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SOCIETÀ ITALIANA DI EMATOLOGIA

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Società Italiana di Ematologia

ROMA,
23-25 Ottobre 2023

Marriott Park Hotel

ABSTRACT BOOK

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BEST ABSTRACTS

B01

THE ITALIAN CART-SIE REAL LIFE EXPERIENCE: A MULTICENTER OBSERVATIONAL STUDY ON CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY FOR LARGE B-CELL (LBCL) AND MANTLE CELL (MCL) LYMPHOMAS

A. Chiappella[1], B. Casadei[2,3], C. De Philippis[4], E. Galli[5,6], S. Ljevar[7], A. Dodero[1], A. Di Rocco[8], M.C. Tisi[9], I. Cutini[10], M.G. Carrabba[11], A. Guidetti[12,1], M. Musso[13], M. Martino[14], A.M. Barbui[15], B. Botto[16], M. Farina[17], G. Grillo[18], J. Olivieri[19], M. Pennisi[1], M. Ladetto[20], L. Arcaini[21], M. Krampera[22], M. Massaia[23], M. Clerico[24], A. Bermema[1], R. Miceli[7], M. Magni[1], P.L. Zinzani[2,3], S. Bramanti[4], P. Chiusolo[5,6], M. Martelli[8], C. Carniti[1], P. Corradini[12,1]

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Axi-cel and tisa-cel are commercially available for LBCL relapsed/refractory (R/R) after at least two regimens, and brexu -cel for R/R MCL failing a BTK inhibitor. CART-SIE is a national observational study evaluating the outcome [overall response rate (ORR), overall survival (OS), progression free survival (PFS)] and the safety [cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS)] of patients treated with CAR-T.

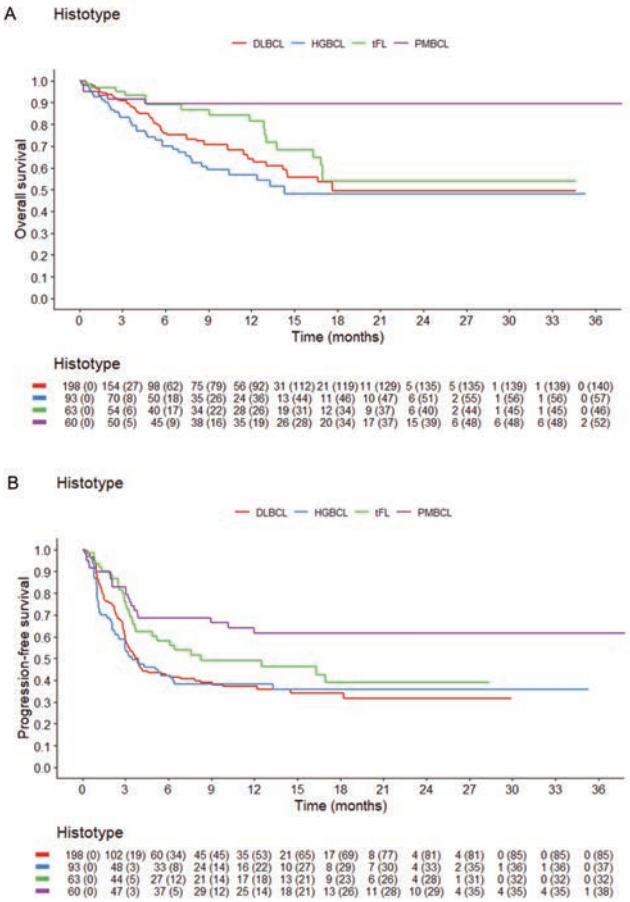

Figure 1.

From March 2019 to April 2023, 564 patients were leukapheresed; 481 were infused (85%) and 461 with adequate follow-up, included into this analysis. Clinical characteristics were as follows: median age 57 years (IQR: 47-65), stage III/IV 323 (70%); bulky disease 155 (34%); 146 (32%) failed prior autologous SCT; 321 (70%) were refractory to the last treatment; 47 (10%) were MCL and 414 (90%) LBCL, including 198 DLBCL, 63 tFL, 93 HGBCL, 60 PMBCL. Bridging therapy was performed in 376 (82%) patients. Median follow-up time for infused patients was 9.51 months (IQR: 4.28, 17.99). In the 414 LBCL, axi-cel was infused in 209 (50%), and tisa-cel in 205 (50%) patients; the ORR at 30-days was 270/ 414 (65%), with 186 (45%) CRs; the 12-months OS was 69% (95% CI: 64-75) and the 12-months PFS was 43% (95% CI: 38-48). OS and PFS by histotype were reported in Figure 1A,B. The ORR at 30-days for brexucel in MCL was 36/47 (77%), with 26 (55%) CRs; the 12-months OS was 84% (95% CI: 70-99) and the 12-months PFS was 70% (95% CI: 53-93). All grade CRS were observed in 384 (83%) patients, with 52 (11%) severe (grade 3-4); ICANS in 114 (25%) patients, with 42 (9%) grade 3-4. Tocilizumab was administered in 299 (65%) and steroids in 119 (26%); 53 patients (12%) were admitted in the intensive care unit. Treatment related mortality was recorded in 9 (2%) patients. A sub-analysis comparing axi-cel and tisa-cel was performed in the LBCL, excluding PMBCL; a propensity score (PS) model estimated for the probability of being treated with tisa-cel (arbitrary) was performed using the same variables of Bachy (Nat Med 2022). The number of patients included were 171, 85 axi-cel and 86 tisa-cel. The PS-weighted univariable cox model for tisa-cel *vs* axi-cel was: OS: HR 1.13 (0.68; 1.88), p 0.6347; PFS: HR 1.22 (0.82; 1.82), p 0.3334. In conclusion, in the CART-SIE study, the outcomes of patients treated with CAR-T were similar to those reported by pivotal trials and real life studies, with manageable toxicities.

B02

MULTIPLE MYELOMA AND SARS-COV-2 INFECTION: AN EUROPEAN HEMATOLOGY ASSOCIATION (EPICOVIDEHA) SURVEY OF SURVIVAL IN 1,221 PATIENTS THROUGH THE DIFFERENT PHASES OF COVID-19 PANDEMIC

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Patients affected by multiple myeloma (MM) have an increased risk of serious COVID-19 and related death. The current epidemiological and therapeutic scenarios suggest that there has been an improvement in severity and survival of COVID-19 during the most recent waves of pandemic in normal population and several cancers, but this has not been tried yet in MM patients. Here we analyzed a cohort of 1,221 patients with MM and confirmed SARS-CoV-2 infection (from 132 centers of 32 countries) included, between February, 2020, and August, 2022, in the EPICOVIDEHA registry, a web-based, open platform for patients with hematological malignancies with SARS-CoV-2. With a median follow-up of 52 days for the entire cohort and 83.5 days for survivors, 303 patients died (24.8%). COVID-19 was a primary reason for death of around 89% of these patients. Overall survival (OS) was significantly higher in vaccinated patients with both stable and active MM versus not vaccinated ones, while only a trend favoring vaccinated patients was observed in subjects with responsive disease. Vaccinated patients with at least 2 doses showed a better OS than those with one single dose or not vaccinated. Patients receiving a combination of antivirals and/or monoclonal antibodies, with or without the adjunct of corticosteroids and/or plasma, also evidenced a better OS. Overall, according to pandemic waves due to SARS-CoV-2 variants, mortality rate decreased over time from 34% to 10.2% (Figure 1).

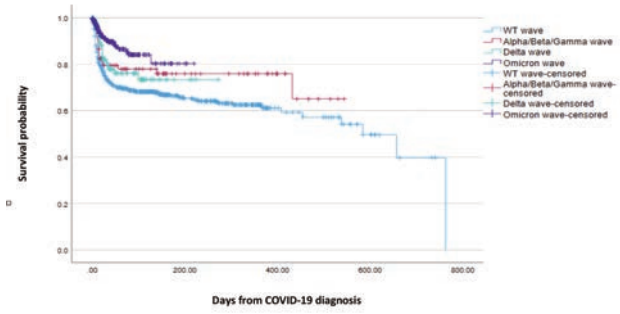

Figure 1. Survival probability by COVID-19 waves (variants of concern).

In particular, differences observed were statistically significant between Omicron and WT waves ($p<0.001$) and between Omicron and Delta waves ($p=0.042$), respectively. At multivariate analysis, age, renal failure, active disease, hospital and intensive cure unit admission, were independently associated with poor survival, while a neutrophil count above $0.5x10^9$/L was found to be protective. This data suggests that OS of MM patients with SARS-CoV-2 infection has significantly improved throughout the different phases of pandemic. However, despite the recent declaration of the end of pandemic by OMS (May 5, 2023), they remain at risk of breakthrough infection and severe complications even in the vaccination era. It is, therefore, still mandatory to maintain attention on these patients, including prevention measures during SARS-CoV-2 outbreaks, appropriate administration of booster doses of mRNA-based, variant-specific vaccines and use of antivirals effective against Omicron subvariants.

B03

IDECABTAGENE VICLEUCEL (IDE-CEL) VERSUS STANDARD REGIMENS IN PATIENTS (PTS) WITH TRIPLE-CLASS–EXPOSED (TCE) RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM): KARMMA-3, A PHASE (PH) 3 RANDOMIZED CONTROLLED TRIAL (RCT)

M. Cavo[1], S. Giralt[2], S. Ailawadhi[3], B. Arnulf[4], K. Patel[5], A. Nooka[6], S. Manier[7], N. Callander[8], L. Costa[9], R. Vij[10], N. Bahlis[11], P. Moreau[12], S. Solomon[13], M. Delforge[14], J. Berdeja[15], A. Truppel-Hartmann[16], Z. Yang[17], J. Felten[17], F. Wu[17], J. Piasecki[17], M. Cook[17,18], P. Otero[19]

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Background. Outcomes are poor in pts with RRMM who are TCE to immunomodulatory (IMiD®) agents, proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies. Ide-cel demonstrated deep durable responses in heavily pretreated TCE RRMM.

Methods. KarMMa-3 (NCT03651128), an open-label RCT, enrolled pts with RRMM who received 2-4 prior regimens, including an IMiD, PI, and daratumumab, and were refractory to the last regimen. Pts were randomized 2:1 to ide-cel or a standard (std) regimen (investigator choice of DPd, DVd, IRd, Kd, or EPd based on prior regimen). Ide-cel was infused at a target dose of 150-450×10^6 CAR+ T cells (≤540×10^6 cells allowed). Primary endpoint: progression-free survival (PFS) assessed by Independent Response Committee (IRC). Key secondary endpoints: IRC-assessed overall response rate (ORR) and overall survival. Other secondary endpoints: duration of response (DOR), health-related quality of life (QoL), pharmacokinetics, and safety. Efficacy assessed per ITT.

Results. Of 386 pts, 225 received ide-cel (median dose 445×10^6 CAR+ T cells) and 126 received std regimens. Baseline characteristics were generally balanced. Median follow-up from randomization to data cutoff was 18.6 months. Ide-cel significantly improved PFS *vs* std regimens (median 13.3 *vs* 4.4 mo; HR 0.49; P<0.0001). Ide-cel significantly improved ORR *vs* std regimens (71% *vs* 42%; P<0.0001), with deep (complete response 39% *vs* 5%), durable responses (median DOR 14.8 *vs* 9.7 mo). PFS and ORR benefit from ide-cel was consistent across multiple pt subgroups. Post–ide-cel infusion, CAR+ T cells underwent rapid multi-log expansion (median 11 d to maximum expansion). In the treated population, grade (gr) 3/4 adverse events (AEs) occurred in 93% and 75% of pts in the ide-cel and std regimen arms, respectively, and gr 5 AEs in 14% and 6%; gr 5 treatment-related AEs in 3% and 1%. In ide-cel-treated pts any-gr cytokine release syndrome occurred in 88%; gr 3/4 in 4%. Any-gr investigator-identified neurotoxicity occurred in 15% of pts; gr 3/4 in 3%. Ide-cel demonstrated clinically meaningful improvements on pt-reported outcomes, including QoL *vs* std regimens (Figure 1).

Conclusions. Ide-cel benefit was consistent across difficult-to-treat subgroups, and the toxicity profile was consistent with prior studies. These results support the use of ide-cel in TCE RRMM, a population with poor survival outcomes. Previously presented at the Transplantation & Cellular Therapy Meetings of ASTCT & CIBMTR, Feb'23.

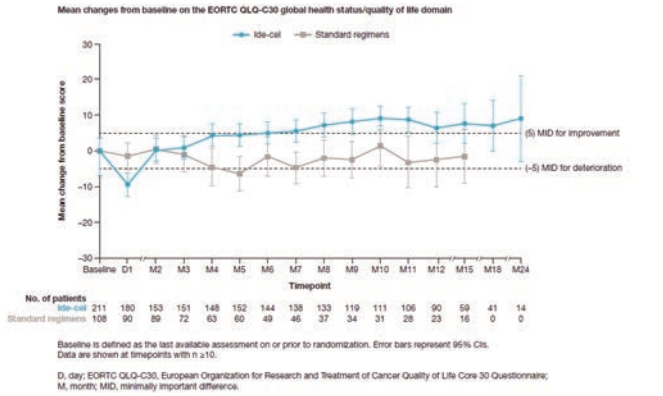

Figure 1.

B04

LUSPATERCEPT *VS* EPOETIN ALFA FOR TREATMENT (TX) OF ANEMIA IN ERYTHROPOIESIS-STIMULATING AGENT (ESA)-NAIVE LOWER-RISK MYELODYSPLASTIC SYNDROMES (LR-MDS) PATIENTS (PTS) REQUIRING RBC TRANSFUSIONS (RBCT): DATA FROM THE PHASE 3 COMMANDS STUDY

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Introduction. There is an unmet need for effective Tx of anemia due to TD LR-MDS. We report interim efficacy and safety results from the COMMANDS trial (NCT03682536) comparing luspatercept *vs* ESA in ESA-naive LR MDS pts.

Methods. Pts ≥18 y, had sEPO <500 U/L and required RBCTs. Pts received luspatercept (1.0–1.75 mg/kg; Q3W) or ESA (450–1050 IU/kg; Q1W) for ≥24 wk. Pts were stratified by baseline RBCT burden, sEPO, and RS status. Primary endpoint was RBC-TI ≥12 wk with concurrent mean Hb increase ≥1.5 g/dL (wk 1–24). Secondary endpoints included HI-E ≥8 wk, RBC-TI 24 wk and ≥12 wk (wk 1–

24), subgroup analyses, response impact of MDS-related gene mutations, safety.

Results. 178 pts were randomized to luspatercept and 178 to ESA (31Aug22); median Tx durations were 41.6 and 27.0 wk. 86/147 (58.5%) luspatercept and 48/154 (31.2%) ESA pts achieved the primary endpoint ($P<0.0001$; Figure 1A); achievement of primary endpoint favored luspatercept or was similar to ESA for all subgroups (Figure 1B). Luspatercept Tx favored achieving HI-E ≥8 wk, RBC-TI 24 wk and ≥12 wk (wk 1–24) (Figure 1A). Median duration of RBC-TI ≥12 wk (wk 1 to end of Tx) was longer with luspatercept *vs* ESA overall (126.6 *vs* 77.0 wk), and for relevant subgroups, including RS+/−. Mutations in *SF3B1*, *SF3B1α*, *ASXL1*, and *TET2* were associated favorably with achievement of clinical benefit with luspatercept over ESA (Figure 1C).

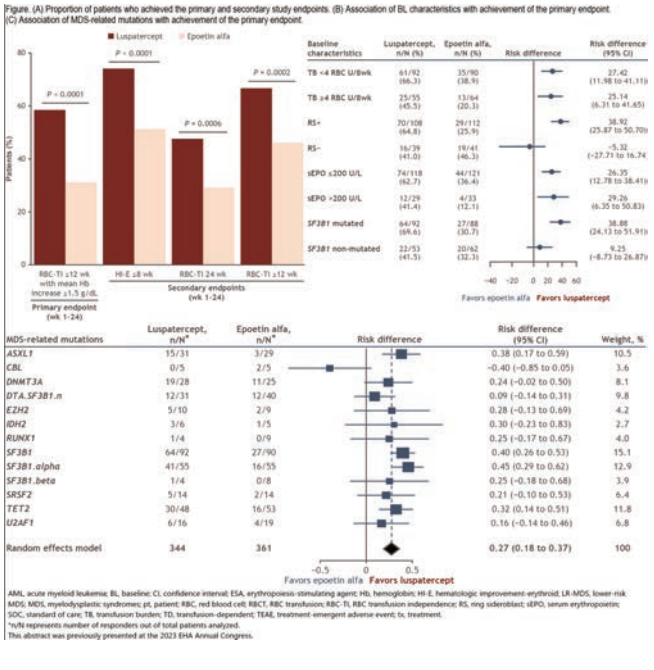

Figure 1.

Luspatercept pts (164 [92.1%]) and ESA pts (150 [85.2%]) reported TEAEs; 8 (4.5%) and 4 (2.3%) pts discontinued due to TEAEs. Most common TEAEs with luspatercept were fatigue (14.6%), diarrhea (14.6%) and hypertension (12.9%), and with ESA asthenia (14.2%), diarrhea (11.4%) and anemia (9.7%); most TEAEs were mild/moderate. 4 (2.2%) luspatercept and 5 (2.8%) ESA pts progressed to AML; death rates were similar (32 [18.0%] *vs* 32 [18.2%]).

Conclusions. Luspatercept showed statistically meaningful HI-E, durable RBC-TI, and favorable outcomes across subgroups and many MDS mutations *vs* ESAs. Luspatercept safety was comparable with previous MDS reports; luspatercept may represent a new standard of Tx in TD LR-MDS.

B05

UPDATED EFFICACY AND SAFETY DATA FROM THE AGILE STUDY IN PATIENTS WITH NEWLY-DIAGNOSED ACUTE MYELOID LEUKEMIA TREATED WITH IVOSIDENIB + AZACITIDINE COMPARED TO PLACEBO + AZACITIDINE

M. Riva[1], B. Bruno[2], F. Ciceri[3], C. Cerchione[4], F. Passamonti[5], P. Zappasodi[6], R. Cairoli[1], S. de Botton[7], P. Montesinos[8], S. Vives Polo[9], E. Zarzycka[10], J. Wang[11], M. Heuser[12], R.T. Calado[13], A.C. Schuh[14], S.P. Yeh[15], J. Hui[16], D.A. Gianolio[16], P. Patel[16], C. Recher[17], H. Dohner[18]

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Background. Ivosidenib (IVO) plus azacitidine (AZA) significantly improved event-free survival (EFS), overall survival (OS) and complete remission + partial hematologic recovery rates *vs* placebo (PBO) plus AZA in the AGILE study (NCT03173248) in patients (pts) with newly diagnosed *IDH1*-mutated acute myeloid leukemia (AML). As of March 2021, median OS (mOS) was 24 months (IVO+AZA) *vs* 7.9 months (PBO+AZA; HR: 0.44; p=0.0005). Long-term follow-up data are presented here.

Methods. In the double-blind, PBO-controlled AGILE study, pts were randomized 1:1 to IVO 500 mg QD + AZA 75 mg/m^2 SC or IV for 7 days in 28-day cycles, or PBO+AZA. Long-term follow-up data (June 2022) for OS, blood count recovery, transfusion independence and safety are described here. As of July 2021, serial bone marrow assessments were not mandated per study protocol, and therefore, updated results for the primary endpoint (EFS) are not available.

Results. 148 pts were randomized: 73 to IVO+AZA; 75 to PBO+AZA. Median treatment duration was 10.8 months (IVO+AZA) *vs* 3.2 months (PBO+AZA). Five PBO+AZA pts crossed over to IVO+AZA after March 2021 and no adjustment was made for crossover for the updated OS analysis. At a median follow-up of 28.6 months, mOS was 29.3 months (95% CI 13.2, not reached) for IVO+AZA *vs* 7.9 (95% CI 4.1, 11.3) for PBO+AZA (HR 0.42 [0.27, 0.65]; p<0.0001). OS rates were 62.9% and 38.3% at 12 months and 53.1% and 17.4% at 24 months, with IVO+AZA and PBO+AZA, respectively. In the IVO+AZA arm, hemoglobin levels steadily increased from baseline (BL; 88.8 g/L) to cycle 8 and then stabilized; mean platelet count recovered from BL values (72.7x 10^9/L) as early as week 8 (171.9x10^9/L) and remained stable; and mean neutrophil counts rapidly increased from BL (0.98x10^9/L) to week 3 (3.99x10^9/L) and week 4 (4.36x10^9/L), and then generally stabilized to within the normal range. Conversion from BL transfusion dependence (red blood cell and/or platelet transfusion dependence) to post-BL transfusion independence was significantly higher with IVO+AZA than PBO+AZA (53.8% *vs* 17.1%, respectively;

p=0.0004). There were fewer neutropenic fever events (27.8% *vs* 33.8%) and infections (34.7% *vs* 51.4%) with IVO+AZA than with PBO+AZA. TEAEs led to discontinuation of IVO+AZA or PBO+AZA in 26.4% and 25.7% of pts, respectively.

Conclusions. Updated data on OS, transfusion independence, blood count recovery and safety confirm the efficacy and safety of IVO+AZA at long-term follow-up.

B06

ORAL THERAPY WITH IPTACOPAN HAS SUPERIOR EFFICACY TO INTRAVENOUS THERAPY WITH ECULIZUMAB OR RAVULIZUMAB AND FAVORABLE SAFETY IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA AND RESIDUAL ANEMIA: PHASE III APPLY-PNH STUDY

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Background. The intravenous (IV) anti-C5 monoclonal antibodies eculizumab and ravulizumab are standard of care (SoC) for hemolytic paroxysmal nocturnal hemoglobinuria (PNH); however, up to 60% of patients (pts) have residual anemia with treatment. Iptacopan is a first-in-class, oral, selective complement factor B inhibitor that showed promising safety and efficacy in two Phase II trials of anti-C5-treated and -naïve pts with PNH.

Methods. The Phase III APPLY-PNH trial (NCT04558918) was a Phase III 24-week multicenter study of the efficacy and safety of iptacopan *vs* continued SoC treatment in adult PNH pts with mean hemoglobin (Hb) <10 g/dL on stable therapy for ≥6 months. Pts were randomized 8:5 to iptacopan 200 mg twice daily or SoC and stratified by prior therapy and red blood cell transfusions (RBCTs) in the preceding 6 months. The two primary endpoints were the proportion of pts with a ≥2 g/dL Hb increase from baseline and the proportion of pts with Hb ≥12 g/dL, each in the absence of RBCTs. Secondary endpoints are listed in the Table 1.

Results. Of 97 pts, 62 and 35 were randomized to iptacopan and SoC, respectively. Baseline disease characteristics were balanced between arms; mean age was 51 years and 69.1% of pts were female. RBCTs were received by 57.7% of pts in the 6 months before randomization. Iptacopan was superior to SoC for both primary endpoints and most secondary endpoints (Table 1). There were no deaths and no serious N. meningitidis, S. pneumoniae or H. influenzae infections. One iptacopan-treated patient had a MAVE (transient ischemic attack; considered unrelated to iptacopan). Headache (iptacopan: 16.1% vs SoC: 2.9%) and diarrhea (14.5% *vs* 5.7%) were more common with iptacopan, whereas infections/infestations (38.7% *vs* 48.6%) and BTH events (3.2% *vs* 17.1%) were more common with SoC. Serious adverse events of hemolysis were reported in two SoC-treated pts compared with no iptacopan-treated pts. No pts discontinued iptacopan or SoC due to adverse events.

Conclusions. In this Phase III trial in PNH pts with residual anemia on IV anti C5 SoC therapy, oral iptacopan resulted in clinically meaningful Hb increases and Hb ≥12 g/dL. These benefits were associated with transfusion independence in almost all pts, clinically meaningful improvements in patient-reported fatigue, and a favorable safety profile. Single agent iptacopan may represent a practice-changing treatment for PNH pts with an inadequate response to IV anti-C5 SoC therapy.

Table 1. Summary of primary endpoints and secondary efficacy and QoL endpoints after the 24-week randomized treatment period of APPLY-PNH.

	Endpoints	Arm	Proportion of patients	Summary statistic	Comparative statistic	Unadjusted *P* value
			*n/M**	*Marginal proportion (% [95% CI])*	*Difference in marginal proportion (% [95% CI])*	
Primary	Proportion of patients with ≥2 g/dL increase in Hb level from baseline† in the absence of RBCTs‡	Iptacopan	51/60	82.3 (73.4, 90.2)	80.3 (71.3, 87.6)	<0.0001
		SoC	0/35	2.0 (1.1, 4.1)		
	Proportion of patients with Hb level ≥12 g/dL† in the absence of RBCTs‡	Iptacopan	42/60	68.8 (58.3, 78.9)	67.0 (56.3, 76.9)	<0.0001
		SoC	0/35	1.8 (0.9, 4.0)		
Secondary	Transfusion avoidance‡	Iptacopan	60/62	96.4 (90.7, 100.0)§	70.3 (52.6, 84.9)§	<0.0001¶
		SoC	14/35	26.1 (12.4, 42.7)§		
			M/N‖	*Adjusted mean change from baseline (95% CI)*	*Adjusted mean difference in change from baseline (95% CI)*	
	Change from baseline in Hb (g/dL)†,¶	Iptacopan	62/62	+3.59 (3.32, 3.86)	+3.63 (3.18, 4.08)	<0.0001
		SoC	30/35	-0.04 (-0.42, 0.35)		
	Change from baseline in FACIT-F scores†,**	Iptacopan	62/62	+8.59 (6.72, 10.47)	+8.29 (5.28, 11.29)	<0.0001
		SoC	31/33	+0.31 (-2.20, 2.81)		
	Change from baseline in ARC (10^9/L)†,††	Iptacopan	62/62	-115.89 (-126.49, -105.30)	-116.26 (-132.17, -100.36)	<0.0001
		SoC	35/35	+0.37 (-13.03, 13.77)		
			M/N‖	*Geometric adjusted mean ratio to baseline*	*Reduction (% [95% CI])*	
	Ratio to baseline in log-transformed LDH (U/L)†,‡‡	Iptacopan	62/62	0.96 (0.90, 1.03)	1.15 (-10.18, 11.32)	No superiority
		SoC	35/35	0.98 (0.89, 1.07)		
			n/N§§	*Adjusted annual rate (% [95%CI])*	*Rate ratio (95% CI)*	
	Rate of clinical BTH‖‖	Iptacopan	2/62	0.07 (0.02, 0.31)	0.10 (0.02, 0.61)	0.0118
		SoC	6/35	0.67 (0.26, 1.72)		
	Rate of MAVEs	Iptacopan	1/62	0.03 (0.00, 0.25)	Not estimable	No superiority
		SoC	0/35	0		

A prespecified testing procedure adjusted for multiplicity; 2-sided P values are reported for significant endpoints only. *n=number of patients with response, M=number of patients with evaluable/non-missing data; †Assessed between D126–168; ‡Between D14–168; §The prespecified methodology for handling of missing data may have underestimated transfusion avoidance in the SoC arm, so a *post hoc* sensitivity analysis was conducted using a more conservative modeling approach. In this analysis, marginal proportions (95% CI) were 96.7% (91.3, 100.0) *vs* 38.9% (23.1, 55.8) for iptacopan and SoC, respectively (P<0.0001); ‖M=number of patients with evaluable/non-missing data, N=overall number of patients; ¶Mean (SD) baseline Hb levels were 8.93 (0.70) and 8.85 (0.90) g/dL in the iptacopan and SoC arms, respectively; **Mean (SD) baseline FACIT-F scores were 34.7 (9.8) and 30.8 (11.5) in the iptacopan and SoC arms, respectively; ††Mean (SD) baseline ARCs were 193.2 (83.6) and 190.6 (80.9) 10^9/L in the iptacopan and SoC arms, respectively; ‡‡Mean (SD) baseline LDH levels were 269.1 (70.1) and 272.2 (84.8) U/L in the iptacopan and SoC arms, respectively; §§n=number of patients with event, N=overall number of patients; ‖‖Events that met the protocol-specified criteria for clinical BTH. ARC, absolute reticulocyte count; BTH, breakthrough hemolysis; CI, confidence interval; D, day; Hb, hemoglobin; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; QoL, quality of life; RBCT, red blood cell transfusion; SD, standard deviation; SoC, standard of care.

B07

THE IMPACT OF ALLOGENEIC STEM CELL TRANSPLANTATION IN PH-LIKE PATIENTS: A REPORT FROM THE NATIONAL TREATMENT PROTOCOLS GIMEMA 1913 AND GIMEMA 2317

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Background. Philadelphia (Ph)-like acute lymphoblastic leukemia (ALL) is characterized by a gene-expression signature resembling true Ph-positive ALL and treated with chemotherapy shows poorer outcomes. The benefit of allogeneic hematopoietic stem cell transplant (alloHSCT) is to be investigated. This study's aim was to investigate the impact of alloHSCT on prognosis of Ph-like ALL in patients enrolled in two consecutive Italian national phase II trials (GIMEMA 1913 & GIMEMA 2317).

Table 1. Patients' characteristics.

Patients' characteristics

Characteristic	Overall, N = 197	Ph like, N = 58	No Ph like, N = 139	P value
Median Age (range)	40 (18 , 65)	39 (18 , 65)	40 (18 , 65)	0,65
WBC >30 x 10^9/L, n (%) WBC <30 x 10^9/L, n (%) Unknown, n (%)	54 (27%) 140 (72%) 3 (1%)	25 (43%) 31 (54%) 2 (3%)	29 (20.3%) 109 (79%) 1 (0.7%)	0,001
Standard risk, n (%) No Standard Risk, n (%) Unknown, n (%)	120 (64%) 68 (36%) 9	28 (54%) 24 (46%) 6	92 (68%) 44 (32%) 3	0.091
ECOG 0-I, n (%) ECOG ≥ II, n (%) Unknown, n (%)	174 (92%) 16 (8.4%) 7	50 (91%) 5 (9.1%) 3	124 (92%) 11 (8.1%) 4	0.60
Ikaros^{plus}, n (%)	41 (27%)	24 (51%)	17 (16%)	<.0001
Protocol LAL2317, n (%) Protocol LAL 1913, n (%)	109 (55%) 88 (45%)	30 (52%) 28 (48%)	79 (57%) 60 (43%)	0.53

Methods. In this analysis, 197 patients, 88 enrolled in the GIMEMA1913 protocol and 109 in the GIMEMA 2317. Ph-like status was evaluated according to "BCR/ABL1-like predictor" but was not part of transplant allocation decision-making. At variance patients were considered eligible to alloHSCT in CR1 based on the joint assessment of conventional disease risk profile at diagnosis and post-consolidation MRD status.

Results. A Ph-like signature was identified in 58/197(29.4%) ALL patients. Patients' features are shown in Table 1. Complete remission (CR) was achieved in 88% of non-Ph-like and 81% of Ph-like patients (p=0.26), while MRD negativity at TP2, after the first 3 chemotherapy cycles, was lower in Ph-like group (61% *vs* 77%, p=0.074). In terms of 2-y. disease-free survival (DFS) and overall survival (OS) Ph-like patients did markedly worse than no Ph-like patients (DFS 48%(95%CI:35-68%) *vs* 78%(95%CI:71-87%), p<0.0001); OS 61%(95%CI:47-78%) *vs* 79% (95%CI:72-87%), p=0.107).

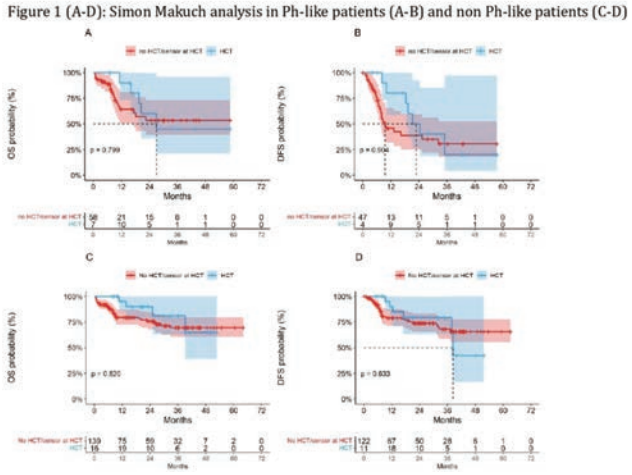

Figure 1.

Among the whole patients' cohort, 45 patients underwent an alloHSCT in CR1: of those 38% were Ph-like and 62% non-Ph-like ALL. To overcome the bias of time to transplantation, the therapeutic efficacy of transplantation was tested by a Simon-Makuch analysis. In both Ph-like and non-Ph-like patients a consolidative alloHSCT overwhelms the unfavorable impact of MRD positivity, which was the main reason to allocate patients to alloHSCT in CR1 according to the study design (Figure 1 A-D).

Conclusions. Ph-like signature defines a very high-risk group of ALL characterized by worse OS and DFS. The benefit gained by an alloHSCT in Ph-like patients at higher risk of relapse due to the persistence of MRD positivity, suggests that transplantation remains a crucial treatment also in this subset of ALL.

B08

REAL-WORLD EFFICACY PROFILE OF ASCIMINIB IN AN ITALIAN, MULTI-RESISTANT CHRONIC-PHASE CHRONIC MYELOID LEUKEMIA (CML-CP) PATIENT POPULATION

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Asciminib (Asc) is the first tyrosine kinase inhibitor (TKI) to Specifically Target the ABL Myristoyl Pocket (STAMP). The recent update of the ASCEMBL study demonstrated a superior efficacy with a good tolerability of Asc compared to bosutinib in chronic phase chronic myeloid leukemia (CP-CML) patients (pts) intolerant or refractory to ≥2 TKIs (Rea *et al.*, 2022)

Here we present the real-world clinical outcomes of 77 3rd + line Italian CP-CMLpts who received Asc through a Managed Access Program (MAP) approved by Novartis in 41 Italian institutions.

BCR::ABL1/ABL ratio was expressed as % IS. Efficacy was analyzed by comparing the best response registered as well as the response at 3 months *vs* the response at baseline

The median number of prior TKIs were 3 (2-5) and 51.7% of pts were reported to have ≥3 comorbidities. Switch to Asc occurred for resistance in 44 pts (57.1%) and for intolerance in 33 pts (42.9%). Eleven pts(14.3%) harbored a T315I mutation. Forty-three pts (55.8%) had a prior exposure to ponatinib and 38 of them (88.4%) had ponatinib as last TKI before switching to Asc. At the time of data cut-off, 60 pts (77.9%) remained on treatment with a median treatment duration of 8.5 months (3-38) Reason for Asc discontinuation was progression (n=5, 6.4%), resistance (n=2, 2.5%), intolerance (n=2, 2.5%), death (n=1, 1.2%) and allogenic transplant (n=7, 9%).

Sixty-eight out of 77 (88.3%) and 70/77 (90.9%) pts maintained or improved their previous response at 3 months and at the best response time point respectively (Figure 1A). After 3 months, 34/77 (44.2%) pts showed an improvement of previous baseline response with approximately 33% of pts, without MMR response at baseline, that was able to reach at least this response. At the same time point, considering pts who enter the MAP without MR2, 51% achieved this response level. Previous ponatinib treated pts showed a reduced probability of reaching MMR when compared to ponatinib naive condition. Specifically, of the 34/43 (79.1%) ponatinib pre-treated pts without an MMR at baseline, 12 (35.3%) reached an MMR whereas of the 30 out of 34 of ponatinib naive pts without MMR at baseline, 19 of them (63.3%) reached an MMR (Figure 1B).

In this heavily pre-treated population of CML pts most of whom with a high comorbidity burden, Asc demonstrated fast and sustained responses. Collectively, these results continue to confirm that Asc has a promising role as standard of care in pts with CP-CML treated with ≥2 prior TKI.

1A. Proportion of patients who maintained, improved or lost response respect to baseline

	MISSING*	WORSENING, n (%)	NO CHANGE, n (%)	IMPROVEMENT, n (%)
3 months (N=77)	3 (3.90)[a]	6 (7.79)	34 (44.16)	34 (44.16)
Best response (N=77)	1 (1.30)[b]	6 (7.79)	24 (31.17)	46 (59.74)

a. Missing results were due to MR value not available at baseline or at month 3, b. Missing results was due to MR value not available at baseline

1B. Patients who reached MMR

	Ponatinib Naive (N=34)	Ponatinib pre-treated (N=43)
Patients with MR<MR3 at baseline, n (%)	30 (88.24)	34 (79.07)
Patients who reached MR3, n (%)	19 (63.33)	12 (35.29)

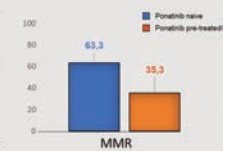

Figure 1.

B09

RUXOLITINIB ADHERENCE IN MYELOFIBROSIS AND POLYCYTHEMIA VERA: THE "RAMP" ITALIAN MULTICENTER PROSPECTIVE STUDY

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Ruxolitinib (RUX) is beneficial in myelofibrosis (MF) and polycythemia vera (PV) patients (pts). Information on adherence (ADH) is scant. After IRB approval, the RAMP Italian prospective study included 189 pts with MF (n. 141, 75%) or PV (n.48, 25%), that received RUX monotherapy in 9 Hematology Centers. Pts completed the Adherence to Refills and Medications Scale (ARMS) and Distress Thermometer and Problem List (DTPL) at the earliest convenient time (wk0), irrespective of the RUX start date, and again after 4, 8, 12, 24 and 48 wks (Table 1). The aims of the RAMP study were to evaluate:1) incidence of/features correlated to LOW-ADH;2) modifications of ARMS/DTPL scores over time;3) impact of ARMS/DTPL scores on spleen response (SR) in MF. LOW-ADH (ARMS>14) was declared by 94 pts (49.7%) (MF: 48.2%; PV: 54.2%); 76 pts (40.2%) (MF: 39.7%; PV: 41.7%) reported a high distress (DT ≥4). Main reason for LOW-ADH was attributed to difficult RUX supply process (49%), intentional (4.3%) or unintentional (46.7%) non-take. Unintentional LOW-ADH was more frequent in PV (65.4% *vs* 39.7% MF, p=0.03). In multivariate regression analysis (MVA), baseline LOW-ADH was associated to male sex (OR: 3.2, p=0.001), high distress (OR: 3.8, p<0.001), and RUX duration >1yr (OR: 2.2, p=0.03). LOW-ADH was associated to male sex & high distress (OR 3.0, p=0.01 & OR 3.4, p=0.005) in MF and to low education level (OR: 3.7, p=0.04) in PV. Considering only the 8 questions directly related to intentional/unintentional non-take, 63/189 (33%) pts had a LOW-ADH (45.9% PV *vs* 29.1% MF, p=0.03) that was mainly unintentional (n. 56, 89%). Among the 138 (73%) pts who completed both tests at all timepoints, 51 (37%) had always a LOW-ADH, which was associated to male sex (OR: 3.1, p=0.006) and high distress (OR: 2.3, p=0.04) in MVA. The risk for stable LOW-ADH was associated to male sex in MF (OR 3.5, p=0.008) and to low educational level (OR 5.5, p=0.05) in PV. Among these 138 pts, LOW-ADH tended to decrease over time (from 53.6% to 49.3% at wk48), while high distress decreased (from 44.2% to 38.4%). Finally, pts who always maintained high ADH & low distress were more likely to obtain/maintain 24 wk SR (Mc Nemar test, p=0.02 & p=0.04). The RAMP study shows that LOW-ADH to RUX remains an unmet clinical need that requires a multifaceted approach based on reasons behind it, pts characteristics and treatment duration. ADH evaluation may distinguish true RUX failure from pts in need of therapy optimization.

Table 1. Baseline characteristics and ARMS/DT scores over time.

Characteristics	
Male sex, n (%)	112 (59.3%)
Age (years), median (range)	70.0 (33.7-88.9)
>70 years, n (%)	95 (50.3%)
Myelofibrosis	141 (74.6%)
Polycythemia Vera	48 (25.4%)
Presence of caregiver, n (%) on 177 evaluable	82 (46.3%)
Education, n (%) on 182 evaluable	
None	2 (1.1%)
Primary	30 (16.5%)
Middle school	53 (29.1%)
High school	71 (39.0%)
University	26 (14.3%)
Employment, n (%) on 181 evaluable	
Retired	101 (55.8%)
Employed	47 (26%)
Domestic work	29 (16.0%)
Unemployed	4 (2.2%)
Visit frequency in the 12 months before wk0, on 181 evaluable	
>4 visits/year every 3 months	50 (27.6%)
2-4 visits/year	126 (69.6%)
1 visit/year	5 (2.8%)
Chronic intake of tablets for other diseases, n (%)	152 (81.3%)
Total number of daily tablets including RUX, median (range)	6 (0-20)
Patients who report being followed by a stable team of hematologists, n (%)	189 (100%)
Patients who report having satisfactory relationship with the hematologists, n (%)	188 (99.5%)
Patients who think too high the number of RUX tablets/day, n (%)	19 (10%)
Patients who think too high the number of RUX administrations/day, n (%)	12 (6.4%)
Patients who think that RUX intake interferes with work, n (%)	7 (3.7%)
Patients who think that RUX intake is relevant for health, n (%)	186 (98.4%)
Patients who think that RUX intake has improved health status, n (%)	171 (91.4%)
Median yrs from RUX start to wk 0, (range)	1.88 (0.02-12.65)
> 1 year from RUX start to wk 0, n (%)	127 (67.2%)
Patients who declare low adherence before taking the first ARMS/DTPL tests, n (%) on 178 evaluable	2 (1.1%)
Median ARMS score (standard deviation)	
wk0	14 (2.0)
wk4	15 (2.3)
wk8	14 (2.3)
wk12	14 (2.1)
wk24	14 (2.0)
wk 48	15 (1.9)
Median distress score (standard deviation)	
wk0	2 (2.8)
wk4	2 (2.7)
wk8	2 (2.7)
wk12	3 (2.8)
wk24	2 (2.5)
wk 48	3 (2.7)

B10

IMPROVED OVERALL SURVIVAL WITH FIRST-LINE BRENTUXIMAB VEDOTIN PLUS CHEMOTHERAPY IN ADVANCED CLASSICAL HODGKIN LYMPHOMA: UPDATED ANALYSIS OF ECHELON-1

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Based on 5-year data from ECHELON-1 (NCT01712490), patients with previously untreated stage III/IV classical Hodgkin lymphoma (cHL) treated with brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) had improved progression-free survival (PFS) *vs* doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD); A+AVD had a manageable long-term safety profile. We report an overall survival (OS) analysis from ECHELON-1 after a median follow-up of 6 years (data cut-off June 1, 2021). Randomized patients (1:1) received ≤6 cycles of A+AVD (n=664) or ABVD (n=670) on days 1 and 15, every 28 days. OS (event-driven, type-1 error controlled) in the intent-to-treat population was a key secondary endpoint. Analysis of OS in prespecified subgroups was exploratory and not adjusted for multiplicity. PFS per investigator was reported for long-term follow-up. Deaths during follow-up and causes of death by investigator assessment were summarized.

In the A+AVD *vs* ABVD arms, 6-year OS estimates were 93.9% (95% confidence interval [CI] 91.6-95.5) *vs* 89.4% (95% CI 86.6-91.7); 39 *vs* 64 deaths were reported (hazard ratio [HR] 0.59; 95% CI 0.40-0.88; p=0.009; median follow-up 73 months). OS was examined in prespecified subgroups; in a multivariable analysis adjusting for baseline demographic and disease factors, OS benefit with A+AVD *vs* ABVD was preserved (HR 0.53; 95% CI 0.34–0.83). PFS was longer with A+AVD *vs* ABVD (HR 0.68; 95% CI 0.53–0.86). Fewer patients treated with A+AVD *vs* ABVD received subsequent therapy (135 [20%] *vs* 157 [24%]) including fewer autologous (44 [7%] *vs* 59 [9%]) and allogeneic (4 [<1%] *vs* 12 [2%]) stem cell transplants; radiation use was similar (55 [8%] *vs* 58 [9%]). There were fewer second malignancies (23 *vs* 32) and deaths related to cHL or treatment complications (32 *vs* 45) or second malignancies (1 *vs* 11) with A+AVD *vs* ABVD. Fertility was not formally assessed; 195 pregnancies were reported by patients and their partners (A+AVD 114, ABVD 81). Peripheral neuropathy (PN) had improved/resolved in most patients at last follow-up (A+AVD 379 [86%], ABVD 249 [87%]); PN incidence was higher with A+AVD (443 [67%]) *vs* ABVD (286 [43%]).

In patients with previously untreated stage III/IV cHL, A+AVD resulted in a significant reduction in the risk of death (41%) *vs* ABVD with a manageable long-term safety profile, consistent with prior reports.

B11

ABSTRACT NOT PUBLISHABLE

B12

FIRST REPORT OF PHALLCON: A PHASE 3 STUDY COMPARING PONATINIB (PON) *VS* IMATINIB (IM) IN NEWLY DIAGNOSED PH+ ALL

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Background. The standard of care in patients (pts) with newly diagnosed (dx) Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) is BCR::ABL1 tyrosine kinase inhibitors (TKIs) with chemotherapy (chemo) or steroids. Treated with 1st- or 2nd-generation TKIs, pts eventually progress due to emergence of resistance. Multiple studies have reported promising minimal residual disease (MRD) negativity (neg) rates and survival outcomes with pon in combination with chemo or chemo-free regimens. PhALL-CON (NCT03589326), the first phase 3 randomized study comparing TKIs in pts with Ph+ ALL, evaluates pon *vs* im in combination with reduced-intensity chemo.

Methods. This open-label trial randomized adult newly dx Ph+ ALL pts 2:1 to pon (30 mg once daily [QD]) or im (600 mg QD) with reduced-intensity chemo through end of induction (EOI; Cycles 1–3), consolidation (Cycles 4–9), and post-consolidation (Cycles 10–20). After Cycle 20, pts received single-agent pon or im until disease progression or unacceptable toxicity. The composite primary endpoint was MRD-neg (*BCR::ABL1* ≤0.01%) complete remission (CR) for 4 weeks at EOI. Event-free survival (EFS: any cause death, failure to achieve CR by EOI, relapse from CR) was a key secondary endpoint.

Table 1.

	Ponatinib	Imatinib
Responses at EOI, n (%)*	**(N=154)**	**(N=78)**
MRD-neg (*BCR::ABL1* ≤0.01%) CR	53 (34)	13 (17)
P value	0.0021	
MR 4 (*BCR::ABL1* ≤0.01%)	64 (42)	16 (21)
MR 4.5 (*BCR::ABL1* ≤0.0032%)	39 (25)	10 (13)
AEs, n (%)	**(N=163)**	**(N=81)**
Grade 5 TEAEs/TRAEs	8 (5)/0	4 (5)/1 (1)
Grade 3–4 TEAEs	139 (85)	71 (88)
TE AOE (any grade)	4 (2)	1 (1)

*Efficacy evaluable.
AE, adverse event; CR, complete remission; EOI, end of induction; MR, molecular response; MRD-neg, minimal residual disease negativity; TE, treatment-emergent; TR, treatment-related

Results. 245 pts were randomized to pon (n=164) or im (n=81); median age was 54 y (37% ≥60 y). At data cutoff (Aug 2022), 78 pts (pon *vs* im: 42% *vs* 12%) were on study treatment; the top 3 reasons for discontinuation were hematopoietic stem cell transplantation (31% *vs* 37%), adverse events (12% *vs* 12%), and lack of efficacy (7% *vs* 26%). Median follow-up was 20 *vs* 18 mo (pon *vs* im). The primary endpoint was met (Table 1) by clinically significantly higher MRD-neg CR rate for pon *vs* im (34.4% *vs* 16.7%; *P*=0.0021). Survival data were not mature, but the median EFS was reached in im and not in pon, with a trend toward improvement (HR=0.652, 95% CI=0.385–1.104). Time to treatment failure also showed a trend toward improvement (HR=0.455). The treatment-emergent adverse event (TEAE) rates (any grade [Gr] and Gr3/4/5) were comparable between treatment arms. Arterial occlusive events (AOEs) were infrequent and similar between the arms (Table 1).

Conclusions. Pon was superior to im in combination with reduced-intensity chemo in pts with newly dx Ph+ ALL, with a clinically significantly higher MRD-neg CR rate at EOI. Pon was associated with deep and durable responses, with a trend toward improved EFS and comparable safety *vs* im.

ORAL COMMUNICATIONS

Anemia and erythrocyte disorders

C001

ORAL COMPLEMENT FACTOR B INHIBITOR IPTACOPAN DEMONSTRATES EFFICACY AND TOLERABILITY AS MONOTHERAPY IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS NAÏVE TO COMPLEMENT INHIBITION: PHASE III APPOINT-PNH STUDY

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Background. The first-in-class, oral, selective complement factor B inhibitor iptacopan demonstrated efficacy and safety in patients (pts) with paroxysmal nocturnal hemoglobinuria (PNH) and residual anemia despite anti-C5 treatment in the Phase III randomized APPLY-PNH trial. We report primary efficacy and safety data from the 24-week core treatment period of the single-arm, open-label, multicenter, Phase III APPOINT-PNH trial in pts with complement inhibitor-naïve, hemolytic PNH (NCT04820530; data cut-off: 2 November 2022).

Methods. Adults with complement inhibitor-naïve PNH with mean hemoglobin (Hb) <10 g/dL and lactate dehydrogenase (LDH) >1.5 x upper limit of normal received iptacopan monotherapy 200 mg twice daily. The primary endpoint was a ≥2 g/dL Hb increase from baseline in the absence of red blood cell transfusions (RBCTs). Secondary efficacy endpoints (Table 1) and safety were also assessed.

Results. Of 40 pts enrolled (mean age: 42.1 years), 42.5% were female. Mean (SD) time since diagnosis was 4.7 (5.5) years; 70% of pts received RBCTs in the prior 6 months. Baseline mean (SD) Hb and LDH levels were 8.16 (1.09) g/dL and 1698.8 (683.3) U/L, respectively. The study met its prespecified success criterion with an estimated 92.2% of pts (95%CI 82.5, 100) achieving a ≥2 g/dL Hb increase from baseline; 62.8% of pts (95% CI 47.5, 77.5) had Hb ≥12 g/dL and 97.6 of pts (95% CI 92.5, 100) had transfusion avoidance by Week 24. Clinically meaningful differences were also observed for other secondary endpoints (Table 1). No clinical breakthrough hemolysis events, major adverse vascular events, or deaths were observed. Four serious adverse events were reported: bacterial pneumonia, COVID-19, cataract and type II diabetes mellitus. Infections/infestations (40.0% of pts, mainly COVID-19 [15.0%]), headache (27.5%) and diarrhea (7.5%) were the most frequent adverse events. No pts discontinued iptacopan.

Conclusions. In this single-arm Phase III trial in pts with complement inhibitor-naïve hemolytic PNH, oral iptacopan monotherapy resulted in clinically meaningful Hb increases with good control of intravascular hemolysis in most pts; transfusion avoidance and patient-reported fatigue also improved. Iptacopan monotherapy demonstrated a favorable safety profile with no clinical breakthrough hemolysis events. Oral iptacopan monotherapy represents a potentially practice-changing outpatient treatment that could become a preferred therapeutic option for pts with hemolytic PNH.

Table 1. Summary of efficacy and quality of life endpoints after the 24-week core treatment period of APPOINT-PNH.

	Endpoints	Proportion of patients	Summary statistic
		*n/M**	Estimated proportion† (% [95% CI])
Primary	Response defined as increase from baseline in hemoglobin of ≥2 g/dL‡ in the absence of RBCTs§	31/33	92.2 (82.5, 100)
Secondary	Response defined as hemoglobin level ≥12 g/dL‡ in the absence of RBCTs§	19/33	62.8 (47.5, 77.5)
	Transfusion avoidance§	40/40	97.6 (92.5, 100)
		M/N‖	Adjusted mean change from baseline (95%CI)
	Change from baseline in hemoglobin level (g/dL)‡,¶	40/40	+4.28 (3.87, 4.70)
	Change from baseline in FACIT-Fatigue score‡,**	40/40	+10.75 (8.66, 12.84)
	Change from baseline in ARC (10^9/L)‡,††	40/40	-82.48 (-89.33, -75.62)
	Percentage change from baseline in LDH level (U/L)‡,§§	39/40	-83.55 (-84.90, -82.08)
		n/N‡‡	Adjusted annual rate (% [95%CI])
	Rate of clinical breakthrough hemolysis¶¶	0/40	0 (0.00, 0.17)
	Rate of MAVEs	0/40	0 (0.00, 0.17)

Response probability was described as proportions of responders with 95%CI computed using bootstrap; missing data were accounted for using Bayesian multiple imputation. *n=number of patients with response, M=number of patients with evaluable/non-missing data; †Estimated proportions reflect the population average probability of a patient meeting the endpoint criteria; ‡Assessed between D126–168 – evaluable if at least one value is non-missing; §Between D14–168; ‖M=number of patients with evaluable/non-missing data, N=overall number of patients; ¶Mean (SD) baseline hemoglobin level was 8.16 (1.09) g/dL; **Mean (SD) baseline FACIT-Fatigue score was 32.78 (10.17); ††Mean (SD) baseline ARC was 154.33 (63.67) x 10^9/L; §§Mean (SD) baseline LDH level was 1698.8 (683.3) U/L; ‡‡n=number of patients with at least one event, N=overall number of patients; ¶¶Events that met the protocol-specified criteria for clinical breakthrough hemolysis. 95%CI, 95% confidence interval; ARC, absolute reticulocyte count; D, day; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; RBCT, red blood cell transfusion; SD, standard deviation

C002

CLINICAL POTENTIAL OF BIOMIMETIC PROTEOLIPID LEUCOSOME VESICLES FOR DELIVERY OF GPI-ANCHORED PROTEINS

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Novel platforms for drug delivery are required to highly increase molecule uptake by specific targeted cells simultaneously reducing off-target effects and to enhance drug efficiency. Liposomes consist of an aqueous volume entrapped by one or more bilayers formed by both natural and/or synthetic lipids, and are promising biocompatible

vesicular carriers, because of their amphipathic nature allowing encapsulation of a wide range of molecules. Membrane protein incorporation within liposome bilayer is a novel promising drug delivery system. In this study, we characterized liposomes functionalized with human membrane proteins and assembled using a microfluidic technology. These biomimetic proteo-lipid vesicles (BPLVs) were then explored for their clinical potential as glycosylphosphatidylinositol (GPI)-anchored protein-delivery system for reverting GPI deficiency in paroxysmal nocturnal hemoglobinuria (PNH).

BPLVs were produced by microfluidic technique using the Nano - Generator Flex (Precigenome) and using an optimized mixture of human membrane proteins from healthy controls and rhodamine-conjugated synthetic lipids. BPLV size, distribution and zeta-potential were measured using a Nano ZS MAlvern Zeta Sizer. Flow cytometry immunophenotyping was carried out to confirm the presence of GPI-anchored proteins correctly inserted within BPLV bilayer. Next, peripheral blood mononuclear cells (PBMCs) from healthy donors and PNH patients were treated with BPLVs for 24h, 48h, and 72h at a final concentration of 0.5 mg/mL. Flow cytometry immunophenotyping was performed to investigate changes in GPI-anchored protein expression after treatment, as well as cell viability to exclude any BPLV-related toxicity.

Produced BPLVs showed high homogeneity and an optimal DLS potential was cell incorporation. Moreover, BPLVs correctly carried human surface proteins, such as CD3. CD14, CD33, CD45, HLA-DR, and FLAER, a molecule that binds the GPI-anchor thus identifying all GPI-linked proteins and being a marker of the presence of post-translational-modified proteins on BPLVs. After treatment, PBMCs show high viability and uptake of BPLV-carried proteins (Figure 1) in both healthy and PNH subjects.

BPLVs are promising nanocarrier delivery system and can be used to deliver human membrane proteins to revert deficiency on targeted cells, such as GPI-anchor proteins on PNH cells. Further *in vitro* and *in vivo* studies are required to validate our preliminary results.

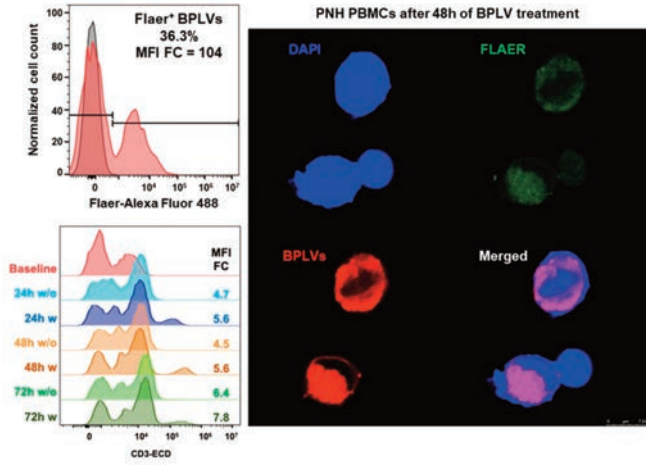

Figure 1.

C003

PREGNANCY IN ACQUIRED BONE MARROW FAILURE SYNDROMES AND PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: A SINGLE CENTER EXPERIENCE

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Onset/relapse of aplastic anemia (AA), hypoplastic myelodysplastic syndrome (hMDS) and paroxysmal nocturnal hemoglobinuria (PNH) during pregnancy are rare events and little is known about management and fetal/maternal outcomes. We conducted a single-center retrospective study evaluating impact of these disorders on pregnancy, focusing on disease severity, treatment need and outcomes. Seventy pregnancies occurring in 52 women were registered between 1989 and 2022 (Table 1).

Table 1.

	Overall	De novo AA/hypoMDS	Previously diagnosed AA/hypoMDS	With PNH clone >10%
N° of women, n	52	17	28	22
N° of pregnancies, n	70	17	38	34
Hemoglobin at onset/relapse, g/l, median (range)	-	73 (49-112)	83 (78-113)	-
Reticulocytes at onset/relapse, x10⁹/l, median (range)	-	50 (32-62)	66 (65-66)	-
Neutrophils at onset/relapse, x10⁹/l, median (range)	-	1.8 (0.1-4.5)	2.5 (1.5-6.6)	-
Platelets at onset/relapse, x10⁹/l, median (range)	-	22 (2-87)	33 (22-65)	-
Transfusion needs during pregnancy, n (%)	40 (57)	16 (94)	14 (37)	21 (62)
- for onset/relapse;	24	16	7	6
- without frank relapse or for PNH-related hemolysis	16	-	7	16
Treatment during pregnancy, n (%)	15 (27)[§§]	8 (47)	7 (18)	-
- CSA, n	12	5	7	-
- Steroids, n	3	3	-	-
- Eculizumab, n	33	1	20	33
Blood counts improvement after delivery, n (%)	29 (41)	9 (53)	17 (45)	14 (41)
Treatment after pregnancy, n (%)	14 (25)[§§]	10 (59)	4 (11)	-
- ATG-based, n	6	5	1	-
- CSA ± eltrombopag, n	6	3	3	-
- Androgens, n	1	1	-	-
- HSCT, n	1	1	-	-
- Eculizumab, n	26	1	12	26
Miscarriage, n (%)	5 (7)	-	4 (11)	5 (15)
- I trimester	4		3	4
- II trimester	1		1	1
Maternal complications, n (%)	17 (24)	5 (29)	9 (24)	9 (26)
- Thrombotic complications	1	-	1	1
- Infective complications	6	1	4	3
- Bleeding complications	4	2	2	-
- Placental complications (pre-eclampsia; retained placenta; PROM)	6 (2; 2; 2)	2 (0; 1;1)	2 (2; 0; 0)	5 (2; 1; 2)
- Needs of urgent cesarean section or delivery before full term (for any causes)	6	2	4	4
- Needs of additional peripartum transfusion support	7	3	1	4
Fetal complications, n (%)	8 (11)	4 (24)	3 (8)	4 (12)
- Prematurity[##]	6	3	2	3
○ Extremely preterm (less than 28 weeks)	2	-	2	2
○ Very preterm (28-32 weeks)	1	-	-	1
○ Moderate-late preterm (32-37 weeks)	3	3	-	-
- Fetal growth restriction	1	1	-	-
- Other (talipes foot)	1	-	1	1

[§§]Percentage calculated excluding pregnancies in patients with isolated PNH (N=55).
[##]According to the WHO definition of prematurity.

AA, aplastic anemia; ATG, anti-thymocyte globulin; CSA, cyclosporin; hypo-MDS, hypoplastic myelodysplastic syndrome; HSCT, allogeneic stem cell transplant; PNH, paroxysmal nocturnal hemoglobinuria; PROM, premature rupture of membrane.

Thirty-three women had a previous hematologic diagnosis (25 AA; 3 hMDS; 5 PNH) while 19 had an onset during pregnancy (14 AA; 3 hypo-MDS; 2 PNH). Among the 33 with a previous diagnosis, 16 women had received ≥1 therapy line (12 ATG; 3 CSA; 1 tacrolimus), 3 ≥2 lines and 5 received eculizumab (ecu). Twenty-two were on treatment at pregnancy onset (3 CSA; 1 eltrombopag; 18 ecu). AA/hMDS relapses occurred in 24% of pregnancies, with 48% dur-

ing the 1st trimester. At the time of onset/relapse, median Hb was 80 g/l (49-113), reticulocytes 59x10^9/l (32-66), ANC 2.27 x10^9/l (0.1-6.6), and PLT 32x10^9/l (2-87). Transfusions were necessary in 57% and CSA was used in 12. Eight patients started CSA during pregnancy, with response in 5. Twenty-two women (7 PNH; 15 AA/hMDS) had a PNH clone >10% and 21/22 received ecu during a total of 33/34 pregnancies, due to active hemolysis in 20 or preemptively (clone>20% and LDH<2xULN) in 13. Ecu dose was increased in 52% of pregnancies and thromboprophylaxis was performed in 94%. Blood counts improvement after delivery occurred in 41% of cases. Post-partum treatment for AA was required in 14 (6 ATG, 6 CSA, 1 transplant and 1 androgens) with 75% response rate. Five (7%) spontaneous miscarriages were reported (4 in the 1st trimester), all in PNH women. Maternal adverse events occurred in 24% of pregnancies (1 Budd-Chiari syndrome, 6 infections, 4 peripartum bleedings, and 6 placental complications). Fetal complications occurred in 11% of pregnancies (6 premature births and 1 fetal growth restriction). Bleedings and infective complications occurred more often in AA/hMDS women, while thrombosis, placental dysfunctions and, preterm births were observed mostly in patients with an underlying PNH clone. In conclusion, this is one of the largest cohorts reported so far and suggests that, even though pregnancy should not be discouraged in these women, it requires a high level of awareness and multidisciplinary approach.

C004

ABSTRACT NOT PUBLISHABLE

C005

TRANSFUSIONS IN AUTOIMMUNE HEMOLYTIC ANEMIA: FREQUENCY AND CLINICAL SIGNIFICANCE OF ALLOIMMUNIZATION

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Autoimmune hemolytic anemia (AIHA) may present acutely and require transfusion support. Few data on the risk of transfusion reactions and alloimmunization are available, also considering the evolving blood selection strategies. Here we analyzed transfusion policy and rate of alloimmunization in a single-center series of 103 patients with AIHA. We included 103 transfused patients from a series of 408 AIHAs followed from 1997 to 2022. Patients were classified as warm (54%), cold (33%), mixed or atypical (IgA positive or negative direct antiglobulin test, 13%). Clinical and laboratory features, antibody specificity, number of red blood cell (RBC) transfusions hematologic parameters pre and post transfusion , and transfusion reactions were retrospectively registered. The median number of RBC units (RBCU) transfused was 4 (1-55). Median pre-transfusion Hb was 6.8 g/dL (2.7-8.6) and 8 febrile transfusion reactions (7%) were registered, none hemolytic. Figure 1 shows the trend in transfusion frequency and alloimmunization rate in 408 patients along time: RBC transfusions and the rate of alloimmunization progressively decreased, particularly after 2010, from 53% to 20% and from 30% to 6% respectively. Overall, anti-RBC alloantibodies were found in 20 patients (19%), associated with higher transfusion burden compared with non-alloimmunized (median 10 *vs* 3 RBCU, p=0.01), and. lower Hb increase post transfusion [0.9 (0.2-3.5) *vs* 1.5 (0-7.1) g/dL, p=0.05]. This was more significant for those transfused before 2010 [0.7 (0.2-1.7) *vs* 1.8 (0.4-4.5) g/dL, p=0.03], possibly due to the improved RBCU selection and allocation procedures over time. Alloimmunized patients also had significantly more transfusion reactions (20 *vs* 4%, p=0.04). Relapsed/refractory patients had a higher transfusion burden and increased rate of alloimmunization [median relapses in allo *vs* non-alloimmunized patients: 2 (0-13) *vs* 1 (0-8), p = 0.05]. These data show that RBC transfusions in AIHA are effective (median Hb increase of 1 g/dL) and generally safe (<10% transfusion reactions).reaction However, subjects developing alloantibodies more often experienced transfusion reactions and showed a reduced post transfusion Hb increase. Finally, we observed a decrease in the transfusion rate and in the frequency of alloimmunization over the last 15 years, likely linked to the implementation of pre-storage leukoreduction, patient-donor molecular typing, and to the use of more restrictive Hb thresholds.

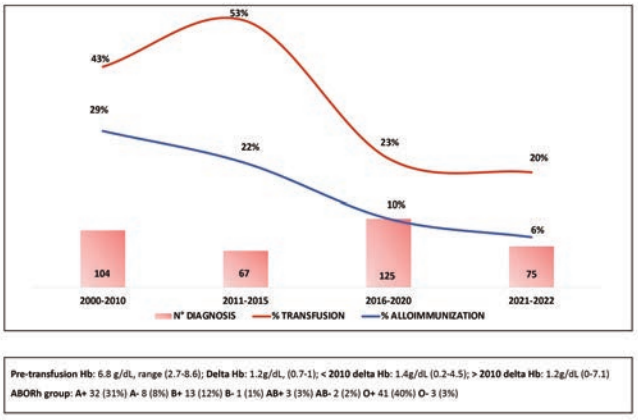

Figure 1.

Chronic lymphocytic leukemia and lymphoproliferative syndromes I

C006

DISSECTING THE AGGRESSIVENESS OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA HARBORING T(14;19) FROM A CLINICAL-MOLECULAR PERSPECTIVE. AN ERIC AND ITALIAN CAMPUS CLL STUDY

A. Visentin[1], E. Gaffo[2], P. Baliakas[3], C. Haferlach[4], K. Plevova[5], D. Oscier[6], Z. Davis[6], F. Nguyen-Khac[7], E. Roncaglia[2], G.M. Rigolin[8], A. Athanasiadou[9], F. Baran-Marszak[10], A. Valiente[11], M.J. Terol[12], P. Abrisqueta[13], B. Espinet[14], A. Puiggros[14], A. Martines[15], L. Bonaldi[15], F. Frezzato[1], V. Ruocco[1], A. Buratin[2], S. Orsi[2], A. Cellini[1], F. Angotzi[1], C.A. Cavarretta[1], I. Zatta[1], A. Serafin[1], F.R. Mauro[16], R. Foà[16], A. Cuneo[9], L. Scarfò[17], K. Stamatopoulos[18], P. Ghia[17], S. Bortoluzzi[2], L. Trentin[1]

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Introduction. Translocation t(14;19)(q32;q13), involving the BCL3 oncogene and the IGH locus, is a cytogenetic abnormality identified in almost 1% of chronic lymphocytic leukemia (CLL) and is associated with poor prognosis. In this study, we aimed at disclosing the clinical-molecular features of CLL harboring t(14;19), that represents a still poorly characterized subtype of CLL.

Methods. Databases of the European Research Initiative on CLL (ERIC, n=5,290) and of the Italian Campus CLL (n=546) were used to identify cases with t(14;19). Treatment-free survival (TFS) and overall survival (OS) were analyzed and compared with the Log-rank tests. For RNA sequencing (RNA-seq), RNA was extracted from 106 purified cells, processed by TruSeq Stranded Total RNA Ribo-Zero Gold and sequenced with Illumina technology at 60 million paired-end. Both linear and circular RNAs (circRNA) were analyzed, using CircomPara2.

Results. Forty-one (0.8%) t(14;19) CLL patients referred to 11 European centers were recruited in this study since 1996, 58% were males, 27% were <50 years old, 85% an unmutated IGHV status (1 stereotype #8), 59% trisomy 12 (+12), 54% a complex karyotype (CK, aberrations >=3 54%,>=5 22%) and 17% TP53 abnormality (abn, deletion and/or mutation). After a median follow-up of 6.7 years, the median TFS and OS was 2 and 7 years. Of note, patients with t(14;19) had a shorter TFS and OS compared to the CLL patients without t(14;19), superimposable to cases with TP53 abn (n=42) or CK (n=99), but shorter than +12 patients (n=82) (Figure 1). Thirty-three t(14;19) samples, 22 control CLL (11 with +12 and 11 with both normal FISH and karyotype, 10 unmutated IGHV) and B-cells from 9 healthy donors (HD) underwent RNA-seq. Gene expression profile (GEP) identified 996 dysregulated genes in t(14;19) CLL, in particular we confirmed that BCL3 was overexpressed compared to control CLL cases. Furthermore, TP63, CDKN2A and CD52 were overexpressed while CD82, CD274 (PD-L1) and TNFAIP3 were downregulated in t(14;19) subset than both controls. Then, we extended the transcriptome by studying over 22,000 circRNAs expressed from 6,113 genes, and obtaining genomic information from RNA-seq data we are moving toward a multi-omics.

Discussion. We herein demonstrated that t(14;19) patients display an adverse clinical outcome, associated with a distinct GEP. The aberrant expression of CD52 and CD274 might be an interesting hint to pursue innovative therapies for this aggressive subset of CLL.

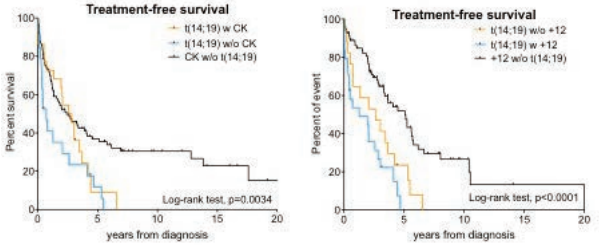

Figure 1.

C007

THE CXCR4-LOW/CD5-HIGH PROLIFERATIVE FRACTION IS ENRICHED IN BTK MUTATIONS AND ANTICIPATES RELAPSE IN IBRUTINIB-TREATED CLL

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CXCR4/CD5 expression on chronic lymphocytic leukemia (CLL) cells identify the proliferative fraction (CD5high/CXCR4dim PF), recently egressed from the lymph node, from the resting fraction (CXCR4high/CD5dim RF) of older quiescent cells. BTK inhibitors affect the proliferative capacity of CLL cells causeing their redistri-

bution from lymph nodes to periphery. Longitudinal monitoring of the PF under ibrutinib (IB) in 31 CLL from the IOSI-EMA-001 study (156 sequential samples, median 6/case) showed rapid depletion, from 17.7% at pre-treatment to 4.75-0.4-1.5-0.6-1.5% at 0.5-6-12-18-24 months ($p<0.001$) with loss of Ki67 expression.

In IB-treated real-world CLL (296 samples, median 3/case; Figure 1A-B), median PF in pre-IB samples was 12.0% (range 0.7-50) dropping to 2.7% and 1.0% at 1-2 years of treatment ($p<0.001$). IB was discontinued within 5 years in 71/100 cases (17 toxicity, 46 progression, 8 other/death).

BTK/PLCG2 mutations were detected in 29/100 cases, 24/29 discontinuing IB due to progression/relapse (23/24) or toxicity (1/24). In samples collected within 12 months before/after IB discontinuation (n=59), mutations were found in progressing cases (22/43, 51%) with a PF higher than wild-type (WT) cases discontinuing for toxicity (8.9% *vs* 2.4%; p=0.012) or still on treatment (2.8%, p=0.015; Figure 1C). Notably, WT progressing cases also showed higher PF compared to cases discontinuing for toxicity (6.9% *vs* 2.4%; p=0.004) or still on treatment (6.9% *vs* 2.8%; p=0.024; Figure 1C).

Sequential dosages of plasmatic B2M in progressing cases (n=5) revealed steady levels below the 3.5 ug/mL threshold, despite the PF increase (median PF 18%; Figure 1D).

Sequencing of PF/RF fractions, sorted from 10 cases with BTK mutations and with PF reappearance after prolonged IB treatment (median 50.7 months), revealed 27 BTK mutations (mean 1.7/sample, range 1-4), with median VAF higher in the PF (23.0%, 0.3-92.3) than in the RF (5.2%, 0.1-84.8; p=0.003); overall, the PF VAF was 2.8-fold larger than the RF (0.01-38). A similar trend was present for PLCG2 mutations (Figure 1E).

Differential expression of paired PF/RF fractions from samples (n=6) at pre-IB and progression, drove co-clustering of post-IB PF/RF with their respective counterparts (Figure 1F), indicating that PF at progression functionally resembles its pre-IB counterpart.

Clinically, longitudinal monitoring of the CXCR4/CD5 fractions by flow cytometry may provide a simple tool helping to intercept CLL progression under IB therapy.

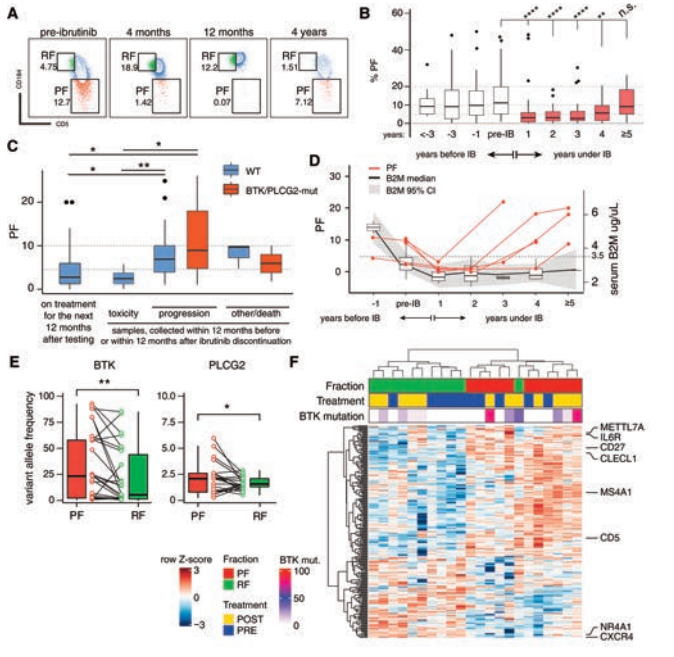

Figure 1.

C008

EFFICACY OF PIRTOBRUTINIB IN COVALENT BTK-INHIBITOR PRE-TREATED RELAPSED/REFRACTORY CLL/SLL: ADDITIONAL PATIENTS AND EXTENDED FOLLOW-UP FROM THE PHASE 1/2 BRUIN STUDY

P. Ghia[1], A.R. Mato[2], J.A. Woyach[3], J.R. Brown[4], K. Patel[5], T.A. Eyre[6], T. Munir[7], E. Lech - Maranda[8], N. Lamanna[9], C.S. Tam[10], J.F. Seymour[10], N.N. Shah[11], C.C. Coombs[12], C.S. Ujjani[13], M.R. Patel[14], B. Fakhri[15], C.Y. Cheah[16], A.J. Alencar[17], J.B. Cohen,[18], J.N. Gerson[19], I. W. Flinn[20], S. Ma[21], D. Jagadeesh[22], J.M. Rhodes[23], F. Hernandez - Ilizaliturri[24], P.L. Zinzani[25], M. Balbas[26], B. Nair[26], P. Abada[26], C. Wang[27], D. Wang[26], D.E. Tsai[26], W.G. Wierda[28], W. Jurczak[29]

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Background. Pirtobrutinib is a highly selective, non-covalent (reversible) Bruton tyrosine kinase inhibitor (BTKi). We report updated CLL/SLL results from BRUIN.

Methods. Pts with previously treated B-cell malignancies, including CLL/SLL, were eligible for pirtobrutinib monotherapy in dose escalation/expansion portions of BRUIN. Key endpoints: ORR per 2018 iwCLL response criteria, PFS, and safety. The reported cohort was CLL/SLL pts enrolled to phase 1/2 who had received a prior covalent BTKi-containing regimen and had undergone their first response assessment/discontinued therapy. The safety cohort was pts with B-cell malignancies who received at least one dose of pirtobrutinib monotherapy (n=725). Data cut was 31 January 2022.

Results. Of 276 pts with CLL/SLL who had received a prior BTKi, (median age: 69 [36-88] years) the median number of prior therapies was 3 (1-11). Additional prior therapies: anti-CD20 antibody (89%), chemotherapy (80%), BCL2 inhibitor (44%), PI3K inhibitor (24%), CAR-T cell therapy (6%), and stem cell transplantation (2%). High-risk features were frequent: del(17p) in 29% (58/197), mutated TP53 in 40% (91/230), unmutated IGHV in 85% (188/220). Most pts (n=206, 75%) discontinued prior BTKi therapy due to disease progression. Overall, 84% (n=232) received the recommended phase 2 dose (200 mg QD) as starting dose. The investigator-assessed ORR was 74% (95% CI, 68-79): 3 complete responses (1%), 174 partial

responses (PR; 64%), 23 PRs with lymphocytosis (PR-L; 8%), and 1 nodular PR (<1%). At a median follow-up of 13.9 months, the median PFS was 19.4 months (95% CI, 16.6-22.3). 12-month and 18-month estimated PFS rates were 68% (95% CI, 62-74) and 54% (95% CI, 46-61), respectively. In the safety cohort (n=725), the most common TEAEs were fatigue (26%, n=191), diarrhea (22%, n=160), and contusion (19%, n=138). The most frequent Grade≥3 TEAE was neutropenia (20%, n=143). Low rates of Grade≥3 TEAEs of hypertension (3%, n=20), hemorrhage (2%, n=16), atrial fibrillation/flutter (1%, n=7) were observed. Overall, 15 (2%) pts discontinued due to a treatment-related AE.

Conclusions. Pirtobrutinib continues to demonstrate durable efficacy in pre-treated R/R CLL/SLL pts treated with a prior covalent BTKi, regardless of prior therapy, reason for prior BTKi discontinuation, age, high-risk TP53 mutations, C481 mutational status, and/or del(17p). It was well tolerated with low rates of discontinuation due to drug-related toxicity.

C009

ABSTRACT NOT PUBLISHABLE

C010

ABSTRACT NOT PUBLISHABLE

Non Hodgkin lymphoma I

C011

PRIMARY MEDIASTINAL B-CELL LYMPHOMA, A NATIONWIDE REAL-LIFE RETROSPECTIVE STUDY FROM FONDAZIONE ITALIANA LINFOMI (FIL)

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Introduction. PMBCL is an uncommon neoplasia showing unique clinic-pathologic and demographic features. Front-line chemo-immunotherapy (R-CHT) plus consolidative radiotherapy (RT) allows a 5yr OS of 80%. However, several issues still need to be debated.

Methods. We designed a retrospective cohort study including 37 hematological centers throughout the national territory to describe presenting features, first-line and consolidation strategies adopted, and the outcomes in a real-world setting. All adult patients were eligible, provided they had a clinical picture coherent with that of the PMBCL, were registered in the local databases from 1/1/2007 to 31/12/2019 with a histological diagnosis of PMBCL, and were treated with an RCHT.

Results. Data from 891 patients with PMBCL were retrieved. The median age was 35 yrs (IQR 28-44), and 62% were females. ECOG>2, Stage >II, LDH ratio > 1, and bulky mediastinum were present in 21%, 22%, 74%, and 72% of patients, respectively. All patients received treatment with rituximab plus CHOP21 (n=98), CHOP14 (n 181), megaCHOP (n 31), VACOPB (n 179), MACOPB (n 225), and DAEPOCH (n 179). In addition, 66 (7.5%) were consolidated with autologous stem cell transplant (ASCT), and 589 patients (66.2%) received RT. The RT consolidation rates significantly differed across therapeutic groups (p=0.01); the lower (31%) and the higher values (90%) were reported in the R-DAEPOCH and in the R-megaCHOP groups, respectively. Final PET response assessment was available in 97% of patients, and CR was recorded in 81%. Both CR and primary failure rates were comparable across the different regimens. With a median follow-up of 5.1 years [QR: 3.5□7.6], the 5-yr PFS and OS of the entire series were 83% (95%CI:80-85) and 91% (95%CI:89-93), respectively. PFS curves according to different therapeutic groups and multivariate Cox proportional-hazards models are shown in Figure 1.

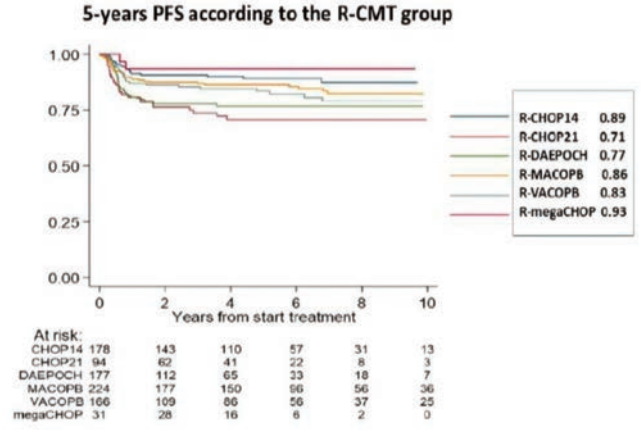

Figure 1.

The 5-yrs PFS and OS rates with R-MACOPB, which is the treatment of choice in Italy, were 86% (95%CI:81-90) and 91% (95%CI:86-94), respectively and comparable to others reported in the literature. In multivariate analysis, compared to the R-MACOPB group, R-CHOP21 treated patients showed a significantly worse PFS (HR=2.00 95%CI:1.08-3.72). Concerning OS, there was no substantial difference among the different R-CMTs. The IPI score (one class increase) was significantly associated with the risk of primary refractoriness, worse PFS, and OS. The presence of > 1 extranodal site conferred a higher prognostic weight than the other IPI parameters.

Conclusions. Our preliminary nationwide real-world analysis indicates that R-CHOP21 is a suboptimal treatment for patients with PMBCL. All other regimens allow PFS and OS rates that do not significantly differ from the original R-MACOPB.

Table 1.

Univariable and multivariable Cox model for PFS.

	HR	95%CI	p
Univariable			
CHOP21	2.34	1.27,4.32	0.006
VACOPB	1.31	0.69,2.50	0.413
MACOPB	1.00	1.00,1.00	.
DAEPOCH	2.09	1.12,3.91	0.021
CHOP14	0.80	0.41,1.58	0.519
megaCHOP	0.34	0.07,1.80	0.206
Multivariable			
CHOP21	2.00	1.08,3.72	0.028
VACOPB	1.23	0.66,2.31	0.514
MACOPB	1.00	...	.
DAEPOCH	1.70	0.92,3.13	0.090
CHOP14	0.76	0.39,1.48	0.421
megaCHOP	0.38	0.08,1.95	0.248
IPI score (1-point increase)	1.57	1.29,1.91	<0.001
AA Stage III-IV	1.56	1.03,2.35	0.034
ECOG PS>=2	1.37	0.91,2.05	0.131
LDH Abnormal	0.82	0.55,1.21	0.315
>1 extranodal site	1.98	1.26,3.12	0.003
Age, per 5-year increase	1.00	0.93,1.07	0.901
Male sex	1.20	0.86,1.67	0.275
Systemic B symptoms	1.53	1.09,2.14	0.014
Bulky mediastinum > 10 cm	1.41	0.91,2.19	0.129
Pericardial or Pleuric effusion	1.20	0.83,1.74	0.342

C012

PIRTOBRUTINIB IN COVALENT BTK-INHIBITOR PRE-TREATED MANTLE CELL LYMPHOMA: UPDATED RESULTS AND SUBGROUP ANALYSIS FROM THE PHASE 1/2 BRUIN STUDY WITH >3 YEARS FOLLOW-UP FROM START OF ENROLLMENT

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Background. Pirtobrutinib is a highly selective, non-covalent (reversible) BTK-inhibitor (BTKi). Here, we report updated results of

pirtobrutinib in patients (pts) with cBTKi pre-treated relapsed/refractory (R/R) mantle cell lymphoma (MCL) and more than 3 years follow-up from start of enrollment.

Methods. Pts with cBTKi pre-treated R/R MCL received pirtobrutinib monotherapy in a multicenter phase 1/2 BRUIN trial (NCT03740529). Efficacy was assessed in the prespecified primary efficacy cohort that comprised the first 90 enrolled pts who had measurable disease, had received a prior cBTKi, and had no known central nervous system involvement. The primary endpoint was overall response rate (ORR) as assessed by independent review committee. Secondary endpoints included duration of response (DOR) and safety. A data cut of 29 July 2022 was utilized.

Results. Among MCL pts who received a prior cBTKi (n=90), median age was 70 years (range, 46-87), median prior lines of therapy were 3 (range, 1-8), 82% discontinued a prior cBTKi due to disease progression, and 78% had intermediate/high risk sMIPI score. Of samples available, 17/36 (47%) had TP53 mutations and 25/34 (74%) had Ki67 ≥30%. The ORR was 57% (95% CI, 46-67), including 19% complete responses (n=17) and 38% partial responses (n=34). At a median follow-up time of 13 months, the median DOR among the 51 responding pts was 17.6 months (95% CI, 7.3-27.2). The 12- and 18-month estimated DOR rates were 58% (95% CI, 41-72) and 45% (95% CI, 27-61), respectively. ORR and DOR by subgroups are shown in the Table. The median progression-free survival was 7.4 months (95% CI, 5.3–13.3). The median overall survival was 23.5 months (95% CI, 15.9-NE). In the MCL safety cohort (n=166), the most frequent treatment-emergent adverse events (TEAE) were fatigue (31%), diarrhea (22%), and anemia (17%). The most common Grade ≥3 TEAE was neutropenia (15%). Grade ≥3 TEAE of hemorrhage (3%) and atrial fibrillation/flutter (2%) were infrequent. Only 5 (3%) pts discontinued due to a treatment-related AE.

Conclusions. Pirtobrutinib continues to show durable efficacy and a favorable safety profile in heavily pre-treated R/R MCL pts with prior cBTKi therapy. Responses were observed in pts with high-risk disease features including pts with blastoid/pleomorphic variants, elevated Ki67 index, and TP53 mutations.

C013

COMBINED USE OF MINIMAL RESIDUAL DISEASE MONITORING AND FDG-PET FOR OUTCOME PRE-DICTION IN FOLLICULAR LYMPHOMA: RESULTS FROM THE FONDAZIONE ITALIANA LINFOMI (FIL) FOLL12 TRIAL

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Introduction. In follicular lymphoma (FL), FDG-PET is employed to evaluate response at the end of induction (EoI), while minimal residual disease (MRD) analysis is reliable in predicting relapse. Nonetheless, scant data are available describing the integration of these prognostic tools for response evaluation. This issue was investigated in the phase III FIL FOLL12 trial.

Methods. Only patients with an available MRD marker and centrally reviewed EoI PET were included. MRD was assessed by RQ-PCR with BCL2::IGH consensus primers in peripheral blood (PB) and bone mar-row (BM), as previously reported. PET scans were classified according to Deauville score (DS) criteria: DS1-3 was negative and DS4-5 positive(-/+).

Results. 394 patients out of 780 were included (51%). This group had a slightly better outcome than excluded cases. At EoI, both BM MRD+ and PET+ were independent predictors of poor PFS in multivariate analysis (HR 1.66, CI 1.01-2.71 and HR 2.03, CI 1.30-3.18). The 68 discordant cases (*i.e.* MRD+/PET- or MRD-/PET+) showed an intermediate outcome (PFS HR 1.93, CI 1.28-2.92) between the 314 double negative and the 10 double positive ones (HR 6.22, CI 2.99-12.9), Figure 1A.

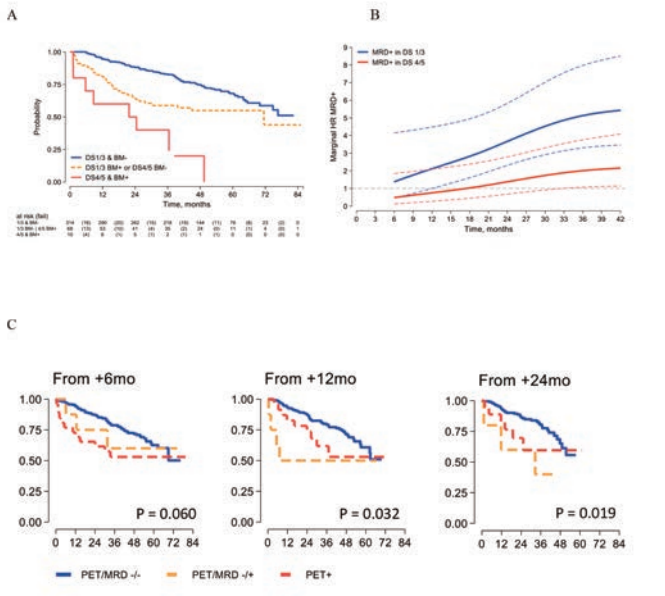

Figure 1.

Both EoI PET+ and the persistence/reappearance of MRD+ in BM during the 18 months of rituximab maintenance/observation were independently associated to a higher risk of POD24 (HR 5.61, CI 2.59-12.1, and HR 2.37, CI 1.15-4.84, respectively). On the other hand, MRD kinetic analysis by PB sampling during the rituximab maintenance/observation period substantially updated the risk status over PET results. The marginal PFS HR for an MRD+ after an EoI PET negative result increased from 1.36 (CI 0.47-3.96) at 6 months, up to 3.60 (CI 2.30-5.64) at 24 months, Figure 1B. Patients scoring PET- at EoI but showing a per-sistent or reappearing MRD+ signal during

the following 24 months had a dismal PFS, superimposable to that of PET+ patients, Figure 1C. Accordingly, in landmark multivariate analysis PB MRD+ either at 12 or 24 months predicted adverse PFS (HR 3.79, CI 1.60-8.96 and HR 5.21, CI 1.88-14.4, respectively), independently from EoI PET result.

Discussion. MRD analysis and PET scan are independent and complementary prognostic tools: a MRD positivity in the two years after treatment is predictive of POD24 and dismal PFS independently from the EoI PET result. Regular and non-invasive MRD monitoring in PB might identify high risk patients even among PET- patients under rituximab maintenance.

C014

REAL-LIFE MULTICENTRE STUDY ON 441 PATIENTS AFFECTED BY WALDENSTROM MACROGLOBULINAEMIA TREATED WITH CHEMO-IMMUNOTHERAPY: WHICH IS THE BEST AND MOST USED FIRST-LINE TREATMENT?

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Waldenström Macroglobulinaemia (WM) is an indolent lymphoma still treated with chemo-immunotherapy, which keeps a role in the treatment of WM in particular in first-line; in fact only recently BTKIs have become an option for untreated patients.

Previous trials have investigated efficacy and safety of the main chemotherapeutic agents. The aim of our study was to assess what are the main schemes used in Italy to further evaluate and compare responses and toxicities of them.

We enrolled frontline WM patients in the period 2008-2022 from 12 haematological Italian centres. This retrospective analysis was conducted on 441 patients: 219 were treated according to BR scheme (bendamustine-rituximab), 104 DRC (dexamethasone-rituximab-cyclophosphamide), 26 Chl-R (chlorambucil-rituximab) and 90 other different schemes that varied from monotherapy with alkylants to more aggressive schemes, as seen in Figure 1A.

We focused our analysis on the two major groups: BR and DRC. The two populations were different for age at treatment (67 *vs* 69 years old, respectively), CIRS (CIRS>6 in 11% and 26%, respectively) and revised IPSSWD (rates of higher risk in BR), so patients treated with BR were younger, more fit but also with a more aggressive disease. No significant differences were seen in the tolerability: we registered a reduction on cycles administered of 15.3% for BR and 21.4% for DRC, a dose reduction of 12.9% for BR and 5.8% for DRC, finding only a trend of significance for dose reduction higher in BR patients (p=0.052). When analysing the curves of progression free survival (PFS, Figure 1B) we noted a PFS at 5-yy 71% for BR and 52.6% for DRC (p=0.0002). Curves of overall survival (OS, figure 1c) did not differ between the two schemes (OS at 5-yy 88.5% for BR and 89.8% for DRC, p=0.8). Multivariate analysis confirmed the main role for the choice of the treatment (BR *vs* DRC) as the unique significant variable to impact on PFS (RR 1.76).

This large Italian retrospective real-life study showed excellent outcomes in unselected patients with WM treated with chemo-immunotherapy, which is not out of fashion, but it is still the best option of treatment in these patients. Survival curves with long follow-up confirmed a better PFS, but the same OS, of BR patients than DRC patients.

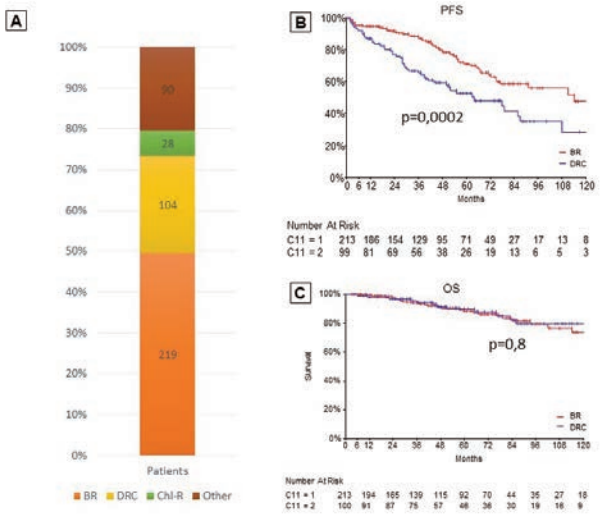

Figure 1.

C015

ABSTRACT NOT PUBLISHABLE

Acute leukemia I

C016

GENE FUSIONS ARE A PUTATIVE MECHANISM THAT DIMINISHES SENSITIVITY TO VENETOCLAX-HYPOMETHYLATING AGENTS COMBINATION IN ACUTE MYELOID LEUKEMIA

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Background. Different mechanisms are responsible for resistance to venetoclax (VEN), but the contribution of rearrangements, also in co-recurrence with genomic events, remains unexplored.

Aims. Within the INTHEMA protocol (NCT04298892), we aimed to discover novel VEN resistance mechanisms.

Methods. After informed consent, we collected samples from 21 consecutive patients with relapsed/refractory acute myeloid leukemia after VEN + hypomethylating agents. We performed TruSight RNA Pan-Cancer searching for fusion genes (capture technology, 1385 genes), RNA expression and expressed mutations on each sample.

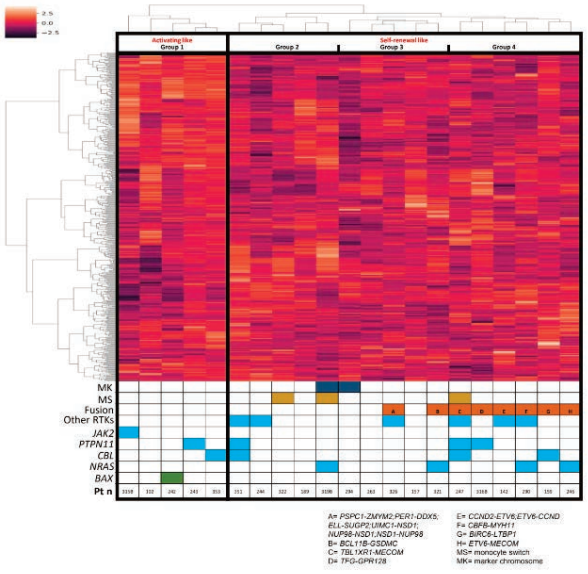

Figure 1.

Results. We identified at least 1 putative mechanisms of VEN resistance in 17/21 (81%) patients (figure) including the co-occurent mutations and genomic rearrangements: 14/21 patients had RTK mutations (67%; NRAS=4, PTPN11=4, CBL=4, FLT3=3, JAK2=1, cKIT=1, EPHB6=1, FGFR=1, PDGFRb=1), 1 had BAX mutation (p.G67R; BH3 domain), 3/21 switched to monocytic phenotype, 2 had marker chromosomes. Gene fusions emerged in 8/21 patients: a cryptic rearrangement of MECOM (TBL1XR1-MECOM and ETV6_MECOM) in 2 patients, a novel BCL11B fusion (BCL11B-GSDMC), a CCND2-ETV6 BIRC6-LTBP1, the reciprocal NUP98-NSD1, the CBFB-MYH11, additional transcripts with a less defined role (PSPC1-ZMYM2; PER1-DDX5; ELL-SUGP2). Interestingly, most of the genes involved in translocations, with a potential driver role in therapy resistance (MECOM, ETV6, CCND2, BCL11B, NUP98, ELL) also showed high expression levels of translocated oncogenes. Unsupervised clustering of RNA expression data distinguished two main groups of patients (Figure 1). A group of 5 patients (24%) showed an "activating like" signature, with CSF3R and IKZF overexpression. The other group presented with a "self-renewal like" signature. Patients carrying gene fusions clustered within the "self-renewal like" group, being enriched in a subgroup (subgroup 4), also characterized by overexpression of HOXA genes.

Conclusions. By the association of a deep transcriptomic characterization to conventional diagnostics, our analysis suggested novel mechanisms of resistance to VEN and detected the established ones. Appealing patterns of resistance emerged from genomic analysis: the "activating like" signature may help define a specific target among tyrosine kinase inhibitors, while "self-renewal like" patients may benefit from histone deacetylase inhibitors (as we previously published). HOXA genes overexpression open a novel therapeutic options for selected patients.

C017

USE OF PERIPHERAL BLOOD TO MEASURE RESIDUAL DISEASE BY FLOW CYTOMETRY (FC) IN ADULT ACUTE MYELOID LEUKEMIA (AML): FINAL REPORT OF PROSPECTIVE AML1310 GIMEMA PROTOCOL

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Based on retrospective analyses, it has been suggested that peripheral blood (PB) can be an alternative and/or complementary source to bone marrow (BM) for detecting measurable residual disease (MRD), in AML. We investigated whether FC detection of MRD in PB by is feasible and has a prognostic value in a large, prospective cohort of younger AML patients treated within the GIMEMA AML1310 protocol. Two hundred ninety-eight patients were monitored for MRD after the achievement of complete remission. Median age was 49.3 years (range 18-61); 118 (36%), 87 (26.5%) and 123 (37.5%) patients received as post consolidation therapy allogeneic

stem cell transplantation, autologous stem cell transplantation or no transplantation, respectively. Overall, in PB MRD was expressed one logarithm lower than BM, being the median value of residual leukemic cells (RLC) 0.118% and 0.029% after induction, and 0.020% and 0.004% after consolidation, respectively ($p<0.001$ for both comparisons). The levels of MRD mesured in 548 and 510 pairs of PB and BM after induction and consolidation, respectively, were significantly concordant (Pearson correlation r=0.69 and 0.77, respectively, $p<0.001$ for both correlations). As a second step of analysis, the levels of PB RLC were tested by the maximally selected log-rank statistics and the optimal prognostic thresholds were set at 0.008% and 0.0004% after induction and consolidation, respectively. Therefore, patients with PB RLC values below or equal/exceeding these cut-offs were classified as PB MRD- and PB MRD+, respectively. The median duration of DFS and OS was not reached among the patients PB MRD-after induction and consolidation, whereas it was 24 and 41 months, 28 and 63 months among those PB MRD+ after induction and consolidation (p=0.023 and 0.0033, 0.094 and 0.037, respectively; Figure 1). In multivariate analysis the variables significantly associated with shorter DFS were PB MRD+ status after induction, ELN high risk, age (p=0.038, <0.0001, 0.003, respectively). By combining PB MRD with BM MRD status after consolidation (BM threshold set at 0.035%) we identified three categories of patient, BM+PB+ (111), BM-PB+ (83), , BM-PB- (61) whose DFS at 2 years was 52.6% (95% CI: 43.8%, 63.0%), 52.6% (95% CI: 42.4%, 65.1%) and 59.9% (95% CI: 48.6%, 73.7%), respectively (p=0.22). In conclusions. (1) MRD levels in PB of AML patients are measurable and correlate to those measured in BM (2) PB MRD determination has a prognostic role.

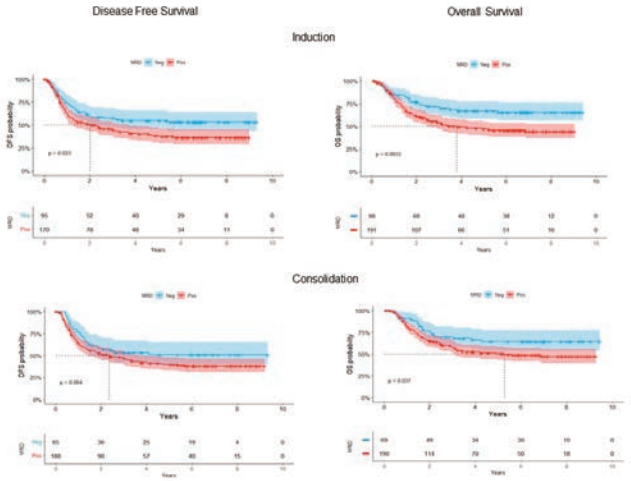

Figure 1.

C018

UPDATED DATA FOR ZIFTOMENIB IN PATIENTS WITH NPM1-MUTATED RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA

C. Papayannidis[1], A. Fathi[2], E. Wang[3], G. Issa[4], J. Altman[5], P. Montesinos[6], S. de Botton[7], R. Walter[8], K.M. Pettit[9], S. Strickland[10], M. Patnaik[11], M. Kremyanskaya[12], M. Baer[13], J. Foran[14], G. Schiller[15], L. Ades[16], M. Heiblig[17], C. Berthon[18], P. Peterlin[19], J. Antonio Perez Simon[20], O. Salamero Garcia[21], M. Tabachri[22], D. Corum[22], M. Leoni[22], S. Dale[22], H. Erba[23]

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The menin and histone-lysine-N-methyltransferase 2A (KMT2A) protein complex, an essential epigenetic regulator of genes critical for maintenance of multiple genetic subtypes of leukemia, is implicated in NPM1 mutant acute myeloid leukemia (AML) (NPM1m; 30% of AML) and AML with KMT2A gene rearrangements (KMT2A-r; 5-10% of AML). The presence of co-mutations (ie IDH1/2 and FLT3) portend a poor prognosis, particularly in the relapsed/refractory (R/R) setting, a high unmet need area. KOMET-001 is a global, open-label Ph1/2 study of ziftomenib, a menin inhibitor, in adult patients (pts) with R/R AML. The dose escalation (P1a) and randomized, multi-dose expansion (P1b) in pts with KMT2A-r or NPM1-m R/R AML are fully enrolled. Ziftomenib is dosed orally, QD, in 28-day cycles until relapse, progression, or unacceptable toxicity. This report provides updates on the Ph1 NPM1-m pts dosed at the 600 mg RP2D (n=20) and on duration of remission (DoR) for a 200 mg pt as of 31JAN2023. Median age for RP2D pts was 70.5 years (22 to 86y). Common co-mutations were FLT3 (35%), IDH1/2 (30%), and IDH1/2+FLT3 (20%). The safety profile for the ziftomenib RP2D is consistent with prior reports. Most (85%) had at least one ≥Gr 3 treatment-emergent adverse event (TEAE), with 30% of TEAEs considered potentially treatment-related. The complete remission (CR) rate for NPM1-m pts treated with 600mg was 30%, composite CR rate (CRc) was 35%, and ORR was 40% (Table 1).

Table 1. Response Rates for NPM1-m Patients treated at the Ziftomenib RP2D.

CR Rate	
n (%)	**6 (30)**
95% (CI)	**(12, 54)**
CR/CRh Rate	
n (%)	**6 (30)**
95% (CI)	**(12, 54)**
CRc Rate (CR+CRh+CRi)	
n (%)	**7 (35)**
95% (CI)	**(15, 59)**
MRD Negativity Rate[1]	
n (%)	**3 (43)**
95% (CI)	**(10, 82)**
ORR Rate (CR+CRh+CRi+MLFS)	
n (%)	**8 (40)**
95% (CI)	**(19, 64)**

[1]Five of 7 patients achieving CRc were evaluated for MRD. Of those evaluated, 60% were MRD negative.

Median DoR for pts achieving CRc, which continues to mature, was 8.2 months (m) per Kaplan-Meier estimate (95% CI: 1.5 to NE). One CR at the 200 mg dose, has an ongoing DoR of 32 cycles. Median time to CR was 70 days (26 to 89). Two pts received SCT and remain in remission at cutoff. Median overall survival for NPM1-m pts treated with 600 mg was 5.1m (95% CI: 2.1 to NE), with a median duration of follow-up of 8.0m. 57.1% of pts achieving CRc at

RP2D remain on treatment or in post-SCT follow-up; those on treatment continue to show evidence of evolving responses. Ziftomenib continues to demonstrate significant clinical activity in heavily pretreated and co-mutated R/R NPM1-m AML pts. The safety profile remains consistent with previous reports and the on-target effect of DS continues to be manageable. Data suggest durable remissions as the DoR continues to mature with 5 of 8 pts with CRc ongoing at cutoff. A single-arm registration-directed Ph 2 study is currently accruing to further evaluate ziftomenib monotherapy in R/R NPM1-m AML.

C019

A NEW MONOCLONAL ANTIBODY PROVIDES INSIGHTS ON NPM1 MUTANT SUBCELLULAR EXPRESSION, INTRACLONAL CELL DIFFERENTIATION AND MRD IN NPM1-MUTATED AML

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Background. NPM1-mutated AML shows unique clinical and molecular features, including cytoplasmic expression of NPM1 mutant that is critical for leukemogenesis and can detected by immunohistochemistry.

Aims. We generated a monoclonal antibody (mAb) specifically recognizing the NPM1 mutant, to study the expression of NPM1 mutant at subcellular level and during maturation, and to assess minimal measurable disease (MRD).

Methods. Immunostainings with the specific mAb and molecular analyses were performed according to standard procedures

Results. The mAb was tumor specific, being reactive with 150/150 NPM1-mutated AMLs (including 32 myeloid sarcomas) but not with 105 AMLs NPM1 wild-type and 150 solid tumors. Positivity was consistently cytoplasmic but about 30% of cases showed also nuclear positivity (especially leukemic proerythroblasts). This is in keeping with the recent observation that the NPM1 mutant can interact with XPO1 bound to chromatin and to exert its leukemogenic activity at nuclear level. Immunostaining of 50 NPM1-mutated AML cases of M4-M5 FAB subtype showed that the NPM1 mutant was variably expressed, the most mature leukemic cells being negative/weakly positive. These cells retained the wild-type NPM1 protein, suggesting that the NPM1 mutant is undergoing degradation more quickly than wild-type NPM1. Because the NPM1 mutant protein is not expressed in the most mature cells (including starry sky macrophages), this probe cannot be used to track clonality. Therefore, we focused our analysis on NPM1-mutated AMLs co-mutated for IDH1 R132H. Staining with a specific anti-IDH1 R132H mAb revealed strong positivity of the NPM1-mutant negative mature macrophages for the IDH1 mutant (Figure 1A), clearly demonstrating for the first time that these cells belong to the leukemic clone. To explore whether the mAb was suitable for monitoring MRD, we immunostained 13 normal BM biopsies and 10 CD34+ purified BM hematopoietic cellì samples with the mAb but no reactivity was observed. Conversely the mAb detected even rare NPM1 mutant-expressing cells in patients in molecular relapse (Figure 1B). Correlation with molecular studies is ongoing.

Conclusions. We demonstrate that: i) the NPM1 mutant is expressed also in the nucleus and is downregulated during monocytic differentiation; ii) cells in the terminal phase of monocytic differentiation may belong to the leukemic clone; and iii) the mAb is tumor specific marker that can be used for monitoring MRD.

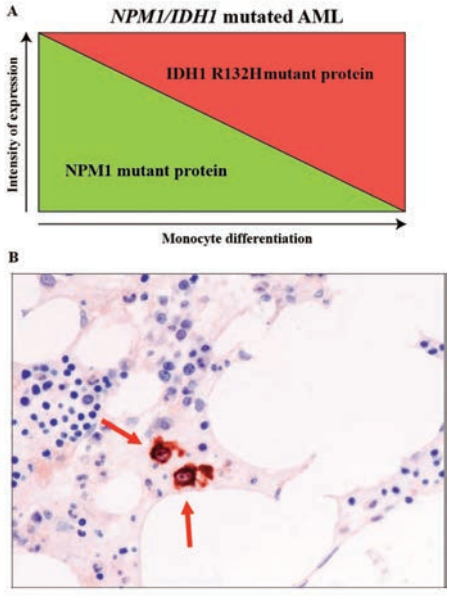

Figure 1.

C020

EXTERNAL VALIDATION OF AN EARLY DEATH RISK SCORE IN ACUTE PROMYELOCYTIC LEUKEMIA: A RETROSPECTIVE ANALYSIS FROM A MONOCENTRIC COHORT

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The prognosis of Acute Promyelocytic Leukemia (ALP) is radically changed by the introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). Despite this, early mortality (ED) remains the leading cause of treatment failure in APL, with 20-25% of deaths for fatal bleeding and thrombosis within 30 days from diagnosis. Sanz risk model, which stratifies patients (pts) in low, intermediate, and high risk based on white blood cells (WBC) and platelet (Plt) count, allows risk-adapted application of therapeutic options, but not specifically predict ED. Österroos et al. proposed and externally validated a risk score based on real-world data, identifying age, WBC and Plt count as the most significant variables to predict ED in APL. By this, pts are stratified in low, high and very high risk for ED, with ED risks of <10%, 10-30% and >30% respectively. The aim of this study was to retrospectively evaluate the predictivity of ED in a monocentric cohort of 220 newly diagnosed APL patients between 1993 and 2022. At diagnosis, median age was 49.9 (19.2-85.4) years, with median hemoglobin, WBC and Plt count of 9.9 (3.2-15) g/dL, 2.3x10^9/L (0.4-280x10^9/L) and 29 (2-302x10^9/L), respectively. The Sanz score was low in 64 (29.1%) pts, intermediate in 98 (44.5%), and high in 58 (26.4%) pts. According to the ED risk score, 111 (50.4%) pts were at low risk, 79 (35.9%) pts at high risk and 30 (13.6%) pts at very high risk. Overall, 158 (71.8%) pts received induction therapy with the AIDA protocol, 38 (17.2%) with

ATO+ATRA, 11 (5.0%) with ATRA and 7 (3.18%) with AIDA+AraC. In the whole cohort, 16 (7.2%) pts died within 30 days, with a median time from diagnosis of 7 days. Of these, 4 (25.0%) died before and 12 (75.0%) during induction therapy. The main causes of death were hemorrhagic or thrombotic complications in 13 (72.3%) patients and infectious in 3 (18.7%) pts. Among 111 pts classified as low risk (0-2 points) the rate of ED was 1.8%, while high risk pts (3-4 points) showed a rate of 8.8%. Finally, among high-risk pts (5-7 points), the mortality rate was 23.3%. The Area Under the Receiver Operating Characteristic (AUROC) curve for ED for our cohort was 0.75 (95% CI 65.2-85.6) *vs* 0.77 (95% IC: 0.72-0.83) of the cohort in the original study. In conclusion, the ED score was able to predict ED in our cohort with adequate discriminatory power, thus being a valid option to take urgent measures to prevent ED.

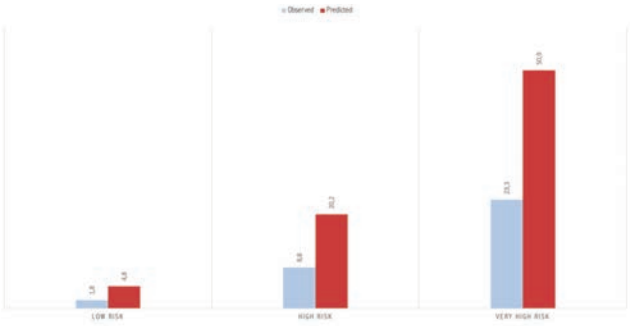

Figure 1.

Myeloma and monoclonal gammopathies I

C021

ARTIFICIAL INTELLIGENCE-ASSISTED DEVELOPMENT OF HIGH AFFINITY ANTI-CD79B CAR-T CELLS FOR THE TREATMENT OF RELAPSED/REFRACTORY B-NON HODGKIN LYMPHOMAS AND MULTIPLE MYELOMA

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Background. Chimeric antigen receptors (CAR) T cells targeting CD19 and BCMA are revolutionizing the therapy of relapsed/refractory (r/r) B non-Hodgkin lymphomas (B-NHL) and multiple myeloma (MM), respectively. However, about 30% of high-grade B-NHLs relapse after CD19 CAR-T cells due to CD19 target antigen escape and efficacy of BCMA CAR-T cells for r/r MM is reduced following BCMA downregulation or complete antigen loss. We recently produced a new monoclonal antibody (mAb) against the conserved extracellular portion of CD79b showing immunohistochemistry and flow cytometry reactivity against both B-NHL and MM cells. However, anti-CD79b CAR-T cells developed from our mAb showed a better cytotoxicity against B-NHL as compared to MM, due to lower CD79b antigen expression on myeloma cells. With the intention to treat both r/r B-NHL and MM patients, we probe to enhance CD79b CAR-T cell affinity through artificial intelligence-assisted docking analysis.

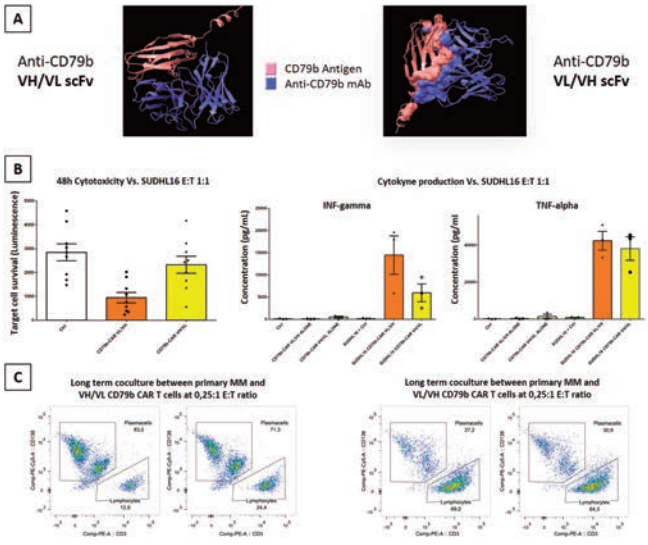

Figure 1.

Methods. The artificial intelligence (AI) Alphafold2 program was used to predict 3D interaction between CD79b and VH/VL or VL/VH orientation of anti-CD79b mAb while the HADDOCK server was exploited for molecular docking analysis. CD79b CAR-T cell activity was tested against the SUDHL-16 B-NHL and KAPPAS 299 MM cell lines and primary MM cells.

Results. The anti-CD79b scFv affinity binding was predicted comparing docking analysis between VH/VL or VL/VH orientation and CD79b antigen. Anti-CD79b VL/VH scFv orientation displayed a

lower binding energy than VH/VL (HADDOCK score 54.2±14 *vs* 72.9± 13.3), suggesting a higher association propensity to CD79b (A). The consistency of in silico results have been confirmed *in vitro*, where VL/VH exhibited enhanced activity compared to VH/VL anti-CD79b CAR-T cells in terms of cytotoxicity after 48h at E:T 1:1 ratio and cytokine production against SUDHL-16 B-NHL (B) and KARPAS 299 MM cell lines. Significantly higher efficacy of VL/VH anti-CD79b CAR-T cells against MM cells was revealed also by long term coculture assays at unfavourable E:T ratio with MM primary cells showing enhanced cytotoxicity and T cell proliferation as compared to controls (C).

Conclusions. The identification of alternative B and plasma cell targets is mandatory to improve CAR-based therapies of r/r B-NHLs and MM. High-affinity CD79b CAR-T cells developed using AI may represent a promising approach to treat subsets of r/r B-NHL and MM patients not responding to commercial CD19 or BCMA-directed CAR T cells.

C022

PREDICTORS OF UNSUSTAINED NEGATIVITY IN MINIMAL RESIDUAL DISEASE (MRD)-NEGATIVE TRANSPLANT-ELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA (MM) PATIENTS ENROLLED IN THE FORTE TRIAL

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Introduction. We analyzed the impact of baseline prognostic factors on the risk of losing the status of minimal residual disease (MRD) negativity in patients (pts) with multiple myeloma (MM).

Methods. We included all pts in the FORTE trial (NCT02203643) who achieved MRD negativity by multiparameter flow cytometry (10^{-5}). MRD was assessed in the bone marrow aspirate of pts with ≥very good partial response at premaintenance and every 6 months (mo) during maintenance. Hemodilution of the first MRD-negative sample was ruled out. The primary endpoint was the cumulative incidence of MRD positivity and/or progression from the first MRD-negative evaluation. Death without progression was a competing event. A multivariate Fine-Grey model was used to evaluate the risk of losing the MRD-negative status over time.

Results. 306/474 (65%) pts achieved MRD negativity. After a median follow-up of 50.4 mo from MRD negativity, 185/306 (60%) pts were still MRD-negative and progression-free, 118 (39%) lost their MRD-negative status and 3 (1%) died without progression. The presence of ≥2 *vs* 0 high-risk cytogenetic abnormalities (HRCA) was associated with a higher risk of unsustained MRD negativity (HR 2.22, *P*=0.01). The 4-year (y) cumulative incidence of unsustained MRD negativity was 59% *vs* 29% in pts with ≥2 *vs* 0 HRCA. Pts harboring gain(1q) (HR 1.50, *P*=0.08) and amp(1q) (HR 2.12, *P*=0.02) showed a higher risk of unsustained MRD negativity *vs* normal 1q. The 4-y cumulative incidence of unsustained MRD negativity was 63% *vs* 49% *vs* 32% in pts with amp(1q) *vs* gain(1q) *vs* normal 1q. The median duration of the MRD-negative status was 27.6 mo in amp(1q) pts. Pts with high circulating tumor cells (CTC) levels at baseline showed a higher risk of unsustained MRD negativity (HR 1.88, *P*=0.01). The 4-y cumulative incidence of unsustained MRD negativity according to CTC levels was 59% *vs* 31% in pts with high *vs* low CTC, with a median duration of MRD negativity of 38.1 mo in the high CTC group. As per protocol, at maintenance pts were randomized to receive carfilzomib (for up to 2 y) +lenalidomide (KR) *vs* R alone. During the 2 y after maintenance randomization, pts receiving KR *vs* R alone had a lower risk of unsustained MRD negativity (HR 0.58, *P*=0.03).

Conclusions. MRD-negative pts with amp(1q), high CTC levels or multiple HRCA were at high risk of losing their MRD-negative status over time. Pts receiving KR maintenance were at lower risk of losing their MRD-negative status *vs* R alone.

C023

LONG-TERM OUTCOMES WITH ISATUXIMAB-CARFILZOMIB-DEXAMETHASONE (ISA-KD) IN RELAPSED MULTIPLE MYELOMA PATIENTS WITH 1Q21+ STATUS: UPDATED RESULTS FROM THE PHASE 3 IKEMA STUDY

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Background. Gain or amplification of 1q21 (1q21+, ≥3 copies), a chromosomal abnormality frequently observed in multiple myeloma (MM), has a negative impact on prognosis due to its potential involvement in resistance to MM therapy and disease progression. In the prespecified, long-term analysis of the Phase 3 IKEMA trial in relapsed MM patients (pts), treatment with Isa-Kd showed

continued, significant improvement in progression-free survival (PFS) *vs* Kd (HR 0.58; 95.4% CI 0.42–0.79), with meaningful increase in depth of response (complete response or better [≥CR] 44.1% *vs* 28.5%; minimal residual disease negativity [MRD-] 33.5% *vs* 15.4%, MRD- ≥CR 26.3% *vs* 12.2%), and a manageable safety profile. In this subgroup analysis of IKEMA, we evaluated efficacy of Isa-Kd in pts with 1q21+ status (with or without high-risk chromosomal abnormalities [HRCA]) and related subgroups – isolated 1q21+ (≥3 copies without HRCA), gain(1q21), amp(1q21) – at long-term follow-up (44.2 months) (NCT03275285).

Methods. Pts with 1–3 prior lines of therapy were randomized to Isa-Kd (n=179) or Kd (n=123). Assessment was prespecified (at 30% cutoff by FISH) for 1q21+ status as ≥3 copies, gain(1q21) as 3 copies, and amp(1q21) as ≥4 copies.

Results. In the Isa-Kd and Kd arms, 41.9% and 42.3% of pts had 1q21+ status, 26.3% and 25.2% isolated 1q21+, 24.0% and 30.1% gain(1q21), 17.9% and 12.2% amp(1q21) respectively. Greater PFS benefit was achieved with Isa-Kd *vs* Kd in pts with 1q21+ status (HR 0.58, 95% CI 0.37–0.92) and in pts with isolated 1q21+, gain(1q21), or amp(1q21) (Table). Responses deepened by adding Isa to Kd, with increased rates of very good partial response or better (≥VGPR), ≥CR, MRD-, and MRD- ≥CR (Table).

Conclusions. 1q21 abnormalities affect PFS in MM pts. Our results at long-term follow-up of pts with 1q21+ status (with or without HRCA) in the IKEMA study continue to show greater PFS benefit and deeper responses with Isa-Kd than Kd, consistent with the overall population and earlier 1q21+ subgroup interim analyses. Thus, they support Isa-Kd as an effective treatment option also for difficult-to-treat, 1q21+ pts with relapsed MM.

Table 1.

	Standard risk		1q21+		Isolated 1q21+ (w/o HRCA)		Gain(1q21)		Amp(1q21)	
	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd
n	65	43	75	52	47	31	43	37	32	15
%	36.3	35.0	41.9	42.3	26.3	25.2	24.0	30.1	17.9	12.2
mPFS, mo (95% CI)	42.4 (26.3–NC)	20.3 (15.2–28.2)	25.8 (17.1–38.2)	16.2 (10.2–24.8)	38.2 (18.8–NC)	16.2 (10.2–25.1)	30.2 (20.8–NC)	18.2 (10.2–25.0)	18.4 (13.1–NC)	14.5 (2.8–NC)
PFS HR vs Kd (95% CI)	0.50 (0.29–0.84)		0.58 (0.37–0.92)		0.50 (0.27–0.92)		0.50 (0.28–0.90)		0.73 (0.33–1.63)	
ORR %	90.8	86.0	86.7	82.7	91.5	87.1	90.7	86.5	81.3	73.3
≥VGPR %	76.9	53.5	73.3	51.9	80.9	51.6	79.1	56.8	65.6	40.0
MRD- %	44.6	18.6	34.7	15.4	40.4	12.9	34.9	13.5	34.4	20.0
MRD- ≥CR %	33.8	11.6	29.3	15.4	36.2	12.9	27.9	13.5	31.3	20.0

C024

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C025

ABSTRACT NOT PUBLISHABLE

Hemostasis, thrombosis, thrombocytopenia and platelet diseases I

C026

EFFICACY AND SAFETY OF VWF CONCENTRATES IN A COHORT OF 93 PATIENTS WITH SEVERE TYPE 3 VON WILLEBRAND DISEASE ENROLLED INTO 3WINTERS-IPS PROJECT: RESULTS OF THE 2-YEAR PROSPECTIVE CLINICAL OBSERVATION

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Introduction. Plasma-Derived von Willebrand factor concentrates (pd-VWFC) are the mainstay of treatment in inherited von Willebrand disease type 3 (VWD3). The aim of 3Winters-Ips was to collect prospective data on the efficacy and safety of these pd-VWFC in a large cohort of VWD3.

Methods. 3Winters-Ips is an investigator-initiated, non-interventional, non-crossover, retrospective and prospective clinical study on VWD3. The type of pd-VWFC used was chosen by local investigators in Europe (EU) and Iran (IR). 108 patients who completed the

2-year prospective observation received pd-VWFC either on demand (OD) or under Secondary Long-Term Prophylaxis (SLTP). The efficacy and safety of these pd-VWFC was assessed according to FDA-agreed objective criteria following regulatory procedures.

Results. Among the pd-VWFC used by EU/IR investigators, HAEMATE-P/VONCENTO were administered in 93/108 (86%) VWD3 patients. 69/93(74%) received OD treatments to manage 629 bleeding episodes [mucosal (83%) - joint bleeds (17%)] with excellent/good efficacy in 96%. Moderate/poor responses were reported in 25 bleeds [Menorrhagia (n=11), GI bleeds (n=7), Joint bleeds (n=4) and epistaxis (n=3)]. 24/93(26%) VWD3 received at enrolment SLTP. When compared to their previous retrospective OD treatments, Annualized Bleeding Rates (ABR) during SLTP were significantly reduced by 66% in these individual patients. Only 2 patients with GI bleeds showed recurrent events. No major side-effects were reported.

Conclusions. Results from this large cohort of VWD3 patients indicate that these pd-VWFC are effective and safe to treat or prevent mucosal and non-mucosal bleeds in the rarest and most severe form of VWD. Patients exposed to SLTP can reduce substantially their ABR.

C027

THROMBOPOIETIN SERUM LEVELS, PLATELET INDICES AND MEGAKARYOCYTE FEATURES FOR THE DIFFERENTIAL DIAGNOSIS OF THROMBOCYTOPENIA

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Background. Thrombopoietin (TPO) serum levels and platelet (plt) indices may help to discriminate different etiologies of thrombocytopenia. In this study we compared TPO serum levels, plt indices and megakaryocyte (MK) features in patients (pts) with a known diagnosis of hyporigenerative (myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML)) and consumption (immune thrombocytopenia (ITP)) thrombocytopenia. The aim was to point out the distinctive features between the two groups, which may be used for differential diagnosis in doubtful cases.

Methods. This was a monocentric, retrospective, explorative study. Blood samples of ITP and MDS/AML pts with plt count < $100x10^9$/L were collected. TPO serum levels were measured with a quantitative sandwich ELISA assay. Immature plt fraction (IPF), mean plt volume (MPV), plt distribution width (PDW), plateletcrit (PCT), plt large cell ratio (P-LCR) were obtained using Sysmex XN-1000 hemocytometer, and were not available for all pts due to technical issues. Features evaluated in bone marrow (BM) aspirates were: MK number (magnification 10x), clusters, size, maturation, number of nuclei, lobes, emperipolesis. Microsoft Excel and Jamovi were used for statistical analysis. Fisher and Student's t-test were used for comparisons between groups. P-value <0.05 was deemed statistically significant.

Results. We enrolled 68 ITP and 41 MDS/AML pts (15 MDS, 26 AML). Table 1 summarizes the results. There was no difference in terms of plt count and PCT. ITP pts had lower TPO serum levels and higher IPF, MPV, PDW and P-LCR compared to MDS/AML pts. TPO and IPF resulted statistically significative also in multivariate analysis (TPO: OR 0.99, CI 0.9907-0.9985; IPF: OR 1.08, CI 1.028-1.139). ROC curves showed that IPF can distinguish the two groups better than TPO (AUC 0.714 *vs* 0.615). BM was evaluated in 21 ITP and 34 MDS/AML. ITP had higher number of MK, emperipolesis, mononucleated MK, clusters of MK, less hypolobated, larger MK. Immature MK were seen only in ITP. TPO and IPF didn't correlate with MK features. Of note, pts with MDS and AML were not different in terms of plt indices and MK features.

Conclusions. In this study we confirmed that ITP displays distinctive characteristics in terms of platelet indices, TPO levels and MK features. These easy to get parameters may become a useful tool for the differential diagnosis of thrombocytopenia.

Table 1. Platelet indices, TPO levels and MK features in ITP compared to MDS/AML paAents.

	ITP	MDS/AML	P value
Number of evaluable patients	68	41	
Mean platelet count ($x10^9$/L)	30	36	0.183
	0-97	3-89	
Mean TPO (pg/mL)	97	208	0.001
Range	6-432	0-1475	
Number of evaluable patients	62	39	
Mean IPF (%)	18	11	0.001
Range	0.04-55	1-38	
Number of evaluable patients	42	22	
Mean MPV (fL)	13	11	<0.001
Range	9-18	9-14	
Mean PDW (fL)	17	13	<0.001
Range	4-25	9-23	
Mean P-LCR (%)	45	33	<0.001
Range	14-61	21-56	
Mean PCT (%)	0.055	0.047	0.287
Range	0-0.14	0.01-0.1	
Bone marrow features			
Number of evaluable patients	21	34	
Mean n° of MK per field (10x)	9	3	<0.001
Range	2-23	0-30	
MK clusters present	28%	6%	0.043
Emperipolesis present	76%	6%	<0.001
Number of evaluable patients	21	24	
Number of nuclei:			
• Mononucleated MK	95%	46%	<0.001
• Multinucleated MK	5%	54%	
MK lobes:			
• Hypolobated	19%	79%	<0.001
• Normolobated	29%	12%	
• Hyperlobated	52%	8%	
MK size:			
• Normal/large	52%	21%	0.045
• Small	19%	50%	
• Variable	29%	29%	

AML = acute myeloid leukemia; IPF = immature platelet frac7on; ITP = immune thrombocytopenia; MDS = myelodysplas7c syndrome; MK = megakaryocytes; MPV = mean platelet volume; PCT = plateletcrit; PDW = platelet distribu7on width; P-LCR = platelet large cell ra7o; TPO = thrombopoie7n.

C028

MATERNAL AND FETAL OUTCOMES IN PREGNANCIES OF WOMEN WITH IMMUNE THROMBOCYTOPENIA: A MULTICENTER RETROSPECTIVE OBSERVATIONAL ITP-NET ITALIAN STUDY ON BEHALF OF THE GIMEMA WORKING GROUP ANEMIA AND THROMBOCYTOPENIA

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Background. Pregnancy (P) might complicate Immune thrombocytopenia (ITP). Bleeding at delivery (D), side effects of treatment (tx), thrombocytopenia (T) of the neonate (N) and worsening of ITP are possible. Evidence-based guidelines for ITP in P are lacking, data about efficacy and safety of tx are limited, especially for thrombopoietin receptor agonists (TPO-RA).

Aims. To evaluate maternal, fetal outcomes, ITP management ITP in P in 9 Italian centers (ITP-NET STUDY)

Methods. Retrospective data review from hospital charts, including need of tx, N plts at birth, maternal and N adverse events (AE).

Results. We recorded data on 95 women, 93 D (2 abortion) and 96 N. 68% of pts had prior ITP and 44% had multiple P during ITP history. 65.3% of P required 1st line tx, 21% 2nd line, 8.4% 3rd line. 15.5% had plt <10x10^9/L at 1st line of tx. One pt was taking cyclosporine before P and received also steroid. Diabetes and hypertension developed in 10% and 7% . WHO Grade 1-2 bleeding (B) in P developed in 26.5%, and WHO 3 in 1.1%. D occurred at a median g.a of 39 wks (20-43) with median plt of 93x10^9/L (7-246). 65.2% of P needed to increase plt at D. 12.9% received TPO-RA (4 Rom, 3 Eltr) as single or combo tx without AE (Table 1).

Table 1. ITP Treatment strategies adopted to prepare delivery.

	Total Pts n (%)	Single agent n (%)	*Combo 1 n (%)	**Combo 2 n (%)
Steroids	35 (56.5)	17 (27.4)	13 (20.9)	5 (8.1)
IgV	34 (54.8)	14 (22.6)	15 (24.2)	5 (8.1)
Ig-antiD	2 (3.2)	2 (3.2)		
TPO-RA	8 (12.9)	5 (8.1)	2 (3.2)	1 (1.6)
PLT transfusion	6 (9.6)		4 (6.4)	2 (3.2)

*Steroids were combined with: IgV (11 pts), or TPO-RA (1 pt), or PLT transfusion(1 pt):

**Steroids were combined with: IgV+PLT (2 pts), or IgV+Azathioprine (1 pt), or IgV+CyA (1 pt), or IgV+ TPO-RA (1 pt)

*PLT transfusion were combined with IgV in 3 patients

Table 2. Factors affecting neonatal thrombocytopenia in univariate analysis.

	P Value	ORR (CI 95%)
Maternal PLT < 50 x 10^9/L at D	0.0376	2.81 (1.1-6.9)
Maternal PLT < 30 x 10^9/L at D	0.0268	3.28 (1.4-7.4)
Maternal PLT < 30 x 10^9/L at presentation	0.0460	2.53 (1.06-6.04)
Maternal need of first line therapy	0.0037	7.64 (1.06-54.74)
ITP before P	0.0328	4.91 (0.69-34.77)
ITP therapy before P	0.0328	2.73 (1-7.6)
Prior newborn with T	0.0041	4.2 (1.3-10.3)
Splenectomy before P	0.001	10 (2.9-33.9)

D: delivery; P: pregnancy; T: thrombocytopenia

Median plt count of their N was 67x10^9/L (8-161). 35.5% of pts received analgesia at labor. Cesarean section was performed in 31.2%. Peripartum B occurred in 11 D(10 WHO 1-2, 1 WHO 3). 15 N (16.6%) had T at birth (12.5% < 30 , 7.3% < 10x10^9/L) and 4 N had mild B (WHO 1-2). 23/81 N received tx: 21 IVIG alone or combined with plt transfusion. Neonatal T is related to the following maternal data: plt count < 30x10^9/L at D, need of first line tx, previous ITP tx, previous splenectomy (S), prior newborn with T (Table 2). N bleeding is related to N plt count at birth and S before P. Median maternal plt count 1 month after D was 86x10^9/L plt (1-562) and 17% showed plt count < 30x10^9/L. Of 70 pts with available follow up after D, 35 continued the last ongoing tx or received new tx included TPO-RA (16 cases alone or combo), rituximab (3) or S (2).

Conclusions. P in ITP pts occurred mostly with mild B, but a single tx or combo tx, including also TPO-RA were frequently used. Despite only a minority of pts having T at labor, analgesia is used only in a small % of pts. Neonatal T is not uncommon, is related mostly to low maternal plt count and the need of ITP tx before/during P and S. A multidisciplinary management of P in ITP pts is suggested

C029

SAFETY AND EFFICACY OF CAPLACIZUMAB RETREATMENT IN A REAL-LIFE MONOCENTRIC COHORT OF PATIENTS WITH THROMBOTIC THROMBOCYTOPENIC PURPURA

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Immune-mediated thrombotic thrombocytopenic purpura (iTTP) presents as an acute disease with an additional 30-50% risk for relapse. Caplacizumab treatment has resulted in a significantly faster iTTP recovery, with a generally safe profile when administered as a first-line treatment; the most common reported adverse event (AE) is represented by mucocutaneous bleeding.

Table 1. Characteristics of patients with iTTP treated and retreated with caplacizumab.

	First-line treatment (n=24)	Retreatment for relapse (n=5)	p value
Sex female, n° (%)	18 (75)	4 (80)	0.81
Age at treatment, median years (range)	37.5 (17-75)	40 (23-40)	0.79
Hemoglobin g/dL, mean (range)	11 (4.7-10.7)	12 (10-13.7)	0.22
Platelet ×10^3/uL, mean (range)	12 (5-30)	32 (9-68)	**0.01**
Creatinine mg/dL, mean (range)	1 (0.4-2.72)	0.8 (0.5-1.6)	**0.03**
LDH mU/mL, mean (range)	1354 (516-3.491)	839 (353-2.292)	0.24
TPE, mean n° (range)	6 (2-15)	7 (6-7)	0.40
Caplacizumab doses, mean n° (range)	24 (11-36)	22 (6-28)	0.55
Rituximab association, n° (%)	3 (12.5)	2 (40)	0.30
Days of hospitalization, mean n° (range)	8 (5-17)	7 (6-8)	0.56
Previous iTTP relapse, mean n° (range)	2 (0-15)	1 (1-8)	0.43
Bleeding adverse event, n° (%)	2 (8.3)	0 (0)	
Cardiovascular adverse event, n° (%)	0 (0)	0 (0)	
Time to relapse, mean months (range)		8 (1-20)	
Follow-up, mean months (range)	16.5 (1-33)	10.4 (5-23)	0.15

TPE, therapeutic plasma exchange; iTTP, Immune-mediated thrombotic thrombocytopenic purpura.

Few data are available on efficacy and safety in patients treated with a second course of caplacizumab. To the best of our knowledge, besides an anecdotical case report, only the post-Hercules study showed safety data on 9 patients retreated with Caplacizumab for iTTP recurrence or relapse, reporting 44% of serious AE. With the aim of analyzing data coming from a real-life monocentric cohort, we considered 24 consecutive iTTP patients treated with caplacizumab from August 2020 to February 2023 at the Hematology Unit, Ospedale Businco Cagliari, with 5 of them (20.8%) underwent a second treatment (Table 1). All retreated patients experienced a re-

lapse defined as recurrent thrombocytopenia requiring initiation of therapeutic plasma exchange (TPE) more than 30 days after the last TPE, confirmed by severe ADAMTS-13 deficiency. Relapse occurred after a mean of 8 months (range 1-20) from the previous iTTP resolution. The hospitalization ranged from 6 to 8 days, with a mean of 7 TPE performed (range 6-7) to obtain platelets and LDH recovery. The second course of caplacizumab was administered for a mean of 22 days, similar to the duration in the previous iTTP occurrence (p=0.55). In 2 out of 5 patients, a concomitant treatment with rituximab was associated. Overall, only two bleeding adverse events were registered in the cohort of patients treated with a first course of caplacizumab (metrorrhagia and upper arm hematoma, that required treatment withdrawn). No bleeding events were registered in the cohort of retreated patients. No cardiovascular AEs were reported in both groups. The mean follow-up of retreated patients was 10.4 months (range 5-23).

In conclusion, these data stemming from a real-life monocentric cohort, further support the evidence that repeated use of caplacizumab presents a safe profile and is efficacy in providing a rapid resolution of iTTP episodes, similar to that observed during the first treatment.

C030

A NATIONWIDE SURVEY ON CLINICAL MANAGEMENT AND ORGANIZATIONAL CHARACTERISTICS OF 33 ITALIAN CENTERS TREATING ITP IN PREGNANCY (ITP-NET PREGNANCY STUDY GROUP), ON BEHALF OF THE GIMEMA WORKING GROUP ANEMIA AND THROMBOCYTOPENIA

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Background. Pregnancy (P) is a non-rare event in ITP and represents a clinical/organizational challenge due to few treatments and the multidisciplinary involvement. Case series and data supporting current guidelines are limited.

Aims. To assess the organizational aspects and the clinical management of Italian centers treating ITP pregnant women.

Methods. ITP-NET Pregnancy Study Group performed a nationwide survey. An electronic multiple-choice questionnaire was administered to 41 Italian Hematology Centers.

Results. 33/41 centers replied to the survey. In 88% of centers was present a dedicate high risk pregnant clinic and in 51% a dedicated hematologist. In the last 5 years a cumulative number of 676 deliveries was reported. In 32% of cases ITP was diagnosed before P. Cesarean section was chosen in 41% of deliveries, mainly for obstetric reasons. Platelet cut off for first line treatment was $30x10^9$/L regardless of symptoms for 60% of centers, $30x10^9$/L only if bleeding symptoms for 21% of centers and $20x10^9$/L regardless of symptoms in 7%. This approach was maintained in almost all centers both for *de novo* and pre-P cases. In 50% of centers the first line steroid dosage was 20-25 mg/die until obtaining a response with a subsequent tapering to maintain platelets higher than $30x10^9$/L. In other 50% of responses the steroid dosage chosen was 1 mg/Kg/die. IVIG were considered a steroid-sparing strategy for 45% of centers and a rescue therapy option for other 44%. In refractory patients TPOra was the most used treatment (7 cases with Romiplostin and 4 with Eltrombopag) followed by Azathioprine (6 cases) and Cyclosporine (3 cases). 3 cases treated with splenectomy were reported. The most frequently recommended platelet cut off for vaginal delivery and cesarean section was $50x10^9$/L, respectively in 60% and 54% of centers. For epidural analgesia the preferred cut off was $80x10^9$/L (48%). In 80% on P there was no AEs. 11 clinically relevant bleeding during P, 9 bleeding in peripartum, 4 thrombosis and 4 infections were reported. The incidence of neonatal immune thrombocytopenia was 7.5%. For women with ITP who wish to become pregnant, counseling is multidisciplinary in 54% of centers. Interestingly splenectomy remains a valid option before P for 57% of centers, even for patients treated with TPOra.

Conclusions. This survey is the first in Italy on the management of ITP in pregnancy and shows a relatively homogeneous approach of the clinical and organizational aspects.

Infections

C031

ATYPICAL SCENARIOS IN PULMONARY INVASIVE FUNGAL INFECTIONS IN HEMATOLOGIC PATIENTS: RESULTS OF A 7-YEAR RETROSPECTIVE STUDY IN BRESCIA

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Invasive fungal infections (IFI) have been considered a complication of acute myeloid leukemia (AML) patients (pts), but more recently, IFI have been frequently documented also in other hematologic diseases. IFI radiological findings not fulfilling the EORTC/MSG criteria were also reported in microbiologically documented IFI. To describe the recent epidemiology, clinical characteristics, and outcome in hematologic pts, we evaluated all the pulmonary microbiologically documented IFI observed in our Institution during a 7-year period. Between 2016 and 2022, 1942 pts were admitted to the Hematology ward of our Institution. Seventy (3.6%) pulmonary IFI were recorded; their characteristics are summarized in Table 1.

Table 1. ITP Treatment strategies adopted to prepare delivery.

Median age (y, range)	61,5 (18-83)
Male gender	45 (64.3%)
Hematological disease	
AML	29 (7.6%)
ALL	9 (10.5%)
Lymphoma	21 (2.6%)
MM	6 (1.3%)
CLD	1 (2.6%)
MDS/MPS	1 (2.2%)
SAA	2 (9.1%)
Non-neoplastic disease	1 (1%)
Neutropenia (PMN<0.5 x 10^9/l)	54 (77.1%)
Active phase of hematological disease	54 (77.1%)
Anti-mold prophylaxis	22 (31.4%)
Atipycal rasiological findigs	20 (28.6%)

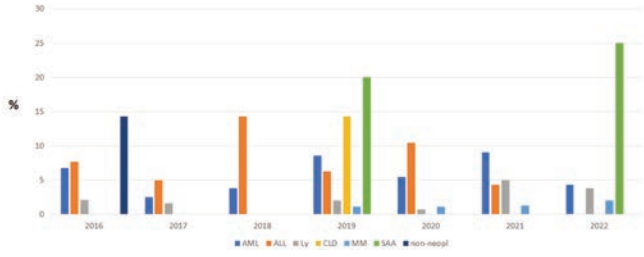

Figure 1. Incidence of pulmonary IFI according to hematologic disease over tyme.

Aspergillus spp was documented in all but one case; Fusarium spp and an Aspergillus spp/Myceliophthora thermophila coinfection were observed in one case each. A coinfection was observed in 32 (45.7%) pts; in particular, 10 (14.3%) were affected by a respiratory virus (RV) infection. Incidence of pulmonary IFI was 29/381 (7.6%) in AML, 9/86 (10.5%) in acute lymphoblastic leukemia (ALL), 21/808 (2.6%) in lymphoma (Ly), 1/39 (2.6%) in chronic lymphoproliferative disorders (CLD), 6/459 (1.3%) in myeloma (MM), 2/22 (9.1%) in severe aplastic anemia (SAA), 1/46 (2.2%) in myelodysplastic/myeloproliferative syndromes (MDS/MPS) and 1/99 (1%) in non-neoplastic hematological diseases. Interestingly, 12 out of 21 IFI observed in Ly were reported in the last 2 years, and no cases were reported in MM pts before 2019. In 20 (28.6%) cases, an atypical radiological finding (aRF) was observed, mainly dense consolidations or interstitial-alveolar infiltrates. An aRF was less frequently observed only in Ly (2/20, 10% *vs* 19/50, 38%; p=0.023). No correlation with phase of hematologic disease, neutropenia or anti-mold prophylaxis was observed, whereas aRF was more frequent in pts with RV coinfection (6/20, 30% *vs* 4/50, 8%, p=0.0267). Thirty-day mortality was higher in pts with aRF (5/20, 25% *vs* 1/50, 2%; p=0.0062); in 3 and 1 cases respectively, death was IFI-related.

A new epidemiologic scenario of pulmonary IFI is outlined in hematologic pts, with significant incidence also in diseases other than AML, particularly in ALL, and, at least in the last years, in Ly and MM pts. As typically RF are lacking in nearly 30% of pulmonary IFI, including AML pts, a redefinition of the diagnostic criteria is mandatory, also considering that mortality is particularly high in this setting.

C032

INFECTIOUS COMPLICATIONS IN AUTOIMMUNE HEMOLYTIC ANEMIA: A MULTI-CENTER ITALIAN EXPERIENCE

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Infections may be the associated with the development/relapse of autoimmune hemolytic anemia (AIHA) or may present as complications of long-term immunosuppression. The prevalence and severity of infection in AIHA are still under-investigated. Here we studied a multi-center series of 331 patients with AIHA followed at 10 Italian centers between 1981 and 2022, focusing on infectious complications and their predictors. At diagnosis, median age was 59 years (range 5-94), most patients (65%) were male, and classified as warm AIHA (53%; Table 1). Median Hb was 7.3 g/dL (2-14) and LDH 621 U/L (174-8681). Among 114 evaluable patients, median serum IgG/IgA/IgM levels were 923(8-6840)/171(1-2350)/94(2-3026) mg/dL, below the lower limit of normality in 37%, 27%, and 23%, respectively. Thirty-one (9%) patients had Evans Syndrome. During a median follow-up of 35 months (1-553 months), patients received a median of 2 therapy lines (1-7), including steroids, rituximab, chemotherapy, and immunosuppressive (IS) drugs in 90%, 44% and 11% of cases, respectively. Sixty-two (19%) patients presented at least one infection episodes, 16 recurrences. Pneumonia was the most frequent (48 cases), and pathogens were isolated in 23 patients (62% viral and 38% bacterial agents); 12 (16%) suffered from SARS-CoV-

2 infection, of whom 7 requiring specific therapy. Eleven (18%) patients were receiving prophylaxis at the time of infection, including acyclovir (18%), cotrimoxazole (18%), both (55%), or entecavir (18%). Most patients (48, 77%) were on active treatment for AIHA at the time of infection (42 steroids and 10 rituximab), and 16 (26%) also experienced a thrombotic event. Patients with infections had received a higher number of AIHA therapy lines *vs* those without infections (p=0,0002), particularly rituximab and IS (p=0,002 and p=0,003, respectively), and had more frequently experienced thrombotic events (p=0,002). Patients with Evans syndrome had a higher incidence of infection (32%, p=0.04). During observation, 55 patients (23%) died, among them 10 for AIHA complications, including 6 infections.

In conclusion, infections complicate about 20% of AIHA. Most episodes occurred during active AIHA-therapy and were more common in patients with prior exposure to rituximab or IS, suggesting an iatrogenic effect. The association with thrombotic events may indicate a relationship with more severe AIHA. Strategies to reduce the burden of IS in AIHA should be pursued.

Table 1. Characteristics of patients with autoimmune hemolytic anemia (AIHA) with and without infections.

	with infections (62)	without infections (269)	
Median Age, years	57 (8-84)	58 (5-94)	ns
Males/Females	17/22	79/123	ns
Type of AIHA			
warm AIHA IgG	26 (19)	109 (81)	ns
warm AIHA IgG+C	13 (33)	26 (67)	p=0,0128
cold AIHA	15 (14)	95 (86)	p=0,05
mixed AIHA	7 (28)	18 (72)	ns
atypical AIHA	1 (5)	21 (95)	ns
Evans Syndrome	10 (16)	21 (84)	p=0,003
Median Hb, g/dL	7,2 (2.1-11.8)	7,25 (2-14.1)	ns
Median Plt, x10^9/L	256 (5-592)	263 (4-695)	ns
Median WBC, x10^9/L	7,1 (1,4-93,7)	7,9 (1,6-87,8)	p=0,011
Median Neutrophils, x10^9/L	5,2 (1,5-52)	5 (0,3-31,8)	ns
Median Lymphocytes, x109/L	1,5 (0,2-90)	1,7 (0,1 – 79,2)	p=0.0883
Median LDH, IU/L	621 (197-4000)	621 (174-8681)	ns
Median IgA, mg/dL	147 (5-970)	180 (1-2350)	ns
Hypogammaglobulinemia IgA	12 (33)	19 (25)	ns
Median IgG, mg/dL	846 (135-6840)	997 (8-4170)	ns
Hypogammaglobulinemia IgG	16 (44)	26 (34)	ns
Median IgM, mg/dL	80 (3-3026)	100 (2-2249)	ns
Hypogammaglobulinemia IgM	11 (31)	15 (20)	ns
Median N. of therapy lines	2 (1-6)	1 (1-7)	p=0,0002
1	22 (34)	146 (54)	
2	18 (30)	77 (29)	
>=3	22 (36)	46 (17)	
Type of therapy			
Steroids	55 (90)	234 (89)	ns
Rituximab	39 (63)	103 (39)	p=0,0007
Splenectomia	7 (11)	16 (6)	ns
CHT	9 (15)	24 (9)	ns
IS	12 (19)	26 (10)	p=0,031
IVIG	13 (21)	33 (12)	p=0,074
Thrombosis	16 (26)	24 (9)	p=0,002
Arterial	5 (18)	4 (12)	
Venous	13 (18)	8 (12)	
Prophylaxis	11 (18)	24 (9)	ns
Cotrimoxazole	8 (13)	20 (7)	
Acyclovir	8 (13)	18 (7)	
Others	2 (3)	0	
Status at last follow-up			p=0,06
Alive	46 (87)	142 (75)	
Dead	7 (13)	48 (25)	

**Hb: hemoglobin; Plt: platelets; WBC: white blood cells; LDH: lactatedehidrogenase; Ig: immunoglobuline CHT: chemotherapy; IS: immunosuppressive; IVIG: intravenous immunoglobuline; ns: not significant *Values are given as number (%) unless otherwise specified*

C033

ANTI-CMV LETERMOVIR PROPHYLAXIS SIGNIFICANLTY REDUCES ACUTE AND CHRONIC GRAFT VERSUS HOST DISEASE AFTER ALLOGENEIC STEM CELL TRANSPLANTATION: REAL LIFE DATA ON 155 PATIENTS

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Cytomegalovirus (CMV) reactivation is the most common viral complication in the allotransplant setting. Letermovir (LET) prophylaxis from day 0 to day +100 has been shown to reduce CMV clinically significantly infections (CMV-csi) and disease, both in the registrative trial and in several real-life experiences. Whether this translates into an improvement of other transplant long-term outcomes remains controversial. With the aim to compare the incidence of CMV-related events, acute and chronic graft versus-host disease (GVHD), relapse (CIR), non-relapse mortality (NRM), and overall survival (OS), we analyzed data on 480 transplants performed in our Center from 2006 to 2022: 325 (68%) belonged to the NO-LET ERA (2006-2018) and 155 (32%) to the LET ERA (2018-2022). In the LET ERA we registered: a major incidence of patients with HCT-CI higher than 2 (48% *vs* 34%; p=0.007), a higher use of haploidentical donors (30% *vs* 11%; p=0.007) and peripheral blood stem cells (90% *vs* 74%; p=0.0002), as well of myeloablative conditioning regimens (63% *vs* 43%; p=0.04).

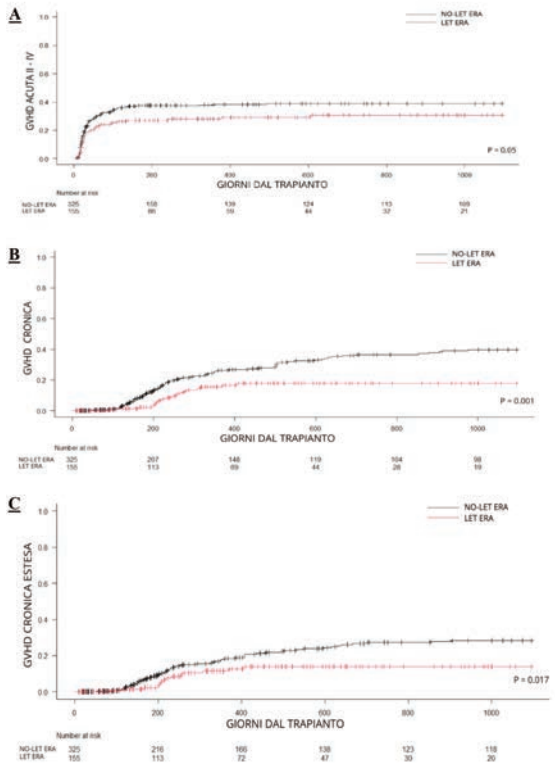

Figure 1. Cumulative incidence of grade II/IV aGHVD (A), cGVHD (B) and extensive cGVHD (C).

The incidence of CMV-csi and disease by day +100 in the NO-LET ERA *vs* LET ERA was 43% and 6% *vs* 8% and 1% (p<0.0001). By day +180 these percentages were 44% and 8% *vs* 20% and 3% (p<0.0001). The incidence of grade II/IV aGVHD at day +100 and at 1 year in the two ERA was 33% *vs* 24% and 38% *vs* 28% (p=0.05; Figure 1A). The incidence of cGVHD at 1 year was 26% *vs* 15% (p=0.001; Figure 1B). Focusing on extensive cGVHD at 1 year, its incidence was 18% in the NO-LET ERA *vs* 11% in the LET ERA (p=0.01; Figure 1C). CIR, NRM and OS were super-imposable in the two groups. Our study confirms that LET significantly reduces the incidence of CMV-related complications as well as the incidence of acute and chronic GVHD. Despite a higher number of risk factors for post-transplant complications in the LET ERA (higher comorbidity score, more haploidentical transplants, more peripheral blood stem cell use and more intensive conditioning), the outcome of the two groups is comparable. Whether this is partially related to LET and the consequent reduction in CMV-related complications has to be confirmed with other studies.

C034

EFFICACY OF TIXAGEVIMAB/CILGAVIMAB (AZD7442) AS IMMUNOPROPHYLAXIS IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES

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AZD7442 is a valid option for Covid-19 immunoprophylaxis in adults who are at higher risk of an inadequate response to Covid-19 vaccination. Therefore, AZD7442 was administered in patients affected by hematologic malignancies (HMs) for Covid-19 prevention. Here, we present the results of a prospective, monocentric, real-world, observational study aimed to compare the incidence and severity of Covid-19 between adult patients affected by HMs, who were treated with AZD7442 *vs* patients who were not. Consecutive adult patients affected by HMs, eligible to AZD7442 administration, were enrolled. Each patient was followed for 6 months. Data regarding demographics, HMs, status of anti-SARS-CoV-2 vaccination, and AZD7442 administration were collected. At data cutoff the cases and features of breakthrough SARS-CoV-2 infections were registered. Differences between categorical variables were tested by Chi-square or Fisher test, while Wilcoxon rank test was used for continuous variables. Kaplan-Meier estimator was used for measuring cumulative risk of outcomes. Cox proportional model, adjusted by age class, sex, HMs, last therapy, active treatment, type and status of anti-SARS-CoV-2 vaccination, was used to estimate the hazard ratio (HR) for the association between AZD7442 administration and outcomes. The incidence rates were expressed as a rate per 10,000 person-days (p-d). Differences between groups were tested with the Z test. In 2022, from June, 1st to September, 1st, 204 patients with HMs were eligible to AZD7442 administration and enrolled in the study: 130 (64%) received AZD7442, 74 (36%) did not. At data cut-off (1st March 2023) the rate of Covid-19 was 21% among patients exposed to AZD7442 *vs* 38% in control group (P 0.01). The incidence of Covid-19 was 14 X 10,000 p-d in AZD7442 group *vs* 28 in control arm, P 0.0069, HR 0.47 (95% CI 0.27-0.81). Administration of AZD7442 significantly reduced the incidence of severe/critical Covid-19: 1.4 *vs* 4.0 X 10,000 p-d, P 0.0495, HR 0.18 (95% CI 0.03-0.99). Need of hospitalization was also significantly lower in patients receiving AZD7442: 1.3 *vs* 4.0 X 10,000 p-d, P 0.038 HR 0.19 (95% CI 0.04-0.91). These results were confirmed by Kaplan-Meier estimator (Figure 1). AZD7442 reduces the incidence and severity of Covid-19. It is crucial to update the neutralizing power of AZD7442, in order to maintain its efficacy against new emerging variants such as XBB.

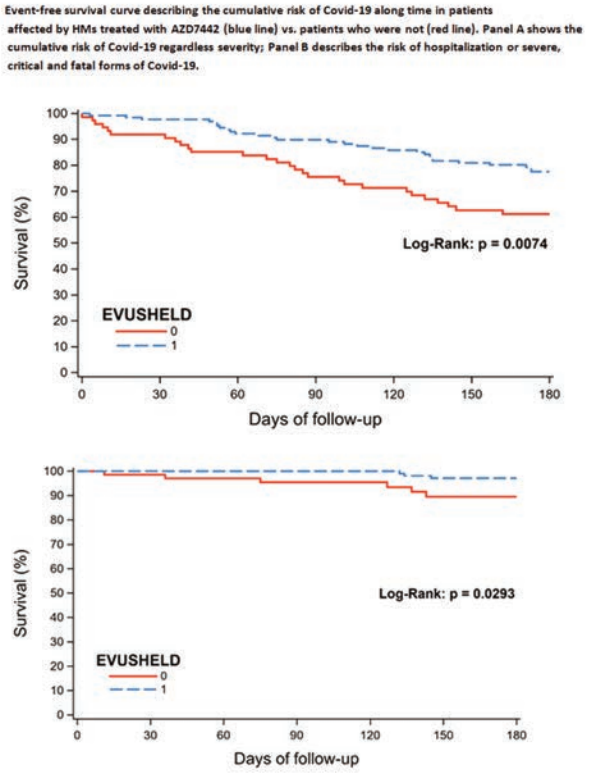

Figure 1.

C035

VACCINATION STRATEGIES FOR PATIENTS WITH LYMPHOMA: A REAL-WORLD PRACTICE SURVEY AMONG FONDAZIONE ITALIANA LINFOMI CENTERS

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Patients with hematological malignancies are at increased risk for various infections, including some (*e.g.*, influenza and invasive pneumococcal disease) that are vaccine preventable. In particular, patients with lymphoma have impaired T cell or B cell immunity, and B cell immunity is further affected by the use of anti-B cell antibodies. The aim of this study was to assess the attitudes on vaccination of different centers affiliated with Fondazione Italiana Linfomi (FIL) in Italy. A survey questionnaire assessing vaccine uptakes and general opinion about vaccination was provided to 144 FIL centers between May

2022 and December 2022. Responses from 67 centers (46%) were received. All respondents reported informations about vaccine strategies in the centers. Prior to starting chemotherapy, 67% of clinicians verify the vaccination history of patients, paying particular attention to the inactivated anti-influenza virus (83%), pneumococcal (71%), and varicella-zoster virus (46%). There is minor attention to vaccinations for diphtheria, tetanus, and pertussis (DTP) or measles, mumps, and rubella (MMR).

In fact, 83% of the centers recommend annual influenza vaccination while pneumococcal vaccination is reserved for 32% of the centers for patients over 65 years of age and 25% of the centers for splenectomized patients or with respiratory comorbidities. Only 7% recommend it to all patients. In 96% of the centers, the vaccination status against SARS-CoV-2 is checked, and 20% also perform anti-Spike antibody testing before starting treatment. 37% of clinicians administer pre-exposure prophylaxis with tixagevimab-cilgavimab (Evusheld) in patients with lymphoma who are candidates for or undergoing treatment, and 20% in patients undergoing treatment with anti-CD20. This practice has allowed to delay the fourth vaccine dose from 1 to 4 months in 46% and 16% respectively, while it does not change the vaccination attitude for 25% of the centers. Almost all centers dispence the anti-SARS-CoV-2 booster dose even during maintenance therapy. In 63% of centers, vaccination with the new recombinant subunit vaccine for Varicella-Zoster Virus is recommended for patients with indolent lymphoma who are candidates for immuno-chemotherapy. This survey shows a a particular sensitivity among hematologists towards the vaccination for SARS-CoV-2 and initial interest towards VZV vaccination. Further effort is needed to make clinicians' attitudes more homogeneous."

Myelodysplastic syndromes

C036

A CARTOGRAPHY OF *UBA1* GENE TESTING, EPIDEMIOLOGY AND CLINICAL-GENOMIC CHARACTERISTICS: THE VEXAS/MDS ITALIAN EXPERIENCE

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VEXAS syndrome is a prototypic hemato-inflammatory disease combining rheumatologic and hematologic disorders as a molecularly defined nosologic entity. Given its multifaceted nature, VEXAS is a challenging masquerade lying at the interface between bone marrow failure syndromes, inflammaging and clonal hematopoiesis. Indeed, this condition displays a tetrad of somatic mutations, morphologic features, inflammatory pathways and immune overshooting. *UBA1* mutations constitute the genomic underpinnings of VEXAS, oftentimes presenting in association with MDS. Herein, we wanted to screenshot the current Italian *UBA1* diagnostic capabilities and clinical-genomic features of VEXAS using a national survey. Overall, 13/26 centers had *UBA1* genomic testing (Figure 1A). This consisted of either Sanger (50%), next-generation sequencing (14%), Droplet Digital PCR (7%), or combination (29%) (Figure 1B). Over a median of 13.7 months from *UBA1* testing availability, the positivity rate achieved 11.5% (n=39/337 total requests). Majority (72%) of VEXAS cases had threonine substitutions at Met41 hotspot, followed by leucine and valine (14% each; Figure 1C). Full information was available for 31 males. Median age at VEXAS diagnosis was 67 years (IQR=63-72). All patients had anemia (median hemoglobin 9.1 gr/dL, IQR=8.3-10.5) with macrocytosis (median MCV 106 fL, IQR=102-109.3). Bone marrow vacuoles were observed in myeloid and erythroid precursors (24% and 4%), or both (72%) (Figure 1D). Recurrent polychondritis was the most common rheumatologic association, accounting for 52% of cases, and 35% of patients showed an MGUS. A concomitant MDS was registered in 68% of cases, all

with low IPSS-R categories (scores <3.5). When re-stratified with IPSS-M, only 1 case was upstaged. Cytogenetics was normal in all patients apart from 3 MDS showing delY, t(12;16)(q13;q24) and trisomy8. *DNMT3A* was the most recurrently mutated gene (n=8), followed by *TET2* (n=3) with a 34.9% median VAF (IQR, 25.75-38.5). At last follow-up (median 8.8 months), 5 patients died following infection. Notably, 1 patient with *ASXL1/SF3B1*-mutant MDS progressed to AML after acquiring *RUNX1* mutation and underwent allogeneic HSCT following remission, whereas another was allografted with subsequent clinical and molecular remission.

This is the first Italian multidisciplinary clinical-genomic cartography of VEXAS. Acute clinical acumen and multidisciplinary interactions are essential for its identification and proper management.

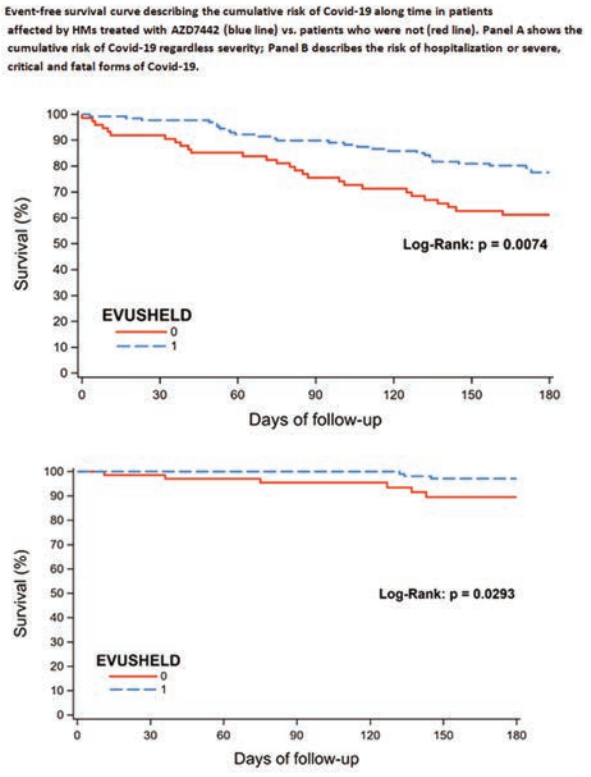

Figure 1.

C037

EFFECT OF CO-ADMINISTRATION OF VENETOCLAX AND AZACYTIDINE ON PLC-RELATED AND APOPTOSIS PATHWAYS IN MYELODYSPLASTIC SYNDROMES (MDS)

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Co-administration of Azacytidine (AZA) and Venetoclax (VEN) is effective in Myelodysplastic Syndromes (MDS) (Bazinet A et al, Curr Treat Options Oncol, 2022). Phospholipases C (PLCs) and PLC-related pathways, which target BCL-2, are implicated in MDS response to therapy (Mongiorgi S *et al.*, Clinical epigenetics, 2023). Here we investigated the effect of AZA/AZA+VEN in higher risk MDS patients and hematopoietic cell lines, focusing on PLC-related pathways and apoptotic markers. MDS patients, collected at baseline and during therapy, were 8 higher-risk (IPSS-R intermediate, high or very high) (Greenberg et al, Blood, 2012) and came from the Institute of Hematology "L e A Seràgnoli", Bologna, Italy. 5/8 patients were treated with AZA alone (75 mg/m2/day, on days 1-7), and in 3/8 patients VEN (400 mg/day, on days 1-14) was added to AZA. In patients treated with AZA alone and considered Responders (R), i.e., achieving Complete Remission (CR), Partial Remission (PR) or Hematological Improvement (HI) (2/5), BCL-2 decreased and BAX (BCL-2-associated X) increased within the first cycles of therapy, while, in Non-Responders (NR, showing Stable Disease SD, 3/5), BCL-2 increased, and BAX decreased. All 3 AZA+VEN patients showed a rapid hematological response (CR or HI), an early BCL-2 decrease and a BAX increase. However, following the 14th cycle of therapy, one CR AZA+VEN patient, which subsequently evolved into Acute Myeloid Leukemia (AML), showed a BCL-2 increased expression (shortly before AML progression) and no significant changes in BAX.

THP-1 and MV4-11 cells, used as resistant and sensitive *in vitro* models, were treated with AZA, VEN or AZA+VEN for 24h. AZA+VEN significantly decreased G2-M cell cycle phase in both cell lines, while it early induced PLCβ1, related with G0/G1 regulation and myeloid differentiation, only in THP-1 cells, where also CD11 and CD14 differentiation markers increased after treatment. Finally, AZA+VEN strongly affected cell death: BCL-2 decreased in MV4-11 cells; BAX, BIM (Bcl-2 Interacting Mediator of cell death), PUMA (p53 upregulated modulator of apoptosis) increased in THP-1 and decreased in MV4-11 cells; and Bcl-2 homologous antagonist killer (BAK1) increased in both cell lines. All in all, our results, that need to be confirmed in a larger number of patients, may help to better understand the molecular mechanisms involving apoptosis regulation and PLCs-related pathways, such as AKT or PLCγ2, in AZA/AZA+VEN response.

C038

IN MYELODYSPLASTIC SYNDROMES HIGHLY SUPPRESSIVE TREGS, EXPRESSING FOXP3-E2 ISOFORM, CORRELATE WITH THE DEGREE OF DYSPLASIA AND WITH THE ABSENCE OF SPLICING MUTATIONS

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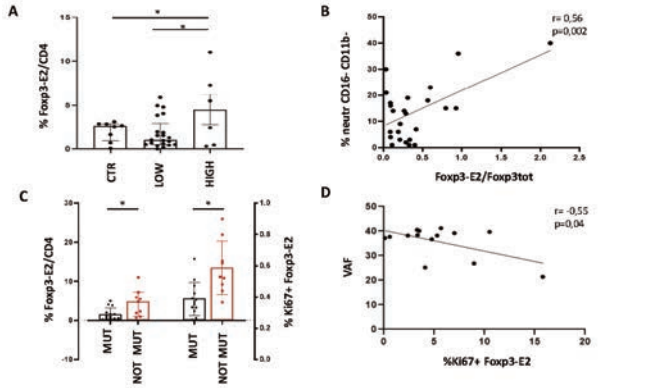
An altered immune-tolerance control, mediated Regulatory T cells (Tregs), has been largely described in MDS. Indeed, in early stage, reduced Tregs levels might favor pro-inflammatory and autoimmune mechanisms while in advanced stages, increased Treg-dependent suppression of immune effectors could probably foster leukemia progression. Treg's immune modulating properties are regulated by the expression of the master regulator gene FoxP3, which alternative splicing mechanisms generate two main isoforms, one containing the exon 2 (Foxp3-E2) and another, shorter, lacking it(Foxp3-Δ2). The expression of Foxp3-E2 has been recently demonstrated to be essential for Tregs suppressive activity; indeed, it is associated with the generation of unstable Tregs and with an autoimmune phenotype in a murine model. It currently lacks data about how alternative splicing of Foxp3 contributes at Tregs' dysfunction in MDS.

27 newly diagnosed MDS patients and 8 healthy donors were recruited in this monocenter study, conducted at Federico II University of Naples, approved by the Local Ethical committee. Immune profile, Foxp3-E2, overall Foxp3 and ki67 expression by Treg have been

evaluated with a multi-parametric flow cytometry approach.

According to IPSS-M, 21 patients were low risk and 6 were high risk. In high risk MDS patients, Tregs had a significantly increased Foxp3-E2 expression, as well as an higher proliferative capability, assessed by ki67 expression, compared to controls and low risk patients. Foxp3-E2/overall Foxp3 ratio was significantly decreased in all MDS patients, both low and high risk groups, as compared to controls. A significative direct correlation between the BM percentage of CD16-CD11b- dysplastic neutrophils and Foxp3-E2/overall Foxp3 ratio has been identified in the MDS cohort. Moreover, separating low risk patients on the basis of acquired splicing mutations, both Foxp3-E2 and overall Foxp3 CD4+ T cells are significantly increased in non mutated patients. Indeed, the proliferative capability of Foxp3-E2 CD4+ T cells is significantly lower in mutated patients and is inversely correlated with the Variant Allele Frequencies (VAF) of the mutated genes. Here we show, for the first time, how highly suppressive Tregs, expressing Foxp3-E2 isoform, characterize high risk MDS patients and are directly correlated with the degree of BM dysplasia. Intriguingly, it seems that mutations in spliceosome are associated with a less immunosuppressive BM microenvironment.



A: Median of the percentages of Foxp3-E2 on CD4 T cells in the Bone Marrow (BM) of Healthy donors (CTR), Low risk patients (LOW), High Risk patients (HIGH). B: Direct correlation between Foxp3-E2/Foxp3tot ratio and the percentage of dysplastic % neutrophils CD16- CD11b- in the BM of all MDS patients. C: Median of percentages of Foxp3-E2 on CD4 T cells in the BM of patients with (MUT) and without (NOT MUT) spliceosome mutations; Median of Ki67 expression on Foxp3-E2 CD4+ T cells in the BM of patients with (MUT) and without (NOT MUT) spliceosome mutations. D: Direct correlation between Ki67 expression on Foxp3-E2 CD4+ T cells in the BM of patients with spliceosome mutations and the Variant Allele Frequencies of the mutated gene. Statistical evaluation of data has been performed by means of the Mann-Whitney test and by Spearman's test for correlations. *=p<0,05

Figure 1.

C039

EXPRESSION OF NEO-201 MAY HELP IN THE DIFFERENTIAL DIAGNOSIS BETWEEN MYELODYSPLASTIC SYNDROMES AND ACUTE MYELOID LEUKEMIA

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Introduction. Differential diagnosis between myelodysplastic (MDS) mature dysplastic neutrophils, promyelocytes, and blasts of acute myeloid leukemia (AML) is currently challenging because of the lack of own markers of dysplastic cells. NEO-201 is an IgG1 monoclonal antibody for the treatment of solid tumors. In this study, the use of NEO-201 in the flow cytometric differential diagnosis between MDS and AML was evaluated. This hypothesis arises from the fact that, following the administration of the antibody to mice, mild neutropenia is observed, which can be explained by the fact that the targeting epitope of NEO-201 core 1 and extended core 1 O-glycans are also expressed on cells of the hematopoietic lineage.

Table 1. Median values of the characteristics at the diagnosis of the patients taken into analysis for NEO-201 expression in myeloid blasts and in the bone marrow. Hb: hemoglobin; PLT: platelets; WBC: white blood count; FC: flow cytometry; BM: bone marrow; MFI: median fluorescence intensity, with arbitrary units scaled from 0 to 262,144; NMFI: absolute number of cells based on CD15 and NEO+. In the figure, the expression of NEO+ cells in MDS contrasts with blast cells in AML.

	AML (27 pts)	MDS (12 pts)
Age (y) [range]	50 [18-80]	65 [40-88]
Sex M/F, %	14/13 [52/48]	8/4 [66.7/33.3]
Kariotype		
- Normal	19 [70.4]	4 [33.3]
- Altered	6 [22.2]	2 [16.7]
- Not available	2 [7.4]	6 [50]
Mutation		
- FLT3-ITD	11 [40.7]	0 [0]
- NPM1	8 [29.6]	0 [0]
- Not available	2 [7.4]	9 [75]
Hb (g/dL)	8.5 [5.8-12.8]	10.9 [6.4-13]
PLT (x 10^9/L)	49 [6-159]	113 [20-267]
WBC (10^3/mmc)	12 [0.1-247]	4.2 [0.7-32]
% blasts		
- Morphology	60 [30-90]	<5 [100]
- FC	54 [20-88]	0.6 [0.1-1.9]
% blasts NEO-201 negative	61.4 [20-88]	0.9 [0.1-3]
% blasts NEO-201 positive	0	0
MFI NEO-201 on blasts	0.6 [0-2]	0.5 [0.3-0.9]
% cells NEO positive in BM	10 [3-32]	50 [23-77]
% NEO positive (gate CD15+)	98.8 [1.4-100]	98.7 [97.1-100]
MFI NEO-201 on CD15+ cells	8 [5.5-13.4]	9.5 [6.4-18]
NMFI CD15+ cells	780 [12-1337]	928 [621-1800]

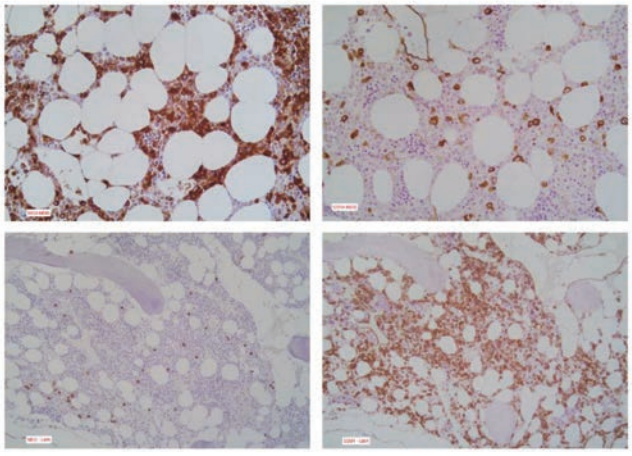

Figure 1.

Materials and Methods. We evaluated by flow cytometry the bone marrow samples of newly diagnosed 21 MDS and 25 AML patients, diagnosed according to the current ELN-working group criteria. The immunophenotypic markers used were CD15, CD45, CD38, CD138, CD14, CD19 and NEO-201. NEO-201 positivity was defined when % of positive cells >10%.

Results. NEO-201 is differentially expressed in the bone marrow. CD15+ neutrophil granulocytes are positive for NEO-201 expression, in contrast to monocytes, where it is negative (98.7% [1.4-100] for AML, 98.7 [97.1-100] for MDS). Instead, NEO-201 antigen is

absent in blasts and in leukemic cells that are positive for AML markers. The 27 AML patients reported a median rate of blast cells of 54 and 60% (in morphology and flow cytometry, respectively), with 0% of these cells expressing NEO-201 and 100 [IQR, 100-190] also NEO-201 negative ($p<0.05$). Rates of total cells NEO-201 positive in BM are 10% [3-32] in AML, and 50% [23-77] in MDS, evidencing the reduction of antigen expression when there is an increase in blast cells. The median fluorescence intensity evaluated in the two populations on CD15+ cells appears superimposable. In Figure 1 are reported two samples of bone marrow biopsies, evaluated both with CD34 and NEO-201 antigens, showing the significant presence of NEO-201 in the context of MDS (upper panel), contrary to AML (lower panel).

Conclusion. Expression of NEO-201 is not found in blasts, immature cells, and monocytes of the analyzed patients, contrary a CD15+ neutrophil granulocytes where NEO-201 is positive, supporting the proposal to integrate NEO-201 as a marker in the differential diagnosis, leaving open the possibility of use as a future antitumor agent.

C040

STAT3 MUTATIONS IMPACT ON MDS ASSOCIATION IN PATIENTS WITH LGL LEUKEMIA (LGLL)

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Background-Aim. Myelodysplastic (MDS) patients are often characterized by clonal expansions of cytotoxic T-Large Granular Lymphocytes (T-LGL) or Natural Killer (NK) cells in peripheral blood, with possible involvement of bone marrow (BM), sometimes meeting the diagnostic criteria of LGL-Leukemia (LGLL). In LGLL, somatic STAT3 mutations represent the main genetic lesions and are extremely relevant due to their clinical association with cytopenias, leading to a reduced overall survival of patients. The nature of the intertwining LGLL/MDS clinical dyad is still unclear, although a pathogenetic nexus rather than an incidental age-related finding has been speculated. In this regard, the potential pathogenetic impact of hyperactivating STAT3 mutations has never been elucidated. The aim of this study was to compare BM histological features between STAT3-mutated and wild-type (WT) LGLL patients, particularly focusing on the incidence and characteristics of concomitant LGLL-MDS cases.

Methods. We retrospectively examined 45 consecutive BM biopsies from LGLL patients, with complete clinical annotations and immunophenotypic data. STAT3 mutations (exons 19–21) were assessed by Sanger sequencing.

Results. In the main cohort, 21/45 (47%) patients harbored somatic STAT3 mutations in the LGL clone. A concomitant MDS was reported in 11/45 (24%) LGLL cases, with a prevalence in the STAT3-mutated group (8/21, 38%), as compared to STAT3-WT cases (3/24, 12%, $p<0.05$). Signs of dysplasia (without meeting MDS diagnosis) were instead similarly observed in both groups (19% *vs* 21%). Focusing on LGLL-MDS cases, 10/11 (90%) were characterized by a TCRαβ/CD8+/CD16+/CD56-/CD57+ T-LGL clone. Notably, expression of the TCR-Vβ9 was shared by 4/10 (40%) T-LGLL-MDS cases ($p<0.05$), suggesting a non-random association with the T-LGL clone. Hypo-cellular BM, suggestive of a massive immune suppression, was observed in 2/11 (18%) cases, both STAT3-mutated. Of novelty, follow-up of 3 MDS-LGLL cases revealed that LGLL diagnosis preceded MDS onset.

Conclusions. Our evidence suggests that STAT3-mutated LGL clones might exert a causative role in MDS pathogenesis. Ongoing analysis of LGL clonotypes in T-LGLL-MDS cases might shed light on LGLL-MDS relationship.

Chronic myeloid leukemia

C041

MULTICENTER, PROSPECTIVE AND RETROSPECTIVE OBSERVATIONAL COHORT STUDY OF PONATINIB IN PATIENTS WITH CML IN ITALY: LONG-TERM FOLLOW-UP RESULTS OF THE OITI TRIAL

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Background. Ponatinib is a 3rd-generation TKI indicated for adults with CP, AP or BP CML R/I or with T315I mutation.

Aims. The goal of the OITI trial was to evaluate treatment patterns and outcomes with ponatinib in pts with CML in Italy.

Methods. This non-interventional study included pts aged ≥18 years with CP, AP or BP CML who started ponatinib in clinical practice across 26 Italian sites. Primary endpoint was the CCyR rate in CP CML pts by 6 months after ponatinib start. We present the updated analysis of all evaluable pts (median follow-up 40.9 mo [IQR 31.6-59.0]).

Results. 120 pts (111 CP, 6 AP, 3 BP CML; median age 60 [19–93] years) were analyzed. 60 (50%) received ponatinib in 2L, 42 (35%) in 3L and 18 (15%) in ≥4L. Most common reasons for switching to ponatinib were intolerance 40 (33%), primary resistance 29 (24%), secondary resistance 19 (16%). Of 70 evaluated pts, 6 (8.6%) had the T315I mutation whereas 17 (24%) had other ABL1 mutations. Ponatinib starting doses were 45mg (36%), 30mg (41%) or 15mg (23%). Median treatment duration was 33.5 (1.3–89.7) mo. Focusing the analyses on CP pts, at baseline, 54 (50%) pts had less than CCyR and 55 (50%) were in CCyR or better. At 6 mo, 82/109 (75%) evaluable pts were in CCyR; 29/54 (54%) achieved and 52/54 (96%) maintained at least a CCyR or improved response *vs* baseline. Additionally, 38/109 (35%) achieved a MR3 and 21/109 (19%) a DMR (≥MR4) (Table 1). PFS rates at 24 and 36 mo were 87.7% (95% CI 81.6-94.2%) and 83.0% (95% CI 75.9-90.8%). Corresponding OS rates were 90.4% (95% CI 84.9-96.3%) and 86.7% (95% CI 80.2-93.8%). In the whole cohort, 64/120 (53%) pts experienced at least one treatment-related AE, most commonly hypertension (8.3%), increased lipase (5.0%) and thrombocytopenia (5.8%). Only 2 treatment-related AOEs were reported. Dose modifications occurred in 76 pts: 29 (38%) due to AEs, of which 4 were CV AEs; 22 (29%) due to medical decisions; 16 (21%) reduced the dose after at least a MCyR; 8 (11%) increased the dose due to lack of efficacy and 1 (1%) for other reasons. 54 pts permanently discontinued ponatinib [main reasons were AEs 19/54 (35%) and progression or death 12/54 (22%)].

Conclusions. Ponatinib confirmed a favorable efficacy and long-term manageable safety profile in pts with CML treated in clinical practice. No new safety signals emerged with ponatinib in longer follow-up. Early ponatinib use and dose optimization appear key to the outcomes observed in this real-world study.

Table 1. Molecular response outcomes in patients with CP CML overall and according to treatment line.

	CP CML			
Cohort	**Overall (N=111)**	**2L (n=56)**	**3L (n=38)**	**>3L (n=17)**
MR2, n/n (%)				
3 mo	12/80 (15.0)	4/44 (9.1)	7/26 (27.0)	1/10 (10.0)
6 mo	23/109 (21.0)	9/55 (16.0)	8/37 (22.0)	6/17 (35.0)
12 mo	10/69 (14.0)	4/33 (13.0)	4/26 (15.0)	2/12 (17.0)
24 mo	7/53 (13.0)	1/22 (4.5)	3/22 (14.0)	3/9 (33.0)
36 mo	6/42 (14.0)	3/15 (20.0)	1/18 (5.6)	2/9 (22.0)
MR3, n/n (%)				
3 mo	18/80 (22.0)	10/44 (23.0)	8/26 (31.0)	0/10 (0)
6 mo	38/109 (35.0)	18/55 (33.0)	14/37 (38.0)	6/17 (35.0)
12 mo	30/69 (43.0)	16/33 (52.0)	9/26 (35.0)	5/12 (42.0)
24 mo	20/53 (38.0)	12/22 (55.0)	4/22 (18.0)	4/9 (44.0)
36 mo	13/42 (31.0)	5/15 (33.0)	4/18 (22.0)	4/9 (44.0)
DMR (MR4–MR5), n/n (%)				
3 mo	13/80 (16.2)	7/44 (15.5)	5/26 (19.7)	1/10 (10.0)
6 mo	21/109 (19.4)	11/55 (19.6)	4/37 (21.8)	2/17 (11.6)
12 mo	18/69 (25.5)	8/33 (25.7)	9/26 (33.8)	1/12 (8.3)
24 mo	21/53 (39.4)	9/22 (41.1)	10/22 (45.1)	2/9 (22.0)
36 mo	21/42 (50.1)	7/15 (46.7)	11/18 (60.6)	3/9 (33.0)

Abbreviations: 2L, 2nd-line; 3L, 3rd-line; 4L, 4th-line; AE, adverse event; AOE, arterial occlusive event; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CI, confidence interval; CML, chronic myeloid leukemia; CP, chronic phase; CV, cardiovascular; DMR, deep molecular response; EMA, European Medicines Agency; IQR, interquartile range; MCyR, major cytogenetic response; MMR, major molecular response; mo, months; MR, molecular response; OITI, Observational study of Iclusig® (ponatinib) Treatment in patients with CML in Italy; OS, overall survival; PFS, progression-free survival; pts, patients; R/I, resistant/intolerant; TKI, tyrosine kinase inhibitor.

C042

A SUCCESSFUL TREATMENT-FREE REMISSION IS ACHIEVABLE ALSO IN CHRONIC MYELOID LEUKEMIA PATIENTS LACKING OPTIMAL REQUIREMENTS

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Achievement of a sustained treatment-free remission (TFR) after tyrosine kinase inhibitors (TKI) discontinuation is of utmost importance in chronic myeloid leukemia (CML). The international recommendations indicate the requirements for accessing TFR, defining circumstances that definitely point towards it ("optimal"), or that allow attempting it only in high priority cases ("minimal"), or strongly advise against it. We aimed to evaluate the impact of these circumstances in a real-world series of 236 CML patients (pts) who discontinued TKIs from 2011 to 2023 in the retro-prospective Triveneto registry.

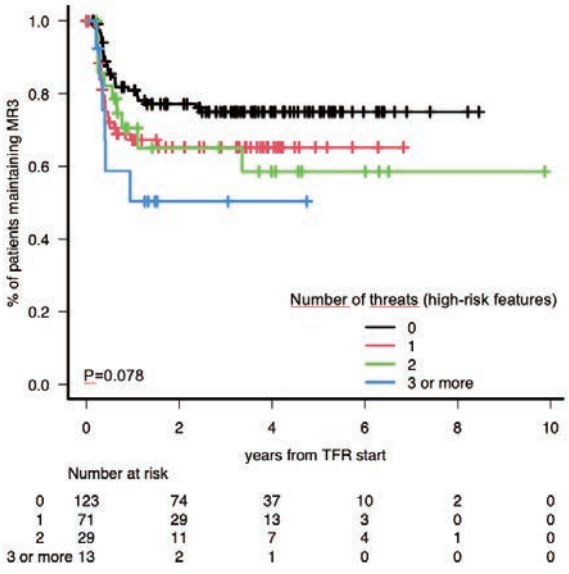

Figure 1.

We defined as threats for discontinuation the followings: (a) high ELTS risk, (b) history of accelerated phase (AP), (c) warning or failure molecular responses (according to ELN2020 definitions) at 3, 6 and/or 12 months of the TKI later discontinued, (d) switch to second line TKI for resistance, (e) total duration of treatment ≤5 years (yrs), (f) duration of deep molecular response (DMR) before TKI stop ≤2 yrs if MR4.5 or ≤3 yrs if MR4.0, (g) use or ≥3 lines of TKI, and (h) history of BCR::ABL1 mutations. The endpoint was the rate of sustained TFR 12 months after discontinuation according to the number of threats. Males were 124 (52.5%), median age at CML diagnosis was 50.4 yrs (range 17-80) and median age at TKI stop was 61.7 yrs (range 23-91). All pts had typical e13a2 and/or e14a2 transcripts. All pts were diagnosed in chronic phase (CP), except one in AP. ELTS risk was L/I/H/unknown in 162/54/9/11 pts respectively. Frontline TKI was imatinib in 201 pts and 2G-TKI in 35 pts. Lines of treatment were 1, 2 or ≥3 in 172, 54 and 10 patients respectively. Optimal response was achieved to all timepoints after start of the TKI leading to TFR in 156 pts while 40 had at least one non optimal response. Four pts had a history of mutations. Total duration of TKI was >5 yrs in 215 and ≤5 yrs in 20 pts, duration of DMR was optimal in 193 and non optimal in 39 patients. The probability of sustained TFR at 12 months was 73.8% (IC95% 67.5-79.1) for the whole cohort and 80.9%, 67.3%, 70.5% and 50.3% for 0, 1, 2, and ≥3 threats, respectively (Figure 1). Only non optimal duration of DMR, history of AP and history of BCR-ABL1 mutations were associated to a significantly lower probability of TFR.

We conclude that CP CML pts may have access to a successful TFR even when lacking one or more optimal features, provided there is an optimal duration of DMR before TKI stop.

C043

BCR-ABL1 TRANSCRIPT LEVEL IN SMALL EXTRACELLULAR VESICLES CORRELATES WITH MOLECULAR RESPONSE AND THE ONGOING THERAPY: A STUDY ON ADULT CML PATIENTS

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Small extracellular vesicles (sEVs) have been shown to play a function in tumor growth and have been studied in Chronic Myeloid Leukemia (CML). Analysis of sEVs and their contents offers a non-invasive strategy that might identify messages transmitted by persisting leukemic cells. The sEVs recovered from CML patients may contain the BCR::ABL1 transcript, but its relationship to clinical and biological factors is still unclear. This study aims to connect the disease status and several clinical features with the BCR::ABL1 transcript levels in sEVs (BCR-ABL1-EV). sEVs were isolated from 65 plasma samples of adult CML patients in molecular response: 12/65 (18%) in MMR and 53/65 (82%) in DMR assessed by RT-qPCR following the international scale. At sampling, 17/65 (26%) patients were treated with imatinib, 9/65 (14%) with nilotinib, 6/65 (9%) with dasatinib, 8/65 (12%) with intermittent TKI therapy, and 11/65 (17%) were in treatment free remission (TFR).

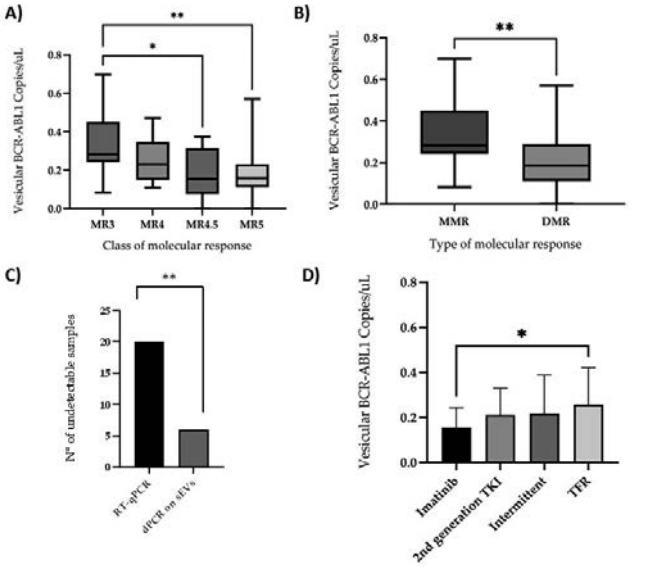

Figure 1.

Taking advantage of digital PCR's (dPCR) sensitivity, it was used to detect the presence of BCR::ABL1 transcript in sEVs. The BCR::ABL1-EV show a decrease at the deepening of the MR classes and there was a significant difference between MR3.0 and MR4.5

and MR5.0 (p = 0.017 and p=0.0035, respectively) (Figure 1A). By gathering overall samples according to MMR and DMR definition, the BCR::ABL1-EV resulted statistically different (p= 0.0017) (Figure 1B). The undetectable samples by RT-qPCR on cells were 20/65 (31%), while by dPCR on sEVs were and 6/65 (9%). This difference resulted statistically significant (p=0.0038) (Figure 1C). A significant difference between BCR::ABL1-EV and the ongoing therapy was observed. For this analysis, nilotinib and dasatinib were considered together as "2nd generation TKI". The BCR::ABL1-EV were significantly higher in samples from patients in TFR compared to those from patients treated with imatinib (p=0.0416). No statistical difference resulted by other comparisons (Figure 1D). This evidence may be due to the therapy duration or to a mechanism activated by the drug. Further analysis will clarify this point. In conclusion, dPCR on sEVs is able to detect transcript reduction at the deepening of the MR classes and to discriminate between MMR and DMR. dPCR associated with sEVs analysis confirmed its higher sensitivity to detect even low levels of target and it is able to identify the presence of leukemic cells releasing BCR::ABL1 positive sEVs.

C044

CIRCRNAS DERIVED FROM THE BCR::ABL1 FUSION GENE ARE POTENTIAL BIOMARKERS OF RESPONSE IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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Background. Circular RNAs (circRNAs) are a type of single-stranded covalently closed non-coding RNAs that play important roles in various biological processes. CircRNAs are more stable compared with linear RNAs due to their special circular structure, which can effectively resist degradation induced by exonucleases. Recent evidences demonstrate that circBA1 are involved in the pathogenesis of cancer, including hematologic malignancies. One relevant consequence of CircRNAs is the sequestration of mirRNAs. It has been demonstrated that circBA1, derived from BCR::ABL1 fusion transcript, is a sponge for miR-148b-3p that is involved in the activation of stemness pathways including WNT and b-catenin and the expression of CD25, a surface marker expressed by Chronic Myeloid leukemia (CML) stem cells. The aim of the study is to correlate the levels of BCR::ABL1 circRNAs at different time points during therapy with the deepness of the response and with the probability of entering the treatment-free remission (TFR) phase and to maintain a sustained TFR without molecular relapse.

Methods. We analyzed the expression levels of circBA1 and circBA9.3 by droplet digital PCR (ddPCR) in bone marrow (BM) and peripheral blood (PB) samples from 20 CML patients with variable levels of BCR::ABL1 at diagnosis and at different time of TKI treatment including patients who obtained BCR::ABL1 negativity. Linear BCR::ABL levels were measured by RealTime PCR according to standard methods.

Results. CircBA1 was found to be expressed in all the CML patients irrespectively of the BCR:ABL1 levels. Interestingly, we detected circBA1 in all the 5 patients in MR5 with levels ranging from 0,03 to 4 copies/uL. Patients in molecular responses MR3 presented levels ranging from 1,8 to 3,13. Patients in MR2 presented levels of circBa1 ranging from 0,3 to 3,62 copies/uL. In the patients at diagnosis of circBA1 is expressed at levels ranging from 3,1 to 4 copies/uL. Regarding circBA9.3, we found that is expressed in 90% of the samples with values ranging from 0,06 to 0,3 copies/uL.

Conclusions. Although data are still preliminary, we detected for the first time the presence of circRNAs in CML patients completely negative for BCR::ABL1 after TKI therapy. We are expanding the study to investigate the correlation with deep molecular responses and with the possibility to obtain and maintain treatment-free remission. CircRNA could represent a novel predictive marker of deep molecular response.

C045

TYROSINE KINASE INHIBITORS DISCONTINUATION IN CHRONIC MYELOID LEUKEMIA: A RETROSPECTIVE ANALYSIS OF 442 ITALIAN PATIENTS

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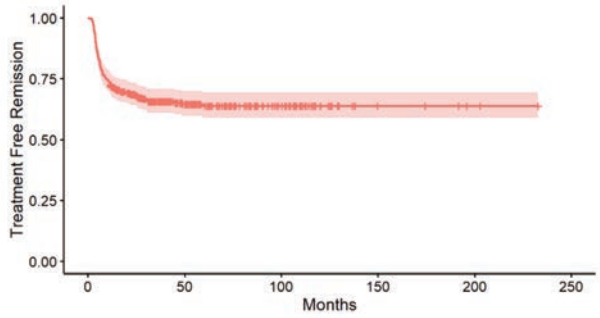
In the last 15 years different studies analyzed the outcome of Chronic Myeloid Leukemia (CML) patients (pts) with sustained deep molecular response (DMR) who discontinued tyrosine kinase inhibitors (TKIs) and demonstrated that it is safe according to the current recommendations.

We proposed a retro-prospective observational study on pts with CML who discontinued TKIs and we present data on 442 pts in 29 centers in Italy. Median age at time of discontinuation was 59 yo (IQR: 48-71). 204 pts (46%) were female; 54%, 34% and 12% were low, int, and high Sokal score respectively. 26% pts carried a b2a2

BCR-ABL1 transcript, 71% pts a b3a2 and 9 pts discontinued with an atypical transcript. 258 pts (59%) discontinued in first line, 155 pts in 2nd line, 25 pts in 3rd line, and 2 pts in 4th line. 241 pts were on treatment with imatinib (54% all frontline). 122 pts with nilotinib (75 frontline, 47 in 2nd or further lines), 72 pts with dasatinib (17 frontline, 55 in 2nd or further lines), 4 pts with bosutinib and 3 pts with ponatinib. Median duration of treatment with the last TKI was 82 mos (IQR: 55-124); median time to DMR (undetectable transcript or MR4/MR4.5/MR5) with the last TKI was of 18 mos (IR 7-35). Median duration of DMR was 64 mos (IQR: 41-97) before stop. 424 pts had a response defined according to molecular standardization: 19 pts (4%) were MR3, 114 pts (27%) were MR4, 170 pts (40%) were MR4.5, 119 pts (28%) were MR5. Reasons for discontinuation were toxicity (22%), pregnancy (6%), pts' desire (6%), other reasons for 28 pts. Median time to restart TKI was 5.8 mos (IQR: 3.8-10.2). No pts progressed. We assessed age, sex, Sokal score, ELTS Risk, type of transcript, duration of TKI therapy, line of therapy at stop, depth of MR, reasons for stop as potential prognostic factors for TFR, and we have identified the level of MMR at stop (MMR *vs* MR4.5, HR: 3.2, p<0.001; MR4 *vs* MR4.5, HR:1.9, p=0.005), the reason of discontinuation (pregnancy *vs* shared decision: HR 2.0, p=0.016), ELTS score (High risk *vs* low risk, HR 3.0, p= 0.034) and age (older *vs* younger HR 0.6, p<0.001). Survival analysis was conducted on pts with at least one year of follow up after treatment discontinuation (N 383), (FIG.1). 130 patients (33.9%) had to resume therapy, most of them (N 105) lost MMR within 12 mos. Our experience confirms that discontinuation may be feasible also in particular condition which are excluded by recommendations.



time	n_risk	n_evens	TFR	0.95 LCL	0.95 UCL
12	279	105	0.73	0.68	0.77
24	206	14	0.69	0.64	0.73
36	154	8	0.66	0.61	0.71
48	122	1	0.65	0.60	0.70

Figure 1. Kaplan-Meier curves for patients who discontinued tyrosine kinase inhibitor (TKI). Estimated treatment-free remission (TFR) and the corresponding 95%CI are reported at 12, 24, 36, and 48 months.

Chronic lymphocytic leukemia and lymphoproliferative syndromes II

C046

ABSTRACT NOT PUBLISHABLE

C047

ABSTRACT NOT PUBLISHABLE

C048

GENOMIC EVOLUTION AND RESISTANCE TO PIRTOBRUTINIB IN COVALENT BTK-INHIBITOR PRE-TREATED CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS: RESULTS FROM THE PHASE I/II BRUIN STUDY

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Background. Pirtobrutinib, a non-covalent (reversible) BTKi, demonstrated efficacy in pts with CLL resistant to cBTKi. Mechanisms of resistance to pirtobrutinib have not been systematically analyzed.

Methods. Pts treated with pirtobrutinib monotherapy in phase 1/2 BRUIN who developed disease progression (PD) were included. Targeted NGS of 74 relevant genes was performed on PBMCs. Somatic mutations were reported with a limit of detection (LoD) of 5% variant allele frequency (VAF).

Results. As of 29 July 2022, 49 cBTKi pre-treated CLL pts who progressed on pirtobrutinib had paired NGS data at baseline and PD. Median age was 69y (36-86), median number of prior lines was 4 (1-10), 41 pts (84%) had discontinued prior cBTKi due to PD. Pts received 1 or more cBTKi: ibrutinib (n=44, 90%), acalabrutinib (n=10, 20%) or zanubrutinib (n=1, 2%). ORR to pirtobrutinib (including PR-L) was 80%. Most common alterations at baseline were mutations in BTK (51%), TP53 (49%), ATM (27%), NOTCH1 (20%), SF3B1 (18%), PLCG2 (10%). BTK C481 VAF decrease/complete clearance was observed at PD in most pts (92%, 22/24, median VAF decrease=100%). At PD, 71% (35/49) pts acquired ≥1 mutation, 55% (27/49) acquiring ≥1BTK mutation. Among these 27 pts, 36 acquired BTK mutations were identified; including gatekeeper mutations (T474I/F/L/Y, 17/49, 35%), kinase-impaired (L528W, 9/49, 18%) and variants of unknown significance (VUS) proximal to the ATP-binding pocket (6/49, 12%; V416L (n=2), A428D (n=2), D539G/H (n=1), Y545N (n=1)) (Figure 1). Manual inspection for acquired BTK mutations at PD in baseline samples revealed 9 mutations (8 pts) pre-existed at baseline at low VAFs (1-

4%): 6 gatekeeper T474I/L, 2 kinase impaired L528W, 1 VUS A428D. These pts responded to pirtobrutinib (6/8, 75%ORR) and received prior ibrutinib (n=5)/acalabrutinib (n=4). Most commonly acquired non-BTK mutations were TP53 (7/49, 14%) and PLCG2 (4/49, 8%).

Conclusions. Pts who progressed on pirtobrutinib showed clearance of BTK C481 clones and emergence/outgrowth of non-C481 clones (T474, L528W mutations) and other VUS. Many acquired BTK mutations were shown to pre-exist at baseline at low VAF, reflecting emergence on prior cBTKi and did not preclude pirtobrutinib efficacy. ~Half the pts did not acquire BTK mutations and 29% did not acquire any in this targeted panel, suggesting alternate resistance mechanisms. Whether similar resistance patterns would manifest if pirtobrutinib was utilized prior to cBTKi treatment remains uncertain.

Figure. Number of patients with acquired mutations according to *BTK* status at baseline and prior type of cBTKi. The color gradient indicates the mean VAF at progression.

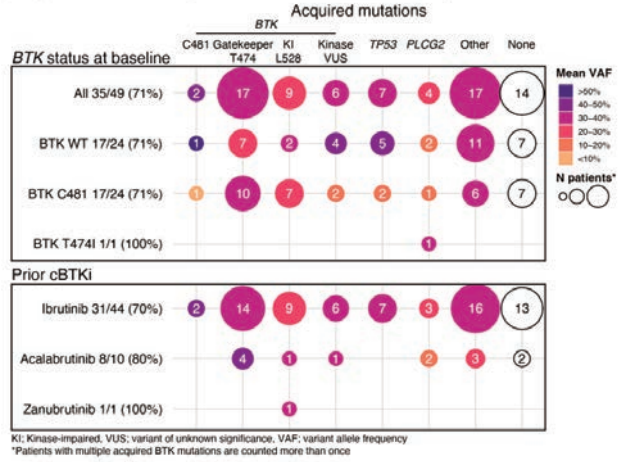

Figure 1.

C049

ABSTRACT NOT PUBLISHABLE

C050

RNA-SEQUENCING OF T-LGLL PATIENTS IDENTIFIES NEW TARGETABLE ONCOGENIC MECHANISMS IN THE MOST SYMPTOMATIC CD8+ STAT3 MUTATED CASES

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Background and Aims. T-Large granular lymphocyte leukemia (T-LGLL) is a heterogeneous disease, including distinct biological and clinical subtypes. By phenotype, a canonical CD8+ T-LGLL and a CD4+ T-LGLL variant can be distinguished. Moreover, additional genetic subgroups can be defined based on the presence of STAT3 or STAT5B-mutations (M), which are particularly relevant for their association with disease clinical manifestations and prognosis.

Robust biological rationales for the treatment of T-LGLL patients are still lacking. The understanding of the biological basis of their different clinical courses is diriment for the development of targeted therapeutic strategies. Although STAT3 and STAT5B are crucial transcription factors in the survival hub of leukemic LGL, the impact of hyperactivating STATs-M on T-LGL transcriptome has never been elucidated yet. This study aims to disclose the gene expression profiles of T-LGLL patients with reference to the subtypes defined by CD8+/CD4+ phenotype and STAT3/STAT5B mutational status.

Methods. RNA-Seq profiling of purified T-LGL was performed in 20 T-LGLL samples and 5 controls (CTR). Differentially expressed genes were assessed using DESeq (adj. $p<0.01$) and validated by RT-qPCR.

Results. STAT3-mutated (M) cases, characterized by symptomatic disease and reduced survival, resulted as a distinct biological entity as compared to the other T-LGLL subtypes and CTR, with deregulation of several oncogenes, cytokines and receptors. Gene Set Enrichment Analyses pointed out a massive activation of distinct signaling pathways, in spite of a global down-regulation of gene expression. Notably, by focusing on LAIR1 depletion, which in turn result in a defective activation of the SHP-1 phosphatase, we discover a new mechanism cooperating in the maintenance of STAT3 activation. We also proved that the LAIR1/SHP-1/STAT3 axis can be restrained by treatment with a SHP-1 agonist (SC-78), inducing apoptosis of malignant T-LGL. By contrast, the impact of STAT5B-M on T-LGL transcriptome was limited. Of novelty, in CD4+ STAT5B-M cases we found the up-regulation of PIM1, a negative regulator of the STAT5B-axis, likely accounting for the mostly indolent course of STAT5B-M patients.

Conclusions. This study significantly advances the knowledge of transcriptome dysregulations in T-LGLL, identifying novel targetable oncogenic axis and players likely linked to disease clinical manifestations, paving the way for new tailored therapeutic approaches.

Hodgkin lymphoma

C051

ABSTRACT NOT PUBLISHABLE

C052

GENETICALLY DISTINCT PATHOGENESIS OF EPSTEIN-BARR VIRUS (EBV)-POSITIVE VERSUS EBV-NEGATIVE CLASSICAL HODGKIN (CHL) LYMPHOMA

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Introduction. Latent EBV infection of the cHL clone is more frequent in the mixed-cellularity (MC) histological subtype, in early childhood and older adulthood, and in developing countries. Based on these and other epidemiologic features, EBV+ cHL was hypothesized to have distinct etiology and pathogenesis compared to EBV- cHL. However, the genomic landscape of EBV+ cHL is incompletely defined.

Methods. We studied 57 cHL cases (10-83 year-old; 41 EBV-, 16 EBV+) by whole exome (WES) and/or whole genome (WGS) sequencing of tumor and normal cells purified from frozen samples, at identical median depths for EBV+ and EBV- cases (WGS 44X; WES 146X).

Results. Clonal nonsynonymous somatic mutations were much fewer in EBV+ *vs* EBV- cHL (median 4.5 *vs* 57; p=0.0013), and the same was for total mutations genome-wide (median 112 *vs* 6826; p<0.0001). Conversely, within EBV- cHL, MC (n=6) and non-MC (n=33) cases had similar mutation load (p=0.56), indicating a link with viral status rather than histology. AID-associated mutational signatures were stronger in EBV- *vs* EBV+ cHL, both genome-wide (SBS9, q=0.069; SBS85, q=0.023) and in the target region of 126 genes known to undergo AID-driven aberrant somatic hypermutation (median of 4 *vs* 0 mutations/Mb; p=0.045). Compared to EBV- cHL, EBV+ cHL had fewer mutations or copy number alterations in ≥1 genes of several pathways (Figure 1A) that drive cHL pathogenesis and can be activated by EBV latent proteins (possibly surrogating cellular genetic lesions): i) JAK-STAT signaling genes STAT6, SOCS1, CSF2RB and JAK2 were altered in 85% EBV- *vs* 47% EBV+ cases (p=0.0057); ii) PI3K-AKT signaling genes GNA13 and ITPKB were mutated in 34% EBV- *vs* 7% EBV+ cases (p=0.047); and iii) NF-κB signaling genes TNFAIP3, NFKBIE and REL were altered in 85% EBV- *vs* 47% EBV+ cases (p=0.0057). EBV- cHL had also more frequent mutations of the MHC-I genes B2M and HLA-A/B/C (56%, *vs* 20% in EBV+ cHL, p=0.0032; Figure 1A), possibly to prevent presentation of tumor neo-antigens generated by the much higher mutation burden. Conversely (Figure 1B), EBV+ cases had germline homozygosity of ≥1 HLA-I genes more often than EBV- cases (53% *vs* 19%; p<0.05), particularly for HLA-C (33% *vs* 2%; p=0.0039), which may favor EBV+ cHL development through a reduced diversity of HLA-I alleles available for viral antigen presentation.

Conclusions. In the largest series characterized to date, EBV+ and EBV- cHL genetically diverged in their germline and somatic routes to lymphoma development.

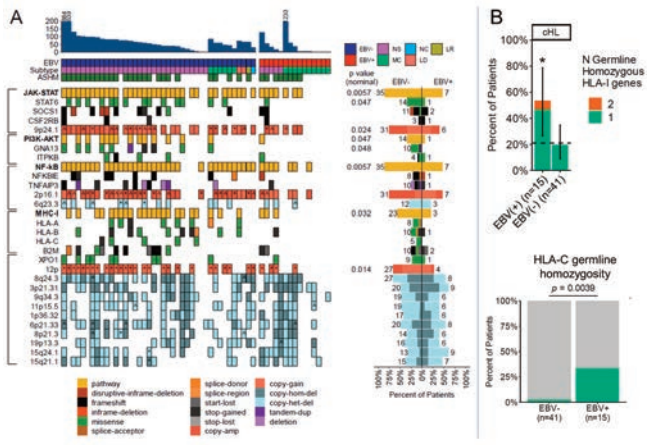

Figure 1.

C053

BRENTUXIMAB-VEDOTIN PLUS AVD CHEMOTHERAPY AS FRONTLINE THERAPY IN PATIENTS WITH STAGE IV CLASSICAL HODGKIN LYMPHOMA: A FIRST REAL-WORLD REPORT FROM THE RETE EMATOLOGICA LOMBARDA

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Brentuximab-Vedotin (BV) plus doxorubicine, vinblastine and dacarbazine (AVD) demonstrated to improve survival compared to ABVD as frontline treatment of advanced stage classical Hodgkin Lymphoma (HL) with a manageable increase of toxicity. Data of HL patients (pts) treated with BV-AVD in 12 centers of Rete Ematologica Lombarda were collected with the aim to describe efficacy and toxicity in a real-world setting. Sixty-seven classical HL pts treated with BV-AVD until March 2023 were included; median age was 39 (range: 18-81) years and 10 pts (14.9%) were older than 65. All pts presented with stage IV disease; 13 (19.7%) pts had B symptoms, 20 (29.9%)

bulky disease and 42 (62.7%) presented with skeletal involvement. Hasenclever score was ≥ 5 in 11 pts (16.4%). All pts were initially treated with BV-AVD; at present, 58 pts (86.6%) underwent PET after 2 cycles (PET2) and 38 pts (56.7%) after 6 cycles (PET6). PET2 was negative (Deauville Score: 1-3) in 45/58 pts (77.6%) and PET6 was negative in 30/38 pts (78.9%). PET2 positive pts had a lower probability to achieve complete response (CR) at PET6 when compared to PET2 negative pts (Odds ratio: 0.06, p=0.002). With a median follow-up of 7.9 months (IQ range: 4.0-11.9), 1-year progression-free survival (PFS) for the whole study population was 70.5% (CI 95%: 50.6-88.7); 1-year PFS was significantly superior in PET2 negative *vs* PET2 positive pts: 80.8% (CI 95%: 65.7-99.2) *vs* 31.5% (CI 95%: 10.6-93.7) (p = 0.0009) (Figure 1). Twenty-eight pts (41.8%) experienced at least one grade ≥ 3 extra-haematological adverse event (AE) for a total of 35 events: infections (10 pts), peripheral neuropathy, constipation and transaminitis (6 pts each) were the more common. Among less frequent AEs, a case of grade 3 pancreatitis and encephalitis were described, in both cases solved without sequelae. Hospitalization was required in 14 pts (20.9%), with a median duration of 11 (range: 1-37) days; 11 pts (16.4%) required transfusions during treatment. Two pts have died so far, 1 due to COVID-19 pneumonia and 1 to ischaemic heart attack in known history of cardiac disease: both of them were over 70 years old and in CR at PET2. In conclusion, BV-AVD confirmed to be effective in this first real-word report; PFS is inferior to that described in the ECHELON-1 trial, likely due to the unfavourable characteristics of the unselected population. The predictive role of PET2 during BV-AVD seems substantial and PET driven approach can be hypothesized.

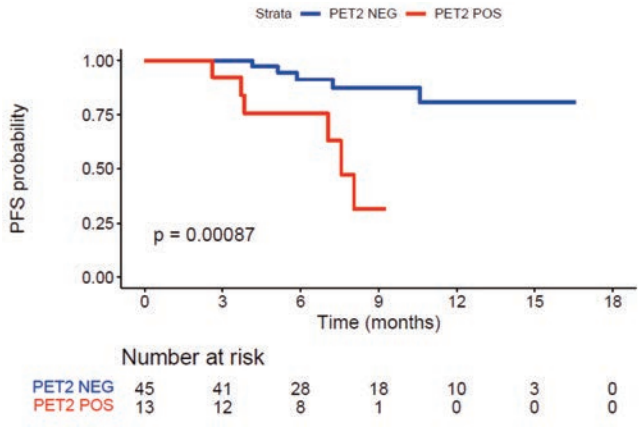

Figure 1. PFS accordingly to PET2 result.

C054

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Acute leukemia II

C056

CAMPUS ALL MULTICENTRE STUDY ON OUTCOME OF 322 ADULT PATIENTS WITH PHILADELPHIA-NEGATIVE ACUTE LYMPHOBLASTIC LEUKEMIA TREATED IN REAL-LIFE ACCORDING TO LAL-1913 PROTOCOL DESIGN, AND COMPARISON WITH THE RESULTS OF LAL-1913 CLINICAL TRIAL

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Introduction. In recent years, a significant improvement in the prognosis of Ph-ALL in adults was achieved using pediatric-inspired regimens that include peg-asparaginase (PegAsp). However, very few data are available regarding the performance and tolerability of

these chemotherapy programs outside clinical trials.

Methods. We analyzed the outcome of 322 adult patients (pts) with Ph-ALL, treated in 27 Italian centers according to the GIMEMA LAL-1913 study design but outside the clinical trial. All patients were treated after this clinical trial was completed. The aim of this study was to compare the real-life data with the LAL-1913 protocol results (Bassan R, *et al*, EHA 2022) in terms of CR rate, OS, DFS and tolerability.

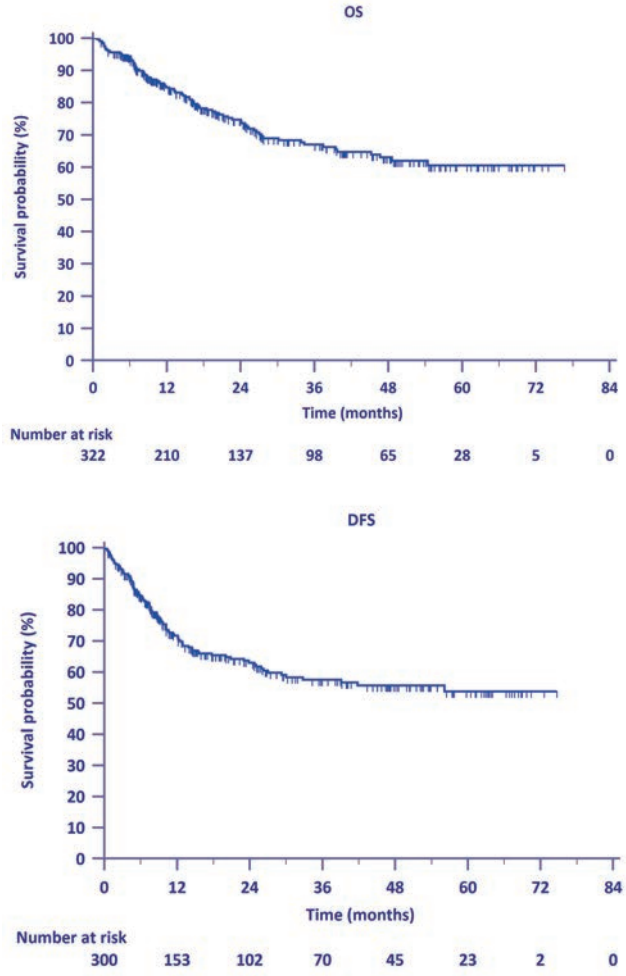

Figure 1.

Results. Median age was 42 (range 18-72), 24% of pts were ≥55 years; 52% had B-ALL, 45% T-ALL and 3% MPAL. According to the LAL-1913 study risk stratification, 51% were SR, 10% HR, 39% VHR; risk was unknown in 2 pts. The CR rate after C1 and C3 was respectively 93.9% (277/295) and 96.4% (244/253) of evaluable patients. MRD negativity after C3 was 74% (186/253). Before C3, 33 pts changed therapy due to refractory ALL or complications, and 10 pts died. Allogeneic stem cell transplantation (AlloSCT) rate after C3 (first line) was 34% (109/322), 70% due to VHR, 23% due to MRD+ and 7% underwent AlloSCT for medical decision; 17% of pts received immunotherapy before AlloSCT due to MRD+. In this real-life population the 3-year OS and DFS were respectively 67% and 58% (median not reached). Post Allo-SCT OS was not different between VHR and MRD+ pts (2-year OS 82% and 75% respectively, median not reached). At C1, a grade ≥3 PegAsp related hepatic toxicity was observed in 16% of pts, a grade ≥3 pancreatic toxicity in 3%, and grade ≥3 thrombotic or hemorrhagic events in 2%. Due to this toxicity, in subsequent courses the dose of PegAsp was reduced or omitted in 30% and 15% of cases, respectively.

Conclusions. In this real-life study we observe similar CR rate and survival results than those of the GIMEMA LAL-1913 clinical trial (CR rate after C1 94% *vs* 91%, 3-year OS 67% *vs* 67% and 3-year DFS 58% *vs* 63%), despite an older population (24% of pts aged ≥55 *vs* 19%) and a higher proportion of VHR cases (39% *vs* 33%). Allo-SCT retains a very important role for VHR and MRD+ pts. Preliminary data regarding PegAsp suggest that dosage must be individualized according to age and comorbidity profile to avoid excessive toxicity and a delay of the therapy program.

C057

INCIDENCE OF OCCULT CENTRAL NERVOUS SYSTEM LOCALIZATION IN ADULT PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA. A CAMPUS ALL PROSPECTIVE STUDY

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Previously, in the framework of the national Campus ALL program, we demonstrated that flow cytometry (FCM) allows to detect occult CNS disease (OCNSD) in acute lymphoblastic leukemia (ALL) and that the presence of OCNSD is associated with poor outcome. Given the retrospective nature of study, the heterogeneity of treatments of our patients and the long period of observation, further prospective studies are needed to confirm these results, also considering that current international guidelines do not mention the use of FCM in cerebrospinal fluid (CSF) for the initial ALL workup. Thus, we designed a multicenter, observational, prospective study, whose primary endpoint is to evaluate the incidence of OCNSD in adult ALL patients. So far, we enrolled prospectively 102 patients (Table 1). Patients were treated according to the GIMEMA/NILG ALL protocols or with the Hyper-CVAD program. Median follow up was 16 months (range 1-35). All CSF samples were evaluated both by conventional cytology (CC) and FCM. A panel of 8-10 monoclonal antibodies was used. On average, 19933 events were acquired (range 0-710151). The presence of >10 clonally restricted or phenotypically abnormal events was regarded as a FCM positivity. Based on the results of CSF examination, three different categories were recognized: manifest CNS+ (MCNSD, CC+FCM+), OCNSD (CC-FCM+) and CNS- (CC-FCM-). Overall, 6 (6%) patients had MCNSD ,14 (14%)

OCNSD and 82 (80%) were CNS-. In the OCNSD group, the median of the total acquired, and the leukemic events were 11272 (60-276339) and 44 (14-993), respectively. Median age, B/T lineage, cytogenetic/genetic features did not differ significantly between the three categories. Compared to CNS- subset, OCNSD patients had more frequent white blood cells count (WBCc)>30x10^9/L (p=.001). Of the 62 evaluable patients, the relapse occurred in 20 (32%) pts and OCNSD patients showed a higher rate of relapse than CNS- [7/11(63%) *vs* 13/45(29%), p=.031). No relapse was observed in the small MCNSD subset. Although preliminary, our data confirm that the frequency of OCNSD is not negligible and impacts on the risk of relapse. In addition, no risk factors predictive of OCNSD seem to emerge in our study, except for WBCc. Our study supports the need for FCM in the CSF examination in ALL patients.

Table 1.

Patients Characteristics	N (%)
Total patients	**102**
Gender	
Male	53 (42)
Female	49 (48)
Age, years	
Median	46
Range	(19,81)
≥45years	52(51)
<45years	50(49)
WBC (10^9/L)	
Median	48
Median [range]	(0.9,512)
Immunophenotype	
B	74(72)
T	28(28)
Cytogenetic (92)*	
Normal	50(55)
t(9;22)	26 (28)
t(4;11)	4(4)
Others	12(13)
Risk Classification	
Standard	35(34)
High	21(21)
Very high	46(45)

WBC; white blood cell

*data

C058

GIMEMA SEIFEM REAL-LIFE STUDY *vs* RANDOMIZED CPX-351 REGISTRATIVE TRIAL FOR OLDER PATIENTS WITH SECONDARY ACUTE MYELOID LEUKEMIA: AN UNANCHORED MATCHING-ADJUSTED INDIRECT COMPARISON OF INFECTION RATES AND SURVIVAL OUTCOMES

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Unanchored MAIC(Matching-Adjusted Indirect Comparison) is an Indirect Treatment Comparison method adjusting for cross-trial heterogeneity in patient demographic features or diseases. In this analysis, 2 trials for adults with secondary acute myeloid leukemia (AML) were compared by an unanchored MAIC. The GIMEMA-SEIFEM (GS) real-life on the use of CPX-351(Fianchi et al–submitted) was weighted for the aggregated patients(pts)' characteristics from the standard arm("7+3") of the CPX-351 trial (Lancet et al–JCO 2018). This analysis aimed to test the feasibility to compare individual pts' data with aggregated published results and evaluate the rate of infections of CPX-351 in real life *vs* the "3+7" regimen and their impact on the survival outcomes. Pts-level data from GS on the use of CPX-351(n=202) and aggregated data from CPX-351 ("3+7" arm, n=156) trials were used to conduct an unanchored MAIC. GS study included pts with AML from 30 Italian hematologic centers who received CPX-351 from July 2018 to June 2021.Pts from the GS study were weighted to balance with baseline characteristics from the trial cohorts. Accordingly, weighted Overall and Event-free survival(w-OS, w-EFS)estimates, as well as rates of febrile neutropenia, pneumonia, CR, and the interval of PMN recovery, were computed.

Table 1.

	GIMEMA-SEIFEM		"3+7"
	Observed	Weighted	
	N = 202	N = 202	N = 156
Age, mean (sd)	64 (8)	65 (6)	68 (4.1)
Male, n (%)	104 (52%)	62%	96 (62%)
tAML, n (%)	52 (26%)	22%	33 (21%)
sAML, n (%)	71 (35%)	53%	86 (55%)
MDR, n (%)	79 (39%)	24%	37 (24%)
HMA, n (%)	41 (20%)	44%	71 (45%)
Febrile neutropenia	74.4%	74.9%	71%
FUO	36.8%	38.4%	
Pneumonia	8.9%	10.6%	14.6%
Sepsis			
Time to PMN recovery days, median	22 (0, 316)	21.8 (0, 316)	29
CR	64.90%	57.40%	33.0%
OS median (95%CI)	17.6 (14.2, 20.4)	14.2 (11.6, 18.7)	6
EFS median (95%CI)	9.8 (7.2, 15.0)	7.4 (3.0, 10.6	1.3
Overall deaths	56%	63%	128 (85%)
Early death - 30 days	4%	3%	11%
Early death - 60 days	8%	8%	21%

4 potential effect modifiers were identified and used for adjustment: age, sex, AML subtype(tAML, sAML, MRC),and prior HMA exposure. Median w-OS and w-EFS were 14.2 (95%CI:11.6-18.7) and 7.4 (95%CI:3.0-10.6) months, respectively. These estimates were

slightly lower than those documented in the most recent report of the GS trial (median OS 17.7 months and median EFS 9.8 months) and higher than the results obtained by the standard arm of the CPX-351 trial (median OS 5.9 months, median EFS 1.3 months). Weighted rates of febrile neutropenia, pneumonia, CR, and interval of PMN recovery were comparable to the observed values and better than observed in the standard arm of the CPX-351 trial for all considered variables, except for febrile neutropenia (Table 1).

The MAIC method allowed a robust comparison of 2 clinical trials for the treatment of AML pts.After adjustment, survival outcomes of the real-life cohort were slightly lower than the observed estimates and higher than the observed in the standard arm of the CPX-351 trial. Pneumonia risk was confirmed lower in CPX-351 matched group than in "3+7" arm.This pilot analysis underlines the potentiality of this statistical method.

C059

CLINICAL IMPACT OF TYROSINE KINASES MUTATIONS IN NPM1 MUTATED ACUTE MYELOID LEUKEMIA: A REPORT FROM THE NORTHERN ITALY LEUKEMIA GROUP (NILG) RANDOMIZED TRIAL 02/06

G. Cavallaro[1], S. Salmoiraghi[1], R. Cavagna[1], E. Oldani[1], T. Intermesoli[1], A. Grassi[1], G. Gianfaldoni[2], F. Mannelli[2], D. Ferrero[3], E. Audisio[3], E. Terruzzi[4], L. De Paoli[5], C. Cattaneo[6], E. Borlenghi[6], I. Cavattoni[7], M. Tajana[8], A.M. Scattolin[9], D. Mattei[10], P. Corradini[11], L. Campiotti[12], F. Ciceri[13], M. Bernardi[13], E. Todisco[14], A. Cortelezzi[15], B. Falini[16], C. Pavoni[1], R. Bassan[1], O. Spinelli[1], A. Rambaldi[1], F. Lussana[1]

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Background. The internal tandem duplication (ITD) of the FLT3 gene mutation has a well-known detrimental effect in nucleophosmin-mutated AML prognosis. Less is known about the clinical impact of other tyrosine kinases (TK), whose deregulation of mechanism of action could possibly cooperate in leukemic cell growth and expansion and the significance of their detection in NPM1 mutated AML remains to be elucidated.

Aims. To investigate the clinical impact at diagnosis of other TK gene mutations in NPM1 mutated AML, when compared to NPM1-FLT3 AML or NPM1 isolated in patients enrolled in the prospective NILG trial 02/06 [ClinicalTrials.gov Identifier: NCT00495287]

Methods. Out of 547 newly diagnosed AML patients enrolled into the trial, 109 had a NPM1 mutation and a normal karyotype. Next-generation sequencing (NGS) was performed at diagnosis on bone marrow samples. TK-mutations were defined as KRAS, NRAS, CBL, CSF3R, JAK2, CDKN2A or PTPN11. All participants received an intensive induction chemotherapy. At the time of this clinical trial, FLT3-inhibitors were not available for clinical practice. Clinical endpoints of this analysis were overall survival (OS), disease-free survival (DFS), cumulative incidence of relapse (CIR).

Results. At least one TK-mutation was reported for 31 out of 109 patients (28%), while 45 (41%) patients had NPM1-FLT3ITD mutation and 33 (30%) were NPM1 isolated. The most recurrent TK-mutation was PTPN11 (n=11/31, 35.5%), followed by KRAS (n= 8/31, 25.8%), NRAS (n=7/31, 22.6%), CBL (n=3/31, 9.7%), CSF3R (n=2/31, 6.5%), JAK2 (n=1/31, 3.2%), CDKN2A (n= 1/31, 4.2%). Median follow-up for the study population was 3.9 years. NPM1-TK mutated patients showed a significant better 5-years OS (66%) and DFS (58%) than NPM1-FLT3ITD (OS 36%, DFS 38%; P<0.001 and P=0.01 respectively). Patients with NPM1-TK mutated AML had a similar OS and DFS as compared to isolated NPM1 AML (P=0.67 and p=0.36, respectively) (Figure 1A and B). NPM1-TK and NPM1 isolated AML patients showed a significant reduced risk of hematologic relapse at 5 years with a CIR of 39% and 27%, respectively compared to 59% of patients with NPM1-FLT3ITD AML. By univariate and multivariate analysis, the presence of TK mutations was independently associated with favorable outcomes compared to NPM1-FLT3ITD group.

Conclusions. TK gene mutations represent a subgroup of NPM1 AML with a favourable outcome, more similar to those of isolated NPM1 mutated as compared to NPM1-FLT3ITD mutated group.

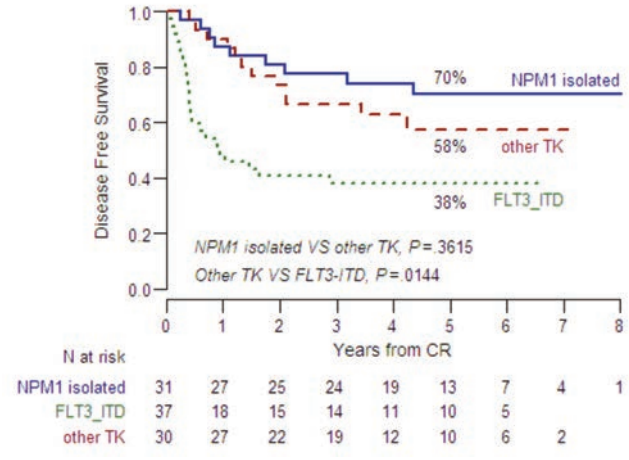

Figure 1.

C060

SIE/SIES/GITMO CONSENSUS CRITERIA FOR UNFITNESS CAN IDENTIFY AML PATIENTS WHO DOES NOT BENEFIT FROM HMA + VENETOCLAX

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The association of Venetoclax (Ven) with Hypomethylating agents (HMAs) in patients with Acute Myeloid Leukemia (AML) improves survival compared to HMAs alone. However, the combination is associated with hematologic toxicities and higher rates of infection. Hence, many elderly AML patients may be unable to tolerate Ven + HMA. We present an Italian multicenter real-life experience on AML patients treated with HMA (azacitidine or decitabine) + Ven (target

dose 400 mg) at Molinette Hospital (Turin) or Cardarelli Hospital (Naples). Our aim was to evaluate if a careful fitness assessment, based on objective criteria, could be useful to predict early mortality and overall survival (OS), helping clinicians to identify who may benefit from the addition of Ven to HMAs and who may not tolerate the higher toxicity of combination.

Patients were retrospectively stratified according to the SIE/SIES/GITMO consensus criteria for unfitness (Ferrara criteria), which define AML patients fit or unfit for intensive (INT-Fit and INT-Unfit) and non-intensive (NINT-Fit and NINT-Unfit) chemotherapy. We included 103 patients, 58 newly diagnosed (ND) and 45 relapsed/refractory (R/R), with a median age of 73 years. Median follow up was 10.5 months and median OS of the whole cohort was 7.9 months (8.6 months for ND and 6.6 months for R/R patients).

In patients treated with HMAs, most were INT-Unfit (57.3%) and 17 were NINT-Unfit (16.5%). Ferrara criteria were predictive of survival both in univariate and multivariate analysis. NINT-Unfit patients showed significantly shorter OS, both in ND or in R/R (Figure 1a-b). In multivariate analysis in ND-patients, NINT-Unfit (HR 26.771; P=0.002), higher white blood cell count (WBC) (HR 1.66; P=0.031) and adverse risk ELN (HR 4.12; P=0.030) were independently associated with shorter OS. In the R/R setting, being NINT-Unfit was the only factor associated with reduced OS (HR 3.40, P=0.026). Ferrara criteria identified patients at higher risk of early mortality: NINT-Unfit patients had higher rates of mortality at 60 and 100 days than NINT-Fit patients (26.7% *vs* 7.5%, P=0.0537 and 71.4% *vs* 13.6%, P<0.0001).

In conclusion, using the Ferrara criteria we identified NINT-Unfit patients as the ones with the poorest prognosis. An accurate fitness assessment, based on Ferrara criteria, is crucial to identify frailer patients with dismal prognosis after Ven-based therapies, who may benefit from a less intensive therapy or from best supportive care only.

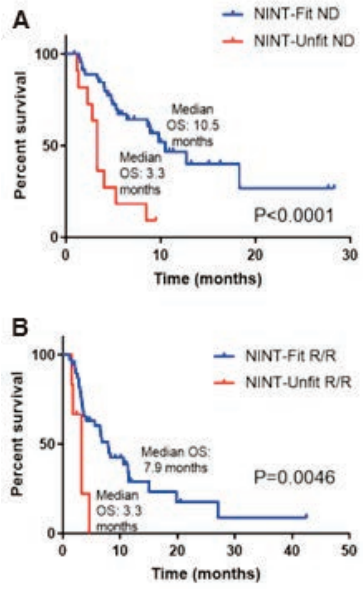

Figure 1.

Myeloma and monoclonal gammopathies II

C061

IDECABTAGENE VICLEUCEL (IDE-CEL) *VS* STANDARD REGIMENS IN PATIENTS (PTS) WITH TRIPLE-CLASS–EXPOSED (TCE) RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM): A KARMMA-3 ANALYSIS IN HIGH-RISK SUBGROUPS

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Background. Despite the combined use of immunomodulatory (IMiD®) agents, proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies in front-line and early relapse, patients (pts) with RRMM become TCE earlier in their treatment course. Outcomes remain especially poor in patients with high-risk disease characteristics. Ide-cel significantly improved progression-free survival (PFS) and overall response rate (ORR) *vs* standard (std) regimens in the overall population of pts with TCE RRMM in KarMMa-3. We assessed efficacy and safety of ide-cel *vs* std regimens in pts with high-risk disease characteristics in KarMMa-3.

Methods. Pts with RRMM who received 2-4 prior regimens, were TCE (IMiD agent, PI, and daratumumab), and had disease refractory to the last regimen were randomized 2:1 to receive ide-cel (target dose range: 150-450×10^6 CAR+ T cells) or a std regimen (DPd, DVd, IRd, Kd, or EPd per investigator). Efficacy (PFS, ORR, and complete response rate [CRR]) was assessed in high-risk groups including pts with cytogenetic abnormalities (del[17p], t[4;14], or t[14;16]), R-ISS stage III disease, high tumor burden (≥50% CD138-positive plasma cells in bone marrow), extramedullary plasmacytoma (EMP; soft-tissue–only and soft-tissue bone-related plasmacytomas), and triple-class refractory (TCR) disease (refractory to ≥1 each of an IMiD, PI, and anti-CD38 antibody).

Results. Baseline demographics and high-risk disease characteristics were balanced between treatment arms. At 18.6-mo median follow-up, median PFS was longer in pts treated with ide-cel *vs* std regimens in all high-risk subgroups: cytogenetic abnormalities (11.9 *vs* 4.2 mo; HR, 0.608), R-ISS stage III disease (5.2 *vs* 3.0 mo; HR, 0.861), high tumor burden (11.0 *vs* 4.9 mo; HR, 0.595), EMP (7.2 *vs* 2.0 mo; HR, 0.401), and TCR disease (11.2 *vs* 3.5 mo; HR, 0.458; Table). Both ORR and CRR improved in pts treated with ide-cel *vs* std regimens in all high-risk subgroups.

Conclusions. Pts treated with ide-cel had a lower risk of disease progression and higher odds of achieving an overall response (with

higher CRRs) compared with pts from std regimens, regardless of baseline high-risk disease. These results support use of ide-cel in pts with TCE RRMM, including those with difficult-to-treat, high-risk disease. Presented previously at European Haematology Association Hybrid Congress, June 2023

Clinical Trial Identification: NCT03651128.

Table 1.

	High-risk cytogenetics		R-ISS stage III		High tumor burden	
	Ide-cel (n = 107)	Standard regimens (n = 61)	Ide-cel (n = 31)	Standard regimens (n = 14)	Ide-cel (n = 71)	Standard regimens (n = 34)
Median (95% CI) PFS, mo[a]	11.9 (8.0–14.5)	4.2 (2.4–5.7)	5.2 (1.8–7.2)	3.0 (0.8–6.1)	11.0 (7.2–16.2)	4.9 (2.3–10.1)
Unstratified HR (95% CI)[b]	0.608 (0.411–0.899)		0.861 (0.387–1.919)		0.595 (0.367–0.965)	
ORR, n (%)[c]	69 (64.5)	23 (37.7)	14 (45.2)	4 (28.6)	46 (64.8)	18 (52.9)
Unstratified OR (95% CI)[d]	3.00 (1.56–5.76)		2.06 (0.53–8.01)		1.64 (0.71–3.75)	
CRR, n (%)[e]	34 (31.8)	3 (4.9)	5 (16.1)	1 (7.1)	22 (31.0)	3 (8.8)
95% CI	23.0–40.6	0.0–10.3	3.2–29.1	0.0–20.6	20.2–41.7	0.0–18.4

	EMP present		Triple-class refractory	
	Ide-cel (n = 61)	Standard regimens (n = 32)	Ide-cel (n = 71)	Standard regimens (n = 34)
Median (95% CI) PFS, mo[a]	7.2 (4.0–11.8)	2.0 (1.3–3.0)	11.2 (8.7–12.5)	3.5 (2.9–4.7)
Unstratified HR (95% CI)[b]	0.401 (0.248–0.649)		0.458 (0.336–0.624)	
ORR, n (%)[c]	34 (55.7)	6 (18.8)	105 (64.0)	28 (31.5)
Unstratified OR (95% CI)[d]	5.46 (1.96–15.15)		3.88 (2.24–6.72)	
CRR, n (%)[e]	14 (23.0)	1 (3.1)	55 (33.5)	1 (1.1)
95% CI	12.4–33.5	0.0–9.2	26.3-40.8	0.0-3.3

[a]Median and 95% CI are based on Kaplan–Meier approach; [b]Unstratified HR based on univariate Cox proportional hazard model. CI is two-sided; [c]Patients with ≥partial response; [d]Cochran–Mantel–Haenszel test with two-sided Wald CI; [e]Complete response or stringent complete response.
OR, odds ratio; R-ISS, Revised International Staging System.

C062

ABSTRACT NOT PUBLISHABLE

C063

PLASMA CELL LEUKEMIA-LIKE TRANSCRIPTOME OF BONE MARROW PLASMA CELLS AND CIRCULATING TUMOR CELL LEVELS IN PERIPHERAL BLOOD COMPLEMENTARILY DEFINE HIGH-RISK IN NEWLY DIAGNOSED MULTIPLE MYELOMA

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Background. We assessed if plasma cell leukemia (PCL)-like status (combined transcriptomic score of 54 genes) and high levels of circulating tumor cells (CTC; >0.07%) in peripheral blood had independent prognostic value in a combined model with conventional risk markers in newly diagnosed multiple myeloma (NDMM).

Methods. At baseline, both PCL-like status and CTC levels were determined in transplant-eligible NDMM patients (pts) enrolled in the phase 2 FORTE trial. RNA Seq data of CD138-enriched BM tumor cells were generated within the MMRF CoMMpass study. CTC quantification was performed with multiparameter flow cytometry (4×10^{-5}). Progression-free survival (PFS) and overall survival (OS) were analyzed, hazard ratios (HRs) were estimated using a Cox proportional hazards model including both PCL-like status and CTC levels and adjusted for ISS, cytogenetic risk, LDH levels and first randomization arm.

Results. PCL-like status was found in 33/122 (27%) pts with available transcriptomic data, with the remainder being classified as intramedullary (i-)MM. PCL-like status was associated with a higher rate of LDH levels above the upper limit of normal (30% in PCL-like MM *vs* 9% in i-MM, *P*=0.007), while no statistically significant differences in the distribution of ISS, cytogenetic risk [del(17p), t(4;14) or t(14;16)], gain(1q), amp(1q), R2-ISS group or randomization arm were found. Of 95/122 (78%) NDMM pts, baseline CTC levels were also available. PCL-like MM pts had higher CTC levels (median 0.97%, IQR 0.28%-1.62%) than i-MM pts (median 0.03%, IQR 0.01%–0.14%, *P*<0.001). 74% of PCL-like pts had high CTC levels *vs* 36% of i-MM pts (*P*=0.002). After a median follow-up of 68 months (mo), in a multivariate model for PFS, both PCL-like status (HR 2.18, 95% CI 1.16-4.11, *P*=0.016) and high CTC levels (HR 2.20, 95% CI 1.09-4.47, *P*=0.028) retained independent prognostic value. Combining these two factors, median PFS was not reached in i-MM pts with low CTC levels, 54.2 mo in PCL-like MM with low CTC levels, 37.9 mo in i-MM with high CTC levels and 23.5 mo in PCL-like MM with high CTC levels (Figure 1). In a multivariate model for OS, a statistically significant effect was found for PCL-like status (HR 3.12, 95% CI 1.26–7.69, *P*=0.014), while a borderline significant effect was found for high CTC levels (HR 2.88, 95% CI 0.93-8.96, *P*=0.068).

Conclusions. PCL-like status and high CTC levels are complementary prognostic markers to define high risk in transplant-eligible NDMM pts.

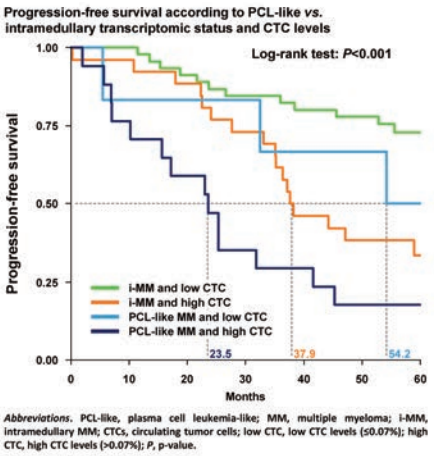

Figure 1.

C064

ISATUXIMAB PLUS CARFILZOMIB AND DEXAMETHASONE IN RELAPSED MULTIPLE MYELOMA: IKEMA SUBGROUP ANALYSIS BY NUMBER OF PRIOR LINES OF TREATMENT

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**All Sanofi authors were employees of Sanofi at the time the original abstract submission*

Introduction. In the Phase 3 IKEMA study, isatuximab (Isa) + carfilzomib (K) and dexamethasone (d), (Isa-Kd) significantly improved progression-free survival (PFS) *vs* Kd in relapsed multiple myeloma (MM) patients (pts) (HR 0.538; 99% CI 0.318−0.889; one-sided *P*=0.0007; NCT03275285). Two years later (cut-off: January 14, 2022), the final PFS analysis confirmed that Isa-Kd improved PFS *vs* Kd with median PFS (months [mo]) 35.65 in Isa-Kd *vs* 19.15 in Kd, with clinically meaningful increase in minimal residual disease negativity (MRD–) (33.5% *vs* 15.4%) and complete response (CR) (44.1% *vs* 28.5%) rates in the intent-to-treat (ITT) population, and a manageable safety profile. Updated efficacy and safety results from IKEMA by prior lines of therapy (1 *vs* >1) are presented.

Methods. Pts with 1–3 prior lines of therapy were randomized 3:2 to receive Isa-Kd (n=179) or Kd (n=123) until progressive disease or unacceptable toxicity. These updated, longer-term data are based on a prespecified final PFS analysis (primary endpoint) of IKEMA at 159 PFS events. Key secondary endpoints included MRD– and CR rates. MRD– and CR rate and safety were also updated.

Results. Of the 302 randomized pts, 134 (79 Isa-Kd, 55 Kd) and 168 (100 Isa-Kd, 68 Kd) received 1 and >1 prior line of therapies, respectively. Median PFS (mo) in pts with 1 prior line of therapy in Isa-Kd *vs* Kd was 38.24 *vs* 28.19 (unstratified HR 0.723; 95.4% CI 0.442–1.184; Figure 1). Median PFS (mo) in pts with >1 prior line of therapy in Isa-Kd *vs* Kd was 29.21 *vs* 16.99 (unstratified HR 0.452; 95.4% CI 0.298–0.686). More pts achieved CR with Isa-Kd *vs* Kd (48.1% *vs* 38.2%, 1 prior line; 41.0% *vs* 20.6%, >1 prior line). Isa + Kd also yielded higher rates of both MRD– (39.2% *vs* 21.8%, 1 prior line; 29.0% *vs* 10.3%, >1 prior line) and MRD– and CR (32.9% *vs* 16.4%, 1 prior line; 21.0% *vs* 8.8%, >1 prior line). The Grade ≥3 treatment emergent adverse events (TEAEs) frequency was generally similar between the subgroups (83.3% [Isa-Kd] and 72.2% [Kd], 1 prior line; 83.8% [Isa-Kd] and 73.5% [Kd], >1 prior line). Serious TEAEs occurred in 66.7% *vs* 51.9% of pts (1 prior line) and 72.7% *vs* 66.2% of pts (>1 prior line) with Isa-Kd *vs* Kd, respectively.

Conclusions. Isa + Kd improved PFS and depth of response in pts with relapsed MM, regardless of the number of prior lines of therapy, with a manageable safety profile. Results from this study are consistent with the benefit observed in the overall IKEMA study population.

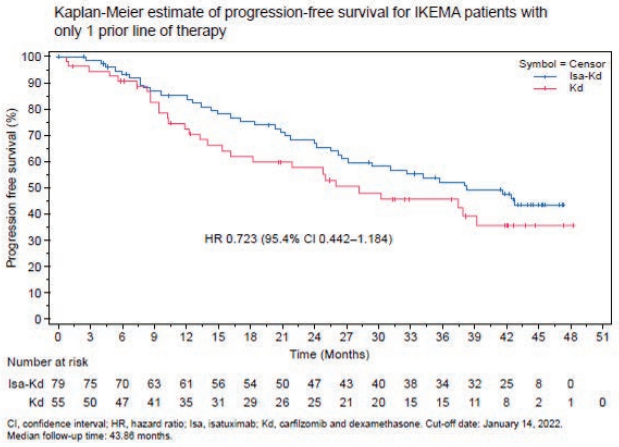

Figure 1.

C065

CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE (KRD) *VS* LENALIDOMIDE-DEXAMETHASONE (RD) IN NEWLY DIAGNOSED FIT OR INTERMEDIATE-FIT MULTIPLE MYELOMA PATIENTS NOT ELIGIBLE FOR AUTOLOGOUS STEM-CELL TRANSPLANTATION: THE RANDOMIZED PHASE III EMN20 TRIAL

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Lenalidomide-dexamethasone (Rd) has represented a standard of care for transplant-ineligible (NTE) newly diagnosed multiple myeloma (NDMM) patients (pts) until the recent introduction of daratumumab (Dara) in the frontline setting. Nonetheless, median progression-free survival (PFS) with Rd was still relatively short, as compared with 3/4-drug regimens, also including carfilzomib (K). The randomized, multicenter EMN20 trial (NCT04096066) compares KRd *vs* Rd in fit or intermediate-fit MM pts according to the International Myeloma Working Group frailty score. NTE NDMM pts were randomized to KRd (28-day cycles, once-weekly K 56 mg/m² on days [dd] 1,8,15 for 12 cycles and on dd 1,15 from cycle 13 onwards, R 25 mg orally on dd 1–21 and d 40 mg on dd 1,8,15,22) or continuous Rd (28-day cycles, R 25 mg on dd 1–21, d 40 mg on dd 1,8,15,22). Pts were stratified based on International Staging System (ISS) stage and fitness status. After 5 years (y), pts in the KRd arm will stop K administration and continue Rd, except for pts achieving sustained minimal residual disease (MRD) negativity after 2 y, who will stop K administration after 2 y and continue Rd. The primary endpoints were MRD after 2 treatment y and PFS. For MRD assessment, the clonoSEQ® assay was used at the sensitivity of $\geq 10^{-5}$. The MRD negativity rate was the proportion of MRD-negative pts (sensitivity $\geq 10^{-5}$) at 2 treatment y. Key secondary endpoints included response rates, overall survival and safety. The protocol was prematurely stopped on 23-11-2021, after the introduction of frontline Dara-Rd. Here we report the demographics of all pts enrolled. A total of 101 pts were enrolled and 82 were randomized (KRd 42 *vs* Rd 40); 19 pts were not randomized due to screening failure (17) and withdrawal of consent (2). Pt characteristics were well balanced between the KRd and Rd arms (Table 1): median age was 73 (IQR 70–76) and 74 y (IQR 72–76), 60% *vs* 58% of pts were fit, 33% *vs* 30% had ISS III and 22% *vs* 22% had high-risk cytogenetics, respectively. Median follow-up was 23 months (IQR 19–28). In the KRd *vs* Rd arms, 33/42 (78.6%) *vs* 19/40 (47.5%) pts are still under treatment; reasons for discontinuation were medical decision (1 *vs* 4), death (2 *vs* 4), adverse events (2 *vs* 1), progressive disease (3 *vs* 10), lost to follow-up (1 *vs* 0) and consent withdrawal (0 *vs* 2). The analysis of the primary MRD endpoint is planned when all pts have received treatment for 2 y (Q4 of 2023): results will be presented at the meeting.

Table 1.

	KRd (n=42)	Rd (n=40)
Median age, years (IQR)	73.0 (70.25–75.75)	74 (72–76.25)
Age category, years (%)		
≤70	11 (26)	5 (12)
71–75	20 (48)	22 (55)
>75	11 (26)	13 (32)
ISS, No. (%)		
I	12 (29)	10 (25)
II	16 (38)	18 (45)
III	14 (33)	12 (30)
R-ISS, No. (%)		
I	10 (25)	5 (13)
II	23 (58)	30 (79)
III	7 (17)	3 (8)
Missing	2	2
ECOG PS – No. (%)		
0	22 (52)	24 (60)
1	16 (38)	15 (38)
2	4 (10)	1 (3)
Serum LDH >ULN, No. (%)	5 (12)	5 (12)
Frailty Score, No. (%)		
Fit	25 (60)	23 (58)
Intermediate fit	17 (40)	17 (42)
Cytogenetic risk by FISH*, No. (%)		
Standard	28 (78)	29 (78)
High	8 (22)	8 (22)
Missing	6	3

**High-risk cytogenetics were defined in accordance with the International Myeloma Working Group (IMWG) criteria: presence of t(4;14) and/or t(14;16) and/or del(17p).*
Abbreviations. K, carfilzomib; R, lenalidomide; d, dexamethasone; IQR, interquartile range; ISS, International Staging System stage; No., number; R-ISS, Revised ISS stage; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; ULN, upper limit of normal; FISH, fluorescence *in situ* hybridization; t, translocation; del, deletion.

Hemostasis, thrombosis, thrombocytopenia and platelet diseases II

C066

EVANS SYNDROME: DISEASE AWARENESS AND CLINICAL MANAGEMENT IN A NATION-WIDE ITP-NET SURVEY

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The management of Evans syndrome (ES, concomitant/subsequent association of two among autoimmune hemolytic anemia AIHA, immune thrombocytopenia ITP, immune neutropenia CIN) is not standardized. To assess disease awareness and clinical management of adult ES in Italy, a pre-defined structured survey including three domains 1) epidemiology, 2) diagnosis, and 3) therapy of ES was administered to Italian Centers participating in the ITP-NET. From December 2022 to February 2023, 30 clinicians from 29 Italian Hospitals completed the survey. They followed a median of 5 (range1-45) ES patients in the last 15 years. AIHA+ITP was the most reported ES type (mean 9 *vs* 2.8 patient/center for AIHA/ITP+CIN, $p<0.001$), and 25% of patients had an underlying condition. Table 1 shows the level of agreement for each diagnostic test: 100% for complete blood count, hemolytic markers, and direct anti-globulin test; >80% for coagulation, smear, electrophoresis and Ig dosage, ANA, ENA, anti-DNA, anti-phospholipid antibodies, and thyroid function and autoantibodies; only 40% for anti-platelets (anti-PLT) and anti-neutrophil (anti-N) autoantibodies; >60% suggested abdomen ultrasound and thorax X-ray, and 77% bone marrow evaluation at diagnosis (80% both aspirate and trephine). Concerning therapy, 96% considered that ES deserves specific approach compared to isolated cytopenias, for risk of relapse/complications (63%) and more complex immunopathology (76%). For ITP relapse, 60% suggested to repeat steroids if >12 months from previous cytopenia (instead of a 2nd line); for AIHA relapse, 80% consider recombinant erythropoietin for inadequate reticulocytosis. >80% indicated that rituximab and splenectomy may have higher infectious risk if associated conditions (i.e. immunodeficiencies) or neutropenia are present; it was also suggested that TPO-RA and splenectomy (66% and 90%, respectively) may have higher thrombotic risk due to concomitant risk factors, active hemolysis, or PLT oscillations. No clear agreement was reached for anti-microbic/G-CSF prophylaxis for CIN. Finally, >60% of clin-

icians advised anti-thrombotic prophylaxis during severe COVID-19 infection, >70% agreed that vaccination is not contraindicated but may be deferred in case of active hemolysis/PLT<30x10^9/L. This survey identifies a suggested workup for adult ES, highlights high awareness regarding thrombotic/infectious complications and the importance of risk assessment to harness therapy.

Table 1. Diagnostic procedures in adult ES patients.

Diagnostic test	N of indications	% of agreement
Laboratory		
Complete blood count	30	100
Direct antiglobulin test	30	100
ANA/ENA/anti-DNA	29	97
Serum electrophoresis	28	93
IgG/IgA/IgM	27	90
Blood smear	25	83
Coagulation parameters	25	83
Anti-phospholipid antibodies	25	83
Thyroid function/antibodies	25	83
Anti-platelet autoantibodies	13	43
Anti-neutrophils antibodies	11	37
Imaging		
Abdomen ultrasound	22	73
Thorax X-ray	19	63
Whole body CT scan	13	43
Bone marrow evaluation		
Bone marrow aspirate	28	93
Bone marrow trephine	26	87
Both tests	24	80
At diagnosis/at relapse	23/7	77/23

C067

LONG TERM COMPLICATIONS AFTER SPLENECTOMY IN PRIMARY IMMUNE THROMBOCYTOPENIA (PITP) PATIENTS

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Background. Splenectomy has usually been considered an efficacious second line therapy for primary Immune Thrombocytopenia (pITP), although bleedings, infections, thromboses and neoplasms can occur as short and long-term complications. After the introduction of rituximab, TPO-receptor agonists and recently fostamatinib, clinicians have decreased the use of splenectomy. Aim of our study is to evaluate the burden of the complications of this procedure in a large ITP cohort and to evaluate if splenectomy still has a role in the treatment of pITP.

Methods. This is a monocentric retrospective case control study, which enrolled patients (pts) followed between 1955 and 2019 in our Centre. Data related to demographics, treatments, infections, infectious prophylaxis, thromboses and neoplasms, were collected.

Results. We enrolled 164 splenectomized pts and 1503 controls. Among controls, 896 underwent at least 1 therapy line, 607 were only observed. After splenectomy, 68.3% of pts obtained a complete and 22% a partial response; 37.8% of responsive cases relapsed. Among splenectomized, 68.3% have been vaccinated against S. Pneumoniae, H. Influentiae and N. Meningitidis at least once in life; 87.2% of patients received antibiotic prophylaxis for at least 1 year after splenectomy. Infections prevalence was higher in splenectomized pts compared either with the whole control cohort (30.5% *vs* 10.7%; p0.001) or with treated and observed subgroups of control pts respectively (30.5% *vs* 13.8% or *vs* 7.7%; p0.001). Prevalence of thromboses was higher in splenectomized cases compared to the subgroup of observed ones (5.5% *vs* 1.3%, p0.03), while was not significantly different when compared to the whole control cohort or with the subgroup of treated pts. Rate of neoplasms was higher in splenectomized pts compared to the subgroup of observed cases (7.32% *vs* 2.14%) and to the subgroup of treated pts (7.32% *vs* 4.7%) (p0.004).

Conclusions. Splenectomy presents a higher risk of infections and neoplasms compared to the controls. The rate of thromboses is not statistically different comparing splenectomized pts with treated subgroup, suggesting a role also for medical therapies in such complications. We think splenectomy still has a role in the management of ITP with some limitations. The choice of this treatment must be shared with patients and tailored on the characteristics of each case. It is necessary a good infections prophylaxis and a long-term follow-up even after splenectomy.

C068

EFFICACY AND SAFETY OF THROMBOPROPHYLAXIS IN HOSPITALIZED HEMATOLOGICAL PATIENTS: A MONOCENTRIC RETROSPECTIVE STUDY

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Background. Current literature has clearly established that patients with Hematological Malignancies (HMs) have an increased risk for Venous Thromboembolic Events (VTEs), despite the frequently associated thrombocytopenia. No Risk Assessment Model (RAM) for VTE prediction was derived and validated in hospitalized hematological patients; as a result, the clinical decision to prescribe thromboprophylaxis is often based on physicians' experiences and on RAMs established for different but similar clinical settings, i.e. Padua Prediction Score (PPS).

Aims and Methods. The aim of this study is to assess the efficacy and safety of thromboprophylaxis in hospitalized hematological patients affected by HMs and to evaluate the predictive power for VTE of PPS in this clinical context. We retrospectively identified patients who were admitted to our Hematology Division between January 1, 2016, and December 31, 2022. Patients with ongoing anticoagulant therapy at any dosage higher than prophylactic ones at admission were excluded. Anticoagulant prophylaxis at standard doses (*i.e.*, Enoxaparin 4000 IU/day) was defined as intention-to-treat for at least 50% of the time of hospitalization. Confounders were adjusted using inverse probability of treatment weighting (IPTW).

Results. Among 1001 hospitalizations, that met the aforesaid criteria, 256 (25,6%) received prophylaxis (Cohort A) while 745 (74,4%) did not (Cohort B). Patients in Cohort A were significantly older with higher platelet count and more thromboembolic risk factors at admission, while patients in Cohort B were significantly more often affected by acute leukemias. VTE rate was 0,8% in Cohort A and 3% in Cohort B (p=0,057) and Hemorrhagic Event (HE) rate was 0,4% in Cohort A and 1,3% in Cohort B (p=0,307), respectively. After weighing for confounders, VTE rate was 0,5% in Cohort A and 2,4% in Cohort B (p<0,001) and HE rate was 0,2% in Cohort A and 1% in Cohort B (p=0,026), respectively. After adjustment for thromboprophylaxis, PPS ≥ 4 was not associated with increased risk for

VTE (Hazard Ratio 1,86 [0,727-4,585], p 0,200). ROC curve for PPS demonstrated that Area Under the Curve (AUC) is 0,692 [0,688-0,696].

Conclusions. Anticoagulant prophylaxis can be safely used in hematological patients with no increase in major or CNS bleeding rates. Current RAMs don't perform in optimal way in hospitalized hematological patients. Based on these data, a new RAM for this setting could be developed.

C069

RESIDUAL VEIN THROMBOSIS UNDER DIRECT ORAL ANTICOAGULANTS: INTERIM ANALYSIS OF A SINGLE CENTER STUDY

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Introduction. Optimal management for the prevention of recurrent deep vein thrombosis (DVT) remains to be determined. Residual vein thrombosis (RVT), alongside clinical and laboratory abnormalities, has been proposed as a risk factor for recurrence. Most data have been collected in the setting of treatment with vitamin K antagonists (VKA) whereas the experience with Direct Oral Anticoagulants (DOACs) is scant. We therefore designed a prospective study to evaluate the rate of RVT during treatment with DOACs (Rivaroxaban/Apixaban) and to find out potential differences between the two drugs.

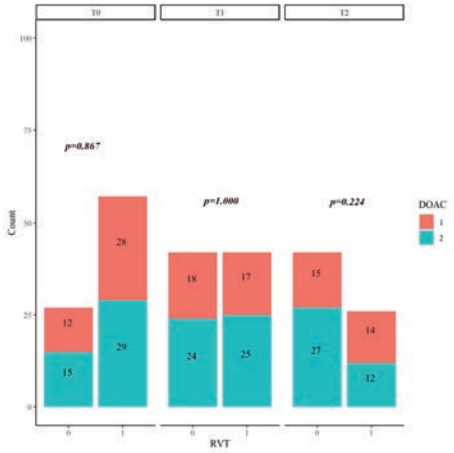

Figure 1. RVT rates under Rivaroxaban *vs* Apixaban at 6 weeks (T0), 3 months (T1) and 6 months (T2).

Materials and Methods. The "READ" ("residual vein thrombosis and DOACs") study was approved by the local Ethics Committee in November 2019. All eligible patients signed informed consent according to the Declaration of Helsinki. RVT was defined as persistent thrombotic material of at least 4 mm in diameter identified by compression ultrasonography (CUS) in common femoral or popliteal veins. The study is still recruiting and 112 patients were enrolled until April 2023. Here, we report an interim analysis on the first 84 and 68 patients with a follow up of at least 3 and 6 months respectively.

Results. Primary endpoint was to evaluate RVT rates at 6 weeks, 3 and 6 months after the start of treatment with either Rivaroxaban or Apixaban for newly diagnosed lower limb DVTs. The choice of the drug was not randomized but based on clinical and laboratory variables. RVT rates were 57/84 (67.9%) at six weeks, 42/84 (50%) at 3 months and 26/68 (38.2%) at 6 months (p=0.001). Secondary endpoint was to compare rates between the 2 drugs. At 6 weeks, 28/40 (70%) patients on Rivaroxaban and 29/44 (65.9%) on Apixaban developed RVT respectively (p=0.867); 17/35 (48.5%) and 14/29 (48.2%) on Rivaroxaban and 25/49 (51%) and 12/39 (30.7%) on Apixaban showed RVT at 3 and 6 months respectively (p values = 1.000 and 0.224).

Conclusions. Our interim analysis shows progressive recanalization of lower limb DVT in patients treated with DOACs, similar to those historically reported with AVK, and with a trend toward complete RVT resolution over time. No statistically significant differences in RVT rates have been observed between Rivaroxaban and Apixaban in this head-to-head comparison.

C070

EARLY USE OF THROMBOPIETIN RECEPTOR AGONISTS (TPO-RAS) IN CLINICAL PRACTICE: RESULTS FROM AN ITALIAN SURVEY ON BEHALF OF THE ITP-NET, GIMEMA WORKING GROUP ANEMIA AND THROMBOCYTOPENIA

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The administration of thrombopietin receptor agonists (TPO-RAs) is currently part of the second line treatment of immune thrombocytopenia (ITP). Since the initial availability of TPO-RAs, the management of ITP has changed, however the optimal timing of administration, tapering and discontinuation of these drugs has not been clearly defined yet. Available data suggest that, even if TPO-RAs have similar efficacy during different disease phases (newly diagnosed, persistent or chronic ITP), their early use may be associated with improved clinical outcomes in the long-term, particularly regarding the sustained response off therapy (SROT). We have recently published a "Nationwide Survey on the use of TPO-RA among Italian haematologists", but it was not related to the early use of TPO-RAs. This survey was therefore specifically focused on the early administration of TPO-RAs, in the current Italian clinical practice. The survey was developed in the frame of a scientific project (ITP-NET) in partnership with the National GIMEMA working party on ITP and it was launched among haematologists from thirty eight italian haematological centres participating in the GIMEMA Foundation. The main topics of the proposed questions on TPO-RAs referred to: timing and schedule of administration, ideal candidate profile, perceived risk factors for their early administration, main factors in favour or against their early use. A full list of the proposed questions is reported in Table 1. Overall, 41 participants answered the survey. Survey results showed that an early use of TPO-RAs is frequently adopted in the common clinical practice, also immediately after a first line therapy with corticosteroids ± immunoglobulins (Ig); the driver for the early use is always the clinical situation, in particular an absent or unsatisfactory response; the choice of the ideal candidate to early treatment with TPO-RAs is mainly defined on the basis of

comorbidities, aiming to avoid corticosteroids-related toxicities, while it is unrelated to age. The opinions of the survey participants were quite heterogeneous as regards some items referring to: the choice of the specific timing of early use; driving reasons in favor or against an early use. Therefore, these results confirm that Italian hematologists adopt an early therapy with TPO-RAs if necessary but also support the need to better (re) define the concept of "early use" of TPO-RAs in an up-to-date management of ITP.

Table 1. Full list of questions and proposed answers.

1) Has the clinical experience you gained with TPO-RAs, changed your approach to the use of these drugs, compared to the time of their initial marketing?	• No; • Yes, both for the timing of the start and for tapering of TPO-RAs; • Yes, but only for the timing of the therapy start; • Yes, but only for the tapering of TPO-RAs therapy; • Yes, for reasons other than the timing of starting therapy and tapering (specify which ones).
2) Has the recent availability of new ITP treatments changed your approach to the choice of a second-line treatment?	• Yes; • No; • Only in selected cases (specify which ones).
3) With reference to the available evidence and your current clinical practice, do you think that TPO-RAs can be administered very early (i.e. within four weeks) after the first diagnosis of ITP?	• Yes; • No; • I don't know.
4)Where do you place treatment with TPO-RAs today?	• First-line therapy, in combination with steroids; • First-line therapy, as an alternative to steroids; • First-line therapy in selected cases (i.e diabetic or elderly or septic patient); • Immediately after a short course (up to two weeks) of appropriately dosed steroid therapy with a scarce or absent increase in platelet count (PLT<30,000/mm3); • Second-line therapy, in all patients; • Second-line therapy, evaluating case by case, pros/cons and patient characteristics.
5)Which features/factors can promote early/extremely early administration of TPO-RAs?	• Home administration/delivery, availability of the molecules; • Non – early response to first-line therapy (corticosteroids +/- Ig) with or without bleeding symptoms; • Age; • Frequent contact with patients; • Time required to reach a safe platelet count; • Easy dose definition; • Intolerance; • Platelet count fluctuations; • Comorbidities/concomitant therapies/patient compliance; • Other (specify what other characteristics/factors could favor the administration of TPO-RA).
6)You Indicate TPO-RAs early more often	• In young patients; • In elderly patients; • Regardless of age.
7)Do you think that the administration of TPO-RAs should take place earlier or later in relation to an age above or below 65 years?	• Yes, I administer TPO-RAs earlier for age > 65 years; • Yes, I administer TPO-RAs earlier for age < 65 years; • No, actually I administer TPO-RAs earlier only in absence of relevant cardiovascular risk factors and comorbidities, regardless of age; • I define the early administration of TPO-RAs based on other criteria (not age and cardiovascular risk) - specify which ones.
8)What features/factors can disadvantage early/extremely early administration of TPO-RAs?	• Costs; • Risk of overtreatment for some patients; • Diagnostic doubts (for patients treated in the first line); • Comorbidity; • Risk of extreme fluctuations in platelet count; • Difficult supply; • Interactions with other drugs/food habits;
9)In your opinion, which is the "ideal" candidate for first-line administration of TPO-RAs?	• Patient not responding within 5 days to steroid therapy + /- Ig; • Patient with major bleeding who does not respond within 1-2 days to steroid therapy + Ig; • All patients with new diagnosed ITP that experience hemorrhagic syndrome at onset; • Patients with ITP and diabetes, as steroid-sparing agents; • If I could, I would use them all on the first line, with the aim of avoiding the side effects of steroid therapy; • None of the above;
10)In the light of the experience gained with the TPO-RAs, you use them with more confidence:	• In the event of thrombosis occurring outside treatment with TPO-RAs because of the need to establish anticoagulant/antiplatelet therapy; • In case of thrombosis occurred during treatment with TPO-RAs because of the need to start anticoagulant/antiplatelet therapy (continue treatment); • No, I do not use TPO-RAs more confidently, but in light of the introduction of new molecules I preferentially use those, in case also discontinuing previous treatment with TPO-RAs; • In both cases of thrombosis that occurred before or during TPO-RAs treatment.
11)In the light of the experience gained with the TPO-RAs, you use them with more confidence in pregnancy:	• Yes; • No.
12)If you answered yes to the previous question	• First quarter; • Second quarter; • Third quarter; • Indifferently during the course of pregnancy.
13)You have had experience using TPO-RAs in the following patient settings:	• Oncology during chemotherapy/radiotherapy; • Onco-hematology during chemotherapy;
	• Post-autotransplant or allo-transplant to promote recovery of platelet values; • Septic patients.

Non Hodgkin lymphoma II

C071

ABSTRACT NOT PUBLISHABLE

C072

ABSTRACT NOT PUBLISHABLE

C073

PET-DRIVEN RADIOTHERAPY IN PATIENTS WITH LOW RISK DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): THE DLCL10 MULTICENTER PHASE 2 TRIAL BY FONDAZIONE ITALIANA LINFOMI (FIL)

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Background. The role of consolidation radiotherapy (RT) after rituximab-chemotherapy (R-CT) in DLBCL is not completely defined. Historically, bulky sites at diagnosis are irradiated after R-CT, whereas residual disease at other sites is considered as treatment failure. Since 2007, complete remission (CR) is defined as PET negativity and some groups postulated that PET negative areas after R-CT do not need consolidation RT.

Aims. To assess the role of RT in PET-negative and in PET-positive low-risk DLBCL patients after R-CT

Methods. The DLCL10 trial was a phase II study of patients >=18 years with DLBCL defined at low risk according to the MiNT study,(aa IPI 0 and bulky , aa IPI 1 with/without bulky) conducted in 19 FIL centers. Patients were treated with 6 courses of RCHOP-14 or R-CHOP-21 and final response was evaluated with FDG-PET. Both pre and post treatment PET scans were centrally reviewed through the Widen web platform by a panel of five nuclear medicine experts. Positive scans were those centrally classified with Deauville score 3-4-5. The first 2 concordant reviewers decided the final results. Patients with one residual FDG-uptaking area (RUA) were planned to receive RT, 36 Gray involved-field, regardless of the presence of bulky disease at diagnosis, while patients with multiple RUA were shifted to salvage systemic therapy. Primary aim was to obtain 2-year PFS of at least 85% for PET negative patients observed after R-CT; secondary endpoints were overall survival and response

Results. From January 2012 to December 2017, 115 consecutive patients were enrolled, and 109 were evaluable. Patients had a median age of 58 yrs (47-65); M:F 60/49; 90% DLBCL *de novo*. Fifteen patients presented with aa IPI 0, and 94 with aa IPI 1, among whom 20 with bulky disease; 72 patients received RCHOP-14 and 37 RCHOP-21. The median follow-up was 36 months and 6 patients died (2 lymphoma, 3 toxicitiy, 1 unknown). A total of 105 patients completed the chemotherapy program, while four were discontinued for lymphoma progression (1), toxicity (2, both died) and unknown cause (1). At the end of treatment 83 patients had negative PET, whereas 17 had single RUA and received RT. In PET-negative patients, PFS was 90.6% (95% CI 81.1-95.4) at 2 years and 88.7% (95% CI 78.4-94.3) at 3 years. After RT, 15 out of 16 evaluable cases reached CR, one PR and one was not evaluable. None of them relapsed. Thus, all patients with positive focal findings after R-CT were cured with focal RT. Concerning the 35 patients with bulky disease, 20 reached negative PET and 15 had RUA after R-CT (1 PD). There were two relapses in the negative PET/non irradiated group and none in the positive PET /RT group. In the total population, 3-year PFS and OS are 85.1% (95%CI 76.4-89.3) and 94% (95% CI 87.3-97.7), respectively.

Summary/Conclusions. Our data suggest that irradiating only sites of unique residual PET uptake, regardless of bulky at onset, can be considered as a reasonable strategy for low risk DLBCL patients. In patients with bulky disease, PET-driven RT allowed RT sparing in approximately half of patients. Moreover, consolidation RT in those with focal residual PET positivity, guaranteed excellent prognosis (17/17 cured) and has to be recommended as a valid option.

C074

THE CAR+CD4/CD8 RATIO IN INFUSED CAR-T PRODUCTS PREDICTS EFFICACY AND ICANS

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**same contribution*

Background and Methods. The definition of precise outcome predictors for patients with LBCL treated with anti-CD19 CAR-T is still incomplete. Some studies support the role of CAR-T subsets in predicting expansion at day 10 and outcomes. The role of the CAR+CD4/CD8 ratio is not defined to date, despite some data reporting superior outcomes for patients with a defined 1:1 CAR+CD4/CD8 ratio. We studied CAR+CD4/CD8 ratio in leftovers collected after CAR-T infusion, from 24 patients with R/R LBCL treated with tisa-cel (13), axi-cel (13), or brexu-cel (5). The major demographic and disease-related characteristics were not different among the three groups.

Results. CAR+CD4+/CD8+ median ratio was 1.44 (range 0.18-7.86). The median ratio on infused products was 0.54, 1.54, and 2.56 in brexu-cel, axi-cel and tisa-cel, respectively (p=0.126). LDH at apheresis (p=0.002) but not age (p=0.528), previous autologous stem cell transplantation (p=0.191) nor CD4/CD8 ratio in PB at the apheresis influenced the CAR+CD4+/CD8+ ratio in the final product. Patients who obtained a response 3 months (M3) after CAR-T had a lower CAR+ CD4+/CD8+ ratio in infused bags when com-

pared with non-responders (median ratio 0.74 *vs* 2.47, p=0.011) (Figure 1A). A ROC analysis identified that a cutoff of 1.12 had 100% sensitivity and 70 % specificity in predicting responses at M3 (AUC 82%, p=0.001), with an Odds Ratio of 23.3 at M3 and 10 at M6. When dichotomized by the CAR+CD4/CD8 ratio cutoff of 1.12, patients had a 6-month progression-free survival (PFS) of 76% *vs* 31% (p=0.047) (Figure 1B). In multivariate analysis, the CAR+CD4/CD8 ratio (OR 16.41)- but not the costimulatory domain (4-1BB *vs* CD28)- of CAR-T products resulted an independent risk factor for progression at M3, while costimulatory domain - but not the ratio- independently predicted PFS. A ratio lower than 1.12 had no impact on the subsequent development of CRS graded 2 or more, but predicted the onset of ICANS of any grade (OR 3.00 p=0.021).

Conclusions. Patients responding 3 months after CAR-T had a lower CAR+CD4/CD8 ratio in infused bags. A cut-off ratio of 1.12 can be useful in predicting PFS, the response at M3 and M6, and the development of neurotoxicity. These data support the role of the CD8-mediated cytotoxic mechanism of action of CAR-T cells and may be useful for strategies of potential empowerment of manufactured products, such as a balanced CAR+ CD4+/CD8+ ratio.

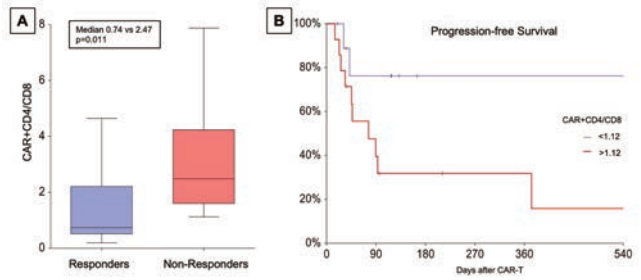

Figure 1.

C075

EPCORITAMAB + R-CHOP IN PATIENTS WITH PREVIOUSLY UNTREATED HIGH-RISK DIFFUSE LARGE B-CELL LYMPHOMA, INCLUDING DOUBLE-HIT/TRIPLE-HIT LYMPHOMA: EPCORE NHL-2 UPDATE

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Patients (pts) with previously untreated (1L) diffuse large B-cell lymphoma (DLBCL) typically receive rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); however, approximately 40% are refractory or relapse. Complete response rates and long-term outcomes are worse for high-risk pts with International Prognostic Index (IPI) 3–5 or double-hit/triple-hit (DH/TH) lymphoma; this underserved population requires better curative options. Results from the pivotal study of single-agent epcoritamab, a T-cell–engaging bispecific antibody, demonstrated impressive efficacy and a manageable safety profile (Thieblemont et al, *JCO* 2022). Preliminary data for epcoritamab + R-CHOP in 1L DLBCL from the EPCORE™ NHL-2 phase 1/2 trial (NCT04663347) showed encouraging efficacy. We present a larger cohort with longer follow-up. Pts with 1L $CD20^+$ DLBCL and IPI ≥3 received subcutaneous (SC) epcoritamab (cycle [C] 1–4, QW; C5–6, Q3W) + R-CHOP for 6 Cs (21 d each) followed by epcoritamab monotherapy Q4W (28 d Cs) for ≤1 y in total. As of Oct 31, 2022, 47 pts (median age, 64 y) had received epcoritamab 48 mg + R CHOP (median follow-up, 11.5 mo; range, 0.8–15.5). All pts had IPI 3–5, 37 (79%) had stage IV disease, and 11 (44%) of 25 pts with FISH data had DH/TH DLBCL. Median time from diagnosis to first dose was 28 d (range, 3–423), and median dose intensity for R-CHOP was ≥95%. The most common treatment-emergent AEs (TEAEs; any grade [G]) were neutropenia (64%), anemia (62%), CRS (60%), fatigue (40%), pyrexia (40%), injection-site reactions (38%), and nausea (38%). TEAEs led to epcoritamab discontinuation in 3 pts, and 1 G5 TEAE was reported (COVID-19, unrelated to treatment). CRS was mostly low grade (57% G1–2, 2% G3) and occurred most frequently after the first full dose (C1D15); all cases resolved. One pt had ICANS (G2, resolved in 4 d). All response-evaluable pts (100%; 46/46) had a response; 76% (35/46) had a complete metabolic response (CMR; Table). Response rates were similar for DH/TH pts (82% [9/11] CMR). Median duration of response, progression-free survival, and overall survival were not reached. Responses were durable; an estimated 96% of pts with CMR remained in CMR at 9 mo. Updated data will be shown. SC epcoritamab + R-CHOP induces high CMR rates with a manageable safety profile in pts with 1L high-risk DLBCL, including DH/TH pts. These results support the ongoing phase 3 trial of epcoritamab + R-CHOP in 1L pts (NCT05578976).

Table 1.

Antitumor activity overall and in double-hit/triple-hit pts

	Overall response %	Complete metabolic response %	Partial metabolic response %	Stable/ Progressive disease %
Total evaluable (n=46)	100	76	24	0
Double-hit/triple-hit (n=11)	100	82	18	0

Myeloproliferative neoplasms I

C076

ASSOCIATION OF HYPOMETHYLATING AGENTS + VENETOCLAX IN THE REAL-LIFE TREATMENT OF MYELOPROLIFERATIVE NEOPLASMS IN BLASTIC PHASE

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Background. Association of hypomethylating agents (HMA) and venetoclax (VEN) is widely used in elderly patients (pts) with de novo Acute Myeloid Leukemia not eligible for intensive chemotherapy, with improvement of survival. However, very few data are available in pts with Myeloproliferative Neoplasms evolved in blastic phase (MPN-BP). In this setting, the survival is dismal and at present no therapy seems to have a role.

Methods. Data of 54 pts with MPN-BP treated frontline with HMA+VEN in 19 hematologic Centers in Italy outside clinical trials from 11/2018 to 3/2023 were retrospectively collected and analysed. Composite overall response rate [ORR; complete remission (CR) + CR with incomplete hematologic recovery (iCR) + partial remission (PR) + hematologic improvement (HI)], duration of response and overall survival (OS) were assessed.

Results. Baseline features at evolution and starting treatment are reported in the Table 1. Median interval from initial MPN diagnosis to evolution was 38.4 months [interquartile range (IQR) 15.4-124.5]. Pts were treated for a median of 3 courses (IQR 2-7): HMA were administered at standard dosage, VEN daily doses in the 1st cycle are reported in the Table 1. On the whole, 40 pts (74.1%) had at least one hematologic toxicity of grade 3-4: in particular, severe neutropenia (PMN < $0.5x10^9$/l) was reported in 37 pts (68.5%). Thirty pts (55.5%) had at least one infective episode during the treatment: pulmonary infections were reported in 13 pts (24.0%). Response to treatment is shown in the Table 1: ORR was 62.7%, with a median response duration of 9.4 months (95%CI 5.8-12.9). After a median follow-up of 6.7 months (IQR 3.2-12.1), 35 pts (64.8%) died, 2 (3.7%) were lost to follow-up and 17 (31.5%) were alive. Median OS of the whole cohort was 10.6 months (95%CI 5.8-15.3), Pts with any response to HMA+VEN had a significantly longer OS compared to pts with progressive/stable disease [11.6 (95%CI 9.4–13.7) versus 5.4 (95%CI 2.1-8.6) months, respectively (p=0.002)].

Conclusions. Our real-life data confirm that HMA + VEN combination could have a role in MPN-BP, with ORR > 50% in pts unfit for intensive therapy: however, this treatment is affected by severe hematologic and infective toxicities and the response duration is short, with a persistently poor median OS. Larger cohorts of pts and a longer follow-up are needed to assess factors predictive of CR/iCR achievement, while addition of other targeted therapies should be explored.

Table 1.

N° of patients	54
M/F, n° (%)	41/13 (75.9/24.1)
Median age, years (IQR)	72.4 (66.2 – 75.2)
Median Hb, g/dl (IQR)	9.1 (7.9 – 10.8)
Median WBC, x 10^9/l (IQR)	8.0 (2.8 – 21.6)
Median PMN, x 10^9/l (IQR)	1.9 (0.7 – 6.4)
Median PLTS, x 10^9/l (IQR)	94 (31 – 233)
Median marrow blasts, % (IQR)	30 (23 – 60)
Treatment, n° (%): Aza + VEN	34 (63.0)
Dac + VEN	20 (37.0)
VEN starting dose (1st cycle), n° (%):	
50 mg	10 (18.5)
100 mg	19 (35.2)
200 mg	4 (7.4)
400 mg	21 (38.9)
Type of response, n° (%):	
CR/iCR	16 (31.4)
PR	12 (23.5)
HI	4 (7.8)
SD	3 (5.9)
PD	13 (25.5)
ED	3 (5.9)
Too early	3

C077

CLINICAL PHENOTYPE, RESPONSE TO THERAPY, AND PROGNOSTIC CORRELATIONS OF PATIENTS WITH POLYCYTHEMIA VERA AT LOW THROMBOTIC RISK TREATED WITH HYDROXYUREA. A PV-NET ITALIAN STUDY

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Recently, ELN recommended cytoreduction in selected patients (pts) with PV at low-risk (LR) according to conventional criteria (age<60 yrs & no previous thromboses) (Marchetti M *et al.*, Lancet Haematol 2022). However, information on the efficacy of HU in pts at LR, at high-risk pts only by age (HR-AGE), or high-risk by thrombosis regardless of age (HR-THRO) is scant. The "PV-ARC" retrospective multicenter Italian study includes 934 WHO2016-defined PV pts followed in 28 Hematology Centers. We evaluated ELN response rates to HU and their influence on thrombosis-free survival (TFS) in LR, HR-AGE and HR-THRO PV pts. Among the 504 pts who received HU, 423 (83.9%) pts were at HR at baseline (HR-AGE, no. 290, 57.5%; HR-THRO, no. 133, 26.4%). In the 81 (16.1%) LR pts, main reason for HU start was: high (≥6/yrs) PHL need/intolerance (56.6%), itching score ≥5/10 (23.0%), PLT ≥1.500x10^9/L and/or WBC ≥15x10^9/L (13.9%), microvascular disturbances (4.9%), progressive splenomegaly (1.6%).

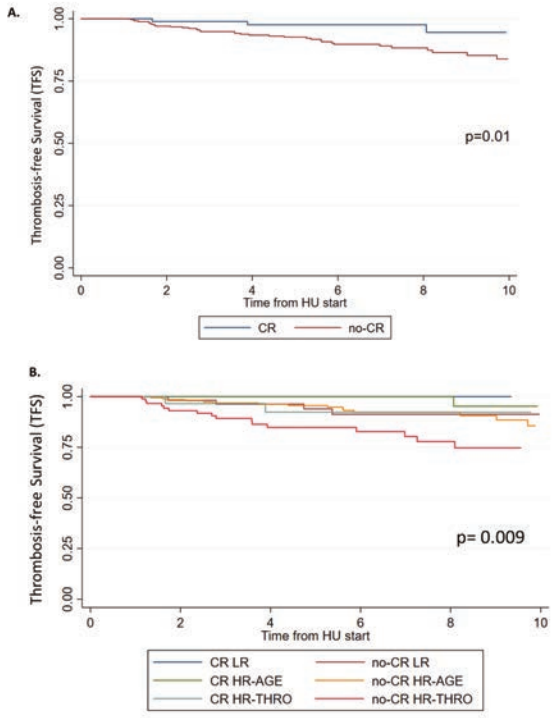

Figure 1. Thrombosis-free survival by complete response to HU at 12 months (landmark analysis). A. TFS at 5 yrs was 98% and 91% in CR and no-CR pts (p=0.01). B. TFS at 5 was 100% in LR and HR-AGE pts in CR; 94%, 96%, and 92% in no-CR LR, no-CR HR-AGE, and CR-THRO pts; 84% in no-CR HR-THRO pts.

Compared to both HR groups, LR pts were more frequently symptomatic, with palpable splenomegaly, and higher WBC/PLT counts. 33.3%, 31% and 35.3% of LR, HR-AGE and HR-THRO pts received median HU dose ≥1 g/d. During HU, 53 pts had a thromboses for an incidence rate (IR) of 1.5 per 100 pt-yrs; 31 bleedings (IR: 0.9), 13 BP (IR: 0.3) and 35 MF (IR 0.9) were recorded. Notably, IR of thrombosis was comparable in LR (0.98) and HR-AGE pts (1.15, p=0.77), but significantly higher in HR-THRO pts (2.58, p=0.006). Conversely, IR of bleedings and MF/BP progressions were comparable in the 3 groups. At 12 mos, 101/475 evaluable pts (21.2%) were in CR. The probability of CR was lower in pts with LR PV (OR [95% CI]: 0.36 [0.15-0.87], p=0.02), itching (OR: 0.44 [0.22-0.95], p=0.02), WBC ≥15x10^9/L (OR: 0.46 [0.22-0.95], p=0.04), male sex (OR: 0.52 [0.32-0.82], p=0.005), and median HU dose <1 g/d (OR: 0.53 [0.33-0.85], p=0.009).

By KM landmark analysis by CR at 12 mos, pts in CR had significantly better TFS compared to no-CR pts (Figure 1A). Specifically, best TFS was observed in LR and HR-AGE pts with CR, while HR-THRO pts without CR had the worse TFR (p=0.009) (Figure 1B).

The equal IR of thrombosis in LR and HR-AGE pts suggests that leukocytosis, thrombocytosis, splenomegaly, and symptoms identify an increased risk phenotype in pts conventionally defined as low risk. Notably, the achievement of a CR at 12 mos correlated with reduced risk of thrombosis across all risk categories.

C078

THE COMBINATION OF NAVITOCLAX AND RUXOLITINIB IN JAK INHIBITOR–NAÏVE PATIENTS WITH MYELOFIBROSIS MEDIATES RESPONSES SUGGESTIVE OF DISEASE MODIFICATION

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Background. Driver mutations in *JAK2*, *CALR*, and *MPL* are potential treatment targets for myelofibrosis (MF), with reduction in variant allele frequency (VAF) and reversal of bone marrow fibrosis (BMF) indicating disease modification. Mutations in *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*, and *U2AF1* p.Q157 are seen as high molecular risk (HMR) due to poor prognosis. We investigated if MF type and risk correlated with clinical responses, thus indicating disease modification in Janus kinase inhibitor (JAKi)–naïve patients treated with combined navitoclax and ruxolitinib.

Methods. Cohort 3 of phase 2 multicenter REFINE study (NCT03222609) enrolled JAKi– and bromodomain and extra-terminal motif inhibitor–naïve patients with primary or secondary MF. Patients initiated navitoclax at 100 or 200 mg QD if baseline platelet count was ≤150×10^9/L or >150×10^9/L, respectively. Ruxolitinib was given BID with starting dose based on baseline platelet count per local label. The primary endpoint was spleen volume reduction of ≥35% (SVR_{35}) at Week 24 (MRI; central review). Key secondary and exploratory endpoints were BMF decrease (BM biopsies; local evaluation) and VAF reduction for *JAK2*^{V617F}, *CALR*, or *MPL* mutations, respectively. Driver gene VAF and HMR mutations were assessed in whole blood with next-generation sequencing.

Results. As of Feb 07, 2022, all 32 patients were biomarker evaluable. Median follow-up duration was 6.1 months (range, 1.9–18.6). At baseline, 22 (69%) patients had *JAK2*, 6 (19%) had *CALR*, and 3 (9%) had *MPL* mutations; 1 (3%) was triple negative; 19 (59%) had

HMR mutations. Median baseline VAF for *JAK2*^{V617} was 66% (range, 36%-96%). SVR_{35} at Week 24 was observed irrespective of baseline *JAK2*^{V617} allelic burden in all subgroups with poor prognosis (aged ≥75; intermediate-2/high DIPSS score; HMR; Figure 1). BMF grade improvement was evaluable in 26/32 (81%) patients; 9/26 (35%) achieved ≥1-grade improvement. Median time-to-improvement was 12.3 weeks (range, 12.1-24.1). Complete BMF resolution was observed in 2/9 (22%) patients (baseline grades 2 and 3). BMF ≥1-grade improvement was achieved by 7/13 (54%) and 2/13 (15%) patients with and without HMR mutations, respectively. VAF reduction >20% in *JAK2*^{V617} was observed in 14/28 (50%) patients (Week 12 or 24); >50% was observed in 5/14 (36%).

Conclusions. In JAKi-naïve patients with MF, navitoclax plus ruxolitinib showed BMF and VAF (*JAK2*^{V617}) reductions, independent of HMR mutations, suggestive of underlying disease modification.

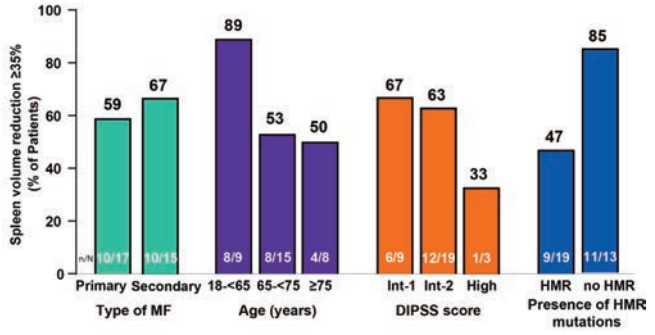

Figure 1. Spleen volume reductions ≥35% (SVR_{35}) in subgroups at Week 24. Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; HMR, high molecular risk; Int, intermediate; MF, myelofibrosis.

C079

DECIPHERING THE PROGNOSTIC CONTRIBUTION OF RAS/MAPK PATHWAY GENES AND TP53 MUTATIONS TO MUTATION-ENHANCED INTERNATIONAL PROGNOSTIC SCORE SYSTEMS (MIPSS) FOR PRIMARY MYELOFIBROSIS

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Background. High molecular risk (HMR) mutations in PMF included *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2* (according to MIPSS70/plus) and *U2AF1* (plus 2.0). Although there is no consensus on how extensive the search for additional mutations should be, the 2022 ICC authors questioned about the utility of including *TP53*, *NRAS/KRAS*, *RUNX1* mutations.

Aim and Methods. Elucidate the prognostic contribution of above mutations on top of original MIPSS variables. This retrospective study included 363 PMF pts at our Institution, annotated for clinical and molecular data at diagnosis or within 1 year.

Results. Median age of PMF pts (59% *JAK2*, 24% *CALR*, 6% *MPL*, and 11% triple negative –TN) was 59 yrs; 60% were males and median follow-up was 4.5 yrs. Deaths and leukemic transformations were 135 and 42, respectively. The frequencies of myeloid-gene mutations were: *ASXL1* (29%), *EZH2* (10%), *IDH1/2* (4%), *SRSF2* (10%), *U2AF1* (5%), *CBL* (5%) *NRAS* (7%), *KRAS* (4%), *RUNX1* (4%), and *TP53* (5%). MIPSS70 scores clinical and laboratory variables were confirmed to have negative impact on OS in univariate analysis: Hb <10 g/dL (HR 3.7; p<0.001), leukocytes >25×10^9/L (HR 2.5; p<0.001), platelets <100×10^9/L (HR 2; p<0.001), BM fibrosis ≥2 (HR 3; p<0.001), blasts ≥2% (HR 4; p<0.001), and symptoms (HR 2.7, p<0.001). Mutations in *CBL* (HR 2.8; p<0.001), *NRAS* (HR 2.4; p<0.001), *KRAS* (HR 2.1; p<0.001) and *TP53* (HR 2.4, p<0.001) had a worst significance, along with HMR ones. Conversely, *RUNX1* mutations were not significant (HR 1.8, p=0.08). HMR, *U2AF1*, *CBL*, *NRAS*, *KRAS* and *TP53* were included under "HMR+" category. Multivariable analysis comprising all adverse mutations only, documented the independent prognostic role of *ASXL1* (HR 1.8, p=0.007), *EZH2* (HR 2.4, p<0.001), *SRSF2* (HR 4.3, p<0.001) and *U2AF1* (HR 2.9, p=0.004). Accordingly, the OS probability was progressively lower in HMR without *U2AF1* (HR 3.6), HMR with *U2AF1* (HR 3.9) and "HMR+" patients (HR 4). Then, we compared MIPSS70 score performances including HMR (+/- *U2AF1*) and "HMR+" categories. As regards MIPSS70, C-indexes were 0.79 and 0.81 for original and enhanced by "HMR+" category models, respectively (Z score= 2.2; p=0.03, Figure 1). Therefore, MIPSS70 plus and plus 2.0 scores and respective "HMR+" enhanced models were superimposable.

Conclusions. whilst original MIPSS70 score confirm to be accurate and powerful to risk stratify PMF patients, *U2AF1*, *CBL*, *NRAS*, *KRAS* and *TP53* mutations should be included as well, if available.

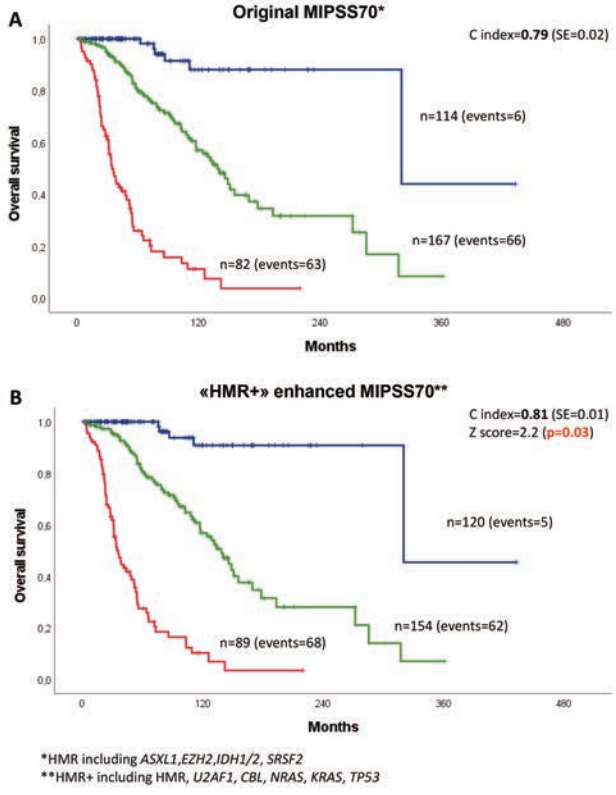

Figure 1.

C080

VALIDATION AND MOLECULAR INTEGRATION OF THE RESPONSE TO RUXOLITINIB AFTER 6 MONTHS (RR6) MODEL

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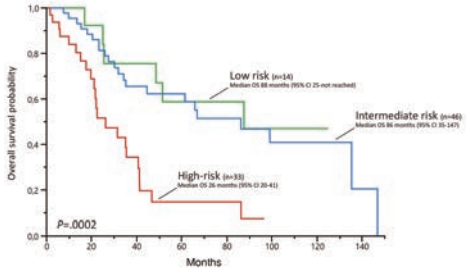
Background. Ruxolitinib (Rux) failure is common and associated with dismal prognosis[1]. Recently, the RR6 model has been developed and proved to be accurate in distinguishing Rux-treated patients (pts) with impaired survival.

Aim and Methods. This retrospective, single center study aimed to validate the RR6, explore the independent contribution of gene mutations, and integrate them into the RR6.

Results. We included 93 Rux-treated MF pts with extensive clinical and molecular data. Median time on Rux was 29 (6-130) mos, median follow-up time 80 (59-99) mos. Rux dose was <40 mg daily in 70%, 82%, and 82% of pts at baseline, 3 and 6 mos, respectively. Transfusion need was reported in 15% of pts at all timepoints and 41% at 3/6 mos. Palpatory spleen reduction <30% at 3 and 6 mos was observed in 29% of pts. While 41 out of 92 (45%) evaluable pts harbored >1 high molecular risk mutation (HMR^{mt}; *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SRSF2*), 7 (8%) harbored >1 mutation in RAS pathway genes (RASp^{mt}; *NRAS*, *KRAS*, *CBL*). According to the RR6, 14 (15%), 46 (49%), and 33 (35%) pts were classified as low (LR), intermediate (IR), and high risk (HiR), respectively. The estimated median OS from 6 mos after Rux start was 88, 86, and 26 mos, respectively (*P*=.0002; Figure 1A).



B

Comparison of the prognostic performance of RR6 model and its integration with high molecular risk signatures

		Events at 12 months		Events at 24 months		Events at 36 months		Events at 48 months	
	C-index	Brier score	AUC	Brier score	AUC	Brier score	AUC	Brier score	AUC
RR6	63.6	0.036	73.7	0.074	73.7	0.115	67.2	0.137	76.9
HMR^{mt}	58.4	0.038	57.9	0.080	60.5	0.123	61.5	0.149	61.2
RASp^{mt}	54.9	0.037	61.4	0.071	62.0	0.114	56.6	0.142	56.5
RR6+HMR4^{mt}	**67.2***	0.036	77.8	0.075	78.1	0.113	71.2	0.133	80.2
RR6+RASp^{mt}	**67.2***	**0.035***	**80.7***	**0.066***	**82.1***	**0.104***	**71.3***	**0.124***	**81.1***

Notes: Asterisk and bold indicate the best values. [1]HMR mutations include pathogenic variants in any of the following genes: *ASXL1, EZH2, SRSF2, IDH1* or *IDH2*. [2]RAS pathway mutations include pathogenic variants in any of the following genes: *NRAS, KRAS* or *CBL*.

Abbreviations: AOU: area under the curve; HMR^{mt}: high molecular risk mutation; RASp^{mt}: RAS pathway mutation; RR6: Response to Ruxolitinib After 6 Months.

Figure 1.

Although HiR pts had a significant higher risk of death compared to both IR (HR 3.1; *P*=.0003) and LR (HR 3.8; *P*=.0046) pts, the latter two showed a superimposable outcome. We next evaluated the contribution of genetic variables independently from the RR6, including driver and additional mutations assessed by NGS. In univariate Cox proportional hazards analysis, inferior OS was predicted by RR6 categories, presence of >1 HMR^{mt}, and >1 RASp^{mt}. Upon multivariate analysis, only RR6 (HiR *vs* IR: HR 4; *P*<.0001; HiR *vs* LR: HR 4.4; *P*=.0022) and RASp^{mt} (HR 6.3; *P*=.0004) remained independent predictors of reduced OS. Finally, we evaluated the prognostic contribution of mutations by computing the C-index, Brier score, and time-dependent AUC of the RR6 and its molecular integration with HMR^{mt} and RASp^{mt} (Figure 1B). The highest values for performance and accuracy were achieved by the RR6-RASp^{mt} combination, that showed to be superior at almost all time points considered.

Conclusions. Our findings suggest that 1) the RR6 effectively identifies HiR pts, but may present inferior performance in discriminating lower risk pts; and 2) RASp^{mt} are an additional risk factor, and their integration in the RR6 enhances the performance of the score.

Myeloma and monoclonal gammopathies III

C081

ABSTRACT NOT PUBLISHABLE

C082

FIRST INTERIM ANALYSIS OF A PROSPECTIVE, MULTICENTER, OBSERVATIONAL STUDY ON THE PREVALENCE OF TYPE 1 GAUCHER DISEASE IN PATIENTS WITH MULTIPLE MYELOMA

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Background. Type I Gaucher disease (GD1) has been associated with increased cancer risk in the International Collaborative Gaucher Group (ICGG) Registry (Rosenbloom et al, 2005). However, due to the retrospective nature of the study and young age distribution of population, cancer risk was likely underestimated. We designed a prospective study to investigate the prevalence of GD1 in a large Multiple Myeloma (MM) patient population.

Aims. Primary end-point of the study is the prevalence of Dried Blood Spots (DBS) test positivity in MM patients. All patients with DBS test positive undergo genetic test to confirm the diagnosis of GD1. If the observed prevalence will be significantly higher than predicted, the identification of potential risk predictors in the selected population will be carried out.

Methods. This is an observational, prospective, cross-sectional, multicentre study. Due to the lack of data on the effective prevalence of GD1 in MM, the sample size has been determined considering clinically relevant a prevalence of the condition > 0.5% for defining as "high risk" the selected population. Considering an alpha error of 5% and a statistical power of 95%, we should enroll 1000 patients overall. All MM patients are screened for GD1 by DBS sampling technique, that was centralized at the Istituto per la Ricerca e l'Innovazione Biomedica CNR-Palermo.

Results. We enrolled 734 patients so far. Median age was 67 years (range 37-90), 58% of patients were male. No patients were Jews, one was Asian and one was Black, all others were Caucasian. Newly diagnosed and relapsed-refractory MM were 60% and 40%, respectively, whereas SMM and MM 12% and 88%, respectively. Monoclonal component was IgG in 54%, IgA in 25%, light chain in 11%. Median Ferritin was 322 ng/ml (range 17-1236) and median Alkaline Phosphatase was 81 U/L (range 29-355). Data of DBS test, enzymatic activity and genetic are reported in the Table. DBS test found single heterozygous in 10 patients and double heterozygous mutation in 1 patient, so the prevalence of test positivity was 11/734 (1.49%). Patients with double heterozygous DBA test underwent genetic test that confirmed GD so the prevalence of GD was 1/734 (0.13%).

Conclusions. After the enrolment of more than a half of the planned patients, the prevalence of DBS 2 variants test positivity was less than 0.5%, but single variant positivity was higher, selecting a not negligible population eventually undergoing the genetic test to confirm the GD (Dardis *et al*., 2022).

Acknowledgment. This study is supported by Sanofi Genzyme

Table 1.

ID	Sex	GBA Enzimatic activity (normal range=0.2-2.5 nMol/h/ml)	Lyso Gb1 (normal range<6.8 ng/ml)	Involved GBA gene
Double heterozygosity				
KA505	M	2.0	14.6	R170C heterozygous L444P heterozygous
Single heterozygosity				
KA492	M	3.9		L444P heterozygous
KA404	M	3.4		N370S heterozygous
KA763	F	2.7		G241R:G202R
KA863	M	3.3	5.4	N370S
KA878	F	2.6	3.6	V53M
KA951	M	3.5	1.8	K13R
KB119	F	2.2	2.2	N370S
KB211	M	4.6	4.6	E365K
KB347	F	4.5	4.5	M369T
KC496	F	2.8	2.8	I441T

C083

ABSTRACT NOT PUBLISHABLE

C084

TIMMING: DEVELOPING AN INNOVATIVE SUITE OF BIOINFORMATIC TOOLS TO HARMONIZE AND TRACK THE ORIGIN OF COPY NUMBER ALTERATIONS IN THE EVOLUTIONARY HISTORY OF MULTIPLE MYELOMA

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Multiple Myeloma (MM) is a hematologic cancer with heteroge-

neous and complex genomic landscape, where Copy Number Alterations (CNAs) play a key role in the disease's pathogenesis and prognosis. It is of biological and clinical interest to study the temporal occurrence of early alterations, as they play a disease "driver" function by deregulating key tumor pathways. This study presents an innovative bioinformatic tools suite created for harmonizing and tracing the origin of CNAs throughout the evolutionary history of MM. To this aim, large cohorts of newly-diagnosed MM (NDMM, N=1582) and Smoldering-MM (SMM, N=282) were aggregated. The tools developed in this study enable the harmonization of CNAs as obtained from different genomic platforms (*i.e.* WGS, ULP-WGS, WES, SNP array) in such a way that a high statistical power can be obtained. By doing so, the high numerosity of patients was harnessed for both the identification (through optimized use of GISTIC tool) of novel of genes characterized as focal "driver" alterations in MM (including BCMA, NFKB2, NOTCH2, MAX, TERC, EVI5 and MYC-enhancer genes), and the generation of an innovative timing model, implemented with the introduction of a statistical method to compute statistical confidence intervals in CN estimation.

By applying this model on both NDMM and SMM cohorts, it has been possible to identify specific CNAs (1q(CKS1B)amp, 13q(RB1)del, 11q(CCND1)amp and 14q(MAX)del) and categorize them as early/driver events (Figure 1). A high level of precision was guaranteed by the narrow confidence intervals in the timing estimates. These CNAs were proposed as critical MM alterations, playing a foundational role in the evolutionary history of both SMM and NDMM. Importantly, among the identified events, CKS1B amp and RB1 del were previously poorly characterized from an evolutionary point of view and uncertainly classified between primary and secondary events, while MAX del represents a completely new discovered MM driver alteration. Finally, a multivariate survival model was employed to identify the independent genomic alterations with the highest effect on patients' survival, including RB1 del, CKS1B amp, MYC amp, NOTCH2 amp and TRAF3 del/mut.

In conclusion, the study highlighted the existence of previously unrecognized "early-drivers" CNAs, whose impact on patients' survival has been demonstrated and that could provide a better disease stratification and an improved prognosis definition.

Acknowledgment: BolognAIL ONLUS, AIRCIG2019.

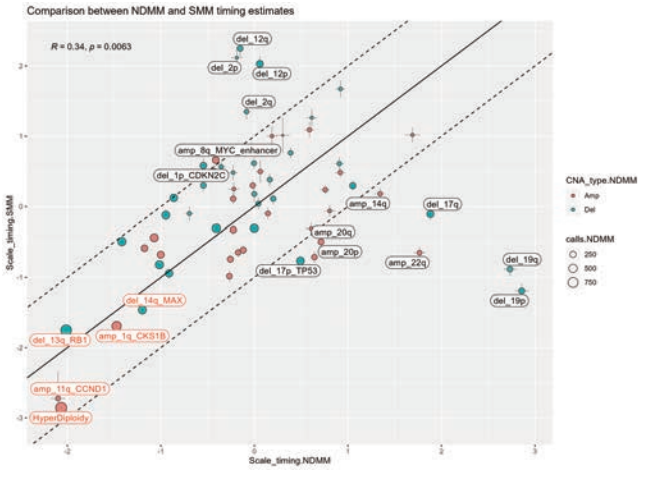

Figure 1.

C085

VENOUS THROMBOEMBOLISM IN MULTIPLE MYELOMA: RISK FACTORS AND IMPACT ON PROGNOSIS. ROLE OF THROMBOPHILIA

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Venous thromboembolism (VTE) is a common complication of multiple myeloma (MM) despite antithrombotic prophylaxis. We retrospectively analyzed the impact on VTE risk of the variables listed in the IMPEDE-VTE score, adding as covariates the family history of VTE and inherited or acquired thrombophilia.

We evaluated 292 MM patients (M/F 163/129, median age 65 years, range 28-89). We recorded 62 VTE events, 41 during the induction phase (first 12 months from diagnosis) and 21 in later phases. We confirmed in the induction phase the risk for VTE associated with immunomodulatory drugs, pelvic/hip/femur fractures, doxorubicin, high dose dexamethasone, personal history of VTE, and antithrombotic prophylaxis. In addition, a family history of VTE, severe inherited thrombophilia, and acquired thrombophilia were significant risk factors for VTE (Table 1).

Table 1. Univariate and multivariate analysis applied to patients in induction phase of treatment, with parameters included in IMPEDE-VTE score adding family history of VTE, acquired and inherited thrombophilia Severe inherited thrombophilia includes deficiency of natural anticoagulants (antithrombin, protein C, and protein S) confirmed with genic sequence or family studies, homozygous and combined alterations; mild inherited thrombophilia includes heterozygous factor V Leiden and prothrombin G20210A; acquired thrombophilia includes hyperhomocysteinemia, antiphospholipid antibodies, and transitory disease-related deficiency of natural anticoagulants. BMI: body mass index; CVC: central venous catheter; IMIDs: immunomodulatory drugs; LMWH: low molecular weight heparin; VTE: venous thromboembolisms.

Covariates	Patients in induction phase (<12 months from diagnosis)			
	Univariate Analysis OR (95%CI)	p	Multivariate analysis HR (95%CI)	p
IMIDs	**2.39 (1.09-5.22)**	**0.02**	**5.06 (2.14-11.92)**	**0.0002**
BMI> 25 kg/m2	0.32 (0.16-0.67)	0.002	0.26 (0.12-0.55)	0.0004
Pelvis/hip/femur fracture	**11.48 (2.63-50.10)**	**0.001**	**5.99 (1.74-20.60)**	**0.004**
Erythropoietin	0.97 (0.48-1.96)	0.94	N.A.	N.A.
Doxorubicin	**5.31 (1.36-20.71)**	**0.01**	**3.81 (1.09-13.24)**	**0.03**
High-Dose Dexamethasone	**2.07 (0.91-4.69)**	**0.07**	2.09 (0.84-5.19)	0.10
Low-Dose Dexamethasone	1.20 (0.52-2.79)	0.66	N.A.	N.A.
CVC	1.59 (0.81-3.10)	0.17	N.A.	N.A.
Personal history of VTE	2.54 (0.85-7.55)	0.09	**2.98 (1.00-8.88)**	**0.04**
Family history of VTE	**4.41 (1.18-16.38)**	**0.02**	**7.25 (2.38-22.10)**	**0.0005**
LMWH prophylaxis	**0.36 (0.18-0.72)**	**0.003**	**0.15 (0.07-0.31)**	**<0.0001**
Therapeutic anticoagulation	0.24 (0.03-1.88)	0.17	N.A.	N.A.
Acquired thrombophila	**1.87 (0.87-4.04)**	**0.10**	**2.35 (1.12-4.90)**	**0.02**
Severe inherited thrombophilia	1.58 (0.50-5.01)	0.06	**10.53 (2.18-50.79)**	**0.003**
Mild inherited thrombophilia	0.86 (0.18-3.96)	0.85	0.70 (0.15-3.26)	0.65

After the first 12 months from MM diagnosis, only a personal history of VTE (hazard ratio HR 4.58 95%CI 1.37-15.23) and mild inherited thrombophilia (HR 5.70, 95%CI 1.84-17.66) were independent risk factors for VTE. From this population, we analyzed only the patients with responding MM, and we recorded 9 VTE events; mild thrombophilia was confirmed as a risk factor for VTE

(HR 16.26, 95%CI 3.94-67.05), while severe inherited thrombophilia showed a trend toward statistical significance (HR 6.39, 95%CI 0.70-57.85, p=0.09). Moreover, we analyzed the progression-free survival of patients who experienced VTE during the maintenance phase compared to patients without thrombosis; patients with VTE had a significantly increased risk for relapse (HR 9.01, CI 95% 2.57-31.53, p=0.0006).

In conclusion, the IMPEDE-VTE variables are reliable only during the induction phase of treatment. A family history of VTE, severe inherited thrombophilia, and acquired thrombophilia enhance the risk of VTE during the induction phase of MM. On the other hand, mild inherited thrombophilia is a strong risk factor for VTE during the maintenance phase. We suggest that during the first phase of active disease, the moderate risk associated with mild inherited thrombophilia was obscured by the stronger clinical or biochemical risk factors dependent on the MM burden disease. Conversely, the constitutional risk due to inherited factors becomes more critical during a stable phase of the disease. Moreover, the occurrence of VTE reduces PFS, suggesting the presence of MM-related thrombophilic alterations as a possible marker of active disease.

Allogenic and autologous transplant

C086

A CLINICAL TRIAL OF MULTIPLE INFUSIONS OF CRYOPRESERVED DONOR-DERIVED REGULATORY T (TREG) CELLS IN STEROID-REFRACTORY CHRONIC GVHD

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Introduction. Chronic GVHD has been associated with selectively delayed Treg cell recovery, leading to the hypothesis that the infusion of healthy Treg cells may improve their recovery and possibly ameliorate chronic GVHD symptoms,.

Methods. In the current trial (NCT02749084) we treated patients with steroid refractory chronic GVHD with multiple infusions of cryopreserved GMP-purified Treg cells. Each patient received three infusions of Treg cells each one month apart. The study had a dose escalating 3+3 design, with three dose levels (0.5, 1 and 2x10e6/kg total dose, respectively) with safety as the primary end point. Treg cells were isolated in a two-step procedure by immunomagnetic depletion of CD8+ and CD19+ cells followed by enrichment of CD25+ cells.

Results. Eleven Treg products have been prepared. Median purity was 94% (IQ 93-96%), 90% (IQ 90-94%) and 71% (IQ 66-77%) as based on identification of CD4+CD25+, CD4+CD25+CD127- and CD4+CD25+CD127-foxp3+ cells, respectively. No contamination (percentage <0.1%) was observed by CD19+, CD8+ and CD56+ cells. Median contamination by effector T cells (defined as CD4+CD25+CD127+ cells) and by Th17 cells (defined as CD161+CD196+) was 11% and 1.6%, respectively, resulting in the infusion of $2.8x10^4$/kg effector T cells and $3.9x10^3$/kg Th17 cells. Nine out of 11 products have received at least one infusion of purified T regs, 3 at the first dose level ($0,5x10^5$ Treg/kg total dose), and 6 at the second dose level (10^6 Treg/kg total dose). No infusion related events were observed. One patient developed a DLT (CMV pneumonia) one month after the last infusion. 5 more SAEs were observed during the 12 months predetermined observation period but were considered unrelated to the infusion. Importantly, no acute GVHD or early flares of chronic GVHD were observed. Disease responses observed in the 8 evaluable patients who received all three Treg infusions are reported in Table 1.

Table 1. NIH-based evaluation of response in the 8 patients who received three T reg infusions. a one of the eight patients missed the 12 month follow up visit due to worsening clinical conditions abbreviations: CR: complete response; PR: partial response; SD: stable disease; Prog: progression.

	3 months			
	CR	PR	SD	Prog
Global	0	7 (87%)	1 (13%)	0
Skin	0	2 (33%)	4 (67%)	0
Mouth	0	2 (33%)	4 (67%)	0
Eyes	0	2 (33%)	3 (67%)	0
Lung	0	0	6 (100%)	0
	12 months[a]			
	CR	PR	SD	Prog
Global	0	5 (71%)	0	2 (29%)
Skin	0	3 (50%)	3 (50%)	0
Mouth	1 (25%)	2 (50%)	2 (25%)	0
Eyes	1 (15%)	1 (15%)	5 (70%)	0
Lung	0	0	4 (71%)	2 (29%)

Interestingly, 5 out patients were able to reduce the dose of prednisone at the 12 month time point, with two patients being able to stop prednisone. While Treg numbers and percentages did not change significantly during the study, NGS analysis of TCR sequences confirmed the persistence of the infused Treg clones for up to 12 months after treatment.

Discussion. Treatment of patients with steroid-refractory chronic GVHD with purified cryopreserved donor T regs appears feasible and safe and may improve disease severity in some patients.

Acknowledgements. The study has received funding from the European Union H2020 research and innovation programme under grant agreement No 643776 ("Tregeneration").

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C089

DYNAMICS OF POLYCLONAL IMMUNO-RECONSTITUTION AFTER ALLOGENEIC TRANSPLANT WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE AND LETERMOVIR

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Background. Cytomegalovirus (CMV) reactivations are known strong stimulators of immune-reconstitution (IR) in hematopoietic stem cell transplantation (HSCT) recipients, which plays a major role in determining transplant outcomes. The advent of letermovir (LTV) determined a significant decrease of CMV-reactivation in the early post-HSCT period. The dynamics of IR during LTV as CMV prophylaxis are still to be defined, especially in patients receiving Post-Transplant Cyclophosphamide (PTCy) as Graft versus Host Disease (GvHD) prophylaxis.

Methods. Herein, we analyzed 317 CMV-seropositive consecutive patients (n=208 LTV-free; n=109 LTV), undergoing HSCT with PTCy and calcineurin inhibitor- (CNI) free GvHD prophylaxis, from August 2017 to March 2021. IR panels with lymphocytes subsets and immunoglobins quantification were performed at day 90 and day 180 after HSCT.

Results. At day 90, median CD19+/mm^3 was higher in the LTV-cohort: 5.5 [0;594] versus 2 [0;294], p=0.008; with no differences in CD4+, CD8+ and NK cells. At day 180 median CD3+, CD4+ and CD8+/mm^3 values were comparable between groups. Higher CD19+/mm^3 counts were still observed in the LTV-cohort: 62 [0; 2983] versus 42 [0; 863]. Significantly higher median NK/mm^3 values were seen in the LTV-cohort: 225.5 [0;763] versus 162 [0;744], p=0.0003. The impact of LTV on B cell IR at 3 months and NK cell levels at 6 months was retained also in multivariate analysis (p<0.01). Regarding the humoral response, we observed at day 90 higher IgA and IgG median values in the LTV cohort. No difference was seen in IgM levels. At day180, IgA values were higher in the LTV treated group, and no difference could be found in IgG and IgM levels. No difference in immunoglobulins supplementation, including CMV specific immunoglobulins, among two groups was observed. Moreover, we confirmed a significant reduction of clinically relevant CMV, and a reduction of moderate-to-severe chronic GVHD in LTV-recipients, confirmed also in multivariate analysis (p<0.001).

Discussion. Overall, in our study the use of LTV was not associated with a delayed T cell immune reconstitution. Conversely, we observed a slight improvement of B cell and NK cells reconstitution in LTV cohort, giving new insights on polyclonal immune reconstitution for HSCT recipients in the letermovir and PTCy era.

Finally, in our cohort, we confirmed a significant reduction of clinically relevant CMV in letermovir-recipients, and a reduction of moderate-to-severe cGVHD.

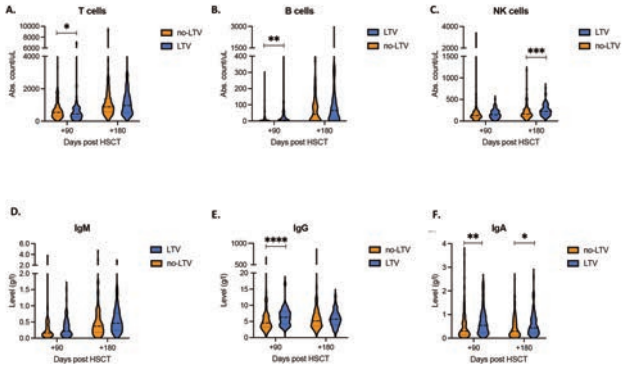

Figure 1. Cellular and humoral immune reconstitution in letermovir and no-letermovir groups. A: Absolute count of CD3$^+$ (T) cells/µl of peripheral blood. B: absolute count of CD19$^+$ (B) cells/µL of peripheral blood. C: absolute count of CD3$^-$CD16$^+$, and/or CD3-CD56+ (NK) cells/µl of peripheral blood. D: IgM peripheral blood quantification (g/L). E: IgG peripheral blood quantification (g/L). F: IgA peripheral blood quantification (g/L). *: P<0.05. **: P<0.01. *** P<0.0001. Abbreviations: LTV: Letermovir, NK cells: Natural Killer cells. Values are reported as median and range. Wilcoxon signed-rank test has been employed for statistical analysis.

C090

TIME OF ORIGIN AND ENVIRONMENTAL DRIVERS OF LEUKEMIA IMMUNE ESCAPE AFTER TRANSPLANTATION

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Background. One of the key questions regarding all cancer therapies is whether treatment-resistant subclones pre-exist therapy or originate at a later time-point from residual cancer cells that were kept under control until that time. Here we addressed this issue in HLA loss leukemia post-transplantation relapses, representing one the best characterized mechanisms of selective immune escape.

Mrthods: We started from the notion that mutations can be employed as molecular clocks to date the age and exposure to mutagens of cells, and combined whole genome sequencing (WGS) with Poisson-based modelling to derive the timing of the HLA loss rearrangement, intersecting results with the patient clinical history.

Results. By high-depth (average 100x) WGS of serial purified acute myeloid leukemia (AML) samples, we were able to successfully reconstruct clonal dynamics leading to 11 HLA loss relapses, and in each subclone to deconvolve mutational signatures. By applying Poisson-based timing models to homozygous (i.e. occurred before the copy neutral-loss of heterozygosity rearrangement) and heterozygous (i.e. occurred after the event) mutations in the rearranged region, in 9/11 HLA loss relapses we confidently dated the event to a post-transplantation time-point. In line with this observation, in all HLA loss subclones we could detect a C>A mutational signature that was absent in pre-transplant samples, and by literature data and *in vitro* experiments this was reconducted to the antiviral drug ganciclovir (GCV). By functional assays followed by immunofluorescence and flow cytometry analyses, we showed that GCV induces DNA damage and homologous recombination repair in AML, and hypothesize that this effect might be potentiated by concomitant exposure to the immunosuppressant mycophenolate. Concordantly, in the retrospective analysis of 35 post-transplantation relapses, incidence of HLA loss was 8/16 (50%) in patients exposed to GCV and 2/19 (10%) in unexposed patients (OR: 8.5, CI 1.7-43.8, p=0.02).

Conclusions. Our data indicate that in the majority of patients HLA loss variants originate after transplant, and that the genotoxicity of the GCV/mycophenolate combination is a potent facilitator of the phenomenon. Defining the time of origin of therapy resistance has fundamental clinical consequences, implying that immune escape clones can only be targeted by post-transplant interventions, and warranting the development of new tools to anticipate their detection.

Non Hodgkin lymphoma III

C091

B-CELL RECEPTOR SIGNALING ACTIVITY IDENTIFIES PATIENTS WITH MANTLE CELL LYMPHOMA AT HIGHER RISK OF PROGRESSION

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Mantle cell lymphoma (MCL) is an incurable B-cell malignancy characterized by high clinical variability, with some patients presenting with indolent disease while others experiencing aggressive clinical course. There is a critical need to define parameters that identify patients at higher risk of progression and therapy resistance for guiding clinical decisions. B-cell receptor (BCR) signaling is crucial for MCL initiation and progression and is a target for therapy. We measured the phosphorylation status of nine BCR signaling phosphoproteins (SYK, LCK, BTK, PLCγ2, p38, ERK1/2, AKT, NF-κB p65, STAT5) using phospho-specific flow cytometry in peripheral blood mononuclear cells (PBMCs) from 30 MCL patients, in the basal condition and following BCR modulation with anti-IgM antibodies. Flow-cytometry data were subjected to unsupervised hierarchical cluster analysis (HCA) within the MCL samples. Progression free survival (PFS) and overall survival (OS) curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Univariate and bivariate models for PFS and OS were generated using Cox proportional hazards regression. BCR modulation with anti-IgM induced activation of BCR signaling that was heterogenous among patients' samples. Unsupervised HCA of BCR responsiveness to anti-IgM modulation within the MCL samples identified two main clusters showing differential responses to BCR stimulation. The cluster comprising samples with higher BCR signaling response (HR) was associated with shorter survival than cluster with lower BCR signaling response (LR) (median PFS: 15 *versus* 40 months, respectively, log-rank test *P*=0.042; median OS: 27 *versus* 52 months, respectively, log-rank test *P*=0.041; Figure 1).

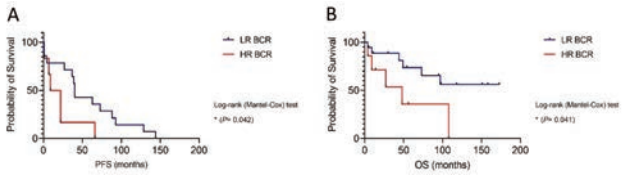

Figure 1. Association of the BCR signaling-based clusters with clinical behavior. Kaplan-Meier curves of PFS (A) and OS (B) expressed in months for the two clusters defined by BCR signaling responsiveness to anti-IgM, i.e. high responder (HR) BCR and low responder (LR) BCR MCL. P values are from the log-rank test.

In conclusion, we identified BCR signaling properties that were associated with poor clinical outcome and resistance to ibrutinib, thus

highlighting the prognostic and predictive significance of BCR activity in MCL and advancing our understanding of signaling heterogeneity underlying clinical behavior of MCL.

We thank Fondazione Italiana Linfomi (PGR Ed. 2019) for funding support.

C092

TUMOR TRANSCRIPTOMIC PROFILING AND MICROENVIRONMENTAL ECOSYSTEMS REFINES THE PROGNOSTIC CLASSIFICATION OF DIFFUSE LARGE B CELL LYMPHOMA

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Diffuse Large B-cell Lymphoma (DLBCL) is the most frequent aggressive lymphoma, and response rate to first-line therapy (R-CHOP) is ~60%. Recently, EcoTyper, a machine-learning algorithm based on transcriptome data, has been proposed for dissecting cellular heterogeneity. Here we aim to validate the clinical impact of EcoTyper on 204 FFPE DLBCL samples homogeneously treated with R-CHOP. Cell-of-origin (COO) classification identified 41% germinal center (GCB) and 59% activated B-cell (ABC) cases (Hans' algorithm), or 47% GCB, 35% ABC, and 18% unclassified cases (Lymph2Cx assay; R=0.719). RNASeq data on 186 DLBCL cases was used as input for EcoTyper. EcoTyper detected 5 malignant B-cell states (S1-S5) corresponding to 5 different transcriptional programs (Figure 1A). State-associated event free survival (EFS) curves showed distinct outcomes (S1 *vs* S5 p=0.0012; Figure 1B). When stratified for COO, S1 and S5 B cell states were mutually exclusive, displaying GCB or ABC signatures, respectively (p<0.0001). By combining B cell states and tumor microenvironment (TME) cells, EcoTyper generated 9 different Lymphoma Ecotypes (LEs) subgroups (Figure 1C). EFS analysis displayed significant differences between LEs (p=0.0028) with LE9 showing the best outcome (Figure 1D). Accordingly, ABC cases were associated with LE1 and LE2, due to high B cell infiltration, whereas GCB cases were linked to LE7, LE8 and LE9 with the strongest TME activity (p<0.0001). As expected, ABC and R-IPI poor groups had the worst clinical outcome. The B cell states or the LE subgroups split into three (S1, S2-S3-S4, S5) or four (LE1-2-3, LE4-5-6, LE7-8, LE9) categories, remained independent EFS predictors (p<0.05) of poor outcome along with R-IPI and COO in two multivariate models (n=138). Interestingly, in R-IPI poor patients only, the S1 B cell state identified patients with an outcome comparable to R-IPI very good/good cases, while the S5 B cell state identified cases with the worst outcome (Fig. EF). Mutational analysis, on RNASeq data, identified on average 4 (0-21) missense variants/patient. According to LymphGen tool, MCD subtype, significant enriched in ABC patients (33%), had the worst outcome, and GCB cases were significantly over-represented in the EZB subtype (21%).

Here we confirm that trascriptome approaches coupled with new deconvolution methods could contribute to refine the prognostic risk of DLBCL patients on R-CHOP, by identifying cases potentially eligible for new therapy approaches.

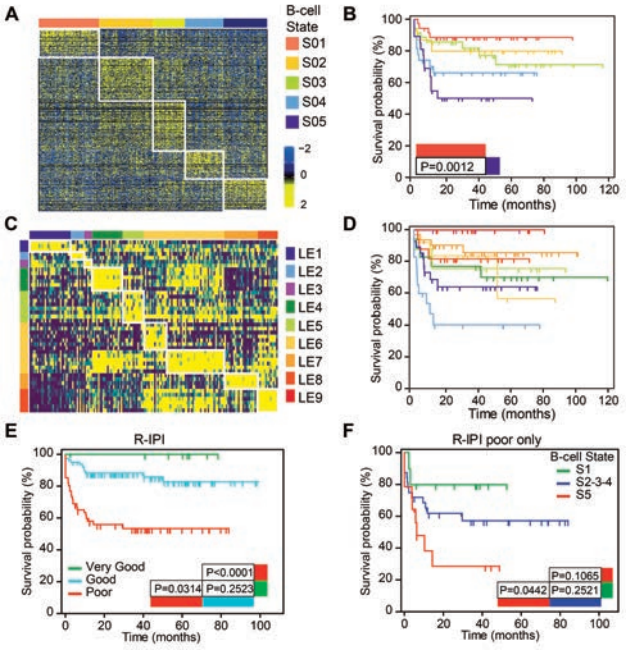

Figure 1.

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Myeloproliferative neoplasms II

C096

AVAPRITINIB IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS (ADVSM): EFFICACY AND SAFETY ANALYSES FROM THE PHASE 2 PATHFINDER STUDY WITH 2-YEAR FOLLOW-UP

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Background. AdvSM is a clonal mast cell (MC) disease driven by the *KIT* D816V mutation. Avapritinib is a potent, selective KIT D816V inhibitor approved for adults with AdvSM in the USA and in Europe after ≥1 prior therapy based on data from EXPLORER and PATHFINDER. We present efficacy and safety data from PATHFINDER with 2 years of follow-up.

Methods. Primary endpoint was overall response rate (ORR) per modified International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis (mIWG) response criteria. Secondary endpoints were time to response (TTR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), mean change from baseline objective disease burden measures (bone marrow [BM] MC burden, serum tryptase level, blood *KIT* D816V variant allele fraction [VAF], spleen volume), safety.

Results. As of September 9, 2022, 107 patients with centrally confirmed AdvSM had initiated avapritinib 200 mg (n=105) or 100 mg (n=2) QD; 64% had received ≥1 prior systemic therapy. In 83 mIWG response-evaluable patients, ORR (95% CI) was 73% (63–83), with 27% achieving complete remission (CR) or CR with partial hematologic recovery. Median TTR (range) was 2.3 months (0.3–15). Median DOR, PFS, and OS were not reached. Benefit was observed regardless of prior therapy or subtype (Table 1). Reductions of ≥50% in BM MC burden (88%), serum tryptase (92%), *KIT* D816V VAF (81%), and ≥35% reduction in spleen volume (70%) were observed. 70% of patients had total clearance of MC aggregates, 61% had serum tryptase <20 ng/mL, 58% had *KIT* D816V VAF <1%, and 74% with palpable spleens became non-palpable. The most frequent (≥25%) treatment-related adverse events (TRAEs; any Grade, Grade ≥3) were thrombocytopenia (39%, 18%), periorbital edema (39%, 6%), peripheral edema (38%, 2%), and anemia (29%, 13%). Treatment-related cognitive effects occurred in 24% of patients, mostly Grade 1–2 (n=22/26) and managed with dose modification. Intracranial bleeds (ICBs) occurred in 3.7% of patients; all discontinued treatment and events resolved. Incidence of ICBs, and general safety, was consistent with previous reports. Dose reductions, interruptions, and discontinuations due to TRAEs occurred in 75%, 64%, and 10% of patients. There were no treatment-related deaths.

Summary/Conclusions. In patients with AdvSM, avapritinib provides robust efficacy with a favorable benefit-risk profile, regardless of prior therapy or disease subtype.

Table 1.

Summary of efficacy patients with AdvSM

	Response-evaluable					
		AdvSM subtype			Treatment-naïve	Previous therapy
Outcome, % (n)	All[a] (n=83)	ASM (n=13)	SM-AHN (n=55)	MCL (n=15)	All[b] (n=30)	All[c] (n=53)
ORR[d]	73 (n=61)	77 (n=10)	75 (n=41)	67 (n=10)	90 (n=27)	64 (n=34)
95% CI	63–83	46–95	61–85	38–88	74–98	50–77
CR	13 (n=11)	0	15 (n=8)	20 (n=3)	20 (n=6)	9 (n=5)
CRh	13 (n=11)	15 (n=2)	16 (n=9)	0	20 (n=6)	9 (n=5)
PR	42 (n=35)	62 (n=8)	36 (n=20)	47 (n=7)	50 (n=15)	38 (n=20)
CI	5 (n=4)	0	7 (n=4)	0	0	8 (n=4)
SD	17 (n=14)	23 (n=3)	15 (n=8)	20 (n=3)	10 (n=3)	21 (n=11)
PD	2 (n=2)	0	2 (n=1)	7 (n=1)	0	4 (n=2)
NE	7 (n=6)	0	9 (n=5)	7 (n=1)	0	11 (n=6)
Median DOR (95% CI)	NR (37–NR)	NR (27–NR)	NR (37–NR)	NR (NR–NR)	NR (37–NR)	NR (NR–NR)
24-month DOR, % (95% CI)	89 (81–97)	89 (68–100)	87 (76–98)	100 (100–100)	92 (81–100)	87 (75–99)
Median PFS (95% CI)	NR (39–NR)	NR (30–NR)	NR (39–NR)	NR (12–NR)	39 (39–NR)	NR (30–NR)
24-month PFS, % (95% CI)	76 (66–85)	100 (100–100)	71 (59–84)	72 (49–95)	89 (78–100)	68 (55–81)
Median OS (95% CI)	NR (NR–NR)	NR (30–NR)	NR (NR–NR)	NR (14–NR)	NR (NR–NR)	NR (NR–NR)
24-month OS, % (95% CI)	79 (70–87)	100 (100–100)	74 (64–85)	72 (49–95)	89 (78–99)	73 (62–84)

[a]Median OS was reported for all enrolled patients (n=107). [b]Median OS was reported for all treatment-naïve patients (n=38). [c]Median OS was reported for all previous therapy patients (n=69). [d]CR + CRh + PR + CI.

95% CI, 95% confidence interval; AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; DOR, duration of response; MCL, mast cell leukemia; NE, not evaluable; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial remission; SD, stable disease; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm.

C097

IMPACT OF HIGHER CALR MUTATION VARIANT ALLELE FREQUENCY IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA

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Background. Calreticulin (CALR) mutations account for 30% of essential thrombocythemia (ET). Few pts have CALR variant allele frequency (VAF) >50%. Recently, we reported that CALR mut MF pts with a higher CALR VAF (CALR-h) have a more anemic phenotype; conversely, little information is available regarding impact of CALR-h in ET.

Aims. The aim of the study was to characterize the hematological and clinical correlates of CALR-h in a large population of pts with ET.

Patients and Methods. Patients with a WHO2022 diagnosis (dx) of CALRmut ET were included. CALRmut was assayed by PCR and capillary gel electrophoresis from granulocytes. Panel mutation analysis of 40 myeloid neoplasm-associated genes was performed by NGS. Nonparametric Wilcoxon rank-sum test, Kaplan-Meier estimate of survival and log-rank test were used as appropriate.

Results. A total of 179 pts were considered. Overall, T1/T1-like (T1) mutation was found in 100 pts (55.8%), T2/T2-like (T2) in 60 (33.5%) and 19 were atypical variants(10.6%). The median CALR VAF was 43.3+15.7%. For the purposes of the analysis, we considered as CALR-h pts having a VAF of >50% versus Lower VAF (CARL-l; <50%). CALR-h was found in 56 pts (31.3%). The frequency of T1 and atypical were increased in CALR-h compared to T2, 39%, 36.8% and 16.7% of the pts, respectively (p=0.001). 24/62 (39.3%) evaluable pts harbored >1 mutation in an NGS-panel (62 pts were analyzed); however no difference was outlined between CALR-h and CALR-l. According to IPSET-rev, CALR-l pts were enriched in the Very Low Risk category. There was no significant difference between CALR-h and CALR-l pts as regarded gender, age, blood counts, karyotype abnormalities, constitutional symptoms, splenomegaly and thrombosis rate, at dx or during follow-up (FU). On the other hand, CALR-h pts harbored more frequently grade 1 BM fibrosis at dx (50% *vs* 13.3%; P=0.03), abnormal LDH level (72% *vs* 50.6%; P=0.049) and reported bleeding episodes during the FU (15.7% *vs* 6.0%;P=0.047). More CALR-h pts developed post-ET myelofibrosis during the FU (32.1% *vs* 16.3%; P=0.015), unlike for thrombosis-free, leukemia-free or overall survival.

Discussion. We found that about 1/3 of CALR mut ET pts harbor a higher VAF, that is associated with a greater risk of developing myelofibrosis and bleeding during the FU, and having G1 reticulin at dx; however, overall-, leukemia- and thrombosis-free survival were not impacted even after stratification based on CALR subtype.

C098

CHARACTERIZATION OF PV AND ET PATIENTS WITH JAK2V617F MOLECULAR RESPONSE UNDER LONG-TERM RUXOLITINIB

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Introduction. In patients (pts) with polycythemia vera (PV) and essential thrombocythemia (ET), an elevated JAK2V617F variant allele fraction (VAF) is associated with more severe disease. Exploratory analysis in pts long-term treated with RUX suggested that ruxolitinib (RUX) provided progressive JAK2VAF reductions in 50% of pts and in those with (C) or deep (D) molecular response (MR), lower risk of progression to secondary MF (sMF) was ascertained [Guglielmelli P ASH 2022]

Aims. Aim of the study was to identify potential surrogate markers associated with CMR/DMR after long-term RUX.

Patients and Methods. Paired samples at different time points (baseline and MR assessment: CMR+DMR, PMR and NR) were investigated by: (i) Mutation analysis of 40 myeloid genes (n=69); (ii) Plasma cytokine assay (n=19, Human XL Cytokine Panel) and RNAseq of GN (n=11).

Results. Of 77 PV and ET pts receiving RUX for a median of 8.8 years, 18% achieved sustained CMR (6.5%) or DMR (11.7%), and 44.2% a PMR. At least one myeloid gene mutation was found in 40% of PV and 33.3% with ET. Two or more mutations were found in 11% of PV and none with ET. At baseline, mutational status was comparable in the three cohorts ranked by molecular response; however, only 3/13 of pts who achieved a JAK2 CMR/DMR displayed an additional myeloid mutation. During the follow-up, the number of mutant clones newly acquired, that increased in VAF or became undetectable, was similar in the cohorts. The % of pts showing any degree of VAF reduction during treatment was 5.6% among those with no-molecular response compared to 50% and 33.3% of PMR and DMR pts. Compared to baseline, there was a general down-regulation of inflammatory cytokines under RUX, but no significant difference was noticed among pts achieving CMR/DMR and PMR/NR, except for IL-9, trend increase (3.3vs1.3 pg/mL, p=0.016) and Leptin, trend decrease (0.7vs1.6 pg/mL,p=0.05) . Principal components analysis of RNAseq dataset revealed that sample at CMR/DMR exhibited significant differences in gene expression profile (DEG) when compared with baseline, while no difference was observed in PMR/NR. Functional analysis of the 20 most DEG in CMR/DMR revealed that DNA replication, cell-cycle transition were the major enriched biological processes.

Discussion. We identified biomarkers of molecular response after JAKi treatment in PV/ET that might shed light on biological mechanisms of response.

C099

CD34+ HEMATOPOIETIC STEM AND PRECURSORS CELLS (HSPC) AND CIRCULATING ENDOTHELIAL CELLS (CEC) SHARED SOMATIC MUTATIONS IN PATIENTS WITH PRIMARY MYELOFIBROSIS BEFORE AND AFTER ALLOGENEIC STEM CELL TRANSPLANTATION (ALLO-SCT)

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Background. Primary myelofibrosis (PMF) is characterized by a high rate of vascular complications (VC). Some studies highlighted the possible role of JAK2+ endothelial cells (EC) in VC development. We explored the role of endothelium in PMF with the MyCEC study aimed at comparing the mutational profiles of Circulating Endothelial Cells (CEC) and paired CD34+ Hematopoietic stem and progenitors cells (HSPC).

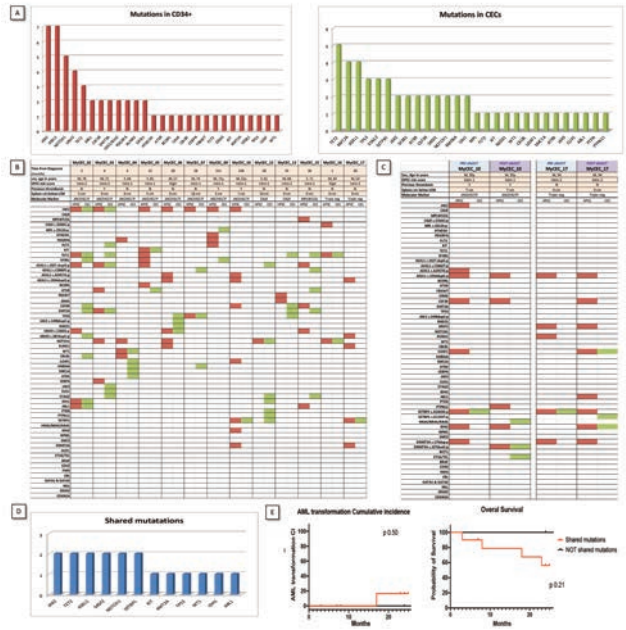

Figure 1. (A) molecular alteration on CD34+HSPC (on the left) and CEC (on the right) from PMF pts; (B) molecular profile of both CEC (green) and HSPC (red) in PMF pts; (C) molecular profile of both CEC (green) and HSPC (red) before and after alloSCT in PMF pts; (D) Mutated genes shared between HSPC and CEC; (E) Impact of harboring shared mutations between CEC and HSPC on clinical outcome of PMF pts.

Methods. 17 PMF patients (pts) untreated with JAK2 inhibitors, along with 5 healthy controls (HC), were enrolled in the study. HSPC were selected using CD34+ immunomagnetic separation. CEC were detected by FDA-approved CellSearch system, combining immunomagnetic selection and fluorophore-labelled antibodies. CEC were identified as CD146+, CD105+, DAPI+ and CD45- cells. Putative CECs were sorted by DEPArray system as previously described. For those pts who underwent allogenic stem cell transplantation (alloSCT), two extra time points were collected: before and after alloSCT. Sequencing data were assessed with the MiSeq Illumina NGS platform using a 54-PMF related genes custom panel.

Results. CEC were successful detected in all samples. PMF pts had a higher number of CEC compared with HC (p: 0.0005). CEC were collected in 13 of 17 pts, in all HC, and after alloSCT in 2 of 3 pts who underwent transplant. HSPC were successfully isolated in all samples. No mutations were found in HSPC and CEC from HC. Conversely, several mutations were found in PMF pts (Figure 1). In HSPC, 27 of the 54 genes analyzed were mutated. Surprisingly, all CEC from PMF pts hold at least 1 mutation (median: 4). 28 genes were mutated on CEC and the JAK2 mutation was found in 2 of the 8 JAK2+ pts. When comparing mutational profiles of HSPC and CEC, 10 of 13 pts shared at least one mutation (up to 4) between the two subpopulations. 2 JAK2+ pts shared the driver mutation, while 8 pts shared only non-driver mutations. Even after alloSCT, pts had both shared and unshared mutations on HSPC and CEC, mostly different from those detected before transplant. No clinical differences were found between pts who shared mutations in HSPC and CEC and those who did not.

Conclusions. The detection of somatic mutations on HSPC and CEC only from PMF pts highlights the role of endothelium in disease development. The high frequency of shared mutations between the two cell populations, even after alloSCT, supports the hypothesis of a common precursors between HSPC and EC, which might act as the cell of origin of PMF.

C100

PREDICTORS OF HEMATOLOGIC RECOVERY IN PATIENTS WITH MYELOFIBROSIS UNDERGOING AN ALLOGENEIC HEMOPOIETIC STEM CELL TRANSPLANT

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Hematologic recovery is slow following allogeneic hemopoietic stem cell transplantation (HSCT) in patients with myelofibrosis (MF). We studied 209 MF patients for risk factors affecting hematologic recovery. Patients were transplanted between year 2000 and 2021 in two transplant Centers (Genova and Rome). Variables studied were: donor and patients gender and age, donor type (HLA matched, mismatched), spleen size, transfusion burden pre-transplant, conditioning regimen. A platelets count>50x10^9/L was achieved in 91%, 66%, 64%, 50% of transplants from respectively HLA=SIBS (SIBS), matched unrelated donors (MUD) mismatched UD (mmUD) and haploidentical family members (HAPLO) (p=0.00001). It was achieved in 76% *vs* 60% of patients with a low or a high transfusion burden (p=0.03), and in 71%, 63%, 53% of patients aged <50, 51-60 or over 60 years (p=0.1). Spleen size influenced neutrophil engraftment (7%,26%,32% in patients with a spleen <15, 15-22 and > 22 cm) (p=0.1) but not platelet counts on day +50. There was a trend for DIPSS to predict platelet recovery (81%, 71%, 61%, with platelets 50x10^9/l on day +50; respectively for In1, int2, high risk) but not statistically significant (p=0.1). There was no effect of complete donor chimerism (achieved in 70% of patients on day +30), on platelet recovery. There was a trend for patients with acute GvHD III-IV to have a lower rate of platelet engraftment (41% *vs* 63%, p=0.1). A platelet count of 50x10^9 on day +50 predicted TRM (9% *vs* 60%; p<0.00001), and 5 year survival (63% *vs* 25%;

p<0.00001). Relapse was higher in patients with a platelet count of $50x10^9$ on day +50 (31% and 12% ; p=0.001). In conclusions an HLA identical sibling donor is the strongest predictor of hematologic recovery in patients with MF, followed by transfusion burden. Platelet recovery on day +50 predicts TRM and survival. Relapse is higher in patients with rapid hematologic recovery, and may call for early reduction of immunosuppressive therapy.

DISCUSSED POSTERS

Lymphomas

DP001

FLOW CYTOMETRIC QUANTIFICATION OF PD-L1 EXPRESSION ON HODGKIN REED-STERNBERG CELLS AND ITS CORRELATION WITH HISTOLOGICAL MACROPHAGE INFILTRATE

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Flow-cytometric (FC) identification of Reed-Sternberg cells (HRS) in cell suspensions generated from lymph node biospies of patients (pts) with Hodgkin Lymphoma (HL) is challenging due to the rarity of the events. Fromm JR described a 6-colour assay to identify cells with HRS features, defined as cells with increased FSC and SSC characteristics expressing CD30, CD40 and CD95, while CD20 and CD45 are usually negative or low. The aim of our study was to quantify the expression of target-therapy antigens CD30 and PD-L1 with FC and correlate them to biological e clinical parameters at diagnosis. Our 8-colour panel consisted of CD20V450/CD45V500/CD64FITC/CD30PE/CD40PECy5.5/PDL1PECy7/CD95APC/CD3 APCH7. We analysed 20 biopsies from pts with a histological diagnosis of HL from June 2020 to January 2023 (median age 32, range 18-75, F/M 9/11). Cell suspensions were obtained by mechanical disaggregation using Medimachine. Data were acquired and analyzed by DXFLEX Cytometer (Beckman Coulter). According to the definition of FC limit of quantification (LOQ) we considered a cluster of at least 50 events with phenotypic features of HRS as diagnostic. Median number of total acquired events was 549200 (43110-2056814). Median percentage of HRS cluster was 0.27% (0.02-4.26) of total events with a median absolute number of 809 HRS events (135-6418). Expression of CD40 and CD95 was always bright, separating HRS cells from the rest of leukocyte populations in the wide dynamic range of DXFlex instrument. PD-L1 was strongly expressed on HRS cells in all samples. Median fluorescence intensity (MFI) expression of PD-L1 was higher in pts with a proportion of macrophages in immunohistochemistry > 5% compared to biopsies with <5% macrophages (median MFI $44x10^4$, range 3-37 *vs* $4.8x10^4$, range 0.6-22, respectively, p=0.0057). There was a trend for a higher CD30-MFI expression in pts with macrophages >5% (p 0.06). PD-L1-MFI and CD30-MFI expression on HRS cells were correlated (Spearman R 0.67, p=0.001). We conclude that HRS cells can be rapidly detected by FC in lymph node suspensions and PD-L1 assessment may add to the accuracy of HRS detection compared to 6-colour panel. Moreover, this assay allows the quantitative assessment of therapeutic target antigens, such as CD30 and PD-L1.

DP002

ABSTRACT NOT PUBLISHABLE

DP003

REAL LIFE USE OF BRIDGING THERAPY BEFORE COMMERCIAL CAR T-CELLS: AN ITALIAN SURVEY ON BEHALF OF GIMEMA IMMUNOTHERAPY WORKING PARTY

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Bridging therapy (BT) plays an important role in the interval between apheresis and infusion for patients (pts) candidate to Chimeric antigen receptor (CAR) T-cell, with the aim to reduce or stabilize the tumour burden without exceeding toxicity. There is not a standard BT, but current practice is guided by physician experience and preference. We designed a national survey with the aim to evaluate the BT strategies used in routine clinical practice and their efficacy. A

questionnaire was sent to CART-SIE study centres in March 2022 and analysed by the GIMEMA Data Center in the framework of the Immunotherapy Working Party activities.

Twenty-two centres completed the survey, and 18 were included in data analysis as effective treating centres. This report is focused on Diffuse, High Grade and Primary Mediastinal B-Cell Lymphomas according to commercial CART indications in Italy at the time of the survey. Out of a total of 328 pts considered in the study, 264 pts (80%) received BT, and 108 pts (41%) were treated in the Referral Center; 137 pts (52%) attained a partial or complete response. 151 (57%) pts received systemic chemotherapy (ST), 60 (23%) pts radiotherapy (RT), and 32 (12%) pts a combined modality (chemo+RT, CMT). The other 21 (8%) patients received other treatments (chemo-free), Figure 1. Reasons for not using BT were preferably the presence of a low tumor burden (38.9% of centres), a low tumor burden but not suitable for RT, a stable or slowly progressing disease (16.7%), a late relapse and a reasonable turn around time for CART manufacturing (11.1%). Physicians often chose RT alone because of: low tumor burden, or in cases of few nodal sites easy to reach in a single RT field (72%), for the presence of bulky disease (22%) and for "low risk" progressive disease (e.g. relapsed DLBCL and not refractory double hit lymphoma), (17%). Focusing on Lenalidomide as single agent, 44% of centres did not choose it, 22% chose it in case of nonGCB histotype, for low kinetics or for low tumor burden disease; 11% preferred it in case of chemo-resistant disease. The list of ST combination was extremely wide.

In conclusion, BT is frequently used by clinicians (80% of patients), with 52% of overall response rate in this high risk group of patients. ST is the preferred choice although there is not a preferred regimen, local disease is often treated with RT, while the CMT or chemo-free agents are less frequently used (12% and 8%).

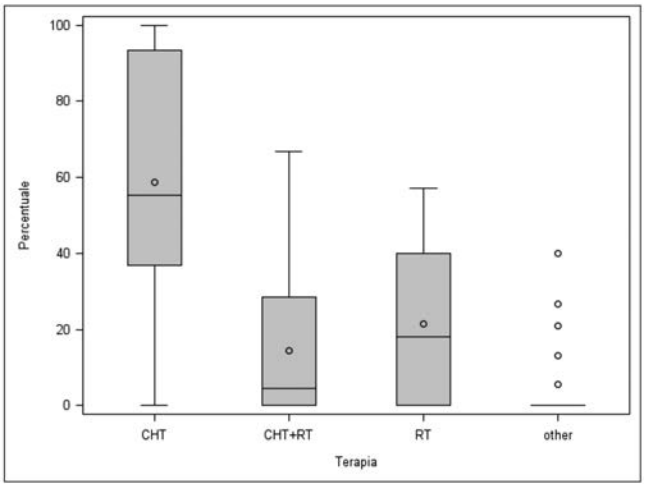

Figure 1. Distribution for centres of the BT approach.

DP004

MOLECULAR CLUSTERING ON CTDNA IMPROVES DLBCL OUTCOME PREDICTION

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Diffuse large B-cell lymphoma (DLBCL) can be classified into molecular clusters that reflect the disease genetic and clinical heterogeneity. These subtypes have been identified on tissue biopsy that might not accurately capture the anatomical variability of DLBCL. The analysis of circulating tumor DNA (ctDNA) in DLBCL is an accurate and non-invasive approach to retrieve molecular information not otherwise detectable in tissue biopsies. Moreover, the quantification of baseline ctDNA stratifies DLBCL outcomes, but its integration with molecular clustering has not been evaluated yet aims to evaluate the role of ctDNA in detecting DLBCL molecular clusters and to assess whether molecular clustering combined with ctDNA levels may improve outcome prediction. A training cohort of 77 newly diagnosed DLBCL patients treated with R-CHOP (provided with tumor gDNA from formalin-fixed paraffin embedded (FFPE) lymph node (LN) biopsies, ctDNA from plasma and germline gDNA from granulocytes), were enrolled in the study. The LyV4.0 CAPP-seq assay consisting of a panel of 59 genes relevant to DLBCL and the LymphGen clustering tool were used. Clustering analysis allowed to classify 40.3% of patients on ctDNA and 46.5% on LN. Patients assigned to ST2/BN2 clusters displayed a favourable outcome, in both ctDNA (p=0.032) and in LN (p=0.007), compared to others. Patients with ctDNA load <2.5log10hGE and/or identified as ST2/BN2 presented superior outcome compared to patients with ctDNA load >2.5log10hGE and not assigned to clusters ST2/BN2 (40-months PFS and OS: 80.4% and 93% *vs* 33.2% and 54.8%); both p<0.001) (Figure 1A). To validate these findings, we analyzed a validation cohort of 89 newly diagnosed DLBCL provided with ctDNA. Consistently, also in the validation cohort, patients with <2.5log10hGE and/or assigned to cluster ST2/BN2 had an excellent outcome compared to others (40-months PFS and OS: 73.2% and 79.7% *vs* 39.2% and 44.8%; both p=0.001) (Figure 1B). By combining the data of the two cohorts (N=166 cases), both low ctDNA (HR 0.27, 95% CI 0.14-0.52, p <0.001) and ST2/BN2 clusters (HR 0.11, 95% CI 0.02-0.83, p=0.033) (Fig.1C) maintained an independent association with an improved PFS in multivariate analysis. Moreover, compared to ctDNA levels only, the addition of BN2/ST2 clusters improved the C-statistics of the model (0.64 *vs* 0.60 for PFS and 0.68 *vs* 0.63 for OS)(Fig.1D). In conclusion, the combination of ctDNA levels and ST2/BN2 clusters improves DLBCL outcome prediction.

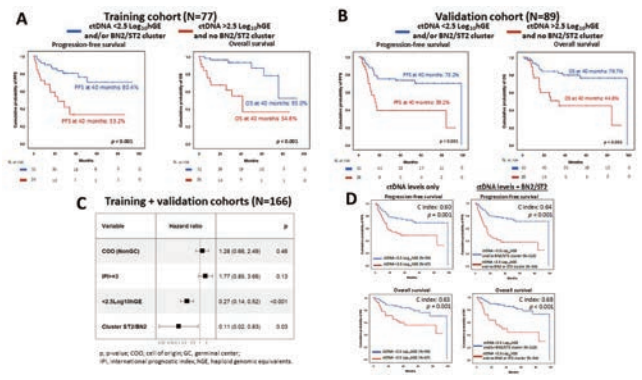

Figure 1.

DP005

IMPACT OF COVID-19 PANDEMIC WAVES ON OUTCOMES OF PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA ENROLLED IN THE URBAN RETROSPECTIVE AND PROSPECTIVE STUDY IN ITALY

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Introduction. URBAN is an observational, retrospective/prospective multicenter study evaluating effectiveness and safety of obinutuzumab-based treatment in the standard care of patients (pts) with previously untreated Follicular Lymphoma (FL). The objective of this analysis was to evaluate the effects of COVID-19 pandemic in terms of infection rates and severity, outcomes, and effectiveness of vaccination strategies in the study population.

Methods. Data on COVID-19 vaccination, infections and outcomes were collected. The following periods were considered: 25Feb20–01Mar21 (from the pandemic outbreak up to vaccination campaign start), 01Mar21–01Nov21 (predominant delta variant), and 01Nov21–31Jan22 (predominant omicron variant). Comparisons of categorical variables were obtained by Chi-square or Fisher exact test.

Results. Information on vaccination status was available for 270 of the 283 enrolled pts; 245 (90.7%) of them had received at least one dose of vaccine (13.5%, 1 dose; 31.4%, 2 doses; 55.1%, 3 doses). Most of doses (503/568, 88.6%) were given during obinutuzumab maintenance, since 207 pts had already initiated this phase in March 2021. Median observation time for pts in the "unvaccinated" status (before vaccination or not vaccinated at all [pre/no-vax]) was 13.3 (8.7-23.2) months, while for pts in the "vaccinated" status (post-vax) was 7.9 (0-10.5) months. Overall, 48 COVID-19 infections were detected in 45 pts, without any statistically significant correlation with clinical variables. Of the 48 infections, 23 occurred in 22/25 (88%) unvaccinated pts and 18 in 17/245 (6.9%) vaccinated pts. There were 10 deaths, including 9 unvaccinated (39.1%) and 1 vaccinated pts (5.9%, p<0.001). Hospitalization was required for 22 infections (45.8%), 14 (60.9%) in pre/no-vax pts, and 5 (27.8%) in post-vax ones (p=0.073). Interestingly, no differences in COVID-19 infection rates have been observed between pts who were receiving maintenance or not (p=1.000). The table summarizes COVID-19 infections and their outcomes.

Conclusions. The URBAN study offered the unique opportunity to follow the impact of SARS-CoV2 variants and vaccination on a population of pts with advanced FL homogeneously treated with frontline obinutuzumab-based induction and maintenance therapy. From our results, the circulation of less aggressive variants and the increased vaccination coverage showed that obinutuzumab-based treatments is safe and feasible.

Table 1. SARS-CoV2 infections and outcomes in newly diagnosed FL patients who received obinutuzumab-based immunochemotherapy and maintenance within the URBAN study.

	Pre/no-vax	Post-vax	p-value
Rate of infections	0.043 infections/month	0.082 infections/month	0.058
Hospitalizations, n (%)	14/23 (60.9%)	5/18 (27.8%)	0.073
Deaths, n (%)	9/23 (39.1%)	1/18 (5.6%)	0.025
	25-Feb-2020 – 01-Mar-2021 (Pre-vaccination period)	After 01-Mar-2021 (Post-vaccination period)	p-value
Rate of infections	0.045 infections/month	0.065 infections/month	0.236
Hospitalizations, n (%)	13/21 (61.9%)	7/25 (28.0%)	0.044
Deaths, n (%)	8/21 (38.1%)	2 /25 (8.0%)	0.028
	Pre 01-Nov-2021 (Presumptive alfa and delta variants)	01-Nov-2021 – 31-Jan-2022 (Presumptive omicron variants)	p-value
Rate of infections	0.036 infections/month	0.187 infections/month	<0.001
Hospitalizations, n (%)	16/27 (59.3%)	4/19 (21.1%)	0.023
Deaths, n (%)	10/27 (37.0%)	0/19 (0.0%)	0.003

Pandemic periods	25/02/2020-01/03/2021 1st phase (First outbreak to start of the vaccination campaign)	01/03/2021-01/11/2021 2nd phase) (Predominant delta variants)	01/11/2021-31/01/2022 3rd phase (Predominant omicron variants)	p-value (1st vs. 2nd)	p-value (1st vs. 3rd)	p-value (2nd vs. 3rd)
Rate of infections	0.045 infections/month	0.021 infections/ month	0.187 infections/month	0.115	<0.001	<0.001
Hospitalizations, n (%)	13/21 (61.9%)	3/6 (50.0%)	4/19 (21.1%)	0.662	0.022	0.299
Deaths, n (%)	8/21 (38.1%)	2/6 (33.3%)	0/19 (0.0)%	1.000	0.004	0.050

DP006

ABSTRACT NOT PUBLISHABLE

DP007

OUTCOME OF HIGH DOSE CHEMOTHERAPY PLUS AUTOLOGOUS STEM CELL TRANSPLANTATION IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA: EXPERIENCE OF A SINGLE ITALIAN INSTITUTION

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Patients with follicular lymphoma(FL) can have long survival times, nevertheless most patients still have a relapse with disease-free intervals progressively shorter. In this chemo-free era it has become challenging to define the right place for high dose chemotherapy plus autologous stem cell transplantation (HDT-ASCT) within current clinical practice. The aim of this analysis was to collect long-term follow-up data on pts treated with HDT-ASCT in our Institution focusing on outcome and toxicity. Relapse/refractory (R/R) FL pts were selected from our Institutional dataset. The inclusion time frame was 18 years. Primary end point was overall survival (OS). Secondary end points included time to progression (TTP), progression-free survival (PFS) and second tumors. Based on Casulo *et al.* (JCO 2015) definition of disease progression within 24 months from first-line treatment (POD24), survival analysis was also conducted on different subgroups of pts divided according to the time of onset of early relapse (POD24) or late (noPOD24). Between 16th October 2003 and 4th May 2021, 87 pts underwent ASCT, of these 70 had complete data and were considered for the analysis. Pts characteristics are reported in Table 1.

Table 1.

	N =70
Median age at ASCT (years)	58 (33-75)
First-line treatment	
ANTHRACYCLINE	32 (46%)
BENDAMUSTINE/FLUDARABINE	28 (40%)
ALKYLATING AGENT	9 (13%)
OTHER	1 (1%)
Rituximab containing regimen in first-line	
Yes	53 (76%)
No	17 (24%)
Rituximab maintenance after first-line	
Yes	23 (33%)
No	47 (67%)
POD24	
Yes	37 (53%)
No	33 (47%)
N° treatments pre-ASCT	
1	56 (80%)
> 2	14 (20%)
Induction therapy	
VACOP-B+R-CV	48 (69%)
DHAP/ESHAP	15 (21%)
OTHER	7 (10%)
Remission status before ASCT	
RC	32 (48%)
RP	34 (52%)
ND	4
Conditioning Regimen	
BEAM	45 (64%)
FEAM	25 (36%)

With a median follow-up of 170,4 months (range, 50,4-366) from diagnosis, the 5years(yrs) and 10yrs OS were 80% and 69%; 5yrsPFS 55% and 10yrs PFS 39%. The 5yrs and 10yrs TTP were 62% and 51%; plateau was reached around 8 years after ASCT (Figure 1). In a cohort of 45 pts transplanted in 2nd-line who received 1st-line therapy within the first year of diagnosis, 5yrs OS was 73% in pts with POD24 versus 87% in pts noPOD24; 10yrs OS was 62% *vs* 79% (p 0.26). Transplant Related Mortality was 0%. Thirty pts (43%) had relapse or progression, 2 pts (3%) had histological transformation into diffuse large B-cell lymphoma. Nineteen pts (27%) developed 2nd tumors [10 (53%) hematological, 8 (42%) solid and 1 (5%) both].Twenty pts (29%) died [4 (20%) for lymphoma, 12 (60%) for 2nd tumors and 4 (20%) for infections]. In our experience ASCT is still an effective and safe treatment for R/R FL with the longest follow-up compared to the nontransplant strategies. We did not find significant differences between POD24 and no POD24 pts in terms of PFS and OS. The plateau of TTP curve suggests that ASCT is potentially curative for a non-negligible subset of pts, that may become larger by the incorporation of novel therapeutic agents able to reduce the occurrence of 2nd tumors.

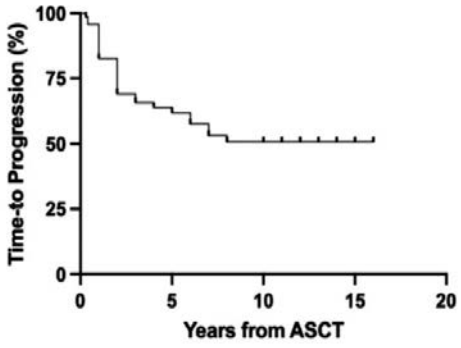

Figure 1.

DP008

GENE EXPRESSION PROFILES OF LK PRODUCTS SUGGEST A PROGNOSTIC ROLE OF MONOCYTES IN PATIENTS RECEIVING CAR-T FOR R/R LBCL

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Introduction. CD19-directed chimeric antigen receptor (CAR)-T cells induce durable remissions in about 40% of relapsed/refractory large B-cell lymphomas (R/R LBCL). Biological factors identifying patients achieving prolonged progression-free survival (PFS) are not fully delineated.

Aims. Aim was to evaluate the impact of transcriptomic and phenotypic features of pre-manufacturing leukapheresis products (LK), on the outcome of LBCL patients treated with tisagenlecleucel (Tisa-cel) and axicabtagene ciloleucel (Axi-cel).

Methods. The immune cell composition of LK prospectively collected from 77 patients receiving either Tisa-cel or Axi-cel was characterized at the mRNA and protein level. RNA of sorted CD3+ cells was analyzed using the nCounter 780-gene CAR-T Characterization Panel (NanoString). For flow cytometry, thawed LK were stained with CD3, CD14, CD16, CD19, CD20, CD56, HLA-DR, CD192, CX3CR1 and VISTA antibodies, to study monocyte subsets. T-cells

were analyzed with CD45, CD3, CD4, CD8, CD45RO, CD62L, CD197 and CD95 antibodies. Disease response was assessed according to Lugano criteria. Statistical analyses were performed by GraphPad Prism v9.00 and R v4.1.2.

Results. A 4-myeloid derived gene model identifies patients characterized by shorter PFS (Figure 1A-B). These patients also display higher levels of monocytes in the LK at cell count (median 22.7% *vs* 16.8%, p=0.0015)(Fig.1C), of intermediate monocytes (iMo, CD14+CD16+) (median 12.5% *vs* 8.5%, p=0.02) (Figure 1D) and of iMo expressing CD192 (median 52.1% *vs* 33.4%, p=0.0054) (Figure 1E). Multivariate analysis showed that the model was the only parameter to retain its significance and was negatively associated with PFS. To assess whether monocytes could contribute to the impairment of T-cell functions, the differentiation state of CD8+ and CD4+ cells in LK was evaluated in patients grouped according to the expression of the 4 genes, but no differences were found. Nonetheless, the expression of the 4 genes negatively affected the presence of central memory T cells in infusion products (median 8.37% *vs* 13.95%, p=0.0069), which we have shown are necessary for CAR-T expansion (Monfrini *et al.,* 2022).

Conclusions. Our study highlights that the expression of the 4-myeloid genes in LK, can serve as an independent prognostic factor for predicting shorter PFS after CAR-T. Additionally our data suggest that the presence of monocytes with peculiar immunophenotypes may have an important role in affecting CAR-T efficacy in LBCL.

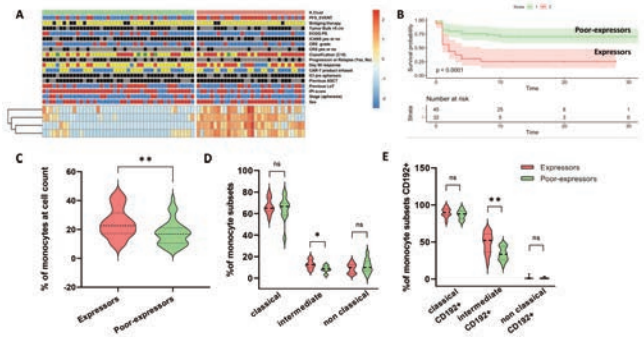

Figure 1. A) Heatmap clustering of patients based on the expression of the 4 genes. Ward and Canberra were used as linkage and distance metrics, respectively. Patients' features are shown alongside the code (ECOG: eastern cooperative oncology group performance status; ICANS: immune effector cellassociated neurotoxicity syndrome; CRS: cytokine release syndrome; classification C_{10}: classification of expanders (yellow) and poor expanders (red) patients according to the number of circulating CAR-T cells at day 10 post infusion (C10); ICI: immune checkpoint inhibitors; ASCT: autologous stem cell transplantation; LoT: lines of therapies prior to LK; IPI: international prognostic index). B) Kaplan Meier estimate of PFS in patients stratified according to the 4-gene model. C) Percentage of monocytes in the LK at cell count in patient expressing the 4-gene signature (Expressors) or not (Poor-expressors). D) Levels of monocyte subsets among lineage negative/HLA-DR positive cells, in the LK of Expressors and Poor-expressors. E) Frequencies of monocyte subsets expressing CD192 in the LK of Expressors and Poor-expressors.

DP009

CELL-FREE DNA IN PERIPHERAL T-CELL LYMPHOMAS: PRELIMINARY DATA FROM THE PHASE IB/II PTCL13 STUDY

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Background. The prospective Phase Ib/II PTCL13 trial tested the combination of Romidepsin with chemotherapy in patients (pts) with newly diagnosed Peripheral T-cell Lymphoma (PTCL), but it failed to improve survival. Here we present preliminary liquid biopsy data obtained from this study.

Methods. Cell-free DNA (cfDNA) was extracted from plasma collected before treatment (N=75). In an exploratory cohort of 25 pts, cfDNA was also obtained after the third and sixth cycle, after transplantation, and eventually at relapse. In this latter cohort, targeted sequencing by the CAncer Personalized Profiling by deep Sequencing of cfDNA was used to detect circulating tumor DNA (ctDNA). Germline DNA and genomic DNA from biopsies were used to filter out germline variants and to distinguish tumor associated mutations, respectively.

Results. Histologies of pts are shown in Figure 1C. The median baseline cfDNA concentration was 19.1 ng/mL plasma, with a strong correlation between elevated cfDNA and: increased Lactate dehydrogenase level, high International Prognostic Index score, and poor performance status (p <0.001). A moderate correlation was found in pts with an high Prognostic Index for T-cell lymphoma score and ≥2 extranodal localizations (p<0.01), while no correlation was found when analyzing stage and bone marrow involvement. A baseline cfDNA concentration >62ng/mL plasma identifies pts characterized by refractoriness at the end of 6 cycles of therapy (p<0.05) and reduced survival (Figure 1A,1B).

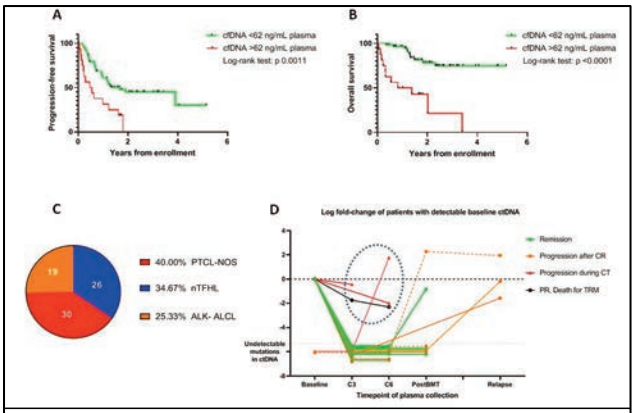

Figure 1. **A-B**: survival curves divided by baseline cfDNA concentrations above (red) or below (green) 62 ng/mL plasma, which include Progression-free survival (**A**) and Overall survival (**B**). **C**: Histology distribution among patients with available pre-treatment plasma samples for cfDNA extraction. **D**: Circulating tumor DNA concentration dynamics. Mutations identified during and after treatment are related to baseline concentration and the ratio is shown in logarithmic scale. Only pts with detectable mutation (either before or during treatment) are shown (n=21). Patients who achieved sustained complete remission (**CR**) are shown in green, those who progressed after initial CR are shown in orange, patients who progressed during therapy are shown in red, and a patient who achieved partial remission (PR) and died of an infectious complication after transplantation is shown in black. Patients with detectable mutations between the third and sixth cycle, who have worse survival, are circled in blue.

Figure 1.

Sequencing of the exploratory cohort identified mutations in 18 and 20/25 pts in ctDNA and biopsies, respectively. 30/56 mutations, identified in 16 pts, were shared, with a sensitivity of the liquid biopsy of 73.2% in identifying mutations present in lymphoma tissue. The most frequently mutated gene was TP53, mutated in 6 pts all affected by PTCL-NOS, resulting in worse survival. Sequencing of cfDNA collected during treatment showed that most pts (N=15) have a disappearance of mutations after the third cycle. In 3 pts, mutations

were still detectable after the third or sixth cycle, while one patient acquires one during therapy (Figure 1D); these 4 cases have significantly worse survival than those in which mutations were cleared.

Conclusions. Elevated cfDNA levels before treatment is associated with high-risk features and worse survival. Liquid biopsy is feasible in PTCLs and allow to detect residual disease during treatment, which is associated with disease progression.

DP010

ABSTRACT NOT PUBLISHABLE

DP011

RADIOTHERAPY CONSOLIDATION REDUCES RISK OF RELAPSE IN DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS WITH BULKY DISEASE IN COMPLETE RESPONSE AFTER FRONTLINE IMMUNOCHEMOTHERAPY: RESULTS FROM A RETROSPECTIVE SINGLE CENTER STUDY

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Introduction. The role of radiotherapy (RT) consolidation upfront in patients (pts) with diffuse large B-cell lymphoma (DLBCL) and bulky disease at diagnosis is controversial, especially in those in complete response (CR) after immunochemotherapy.

Methods. All pts with DLBCL diagnosed between January 2010 and June 2021 at AOU Città della Salute e della Scienza di Torino and treated frontline with RCHOP-like regimens were retrospectively selected. Pts with primary mediastinal lymphoma were excluded. Clinical and biological features as well as treatment and survival data for the whole population were collected. All pts with bulky disease (defined as ≥6 cm) at diagnosis who obtained CR (defined as PET/TC Deauville score ≤ 3) at the end of systemic treatment were further selected. Progression free survival (PFS) and overall survival (OS) were compared between pts receiving consolidative RT on initial bulky mass and those who did not.

Results. A total of 453 pts with DLBCL were identified. Median age was 68 years (IQR 58-77), 56% were males, 74% stage ≥3, 52% IPI ≥3. 140/451 (31%) had bulky disease at diagnosis. Median follow-up was 5 years (y). 5-y PFS and OS for the whole cohort were 59% and 66%, respectively. Bulky disease correlated with a significantly lower 5-y PFS (bulky 50% *vs* no bulky 64%, p=0.0005) and OS (bulky 68% *vs* no bulky 60%, p=0.01). 82 out of 140 pts with bulky disease (68/82 with a bulky ≥7 cm) were in CR after immunochemotherapy: 19/82 (23%) received RT (16/19 on bulky ≥7 cm), 63/82 (77%) did not (55/63 with a bulky ≥7 cm). There were no significant differences between the two groups regarding age, stage, ECOG PS, LDH levels, extranodal involvement and IPI. RT dose was 30 Gy in most pts (17/19), two pts received 36 Gy and 40 Gy. The 5-y PFS was 95% in the RT cohort and 58% in the no-RT cohort (p=0.004); the 5-y OS was 95% in the RT cohort and 69% in the no-RT cohort (p=0.038) (Figure 1). A propensity score matching analysis confirmed the benefit of RT on PFS (HR 0.1, 95%IC 0.01-0.68, p=0.019), and showed a non-statistically significant trend of better OS (p=0.06). 14/24 relapses in the no-RT cohort occurred on the site of bulky disease.

Conclusions. With the limit of a non-randomized retrospective study, our data showed a benefit of RT consolidation on bulky disease in pts with DLBCL in RC after frontline immunochemotherapy, significantly prolonging PFS and with a trend of improved OS in a propensity score matching analysis.

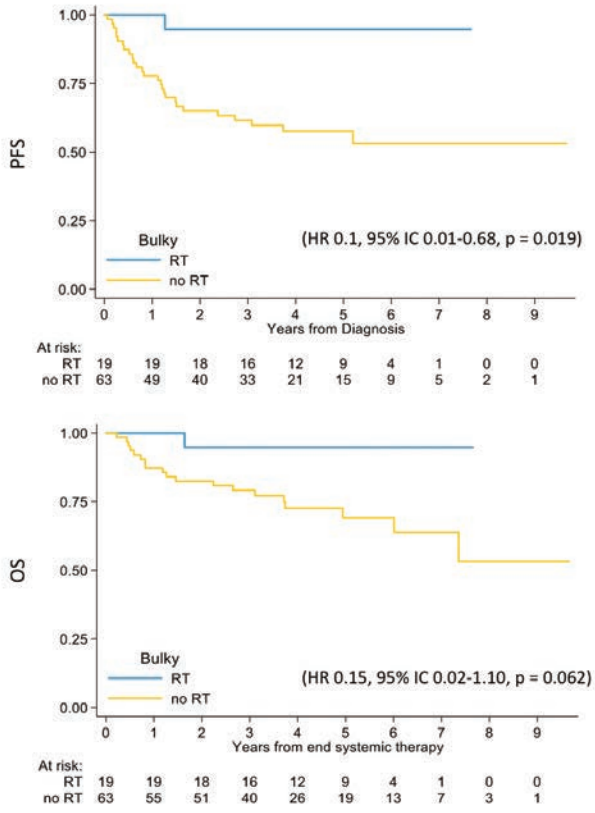

Figure 1.

DP012

A SINGLE CENTER RETROSPECTIVE STUDY ON VITREORETINAL LYMPHOMA

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Background. Vitreoretinal lymphoma (VRL) is a high-grade extranodal non-Hodgkin lymphoma, regarded as a variant of primary central nervous system lymphoma (PCNSL), involving the retina, the vitreous or both structures. It is considered primary VRL (PVRL) in case of no brain parenchyma infiltration. While in case of CNS involvement, high-dose systemic chemotherapy is recommended, there is no established treatment protocol for PVRL patients.

Methods. We describe clinical and diagnostic features, treatment and outcomes of VRLs diagnosed between 2013 and 2023, at Azienda USL-IRCSS of Reggio Emilia.

Results. We identified 30 VRL patients with a median age of 62.5 years (range 46- 79); 16 patients (53%) were female and 24 (80%) had PVRL. Among non PVRLs, 3 patients had positive MRI for CNS involvement, 1 had lymphomatous infiltration of cerebrospinal fluid (CSF) and 2 had systemic lymphoma. Diagnosis of VRL was supported by positive vitrectomy in all patients. All but one had a IL10/IL6 ratio greater than one and 16/17 had positive rearrangement of IGVH genes in vitreous humor. 13/21 tested positive for MYD88 L265P mutation in vitrectomy. MYD88 mutations were also found in CSF in 3/7 cases of whom 2 were considered PVRLs. Ocular Computed Tomography (OCT) was consistent for bilateral involvement in 24 cases. All patients received intravitreal therapy with Methotrexate (MTX); 29/30 also received systemic therapy. The most frequent regimen (25 cases) was R-MTX-Cytarabine (ARAC) which was combined with Thiotepa or temozolamide in 13 and 4 cases, respectively. Consolidation with ASCT was administered in 4 non PVRL patients. 4/30 cases were treated with less intensive regimens (R-MTX, R-temozolamide), due to advanced age or comorbidities. All patients treated with R-MTX-ARAC reached a CR at the end of induction therapy, 2 cases were lost to follow up and 3 patients are still on therapy. Only 1 out of 4 treated with less intensive therapy had a Complete Remission. After a median follow up of 21 months (2-121), 2 patients had an ocular relapse and 6 a CNS relapse; 7 died, all due to disease progression at CNS. Five-year-OS was 68%.

Conclusions. The high response rates reported in our retrospective study support the role of chemotherapy regimens containing R-MTX-ARAC as the most suitable upfront therapy for all VRL patients. CNS involvement remains the first cause of death in R/R VRLs. Collaborative studies on this rare lymphoma are warranted.

DP013

ABSTRACT NOT PUBLISHABLE

DP014

ABSTRACT NOT PUBLISHABLE

DP015

NON-INVASIVE MINIMAL RESIDUAL DISEASE ANALYSIS BY IMMUNOGLOBULIN GENE REARRANGEMENTS ON CIRCULATING TUMOR DNA PREDICTS THE OUTCOME OF PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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In diffuse large B-cell lymphoma (DLBCL) the response to therapy relies on PET/CT scan. The analysis of clonal immunoglobulin (IG) gene rearrangements using a next-generation sequencing (NGS) approach could be used to track minimal residual disease (MRD) on circulating tumor DNA (ctDNA) from plasma samples, a potential tool to identify patients at high risk of recurrence.

Aims. To identify IG heavy (IGH) and kappa light (IGK) chain gene rearrangements by NGS on formalin-fixed paraffin embedded (FFPE) lymph node (LN) biopsies and on ctDNA; to explore if tracking clonal IG by NGS on ctDNA can be a tool to monitor MRD; to correlate the MRD results with radiologic disease assessment during (at interim) and at the end of treatment (EOT). A multicenter cohort of 73 newly diagnosed DLBCL treated with R-CHOP was included in the study. NGS clonality testing was performed using the LymphoTrack assay (Invivoscribe Inc) for IGH and IGK on DNA from LN and on ctDNA. MRD was analyzed by tracing the disease-specific clonotypes in plasma samples collected at interim and at the EOT. At diagnosis, clonal IG were detected in 52/57 available FFPE LN and in 68/73 ctDNA samples. Identical IG markers on paired LN and ctDNA were found in 36/52 cases; in 11 cases different clonal IG were found in ctDNA and in 5 cases no clonality was detected on ctDNA. At interim, ctDNA MRD was positive in 10/38 so far evaluated cases and 60% of them subsequently relapsed; it was negative in 28/38 and 14% of them relapsed ($p<0.0001$). MRD at interim allowed to better categorize the 22 cases in partial response (PR) by CT scan: 14 patients were MRD negative and 3 relapsed, while 8 were MRD positive and 4 relapsed ($p=0.09$) (Figure 1A). At EOT, MRD was positive in 10/48 so far evaluated cases and 9 of them relapsed; 7/10 had a negative PET/CT, 2 had a PR and 1 showed a progressive disease at EOT. MRD was negative in 38/48 cases and 2/38 have so far relapsed ($p<0.0001$); both cases had a negative PET/CT (Figure 1B). After a median follow-up of 37 months (range 2-59), at EOT patients achieving a complete response at PET/CT had 82.8% progression-free survival (PFS), while patients achieving an MRD negativity had 94.7% PFS. The prognostic value of the latter resulted significant on multivariate analysis ($p<0.0001$, HR 38.1, CI 95%, range 7.9-183). The impact of ctDNA MRD detection on prognosis deserves to be validated in larger series of DLBCL patients, in order to explore the possibility of MRD-adapted therapies.

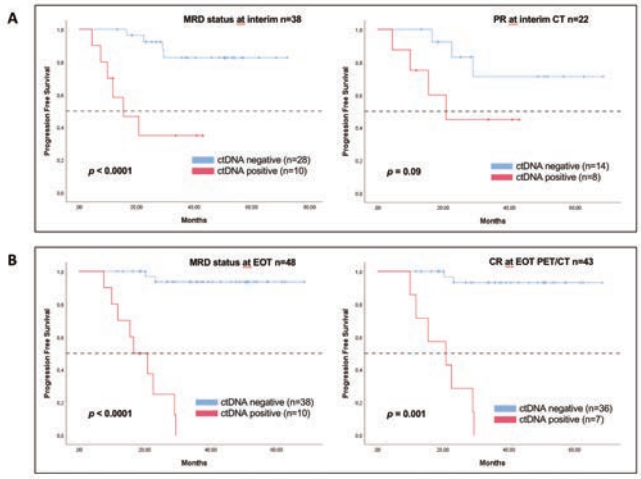

Figure 1.

DP016

EPCORITAMAB + R² LEADS TO HIGH CMR RATES IN HIGH-RISK RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA, INCLUDING PATIENTS WITH POD24

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In follicular lymphoma (FL), early progression after initial treatment (tx) with chemoimmunotherapy (POD24) occurs in approximately 20% of patients (pts) and is a strong predictor of poor outcomes. There is no standard tx approach for high-risk, relapsed or refractory (R/R) FL (high-risk subgroups in Table), and novel tx options are needed to improve efficacy. Epcoritamab, a subcutaneous (SC) T-cell–engaging bispecific antibody, demonstrated impressive single-agent antitumor activity and a manageable safety profile in R/R FL and shows promise in combination with standards of care. Here we present pooled analyses of epcoritamab with rituximab + lenalidomide (R^2) from cohorts 2a and 2b of the ongoing phase 1/2 EPCORE™ NHL-2 trial (NCT04663347). Pts with R/R $CD20^+$ FL received SC epcoritamab + R^2 for 12 cycles (Cs; 28 d each). Epcoritamab was dosed as follows: QW in C1-3, Q2W in C4-9, and Q4W in C≥10 (2a) or QW in C1–2 and Q4W in C≥3 (2b) for ≤2 y. As of Oct 31, 2022, 109 R/R FL pts (median age, 65 y) had received epcoritamab 48 mg + R^2 across cohorts 2a and 2b.

Table 1.

Table. Response rates, overall and in high-risk R/R FL subgroups

Population	ORR %	CMR %
Efficacy evaluable (n=101)	97	86
Primary refractory[a] (n=39)	97	87
Double refractory[b] (n=39)	92	79
Refractory to last line of tx (n=40)	93	80
Refractory to prior anti-CD20 tx (n=49)	94	84
POD24[c] (n=38)	95	82
POD24[c] 2L[d] (n=20)	95	90

[a]No response or relapse within 6 mo after first-line tx.
[b]Refractory to anti-CD20 and an alkylating agent.
[c]Progression within 2 y of first-line tx with chemoimmunotherapy.
[d]Pts received epcoritamab in second line.

Overall, 56% of pts had FLIPI 3-5, 61% had stage IV disease, and 59% had only 1 prior tx line. Most had received alkylating agents (92%) or anthracyclines (62%), and 2 had prior CAR T. With a median follow-up of 8.8 mo (range, 1.2-18.5), tx was ongoing in 82% of pts. The most common tx-emergent AEs were CRS and neutropenia (48% each), injection-site reactions (38%), and fatigue (33%). CRS events were mostly low grade (G; 46% G1–2, 2% G3) and most commonly occurred following the first full dose on C1D15. All resolved; none led to discontinuation. Two pts had ICANS (G1, G2), which resolved. In 101 efficacy-evaluable pts, overall response rate (ORR) was 97%, with a complete metabolic response (CMR) rate of 86% (median time to any response and CMR, 1.4 mo). In second-line pts with POD24, ORR/CMR rates were 95%/90% (additional subgroup data in Table 1). Estimated progression-free survival at 6 mo was 93%. Longer follow-up and additional data will be presented. Epcoritamab + R^2 showed potent antitumor activity with a manageable safety profile in a large R/R FL population. Encouraging responses were observed in high-risk pts, suggesting SC epcoritamab may abrogate negative effects of high-risk features. A separate POD24 cohort is planned, and the phase 3 EPCORE FL-1 trial of epcoritamab + R^2 (NCT05409066) is ongoing.

DP017

ABSTRACT NOT PUBLISHABLE

Myeloproliferative neoplasms

DP018

ABSTRACT NOT PUBLISHABLE

DP019

ABSTRACT NOT PUBLISHABLE

DP020

THE PROGNOSTIC NUTRITIONAL INDEX (PNI), A MARKER OF INFLAMMATION AND NUTRITIONAL STATUS, IS A PREDICTOR OF SURVIVAL IN PATIENTS WITH PRIMARY MYELOFIBROSIS IN THE PRE-FIBROTIC PHASE

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Background. Systemic inflammation and cachexia have been shown to be associated with negative outcomes in cancer patients. The abnormal expression of inflammatory cytokines is responsible for the constitutional symptoms experienced by individuals with primary myelofibrosis (PMF), which reflects the hypercatabolic and cachectic state of the disease. Laboratory biomarkers of cachexia and inflammation, such as albumin (ALB) and absolute lymphocyte counts (ALC), respectively, can provide valuable information regarding the prognosis of PMF. The Prognostic Nutritional Index (PNI) integrates data on ALB and ALC to reflect a patient's inflammatory, nutritional, and immune status.

Aims. Our objective was to investigate the role of the PNI as a predictor of survival in patients with prefibrotic primary myelofibrosis (prePMF).

Methods. A total of 225 patients, affected by prePMF, followed at 8 Italian Hematology Centers, were enrolled in the INFLA-ME observation protocol. Out of these pts, data on ALC and ALB were available for 120 individuals: therefore, the analysis was conducted on this pts cohort. PNI value is obtained by adding the serum ALB level (g/L) to the ALC (*10^3/uL) multiplied by 5. The optimal cut off value of PNI (50) was identified by a ROC analysis. Statistical analyses for categorical variables were performed using the chi-square test and Fisher's exact test, while the Mann-Whitney and log-rank tests were used for continuous variables.

Results. The median age of pts at diagnosis was 59.2 years (range 26.6-80.7); 56 pts (46.7%) were male. The majority of pts were JAK2 V617F mutated (75%). The median value of ALB levels at diagnosis was 4.2 g/dl (range 2.5 - 5.4), while the median value of ALC was 1,95x10^3/uL (range 0,17-4,39*10^3/uL). After a median follow-up of 6 (range 0,5-28) years, 18 pts (15%) died. 17 pts (14.1%) had a disease progression: of them, 12 (10%) experienced overt PMF and 5 (4.1%) evolved to an accelerated or blast phase. Pts with PNI < 50 at diagnosis had a significant shorter overall survival (OS) compared to the group with PNI > 50 (median OS 9.9 years *vs* not reached respectively, p=0.04). No differences were observed between the two PNI groups regarding age, IPSS risk category, and degree of bone marrow fibrosis.

Conclusions. Our preliminary data suggests a potential predictive role of PNI, a marker of nutritional and inflammatory status, for OS in prePMF pts: further studies on larger scale are needed to confirm these data.

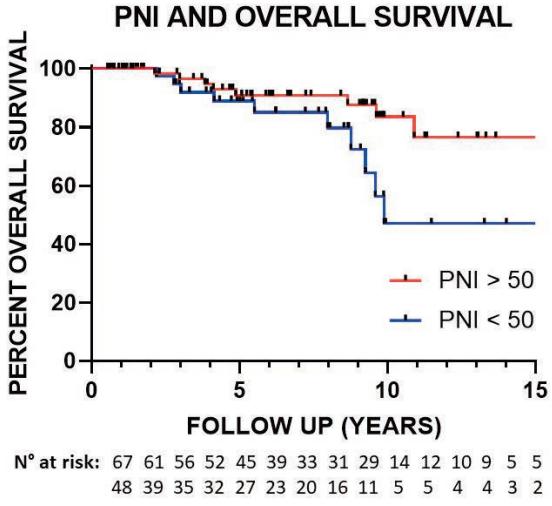

Figure 1.

DP021

A PROGNOSTIC MODEL TO PREDICT TREATMENT DISCONTINUATION AND DEATH ON RUXOLITINIB (RUX) IN PATIENTS (PTS) WITH MYELOFIBROSIS (MF)

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50-70% of MF pts discontinue RUX within 3-5 yrs. The Response to RUX After 6 Months (RR6) model may identify RUX-treated MF pts with worse overall survival (OS). We investigated predictors of early Rux discontinuation and death on therapy in 889 pts included in the "RUX-MF" retrospective study. This analysis focused on 410 pts: 172 pts (19.3%) who were alive on RUX after ≥5 yrs from RUX start (long-term RUX, LTR); 115 (12.9%) who were alive off RUX after ≥5 yrs (short-term RUX, STR); 123 (13.8%) who died while on RUX after <5 yrs (early death on RUX, EDR). At baseline, LTR pts had more frequently secondary MF (SMF) (p=0.02), PLT≥100x10^9/L (p=0.03), Hb ≥10 g/dL (p<0.001) and no transfusion request (p=0.003) than STR pts. ERD pts were older (p<0.001), more frequently males (p=0.005), with higher DIPSS/MYSEC-PM (p<0.001), WBC count (p=0.02) and transfusion requests (p=0.003) compared to LTR/STR pts. Rates of IWG-MRT spleen response (SR) were comparable in LTR and STR at 3 and 6 mos; EDR pts had significantly lower rates of SR (18.4% *vs* 35.2%/24.2%, p=0.009 at 3 mos and 17.5% *vs* 39.5%/32.6% at 6 mos, p=0.001). Rates of treatment-emergent anemia/thrombocytopenia were comparable in the 3 groups.

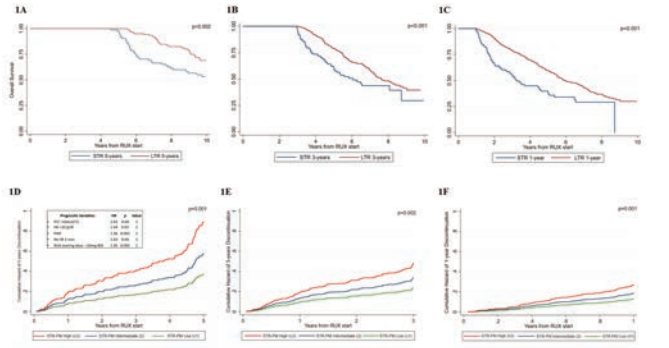

Figure 1. OS adjusted for delayed entry according to STR/LTR phenotype at 5 yrs (1A), 3 yrs (1B) and 1 yr (1C). Probability of early RUX discontinuation based on the STR-PM considering pts who discontinued at 5 yrs (1D), 3 yrs (1E) and 1 yr (1F). STR probability was: 37.6%, 58.2% and 90.4% at 5 years (p=0.001), 23.9%, 33.9% and 48.1% at 3 years (p=0.002), 12.6, 18% and 26.8% at 1 year (p=0.001).

At last contact, 285 (69.5%) pts discontinued RUX, 14 (8.7%) had a blast phase (BP) and 226 (55.1%) died. Cumulative incidence of BP with death as competing event was similar in LTR and STR pts (p=0.08). OS was significantly longer in LTR pts (p=0.002) (Figure 1A). OS improvements were also observed in pts continuing RUX over pts who discontinued within 3 yrs (Figure 1B) and within 1 yr (Figure 1C). In multivariate analysis, PLT<100x10^9/L, Hb<10 g/dl, PMF, no SR at 3 mos and RUX starting dose <10 mg BID were associated to higher probability of STR. Assigning 1 point to each significant variable, a prognostic model for STR (STR-PM) was built and 3 groups were identified: low (score 0-1, 48.1% of the pts); intermediate (score 2, 36.2%); and high risk (score ≥3, 15.7%) (Figure 1D). The STR-PM also applied considering earlier time-points for RUX discontinuation (Figure 1E and 1F). The STR-PM including RUX dose <10 mg BID, cytopenia, PMF and no SR at 3 mos may identify those pts less likely to receive prolonged RUX resulting in reduced OS. With the RR6 score, the STR-PM underscores the need for RUX dose optimization and early evaluation of SR. Personalized front-line approaches are required for pts with high-risk STR-PM and with anemia/higher risk MF, which are associated to early death on RUX.

DP022

SYSTEMIC MASTOCYTOSIS WITH AN ASSOCIATED HEMATOLOGIC NEOPLASM: FIRST REPORT OF AN OBSERVATIONAL, MULTICENTRIC, RETROSPECTIVE ITALIAN STUDY

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Systemic mastocytosis (SM) is a hematologic neoplasm characterized by the abnormal proliferation and accumulation of mast cells in the bone marrow (BM), skin and/or other extracutaneous organs. SM with an associated hematological neoplasm (SM-AHN) is an advanced variant, that constitutes about 20% of all cases of SM. AHN are mostly myeloid and their prognosis depends on the hematologic disease and the SM variant. We retrospectively reviewed 73 cases of SM-AHN, diagnosed according to the WHO 2016 criteria and treated in 3 Italian centers between 2011 and 2022, to evaluate frequency, characteristics and outcome of SM-AHN subtypes. Forty-four patients (pts) were males (60%) and the median age was 66 yrs. In 58 cases AHN was myeloid (79%) (14 Chronic Myelomonocytic Leukemia (CMML), 13 Myelodysplastic syndromes (MDS), 6 Acute Myeloid Leukemia (AML), 25 Myeloproliferative Neoplasm (MPN)) and in 15 (21%) Lymphoid. Main characteristics of pts are summarized in Table 1.

SM component was classified as advanced in 12 (16%) pts (8 Aggressive SM e 4 Mast Cell Leukemia (MCL)). The AHN component in these pts was CMML (6; 50%), AML (2; 17%), MDS (2; 17%), MPN (1) and Multiple Myeloma (1).

KIT D816V mutation was documented in 51/63 tested pts (81%): 39/49 (79%) in the BM and 12/14 pts (86%) on peripheral blood. In 3/12 D816V KIT negative pts, NGS study was performed without detecting alternative KIT mutations. Cytogenetic abnormalities were identified in 13/50 tested pts (26%), mainly SM-MDS (n=4/8, 50%). JAK2 V617F mutation was found in 26/58 tested pts (48%), mainly SM-MPN (77%).

The median follow-up was 26 months (range 1-138). Median survival was shorter in pts with associated AML and CMML (21 and 26 months, respectively) than pts with other associated AHN (not reached) (p=0.01). Treatment for AHN mainly included: hydroxyurea, ruxolitinib, azacytidine, polichemotherapy, immunotherapy, chlorambucil. The treatment directed to SM was: midostaurin (n=10), avapritinib in (n=1), α-interferon (n=2) and cladribine (n=3). Two AML and 2 CMML pts underwent allogeneic hematopoietic stem cell transplantation: all of these pts were alive at the last follow up.

In conclusion, in our series SM-AML and SM-CMML had poorer survival than SM-MPN and SM-Ly, consistent with a higher fre-

quency of associated advanced SM variant and poor prognostic mutations. Extensive NGS study in a larger group of pts will help us to better evaluate this heterogeneous disease from a prognostic point of view.

Table 1. Clinical, molecular and treatment characteristics of 73 patients with Systemic Mastocytosis with an Associated Hematologic Neoplasm (SM-AHN).

Characteristics	All pts n = 73	AML n = 6	MDS n =13	CMML n =14	MPN n =25	LyN@ n =15
Males n°(%)	44 (60)	4 (67)	9 (70)	6 (40)	19 (76)	6 (40)
Median Age, years (range)	66 (23-80)	65 (46-73)	71 (23-80)	71 (55-78)	62 (35-72)	57 (27-76)
Median follow-up from diagnosis, months (range)	26 (1-138)	21 (1-105)	29 (1-127)	28 (1-49)	44 (2-138)	41 (0-108)
Median overall survival, months	NR	21	NR	26	NR	NR
Diagnosis of advanced SM component n° (%)	12 (16)	2 (33)	2 (15)	6 (43)	1 (4)	1 (7)
Serum basal tryptase, median (ng/ml) **(range)**	36.0 (2-996)	44.5 (30-90)	33.7 (12-996)	110.0 (10-381)	25.5 (8-179)	39.5 (2-255)
Abnormal karyotype n° (%) **N° evaluable**	13 (26) n=50	1 (20) n=5	4 (50) n=8	3 (25) n=12	4 (24) n=17	1 (11) n=9
D816V KIT mutation (%) N° evaluable	51 (81) n=63[#]	4 (100) n=4	8 (62) n=13	11(85) n=13	16(80) n=20	12(86) n=14
V617F JAK2 mutation (%) N° evaluable	26 (21) n=58	0 (0) n=3	2 (29) n=7	2 (17) n=12	20 (80) n=25	2 (18) n=11
Additional Myeloid mutations n° tested pts (%)†	26 (32)	2 (33)	4 (31)	10 (67)	6 (24)	2 (13)
ASXL1 n° (%)	8 (31)	1 (50)	0 (0)	6 (60)	1 (14)	0 (0)
RUNX1 n° (%)	4 (15)	0 (0)	0 (0)	4 (40)	0 (0)	0 (0)
SRSF2 n° (%)	6 (23)	1(50)	1 (25)	4 (40)	0 (0)	0 (0)
DNMT3A n° (%)	3 (12)	0 (0)	2 (50)	0 (0)	1 (14)	0 (0)
SF3B1 n° (%)	2 (8)	0 (0)	2 (50)	0 (0)	0 (0)	0 (0)
TET2 n° (%)	12 (46)	2 (100)	2 (50)	6 (60)	1 (14)	1 (33)
U2AF1 n° (%)	3 (12)	0 (0)	0 (0)	3 (30)	0 (0)	0 (0)
TP53 n° (%)	8 (31)	0 (0)	1 (25)	1 (10)	6 (86)	0 (0)
Treatments						
Pts treated for AHN n° (%)	40 (55)	6 (100)	6 (46)	9 (65)	12 (50)	7 (47)
Pts treated for advanced SM n° (%) £	11 (15)	2 (33)	2 (15)	6 (43)	1 (4)	1 (7)
Pts undergoing Allo-HSCT n° (%)	4 (5)	2 (33)	0 (0)	2 (14)	0 (0)	0 (0)

SM, Systemic mastocytosis; AML acute myeloid leukemia; MDS myelodysplastic syndrome; CMML chronic myelomonocytic leukemia; MPN, myeloproliferative neoplasm, LyN, lymphoid neoplasm, Pts, patients; Allo-HSCT allogeneic hematopoietic stem cell transplant; ✣ MPN includes polycythemia vera (n=6), essential thrombocythemia (n=13), primary myelofibrosis (n=6), chronic myeloid leukemia (n=1) and myeloproliferative neoplasm NOS (n=1) @ LyN includes multiple myeloma (n=4), Diffuse Large B cell lymphoma (n=2), follicular lymphoma (n=1), mantle cell lymphoma (n=1), B-chronic lymphocytic leukemia (n=1) and other indolent lymphomas (n=6). #49 patients had evaluation of mutation on bone marrow and 14 on peripheral blood. †evaluated with QIAseq Targeted DND Custom Panel (CDHS-33828Z-1177) (Florence), Pipeline ILL1XG1S4_CNV / v5.5.75 / GEN1GN1FSQ2 (Sophia Genetics) (Verona). Reference Genome: GRch37/hg19). ▵Hydroxyurea, ruxolitinib, azacytidine, R-CHOP, RT, idarubicin, cytosine-arabinoside, chlorambucil, temozolamide, lenalidomide, daratumumab, bortezomib, elotuzumab, pomalidomide, isatuximab. £ Midostaurin, avapritinib, cladribine, alpha-interferon,

DP023

TREND OVER TIME OF SERUM TRYPTASE LEVELS IN 332 PATIENTS WITH INDOLENT VARIANTS OF SYSTEMIC MASTOCYTOSIS: A RETROSPECTIVE, SINGLE-CENTER STUDY

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The prognostic significance of serum tryptase (sT) level changes over time in patients (pts) with indolent variants of Systemic Mastocytosis (SM) is still unclear. Some studies suggested their association with a higher risk of progression and a poor outcome. We monitored and compared sT levels variations in pts with Indolent SM (ISM) n=147 and Bone Marrow Mastocytosis (BMM) n=185 diagnosed according to the 2022 WHO classification, to identify differences in progression free survival (PFS). All pts in our study had at least four consecutive sT determination with a median interval between two sT points of 16 months. As expected, median sT at diagnosis was lower in BMM than ISM pts (19.1 *vs* 31.6 ng/mL, p<0.0001). At the time of the 4th sT determination the median follow-up (FU) was 51 (range 16-213) and 53 months (range 20-119) for ISM and BMM pts, respectively. BMM pts displayed a significant higher median sT decrease than ISM pts (-1.3 *vs* -0.1 ng/ml, respectively; p=0.03) and median percentage change over time (-8.47 *vs* - 1.16%, respectively; p=0.001). We divided pts into three different groups, according to sT variation over time: >10% decrease (group A), stable or < 10% variation (group B), >10% increase (group C). With a median FU of 51 months (range 16-213) no significant differences in PFS were found among the three groups (p=0.38) in the entire cohort. Nevertheless, we observed a trend towards a better PFS in pts with ISM in the group A compared to other groups (p=0.25) (Figure 1).

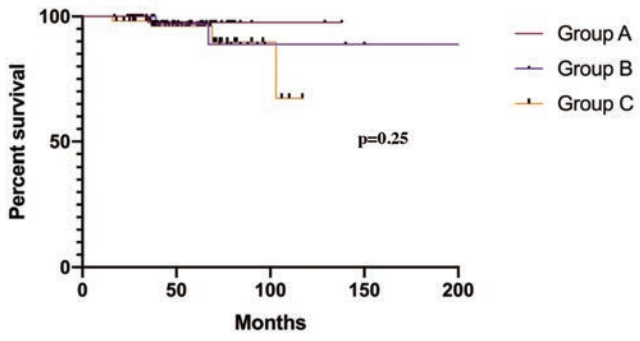

Figure 1.

In particular a progression to smoldering SM (SSM) was documented in one out of 48 pts in group A (2 %) and in 2/ 42 pts in group B (4,8 %), whereas four out of 57 pts in group C (7.5%) progressed to an advanced form [SSM, n=2; aggressive SM (ASM), n=1; BMM with an associated acute myeloid leukemia (BMM-AML), n=1]. Only two out of 185 BMM pts (1.1%) progressed (one to BMM associated to chronic myeloid leukemia and one to BMM associated to essential thrombocythemia). In our knowledge, this is the largest observational study describing the sT levels modification over time in pts with indolent variants of SM. Although statistically significant differences would require a longer observation period, our data confirm the importance of monitoring sT. Also, a closer FU might be needed for ISM pts with significantly increasing sT values over time (>10%), while reducing the frequency and psychological stress of periodic diagnostic examinations in other ISM and BMM pts.

DP024

PHENOTYPIC AND PROGNOSTIC CORRELATES OF NON-CANONICAL *JAK2*, *MPL* AND *CALR* MUTATIONS IN PATIENTS WITH CLASSICAL PHILADELPHIA-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS (MPNS)

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Background. Besides *JAK2*, *MPL*, and *CALR* (*JMC*) driver mutations, non-canonical variants (NCVs) have been reported in patients (pts) with MPNs, and may occur in association with *JMC*-mutations (JMC/NCVs) as well as triple negative (TN) diseases.

Table 1. List of the 57 non-canonicall variants.

Case	NCV gene	Amino acid change	Nucleotide change	Mutation type	VAF	COSMIC	gnomAD AF	Disease	Driver mutation
FI_180	*MPL*	C322G	964T>G	Missense	8%	/	/	PMF	*CALR* type 2
FI_331	*MPL*	C322Y	965G>A	Missense	49%	/	0.00000398	ET	*CALR* type 2
FI_142	*MPL*	E259K	775G>A	Missense	42%	COSM6931318	0.0000239	PMF	*JAK2* V617F
FI_208	*MPL*	E259K	775G>A	Missense	42%	COSM6931318	0.0000239	ET	*MPL* W515S
FI_345	*MPL*	E259K	775G>A	Missense	67%	COSM6931318	0.0000239	PMF	*MPL* W515L
FI_464	*MPL*	E259K	775G>A	Missense	51%	COSM6931318	0.0000239	PMF	*MPL* W515L
FI_174	*MPL*	F315C	944T>G	Missense	51%	/	0.00000398	ET	TN
FI_360	*MPL*	G540S	1618G>A	Missense	51%	COSM142842	0.00000398	PMF	*CALR* type 1
FI_411	*MPL*	H353R	1058A>G	Missense	50%	/	0.0000358	PMF	*JAK2* V617F
FI_269	*MPL*	P200R	599C>G	Missense	38%	/	/	PMF	*JAK2* V617F
FI_182	*MPL*	Q516R	1547A>G	Missense	24%	/	/	ET	*MPL* S505N
FI_392	*MPL*	Q516R	1547A>G	Missense	43%	/	/	PMF	*MPL* S505N
FI_025	*MPL*	R592Q	1775G>A	Missense	45%	COSM2170465	0.0000159	PV	*JAK2* V617F
FI_133	*MPL*	R592Q	1775G>A	Missense	13%	COSM2170465	0.0000159	ET	*JAK2* V617F
FI_176	*MPL*	R592Q	1775G>A	Missense	66%	COSM2170465	0.0000159	PMF	*JAK2* V617F
FI_188	*MPL*	R592Q	1775G>A	Missense	7%	COSM2170465	0.0000159	PMF	*CALR* type 1
FI_216	*MPL*	R592Q	1775G>A	Missense	3%	COSM2170465	0.0000159	PV	*JAK2* V617F
FI_459	*MPL*	R592Q	1775G>A	Missense	6%	COSM2170465	0.0000159	ET	*MPL* W515A
FI_523	*MPL*	R592Q	1775G>A	Missense	5%	COSM2170465	0.0000159	PMF	*JAK2* V617F
FI_077	*MPL*	R592X	1774C>T	Missense	28%	/	0.0000239	PMF	*JAK2* V617F
FI_282	*MPL*	S204F	611C>T	Missense	3%	COSM28996	/	PMF	*CALR* type 2
FI_044	*MPL*	V501A	1502T>C	Missense	92%	COSM86964	/	PMF	*MPL* W515R
FI_338	*MPL*	V501L	1501G>T	Missense	36%	COSM142840	/	PMF	*MPL* S505N
FI_099	*MPL*	V501M	1501G>A	Missense	47%	/	/	PMF	*MPL* S505N
FI_212	*MPL*	V501M	1501G>A	Missense	6%	/	/	ET	*MPL* S505N
FI_163	*MPL*	Y591D	1771T>G	Missense	3%	COSM28997	0.0000131	ET	*JAK2* V617F
FI_213	*MPL*	Y591D	1771T>G	Missense	63%	COSM28997	0.0000131	PV	*JAK2* V617F
FI_373	*MPL*	Y591D	1771T>G	Missense	100%	COSM28997	0.0000131	PMF	*JAK2* V617F
FI_526	*MPL*	Y591D	1771T>G	Missense	28%	COSM28997	/	PV	*JAK2* V617F
FI_165	*MPL*	Y591H	1771T>C	Missense	44%	/	0.00000398	PV	*JAK2* V617F
FI_167	*MPL*	Y591H	1771T>C	Missense	45%	/	0.00000398	PV	*JAK2* V617F
FI_331	*MPL*	Y591N	1771T>A	Missense	19%	/	/	ET	*CALR* type 2
FI_233	*JAK2*	C618R	1852T>C	Missense	32%	COSM29118	/	PMF	*JAK2* V617F
FI_351	*JAK2*	E621K	1861G>A	Missense	50%	COSM5411124	0.00000805	PMF	*JAK2* V617F
FI_524	*JAK2*	E621K	1861G>A	Missense	49%	COSM5411124	0.00000805	PMF	*JAK2* V617F
FI_250	*JAK2*	G281A	280+1G>C	Missense	5%	/	/	PMF	*JAK2* V617F
FI_235	*JAK2*	G281C	841G>T	Missense	80%	/	/	PMF	*JAK2* V617F
FI_128	*JAK2*	G301R	901G>C	Missense	30%	/	/	PV	*JAK2* V617F
FI_355	*JAK2*	G301R	901G>C	Missense	66%	/	/	PV	*JAK2* V617F
FI_390	*JAK2*	G301R	901G>C	Missense	47%	/	/	PV	*JAK2* V617F
FI_503	*JAK2*	G301R	901G>C	Missense	44%	/	/	PV	*JAK2* V617F
FI_248	*JAK2*	G571S	1711G>A	Missense	50%	COSM29107	0.000471	ET	*CALR* type 2
FI_457	*JAK2*	I801S	2402T>G	Missense	50%	/	0.00000418	PMF	*CALR* type 2
FI_056	*JAK2*	I951T	2852T>C	Missense	91%	/	0.0000369	ET	*JAK2* V617F
FI_139	*JAK2*	I951T	2852T>C	Missense	75%	/	0.0000369	PMF	*JAK2* V617F
FI_461	*JAK2*	I951T	2852T>C	Missense	84%	/	0.0000369	PV	*JAK2* V617F
FI_526	*JAK2*	Q572H	1716A>T	Missense	98%	/	0.00000399	PV	*JAK2* V617F
FI_513	*JAK2*	S1115C	3344C>G	Missense	51%	/	0.00000799	ET	*CALR* type 1
FI_502	*JAK2*	S277G	829A>G	Missense	19%	/	/	PMF	*JAK2* V617F
FI_308	*JAK2*	S958A	2872T>G	Missense	49%	/	/	ET	*JAK2* V617F
FI_309	*JAK2*	S958A	2872T>G	Missense	49%	/	/	ET	*JAK2* V617F
FI_341	*JAK2*	T810I	2429C>T	Missense	86%	/	/	PMF	*JAK2* V617F
FI_302	*JAK2*	T875N	2624C>A	Missense	5%	COSM23940	/	PMF	*JAK2* V617F
FI_534	*JAK2*	Y613C	1838A>G	Missense	13%	COSM9991425	/	PV	*JAK2* V617F
FI_094	*JAK2*	Y813C	2438A>G	Missense	38%	/	/	PMF	*JAK2* V617F
FI_334	*CALR*	D125E	375C>G	Missense	52%	/	0.0000239	PV	*JAK2* V617F
FI_018	*CALR*	D302N	904G>A	Missense	50%	COSM2817017	0.0000318	ET	*JAK2* V617F

Abbreviations: COSMIC: catalogue of somatic mutations in cancer; ET, essential thrombocytemia; gnomAD: genome aggregation database; NCV, non-canonical variant; PMF, primary myelofibrosis; PV, polycythemia vera; VAF, variant allele frequency.

Aims and Methods. To study the prevalence and clinical implications of JMC/NCVs in MPN pts, we interrogated the molecularly integrated database of CRIMM. Each variant was manually annotated to assess pathogenicity excluding benign and likely-benign variants, as described[1].

Results. Among 476 MPN pts, we selected 57 NCVs occurring in 55 (12%) pts, including 13 (24%) PV, 14 (25%) ET, and 28 (51%) PMF (Table 1). Two pts harbored >2 NVCs. All variants were missense. *MPL* variants were the most frequent (n=32, 56%), followed by *JAK2* (n=23, 40%) and *CALR* (n=2, 4%). Of the 32 *MPL* variants, 19 (59%) were located in the intracellular domain, 10 (31%) in the extracellular domain, and 3 (9%) in the transmembrane domain. Pts with *MPL* NCVs were diagnosed with PV in 6 (19%) cases, ET in 8 (26%), and PMF in 17 (55%). While one pt was TN, 15 (48%) were JAK^{VF}-mutated, 10 (32%) had canonical *MPL* mutations, and 5 (16%) were *CALR*-type 1/2-mutated. Of note, among *MPL* mutated pts, 4 were MPL^{S505N} and 6 MPL^{W515}. *JAK2* NCVs were located in the FERM (n=8; 35%), JH2 (n=7; 30%), and JH1 (n=8; 35%) domain. Among the 23 pts harboring *JAK2* variants, a diagnosis of PMF, PV, and ET was reported in 11 (48%), 7 (30%), and 5 (22%), respectively. *JAK2* NCVs co-occurred with JAK^{VF} in 20 (87%) cases and with *CALR* mutations in 3 (13%). *CALR* NCVs were located within the proline-rich (n=1) and N-terminal (n=1) domains. Of the 2 pts harboring *CALR* NCVs, 1 was diagnosed with ET and 1 with PV; all 2 had the JAK^{VF} mutation. Finally, we performed 1:3 propensity score-matching for disease type, gender, and disease duration in 39 selected NCV pts with available data. In ET, NCVs were associated with higher venous thrombosis rate (29% *vs* 6%, P=.0269). We found no difference in the PV and PMF cohorts. While OS was similar both in the entire MPN cohort and the single MPN entities, ET pts with NCVs had a higher risk of evolution to MF, with 7/ 8 evaluable pts who progressed; fibrotic PFS was shorter compared to pts without NCVs (median 97 *vs* 241 mos, P=.0021).

Conclusions. Our study provides a comprehensive overview of the prevalence of JMC/NCVs in a large cohort of MPN pts, supporting the hypothesis of a possible genotype-phenotype effect, especially in ET.

DP025

REAL-WORLD EXPERIENCE OF ROPEGINTERFERON IN POLYCYTHEMIA VERA

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Introduction. Ropeginterferon alfa-2b (Ropeg) is a novel long-acting mono-pegylated proline-IFN-alfa-2b that was recently approved in Italy for treating polycythemia vera (PV) patients without symptomatic splenomegaly intolerant to hydroxyurea, woman of childbearing potential and subject with skin cancer history. In the phase 3 studies Ropeg was efficacious and safe. However, little is known about this agent in real-world practice.

Methods. We collected clinical data and assessed the safety and preliminary efficacy of Ropeg in 20 PV patients treated across the Federico II University. Ropeg was adminstered according to data sheet. Complete blood counts and biochemestry panels were ordered every 2 weeks, with less frequent monitoring thereafter.

Results. A total of 20 PV patients were included in this series. Median age at Ropeg initiation was 53 years (range 33-87), and 63.2% of patients were male. 18 patients were transitioned from a prior HU therapy (median time under HU treatment was 12 months, range 1-171) indications for starting Ropeg included leg ulcers (n=3), colitis (n=3), skin dryness (n=2), melanonychia (n=2), oral stomatitis (n=2), fever (n=2), actinic cheratosis (n=2), skin cancer (n=1), cytopenia (n=1) appeared on HU treatment. One female of childbearing potential and one patient with previous skin cancer start Ropeg as first line

therapy. The median time between PV diagnosis and Ropeg starting was 45 months (range 2-345). The median phlebotomy number for year before Ropeg starting was 2 (range: 1-5). One patient had grade 1 increases in liver function tests, resolved after dose reduction. Three patients discontinued Ropeg after 3 months of therapy, one for depression (likely Ropeg related, 5%), one patient due to gastrointestinal bleeding, one for progressive symptomatic splenomegaly. Overall, flue-like symptom or injection site reaction were not reported. The median time on Ropeg was 6,5 months, and the median dose was 125 mcg. Three patients (15%) required an additional phlebotomy session after starting Ropeg. We didn't found significant decreases in hematocrit, WBC counts or platelet counts compared to baseline. Three patients had obtained a complete hematologic response.

Conclusions. Overall, we found that Ropeg is remarkably well-tolerated with improvements in hematologic parameters. However, responses are slow, which is consistent with published data and the short follow-up of our cohort.

DP026

EFFECTIVENESS AND SAFETY OF THIENOPYRIDINES AS ANTITHROMBOTIC PROPHYLAXIS IN PHILADELPHIA-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS IN COMPARISON WITH ASPIRIN

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Patients (pts) with Philadelphia-negative myeloproliferative neoplasms (MPN) intolerant or allergic to aspirin commonly receive thienopyridines (TP) as antithrombotic prophylaxis, even without evidence of efficacy and safety in this setting. We conducted a monocentric retrospective study to investigate the effectiveness and safety of clopidogrel (CPG) and ticlopidine (TKL) in MPN pts compared to standard treatment with low-dose aspirin (LD-ASA). We recorded 689 MPN pts receiving primary prophylaxis with LD-ASA (n= 641) or TP (CPG n=22 and TKL n=26). Pts receiving TP had a higher incidence rate (IR) per 100 pt-years of thrombosis (6.1) compared to LD-ASA pts (2.0, p=0.0001).

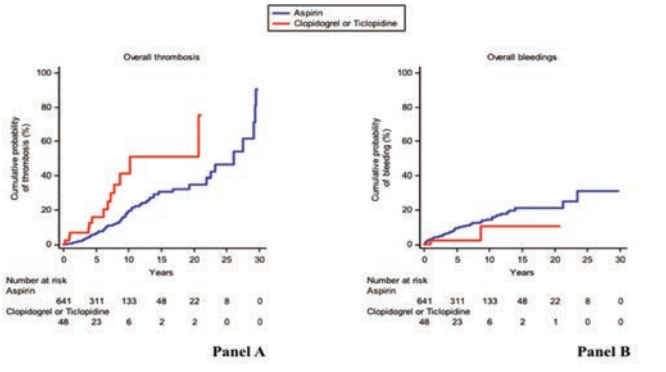

Figure 1.

Both venous thromboembolism (VTE) and arterial thromboses (AT) have a higher IR per 100 pt-years in the TP group compared to the LD-ASA group (VTE 2.8 *vs* 1.2, p=0.03; AT 3.3 *vs* 0.8, p=0.0002). Cox analysis showed a higher thrombotic risk in the TP group than in the LD-ASA group (Hazard Ratio HR 5.2, 95%CI 2.1-12.7, p=0.0003) [Figure 1, panel A]. The risk in the TP group was increased for VTE (HR 3.6, 95%CI 1.1-12.4, p=0.04) and AT (HR 15.0, 95%CI 3.6-63.4, p=0.0002) compared to the LD-ASA group. There was no difference in major or clinically relevant bleedings between the two groups (HR 0.5, 95%CI 0.2-1.4, p=0.22) [Figure 1, panel B]. LD-ASA seems more effective than TP in preventing thrombosis in polycythemia vera (PV) and essential thrombocythemia. Multivariate analysis identified age >65 years (HR 3.03, 95%CI 1.87-4.91, p<0.0001), JAKV617F mutation (HR 2.88, 95%CI 1.52-5.48, p=0.0012), and TP intake (HR 2.85, 95%CI 1.54-5.26, p=0.0008) as independent risk factors for all thrombotic events. Cytoreductive therapy was protective (HR 0.54, 95%CI 0.33-0.89, p=0.017). Furthermore, we analyzed 115 pts with a first arterial event receiving secondary antiplatelet prophylaxis (LD-ASA n=82 and TP n=33). The multivariate analysis identifies only age>65 years (HR 3.6, 95%CI 1.5-8.3, p=0.003) and PV diagnosis (HR 2.5, 95%CI 1.1-5.9, p=0.03) as independent risk factors for recurrent thrombosis, and cytoreductive treatment as a protective factor (HR 0.2, 95%CI 0.3-2.1, p=0.004). Recurrent thrombosis- and bleeding-free survival are not different between the two groups.

In conclusion, in MPN pts TP are less effective than LD-ASA as primary antithrombotic prophylaxis. On the other hand, the effectiveness of secondary antithrombotic prophylaxis after arterial events is similar for TP and LD-ASA.

DP027

NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) IN MYELOFIBROSIS PATIENTS TREATED WITH RUXOLITINIB MAY PREDICT PROGNOSIS AND RATE OF DISCONTINUATION

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After their introduction in clinical practice, JAK inhibitors have become the cornerstone of treatment for primary (PMF) and secondary myelofibrosis (SMF). Ruxolitinib (ruxo) proved to be active in improving symptoms and achieving spleen responses. Common prognostic scores like IPSS and DIPSS/DIPSSplus focus on all MF patients and not just on ruxo-treated patients. Nevertheless, the recently developed Response to Ruxolitinib after 6 months (RR6) risk model predicts survival in this specific patient's cohort, evaluating clinical-only variables. However, few data are available in literature regarding full blood count parameters to predict outcome of ruxo-treated patients. The ratio between absolute neutrophils count (ANC) and absolute lymphocyte count (ALC), called NLR, was found to be a simple predictive factor for progression free survival (PFS) and overall survival (OS) in various malignancies. In our retrospective single center analysis, we evaluated 140 patients diagnosed with intermediate-2 or high IPSS risk PMF/SMF treated with ruxo from 2011 to 2022. At baseline evaluation before ruxo start, the median NLR was 4.7 (range 0.2-29.3; IQR 2.9-8.2). At 6-months, the median NLR was 3.4 (range 0.3-43). Baseline or 6-months NLR was not significantly associated with spleen response (p=0.109 - p=0.278). After a median follow up of 38 months, 28 patients died (20%). Patients with a baseline NLR <2 *vs* ≥2 had a median overall survival (OS) of 48.7 months (95%CI 16.4-81.1) *vs* not reached (p<0.001) [HR 4.6 (95%CI 2.0-10.9)]. Moreover, patients with 6-months NLR <2 *vs* ≥2 had a median OS of 56.4 months (95%CI 44.0-68.4) *vs* not reached (p=0.011) [HR 3.0 (95%CI 1.2-7.2)]. Baseline and/or 6 months NLR < or ≥ 2 was not associated with infection rate (p=0.360 - p=0.702). In our cohort, the median treatment duration was 26.9 months (range 2-110; IQR 11-44.1) with 54 patients (39%) who have discontinued

ruxo. Major discontinuation causes were death [10 (18.5%)], lack of response [9 (16,6%)] and allotransplant [15 (27.8%)]. Censoring for patients undergone allotransplant, baseline NLR <2 is predictive of an earlier ruxo any-other-cause discontinuation (27.4 months *vs* not reached, p<0.001) [HR 4.1 (95%CI 1.8-8.9)]. NLR evaluation before ruxo start and at 6 months may be a useful and simple tool to predict OS and treatment discontinuation in MF patients.

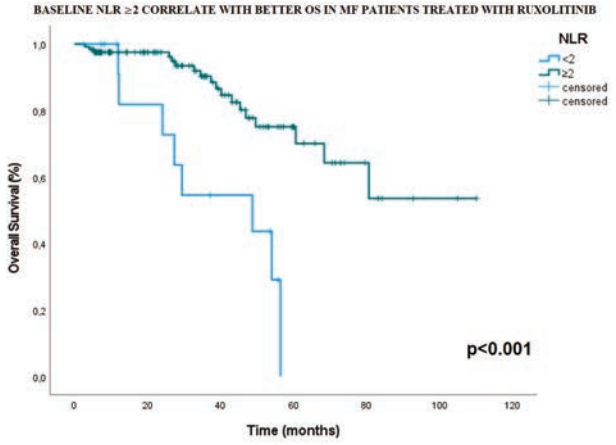

Figure 1.

DP028

INCIDENCE OF BLAST PHASE IN RUXOLITINIB-TREATED MYELOFIBROSIS PATIENTS ACCORDING TO ANEMIA SEVERITY

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Anemia is associated to higher risk of blast phase (BP) and death in patients (pts) with primary (PMF) or secondary myelofibrosis (SMF).

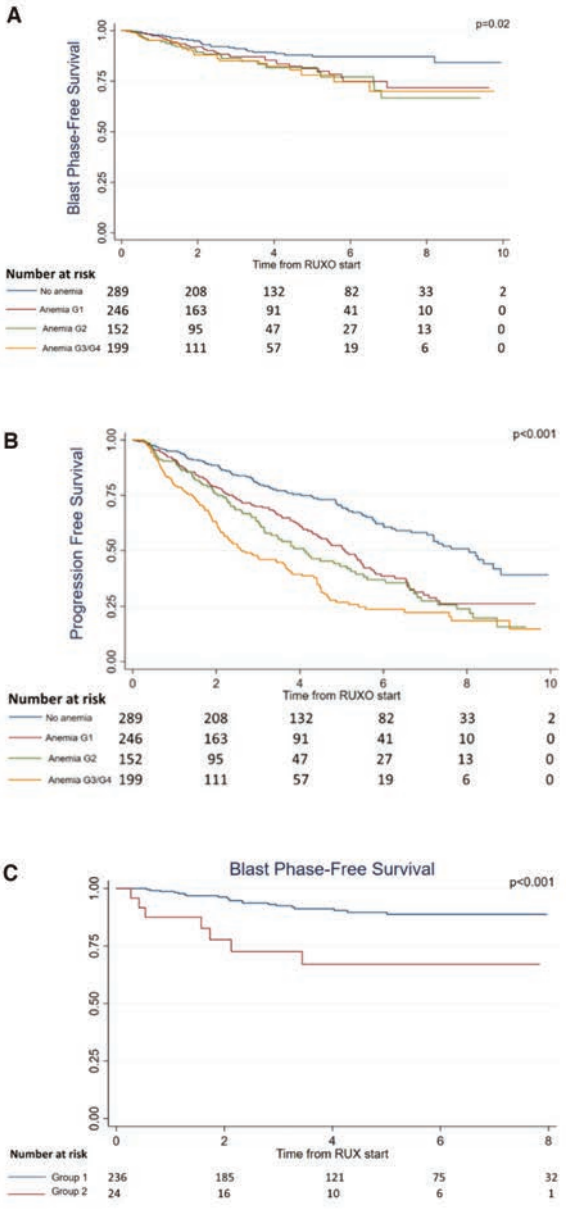

Figure 1. Kaplan-Meier curves of blast-phase free survival (Figure 1A) and progression-free survival (PFS) (Figure 1B) of patients within different anemia classes, as for CTCAE. Blast Phase Free Survival in patients without baseline (BL) anemia, according to the occurrence of anemia after 6 months of RUX therapy (Figure 1C). Fig 1b. PFS was calculated from RUX start to the date of BP, death or last contact; 74 pts were censored at the time of ASCT. No anemia significantly different from all other anemia categories; grade 2 anemia significantly different from grade 3/4 anemia (p=0.01) but was comparable to grade 1 anemia. Figure 1C. Group 1: Patients without BL anemia who had no or G1/2 anemia after 6 months of RUX therapy. Group 2: Patients without BL anemia who had grade 3/4 anemia after 6 months of RUX therapy.

Anemia is present in 1/3 of pts at diagnosis and its frequency increases with time. Also, JAK2 inhibition by ruxolitinib (RUX) and fedratinib may cause anemia, severe in around 40% of pts. Information on the prognostic role of anemia at RUX start or during therapy is limited. We explored prognostic correlates of anemia in 886 RUX-treated pts included in the "RUX-MF" retrospective study. RUX was started after a median of 1.07 yrs (range, 0-32.9) from MF diagnosis. Median duration of RUX treatment was 2.36 yrs (0.1-12.4). At RUX start, 597 (67.5%) pts had anemia, which was significantly more frequent in pts with overt-PMF diagnosis, older age, lower WBC and PLT counts, higher DIPSS/MYSEC-PM risk and greater symptoms burden. Overall, 414 (46.8%) pts died and 117 (13.2%) had a BP, with a BP incidence of 3.74 per 100 pts year (% p-y). BP rate was 2.34 in pts with no anemia (32.5%) and reached respectively 4.22, 4.89 and 4.93% p-y in pts with CTCAE grade 1 (27.8%, Hb >10 g/dL), 2 (17.2%, Hb 8-10 g/dL) and 3/4 (22.5%, Hb <8 g/dL) anemia. Considering the sex- and severity-adjusted Hb thresholds, BP incidence was 2.85, 4.97 and 4.89 in pts with mild/no anemia, moderate (Hb 8-9.9/9-10.9 g/dL in f/m), severe (Hb <8/<9 g/dL in f/m). BP-free survival (BP-FS) rate at 5 years were 89%, 81%, 82% and 78% for pts with no, G1, G2 and G3/G4 anemia, respectively (p=0.02) (Figure 1A) and 86%, 79% and 78% for pts with no/mild anemia, moderate and severe anemia (p=0.02). 5-yr progression-free survival (PFS) (including BP and death) was 70%, 52%, 43% and 27% in pts with no, G1, G2 and G3/G4 anemia, respectively (Figure 1B). 5-yr PFS was 64%, 44% and 29% in pts with no/mild anemia, moderate and severe anemia, respectively. All 3 categories were significantly different from the others (no/mild *vs* moderate and *vs* severe anemia, p<0.001; moderate *vs* severe, p=0.009). At the 6-mos timepoint, 260/289 pts with no baseline anemia were on RUX therapy, and 24 (9.2%) presented a G3-4 anemia. By landmark analysis considering only BP occurring after the 6-mos timepoint, BP-FS was significantly worse in pts acquiring anemia (Figure 1C). Our study highlights that anemia correlates with an increased risk of evolution into BP, both if present at baseline and if acquired during RUX monotherapy. In these pts, innovative anemia therapies and disease-modifying agents are warranted.

DP029

NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) AT DIAGNOSIS IN ESSENTIAL THROMBOCYTEMIA (ET) PREDICTS THROMBOTIC EVENTS

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Myeloproliferative diseases (MPNs) are characterized by an inflammatory process involved in symptom burden of the patients (pts), progression to myelofibrosis (MF) or leukemia, and thrombotic complications. Neutrophil-to-lymphocyte ratio (NLR) is a prognostic biomarker that reflects the imbalance between systemic inflammation and immunity in several diseases, including hematological ones. We analyzed retrospectively the relationship between NLR value at ET diagnosis and the risk of thrombotic events (TEs), disease progression into MF and overall survival (OS). 473 pts with diagnosis of ET, between 1995 to 2022, were enrolled in the INFLA-ME (INFLAmmation in myeloproliferativE disease) trial. NLR value was calculated as the ratio between absolute neutrophil count (ANC) and lymphocyte count (ALC) at diagnosis and the best threshold was identified by ROC analysis. TEs included both arterial (ischemic stroke, myocardial infarction, peripheral arterial disease) and venous (deep vein thrombosis, pulmonary embolism, cerebral and splanchnic vein thrombosis) events. Median age at diagnosis was 64.7 years (range:18-92). Most of pts was JAK2 V617F mutated (69%) and 372 pts (78%) classified as intermediate-high IPSET score. 73 TEs occurred (47 arterial and 26 venous) in 14.5% pts, with an incidence rate of 1.7 x 100 pts/year. 4 was identified as the best cut-off value to dichotomize pts based on NLR. Age≥65 years(p=0.04), IPSET score intermediate-high(p=0.03), prior/at diagnosis thrombosis (p<0.0001) were associated with a significant risk of TEs. NLR value ≥4 at diagnosis was associated with higher thrombotic risk (p<0.0001, both arterial and venous) with a shorter thrombosis free-survival (TFS) compared with NLR < 4 (p<0.0001, Figure 1). With a median follow-up of 7.8 years (range: 0.6-21), 48 pts progressed to MF (10%). NLR ≥4 was not associated with evolution to MF and OS. Multivariate analysis confirmed that NLR ≥ 4 was predictive for thrombosis (p<0.0001 HR=2.7, IC 1.6-4.3) as well as age ≥65 years (p=0.003, HR=2.8, CI1.6-5.06); CALR mutation seemed to be protective against TEs (p=0.05, HR=2, CI1.06-5.54). NLR value is a simple, cost-effective and easy to obtain inflammatory marker can predict at diagnosis the risk of thrombosis in ET. We found that pts with NLR value ≥4 have a significant higher risk of TEs. Despite the retrospective nature of the study, these data are promising but require to be validated in larger and prospective studies.

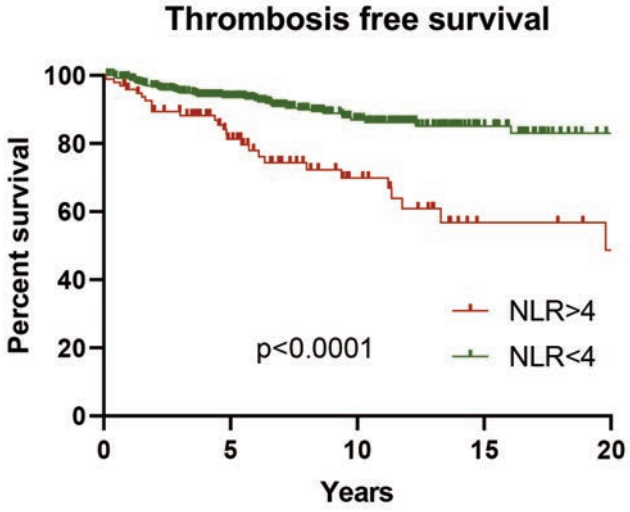

Figure 1. Thrombosis free survival according to NLR value.

DP030

INCIDENCE AND RISK FACTORS FOR HEMORRHAGIC EVENTS IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA

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Background. Essential thrombocythemia (ET) is characterized by increased risk of thrombotic and hemorrhagic events, that represent their leading causes of mortality and morbidity. While the risk of thrombosis is assessed through the IPSET score, there is no specific prognostic tool used to predict hemorrhagic risk in ET. Aim of the study was to analyze incidence and main risk factors connected to hemorrhagic events onset in ET patients.

Methods. We retrospectively analyzed 308 patients diagnosed with ET between 1984 and 2022 at the Division of Hematology of Udine, treated according to the current international guidelines.

Molecular status (JAK2, CALR and MPL mutations) was defined as soon as analysis were available.

Results. Median age at ET diagnosis was 57.2 years (range: 17.7-87.6), with a slight prevalence of females (53.6%). According to molecular status, 193 patients (62.7%) were JAK2 mutated, 66 (21.4%) had a CALR mutation (type 1 in 40/66, 60.6%), and 14 (4.5%) had a MPL mutation (W515L in 12/14, 85.7%), 21 patients (6.8%) were "triple negative", and in 14 patients (4.5%) were not evaluable. According to IPSET-thrombosis score, 49.7% patients were at high, 24.3% at intermediate and 26.0% at low risk, respectively. Twenty-four patients (7.8%) experienced a hemorrhagic event after ET diagnosis, at a median time of 117 months (range: 1-316); event was defined as minor in 8 cases, moderate in 10 cases, and severe in 6 cases, with 2 CNS bleeding and 4 g.i. bleedings. Cumulative incidence of hemorrhage at 10 and 20 years was 6.0% (95% confidence interval [CI]: 3.5-10.3) and 12.0% (95% CI: 7.7-22.9), respectively. At hemorrhage, 18 patients received cytoreduction (HU in 15), 19 antiplatelet therapy (ASA in 14) and 4 were under anticoagulants. There was a significant correlation between hemorrhagic risk and IPSET score: cumulative incidence of hemorrhage at 10 years was 3.2% (95% CI: 0.8-12.7) for low-risk, 2.9% (95% CI: 0.7-111.1) for intermediate-risk and 9.8% (95% CI: 5.1-18.4) for high-risk patients, respectively (p=0.002 – Figure 1). We found no correlation between hemorrhagic risk and gender (p=0.2) and mutational status (p=0.54).

Conclusions. Results of our study highlight the validity of IPSET score in predicting individual hemorrhagic risk among ET patients, suggesting a possible role of IPSET scoring system as a global evaluator for vascular events in ET patients.

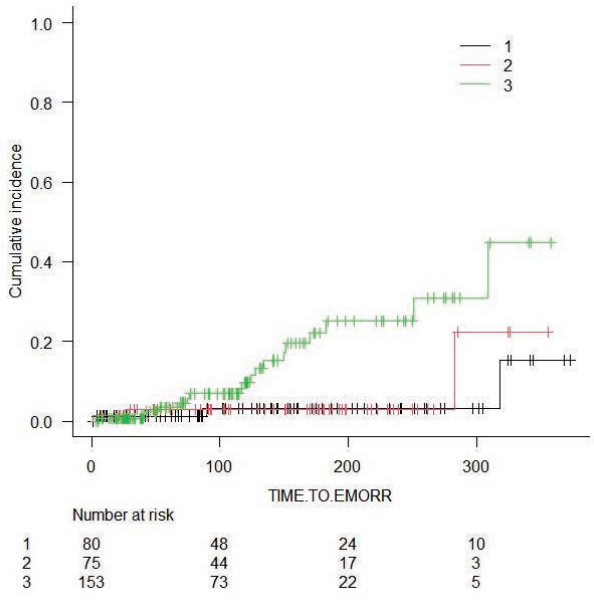

Figure 1.

DP031

INCIDENCE OF SUPERFICIAL VEIN THROMBOSIS IN PHILADELPHIA-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS AND RISK OF RECURRENCE

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Superficial vein thrombosis (SVT) is a well-established paraneoplastic condition. SVT is common among patients with Philadelphia-negative myeloproliferative neoplasms (MPN); however, no precise data about its incidence in MPN is available. Our study aims to determine, in an MPN population, SVT incidence and the risk of recurrence after index SVT. We retrospectively analyzed MPN patients referring to our center from 1978 to 2022. We recorded 50 cases of first SVT among 1,319 MPN patients (10,181 patient-years of observation), corresponding with an SVT incidence rate (IR) of 0.49 per 100 pt-years (95%CI 0.36-0.64). We compare them with 84 patients (9,960 patient-years of observation) who developed a first DVT/PE after MPN diagnosis (IR 0.84 per 100 pt-years, 95%CI 0.67-10.4). The SVT IR is significantly lower than DVT/PE IR (p=0.003). A second thrombotic event occurred in 25 (50%) SVT patients and 34 (41.7%) patients in the DVT/PE group corresponding with an IR of 7.4 per 100pt-years and 6.9 per 100 pt-years, respectively (95%CI 0.6-1.6, p=0.9).

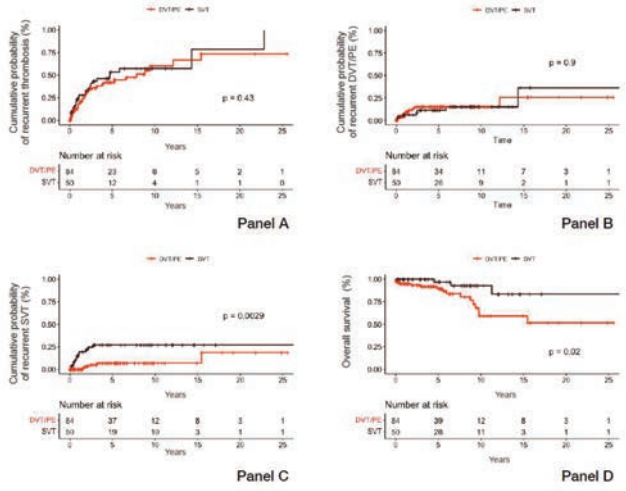

Figure 1. Cumulative probability of recurrent thrombosis (panel A), recurrent DVT/PE (panel B), recurrent superficial vein thrombosis (SVT) (panel C), and overall survival in MPN patients with a first SVT or a first DVT/PE.

Regarding venous recurrence, the IR per 100 pt-years of recurrent DVT/PE was 2.1 after the first SVT and 2.3 after the first DVT/PE, with no difference between the two groups (95%CI 0.4-3.4, p=0.9). The IR per 100 pt-years of recurrent SVT was significantly higher after the first SVT (IR 3.5) than after the first DVT/PE (IR 1.0, 95%CI 0.08-0.9, p=0.02). The two groups had no significant differences regarding arterial or unusual site thrombosis (*data not shown*). Cumulative probability of a recurrent thrombosis (Hazard Rate HR 1.2, 95%CI 0.7-2.1, p=0.4) [Figure 1, Panel A] or of a recurrent DVT/PE (HR 0.94, 95%CI 0.36-2.43, p=0.9) [Figure, Panel B] is similar between the two cohorts. Conversely, Cox analysis shows a

four-fold higher risk of a second SVT in the SVT group than in the DVT/PE group (HR 4.3, 95%CI 1.5-12.2, p=0.0029) [Figure 1, Panel C]. Finally, our data show a higher overall survival rate in the SVT group than in the DVT/PE group (HR 0.25, 95%CI 0.07-0.88, p=0.02) [Figure 1, Panel D]. In conclusion, the incidence of SVT in MPN patients seems to be increased compared to the general population. Patients with a first SVT show a risk of recurrences as high as after a first DVT/PE; moreover, they are particularly prone to recurrence in the superficial vein system. Therefore, the occurrence of an SVT should be considered predictive of major events, and special attention should be paid to those patients.

Chronic lymphocytic leukemia and lymphoproliferative syndromes

DP032

NATURAL CLONAL EVOLUTION OF CHRONIC LYMPHOCYTIC LEUKEMIA WITH BIMODAL CD49D EXPRESSION REVEALS CD49D PLASTICITY

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In chronic lymphocytic leukemia (CLL), expression of CD49d, the alpha-chain of the integrin VLA-4, is either homogenously negative (homCD49d-) or positive (homCD49d+), or (~20%) bimodal (bimCD49d), i.e. with CD49d- and CD49d+ subpopulations, the latter increasing overtime given its propensity to proliferate and segregate in tissue sites (Tissino *et al.*, Blood, 2020). By a whole-genome-sequencing (WGS) approach, we studied the interplay of natural clonal evolution with the dynamics of epigenetic regulation of CD49d expression in bimCD49d CLL. We collected 2-3 longitudinal samples (mean time interval: 3.3 y, range 1.3-7.0) from 8 untreated bimCD49d CLL with overtime increase of the CD49d+ component.

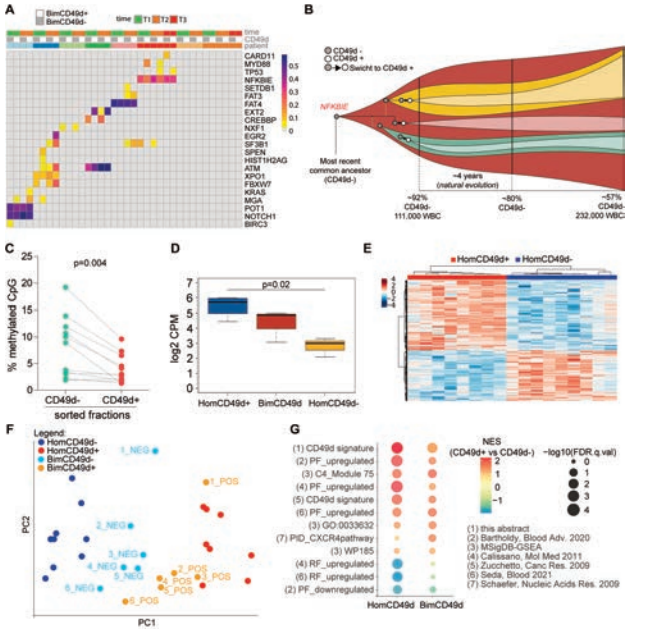

Figure 1.

WGS was carried out from sorted CLL cells (CD5+/CD19+) split

into CD49d+/CD49d- fractions in order to keep clonal dynamics of CD49d+/CD49d- subpopulations distinguishable. WGS analysis revealed 4,815 median heterozygous SNVs (range: 3,177-15,547) and 61 driver mutations in 22 genes (Figure 1A). Two or more branching subclones with identical genetic origin were present in both CD49d+ and CD49d- sorted subpopulations suggesting CD49d expression rewiring, these transitions occurring mainly toward the upregulation of CD49d expression in CD49d- cells (Figure 1B). DNA methylation in 119 CpG island of the ITGA4/CD49d gene promoter was done by NGS on bisulfite converted DNA. A higher degree of ITGA4 methylation was observed in CD49d- *vs* CD49d+ CLL fractions (p=0.004), indicating a methylation-driven epigenetic regulation (Figure 1C), as observed in other CLL settings (Zucchetto *et al*., Blood 2013). ATAC-seq of the ITGA4 promoter (according to Illumina protocol) showed higher chromatin accessibility in homCD49d+ (n=7) compared to homCD49d- cases (n=3, p=0.02), bimCD49d cases showing intermediate levels (n=3; Figure 1D); accessibility of the ITGA4 promoter correlated with the amount of ITGA4 mRNA (p<0.0001, r=0.93). The CD49d- and CD49d+ fractions from bimCD49d cases expressed a transcription signature respectively similar to homCD49d- and homCD49d+ cases (Figure E-F), CD49d+ cells over-expressing the transcription signatures of CLL proliferating fraction (PF; Figure 1G), including the CXCR4dim/CD5bright phenotype of cells recently egressed from lymph nodes, distinct from cells from the resting fraction (RF) bearing a CXCR4high/CD5dim profile (p=0.001). In conclusion, CD49d expression is plastic in CD49d bimodal CLL, its plasticity driven by a combination of genetic and epigenetic events.

DP033

MEASUREMENT OF INTRACLONAL DIVERSIFICATION REFINES THE PROGNOSTIC IMPACT OF THE IGHV MUTATIONAL STATUS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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The mutational status of the heavy chain variable region of the immunoglobulin (IGHV) gene is a prognostic/predictive marker in chronic lymphocytic leukemia (CLL). Despite the categorization in mutated (M) and unmutated (UM) IGHV, some CLL exhibit an ongoing introduction of mutations, in a process known as intraclonal diversification (ID). Here, we aimed to develop a bioinformatic workflow to quantify ID from IGHV repertoire sequencing data (RepSeq) and evaluate its clinical impact. IGHV RepSeq data of 983 CLL patients was analyzed with an original error-suppression pipeline to avoid ID overestimation. To measure ID, we extracted the inverse Simpson Index (iSI) from rarefaction curves; an iSI cutoff of 1.2 was used to discriminate between samples with ID from samples without ID. iSI calculated from RepSeq data (n=52) with Unique Molecular Identifier (UMI) highly correlated with iSI of RepSeq data corrected with our pipeline (p<0.0001, Figure 1A). RepSeq data from other lymphoproliferative disorders showed the highest iSI values in DLBCL and FL, according to their germinal center origin, while MCL showed the lowest values, as expected from the naïve B cell origin, and HCL has mixed values suggesting disease heterogeneity (Figure 1B). Among 983 CLL (508 M-CLL and 475 UM-CLL), we identified 144 with ID (14%) and 839 without ID CLL (iSI range 1.0-20.4; Fig.B). A significant overrepresentation of cases with ID was found in M- over UM-CLL (92 *vs* 53; p=0.002), without correlation with IGHV families or genes. Conversely, cases without ID were 422 *vs* 417 in UM- *vs* M-CLL, respectively. Strikingly, M-CLL patients with ID had significantly longer time-to-first treatment (TTFT) respect to M-CLL patients without ID (P=0.015; Figure 1C). A multivariate analysis on M-CLL only, identified ID classification as independent variable along with Rai Stage, CD49d, and del 11p/del 17p (Figure 1D). RNASeq performed on 14 M-CLL (8 with ID, 6 without ID) revealed that M-CLL with ID upregulated genesets related to BCR downstream signalling, T/NK cell activation and cellular apoptosis, while downregulated protein synthesis and transcription genesets (Figure 1E,F). Altogether, by reporting a novel UMI-independent method to assess ID in CLL, we provide evidence that: i) ID prevalently affects M-CLL; ii) patients affected by M-CLL with ID have better outcome than M-CLL cases without ID; iii) ID identifies a subset of M-CLL with specific molecular/biological features and clinical characteristics.

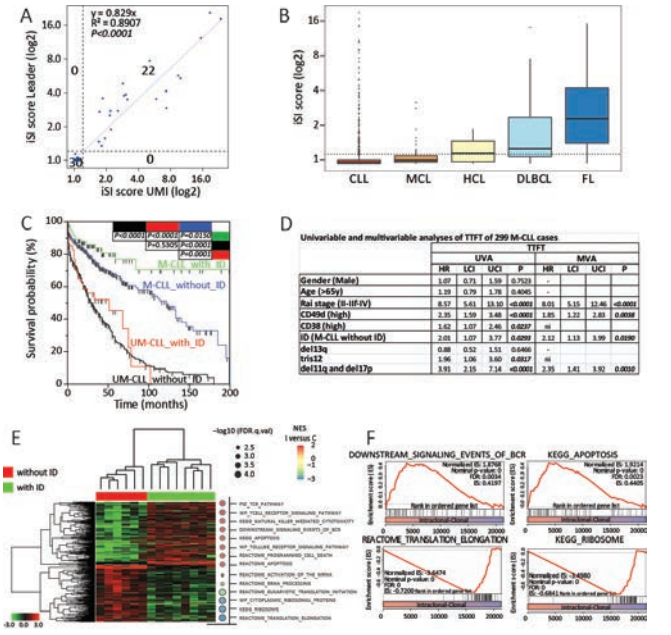

Figure 1.

DP034

CAT RS1001179 SINGLE NUCLEOTIDE POLYMORPHISM IDENTIFIES AN AGGRESSIVE CLINICAL BEHAVIOR IN CHRONIC LYMPHOCYTIC LEUKEMIA

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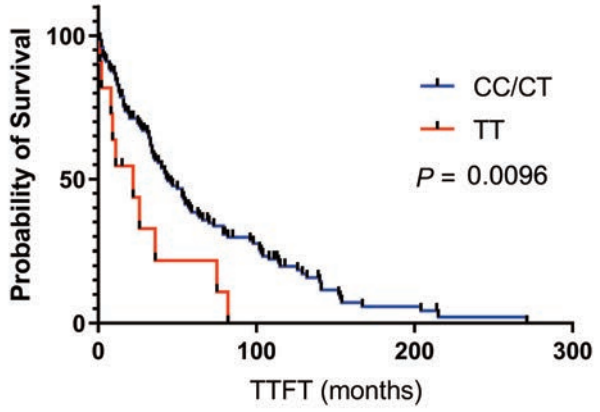
Chronic lymphocytic leukemia (CLL) is an incurable disease characterized by a highly variable clinical course, with some patients having indolent disease and others experiencing a more accelerated course, treatment resistance and a dismal outcome. We have recently identified low catalase (CAT) expression as a major antioxidant element that identifies an indolent clinical behavior in CLL. In contrast, high CAT expression is associated with a more aggressive disease course. Moreover, we have shown that CLL cells harboring the rs1001179 single nucleotide polymorphism (SNP) T allele in the CAT promoter exhibit a significantly higher CAT expression compared with cells bearing the CC genotype. The objective of this study was to investigate the prognostic significance of the CAT rs1001179 SNP in CLL. We studied 235 patients with CLL and 123 healthy donors (HDs). Genotyping was assessed by restriction fragment length polymorphism (RFLP)-PCR. Time to first treatment (TTFT) curves were estimated using the Kaplan-Meier method and compared using the log-rank test. The distribution of genotypes was consistent with the Hardy–Weinberg equilibrium among CLL patients and HDs (χ^2=0.156, P>0.05; χ^2=0.099, P>0.05; respectively), and no significant differences in genotype frequencies was found. The mutant homozygous TT genotype identified a subgroup of CLL patients with a more aggressive disease and a shorter TTFT whereas the CC and CT genotypes were associated with an indolent disease course (CC/CT *vs* TT: P=0.0096; Figure 1).



Kaplan-Meier curves of TTFT for subgroups of CLL patients distinguished by CC/CT (n = 122) and TT (n =11) genotypes of rs1001179 SNP. Difference between the two curves was calculated with log-rank test. TTFT: time to first treatment.

Figure 1.

Furthermore, TT genotype refines risk stratification in patients with indolent disease, defined by low ZAP70 expression (CC/CT *vs* TT: P<0.0001), favorable/neutral cytogenetics (CC/CT *vs* TT: P=0.0004) and Binet A stage (CC/CT *vs* TT: P=0.0383). Consistently, we have documented that patients bearing the TT genotype were characterized by a higher % of lymphocytes; a lower count of red blood cells, hemoglobin, and platelets at diagnosis compared with patients bearing the CC/CT genotype. Remarkably, the TT genotype identified a subgroup of CLL patients with a faster clinical progression within early-stage disease subgroups of patients characterized by lower CD38 expression and wild-type p53 (CC/CT *vs* TT: P=0.0514; CC/CT *vs* TT: P=0.0560; respectively). This study shows for the first time that the TT genotype of CAT rs1001179 SNP identifies CLL patients with a poor prognosis and provides prognostic information on disease progression in patients with early-stage disease.

DP035

PROGNOSTIC AND PREDICTIVE IMPACT OF NOTCH1 MUTATIONS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA. A SINGLE CENTER EXPERIENCE ON 271 PATIENTS

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Background. *NOTCH1* mutations (*NOTCH1*^{m}) are recurrently detected in patients with Chronic Lymphocytic Leukemia (CLL) and associated with poor outcomes. Although patients harbouring *NOTCH1*^{m} express lower levels of CD20 and do not benefit from the addition of rituximab (R) to chemotherapy or venetoclax (VEN), its assessment is not recommended.

Aims. In this study we explored the prognostic and predictive impact of *NOTCH1*^{m} in a real-life cohort of CLL patients.

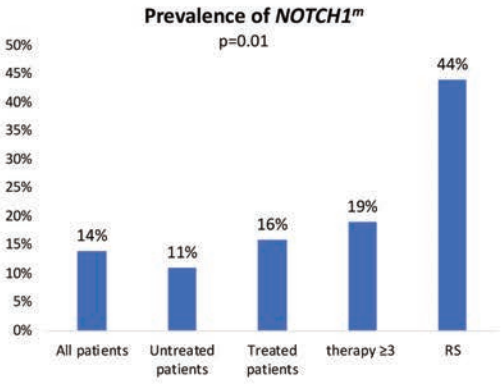
Methods. We included 271 CLL patients admitted to the Hematology Unit of Padua University Hospital between 1999 and 2023. *NOTCH1*^{m} in the C-terminal PEST domain were analyzed at the time of diagnosis and/or progression by DNA Sanger sequencing. Patients were treated with chemoimmunotherapy (CIT) such as fludarabine-cyclophosphamide-R, bendamustine-R, obinutuzumab (G) or R+chlorambucil, with BTK inhibitors (BTKi) or VEN-based treatments (VEN±R or G). The impact of *NOTCH1*^{m} was evaluated by time to first treatment (TTFT), time to next treatment (TTNT) and overall survival (OS).

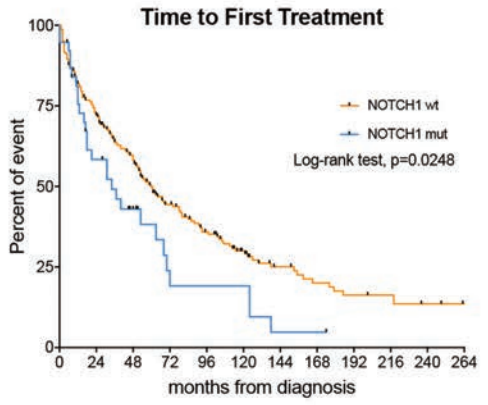
Results. The median age was 73 years, 51% patients harboured unmutated IGHV, 17% trisomy 12, 63% TP53 disruption (deletion or mutation) and 35% a complex karyotype. Overall *NOTCH1*^{m} were detected in 39 (14%) patients (c.7541-7542delCT in 87% of cases), 4 (11%) of them were untreated, 7 (19%) received ≥3 lines of therapy and 17 (44%) developed Richter's syndrome (RS, Figure 1). The rate of RS transformation was higher in *NOTCH1*^{m} patients (p=0.01).

After a median follow-up of 118 months (m), *NOTCH1*^{m} patients displayed a significantly shorter TTFT (median TTFT, 34 *vs* 60 m, HR 1.57 95%CI 1.07-2.82; p=0.02) and OS (median OS, 244 m *vs* not reached, HR 3.18, 95%CI 1.35-7.51, p=0.008) compared with wild-type ones (Figure 1). To explore the predictive impact of *NOTCH1*^{m} we analyzed its relation to different treatments. Patients with *NOTCH1*^{m} treated with CIT (n=108) had a shorter TTNT (median TTNT 46 *vs* 58 m, HR 2.41, 95%CI 1.11-5.24, p=0.0260). Conversely, no shorter duration of response was observed in *NOTCH1*^{m}

patients receiving BTKi (n=88, p=0.4539) but we observed a negative trend with VEN-based treatments (n=42, median TTNT 34 *vs* 58 m, p=0.3046).

Conclusions. *NOTCH1*^{m} had a negative impact on prognosis and on response to CIT and VEN-based treatments in CLL patients. Since an increasing number of patients will receive VEN-based fixed duration treatments, our results suggest that analysis of *NOTCH1*^{m} should be incorporated in the clinical practice.





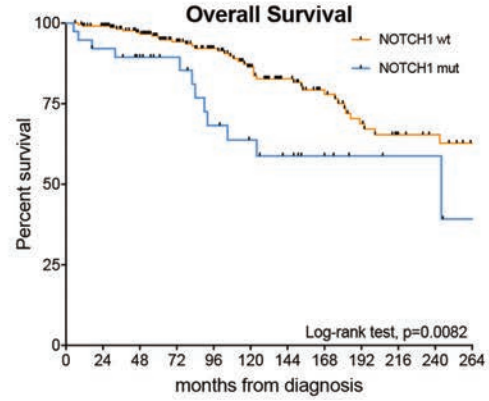


Figure 1.

DP036

ABSTRACT NOT PUBLISHABLE

DP037

PET/CT IN THE CLINICAL MANAGEMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TREATED WITH BTK INHIBITORS

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FDG positron emission tomography-computed tomography (PET/CT) is a sensitive method for detection of aggressive lymphomas, other cancers, and systemic infections. Between September 2014 and March 2023, 95 patients with chronic lymphocytic leukemia (CLL), 36 treatment-naïve and 59 relapsed/refractory, had PET/CT assessed before treatment with Bruton tyrosine kinase inhibitors (BTKi) at the Hematology Institute of the Sapienza University of Rome. PET/CT was considered in presence of at least two risk-factors suggesting the presence of an aggressive disease: B symptoms, lymph nodes with fast increase in size and diameter ≥5 cm; R/R disease, severe cytopenia, increased LDH or beta-2 microglobulin. This observational/retrospective study aimed at defining whether baseline SUVmax levels of <5 *vs* ≥5 could have an impact on the probability of achieving a clinical CR (normal blood count, no enlarged nodes nor hepatosplenomegaly), on PFS, EFS and of predicting RT or SM.

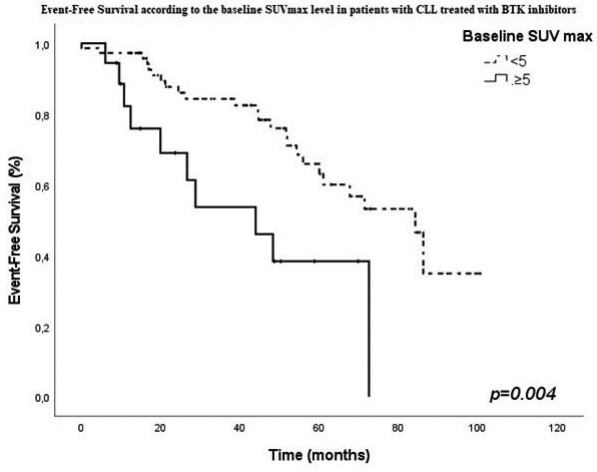

Figure 1.

The median age of patients was 68 (41-83) years; 59% had unmutated IGHV, and 35% TP53 disruption. The median SUVmax value at baseline was 2.4 (1.1-31) with SUVmax levels ≥5 in 22 patients (23%).The need for a biopsy to exclude a more aggressive disease was considered in 34 (36%) patients, in 23 (68%) before starting BTKi treatment and 11 (32%) during BTKi treatment. A more aggressive disease, RT or SM, was diagnosed in 14 (41%) biopsied patients, and included RT in 4 (11%) and a SM in 10 (29%; lung 3; breast, 1; prostate, 1; stomach, 1; bone, 1; liver, 1; kidney, 1; rectum, 1). SUVmax values ≥5 or <5 predicted RT or SM in 13/24 (54%)

and 1/10 (10%) biopsied patients, respectively (p=0.024). The best response recorded in the 91 patients who were treated with BTKi included a clinical CR in 29 (32%), a PR in 42 (46%), and a PR-L in 15 (17%), while 5 (5%) did not respond. Compared to patients with higher SUVmax values, those with baseline SUVmax <5 achieved a higher rate of clinical CR (37% *vs* 11%; p=0.047), a higher median PFS (84.3 *vs* 48.4 months; p=0.014) and EFS including RT and SM events (84.3 *vs* 44 months; p=0.004). In conclusion, in this study, SUVmax values significantly impacted the quality of response, PFS and EFS of CLL patients treated with BTKi. Moreover, our results confirm the significant value of SUVmax levels in predicting RT or SM. Controlled and prospective trials are needed to validate the prognostic role of PET/TC in the clinical management of patients treated with BTK inhibitors

DP038

LYMPHOMA AND CHRONIC NON-CLONAL LYMPHOPROLIFERATION…BE AWARE OF THE IMMUNE SYSTEM!

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*contributed equally to this work.

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Introduction. Systemic chronic non-clonal lymphoproliferation can be the presenting feature of inborn errors of immunity (IEIs) or may develop during the disease course. Data are scarce on management, disease evolution and risk factors for malignant degeneration.

Methods. We retrospectively enrolled patients followed for systemic non-clonal lymphoproliferation and IEI at the IRCCS Azienda Ospedaliero-Universitaria di Bologna and the Bambino Gesù Pediatric Hospital of Rome from 1996 to 2022.

Results. We included a total of 47 patients. The median age of symptoms onset was 7 years (range 0,1-53 years) and of IEI diagnosis 14 years (0,5-60 yrs), with a median diagnostic delay of 3 years (0-30 yrs). 34% had isolated lymphoproliferation at onset. Of them, 21,3% were >18 years at symptoms onset and 29,8% at diagnosis. 25,5% were diagnosed as Common Variable Immunodeficiency (CVID), 40,4 % received a genetic diagnosis, 8,5% as Autoimmune Lymphoproliferative Syndrome (ALPS) and 8,5% as Activated PI3K delta Syndrome (APDS). After a median follow-up of 10 years from IEI diagnosis, 31,9% of patients developed lymphoma (53,3% Hodgkin Lymphoma) and 46,8 % developed autoimmune (AI) and/or autoinflammatory disorders. 43% of patients were treated with immunomodulant therapies. Patients developing lymphoma were less likely to have an AI and/or autoinflammatory manifestations compared to patients without malignant lymphoproliferation (20,0% *vs* 59,4%; p=0,015) and more frequently received antibiotic prophylaxis during the disease course (73,3% *vs* 15,6%; p=0,001). On the contrary, patients with AI and autoinflammation less frequently had lymphoproliferation at disease onset (46,7% *vs* 72%; p=0,006) and presented a higher frequency of gastrointestinal and endocrinological complaints. Significantly lower absolute lymphocyte, CD3+CD4+, CD3+CD8+ and CD16+56+ counts with a higher percentage of CD3+CD4+ central memory at disease onset were observed in AI patients.

Conclusions. Chronic non-clonal lymphoproliferation may underly an IEI also in adulthood. These patients are at high risk of developing lymphoma. Providing a proper immune workup and building multidisciplinary diagnostic pathways are pivotal in delivering appropriate follow-up and targeted therapies. We observed an inverse association between lymphoma and AI/autoinflammatory manifestations, that should be confirmed in further studies. Expanding the cohort will help identify more indicators of disease progression and risks.

DP039

ABSTRACT NOT PUBLISHABLE

DP040

PROLONGED TREATMENT WITH IBRUTINIB MODULATES PHENOTYPIC AND FUNCTIONAL FEATURES OF IMMUNE CELL COMPARTMENTS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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CLL is characterized by a wide range of immune alterations, responsible for the increased susceptibility to infections, the occurrence of autoimmunity and the failure to control disease progression. Besides its direct anti-tumor activity, ibrutinib has shown to exert immunomodulatory effects. The aim of this study was to analyze immune changes occurring in CLL patients treated with ibrutinib. Thirty-one patients with progressive CLL and the indication to start ibrutinib therapy were included. Peripheral blood samples were collected before and after 1, 6, 12 and 24 months of ibrutinib treatment. Fifteen additional patients with early-phase disease (EP-CLL) and 10 healthy donors (HD) were analyzed. Immune cell counts, the expression of surface markers and functional assays were performed by flow cytometry. At the 6-month timepoint, we observed a significantly lower value in the number of CLL cells, which persisted after 12 and 24 months of ibrutinib treatment. We detected a significant reduction of CD3+ and CD4+ T-cell counts at month 12, and a decrease of CD8+ T-cell number already at month 6 of therapy. Regarding γδ T-cell compartment, the count of Vδ1 T cells – but not Vγ9Vδ2 T cells – significantly decreased by 12 months of treatment. A prolonged (*i.e.* 24-month) therapy with ibrutinib also favored the normalization of Tregs, NK and NKT-cell counts. Before treatment, we found a higher expression of the activation marker CD69 on T cells from pre-treatment compared to EP-CLL and HD, which nor-

malized after 6 months of therapy. Phenotypic analysis revealed that PD-1 expression on CD8+ T cells was significantly lowered by 6 and 12 months of ibrutinib treatment. Ibrutinib also induced a significant downmodulation of other inhibitory checkpoints expressed on T cells: CTLA-4, CD96, Tim-3 and TIGIT. Similar to T cells, CD69, CD96, TIGIT and Tim-3 were significantly decreased overtime by ibrutinib therapy on NK cells. Functional data showed that 12 months of ibrutinib treatment enhanced Vγ9Vδ2 T-cell cytotoxicity and NK-cell-mediated ADCC of obinutuzumab towards MEC-1 cells. An improvement in the proliferation of both CD4+ and CD8+ T cells was also detected at month 24. The correlation of phenotypic changes with clinical response at 12 months demonstrated that the positive immunomodulatory effects of ibrutinib were mainly observed in patients achieving a partial (n=21) or complete (n=2) response and not in patients with a stable disease (n=8).

DP041

ABSTRACT NOT PUBLISHABLE

DP042

SERUM SOLUBLE INTERLEUKIN-2 RECEPTOR (SIL-2R) LEVELS IN HAIRY CELL LEUKEMIA (HCL) AS MARKER OF TUMOR BURDEN WITH PROGNOSTIC IMPLICATIONS FOR DISEASE MONITORING

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Background. Neoplastic cells of hairy cell leukemia (HCL) express the interleukin-2 receptor on their surface, and its alpha-chain is secreted in large amounts in the serum in a soluble form (sIL-2R). Serum sIL-2R levels have been previously investigated as a marker of tumor burden in HCL patients treated with interferon-α. To expand on this knowledge, we aimed to assess the usefulness of sIL-2R as a marker of disease burden in patients treated with purine analogs, its relationship to minimal residual disease (MRD) status, and its prognostic utility in disease monitoring.

Methods. We collected data over 59 patients with HCL from the Hematology Unit of the University of Padova from 2002 to 2023, who underwent yearly serial sIL-2R measurements after diagnosis (n=5, 8.4%) or disease remission after first-line therapy (n=54, 91.5%). We correlated sIL-2R kinetics with time to cytopenia (TTC) (neutrophils < 1000/μL or platelets <100.000/μL) and time to next treatment (TTNT). In 50 patients we explored the correlation of post-therapy sIL-2R levels with response and MRD status evaluated by immunohistochemistry according to guidelines. The correlation of pre-therapy sIL-2R levels with other hematologic features (leukocyte count, splenomegaly, β-2 microglobulin, circulating hairy cells %, and % of bone marrow infiltration) was also investigated.

Results. Mean age was 60.6 years, 16.9% of patients were females and 83.1% males. 88% were treated with cladribine and 12% with pentostatin. sIL-2R levels before therapy correlated with leukocyte count (p=0.009), β-2 microglobulin levels (p<0.001), circulating hairy cells (p=0.017), and bone marrow infiltration (p=0.009), but not splenomegaly. Median sIL-2R levels were significantly different between patients achieving a complete response versus those who did not (median 568 for CR *vs* 3272 for PR/SD; p=0.002). A statistically significant difference was observed in post-therapy sIL-2R levels between MRD- and MRD+ patients (median 502 *vs* 724; p=0.003) (Figure 1A). A rise in sIL-2R levels ≥ 25% between two samples taken 1-year apart during follow-up, was associated with shorter TTC (HR 26.2; 95%CI 3.44-200; p<0.001) (Figure 1B) and TTNT (HR 8.83; 95%CI 1.9-40.9; p<0.001).

Conclusions. sIL-2R is a reliable marker of disease burden and depth of response in HCL. Given its ability to predict the onset of cytopenias, sIL-2R may also represent a cheap and reliable marker for disease monitoring with relevant prognostic implications.

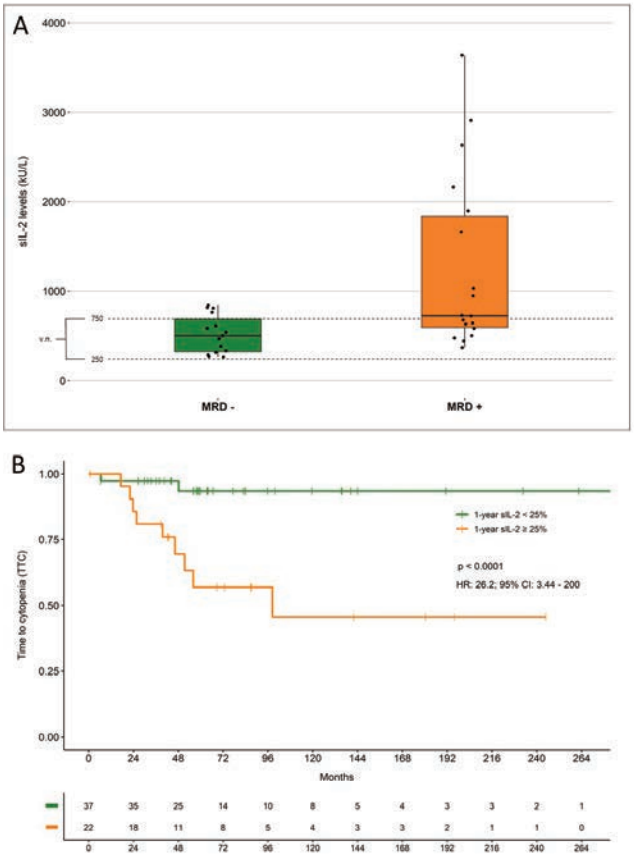

Figure 1.

DP043

CASTLEMAN DISEASE AND CASTLEMAN-LIKE LYMPHADENOPATHIES: A 20-YEAR RETROSPECTIVE ANALYSIS OF CLINICAL AND PATHOLOGICAL FEATURES AT SANT'ANDREA UNIVERSITY HOSPITAL, SAPIENZA OF ROME

S. Pelliccia[1], E. Rogges[2], A. Cardoni[3], G. Lopez[2], M.P. Bianchi[1], E. Conte[1], A. Faccini[1], C. Togni[1], S. Scarpino[2], F. Del Porto[4], F. Di Gregorio[5], A. Di Napoli[2], A. Tafuri[1]

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Background. Castleman disease (CD) comprises a group of rare and heterogeneous hematologic disorders including unicentric (UCD) and multicentric forms (MCD), divided into HHV8-MCD, POEMS-MCD and idiopathic-MCD. Recently great progress has been made in the diagnosis and treatment of CD thanks to the publication of the Castleman Disease Collaborative Network guidelines. According to diagnostic criteria, we performed a retrospective revision of lymphadenitis with histopathological findings reminiscent of CD diagnosed in the years 2003-2022 by applying a multidisciplinary approach that integrated histology with clinical, serological and imaging findings, in order to re-classify the lymphadenopathy and to extrapolate the "true" CD cases.

Methods. Thirty-seven patients with a diagnosis of reactive lymphadenopathy with histological CD-like performed at our center in the years from 2003 to 2022, were enrolled in the study. Patients data, clinical history, radiological findings, laboratory results and virologic status, were collected retrospectively. Histological revision of each case was conducted by three different pathologists according to Dispenzieri's criteria.

Results. The revision of the 37 enrolled patients with a diagnosis of reactive lymphadenitis with CD-like histology confirmed the diagnosis of CD in 20 cases (54%). In particular, 10 (27%) involving a single lymph node station were confirmed as UCD, whereas among 27 (73%) patients with multiple enlarged lymph nodes only 10 (37%) cases were confirmed as MCD: 3 HHV8-MCD (30%), 2 POEMS-MCD (20%), 5 iMCD (50%), respectively. Among the remaining 17 cases, 6 were re-classified as autoimmune diseases, 9 reactive lymphadenitis, 1 was a reactive lymphadenitis associated with HIV-infection, and 1 nodal marginal zone lymphoma with CD-like features. All patients with UCD were treated surgically resulting in excellent prognosis. The treatment for patients with iMCD was instead heterogeneous over the years. In fact, 2 received siltuximab, 1 rituximab, 1 was treated with surgical removal of the bulky mass, and 1 did not received any treatment. These 5 patients all died, except one.

Conclusions. We confirm the crucial role of the multidisciplinary approach to the diagnosis of reactive lymphadenitis. Moreover, we provide evidence that applying the recently established consensus clinic-pathological criteria for Castleman disease, the diagnostic accuracy is significantly improved.

Acute leukemias

DP044

IS FLT3 INHIBITION A THERAPEUTIC OPTION FOR TRIPLE NEGATIVE B-CELL ADULT ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS?

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Introduction. The prognosis of B cell Acute Lymphoblastic Leukemia (B-ALL) patients (pts) relapsing after Hematopoietic Transplant is poor and new drugs are needed. In acute myeloid leukemia, FLT3-inhibitors (FLT3i) are showing promising results in *FLT3*-mutated (mut) cases. Their potential use in *FLT3*-mut B-ALL has been poorly investigated.

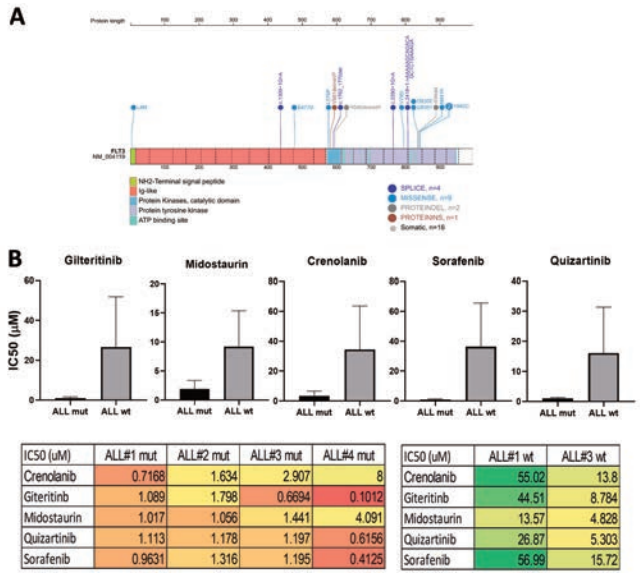
Methods. We sequenced 183 adult B-ALL [n=131 Triple-Negative (TN) for Ph, t(4;11) and t(1;19); n=52 Positive for Ph or t(4;11) or t(1;19); TruSight RNA Pan-Cancer, Illumina-1385 genes] and 15 healthy subjects. 12 *FLT3* mut B-ALL available samples were further sequenced with Extended Myeloid Solution (98 genes; SOPHiA; *FLT3* covered full sequencing).

Results. We found 16 *FLT3* mut in 11.5% (15/131) TN B-ALL and in one Ph+ case (1/43): 43.8% were TKD mut, 3 ITD mut, 3 splicing site mut,1 N-terminal, 1 juxta-membrane domain and 1 Immunoglubulin-like site mut (Figure 1A). *FLT3* mut were confirmed in 12/13 pts with available DNA. *FLT3* expression was increased in 11/15 cases compared to healthy subjects. Targeted NGS revealed the co-occurrence with other mutations (range 1-15), and in particular with *KMT2D, CREBBP* and *CSMD1* alterations. Moreover, 11/13 samples carried copy number alteration (mean 12), mostly amplifications (87 gains *vs* 43 losses). *CDKN2A* & *IKZF1* were the most frequently altered genes (n=8 and n=5 CN-loss). *ATM* and *MYC* were amplified in 3 cases. Differential expression analysis revealed mutual exclusivity of *FLT3*mut and upregulation of *CRLF2/LRRC37A2/PTPRC*. To evaluate the effect of FLT3 inhibitors in ALL, we treated *ex vivo* primary leukemic cells of 6 adult ALL patients (*FLT3* mut n=4; *FLT3* wt n=2) with increasing concentrations of Gilteritinib, Midostaurin, Crenolanib, Sorafenib and Quizartibin for 24, 48 and 72h. We observed a trend towards greater response of *FLT3*-mut ALL

cells compared to wt ones. The average IC_{50} values in response to the five FLT3i was 1.6 uM and 24.5 uM after 72h of treatment in *FLT3*-mut and *FLT3*-wt B-ALL, respectively (Figure 1B).

Conclusions. *FLT3* mutations identify a novel subgroup of TN B-ALL with therapeutic potential in combination regimens.

Acknowledgements. AIRC IG 2019 (Project Code: 23810).



IC50 (uM)	ALL#1 mut	ALL#2 mut	ALL#3 mut	ALL#4 mut
Crenolanib	0.7168	1.634	2.907	8
Giteritinib	1.089	1.798	0.6694	0.1012
Midostaurin	1.017	1.066	1.441	4.091
Quizartinib	1.113	1.178	1.197	0.6156
Sorafenib	0.9631	1.316	1.195	0.4125

IC50 (uM)	ALL#1 wt	ALL#3 wt
Crenolanib	55.02	13.8
Giteritinib	44.51	8.784
Midostaurin	13.57	4.828
Quizartinib	26.87	5.303
Sorafenib	56.99	15.72

Figure 1.

DP045

A SIMPLE PROGNOSTIC SCORE CAN PREDICT THE MEDIAN OVERALL SURVIVAL IN AML RECEIVING FIRST LINEE THERAPY WITH VENETOCLAX AND AZACITIDINE

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Introduction. The Azacitidine+Venetoclax regimen (AZA/VEN) is now the standard of care for first line therapy in patients (pts) with AML and unfit for intensive chemotherapy. The real word data confirmed the results of the VIALE-A registrative study in terms of Complete Remission Rate (CR) and Overall Survival (OS). However, as the number of pts treated with this combination continues to increase, there is a clinical need to predict the probability of OS based not only on the AML biological parameters but also according to other pts related characteristics (such as age at diagnosis, concomitant comorbidities, presence of infection at baseline).

Methods and Results. We analyze the probability of survival of 255 pts with AML treated with AZA/VEN in the first line (median age, 74 years, range 41-85) in 8 Italian Hematology Centers, according a predictive score including 7 already validated and easy pre-therapy prognostic parameters (patient' age, secondary AML, karyotype, WBC>30,000/mmc, presence of cardiac comorbidity, presence of pulmonary comorbidity, documented pre-therapy Infection). Based on these parameters, 3 classes of pre-AZA/VEN treatment Scores were defined: LOW (0-1.5 points), INTERMEDIATE (2-2.5 points) and HIGH (> 3 points). Each single parameter has recently been identified to predict survival in a large AML population (Cancer 2023; 1-13). We did not take into consideration neither the chart reported performance status (its report is often inaccurate) nor the value of platelets or hemoglobin prior to treatment (that could be affected by transfusional support). In comparison with what has been published previously, our survival predictive score has been further simplified. The OS curves according to the 3 Score classes are shown in Figure 1 and documented significantly different median OS in the 3 groups: in the group with LOW-SCORE(1), median OS was 13.5 months; in the group with INT-SCORE(2), 7.6 months and in the group with HIGH-SCORE(3), only 5.3 months (log-rank p=0.001). The 2-year survival rates were 31%, 22% and 0%, in the low, intermediate and high-risk score category, respectively.

Conclusions. The calculation of this simplified predictive OS score (including 7 easily and widely available parameters) allows a significant stratification of the median OS probability in pts treated with AZA/VEN. These results, if confirmed in a larger population, may represent a useful information in clinical practice and may help to discuss, with pts and their caregivers, the AML outcome, particularly in those with older age and comorbidities.

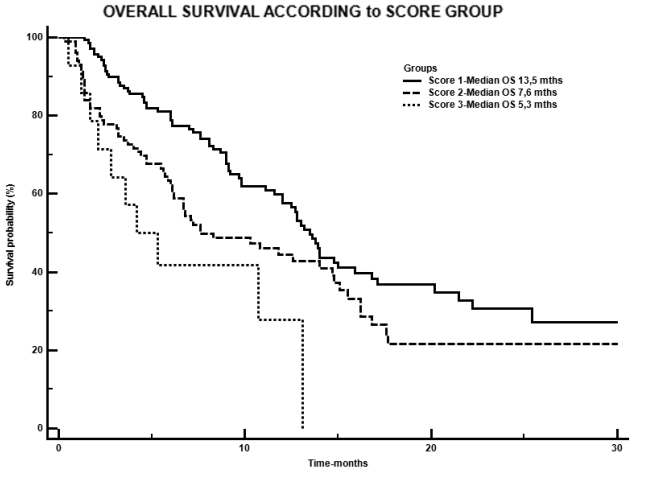

Figure 1.

DP046

DIFFERENCES IN IMMUNE TRANSCRIPTOMIC PROFILE ARE ASSOCIATED WITH RESPONSE TO FLT3 INHIBITORS IN FLT3-MUTATED ACUTE MYELOID LEUKEMIA PATIENTS AND MAY CONTRIBUTE TO THERAPY RESISTANCE

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Background. Despite significative improvements in FLT3-mutated Acute Myeloid Leukemia (AML) prognosis since FLT3 inhibitors (FLT3i) adoption, still a significant percentage of patients results refractory or relapses. Thus, the investigation of novel resistance mechanisms to FLT3i is crucial.

Aims. This study aims at investigating intrinsic and potential novel immunological extrinsic mechanisms of resistance to FLT3i-containing regimens.

Methods. Two cohorts of FLT3-mut AML patients treated either with Midostaurin in combination with intensive chemotherapy (M cohort) as induction or Gilteritinib (G cohort) as salvage at Seràgnoli Hematology Institute of Bologna were enrolled. Bone marrow (BM) samples were analysed pre-therapy and at response assessment by using a custom NGS panel covering the full-cds of 28 genes and the PanCancer IO 360 Nanostring GEP Panel.

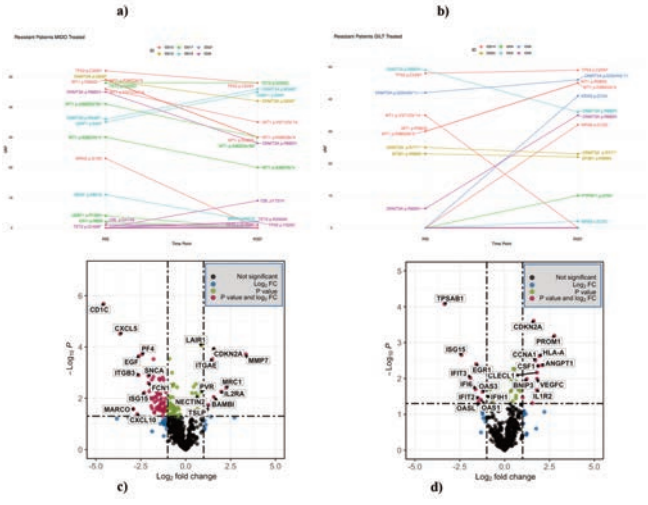

Figure 1. a) Evolutionary trajectories of non-FLT3 pathogenic mutations in patients refractory to Midostaurin in combination with intensive chemotherapy; b) Evolutionary trajectories of non-FLT3 pathogenic mutations in patients refractory to Gilteritinib single-agent therapy. c) Volcano plot showing the differential genes among resistant (Log2 fold change positive) versus sensitive (Log2 fold change negative) patients to Midostaurin plus intensive chemotherapy (p<0.01, FDR <0.01). d) Volcano plot showing the differential genes amongmresistant (Log2 fold change positive) versus sensitive (Log2 fold change negative) patients to Gilteritinib (p<0.01, FDR <0.01).

Results. Twelve Newly-Diagnosed (ND) FLT3-mutated AML patients and 13 Relapsed/Refractory (R/R) patients were enrolled in the M and G cohorts, respectively. Patients were divided into Sensitive (S)(n=6 in M and n=7 in G cohort) and Resistant (R)(n=6 in both M and G cohort) according to morphologic BM response. Firstly, FLT3 full-coding sequencing did not detect any clearly pathogenetic non-canonical mutation. M737I, M837I, P890L and P534L were 4 detected NC variants. Secondly, evaluating non-FLT3 variants detected pre- and post-therapy we observed different evolutionary trajectories. Particularly, resistance was frequently associated with the persistence of pathogenic variants (*e.g.* tp53, U2AF1, WT1) at high VAFs (> 10 %) in M cohort (Figure 1a), whereas among Gilteritinib R patients a variant onset was observed in 4/6 (66.7 %) patients, affecting RAS pathway in all cases (Figure 1b). Of note, differences in the immune transcriptomic profile have been observed between S and R patients. A higher activation of genes belonging to pathways involved in innate immune response was present in S patients (*e.g.* CD1C, CXCL5 and PF4 in patients S to Midostaurin (Figure 1c), specifically linked to interferon alfa and beta in Gilteritinib cohort (e.g. ISG15, IFIT3 and IFI6)(Figure 1d). Some genes with a potential immune tolerogenic role (IL2RA and IL1R2) were upregulated in R patients.

Conclusions. This study portrays evolutionary trajectories under FLT3i-containing regimens pressure and highlights novel preliminary differences in immune transcriptomic profile associated with FLT3i effectiveness.

DP047

CPX-351 EFFICACY IN YOUNG AML PATIENTS (<60 YEARS OLD): ANALYSIS OF A MULTICENTER REAL-LIFE EXPERIENCE

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Data on young acute myeloid leukemia (AML) patients (pts) treated with CPX-351 are limited. The aim of this study is to explore CPX-351 efficacy in younger pts (<60 years old) in real-life.

From October 2018 to February 2023, 113 pts were treated with CPX-351. Median age was 54 (range 32-59). Baseline characteristics are reported in Table 1.

Table 1. Baseline characteristics.

Variable	t-AML (n=33)	MRC-AML (n=80)
complex karyotype	8 (24%)	27 (34%)
-7/del(7q)	3 (9%)	11 (14%)
del(5q)	0	2 (2%)
intermediate risk karyotype	19 (58%)	36 (45%)
inv(16)	1 (3%)	0
not evaluable	2 (6%)	4 (5%)

Caption: 33 pts had t-AML, 8 of them with complex karyotype (CK), 3 had del(7q), 19 intermediate risk K (int K), 1 inv(16) and 2 not evaluable K.
80 pts had MRC-AML: 27 had CK, 11 monosomy of chromosome 7 or del(7q) and 2 del(5q). 36 had int K, 10 of them with AML secondary to MDS or MDS/MPN (sec-AML). K analysis failed in 4 cases, 1 of them with sec-AML. Accounting the de novo AML with int K (26) or failed K (3), 29 pts had a morphological MRC-AML.
t-AML: therapy related acute myeloid leukemia
AML-MRC: AML with myelodysplasia-related changes

All pts received 1st induction, with 2 dying early because of lung infection and 1 not yet evaluable. Therefore, 110 pts were evaluable for response assessment after 1st induction. Seventy pts (64%) achieved complete remission (CR), 40 (36%) had a refractory disease (RD). Seventeen with RD received a re-induction and 8 reached CR. One additional pt with RD achieved CR after 1st consolidation (cons), given instead of re-induction. Cumulative CR rate was 72% (79/110 pts). Sixty-1 pts received 1st cons and 18 of them also a 2nd cons. Forty-6 of 79 pts in CR (58%) underwent allogeneic stem cell transplant (HSCT); of these 46, 6 received a 2nd induction. One or 2 courses of cons were given to all but 6 pts. Five (11%) of 46 pts relapsed after HSCT. Of the 31 pts who did not undergo HSCT, 11 (38%) relapsed and 4 of them (33%) were transplanted in 2nd CR. At a median follow-up of 21 months (mos), median disease-free survival (DFS) was not reached (NR) with 62 pts (78%) being still in CR. DFS was negatively influenced by complex karyotype (CK) (median DFS 13,5 mos for CK *vs* NR for no-CK, p=0.046). Pts who received HSCT in 1st CR had a median DFS not yet reached while median DFS for those not allografted was 11,3 mos (p<0.001). Median OS was NR for pts in CR, with 55 (70%) of them being still alive, while those with RD had a median OS of 7 mos. Pts with CK had a median OS of 9.6 mos *vs* NR for those no-CK, p=0.007. Median OS of pts undergoing HSCT in 1st CR was NR while it was 21 mos for those not transplanted. In univariate analysis CK (HR 2.3; 95% CI 1.2-4.2, p=0.008); CR status (HR 0.2; 95% CI 0.1 – 0.5, p<0.001); HSCT in 1st CR (HR 0.2; 95% CI 0.1-0.5, p<0.001) were factors affecting OS. In multivariate analysis only CR status (HR 0.3; 95% CI 0.2 – 0.7, p=0.005) and HSCT in 1st remission (HR 0.4; 95% CI 0.2 – 0.9, p=0.03) were factors independently associated with OS. In conclusion, CPX-351 appears to be an effective treatment even in younger pts, in whom the successful achievement of CR should be consolidated as soon as possible with HSCT. This observation emphasizes the need of a timely activation of a donor search.

DP048

THE COMPARISON OF V-FLAI, FLAI AND 3+7 REGIMENS BY MULTILEVEL PROPENSITY SCORE HIGHLIGHTS THE BENEFIT OF THE ADDITION OF VENETOCLAX IN NO LOW-RISK AML TREATED IN GIMEMA CLINICAL TRIALS AND REAL WORLD

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Background. To evaluate the advantage of the addition of venetoclax to chemotherapy, the GIMEMA AML1718 - based on venetoclax-FLAI in intermediate/high-risk ELN2017 AML - was compared to GIMEMA AML1310, which entailed a "3+7"-like induction and a risk-adapted, MRD-directed post-remission transplant allocation (Venditti 2019), and to FLAI real-life single center experience (Guolo 2016).

Methods. To perform a reliable comparison, patient-level data from AML1718 (n=57), AML1310 (n=445) and real-life FLAI experience (n=155) with ELN2017 risk classification available were used to conduct a multilevel propensity score weighting analysis. Since age, gender, ELN2017 risk and allogenic transplant rate significantly differed among the 3 cohorts, these variables were included in the propensity score. AML1718 median follow-up was shorter than AML1310 and FLAI treatment (10.5 *vs* 75.8 *vs* 104.8 months). Weights were calculated with a multinomial logistic regression model. Odds Ratio (OR) were estimated using logit models. Survival curves were compared by standard and pairwise Log-rank test.

Table 1. Comparison of characteristics and outcomes of V-FLAI, FLAI and 3+7 patients after weighting using propensity score method.

Characteristic, Overall, N = 392	3+7, N = 183	FLAI, N = 155	V-FLAI, N = 54	OR	p-value
Age, median (range)	50 (18, 61)	50 (17, 75)	51 (18, 66)		0.99
Male, n (%)	113 (62%)	88 (57%)	39 (72%)		0.98
Graft, n (%)	90 (49%)	68 (44%)	29 (54%)		0.99
ELN2017 High Risk, n (%)	79 (43%)	55 (35%)	28 (51%)		0.98
CR, n (%)	159 (63%)	124 (80%)	48 (84%)	V-FLAI vs FLAI: 0.36	0.34
				V-FLAI vs 3+7: 0.91	**0.01**
				FLAI vs 3+7: 0.55	**0.03**
MRD- (<0.1%), n (%)	44 (40%)	59 (48%)	28 (74%)	V-FLAI vs FLAI: 1.18	**0.005**
				V-FLAI vs 3+7: 1.40	**0.001**
				FLAI vs 3+7: 0.22	0.48
12 months-OS, estimate (95%CI)	66.3% (60.7%, 72.4%)	64.4% (57.2%, 72.4%)	75.7% (64.1%, 89.5%)		0.39
12 months-DFS, estimate (95%CI)	62.2% (55.0%, 70.4%)	53.3% (46.0%, 61.8%)	80.7% (67.9%, 95.9%)		**0.048**

Results. Among the balancing weights methods, the matching weights produced the best balance, with standardized mean differences <0.18 for all variables. The final weighted sample sizes on which the analysis has been carried out are 183 (3+7), 54 (V-FLAI) and 155 (FLAI). After weighting (Table 1), the CR and MRD-negativity rates in the V-FLAI group were higher than FLAI and 3+7. In terms of OR, the probability of achieving CR in V-FLAI and FLAI

was significantly higher compared to 3+7 patients (p=0.01 and p=0.03,); while V-FLAI and FLAI did not differ significantly. Also, in the V-FLAI group the probability of achieving MRD-negativity was significantly higher in comparison to both FLAI (p=0.005) and 3+7 (p=0.001) treatment. Survival estimates at 12 months, were higher in the V-FLAI group than the other two, though a slight statistical significance was reached only on DFS (p=0.048).

Conclusions. Combining venetoclax with chemotherapy in newly diagnosed AML patients resulted in improved outcomes compared to FLAI and to 3+7 regimens in terms of MRD-negativity. In terms of CR, venetoclax-based therapy was preferable only to 3+7. With regards to survival outcomes, a solid conclusion will be drawn when a longer AML1718 follow-up is available. These results highlight the incremental benefit of venetoclax added to intensive chemotherapy and pave the way to novel combination regimens.

DP049

EFFICACY OF HYPOMETHYLATING AGENTS PLUS VENETOCLAX AS A "BRIDGE" TO ALLOTRANSPLANT IN RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA: A SUBANALYSIS OF THE AVALON STUDY

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Venetoclax (VEN) in combination with hypomethylating agents (HMA) is revolutionizing the therapy of acute myeloid leukemia (AML). We recently published the results of AVALON (Todisco et al. Cancer 2022), an Italian observational cohort study on patients (pts) with AML receiving VEN-based therapies between 2015 and 2020. In this subanalysis we investigated the efficacy of VEN+HMA as "bridge" to allo-transplant (alloSCT) in relapsed/refractory (R/R) pts (n=147). Overall, 38/147 (26%) pts underwent alloSCT. The median age was 56 years (y) [I-III quantiles: 48-65]; the median number of previous chemotherapy lines was 2; 30 (79%) had de novo AML and 34 (89%) were fit for intensive chemotherapy; 21 (55%) received azacitidine and 17 (45%) decitabine; 5 (13%) pts received a prior line with HMA for a previous MDS while all pts were VEN "naïve". Median time between VEN+HMA and alloSCT was 4 months (m) [I-III quartiles: 3-5]. Eighteen (47%) pts underwent haploidentical alloSCT, 15 (39%) unrelated and 5 (13%) sibling; 31 (82%) pts received peripheral blood stem cells and 22 (58%) a myeloablative conditioning. At the time of conditioning, 28 (74%) pts were in composite CR (cCR). Among non-transplanted (NT) pts (n=109), 26 (24%) achieved cCR. Of these, 81% had median time to PD/death of 6.8 m [I-III quartiles: 1.6-4.3] whereas for non-responders it was 2.3 m [I-III quartiles: 1.5-4.7]. NT responders as compared to transplanted responders were older (81% over 60 y as compared to 33%), and had a higher prevalence of unfit pts (35% *vs* 15%). The median overall survival (OS) for all R/R pts (n=147) was 8 m [95% CI: 5-10] and the median follow-up time was 21 m [95%CI: 17-26]. A standard landmark analysis using the Cox model was performed. Moreover, a dynamic prediction model for 1-year OS considering a two-week grid of landmark (prediction) time points from zero to 6 m with stratification on the landmark, was fitted. At the landmark time point of 4-m, 15 (10%) pts had received alloSCT. Figure 1 shows the Kaplan-Meier curves for OS by alloSCT status. The HR for alloSCT, after including the R/R status, age at start of treatment, type of AML and ELN risk classification, in the 4-m landmark model was 0.34 (95%CI: 0.13-0.87, p=0.026). From the dynamic prediction model including these factors, the resulting HR for alloSCT was equal to 0.50 (95%CI: 0.26-0.95, p=0.033). Our data show that VEN+HMA may represent an effective rescue therapy as bridge to alloSCT for R/R AML pts.

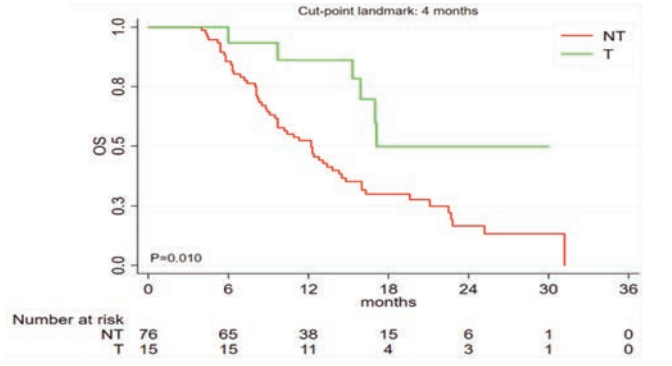

Figure 1.

DP050

ASSOCIATION OF COMORBIDITY AND HEALTH-RELATED QUALITY OF LIFE PROFILE IN LONG-TERM SURVIVORS OF ACUTE MYELOID LEUKEMIA

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There is paucity of evidence-based data on long-term survivors of acute myeloid leukemia (AML). The primary objective of this study was to investigate the association of comorbidity and health-related quality of life (HRQoL) profile in long-term AML survivors. Analysis was based on 225 long-term adult AML survivors (at least 5 years after diagnosis, without current relapse or AML treatment) who were enrolled in a GIMEMA/EORTC Leukemia and Quality of Life Groups multicenter international study. Cancer specific HRQoL issues were assessed with the EORTC QLQ-C30 questionnaire. Comorbidity was assessed with a slightly modified version of the validated Self-Administered Comorbidity Questionnaire including additional leukemia-specific late effects. Comorbidity burden was defined as having at least one health problem *vs* none. Mean score differences were calculated between groups (i.e., having at least one health problem *vs* none) for each scale of the QLQ-C30 questionnaire. Statistical significance was determined by means of a Wilcoxon rank sum test and clinical significance of differences in HRQoL scores was based on previously defined thresholds. Median age at AML diagnosis was of 48.3 years (IQR 39.4-58.1) and there were 106 men (47.1%) and 119 (52.9%) women, and median time since AML diagnosis was of 8.8 years (IQR 6.4-11.9). There were 195 AML survivors (86.7%) reporting at least one comorbidity and 25 AML survivors (11.1%) reporting no health problem/comorbidity. Cancer specific HRQoL outcomes measured with EORTC QLQ-C30 showed that AML survivors with one or more comorbidities had statistically and clinically significant worse scores for the following functional outcomes: cognitive functioning, and global health status/QoL and the following two symptom scales: fatigue, insomnia. The top three largest clinically meaningful differences, favoring patients without concomitant comorbidities, were observed for: cognitive functioning (Δ=11.4 points, P=0.004), global health status/QoL (Δ=11.5 points, P= 0.004) and insomnia (Δ= 12.4 points, P=0.027). The assessment of comorbidity in long-term AML survivors is important to facilitate identification of vulnerable individuals most in need of HRQoL improvements.

DP051

CPX-351 INDUCTION IS ABLE TO INDUCE MRD NEGATIVE COMPLETE REMISSION IN AML WITH HIGH RISK MOLECULAR PROFILE ASSESSED BY NGS

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Minimal residual disease (MRD) assessment in Acute Myeloid Leukemia patients (AML) undergoing intensive induction therapy has a high prognostic value in the prediction of relapse and survival. MRD clearance in AML is influenced by different factors. Recent studies showed that mutations in critical genes or high mutational burden predict a dismal outcome when conventional chemotherapy is administered. Those mutations are particularly frequent in AML arising from MDS (s-AML) or secondary to chemotherapy (t-AML). CPX-351 was recently approved for the treatment of s-AML and t-AML but only a limited amount of data is available on the prognostic impact of specific mutations and the correlation with MRD clearance probability in this setting. The aim of this study was to assess the prognostic impact of mutational burden at diagnosis and correlation with MRD clearance in a cohort of patients receiving CPX-351. 61 elderly (median age 68, range 60-77) s-AML or t-AML patients treated in our Center with CPX-351 were included. NGS was performed using the Myeloid Solution panel by SOPHiA Genetics, encompassing 34 genes mutations on Illumina MiSeq platform analysed with SOPHiA DDM® Software. MRD was analysed in all patients achieving complete remission (CR) with multicolour flow-cytometry (MFC), with a threshold of 0.1%. ELN 2022 risk score was high, intermediate and low risk in 31, 27 and 3 patients, respectively.

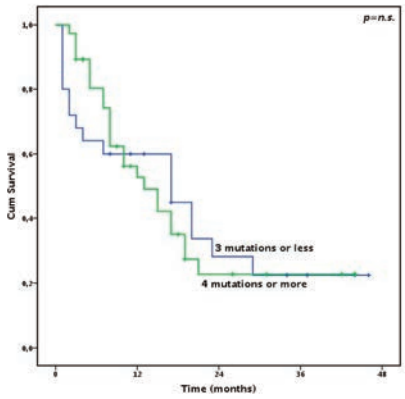

Figure 1.

Median mutational burden in NGS analysis was 4 (range 2-8). Most frequent mutations were: RUNX1 (40%), ASXL1 (35%), IDH1 (20%), IDH 2 (15%), TP53 (30%), DNMT3A (12%), TET2 (9%). After first induction cycle, 50 patients (81%) achieved CR, MFC MRD was negative in 25/50 CR patients (50%). Both CR rate and MRD negativity probability were not affected by ELN risk group, specific mutations, mutational burden or other analysed variables. After a median follow up of 34 months (CI 95%; 21.7 -46.3 months), median OS was 17 months (CI 95% 13-21), whereas 2-year OS was 25%. MFC MRD was the strongest prognostic variable in multivariate OS analysis ($p<0.05$). Notably, OS was not affected by mutational burden (p=n.s, Figure 1). In landmark analysis, patients achieving

CR and proceeding to allogeneic stem cell transplantation consolidation (HSCT) within 3 months from CR (N=12) had a significantly better outcome (p<0.03). CPX-351 resulted in high CR rate with deep MRD responses, regardless of mutational burden, allowing a high number of elderly AML patients to proceed to HSCT.

DP052

TOWARDS AN MFC-MRD STANDARDIZATION IN ACUTE MYELOID LEUKEMIA: COMPARISON OF TWO ANALYSIS TECHNIQUES BY EVALUATING THE CONCORDANCE WITH RT-QPCR RESULTS FOR NPM1 MUTATIONS

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Minimal residual disease (MRD), assessed by multicolor flow cytometry (MFC), is an important prognostic/predictive biomarker in acute myeloid leukemia (AML). However, in contrast to other diagnostic tests for MRD evaluation, MFC assay has suffered from large interlaboratory variations in terms of sample processing and data acquisition/interpretation. Standardization of the MFC technique is still limited, compromising the comparability and clinical interpretation of MFC-MRD results. This study aimed to compare two different MFC-MRD analysis approaches according to the concordance with RT-qPCR results for NPM1 mutations. Using the sequential gating technique, we prepared a patient(pt)-specific template analysis at diagnosis. Based on the template analysis, we explored the accuracy of two methods for MRD evaluation: 1) Template-Method, all cells within the pt-specific template are counted without further gate manipulation; 2) Restricted-Method, cells positive for leukemia-associated-immunophenotype (LAIP)-specific aberrant markers are selected. A total of 125 bone marrow samples from 25 AML pt were studied for MFC-/NPM1-MRD (n=62 post-chemotherapy (CHT); n=58 post-hypomethylating agents-based regimens (HMA); n=5 post-Allogeneic stem cell transplant). To statistically evaluate the accuracy of the two MFC-methods we performed a Receiver Operating Characteristic (ROC) analysis based on NPM1-MRD outcomes. ROC curves showed that the restricted-method is more accurate (area under curve (AUC)=0.75; p<0.0001) than the template-method (AUC=0.69; p=0.0014)(Figure 1A).

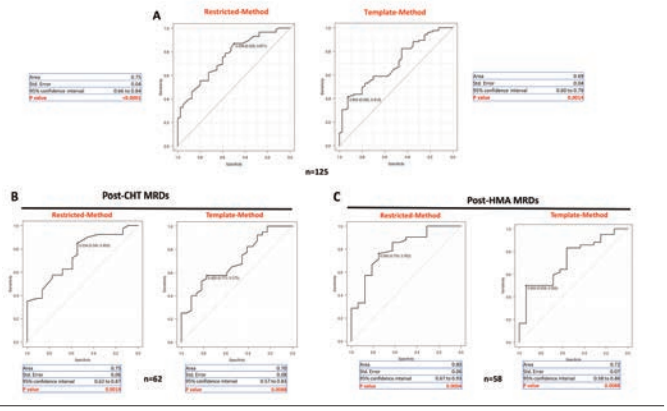

Figure 1.

Moreover, we determined that the cut-off value for the restricted-method is 0.034% of LAIP+ cells. Next, we evaluated whether different therapies might affect the MFC-MRD. The restricted-method showed a higher AUC than the template-method in both post-CHT/-HMA MRDs. Of note, ROC analysis identified a cut-off of 0.034% for post-CHT MRDs and a cut-off of 0.095% for post-HMA MRDs (Figure 1B-C). We also found different degrees of accuracy based on the LAIP-specific aberrant markers used for MRD assessment. Our data demonstrate that restricted approach improves the accuracy of the MFC-MRD and its comparability with molecular-MRD results. These results further contribute to redefine/confirm an MFC-MRD analysis approach and threshold, highlighting the key role of subdivision of MRD assays according to therapeutic settings and the importance to define a LAIPs classification based on their specificity/sensitivity.

DP053

OUTCOME OF ADULT ACUTE MYELOID LEUKEMIA PATIENTS WITH EXTRAMEDULLARY DISEASE AFTER TREATMENT WITH VENETOCLAX/HYPOMETHYLATING AGENTS

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Background. Extramedullary (EM) manifestations of AML have traditionally been approached with conventional chemotherapy (CTX) and/or radiation. Currently, VEN/HMA treatment is standard of care in older/unfit AML pts. Whether EM AML responds to VEN/HMA is unknown.

Aims. To evaluate outcome of EM AML patients treated with VEN/HMA within an international retrospective cohort.

Methods. We studied 41 pts (median age, 66 years; range, 19-81 years, M/F 26/15, ECOG≤2) treated between 2017 and 2022. Eighteen (44%) of 41 pts were relapsed or refractory after intensive CTX or allo-SCT (n=10/18) prior to VEN/HMA. Up to 31 VEN/HMA cycles (median, 2 cycles) were administered. EM response assessment was performed by CT or PET-CT and BM and/or cerebral fluid/MRI in case of CNS involvement.

Results. AML was de novo in 23 (56%), secondary after MDS/MPN in 17 (41%), and therapy-related in 1 (3%) pt. Median WBCs and PLTs counts at time of EM onset were 6.6/nl (range, 0.6-131.2/nl) and 66/nl (range, 6-307/nl), respectively. Pts had in median 2 EM manifestations (range, 1-5; Table 1). Thirty-four (83%) pts had also BM involvement. Karyotype was complex in 17 (41%) pts. NPM1 was mutated in 8 (20%) and three (7%) pts had a FLT3-ITD mutation. TP53 mutations were detected in 11 (27%). According to ELN 2022, 20 pts (49%) had a high risk AML. After VEN/HMA treatment, 18 (44%) pts achieved CR/CRi, of whom 3 had already received allo-HCT. Five (12%) pts achieved a PR and 4 (10%) a SD. The overall response rate (ORR; including CR/CRi/PR/SD) was 66% (n=27). Six pts went on to allo-SCT (CR/CRi, n=4; PR, n=2). Prior to allo-HCT all pts received ≤3 cycles. Conditioning was myelo-ablative in 2 pts. Median follow-up was 28.8 months (95%-CI, 11.5 months - not reached) and median OS 6.4 months (95%-CI, 3.9-12 months). One-year and 2-years OS rates were 26.4% (95%-CI, 15-47%) and 14% (95%-CI, 5-36%), respectively. Age with a cut-off of 60 years had no impact on OS (P=0.80). Relapse occurred in 11 of 18 (61%) pts who had achieved CR/CRi after VEN/HMA treatment. Of those, all except than two succumbed of their disease. Five (28%) pts are in ongoing CR/CRi and 2 died in CR. All pts who did not respond died due to disease progression.

Conclusions. VEN/HMA resulted in an encouraging ORR of 66% with a CR/CRi rate of 44% in a high risk EM AML population. However, long-term efficacy is limited. Whether allo-HCT after disease control with VEN/HMA is a veritable option needs to be evaluated in the future.

Table 1.

Localization of extramedullary disease	Number
Liver / spleen	9
Genito-urinary tract	9
Skin lesions	8
Lung / pleural effusion	7
Head / neck	6
Central nervous system / cerebral fluid	6
Lymph nodes	5
Muscles	5
Bones	2
Heart / pericardial effusion	2
Paravertebral mass	1
Extra-axial mass	1
Mediastinal mass	1
GI tract	1

*Overall, patients had in median 2 extramedullary disease manifestations (range, 1-5). Each localization of extramedullary disease was counted separately; thus, the total number does not add up to the total number of patients.

DP054

PRELIMINARY RESULTS OF MRD ANALYSIS OF AML1718, A PHASE 2 OPEN-LABEL STUDY OF VENETOCLAX, FLUDARABINE, IDARUBICIN AND CYTARABINE (V-FLAI) IN THE INDUCTION THERAPY OF NON LOW-RISK AML

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Background. The AML1718 trial (NCT03455504) investigates safety and efficacy of BCL-2 inhibitor venetoclax in combination with fludarabine/high dose cytarabine/idarubicin induction (FLAI) for newly diagnosed non low-risk Acute Myeloid Leukemia. Results from the Interim Analysis of Safety Run-in and Part 1 were presented at 2022 ASH Meeting. With a median follow-up of 10.5 months median overall survival (OS) was not reached; probability of 12-month OS was 76%. Median disease-free survival was not reached. We report the preliminary results of the centralized multicolour flow cytometry minimal residual disease (MFC-MRD) analysis performed during the phase 2, part 2 of the study (confirmatory cohort), with the aim of identify the most informative time-points (TPs) for MRD evaluation.

Methods. Bone marrow samples obtained at diagnosis were analysed to identify the leukemia-associated phenotype for MRD analy-

sis. Eight colour flow cytometry analysis was performed at pre-defined TPs (TP1: post-induction I, TP2: post induction II/consolidation I, following TPs: post consolidation/pre-transplantation) (FACSCantoII; BD Facs Diva Software V6.1.3). A positive flow MRD was defined by the presence of no less than 10 clustered leukemic cells/10^4 total events.

Results. 67 patients were enrolled in phase 2, part 2. Risk stratification (ELN 2017) was intermediate in 46% and high risk in 54%. Fifty-eight/67 patients (87%) obtained CR after induction I. For centralized MRD analysis 144 samples from 67 patients treated in 11 different centers has been collected so far. Baseline samples were available in 65/67 patient (97%). TP1 was available in 56/58 patient achieving CR (97%), and TP2 was available in 29/58 patient (50%), so far. In 11/144 (8%) of the samples haemodiluition was present, mostly collected at TP1(10/11, 91%) in patients with delayed haematological recovery. MFC-MRD negativity was obtained in 40/56 (71.4%) at TP1 (post V-FLAI). An increase in MFC-MRD negativity rate was observed at TP2 (post Induction II or consolidation I) with 28 MFC-MRD negative patients/29 available samples (96.5%).

Conclusions. Preliminary results from centralized MRD analysis confirm that V-FLAI is able to induce high percentage of MFC-MRD negative CR in a difficult cohort of patients. As post induction delayed haematological recovery is observed, TP2 appears to be the most reliable for MRD assessment. Correlation with survival will be performed as data collection will be complete.

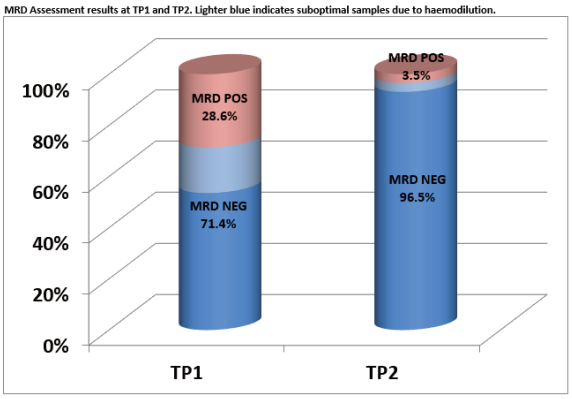

Figure 1.

DP055

THE EXTRACELLULAR VESICLES OF ACUTE MYELOID LEUKEMIA PATIENTS HAVE MORE CIRCPVT1 CARGO AND EXPRESS MORE LEUKEMIC CELL MARKERS

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Extracellular vesicles (EVs) act as molecular mediators in the tumor microenvironment, by shuttling information contained within malignant cells and functioning as regulators of the immune system. Circular (circ)RNAs are characterized by a closed loop-like structure that makes them more stable in the extracellular milieu and suitable to be packaged inside EVs. circPVT1 (hsa_circ_0001821) showed an oncogenic role in several cancer types. Moreover, circPVT1 could suppress anti-tumor immune responses by acting on diverse cell populations, according to the physiological or pathological context. So far, 8 PVT1 isoforms have been detected in exosomes from cell lines, primary tumors and/or serum of patients with active tuberculosis (http://www.noncode.org). We can therefore hypothesize that circPVT1 can also instruct the tumor microenvironment towards immune suppression as extracellular entities. In this study, we analyzed extracellular vesicles (EVs) recovered from peripheral blood plasma of AML patients (n=20) compared to age and sex-matched healthy donors (n=12). We characterized EVs in terms of size, concentrations using size exclusion cromatography for EVs isolation, followed by Nanoparticle Tracking Analysis. In addition, we tested surface markers through MACSPlex Exosome Kit and circPVT1 cargo, using digital-PCR. Finally, we also evaluated the expression level of circPVT1 in BMMCs of AML patients compared to healthy controls. We showed that circPVT1 is overexpressed by primary blast cells from newly-diagnosed AML patients compared with hematopoietic stem-progenitor cells and is released as cell-free RNA in the plasma. EVs analysis showed that EVs are increased in number (median concentration: 0.31 (0.08-0.54) *vs* 0.17 (0.11-0.31) and have a larger diameter (median diameter: 135.64 (85.27-174.72) *vs* 111.86 (103.60-132.63)) in AML plasma's patients than in healthy donors. Moreover, their surface profile is characterized by higher levels of the leukemic cell markers CD133, CD105, CD49e and other immune-related epitopes, with differences according to AML molecular profile. Digital PCR analysis revealed that circvPVT1 is more abundant inside EVs from the plasma of AML patients compared with healthy subjects. Our findings provide new insights on the features and content of AML EVs and suggest a role of circPVT1 in the crosstalk between AML cells and the tumor microenvironment.

DP056

INVESTIGATING THE ORIGINS OF FLT3-ITDMUT ACUTE MYELOID LEUKEMIA: A DEEPER CHARACTERIZATION OF LEUKEMIC PROGENITOR CELLS

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Despite major treatment advances, FLT3-ITD mutated acute myeloid leukemia (FLT3-ITDmut AML) still remains an unmet clinical need. Particularly, we have previously shown that FLT3-ITDmut leukemic progenitor cells (LPCs), characterized by the CD34/CD123/CD25/CD99+ immunophenotype, may persist after induction treatment and be responsible for drug resistance and disease progression. However, the rarity of these leukemic precursors impairs their deep characterization. In this scenario, we aimed at the functional characterization FLT3-ITDmut LPCs and at investigating their transcriptomic profile, to identify survival gene signatures and potential vulnerabilities.

Paired blasts and LPCs, purified from 13 FLT3-ITDmut AML samples by cell sorting, were available for xenotransplantation in NSG mice and RNA sequencing. Differential expression was studied out using DESeq2 and validated by qRT-PCR. The anti-proliferative effects of dasatinib, alone and in combination with gilteritinib, was also tested on FLT3-ITDmut MV4-11 cells and 3 primary AML samples. Sorted LPCs showed a higher potential to engraft mice and induce leukemia as compared to paired blasts, confirming the self-renew and initiate leukemia capacity (Figure 1). RNAseq showed upregulation of signaling by receptor tyrosine kinases as the most significantly enriched pathway in LPCs. Among kinases, we found a higher LCK expression in an extended series of primary AML samples (n=55; FLT3-ITD=30, FLT3wt=25), as compared to HDs (n=8) (Figure 1B), particularly in FLT3-ITDmut AML. In this line, the LCK inhibitor dasatinib, showed a clear anti-proliferative effect *in vitro*, on MV4-11 and primary FLT3-ITDmut AML cells. Interestingly, after 72h, Dasatinib induced a significant reduction in the expression of FLT3 and STAT5 both at the transcriptional and protein levels, also confirmed by confocal microscopy analysis. Furthermore, the combination of dasatinib and gilteritinib proved most effective at decreasing cell proliferation in FLT3-ITDmut AMLs, also reducing the IC_{50} of gilteritinib.

In summary, we deeply characterized the FLT3-ITDmut stem cell compartment in AML, providing the first evidence that FLT3-ITDmut LPCs may engraft NSG mice and maintain the stem cell potential. Furthermore, we propose a new treatment combination which may be helpful to eradicate residual LPCs in FLT3-ITDmut AML.

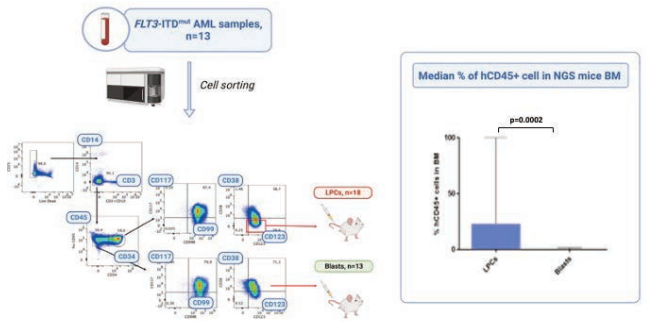

Figure 1.

DP057

PROSPECTIVE MULTICENTRIC STUDY ON OUTCOME OF POST-CONSOLIDATION CHEMOTHERAPY APLASIA IN 211 ACUTE MYELOID LEUKEMIA PATIENTS MANAGED AS INPATIENT OR AS OUTPATIENT. A PROSPECTIVE STUDY BY THE NETWORK "RETE EMATOLOGICA LOMBARDA (REL)

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Consolidation chemotherapy (cons-T) in acute myeloid leukemia (AML), including high doses (HD) or intermediate doses (ID) of ara-C (AC), is burdened by a low rate of severe infectious and, consequently, of mortality. Historically, AML patients (pt) undergoing cons-T have been managed as inpatient. An increasing interest in outpatient management has emerged to improve quality of life of pt, to reduce nosocomial infections and hospitalization costs. We conducted a prospective multicenter study within the "Rete Ematologica Lombarda" to investigate the infectious events, fever of unknown origin (FUO) and G4-G3 non-infectious events during the aplastic phase post cons-T in three cohorts: pt managed as inpatient (cohort 1), pt discharged early post therapy but hospitalized for the aplastic phase (cohort 2); pt managed as outpatients (cohort 3). The management policy was according to institutional clinical practice. We enrolled 211 pt [no M3; median age 54 (18-77)] responding to induction and treated with cons-T, from 01.18 to 01.22. The recruitment began before SARS COV2 pandemic, that has markedly influenced the Centers policy, especially in cohort 3. We focused on 1st and 2nd cons-T, including HD, ID and low dose AC, anthracycline plus AC and other approved regimens.

Table 1.

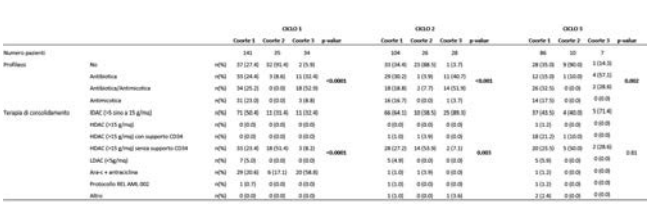

Table 1 shows the sample size by cons-T and by cohort. In cohort 3, 47,1% during 1st and 35,7% during the 2nd cycle were admitted in hospital for complications. The three cohorts differ in antimicrobic prophylaxis and in cons-T. No significant differences in age, sex, ELN 2017, comorbidity, non-haematological toxicity in ind-T and

response to ind-T, were observed. In the three cohorts, there were no differences in term of G3-G4 infections during 1st cons-T (34,7%; 40%; 26,5% in cohort 1, 2 and 3 respectively) and during 2nd cons-T (35,6%; 38,5%; 18,5%). Concerning G2-G1 infections, during the first cons-T, incidence was lower in cohort 3 (2,9%) *vs* cohort 2 (20%) and 1 (25,5%), maybe due to failure to report minor infectious events in outpatients. In term of FUO, there were no differences during 1st cons-T but it is statistically different during 2nd cons-T (41,4%; 34,6%; 10,7%; p 0.01). In conclusion, even considering the difference in sample size, due to a change in pt management during the COVID pandemic there were no significant differences in severe complications, particularly G3-G4 infectious events in the 3 cohorts even comparing cohorts 2 and 3 and most importantly there were no toxic deaths.

DP058

RARE NUCLEOPHOSMIN-1 (NPM1) GENE MUTATION SUBTYPES IN ADULTS WITH ACUTE MYELOID LEUKEMIA (AML): CLINICAL FEATURES AND PROGNOSTIC IMPACT IN A RETROSPECTIVE SINGLE-CENTER STUDY

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Although nearly 90% of NPM1 gene mutations in AML correspond to the 3 most frequent subtypes (A/B/D), more than 140 different mutations, mainly occurring in exon 12, have so far been described, with controversial data on their prognostic impact. We retrospectively found NPM1 mutations in 88 of 263 (33.5%) consecutive AML patients (pts) observed over a 13-year period (2010-2022). Of note, 80 (90.9%) had A/B/D mutations (group 1), while 8 (9.1%) pts (group 2) showed rare non-A/B/D variants (Table 1), different for each case, namely 13/Iy, G, Gm, Nm, I*, type I/Pm/4/H†, L/Om and exon 11 abnormalities. Compared to the A/B/D NPM1-mutated group, pts in group 2 are significantly younger with median age 45 years (p=0.02). Both groups have BM hypercellularity and similar BM blast percentage, whereas a trend for lower WBC and circulating blast counts were documented in group 2. Normal karyotype was observed among pts with available cytogenetics in 84.1% and 71.4% of cases from groups 1 and 2, respectively (p=0.59). No adverse-risk abnormalities were detected, with trisomy 8 as the most represented lesion in the minority of cases showing abnormal karyotype. FLT3-TKD mutations were significantly more frequently observed (p=0.01) in non-A/B/D NPM1-mutated subtypes (50%), compared to pts belonging to group 1 (11.9%). Conversely, FLT3-ITD were not documented in group 2, while frequently occurring (35%) in cases harboring A/B/D NPM1 mutations. NGS analysis was performed in 41 and 6 pts from group 1 and 2, respectively. No differences were noted in frequency of DNMT3A, IDH2, N/KRAS, PTPN11 gene mutations between the 2 subgroups. Moreover, no variants in IDH1, TET2, ASXL1 and SRSF2 were found in pts with rare NPM1 mutations. Since all non-A/B/D NPM1-mutated AML pts from our series were younger than 65 years, negative for FLT3-ITD and received intensive remission induction chemotherapy, we selected a matched 34 patient subgroup, showing these same features, among cases with A/B/D NPM1 mutations, in order to compare clinical outcomes. Despite similar CR rates between the 2 groups, non-A/B/D NPM1 mutations correlated with significantly worse survival outcomes (median OS and PFS 24 and 8 months, respectively). The unsatisfactory prognosis documented in our small cohort confirms pitfalls in management of AML pts with rare NPM1 mutations, raising the need for larger studies to further characterize their molecular and prognostic features, concurrently improving MRD monitoring.

Table 1. Clinical characteristics and outcomes of NPM1-mutated AML patients.

	A/B/D *NPM1* mutations (group 1)	Rare (non-A/B/D) *NPM1* mutations (group 2)	*p* value
Number of patients (%)	80 (90.9%) 65 A (73.9%)/8 B (9.1%)/7 D (7.9%)	8 (9.1%)	-
Age at diagnosis (years, range)	60 (33-86)	45 (21-65)	0.02
Sex M/F (number of patients, %)	35 M (43.8%)/45 F (56.2%)	5 M (62.5%)/3 F(37.5%)	0.46
Bone marrow cellularity (%), median (range)	95 (30-100)	95 (90-100)	0.39
WBC count (x 10^9/L), median (range)	35.2 (1.1-280.3)	12.6 (1.1-43)	0.08
Hemoglobin level (g/dl), median (range)	9.5 (4.1-18)	9 (6-11.7)	0.79
Platelet count (x 10^9/L), median (range)	68 (5-516)	60 (39-227)	0.67
Peripheral blood blasts (%), median (range)	44 (0-97)	17 (0-65)	0.12
Bone marrow blasts (%), median (range)	65 (2-100)	60 (10-80)	0.24
Extramedullary disease, number of cases (%)	7 (8.8%)	0	-
Normal karyotype, among cases with available cytogenetics (%)	53/63 (84.1%)	5/7 (71.4%)	0.59
***FLT3*-ITD mutation**, number of cases (%)	28 (35%)	0	-
***FLT3*-TKD mutation** number of cases (%)	9 (11.3%)	4 (50%)	0.01
Next generation sequencing (NGS) on BM aspirate, available results (%)	41 (51.3%)	6 (75%)	-
Patients receiving intensive induction chemotherapy (%)	73 (91.2%)	8 (100%)	-
CR post induction, number of cases (%)	63 (86.3%)	8 (100%)	0.59
Subgroup of patients <65-year old, without *FLT3*-ITD, undergoing induction chemotherapy, number of cases	34	8	
CR after remission induction, number of cases (%)	32 (94.1%)	8 (100%)	1
Allogeneic HSCT in 1st CR, number of cases (%)	9 (26.5%)	1 (12.5%)	0.65
Allogeneic HSCT in any phase, number of cases (%)	16 (47.1%)	2 (25%)	0.43
Median OS (months)	Not reached	24	0.03
Median PFS (months)	Not reached	8	0.003

DP059

APL-LIKE SUBSET WITHIN NPM1-MUTATED ACUTE MYELOID LEUKEMIA: A DISTINCT PHENOTYPIC SIGNATURE CORRELATING WITH EARLY-ONSET VASCULAR COMPLICATIONS

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Background. NPM1 mutations is the most common gene mutation in acute myeloid leukemia (AML). There is evidence of distinct immunophenotypic subsets driven by co-occurring mutations in NPM1+ AML, accounting for the heterogeneity of clinical picture and outcome. A subtype of NPM1+ AML is characterized by a phenotypic profile resembling acute promyelocytic leukemia (APL-like).

Aims. We studied a series of patients with APL-like NPM1+ AML,

focusing on the incidence of vascular events at onset, and investigated the impact of some markers reported to correlate with coagulopathy.

Methods. Patients diagnosed with NPM1+ AML at our Centre according to conventional criteria from March 2011 to January 2023 were included in the study. APL-like definition relied on negativity for CD34 and HLA-DR.

Table 1. Clinical, molecular and treatment characteristics of 123 patients with *NPM1* mutated AML.

	Overall	*NPM1*+ apl like		*NPM1* +non apl like		P
Total %	123	28/123	22.76%	95/123	77.23%	
Age ys	59 (47-67)	64	56-70	56	44-66	**0.003**
Female % Male %	67/123 (55%) 53/123 (44%)	11/28 16/28	39.3% 57.1%	56/95 37/95	58.9% 38.9%	 0.126
WBC (x 10^9)	38.4 (13.4-93.5)	41.15	13-132	38.4	16.4-78	0.577
WBC>25 (x10^9) %	78/123 (63.4%)	16/28	57.1%	62/95	65.3%	0.505
Hb g/dl	8.9 (7.9-9.7)	8.9	7.7-9.6	8.9	7.9-10.07	0.645
Plt (x10^9)	50 (32-79)	49	31-101	52	33--84	0.859
Plt<40 (x10^9) %	49/123 (39.8%)	13/28	46.4%	36/95	37.9%	0.511
LDH u/L	604.5 (386-974.5)	450	361-619	699	443-1111	0.005
LDH>2 ULN %[1]	80/117	13/27	48.1%	67/90	74.4%	**0.017**
PT s	67 (60-77)	69	58-79	66.5	60-77	0.960
PT<70 s %	63/117	14/27	51.9%	49/90	54.4%	0.829
INR	1.3 (1.2-1.4)	1.3	1.2-1.5	1.3	1.2 -1.4	0.817
INR ≥1.3-<1.5% INR ≥1,5 %	48/117 (41%) 19/117 (16.2%)	7/27 7/27	25.9% 25.9%	41/90 12/90	45.6% 13.3%	0.075 0.140
Fibrinogen (mg/dl)	413 (303.5-484)	398	217-465	421.5	322.25-489.25	0.336
Fibrinogen<150 %	14/117 (12%)	4/27	14.8%	10/90	11.1 %	0.735
Antithrombin (AT) III	91 (80.75-97)	93	87-98	90	79-97	0.089
AT III low %[2]	7/114 (6.1%)	0/25	0%	7/89	7.9%	0.344
D dimer ng/ml	2936 (1032-14450)	7499	2763-32909	2319	896-6832	**0.001**
D dimer >4000 %	45/115 (39.1%)	18/26	69.2%	27/89	30.3%	**0.001**
DD/FBG (all cases)	6.79 (2.48-45.13)	21.28	5.92.-149.28	4.62	1.94-21.53	**0.003**
DD/FBG (only cases with vascular complications)	81.60 (12.26-445.2)	349.28	69-630.31	18.82	5.67-239.08	**0.013**
Coagulopathy %[3]	23/117 (19.7%)	7/27	25.9%	16/90	17.8%	0.409
Vascular complications%[4]	22/117 (18.8%)	9/27	33.3%	13/90	14.4%	**0.046**
Bleeding (BC) Thrombotic (TC)	20/22 (90.9%) 2/22 (9.1%)	8/27 1/27	88.9% 11.1%	12/90 1/90	92.3% 7.7%	1
WHO grading BC% G1-G2 G3-G4	 17/20 (85%) 3/20 (15%)	 7/27 1/27	 25.9% 3.7%	 10/90 2/90	 11.11% 2.22%	
CTCAE TC% G1-G2 G3-G4	 0 2/2 (100%)	 0 1/27	 0% 3.7%	 0 1/90	 0% 1.1%	
Days before vascular events (median)	4(1-9)	7	(1-11.5)	3	(3-8)	0.357
Vascular events within 15 days % over 15 days %	 17/21 4/21	 7/9 2/9	 77.8% 22.2%	 10/12 2/12	 83.3 16.7%	1
DIC Score[5]	3 (2-4)	4	3-5	3	2-4	0.217
DIC score≥5 %	24/117	8/27	29.6%	16/90	17.8%	0.186
FLT3 any TKD ITD	76/123 (61.8%) 19/123 (15.4%) 64/123 (52%)	19/28 2/28 18/28	67.9% 7.1% 64.3%	57/95 17/95 46/95	60% 17.9% 48.4%	0.512 0.238 0.196
IDH1	11/81 (13.6%)	7/17	41.2%	4/64	6.3%	**0.001**
IDH2	14/87 (16.1%)	8/19	42.1%	6/68	8.8%	**0.002**
TET2	15/64 (23.4%)	3/14	21.4%	12/50	24%	1
Karyotype (normal)%	85/99	18/20	90%	67/79	84.8%	0.729
CR1 %[6] CR % anytime	88/116 (75.9%) 98/117 (83.8%)	20/24 23/24	83.3% 95.8%	68/92 75/92	73.9% 81.5%	0.428 0.358
Relapse	53/100 (53%)	14/23	60.9%	39/77	50.6%	0.478
HSCT[7]	39/122 (32%)	7/27	25.9%	32/95	33.7%	0.493

[1]Antithrombin III low: <60%. [2]LDH ULN: the upper limit of normal for LDH was 214 U/L [3]Coagulopathy: including INR>1,5 and/or fibrinogen lower than 150 mg/dl. [4]Vascular events: defined according to the revised World Health Organization (WHO) bleeding scale and to the CTCAE grading of thromboembolic events. [5]DIC: ISTH Criteria for Disseminated Intravascular Coagulation. [6]CR: complete remission.[7]HSCT: hematopoietic stem cell transplantation.

Results. Of a total of 123 patients with NPM1+ AML, 28 (22.77%) were defined as APL-like. They were older (64 y) than non-APL-like (56 y, P=0.003) patients (Table 1); no further difference emerged for hemochrome parameters. Vascular complications were significantly more frequent in the APL-like (n=9, 33.3%) than non-APL-like (n=13, 14.4%, P=.046) group (Table 1). D-dimer was significantly higher in APL-like (median 7,499 ng/ml) than non-APL-like (2,319 ng/ml, P=.001) patients. Also, D-dimer/fibrinogen ratio (DD/FBG), a predictor of vascular events, showed higher level in APL-like (median 21.28) than non-APL-like (4.62, P=.003) patients. Furthermore, among patients with vascular complications higher levels were found in the APL-like group (median 349.28 *vs* 18.82, P=.013). In multivariate analysis, the impact of APL-like phenotype maintained an independent value (OR=2.77, P=.041) from age (OR=1.01, P=.61) on the incidence of vascular complications. The analysis of molecular data demonstrated a significant enrichment in both IDH1 (P=.001) and IDH2 (P=.02) in APL-like patients. As regards outcome, complete remission rate was 85.7% and 78.9% in APL- and non-APL-like (P=.43). We did not observe any significant difference between APL- and non-APL-like patients in disease-free (13.2 *vs* 22.0 months; P=.83) or overall (15.9 *vs* 15.1 months, respectively; P=.57) survival.

Conclusions. Our findings suggest APL-like signature to be a potential predictor of susceptibility to vascular events within NPM1-mutated AML. Our results deserve validation in a larger patient set and might indicate the utility of an intensive monitoring and supportive care to prevent early vascular events in this patient category.

DP060

INTERIM RESULTS FROM CLEVO: A NON-INTERVENTIONAL COHORT STUDY INVESTIGATING THE CLONAL EVOLUTION OF *FMS-LIKE TYROSINE KINASE 3 (FLT3)* MUTATIONS DURING DISEASE PROGRESSION IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

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Within the general acute myeloid leukemia (AML) population, ~30% have mutations in the gene *FMS-like tyrosine kinase 3 (FLT3)*. The dynamics of *FLT3* clonal evolution and the clinical consequences are not fully understood. This ongoing study aims to characterize the natural history of *FLT3* mutations in AML from diagnosis through treatment over 36 months. This is a non-interventional, prospective study of adults (≥18 years) diagnosed with AML within 30 days of enrolment at sites in Belgium, France, Germany, Israel, Italy, Spain, the UK and the USA. Patients with relapsed/refractory (R/R) AML at enrolment, acute promyelocytic leukemia, or central nervous system leukemia are excluded. Treatment is given at the physician's discretion. Routine *FLT3* genetic testing was performed at initial diagnosis (ID) and at each R/R event. The primary objective is to determine the proportion of relapsed/refractory AML patients with *FLT3* clonal evolution (gain/loss of *FLT3* mutations) from ID; we present results from the first interim analysis conducted 12 months after study initiation. At data cut-off (Sep 30, 2021), 272 patients were enrolled; 245 were included in the full analysis set. Most patients were male (56.3%, 138/245), and the median (min, max) age was 63.0 (22, 89) years. At baseline, 29.0% (71/245) of patients tested positive for *FLT3* mutations (*FLT3*+); of these, 71.8% (51/71) had an *FLT*3-ITD mutation. Preliminary findings for *FLT3* clonal evolution by R/R event are shown in the table. After first-line treatment, 15/245 ([6.1%] 6 *FLT3*+, 9 *FLT3*− at ID) patients had relapsed and 27/245 ([11.0%] 13 *FLT3*+, 14 *FLT3*− at ID) patients were refractory. Of the primary refractory patients, 2/27 ([7.4%] both *FLT3*+ at ID) were refractory after second-line treatment and 2/27 ([7.4%] 1 *FLT3*+, 1 *FLT3*− at ID) experienced a relapse after sec-

ond-line treatment. The number of patients and relapse/refractory events in this first interim analysis is very limited; *FLT3* test results were not available for 40% of the patients who relapsed and 59% of those refractory after first-line treatment. Therefore, the full extent of *FLT3* clonal evolution still remains uncertain and will need to be further analyzed in later data cuts. This ongoing study, which has now enrolled all 650 patients, will help to better understand the magnitude of *FLT3* clonal evolution throughout the AML disease course.

Table 1. FLT3 clonal evolution (preliminary data).

	FLT3 mutation status at previous assessment[a]		
	Positive	Negative	Total
***FLT3* mutation status at event assessment[b]**			
Patients with relapse after first-line treatment, n (%)	6	9	15
FLT3+	0	1 (11.1)	1 (6.7)
FLT3–	2 (33.3)	6 (66.7)	8 (53.3)
Missing	4	2	6
Patients with relapse after second-line treatment, n (%)	1	1	2
FLT3+	0	0	0
FLT3–	1 (100.0)	0	1 (50.0)
Missing	0	1	1
Patients refractory to first-line treatment, n (%)	13	14	27
FLT3+	7 (53.8)	0	7 (25.9)
FLT3–	2 (15.4)	2 (14.3)	4 (14.8)
Missing	4	12	16
Patients refractory to second-line treatment, n (%)	2	0	2
FLT3+	0	0	0
FLT3–	1 (50.0)	0	1 (50.0)
Missing	1	0	1

[a]For patients who relapsed after second-line treatment or were refractory to second-line treatment, the previous assessment could be either diagnosis or the previous post-treatment assessment. [b]Denominators for percentages represent the overall number of patients at each event assessment.

Anemias, myelodysplastic syndromes and chronic myeloid leukemia

DP061

SAFETY AND EFFICACY OF TKIS IN VERY ELDERLY PATIENTS (≥75 YEARS) WITH CHRONIC MYELOID LEUKEMIA: A RETROSPECTIVE ANALYSIS

A. Costa[1], E. Abruzzese[2], R. Latagliata[3], O. Mulas[1], I. Carmosino[4], E. Scalzulli[4], C. Masucci[4], M. Passucci[4], M. Capriata[4], C. Ielo[4], M. Martelli[4], G. Caocci[1], M. Breccia[4]

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The treatment paradigm and prognosis of Chronic Myeloid Leukemia (CML) are radically changed since the introduction of tyrosine kinase inhibitors (TKIs). Outcomes of CML patients (pts) with >65 y at diagnosis have been already investigated in real-life experiences, but few have included very elderly pts (age ≥75 y). The aim of this study was to retrospectively evaluate safety and efficacy of TKIs in a multicentric cohort of 123 newly diagnosed CML very elderly pts between 2003 and 2023. The median age at diagnosis was 80 (75-96) y, with >48% (n=60) aged ≥80 y. All pts were in chronic phase, and ELTS risk score was intermediate and high in 76 (61.8%) and 43 (34.9%) pts, respectively. At least one comorbidity was recorded at baseline in 95.9% of pts, mainly represented by cardiovascular (CV) comorbidities in 82.1% of them. In 1st line, pts were treated with imatinib (n=101; 86.1%), nilotinib (n=7; 5.69%), dasatinib (n=9; 7.13%) and bosutinib (n=1; 0.81%).

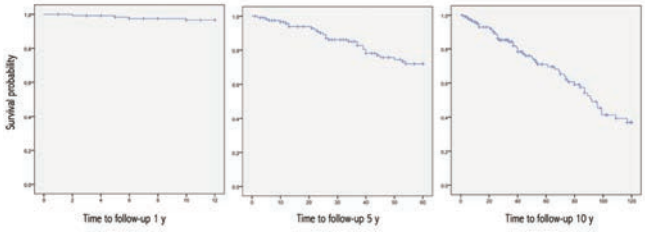

Figure 1.

Thirty-one pts (25.2%) switched to a 2nd line: 13 changed to dasatinib (41.9%), 9 to bosutinib (29.0%), 6 to nilotinib (19.35%), 2 to ponatinib (6.45%) e 1 to imatinib (3.22%). In 3rd line, ponatinib was administered in 5 patients, while 2 pts switched to nilotinib, and other 2 to dasatinib and bosutinib. Only one pts switched to a 4th line and started asciminib. Resistance to treatment was the main cause of switching TKIs both in 1st (64.5%) and 2nd line (77.7%). Dose-reduced TKIs were administered in 36.58% of pts in first line and in all pts in subsequent line. Overall, 3 months cytogenetic response was evaluated in 75 pts, with complete cytogenetic response (CCyR) achieved in 45.3% of them. After a median follow-up of 58 months (1-202), 64.2% of pts reached a major molecular response (MMR), and 45.5% obtained a deep molecular response (DMR). Treatment free remission (TFR) was successfully attempted in 11 pts. During follow-up, adverse events (AEs) were observed in 78.8% of pts, including 12 cases of CV AEs, and 43 pts died mainly for causes unrelated to CML; 3 pts died for progression to advanced (n=1) and blastic (n=2) phase of disease. Overall survival (OS) for the whole

cohort was 96,6±1,7%, 71,9±4,7% and 37±6,2% at 1 y, 5y and 10 y of follow-up. In conclusion, TKIs appear quite safe and effective even in very elderly CML pts, and dose optimization strategies lead to sufficiently deep molecular responses for adequate disease control.

DP062

LONG TFR IN CHRONIC MYELOID LEUKEMIA: RT-QPCR VERSUS DIGITAL DROPLET PCR AND ROLE OF CD26+ CELLS AND NK

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Tyrosine kinase inhibitors (TKIs) and standardization of molecular response (MR) have changed the history of CML patients and hematological therapies. MR measured by RT-qPCR has led to discontinuation of therapy. Digital PCR is proposed as a method with higher sensitivity to evaluate MR at time of treatment interruption and during therapy discontinuation. There is currently much interest in the role played by microenvironment in disease control at the time of diagnosis, during therapy and in treatment free remission (TFR), particularly CD26+ cells and NK cells. We analyzed results of RT-qPCR and ddPCR of peripheral blood samples of 12 CML patients in long TFR and deep molecular response from January 2022 to March 2023. Nine patients were treated with Imatinib (six until discontinuation, two switched to Nilotinib, one to Dasatinib); three with IFN (one until withdrawal, two switched to Imatinib). CD26+ cell analysis was conducted using a four-color staining protocol that acquires at least 1x10*6 cells. NK cell analysis was conducted using an eight-color staining protocol that acquires 3x10*4. No significant differences emerged between RT-qPCR and ddPCR according to t-Test (t=0.531; p=0.606). Inverse significant correlation emerged between length of treatment and CD26 levels (r2=-.724, p=0.008). According to Anova, first line of therapy had a significant effect on the length of treatment (F=6.424; p=0.03; eta squared=0.391). NK cell events did not correlate with CD26 cell events nor with the lines of treatment. Our results show that RT-qPCR is still a valid, reliable and economic method, not inferior to ddPCR in MR monitoring in TFR patients. An inverse correlation was found between duration of treatment and CD26+ cells in peripheral blood, regardless of the drug and the number of lines. Patients treated with imatinib presented higher number of NK cells in our samples. In our small series patients with a longer duration of treatment before weaning were taking first-line IFN, which has a well-known immunomodulating role in the CML microenvironment. The results obtained are limited by the size of our sample. A baseline evaluation and a targeted follow up of the patients would be necessary.

DP063

HIGH BCR-ABL1 EXPRESSION DEFINES CD34+ CELLS WITH SIGNIFICANT ALTERATIONS IN SIGNAL TRANSDUCTION, SHORT-PROLIFERATIVE POTENTIAL AND SELF-RENEWAL ABILITY

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Chronic Myeloid Leukemia (CML) is a clonal disorder of the hematopoietic stem cell caused by the expression of the BCR-ABL1 oncoprotein. High BCR-ABL1 levels have been associated to proliferative advantage of leukemic cells, blast crisis progression and tyrosine kinase inhibitors (TKIs) inefficacy. We previously showed that high BCR-ABL1/GUS^{IS} transcripts measured at diagnosis are associated with inferior responses to standard dose Imatinib (IM). However, the mechanisms underlying the higher rates of disease progression and development of TKIs resistance dependent on high BCR-ABL1 levels remain still unclear. Leukemic cells were collected at diagnosis from bone marrow and peripheral blood samples of 26 CML patients showing either high or low BCR-ABL1/GUS^{IS} levels. BCR-ABL1 expression was measured by Real-Time PCR. Short-term cultures and Long-Term Culture-Initiating Cells assays were employed to investigate the role of BCR-ABL1 gene-expression levels on proliferation, clonogenicity, signal transduction, TKIs responsiveness and self-renewal ability. Cell division were performed by carboxyfluorescein-succinimidyl ester (CFSE) assays. We observed that: (i) BCR-ABL1 oncogene expression levels correlate in both PMNs and CD34+ cells, (II) high oncogene levels increased both proliferation and anti-apoptotic signaling via ERK and AKT phosphorylation, (iii) high BCR-ABL1 expression reduced the clonogenicity of leukemic CD34+ cells and increased their sensitivity to high doses IM but not to those of dasatinib. Further, we also observed that high BCR-ABL1 levels are associated with a reduced self-renewal of primitive leukemic cells and that these cells showed comparable TKIs responsiveness with cells expressing lower BCR-ABL1 levels. Interestingly, we found a direct correlation between high BCR-ABL1 levels and reduced number of quiescent leukemic cells, caused by increasing their cycling. In conclusion our findings support the notion that high BCR-ABL1 expression levels lead to increased proliferation and anti-apoptotic signaling in CD34+ committed leukemic progenitors, promoting also stem cell division.

DP064

MULTIPARAMETRIC ANALYSIS OF THE EFFECTS OF DIFFERENT TYROSINE KINASE INHIBITORS COMBINED WITH LITHIUM ON *IN VITRO* MODELS OF CHRONIC MYELOID LEUKEMIA

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Hematopoietic effects due to lithium (Li) administration have been known since the 1980s. However, in the context of CML only one study analyzed the combination of Li and one TKI (nilotinib). Therefore, we performed a multiparametric analysis on *in vitro* CML models (K562 and LAMA84 cells) cultured with different combinations of TKIs +/- Li. The proliferation resulted reduced by TKIs compared to controls (CTR *vs* TKIs p=0.0005 in K562 and p<0.0001 in LAMA84), even more when combined with Li (CTR *vs* TKIs+Li p<0.0001 in both K562 and LAMA-84). The proliferation reduction was statistically significant comparing TKI and TKI+Li only in K562 (p<0.0001). Similarly, the cell viability was decreased by TKIs when compared to controls (CTR *vs* TKIs p<0.0001 in both K562 and LAMA84), with higher reduction by TKI+Li (CTR *vs* TKIs+Li p<0.0001 in both K562 and LAMA84). Then, the expression of the CML hallmark BCR::ABL1, and the differentiation markers CD33 and CD11b was analyzed by digital PCR transcripts quantification. As expected, BCR::ABL1 resulted strongly reduced by TKIs. Surprisingly, TKI+Li increased the expression of BCR::ABL1 in K562 (TKIs *vs* TKIs+Li p=0.0312). So, in this cell line the trend was CTR > TKI+Li > TKIs. The same results were observed quantifying CD33 (TKIs *vs* TKIs+Li p=0.0037) and CD11b (TKIs *vs* TKIs+Li p=0.001). Conversely, LAMA84 presented the lowest expression of the considered markers when treated with TKI+Li (BCR::ABL1, CD33 and CD11b: CTR *vs* TKIs *vs* TKIs + Li p<0.0001). In this case, the trend was CTR > TKIs > TKI+Li. This difference, together with the one reported in proliferation, highlighted that the considered *in vitro* models are diverse and reflect the variability observed in CML patients. This aspect should be considered during *in vitro* experiments analysis. Finally, we evaluated the intake of glutamate (Glu), altered by both Li and CML pathogenesis. The extracellular Glu concentration analysis revealed that TKIs led to a higher intake of Glu, that is increased by Li (CTR *vs* TKIs, CTR *vs* TKIs+Li, TKIs *vs* TKIs+Li p<0.0001 in both K562 and LAMA84). Furthermore, a linear correlation between cell proliferation and extracellular Glu concentration emerged. These data highlighted the need to compare multiple *in vitro* models to increase the robustness of the results. Moreover, these interesting insights suggested a synergy of TKIs and Li and further analysis on ex vivo and *in vivo* models will clarify the mechanisms underlying the reported effects.

DP065

TKI DOSE OPTIMIZATION: IMPACT ON MOLECULAR RESPONSE AND SURVIVAL IN CHRONIC MYELOID LEUKEMIA

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Targeted therapy for chronic myeloid leukemia (CML) has allowed a near-normal patient life expectancy; however, continuous TKI treatment often encompasses low-grade side effects, which adversely affect normal activities. In clinical practice, dose reduction (DR) is a well-utilized approach to spare the toxicity of TKI. We analyzed 93 chronic phase CML patients (pts) receiving lower than standard dose (LD) TKI in order to assess the safety and impact on molecular responses. Male and female pts were 56% and 44%, with a median age at diagnosis of 62 years. ELTS risk was low/intermediate/high in 74%, 25% and 1% of cases. We considered 4 groups of pts: pts who started LD TKI frontline or during subsequent lines (group 1: 24 pts; group 3: 18 pts); pts who initially received standard dose TKI, experiencing dose reduction (DR) during first or subsequent lines (group 2: 31 pts; group 4: 20 pts). DR occurred after a median of 15.3 and 17.6 months from the TKI start in group 2 and group 4, respectively. LD Imatinib was given in 48/93 pts (51.6%), Dasatinib in 14 pts (15%), Nilotinib in 9 pts (9.6%), Bosutinib in 15 pts (16.1%) and Ponatinib in 7 pts (7.52%). Reasons for DR included patient fragility in 33 cases (35.4%), any degree of adverse event deemed significant by the clinician in 47 cases (50.5%), dose optimization due to low-grade persistent intolerance in 13 cases (13.9%). In the group 1, mostly receiving LD Imatinib frontline for fragility, 3/24 (16.6%), 8/24 (37.5%) and 11/24 (45.8%) cases obtained MR3 at 3, 6 and 12 months. At 24 months, MR3 was maintained in 5/11 pts, while 4/11 pts obtained a DMR. Loss of MR3 was observed in 2/11 cases. Excluding group 1, 40/ 69 cases (57.9%) were at least in MMR at the moment of DR. This response was maintained in 33/69 cases (47.8%) after 12 months. The evaluation at 24 months from DR showed 43/69 (62.3%) pts at least in MMR, including 33/69 (31.8%) pts in DMR. Median observation times of patients from diagnosis until last follow-up and from first DR until last follow-up were 112.1 and 56.3 months. The median overall survival (OS) was of 90.2 months for group 3, not reached for groups 1/2/4 (p=0.006) (Figure 1). Our data showed that TKI dose optimization could be an acceptable and safe strategy for patients who are unable to tolerate standard doses of TKI and in whom continuing these doses may lead to drug cessation or poor compliance, all of which may compromise the achievement of molecular responses.

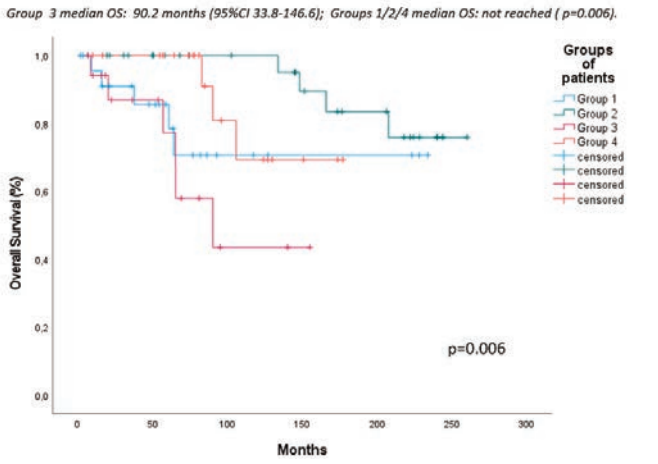

Figure 1.

DP066

SUBCLONES CARRYING VARIANTS WITH KNOWN OR UNKNOWN CLINICAL SIGNIFICANCE MIGHT UNDERLIE GENOMIC INSTABILITY IN MYELODYSPLASTIC SYNDROMES AND ACUTE MYELOIDE LEUKEMIA

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Genetic and epigenetic alterations are considered the main pathogenetic events for development of myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). In this study, we retrospectively investigated clinical significance of mutations in leukemia-related genes of known pathogenetic significance and of

variants of uncertain clinical significance (VUS) in MDS and AML.

A total of 191 (M/F, 104/87; mean age, 63 years old) consecutive subjects were included in this retrospective study. Of total subjects, 59 (30.9%) with MDS and 48 (25.1%) with AML were further studied, while a total of 26 subjects were used as a control cohort. Next-generation sequencing analysis was performed using SOPHIA Genetics Myeloid Solution panel (Sophia Genetics), and fastq files were loaded on SophiaDDM software for alignment and analysis.

A total of 495 genetic alterations were identified in 95% of subjects, and most subjects were found to have pathogenetic or VUS variants in at least two AML-related genes, especially TET2 and SETBP1, SRSF2, EZH2, DNMT3A, and CEBPA. For SETBP1, MDS patients showed a higher genetic complexity compared to controls, as MDS subjects more frequently showed the presence of two or more variants on SETBP1 (P = 0.0402). Similar for TET2, MDS patients tended to have a greater genetic heterogeneity compared to controls (P = 0.0515). Next, prognostic significance of genetic mutations in SETBP1 and TET2 was investigated, and AML and MDS patients were divided based on: SETBP1 wild type (WT) or =>2 variants + TET2 single variant (N = 14); SETBP1 WT or =>2 variants + TET2 WT or =>2 variants (N = 34); SETBP1 single variant + TET2 single variant (N = 10); and SETBP1 single variant + TET2 WT or =>2 variants (N = 28). Patients carrying SETBP1 single variant and at least one TET2 variant displayed a significant shorter progression-free survival (PFS) compared to other groups (P = 0.0478), regardless the small number of subjects per group.

Our preliminary data suggest that MDS patients might have a greater genomic heterogeneity as demonstrated by increased presence of SETBP1 and TET2 variants, predisposing to genomic instability. Moreover, even if reported as benign in other conditions, the presence of VUS in AML-related genes in MDS might underlie impaired protein function in a context of ineffective hemopoiesis, that could increase the risk of AML progression. However, our preliminary findings need further validation in larger prospective studies.

DP067

ABSTRACT NOT PUBLISHABLE

DP068

ASSOCIATION OF HYPOMETILATING AGENTS (HMA) + VENETOCLAX (VEN) IN THE THERAPY OF ACUTE MYELOID LEUKEMIAS EVOLVED FROM MYELODYSPLASTIC SYNDROMES (AML-MDS) ALREADY TREATED WITH AZACYTIDINE

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Background. Survival of high-risk Myelodysplastic Syndromes (MDS) treated with azacytidine during the dysplastic phase and then evolved in Acute Myeloid Leukemia (AML-MDS) is very poor. While the association of hypometilating agents (HMA) and venetoclax (VEN) is widely used in de novo AML not eligible for intensive chemotherapy, very few data are available in patients (pts) with AML-MDS.

Methods. Data of 42 pts with AML-MDS treated frontline with HMA+VEN in 19 hematologic Centres in Italy outside clinical trials from 5/2018 to 3/2023 were retrospectively collected and analysed. Composite overall response rate [ORR; complete remission (CR) + CR with incomplete hematologic recovery (iCR) + partial remission (PR) + hematologic improvement (HI)], duration of response and overall survival (OS) were assessed.

Table 1. Clinical features at AML evolution, type of treatment and treatment response.

N° of patients	42
M/F, n° (%)	28/14 (66.7/33.3)
Median age, years (IQR)	74.8 (70.7 – 77.5)
Median Hb, g/dl (IQR)	8.1 (7.6 – 10.0)
Median WBC, x 10^9/l (IQR)	3.0 (1.4 – 9.3)
Median PMN, x 10^9/l (IQR)	0.5 (0.2 – 3.3)
Median PLTS, x 10^9/l (IQR)	41 (23 – 92)
Median marrow blasts, % (IQR)	25 (20 – 40)
Treatment, n° (%): Aza + VEN	24 (57.1)
Dac + VEN	18 (42.9)
VEN starting dose (1st cycle), n° (%):	
50 mg	7 (16.7)
100 mg	22 (52.4)
200 mg	5 (11.9)
400 mg	8 (19.0)
Type of response, n° (%):	
CR/iCR	11 (26.2)
PR	10 (23.8)
HI	1 (2.4)
SD	5 (11.9)
PD	11 (26.2)
ED	4 (9.5)

CR: complete remission – iCR: CR with incomplete recovery – PR: partial remission – HI: hematological improvement – SD: stable disease – PD: progressive disease – ED: early death (<30 days from treatment start).

Results. Baseline characteristics at evolution in AML are reported in the Table 1. Median interval from initial MDS diagnosis to evolution was 16.7 months [interquartile range (IQR) 8.2–30.1]. Pts were treated for a median of 3 courses (IQR 2-6): HMA were administered at standard dosage, VEN daily doses in the 1st cycle are reported in the Table 1. On the whole, 34 pts (81.0%) had at least one hematologic toxicity of grade 3-4: in particular, severe neutropenia (PMN < 0.5 x 10^9/l) was reported in 32 pts (76.1%). Eighteen pts (42.8%) had at least one infective episode during the treatment: pulmonary infections were reported in 9 pts (21.4%). Response to treatment is shown in the Table 1: ORR was 52.4%, with a median response duration of 17.8 months (95%CI 3.3-32.2). After a median follow-up from AML evolution of 6.1 months (IQR 2.2–11.6), 31 pts (73.8%) died and 11

(26.2%) were alive. Median OS from AML evolution of the whole cohort was 6.9 months (95%CI 4.7-9.1), Pts with any response to HMA+VEN had a significantly longer OS compared to pts with progressive/stable disease [15.6 (95%CI 11.3–19.8) versus 3.3 (95%CI 0.7–5.8) months, respectively (p<0.001)].

Conclusions. Our real-life data suggested that HMA + VEN combination could be useful also in AML-MDS already treated with azacytidine in the dysplastic phase, with an ORR of about 50% in pts unfit for intensive approaches: however, hematologic and infective toxicities were severe and the response duration was short, with a persistently poor median OS. As a consequence, addition of other targeted therapies driven by NGS should be explored in the next future.

DP069

UBE2O DEFICIENCY AS A MECHANISM OF INEFFECTIVE ERYTHROPOIESIS IN MYELODYSPLASTIC SYNDROMES

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Myelodysplastic syndromes (MDS) are heterogeneous clonal hematological diseases characterized by inefficient hematopoiesis, bone marrow dysplasia and risk of progression to acute myeloid leukemia (AML). Anemia is the main feature of low risk MDS. Therefore, new therapies, including Luspatercept, have been developed to reduce or avoid red blood cell transfusion requirement. The mechanisms underlying anemia in MDS are not fully understood. Erythropoiesis is a finely regulated process in which several factors are involved. The ubiquitin-conjugating enzyme E2O (UBE2O) is involved in the proteome remodeling during terminal erythroid differentiation. It allows to degrade most of the proteins, except for globin, to generate mature red blood cells. Since UBE2O has been shown to regulate the erythrocytes maturation under physiological conditions, we hypothesized that it could be implied in MDS pathogenesis. The aim of the study is to assess UBE2O expression levels in a panel of MDS and its potential role in ineffective erythropoiesis.

We analyzed the expression levels of UBE2O in bone marrow samples collected from low risk MDS patients. We observed a downregulation of UBE2O in patients with MDS, including MDS with SF3B1 mutation, compared to healthy controls. Interestingly, UBE2O expression is upregulated in MDS with SF3B1 mutation after *in vivo* treatment with Luspatercept. These data suggest that UBE2O deficiency may be associated with alterations of splicing mechanisms. Luspatercept treatment leads to an increase in GATA1 by the inhibition of SMAD pathway and therefore an increase in UBE2O expression. Consistently, the use of Erythropoietin (EPO) on leukemia cell lines (K562, OCI-AML-3 and MOLM-13) showed increased levels of UBE2O and a significative positive correlation between UBE2O and GATA1. Additionally, preliminary data on cell lines under stress conditions (36 hours of nutrient depletion or 6 hours of heat shock) showed no significant differences in the UBE2O levels, suggesting an exclusive role of UBE2O in myeloid lineage and erythroid differentiation. Our data indicate that UBE2O may be a player in the erythroid maturation defect, with an association with splicing machinery alterations, and that Luspatercept can restore normal red blood cell maturation by upregulating UBE2O. Although further studies are needed to establish the role of UBE2O in MDS, the ubiquitination process seems a promising target to improve erythropoiesis in MDS.

DP070

REDUCED COMPLEMENT LEVELS IN PATIENTS WITH LOW-RISK MYELODYSPLASTIC SYNDROMES

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The complement system is a collection of soluble proteins and membrane receptors which belong to both innate and adaptive immunity. Its activation may be associated with cytopenias, including autoimmune cytopenias and PNH. Myelodysplastic syndromes (MDS) are marked by ineffective erythropoiesis with a proinflammatory/proapoptotic bone marrow microenvironment. The aim of this study was to evaluate the activity of the complement's pathways in patients with MDS. Serum levels of C3 and C4 in patient with low risk MDS and myelodysplastic/myeloproliferative neoplasms (MDS/MPN) were sampled, and treatment features were retrospectively collected. Student's t-test, Chi-squared test and Fisher's exact test were used for statistical analysis. A total of 57 patients were included in the study: 18 MDS-SF3B1, 7 MDS-5q deletion, 28 MDS-LB, 2 MDS-F, 1 CMML-1 and 1 MDS-MPN with SF3B1 mutation and thrombocytosis according to WHO classification 2022 (Table 1).

Table 1.

	All patients	Reduced complement levels	Normal complement levels
Median Age, years (range)	79 (57-94)	80 (62-92)	79 (57-94)
M/F	37/20	24/10	13/10
Median follow up, years (range)	3 (1-22)	4 (1-22)	2 (1-11)
WHO 2022 type			
MDS-SF3B1	18	16	2
MDS-5q	7	3	4
MDS-LB	28	13	15
MDS-F	2	0	2
CMML-1	1	1	0
MDS-MPN-SF3B1 and thrombocytosis	1	1	0
IPSS-R VL/L/I nd	17/22/13 4	9/16/7 2	8/8/6 2
Blood counts at diagnosis			
Median Hb, g/dl (range)	9,8 (6,5-16,4)	9,7 (7,5-12,6)	10 (6,5-16,4)
Median PLTx10^9/L (range)	205,75 (25-580)	227 (63-580)	127 (25-303)
Median ANCx10^9/L (range)	2030 (161-7190)	2020 (500-7190)	2210 (161-4410)
Transfusion dependent, N (%)	30 (53)	20 (59)	10 (43)
Treated, N (%)	48 (84)	32 (94)	16 (70)
ESAs, N (%)	46 (81)	31 (91)	16 (70)
Overall response, N (%)	28 (61)	18 (58)	10 (63)
Lenalidomide, N (%)	5 (9)	1 (3)	4 (17)
Overall response, N (%)	2 (40)	1 (100)	1 (25)
Luspatercept, N (%)	18 (32)	17 (50)	1 (4)
Overall response	10 (56)	10 (59)	0 (0)
Iron chelation, N (%)	18 (32)	17 (50)	1 (4)
Leukemia evolution, N (%)	1 (2)	1 (3)	0 (0)
Death, N (%)	2 (4)	1 (3)	1 (4)

M = male, F = female; VL = very low; L = low; I = intermediate; nd = not detected; N = number; ESAs = erythropoiesis-stimulating agents

Median age of patients at sampling was 79 years (57-94); the majority were males (65%); and mostly belonged to IPSS-R very low or low (68%). Median Hb, PLT and ANC at diagnosis were 9,8 g/dl (6,5-16,4), 206x10^3/mmc (25-580) and 2030/mmc (161-7190), respectively. Thirty patients were transfusion dependent on RBC (53%). Most of them (n=48; 84%) received at least one line of therapy including erythropoiesis-stimulating agents (ESAs, n=46), lenalidomide (n=5), and luspatercept (n=18), and iron chelation therapy was administered in 18 patients. A patient progressed to acute myeloid leukemia; 2 patients died. Thirty-four patients (60%) had reduced levels of C3 and/or C4 (33 with low C4 and 6 low C3). These subjects more frequently belonged to MDS-SF3B1 subgroup (47% *vs* 9%, p=0.003). Additionally, they were more frequently treated compared to those with normal C3/C4 levels (94% *vs* 70%; p=0.03). Specifically, more patients with reduced C3/C4 were treated with ESAs (p=0.01) and luspatercept (p=0.001). In contrast, patients with MDS-5q- and reduced C3/C4 were less frequently treated with

lenalidomide (p=0.04). No differences were noted in terms of response to treatment nor regarding Hb, PLT and ANC at the time of sampling. In conclusion, serum complement levels were reduced in two third of low risk MDS patients with an association with MDS-SF3B1 and treatment requirement. This observation may be linked with the higher degree of dyserythropoiesis and immune activation in this subgroup and may give hints for treatment approach.

Allogenic and autologous transplant

DP071

IMPACT OF VIRAL INFECTION ON EXTRACELLULAR VESICLE PHENOTYPE AFTER HAPLOIDENTICAL STEM CELL TRANSPLANTATION AND POST-TRANSPLANT CYCLOPHOSPHAMIDE

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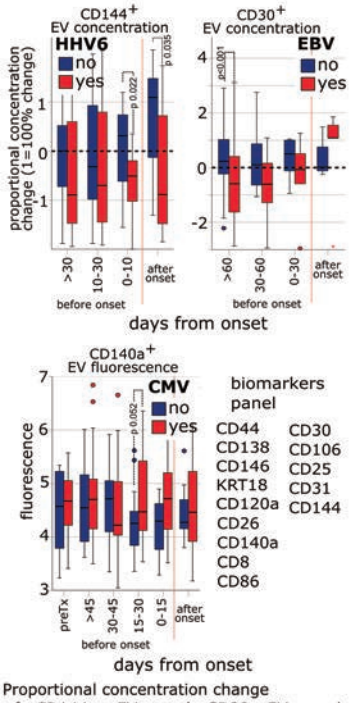
Introduction. Reactivation of Cytomegalovirus (CMV), Human herpesvirus 6 (HHV6) and Epstein-Barr virus (EBV) remains an important cause of post-transplant morbidity and mortality in hematopoietic cell transplantation (SCT) recipients. We recently reported on the potential use of serum and plasma extracellular vesicles (EVs) as "non-invasive" biomarkers of acute GVHD (Lia G. Frontier Immunol 2022). In this study, we investigated the potential correlation of plasma EVs with CMV, EBV, and HHV6 reactivations in the setting of haploidentical-SCT (Haplo-SCT) with post-transplant cyclophosphamide.



Proportional concentration change of CD144+ EVs and CD30+ EVs, and fluorescence level of CD140a+ EVs at different time points before and after viral reactivation in patient with (blue) and without (red) viral reactivation (HHV6, EBV and CMV, indicated on plot). Panel of 14 EVs surface biomarkers characterized in this study.

Figure 1.

Methods. Plasma samples were collected at given time points (pre-transplant, on day 0, 3, 7, 14, 21, 28, 35, 45, 60, 75, and 90 after Haplo-SCT) from thirty-two consecutive patients (2011-2015). After extraction by precipitation methods, EVs were analysed by flow-cytometry with a panel of 14 antibodies as previously described. The correlation between EVs and viral reactivation was evaluated by multivariate logistic regression models (LRM) using STATA 15.

Rsults. Overall, CMV, EBV and HHV6 reactivations were observed in 62.5% of the patients at a median of day 50 (r 10-275), in 34% at day 96 (r 54-314) and in 53% at day 34 (r 11-280), respectively. CMV reactivation was significantly associated with the absolute fluorescence of CD86 in the entire post-transplant period. CD140a and CD44 after day 7, and CD144 after day 14 (OR 1.609, p 0.012; OR 1.466, p 0.006; OR 1.373, p 0.012; and OR 1.777, p 0.012 respectively). EBV reactivation was associated with CD30 in the entire post-transplant period and KRT18 after day 7 (OR 0.573, p 0.007; and OR 1.595, p 0.028 respectively). HHV6 reactivation was associated with CD26 and CD86 fluorescence the entire post-transplant period, and CD120 and CD144 after day 7 (OR 1.361 p 0.006; OR 0.596, p 0.010; OR 1.430, p 0.026; and OR 0.679, p 0.051 respectively). Multivariate LRM showed that correlation was not affected by acute GVHD.

Conclusions. Alteration of endothelial and immune cell functions that precedes clinical detection of viral reactivation have been correlated with a dynamic change in biomarkers involved in endothelium and immune cell interactions and crucial for viral tropism control.

DP072

SIMPLIFIED PATIENTS RISK STRATIFICATION TO PREDICT STEROID REFRACTORY AGVHD AND MORTALITY

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Acute Graft-versus-Host disease (aGvHD) represents a major cause of morbidity and mortality after allogeneic stem cell transplantation (HSCT). The Minnesota risk score proved to offer a reliable stratification of patients (pts) with reference both to probability of response to 1st-line steroid therapy and to transplant related mortality (TRM). Recently, Hospital St. Louis (HSL) group demonstrated that the benefit of adding biomarkers to clinical parameters was marginal for the day-28 non-response and mortality endpoints, proposing a new simplified risk stratification score which categorized at high risk (HR) patients with either age ≥50 years old or initial G3 GvHD or initial liver involvement. We conducted a retrospective single-center study, involving 315 consecutive HSCT performed with a PTCy-based GvHD prophylaxis in our center for any disease and donor type between Jan-2016 and Jun-2020. Acute GvHD was diagnosed in 139 pts. At steroid initiation, 104 pts were classified as HR according to HSL risk score, with one single risk factor (SRF-HR) in 64 cases (51 were aged ≥50, 12 presented G3 GvHD and one liver involvement) and multiple risk factors in 40 very-HR pts. Low risk (LR) pts in absence of risk factors were 35. The day-28 overall response rate (ORR - complete and partial response) to 1st-line therapy was lower among HR pts versus LR (p0.05). Comparing LR *vs* SRF-HR *vs* very-HR, ORR was superimposable between LR and SRF-HR subgroups (95%), while more than 40% of very-HR did not respond (p<0.001) – Figure 1a. The 2-year overall survival (OS), TRM and progression free survival (PFS) for LR pts were respectively 72%, 0% and 68% while for HR were 52% (p0.02), 35% (p<0.001) and 51% (p0.048). There was no significant difference in respect to 2-year OS and PFS between LR and SRF-HR subgroup, while survival outcomes for very-HR were significantly lower (2-y OS and PFS 30% p<0.0001). Of note, TRM was different for the three subgroups: LR 0%, SRF-HR 19% and very-HR 60% (p<0.0001) – Figure 1b-c-d. In conclusion, age as single risk factor seems not sufficient in predicting steroid refractory aGvHD and mortality. Notably, when age accompanies a marker of disease presentation severity, the simplified HSL aGvHD risk definition appears to be a more reliable predictor of steroid response, PFS, TRM and OS. This may foster for a prompt intervention, tailoring therapy to increase response for pts with HR disease or to minimize side effects for patients with LR disease.

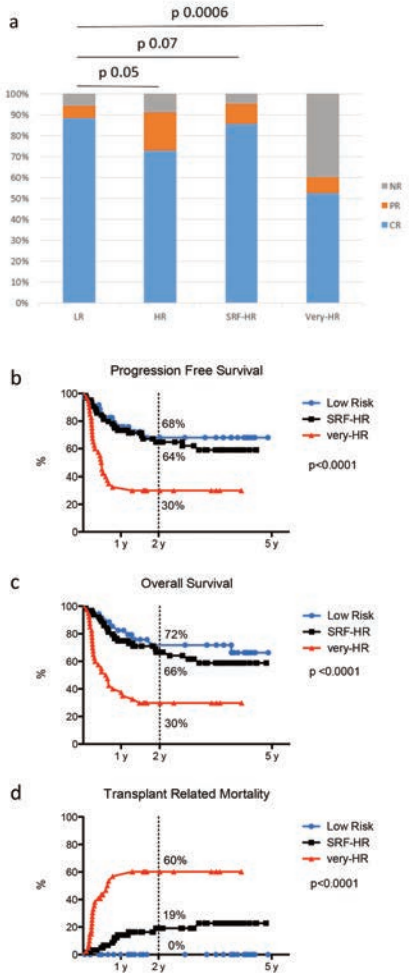

Figure 1. a) day-28 overall response rate; b) progression free survival; c) overall survival; d) transplant related mortality.

DP073

REDUCING THE DOSE OF BUSULFAN IN TBF CONDITIONIG, FOR AML OVER THE AGE OF 60: IS IT ENOUGH TO REDUCE TRANSPLANT RELATED MORTALITY?

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Background. Transplant related mortlity (TRM) remains an important issue in patients with AML above the age of 60 undergoing an allogeneic hemopoietic stem cell transplant (HSCT). Reduced intensity regimens (RIC) have been used, although the problem is an increased incidence of leukemia relapse. One is therefore confronted with the opposing requirement of reduced intensity conditioning to control toxicity, but maintain some degree of myeloablation to control leukemia. We have used the combination of thiotepa, busulfan, fludarabine (TBF) with 3 days of busulfan (total dose 9.6 mg/kg) (TBF3) for patients under the age of 60. Over the age of 60, and for patients considered unfit, we have reduced the dose of busulfan to 3.2 mg/kgx2 (TBF2). We are now reporting 107 patients with remission AML receiving TBF2 compared with 175 remission AML receiving TBF3. Donors were matched siblings, matched unrelated, 7/8 unrelated, and haploidentical .

Patients: All patients had acute myeloid leukemia in first (CR1) or second (CR2) remission. The proportion of CR1 was 75% for TBF3 and 69% for TBF2 (p=0.5). The median age of TBF3 was 46 years (range 18-64), and for TBF2 it was 61 years (31-73) (p<0.00001). HAPLO donors comprised 61% in both groups (p=0.9) . And post transplant cyclophosphamide GvHD prophylaxis was used in 71% and 72% of patients respectively (p=0.7).

Results. The 8 years disease free survival (DFS) was 78% and for TBF3 and 42% for TBF2 (p<0.0001). The Overal survival was 82% and 41% (p<0.0001)- You will then ask the question: is this due to more relapse or more TRM in older patients receiving TBF2. The cumulative incidence of relapse at 8 years . was 12% for TBF3 and 16% for TBF2 (p=0.5). The cumulative incidence of TRM at 8 years was 9% for TBF3 and 41% for TBF2 (p=0.00001). Causes of death were respectively for TBF3 and TBF2 as follows : relapse 7% and 10%; GvHD 3% and 7%; infections 3% and 15%; multiorgan failure 1% and 4%.

Conclusions. We conclude that the reduction of TBF3 to TBF2 for older patients is insufficient to control the toxicity of the conditioning regimen, whereas control of leukemia is satisfactory, and not statistically different from TBF3 . The regimen needs to be further reduced in AML patients over the age of 60. Alternative options could be one day of busulfan (TBF1) with the addition of total marrow irradiation (Pieri *et al.*, Blood Advance 2021)

DP074

PRE-EMPTIVE IMMUNOTHERAPY WITH DONOR LYMPHOCYTE INFUSION IS THE MOST EFFECTIVE TREATMENT FOR ACUTE MYELOID LEUKEMIA AND MYELODISPLASTIC SYDROME RELAPSED FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION: A SINGLE CENTER RETROSPECTIVE ANALYSIS ON 61 PATIENTS

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Disease relapse is the main cause of treatment failure after allogenic stem cell transplantation (allo-HSCT) for acute myeloid leukemia (AML) and myelodysplastic syndromes (MDSs). Nowadays there is the possibility to identify end treat early relapse (e.g. molecular relapse and mixed chimerism) with pre-emptive therapies, based on drugs and/or immunotherapies like donor lymphocyte infusions (DLIs). This study aims to collect outcome data according to different relapse treatments. We retrospectively analysed 133 patients transplanted for AML/MDS between 2015 and 2021 at our institution.

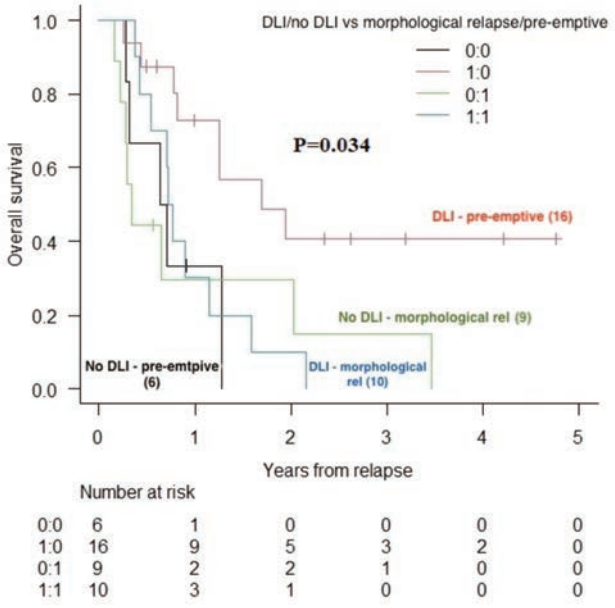

Figure 1. OS of the 41 patients according to type of treatment (DLI *vs* no-DLI) and setting (pre-emptive *vs* morphological).

Sixty-one patients relapsed (45%) and 41 of these were treated for relapse according to clinical conditions. We compared the overall survival (OS) of 26/41 (63%) patients who received DLI-based therapies with the OS of 15/41 (37%) patients who were treated without DLI. Then we compared the OS of 22/41 (54%) patients who received pre-emptive therapies with the OS of 19/41 (46%) patients treated for a morphological relapse. The 5 years OS from relapse of the whole population was 7%, and it was higher in treated than untreated patients (17% *vs* 0%; p<0.001). Moreover, the OS was significantly better in patients undergone pre-emptive therapies than in those treated for a morphological relapse (30% *vs* 0% at 5 years; p=0.016). Likewise, patients receiving DLI-based therapies had

longer OS, than those treated without DLI (20% *vs* 0% at 5 years; p=0.027). Finally, the best OS was observed in patients treated in pre-emptive setting with DLI-based therapies (40% at 5 years; p=0.034; Figure 1). Multivariable analysis showed that chronic Graft versus Host Disease (GVHD) and relapse after more than one year from allo-HSCT were independently factors associated with better OS (p=0.022 and p=0.012). Our results confirm that relapse treatment with pre-emptive therapies is associated with better outcome. Moreover, DLI-based therapies are the most effective, and this is even more evident combining the pre-emptive setting with cellular therapies DLI-based. These results confirm the primary role of Graft versus Leukemia in the treatment of relapses, and the importance of its early identification through minimal residual disease monitoring.

DP075

UNMANIPULATED HAPLOIDENTICAL BONE MARROW TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA IN REMISSION FOLLOWING TBF3 CONDITIONING AND PTCY PROPHYLAXIS: A TEN YEAR FOLLOW UP

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We are reporting a ten year follow up of 98 patients with intermediate/high risk acute myeloid leukemia (AML), who underwent an unmanipulated haploidentical (HAPLO), bone marrow transplant (BMT). All patients received a myeloablative regimen, consisting of thiotepa (10 mg/kg), busulfan (9.6 mg/kg), fludarabine (150 mg/m^2) (TBF3). Graft versus host disease (GvHD) prophylaxis was cyclosporine on day 0, mycophenolate on day +1, and post- transplant cyclophosphamide (PT-CY) 50 mg/kg, on days +3 and +5. The median age was 43 years (18-66); patients were in first (n=78) or second remission (n=20); 70% of first remission (CR1) patients had high risk AML. Two patients died before day 18 of infection; 5 patients failed to engraft and received a second HAPLO transplant- 4/5 engrafted after a secondf HAPLO. The overall number of trilineage engraftment was therefore 95/98 patients (95%), including the 2 early failures. The median time for neutrophil engraftment was 18 days (13-76) ; the cumulative incidence (CI) of acute graft versus host disease (GVHD) grade II-IV and moderate/severe chronic GvHD was respectively 8% and 17%. The 10 year CI of transplant related mortality (TRM) and of relapse is respectively 8% (95% CI 4-16%) and 14% (95% CI 8-24%). Ten year disease free survival (DFS) is 77%. DFS is 80% and 67% for CR1 and CR2 patients. The overall graft-relapse free survival (GRFS) is 70%. In conclusion, unmanipulated HAPLO BMT for remission patients with AML, following TBF3 conditioning, with modified PTCY GvHD prophylaxis, allows for very encouraging long term DFS and GRFS, with a low (17%) 10 year relapse rate.

DP076

SELECTION OF THE BEST HEMATOPOIETIC STEM CELL DONOR BY ANALISIS OF LOCAL OWN REAL-DATA: OLD METHODS FOR A NEW TOOL FOR TRANSPLANT PHYSICIANS

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Introduction. The selection of the best allogeneic donor for each specific patient is crucial for the success of allogeneic hematopoietic stem cell transplantation (HSCT). Besides well-known patient's characteristics, donor-related variables such as HLA matching and donor age are of utmost importance for the outcome of patients after HSCT. Since the selection of the best donor is usually performed among multiple potential donors, a tool extrapolating real-data results from each center would be of interest in guiding the donor selection.

Methods. By using real-data from two transplant centers, we developed a calculator able to provide the 2-year patients' overall survival (OS) estimates associated to each potential donor evaluated during the selection process. Through ProMIse extraction, data on n=737 HSCTs performed from January 2010 to July 2022 have been obtained. Only first HSCTs were considered. Donors were HLA-identical siblings, adult unrelated and haploidentical. Cord blood were excluded due to few numbers.

Results. Both Cox regression and parametric model indicates patient's age, disease, comorbidity index and donor type as significant variables ($p<0.05$) able to predict 2-year OS after HSCT with robustness, with a concordance index of 0.677. Diagnosis was grouped into three categories based on risk and comorbidities into three groups: HCT-CI of 0, 1-2 and >2. The calculator allows for the visualisation of the 2-year OS estimates associated to each donor type for a specific patient during the donor selection process. An example is provided in Table 1 for two hypothetical patients (#1 and #2). Estimates are shown for the three donor options: HLA-identical sibling, unrelated and haploidentical. Of note, estimates express real data of the two transplant centers and reflect their actual experience.

Conclusions. We here present a prototype of a new tool for the a priori calculation of patients' outcome after HSCT according to the donor type. The novelty of this approach relies on the use of real-data analysis from the investigating centers only, therefore being sure that results are applicable to those centers and that they are empirically-based. By this calculator, transplant physicians can visualise the OS estimate for each potential donor under selection and may be guided to choose the donor associated with the best patient's survival expectation. Improvements are planned by filling additional information and pooling data from more transplant centers.

Table 1. Example of calculator outputs for two hypothetical patients.

Pt.	Age	Disease group	Donor type	HCT-CI	2y-OS	Lower 95%CI	Upper 95%CI
#1	50	1	HLA-identical Sibling	0	0.9035	0.8747	0.9259
#1	50	1	Unrelated	0	0.8622	0.8215	0.8943
#1	50	1	Haploidentical	0	0.8509	0.8108	0.8831
#2	50	1	HLA-identical Sibling	3	0.7939	0.6966	0.8631
#2	50	1	Unrelated	3	0.7139	0.5928	0.8047
#2	50	1	Haploidentical	3	0.6927	0.5648	0.7898

DP077

ABSTRACT NOT PUBLISHABLE

DP078

SORAFENIB MAINTENANCE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELLTRANSPLANT FOR FLT3+ ACUTE MYELOID LEUKEMIA: A SINGLE CENTER EXPERIENCE

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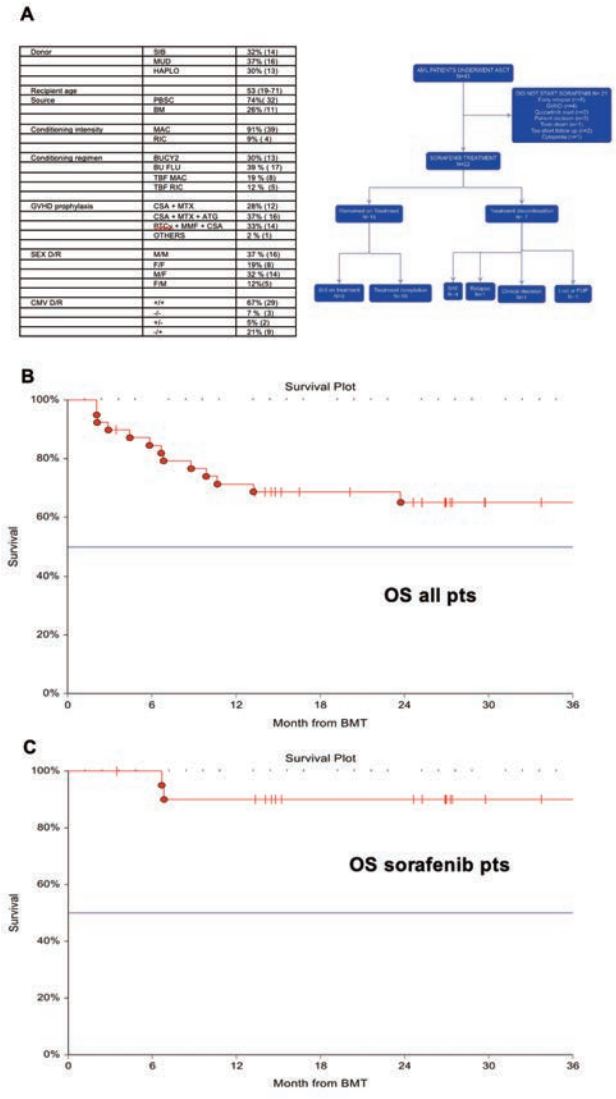
Background. Acute myeloid leukemia (AML) relapse is the main cause of death after allogeneic stem cell transplant (allo-SCT). In AML FLT3+, it was shown that Sorafenib (SOR) used as maintenance therapy after allo-SCT, significantly reduces the risk of relapse and death.



Figures 1 and 2. Table 1.

Methods. This is a retrospective analysis aimed to evaluate the feasibility, safety and outcome of maintenance with SOR in patients with FLT3+ AML who underwent allo-SCT. The majority of patients received a myeloablative conditioning regimen and peripheral blood stem cells. Donor types were equally distributed between HLAid sibling MUD and haploidentical donors. SOR was started at different time points after allo-SCT based on hematological reconstitution, performance status, infectious complications and disease evaluation. The starting dose was 400 mg/day. For survival analysis we used the Kaplan Meier method. All statistical analyses were performed using NCSS 2019 software.

Results. From 2017 to 2022, 43 patients with FLT3+ AML received allo-SCT. 95% (n=41) were FLT3 ITD mutated and 5% (n=2) TKD mutation. Patient flow and characteristics are depicted in Figure 1 and the Table 1. Median age was 53 (range 19-71). 62% (n=27), 14% (n=6) and 2% (n=1) of patients had NPM1, IDH2 and DNMT3A mutations, respectively. 95% of patients were in CR (CR1 83%, CR2 9%, CR3 2%) and 80% were MRD negative at time of allo-SCT. 2 patients underwent allo-SCT with active disease. Grade 2-4 acute GVHD incidence was 38%. 51% (n=22) of patients received SOR. The most frequent reasons for not starting SOR were relapse (19%) and GVHD (9%). Considering patients in CR before allo-SCT (n= 41), 8 patients (19%) relapsed before the start of SOR and median day of relapse was 93 days (range 30-153). Median day to start SOR was 120 days (range 59-279). SOR was discontinued because of adverse events in 18% (2 developed heart toxicity, 1 gastrointestinal toxicity and 1 skin toxicity). With a median follow up of 27 months, 3-year overall survival of the whole cohort was 65% and 90% for patients treated with SOR (Figure 2A and B). No patients relapsed during SOR treatment. 10 patients completed the treatment and the median of SOR exposition was 731 days (range 575-752). 5 patients are still on treatment (median time of SOR exposition 422 days (27-638).

Conclusions. Post-transplantation SOR reduces the risk of relapse in FLT3+ AML. In our experience SOR was well tolerated even if 4 patients stopped the treatment because of toxicity. Early relapse, observed in 19% of patients, mostly in the first 3 months after allo-SCT, was the most important factor that impacted treatment feasibility. This underlines that the timing of SOR start should be as early as possible after allo-SCT.

DP079

PROSPECTIVE ANALYSIS OF THE PROGNOSTIC IMPACT OF HIGH MOLECULAR RISK MUTATIONS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION IN MYELOFIBROSIS

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Introduction. Allogeneic hematopoietic stem cell transplantation (HSTC) is the only curative approach for Myelofibrosis (MF). The presence of high molecular risk (HMR) mutations (ASXL1, SRSF2, EZH2, IDH1, IDH2 and U2AF1), confers a detrimental effect on survival. The aim of this study was to prospectively evaluate the impact of HMR mutations on transplant outcomes. Furthermore, preliminary results of an ongoing study on post-transplant minimal residual disease (MRD) monitoring will be presented.

Methods. We studied a cohort of 31 patients who underwent allogeneic HSTC at the Bergamo Bone Marrow Transplant Unit from 2017 to 2022. Median age at transplant was 61 years (36-67). Patients received a reduced intensity conditioning with Thiotepa 5 mg/kg, Fludarabine 150 mg/kg, and Busulfan 8 mg/kg. GVHD prophylaxis was based on CSA, MTX and ATG 5 mg/kg. Pre transplant mutational profile was performed by sequencing 30 myeloid related genes by applying SOPHia GENETICS Myeloid Solution on Illumina MiniSeq platform. Post transplant MRD monitoring was performed by digital droplet PCR (ddPCR). The target genes of MRD monitor-

ing were JAK2V617F, MPL, ASXL1, U2AF1 and IDH1.

Results. A driver mutation was detected in all patients (16 JAK2V617F/ 8 CALR / 7MPL). At least one HMR mutation was detected in 50% of patients. According to the Mutation-Enhanced International Prognostic Scoring System 70 plus (MIPPS70+) scoring system, 59% of patients were allocated in the high/very high-risk group, while 29% of patients were classified in the high/very high-risk group according to the MTSS risk score. After a median follow up of 20 months, the 2-years OS and PFS were 69% and 62% and the 2-years NRM and CIR were 28% and 11% respectively. The presence of HMR mutations did not significantly affect OS, PFS (Figure 1), NRM or CIR. A cohort of 13 patients was evaluated by for post-transplant MRD monitoring by ddPCR. At day +90 post-transplant, 11 patients (85%) had an MRD positive test. Of these, 3 patients relapsed, and relapse was always preceded by an MRD positive test > 0.1%; 7 patients achieved spontaneous MRD negativity during follow up and 1 patient achieved MRD negativity after DLI infusions.

Conclusions. In this study we prospectively confirmed that HSTC can lead to a significant cure rate of MF patients regardless the presence of HMR mutations. ddPCR is a promising method for MRD monitoring after transplant.

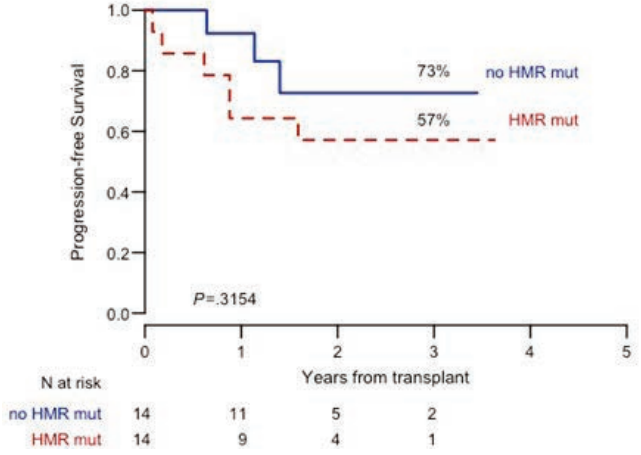

Figure 1.

DP080

ABSTRACT NOT PUBLISHABLE

Monoclonal myeloma and gammopathies

DP081

ELOTUZUMAB, POMALIDOMIDE E DESAMETASONE NEL MIELOMA MULTIPLO RECIDIVATO/REFRATTARIO: ESPERIENZA MULTICENTRICA, RETROSPETTIVA E IN REAL-LIFE SU 200 CASI TRATTATI AL DI FUORI DI STUDI CLINICI CONTROLLATI

M. Gentile[1,2], E. Vigna[1], S. Palmieri[3], M. Galli[4], D. Derudas[5], R. Mina[6], R. Della Pepa[7], R. Zambello[8], E.A. Martino[1], A. Bruzzese[1], S. Mangiacavalli[9], E. Zamagni[10,11], C. Califano[12], M. Musso[13], C. Conticello[14], C. Cerchione[15], G. Mele[16], N. Di Renzo[17], M. Offidani[18], G. Tarantini[19], G.M. Casaluci[20], A. Rago[21], R. Ria[22], G. Uccello[23], G. Barilà[24], G. Palumbo[25], A. Pompa[26], I.D. Vincelli[27], M. Brunori[28], F. Accardi[29], V. Amico[30], A. Amendola[31], R. Fontana[32], V. Bongarzoni[33], B. Rossini[34], E. Cotzia[35], A. Gozzetti[36], R. Rizzi[37], N. Sgherza[37], E. Ferretti[38], G. Bertuglia[6], D. Nappi[15], M.T. Petrucci[39], F. Di Raimondo[14], A. Neri[38], F. Morabito[40], P. Musto[37]

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In the ELOQUENT-3 trial, the combination of elotuzumab, pomalidomide, and dexamethasone (EloPd) proved a superior clinical benefit over Pd with a manageable toxicity profile, leading to its approval in relapsed/refractory multiple myeloma (RRMM), who had received at least two prior therapies, including lenalidomide and a proteasome inhibitor (PI). We report here a real-life series of 200 RRMMs treated with EloPd in 35 Italian centers outside of clinical trials (Table 1).

Table 1. Main characteristics of patients at baseline.

	No. of patients (%)
Age, (years)	
<70	86 (43)
≥70	114 (57)
Sex	
Male	108 (54)
Female	92 (46)
Paraproteins (isotype)	
Immunoglobulin G	121 (60.5)
Immunoglobulin A	44 (22)
Immunoglobulin D	3 (1.5)
Immunoglobulin M	2 (1)
Light chain only	30 (15)
Creatinine clearance (mL/min)	
≥60	132 (66)
<60	68 (34)
Stage ISS, (%)	
I	61 (30.5)
II	86 (43)
III	53 (26.5)
LDH	
Normal	142 (71)
Elevated	58 (29)
Previous lines of therapy	
2	101 (50.5)
3	57 (28.5)
≥4	42 (21)
Previous ASCT	
No	99 (49.5)
Yes	101 (50.5)
Previous daratumumab	
No	54 (27)
Yes	146 (73)
Lenalidomide refractory	
No	5 (2.5)
Yes	195 (97.5)
Disease status	
Biochemical relapse	30 (15)
Symptomatic relapse	94 (47)
Refractory to last treatment	76 (38)
FISH analysis available (n= 80)	
Standard Risk	43 (53.8)
High Risk	37 (46.2)

In our dataset, the median number of prior lines of therapy was 2, with 51% of cases undergoing autologous stem cell transplant (ASCT) and 73% exposed to Daratumumab. After a median follow-up of 9 months, 126 patients stopped EloPd, most of them (88.9%) because of disease progression. The overall response rate (ORR) was 55.4%, in line with the 'registration' trial results. Major adverse events (AEs) include grade 3/4 neutropenia (21.5%), anemia (11%), lymphocytopenia (9.5%), and thrombocytopenia (9.5%), while infection rates and pneumonia were roughly 14% and 6.5%, respectively. Thus, our cohort experienced a toxicity profile similar to the ELOQUENT-3 trial, with no significant differences between younger (<70 years) and older patients. The median progression-free survival (PFS) was 7 months, shorter than that observed in the ELOQUENT-3, probably due to the different clinical characteristics of the two cohorts. Interestingly, the ISS stage III (HR:2.55) was associated with worse PFS. Finally, our series's median overall survival (OS) was shorter than that observed in the ELOQUENT-3 trial (17.5 versus 29.8 months). Notably, in the Cox multivariable analysis, advanced ISS stage (III) (HR=1.87), symptomatic relapse (HR=2.5) and refractory disease at EloPd beginning (HR=2.4) maintained an independent prognostic impact on the survival outcome. Moreover, in our experience, Daratumumab exposure neither impacted the probability of achieving a response nor the outcome indicators in RRMM patients treated with EloPd.

In conclusion, our real-world study confirms EloPd as a safe and possible therapeutic choice for RRMM who received at least two prior therapies, including lenalidomide and a PI.

DP082

SINGLE-CELL DNA AMPLICON SEQUENCING REVEALS AN EVOLUTIONARY PATTERN OF CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL (CHIP)'S SOMATIC MUTATIONS PROFILE IN TRANSPLANT ELIGIBLE MULTIPLE MYELOMA PATIENTS

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Clonal hematopoiesis of indeterminate potential (CHIP) is a common age-related phenomenon in which hematopoietic stem cells acquire leukemogenic mutations resulting in the selection and expansion of a genetically distinct subpopulation of blood cells. CHIP is common in patients (pts) with plasma cell neoplasms, with some studies suggesting that up to 30% of treated pts with Multiple Myeloma (MM) may harbour CHIP mutations. We used a single-cell (sc)-based approach to explore the presence of Single Nucleotide Variants (SNVs) in 20 myeloid-related genes, associated with CHIP, in the MM stem cell compartment. To this aim, we used the Tapestri technology to perform scDNA sequencing both at the onset of the disease, at the time of transplantation and after treatment in 12 MM pts. High throughput amplicon-based scDNA sequencing of apheresis-derived CD34+ cells, collected before autologous stem cell transplantation, detected CHIP in 6/12 MM pts. Notably, we found that the apheresis MM CD34+ cells' clonal architecture was typically composed by a major clone, harbouring just one SNV, carried by 3% to 63% of the cells, and 1 to 2 minor sub-clones carried by less than 20% of the cells. For two pts, we also showed the presence of minor doublets-mutated sub-clones affecting genes involved in epigenetic modifier and/or splicing machinery and/or tyrosine kinase receptor.

Moreover, in 4 MM pts, longitudinal analysis of paired samples revealed an over-time positive selection of sub-clones carrying high-fitness SNVs, emerged from baseline either as major or minor sub-clones. Since MM pts commonly present with both chromosomal abnormalities and somatic SNVs, the copy number alterations profile of the 20 genes was also studied, to explore whether chromosomal abnormalities can co-occur with SNVs, as part of CHIP. The analysis showed that neither loss nor gain of gene copies could be highlighted in CHIP-positive samples.

Finally, we observed that pts with CHIP tended to achieve a sub-optimal response to therapy, as compared to those without. Notably, three pts with CHIP relapsed during maintenance therapy.

In conclusion, by employing a scDNA technology, we have been able to identify rare pathological SNVs in the CD34+ compartment collected and subsequently re-infused in MM pts. A sub-clone dynamic of high-fitness SNVs over time was confirmed. These findings suggest that pts' clinical management might benefit from a close monitoring of CHIP dynamics.

Thanks: BolognAIL, AIRCIG2019

DP083

CYTOMEGALOVIRUS REACTIVATION IN MULTIPLE MYELOMA PATIENTS TREATED WITH DARATUMUMAB: A SINGLE-CENTER RETROSPECTIVE EXPERIENCE

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Introduction. Viral reactivations are important causes of morbidity and mortality in hematologic malignancies, because of their cancer-related and drug-induced immunosuppressive status. Daratumumab, an anti-CD38 monoclonal antibody, is approved for multiple myeloma (MM) treatment, and targets neoplastic plasma cells, and CD38-expressing lymphocytes, eventually leading to immunosuppression. Studies on CMV reactivation during daratumumab-based therapies are lacking in literature. In our real-life experience, we evaluated incidence of CMV reactivation in MM patients treated with daratumumab-based regimens as first- or second-line therapy.

Materials and Methods. A total of 99 MM patients were included in this single-center retrospective study and were divided in two cohorts: daratumumab and non-daratumumab based (control) regimens. Patients treated with >2 lines of therapies were excluded to reduce the confounding factor of multi-treated cases. The control group was included to investigate additional effects of other agents involved in viral reactivation, such as dexamethasone. Primary endpoint was CMV reactivation, defined as detectable CMV-DNA by polymerase chain reaction, monitored monthly for the entire population.

Results. Clinical characteristics are summarized in Table 1. CMV reactivation rate was significantly increased in daratumumab cohort compared to control group (31% *vs* 4%; P<0.001), also with higher CMV-DNA levels (>137 or >1000 UI/mL in 8% and 4% of cases; all P<0.05). However, only one subject developed a CMV disease with severe pneumonia, while 10% of patients were treated with pre-emptive therapy with valganciclovir. No subjects in the control cohort required anti-CMV agents (P=0.02).

Discussion. Our single-center retrospective experience showed that daratumumab administration might significantly increase the risk of CMV reactivation in MM, likely because of a deep immunosuppression caused by removal of residual CD38-expressiong lymphocytes. To our knowledge, this is the first study reporting CMV reactivation risk in daratumumab-treated patients. Further validation on larger and prospective clinical trials are required.

Table 1. Patients' characteristics at baseline.

Characteristics	Daratumumab cohort N = 49	Control cohort N= 50	P value
Median age, years (range)	66 (44-86)	67 (45-83)	0.47
Gender, n (%)			
Male	29 (59)	29 (58)	0.9
Female	20 (41)	21 (42)	
M-protein type, n (%)			
IgG	38 (78)	37 (74)	
IgA	7 (14)	2 (4)	0.19
Micromolecular	3 (6)	11 (22)	
Not secernent	1 (2)	-	
Light chain type, n (%)			
Kappa	29 (59)	36 (72)	0.17
Lambda	20 (41)	14 (28)	
Median glomerular filtration rate, ml/min (range)	78 (4-117)	80 (4-118)	0.71
Glomerular filtration rate < 40 ml/min, n (%)	12 (25)	9 (18)	0.39
Dialysis, n (%)	2 (4)	3 (6)	0.68
Diabetes, n (%)	9 (18)	10 (20)	0.83
Body weight, median, kg(range)	70 (45-120)	70 (45-98)	0.56
Association regimens, n (%)*			
Dara-VTD	21 (43)		
Dara-VMP	6 (13)		
Dara-RD	9 (18)		
Dara-VD	4 (8)		
Dara-PD	1(2)		NV
Daratumumab	8 (16)		
VRD		41 (82)	
KRD		7 (14)	
VMP		1 (2)	
KD		1 (2)	
Therapy setting, n (%)			
First line	35 (71)	42 (84)	0.13
Second line	14 (29)	8 (16)	
Prior ASCT,	3 (6)	5 (10)	0.23
Lowest lymphocyte count, median, x 10^3/µL (range)	0.47 (0.1-1.8)	0.48 (0.2-1.19)	0.25
Overall IgG, median, mg/dl (range)	346 (37-2470)	490 (79-1150)	0.39
Antiviral prophylaxis with acyclovir, n(%)	30 (61)	43 (86)	**0.017**
CMV reactivation, n (%)	15 (31)	2 (4)	**<0.001**
CMV DNA at peak, median UI/mL(range)	152 (34.5-141,000)	137 (137-137)	0.64
CMV DNA at peak > 137 UI/mL	8 (16)	0	**0.003**
CMV DNA at peak > 1000 UI/mL	4 (8)	0	**0.04**
Time to CMV reactivation, median, days (range)	29 (10-184)	54 (48-59)	0.64
Clinical features of CMV reactivation , n (%)			
- Pneumonia	1 (2)	0	0.31
- Blood reactivation	14 (29)	2 (4)	**<0.001**
- Treatment with anti-CMV agents	5 (10)	0	**0.02**

*Dara-VTD, daratumumab-bortezomib-thalidomide-dexamethasone; Dara-VMP, daratumumab-bortezomib-melpgalan-prednisone; Dara-RD, daratumumab-lenalidomide-dexamethasone; Dara-VD, daratumumab-bortezomib-dexamethasone; Dara-PD, daratumumab-pomalidomide-dexamethasone; VRD, bortezomib-lenalidomide-dexamethasone; KRD, carfilzomib-lenalidomide-dexamethasone; KD, carfilzomib-dexamethasone

DP084

EFFECT OF DARATUMUMAB ON STEM CELL YIELDS IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: A MULTICENTRIC ITALIAN EXPERIENCE

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The inclusion of the anti-CD38 antibody daratumumab (dara) into induction therapy improved outcomes for patients (pts) with newly diagnosed multiple myeloma.

Table 1. Baseline patient's clinical characteristics and the frontline induction therapy. *NA= not available

Characteristics	Patients (N= 78)	%
Gender		
Male	48	62
Female	30	38
Age (years)		
Median (range)	61 (56-66)	
Type of Heavy chain		
G	46	59
A	18	23
Absent	14	18
Type of Light chain type		
κ	54	69
λ	24	31
ISS		
I	31	40
II	27	35
III	19	24
NA	1	1
Cytogenetic abnormalities, n (%)		
High risk	34	43
Standard risk	31	40
Not evaluable/missing	13	17
CRAB		
Hypercalcemia	13	17
Renal insufficiency	12	15
Anemia	35	45
Osteolytic bone lesions	70	90
R-ISS		
I	22	28
II	29	37
III	17	22
NA	10	13
Mobilization regimen, n (%)		
G-CSF	3	3.8
CTX + G-CSF	70	90
G-CSF + PLERIXAFOR	1	1.3
CTX + G-CSF + PLERIXAFOR	4	5.1
Total dose of CTX (gr), median (range)	3.2	3.6 - 5
Number of days of CTX, n (%)		
1	42	55
2	34	45
Number of plerixafor dose, n (%)		
1	17	71
2	7	29
Response after induction therapy		
sCR	10	13
CR	16	21
VGPR	40	51
PR	12	15
Bone marrow plasma cell infiltration		
Median (range)	60 (35-75)	
Bone marrow function pre-mobilization therapy, median (range)		
Hb, g/dl	12.7 (12.1-13.7)	
Platelets, mm³	234 (185-310)	
Neutrophils, mm³	3000 (2120-4178)	
Induction therapy toxicity		
Haematological		
Anemia	1	2
Thrombocytopenia	2	4
Leucopenia	4	8
Non-Haematological		
Neuropahty	14	27
Infections	1	2
Gastroenteric	7	14
Skin rash	3	6
Cardiac	2	4

Recent studies have indicated a potential reduction in stem cell yields in pts exposed to dara prior to stem cell mobilization1.

The aim of this study is to investigate the possible impact of dara on stem cell yields with mobilization therapy.

We retrospectively evaluated 78 pts with NDMM managed at 12 Italian Hematology Centers who underwent induction therapy based on dara-bortezomib, thalidomide and dexamethasone (D-VTD) between November 2021 and March 2023. Following induction, pts underwent mobilization therapy as per institutional guidelines.

The baseline clinical characteristics and the frontline induction therapy were summarized in Table 1. Globally, 73/78 pts (93%) met the collection goal after mobilization therapy, however for 5/73 pts (7%) and 2/73 pts (3%) a second and third mobilization attempt was required, respectively. In the majority of pts (90%), a combination of cyclophosphamide (CTX) with granulocyte colony stimulating factor was used as the first mobilizing regimen attempt. Plerixafor on demand was administered in 24/78 pts (30%) failing to achieve the desidered collection goals, confirming that a higher use of plerixafor was necessary in the dara-based induction therapy1. The median number of CD34+ stem cells collection yield was 7.6 x 106 cells/Kg (5.9-9.9). The median time between the last day of induction therapy and the first day of mobilization therapy was 31 days (21-45). Univariate analysis showed that a baseline plasmacytoma was associated with a lower rate of collection goal, after the first mobilization attempt (p=0.028). Pts with a median lower pre-mobilization therapy level of neutrophils showed a significantly lower rate of collection goal after the first mobilization attempt (p=0.021), possibly due to prolonged hematological toxicity after induction therapy. Pts who received a full dose of CTX in 1 day have a higher rate of collection after first mobilization attempt compared to pts who split the dose over 2 days (p=0.003).

On introducing dara to the induction treatment, we observed that a higher use of plerixafor is required to meet the collection goal at the first mobilization attempt. A larger cohort of pts are needed to confirm our results and to evaluate a new mobilization therapy schedule to guarantee adequate stem cell yields.

Reference

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DP085

THE ROLE OF CIRCULATING MULTIPLE MYELOMA CELLS (CMMC) AS MARKER OF DISEASE DYNAMICS UNDER TREATMENT

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Aim of the study was to analyze circulating multiple myeloma cells (CMMCs) in newly diagnosed (ND) MM pts, by CELLSEARCH system® (Menarini Silicon Biosystems), to correlate CMMCs count with both the bone marrow (BM) tumor burden at baseline and its dynamics under treatment. 44 NDMM patients (pts) were included in the study, and from 40 of them, a total of 94 peripheral blood (PB) samples were collected every 3 months (m) (median follow-up: 6m, range 0-18m) throughout their sequential treatment phases. In 17/44 pts, PB samples were collected also at di-

agnosis. In 4 pts, single cell (sc) DNA analysis was performed to study the Copy Number Alterations (CNAs) profile of CMMCs under treatment. At diagnosis, a wide range of CMMCs (1-39940, median 349) was counted, though significantly correlated with the percentage of BM-plasma cells (PCs) and serum β2 microglobulin levels (p=0.06 and 0.032, respectively), suggesting that CMMCs count reflects BM tumour burden. During induction therapy, a median of 2 CMMCs (0 to 5432) was found in 52 samples, whereas, in the subsequent pre-maintenance phase, a narrower range of CMMCs (0-180, median 0) was counted in 42 samples. Under treatment, CMMCs were repetitively detectable in 15/40 analyzed pts (referred as G1), or constantly undetectable or increased or decreased over time in the remaining 25 pts (referred as G2). High quality response rates were significantly lower in G1, as compared to G2: 6/15 (40%) pts in the G1 group and 19/25 (76%) G2 pts achieved at least a very good partial response (p=0.04). Similarly, BM-measurable residual disease analyses by Next Generation Sequencing at a sensitivity level of 10-5 were positive in 8/10 (80%) and 9/23 (39%) G1 and G2 pts, respectively (p=0.05), suggesting that either persistence or continuous CMMCs release correlates to suboptimal clinical and molecular responses. Finally, genomic analysis of residual CMMCs collected from 4 pts showed that CMMCs CNAs profiles mirrored the baseline BM-PCs one, though minutely disclosing its sub-clonal composition and highlighting that, in 3/4 pts, the main-ploidy was 4 (i.e., suggestive of whole-genome doubling events), which represents a not-feasible finding in BM-PCs. In conclusion, these results suggest that CMMCs count might reflect the BM tumor burden dynamics, possibly providing a minimally-invasive tool to monitor MM pts' clinical course.

Thanks to: AIRC19-IG22059, AIL Bologna ODV, RC 000599/22

DP086

PROLONGED OVERALL SURVIVAL IN MULTIPLE MYELOMA PATIENTS RELAPSING AFTER ALLOGENEIC TRANSPLANT AND RECEIVING NOVEL DRUGS

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Even if allogeneic stem cell transplantation (allo-SCT) is curative for a minority of patients with multiple myeloma (MM), the patients who have relapsed after allo-SCT can experience long term survival.We evaluated 202 multiple myeloma (MM) pts reported to the Gruppo Italiano Trapianto Midollo Osseo (GITMO) registry who underwent allogeneic stem cell transplantation (allo-SCTs) between 2009 and 2018 and survived at least 3 months after transplantation in order to identify predictors for long term outcome in the whole population and for prolonged OS after relapse in the subgroup of relapsed pts. Median age at transplant was 54 years (range 29-77). ISS stage 3 was detectable in 49/121 pts (40%). High risk FISH was present in 53 out of 117 evaluable pts (45%). Allo-SCT was performed after more than 2 lines of treatments in 92 pts (49%). Myeloablative conditioning was administered to 119 allo-SCTs (60%). Stem cell source was peripheral blood for 177 allo-SCTs (88%). Donors were: 92 HLA-identical sibling (45%), 104 unrelated (51%) and 6 haploidentical (4%). Median overall survival (OS) and progression free survival (PFS) of the whole population were respectively 39.4 and 19 months from allo-SCT. Grade 2-4 GVHD incidence was 22.6% and moderate or severe chronic GVHD occurred in 35.4 % of the pts. In the multivariate model, > 2 lines of therapy before allo-SCT (p=0.012), older age (p=0.015), acute GVHD (p=0.002) and high risk FISH (p=0.017), were significant factors associated with reduced OS. Relapse after allo-SCT occurred in 119 (59%) pts at a median of 14.3 months (IQR 7.2-26.9).Thirty-seven pts (31%) were observed without treatment or received chemotherapy or radiotherapy, 9 pts (8%) received at least one salvage treatment including immunomodulating agents, 43 pts (33%) were treated with at least one salvage therapy including proteasome inhibitors, 34 pts (29%) received at least one salvage treatment including monoclonal antibodies (33 daratumumab, 1 elotuzumab). Median OS of relapsed pts was 38.5 months from allo-SCT and 20.2 months from relapse. In multivariate analysis OS after relapse was significant longer in pts who had received at least 3 salvage treatment lines (p<0.001) and/or donor lymphocyte infusions (DLI) (p=0.011). Our results suggest a synergy between anti-myeloma drugs administered after allo-SCT and donor T cells inducing a long term disease control.

DP087

EFFECT OF DARATUMUMAB-BASED INDUCTION THERAPY ON AUTOLOGOUS PERIPHERAL BLOOD STEM CELL (PBSC) COLLECTION AND POST-TRANSPLANT ENGRAFTMENT IN NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM) PATIENTS (PTS)

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Concerns have been raised about the potential interference of daratumumab (D)-based induction therapies with collection of peripheral blood stem cells (PBSC) and their engraftment after auto-transplantation (ASCT) in MM. We retrospectively analysed 44 NDMM pts who received 4 (N=34) or 6 (N=10) cycles of DVTD (D-bortezomib-thalidomide-dexamethasone, N=26) or DVCD (D-bortezomib-cyclophosphamide-dexamethasone, N=18) as induction therapy before ASCT, and compared them with a series of 50 VTD-treated NDMM pts who were matched for age and cytogenetic risk. After induction, pts received mobilisation therapy with cyclophosphamide (CY) at either 2 g/sqm (59% *vs* 80% in the two groups, respectively) or 3 g/sqm (41% *vs* 20%) plus G-CSF 10 mg/sqm/day. The collection target was $3x10^6$ PBSC/kg for each planned ASCT, most of pts aimed at receiving at least 2 ASCTs (91% *vs* 98%). A maximum of 2 doses of Plerixafor (PLX) were administered before collection in poor mobilisers (<20 PBSC/uL) or during collection in case of unsatisfactory yield. A trend of lower median collected CD34+ cells (6.74 *vs* 8.03 $x10^6$/kg, p=0.074) and higher rates of mobilisation failure (7% *vs* 0%, p=0.198) or target failure (23% *vs* 16%, p=0.572) were noted in

the D-treated *vs* control groups, although the small sample sizes might have influenced the statistical power. Failures to achieve the collection goal in the D group were more frequent in females *vs* males (p=0.033); other baseline characteristics, type of induction quadruplet, number of cycles, response to therapy, D-free interval before CY and CY dose were not significantly related. The median number of days of collection was 3 in both groups. Use of PLX was frequent in the D group (52% *vs* 20%, p=0.002), with higher incidence (p=0.04) in pts older than 60 years. Despite similar mean numbers of PBSC reinfused in the two groups (3.24 *vs* 3.64 x10^6/kg, p=0.097) and better PBSC vitality in the D group (73% *vs* 68%, p=0.047), D pts had slower neutrophil (12 *vs* 11 days, p<0.001) and platelet (14 *vs* 12 days, p<0.001) engraftment, requiring more red cell transfusions (p=0.029) after the first ASCT than controls. No higher rates of febrile neutropenia (47% *vs* 38%, p=0.596) or longer hospitalisation (median: 20 days in both groups) were observed. In summary, D-based treatment was likely to interfere with PBSC collection and engraftment; however, the impact was not clinically relevant and potentially mitigated by PLX.

DP088

THE COMPOSITION OF IMMUNE CELLS IN BONE MARROW REFLECTS THE PROGRESSION OF MULTIPLE MYELOMA AND INFLUENCES TREATMENT RESPONSE

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Multiple myeloma (MM) is the second most common incurable hematologic malignancy, characterized by the accumulation of aberrant clonal plasma cells in the bone marrow (BM) and the occurrence of myeloma-defining events and end-organ damage (SLiM-CRAB features). The symptomatic disease is preceded by two premalignant conditions: monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM), with evolution rates of 1% and 10% per year, respectively. Currently, these patients enter follow-up programs which depend upon progression risk models based on (tumor-derived) clinical laboratory data. Thus, elucidating the key factors that trigger neoplastic transformation and managing high-risk patients to improve their clinical outcomes and implement early therapeutic interventions are crucial. Because the genomic landscape often overlaps between premalignant conditions and active MM, the latest research has focused on the role of the BM immune microenvironment. The purpose of this study is to characterize the alterations in BM immune cell composition along the MGUS-MM progression and to determine their association with the therapeutic response of MM patients. We used FlowCT, a recently developed semi-automated pipeline for flow cytometry data analysis, to compare the immune compartment in the BM of 12 MGUS, 12 SMM, and 63 MM patients stained with two common diagnostic tubes. Progression to clinical MM was associated with a decrease in granulocytes (mean, 74.18% MGUS *vs* 73.86% SMM *vs* 65.59% MM; p<0.05) and an increase in monocytes (mean, 4.97% MGUS *vs* 4.62% SMM *vs* 6.77% MM; p<0.01), T lymphocytes (mean, 6.29% MGUS *vs* 7.56% SMM *vs* 11% MM; p<0.01), and NK cells (mean, 0.88% MGUS *vs* 1.51% SMM *vs* 2.13% MM; p<0.001). Effector CD38+CD81+CD28- NK/T lymphocytes were abundant in MM patients (mean, 2.50% MGUS *vs* 2.28% SMM *vs* 4.31% MM; p<0.05) and CD27- *vs* CD27+ NK/T lymphocytes ratio augmented during disease progression (p<0.05). We further evaluated the progression-free survival (PFS) of 50 patients with active MM and found that the abundance of granulocytes in the BM was associated with a longer PFS (HR: 0.15; p<0.05). Furthermore, patients treated with daratumumab who had a high BM neutrophil/T lymphocyte ratio showed a substantially longer 1-year PFS (HR: 0.07; p0.01) than those who had a low ratio (86% *vs* 33%, respectively). These findings suggest that changes in the BM immune cell composition have a role in MM evolution and disease outcome.

DP089

ESTABLISHMENT OF AN ITALIAN "MM MRD NETWORK" FOR THE HARMONIZATION OF NEXT GENERATION METHODS FOR MINIMIMAL RESIDUAL DISEASE ASSESSMENT IN MULTIPLE MYELOMA

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The International Myeloma Working Group (IMWG) has recently established criteria for the analysis of Minimal Residual Disease (MRD) results in Multiple Myeloma (MM), as obtained either by Next Generation Flow (NGF) or by Next Generation Sequencing (NGS). However, the employment of MRD next generation techniques in the daily management of MM raises the need of both flow cytometry (FC) and molecular biology (MB) methods' harmonization in order to avoid possible discrepancies emerging among different laboratories. Aim of this study was to build a "MM MRD network" to harmonize both FC and MB next generation methods for MRD analysis in MM patients among Italian Hub-Hematology Centres. The study has been approved by an Ethic Committee. The experimental plan included a preliminary survey among Italian centres, conducted in order to map the currently used MRD methods and the willingness to participate to the study. Methods harmonization, samples' management between laboratories, definition of quality controls (QC) rounds have been planned and discussed in both FC and MB groups. Here we report the preliminary results of MB method harmonization. For MB MRD assessment, IgH

and Igk genes were sequenced by using the Lymphotrack assays (Invivoscribe) on the MiSeq platform (Illumina) in all centres. Eight newly diagnosed MM patients were included in the study after signing an informed consent. Both screening and MRD mock samples (corresponding to 10-3 and 10-5 residual cells) were prepared in collaboration with University of Milan. The screening phase (QC1 – Clonotype Identification) was completed with a low number of failed reactions ranging from 0 to 31% of the total reactions. By excluding these samples, centres attained a high concordance rate for the definition of the patient-specific clonotype (32/32 rearrangements = 100% concordance). However, some discrepancies arose in the choice of the trackable clonotype(s), that allowed a discussion and definition of shared criteria for their selection. The next phases (QC2 and QC3) devoted to MRD tracking are currently ongoing: the measurement of MRD levels will be compared between the participant centres and results will be reported. In conclusion, this study is supposed to pave the way for a diffuse employment of MRD next generation technologies in the daily management of MM, thanks to the definition of shared criteria and guidelines, as defined by Italian experts.

This study is sponsored by Janssen-Cilag SpA.

DP090

MODELING DYNAMIC EVOLUTION OF MULTIPLE MYELOMA UNDER IMMUNOTHERAPY PRESSURE: A SYSTEMS-THINKING BASED APPROACH

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Clinical behavior of multiple myeloma (MM) arises from a complex system, where neoplastic and immune cells interact together at different hierarchical levels, conveying emergent properties, not yet identified by current deterministic and probabilistic approaches. Bispecific T cell engagers (TCE) are a new immunotherapeutic class of agents that concomitantly engage a target on the surface of cancer cell and CD3 on the surface of T-cells, promoting T cell activation and lysis of tumor cells. In this work, we set up minimal stock-flow models of dynamic MM evolution under TCE, using a Systems Thinking (ST) approach within the framework of non-equilibrium thermodynamics constraints to identify the systemic configurations of TCE response. In the ST diagram of MM treated with TCE, inflows and outflows of resources (energy, matter and information) are conceived as the components of an ideally- confined (open) "disease system". The energy amounts, stored in the system components (namely, state variables), can vary over time and are used to capture the system dynamics. According to this approach, achieving a clinical remission (*e.g.* negative MRD status) is not a (plasma)cell state, but a system at a transitory steady state, where inflows and outflows are balanced. Conversely, clinical relapse is the transition state in which inflows and outflows are not balanced, since neoplastic plasma cell proliferation leads to increase of matter coupled to reduction of information and energy required for the system survival. The competition for resource use and ATP production between T-cell subpopulations and different MM subclones exhibits a class of regime shifts to more stable and dissipative states for selective advantaged populations operating closer to the thermodynamic limit. The critical time for the transitions is controlled by the strength of the actual biochemical interaction. In conclusion, we described the first systemic stock-flow diagram addressing trade-offs operating at the cell population level in MM upon TCE. The proposed approach directly links cell population modeling with non-equilibrium thermodynamics for observable flows, opening to possible experimental validation of the models for further applications in systems medicine.

DP091

SRY-BOX TRANSCRIPTION FACTOR 4 AS A NEW TARGET IN MULTIPLE MYELOMA

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Introduction. Multiple Myeloma (MM) is incurable and characterized by the accumulation of malignant plasma cells in the bone marrow, new therapeutic strategies are needed. Increased expression of the Sex-determining region Y-related high-mobility-group box transcription factor 4 (SOX4) has been correlated with tumor development, progression, and maintenance of cancer-initiating cells. We previously demonstrated that SOX4 and hypoxia-inducible factor 1-alpha (Hif1-α) are functionally coupled. MM cell line U266B1, transfected with miR-335, showed downregulation of SOX4, activation of HIF1α, and apoptosis. Starting from these results, we studied SOX4 expression in plasmacells of MM patients in different stages of the disease and we proved that this gene could be modulated by miRNA-335.

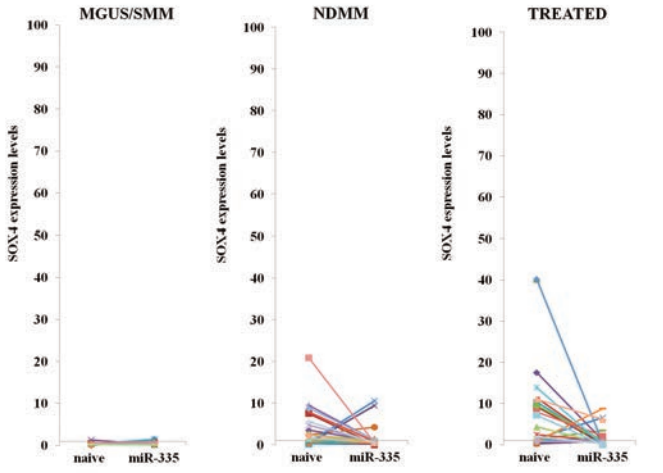

Figure 1.

Methods. Since SOX4 is a known target of miR-335, we used miR-335 to assess whether SOX4 modulation could promote apoptosis in immune-sorted CD138+ plasma cells from MM patients. MM CD138+ cells were divided into two aliquots each, one used as a control to check the SOX4 constitutive level and the other treated with miR-335 to modulate it. Gene expression was analyzed after 72 hours by RT-PCR, protein levels by Wester-blotting, and functionality by vitality assay. SOX4 expression was correlated to the MM follow-up standard assay panel.

Results. miR-335 acts on SOX4 and on SOX4-related genes such as AKT, PI3K, and Hif1-α and promotes apoptosis. SOX4 was found

to be expressed in plasma cells obtained from the bone marrow of MM patients. Patient samples were divided into pre or early MM forms (MGUS/SMM, n=10), newly diagnosed MM (NDMM, n=22), and treated MM (n=27). The data proves that SOX4 is low expressed in MGUS and SMM and increases during the disease progression. In addition, miR-335 transfected plasmacells from MM patients showed clear modulation of SOX4 expression in established disease with or without treatment (Figure 1).

Conclusions. SOX4 increase is related to the stage of the disease. Due to these observations, we propose SOX4 as a new putative marker in MM development and target in the new therapeutic frontiers.

DP092

SAFETY OF SUBCUTANEOUS DARATUMUMAB IN PLASMA CELL DISORDERS: A RETROSPECTIVE MULTICENTER REAL-LIFE EXPERIENCE

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Introduction. Daratumumab, an anti-CD38 monoclonal antibody, is approved for treatment of multiple myeloma (MM) and light chain amyloidosis at an intravenous (IV) dosage of 16 mg/kg; however, a high rate of infusion-related reactions (IRRs; 45-56%), especially during first administrations, is reported. A subcutaneous (SC) formulation at a fixed dosage of 1800 mg has been designed to decrease incidence and severity of IRRs, with similar efficacy and short administration time (3-5 minutes). Real-life data on daratumumab safety are still few, therefore in this multi-center retrospective real word experience, we investigated safety of SC daratumumab in plasma cell disorder treatment.

Materials and Methods. A total of 189 patients diagnosed with MM or light chain amyloidosis from December 2021 were included in this retrospective trial. Enrolled subjects were daratumumab-naïve and were treated with at least one dose of SC formulation in combination or monotherapy regimens as first-line treatment. Primary endpoint was safety of SC daratumumab, especially for IRR incidence and severity.

Results. Clinical characteristics are summarized in Table 1. All patients were premedicated with dexamethasone, paracetamol, and antihistamine, while montelukast was used in 85% of cases, and enrolled patients received a median number of SC daratumumab administrations of 11 (range, 1-23). Four patients (4%) experienced IRRs, and of those, only one subject experienced two consecutive grade III-IV reactions. However, once switched to IV formulation, no IRRs were observed, suggesting intolerance to some SC formulation excipient. Grade I-II hematological and gastroenteric toxicities were observed in 25 cases (13%), and were: 32% (N = 8), thrombocytopenia; 40% (N = 10), neutropenia; 28% (N = 7), lymphopenia; and 2% (N = 4), diarrhea.

Discussion. In our multicenter retrospective real-life experience, SC daratumumab safety profile showed high tolerability with a very low (4%) IRR incidence, even lower than that reported in phase II-III trials, and regardless patient's comorbidities and disease stage. Therefore, SC daratumumab is highly manageable even in a real-life setting with an excellent safety profile and short administration time. Further validation on larger and prospective clinical studies are needed.

Table 1. Patients' characteristics at enrollment.

Characteristics	N = 189
Median age, years (range)	67 (36-85)
Gender, n (%)	
Male	97 (51)
Female	92 (49)
Diagnosis, n (%)	
Multiple Myeloma	189 (95)
Light chain amyloidosis	9 (5)
M-protein type, n (%)	
IgG	129 (68)
IgA	42 (22)
Micromolecular	15 (8)
Not secernent	3 (2)
Light chain type, n (%)	
Kappa	118 (62)
Lambda	68 (36)
Body weight, n (%)	
≤ 65 kg	60 (32)
> 65 kg	129 (68)
Median glomerular filtration rate, ml/min (range)	73 (4-125)
Glomerular filtration rate ≥ 40 ml/min, n (%)	
Yes	156 (83)
Not	33 (17)
Montelukast premedication, n (%)	
Yes	161 (85)
Not	28 (15)
Association regimens, n (%)	
Daratumumab-bortezomib-Thalidomide-dexamethasone	70 (37)
Daratumumab-lenalidomide-dexamethasone	68 (36)
Daratumumab-melphalan-prednisone	8 (4)
Daratumumab-bortezomib- dexamethasone	14 (7)
Daratumumab-ciclophosphamide-bortezomib-dexamethasone	9 (5)
Daratumumab-pomalidomide-dexamethasone	2 (1)
Daratumumab as single agent	18 (10)
First line (%)	123 (65)
1 prior therapy (%)	44 (23)
≥ 2 prior therapies (%)	22 (12)
SC Daratumumab administrations, median for single patient, (range)	11 (1-23)
SC Daratumumab administrations, total	2078
IRR rate for patient, n (%)	
Yes	8 (4)
Not	181 (96)
IRR rates for total SC administrations, n (%)	
Yes	8 (0.4)
Not	2070 (99.6)

Abbreviations. Ig, immunoglobulin; IRR, infusion-related reaction; SC, subcutaneous.

DP093

CONTINOUS CARFILZOMIB, LENALIDOMIDE AND DEXAMETHASONE (KRD) FOR RELAPSED-REFRACTORY MULTIPLE MYELOMA: A LONG-TERM FOLLOW-UP, A MULTICENTER, RETROSPECTIVE REAL-LIFE STUDY FROM EUROPEAN MYELOMA NETWORK (EMN) ITALY

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Introduction. Based on results of the ASPIRE trial, the KRd regimen (carfilzomib, lenalidomide and dexamethasone) was approved in Italy for relapsed/refractory multiple myeloma (RRMM) patients (pts) since 2016. The published KRD schedule calls for this combination to be administered for 18 cycles. However, in Italy, there is no set limit to the number of KRd cycles

Methods. We evaluated safety and feasibility of KRd given up to 18 cycles *vs* continuously (cKRd) outside of clinical trials, based on a retrospective collection of real-world data from 348 pts treated in 20 EMN Italian centers from October 2016 to December 2022.

Results. Baseline characteristics are summarized in Table 1.

Table 1.

Patients	N. 348
Sex, n (%)	
Male/Female	184 (53) /164 (47)
Median Age (range)	64 (34-87)
Age > 70 ys, n (%)	75 (22)
Age ≤ 70 ys, n (%)	273 (78)
Interval KRD-diagnosis, median (range)	3.2 (-3.2 - 24.2)
Unknown	7
ISS, n (%)	
I	89 (32)
II	93 (33)
III	99 (35)
Unknown	67
Line of therapy (LOT) ≥ 3	174 (53)
AuSCT, n (%)	221 (68)
Unknown	21
Histology, n (%)	
IgG	191 (70)
IgM	4 (1.5)
IgA	76 (28)
IgE	2 (0.7)
IgD	1 (0.4)
Unknown	74
Light Chain, n (%)	
Lambda	114 (35)
Kappa	211 (65)
Unknown	23
Dialysis , n (%)	13 (4)
Unknown	27
Extramedullary disease,n (%)	46 (15)
Unknown	31

Most frequent comorbidities included arterial hypertension (14%) and diabetes (5%). The median number of previous lines of therapy (LOT) was 3 (range 1-11), including 221 (68%) pts undergone to autologous stem-cell transplant (ASCT). Based on physician's choice, 131 (38%) pts received cKRd, including 81 (23%) pts treated with 24 cycles or more. The median onset of hematological and non-hematological adverse events (AEs) was 6 cycles. Most frequent hematological AEs included anemia (28%), neutropenia (45%), and thrombocytopenia (49%), with grade 3-4 events in 46% of pts. Most frequent non-hematological AEs were infections (32%), cardiovascular toxicities (11%), hypertension (8%) and neuropathy (6%). We did not observe any worsening of hematological or non-hematological AEs in cKRd pts. After a median follow-up of 3.9 years (range 2.2-5.0), the best overall response rate (ORR) was 83%, obtained after a median of 4 cycles (range 1-35). Responses improved over time and were positively influenced by depth of response and number of KRd cycles ($p<0.001$), being lower in pts treated with 3 or more LOTs (<0.001). Overall 3-year median PFS of the entire series of pts was 54.9% (95% CI 49.7%-60.7%) while it was 68.8% in pts treated with cKRd. Overall 5-years median OS (mOS) was 55.1% (95% CI 49.1%-61.9%), and it was significantly longer in pts previously exposed to less than 3 LOTs *vs* those who received more than 3 previous LOT (64.3% versus 46.2%, $p<0.001$).

Conclusions. With a long term follow-up, a prolonged administration of KRD compared with the conventional schedule showed to be effective and safe. Such a new schedule could be a reasonable option for second-line treatment for pts refractory to daratumumab (D) and not exposed to R (D-VMP and D-VTD-ASCT), which is one of the most important challenges in the near future.

DP094

RISK OF INFECTION IN NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM) PATIENTS RECEIVING DARATUMUMAB BASED REGIMENS: A MULTICENTRIC ITALIAN EXPERIENCE

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Patients with multiple myeloma are at higher risk for infections due to disease pathogenesis and administered therapies. Infection is a significant cause of morbidity and the leading cause of death in patients (pts) with newly diagnosed multiple myeloma (NDMM). The risk of infection may be associated with neutropenia, hypogammaglobulinemia, and NK cell depletion. Daratumumab is approved for NDMM or relapsed/refractory multiple myeloma (RRMM). The use of daratumumab (dara) has improved patient outcomes but has changed the frequency and epidemiology of infections. The overall risk of infection with daratumumab treatment is around 38%, being upper respiratory tract infections the most common. The purpose of this study was to evaluate the number, the type and risk of infection events (IE)

associated with the use of dara in patients with NDMM in the induction phase of transplant eligible and transplant ineligible NDMM patients. We retrospectively evaluated 308 pts with NDMM treatment in 8 Italian Hematology Centers who underwent induction therapy based on dara-bortezomib, thalidomide and dexamethasone (D-VTD), dara-lenalidomide and dexamethasone (D-Rd) and dara-bortezomib and dexamethasone (D-VMP) between 2020 and 2023.. Overall, 105/308 (34%) developed an infection of any grade, 30/105 in D-VTD, 61/105in D-Rd and 14/105 in D-VMP arm. There was no difference on antiviral and antimicrobial prophylaxis in the 3 treatment groups. The median time to infection events was similar between the 3 groups D-VMP 161 days (104-243), D-Rd 156 days (97-370) and D-VTD 82 days (44-184) (p=0.064). Type of IE were upper respiratory tract infection in 81/105 pts (77%), SARS-COV2 infection 12/105 pts (11%), herpes simplex and varicella zoster virus (VZV) in 2/105 pts (1.9%), abdominal infection 3/105 pts (2.8%) and infection of urinary tract 2/105 pts (1.9%) of any grade. No differences were present in the grade and in the duration of IE. In all groups a statistically significant reduction was seen in the IgA level at the time of the IE (p=0.006), while no differences were present for IgG and IgM level in 3 treatment group. Moreover, a significant difference in neutropenia (p=0.002) and lymphocytophenia pre and post IE (p=0.006) resulted in all three groups. In our experience, no significant differences were found between the three treatment groups in terms of incidence, type and degree of infections, while significant differences were found between baseline IgA levels, neutropenia and lymphopenia at the time of the IE. A larger patient cohort and further studies are warranted to confirm these data and to identify patients at higher risk for infection, understanding the potential benefit of infectious prophylaxis in the clinical management in this setting of NDMM.

DP095

AUTOLOGOUS CD34+ MOBILIZATION FOLLOWING DARATUMUMAB- AND NON-DARATUMUMAB-BASED THERAPY: A REAL-LIFE COMPARISON OF TWO CONSECUTIVE COHORTS OF MULTIPLE MYELOMA PATIENTS

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Introduction. Induction therapy with Daratumumab-based regimens (Dara) followed by autologous stem cell transplantation is the standard of care for patients (pts) with newly diagnosed multiple myeloma who are eligible to high-dose chemotherapy. Lower CD34+ mobilization efficacy after Dara has been reported, although in most cases Plerixafor allows to reach the target. However, data on patients with no upfront Plerixafor exposure are lacking.

Aim. To assess autologous CD34+ mobilization efficacy after Dara without upfront plerixafor administration as compared to non-Dara-pts.

Materials and Methods. Retrospective study of 41 consecutive multiple myeloma pts who underwent mobilization at ASST GOM Niguarda. We analyzed demographic data, mobilization yields, CD34+ peak, number (n.) of apheresis attempts and plerixafor use following Dara and non-Dara therapy. Cyclophosphamide monotherapy at a dose of 2-3 g/m^2 was administered as mobilizing regimen to all pts unless contraindicated.

Results. 41 consecutive pts have been analyzed: median age 62 (range 39-72), 12 females (29%), 29 males (71%). Twenty pts received Dara, while 21 non-Dara. A correlation emerged between therapy and n. of apheresis needed to reach the set target (6x10^6 CD34+/kg). Seventy-five % of Dara-pts underwent >1 apheresis, compared to only 24% of non-Dara (p=0.0017). Moreover, Dara-pts had significantly lower CD34+ peak than non-Dara-pts (mean 38 *vs* 79; p=0.0011) Figure 1. Interestingly, a CD34+ peak value of 54.37/µL appeared to be the most effective predictor of target achievement probability within our cohort (ROC curve: sens.78%; spec.76%). Median CD34+ harvest was 3.98x10^6/kg (range 1.68 – 9.18) in Dara-pts, while 6.87x10^6/kg (range 1.63 – 16.85) in non-Dara-pts. Plerixafor was administered to 25% of pts who underwent >1 apheresis, 80% (4/5) being Dara-pts. In multivariate analysis the likelihood of undergoing >1 apheresis was significantly increased in older pt (OR 1.2, CI 1-1.4, Z=2.10, p=0.03) and Dara-pt (OR 15, CI 2.8-129, p=0.004).

Conclusions. This is the first analysis on autologous CD34+ mobilization following Dara and non-Dara-pts without upfront plerixafor use. In our hands, Dara-pts were at increased risk of failing the set CD34+ target by the first mobilization procedure, necessitating >1 apheresis attempt. Further studies with larger number of pts are warranted to confirm these results and to eventually optimize the mobilization strategy in Dara-pts.

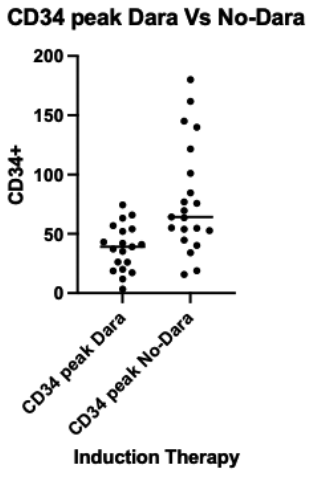

Figure 1.

DP096

REAL-LIFE STANDARDS OF TREATMENT IN PATIENTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA IN ITALY: SUBANALYSIS FROM THE LOCOMMOTION PROSPECTIVE STUDY

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Introduction. LocoMMotion (NCT04035226) is a prospective observational study assessing effectiveness, safety, and treatment (tx) patterns of real-life standard of care (SOC) in triple-class exposed (TCE) patients (pts) with relapsed/refractory multiple myeloma. We report final results from the Italian subset of pts at study end (24 months after first dose of last enrolled pt).

Table 1. Baseline characteristics and SOC therapies.

Characteristic	LocoMMotion (Italy) (N=59)	LocoMMotion (not Italy) (N=189)	Standardized difference[a]	Overall LocoMMotion population (N=248)
Age, median (range), years	69 (47–82)	68 (41–89)	0.0436	68 (41–89)
Sex, n (%)			−0.0395	
Male	33 (55.9)	102 (54.0)		135 (54.4)
Female	26 (44.1)	87 (46.0)		113 (45.6)
ECOG performance status, n (%)			−0.003	
0	17 (28.8)	48 (25.4)		65 (26.2)
1	40 (67.8)	138 (73)		178 (71.8)
≥2	1 (1.7)	3 (1.6)		4 (1.6)
Missing	1 (1.7)	0		1 (0.4)
Years from MM diagnosis, median (range)	5.6 (0.8–14.5)	6.4 (0.3–22.8)	−0.2098	6.3 (0.3–22.8)
Number of prior LOT			**−0.3179**	
Median (range)	4.0 (2–11)	4 (2–13)		4.0 (2–13)
≤4, n (%)	37 (62.7)	89 (47.1)		126 (50.8)
>4, n (%)	22 (37.3)	100 (52.9)		122 (49.2)
ISS stage at study entry, n (%)			0.2003	
I	17 (28.8)	52 (27.5)		69 (27.8)
II	21 (35.6)	48 (25.4)		69 (27.8)
III	17 (28.8)	61 (32.3)		78 (31.5)
Missing	4 (6.8)	28 (14.8)		32 (12.9)
Cytogenetic risk, n (%)			**0.3793**	
Standard risk	13 (22.0)	63 (33.3)		76 (30.6)
High risk	16 (27.1)	64 (33.9)		80 (32.3)
Not tested	30 (50.8)	62 (32.8)		92 (37.1)
Extramedullary disease, n (%)	7 (11.9)	28 (14.8)	0.0869	35 (14.1)
Previous transplant, n (%)	33 (55.9)	127 (67.2)	0.2331	160 (64.5)
Creatinine clearance, n (%)			**0.2762**	
<60 mL/min/1.73 m²	17 (28.8)	67 (35.4)		84 (33.9)
60 to <90 mL/min/1.73 m²	15 (25.4)	66 (34.9)		81 (32.7)
≥90 mL/min/1.73 m²	14 (23.7)	38 (20.1)		52 (21.0)
Missing	13 (22.0)	18 (9.5)		31 (12.5)
Refractory status, n (%)			0.139	
Less than triple refractory	13 (22.0)	53 (28.0)		66 (26.6)
Triple refractory or more	46 (78.0)	136 (72.0)		182 (73.4)
Refractory to PI	48 (81.4)	149 (78.8)		197 (79.4)
Refractory to IMiD	59 (100)	174 (92.1)		233 (94)
Refractory to anti-CD38 mAb	57 (96.6)	172 (91.0)		229 (92.3)
Refractory to last LOT	56 (94.9)	173 (91.5)		229 (92.3)
Index SOC regimens, n (%)[b,c]				
Monotherapy	5 (8.4)	–		22 (8.9)
Doublet therapy	21 (35.6)	–		106 (42.7)
Combination of ≥3 drugs	33 (56)	–		162 (65.3)
Most common index SOC regimens, n (%)[b]				
Pomalidomide-dexamethasone	12 (20.3)	–		29 (11.7)
Lenalidomide-dexamethasone-ixazomib	11 (18.6)	–		14 (5.6)
Carfilzomib-dexamethasone	10 (16.9)	–		35 (14.1)
Pomalidomide-cyclophosphamide-dexamethasone	9 (15.3)	–		35 (14.1)

[a]Bold characters are variables with standardized mean differences >0.25 between Italian patients and patients from other countries in the LocoMMotion study. [b]Participants could be counted in >1 regimen since some received different drugs within the index SOC regimen (eg, patients could start with a triplet regimen then de-escalate to a doublet regimen due to toxicity issues). [c]The Italian cohort is presented as intention-to-treat and patients are counted once, in the group corresponding to the most intensive treatment received in their index LOT. ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; ISS, International Staging System; LOT, line of therapy; mAb, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; SOC, standard of care.

Methods. Pts were TCE, double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD) or had ≥3 prior lines of therapy (LOT), had disease progression since last LOT, and ECOG performance status ≤1. Pt-level data for first tx at study enrollment (index LOT) were analyzed. Primary endpoint was overall response rate (ORR).

Results. The Italian cohort comprised 59 of 248 pts; characteristics were consistent with the overall LocoMMotion population (Table 1). Median follow-up was 22.6 months (mo) (95% CI, 21.0–32.4). At baseline, pts had a median of 4 prior LOT (range, 2–11; 37.3% >4). In index LOT, 20 unique regimens were used (see Table for most common). 57.6% of pts had a combination of ≥3 drugs, and 74.6% were re-exposed to the same mechanism of action (MOA) as in prior LOTs (IMiD [28.8%], PI [23.7%], PI and IMiD [20.3%], PI and anti-CD38 antibody [1.7%]). ORR by response review committee (RRC) assessment was 23.7% and included partial response (PR; 10.2%) and very good PR (13.6%); no pts had complete response or better. Median duration of response was 4.7 mo (95% CI, 3.7–NE) and median time to next tx was 4.6 mo (95% CI, 3.9–6.4). Median progression-free survival (PFS) by RRC was 5.1 mo (95% CI, 3.3–6.1). Median overall survival (OS) was 8.3 mo (95% CI, 5.4–15.3). PFS and OS were not statistically different in pts with >4 *vs* ≤4 prior LOT (median [95% CI] PFS, 5.1 mo [1.9–6.1] *vs* 5.4 mo [2.2–6.4]; median OS, 11.8 mo [4.5–27.9] *vs* 7.4 mo [5.1–15.3]), but interpretation requires caution due to small sample size. In index LOT, 44.1% of pts had grade 3/4 tx-emergent adverse events (TEAEs), most commonly neutropenia (13.6%) and thrombocytopenia (10.2%). Of 41 study deaths, 20 pts (48.8%) died during index LOT, 11 of these from a TEAE.

Conclusions. Italian TCE pts in LocoMMotion showed rapid disease progression and poor survival, confirming poor outcomes in real-life pts receiving third-line tx or later. Most were treated with regimens based on the same drug class previously received, highlighting the need for approval of effective tx options based on different MOAs.

DP097

SECOND CANCER IN PATIENTS WITH SYMPTOMATIC MULTIPLE MYELOMA: A RETROSPECTIVE MONOCENTRIC STUDY

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The association between multiple myeloma (MM) and second cancer (SC) has been reported, especially in patients (pts) exposed to the sequence melphalan/lenalidomide. However, practice guidance is lacking. We studied in our center the MM pts diagnosed with SC within 6 months of MM diagnosis (synchronous) and after 6 months (metachronous). From a cohort of 725 patients, we collected 51 symptomatic pts with SC. The distribution of neoplasms mirrors that of the Italian population: cancer of the colon in 9 pts (17.6%), lung in 7 (13.7%), breast in 4 (7.8%), prostate in 3 (5.8%), and bladder in 3 (5.8%). The prevalence of non-Hodgkin's lymphomas is higher than in the general population (n=4, 7.8%) [AIOM, 2022]. Pts with synchronous SC were 16 (M/F 9/7, median age 72 years, range 57-85). In 10 (62.5%), a diagnosis of SC was made by MM staging exams. Only 1 patient was considered untreatable; 8 started MM treatment, and 7 delayed treatment to allow cancer therapy. In pts <65 years, the overall survival (OS) was unaffected by a diagnosis of synchronous SC (SC 67 months *vs* no-SC 59 months, p=0.35). In pts ≥ 65, the OS was significantly reduced (SC 28 months *vs* no-SC 37.5 months, p=0.047). In pts with synchronous SC, 38.4% of deaths

were attributable to MM (n=1) or SC (n=4).

Pts with metachronous SC were 35 (annual incidence rate IR 0.97%) (median age at MM diagnosis 68 years (40-78), M/F 22/13). The median time to SC diagnosis was 56 months (range 13-216). The annual IR per 100 pt-years of SC was higher in pts who have undergone autologous bone marrow transplantation (1.04 in those with 1 procedure and 1.58 in those with 2 or more procedures), with an odds ratio for SC in transplanted pts of 2.25 (95% CI 1.14-4.45, p=0.01). In 65% of pts, the cancer was symptomatic; 62.8% of pts had an advanced stage at diagnosis, and 31% received palliative treatments. At the time of SC diagnosis, 21 pts were on MM treatment, and half discontinued therapy. The median survival after SC diagnosis was 7 months, and SC was the leading cause of death (70%).

In conclusion, the treatment of a synchronous SC can be included in the therapeutic path of MM pts < 65 yrs without significant impact on prognosis compared to age-matched pts. In pts ≥ 65 yrs, diagnosis of a synchronous SC reduces OS compared to age-matched pts. Diagnosis of metachronous SC is associated with a poor prognosis. We suggest active surveillance for early diagnosis, particularly in transplanted pts.

Infections, cytogenetic and quality of life

DP098

CLINICAL INTRODUCTION AND PROGNOSTIC IMPACT OF NEXT GENERATION SEQUENCING IN ACUTE MYELOID LEUKEMIA PATIENTS AT DIAGNOSIS: SINGLE CENTER REAL-LIFE EXPERIENCE

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The genetic prognostic evaluation of acute myeloid leukemia (AML) patients (pts) is rapidly evolving. In addition to classical cytogenetic and molecular methods, next generation sequencing (NGS) platforms have been progressively introduced with the purpose of expanding the panel of target genes and consequently improve AML risk stratification. Aim of the present study was to report the real-life challenges of NGS introduction in the clinical practice of an Italian center and to analyze its impact on AML prognosis. A total of 130 actively treated AML pts (median age 65 years), diagnosed between January 2020 and December 2022 at the Hematology Unit of "Città della Salute e della Scienza di Torino", were included. Seventy-four pts (57%) received intensive chemotherapy, 37 (28%) the association of venetoclax and hypomethylating agent (HMA) and 19 (15%) only HMA. Cytogenetic and molecular baseline characteristics, in addition to genetic information derived from NGS analysis, when available, were collected; we analyzed how NGS data could have possibly changed our therapeutic choices. Cytogenetic abnormalities were detected in 61 pts (47%): driver fusions in 13, mon5/del5q in 17, mon7 in 9, abn17p in 14, complex karyotype in 19. Concerning molecular biology, we detected NPM mutations (mut) in 34 pts (26%), FLT3-ITD or TKD mut in 25 (19%), and IDH1/2 mut in 24 (19%). NGS was performed in 52% of the pts (n=68): 32% (12/37) in 2020, 53% (24/45) in 2021, 67% (33/49) in 2022. In 2022, NGS was performed in 25/29 intensively treated and in 8/20 less intensively treated pts. Applying NGS, we found additional mutations in DNMT3A in 24 pts (18%), TET2 in 21 (16%), ASXL1 in 15 (12%), RUNX1 in 13 (10%), SRSF2 in 8 (6%), TP53 in 7 (5%), EZH2 and ZRSR2 in 6 (5%). According to NGS evaluation, 19 of 68 (28%) pts would be reallocated in a different prognostic category, particularly 17 pts from the intermediate risk group to the adverse one. In conclusion, we report the effective introduction of NGS in a real-world setting, with a progressive increase in the percentage of patients tested at diagnosis with NGS over the last three years. In our cohort we confirmed that NGS data are useful to better classify AML pts risk and, consequently, to guide informed therapeutic choices. The integration of genomic data given by NGS with clinical and treatment variables in a knowledge bank approach is likely to be the further step toward a more accurate prognostication in AML.

DP099

FAMILIAL HEMATOLOGIC NEOPLASMS: NGS TECHNIQUES FOR IDENTIFYING NOVEL PREDISPOSING GERMLINE VARIANTS

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Background. Thanks to next-generation sequencing (NGS) techniques, several familial forms of hematologic malignancies have been highlighted in recent years, some of which are also recognized in the WHO2016 classification. However, in most familial clusters, known mutations have not yet been identified, highlighting the need to search for additional variants and genes involved. Our hypothesis is that a careful family history at onset may help to identify a population more likely to be carriers of these mutations.

Materials and Methods. We analyzed 9 families in which individuals with hematologic malignancies of both myeloid and lymphoid origin were first-degree relatives. We collected and analyzed blood samples from both affected family members and confirmed the germline origin of the mutations found by analyzing saliva samples. NGS analysis was performed using a custom panel of 70 genes described in inherited forms of solid and/or hematologic malignancies. Software such as ClinVar was used for variant interpretation. In our study, we focused on germline variants classified as pathogenic, likely pathogenic, or of uncertain significance (VUS) according to the American College of Medical Genetics and Genomics guidelines.

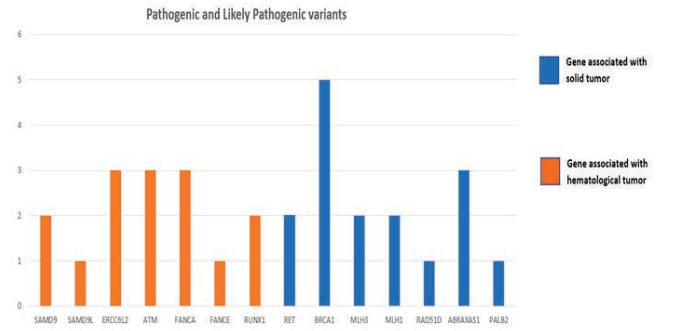

Figure 1.

Results and Discussion. In our families, 31 pathogenic or likely pathogenic germline variants were highlighted in 14 different genes, 7 of which have been described in inherited forms of hematologic malignancies and 7 of which have been associated in the literature with solid tumors. Finally, 62 VUS mutations were identified in 21 different genes. It seems clear that NGS allows the identification of significantly more variants. In our study, several new variants were identified in genes known to be associated with familial forms of hematologic disorders, confirming their role. The interpretation of the remaining mutations is very complex: some mutations were found in only one of the family members; others were found in diseases different from those classically associated in the literature. Studies such as this one highlight the need for continuous updating of international databases, both to identify new variants and to allow proper reclassification of VUS, which deserves a separate chapter. It may also be important to study unaffected family members to better understand the role of these mutations, which also have important therapeutic implications for the management of the allogeneic transplant and for the follow-up of the family members.

DP100

TIXAGEVIMAB-CILGAVIMAB HAS A REDUCED PROPHYLACTIC EFFECT IN THE OMICRON ERA IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES AND WITHOUT ANTIBODY RESPONSE AFTER SARS-COV-2 VACCINATION

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Introduction. Pre-exposure prophylaxis against SARS-CoV-2 with tixagevimab-cilgavimab (AZD7442) has become a clinical practice, especially in patients receiving B-cell depletion or immunosuppressive therapy. However, data regarding AZD7442 specific preventive effect in the onco-hematological population, in the Omicron era, are limited and in the registrative study (PROVENT-NCT04625725) the number of hematologic patients included are not specified and only 7% of participants had cancer.

Patients and Methods. We evaluated the prophylactic efficacy of AZD7442 in patients with hematological malignancies and without antibody response after SARS-CoV-2 vaccination. Between April 2022 and October 2022, 93 onco-hematologic patients (77 NHL or CLL, 10 MM, 6 AML) with a median age 72 yrs (range, 27-88) received AZD7442 prophylaxis (150 mg tixagevimab/150 mg cilgavimab). All patients had inadequate humoral vaccination response with Ab anti SARS-CoV-2 less than 10 UI/mL in 83% of cases (and less than 100 UI/mL in the other 17%) despite 2 (15%) or > 3 (85%) anti SARS-CoV-2 vaccination doses

Results. The AZD7442 administration was well tolerated and no side effects grade CTC≥2 were reported. The median value of the anti-SARS-CoV-2 spike protein IgG Ab in blood samples (neutralizing antibody titer), collected after 1, 2 and 4 months from prophylaxis administration was 2500 UI/mL, 2047 UI/mL and 1193 UI/mL, respectively. These data confirmed a high level of post-prophylactic Ab after administration of AZD7442 lasting for over 4 months. Within 6 months of AZD7442 prophylaxis, 20.4% (19/93) of patients developed symptomatic SARS-CoV-2 infection with 5/19 (26%) severe cases (with pneumonia and respiratory failure). The 21% (4/19) of cases with symptomatic infection died from COVID-19 as a primary cause of death.

Conclusions. We found that, in the Omicron era, the prophylactic effectiveness of AZD7442 was significantly lower than reported in the registrative study (20.4% of symptomatic SARS-CoV-2 infection within 6 months of prophylaxis compared to 0,2% cases of registrative study). In addition, 4,3% (4/93) of our patients died from COVID-19 despite AZD7442 prophylaxis. These results underline: 1) the importance to maintain a close monitoring of SARS-CoV-2 infection in onco-hematological patients, 2) the need to promptly start a specific therapy in this patient population and 3) the need to update the prophylactic Ab mixtures according to the new prevalent SARS-CoV-2 variants.

DP101

EFFECT OF HLA MISMATCH ON INFECTIONS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE

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Post-transplant cyclophosphamide (PTCy) has increased the use of haploidentical (HAPLO) donors. While early data associated HAPLO transplants with increased infections, in those studies, only HAPLO patients had received PTCy. We compared infections in 184 consecutive patients at our center with a HAPLO (n=116) or 8/8 MATCHED (n=68) donor and uniform GvHD prophylaxis with PTCy, mycophenolate, and cyclosporine from 2016 to 2020. Stem cell source was bone marrow for HAPLO and peripheral blood for MATCHED transplants. The groups were similar in age, sex, diagnosis, conditioning, and disease status but differed in transplant date, with MATCHED transplants with PTCy starting in 2019. Risk of infections was compared using competing risk analysis with mortality as the competing risk. A confirmatory analysis with propensity matching was performed, limited to 68 HAPLO and 68 MATCHED transplants. Criteria for matching included donor and recipient age, disease status, and conditioning. Average time to leukocyte and neutrophil engraftment was 20 days in both groups. Risk of bloodstream infections (BSI) was increased in HAPLO grafts (HR 2.54; 95% CI 1.39-4.62; p=0.002) (Figure 1A).

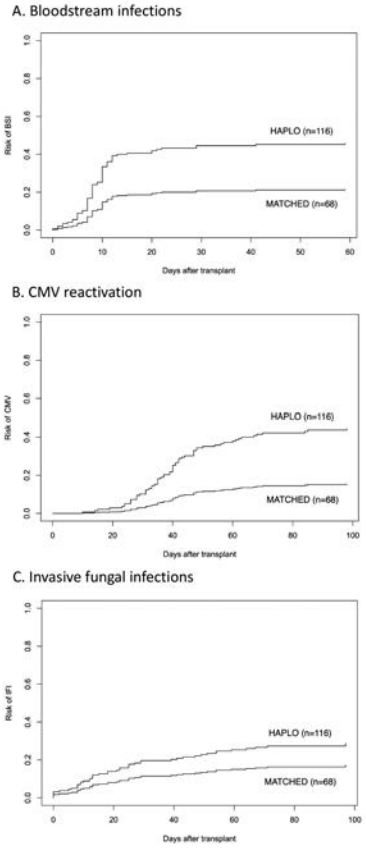

Figure 1.

From day 0 to +20 days, the most frequent pathogens were gram-negative bacteria. From day +21 to +100, BSI were less frequent, and the most frequently isolated pathogens were gram-positives. CMV reactivation occurred in 52/116 (48%) of HAPLO grafts and 10/68 (15%) of MATCHED grafts (Figure 1B). Among the 151 patients who did not receive CMV prophylaxis with letermovir, there was increased CMV reactivation in HAPLO grafts (HR 3.55; 95% CI 1.77-7.12; p<0.001). In the 33 CMV seropositive patients treated with letermovir, CMV reactivation was documented in only 1/33 (3%). EBV reactivation occurred in 8/116 (7%) of HAPLO transplants *vs* 1/68 (2%) of MATCHED transplants. Invasive fungal infections (IFI) occurred in 34/116 (29%) of HAPLO grafts *vs* 11/68 (16%) of MATCHED grafts (Figure 1C). Infection-related mortality (IRM) occurred in 11/116 (9%) of HAPLO *vs* 1/68 (1%) of MATCHED grafts (p=0.03). IRM in HAPLO grafts included 5 gram-negative BSI, 2 gram-positive BSI, 3 IFI, and 1 pulmonary infection. The only IRM in MATCHED grafts was a gram-negative catheter-related BSI. In conclusion, patients with HAPLO donors have increased risk of post-transplant infections and IRM, compared with patients with MATCHED donors. Our findings call for diligent monitoring in patients undergoing a HAPLO transplant.

DP102

MIDOSTAURIN PLASMA EXPOSURE IN PATIENTS WITH FLT3-MUTATED ACUTE MYELOID LEUKAEMIA UNDERGOING POSACONAZOLE PROPHYLAXIS DURING INDUCTION TREATMENT: A PROSPECTIVE MULTICENTER STUDY FROM THE SEIFEM GROUP

F. Marchesi, P. Menna, C. Cattaneo, A. Candoni, M. Delia, G. Nadali, A. Vatteroni, C. Pasciolla, S. Perrone, L. Verga, D. Armiento, M.I. Del Principe, N.S. Fracchiolla, E. Salvatorelli, S. Lupisella, I. Terrenato, A. Busca, L. Pagano

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FLT3-mut AML patients should be exposed to concomitant posaconazole (PCZ) and midostaurin. However, PCZ is a strong CYP3A4 inhibitor that could inhibit midostaurin metabolism resulting in its overexposure. A post-hoc analysis from the RATIFY trial showed that in patients concomitantly treated with midostaurin and strong CYP3A4 inhibitors only emerged a shorter time of toxicities occurrence. However further confirmations are needed. This is a prospective multicenter study within the SEIFEM group aiming to monitor midostaurin plasma exposure in FLT3-mut AML patients concomitantly exposed to PCZ during induction chemotherapy. The study enrolled 37 adult patients with newly diagnosed FLT3-mut AML suitable for induction treatment with CHT plus midostaurin. All blood samples were drawn at day +8 and +21 from the beginning of CHT before, at 3 and 12 hours from midostaurin administration. Midostaurin, its metabolites and PCZ were measured by validated quantitative liquid chromatography tandem mass spectrometry methods. At day+8 patients treated with PCZ were exposed to a total and relative plasma exposure of midostaurin-related material similar to that of patients who did not receive PCZ (Figure 1, Panel A and B). However, at day +21 midostaurin plasma exposure was significantly higher in patients treated with midostaurin and PCZ (P=0.001, Figure 1, Panels C). Moreover, these patients were exposed to approximatively 50% increase of midostaurin relative plasma exposure that was consistent of an approximatively 50% decreased relative plasma exposure to metabolites (P=0.002, Figure 1, Panel D). The total plasma

exposure ratio in PCZ-treated/untreated patients was of 1.78 (P=0.008). In all patients of PCZ group, PCZ reached the target plasma concentration of >0.7 μg/mL. Twenty-nine patients achieved a complete remission, with no significant differences between patients exposed or not to PCZ (84% *vs* 81%, respectively). No significant differences in terms of midostaurin-related AEs, midostaurin discontinuation or dose reduction were observed between the two groups. Toxicity was responsible for midostaurin discontinuation/dose reduction in 4 patients (21%) during PCZ prophylaxis and in 3 patients not exposed to PCZ (19%). We observed three cases of invasive fungal infections (8.5%), once again with no differences between the two groups. Our study suggest that the concomitant administration of PCZ and midostaurin results effective and safe for FLT3-mut AML patients.

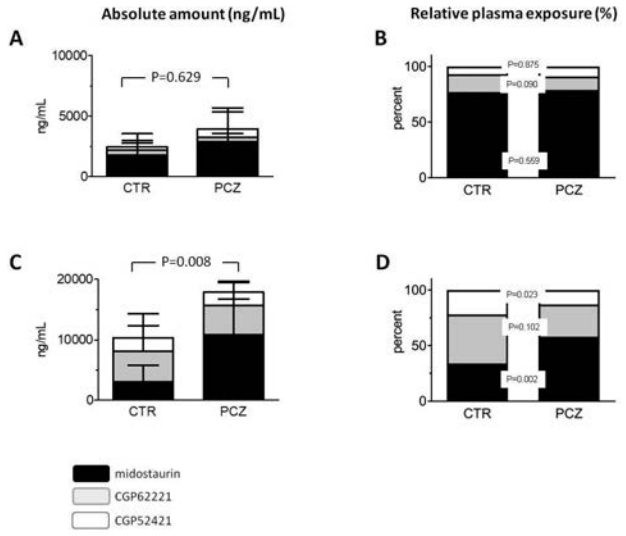

Figure 1.

DP103

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND PREVIOUS INFECTIONS HAVE IMPACT ON INFECTIOUS COMPLICATIONS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TREATED WITH VENETOCLAX: A MULTICENTRE SEIFEM STUDY

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Infections are a major source of morbidity and mortality in patients (pts) with Chronic Lymphocytic Leukemia (CLL). The development of targeted agents decreased the rate but pts, often elderly, with comorbidities, heavily treated, experienced serious infectious complications. The aim of our study was to evaluate the incidence of infections in CLL pts treated with venetoclax. This retrospective multicenter analysis was conducted on 287 CLL pts: on whom 151 single-agent and 136 associated to antiCD20 antibody. Pts of the first group were older, more frequently had del17/TP53mut, renal impairment and lower basal IgG levels. We recorded 181 events of infections grade 1-2, occurred in 114 pts (40%): 106 events involved the respiratory tract and in 57 cases pathogens were isolated (36 viral, 18 bacterial, 3 fungal). We recorded 103 episodes of infections grade 3-4, occurred in 73 pts (25%): 71 respiratory infections, 13 sepsis and 7 gastrointestinal infections. Pathogens implicated in the infections were isolated in 64 cases (40 viral, 21 bacterial, 3 fungal). We registered a trend toward a higher rate of infections in the group of venetoclax plus antiCD20 antibody after the first year (p=0.066). Risk factors for infection in univariate analysis were chronic obstructive pulmonary disease (COPD), CrCl<70, stage A, prior treatments, infections in the previous 12 months; in multivariate resulted COPD (OR 5.39) and previous infections (OR 2.57). Stratifying pts according to COPD and previous infections in the last 12 months we obtained 3 groups significantly different in terms of risk for infection (p<0.001; Figure 1). The cumulative incidence of infection was 69% in the first year if pts showed both characteristics. If considering only grade 3-4 infections, COPD was the unique significant variable in multivariate analysis (OR 2.62). We recorded a median OS of 55 months with 83 deaths, of whom 22 due to infections. Venetoclax was withdrawn for infections in 80 pts (27.9%): 58 temporary and 22 definitive. Considering the 22 definitive withdrawals, the infectious causes were mainly pneumonia (12 cases, of whom 6 SarS-CoV2) and sepsis (8 cases, in 5 after a SarS-CoV2 infection); 16 pts in this subgroup died for these infections in venetoclax. This large study showed a significant rate of infections, most of grade 1-2, sometimes serious. We found as risk factors comorbidities such as COPD and previous infections; COPD resulted a risk factor also for infections of grade 3-4.

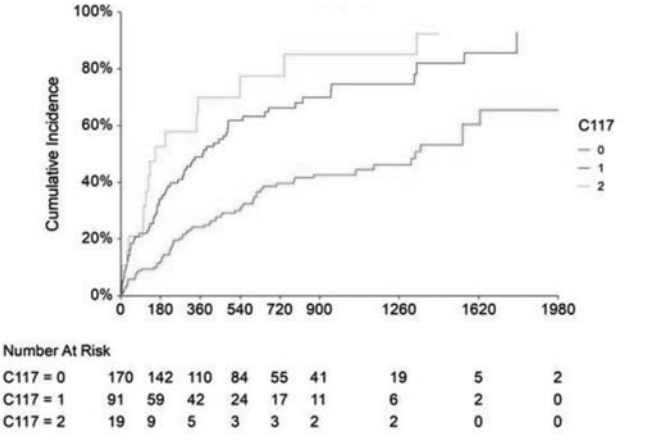

Figure 1. Stratification of patients according to the two risk factors for infections COPD and previous infections in the last 12 months: none risk factor (group 0), one of the two risk factors (group 1), both the risk factors (group 2), p<0.001.

DP104

EFFICACY AND SAFETY OF TIXAGEVIMAB-CILGAVIMAB VERSUS SARS-COV-2 BREAKTHROUGH INFECTION IN THE HEMATOLOGICAL CONDITIONS

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Introduction. Despite the development of anti-COVID-19 messenger RNA vaccines, several immunocompromised patients (above all affected by hematological disorders) were unable to produce anti-SARS-CoV-2 spike antibodies in response to vaccination. In this context, preexposure prophylaxis with tixagevimab-cilgavimab (TIX-CIL, a monoclonal antibody able to avoid attachment of the SARS-CoV-2 spike protein to the surface of cells approved in 2022 by FSA and EMA) has resulted in an alternative strategy, based on the promising results of the phase III PROVENT study.

Table 1. Clinical characteristics and treatment overview in 202 hematological patients distinguished on the occurrence or not of breakthrough infection. ALL-B: acute lymphoblastic leukemia-B; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma; CLL: chronic lymphocytic leukemia; MM: multiple myeloma; AML: acute myeloid leukemia; MPN: myeloproliferative neoplasm; BMT: bone marrow transplant; MoAb: monoclonal antibody; BTKi: Bruton's tyrosine kinase inhibitor; JAKi: Janus kinase inhibitor; IST: immunosuppressive therapy; PI: proteasome inhibitors; TIX-CIL: tixagevimab-cilgavimab.

	SARS-CoV-2 positive 44 patients (%) [range]	SARS-CoV-2 negative 158 patients (%) [range]	*p*
Age, years	72 [46-87]	69 [24-87]	0.035
Sex, male/female	26 / 18 (25 / 18.4)	78 / 80 (75 / 81.6)	0.307
Hematology condition			
- B-lymphoproliferative disorders	42 (28.2)	107 (71.8)	<0.001
○ ALL-B	0 (0)	3 (100)	NA
○ NHL	3 (9.4)	29 (90.6)	0.099
○ HL	0 (0)	4 (100)	NA
○ CLL	17 (27)	46 (73)	0.27
○ MM/Amyloidosis	22 (46.8)	25 (53.2)	<0.001
- T-lymphoproliferative disorders	0 (0)	2 (100)	NA
○ NHL	0 (0)	2 (100)	NA
- Myeloid disorders	2 (5.3)	36 (94.7)	0.004
○ AML	0 (0)	6 (100)	NA
○ MPN	2 (6.3)	30 (9.7)	0.019
- Autoimmune disease	0 (0)	4 (2.5)	NA
- Recent BMT	0 (0)	9 (5.7)	NA
Ongoing treatment, Yes/No	43 / 1 (27.9 / 2.1)	111/ 47 (72.1 / 97.9)	<0.001
- MoAb (no anti-CD20)	15 (44.1)	19 (55.9)	0.001
- Anti-CD20 MoAb	4 (33.3)	8 (66.7)	0.298
- BTKi	9 (27.3)	24 (72.7)	0.489
- JAKi	1 (4)	24 (96)	0.019
- IST	2 (18.2)	9 (81.8)	1
- IP	4 (50)	4 (50)	0.07
- Chemotherapy	0 (0)	5 (100)	NA
- Other	8 (30.8)	18 (69.2)	0.307
Prior SARS-CoV-2 vaccine	32 (20.1)	127 (79.9)	0.527
Prior SARS-CoV-2 infection	20 (33.3)	40 (66.7)	0.015
Anti-spike IgG values, AU/mL	23 [0-3663]	414.6 [0.9-40000]	0.033
Time-to-infection from TIX-CIL, days	75.5 [2- 236]	/	/
Duration of infection after TIX-CIL, days	11 [5-50]	/	/
Antiviral treatment for infection, Y/N	17 / 27 (38.6 / 61.4)	/	/

Material and Methods. This retrospective observational report aims to collect the clinical data of 202 patients affected by hematological diseases and treated in a single center with prophylactic therapy with TIX-CIL, evaluating the incidence of breakthrough infections and, in infected patients, the duration, the severity (potential reduction of severe forms), and the outcome. We divided the patients according to the type of disease, treatment, and clinical SARS-CoV-2 features.

Results. We reported an incidence of 44 breakthrough infections (21.8%) with no prophylaxis-related adverse effects. During a median follow-up of 249 [45-325] days, age ≥70 years old, ongoing treatment (above all with monoclonal antibodies -MoAb-), baseline lymphoproliferative disorders, and prior virus-exposure are identified as risk factors related to subsequent infection ($p<0.05$). Moreover, the incidence is higher in low/non-response to prior vaccination ($p = 0.033$). Patients treated with TIX-CIL had a mild course of the infection and a reduction of the duration compared to pre-prophylaxis infection (11 *vs* 15 days, $p<0.001$). The concurrent treatment with anti-CD20 MoAb and B-non-Hodgkin lymphoma still confer a higher duration of infection despite prophylaxis. Considering the patients who experienced SARS-CoV-2 infection for a second time after a prior exposure, the days of infection were statistically lower at the second infection event, with a median duration of 13 *vs* 14 days ($p=0.022$). No deaths attributable to the infection occurred. The complete cohort's data are reported in Table 1.

Conclusions. Prophylaxis treatment seems to be a valid and safe strategy, although not preventing breakthrough infection, but the severe complications associated with the infection and the possible delays in the administration of life-saving therapies due to the long-positivity.

DP105

EFFECT OF IMMUNOSUPPRESSIVE REGIMEN WITH ANTI-CD20 MONOCLONAL ANTIBODY AND BENDAMUSTINE ON CELLULAR AND HUMORAL IMMUNE RESPONSES TO SARS-COV-2 VACCINATION IN PATIENTS WITH NON-HODGKIN B LYMPHOMA (NHL-B)

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Background. While COVID-19 vaccination has been shown effective in reducing the incidence of a severe disease, vaccinated patients with lymphoma may not be protected as they often fail to develop a sufficient antiviral response. This is why a study of the immune response status of this subjects, in terms of specific antibodies production and T cell compartment evaluation, is essential for the improvement of a vaccination strategy.

Aims and Methods. We enrolled two cohorts of 38 patients with non-Hodgkin lymphoma B (NHL-B), [median age 69 yo, M:F ratio 3] undergoing anti-SARS-CoV-2 vaccination. In the first one 22 patients (pts) were vaccinated during treatment with anti-CD20 monoclonal antibody rituximab (RTX), while in the second one 16 pts received vaccination between 3 and 24 months post RTX therapy. These pts were further divided based on the type of chemotherapy: 20 pts had bendamustine associated with RTX (BENDA) while 22 pts had another chemotherapy regimen (CHOP/COMP/DA-EPOCH: no-BENDA). In all of them we evaluated the immunologic memory response towards SARS-CoV-2 after standard vaccination and/or a vaccine booster dose. We assessed the frequency of CD4+cells specific for SARS-CoV-2 spike protein by multiparametric flow cytometry after 8h *in vitro* stimulation and serum levels of SARS-CoV-2 specific IgGs.

Results. The cohort that completed the standard vaccination cycle at least 3 months after the end of treatment showed a higher humoral spike-specific response compared to pts vaccinated under RTX treatment (Figure 1). BENDA treated pts showed lower levels of S-spe-

cific IgG compared to pts treated without BENDA [4,81 *vs* 7760 BAU/mL, R 2 : 0,635; p=0.017] (Figure 1). Pts in both cohorts had a robust cell-mediated response with a trend to higher level of spike-specific CD4+T cells compared to healthy subjects. BENDA-treated patient had a higher frequency of CD4+ spike-specific T cells compared to no-BENDA pts [Range: 0-1,8%, p=0,08]; these pts developed a worse Covid-19 infection compared to no-BENDA pts.

Conclusions. Our results show that in NHL-B pts under RTX therapy, anti-SARS-CoV-2 vaccination induce a high T-cell mediated response, counterbalancing the lack of the humoral counterpart. Obtained data demonstrate that Bendamustine further reduce pts ability to mount a S-specific humoral response. These results question whether immunocompromised pts, particularly those treated with BENDA, need interventions to improve vaccine-induced immune response.

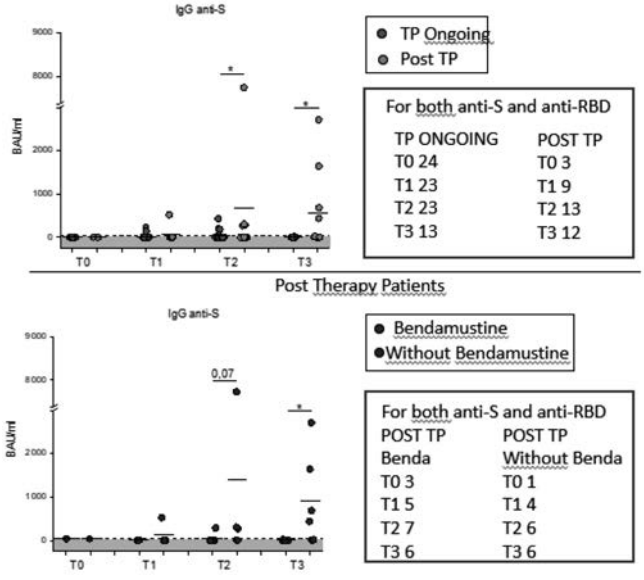

Figure 1.

DP106

HEALTH-RELATED QUALITY OF LIFE IN TRANSPLANT-INELIGIBLE REAL-LIFE MULTIPLE MYELOMA PATIENTS TREATED WITH FIXED-DURATION BORTEZOMIB-MELPHALAN-PREDNISONE VS CONTINUOUS LENALIDOMIDE-DEXAMETHASONE

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Background. Bortezomib-melphalan-prednisone (VMP) and lenalidomide-dexamethasone (Rd) were standards for transplant-ineligible (NTE) newly diagnosed multiple myeloma (NDMM) before daratumumab upfront. We analyzed patient-reported outcomes (PROs) in the Real MM phase IV trial (NCT03829371, funded by the Italian Medicines Agency AIFA, Independent Research) to compare health-related quality of life (HRQoL) with VMP *vs* Rd in a real-life MM population.

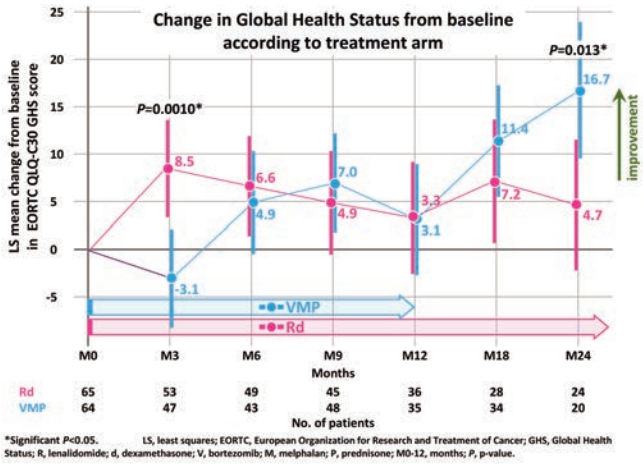

Figure 1.

Methods. NTE NDMM pts were randomized to standard VMP *vs* Rd. PROs were analyzed using validated EORTC QLQ-C30 scales and the EQ-5D-5L visual analog scale (VAS). PROs were collected at baseline, every 3 mo during the first year and every 6 mo thereafter. The PRO analyses included pts who had at least a baseline and a follow-up questionnaire available. Data until +24 mo from randomization were assessed. Change in HRQoL from baseline in VMP *vs* Rd pts were analyzed in a linear mixed model adjusted for IMWG frailty score and cytogenetic risk. Results are presented as least squares (LS) mean changes from baseline.

Results. 129 pts (64 in the VMP and 65 in the Rd arms) had available PROs, 47% were >75 years, 44% were frail. Pt characteristics at screening and response rates were similar in VMP and Rd arms. No significant differences in the mean baseline values of PROs were found in the two arms; the markedly impaired baseline HRQoL reflected a NTE NDMM population. Median follow-up was 28 mo. Changes from baseline values of the different HRQoL scales were analyzed focusing on the time points after VMP completion (+18 and

+24 mo). Global Health Status (GHS) was significantly better with VMP *vs* Rd at 24 mo (+16.7 *vs* +4.6; *P*=0.013). VMP was associated with lower fatigue (-10.5 *vs* +0.9; *P*=0.052), pain (-22.8 *vs* -2.7; *P*=0.003) and insomnia (-12.4 *vs* +5.3; *P*=0.013) at 24 mo. The EQ-5D-5L VAS scale behaved similarly, with a significantly higher score in the VMP *vs* Rd arm at 24 mo (+10.0 *vs* +1.5; *P*=0.041).

Regardless of treatment, best response was not associated with changes in GHS or EQ-5D-5L VAS scale, while frail pts had a long-lasting impairment in GHS and EQ-5D-5L VAS scale (vs fit and intermediate-fit pts) that was still preset at +24 mo.

Conclusion. After an initial impairment of HRQoL with VMP *vs* Rd, the treatment-free interval after VMP was associated with a significant improvement of HRQoL as compared with continuous Rd. Frail pts had poor HRQoL improvements over time, as compared with fit and intermediate-fit pts.

DP107

FERTILITY PRESERVATION AND MONITORING IN ADULT PATIENTS DIAGNOSED WITH LYMPHOMA: A CONSENSUS-BASED POSITION PAPER BY THE FONDAZIONE ITALIANA LINFOMI (FIL) & SOCIETÀ ITALIANA DELLA RIPRODUZIONE UMANA (SIRU)

C. Minoia[1], S. Viviani[2], E. Silvestris[3], S. Palini[4], F. Parissone[5], G. De Palma[6], A. Fedina[7], G. Cormio[8], A. Guarini[1], G. Gini[9], L. Montano[10], F. Merli[11], F.A. Peccatori[12]

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Background. In this consensus-based position paper, the scientific societies Fondazione Italiana Linfomi (FIL) and Società Italiana della Riproduzione Umana (SIRU) identified the optimal paths aimed to preserve and monitor fertility in patients diagnosed with lymphoma (NHL and HL).

Methods. The multi-disciplinary panel (5 onco-hematologists, 4 gynecologist or andrologists, 1 embryologist and 1 biologist, with the supervision of an international expert leader) for this consensus-based position paper proposed a series of rank-ordering key questions according to the clinical relevance and literature review. The agreement was scored by a web-based questionnaire according to the Delphi methodology. All statements were discussed in a round robin way and confirmed for the final recommendations.

Results. Chemotherapy-induced gonadotoxicity is influenced by the type of agent, the dose intensity, and in women, also by age at treatment. The correct timing for onco-fertility counseling is as soon as possible, in order to to allow timing optimization to apply fertility preservation techniques. An urgent referral pathway needs to be established between the Hematological and The Reproductive Centers with the aim to offer the onco-fertility counseling within 24-48 hours. Blood and specialist exams to be performed during the pre-therapy counseling have been summarized. Oocyte cryopreservation is a well-established FP technique to be proposed when it is safe to delay treatment of 10-14 days. Ovarian tissue cryopreservation could be proposed as a unique technique in patients with: therapeutic urgency, when there is a high/moderate gonadotoxic risk, feasibility for surgery. Ovarian samples should be analyzed in order to exclude the presence of neoplastic cells by using molecular and histological analyses prior to graft, especially for aggressive NHL. Post-pubertal males should be offered sperm cryopreservation. GnRHa should not be considered an alternative option for FP with cryopreservation techniques. Indications on fertility tests to be carried out in the period following chemotherapy (1-5 years and > 5 years) has been also discussed.

Conclusions. These recommendations would be useful for clinicians who take care of young lymphoma patients to guarantee an evidence-based onco-fertility assessment and treatment during the oncologic pathway.

DP108

EFFICACY OF ORAL NETUPITANT/PALONOSETRON PLUS DEXAMETHASONE IN PREVENTING CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING IN PATIENTS AFFECTED BY HODGKIN LYMPHOMA TREATED WITH ABVD: A RETROSPECTIVE SINGLE CENTER STUDY

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Background. ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) is a highly emetogenic but commonly used chemotherapy regimen for the treatment of patients with Hodgkin lymphoma (HL). Despite current guidelines recommend a combination of dexamethasone (DEXA), NK1 and 5-HT_3 receptor antagonists as primary prophylaxis of chemotherapy-induced nausea and vomiting (CINV), the optimal drug has not been identified. NEPA, an oral long-acting combination of netupitant and palonosetron, has been studied in solid cancer while very few data are available in hematology, particularly in HL.

Aims. to analyze the efficacy of NEPA in preventing CINV in HL patients treated with ABVD.

Methods. NEPA has been introduced for the primary prophylaxis of CINV in 2017 at the Hematology Unit of Padova University Hospital. We enrolled patients until Mar 2023. NEPA was given at single dose 300/0,5mg plus 8mg of DEXA before ABVD, followed by DEXA 4mg days for the next 3 days and 1mg the 4th day. The inclusion criteria were: diagnosis of HL treated with ABVD/R-ABVD/AVD, oral CINV prophylaxis with NEPA+DEXA, age ≥18. We included R-ABVD and AVD due to the low emetogenic risk of rituximab and bleomycin. Patients with a positive interim PET-CT who shifted to BEACOPPescalated or BEGEV were censured. The primary endpoint was the rate of complete remission, defined as no emesis and no rescue medications. While secondary endpoints were complete control (complete remission and no more than mild nausea) and nausea.

Results. We enrolled 98 patients: 62.24% females, the median age was 32.5 years, 36.7% stage III-IV, 18.4% bulky. Patients received

420 cycles of ABVD, corresponding to 840 chemotherapies. All patients received NEPA, but in 391/840 chemotherapies (46.5%) DEXA was omitted. Emesis occurred in 2/840 (0.24%) events, one in cycle IA and one in cycle IVA (respectively one female and one male). The complete remission was 99.7% (Figure 1). Thirty-six (36.7%) patients reported 73/840 (8.7%) events of nausea until 120 hours after ABVD. Overall, the rate of complete control was 91.31%, being lower during cycle IA (79.7%) and higher during the last VIB (100%, p=0.002, Figure 1). Nausea was more common in females (44% *vs* 24%, p=0.047) but no impact had age (p=0.207) or if DEXA was administered after ABVD (p=0.222).

Summary. We reported the largest real-life study on antiemesis in patients with HL. Our findings support the greater efficacy of NEPA in preventing CINV in HL patients treated with ABVD.

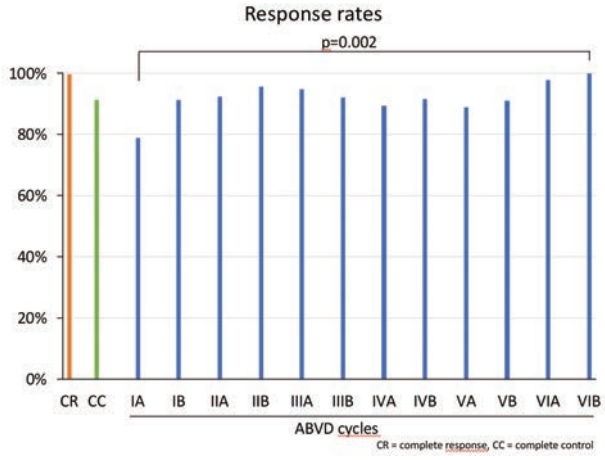

Figure 1.

DP109

MARGHERITA STUDY: IMPROVING THERAPEUTIC ADHERENCE IN ONCOHEMATOLOGICAL PATIENTS WITH A SPECIFICALLY DESIGNED SOFTWARE APPLICATION

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Background. Therapeutic adherence has a key role in the treatment outcome. Novel technologies can potentially support patients (pts) in the treatment journey, and, thus, improve therapeutic adherence. Furthermore, technology support can help collection of patient-reported outcomes (PROs).

Aim of the study. To evaluate whether a software application specifically designed to support oncohematological pts can improve therapeutic adherence. A comparison with a matched historical cohort was also performed. This study supports the registration of RITA as a class IIA medical device.

Methods. We conducted a phase II monocentric prospective study, enrolling oncohematological pts affected by different diseases. Pts were monitored and supported in the management of complications by using a specifically designed APP, called RITA (Remote Intelligence for Therapeutic Adherence) for 3 months. Besides, RITA allowed collection of quality-of-life (QoL) data, through the EQ-5D-5L questionnaire, activity of daily life (ADL) and instrumental activity of daily life (IADL) scale data, and PROs. RITA supported pts providing information pertinent to the management of the reported complaints. RITA also connected patient and doctor when needed. The primary endpoint was therapeutic adherence of at least 80% of the relative dose intensity.

Results. Sixty-two pts received support with RITA. Median age was 72 years (range 19-94), 45 pts had a lymphoproliferative disease, and 17 pts a myeloproliferative disease; 10 pts were enrolled at treatment start, while 52 were still on treatment. After 1 months 82.8% pts had a therapeutic adherence >80%, after 2 months 81.5%, and after 3 months 85.2%. The likelihood of being adherent tends to be higher at all time points in pts supported by RITA compared to matched historical controls: after 3 months, the OR in multivariate analysis of the RITA group was 3.02 (95% CI, 1.04-8.76). Overall, 4626 access were registered, 2410 in the older half, and 2216 in the younger half of the population; 63% of pts completed the QoL questionnaires; 1560 PROs were reported, the more common were fatigue (879), itching (125), and vision decline (107); 9296 clinical parameters were collected.

Conclusions. This is the first study demonstrating the efficacy of an APP in improving the therapeutic adherence in oncohematological patients. Furthermore, RITA allowed collection of relevant QoL data and PROs. (Founded by Advice Pharma, NCT05260203).

DP110

THE PAP SCORE (PALLIATIVE PROGNOSTIC SCORE), A TOOL FOR PREDICTING SHORT-TERM SURVIVAL IN A COHORT OF HAEMATOLOGICAL PATIENTS

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Introduction. Providing palliative care to Haematological patients regardless of diagnosis and prognosis is a concept emphasized by recent reports from the European Hematology Association (E.H.A.) and the World Health Association (W.H.O.). Accurate prediction of survival is necessary for clinical, organizational, ethical reasons and for planning specific care strategies. Many tools have been validated to help physicians estimate survival.

Purpose. Palliative Prognostic Score (PaP score) is based on 6 items and is recommended by the European Association of Palliative Care (E.A.P.C.) for its high accuracy in predicting short-term survival in terminal solid cancer patients. However, no information are available about the accuracy of Pap score in patients with hematologic malignancies, as these patients were excluded from the score validation study. This study aimed to assess the feasibility and accuracy of PaP score in prospective a cohort of hematological patients.

Methods. The survival prediction based on the PaP score was performed on routinely collected clinical data from patients with aggressive hematological disease admitted at an Italian hospital between January and December 2022. All the multidimensional domains of the score were evaluated, including dyspnea, anorexia, Karnofsky Performance Status score (KPS), Clinical Prediction of Survival (CPS), total WBC and lymphocyte percentage. The patients were categorized in the three different risk groups of PaP score according to their 30-day survival probability: group A, >70%; group B, 30-70%; group C, <30%. The CPS item was estimated by the physician who was taking care of the patient.

Results. 143 patients were enrolled. 78 (54.5%) had high grade lymphoma, (27.3%) 32 acute leukemia and 18 (12.6%) with multiple

myeloma. The mean age was 73.5 years (range 20-88). At the 30-days follow-up 41 (28.7%) patients had died. The PaP identified three groups with 30 days actual survival (AS) rates of 88.3% (A group), 50% (B group), and 26% (C group), respectively (Figure 1A). The probability of survival between A and B and C group resulted statistically significant (p<0.0001). The observed 30-days probabilities of surviving are in good accordance with those predicted by PaP score, suggesting a good calibration (Figure 1B).

Conclusions. These data suggest that the PaP scoring system is a reasonably robust method for prognostication also in hematological patients and can help physicians with advanced care planning (ACP).

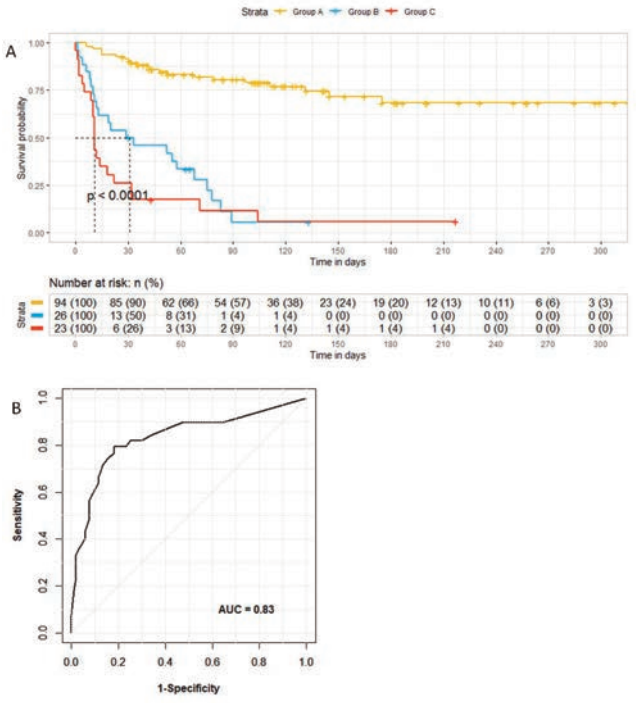

Figure 1.

Hemostasis, thrombosis, thrombocytopenia and platelet diseases

DP111

LONG-TERM HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA

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Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare but potentially life-threatening disorder in which an acquired deficiency of ADAMTS13 leads to generalised microvascular thrombosis with organ failure. Although treatment has significantly reduced the rate of morbidity and mortality, the risk of iTTP relapse is around 30%. The long-term consequences of the acute event and the perception of a possible relapse may be responsible for reducing the patient's health-related quality of life (HRQoL). Limited evidence has been published in this field. The present study aimed to investigate the HRQoL in a cohort of iTTP patients and compare it with the general population. Generic HRQoL was assessed by the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and the FACIT-Fatigue Scale (FACIT-F) version 4. Standardized scores of iTTP patients were compared with norm-referenced data from the Italian population [1]. Thirty-five patients with iTTP were evaluated. The median age at study inclusion was 50.7 years. and the median follow-up from the last iTTP episode was 10.8 years. Twenty-eight (80%) were female, and 15 (42.8%) had one or more recurrences before the survey compilation. The results of SF36 are shown in Table 1.

Table 1. Health-Related Quality of Life Profile by the SF-36 of iTTP patients and the general population. SD, standard deviation; CI, confidence interval.

SF-36 scales	iTTP mean (SD)	General population mean (SD)	Mean difference (95%CI)	P value
Physical health				
Physical functioning	74.14 (25.53)	84.46 (23.18)	-10.32 (-19.14;-1.49)	0.02
Role physical	51.42 (40.19)	78.21 (35.93)	-26.79 (-40.67;-12.9)	<0.01
Bodily pain	61.71 (30.50)	73.67 (27.65)	-11.96 (-22.5;-1.41)	0.02
General health	51.14 (4.03)	65.22 (22.18)	-14.08 (-15.75;-12.4)	<0.01
Mental health				
Vitality	60.28 (23.82)	61.89 (20.69)	-1.61 (-9.83;6.61)	0.69
Social functioning	76.07 (23.75)	77.43 (23.34)	-1.36 (-9.57;6.85)	0.73
Role emotional	60.95 (44.63)	76.16 (37.25)	-15.21 (-30.61;0.19)	0.05
Mental health	71.88 (25.45)	66.59 (20.89)	5.29 (-3.49;14.07)	0.22

Overall, both physical and mental domains were lower in the iTTP group compared with the general population. In particular, they reported significant differences in the Physical Function scale (PF) (mean difference -10.32; 95%CI: -19.14. -1.49; p=0.02), Role Physical (RP) (mean difference -26.79; 95%CI: -40.67. -12.9; p<0.01), Bodily Pain (BP) (mean difference -11.96; 95%CI: -22.5. -1.41; p=0.02), General Health (GH) (mean difference -14.08; 95%CI: -15.75. -12.4; p<0.01) and Role Emotional (RE) (mean difference -15.21; 95%CI: -30.61. -0.19; p=0.05). Among iTTP patients, females reported lower scores in all domains with significant differences in FACIT-F (mean difference -12.46; 95%CI: -18.32. -6.60; p<0.01) and in Mental Health (MH) (mean difference -18; 95%CI: -31.14. -4.85; p<0.01). The use of rituximab was associated with lower scores in the MH domain (mean difference -22.66; 95%CI: -41.39. -3.93; p=0.02), but no other differences were assessed according to the

treatment used. In conclusion, the long-term HRQoL of iTTP patients was lower in comparison with the Italian population. Female gender and use of rituximab were found to be associated with HRQoL lower scores.

Reference

1.Doi:10.1016/s0895-4356(98)00094-8.

DP112

MANAGEMENT OF MYH9-RELATED PLATELET DISORDERS (MYH9 RDS) IN A SINGLE CENTRE: FOCUS ON DIAGNOSIS AND OFF-LABEL THERAPY WITH TPO-MIMETICS

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MYH9-related platelet disorders (MYH9□RDs) are autosomal dominant, syndromic thrombocytopenias caused by mutations of MYH9, the gene encoding for the non-muscular myosin heavy chain IIA (NMMHC-IIA). MYH9-RDs may be associated with varying degrees of high-frequency neurosensory deafness, presenile cataracts, nephrotic syndrome or kidney failure, and presence of Döhle-like bodies within leukocytes. Six patients (pts) with MYH9-related thrombocytopenia are followed in our department (M/F: 1/5). The median age at diagnosis was 35 years (range 31-63). Median patient follow-up is 8 years (range 4-35).

Patients	Platelets at thrombocytopenia presentation (x 10^9/L)	Age at thrombocytopenia presentation (years)	Syndromic features	MYH9 mutations	Follow-up (years)
1 (M)	3	4		c.5521G>A (p.Glu1841Lys)	8
2 (F)	24	24	nephrotic syndrome; Nonalcoholic Fatty Liver Disease (NAFLD); anterior and posterior cataracts	c.5521G>A (p.Glu1841Lys)	8
3 (F)	73	5		c.5797c>T (p.Arg1933Ter)	23
4 (F)	40	24	bilateral neurosensorial hearing loss	c.3464C>T (p.Thr1155Ile)	8
5 (F)	95	3 days from birth		c.4270G>A (p.Asp1424Asn)	4
6 (F)	30	23	bilateral neurosensorial hearing loss	c.5797C>T (p.Arg1933Ter)	35

Figure 1.

Before arriving to our centre, 5/6 pts had been previously misdiagnosed with Immune Thrombocytopenia. At the time of presentation, all pts were asymptomatic and had been referred to hematologists because of isolated thrombocytopenia; 4/6 underwent invasive diagnostic procedures as bone marrow aspiration and biopsy. Three/6 pts were unsuccessfully treated with prednisone (0.5-1 mg/kg/day); two had been previously transfused with platelet concentrates and one received intravenous immunoglobulins. When pts arrived in our clinic, we suspected congenital thrombocytopenia based on personal and family history, clinical presentation, and laboratory parameters. The venous blood smear showed giant platelets and the presence of Dohle-like bodies in the neutrophil's cytoplasm. Upon genetic testing, mutations in the MYH9 gene were detected. Two pts presented with bilateral sensorineural hearing loss and 1 other suffered from nephrotic syndrome and anteroposterior cataracts. During our follow-up, three/6 pts required treatment: 1 to undergo an ovarian cyst removal, 1 for repeated oocyte pick-up procedures, and the last one due to ulcerative colitis bleeding complications. Based on recent literature data, we started off-label therapy with eltrombopag (TPO-mimetic) at a dosage of 50 mg/day. The baseline platelet levels were $39x10^9$/L in two cases and $11x10^9$/L in the other one. Within twenty days from therapy initiation, all 3 pts reached platelet values $>90x10^9$/L. Two pts underwent the procedures without complications, whereas the 3rd one experienced reduction and eventually halting of rectal bleeding. Hence, our cases highlight the importance of considering inherited thrombocytopenias in the diagnostic algorithm to correctly identify these diseases, avoid useless, invasive procedures and therapies, and adopt safe and effective treatment strategies in case of need.

DP113

MANAGEMENT OF IMMUNE THROMBOCYTOPENIA (ITP) DURING THE COVID-19 PANDEMIC IN ITALY: A NATION-WIDE ITP NET COLLABORATION SURVEY ON BEHALF OF THE GIMEMA WORKING GROUP ANEMIA AND THROMBOCYTOPENIA

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Several reports of immune thrombocytopenia (ITP) following SARS-CoV-2 infection or vaccination have been reported worldwide. Available recommendations are based on expert opinion, although some topics about the management of ITP in the COVID-19 era remain unanswered. We conducted a nation-wide electronic survey containing 7 single/multiple-choice questions (Table 1) among 42 hematologists from 40 ITP NET Italian Centers. A SARS-CoV-2 molecular test at ITP onset (Q1) is performed by 81% of participants, half of whom only in case of fever/respiratory symptoms. If ITP occurs during SARS-CoV-2 infection (Q2), 41% use the same first-line therapy as in COVID-negative cases, whilst others prefer intermediate-dose steroids (19%) + intravenous immunoglobulins (IVIG, 33%), the latter rarely used alone (7%). Regarding the second line (Q3), 50% use thrombopoietin-receptor agonists (TPOra) associated with thromboprophylaxis when PLT count is safe, 26% prefer immunosuppressants (rituximab excluded), whilst 24% treat COVID+ patients as negative ones. Thromboprophylaxis in COVID+ patients (Q4) is suggested by 24% of participants if anti-phospholipid antibodies are positive (d), 22% if hospitalized (a), 19% if under TPOra (b), 12% if a+b, 2% if splenectomised (c) or other combinations: 10% a+b+c, 5% a+c, 2% b+c, 2% a+b+c+d, 2% a+d. In case of ITP relapse during COVID-19 (Q5), 50% increase/add a small dose of steroids, 29% increase/add a small dose of TPOra, and 21% use IVIG. All participants recommend COVID-19 vaccination (Q6), 64% monitoring PLT count before/after exposure for patients under treatment/with baseline PLT <50,000/mcL, and 36% only if stable PLT count >30,000/mcL. In case of ITP onset/exacerbation following vac-

cination (Q7), only 12% discourage additional doses, whilst the remaining recommend vaccination if PLT count is monitored (48%), if baseline PLT >50.000/mcL (21%) or if the previous event resolved with a low therapeutic burden (19%).

In summary, this survey shows a high agreement among Italian hematologists about testing any new ITP for SARS-CoV-2 and recommending a complete vaccination schedule, with some concern for severe/refractory cases. The therapeutic choices in COVID+ ITP patients are more variable, especially regarding the indications for thromboprophylaxis. All in all, half of participants use lower steroid doses, and TPOra in COVID-19, a well-known thrombo-inflammatory disease, are not discouraged if given with adequate thromboprophylaxis.

Table 1. Electronic questionnaire regarding the management of patients with immune thrombocytopenia (ITP) during the COVID-19 pandemic. Questions with multiple-choice answers are marked with (M) at the end of the sentence. IVIG intravenous immunoglobulins, TPOra thrombopoietin-receptor agonists, PLT platelet.

Question	Answers
Q1. Do you perform a SARS-CoV-2 molecular test at the onset of ITP?	a. Yes b. No c. Only if the patient shows fever or respiratory symptoms
Q2. Do you change the first-line treatment of a patient with ITP onset during COVID-19 infection, compared with a SARS-CoV-2 negative ITP?	a. No b. Yes, I prefer intermediate corticosteroid doses (20-40 mg/day, flat dose) in association with IVIG c. Yes, I prefer starting with intermediate corticosteroid doses, to be increased after 3-4 days if ineffective d. Yes, I use only IVIG
Q3. Do you change the second-line treatment of a refractory patient with ITP onset during COVID-19 infection, compared with a SARS-CoV-2 negative ITP?	a. No b. Yes, I use TPOra but adding thromboprophylaxis when PLT count is >50,000/mcL c. Yes, I prefer other immunosuppressive drugs (fostamatinib included) than rituximab or TPOra d. Yes, I avoid TPOra
Q4. Do you consider heparin prophylaxis in a chronic ITP patient who gets COVID-19? (M)	a. Yes, if hospitalized b. Yes, if treated with TPOra c. Yes, if splenectomised d. No, unless anti-phospholipid antibodies are positive
Q5. How do you treat an ITP exacerbation due to COVID-19?	a. I increase the dose of steroid (if the patient is already treated with steroids) or I add a small dose of steroid (if steroid-free) b. I increase the dose of TPOra (if the patient is already treated with TPOra) or I start a small dose of TPOra (if TPOra-free) c. I use IVIG
Q6. Would you recommend a patient with chronic ITP to receive anti-SARS-CoV-2 vaccination? (M)	a. I recommend every patient to get mRNA-vaccines without specific monitoring b. I recommend vaccination, monitoring PLT count before and after the administration for patients under specific treatment and/or with baseline PLT count <50,000/mcL c. I temporalily discourage vaccination if PLT count is <30,000/mcL or not stable
Q7. What do you suggest to do after an ITP onset/exacerbation following anti-SARS-CoV-2 vaccination?	a. I suggest completing the vaccination schedule with a close monitoring of PLT count b. I suggest completing the vaccination schedule only if baseline PLT count is stable and >50,000/mcL c. I suggest completing the vaccination schedule only if the previous ITP event was responsive to a low burden of therapy d. I discourage from repeating the vaccination

DP114

ACQUIRED VON WILLEBRAND SYNDROME: A RETROSPECTIVE STUDY ON THE DIAGNOSIS, CLINICAL MANAGEMENT AND OUTCOME FROM 2 ITALIAN CENTERS

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Background. Acquired von Willebrand syndrome (AWVS) is a rare acquired coagulopathy, often associated to underlying disorders (lymphoproliferative, cardiovascular, myeloproliferative, neoplastic, autoimmune). The diagnosis is difficult and relies on a negative familiar and personal clinical bleeding history and a late onset in life of bleeding symptoms, associated with a laboratory pattern of Von Willebrand Disease (VWD). Aim. To describe diagnosis and management of AVWS patients (pts) in two Italian centers. Patients and **Methods.** Between 2004-2022 we diagnosed and managed 20 AVWS pts [9F, 11M; median age at diagnosis 62.45 years (42.9-85.9)]. The diagnosis was made based on clinical and laboratory features suggestive of AVWS (Table 1).

Table 1. Laboratory characteristics of the patients.

	Median	Mean	Range	Normal Values
VWF:Ag	13%	19.78%	1.6-67%	0 blood group : 41-101%//non 0: 50-130%
VWF:RCo	13%	14.62%	3.5-33%	0 blood group: 41-97%//non 0: 52-124%
RCo/Ag	0.75	1.067	0.331-6.25	0.9-1.1
FVIII:C	19.20%	23.64%	2.08-61.9%	58-130%
RIPA	1.4 mg/ml	1.55 mg/ml	0.84-3.49 mg/dl	0.7-1.2 mg/ml
VWF:pp	83%	97.45%	42.84-154.32%	70-140%
pp/Ag	6.62	11.28	2.39-51.87	<3
aPTT ratio	1.45	1.46	1-1.87	0.82-1
VWF:RCo inhibitor	Performed in 11 pts: negative			

Results. Reasons for diagnosis were recent onset of bleeding symptoms in 11 pts, increased aPTT in 9. Nineteen/20 cases showed a concomitant disorder: 1 gastric B cell MALT lymphoma, 1 indolent B cell lymphoma, 13 MGUS, 2 Waldenstrom Disease (WD), 1 Polyglandular Autoimmune Syndrome (APS-1), 1 prostate cancer. In 1 case AVWS was idiopathic. The management of the pts with lymphoproliferative disorders is described in Table 2.

Table 2. Therapeutic management AVWS pts.

Lymphoproliferative disorders associated AVWS pts		
Type of disorder	**Treatment**	**Response**
Gastric B cell MALT lymphoma 1 pt	Rituximab	Complete remission of lymphoma and AVWS
Waldenstrom Disease 1st pt	R-CVP Ibrutinib	After 2nd line, progression of lymphoproliferative disease and persistent AVWS
Waldenstrom Disease 2nd pt	Rituximab After two years for disease progression: Rituximab+-Bendamustine	Partial response Persistent AVWS and partial response of lymphoma
Indolent B cell lymphoma 1 pt	Watch and wait strategy Rituximab	 Complete remission of lymphoma and AVWS
All the other AVWS pts		
Type of disorder	**Treatment**	**Response**
MGUS 1 pt	PDN + CTX and then IvIg	No response to both therapies
MGUS 3 pts	IvIg (2 cases have been under chronic treatment with IvIg every 6-8 weeks for 2-3 years) Thalidomide	Transient CR as measured by VWD laboratory parameters, good control of gastrointestinal bleedings and anemia Good control of gastrointestinal bleedings and anemia in 3/3
MGUS 6 pts	No treatment	
APS 1 pts	No treatment	
MGUS and breast cancer plus 2 pts	PDN	Response to bleeding's symptoms in 1 pt The other pt underwent prophylactic hemostatic therapy before surgery
MGUS and prostate cancer + 1 pt	CHT and RTX	Stable disease
prostate cancer/splenic artery aneurysm 1 pt	No treatment	
Idiopathic AVWS 1 pt	PDN At relapse PDN + CTX	CR on VWD laboratory parameters CR on VWD laboratory parameters

Remission of the lymphoproliferative disorder induced remission of AVWD. Strategies to manage pts with MGUS-associated AVWS are detailed in Table 2: 1 pt received PDB, PDB/CTX, IvIg with no response; 3 pts received IgIv with temporary complete normalization of VWD laboratory parameters, two of them received chronic treatment with IvIg with good control of GI bleeding; no specific treatment was performed in the other MGUS. Four MGUS-associated AVWD patients with persistent GI bleeding (GIB), were treated with thalidomide, 3/4 with good control of GIBs and anemia. The idiopathic AVWS case was treated with PDN and with PDN+CTX at

onset and at relapse of AVWD, respectively, with CR on VWD parameters in both cases. Hemostatic treatments included desmopressin, tranexamic acid, VWF/FVIII concentrate that wereused as prophylaxis/treatment of bleedings, with variable responses on clinical symptoms. Conclusions. AVWS is a rare syndrome, probably underdiagnosed because unrecognized. It is mandatory to search for concomitant diseases, especially hematological, whose treatment can induce remission of AVWD. Treatments of AVWD includes hemostatic treatments, similarly to congenital VWD, immunosuppressive therapies and thalidomide as antiangiogenic drug for the control of recurrent refractory GIBs.

DP115

EVALUATION OF HLA-DRB1*11 EXPRESSION IN PATIENTS WITH THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

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Background. The HLA system plays a decisive role in the genesis of the immune response and many of class II MHC molecules have been associated with the predisposition to the onset of autoimmune diseases.Both DRB1 and DRQ1 are implicated in the presentation of antigens derived by ADAMTS13,some common antigens exist while others are specific. Evaluation of the importance of each peptide derived by ADAMTS13 in the induction of immune response is being studied.Different studies have reported the presence of HLA-DRB1*11 as a risk factor for the development of acquired TTP due to its ability to present the FINVAPHAR peptide to the dendritic cells. In 2018 we have reported the presence of HLA-DRB1*11:04 in 7 patients (pts) in remission of TTP and without clinical and laboratory signs of disease.

Materials and Methods. We evaluated the HLA system in 18 pts (3M and 15F),16 with primary TTP and 2 with complex autoimmune disease,comparing it with 865 Basilicata register IBMDR donors. The molecular study of the HLA phenotype was performed according to the following methods. PCR-sequence-specific-oligonucleotide R-sequence-specific-primers (SSP).

Results. The DRB1*11 allele was present in all 16 pts with primary TTP(12 DRB1*11:04,3 DRB1*11:01,1 both DRB1*11:04 and DRB1*11:01). The DRB1*11 allele was not present in 2 pts,one of them showed DRB1*7:01 and 14:54 phenotype while the other DRB1*3:01 and 10:01.Both of these pts were affected by complex autoimmune disease. One had been in therapy for many years for SLE,the other one, despite not having previously shown symptoms of rheumatological pathology,had high positivity of ENA antibodies.Among 865 potential donors,the expression of at least one HLA DRB1*11 allele was present in 490(56.6%):DRB1*11:01 in 197,DRB1*11:04 in 265 , DRB1*11:02 or 03 in 28,41 pts have HLA DRB1*11 on both HLA DRB1 alleles.The comparison between pts with TTP and the control group shows a significance of 0.08.The association between HLA DRB1*11 and TTP is therefore confirmed, unlike what occurs in other autoimmune pathologies. These differences could explain the particular characteristics of TTP,which requires immediate,complex and aggressive therapy, but which can undergo prolonged periods of remission even with relatively short-term treatments.The outcome of two pts with TTP and complex autoimmune disease who do not show HLA DRB1*11 allele should be monitored and compared with pts who present DRB1*11 allele with a longer follow up.

DP116

EFFICACY AND SAFETY OF FOSTAMATINIB IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA AT HIGH RISK OF THROMBOSIS: A MONOCENTRIC EXPERIENCE

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Fostamatinib is a spleen tyrosine kinase inhibitor recently approved for treating immune thrombocytopenia (ITP); it seems to be associated with a lower incidence of thrombotic events compared to other drugs, particularly TPO-receptor agonists (TPO-RA). Due to different mechanisms of action, a synergy between fostamatinib and other drugs could be hypothesized. We performed a retrospective review of 15 ITP patients who started fostamatinib (M/F 8/7, median age 68 years, range 25–83). Patients had a diagnosis of ITP since a median of 5 years (range 5 months–49 years) and experienced a median of 3 prior lines of therapy (range 1-7). Nine patients had primary ITP, 4 had antiphospholipid antibodies (aPL), and 2 had ITP associated with myeloproliferative neoplasm (MPN). Only 1 patient was treated with splenectomy. Five had a previous thrombotic event (2 with primary ITP, 2 with aPL, 1 with MPN), and 7 were on anticoagulant/antiplatelet therapy (5 for previous thrombosis, 2 for aPL), with increased thrombotic and hemorrhagic risk. At start time, 12 were receiving a combined ITP therapy (TPO-RA, steroids, intravenous immunoglobulins, vincristine, cyclophosphamide). When starting fostamatinib, the median platelet count was 34×10^9/L (range 3–68). The reasons for beginning fostamatinib were the need to achieve a platelet count of at least 50×10^9/L to allow anticoagulant/antiplatelet therapy (7 patients), unstable platelet count or $< 30\times10^9$/L (5 patients), steroid intolerance (3 patients). Twelve patients out of 15 (80%) obtained a response (defined as any first platelet count $> 50\times10^9$/L) in a median time of 17 days (range 7–41 days). Seven patients discontinued fostamatinib for loss of efficacy (unstable platelet count or $< 30\times10^9$/L). Three patients discontinued therapy for gastrointestinal intolerance and 1 for allergic reaction. Four patients (26% *vs* the rate of 18% reported in the registration studies) had a persistent response; 3 received combined therapy with TPO-RA obtaining a dose reduction and a more stable platelet count. Among persistent responders, 2 patients had aPL. No thromboembolic or hemorrhagic event was recorded during a total exposure time of 7.2 years (range 1 month-1.1 year). In conclusion, fostamatinib is effective and safe in ITP patients unresponsive to steroids and TPO-RA, even in patients with high thrombotic risk.

DP117

THROMBOTIC EVENTS IN ITP PATIENTS TREATED WITH TPO RAS: A SINGLE CENTER EXPERIENCE

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Background. One possible effect of thrombopoietin receptor agonist (TPO-RAs) is thrombosis.

Aims. To observe the rate of thrombotic events in ITP patients (pts)

treated with TPO-RAs in our center and and to identify predictive factor of thrombosis in order to choose the optimal therapy for each ITP patient .

Patients ad Methods. We retrospectively evaluated 82 ITP pts (36F/46M)treated with TPO-RAs from June 2010 to April 2023. The median age at the start of TPO was 67 years (y) , 81 pts received Eltrombopag (E), 1 pt only Romiplostim(R), 19 pts were treated with E and R, (101 total treatmens) 14 pts were previously splenectomized, 45 pts were allocated to chronic IPT, 30 to persistent, 16 to newly diagnosed, the median of previous therapy was 1, 25 pts were on anticoagulant or antiplatelet prophylaxis

Results. We observed 10 thrombotic events in 10 pts: 2 pulmonary embolisms, 1 transient ischaemic attack, 1 arterial thrombosis, 1 portal splenic vein thrombosis, 2 superficial venous thrombosis, 3 acute myocardial infarctions. At starting TPO –RAs 5 pts were male , their median age was 74 y (range 56-89) , the ITP stage was newly diagnosed in 2 pts, persistent in 2 pts, chronic in 6 pts, the median of previous lines of therapy was 1,5 , including splenectomy in 2 pts and E in 3 pts, the median time of exposure to TPO RAs (6 pts with E, 4 pts with R treatment) until the thrombotic event was 70 days (respectively 15,12,11, months,100,85,55, 23,21,15,12 days). At the time of thrombotic event all pts obteined a response (9 complete responses , 1 response) the median platelet count was 243000/mmc, no pts were on antiplatelet or anticoagulant prophylaxis , 3 events occurred in pts who had discontinued prophylaxis due to platelet count fluctuation, 2 of whom had previously treated with E with antiplatelet or anticoagulant prophylaxis and both previously vaccinated for SARS COVID respectively 12 and 18 days before the event. Before the thrombotic event, patients had the following thrombotic risk factors: 7 pts were suffering from hypertension, 3 pts from hypercholesterolemia, 2 pts from peripheral arterial disease, 1 pt from lung cancer, 1 pt from previous vein thrombosis, 1 pt from atrial fibrillation, 1 pt was a smoker, 2 pts had no known thombotic risk. After the thrombotic event 5 pts continued the TPO –RA with adequate prophylaxis, 3 pts suspended the treatment, 2 pts died of acute myocardial infarction

Conclusions. In our court the elderly age at starting TPO (67 y in whole court , 63 y in whole court excluding the 10 patients who developed the event, 74 y in the group of thrombosis) and the absence or discontinuation of anticoagulant or antiplatelet prophylaxis were predictive factor of thrombosis and the event has occurred early since the start of therapy (70 days).

DP118

THROMBOPOIETIN RECEPTOR AGONIST (TPO-RA) IN IMMUNE THROMBOCYTOPENIA: LONG TERM FOLLOW-UP

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Background. Immune thrombocytopenia (ITP) is an acquired bleeding disorder caused by autoantibodies who increased platelet destruction. Treatment goal consists in obtaining a safe platelet count to manage and prevent bleeding. While first-line is still glucocorticoids plus intravenous immune globulin, the second one has changed after introduction of thrombopoietin receptor agonists (TPOra) who have been licensed in 2009 and 2010 in Italy (Romiplostim and Eltrombopag respectively). Long-term follow-up data are currently limited.

Methods. Data on a subgroup of patients (pts)affected by ITP treated with TPOra between 2009 and 2023 with an at least 10 years follow-up was retrospectively collected and analyzed.

Results. About 180 pts affected by ITP have been treated at our Center during last 14 years; 77 of them required TPOra. Of these, 25 pts were treated between 2009 and 2023. 68% were female, 32% males with a medium age at ITP diagnosis of 42 years old (10 – 78 years). Before TPOra, the cohort was treated with a median of 3 previous lines of therapy (IQR 2-3) and 10 pts (40%) underwent splenectomy. After a medium time of 118 months from ITP diagnosis (0 – 470 months) 7 pts (28%) started Eltrombopag and 18 (72%) Romiplostim. 14 pts (56%) experienced at least a relapse during TPOra, of which 12 cases (85%) requiring rescue therapy. 6 pts (24%) switched from one TPOra to the second one after a medium time of 59 months (2-96 months): 5 pts switched because of loss of response, 1 for intolerance. 5 pts (20%) experienced an adverse event during TPOra treatment: one case of unstable angina, one ischemic stroke, one allergic reaction and 2 cases of persistent myalgia.3 pts repeated a bone marrow biopsy after a medium time of 6 years from starting TPOra: no marrow fibrosis was detected. After a medium time of 71 months (2-171 months), 14 pts (56%) stopped TPOra and maintained a durable remission. 11 pts (44%) are currently on TPOra. After a medium follow-up time of 11 years (range 9-14 years) 3 pts died for causes different from ITP, 5 resulted lost at follow-up; the remaining 17 (68%) are alive. 6 (24%) are in complete remission, in follow-up with their family doctor.

Conclusions. After more than 10 years from their introduction, the time has come to collect long-term data on TPOra (Eltrombopag and Romiplostim) in ITP pts. Our data show that TPOra are an effective and safe treatment, maintaining a low rate of adverse events even in the long-term.

DP119

DARATUMUMAB AND BORTEZOMIB SALVAGE TREATMENT FOR THROMBOTIC THROMBOCYTOPENIC PURPURA RELAPSED AFTER RITUXIMAB: DESCRIPTION OF A COHORT OF MULTIREFRACTORY-RELAPSING PATIENTS

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Background. Recent update on management of Immune Thrombotic Thrombocytopenic Purpura (TTP) suggests to give elective therapy in patients developing a drop in ADAMTS13 (A13) activity (< 20%) to prevent clinical relapse (CR).

Aim. To retrospectively describe the A13 relapse (A13R), CR and pre emptive treatment in a cohort of TTP pts , with a focus on multirefractory pts treated with bortezomib (B) and daratumumab (D) as salvage therapies.

Methods. Chart of consecutive pts with previous acute TTP and clinical/lab follow up available in a single center were reviewed.

Results. 25 pts (20 F), median age at diagnosis 35(17-79) had TTP and received PEX + prednisone as acute tx; 2 pt received caplacizumab. With a median f-up of 12 yrs (1-33) we registered 12 clinical relapses in 8 pts and 25 A13 relapses in 11 pts. (Table 1). Pts with CR received mainly PEX+PDN and RTX (5/8 episodes) with complete response . We defined "multirefractory" a pt who need >1 immunosuppressant to obtain A13 recovery in a single episode or had subsequent A13 drop after a previous A13R. We observed 11 multirefractory pts who need 18 cycles of RTX, 2 of B and 2 of D. Patient # 5 had 3 A13R : first A13 R was treated with RTX and cyclophosphamide; second A13 R occurred after 8 months and she re-

ceived B with a complete recovery of A13 lasting 16 months; 3rd A13R was treated with RTX. Patient #25 had 9 episodes of A13 relapses (Figure 1), 2 with clinical symptoms (headache and mild drop in plt count without anemia, no need of PEX) and she received 6 courses of RTX, azathioprine, one cycle of B and 2 of D. B was given after 13 months of a previous RTX. This cycle of RTX was complicated with chest pain (no evidence of cardiac toxicity). After B she had complete recovery of A13, but developed a G2 neuropathy. 10 months later she had another A13 R, she received RTX with a brief response (6 months), then we gave D with complete recovery lasting only 3 months, without adverse events. Another cycle of D is ongoing with initial increase of A13. Overall 1 VTE developed in 1 pt at first TTP episode; peripheral neuropathy grade 2 (1 pt) chest pain (1pt), fatigue (3) and malaise (3) developed in pts during CR or A13R. No infectious have been observed.

Conclusions. RTX is a well established tx in A13R, with high rate of remissions but sometimes brief. B and D might be used in relapsed TTP with some efficacy. Extensive data collection is needed to establish efficacy and safety of immune therapy other than RTX.

Table 1.

Table 1: Characteristics and clinical hystory of patients

N	Sex, age @ 1st episode	Therapy at diagnosis	Clinical relapse: time after 1 episode	Therapy @ Clinical Relapse	A13 Relapse: time after 1 episode	Therapy @ A13 R	Duration of Follow up	Status at last Follow up
1	F, 24	PEX, PDN	yes, 2 yrs and 32 yrs	PEX- PDN	no	n.a	33 yrs	lost
2	F, 56	PEX, PDN, capla	no	n.a	yes, 10 months	RTX	1 yr	complR
3	F, 36	PEX, PDN	yes, 18 yrs and 20 yrs	PEX, PDN, RTX	yes, 19 and 21 yrs	RTX	30 yrs	complR
4	M, 66	PEX,PDN	no	n.a	yes, 8 yrs	RTX	7 yrs	complR
5	F, 33	PEX, PDN	yes, 4 yrs; 6 yrs; 12 yrs	PEX, PDN, Vinc, CTX	no	n.a	19 yrs	dead: AML in 2021
6	F, 22	PEX, PDN, RTX	no	n.a	yes 4 yrs, 5 yrs, 6 yrs	RTX, CTX, B, RTX	7 yrs	complR
7	F, 42	PEX, PDN	no	n.a	no	n.a	12 yrs	complR
8	F, 34	PEX,PDN	no	n.a	no	n.a	18 yrs	complR
9	M, 33	pex,PDN	yes, 12 yrs	PEX, PDN, RTX	16 yrs and 18 yrs and 21	RTX @any A13R	27 yrs	complR
10	F, 19	PEX, PDN	yes, 14 yrs	PEX, PDN, RTX	yes 20 yrs	RTX	13 yrs	complR
11	F, 48	PEX, PDN, capla	no	n.a	yes 1yrs	RTX	3 yrs	complR
12	F, 37	PEX, PDN	yes, 2 months	PEX, PDN, RTX	no	n.a	12 yrs	complR
13	F, 33	PEX, PDN	no	n.a	no	n.a	4 yrs	complR
14	F, 25	PEX, PDN	yes 22 yrs	PEX- PDN	yes 12 yrs, 17 yrs	vincristine, RTX,	17 yrs	complR
15	M, 48	PEX, PDN, RTX	no	n.a	no	n.a	5 yrs	complR
16	F, 23	PEX, PDN	28 yrs	PEX, PDN, RTX	yes 15 yrs	RTX	13 yrs	complR
17	F, 17	PEX, PDN	no	n.a	no	n.a	10 yrs	complR
18	F, 38	PEX, PDN	no	n.a	no	n.a	10 yrs	complR
19	M, 35	PEX, PDN, RTX	no	n.a	no	n.a	12 yrs	complR
20	F, 44	PEX, PDN	no	n.a	no	n.a	10 yrs	complR
21	F, 33	PEX, PDN	no	n.a	no	n.a	12 yrs	complR
22	F, 38	PEX, PDN, RTX	no	n.a	yes, 11 yrs	RTX	14 yrs	complR
23	M, 49	PEX, PDN	no	n.a	no	n.a	23 yrs	complR
24	F, 79	PEX, PDN, RTX	no	n.a	no	n.a	2 yrs	lost
25	F, 38	PEX, PDN, RTX	no	n.a	9 episodes*	see figure	15 yrs	ongoing D

Legenda:
PEX: plasma exchange, PDN: prednisone
A13 R: ADAMTS13 relapse; n.a: not applicable; capla: caplacizumab; RTX: rituximab, B: bortezomib, D: daratumumab
A: azathioprine; Vinv: vincristine, CTX: cyclophospamide; complR: complete response; AML: acute myeloid leukemia
* see figure 1 for details about relapses and treatment of patient #25

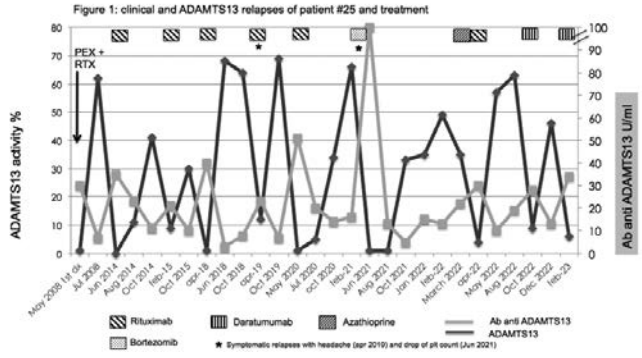

Figure 1.

DP120

PREGNANCY AND CHILDBIRTH OUTCOMES IN WOMEN WITH HEMOPHILIA A AND B

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Background. There are no specific guidelines for the management of carriers of hemophilia (HC) A and B during delivery and/or postpartum in Italy. Conflicting data on the correlation between hemorrhagic symptoms and FVIII/IX levels have been reported, particularly during delivery and postpartum. The optimal mode (cesarean or vaginal) of delivery for a HC is still debated. Current guidelines, despite not referring to the optimal mode of delivery, recommend against instrumental aid.

Aims. This retrospective, observational study aims to describe how HC are managed during pregnancy and delivery, by evaluating clinical and laboratory parameters, in order to stratify the hemorrhagic risk and the need for prophylaxis and replacement therapy of these women

Methods. Following the approval of our Ethics Committee, HC were enrolled, through informed consent, between January 2022 and October 2022. The following data were collected: age, ISTH bleeding score, genetic testing, age of menarche, characteristics of menses, patients' insight, prenatal diagnosis, number and course of pregnancies, type of delivery and any related complication, fluctuations in FVIII/FIX levels during pregnancy. We divided the study population into two groups on the basis of coagulation factor VIII (FVIII:c) and Factor IX(FIX:c) levels: Group A ,with levels less than or equal to 40%; Group B with levels higher than 40%.

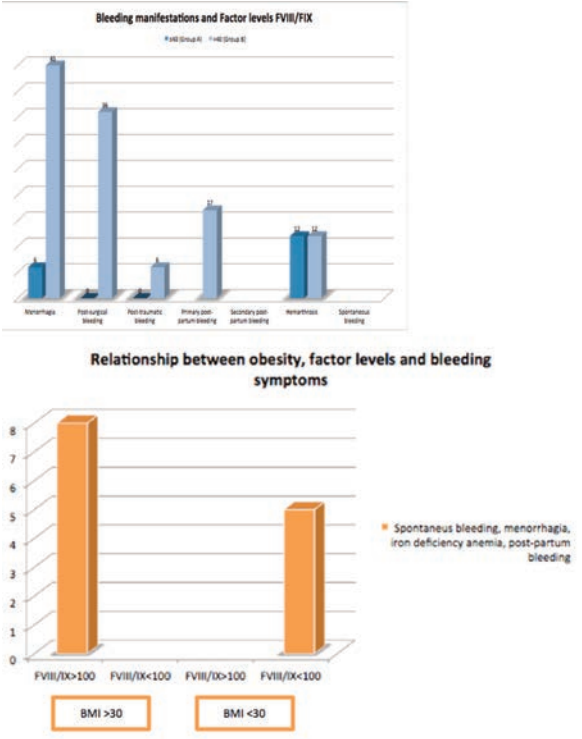

Figure 1.

Results. Eighteen subjects were enrolled. HC women had an in-

creased bleeding risk, regardless of FVIII/FIX levels (Figure 1), instead a significant correlation ($p<0.05$) between BMI and bleeding symptoms was observed (Figure 1). In women with more than one pregnancy, the management of pregnancy and childbirth did not vary after the diagnosis of hemophilia carrier status

Conclusions. The most frequent hemorrhages in HCs are those secondary to excessive menstrual blood losses, pregnancy, childbirth, and postpartum. Women with a BMI>30 and Factor VIII/IX levels above 100% have a higher bleeding tendency than the others, experiencing moderate-severe bleeding symptoms requiring a higher frequency and dosing of pharmacological interventions. Pregnancy and delivery management did not change after carrier status was confirmed.

POSTERS

Lymphomas

P001

AUTOLOGOUS STEM CELL TRANSPLANT SALVAGE IN CLASSICAL HODGKIN LYMPHOMA PATIENTS FAILING FRONT-LINE THERAPY GIVEN IN THE ERA OF PET-ADAPTED STRATEGIES

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Background. High-dose chemotherapy (HDCT) followed by ASCT is still considered the standard of care for adult patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL). However studies evaluating the outcome of patients failing front-line chemotherapy (CT) given according to a PET-2-driven strategy are limited.

Objectives. Aims of this study were to evaluate the efficacy of HDCT and ASCT and risk factors in R/R patients with cHL failing first-line CT given in the era of PET-driven strategies.

Study Design: This was a retrospective multicenter study on individual anonymized data of adult cHL patients collected by an electronic database. The study was approved by the ethical committees of the participating centers and by the European Institute of Oncology ethical and review board. Survivals were estimated using the Kaplan-Meier method and the association between several prognostic factors and survival was evaluated by Cox regression models.

Results. Two hundred and twenty patients who underwent ASCT from 2009 to 2021 at 11 participating centers in Italy were identified. A positive PET-2 (PET-2+) during front-line CT was reported in 59 (32.1%) patients out of 185 with available data. Overall, at relapse or progression 49.5% had refractory disease; 23.2% relapsed within 12 months and 27.3% after ≥12 months from end of frontline CT. Prior to ASCT, 83.6% patients received ≤2 and 16.4% >2 lines of salvage therapy. The 3-year PFS and OS were 74.1% (95%CI, 67.2–79.8) and 89.5% (95% CI, 84.0–93.2), respectively. PET-2+ during first-line CT was associated with a higher risk of failure after ASCT (HR 2.68, P=0.001) as well as having anemia at relapse or progression (HR 2.25, P=0.017) or refractory compared to relapsed disease (HR 1.74, P=0.049). The 3-year PFS was significantly lower also for patients undergoing ASCT in less than CR compared to their counterpart (HR 3.13, p<0.001) and for patients receiving >2 *vs* ≤2 lines of salvage therapy (HR 2.55; p=0.003).

Conclusions. HD-CT and ASCT is an effective salvage approach for cHL patients failing front-line treatment given according to a PET-driven strategy. Receiving ≤ 2 salvage therapy lines and being in CR at ASCT confers the most favorable outcome, whereas a PET-2+ during first-line CT seems an early unfavorable predictor for subsequent salvage ASCT procedures.

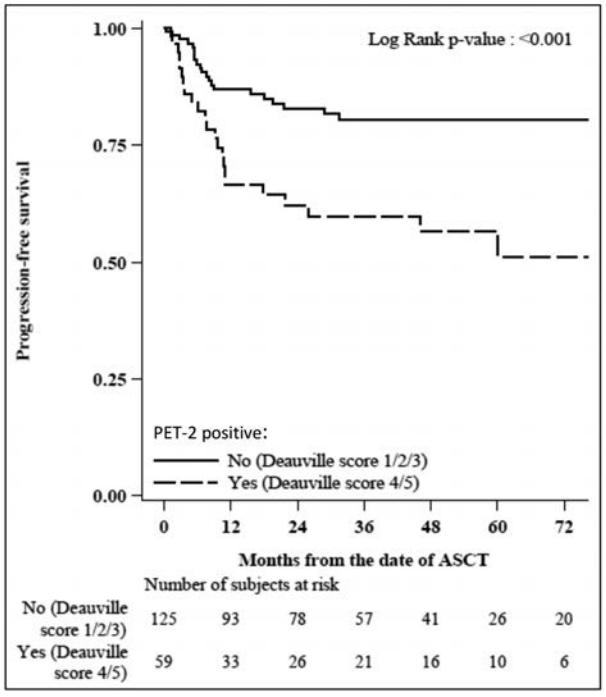

Figure 1. Progression-Free Survival according to PET-2 results during front-line therapy.

P002

TOXICITY AND FEASIBILITY OF FRONT-LINE TREATMENT OF CLASSICAL HODGKIN LYMPHOMA WITH BRENTUXIMAB VEDOTIN (BV)+AVD IN THE REAL-LIFE: A MULTICENTRIC RETROSPECTIVE STUDY

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Background. Brentuximab Vedotin (BV) in combination with AVD, has been approved for front-line treatment of advanced classical Hodgkin Lymphoma (cHL) after the results achieved in the ECHELON-1 study. Beside an advantage in terms of efficacy and survival compared to conventional ABVD, a higher rate of neuropathy and severe neutropenia emerged.

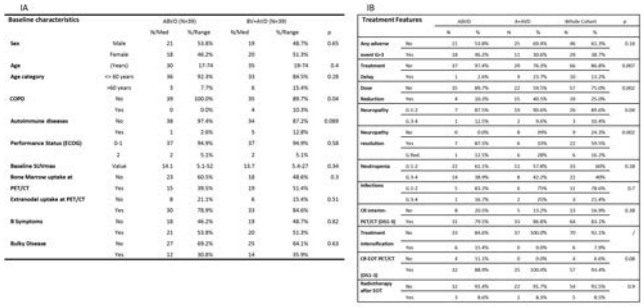
Aims. To assess toxicity and efficacy of BV+AVD in the real-life.

Methods. We started a retrospective multicentric study on patients with cHL, advanced stage, age >18 years, treated upfront with

BV+AVD or ABVD (1:1) outside clinical trials.

Results. Until April 2023, we collected 78 patients: 39 treated with ABVD and 39 treated with BV+AVD. Baseline characteristics were equally distributed, except for a higher incidence of chronic respiratory disease (0 *vs* 10.3%, p=0.04) and autoimmune disease (2.6% *vs* 12.8%, p=0.08) in the BV+AVD group (Table 1A).

Table 1A. Characteristics of cHLpatients treated with BV+AVD versus ABVD. Table 1B. Toxicity and response to treatment in patients treated with BV+AVD versus ABVD.



The median follow-up was significantly longer in the ABVD group (29 months, 7-58) compared to BV+AVD group (8 months, 2-17, p=0.0001). Neuropathy grade (G) 2 (NCTCAE) was higher in the BV+AVD group (66.7% *vs* 37%, p=0.04), as well as treatment schedule delay (23.7% *vs* 2.6%, p=0.007) and dose adjustment (40.5% *vs* 10.3%, p=0.002) (Table 1B). No significant difference was observed in G3-4 neuropathy (p=0.16). Support therapy of neuropathy was heterogenous (acetyl-L-carnitine, pregabalin, etc.). Resolution of neuropathy was more frequent in the ABVD group (87.5% *vs* 33.3%, p=0.03) likely due to the longer follow-up. Neither neutropenia nor infections were significantly different (p=0.18 and p=0.7, respectively). All patients in the A-AVD received G-CSF. So far, 98.7% (77/78) patients underwent interim PET/CT and 78.2% (61/78) the end of treatment (EOT) PET/CT. At interim PET/CT, no difference was observed in CR rate (Deauville score 1-3) (79.8% ABVD *vs* 86% A+AVD, p=0.38); 6 out 39 patients treated with ABVD underwent treatment intensification. Of note, a trend for a better CR rate with BV+AVD was observed at the EOT evaluation (100%, 25/25 *vs* 85%, 32/39 p=0.08). One death was observed for each group.

Conclusions. These preliminary results confirm the efficacy and the toxicity data reported in the clinical trials. Mild neuropathy represents an issue in the BV+AVD regimen that requires dose adjustment and/or dose delay to complete treatment. Extended follow-up and larger series are mandatory to assess treatment efficacy and to define the best clinical management of adverse events.

P003

POST-TRANSPLANT NIVOLUMAB PLUS UNSELECTED AUTOLOGOUS LYMPHOCYTES IN REFRACTORY HODGKIN LYMPHOMA RESULTS IN VERY HIGH REMISSION RATE AND EXCELLENT SURVIVAL AND IT IS ASSOCIATED WITH NK CELL EXPANSION

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Immune checkpoint inhibitors (CI) are approved for treatment of relapsed/refractory Hodgkin Lymphoma (RHL) patients. However, only 20% complete response (CR) rate is observed. In the RHL setting, CR is fundamental for subsequent autologous (ASCT) or allogeneic stem cell transplantation (HSCT) consolidation. To improve the efficacy of CI in RHL, we tried to enhance early post-ASCT CI therapy with the reinfusion of unselected autologous lymphocytes infusions (ALI). The rationale of this approach is to achieve a disease debulking through ASCT conditioning; the early administration of CI is thus performed with a minimal disease burden, and ALI are administered in order to reduce post ASCT immune depression which hamper CI efficacy.

The aim of this study was to evaluate the efficacy of the procedure in terms of CR rates and overall (OS) and disease free survival (DFS). Biological endpoint was to investigate the lymphocyte subpopulations involved in the mechanism of response.

21 patients with RHL (median age 32 years; range 18-65) were enrolled after failure of 1st line chemo and underwent autologous lymphocyte apheresis. All patients then proceeded to 2nd line chemotherapy followed by 3rd line Brentuximab-Vedotin (BV) in non-responding patients. 13 patients failing to achieve CR were enrolled in the treatment arm and proceeded to ASCT + CI and ALI, whereas 8 patients achieving CR after 2nd line chemo (n=6) or 3rd line BV (n=2) received ASCT followed by ALI alone, as a control cohort (Figure 1A). No adverse events were recorded.

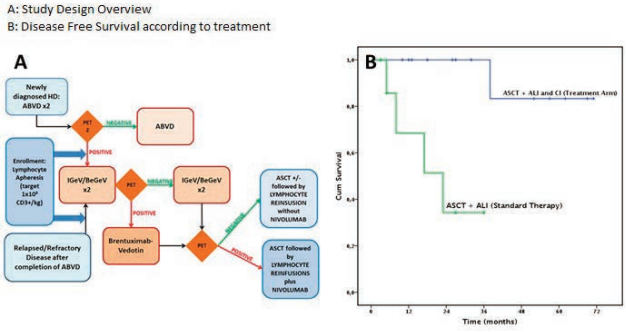

Figure 1.

All patients receiving ALI + CI (treated patients) achieved negative PET scan CR. 8 of them received HSCT consolidation. One patient refused HSCT and relapsed but achieved a 2nd CR with CI retreatment. All patients in the treatment arm are alive and disease free after a median follow-up of 32 months. Median DFS was not reached in treatment arm (Figure 1B).

Four of the patients in the control arm relapsed (50%), 2 of them died because of progressing disease. Median DFS in the control arm was 22 months (Figure 1B). Phenotypic analysis of circulating cells showed a faster expansion of highly differentiated NK cells in ALI plus CI-treated patients. Our data showed high activity of ALI + CI for RHL, allowing most patients to proceed to HSCT in CR. RHL patients who received ASCT in a progressive disease status in the treatment arm had an excellent outcome, especially when compared to the control arm, were patients received ASCT in a CR status.

P004

ROLE OF SEMIQUANTITATIVE PARAMETERS ON INTERIM 18F-FDG PET/CT IN PREDICTING RESPONSE TO SALVAGE BENDAMUSTINE, GEMCITABINE, VINORELBINE (BEGEV) REGIMEN IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA (R/R HL)

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Achieving complete remission (CR) after salvage therapy prior to transplantation with autologous stem cells (ASCT) remains one of the most relevant prognostic factors in patients with R/R HL. The Bendamustine, Gemcitabine, Vinorelbine (BEGEV) regimen is highly effective in inducing CR following 4 cycles. This study aims to explore if the Deauville Score (DS) and semiquantitative parameters on interim positron emission tomography-computed tomography (iPET) with 18F-fluorodeoxyglucose after 2 cycles of BEGEV could predict DS on end-of-treatment PET (EOT-PET) after 4 cycles of BEGEV before ASCT. We retrospectively analyzed the 23 patients with R/R HL treated at our center from April 2017 to October 2022 who completed 4 cycles of BEGEV and performed iPET and EOT-PET. In addition to DS, analysis of the iPET included the following semiquantitative parameters: Lesion SUV (standard uptake volume)max, SUVpeak, SUVmean, ΔSUVmax, MTV40% (metabolic tumor volume with threshold of SUV 3.5), TLG40% (total lesion glycolysis, MTV40% x SUVmean), Liver SUVmax, Liver SUVmean, rPET (lesion SUVmax/liver SUVmax) and qPET (SUVpeak/liver SUVmean). 11/23 (48%) patients achieved a metabolic CR (DS≤3) on iPET. All 11 patients mantained CR on EOT-PET. Of 12/23 (52%) patients with DS≥4 on iPET, 6/12 (50%) achieved DS≤3 on EOT-PET, while 6/12 (50%) had DS≥4 on EOT-PET. Among patients with DS≥4 on iPET, patients who converted to DS≤3 on EOT-PET had significantly lower SUVmax (p=0.004), SUVmean (p=0.002), SUVpeak (p=0.024), rPET (p=0.006), qPET (p=0.026) compared with patients who maintained DS≥4 (Mann-Whitney U test). Using a receiver operating characteristic (ROC) approach, we identified a threshold SUVmean of 3.5 (AUC=1; p=0.002), rPET of 1.97 (AUC 0.97; p=0.02), qPET of 1.90 (AUC 0.89; p=0.02), SUVmax of 6.01 (AUC 0.97; p=0.02), and SUVpeak of 3.88 (AUC 0.90; p=0.06) on iPET as cutoffs that distinguished patients converting to DS≤3 on EOT-PET from patients who still were DS≥4 on EOT-PET. 24-month progression free-survival (PFS) was 90% in patients with DS≤3 on iPET, 100% in patients who converted to DS≤3 and 50% in patients who were still DS≥4 on EOT-PET (p=0.03). Our preliminary analysis shows that semiquantitative parameters on iPET may be helpful in predicting early response to salvage therapy in R/R HL. The precise threshold values need to be confirmed in larger patient cohorts.

P005

ADVANCED-STAGE CHL INTERNATIONAL PROGNOSTICATION INDEX: EXTERNAL VALIDATION AND APPLICATION TO RELAPSED/REFRACTORY PATIENTS

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Background. Since novel targeted therapies are being tested in the frontline setting for Hodgkin Lymphoma (HL), the identification of patients who have a lower chance of being cured with standard PET/CT-guided ABVD, such as patients with a refractory disease, becomes of paramount importance. The Advanced-Stage cHL International Prognostication Index (A-HIPI) has recently been proposed, making use of a mix of dichotomous and continuous variables as risk factors to predict individual patients' prognosis instead of identifying risk groups.

Aims. To validate the A-HIPI prognostic model for HL and evaluate its ability to identify patients at risk for primary refractoriness to first line therapy.

Methods. We included advanced stage HL patients diagnosed at the University Hospital of Padova between 2005 and 2022, treated with PET/CT-guided ABVD. Refractory disease was defined as relapse <3 months from the end of first line treatment. Prognostic Index (PI) for the A-HIPI was calculated as previously reported [Rodday *et al*., JCO 2022].

Results. Of the 157 patients included in the analysis, 46 (29%) patients relapsed, of which 25 (54%) had a refractory disease. Twelve (48%) and 6 (29%) of the refractory and relapsed patients had a second relapse requiring further therapy, respectively. After a median follow-up of 57 months, the 5-year OS and PFS were 94% (95CI 87-97) and 67% (95CI 58-74), respectively. Five-year PFS was 40% (95CI 18-61) for refractory patients and 71% (95CI 46-86) for relapsed patients. When applied to our cohort, the A-HIPI yielded a C-index of 0.644 (95CI 0-56-0.73) for 5-year PFS and 0.78 (95CI 0.63-0.92) for 5-year OS. The PI averages were 1.38-1.23 and 1.53-0.93 for 5-year OS and 1.09-0.37 and 1.18-0.29 for 5-year PFS in the entire cohort and in all relapsed patients, respectively. The calculated PI was not significantly different between refractory and relapsed patients (Figure 1).

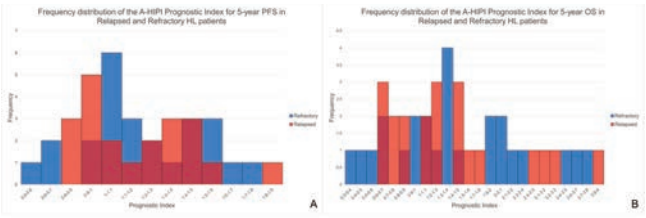

Figure 1. Frequency distribution of calculated A-HIPI PI values for 5-year PFS (Panel A) and OS (Panel B). Refractory patients are shown in blue, relapsed patients are shown in orange. Overlap areas between the two distributions are shown in red. HL: Hodgkin Lymphoma OS: Overall survival; PI: Prognostic Index; PFS: Progression-free survival.

Figure 1.

Summary/Conclusions. In this study we externally validated the A-HIPI prognostic score in an independent retrospective cohort of patients treated within the modern era. We have further confirmed

the prognostic impact harbored by disease refractoriness in HL, showing that the A-HIPI is not able to separate potential refractory patients in a higher-risk cluster. The A-HIPI needs to be further validated in patients undergoing Brentuximab or anti-PD1-based frontline therapies, and its ability to identify higher risk patients requires further investigation.

P006

CK2 INHIBITION DECREASE LIMPHOCYTES MIGRATION IN HODGKIN'S LYMPHOMA

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Introduction. In classic Hodgkin lymphoma (cHL) the tumor microenvironment (TME) is characterized by a massive inflammatory infiltrate of non-tumor cells that surround the Hodgkin's and Reed-Sternberg (HRS) cells. TME plays a central role in cHL pathogenesis, as well as immune evasion and dysregulation of multiple signaling pathways. CK2 is a pleiotropic kinase consisting of 2 alpha (catalytic) and 2 beta subunits which apparently plays a role in both tumor survival and TME formation in hematological malignancies. Given the pivotal role of CK2 in HRS survival, we aim to study the role of this kinase in the modulation of the TME.

Methods. Experiments were performed on 4 cHL cell lines (L-428, L-540, KM-H2, and HDLM-2) cultured for 24/48h with or without CX-4945 (CX), a CK2 alpha inhibitor. Migration assays were performed by transwell: purified normal T or B lymphocytes were seeded at the top of the wells. Conditioned medium (CM) derived from HL cell lines treated or not with 10 μM CX for 24/48h, was added to the bottom of the wells. Migrated T or B cells were detected by flow cytometry.

Results. Using CM obtained from the L-540, HDLM-2, L-428 and KM-H2 cell lines after 24h treatment with CX, the percentage of T lymphocytes chemo-attracted by the CM decreased by 30.2%, 25.3%, 46.2% and 34% respectively, compared to the untreated conditions ($p<0.0001$, one-way ANOVA). In the same conditions, the percentage of migrated B cells toward the CX-treated CM decreased by 14.8%, 9.6%, 13.4%, and 18.5%, respectively, compared to untreated conditions ($p<0.001$, one-way ANOVA). We highlighted that CK2 inhibition decreases the attraction effect of CM enriched by chemokines and cytokines released by HRS cells on normal T- and B-cells.

Conclusions. Blocking CK2 activity counteracts the ability of HL cells to chemoattract T- and B-lymphocytes due to the release of chemokines in the mileau. This effect is probably due to the modulation of soluble factors involved in TME formation. In conclusion, these preliminary data suggest that CK2 could be involved in the tumor niche formation and immunological evasion of HRS cells.

P007

MRNA IDENTIFICATION OF TIGIT IN PERITUMORAL LYMPHOCYTES IN CLASSICAL HODGKIN DISEASE

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Hodgkin lymphoma is a rare B-cell malignant neoplasm represents approximately 11% of all lymphomas and with current treatment, about 90% of all patients diagnosed with HL will be long-term survivors. T cell Ig and ITIM domains (TIGIT) has been recognized as an immune checkpoint receptor able to negatively regulate T cell functions. Aim of this study was to assess the in situ TIGIT mRNA expression in CHL, to verify the effective intracellular transcription of TIGIT receptor in peritumoral lymphocytes that resulted positive at immunohistochemical analysis. 34 formalin fixed-paraffin embedded samples, in which was tested TIGIT protein expression, were selected. The TIGIT protein expression status was determined by immunohistochemical investigations with TiGIT antibody, as previously described. Seriate sections from FFPE lymph nodes were submitted for RNAscope Assay. Among 34 enrolled cases, 15 resulted negative for TIGIT immunohistochemistry on lymphocytes within the tumor environment and were classified score 0. Ten cases showed a sparse, faintly stained non-tumoral lymphocytes within the tumor environment, near the HRS cells and were classified as score 1. Five cases showed the presence of a discrete quote of non-tumoral lymphocytes with moderate membrane staining around the HRS cells and were reported as score 2. Four cases demonstrated evidence of a circle of non-tumoral lymphocytes with intense membrane staining, surrounding the HRS cells corresponding to the score 3. RNAscope was successfully applied to the whole FFPE histological sections of the 34 Hodgkin's lymphoma cases. After slides were visualized, each case was assigned a semi-quantitative score based on the mRNA expression level of the TIGIT gene according to the scoring system provided by the RNAscope manufacturer. The remaining cases scored a "0" with no mRNA probe signals observed in the lymphocytes. Low mRNA expression was observed in ten cases marked as "1" which is equivalent to 1-3 probe signals per positive lymphocyte. Five cases showed moderate mRNA expression with a score of "2" representing 4-10 probe signals per positive lymphocyte. Four cases showed high mRNA expression with a score of "3," representing > 11 probe signals per positive lymphocyte. Our results confirm the presence of immunoescape through the expression of TIGIT in patients with Hodgkin's lymphoma, based on the expression of the mRNA coding for TIGIT.

P008

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P010

FEASIBILITY AND EFFICACY OF CHLAMYDIA PSITTACI ERADICATION WITH PROLONGED DOXYCYCLINE THERAPY IN LOCALIZED OCULAR ADNEXAE MARGINAL ZONE LYMPHOMA (OAMZL): 7-YEAR RESULTS OF THE IELSG39 MULTICENTER TRIAL

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Background. Chlamydia psittaci (Cp) infection is detected in 75% of pts with OAMZL in Italy. Upfront treatment with 3-week doxycycline regimen is associated with a 65% ORR and a 2-yr PFS of 60% (Ferreri et al. JCO 2012). However, the persistence of Cp as elementary bodies within macrophages may lead to antibiotic refractoriness and be responsible for low remission rates. Herein we report the results of the multicentre phase II trial (IELSG39) that explored feasibility and efficacy of an extended doxycycline regimen, designed to improve lymphoma control rate through an increased bacterial eradication rate.

Methods. Adults with newly diagnosed, stage-IEA OAMZL were enrolled and treated with doxycycline 100 mg twice daily for 4 weeks followed by 4 weeks rest, repeated for 3 cycles. The presence of Cp DNA on tumor tissue, conjunctival swab and PBMC was assessed by Real-Time PCR as parameter of infection prevalence and eradication. Tumor response was assessed by orbit MRI and ophthalmological evaluation every 6 months. The primary endpoint was the 2-year PFS; to demonstrate the improvement of 2-yr PFS from the 60% reported in the IELSG27 trial (P0) to 75% (P1), 30 pts with Cp-positive OAMZL were needed; treatment would be considered as effective if 17 were progression-free at two years of follow-up.

Results. 42 pts (median age 58, range 31-85; M:F ratio=0.63) were enrolled between 2013 and 2016, in 7 Centres. Cp DNA was detected in 23 (70%) of the 33 assessed patients; PCR is ongoing in 11. Doxycycline was well tolerated, without any adverse event. ORR was 64% (CR=14, PR=14, SD=11, PD=5). The median time to the best response was 9 months (range 3-34). The primary endpoint was met: 32 pts were relapse-free at 2 years: 21 had a Cp-pos OAMZL, 4 were Cp-neg, and PCR results are pending in 7. At a median follow-up of 86 months (range 5-126), 23 pts remain relapse-free, with a 2- and 5-yr PFS of 75% (95%CI= 74-77) and 55% (95%CI= 49-59), respectively. Considering only Cp-positive OAMZL, the 2- and 5-yr PFS were 90% (95%CI= 90-91) and 64% (95%CI= 60-68), respectively. Eighteen of the 21 pts with relapsing/progressive disease received a second line treatment, with a CR in 14 (78%) of them. Further analyses on Cp status and monitoring are ongoing and will be presented at the meeting.

Conclusions. The IELSG39 trial demonstrates that a prolonged exposure to doxycycline is associated with improved lymphoma control rate, without unexpected toxicity, in OAMZL.

P011

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P012

CIRCULATING TUMOR DNA FOR DISEASE GENOTYPING AND MONITORING IN RELAPSED/REFRACTORY PRIMARY MEDIASTINAL B CELL LYMPHOMA RECEIVING CAR T THERAPY

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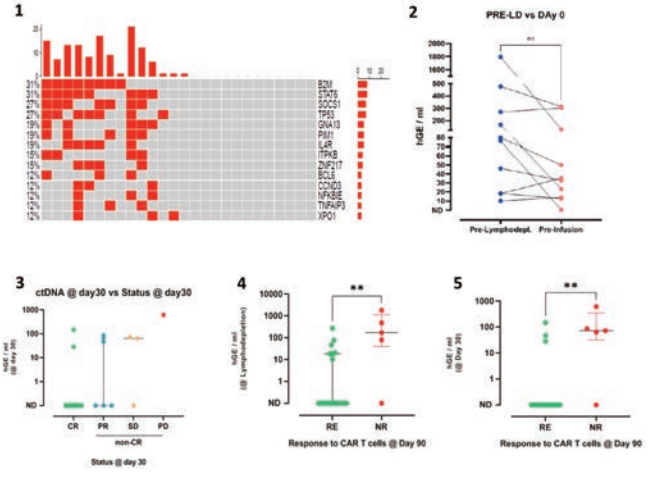
Background. Response to CAR (Chimeric Antigen Receptor) T is currently evaluated by PET/CT but post treatment inflammatory responses can result in false-positive results. Circulating tumor DNA (ctDNA) may represent a useful tool for monitoring disease response post CAR T however, limited data exist on the relevance of ctDNA in primary mediastinal B-cell lymphomas (PMBCL). We aimed at assessing ctDNA in PMBCL patients (pts) receiving CAR T.

Methods. Cell free DNA (cfDNA) was obtained from plasma of 26 PMBCL pts treated with axicabtagene ciloleucel and from paired granulocytes as a source of germline DNA. A total of 95 plasma samples collected at the time of apheresis (AP,n=3), of lymphodepletion (LD,n=24), of infusion (day 0,n=25) and on days 14 (n=18) and 30 (n=25) were profiled. A targeted sequencing panel including the coding exons and splice sites of 154 genes was applied to identify somatic mutations.



Figures 1, 2, 3, 4, 5.

Results. Somatic mutations pre-infusion (at AP, LD or day 0) were detected in 14/26 pts (53.8%, median number of non-intronic and non-synonymous variants=10, range 1-38). At least one somatic mutation at any time point was identified in 15/26 pts (57.7%). The most fre-

quently mutated genes were B2M and STAT6 (8/26, 31%), SOCS1 and TP53 (7/26, 27%), IL4R, PIM1 and GNA13 (5/26, 19%), ITPKB and ZNF271 (4/26, 15%) and BCL6, CCND3, NFKBIA and XPO1 (3/26, 12%)(Figure 1). When levels of ctDNA, defined as haploid genomic equivalents/ml of plasma (hGE/mL) were determined for each time point, a moderate reduction, albeit not statistically significant, in ctDNA was observed between LD and day 0, supporting the role of lymphodepleting agents in reducing tumor burden (Figure 2; n=10 pts, p>0.05; Wilcoxon test). Considering pts not achieving CR by PET/CT at day 30 (n=9), 5 had detectable ctDNA and 4 of them eventually relapsed, while 4 pts with undetectable ctDNA ultimately achieved a CR at day 90(Fig 3). Overall, significantly higher ctDNA levels were detected at both LD and on day 30 in pts not responding to CAR T at day 90 (non responders (NR), n=5) when compared to those responding (responders, RE, n=21) (median hGE/mL 168.8 in NR *vs* 0 in RE at LD;p<0.01 and median hGE/mL 72.1 in NR *vs* 0 in RE, day 30;p<0.005)(Figures 4 and 5).

Conclusions. Our results indicate that cfDNA analysis in PMBCL pts can identify tumor-associated mutations and track tumor levels during therapy. The complementary use of ctDNA and PET/CT could be of use for monitoring disease in PMBCL pts treated with CAR T.

P013

A FIL COHORT STUDY OF R-MINICOMP VERSUS R-MINICHOP IN OLDER UNFIT AND FRAIL PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction. The R-miniCHOP regimen is the reference upfront treatment of diffuse large B-cell lymphoma (DLBCL) for patients older than 80 years or with comorbidities. Some reports showed that the substitution of conventional doxorubicin with its non-pegylated liposomal formulation (NPLD) is safe and equally effective in DLBCL patients; moreover NPLD allows a curative therapy in patients with contraindications to anthracyclines. No study has ever evaluated the outcome of patients with DLBCL treated with NPLD in the setting of reduced intensity regimens.

Patients and Methods. We describe the characteristics and outcomes of DLBCL patients enrolled in the Elderly Project by the Fondazione Italiana Linfomi, prospectively defined as unfit or frail by the simplified geriatric assessment (sGA) and treated with R-miniCHOP or R-miniCOMP per local practice. Primary study endpoint was overall survival (OS); secondary endpoint was progression free survival (PFS).

Results. Starting from a dataset of 1163 cases, 176 patients classified as unfit or frail were treated with R-miniCHOP (89) or R-miniCOMP (87). The clinical characteristics of the two groups did not show statistically significant differences. In particular median age was 82 years, IPI was 3-5 in 56%, 26% had B-symptoms and 32% had bulky lesions; 62% were unfit and 38% frail. Similar frequency of the different comorbidities by Cumulative Illness Rate Scale (CIRS) categories was also observed with the exception of musculoskeletal comorbidities which was more frequent in the R-miniCOMP group (11% *vs* 2%; p=0.017). The elderly prognostic index (EPI) score was intermediate and high in 41% and 59%. After a median follow up of 27 months, the 3-year OS rate was 61% (95% CI 51-69) without difference between the two groups [HR for R-miniCOMP: 1.07 (95% CI 0.63 – 1.82)]. In multivariable analysis high-risk EPI and B-symptoms were independently associated with worse OS. 3-year PFS was 54% (95% CI 44-62. HR for R-miniCOMP was 1.0 (95%CI 0.62-1.61). In multivariable analysis high-risk EPI and B-symptoms were identified as poor prognostic factors. Evaluation of safety profile is ongoing.

Conclusions. With the limitations of a non-randomized comparison, our study suggests that R-miniCOMP has similar efficacy as R-miniCHOP in non-fit elderly patients with DLBCL.

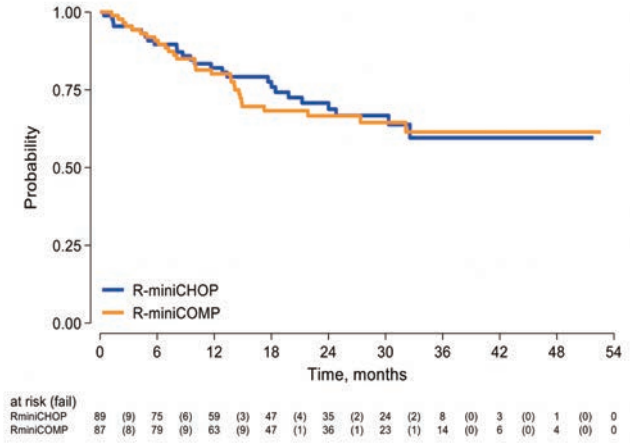

Figure 1.

P014

MARGINAL ZONE LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (MZL-IPI): A PROGNOSTIC SCORE FOR THE ENTIRE SPECTRUM OF MARGINAL ZONE LYMPHOMAS. A FIL AND SPORE-MER STUDY

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Marginal zone lymphomas (MZL) include extranodal (ENMZL), nodal (NMZL) and splenic (SMZL) subtypes. While MZL subtypes have been studied as separate entities, most clinical trials evaluate MZL as a single entity. In this setting, a prognostic score for all MZL is needed. We analyzed patients with MZL prospectively enrolled in the NF10 observational study and who started a systemic therapy. Patients were classified as SMZL, ENMZL and NMZL according to histology and disseminated MZL (dissMZL) for those without a clear pattern of organ involvement. The primary study endpoint was progression-free survival (PFS). For validation, we applied the same inclusion criteria and model used for the NF10 study to an independent cohort of patients from the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE) Molecular Epidemiology Resource (MER). In NF10 study, we identified 501 eligible patients: 166 SMZL (33%), 197 ENMZL (39%), 60 NMZL (12%) and 78 dissMZL (16%). At diagnosis, 40% of the patients were >70 years old, 80% were stage III-IV, 31% had elevated LDH, 41% had Hb <12 g/dl, 20% had lymphopenia, 14% had plt<100x10^9/L. After a median follow-up of 61 months, 5y-PFS was 72% (95%CI 68-76%). In the multivariate model, elevated LDH, anemia, lymphopenia, thrombocytopenia and subtype (NMZL or dissMZL) were independently associated with a worse PFS. A prognostic model was built with those 5 factors and patients were classified into low (LRG, 0 factors, 27%), intermediate (IRG, 1-2 factors, 57%) and high (HRG, 3+ factors, 16%) risk groups. 5y-PFS was 85% for the LRG, 66% for IRG, and 37% for HRG (Fig.), with c-Harrell=0.64 and robust internal validation and calibration. Compared to the LRG, the IRG (Hazard Ratio [HR]= 2.30, 95%CI 1.39-3.80) and HRG (HR=5.41, 95%CI 3.12-9.38) had inferior PFS. In the MER cohort of 192 MZL patients, 5y-PFS was 57% (95%CI 51-64). Applying the MZL-IPI to the MER, 41(21%), 113 (59%) and 38 (20%) patients were classified as LRG, IRG and HRG, respectively. The MZL-IPI was associated with PFS (log-rank test p=0.043;c-Harrell=0.60, 95%CI 0.55-0.66); compared to the LRG, the IRG (HR=1.57, 95%CI 0.97-2.54) and HRG (HR=2.04, 95%CI 1.15-3.62) had inferior PFS. In both the training and the validation studies, MZL-IPI was associated with the best prediction performance and was prognostic for overall survival.

MZL-IPI is a new validated prognostic score for all patients with MZL considered for systemic treatment.

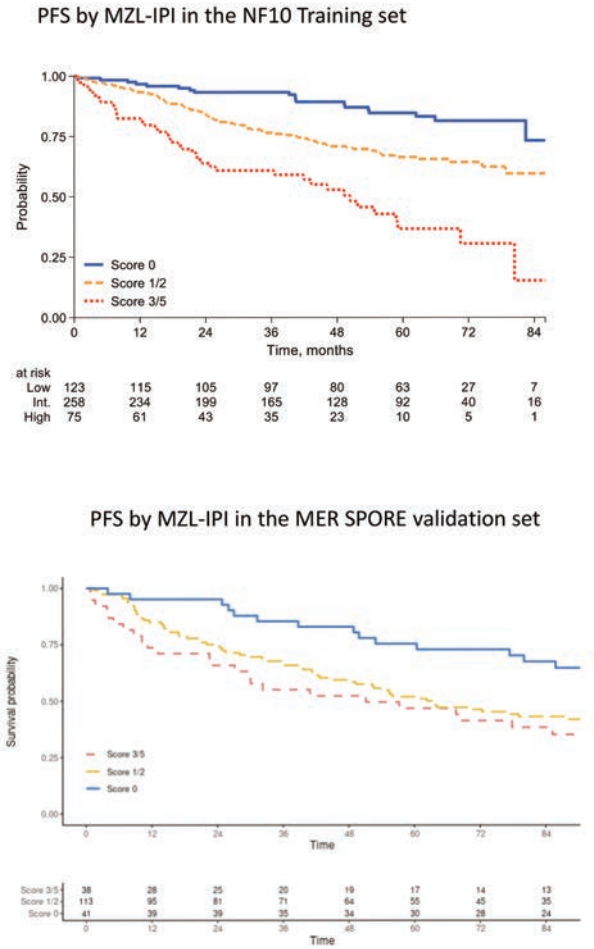

Figure 1.

P015

ABSTRACT NOT PUBLISHABLE

P016

COPANLISIB IN COMBINATION WITH RITUXIMAB AND BENDAMUSTINE FOR TRANSPLANT-INELIGIBLE RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS: RESULTS FROM THE PHASE II MULTICENTER FIL_COPA-RB TRIAL FROM FONDAZIONE ITALIANA LINFOMI (FIL)

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Background. 60% of Diffuse large B-cell lymphoma (DLBCL) are cured with R-CHOP. Treatment options for relapsed/refractory (R/R) patients (pts) not eligible to ASCT or CAR-T are limited. The PI3-K inhibitor copanlisib showed activity in B-cell lymphomas including DLBCL. We reported the results of the phase II single arm multicenter FIL Copa-RB trial which investigated the combination copanlisib plus rituximab and bendamustine (copa-RB) in transplant-ineligible R/R DLBCL.

Methods. Pts with R/R DLBCL previously treated with 1-3 prior lines, not eligible to ASCT and CAR-T were enrolled to receive 6 cycles of copa-RB q28 days (induction: copanlisib 60 mg i.v. days 1,8,15. Rituximab 375 mg/m^2 i.v. day 1, Bendamustine 90 mg/m^2 i.v. days 1,2). Pts with at least stable disease continued with a maintenance phase up to 12 q28 day cycles of Copanlisib (60 mg i.v. days 1,15). The primary end point was 12-month progression free survival (PFS) with an expected improvement from 20% to 35% and a calculated sample size of 81 pts.

Results. From 11/2019 to 7/2022, 37 pts were enrolled. Median age was 76 years (68-87), 62% IPI ≥3, 68% stage IV, 62% and 38% 1 and 2 prior lines and 35% refractory. The best overall response rate (ORR) was 51%, with 22% CR. With a median follow-up of 12 months, the 12-mo PFS was 25.2% (13.6-38.5%) and median PFS 5.5 months (3.7-10.0). The 12-mo overall survival (OS) was 49.4% (30.7-65.7%) (Figure 1). Nine patients were alive and in continuous response at time of the data cut-off. 91% of pts experienced grade > 2 adverse events (AE): neutropenia (58%), infections (28%), gastrointestinal (19%), skin (16%) and thrombocytopenia (13%). SARS-COV-2 infection occurred in 19% with 5 deaths. CMV reactivation occurred in 47%, but without infection. Febrile neutropenia was recorded in 2.8%. AEs led to dose interruptions in 19%. Since the slow recruitment, the unfavorable safety profile and the emerging of potentially more effective new treatments, the study was interrupted prematurely by steering committee decision.

Conclusions. Copa-RB study was conducted in a difficult-to treat R/R DLBCL cohort (elderly, advanced stage) during COVID pandemic that affected its management. Copa-RB induced a good ORR, but it was short lasting with unfavorable safety profile, so the overall activity was modest. A subset of pts had a long-lasting response. A mutational study is ongoing to identify molecular pathways potentially predictive of response to the combination.

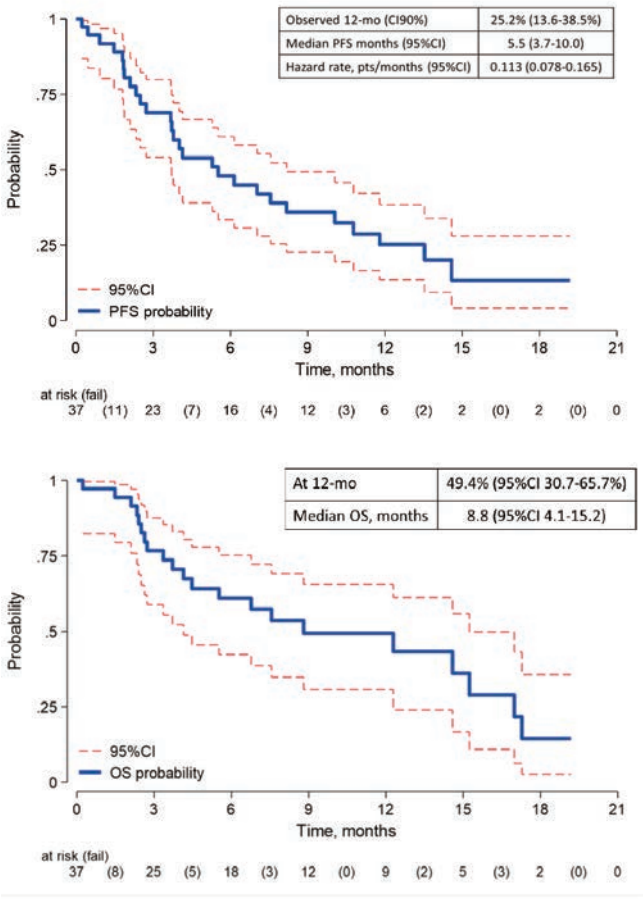

Figure 1. 12-month progression free survival (PFS) and overall survival (OS).

P017

ABSTRACT NOT PUBLISHABLE

P018

PRIMARY DIFFUSE LARGE B CELL LYMPHOMA OF FEMALE GENITAL TRACT: A RETROSPECTIVE MULTICENTER OBSERVATIONAL STUDY

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Introduction. Primary lymphoma of the female genital tract (PLFGT) is a rare extranodal lymphoma. Diffuse large B cell lymphoma (DLBCL) is the most frequent histological subtype.

Methods. Data of presentation, treatment and outcome of PLFGT DLBCL were retrospectively collected and analyzed to defining clinical features and outcome in pre- and post-rituximab era.

Results. Forty-four females were enrolled between 1982 and 2012 (Table 1).

Table 1. Patient's characteristics (n=44). IPI; international prognostic index score (age> 60years; EGOG>2; above normal range of LDH; 1involved extranodal sites >1 ; stage> II); CNS IPI score; central nervous system (age> 60years; EGOG>2; above normal range of LDH; involved extranodal sites >2; stage>2; kidney or/and adrenal involvement); FIGO staging (stage I=confined to the organ of origin; stage II= invasion of surrounding organs or tissue; stage III= spread to distant nodes or tissue within the pelvis; stage IV= distant metastasis).

Patients' Characteristics	N	%
Age		
Median, 52 years (range, 25-87)		
Stage (according to FIGO staging)		
localized	15	34%
advanced	29	66%
Stage (according to Ann Arbor staging)		
I-II	22	50%
III-IV	22	50%
Menopausal status		
Yes	19	44%
No	16	36%
Unknown	9	20%
Primary gynecological site		
Ovary	18	41%
Uterus	21	48%
Vagina	5	11%
IPI or R-IPI score		
Low (0-1)	20	45%
Intermediate-low/intermediate-high (2-3)	22	50%
High (4-5)	2	5%
CNS IPI score		
Low	21	48%
Intermediate	16	36%
high	7	16%

Median age at diagnosis was 52 years, 50% had limited stage (I-II according to Ann Arbor system) and 52% had bulky lesion (>7 cm). Most of them had uterus as primary gynecological site (48%), 41% the ovary, 11% the vagina. Ten patients (23%) had multiple gynecologic involved sites. All but 2 received CHOP-like first line chemotherapy (CT), with Rituximab (28/42), one was treated with rituximab alone and 1 with R-CVP. In 11 cases a major surgery was firstly performed. Consolidation radiotherapy was applied in 11 cases, all but 1 on pelvic lesion. Five patients received central nervous system (CNS) prophylaxis (3 with high dose methotrexate, 1 intrathecal methotrexate, 1 NOS). Forty responded (38 CR, 2 PR), 14 progressed/relapsed after a median time of 7.14 months from therapy start. Six patients experienced CNS relapse, all but 1 had ovary involvement, 3 had bulky disease; none of them had received previous CNS prophylaxis. As second line, 2 received high-dose methotrexate-based CT, 3 high-dose cytarabine -based CT, 2 standard dose CT, 2 palliative cares. One was consolidated with autologous stem cell transplantation. At last follow up, 32/44 are alive (30 in CR), 9 dead for progression disease and 2 for causes not related to lymphoma, 1 was lost at follow up. After a median follow up of 11, 33 years, median progression free and overall survival (PFS and OS) were not reached, 5-year PFS and OS were 66% (95%CI, 58-69%) and 73% (95%CI, 64-77%), respectively. By multivariable analysis FIGO stage (limited versus advanced) resulted to the only clinical factor able to predict the OS and PFS.

Conclusions. The most frequent gynecological site involved by DLBCL are uterus and ovary. The outcome of our population was similar to the counterpart of systemic DLBCL. The risk of CNS relapse was of 14%. A higher risk of CNS relapse was observed in the subgroup of the patients with ovarian involvement. These findings need to be confirmed by larger study, before to support recommendations from scientific societies for the management of PLFGT patients.

P019

ULTRASONOGRAPHY-GUIDED CORE-NEEDLE BIOPSY OF LYMPHADENOPATHIES SUSPECTED OF LYMPHOMA: ANALYSIS ON DIAGNOSTIC EFFICACY AND SAFETY OF 1000 FRONT-LINE BIOPTIC PROCEDURES IN A MULTICENTER ITALIAN STUDY

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Patients with clinical suspect of lymphoma require prompt and correct diagnosis histologically. The aim of this study was to evaluate the reliability and safety of front-line ultrasonography guided core needle biopsy (UG-CNB) of the lymphadenopathies suspected of lymphoma in a large series of patients collected over a 12-year period. We retrospectively checked the findings concerning the application of lymph nodes UG-CNB from four Italian clinical units that utilized specific uniform approach for an extended period. A data schedule was sent to all centers to investigate the information regarding techniques, results, and complications of lymph node UG-CNB in untreated patients. Inclusion criteria were: i) lymphadenopathy power Doppler-U retrospective assessment on recorded video clips and/or images; ii) 16-gauge CNB with powered automatic suction and 1.6 mm needle diameter sample; iii) availability of lymph node sections fixed in formalin and embedded in paraffin; iv) morphological and immunohistochemical information (assessed retrospectively by haematopathologists); and v) information of an accepted diagnostic reference standard (either the lymphadenopathy surgical resection or follow-up assessment with 2-deoxy-2[F-18] fluoro-D-glucose positron emission tomography [FDG PET]-computed tomography [CT] showing decreased FDG uptake and/or decreased size after specific antineoplastic treatment according to the histological subtype, as well as spontaneous regression for the benign conditions). There

was excellent interobserver reproducibility of ultrasonographic and histological examinations. Overall, 1000 (superficial target, n= 750; deep-seated target, n= 250) biopsies performed by using 16-gauge diameter modified Menghini needle under power-Doppler ultrasonographic guidance were evaluable in 1000 patients. The overall accuracy of micro-histological sampling was 97% (95% confidence interval: 95% to 98%) for the series. Most patients were suffering from lymphomas (aggressive B-cell non-Hodgkin lymphoma [aBc-NHL], 309 cases; indolent B-cell [iBc]-NHL, 266 cases; Hodgkin lymphoma [HL], 198 cases; and nodal peripheral T-cell [NPTC]-NHL, 27 cases) and 100 cases from metastatic carcinoma; 70 patients were negative for malignancy (diagnosis of atypical lymphadenopathies mimicking lymphomas [ALML]). The sensitivity rate for the detection of aggressive B-cell non-Hodgkin lymphoma (NHL) was 100%, for indolent B-cell NHL 95%, for Hodgkin lymphoma 93%, and for nodal peripheral T-cell NHL 90%, with an overall false negative rate of 3.3%. The complication rate was low (6% for all complications); nobody suffered from biopsy-related complications of grade >2 according to the Common Terminology Criteria for Adverse Events. Lymph node UG-CNB as mini-invasive diagnostic procedure is effective with minimal risk for the patient.

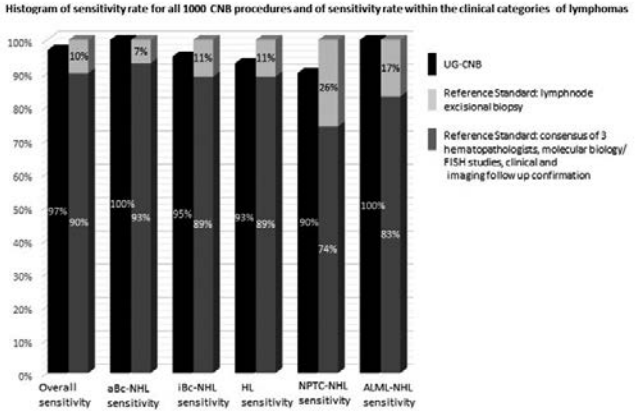

Figure 1.

P020

CLINICAL MANAGEMENT OF T-CELL LYMPHOMA IN REAL LIFE: A SURVEY OF THE FONDAZIONE ITALIANA LINFOMI

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Peripheral T cell Lymphomas(PTCLs) represent 10-12% of all non-Hodgkin lymphomas.PTCLs have a poor outcome,with heterogeneous behaviors among centers.In order to collect data on the clinical management of PTCLs in the Italian centers,we conducted a survey on the 143 centers of the Fondazione Italiana Linfomi.We submitted 45 questions;47 centers participated,reporting 352 PTCLs diagnoses/year. The results of the survey are:histological review by expert hemopathologists is routinely performed in 13(28%) of the centers;additional pathological tests,such as FISH for DUSP22 and/or TP63 rearrangements in ALK-ALCL,TET2 mutation and associated clonal hematopoiesis of indeterminate potential in AITL are assessed in 13(28%), 11(23%) and 10(21%),respectively;only 6 centers(13%) evaluated GATA3/TBX21 expression by immunohistochemistry and CDNK2A deletion in PTCL-NOS. Regarding patients(pts)≤65 years first line treatment:43(91%)centers usually perform CHOEP,4(8%)CHOP and 44(94%)propose a consolidation with autologous stem cell transplantation(ASCT).Upfront allogenic transplant is the standard in 13(28%) centers for hepatosplenic lymphoma and advanced stage NK nasal type.In >65 years pts CHOP is the most common first line regimen in 37(79%) centers,whereas a gemcitabine-based therapy is used in 5(11%).Regarding salvage treatment,only in 8(17%) centers clinical trials with novel agent are available;in ≤65 years old pts 43(87%) centers candidate pts to allogeneic transplantation, after achieving a response with bendamustine-containing regimens in 8(17%),brentuximab-vedotin(BV)(if CD30+ PTCL) in 10(21%) or gemcitabine-based regimen in 23(49%) respectively. For pts not eligible to high-dose therapy and ASCT,29(62%) treat pts with gemcitabine +/- bendamustine regimens.By different subtypes,ALCL ALK- and ALK+ are quite frequently treated with BV in first or second lines; only 9(19%) of centers experienced the use of crizotinib in relapsed ALK+, 7(15%) azacitidine in AITL and 4(8%) lenalidomide in AITL. In Extranodal NK lymphoma SMILE regimen +/-radiotherapy is the most common scheme adopted;in relapse setting, BV is used in 6(13%) centers and immune-check-point inhibitors in 7(15%) centers.In conclusion,while first line CHOEP+ASCT represents the standard of care for young pts,management is less standardized for elderly and relapsed pts and a complete pathological diagnosis is often difficult to obtain.Our survey should be the first step for designing new clinical trials.

P021

LIMITED-STAGE DIFFUSE LARGE B-CELL LYMPHOMA IN ELDERLY PATIENTS: COMPARISON BETWEEN CHEMOIMMUNOTHERAPY PLUS RADIOTHERAPY AND CHEMOIMMUNOTHERAPY ALONE. AN AD HOC ANALYSIS OF THE ELDERLY PROJECT STUDY BY THE FONDAZIONE ITALIANA LINFOMI (FIL)

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Introduction. Limited-stage diffuse large B-cell lymphomas (LS-DLBCL) represent 25-30% of all DLBCL. The standard first-line therapy consists of 6 cycles of immunochemotherapy (CT) alone or 3-4 cycles of CT followed by involved site radiotherapy (RCT). The optimal approach is controversial, particularly in elderly patients (pts).

Methods. We describe the characteristics and outcomes of LS-DLBCL patients enrolled in the Elderly Project, prospectively defined as fit, unfit or frail by a simplified geriatric assessment (sGA) and treated with CT or RCT per local practice. The primary endpoint was overall survival (OS); secondary endpoints were Progression Free Survival (PFS) and the evaluation of survival outcomes according to different geriatric categories. We considered only pts treated with full or reduced dose of R-CHOP/R-COMP.

Results. We identified 197 LS-DLBCL out of 1163 pts enrolled in EP; 146 pts were treated with 6 cycles of CT, 51 pts were treated with RCT. The clinical characteristics were not statistically different in the two groups of treatment, except for stage II (27% RCT *vs* 71% CT, p<0.001) and bulky sites (12% RCT *vs* 30% CT, p=0.009). Median age was 75 years (17% of pts >80 years); 68% of pts were fit, 26% unfit and 7% frail. The median total dose of RT was 30.6 Gy (range 30–44 Gy); we observed only one case of grade 3 acute toxicity post RT and no long term adverse events. The overall response rate (ORR) was 97% for CT and 92% for RCT, with complete response rate (CRR) 87% *vs* 82% (p=0.485). The 5-year OS was 74% for the CT group and 67% for the RCT group (p=0.083); the 5-year PFS was 71% for the CT group and 65% for the RCT group (p=0.249) (Figure 1).

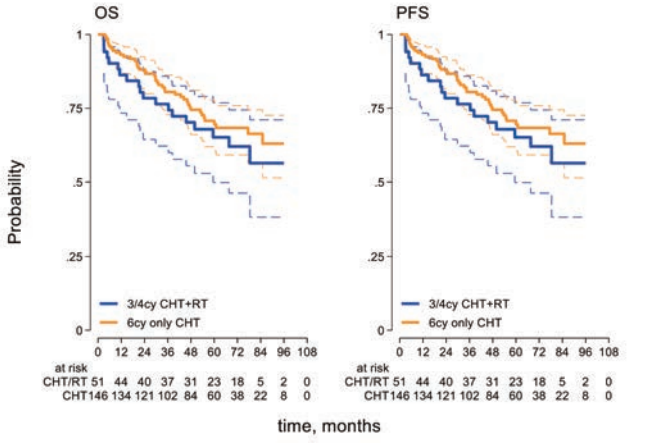

Figure 1. Overall Survival (OS) and Progression Free Survival (PFS) of elderly patients with LS-DLBCL treated with 3-4 cycles of immunochemotherapy plus RT versus 6 cycles of immunochemotherapy without RT.

The 5-year OS according to sGA was 80% in fit pts, 61% in unfit and 39% in frail (p<0.001). The 5-year PFS was 78% in fit pts, 57% in unfit and 29% in frail (p<0.001). The 5-year OS according to the Elderly Prognostic Index (EPI) score was 80% in low-risk pts, 62% in intermediate-risk and 29% in high-risk (p 0.003). The 5-year PFS was 78% in low-risk pts, 59% in intermediate-risk and 25% in high-risk (p<0.001).

Conclusions. In elderly pts with LS-DLBCL, a combined treatment with 3-4 cycles of CT followed by involved site RT may be as effective as 6 cycles of CT and permits to achieve a good outcome with limited toxicity. The sGA and the EPI are confirmed as valuable tools to identify different risk categories of elderly pts with DLBCL, also in limited stage

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CENTRAL NERVOUS SYSTEM INVOLVEMENT AT DIAGNOSIS AND AT RELAPSE IN PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA: A RETROSPECTIVE ANALYSIS OF THE "RETE EMATOLOGICA VENETA" (T-REV PROJECT)

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Background. Peripheral T-cell lymphoma (PTCL), is a heterogeneous and rare entity (5-10% of all lymphomas). Central nervous system (CNS) involvement at diagnosis and at relapse in patients with PTCL ranged from 2-9%, with a well-known dismal prognosis. We retrospectively collected clinicopathologic and treatment data in 217 PTCL patients, diagnosed between 2000 and 2022, who underwent induction chemotherapy in six Italian centers.

Aims. To characterize the rate and survival outcome of CNS involvement in newly diagnosed PTCL.

Methods. Routine staging investigations and response was evaluated using the 2014 Lugano criteria. The diagnosis of PTCL was histologically confirmed and categorized according to the classification at the time of diagnosis. Patients with primary cutaneous T-cell lymphoma, T-cell lymphoblastic leukemia/lymphoma, T-cell prolymphocytic leukemia, adult T-cell leukemia/lymphoma and extranodal NK/T-cell lymphoma were excluded from this study. Only 6 patients received CNS prophylaxis, 3 with intrathecal therapy and 3 with high-dose methotrexate.

Results. Baseline characteristics are shown in Table 1. With a median follow up of 24 months, 10 out of 217 had CNS disease: four patients (1.5%) had CNS involvement at initial diagnosis and six patients (2.5%) had a CNS relapse. At the end of first line treatment, ORR was 65% (with 55% CR and 10% PR) in patients without CNS involvement at diagnosis, and only one CR (25%) in patients with CNS involvement at diagnosis. Median overall survival (OS) of the entire population was 35 months; primary refractory and early relapsed disease were 79 (36%) and 35 (16%), with a median OS of 7.5 and 21 months, respectively. Median OS for patients with CNS relapse were 8 months, and median OS for cases with CNS involvement at diagnosis were 13 months. CNS relapse were all stage IV, had an elevated LDH with extranodal involvement ≥ 1 site; five out of six of CNS relapse were primary refractory patients.

Conclusions. We confirmed previous data that patients with PTCL, who developed CNS relapse, had a higher burden of disease at baseline with a very poor prognosis. PTCL is a group of disease with generally low risk of CNS relapse and prophylaxis should be stratified by histologic subtypes and risk factors. Further studies are needed to prevent and treat this condition, maybe with a more individualized therapeutic approaches.

P027

FIRST LINE TREATMENT WITH IMMUNOTHERAPY OR CHEMO-IMMUNOTHERAPY IN HELICOBACTER PYLORI-NEGATIVE GASTRIC MARGINAL ZONE LYMPHOMA

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Gastric marginal zone lymphoma (MZL) is the most common subtype of extranodal MZL. Despite a close association with Helicobater pylori (HP) infection, an increasing proportion of HP-negative cases has been reported in recent years. Therefore, therapeutic approaches other than HP eradication are used, like immunotherapy (IT), chemoimmunotherapy (CIT), local radiotherapy and surgery. Since available data on these treatments are limited, we performed a retrospective analysis of patients (pts) with HP-negative gastric MZL diagnosed in our Center and treated in first line with IT or CIT. Data on 54 pts with HP-negative gastric MZL were collected (67% males); median age at diagnosis was 68 (range 36-86) years. Stage was I-II in 74% and IV in 26% of pts. The median follow-up for this analysis was 5.5 years.

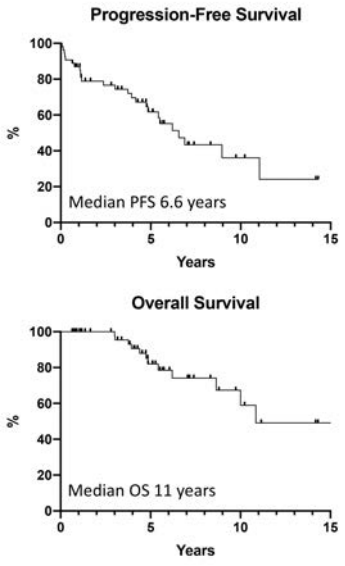

Figure 1.

First-line treatment was IT (rituximab) in 24 (44%) pts, CIT (RFN, R-bendamustine, or R-COMP) in 21 (39%) pts, CT alone in 8 pts (15%), or radio-immunotherapy in 1 patient. A CT-based regimen was preferred for stage IV pts; the median age was similar in the different treatment groups. The median progression-free survival was 6.6 years, the median disease-free survival was 8.5 years and the median overall survival (OS) was 11 years, respectively. Five-year OS was higher for pts treated with IT alone compared to those treated with CIT (94% *vs* 62%; p=0.055). Response to first-line treatment was: complete (CR) in 42 (78%) pts, partial in 9 (17%) pts and stable disease in 3 (5%) pts. CR rates in pts treated with IT and CIT were 63 and 95% (p=0.01), respectively. Eleven pts with CR subsequently relapsed. At last contact, 25 (46%) pts were alive and in continuous CR after first-line treatment, with a median duration of response of 5 years. Second and third-line treatments were required in 18 (33%)

and 3 (5%) pts, respectively. Adverse events (AE) during first-line treatment were generally manageable; 3 pts discontinued treatment (CIT) early due to severe AEs. Late AEs included a second malignancy in 7 (13%) pts (at a median age of 78 years); all of them were previously treated with CT/CIT. Overall, 12 (22%) pts died, only 2 due to lymphoma progression; all but one previously received CT/CIT. In conclusion, first-line IT or CIT in pts with HP-negative gastric MZL yielded high rates of response and a good OS. Response rates but also early and late AEs, including deaths, were higher in pts treated with CIT than pts receiving IT alone.

P028

THE ADDITION OF HIGH-DOSE SYSTEMIC TO INTRATHECAL METHOTREXATE AS CNS PROPHYLAXIS IN AGGRESSIVE B CELL LYMPHOMAS: RESULTS OF A PROPENSITY SCORE MATCHED ANALYSIS OF A LARGE SINGLE INSTITUTION COHORT

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Introduction. Disease progression or relapse in the central nervous system (CNS) is a serious and nearly always fatal event in patients (pts) with aggressive B cell lymphomas including diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL).

Objectives. The study compared 2 CNS prophylaxis strategies in pts affected by DLBCL and HGBL treated in first-line therapy at the Department of Hematology of the Catholic University of the Sacred Heart, Gemelli Foundation, in Rome between January 2006 and August 2022.Pts received either intrathecal Methotrexate(IT-MTX) with the first 4 cycles of R-CHOP or IT-MTX with additional 2 cycles of systemic high-dose Methotrexate(MTX-HD). We compared the effect of the type of prophylaxis onto CNS relapse and overall survival (OS) in pts considered at high risk for CNS relapse.

Methods. We retrospectively assessed 1087 pts with DLBCL and HGBL. After excluding pts with primary CNS involvement at the onset of the disease, 279 pts were deemed to be at risk for CNS progression according to the 2006 SIE/SIES/GITMO guidelines:228 pts received IT-MTX alone and 51 pts both MTX-HD and IT-MTX. A propensity score (PS) matching analysis was used to overcome the bias constituted by the difference in selection of pts groups and balance the baseline pts characteristics, in particular the CNS-IPI score.

Results. Among the 279 pts receiving CNS prophylaxis,15 isolated CNS relapses (5.4%), 4 CNS relapses with concomitant systemic relapse (1.4%) and 62 systemic relapses(22.2%) were found. The median time to CNS relapse was 7.8 months(range 1-44 months), not different from the median time to systemic progression(7.7 months, range 1-80 months). PS matching resulted in selection of 46 pts treated with HD-MTX and 46 pts with IT-MTX for further statistical analysis. In the PS matched cohort, no significant differences emerged regarding the rate of CNS relapse, systemic relapse or OS between the 2 CNS prophylaxis regimens. The cumulative incidence of CNS disease was 11% at 48 months(95%C.I. 0.02–0.28) for the group that received MTX-HD and 7%(95% C.I. 0.04–0.27) for the only IT-MTX group (p=0.26). OS does not differ between the cohorts (p=0.53) with a survival of 72% at 48 months(95%C.I. 0.59–0.85) for pts who received IT-MTX and 79% at 48 months(95%C.I. 0.66–0.92) for pts receiving MTX-HD.

Conclusions. The addition of 2 cycles of intravenous HD-MTX to prophylaxis with IT-MTX appears not effective to reduce the incidence of CNS relapse.

P029

CD79B EXPRESSION IN DIFFUSE LARGE B CELL LYMPHOMA AS ASSESSED BY FLOW CYTOMETRY OF LYMPH NODE BIOPSIES

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The CD79b constitutes the B cell receptor complex (BCR) with CD79a and surface immunoglobulin. The efficacy of Polatuzumab, an anti-CD79b antibody drug conjugate, in the treatment for diffuse large B cell lymphoma (DLBCL) and the scarcity of data about its expression in immunohistochemistry (IHC) and flow cytometry (FC) raised our attention. The aim of our study was to assess CD79b expression in lymph node biopsies with IHC diagnosis of DLBCL using FC. We analysed 101 biopsies between Dec-2015 and Feb-2023. Cell suspensions were prepared by mechanical disaggregation and incubated with 8 surface markers: Kappa/CD45/CD20/CD79b/CD5/CD19/CD10/Lambda. Data were acquired with BDFACSCanto for the first 45 patients (pts) and with DXFlex (Beckman Coulter) for other 56. For each antigen we measured Median Fluorescence Intensity (MFI) on pathological CD19+ B cells and CD5+ T cells (negative control population) and we calculated the relative MFIratio (RMFI) between these two clusters. In the group of 56 pts the median percentage of CD79b expression on lymphoma cells was 72.5% (2-98). CD79b was strongly positive (>70%) in 50% (28/56), partially positive (20-70%) in 16% (9/56), weakly positive (1-19%) in 19.6% (11/56) and <1% in 14.2% (8/56) of pts. CD79b was positive in residual normal B cells in pts with CD79b negative lymphoma cells. We observed a positive correlation between CD79bRMFI and clonal light-chainRMFI (Spearman R=0.55, p=0.0001). Clonal light-chainRMFI was significantly lower in pts with CD79b <20% compared to others (Mann-Whitney median value 6.3 versus 30.3, p=0.01). Similar results were found in the 45 pts analysed with FACSCanto. Spearman test confirmed a positive correlation between CD79bRMFI and clonal light-chainRMFI (R 0.7, p 0.0001). Clonal light-chainRMFI was lower in pts with CD79b <20% (p=0.006). We further analyzed intracytoplasmic expression of CD79b and light chains in two pts with negative surface staining for these antigens. We observed a positive expression of CyCD79b and a clonal restriction for light chains (Cykappa in one case and Cylambda in other). Our results suggest a co-regulation of CD79b surface expression together with other BCR components and indicate a high variability of CD79b expression in DLBCL as previously supposed in literature. It will be interesting whether the quantitative study of CD79b using FC could be helpful to explore associations between the level of surface expression and response to target therapy.

P030

ICANS IN PATIENTS TREATED WITH ANTI-CD19 CAR-T CELLS: CORRELATION WITH SERUM NEUROFILAMENT LIGHT CHAIN (NFL), GLIAL FIBRILLARY ACIDIC PROTEIN (GFAP) AND MARKERS OF ENDOTHELIAL IMPAIRMENT

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Immune effector cell-associated neurotoxicity syndrome (ICANS) is the most frequent neurological toxicity occurring after treatment with chimeric antigen receptor T-cells (CAR-T), with a reported incidence of around 30-50% according to different settings and products. Clinical manifestations may widely range from dizziness to seizures, and tend to respond to high-dose steroids. The pathogenesis of ICANS is unclear, despite some data suggest a role for endothelial activation and impairment of the blood-brain barrier (BBB). Glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL) are reliable biomarkers of astroglial and axonal neuronal damage, respectively.

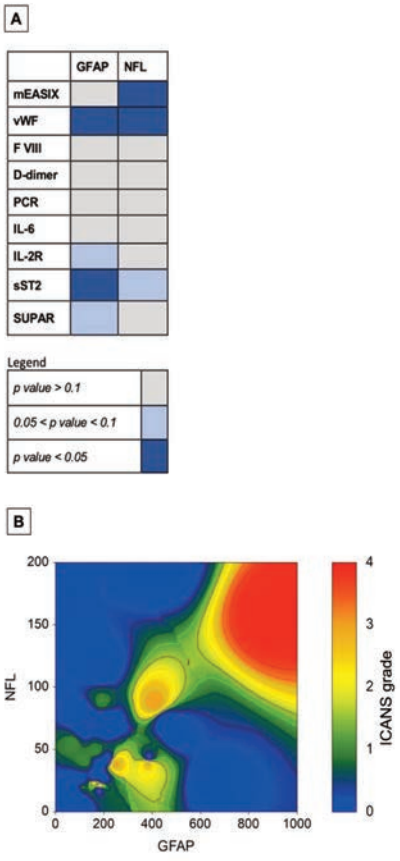

Figure 1.

Recently, preliminary studies reported that NFL serum levels correlate with the severity of neurotoxicity after CAR T-cell treatment. In our study, we measured GFAP and NFL both at baseline and at day 7 in 34 patients with R/R B-cell malignancies treated with CD19 CAR-T cells (15 Axi-cel, 12 Tisa-cel, 7 Brexu-cel), and explored their association with clinically relevant neurological toxicities and markers of endothelial impairment. Elderly patients tended to have higher values of GFAP at day 0 and these levels raised after CAR-T infusion. When measured after infusion, GFAP positively correlated with endothelial biomarkers such as von Willebrand factor (p=0.041) and sST2 (p=0.015) and showed a trend for associations with IL-2R (p=0.050) and SUPAR (p=0.074). NFL positively correlated with the vWF (p=0.021) and with the endothelial activation score mEASIX (p=0.015) (Figure 1A). Overall, 11/34 patients (33%) developed ICANS. Baseline GFAP and NFL values did not impact the subsequent development of CRS or ICANS. When compared to the baseline, an increase in NFL was observed in 50% of cases. Patients experiencing an increase in NFL values after CAR-T infusion were more likely to develop ICANS of higher grades (p=0.046, OR 4.14) and to receive treatment with steroids (p=0.023). Designing a heatmap with GFAP and NFL levels measured after CAR-T infusion, it becomes evident that a pattern with both higher GFAP and NFL values associates with ICANS of a higher grade (Figure 1B). In conclusion, our data confirm a correlation between severe ICANS and elevated serum levels of NFL and G-FAP. Interestingly, these data also correlate with markers of endothelial activation, suggesting an active role of BBB impairment and axonal neuronal damage in the pathogenesis of ICANS.

P031

REAL-LIFE ELDERLY PROGNOSTIC INDEX USEFULNESS FOR GUIDING TREATMENT CHOICES IN ELDERLY DLBCL PATIENTS

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Background. Treatment of DLBCL elderly patients (pts) is challenging due to comorbidities and increased toxicity. Multidimensional geriatric assessment aims to better stratify pts and guide treatment choices.

Methods. We retrospectively applied the elderly prognostic index risk (EPI, *Merli et al. JCO 2021*) in 101 consecutive pts with newly diagnosed DLBCL aged ≥65 years treated between January 2018 and December 2022 at our Institution. Clinical features, treatment outcomes and toxicities were collected. Chi-square (χ^2) test was used for comparison of categorical data. Survival curves were estimated using the Kaplan-Meier method and compared by log-rank test. P<0.05 was deemed statistically significant.

Results. Pts' clinical features, treatment choice and outcomes are summarized in Table 1. 10% pts resulted EPI low-risk, 41.5% EPI intermediate-risk and 48.5% EPI high-risk. All EPI low-risk pts had received standard R-CHOP/COMP. Most (76%) EPI intermediate-risk received R-CHOP/COMP, 12% received R-mini-CHOP/COMP and 12% palliative therapy (*i.e.* chemotherapy without anthracyclines or radiotherapy/surgery only). 45% of EPI high-risk pts were treated with R-CHOP/COMP, 33% with R-mini-CHOP/COMP and 22% received palliative therapy only. Dose reduction was necessary in 39% of R-CHOP/COMP-treated pts and 38% of R-mini-CHOP treated pts. EPI risk was correlated with percentage of dose reduction (0% EPI low, 32% EPI intermediate, 55% EPI high; χ^2-test p=0.004). ORR was 100% in EPI low-risk (all CR), 83% in EPI intermediate-

risk (74% CR) and 82% in EPI high-risk (53% CR). Compared to EPI low and intermediate-risk, pts with EPI high-risk had lower PFS (not reached *vs* 22 months *vs* 15 months p=0.044) and OS (not reached *vs* 32 months *vs* 16 months p=0.0029), with no difference for pts treated with R-CHOP/COMP or R-mini-CHOP (22 *vs* 21 months; p=0.63). EPI stratification resulted predictive of treatment intensity (R-CHOP/COMP *vs* R-mini-CHOP/COMP *vs* palliative; p=0.003) and lower CR rate (p=0.007), PFS (p=0.044) and OS (p=0.0029).

Conclusions. EPI remains a useful tool in stratifying elderly DLBCL pts, and predicts survival. However, it has some limitations, particularly for the EPI high-risk group where it may lead to under-treat a significant proportion of pts. Further investigations are needed to better define within this high-risk-group, those pts that can tolerate a curative treatment approach.

Table 1. Patients' clinical features, treatment modalities and outcomes.

	All patients	EPI low (n=10)	EPI intermediate (n=42)	EPI high (n=49)	P
M vs F	55 vs 46	4 vs 6	21 vs 21	30 vs 19	
Median age, years Range Age ≥75 years	76 65-101 60 (60%)	73 65 – 78 3 (30%)	75 65 – 101 17 (40%)	80 66 – 90 40 (82%)	<0.001 <0.001
ECOG PS 0-1 ≥2	 68 (68%) 33 (32%)	 10 (100%) 0	 38 (90%) 4 (10%)	 20 (41%) 29 (59%)	 <0.001
COO • GCB • Non-GCB • Not available	 38 (38%) 46 (45%) 17 (17%)	 6 (60%) 3 (30%) 1 (10%)	 14 (34%) 19 (45%) 9 (21%)	 18 (37%) 24 (49%) 7 (14%)	 0.393
Stage • I-II • III-IV	 20 (20%) 81 (80%)	 6 (60%) 4 (40%)	 11 (26%) 31 (74%)	 3 (6%) 46 (94%)	 <0.001
Symptoms A vs B	65 vs 36	8 vs 2	29 vs 13	28 vs 21	0.275
IPI • Low • Low-intermediate • High-intermediate • High	 12 (12%) 22 (22%) 32 (31%) 35 (35%)	 6 (60%) 4 (40%) 0 0	 6 (14%) 11 (26%) 17 (40%) 8 (20%)	 0 (0%) 7 (14%) 15 (31% 27 (55%)	 <0.001
Treatment					
R-CHOP/COMP Required dose reduction	64 (64%) 25 (39%)	10 (100%) 0	32 (76%) 10 (3%)	22 (45%) 15 (68%)	<0.001
R-miniCHOP/COMP Required dose reduction	21 (21%) 8 (38%)	0 	5 (12%) 2 (40%)	16 (33%) 6 (37%)	0.012
Palliative	16 (15%)	0	5 (12%)	11 (22%)	0.137
Median PFS (months)	20	Not reached	22	15	0.044
Median OS (months)	35	Not reached	32	16 No difference in R-CHOP/COMP and R-mini-CHOP/COMP treated patients	0.0029

COO = cell of origin; EPI = Elderly Prognostic Index; F = female; GCB = germinal-center B-cell; IPI = international prognostic index; M = male; OS = overall survival; PFS = progression-free survival; PS = performance status.

P032

PLENTIPLEX MYD88 WALDENSTRÖM LYMPHOMA QPCR ASSAY: A HIGHLY SENSITIVE METHOD FOR DETECTION OF MYD88 L265P MUTATION

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Introduction. Lian Xu *et al.* in 2013 identified a somatic mutation (MYD88 L265P) that stimulates nuclear factor-κB activity and is present in >90% of Waldenström macroglobulinemia (WM) patients. Lian Xu et al. developed agarose gel-based conventional and real-time allele-specific polymerase chain reaction (AS-PCR) assays for sensitive detection and quantification of MYD88 L265P for diagnostic discrimination and response assessment. The assays are used to detect MYD88 L265P mutation in WM, IgM Monoclonal Gammopathy of Unknown Significance (MGUS), Marginal Zone Lymphoma (MZL), Chronic Lymphocytic Leukemia (CLL), and multiple myeloma (MM). Despite the conventional AS-PCR assay being highly sensitive and specific for MYD88 L265P, the assay sometimes leads to ambiguous sample results as it is determined from a visual inspection of an agarose gel.

Methods. Here we propose a new assay that utilizes Plentiplex qPCR assay which vastly increases both affinity and specificity of assay oligonucleotides towards the target region compared to assays based on standard DNA. In this clinical study, we compare PlentiPlex MYD88 Waldenström Lymphoma qPCR Assay, a semi-quantitative real-time PCR assay intended for *in vitro* diagnosis of MYD88 L265P in genomic DNA (gDNA) obtained from FFPE tissue or blood samples, with the conventional AS-PCR. The discrepant cases were evaluated by digital droplet PCR (ddPCR). PlentiPlex MYD88 Waldenström Lymphoma qPCR Assay utilizes a unique, proprietary DNA technology to vastly increase both affinity and specificity of the assay oligonucleotides towards the target region compared to standard. We included peripheral and bone marrow blood samples from 100 patients in total from September 2020 until January 2023: 50 adult patients wild-type for MYD88 L265P (4 IgM MGUS patients, 14 CLL patients, 12 splenic MZL (SMZL) patients, and 20 MM patients), and 50 WM adult patients from 47 to 87 years old. The patients' characteristics are summarized in Table 1.

Table 1. Cohort information.

	WM	MGUS	CLL	Marginal Zone Lymphoma (MZL)	Multiple Myeloma (MM)
Number	50	4	14	12	20
Age at diagnosis Median (y)	62	45	69	64	66
Gender male female	 32 (64) 18 (36)	 3 (75) 1(25)	 11 (78) 3 (22)	 7 (58) 5 (42)	 9 (45) 11 (55)
IgM at diagnosis <1500 1500-3000 >3000	 12 (24) 7 (14) 31 (62)	 4 (100) 0 0	 11 (78) 3 (22) 0	 4 (33) 8 (66) 0	 13 (65) 7 (35) 0
Hemoglobin at diagnosis g/dl	10.3 (8-15.2)	14.2 (11.6-18.7)	11.5 (9-14.2)	12.5 (10-16.8)	9.5 (8-13.5)
WBC at diagnosis Cell/mmc	1800 (1120-3600)	3492 (2600-4897)	3139 (1890-5512)	3589 (2560-3648)	3450 (2864-5562)
Platelet at diagnosis/mmc	115000 (74000-279000)	241000 (115000-450000)	145200 (78000-248500)	165000 (98520-202250)	225400 (145000-396000)
B2 microglobulin >3 mg/L	16 (32)	0	5 (35)	4 (33)	15 (75)
LDH >250 UI/L <250 UI/L	 36 (72) 14 (28)	 1 (25) 3 (75)	 12 (85) 2 (14)	 8 (66) 4 (33)	 4 (20) 16 (80)
Bone marrow infiltration Yes No	 17 (34) 33 (16)	 Nd Nd	 Nd Nd	 4 (33) 8 (67)	 20 (100) 0
Hyperviscosity syndrome Yes No	 15 (30) 35 (70)	 Nd Nd	 Nd Nd	 Nd Nd	 Nd Nd
Smoldering Symptomatic	17 (34) 33 (66)	4 (100) 0	9 (64) 5 (35)	5 (41) 7 (59)	6 (30) 14 (70)

Table 2. Confusion matrix of the MYD88 L265P -positive, -negative, and -ambiguous cases.

Clinical performance: MYD88 L265P detection		PlentiPlex™ MYD88 Waldenström Lymphoma qPCR Assay			
		Positive	Negative	Ambiguous	Total
Conventional AS-PCR	Positive	44	0	0	44
	Negative	0	50	0	50
	Ambiguous	6*	0	0	6
	Total	50	50	0	100

Six (6) samples were collected from peripheral blood and ninety-four (94) were collected from bone marrow blood. All samples were

analyzed using the homemade conventional AS-PCR assay and the PlentiPlex MYD88 Waldenström Lymphoma qPCR Assay. The discrepant and ambiguous cases were reanalyzed and in addition, confirmed using Droplet Digital PCR as a third method. For the conventional AS-PCR, 50 ng/µL of gDNA was used, whereas 1-10 ng/µL of gDNA was used for the PlentiPlex assay. Sometimes it can be difficult to determine whether a visible band is present, and if its appearance is enough to establish the sample as positive for the mutation. In the PlentiPlex MYD88 Waldenström Lymphoma qPCR Assay, the MYD88 L265P status is determined from a ΔCt value (it is positive for MYD88 L265P when $\Delta Ct \leq 9$ and negative when $\Delta Ct > 9$). The sensitivity and specificity of the PlentiPlex™ MYD88 Waldenström Lymphoma qPCR Assay on this cohort were calculated as described by Baratloo et al., and the confidence intervals were calculated using the Wilson score method.

Results. The PlentiPlexTM MYD88 Waldenstrom Lymphoma qPCR Assay is able to detect 0,6% MYD88 L265P in whole blood. According to Lian Xu *et al*., the comparator method has been demonstrated to detect MYD88 to a dilution of 0,1%. However, the results from the comparator method are qualitative so based on a rather subjective evaluation of the agarose gel. Sometimes it can be difficult to determine if a visible band is present or not and if its appearance is enough to call the sample positive for the mutation. Conventional AS-PCR was applied on all 100 patient samples, whereof 50/50 (100%) negative samples were wild-type for the MYD88 L265P mutation (IgM-MGUS, CLL, SMZL and MM) and in the other 50 cases, the MYD88 L265P mutation was detected in 44/50 (88%) patients with WM. Furthermore, six (6) samples were ambiguous as a faint band appeared on the agarose gel. See Figure 1, where the faint bands of the six cases are compared to a distinct band from a positive sample control. These six cases were the onset of the pathology and we expect on the agarose gel a strong band at the positive control. The six ambiguous cases were found positive for the MYD88 L265P mutation with the PlentiPlex MYD88 Waldenström Lymphoma qPCR Assay (Figure 2) and confirmed positive with ddPCR (Figure 3) with a fractional abundance between 5-10%. The PlentiPlex MYD88 Waldenström Lymphoma qPCR Assay detected the MYD88 L265P mutation in the remaining 44/50 positive cases resulting in 50/50 (100%) of the WM patients being positive for the mutation. Moreover, 50/50 (100%) of the negative samples were confirmed negative with the PlentiPlex MYD88 Waldenström Lymphoma qPCR Assay. See Figure 3 for a matrix of the comparison. Besides, the PlentiPlex MYD88 qPCR assay being more sensitive than the conventional AS-PCR, the method is also very fast (qPCR run time around 1.5 hours), semi-quantitative, and is less operator dependent.

Conclusions. Comparing PlentiPlex MYD88 Waldenström Lymphoma qPCR Assay to the conventional AS-PCR assay, we found a Positive Percent Agreement (PPA) of 100% [95% CI 0.92 to 1.0] and a Negative Percent Agreement (NPA) of 89% [95% CI 0.79 to 0.95], as six of the cases had ambiguous outcomes using the conventional AS-PCR assay. Taking the ddPCR results into account, the sensitivity and specificity of PlentiPlex MYD88 Waldenström Lymphoma qPCR Assay on this cohort were 1.0 [95% CI 0.93 to 1.0]. Our data demonstrate that PlentiPlex MYD88 Waldenström Lymphoma qPCR Assay is a fast, highly sensitive and specific method for distinctly detection of MYD88 L265P compared to conventional AS-PCR.

Figure 1. AS-PCR.

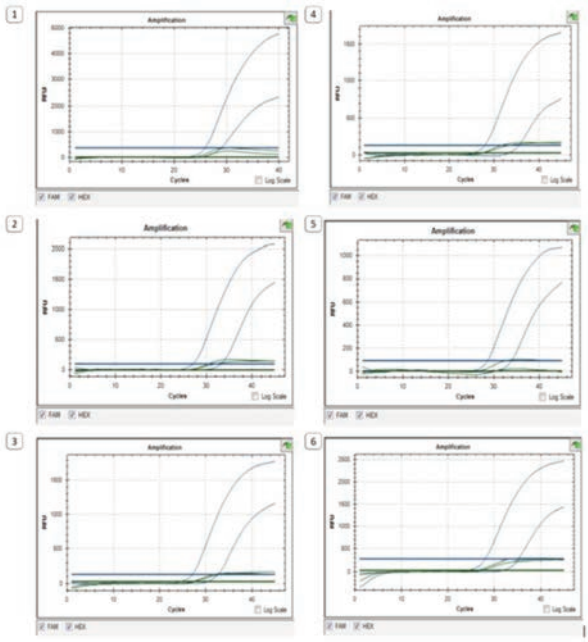

Figure 2. PlentiPlex MYD88 Waldenström Lymphoma qPCR reference assay.

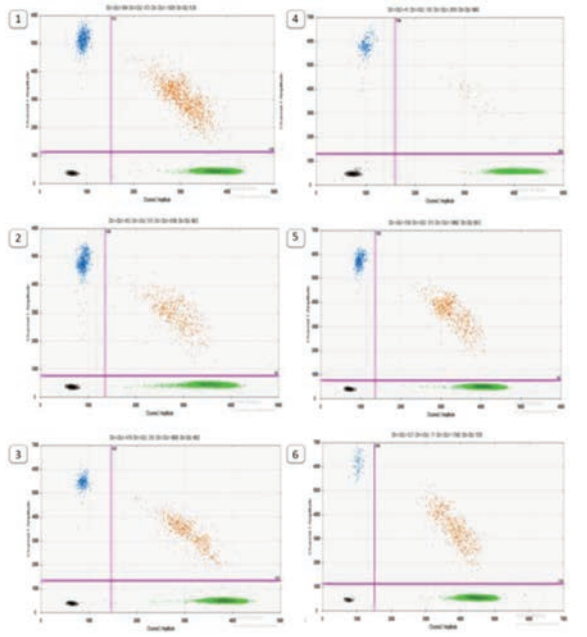

Figure 3. ddPCR.

P033

CLINICAL/IMMUNOHISTOCHEMICAL FEATURES AND PROGNOSTIC FACTORS OF CD5-POSITIVE LARGE B CELL LYMPHOMAS: A RETROSPECTIVE ANALYSIS

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Diffuse Large B cell lymphoma (DLBCL) is a heterogeneous entity. CD5 expression may identify a distinct subgroup of DLBCL with high risk characteristics and poor prognosis, whose clinical presentation and outcome are not well defined. We retrospectively collected data of all consecutive cases of adult patients > 18 years with CD5+ DLBCL diagnosed from 2010 to 2022 in two centers. Among 859 patients diagnosed with DLBCL, 41 (4.8%) were CD5+. At presentation, median age was 65 years (32-86), 24 (56%) patients were females. Twenty-six (63%) cases had stage III-IV, 36 (88%) presented extranodal disease, with gastric and central nervous system involvement in 5 and 1 case respectively.

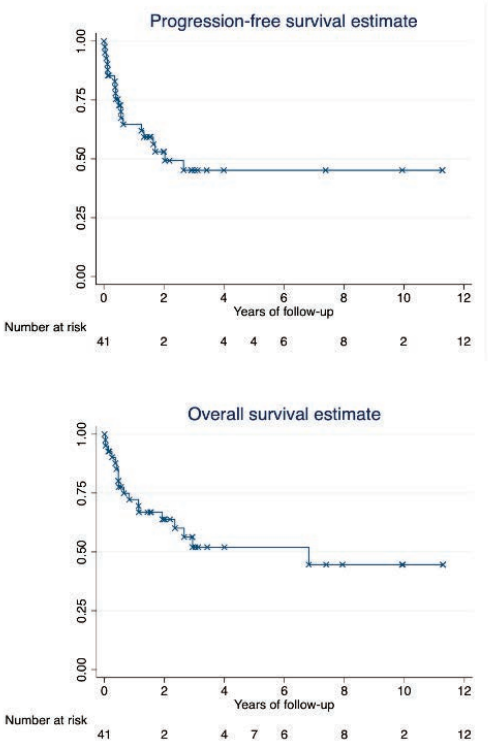

Figure 1.

Twenty-four patients (59%) had IPI 3-5. LDH and ß2microglobuline was elevated in 20 (80%) and 16 (64%) cases respectively. By immunohistochemistry, 14 (63%) patients had activated B-cell-like phenotype according to Hans algorithm, 28 (68%) expressed MUM1 and 29 (71%) BCL2 > 50% (among them 14/22 were double expressor with MYC>40%). P53 was detected in 7/14 (50%) cases, with a median expression of 20% (10-100%). One out of patients had rearranged BCL2 and MYC. DLBCL not otherwise specified (DLBCL-NOS) was the most frequent (63%) histology, followed by 13% transformed DLBCL, 7% post-transplant DLBCL, 6% leg-type, 5% EBV+, 2% high-grade, 2% primary testicular and 2% intravascular DLBCL. Thirty-two (78%) patients were treated with R-CHOP/R-CHOP-like regimen, 3 (7%) with intensified chemotherapy and 4 (10%) handled palliative. The overall response rate was 82% with complete remission (CR) in 74%. Regarding prognostic factors, in the univariate analysis, presence of gastric involvement (p=0,0015), advanced stage (p=0,04), high IPI (p=0,0017) and P53 expression (p=0,018) were associated with lower CR rate. Fourteen (34%) patients progressed/relapsed at a median time of 10 months (1-19), involving CNS in 2 cases. With a median follow-up of 2 years (0-11), 13 (56%) patients maintained CR while 13 (31%) died, among them 9 (70%) of lymphoma. Progression-free survival (PFS) and overall survival (OS) at 2 years were 54% (CI 95%, 37-69%) and 64% (CI 95%, 47-77%), respectively (Figure1). Our data confirmed that these patients presented with some aggressive features as extranodal disease and higher LDH. To date, a more heterogeneous histological subtypes emerged, with PFS and OS at 2 years lower than expected in DLBCL. Further comparison between CD5- and CD5+ DLBCL should be pursued.

P034

DIFFERENT MICROENVIRONMENTAL PATTERNS OF T-CELL INFILTRATION CAN IDENTIFY MANTLE CELL LYMPHOMA PATIENTS WITH DISTINCT CLINICAL OUTCOMES. RESULTS FROM A PILOT CLINICAL-PATHOLOGICAL STUDY

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Mantle Cell Lymphoma (MCL) has well-defined histological features associated with prognosis. Although intrinsic mechanisms of MCL pathogenesis have been elucidated, extrinsic mechanisms regulated by tumor microenvironment (TME) are less known. Investigation of crosstalk between MCL and TME is of preeminent importance to identify mechanisms of early relapse and improve treatment efficacy. Our objective was the histopathological evaluation of relapsed/refractory (R/R) MCL with focus on T-cells and histiocytes infiltration. Correlation between TME, lymphoma characteristics and outcome was attempted. This pilot study is part of the MANTLE-FIRST BIO study. Thirty-eight samples of 28 R/R MCL (22 at diagnosis, 16 at relapse) from 3 Italian centers were evaluated by a hemopathologists consensus group. Histopathological evaluation was performed on lymph nodes sections and included cell morphology, patterns of growth, expression of CD20, CD5, Cyclin D1, Sox11, Bcl2, p53, cMyc, IgM and Ki67 by immunohistochemistry. TME study included histiocytes infiltration by morphology and T-cells evaluation by CD3, CD4 and CD8 stains. Patients with avail-

able clinical data (N=11) were classified as early (N=5) or late (N=6) progressors by the 24 months threshold (Progression of Disease, POD). By comparing lymphoma samples at diagnosis and relapse, classic morphology and non-diffuse patterns of growth were most common in the first group. Samples at relapse were characterized by higher occurrence of diffuse cyclin D1 expression, higher Ki67 and histocytes infiltration and lower CD4/CD8 ratio. In the early-POD group the most represented pattern was diffuse; cyclin D1 was mostly diffuse; Ki67 and p53 were higher. In late-POD group, nodular, diffuse and combined patterns were equally represented; cyclin D1 was occasionally modulated, cMyc was higher. Bcl2 ad IgM were diffusely expressed in all cases. The histocytes score was similar in the two groups (1+ in most cases). Median CD3 infiltration was higher in early- than in late-POD and CD4/CD8 ratio was lower in early-POD, indicating a higher prevalence of CD8 cells in patients that relapsed earlier (Figure 1). Due to the pilot nature of the study differences were not statistically significant. Though, our results suggest that individual differences in TME can reflect clinical outcomes and therapy response thus highlighting a possible predictive significance of TME infiltration patterns in MCL. We thank FIL (PGR Ed.2019) for funding support.

A

Features/Markers	Status	Median (min-max) in early-POD [n=5]	N. (%) in early-POD [n=5]	Median (min-max) in late-POD [n=6]	N. (%) in late-POD [n=6]
Hstiocytes score	0		1 (20)		0 (0)
	1+		3 (60)		4 (67)
	2+		0 (0)		2 (33)
	3+		1 (20)		0 (0)
CD3 in neoplasia	%	15 (5-20)		9 (5-20)	
CD4/CD8 ratio x 100		33 (10-100)		100 (20-100)	
	10		1 (20)		0 (0)
	20-33		3 (60)		2 (33)
	100		1 (20)		4 (67)

B

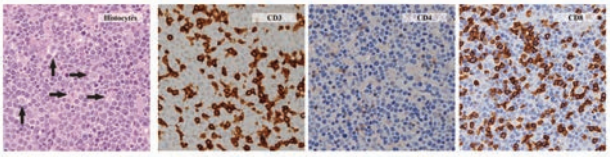

Figure 1.

P035

LIPOSOMAL DOXORUBICIN SUPERCHARGE-CONTAINING FRONT-LINE TREATMENT IN PATIENTS WITH ADVANCED-STAGE DIFFUSE LARGE B-CELL LYMPHOMA OR CLASSICAL HODGKIN LYMPHOMA: PRELIMINARY RESULTS OF A SINGLE-CENTRE PHASE II STUDY

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Myocet™ (NPLD) was suggested for the treatment of elderly or cardiopathic patients with DLBCL or c-HL, instead of hydroxydaunorubicin, constituting new regimens of R-COMP (Rituximab, cyclophosphamide, NPLD and vincristine) and MBVD (NPLD, bleomycin, vinblastine and dacarbazine) respectively. We designed a dose-intensified (DI) version of both R-COMP and MBVD scheme with a supercharge dose of NPLD (named R-COMP-DI and MBVD-DI). In this prospective study, patients with newly diagnosed advanced-stage DLBCL received 3 cycles of R-COMP-DI (NPLD at 70 mg/m^2) followed by 3 cycles of R-COMP (NPLD at standard dose of 50 mg/m^2), and patients with newly diagnosed advanced-stage c-HL received 2 cycles MBVD-DI (NPLD at 35 mg/m^2) followed by 4 cycles of NPLD at standard dose of 25 mg/m2. The primary end-point was the activity of this strategy in terms of interim-FDG-PET negativity (according to the Deauville scale [DS] 5-point scoring system). Secondary end-points were end-of-treatment (EoT) responses, toxicity (including cardiologic side-effects by using the echocardiography [ECG] assessment of global systolic longitudinal myocardial strain [GLS], as well as left ventricular ejection fraction [LVEF]), feasibility and Progression Free survival (PFS). In this phase II study (2016–2022), 92 adult patients, admitted to the Federico II Hematology Department, with advanced-stage DLBCL (n = 60) and c-HL (n = 32) were enrolled. Patients underwent R-COMP-DI and MBVD-DI with a median dose intensity of 91% and 94% respectively. At interim-FDG-PET, 81/92 patients (one failed to undergo i-FDG-PET due to early death) had a Deauville score of ≤3 reaching the primary end-point of the trial in terms of complete response incidence with a Complete Metabolic response rate significantly higher (89% [95% CI 83%–96%]; p = 0.0015) than the pre-specified minimum efficacy threshold. At end of treatment, 90% of patients reached complete responses. In all, 20 patients had Grade ≥3 adverse events, and four of them required hospitalization. According to the definition of cardiotoxicity for cancer treatment of ESC, there were very small changes, *i.e.* <10% point reductions in median values of GLS and LVEF at interim, EoT and 6-month follow-up, when they were compared with the median values at baseline. At a median 21-months of follow-up, the progression-free survival of the entire population was 77.3% (95% confidence interval 68%–88%). Our data suggest that the NPLD supercharge-driven strategy in high-risk DLBCL/c-HL may be a promising option to test in phase III trials, for improving negative interim-FDG-PET cases incidence.

Table 1.

Main efficacy results of liposomal doxorubicin supercharge-based front-line strategy for advanced-stage DLBCL or c-HL.

	Total	R-COMP-(DI)	MBVD-(DI)
Patients	92	60	32
At interim			
i-FDG-PET cases	91	59	32
Negative	82/91 (89) [82-95]	51/60 (85) [75-95]	31/32 (96) [89-100]
Positive	9 (10) [3-17]	8 (13) [4-22]	1 (4)
Not done	1 (1)	1 (2)	0
At the end-of-treatment			
EoT-FDG-PET cases	90	58	32
CR	82/91 (90) [83-96]	51/58 (87) [78-96]	31/32 (96) [89-100]
PR	2 (2.5)	1 (2)	1 (4)
PD	4 (5)	4 (8)	0
Not done	2 (2.5)	2 (4)	0

Data are reported as n (%) [CI%] if not indicated otherwise.

DLBCL: Diffuse large B-cell lymphoma; c-HL: Classic-Hodgkin lymphoma; R-COMP-(DI): Rituximab, Cyclophosphamide, MyocetTM, Vincristine and Prednisone (dose-intensified); MBVD-(DI): MyocetTM, Bleomycin, Vinblastine and Dacarbazine (dose-intensified); CI: Confidence interval; i-FDG-PET: interim-2-deoxy-2[F-18] fluoro-D-glucose positron emission tomography; EoT: end-of-treatment; CR: complete response; PD: disease progression; PR: partial response.

P036

EFFECTS OF IL6 ON DIFFERENTIATION OF MONOCYTES: UNDERSTANDING MYELOID DERIVED SUPPRESSOR CELLS IN DIFFUSE LARGE B CELL LYMPHOMA

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Background. Since the introduction of immunotherapy, the accuracy of IPI in predicting relapse of diffuse large B cell lymphoma

(DLBCL) has decreased. The tumor microenvironment may unveil new biomarkers to strengthen prognostic stratification. Myeloid derived suppressor cells (MDSCs) represent an immunosuppressive myeloid subpopulation, whose rate correlates with survival, disease stage, and IPI in DLBCL. Interleukin 6 (IL6) is a pleiotropic proinflammatory cytokine, elevated at first diagnosis of DLBCL and associated with poor prognosis. A role of IL6 in recruitment and activation of MDSCs was identified, but its role in their differentiation is unexplored.

Aims. Our experiment investigates the impact of IL-6 on differentiation of human monocytes into MDSCs *in vitro*.

Methods. We isolated CD14+ monocytes from the peripheral blood of ten healthy donors by plastic adhesion. We plated the monocytes in RPMI medium enriched with cytokines, namely GM-CSF or M-CSF (50 ng/ml), with or without IL6 (20 or 50 ng/ml) and incubated them for 6 days. Samples were analyzed by flow cytometry, defining MDSCs as CD14+ CD11b+ HLA-DR- cells.

Results. We found expected high rates of MDSCs in the peripheral blood of DLBCL patients at first diagnosis and even higher rates at relapse. Interestingly, MDSCs persisted after achieving complete remission, compared to healthy controls. IL6 was elevated in all disease phases including patients in complete remission which correlated positively with the levels of MDSCs (p=0.01). In our *in vitro* assay, GM-CSF stimulation induced 42% of MDSCs. Addition of IL6 to GM-CSF led to higher MDSC rate (59% with 20 ng/ml, p=0.004; 71% with 50 ng/ml, p=0.001), in a dose dependent manner (p=0.03). Likewise, for M-CSF stimulation, addition of IL6 increased the rate of MDSC from 25% with M-CSF alone to 56% with 20 ng/ml (p<0.0001) and 58% with 50 ng/ml (p<0.0001). Moreover, markers of macrophage polarization decreased. For GM-CSF stimulated cells, addition of IL-6 reduced classically activated macrophages (CD80+ CD86+) to 0.5-fold (p=0.005), whereas the rate of M-CSF stimulated alternatively macrophages (CD163+ CD206+) did not change significantly adding IL6 (p=0.2).

Conclusions. Our results suggest that the clinically found positive correlation of IL6 levels and higher MDSCs may be sufficiently explained by IL-6, which drives monocyte differentiation towards more HLA-DR low MDSCs. Next to more MDSCs, IL 6 also reduces proinflammatory macrophages.

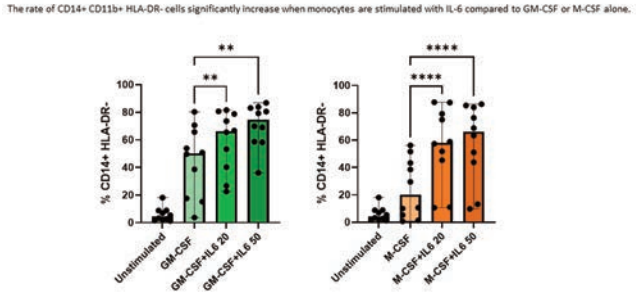

Figure 1.

P037

HISTOLOGICAL TRANSFORMATION FROM INDOLENT NON-FOLLICULAR LYMPHOMAS: REAL WORLD DATA FROM A SINGLE INSTITUTION

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Histological transformation (HT) can occur in the clinical course of indolent lymphomas. Most of the studies focus on follicular lymphoma (FL), and few data are reported in indolent non-follicular lymphomas (iNFLs). Aim of this study was to analyse the characteristics and outcome of the latter group of patients (pts) in order to define their best clinical approach and treatment. We retrospectively evaluated data collected from ward database and clinical documentations. Overall survival (OS) and progression free survival (PFS) were analysed using the Kaplan-Meier method; p-values <0.05 were considered statistically significant. Sixty-four pts with HT consecutively seen in our department between 1996 and 2021 were included: they had a previous nodal (NMZL, 13) or splenic (SMZL, 15) marginal zone lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma (19), lymphoplasmacytic lymphoma (LPL, 15), and 2 not otherwise specified (NOS) iNFLs. Median age was 68.5 (45-86) years; International Prognostic Index (IPI) was intermediate-high or high in 27 pts (42%).

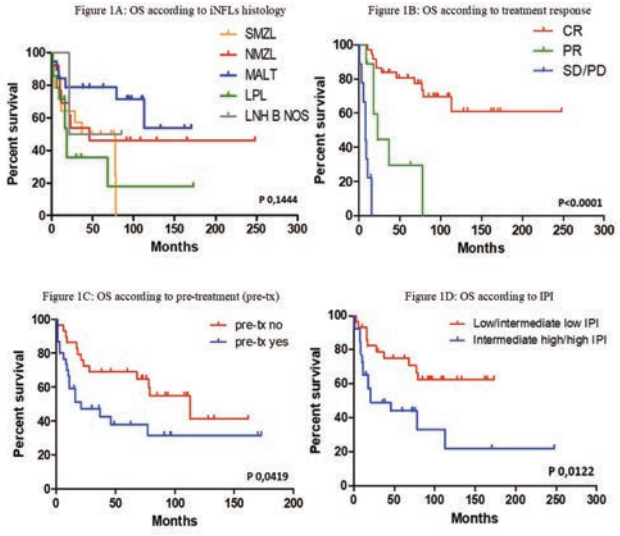

Figure 1.

Sixty pts were treated, while 4 died before treatment. Thirty-seven pts (54%) achieved complete remission (CR); 9 (16) partial remission (PR), 12 (18%) had stable or progressive disease (SD/PD) and 2 died before restaging. With a median follow-up of 42 (9-248) months, the median PFS and OS of the whole population were 20 and 37 months respectively. Different iNFL hystotypes had no significant impact on OS (Figure 1a), despite LPL showed a trend toward worst outcome. Thirty-tree pts (52%) died, most of theme (82%) for lymphoma-related causes, with a 3-year post-transformations survival rate of 59%. Patients achieving CR had a significantly better OS, with 82% oof pts being alive at 42 months from HT (Figure 1b). Previous treatment for iNFLs and IPI were significantly associated with worst outcome (Figure 1c, 1d). Different treatments (CHOP-like or platinum-based), autologous stem cell transplantation or transformation of disease after or before 24 months (TOD24) did not show any impact on sur-

vival. HT is a rare event that can occur in any hystotype of iNFLs. As for follicular lymphomas, the previous treatment was confirmed as unfavourable prognostic factor, while timing of transformations has no impact. A multicenter prospective study should be advisable to identify clinical and molecular risk factors for HT and to establish the best therapeutic approach.

P038

TUMOR MICROENVIRONMENT OF DIFFUSE LARGE B CELL LYMPHOMA IS ENRICHED OF EXTRACELLULAR VESICLES WITH THE POTENTIAL TO AFFECT TUMOR BIOLOGY

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Introduction. Diffuse Large B-cell lymphoma (DLBCL) is an aggressive malignancy of mature B lymphocytes. The tumor microenvironment (TME) surrounding cancer cells consists of immune cells, stromal cells, blood vessels and extracellular matrix. Mechanisms regulating the interactions between tumor cells and TME are partially understood. Extracellular vesicles (EVs) are cell-derived particles that play a central role in cell-cell communication within the TME. According to size and biogenesis, they can be subdivided into Small (S-; 30-200 nm) and Large (L-; 0.2-10 μm) EVs. However, the role of EVs within DLBCL TME is still unknown. Here, for the first time, we aimed to characterize circulating DLBCL S- and L-EVs.

Methods. Peripheral blood was collected from DLBCL patients at diagnosis and matched Healthy Donors (HD). S- and L-EVs were purified from platelet-free plasma by differential ultracentrifugation (20.000g for 20K L-EVs, and 100.000g for 100K S-EVs). Isolated EVs were characterized by tunable resistive pulse sensing analysis, transmission electron microscopy, western blot and MACSPlex Exosome Kit array.

Results. We found that circulating DLBCL and HD L- and S-EVs did not differ in morphology and size distribution and expressed EV markers as CD81, TSG101 and ARF6. However, DLBCL L-EVs were enriched with CD63 and B-cell markers CD19 and CD20. Also, L-EVs overexpressed CD69 lymphocyte activation marker which is involved in the regulation of adaptive immune response, including T-cell exhaustion. In L-EVs, we also found enrichment of the CD49e adhesion molecule, whose aberrant upregulation is implicated in various malignancies and correlated with poor prognosis. Notably, L-EVs showed increased expression of ROR-1 tumor-related marker, a prognostic marker for DLBCL survival that significantly promotes DLBCL tumorigenesis by regulating the PI3K/Akt/mTOR signaling pathway. No differences were observed when selected immune markers (CD1c, CD3, CD4, CD14, CD25, CD40, CD86) were investigated. Conversely, S-EVs showed reduced expression of CD20 and ROR-1.

Conclusions. These results indicate that DLBCL L- and S-EVs show a different phenotypic profile. Notably, even though to be confirmed in a larger casistic, these data demonstrate that circulating L-EVs from DLBCL patients express tumor-related markers with the potential to affect tumor aggressiveness.

Funding: Italian Ministry of Research's PhD scholarship (F.M.-University of Bologna), RC 22000388/RC-2022-2773276.

P039

CENTRAL NERVOUS SYSTEM RELAPSE IN DIFFUSE LARGE B-CELL LYMPHOMA AND ROLE OF CNS PROPHYLAXIS: A 10-YEARS SINGLE INSTITUTION EXPERIENCE

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Introduction. Central nervous system (CNS) relapse of diffuse large B-cell lymphoma (DLBCL) is a rare event, and correlates with a dismal prognosis. The usefulness of strategies that would avert CNS disease recurrence such as high-dose intravenous methotrexate (HD-MTX) and intrathecal prophylaxis (IT) is controversial. Our study focuses on pts with CNS relapse of DLBCL in order to evaluate their clinical and biological features, the validity of prognostic scores and the efficacy of CNS prophylaxis.

	HR	IC 95%	p-value
ECOG PS ≥ 2	3.41	1.07; 10.82	0.038
CNS-IPI ≥ 3	2.51	0.69; 9.09	0.161
Profilassi IT e/o EV	0.32	0.07; 1.51	0.149

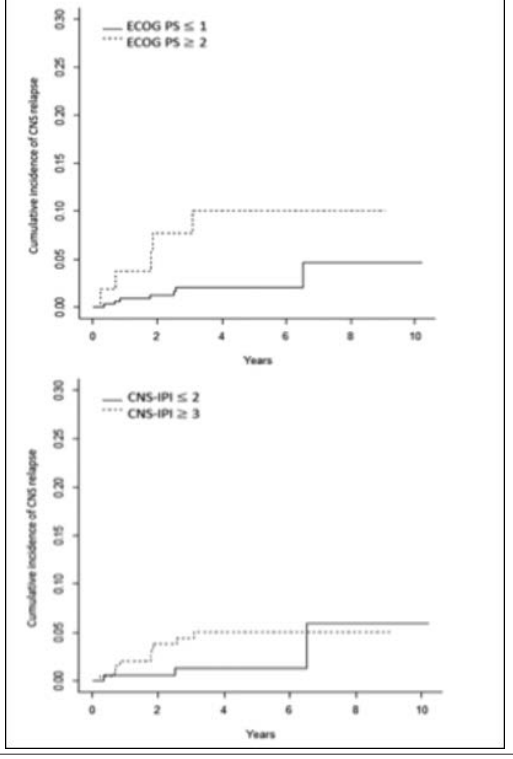

Figure 1.

Methods. All pts with DLBCL diagnosed between January 2010 and December 2021 at AOU Città della Salute e della Scienza di Torino and treated with curative intent were selected. Pts with primary mediastinal lymphoma, primary testicular lymphoma or CNS disease at diagnosis were excluded.

Results. The case series included 406 pts. Mean age was 67 years,

56/400 had ECOG PS ≥ 2 (14%), 231/400 elevated LDH (58%), 251/404 were stage IV (62%), 192/374 IPI score ≥ 3 (51%), 189/373 CNS-IPI 2-3 (51%), 91/373 CNS-IPI 4-6 (24%). 95/397 pts received CNS prophylaxis (24%): 59 by IT route only (15%) (26 CNS-IPI 2-3; 29 CNS-IPI 4-6), 25 by intravenous (iv) MTX only (6%) (17 HD-MTX ≥3 g/mq; 6 CNS-IPI 2-3; 16 CNS-IPI 4-6), and 11 by combined route (3%) (5 CNS-IPI 2-3, 6 CNS-IPI 3-6). 12 pts experienced CNS relapse (8 CNS only, 4 CNS + systemic recurrence). The cumulative incidence at 3 years was 2.8%. In univariate analysis, CNS relapse risk was significantly influenced by ECOG PS and elevated LDH levels but not by the use of CNS prophylaxis. However, none of the pts receiving iv MTX had subsequent CNS disease while 2/59 pts receiving exclusive IT had CNS relapse with an incidence superimposable to the whole cohort (3.3%). In multivariate analysis, only ECOG PS confirmed significant correlation with the risk of such disease recurrence (Figure 1). The 3-year overall survival for pts with SNC recurrence was 30%.

Conclusions. Data from our case series confirm the limited benefit of IT prophylaxis. Although a statistically significant benefit from the use of HD-MTX prophylaxis is not shown, probably due to the limited sample size and the number of overall events, the abandonment of this therapeutic strategy is not justified. Univariate and multivariate regression analyses agree in reporting that the CNS-IPI score is not always reliable. The identification of new predicting factors of CNS relapse may help in directing prophylactic strategies on a more selected very high-risk population.

P040

AUTOLOGOUS STEM CELL TRANSPLANTATION BEFORE LYMPHOCYTE APHERESIS FOR CAR-T CELLS THERAPY NEGATIVELY IMPACTS ON T-CELLS FITNESS IN DLBCL PATIENTS

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Background. Chimeric antigen receptor T (CAR-T) cells are an effective therapy in Diffuse large B-cell Lymphoma (DLBCL). However, more than half of patients (pts) still relapse. CAR-T cells from T-lymphocytes (T-Ly) enriched for early lineage T-cells have shown higher replicative potential and better efficacy. In the BioCART BS study, we assessed the T-cell subpopulations at Ly-apheresis evaluating the impact of previous treatments on T cells fitness.

Methods. Since April 2021, 37 pts underwent Ly-apheresis (25 DLBCL, 6 MCL, 5 PMBCL, and 1 ALL). DLBCL pts with poor prognostic risk factor (primary refractory; PET positivity before Autologous Stem Cell Transplantation [ASCT]; relapse within 12 months) were enrolled in a "pre-emptive" Ly-apheresis program, scheduling leukapheresis as soon as possible. Combinations of monoclonal antibodies were used by Flow Cytometry to evaluate the CD4+/CD8+ T-subsets: Naïve (CD45RA+CCR7+); Central Memory (CM, CD45RA-CCR7+); Effector Memory (EM, CD45RA-CCR7); Terminally Differentiated (TD, CD45RA+CCR7-). CAR-T cells expansion was evaluated using specific CD19 CAR reagent.

Results. 9 out of the 25 DLBCL pts underwent pre-emptive Ly-apheresis, while 16 were enrolled in the standard program, after at least two lines of treatment. The latter have been divided into 2 groups: pts who had received ASCT (n=10) and those who did not (n=6). Comparing T-cell subpopulations before Ly-apheresis, pts who underwent ASCT presented more "exhausted" T-Ly (Figure 1). They had lower CD4/CD8 ratio compared with pre-emptive or standard group without a history of ASCT, as well as lower CD4+ Naïve T cells and higher CD4+ EM T-Ly. They also had lower CD4+ CM T Ly compared with pre-emptive group. Conversely, pts who didn't receive ASCT had more "fit" T-Ly and this seems to impact on CAR-T cells expansion too. In fact, pts who didn't undergo ASCT (pre-emptive and standard group without ASCT) more frequently have adequate CAR-T cell expansion ("expander" pts: 76% *vs* 20%) and a higher percentage of CAR+ cells at the expansion peak (19.2% *vs* 3.1%, p 0.05). Notably, 5 out of 9 (56%) pts in the pre-emptive group had already activated a CAR-T cell program, showing its feasibility.

Conclusions. ASCT before Ly-apheresis results in more "exhausted" T-Ly profile at the time of leukapheresis. Timely pre-ASCT Ly-apheresis, as well as the use of CAR-T in second line would help to collect more "fit" Ly, and this may result in higher CAR-T cells expansion and efficacy.

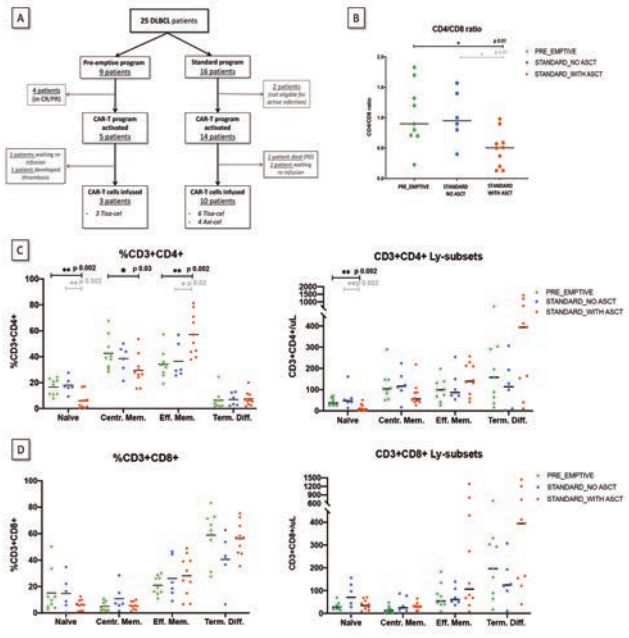

Figure 1: (A) Flow chart of patients enrolled in the Bio-CART BS study; (B) CD4+/CD8+ ratio in DLBCL pts enrolled in the pre-emptive Ly-apheresis group (green), or standard group with previous history of ASCT (red) or not (blue); (C) CD4+ T cells subset analysis; (D) CD8+ T cells subset analysis.

P041

THE ACCURACY OF CORE NEEDLE BIOPSY (CNB) IN THE DIAGNOSIS OF LYMPHPROLIFERATIVE DISORDERS: NEEDLE SIZE COULD MAKE THE DIFFERENCE

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Background. Surgical excision biopsy of the lymph node is still considered as the gold standard for histological diagnosis of suspect lymphoproliferative disorders, but recent current clinical practice has seen an increasing reliance on core needle biopsy (CNB). The aim of this study is to investigate the diagnostic accuracy of CNB and the impact on needle size on the diagnostic yield.

Methods and Materials. This is a unicentric retrospective study reporting data of patients referred to a tertiary centre for hematologic disorders with the suspect of a new or relapsing lymphoproliferative disorder. All the patients underwent image-guided CNB of the target lesion. The primary endpoint of the study was the diagnostic outcome (certain diagnosis according to international guidelines -including cytogenetic characterization- *vs* need for a subsequent excisional biopsy).

Fig.1 Proportion of diagnostic, not diagnostic and not trusted for diagnosis CNBs in cohort 1 (fig.1 A) and cohort 2 (fig. 2A)

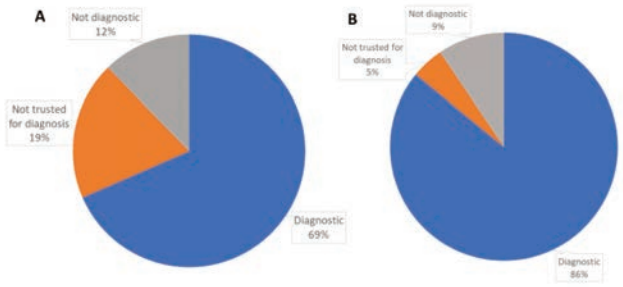

Figure 1.

Results. We enrolled 478 consecutive patients undergoing CNB, who were divided into two cohorts. The first included patients referred to our centre from January to December 2017 (130 patients); CNB was performed using 18-20G Menghini needles; the median dimension of the histological fragments was 1 cm, the CNBs in profound sites were 40 (30%). No complications occurred. The second included patients referred to our centre from October 2019 to April 2022 (348 patients); CNB was performed with 16-18G guillotine needles; the median dimension of the histological fragments was 1.5 cm, the CNBs in profound sites were 84 (24%). There were one grade 1 (according to CTCAE, 5.0.) complication and 3 grade 3 complications (0.8%), all conservatively managed. As for the diagnostic accuracy, in cohort 1 and 2 the rates of diagnostic and non diagnostic (*i.e.* requiring surgical excision) CNBs were, respectively, 89 (69%) *vs* 41 (31%) in cohort 1 and 299 (86%) *vs* 25 (14%) in cohort 2.

Conclusions. The type and the size of the needle used for CNB may affect its accuracy in the diagnosis of lymphoproliferative disorders. If properly optimized, since it safer and quicker to perform as compared to surgical lymph node excision, this technique could be beneficial in shortening the diagnostic/therapeutic *iter* of patients with a suspect lymphoproliferative disorder. In the authors' opinion, surgical excision would still need to be considered the first option in the case of suspect histologic transformation and should be required when the diagnosis offered by CNB is not coherent with the clinical presentation.

P042

ABSTRACT NOT PUBLISHABLE

P043

CLINICAL USE OF CORE NEEDLE BIOPSIES IN THE DIAGNOSIS OF LYMPHOMA: DIAGNOSTIC ACCURACY OF IMMUNOHISTOCHEMISTRY AND FLOW CYTOMETRY

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Histopathological diagnosis on excisional biopsies is a prerequisite for therapy in malignant lymphoma. Planning of surgical procedures may delay diagnostic work-up, and in case of deep lymphadenopathy invasive procedures may be associated with a higher morbidity. Image-guided core needle biopsy (CNB) has become an important tool in the diagnosis of superficial and deep masses and can frequently avoid the need for open biopsy. Velocity and lower invasiveness of CNB have to be weighted against accuracy of the diagnosis. To investigate the clinical usefulness of CNB and the contribution of flow cytometry (FC) to diagnostic work-up, we analysed immunohistochemistry (IHC) and FC results on 160 CNB performed for the suspect of lymphoma (106 ultrasound-guided for superficial lymph nodes and 54 CT-guided for deep masses, respectively) between September 2018 and February 2023. For FC analysis, cell suspensions were prepared by manual disaggregation and cells were incubated with two 8-color antibody combinations for B-cell and T-cell lymphoproliferative diseases (Kappa/CD45/ CD20/CD79b/ CD5/CD19/CD10/Lambda and CD3/CD45/CD7/CD30/CD5/CD8/ CD10/CD4) using FACSCanto (Becton Dickinson) or DXFlex (Beckman Coulter) cytometers. The proportion of samples that were not evaluable in IHC or FC were similar (8.75%, 14/160 and 14.3%, 23/160 respectively, p=0.15). This proportion was not different between superficial or deep biopsies (p=1). Histological diagnoses included 110 lymphomas, 14 reactive lymph nodes, and 10 solid tumors. Among lymphomas, 99 were B-NHL, 7 T-NHL and 4 HL. Diagnostic concordance between IHC and FC was 87.6% (128/146). Using FC, we identified a pathological B-cell cluster with either clonal restriction or absence of sIg light chain expression on mature B cells in 89.9% of B-NHL. An aberrant T cell population was observed in 57% of T-NHL. No aberrant cluster was identified in HL cases. A variable amount of CD45 negative cells with high cellular complexity was observed in metastatic carcinoma. The 14 biopsies of reactive lymph nodes showed polyclonal B cells. FC revealed a pathological clonal B-cell cluster in 3 cases that were not evaluable in IHC (a second biopsy confirmed a B-NHL in one case). We conclude that image-guided CNB performed for the suspect of lym-

phoma can provide diagnostic material in 91.2% of procedures, and that FC can be helpful to direct further diagnostic work-up with a short turnaround time.

P044

T CELL/HISTIOCYTE-RICH LARGE B-CELL LYMPHOMA: CLINICO-PATHOLOGICAL FEATURES AND RESPONSE TO IMMUNE CHECKPOINT INHIBITORS

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T-cell/histiocyte-rich large B-cell Lymphoma (THRLBCL) is an uncommon variant of diffuse large B cell lymphoma (DLBCL), characterized by extensive immune infiltrate composed of T-cells and histiocytes; these features excluded THRLBCL by most clinical trials with CarT-cell, creating a strong need for different salvage therapies in this DLBCL variant. We retrospectively reviewed all cases of DLBCL, NOS, treated with curative intent, who were diagnosed in our Institution between Jan 2010-Jan 2022, and we selected patients with THRLBCL morphological features.

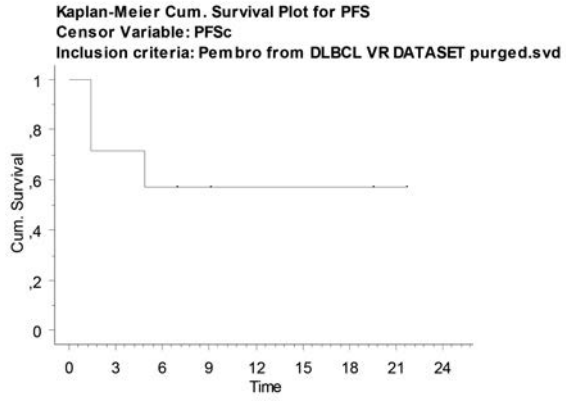

Figure 1. Progression-free survival of 7 patients with R/R THRLBCL treated with pembrolizumab.

Diagnostic specimens of THRLBCL were reviewed for the purpose of this study. Furthermore, we report of a pilot study conducted at our Institution on 7 patients with THRLBCL, that were relapsed or refractory (R/R) after more than 2 lines of conventional immunochemotheraphy, that were treated off-label with the immune check point inhibitor pembrolizumab. Of 324 patients with DLBCL, NOS diagnosed at our Institution between 2010 and 2022, 27 (8%) were THRLBCL. No difference between DLBCL, NOS and THRLBCL was observed in terms of clinical characteristics, type of induction therapy, rate of complete response (CR, 76% and 85%, respectively, p=0.13), progression-free survival (PFS, p=0.72), or overall survival (OS, p=0,20). Of note, THRLBCL were more frequently non-GCB by Hans algorithm (78% *vs* 47%, p=0.002), EBER+ (36% *vs* 4%, p<0.0001) and CD30+ (56% *vs* 22%, p=0.0007) than DLBCL, NOS. Seven patients with THRLBCL were treated with pembrolizumab 200 mg, every 3 weeks. All of them were R/R and had received a median of 2 prior therapies (2-5), and all had no available alternative therapeutic options. Median duration of treatment with pembrolizumab was 7 months (range 1-25). Overall response was 71% (all CR), with two patients that are still on active treatment. Median PFS was not reached (Figure 1). Only one patient who had achieved CR relapsed during treatment. Pembrolizumab was well tolerated overall, with only one patient that interrupted after 3 doses due to autoimmune hemolytic anemia. In conclusion, we report a monocentric series of patients affected by THRLBCL, showing that these patients have similar clinical characteristics of DLBCL, NOS. We also show, in a pilot setting, that patients with THRLBCL, who are not readily candidate to CarT-cell therapy, may benefit of treatment with checkpoint inhibitors.

P045

DIFFERENT GENOME-WIDE APPROACHES TO IDENTIFY MICRORNAS RELATED TO DLBCL RESISTANCE TO IMMUNE-CHEMOTHERAPY

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MicroRNAs (miRNA), small non-coding RNAs that regulate gene expression, are involved in various biological and pathological processes, including lymphomagenesis. Through interactions with signaling pathways, miRNAs modulate many cancer-related processes, such as drug resistance. MiRNAs are deregulated in many cancers including diffuse large B-cell lymphoma (DLBCL) and are easily detected in tumor tissue. They are also released in body fluids such as serum/plasma, where they circulate in a very stable form, thus representing interesting candidates as biomarkers. In this regard, we have previously identified serum miR-22 as a promising non-invasive prognostic biomarker significantly correlated with DLBCL patient progression free survival. Several molecular features have been associated with prognosis in DLBCL but they cannot entirely predict response to conventional treatment with R-CHOP, and some mechanisms underlying drug resistance still need to be clarified. Thus, to better understand the role of miRNAs in DLBCL response to treatment we performed: (i) a genome-wide miRNA profiling, by small-RNA Seq, in serum samples of DLBCL patients to identify miRNAs differentially expressed in R-CHOP refractory and responding subjects and (ii) a global loss-of-function screening, by using a miRNA specific CRISPR-Cas9 library, to study the miRNA role in response to treatment from a mechanistic point of view. From the serum miRNA profiling, among the circulating miRNAs significantly deregulated in samples of responding *vs* non-responding patients, we identified two miRNAs that showed also a functional involvement in DLBCL cell growth decreasing cell proliferation and viability thus suggesting a role as tumor suppressors. By an in silico target and pathway analysis we identified several genes as common target of these identified miRNAs, involved in DLBCL relevant pathways such as the Myc signaling. Lastly, to understand the role of miRNAs in the mechanisms underlying DLBCL response to treatment, we have produced cell models of DLBCL resistance to R-CHOP. A high-throughput functional screening on these in-vitro model led us to the identification of miRNAs potentially involved in drug resistance. Altogether our data may delineate miRNAs with a notable impact on DLBCL response to treatment offering also the possibility to translate these scientific findings into therapeutic interventions.

P046

ABSTRACT NOT PUBLISHABLE

P047

CAR-T CELL THERAPY FOR REFRACTORY LYMPHOMA AND SLE: A PROMISING BREAKTHROUGH

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Introduction. The chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of relapsed/refractory large B-cell lymphoma (R/R LBCL) and it is emerging as a novel therapeutic approach to treat autoimmune disorders as systemic lupus erythematosus (SLE). Based on the excellent results of two preclinical studies, Mackensen et al. showed in a small group of patients with highly pretreated SLE that all patients seroconverted after anti-CD19-CART-cell therapy, remaining in drug-free remission despite the subsequent B-cell reconstitution.

Case Presentation. We present a case of a 55-years-old female patient with a germinal center LBCL diagnosed at stage II-B in December 2019. The patient was concurrently affected by LES and antiphospholipid syndrome since 1994, complicated with pleuropericardits, recurrent episodes of deep vein thrombosis and chronic ischemic cardiomyopathy. At diagnosis the patient was on continuous treatment for SLE with hydroxychloroquine since 2008. She received R-CHOP and R-GDP and was refractory to both treatments. Due to severe heart failure, the patient was not eligible for a clinical trial or more intensive therapies such as allogeneic stem cell transplantation. Therefore she was candidate to anti-CD19 CAR-T cell therapy and received Axicabtagene ciloleucel infusion on December 1, 2020 with standard lymphodepletion chemotherapy based on fludarabine/cyclophosphamide. The patient presented a grade 1 cytokine release syndrome and grade 2 neurotoxicity requiring dexamethasone administration. PET/TC evaluation at 1 month showed a partial response that converted to a complete response at 6 months and persisted at 2 years evaluation. Regarding SLE follow-up, blood tests showed a normalization of complement factor and a significant decrease in the anticardiolipin and anti-beta-2-glycoprotein antibodies levels at 2 months after CAR-T cell infusion. At 12 months the patient showed a SLEDAI-2K score of 1 and at 16 months DORIS remission criteria was fulfilled. Therefore hydroxychloroquine was discontinued and a drug free remission was achieved.

Conclusions. Our case demonstrates not only the efficacy of CART cell therapy in R/R LBCL and but also endorses the idea that a complete regeneration of the immune system may be achievable with this "one-shot" therapy. Further efforts are necessary to establish the long-term efficacy of CART cell therapy for the treatment of SLE.

P048

TAFASITAMAB IN COMBINATION WITH METRONOMIC VINORELBINE OR ETOPOSIDE FOR THE TREATMENT OF AGGRESSIVE B-CELL LYMPHOMAS: A PRECLINICAL STUDY TO BUILD FUTURE CLINICAL TRIALS

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Introduction. Metronomic chemotherapy (mCHEMO) in treatment-naïve DLBCL, was recently reported to allow, an OS and DFS at 24 months of 56% and 74%, respectively. The aim of this study is to evaluate and enhance the activity of tafasitamab (TAFA), an anti-CD19 monoclonal antibody, in concomitant combination with metronomic vinorelbine (mVNR) and etoposide (mETO) on human DLBCL cells and in a mouse model.

Methods. Proliferation assays were performed on three human CD19+ DLBCL cell lines: Toledo, OCI-LY3 and SU-DHL10, exposed to a single dose of TAFA, mVNR thrice a week and daily mETO, alone and their concomitant combination for 144h. Synergism was evaluated by the combination index (CI) and the Loewe additivity model. Apoptosis assay was evaluated by ELISA at 48h. DLBCL subcutaneous xenograft and systemic tumor models were treated with TAFA, mVNR, and their concomitant combination.

Results. The 144h mETO exposure inhibited the Toledo, OCI-LY3 and SU-DHL10 cell proliferation in a concentration-dependent manner with an IC50 of 9.81±1.14 nM, 7.92±3.6 nM and 8.19±0.29 nM, respectively. A higher antiproliferative effect was found using mVNR on Toledo, OCI-LY3 and SU-DHL10 cell lines, as demonstrated by the calculated IC50s of 692±135 pM, 36±13 pM and 511±133 pM, respectively. The 144h TAFA exposure inhibited the Toledo, OCI-LY3 and SU-DHL10 cell proliferation with an IC50 of 1472±351 nM, 906.9±50.87 nM and 57.84±22.14 nM, respectively. In all cell lines, the concomitant treatment TAFA plus mVNR and mETO showed a marked synergism for all the fractions of affected cells (Fa) (CI<1 and DRI>1), except for TAFA + mETO on SU-DHL10 cell line. These findings were confirmed by Loewe analysis. A significant pro-apoptotic activity was found in all DLBCL cell-lines treated with TAFA alone for 48h, while the combination of TAFA with mVNR and mETO further enhanced apoptosis. In all three subcutaneous tumor models, the mVNR and TAFA combination significantly reduced the subcutaneous tumor volumes without causing significant toxicity and significantly increase the overall survival of mice affected by a systemic disease.

Conclusions. We report, for the first time, the synergistic activity of TAFA, with mVNR or mETO in DLBCL cells *in vitro* and *in vivo*. These results prompt a rapid translation of this combination schedule into future clinical trials.

P049

REAL LIFE CLINICAL OUTCOMES OF RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B CELL LYMPHOMAS IN THE RITUXIMAB ERA: THE STRIDER STUDY

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Relapse and refractory rates after first-line treatment with R-CHOP in diffuse large B cell lymphomas (DLBCL) are ~40% and ~15% respectively. The "STRIDER" ("strategies of treatment in diffuse large B cell lymphoma in the era of Rituximab") study is a retrospective analysis aimed at evaluating clinical outcomes of relapsed/refractory (R/R) DLBCL patients after first-line R-CHOP in a real-world setting. Between Jan. 2010 and Dec. 2019, 390 consecutive patients older than 18 years treated at 2 Tertiary Referral Centers (Division of Hematology – University of Torino, and Division of Hematology, Città della Salute e della Scienza – Torino, Italy), with a follow up of at least 12 months, were enrolled. At follow up, after first-line R-CHOP, 256 patients (63%) were still in first response, whereas 134 (33%) had either relapsed (no. 46, 11%) or were refractory (no. 88, 22%). After a median follow up of 50 months, OS at 5 years from diagnosis was 66%. Median OS for non relapsed-refractory (NRR) patients was not reached, and 243 NRR patients (95%) were still alive at last follow up. Median OS from diagnosis was 40 months for relapsed and 11 months (IQR 6-20) for refractory patients (Figure 1a). Median PFS was 20 months for relapsed and 6 months for refractory patients (Figure 1b). Salvage treatments consisted of platinum salts-based chemotherapy in 45/134 (33%), lenalidomide in 14 (10%); 43 (32%) received other treatments (no.34) or were enrolled in clinical trials (no.9). Only 6 (4%) underwent autografting and 32 (24%) underwent palliation. Median OS after second-line therapy was 11 (1-28) months for relapsed patients and 4 months for refractory patients (Figure 1c) while median second PFS was 10 months and 4 months respectively (Figure 1d). By univariate analysis, IPI score at diagnosis, age and response after R-CHOP were significantly associated with better OS and PFS (p<0,001). Baseline hemoglobin level > 10 g/dL showed a trend towards increased OS (p= 0.06), and a significantly better PFS (p=0.014). By multivariate analysis, response after R-CHOP was significantly associated with better OS and PFS. The STRIDER study confirmed very poor outcomes of R/R DLBCL in the rituximab era. The Italian Medical Agency recently approved CAR T Cells for the treatment of DLBCL after second relapse and/or 2 therapy lines, whereas bipecific antibodies largely remain investigational. Approval of these novel treatments as second-line is eagerly awaited to improve outcomes.

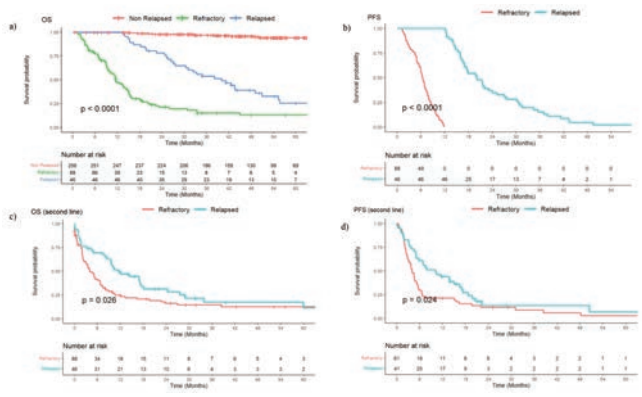

Figure 1. OS for NRR, relapsed and refractory patients (a) and PFS for relapsed and refractory patients. Median OS (c) and median PFS (d) for relapsed and refractory patients.

P050

OUTCOME OF RELAPSED/REFRACTORY B-CELL LYMPHOMAS TREATED IN PHASE I TRIALS: A SINGLE CENTER EXPERIENCE

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Background. Phase I trials usually enroll patient refractory to standard treatment in order to evaluate the toxicity, pharmacokinetic and preliminary efficacy of new therapeutic agents. However, in the last decade, the emergence of targeted and immuno-therapy has rapidly expanded the scope and eligibility of phase I trials towards efficacy assessment. This is particularly evident in B-cell non-Hodgkin lymphomas (NHL), were several new classes of drugs proved substantial efficacy in the relapsed/refractory (R/R) setting. Aim of this study is to review the outcome of patients (pts) with B-cell NHL enrolled in phase I trial at ASST Papa Giovanni XXIII Hospital of Bergamo, Italy.

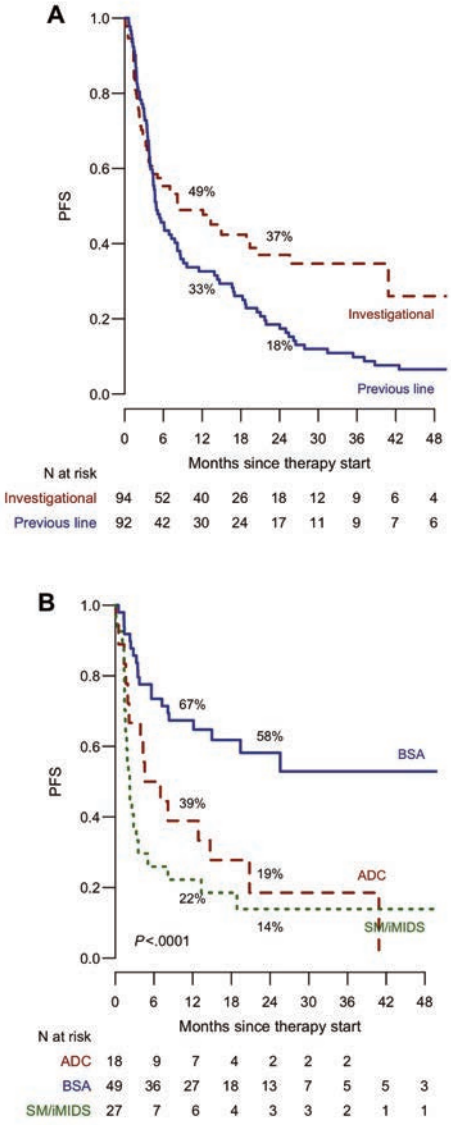

Figure 1.

Methods. 94 R/R B-NHL pts were enrolled and treated in 11 phase I trials from September 2016 to May 2022. Investigational treatments were grouped according to the class of drug in T-cell engaging bispecific antibodies (BSA), antibody-drug conjugate (ADC), or small molecules/immunomodulatory agents (SM/iMIDS). Outcome was assessed in terms of PFS and OS after investigational treatment. Additionally, the PFS of the line of treatment prior to enrollment in phase I trial was reported.

Results. Pts population included 66 pts with aggressive NHL (DLBCL=53, MCL=3) and 28 pts with indolent NHL (FL=26, MZL=2). At enrollment, most of the pts were in advanced stage (78%) and with IPI or FLIPI >2 (67%). Median previous treatment lines were 3 (range 1-8) including 28% relapsed after autologous SCT and 9% after CD19-CAR-T cells. Most of the pts were primary refractory (62%) and/or refractory to the last line of treatment (57%). The PFS after last line of treatment (*i.e.* prior enrollment) was 33% and 18% at 12 and 24-months (Figure 1). Investigational treatment included BSA, SM/iMIDS and ADC in 52%, 29% and 19% of the pts, respectively. ORR and CR according to treatment was 59% (45%), 37% (22%) and 50% (11%) for BSA, SM/iMIDS and ADC, respectively. Twelve and 24-months PFS after investigational treatment was 49% and 37%. Pts treated with BSA showed a better PFS compared with ADC and SM/iMIDS (Figure 1). OS at 12 and 24 months after start of investigational treatment was 64% and 55%.

Conclusions. This study shows the improved outcome of pts with R/R B-cell NHL enrolled in phase I trials, with substantial response rates and durable disease control, mainly driven by the use of T-cell redirecting BSA. These results confirm the efficacy of innovative therapeutic agents that is emerging early in phase I trials.

P051

A RISK-ADAPTED STRATEGY TO SELECT AUTOLOGOUS OR ALLOGENEIC TRANSPLANT CONSOLIDATION IS EFFECTIVE IN MATURE T-CELL LYMPHOMA: A IEO SURVEY OVER THE LAST 26 YEARS

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Treatment consolidation with either autologous or allogeneic stem cell transplantation (ASCT or alloSCT) has been proposed in order to improve outcome in Mature T-cell lymphomas (MTCL), with no consensus on the optimal transplant strategy. In this study we retrospectively reviewed the outcome of MTCL patients treated at the European Institute of Oncology (IEO) since 1995, with the aim of determining the impact of different consolidation strategies adopted in clinical practice over time. Clinical data of MTCL pts treated at IEO from 1995 to 2021 were retrospectively reviewed. While in the first 2 decades (1995-2004 and 2005-2014) ASCT was increasingly used as first-line consolidation, starting from 2015 we introduced a risk-adapted strategy for transplant eligible pts ≤65 years, reserving ASCT consolidation only for pts in complete remission (CR) with no evidence of lymphoma contamination in the apheresis products. All patients achieving less than CR at the end of induction treatment (EOT), or with evidence of apheresis contamination underwent allo-SCT consolidation. Ninety-two MTCL pts were diagnosed and treated at IEO between 1995 to 2021 (Table 1). Median follow-up was 6.7 years (1-25). Excluding ALK pos ALCL, 55 transplant-eligible pts ≤65 years were considered, of whom 30 received transplant consolidation (23 ASCT, 7 allo-SCT). Response to induction therapy was a powerful outcome predictor (5-y OS 80% in CR pts *vs* 46% in PR pts *vs* 21% in non-responders, p=0.0032). Notably, the CR rate at the end of induction did not change significantly over time (30% *vs* 34% *vs* 43% in the 1st, 2nd and 3rd period respectively p=0.7); however in the 1st decade only 4 of 18 pts received transplant consolidation (ASCT in all cases) *vs* 13 of 23 pts in the 2nd decade (13 ASCT, with 1 tandem ASCT-alloSCT) *vs* 13 of 14 pts in the 3rd period (6 allo-SCT and 7 ASCT) (p<0.0001). The 5-year OS of pts treated in the 3rd period was significantly higher (63%) compared to the 1st (37%) and 2nd decade (46%) (p=0.04). Accordingly, while transplant consolidation considered per se did not improve OS compared to the sole observation, the risk-adapted consolidation strategy was associated with a superior outcome compared to either observation or ASCT consolidation given before 2015, with 5-y OS of 63% *vs* 36% *vs* 43% respectively (p=0.04 and 0.02).

In conclusion, these data suggest that a risk adapted first-line consolidation strategy including allo-SCT could improve outcome in MTCL.

Table 1.

Factor	N (%)
Sex	
Male	50 (54%)
Female	42 (46%)
MTCL subtype	
ALCL ALK pos	10 (11%)
ALCL ALK neg	19 (21%)
PTCL-NOS	49 (53%)
Other	14 (15%)
Age, median (range)	59 (18-82)
Transplant eligible	55 (60%)

Legend: MTCL, Mature T-cell lymphomas; ALCL ALK pos, Anaplastic Lymphoma Kinase (ALK)-positive; ALCL ALK neg, Anaplastic Lymphoma Kinase (ALK)-negative; PTCL-NOS, Peripheral T-cell Lymphoma not otherwise specified.

P052

CORRELATION OF PROGRAMMED DEATH LIGAND 1(PD-L1) EXPRESSION WITH HISTOLOGICAL GRADE ,STAGE , BCL2 TRANSLOCATION , METABOLIC TUMOR VOLUME (MTV) AND RESPONSE TO FIRST LINE THERAPY IN FOLLICULAR LYMPHOMAS (FL)

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We performed a retrospective study to evaluate the correlation between the expression of PD-L1 with clinical and genetic features, Metabolic Tumor Volume (MTV) and response to the first line of therapy in a group of consecutive patients affected by FL . From January 2014 to December 2019, we observed 43 cases of FL (20 female, median age 62 year [range 30-90]) with a median follow-up of 47 months (range 9-66) . Six patients with localized disease were treated with radiotherapy and 37 with rituximab associated with ciclophosphamide, doxorubicin, vincristine, and prednisone. 18fluorodeoxyglucose positron emission tomography (FDG-PET) was used for staging and MTV was calculated at diagnosis . MTV was defined as the volumetric sum of FDG positive metabolic volumes of lymphoma lesions after applying local SUV max thresholds of 28%. BCL2 translocation was determined by fluorescent in situ hybridization on nodal biopsy. Membranous PD-L1 immunoreactivity in neoplastic cells was evaluated using a three-tiered score established as

follows: score 0, no immunostaining; score 1, presence of immunostaining in neoplastic follicles, comparable for intensity and number of stained cells to lymphoid cells of hyperplastic follicles; score 2, presence of immunostaining in neoplastic follicles, at least double for intensity and number of stained cells compared to hyperplastic follicles; score 3, presence of intense and diffuse immunostaining in neoplastic follicles. In our cohort 24 biopsies over 43 (56%) were positive for PD- L1. In 17/24 (70%) biopsies, PD-L1 score was 1, and in 7/24 (30%) was 2 or 3.The patients with PD-L1 expression have statistically significant reduced presence of Bcl2 translocation, a prevalence of grade 3 histology , a lower MTV and an increased incidence of early clinical stage (stages I/II). There were no difference for sex, age, Follicular Lymphoma Prognostic Score (FLIPI). Twenty PD-L1 positive patients (83%) and 10 PD-L1 negative patients (53%) obtained a complete response after first line therapy ($p<0.05$) . The expression of PD-L1 seems to be significantly related to high histologic grade($P<0.01$). In PD-L1 positive patients the better response to the first line therapy may be related with the prevalence of early stages and a reduced MTV at the diagnosis. In conclusion, our data suggest that , grade III FLs have a more intense expression of PD-L1 and may be candidate to test efficacy of PD-L1 inhibitors.

Table 1.

		PD-L1 positive	PD-L1 negative	
Sex	male-female	13-11	10-9	P:ns
Age	>65-<65 years	7-17	11-8	P:ns
Bcl2 (FISH)	Positive -Negative	8-16	14-5	P<0.01
Grade	I/II- III	6-18	15-4	P<0.01
Stage	I/II - III/ IV	16-8	2-17	P<0.01
FLIPI	0/1 - 2/3	11-13	9-10	P:ns
MTV cm3	St I/II	181 (13-226)	282 (7-311)	P<0.05
MTV cm3	St III/IV	220 (66-575)	736 (47-2457)	P<0.01
Response to I line therapy	CR -PR	20-4	10-9	P<0.05
Death		4	2	P:ns

P053

ALTERED IMMUNE PHENOTYPE PERSISTS IN PATIENTS WITH DLBCL AFTER ACHIEVING COMPLETE REMISSION

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Introduction. Myeloid-derived suppressor cells (MDSC) are a myeloid subpopulation, integral to immunosuppression in the tumor microenviroment (TME). In diffuse large B cell lymphoma (DLBCL), high MDSCs correlate with stage and are associated with poor outcome. Despite the evolution of DLBCL treatment, the consequences of changes in the TME during active disease and in complete remission (CR) remain unclear.

Methods. We established a flow cytometry-based immunophenotype analysis of fresh blood samples to compare patients at first diagnosis DLBCL, cured from DLBCL, and healthy donors. To examine the immune status within the cured cohort after COVID-vaccination, T cell vaccine response following *in vitro* stimulation, Covid antibody titers, and serum cytokines were measured. To prove inhibitory properties of MDSCs, we performed T cell co-culture assays.

Results. At first diagnosis, patients displayed increased numbers of monocytic MDSCs compared with healthy donors. At CR, high MDSCs persisted and didn´t return to healthy levels. The increased rate of MDSCs was independent of therapy lines, Ann Arbor stage, or risk group (IPI). Classic serum chemokines associated with active disease were no longer elevated in complete remission. Furthermore, T cells of cured patients were significantly activated and senescent, which, together with elevated IL-6 levels resembles patterns of chronic inflammation. For patients that were COVID-vaccinated after cure from DLBCL, the amount of MDSCs correlated negatively with serum levels of Anti-Spike IgG. Additionally, their T cells were less responsive to specific stimulation with SARS-CoV2-peptides. Just as MDSCs in active disease, MDSCs from cured patients were able to suppress the proliferation of stimulated T cells.

Conclusions. Altogether, the presence of inhibitory myeloid cells and hyperactivated, senescent T cells, supports the conclusion of systemic immune dysfunction. Functionally, impaired vaccine responses indicate that DLBCL survivors are vulnerable to infection due to persisting alterations of immune cells. Despite the lasting immune changes being not directly lymphoma-dependent, their exact origin still remains unclear. To examine the universality of this phenomenon in cancer, we will establish a collaboration with the university hospital "A. Gemelli" in Rome to extend our measurements to other types of lymphoma.

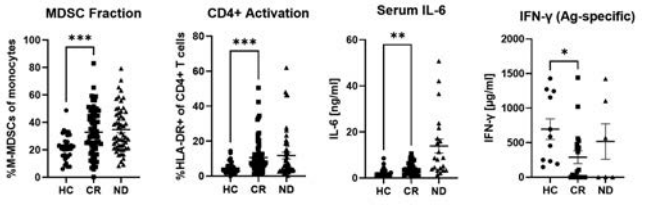

Figure 1.

P054

R-CODOX-M/IVAC-R IS A SAFE AND EFFECTIVE FRONTLINE THERAPY FOR BIOLOGICALLY UNFAVORABLE DLBCL

C. Salvetti[2], L. Manconi[1], F. Santoro[1], M. Schirru[1], L. Bianchi[1], G. Francia[1], E. Montanari[1], E. Fioribello[1], A. Incorvaia[1], C. Martelossi[1], A. Todiere[2], F. Guolo[1,2], F. Ballerini[2], R.M. Lemoli[1,2]

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Background. Diffuse Large B-cell Lymphoma (DLBCL) represents a challenging disease as only 60% of DLBCL can be cured with R-CHOP. R-CODOX-M/R-IVAC is an effective and manageable intensive chemotherapy which constitutes the preferred regimen for Burkitt's Lymphoma treatment. In this study, we aimed to identify subgroups of patients with DLBCL with aggressive biological features, including high risk of central nervous system (CNS) involvement, that may benefit from an intensified regimen.

Methods. 42 consecutive patients with DLBCL were treated in first line with R-CODOX-M/IVAC from 2008 to 2022. Treatment criteria were: eligibility for intensive chemotherapy, ECOG <3, histological diagnosis of DLBCL and at least one of the following unfavorable features: IPI score ≥4; Ki67>90%; non-GC type; MYC, BCL2 or BCL6 rearrangements identifying Double Hit (DH) or Triple Hit (TH) lymphomas; c-MYC and BCL2 over-expression, identifying Double Expressor Lymphoma (DEL). The median age was 52 years (range: 23-63) and the median FUP was 29 months. 22% of patients had IPI score ≥4, 71,4% of patients had a ki67>90%, 78,6% had Ann Arbor stage 4, 45% of patients had non-CG type lymphoma,23% had high risk CNS-IPI; 3 patients had DH/TH lymphoma; 4 patients had DEL; 3 patients had CNS involvement at the diagnosis.

Results. Toxicity was acceptable, with no G>3 renal impairment; 3 patients did not complete the planned therapy due to AEs. No therapy-related deaths occurred. The ORR was 95,2% (CRR 85.7%) and the 2-year OS and PFS were 78% and 70% (Figure 1A). No differences in 2-year OS were seen according to IPI score (65% *vs* 79% for IPI ≤3 or >3, p=n.s.), non-CG type (70% *vs* 85% for non-CG or GC type, p=n.s.), ki67 (72% *vs* 90% for patients with ki67>90% or lower, p=n.s.), DH/TH (68% *vs* 74.5% for DH/TH or non-DH/TH, p=n.s.), DEL (100% *vs* 63%, for DEL or non-DEL, p=n.s.). 2-year-OS was inferior for patients aged >55 (50% *vs* 89%, for age>55 or <55, p=0.001, figure 1B), while no differences were seen for patients aged >50 or <50 (70% *vs* 84%, p=n.s.). No CNS relapse occurred in patients without CNS localization at onset.

Conclusions. Our data show that R-CODOX-M/IVAC is effective and results in a very favorable CRR, OS and PFS, regardless of classical unfavorable prognostic features with manageable toxicity. Moreover, this regimen proved to be effective in preventing CNS relapse. In conclusion, R-CODOX-M/IVAC may be a good first line treatment for younger patients with aggressive DLBCL.

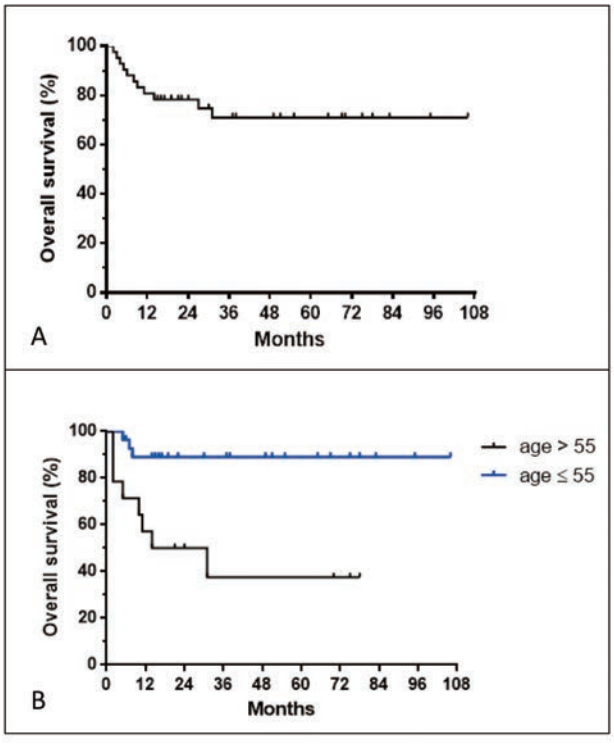

Figure 1.

P055

EXTRACELLULAR VESICLES AS POTENTIAL BIOMARKERS OF TOXICITIES AFTER CAR T-CELL INFUSIONS

B. Bruno[1,2], G. Lia[1,2], S. Bruno[3], A. Evangelista[4], A. Melis[1,2], G. Gabrielli[1,2], I. Dogliotti[1,2], C. De Philippis[5], D. Mannina[5], D. Taurino[5], B. Sarina[5], I. Mariotti[5], L. Giaccone[1,2], S. Bramanti[5]

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Introduction. Chimeric antigen receptor (CAR) T-cell therapy has shown very promising results in lymphoid malignancies. However, it is associated with peculiar toxicities that could limit their wide application. No validated biomarker has been identified to timely predict the onset of cytokine release syndrome (CRS) and neurotoxicity (NT). Potential attractive biomarkers may be represented by extracellular vesicles (EVs): exosomes (EXs), microvesicles (MVs), and, in particular, EVs of endothelial origin. The aim of this study was to investigate the immunophenotype changes of plasma EVs and their correlation with CAR T associated toxicities.

Methods. Twenty-seven patients with aggressive lymphomas treated with autologous anti-CD19 CAR T-cells after two lines of therapy according to the A.I.F.A. indications were studied. Plasma samples were collected at given time-points (before lymphodepletion, and at day 1, 3, 7, 10, 14, and 30 after CAR T-cell infusion). EVs were extracted by precipitation method and the expression of 37 EVs surface biomarkers (Figure 1) were characterized by flow-cytometry bead-based assay (Miltenyi Biotec). Biomarker expression was measured in total EXs, in total MVs, and in EVs of endothelial origin (End). The risk of developing CRS and/or NT was evaluated by multivariate logistic regression models.

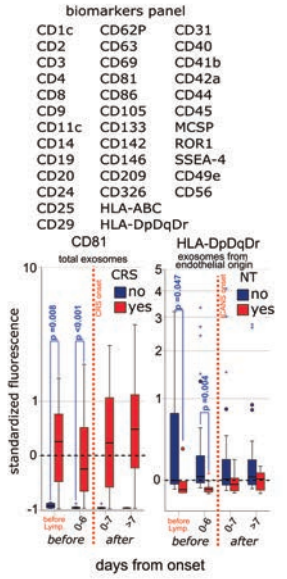

Figure1. Panel of 37 EV biomarkers used in the study. Standardized fluorescence of CD81 in total EXs at different time points before and after CRS onset in patient with (blue) and without (red) CRS. Standardized fluorescence of HLA-DpDqDr in End EXs at different time points before and after NT onset in patient with (red) and without (blue) NT.

Figure 1.

Results. CRS and NT were respectively observed in 23 and 6 patients at a median of day 3 (range 0-9) and day 5 (range 3-9). Grade III CRS and NT were observed in 1 and 2 patients respectively. Overall, 22/27 patients required tocilizumab. The most predictive biomarkers (AUROC >.950) associated with CRS onset included CD81, CD63 and CD69 in total EXs (OR >100 p .032, OR 2.377 p .039, and OR >100 p .001, respectively). CD2 in total MVs (OR 1.903 p .023), and HLA-DpDqDr in End EXs and SSEA4 in End MVs (OR .157 p .02, and OR .003 p <.001, respectively) were associated with the onset of ICANS. Pre-treatment levels of CD2 in total MVs in combination with expression levels of CD69 in End EXs and CD49e in MVs were the most predictive biomarkers for NT development post-CAR T infusion.

Conclusions. The increased level of exosomes agrees with the higher level of exosomal biomarkers expression (CD81 and CD63) stimulated by inflammatory stimuli observed in EVs from patient with CRS. Pre-treatment CD2, SSEA4 and HLA-DpDqDr are likely associated to the damage-repair process of blood-brain barrier. A prospective study has been designed to further confirm these observations.

P056

WALDENSTRÖM MACROGLOBULINEMIA IN THE VERY ELDERLY (OVER 75 YEAR-OLD): DESCRIPTION OF CLINICAL FEATURES AND SURVIVAL OUTCOMES IN A MONOCENTRIC CASE SERIES

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Background. Waldenström macroglobulinemia (WM) is a rare indolent non-Hodgkin lymphoma. Little is known on survival outcomes, causes of death and characteristics of patients ≥ 75 years old at diagnosis. Recently, an "inflammatory" variant of WM with worse survival outcomes has been described. Whether very elderly patients are more affected by the inflammatory WM form and what is their prevalent cause of death are open questions.

Aim. To describe clinical, biological and molecular features of two age-stratified subcohorts of WM patients and to evaluate the impact of various variables on OS and EFS outcomes in the very elderly.

Methods. We retrospectively collected data from WM patients (n=153) diagnosed between 1990-2022 at the Hematology Unit of Padua University Hospital, Italy. We compared two subcohorts distinct by age at diagnosis (≥ 75 *vs* < 75, n=33 *vs* n=120) with regards to WM-related characteristics, comorbidities and survival outcomes (OS, EFS). The impact of variables on survival outcomes in very elderly WM patient was studied with Cox proportional hazards regression model.

Results. The elderly patients subcohort displayed a higher frequency of renal dysfunction (p=0.05), a trend towards other malignancies (p=0.06), higher median values of monoclonal component (p=0.06), β2-microglobulin levels (p=0.04) and cytogenetic aberrations (p=0.0006) with lower median values of albumin (p=0.02). No differences were observed in terms of first-line therapy regimens adopted. Elderly patients displayed a higher rate of progressing disease and an inferior median EFS (not reached *vs* 166 months, p=0.02) and OS (79 *vs* 198 months, p=0.008) compared to the younger cohort (Figure 1). In univariate analysis we found no specific characteristics determining an inferior OS outcome in the very elderly. At variance, a worse EFS was associated with neuropathy (p=0.03), wild type MYD88 (p=0.03) elevated b2-microglobulin (p=0.02). Interestingly, the older subcohort was characterized also by a trend towards having lower levels of serum albumin (p=0.09) and elevated CRP blood concentrations (p=0.06).

Conclusions. This work suggests that some inflammation-related WM features (CRP, albumin, neuropathy) may impact on EFS in very elderly WM patients. However, we have not found any WM-related or unrelated features determining a worse OS outcome. Likely, the main causes of death in the very elderly WM patients subgroup are due to other comorbidities that deserve further analysis.

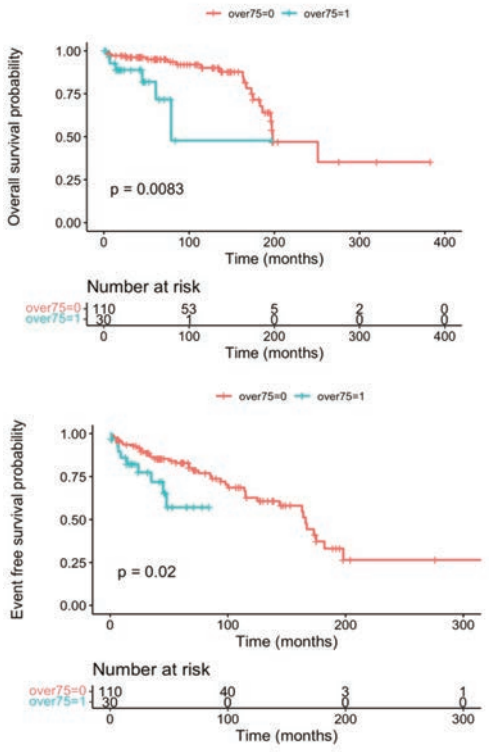

Figure 1.

P057

EFFICACY AND SAFETY OF INTENSIFIED FIRST-LINE THERAPY WITH B-ALL/NHL 2002 GMALL REGIMEN IN HIGH-GRADE B-CELL LYMPHOMA WITH GENOMIC ALTERATIONS OF MYC, BCL2 AND/OR BCL6

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High-grade B-cell lymphoma (HGBCL) with rearrangements MYC and BCL2 and/or BCL6, known as double-hit lymphoma (DHL), are clinically aggressive neoplasms with a poor prognosis. HGBCL with coexistence of rearrangements and amplifications/copy gains of MYC, BCL2 and/or BCL6 are defined as atypical double hit lymphoma (aDHL) and have similar outcome. Less is known on the prognosis of HGBCL with isolated MYC rearrangements, de-

fined as single hit lymphoma (SHL). DHL, aDHL, and SHL are often treated with aggressive induction regimens, however the optimal treatment is still undefined. Here we report our experience with the B-ALL/NHL 2002 GMALL regimen. 28 HGBCL with MYC BCL2 and BCL6 abnormalities confirmed by FISH analysis were treated with the B-ALL/NHL 2002 GMALL protocol at 2 italian Institutions from 2012 to 2023. 16 pts had DHL, 6 aDH and 6 SHL. All pts were treatment-naïve. Median age was 60y (range 43-77); 17 pts were male (61%); 22 had stage IV and 9 had bone marrow (BM) involvement. Pts received a median of 6 courses (range 2-6). Median follow-up was 50 months (range 6-87). The most common adverse event was hematological toxicity grade (G) 3-4: 11 (39%) pts had G3 anemia and 11 had G3-4 thrombocytopenia; 22 (79%) had G4 neutropenia, and 5 (19%) developed febrile neutropenia with 1 treatment-related death (pneumonia). 5 (19%) pts required dose reduction due to gastrointestinal toxicity G2-4. In the DHL/aDHL group 15 (68%) pts achieved a complete metabolic response (CR) at the end of treatment (EOT), 2 (9%) had partial response (PR). 5 (23%) DHL/aDHL pts were primary refractory: 4 died of disease progression, 1 is on salvage therapy. Among the 15 pts in CR, 6 (40%) relapsed and 4 responded to salvage treatment. All SHL pts obtained CR at EOT, only 1 relapsed. In DHL/aDHL, 3-y PFS and OS rates were 43% and 71%. Interestingly BM involvement emerged as a powerful outcome predictor, with 3-y PFS of 14% *vs* 58% (p=.0.0028) and 3-y OS of 22% *vs* 92% (p=0.0048) in pts with or without BM involvement respectively. In the SHL group, 3-y PFS and OS rates were 75% and 100%. With the limits of the small sample size our data suggest that B-ALL/NHL 2002 GMALL regimen has an acceptable safety profile, with excellent outcome in SHL and DHL/aDHL without BM involvement. ASCT consolidation could be considered in pts achieving CR, and early shift to alternative strategies such as CAR-T cell therapy should be considered in DHL/aDHL patients with BM involvement.

P058

LYMPHOCYTE RECOVERY AFTER BENDAMUSTINE THERAPY IN PATIENTS WITH MANTLE CELL LYMPHOMA (MCL). RESULTS OF A RETROSPECTIVE ANALYSIS

L. Donzelli[1], M. Antonacci[1], N. Zhdanovskaya[1], L. Petrucci[1], M. Di Palma[1], M. Martelli[1], A. Di Rocco[1]

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Background. Bendamustine in combination with rituximab (BR) or with rituximab and cytarabine (R-BAC) is the standard first-line immunochemotherapy in MCL for elderly pts (>65 years) or pts ineligible for intensive regimens or autologous transplantation. Bendamustine is known to cause prolonged lymphopenia, but there is a lack of evidence in literature about its persistence in MCL pts. This retrospective analysis is aimed at estimating the time of lymphocyte recovery, also in view of potential CAR-T cell immunotherapy.

Methods. Data were collected from 44 pts who received bendamustine (BR or R-BAC) as first-line therapy at our center between May 2011 and April 2022. Pts received bendamustine at 70 mg/mq/day or 90 mg/mq/day for 2 consecutive days every 28 days for up to 6 treatment cycles, depending on response and toxicity. Only 2 pts received rituximab maintenance. We analyzed their peripheral blood lymphocytes before, during and after bendamustine treatment.

Results. The median age at diagnosis was 72 years (range: 56-85), 75% pts were ≥65 years, 66% were male, 73% had advanced disease. BR was administered to 24 pts (55%) and R-BAC to 20 pts (45%). The median number of bendamustine cycles was 6 (range: 1-6) and the median cumulative dose was 840 mg/mq (range: 140-1080 mg/mq). The median follow-up period was 32 months. Before the 12-month follow-up, 10 pts died. At baseline, the median lymphocyte count was 1795/µl (range: 370-11730/µl). One month after the end of therapy it was 450/µl (range: 50-3300/µl; grade 3 adverse event according to CTCAE v5.0) and 3 months after 768/µl (range: 260-1650/µl; grade 2). After 6 and 9 months we observed a gradual increase in median lymphocyte count of 900/µl (range: 370-2560/µl and 130-2770/µl, respectively). After 12 months median lymphocyte count was 1256/µl (range: 240-4140/µl) (Figure 1).

Conclusions. The recovery of lymphocyte in our pts occurred 12 months after the completion of chemotherapy. This raises the question on the role of bendamustine before CAR-T cell therapy, which is indicated without age limits for the treatment of relapsed or refractory MCL after two lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor. Considering the key role played by lymphocytes in CAR-T cell therapy and that BTK inhibitor does not impact on lymphocytes, our data collected in first-line therapy are intriguing, although they need to be confirmed in larger datasets and by analyzing CD4-positive T-cell count.

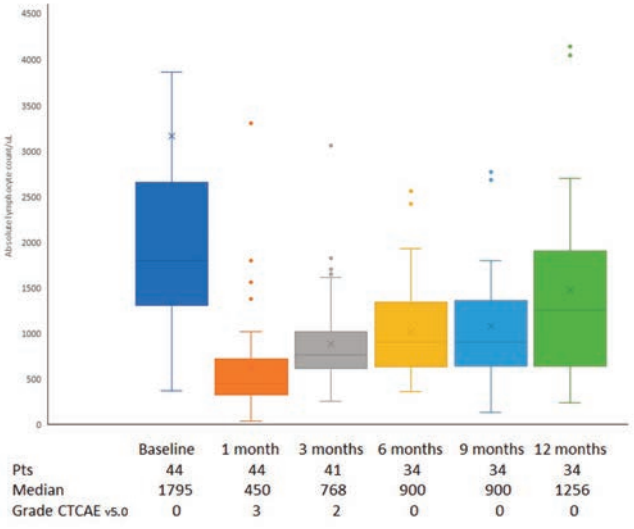

Figure 1.

P059

LONG-TERM FOLLOW UP IN A MONOCENTRIC RETROSPECTIVE FOLLICULAR LYMPHOMA (FL) COHORT: CHANGES IN PATIENT CLINICAL APPROACH AND OUTCOMES

R. Murru[1], C. Chessa[2], A. Galitzia[2], V. Oggianu[1], M.P. Simula[1], D. Dessì[1], S. Usai[1], S. Oppi[1], B. Mola[2], O. Mulas[1,2], G. Caocci[1,2], G. La Nasa[1,2]

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Background. Follicular lymphoma (FL) is characterized by considerable biological and clinical heterogeneity, with a recurrent course and potential aggressive evolution. Despite FL usually responds to therapies, it requires long-term management of patient (pts) throughout life course.

Aims. We sought to determine biological and clinical characteristics, treatment choices, and outcomes in a monocentric FL cohort with long-term follow-up (FU).

Methods. We retrospectively analyzed 340 unselected FL pts diagnosed at our institution between 01/1985 and 12/2022.

Biological and clinical characteristic (>65yrs, stage, grade, FLIPI, LDH, B2M, bulky, extranodal, ECOG, CIRS>6, lines of therapy, MoAb, maintenance, infection, POD24) were analyzed for their impact on OS and PFS.

Results. 54% (181) were female, median age at diagnosis 62 yrs (range: 19-94). Stage I- II was defined in 171 pts (52%), III-IV in 160 (48%) with bulky disease(GELF criteria) in 48 pts (15%). FLIPI score was 0-1 in 49% (133), 2 in 25% (68), ≥ 3 in 26% (72). At the time of the last FU (04/2023), 79% (266) of pts received at least 1 therapy (range: 0-5). After a median FU of 5.6 yrs (range: 0.15-36), the median OS was 33.7 yrs for the entire cohort. In univariate analysis, lower OS was associated with age>65 (p<0.0001), stage (p=0.002), BM involvement (p=0.008), FLIPI (p<0.0001), FLIPI-2 (p<0.0001), bulky (p=0.02), CIRS>6 (p=0.0007), ECOG>1 (p<0.0001), POD24 (p<0.0001), secondary malignancies (p<0.0001). Regarding upfront CIT *vs* RT, we found a statistical advantage in pts receiving RT +/- MoAb for OS (p=0.0002). Age (p=0.001), FLIPI-2 (p=0.03), POD24 (p<0.0001), secondary malignancies (p<0.0001) retained their unfavorable impact on the outcome in multivariate analysis. PFS at 24 months was 98% in patients receiving maintenance therapy *vs* 89% in pts not receiving maintenance therapy (p=0.03). The median PFS was 210 mos. Predictive factors affecting PFS in univariate analysis were BM involvement, FLIPI, male gender, B symptoms, stage. Next, we focused on potential risk factors for solid tumors diagnosed during the disease (16%, 44) and found no association between age, gender, stage, POD24, CIT, G-CSF. Infections, including COVID -19, were the most frequently reported cause of death in our cohort (17%).

Conclusions. Careful judgement of the need of treatment and proper modality of therapy are the cornerstones to influence the natural course of FL and to prolong life expectancy despite recurrent disease.

P060

THE ROLE OF PET IN PATIENTS WITH HISTOLOGICALLY CONFIRMED RECURRENCE OF AGGRESSIVE LYMPHOMA FOLLOWING CAR-T THERAPY

M. Palazzo[1], B. Puccini[2], E. Abenavoli[3], I. Cutini[4], C. Nozzoli[4], R. Boncompagni[4], A. Gozzini[4], L. Nassi[2], G. Simontacchi[5], R. Santi[6], M. Ciceri[1], B. Sordi[1,9], L. Mannelli[7], A. Fabbri[8], V. Berti[3], A.M. Vannucchi[1,2,9], R. Saccardi[4]

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Introduction. 18F-FDG PET (PET) is the imaging reference tool used to assess chimeric antigen receptor T-cell (CAR-T) therapy response in aggressive non-Hodgkin lymphoma (NHL) patients (pts). This study investigates whether specific PET features may identify pts at high risk for relapse after CAR-T.

Methods. We retrospectively analysed data of 15 NHL pts who received CAR-T at our Institution from 2020 to 2022. Baseline and after 1 month (M1) PET were centrally revised. All pts suspected for CAR-T failure with Deauville score (DS)>3 underwent targeted lesion biopsy. Kaplan-meier log-rank test was performed to assess M1 metabolic parameters together with DS impact on progression free survival (PFS) and overall survival (OS), defined as the time from CAR-T infusion to histologically confirmed relapse and death, respectively.

Results. Among all pts, 13 were affected by diffuse large B-cell lymphoma and 2 by transformation from follicular lymphoma. Median age was 66 years. Most pts received 2 prior therapy lines, except for one heavily pretreated with 5 lines. Axi-cel was infused in 12 pts, tisa-cel in 3. Before infusion, 13 pts received bridging therapy: 5 radiotherapy and 8 chemotherapy. Response was assessed according to Lugano criteria: at M1, 8 pts showed DS≤3, of which 6 maintained a response, while two DS3 pts progressed to DS4 and DS5. Relapse was histologically confirmed in all but one pts, who showed inflammatory infiltration and is still in remission. At a median follow□up of 17 months, 9 pts relapsed, 10 pts are alive, 5 died of disease progression, with an estimated median PFS and OS of 9 and 14 months, respectively. Among metabolic parameters, DS value and variation of maximum standardized uptake value (ΔSUVmax) between M1 and baseline significantly predicted PFS and OS (p<0.05). Dividing pts according to DS, survival curves showed that DS3 pts behave similar to DS4-5 (Figure 1). Although this data has not reached statistical significance, probably due to small sample size, in order better

stratify DS3 pts, we performed a subanalysis using ΔSUVmax: pts with DS1-2 and DS3 with decreased ΔSUVmax had a similar PFS, while DS4-5 pts and DS3 pts with increased ΔSUVmax had a poorer outcome (p=0.04).

Conclusions. With the limitations of a retrospective monocentric analysis, our study shows that DS correlates with survival but does not substitute the need of histological confirmation of relapse, which may also be useful to tailor therapy after CAR-T failure.

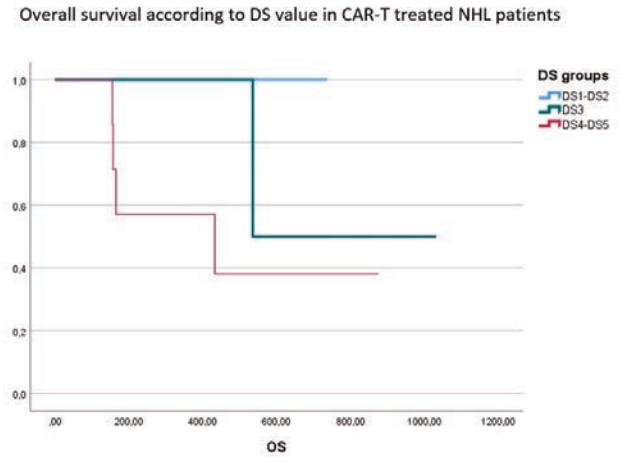

Figure 1.

Myeloproliferative neoplasms

P061

NEXT GENERATION SEQUENCING FOR DEFINIG THE BASELINE CLINICAL PHENOTYPE OF PH- MYELOPROLIFERATIVE NEOPLASMS

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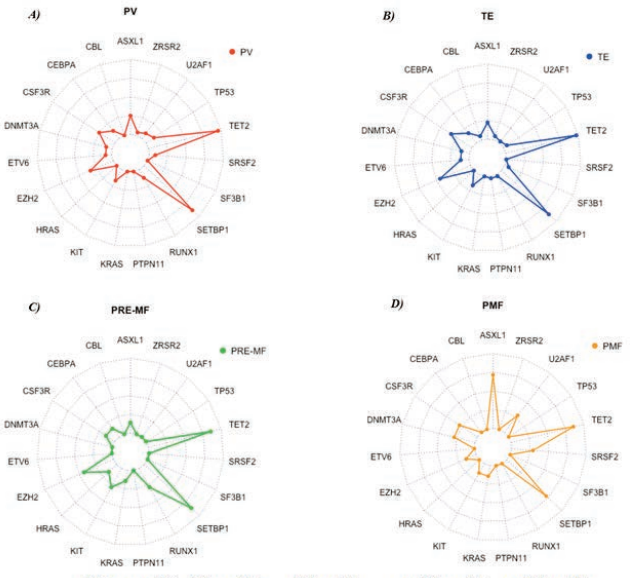
In the era of NGS, the molecular status of Ph- MPN patients is becoming more relevant for clinical and prognostic implications. We studied the performance of a 30-genes panel in defining the baseline features of MPNs and prognosis. The NGS panel was "Myeloid Solution" of Sophia Genetics v5.3.1. Our cohort included patients who received MPN diagnosis between 2017 and 2022 in our center. We described the distribution of mutations and the association of each gene with the following variables at baseline: age, splenomegaly, previous thrombotic events, CBC, LDH, peripheral CD34+ count. We also explored the association between each gene and post-ET and post-PV myelofibrosis. Our cohort included 101 patients, 63 males and 38 females. The most frequent diagnosis was ET (50%), followed by PV (33%), preMF (9%) and MF (8%). Median age was 57 (17-82), but MF had higher median age (70; 56-82).

JAK2 V617F was the most frequent driver mutation (78%), followed by CALR type I (10%), CALR type II (4%), MPL (2%) and JAK2 exon 12 (2%).

*Distribution of non-driver mutations in **A)** PV, **B)** ET, **C)** preMF and **D)** MF and all significative differences among subgroups.*



	MF vs. preMF	MF vs. PV	MF vs. ET	preMF vs. ET	preMF vs PV
ASXL1	p 0,02	p < 0.001	p < 0.001	Not significative	Not significative
U2AF1	p 0,05	p < 0.001	p < 0.001	Not significative	Not significative
RUNX1	Not significative	Not significative	Not significative	p 0.01	Not significative
HRAS	Not significative	Not significative	Not significative	p 0.02	Not significative
KRAS	Not significative	p 0.05	p 0.02	p 0.01	p 0.04

Figure 1.

We found 273 mutations in non-driver genes: 3 genes (TET2, SETB1, EZH2) were mutated in more than 10% of patients, while other 3 genes (CSF3R, ASXL1 and cKIT) were mutated in more than 5% of patients. The median number of mutations per patient was 3 (0-7), but MF patients harbored more mutations: 50% of patients with MF had ≥ 4 mutations *vs* PV 18.2%, ET 23.5% and preMF 22.2% (p 0.0034). The distribution of non-driver mutations can be seen in Figure 1. ASXL1 mutations were associated with lower Hb (p 0.01) and older age (median 65 *vs* 53, p 0,006), even if MF patients were excluded (age p 0.03 and Hb p 0.04). U2AF1 mutations were associated with post-ET and post-PV MF (p 0.01), higher LDH (median U/L 498 *vs* 316, p 0.01), more circulating CD34+ cells (0.25% *vs* 0.03%, p 0.03). RUNX1 mutations were associated with higher WBC count (median x10^3/mm^3 12.5 *vs* 8.9, p 0.02), particularly neutrophils (median x10^3/mm^3 10.2 *vs* 6.3, p 0.006), and advanced age (median 68 *vs* 55, p 0.04). cKIT mutations were associated with splenomegaly (p 0.05) and higher LDH (median U/L 404 *vs* 314, p 0.04). CEBPA was the only gene associated with thrombotic events: 25% of patients with previous thrombosis had CEBPA mutations (p 0.02). NGS testing is increasing in routine practice and promises to improve the accuracy and efficiency of pathological diagnosis and prognosis. Additional studies would be needed to assess the role of these genes in defining MPN phenotypes.

P062

CLINICAL IMPACT OF NUTRITIONAL STATUS AND NUTRITIONAL MONITORING IN PRIMARY MYELOFIBROSIS PATIENTS: PRELIMINARY RESULTS OF NUTRIMY STUDY

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Primary myelofibrosis (PMF) is a myeloproliferative neoplasm characterized by stem cell-derived clonal proliferation (often associated with driver mutations JAK2, CALR or MPL) and fibrosis on bone marrow biopsy. PMF clinical manifestations responsible of a poor quality of life include splenomegaly and anemia, that with an inflammatory cytokine status, induce constitutional symptoms. This condition leads often to an unintentional weight loss. For this reason, studies exploring the influence of dietary factors in this setting of patients (pts) are required, although they have not been performed yet.

Table 1.

	CONUT[1]	NRS-2002[1]	BMI[1]	BCM[1,2]	FFM[1]	FM[1]	PhA[1]	TBW/FFM[1]
Hb > 11 g/dl (12/30 pts)	2 (0-5)	2,5 (2-4)	24,55 (19,2-41,6)	M 15,1 (9-27,3) F 12,35 (3,9-14,7)	30,65 (23,4-53,1)	12,1 (3,6-34,7)	4,5 (2,4-6,8)	73,75 (73,4-90)
Hb < 11 g/dl (18/30 pts)	3 (0-4)	3 (3-5)	23,2 (18,3-27,8)	M 13,9 (11,3-20,7) F 12,2 (10,8-17,3)	31,5 (20,4-39,9)	8,5 (5,7-17,6)	4,3 (1,9-5,6)	76,2 (72,7-83,7)
Spleen length[3] < 5 cm (13/30 pts)	2 (0-5)	3 (2-5)	21,8 (18,3-41,7)	M 16,5 (11,3-27,7) F 13,7 (3,9-14,7)	30,4 (20,4-53,1)	10,7 (3,6-25,9)	4,8 (1,9-6,8)	73 (72,7-85,5)
Spleen length[3] > 5 cm (17/30 pts)	3 (0-4)	3 (2-4)	24,8 (19,2-31,6)	M 14,5 (13,1-20,7) F 11,8 (10,4-17,3)	32,85 (23,6-39,9)	9,9 (5,7-16,7)	4,5 (3,7-5,6)	74,4 (73,4-82,8)
Favourable[4] DIPSS (22/30 pts)	2,5 (0-5)	3 (2-5)	24,45 (18,3-41,6)	M 14,5 (9-27,7) F 12,9 (3,9-14,7)	30,65 (20,4-53,1)	11,1 (3,6-25,9)	4,5 (1,9-6,8)	73,85 (72,7-90)
Unfavourable[5] DIPSS (8/30 pts)	3 (0-4)	3,5 (2-4)	23,95 (19,2-41,7)	M 14 (11,3-20,7) F 12 (10,4-17,3)	30,95 (23,6-39,9)	8,9 (7,6-34,7)	4,3 (3,5-5,6)	76,15 (73,4-85,5)

1. Median value
2. Suddivided in Male (M) and Female (F)
3. From costal margin
4. Low and Intermediate 1 DIPSS
5. Intermediate 2 and High DIPSS

The aim of prospective NUTRIMY study is two-fold: first, to evaluate dietary as part of an all-round assessment of PMF pts; second, to assess the Controlling Nutritional Status (CONUT) and Nutritional Risk Screening (NRS) 2002 score as a prognostic marker in this setting. At baseline pts are assessed for patient-specific and disease-specific items, including the Dynamic International Prognostic Scoring System (DIPSS). Additionally, NRS-2002 score and CONUT score are collected to predict malnutrition. Nutritional status monitoring is performed at baseline and every 3 months by a dedicated dietitian using physical/anthropometric parameters (Body Mass Index, BMI) and bioimpedance analysis, including calculation of Fat Free Mass (FFM), Fat Mass (FM), Body Cell Mass Index (BCM), Phase Angle (PhA) and the ratio of Total Body Water (TBW) to FFM. Up to now, a total of 30 PMF pts (13 female and 17 male) with a median age of 71,5 (45-93) years have been enrolled. At baseline, 18/30 pts suffer from marked anemia (hemoglobin, Hb <11 g/dl), 17/30 pts show massive splenomegaly (palpable spleen length >5 cm from costal margin), and 22/30 pts present DIPSS low or intermediate 1 risk and 8/30 pts DIPSS intermediate 2 or high risk (HR). Nutritional risk at enrollment, expressed by NRS-2002 score and CONUT score, resulted (≥3) in HR categories (marked anemia, massive splenomegaly and unfavourable DIPSS). All the results of nutritional screening tools and bioimpedance analysis performed at baseline are summarized in Table 1. Preliminary results showed that malnutrition and inadequate nutritional status are a common event in PMF pts, especially in those with more severe disease. This could play a crucial role on the wellness of PMF pts as well as on the clinical outcome. Patients accrual is ongoing and a multicenter study, involving several Italian institutions, is in the plan.

P063

AIPSS-MF AND RR6 IDENTIFY MORE ACCURATELY THE PROGNOSIS IN A SETTING OF PATIENTS WITH MYELOFIBROSIS AND TREATED WITH RUXOLITINIB DURING FOLLOW-UP THAN COMMON PROGNOSTIC SCORE

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Introduction. In myelofibrosis (MF), new model scores are continuously proposed to improve the ability to better identify patients with worst outcomes. In this context, the Artificial Intelligence Prognostic Scoring System for Myelofibrosis (AIPSS-MF), based on machine learning, at diagnosis, and the Response to Ruxolitinib after six months (RR6) during the ruxolitinib (RUX) treatment, could play a pivotal role in stratifying these patients.

Material and Methods. This retrospective observational report aimed to validate AIPSS-MF in patients with MF who started RUX treatment, compared to the standard prognostic (IPSS and MYSEC-PM) and the RR6 scores, considering the possible difficulties existing in collecting genetic data available, especially in small centers. Our cohort was based on 103 adult patients affected by MF and treated with RUX during the follow-up. The discriminative capacity of the models was evaluated with out-of-bag estimates of the concordance index (C-index). The precision of the AIPSS-MF score was assessed using cross-validated time-dependent areas under the curve (AUCs) and evaluated in four different time points (2.5, 5, 7.5, and 10 years) derived from Cox survival models.

Results. At diagnosis, in the whole cohort, the AIPSS-MF performs better than the widely used and recognized IPSS (Figure 1A). Splitting patients into PMF and SMF, the AIPSS-MF model confirms its superiority versus IPSS for patients with PMF (C-index 0.636 versus 0.596). We assist in a model failure in the SMF setting due to the

small sample size. However, the AIPSS-MF model, compared to MYSEC-PM, maintains a better ability to predict OS at diagnosis On the other hand, the analyses performed 6 months after RUX therapy started confirmed the leading role of RR6 in predicting an inadequate response by these patients to JAKi therapy. The RR6 model achieved a higher AUC at all evaluated times points compared with the AIPSS-MF, reaching a superimposable rate for both models at 10 years (Figure 1B). The 2.5 and 5-year AUCs of the RR6 model were 75.30% and 77.53%, compared to 60.42% and 54.17% of AIPSS-MF. The C-index confirmed the superiority of RR6 (0.682 versus 0.571).

Conclusion. Based on these findings, the new AIPSS-MF prognostic score confirms that it can adequately stratify this subgroup of patients already at diagnosis better than standard models. Moreover, as expected, RR6 confirmed its superiority built to identify poor responders to RUX.

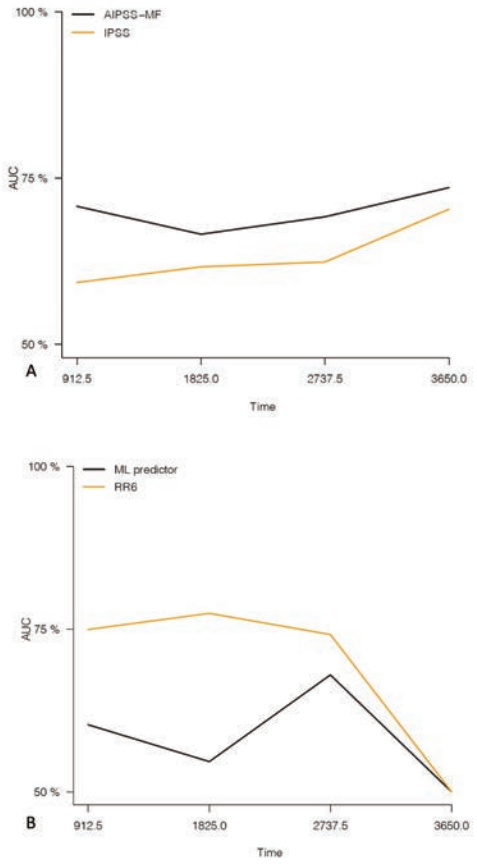

Figure 1.

P064

ABSTRACT NOT PUBLISHABLE

P065

CIRCULATING POLYMORPHONUCLEAR (PMN)- MYELOID-DERIVED SUPPRESSOR CELLS (PMN-MDSCS) ARE STRONGLY CORRELATED WITH DISEASE SEVERITY IN PATIENTS WITH PRIMARY MYELOFIBROSIS (PMF)

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Background. MDSCs are immature myeloid cells that accumulate in patients with malignancies, sepsis or chronic inflammation and are conventionally divided in polymorphonuclear (PMN)- and monocytic (M)-MDSCs. These cells have to ability to reduce cytotoxic functions of T/NK cells and the potential to differentiate into endothelial cells favoring neoangiogenesis. PMF is characterized by clonal expansion of a hematopoietic stem cell, extramedullary hematopoiesis, bone marrow fibrosis, splenomegaly, neoangiogenesis and acquired somatic mutations (JAK2, CALR or MPL genes). Inflammation plays a relevant role in PMF pathogenesis, as proven by high levels of inflammatory cytokines with prognostic significance and by a state of chronic oxidative stress.

Aims. Characterize circulating MDSCs and assess their correlation with the disease progression.

Methods: PBMCs from PMF patients (n=40) and healthy subjects (HDs; n=10) were stained with surface/intracellular markers and analysed by flow cytometry. The statistical analysis was performed using Statistica softyware.

Results. We found that circulating PMN-MDSCs (CD11b+CD15+ Lox1+Arg-1+) were higher (p=0) in PMF (regardeless to the mutational status) than in HDs and directly correlated with the allelic burden (R=0.67, p=0) in JAK2-mutated PMF. The expression of the CXCR4 on PMN-MDSCs was lower (p=ns) in PMF (median 0.7, range 0-10) than in HDs (median 5, range 0-57); besides, CXCR2 was lower (p=ns) on PMN-MDSCs of PMF (median 73, range 13-98) than in HDs (median 83 , range 65-89). Interestingly, PMN-MDSCs in PMF were directly correlated with age, disease duration, circulating CD34+, WBC, severity score and inversely correlated with hemoglobin, platelets count and %CXCR4 on CD34+ (Table 1). Cytokines/chemokines dosages and gene expression studies are ongoing.

Table 1.

	n	R	p
JAK2 allelic burden	26	0,67	0
Age	39	0,61	0
Disease duration	39	0,34	0,03
% CD34^{+}	39	0,49	0,001
CD34 absolute number/µl	38	0,60	0
WBC count (x10^{9}/L)	39	0,42	0,008
severity score*	39	0,44	0,004
Hb level (g/L)	39	-0,52	0
Platelet count (x10^{9}/L)	39	-0,49	0,001
% CXCR4^{+} (on gated CD34^{+})	39	-0,59	0

* defines the severity of PMF considering myeloproliferative and myelodepletive indexes of the disease
[Barosi G et al. Leuk Lymphoma 2002; 43:2301-7]

Conclusions. The increased number of PMN-MDSCs in PMF patients, compared to HDs, and their relation with the mutational status, suggest an involvement of this cell subset in PMF pathogenesis. Interestingly, the correlation between PMN-MDSCs and various clinical parameters suggests an important role of these cells in the disease worsening, likely related to the inflammatory status that characterizes PMF. Moreover, the low expression of CXCR4 on PMN-MDSCs could be, on one hand, related to the low expression of this receptor on CD34+ cells or suggest a PMF-specific recruitment mechanism (maybe CXCR2-related) other than that observed in solid tumors.

P066

SERUM FERRITIN AT DIAGNOSIS IS A PREDICTOR OF BONE MARROW FIBROSIS IN PH- CHRONIC MYELOPROLIFERATIVE NEOPLASMS

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Among hematologic malignancies, the Philadelphia-negative chronic myeloproliferative neoplasms (MPNs) are considered a model of inflammation-related cancer development. Serum ferritin can be considered a widely used surrogate inflammation marker. Here we described the distribution of *serum ferritin levels* (FER) at baseline among all four MPNs subgroups (ET, PV, preMF, MF) and the association of FER with bone marrow (BM) fibrosis, splenomegaly and both *driver* and *non-driver* mutations. Our cohort included 101 patients with no history of blood transfusions who received MPN diagnosis between 2017 and 2022 at AOU Federico II (IT) with the availability of a baseline NGS performed on peripheral blood or BM.

The NGS "myeloid panel" by Sophia Genetics included 30 genes. Splenomegaly was assessed by baseline ultrasound. BM fibrosis was evaluated at histological examination according to Thiele grading. Our cohort included 63 males and 38 females. The most frequent diagnosis was ET (50%), followed by PV (33%), preMF (9%) and MF (8%). Median age was 57 (17-82), but MF had higher median age at diagnosis (70, range 56-82). Median FER (ng/mL) at diagnosis were 27.5 in PV (4-336), 74.5 in ET (5-420), 202 in preMF (5-545) and 233 in MF (43-930). MF had higher FER compared to PV (p .004) and ET (p 0.01) and pre-MF compared to PV (p 0.005) and ET (p 0.02); there was no difference between MF and pre-MF (p 0.79). Higher FER were also associated with splenomegaly (median FER 140.4 for splenomegaly *vs* 76.6 for normal spleen volume, p 0.02) and ASXL1 mutations (median FER 170.5 for mutated *vs* 85.2 for unmutated, p 0.011); incidentally, ASXL1 mutations were more frequent in MF compared to PV (p<.001), ET (p<.001) and pre-MF (p 0.02). Furthermore, a linear correlation was observed between baseline ferritin and BM fibrosis grading (Table 1).

Table 1.

Serum ferritin levels at baseline according to bone marrow fibrosis

	Ferritin, median (ng/mL)	P-value
Fibrosis grade according to Thiele		
G0 (MF-0)	73,2	P < 0,001
G1 (MF-1)	162,9	
G2 (MF-2)	260,7	

In this study we reported increased FER in MF and preMF compared to PV and ET and the association between FER and splenomegaly, BM fibrosis and ASXL1 mutations. Low iron stores usage due to MF and preMF ineffective erythropoiesis could explain these data. However, ASXL1 gene is known for modifying TGF-ß expression: more studies are needed to clarify this association, but TGF-ß is a cytokine reported to be involved both in the BM fibrosis pathogenesis and in regulating the expression of epcidin mRNA, a regulator of iron metabolism. Therefore, the strong association found between FER and BM fibrosis could be explained by cytokine dysregulation.

P067

FEDRATINIB USE IN REAL-LIFE CLINICAL PRACTICE: A SINGLE-CENTER EXPERIENCE

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Background. Fedratinib (FEDR) has recently been approved for ruxolitinib (RUX)-resistant/intolerant and/or JAKi-naïve MF patients (pts). However, information on its use in a real-world setting is quite scarce.

Aims and Methods: To evaluate FEDR efficacy and safety profile in a real-life series of 13 MF pts who started treatment between July 2022 and February 2023.

Results. Main clinical-laboratory features of the pts are shown in Table 1.

Table 1. Clinical-laboratory characteristics of the patients.

	Patients n. 13
Male/female	8/5
Age at diagnosis (years), median (range)	72.1 (51.0 - 81.1)
MF subtype, n (%)	
- overt PMF	5 (38.5)
- SMF	8 (61.5)
- PPV-MF	7 (53.8)
- PET-MF	1 (7.7)
Driver gene mutations, n (%)	
- *JAK2V617F*	11 (84.6)
- *JAK2V617F* allele burden (%), median (range)	82.5 (14.3 – 98.0)
- *CALR type 1*	1 (7.7)
- *MPLW515L*	1 (7.7)
NGS (N = 7), n (%)	
Wild-type	2 (28.6)
TET2	4 (57.1)
DNMT3A	1 (14.3)
Cytogenetic abnormalities, n (%)	8 (61.5)
- unfavorable karyotype	3 (23.1)
Palpable splenomegaly at diagnosis, n (%)	13 (100.0)
- Spleen diameter (cm BCM), median (range)	10 (2 – 21)
Previous RUX treatment, n (%)	8 (61.5)
Reasons for RUX failure (N = 8), n (%)	
- primary resistance	1 (12.5)
- loss of response	6 (75.0)
- intolerance	1 (12.5)
Last RUX dose (mg BID) (N = 8), n (%)	
- 5	7 (87.5)
- 20	1 (12.5)
Age at FEDR start (years), median (range)	73.7 (59.9 – 88.0)
Time from MF diagnosis to FEDR start (months), median (range)	24.8 (1.4 – 116.0)
DIPSS model at FEDR start (N = 5), n (%)	
- Intermediate-2	5 (100.0)
MYSEC-PM model at FEDR start (N = 8), n (%)	
- Intermediate-2	2 (25.0)
- High	6 (75.0)
PLT count at FEDR start (x10^9/L), n (%)	
- 50 to <75	7 (53.8)
- 75 to <100	2 (15.4)
- ≥100	4 (30.8)
FEDR starting dose (mg/day), n (%)	
- 200	1 (7.7)
- 300	6 (46.1)
- 400	6 (46.1)
Baseline thiamine levels (mcg/L), median (range)	54 (31 – 126)
Follow-up from FEDR start (months), median (range)	3.8 (1.9 – 7.9)
FEDR dose reduction, n (%)	8 (61.5)
FEDR permanent discontinuation, n (%)	3 (23.1)
Last FEDR dose (mg/day) (N = 10), n (%)	
- 200	3 (30.0)
- 300	4 (40.0)
- 400	3 (30.0)

Abbreviations: PMF, primary myelofibrosis; SMF, secondary myelofibrosis; PPV-MF, post-PV myelofibrosis; PET-MF, post-ET myelofibrosis; NGS, next-generation sequencing; BCM, below left costal margin; RUX, ruxolitinib; FEDR, fedratinib; PLT, platelets.

8 pts had previously been treated with RUX for a median time of 36.2 months (mts), then suspended mainly for primary/secondary resistance and only in 1 case for intolerance. FEDR was started after a median time from MF diagnosis of 24.8 mts at an average dose of 338.5 mg/day: in detail, 400 mg/day in 6 pts and <400 mg/day in 7 pts, mainly due to pre-existing thrombocytopenia (in all pts) together with transfusion-dependent anemia (5/7 cases). After a median follow-up from FEDR start of 3.8 mts (range, 1.9–7.9), 3 pts permanently discontinued the drug, due to progressive splenomegaly and pancytopenia in 1 pt each, while in the remaining pt it was discontinued after post-traumatic splenectomy. Spleen measurements decreased progressively during the first mts of FEDR: specifically, the spleen was palpable at a median of 12 cm below left costal margin at FEDR start and 9 cm after 1 mts of therapy. Conversely, it increased only modestly to 10 cm after 2 and 3 mts. No pt suffered gastrointestinal (GI) toxicity using prophylactic antiemetics (implemented according to FREEDOM-2 study design) during the first few days; conversely, the most common non-hematological adverse event (AE) was increased creatinine in 4 pts: in all cases FEDR dose reduction was required, leading to renal function improvement. At FEDR initiation, median thiamine level was 54 mcg/L (normal range, 28–85); nevertheless, we decided to start vitamin supplementation in all pts and no case of Wernicke's encephalopathy was recorded. Thrombocytopenia was the most frequent hematological AE (6/13, all Grade 3 according to CTCAE), followed by anemia and neutropenia (2/13 each).

Conclusion. FEDR is effective in reducing splenomegaly and symptom burden in MF pts even in a real-life setting. In addition to GI and neurological AEs, clinicians should also be aware of its potential hematological toxicity (mainly thrombocytopenia), as well as other extra-hematological AEs, i.e., increased creatinine, particularly in an elderly population with comorbidities requiring concomitant medications.

P068

METABOLIC AND NUTRITIONAL EFFECTS OF RUXOLITINIB IN MYELOFIBROSIS PATIENTS

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Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by splenomegaly, cytopenias, bone marrow fibrosis, constitutional symptoms and cachexia, a multifactorial syndrome due to the loss of skeletal muscle and fat mass with detrimental consequences on quality of life, morbidity and mortality. The causative factors underlying cachexia in MF may include reduced nutritional intake due to massive splenomegaly and metabolic disturbances caused by proinflammatory cytokines such as IL-6 and TNF-α. Ruxolitinib (ruxo) treatment is associated both to clinical benefit in reducing splenomegaly, constitutional symptoms, and in improvement of cachexia (reduced proinflammatory cytokines levels with modification of metabolic parameters). Aim of the study is to explore metabolic and nutritional changes in patients with MF treated with ruxo. Malnutrition (GLIM criteria), anorexia (FAACT score) and body composition (BIA) were evaluated at baseline (T0), 3 months (T1), 6 months (T2) and 12 months (T3) from ruxo start. The MPN-SAF-TTS was administered to all patients. Response to ruxo was assessed using IWG-MRT criteria. We evaluated 23 MF patients treated with ruxo according to clinical practice and baseline platelet count, between May 2021 and April 2023. Median age at diagnosis was 64.7 years. At baseline unintentional weight loss, malnutrition and anorexia were present in 70%, 50% and 22% of patients, respectively, with a median BMI of 23.8. Ruxo treatment showed an improvement of anorexia score for all patients (p=0.0005) and for anorexic ones (T0 26.2±6.3; T1 37.6±6; T2 39.2±6.2) (p=0.01), body weight (kg) (T0 68.6±14.22; T2 71.8±15.2, T3 77.3±12.4, p=0.04), fat mass (kg) (from T0 15.8±5.8; to T2 20.3±8.11 and to T3 23.4±7.6, p=0.01) and with preservation of lean body mass (kg) (T0 52.8±12; T2 52.1±12.1; T3 54.3±12.4, p>0.05). In terms of response to ruxo, at last follow up, according to IWG-MRT criteria, 10 patients achieved both a symptoms and spleen response, with splenomegaly not palpable below the left costal margin, 1 a clinical improvement in terms of symptoms response, 9 a stable disease, 3 a progressive disease.

In conclusion, preliminary data show that ruxo may induce clinically significant improvement in nutritional status and body composition, in anorexia score and body weight, mainly due to increased fat mass and preservation of lean body mass, regardless response criteria.

Table 1.

	T0 N= 23	T1 N= 23	T2 N= 19	T3 N= 19
FAACT	33.8 ± 7.3	39.3 ± 4.5	39.9 ± 4.2	40.7 ± 4.1
Weight (Kg)	68.6 ± 14.22	79.8 ± 15.3	71.8 ± 15.2	77.3 ± 12.4
FM (Kg)	15.8 ± 5.8	17.7 ± 7.3	20.3 ± 8.11 (p=0.05)	23.4 ± 7.6 (p=0.01)
LBM (Kg)	52.8 ± 12	52.9 ± 12.1	52.1 ± 12.1	54.3 ± 12.4

P069

CLINICO-PATHOLOGICAL CHARACTERISTICS OF MYELOPROLIFERATIVE NEOPLASMS ASSOCIATED WITH UNUSUAL SITE THROMBOSIS: THE EXPERIENCE WITH 66 CONSECUTIVE CASES

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Unusual site thrombosis, including SVT and CVT usually are associated with presence of underlying myeloproliferative neoplasms (MPN). We conducted a retrospective cohort study with the aim of reviewing clinical characteristics, molecular features and outcome data in MPN in patients who have experienced an unusual site thrombosis. The current study constitutes the "Azienda Ospedaliera Universitaria delle Marche" and "Ospedale Santo Spirito -Pescara" experience with 66 consecutive cases of US-VTE in patients with MPN. Diagnosis of MPN was according to World Health Organization diagnostic criteria and CVT and SVT was confirmed in all cases by imaging studies.

Results. We identified 24.2% of PV, 31.8% of ET, 31.8% of MF, and 12.1% of MPN-U. Most cases (85.9%) carried JAK2V617F mutation, followed by CALR 9.4%, and MPL 3.1% (Table 1). The diagnosis of MPN was concomitant to thrombosis in 36 patients and median time from initial diagnosis of MPN to diagnosis of SVT was 5.6 years in the remaining 30 cases. Differences between these two groups were observed in terms of median platelet levels ($354x10^9$/L *vs* $461x10^9$/L, pV= 0.023); presence of splenomegaly (58.3% *vs* 86.7%, pV= 0.004); and presence of vascular risk factors including diabetes, hypertension, active smoke (47.2% *vs* 17.7%, pV= 0.009).

Most patients included in this analysis experienced SVT, followed by CVT in 22.7%. Initial treatment included systemic anticoagulation (SA) only in 7.6% of the patients and SA+cytoreductive drug in 92.6% of patients. All patients were reported to have received LMWH therapy followed by AVK therapy in the majority (68.1%) or by novel oral anticoagulants in 18% of cases. At a median follow up of 7.4 years, 10 deaths and 2 leukemic transformations were recorded. Post-US-VTE survival was significantly shorter in patients with MF, compared to those with PV or ET (pV = 0.0075, HR 5.4, 95% CI 1.4-12.6). Other significant risk factors for overall survival, in multivariable analysis, included older age (HR 4.2, 95% CI 1.6–12.5), splenomegaly (HR 1.6 95%, C.I. 1.1-2.3) and lower Hb level (HR 1.5, 95% CI 1.2–2.4). Recurrent thrombosis was reported in 12.1% of patients, including 3 (4.5%) with recurrent SVT.

In the current study, post-US-VTE survival in MPN was primarily influenced by the expected natural history of the underlying MPN rather than the SVT event, emphasizing the importance of proper risk-adapted management of MPN patients.

Table 1.

Table 1. Clinical and laboratory characteristics of 66 patients with myeloproliferative neoplasms (MPN) and unusual site thrombosis (US-VTE), stratified by type of MPN

Variables	All patients n=66	Myelofibrosis n=21	Polycythemia Vera n=16	Essential Thrombocythemia n=21	pValue
Age at diagnosis in years, median (range)	50 (11-80)	62 (28-80)	54 (19-71)	43 (11-65)	**0.001**
Age at thrombosis in years, median (range)	52.5 (16-82)	64 (28-82)	41.5 (17-81)	45 (23-77)	**0.004**
Male sex, n (%)	29 (43.9)	7 (33.3)	8 (50)	9 (42.8)	0.584
Type of thrombosis, n (%)					0.455
CVT	15 (22.7)	3 (14.3)	4 (25)	5 (23.8)	
SVT	51 (77.3)	18 (85.7)	12 (75)	16 (76.2)	
PVT	20 (30.3)				
PVT+MVT	9 (13.6)				
BCS± other SVT	6 (9.1)				
Other SVT	16 (24.2)				
Driver mutation, n (%)	N tot = 64	N tot=21	N tot = 16	N tot=19	
JAK2	55 (85.9)	16 (76.2)	16 (100)	16 (84.2)	0.085
CALR	6 (9.4)	2 (9.5)	0	3 (15.8)	
MPL	2 (3.1)	2 (9.5)	0		
Triple negative	1 (1.5)	1 (4.8)	0		
Karyotype, n (%)	N tot= 54	N tot=19	N tot =14	N tot= 16	
normal	48 (88.9)	15 (83.3)	14 (100)	15 (93.8)	0.374
abnormal	6 (11.1)	4 (16.7)		1 (6.2)	
Hemoglobin g/dl, median (range)					
at diagnosis	14.5 (8.6-49.5)	11.4 (8.6-18.6)	16.9 (13.8-20.5)	13.1 (9.2-15.8)	**<0.001**
at thrombosis	13.3 (8.5-18.6)	11.6 (8.8-18.6)	16.3 (11-18)	13.1 (9.2-15.8)	**< 0.001**
Leukocytes x 10*9/L, median (range)					
at diagnosis	7.67 (3-17.77)	6.21 (3.3-17.77)	10.84 (3-16.8)	7.05 (4.58-11.46)	**0.0231**
at thrombosis	9.18 (1.4-30.96)	7.75 (3.3-30.96)	10.80 (1.4-19.5)	8.54 (4.9-19.7)	0.922
Platelets x 10*9/L median (range)					
at diagnosis	362 (44-1384)	288 (44-661)	365 (164-828)	666 (388-1384)	**<0.001**
at thrombosis	361 (44-1632)	246 (44-661)	370 (164-800)	568 (263-1632)	**< 0.001**
Thrombosis concomitant to diagnosis, n (%)	36 (54.5)	13 (61.9)	9 (56.3)	9 (42.9)	0.606
Splenomegaly, n (%)	47 (71.2)	19 (90.1)	13 (81.2)	9 (42.9)	**0.025**
Hereditary thrombophilia, n (%)	N tot= 49	N tot= 14	N tot= 12	N tot= 16	0.263
	28 (57.1)	6 (42.9)	9 (75)	9 (56.3)	
Other vascular risk factors, n (%)	22 (33.3)	10 (47.6)	4 (25)	5 (23.8)	0.193
History of thrombosis, n (%)	9 (13.6)	4 (19.0)	2 (12.5)	2 (9.5)	0.801
arterial	4 (6.1)	1 (4.7)	1 (6.3)	1 (4.8)	
venous	5 (7.5)	3 (14.3)	1 (6.3)	1 (4.8)	
Management, n (%)					0.534
SA only	5 (7.6)	1 (4.7)	2 (12.5)	1 (4.7)	
SA+ cytoreduction	61 (92.6)	20 (95.3)	14 (87.5)	20 (95.3)	
Death, n (%)	10 (15.2)	6 (28.6)	1 (6.3)	3 (14.2)	0.175
Myelofibrosis evolution, n (%)	9 (13.6)	0	2 (12.5)	6 (28.6)	0.289
Leukemic transformation, n (%)	2 (3.0)	2 (9.5)	0	0	**0.019**
Recurrent thrombosis, n (%)	8 (12.1)	2 (9.5)	4 (25)	1 (4.7)	
arterial	2 (3.0)	0	1 (6.3)	1 (4.7)	0.195
venous	3 (4.5)	1 (4.7)	1 (6.3)	0	
SVT	3 (4.5)	1 (4.7)	2 (12.5)	0	

CVT: cerebral vein thrombosis; SVT: splanchnic vein thrombosis; PVT= portal vein thrombosis; MVT: mesenteric vein thrombosis; BCS: Budd Chiari syndrome; SA: systemic anticoagulation.

P070

THE -251A>T (RS4073) SINGLE NUCLEOTIDE POLYMORPHISM OF CXCL8 IS ASSOCIATED WITH THE SEVERITY OF THE FIBROTIC STAGE IN MYELOFIBROSIS

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Several pro-inflammatory cytokine/chemokine axes have been recently proved to contribute to the pathophysiology of myelofibrosis (MF), specifically: CCL2/CCR2, IL-1/IL-1R, CXCL8/CXCR-1/2 and IL-4/IL-13 axis) (Masselli 2021, Rahman 2022, Dunbar 2023, Melo-Cardenas 2022). Among them, CXCL8/CXCR-1/2 chemokine system is emerging as crucial determinant of MF phenotype, since: i) increased plasma levels were associated with reduced PMF survival (Tefferi 2011) ii) MF CD34+ cells are enriched in CXCL8/CXCR2 gene signature; iii) percentage of CXCL8-secretingCD34+ cells correlated with bone marrow fibrosis; iv) CXCR2 blockage ameliorates the fibrotic phenotype of MF mouse models (Dunbar 2023). The -251A>T (rs4073) single nucleotide polymorphism (SNP) of *CXCL8* has been extensively investigated in chronic inflammatory conditions, including cancer. The T allele is predominant in Caucasian population and accounts for higher production of CXCL8 (Paximadis 2021). We performed an allele-specific PCR to assess genotypic and allelic frequency of the rs4073 SNP on samples collected from 99 MF Caucasian patients (57.6% males, median age at diagnosis 68 yrs, range 29-84, median follow-up 8 yrs, of which 45 prePMF, 27 overtPMF, 27 sMF) and 309 matched healthy subjects. Genotype-phenotype correlations were performed according to a dominant genetic model (AT+TT *vs* AA). No significant differences in genotypic and allelic frequencies between MF and control were found. SNP genotyping on epithelial cells from buccal swabs in 9 MF harboring the T allele demonstrated that the SNP was germline. Focusing on MF, we found that both overtPMF and sMF patients were significantly enriched in polymorphic genotypes (25/27, 92.6% in both disease categories) as compared to prePMF (32/45, 71.1%, P=0.037). In line with these findings, the presence of the T allele was associated with higher grading (≥II) of marrow fibrosis (P=0.014). Intriguingly, all prePMF who evolved into overtPMF during the follow-up were polymorphic. We also found that presence of the SNP was associated with leukocytosis in MF (12.6±9.7 *vs* 8.0±3.2x10^9/L, P=0.017). Our results are consistent with the paper by Dunbar et al, in which increased CXCL8-secreting cells correlated with the degree of fibrosis and leukocytosis in MF and suggest that germline predisposition to produce higher levels of CXCL8 (due to the rs4073 SNP) may configure as a host genetic determinant that favors fibrotic progression in MPN.

P071

CLINICAL AND BIOLOGICAL RELEVANCE OF JAK2V617F VARIANT ALLELE FREQUENCY ≤2% IN A MONOCENTRIC SERIES OF CASES OF SUSPECTED MYELOPROLIFERATIVE NEOPLASMS

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The JAK2V617F mutation represents a hallmark of Philadelphia-negative myeloproliferative neoplasms (MPNs). JAK2V617F mutation is detected in >95% of Polycythemia Vera (PV) and 50-60% of

Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF). Highly sensitive molecular assays allow to detect JAK2V617F variant allele frequency (VAF) very low (<1%). Recent studies have shown that JAK2V617F VAF <1% may be present also in healthy subjects. Therefore, we analyzed retrospectively clinical and laboratory data of individuals with a suspected MPN that presented a low (≤ 2%) JAK2V617F VAF, with the aim to define its frequency and significance in the clinical practice. In the period from January 2009 and February 2023 we tested 1260 subjects with a suspected MPN; only 41 (3,3%) individuals had a VAF ≤2%. In particular 22 (1,7%) individuals (group A) had ≤1% VAF (range 0.1-1) and 19 (1,5%) individuals (group B) had VAF between 1,1% and 2%. Group A included 12 males and 10 females with a median age of 62 years (range 44-86). Group B included 8 males and 11 females with a median age of 60 years (range 20-82). In group A, 8 subjects were evaluated for erythrocytosis, 11 for thrombocytosis and 3 for splenomegaly. In group B, 4 subjects were tested for erythrocytosis, 14 for thrombocytosis and 1 for splenomegaly. Figure 1 summarizes the final diagnosis. Overall, 14/22 (64%) patients with JAK2V617F VAF <1% and 12/19 (63%) with JAK2V617F VAF between 1.1% and 2% received diagnosis of MPN according to WHO criteria. In 4 patients JAK2V617F test was repeated; in 2 patients VAF increased (1 with 46/1 Haplotype and 1 with MPN-U), in one patient with ET it decreased and in another with reactive erythrocytosis it remained stable. Other mutations in JAK2 exon 12, MPL and calreticulina (CALR) genes were evaluated in 8 patients. In one patient with ET was detected type 1/like CALR mutation. In two patient was detected JAK2 46/1 Haplotype (rs56241661). Our data confirm that the rate of diagnosis of MPNs is not different between patients with JAK2V617F VAF ≤1% and those with JAK2V617F VAF between 1,1% and 2%. Therefore in patients with JAK2V617F VAF ≤1% clinical, histopathological and genetic data must be integrated for a proper assessment. Patients with JAK2V617F VAF ≤1% and no overt MPN should be monitored to evaluate possible development of hematological malignancies and/or complications such as thrombotic events and solid tumors.

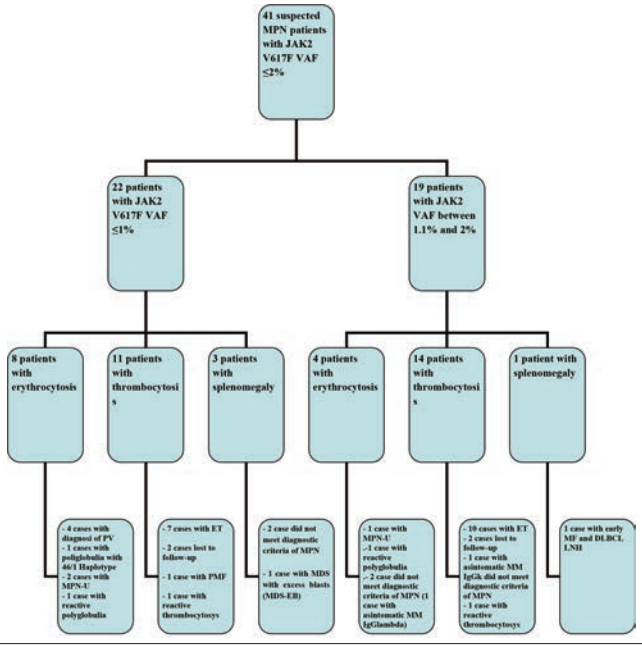

Figura 1. Patients' characteristcs and diagnosis JAK2 V617F VAF<2%.

P072

MONOCYTES FROM ESSENTIAL THROMBOCYTHEMIA PATIENTS ARE RESISTANT TO THE ANTI-INFLAMMATORY ACTIVITY OF LEMON-DERIVED EXTRACELLULAR VESICLES

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Introduction. Essential Thrombocythemia (ET) is a clonal disorder of the hemopoietic stem cell characterized by abnormal expansion of the megakaryocytic lineage. Driver mutations in JAK2, Calreticulin and MPL genes have been previously described. In addition to the molecular pathogenesis, the inflammatory/senescent microenvironment plays a strong role in nurturing the malignant hemopoietic clone. Therefore, strategies to counteract the inflammatory niche are worth of investigation. Plant-derived extracellular vesicles (EVs) are gaining growing interest. Specifically, lemon juice-derived EVs (L-EVs) have been described to have anti-proliferative and anti-inflammatory activity. However, their role in the regulation of the immune microenvironment of ET has never been investigated.

Methods. Peripheral blood was collected from patients with ET at diagnosis and from sex-age matched healthy donors (HD). Extracellular vesicles were isolated from Citrus limon L. juice by differential centrifugation and then stored at -80°C. Freshly isolated mononuclear cells from patients/HD have been incubated for 18 hours at 37°C in the presence or the absence of titrating doses (5, 10, 20 μg/ml) of L-EVs. After incubation, we investigated by flow cytometry: 1) the monocyte/lymphocyte ability to produce intracytoplasmic interleukin 1-β; 2) the effect of L-EVs on monocyte and lymphocyte viability (7-AAD) and apoptosis (Annexin-V); 3) the expression of the CD57 senescence-associated marker on monocytes and lymphocytes.

Results. Here we found that the viability of monocytes and lymphocytes from patients/HD was not affected by the treatment with increasing doses of L-EVs. In addition, L-EVs did not significantly modify the percentages of early and late apoptotic monocytes and lymphocytes. Interestingly, at variance with normal monocytes, monocytes from ET were resistant to the L-EV-driven inhibition of intracytoplasmic interleukin 1-β production. Conversely, lymphocytes from patients/HD did not produce interleukin 1-β at baseline and L-EVs did not significantly modified this behavior. Finally, L-EVs, even at the highest concentration, did not significantly modified the expression the CD56 senescence-associated marker.

Conclusions. Here we demonstrate that L-EVs are unable to modulate the inflammatory activity of immune cells from ET patients. Whether this is due to the intrinsic characteristics of the malignant clone remains a matter of speculation and investigation.

P073

INCREASED PLATELET EXPRESSION OF FCGAMMARIIA AND ITS POTENTIAL IMPACT ON PLATELET ACTIVATION IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA

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Essential Thrombocythemia (ET) is a myeloproliferative neoplasm

characterized by platelet activation, autoimmunity and thrombotic risk. In the autoimmune disorders such as heparin-induced thrombocytopenia (HIT) and vaccine-induced immune thrombotic thrombocytopenia (VITT) there are polyanions that cause the conformational change of platelet factor 4 (PF4) generating anti-platelet factor 4 (PF4)/polyanions immunoglobulin G (IgG) antibodies that cause platelet aggregation. These immune complexes are able to activate the platelets through stimulation of the Fc_{γ}RIIA. In ET there are platelet surface polyanions. Whether there are anti-platelet factor 4 (PF4)/polyanions IgG antibodies in ET have to be investigated. We measured platelet count by automated analyzer, the phosphatidylserine (PS) polyanion and P-selectin expression by flow cytometry, IgG-specific PF4/polyvinylsulfonate (PVS) ELISA and Fc_{γ}RIIA expression by flow cytometry. Platelet aggregation was performed by multiple electrode aggregometry (MEA) without or with the CD32 (anti-Fc_{γ}RIIA) antibody AT10 to show the mediated-Fc_{γ}RIIA platelet aggregation. We studied 15 JAK2V617F positive ET patients (WHO criteria) (6 men, 9 women, mean age 56 years) at low risk. All patients were on low dose aspirin (LDA). None of the patients had cardiovascular risk factors. Fifteen healthy blood donors were controls. All patients had thrombocytosis (720±50 x10^9/L) and allele burden greater than 20%. We found high PS expression (95±5 % *vs* 25±5 %) and P-selectin (650±100 nm *vs* 450±30 nm, high optical density (OD) of anti-PF4 IgG (> 0.400 *vs* < 0.400) and high mean fluorescence intenstity (MFI) Fc_{γ}RIIA (> 1.2 *vs* < 1.2). In addition, we showed increased platelet aggregation without or with CD32 antibody AT10 (> 250 AU/min *vs* < 250 AU/min, respectively). The statistical differences and correlations between PS and P-selectin and PS and anti-PF4 IgG. were < 0.05. These results suggest a potential mechanism of platelet Fc_{γ}RIIA stimulation by anti-PF4 IgG. Future studies are warranted to investigate whether the platelet activation as described in the present study might be a marker of thrombotic risk in ET.

P074

REAL WORLD DATA OF CHRONIC MYELOMONOCYTIC LEUKEMIA: A SINGLE CENTER RETROSPECTIVE EXPERIENCE

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Background. Chronic myelomonocytic leukemia (CMML) is a rare and progressive myeloid neoplasm with overlapping myelodisplastic and myeloproliferative features that primarily affect older adults. Its prognosis is influenced by various factors, including molecular, cytogenetic, and phenotypic characteristics, that are appraised at the onset of disease and integrated into prognostic scores such as CMML Prognostic Scoring System (CPSS) and CPSS molecular score. However, the prognostic role of nutritional status in this setting is still unknown, in contrast to other myeloid neoplasms.

Aims. The aim of this study is to evaluate the impact on overall survival (OS) and progression free survival (PFS) of clinical, laboratory, nutritional and molecular biology characteristics in a monocentric cohort of CMML patients (pts).

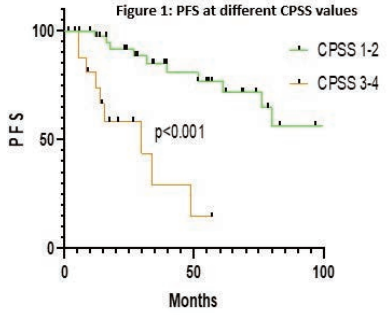
Methods. We retrospectively included 60 consecutive pts followed at our institution between 2007 and 2023, with a diagnosis of CMML (according to current World Health Organization criteria). We collected data about clinical and biological features of disease at diagnosis, including CPSS score, GNRI (geriatric nutritional risk index), type of treatment and variables of outcome. Conventional statistical tests were performed.

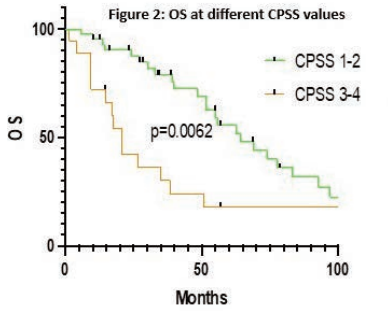
Results. The principal features of CMML pts were recorded in Table 1. Median age was 69,1 years (range 24-83); about 30% of pts were classified as CPSS intermediate-2 high risk. 15 pts (25%) were transfusion-dependent at diagnosis. Most pts (73%) had a normal/low risk karyotype. 33 pts (55%) received hypomethylating agents for a median time of 14.9 months (range: 3-59). With a median follow-up of 36.6 months (range 2-156), 44 (73.3%) pts died and 22 pts (36.7%) evolved into acute leukemia.

Table 1. Principal features of CMML patients.

Variables	N =60
SEX N (%)	
Male	14 (23.3%)
Female	46 (76.7%)
AGE AT DIAGNOSIS Median (range)	69.1 years (24-83)
BLOOD COUNTS AT DIAGNOSIS Median (range)	
Hb (g/dl)	10.6 (6.7-16.2)
WBC /mm3	14000(2500-124800)
AMC /mm3	2853 (282-27100)
PLTs /mm3	104000 (14000-1081000)
Blasts in PB %	0 (0-17)
SUBTYPE AT DIAGNOSIS N (%)	
MDS-CMML	32 (53.3%)
MPN-CMML	28 (46.7%)
CPSS SCORE N (%)	
Low-Int1	42 (70%)
Int2-High	18 (30%)
CYTOGENETIC RISK N (%)	
Low	43 (72.9%)
Int-High	16 (27.1%)
ND	1 (1.7%)
GNRI AT DIAGNOSIS Median (range)	104 (73.1-140.6)
TREATMENT N (%)	
Azacytidine	33 (55%)
Hydroxyurea	18 (30%)
Other	4 (6.7%)
None	5 (8.3%)
LAM EVOLUTION N (%)	
Yes	22 (36.7%)
No	38 (63.3%)
DEATHS N (%)	
Yes	44 (73.3%)
No	16 (26.7%)

Legenda:
Hb: hemoglobin
WBC: white blood cells
AMC: absolute monocyte count
PLTs: platelets
ND: data not available
PB: peripheral blood





Figures 1 and 2.

The 3-years survival for the entire cohort was 33.5%. In univariate analysis higher CPSS (p=0.006, Figure 1), transfusion-dependent (TD) anemia (p=0.023) and the presence of blasts on peripheral blood (PB) at diagnosis (p=0.009) were associated with a worse survival. Therefore, higher CPSS (P=0.0001, Figure 2) and adverse karyotype (p=0.03), correlated with a shorter PFS. The nutritional status at diagnosis evaluated according to GNRI did not influence a different outcome or response to treatment.

Conclusions. In our experience, we confirmed that clinical and biological features at diagnosis, such as CPSS, blast count and TD anemia, are more effective in predicting a different clinical outcome in CMML setting than nutritional scores.

P075

ROLE OF LOW JAK2 V617F ALLELE BURDEN IN PH-NEGATIVE MYELOPROLIFERATIVE NEOPLASM (MPN)

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Diagnosis and risk stratification of Ph-negative MPN are based not only on histological analysis but also on genetic data. Essential gene markers for primary and differential diagnosis of MPN include molecular variants associated with hyperactivation of tyrosine kinases or cytokine receptor abnormalities. Molecular diagnostic routine for Ph- negative MPN involves firstly the research of the V617F variant in JAK2 gene and only in case of negativity it goes ahead with analysis of JAK2 exon 12, CALR and MPL genes. 295 patients were analysed for suspected MPN by quantitative RT-PCR analysis (LoD>0.0099%). Some of the V617F negative patients were analysed with multigenic NGS panel related to myeloid disorders for variants in the remaining targets. 24% of patients tested V617F positive. Among these, 12 samples presented a low Variant Allele Frequency (VAF) 0.1%-2.5%. For 3 of these samples a NGS examination was performed. A case diagnosed with polycythemia vera V617F 0.8% has no further variants; one case with undefined anaemia and platelets with 0.18% V617F has Tier I variants in IDH2 and SF3B1 genes and the third sample with suspected MPN shows 0.13% of V617F and Tier I variants in CALR (type I) and DNMT3A genes. These results seem to support the hypothesis that a low VAF of V617F reflects the presence of a mutated subclone within a polyclonal hematopoiesis, suggesting that it represents an early molecular start and likely sufficient to induce MPN phenotype. These data recommend the value of a high sensitive analysis in suspected Ph- negative MPN cases, because it can detect promptly the expansion of clonal hematopoiesis and diagnose a full-blown disease, although the V617F detection at low levels remains difficult to interpret in daily clinical practice. Molecular monitoring over time can discriminate between a temporary clone (likely benign condition) or an expanding clone and give rise to the disease. Moreover, in cases with low allele burden V617F, it is advised to analyse variants in other genes, normally considered mutually exclusive, as demonstrated by recent studies, although the meaning remains to be defined.

P076

BONE HEALTH IN SYSTEMIC MASTOCYTOSIS

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Systemic Mastocytosis (SM) is a rare myeloid hematologic neoplasm characterized by the abnormal proliferation and accumulation in organs and tissues of clonal mast cells. The WHO classification distinguishes SM in: indolent SM (iSM); smoldering SM (sSM); advanced SM (AdvSM). SM typically affects adults and is characterized by the involvement of one or more extracutaneous organ (bone marrow, liver, gastrointestinal tract, others). One of the main clinical manifestations of SM is bone involvement presenting as localized pain, osteopenia, osteoporosis, pathological fractures and skeletal deformities. Mast Cells Activation Syndrome (MCAS) is diagnosed when symptoms related to mast-cell-released substances are present without reaching WHO 2016 criteria for SM diagnosis. Literature on bone alterations in patients with SM is only anecdotal. Osteoporosis represents the most frequent bone manifestation in SM. Bone loss seems to affect the trabecular bone, considering of the prevalence of osteoporosis in the lumbar spine compared to the hip and the much higher rate of vertebral fractures. Osteoporosis in SM seems to depend on neoplastic infiltration of MCs or their release of mediators, including histamine, heparin, tryptase, cytokines. Activated MCs also synthesize proinflammatory factors, which promote osteoclastic activity. Fractures also represent a typical clinical manifestation of patients with SM. We can consider fragility fractures (FF) as the consequence of osteoporosis and pathological fractures due to focal lytic lesions. FF are the most frequent, and in particular, involve the vertebrae. We revised the literature and then collected data from 8 patients with SM (7 iSM and 1 advSM) and 7 patients diagnosed with MCAS referring to our Hematology center. Median age at diagnosis was 40 years for SM and 52 years for MCAS. Of these cases, 4 SM reported osteoporosis and 2 MCAS reported osteopenia. 2 of the osteoporotic patients with SM reported vertebral fractures, diagnosed between 6 months and 2 years before the diagnosis of SM, and one of the 2 patients with MCAS and osteopenia, reported 4 non-vertebral fractures, all of which occurred before the suspicion of mast cell disease was formulated. Bone health is a serious point of interest and a crucial outcome of the management and treatment in patients with SM, as it is frequently altered and often depresses quality of life and requires bone specialist supervision and prescriptions, and drug and non-drug therapies.

Chronic lymphatic leukemias and lymphoproliferative syndromes

P077

AN UNSUPERVISED MACHINE LEARNING METHOD STRATIFIES CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS IN NOVEL CATEGORIES WITH DIFFERENT RISK OF EARLY TREATMENT

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Conventional hierarchical models for improvement of prognostication of chronic lymphocytic leukemia (CLL) always rely on discretized/dichotomic values of clinical and biological markers. Here we analyzed the immunophenotypic and (immuno)genetic profiles of a multicentric CLL cohort (n=981), applying unsupervised machine learning methods and elaborating prognostic factors as continuous variables. Among several laboratory-based markers (n=15), univariate Cox regression to estimate treatment-free-survival (TFS) selected FISH del11, del17, tris12, TP53 mutation (by NGS as % variant allele fraction, VAF), IGHV % mutation, expression by flow cytometry of CD49d (% of positive cells) with a fit p-value <0.001).

Unsupervised k-means partitioned cases in 6 clusters (C1-C6), and centroid analysis defined their most representing features (Figure 1A):

C1 (n=275) was heavily IGHV-mutated (4.5-22.0%) without other features;

C2 (n=208) was mostly IGHV-unmutated or intermediate (up to 4.5% mutations) in the absence of other features;

C3 (n=169) were CD49d-expressing cases, with low representation of other features;

C4 (n=127) were trisomy 12 cases co-expressing CD49d and CD38;

C5 (n=48) were cases with highly clonal del11 (44-98%) and IGHV-unmutated, mutually exclusive with TP53 disruption;

C6 (n=34) contained TP53-disrupted cases with high mutation burden (VAF 16-97%) and del17 (range 40-96%), skewed towards IGHV-unmutated, all of the other features with low importance.

Kaplan-Meier analysis revealed heterogeneous behaviors: clusters 3-4-5-6 presented a 50% TFS of 59, 22, 7, 5 months respectively whereas it was not reached for clusters 1-2. Hierarchical agglomerative clustering aggregated 3 major risk classes: high (C5-6), intermediate (C2-3-4) and low (C1), with 50% TFS of 7, 55 and not reached, respectively (Figure 1B). Multivariate Cox analysis with Rai staging demonstrated that the 3-tier risk score contributed significantly and independently to TFS estimate (p<0.0001).

In conclusion, our machine-learning-driven, laboratory-based classification identifies clusters at different risk of early treatment, suggesting a diverse impact of biological markers; in details: i) IGHV mutation was relevant if >4% in the absence of other markers (e.g. CD49d); ii) TP53 disruption and del11q was relevance only if present in the majority of the clone; iii) low burden IGHV mutations along with CD49d expression and/or tris12 identifies patients at intermediate risk.

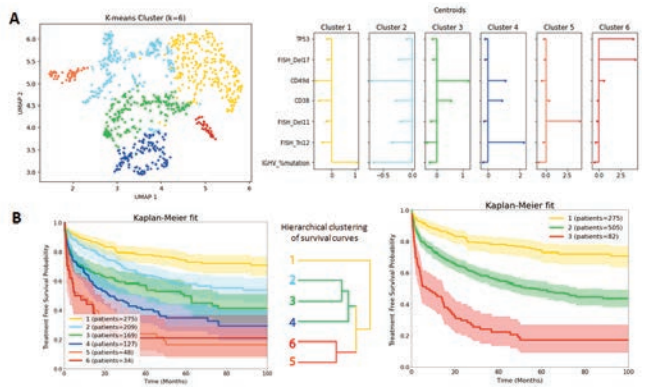

Figura 1.

P078

APPLICATION OF MEASURABLE RESIDUAL DISEASE (MRD) IN CHRONIC LYMPHOCYTIC LEUKEMIA IN THE REAL-LIFE SETTING: A SINGLE CENTER STUDY

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Background. The assessment of measurable residual disease (MRD) has been shown to be a successful tool to predict the outcome of patients with chronic lymphocytic leukemia (CLL), but according to international guidelines, it is used only as a surrogate endpoint in clinical trials.

Aims. This study was aimed at evaluating the role of MRD assessment in clinical practice and at identifying factors related to undetectable-MRD (uMRD) achievement.

Methods. We evaluated CLL patients treated at University Hospital of Padova with chemo-immunotherapy (CIT) or targeted therapies and subjected to MRD assessment between 2014 and 2022. MRD was assessed in the peripheral blood and/or bone marrow by using flow-cytometry, with the standardized four or six-color assay, and analyzed with Infinicyt™. At least 1-2x106 events were acquired. uMRD was defined as less than 1 CLL cell per 10.0000 leukocytes.

Results. We collected data from 83 patients, the median age was 68 years, 37% were females, 60% were treatment-naïve. Thirty-eight percent were treated with CIT (i.e. FCR, BR or G-CHL), 37% with venetoclax-based combinations and 25% with other targeted therapies (venetoclax alone; ibrutinib+/-R; R-idelalisib). At assessment, 60% of patients achieved a complete response (CR) and 35% a partial response (PR); 51% of patients achieved uMRD. TP53 mutation (p=0.0133) or deletion (p=0.0119), unmutated IGHV gene (p=0.0064) and complex karyotype (p=0.0237) were significantly associated with lower rates of uMRD. After a median follow-up of 45 months, patients achieving uMRD had better relapse free survival (RFS, 4-year 84% *vs* 57%, p=0.0297) and overall survival (OS, 4-year 94% *vs* 68%, p=0.0054) than those with detectable-MRD (dMRD). Patients treated with CIT or venetoclax-combination regi-

mens achieved higher rates of uMRD than patients receiving other target therapies (68% *vs* 58% *vs* 19%, p=0.0018), but among uMRD cases there were no differences in terms of RFS between the groups (p=0.2282, Figure 1). Conversely, among the dMRD patients, those treated with venetoclax-combination regimen showed a longer RFS than those treated with CIT or other targeted therapies (the median RFS was 58, 25 and 32 months, respectively, p=0.05, Figure 1).

Conclusion. We herein provide evidence that i) patients achieving uMRD had a better RFS, ii) TP53 abnormalities and complex karyotype negatively correlate with uMRD rates, iii) the outcome of uMRD patients are similar despite the employed treatment.

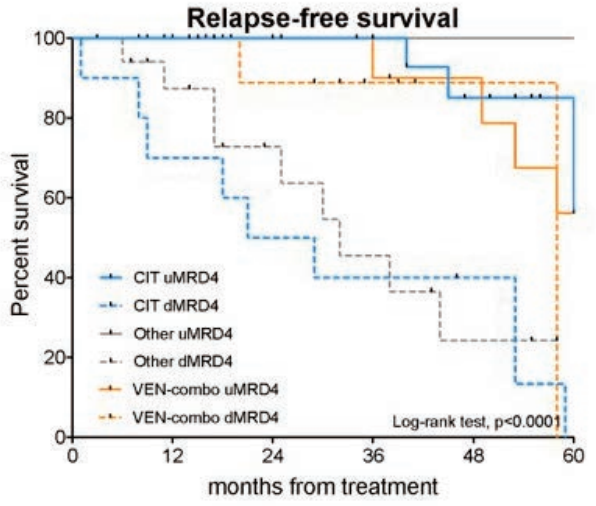

Figura 1.

P079

CIRCULATING EXTRACELLULAR VESICLES FROM PATIENTS WITH CLASSIC HAIRY CELL LEUKEMIA CARRY DISTINCT CANCER-RELATED SIGNALS

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Introduction. Classic Hairy Cell Leukemia (HCL) is a rare indolent but still incurable clonal B-cell disorder characterized by a variable degree of bone marrow (BM) fibrosis, splenomegaly, pancytopenia with abnormalities of innate and adaptive immunity and susceptibility to infections. HCL is characterized by a distinctive pattern of infiltrating hairy cells (HCs) in the BM, liver and spleen. Along with BRAFV600E mutation, HCs express CD19, CD20, CD22, CD11c, CD103, CD123, and CD25. A strong dependence of HCs on tumor microenvironment (TME) (stromal cells, endothelial cells and extracellular matrix) has been described. Extracellular vesicles (EVs), small particles involved in cell-cell communication, are key players within TME. However, their role in HCL has never been investigated.

Methods. Circulating EVs were purified from platelet-free plasma of HCL patients at diagnosis and healthy donors (HD) by size exclusion chromatography and ultrafiltration. Size, morphology and EV-related markers were analyzed by tunable resistive pulse sensing analysis, transmission electron microscopy and western blotting. Then, MACSPlex Exosome Kit was used to simultaneously assess 37 EV surface markers mainly related to immunity, cancer and stemness.

Results. Morphology and size of HCL EVs were superimposable to HD EV. Interestingly, the analysis of HCL EV protein profile highlighted the overexpression of B-lineage cell marker namely CD19 along with high expression of molecules related to cancer and involved in mechanisms of adhesion/migration/invasion (CD44, CD24 and CD146) and tumor angiogenesis (CD146 and CD105). Of note, CD44 is expressed on HCs and, as receptor for hyaluronan, has been described to be involved in mechanisms contributing to HCL-associated fibrosis. Additionally, CD44, having a role in cytoskeleton reorganization through the RhoGTPases (RhoA, Cdc42 and Rac1, all constitutively overexpressed in HCs), might contribute to HC-associated cytoplasmic projections. CD24 is known to promote tumor immune evasion through suppression of cytotoxic T cell function. Finally, HCL EVs were also enriched of CD25, which is a well-known HC-associated marker.

Conclusions. Here we show that EV-based liquid biopsy provides pathogenesis-related and clinically-relevant information on HCL TME which can be exploited as disease marker and potential therapeutic target.

Funding. Italian Ministry of Research's PhD scholarship (F.M.-University of Bologna), RC 22000388/RC-2022-2773276

P080

REPEATED COVID-19 EVENTS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Omicron variants are highly transmissible and the antibody escape due to mutations in the spike proteins exposes patients at an increased risk of subsequent COVID-19 event. To evaluate the morbidity and severity of subsequent SARS-CoV-2 infections we carried out a prospective/retrospective study in 210 patients with chronic lymphocytic leukemia (CLL) who had experienced a COVID-19 event, between March 2020 and March 2023. The median age was 69 years, 38% had unmutated IGHV, 12% TP53 disruption and 20% hypogammaglobulinemia. Ninety-two (44%) patients were previously treated (BTK inhibitors, 23%; venetoclax, 7%; chemoimmunotherapy, 13%). The first COVID-19 event occurred before January 2021 in 22 (10%) patients, during the Alpha pandemic in 11 (5%), the Delta wave in 17 (8%) and the Omicron phase in 160 (76%). The median number of the administered doses of the SARS-CoV-2 vaccine was 3 (range, 0-5). At the time of the first COVID-19, 36 (17%) patients were still unvaccinated, 52 (25%) required hospitalization and 9 died (unvaccinated, 11% *vs* vaccinated, 3%; p=0.045). Two hundred one patients survived the first event and, during the Omicron pandemic, 36 (18%) had a second event, including 2 with a third event. As compared to the first event, subsequent infections had better, though not significantly better, outcomes in terms of patients requiring hospitalization (17% *vs* 25%; p=0.398), interstitial pneumonia (8% *vs* 21%; p=0.066) and fatal cases (0% *vs* 4%; p=0.362). In multivariate analysis, no prior treatment (HR 0.37; p=0.007); ≥ 4 doses of the SARS-CoV-2 vaccine before the second event (HR 0.16; p<0.003) and unmutated IGHV (HR 6.37; p=0.020) emerged as significant and independent factors with an impact on the second COVID-19 event-free survival (Figure 1). The results of this study show that a high rate of CLL patients, 18%, experienced more than one COVID-19 event. Previously treated patients, those who received less than 4

doses of the vaccine before the second COVID19 infection and IGHV unmutated were significantly more vulnerable to a subsequent event. Thanks to prior immunization, the decreased virulence of Omicron variants and the availability of better therapeutic options, no fatal cases were observed. However, a not negligible proportion of patients required hospitalization. Due to the continue emergence of SARS-CoV-2 variants, preventive measures and new vaccine strategies are needed to prevent and mitigate subsequent COVID-19 events in patients with CLL.

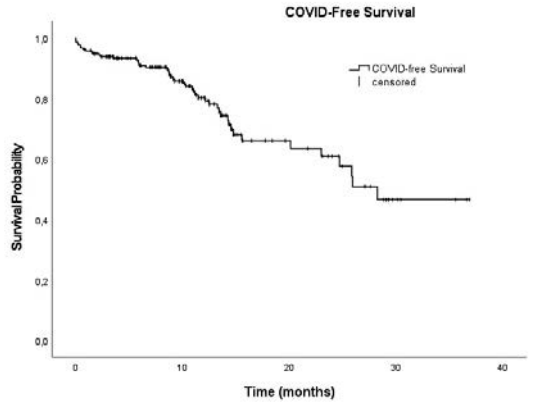

Figura 1.

P081

IBRUTINIB IN 3306 PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): A NATIONWIDE REGISTRY STUDY FROM THE ITALIAN MEDICINES AGENCY (AIFA) AND THE GIMEMA WORKING PARTY (WP) ON CHRONIC LYMPHOPROLIFERATIVE DISORDERS

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The BTK inhibitor ibrutinib is a standard of care treatment for patients with CLL. Ibrutinib administration in a real-world population has shown high discontinuation rate, mainly due to tolerability issues. The GIMEMA WP on CLL established a collaboration with AIFA to analyze the effectiveness of ibrutinib in R/R CLL patients included in the AIFA registry, which has a 100% capture of the patients treated with the drug in Italy. The endpoints were time to discontinuation (TTD) and overall survival (OS) from initiation of ibrutinib. Between 2016 and 2020, 3306 patients received ibrutinib (median time from diagnosis 75.6 months). Median age was 72 y (range 30-95); ECOG-PS 0,1,2,3 were reported in 47.97%, 42.53, 8.83%, 0.64% of the patients, respectively. Duration of response after last treatment was >12 months in 57.37% of the cases and ≤12 months in 29.35% with 13.28% of the patients refractory to last treatment. Rai stages 0,1,2,3,4 were reported 7.53%, 19.6%, 27.59%, 21.84%, 23.44% of the cases; 57.44% of the patients had received 1 previous line of treatment, 28.68% 2 lines, 10.07% 3 lines and 3.81% 4+ lines. 13q- was present in 21.81% of the cases; + 12 in 9.9%, 11q- in 14.3%, 17p- in 16.3%, no aberrations in 28.5%. TP53 mutations were detected in 20.7% of the cases (data available in 1942 patients). Pre-existing renal impairment, atrial fibrillation, severe cardiac disease and use of anticoagulants were reported in 7.99%, 2.75% and 2.63% and 3.63% of the patients respectively. Data cut-off was May 2022. With a median follow-up of 41 months (IQR 29.95-53.59) the median TTD was 31.30 months (0.95% CI: 29.49-33.47), with a 57.94% probability of treatment retention at 24 months. Median time to progression, unacceptable toxicity or death was 53.36 months (95% CI: 50.17-57.04), with a 26.3% probability of progression, unacceptable toxicity or death at 24 months. Median OS was 61.87 months (95% CI 58.95-66.12) with a 76.63% probability of being alive at 24 months (95% CI: 75.19-78.11%). Median OS were 12.16 months (95% CI: 10.45-15.16) post progression and 20.32 months (95% CI: 15.02-23.51) post discontinuation for toxicity or other reasons. Multivariable analysis of prognostic factors will be presented at the congress. In conclusion, these data show that ibrutinib is an effective treatment in R/R CLL treated in a real-world setting an compare favorably with previous real-world analyses.

P082

SF3B1 AND SUBSET#1: NOVEL GENE MUTATION ASSOCIATED WITH POOR PROGNOSTIC STEREOTYPED SUBSET#1 OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) AMONG SARDINIA PATIENTS

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Introduction. Recent studies show the role of antigenic stimulation in evolution of Chronic lymphocytic leukemia (CLL). In brief, CLL patients shows highly skewed repertoire, and good prognosis is associated with somatic Hypermutation status of IGHV genes. Unmutated subset #1was identified in 6% of poor clinical outcome CLL patients. Moreover, patients with subset#8, have poor outcome, and at high risk of Richter transformation among all CLL cases. On the other hand, SF3B1 mutation was reported to be associated with poor prognosis in CLL.

Aim of study. Correlation between different subsets# and SF3B1 gene mutation in 166 CLL Sardinian people cases from 2016 to 2022.

Materials and Methods. Patients and subsets: the study included a total of 166 South Sardinia CLL patients (124 were male and 42 were female) diagnosed at Hematology Department of Cancer Hospital of Cagliari from 2016 to 2022.

Methods. 166 DNA samples were tested by Polymerase chain reactions amplifications, and Sanger sequencing analysis were used to evaluate IGHV somatic mutational status. IGHV gene mutational analysis was performed according to ERIC recommendation. Antigen Receptor Research Tools (ARRes T) were used for Subsets# analysis. For NGS study, 32 CLL genes were customized in a panel for sequencing using Miniseq 100 of Illumina. Cut off over 5% was used as to define pathogenicity levels of genes.

Results. Unmuted IGHV represented 52.4% of the total 166 patients, only 10.2% of them display subset CLL# expression (52.9% were CLL subset#1, 11.8% were CLL subset#6, 5.8% were CLL#7, 5.8% were CLL#64b and 5.8% were CLL#8. Sequence analysis showed that 26.65% of CLL#1 subset was on VH1 family.

Conclusions. The SF3B1 pathogenic variant gene was associated with Subset #1 and subset #8. All variants were pathogenetic asTier3 and Tier 2C, and allelic fraction was major between 2% and 36%. In our study group, majority of unmutated patients express the CLL#1 subset (52.95%) which is one of the poor prognosis subsets if associated with SFB1 gene expression. Moreover, 33% of them combined with NOTCH 1 positive expression associated with more aggressive disease biology.

P083

IMPACT OF AGE AND DRUG DOSAGE IN PATIENTS WITH CLL TREATED WITH VENETOCLAX: A REAL-LIFE EXPERIENCE

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Background. Venetoclax (Ven) is widely used in Chronic Lymphocytic Leukemia (CLL) with a good safety profile. Although Ven is administered regardless of age, only a few studies analyzed the impact of age on patients' outcome. The purpose of this retrospective study was to study the influence of age in patients treated with Ven

Methods. Patients with CLL who received Ven-based treatment in any lines at Padova University Hospital from 05/2015 to 11/2022 were recruited. Ven was administered following a ramp-up from 20mg to 400mg, succeeded by rituximab (R) or preceded by obinutuzumab (G) according to the protocols. Response rates, survivals and adverse events were analyzed. The population was split into two groups: A <70 years and B >70 years

Results. Sixty-one patients were recruited, 33% treated with Ven alone, 59% with VenR and 8% with VenG. In group A 62% of patients received at least one previous line of therapy *vs* 84% in group B (p=0.008); median CIRS score was 3 *vs* 7; low IgG levels were found in 24% *vs* 34% and 41% *vs* 50% before and after Ven respectively. In group B, less patients reached (p=0.029) and maintained (p=0.001) the full dose of 400 mg, and the ramp-up lasted more than 5 weeks in 63% of cases (p=0.001). ORRs in the two groups were 93% *vs* 84%, including 59% and 47% complete remissions. We observed a shorter OS (median not achieved *vs* 23 months, p=0.025) and a trend for a shorter PFS (p=ns) in group B (Figure 1).

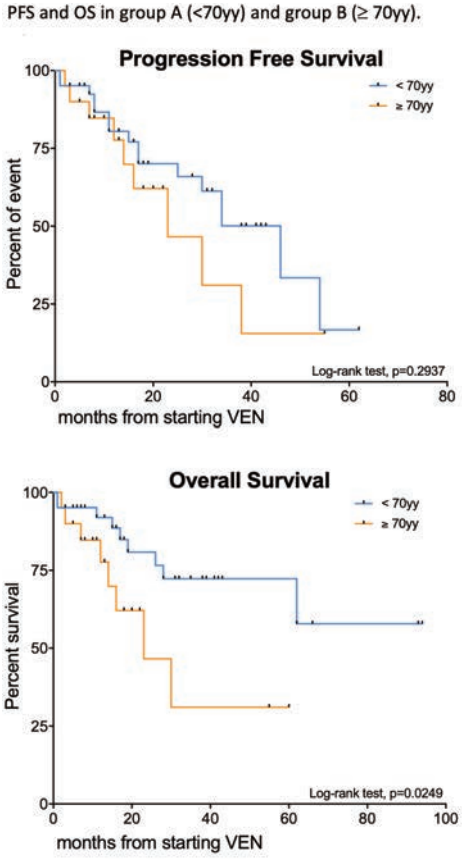

Figura 1.

No differences were observed in the number of temporary drug discontinuations, although more toxicity-related permanent discontinuations were observed in group B (p=0.025). The most frequent grade 1-2 adverse events (AE) were neutropenia (28% *vs* 13%), thrombocytopenia (31% *vs* 28%), asthenia (41% *vs* 31%) and infections (34% *vs* 31%, bacterial 14% *vs* 19%, viral 28% *vs* 16%), mainly of the upper respiratory tract; grade 3-4 AEs were neutropenia (52% *vs* 56%) and infections (38% *vs* 31%, bacterial 14% *vs* 22%, viral 21% *vs* 22%) mainly of the lower respiratory tract. Four cases of febrile neutropenia were observed only in group B. No patients developed TLS. 7% *vs* 24% patients died for an infection in Ven (p=0.09). Remarkably, 66% of patients who died in group B reached a dosage of 400 mg

Conclusions. In the elderly population the management of Ven full dose has been shown to be challenging. While ORRs were similar among the two groups, OS was significantly lower in the elderly group, due to a higher number of infection-related deaths in Venetoclax.

P084

DETECTING MEASURABLE MINIMAL RESIDUAL DISEASE BY NEXT-GENERATION SEQUENCING AT 10^{-4} IS FEASIBLE IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TREATED WITH VENETOCLAX-BASED THERAPIES

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Detection of measurable residual disease (MRD) after treatment with venetoclax-based therapies predicts clinical outcome in patients with chronic lymphocytic leukemia (CLL). Few data are available on the feasibility and sensitivity of next-generation sequencing (NGS) approach to detect MRD in this context. We prospectively collected 18 patients with CLL treated with venetoclax-based therapies. Mean age at diagnosis was 58 years (range 40-74). Previous treatments comprised chemo-immunotherapies (FC, FCR, BR, CHLR) in 12 cases and ibrutinib in 8 cases (range, 1-3). Sixty-one percent of patients had unmutated immunoglobulin genes, TP53 aberrations (deletion/mutations) were detected in 2 cases (11%). Two patient experiencing progressive disease during ibrutinib showed BTK mutations in cysteine 481. An NGS approach by using LymphoTrack FR1 CE IVD kit was applied for definition of patient-specific leukemic clonotype in pre-treatment sample and for MRD assessment in bone marrow and/or peripheral blood samples collected at the end of combination (EOCT) and at the end of treatment (EOT). The NGS approach allowed the definition of CLL clonotype in all 18 cases. We found a predominant unique clonotype in 16/18 CLL (89%), two cases showed multiple clonotypes that were all evaluated by NGS in the MRD assessment. Fourteen patients had samples available at EOCT. Each sample was sequenced in triplicate using 1.5 µg of DNA. All but one sample were successfully analyzed for MRD assessment of CLL clonotype, reaching a 10^{-4} sensitivity. Suboptimal library preparation was obtained in all samples at EOCT due to B-cell depletion related to effects of therapeutic agents, but technical adjustment allowed the achievement of a sensibility at least 10^{-4} in all but one case. Only 4 patients (28%) treated with venetoclax-based therapies reached the molecular MRD negativity at the EOCT. All

patients at the EOCT were negative at morphological examination. However, persistence of enlarged lymph nodes was detected in 43% of cases, of which 2 were negative for molecular MRD. To date, only 5 CLL patients reached the EOT and persistence of a positive molecular MRD by NGS was found in two cases. Richter transformation was present in 2 out of 18 treated patients at 2 and 10 months after the initiation of venetoclax and one patient had progressive disease.

Our data show the feasibility of NGS-based MRD assessment in a prospective cohort of patients with CLL treated with venetoclax-based therapies.

P085

CLINICAL BENEFIT OF SUBCUTANEOUS, MONTHLY IMMUNOGLOBULINS (SMI) IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) AND HYPOGAMMAGLOBULINEMIA (HGG)

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A variable condition of immunodeficiency involving both humoral and cellular immunity is observed in patients with chronic lymphocytic leukemia (CLL). Hypogammaglobinemia (HGG) is a common abnormality associated with relevant morbidity and mortality due to infections. In several studies, HGG emerged as a significant factor associated with increased vulnerability to COVID-19. Reduced morbidity due to infections was observed in CLL patients receiving intravenous (IgIV) or weekly, or bi-weekly, subcutaneous immunoglobulins. We carried out an observational, retrospective, multicenter, study focused on 52 CLL patients with HGG who received monthly subcutaneous immunoglobulins (SMI) during the SARS-CoV-2 pandemic, between January 2020 and March 2023. Our study was aimed at evaluating the morbidity due to infections, in particular, COVID-19 in this patient population. Exposure-adjusted incidence rates for infections and hospitalization were defined as the number of patients experiencing an event per 100 person-years (100 PYs). The median age of patients was 76 years and the median IgG level measured on SMI was 709 mg/dl. Fifty two% of patients had unmutated IGHV, and 37% TP53 disruption. Thirteen (60%) patients had been previously treated with chemoimmunotherapy, 4 (18%) were on ibrutinib, and 4 (18%) on venetoclax (Ven; VenR, 1; continuous Ven, 3). Forty-six (90%) patients received a median number of 3 doses of the SARS-CoV-2 vaccine, with a serologic response in 14/26 (54%) tested patients. Sixty-three% patients were able to self-administer SMIs. Two patients experienced grade 3 hypotension at the time of the first SMI administration. Thirty-four (65%) patients developed at least one infectious event (IR 27.5 per 100 PYs), and 15 (29%) at least one grade ≥3 infection (IR 12.8 per 100 PYs). Thirteen (25%) patients required hospitalization due to infection (IR 9.7 per 100 PYs). Pneumonia was the most frequently recorded grade ≥ 3 infection (87%). COVID-19 was diagnosed in 22 (42%) patients, 20 previously vaccinated. Three patients experienced a second infection. Hospitalization was required by 8 (36%) patients with severe COVID-19 and two of them, heavily pre-treated and unvaccinated, died (1/22, 4,5%; 1/52, 2%). Despite the high vulnerability to infections and COVID-19 described in CLL patients with HGG, the outcomes of patients on SMI replacement were relatively favorable. Our data support the clinical benefit of SMI replacement in patients with CLL and HGG.

P086

THE ROLE OF CLADRIBINE FOR THE TREATMENT OF HAIRY CELL LEUKEMIA: RESULTS FROM A SINGLE-CENTER ANALYSIS

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Introduction. Hairy cell leukemia (HCL) is a rare lymphoproliferative disorder characterized by an indolent course but frequent need of therapy at time of diagnosis, where purine analogues still represent first-line standard of care.

Methods. We collected clinical records of patients diagnosed with HCL between 1977 and 2022 visited at our clinic between Jan/2019 and Apr/2023 . Clinical history and laboratory data were retrospectively analyzed. For dichotomic variables, a two-tailed Fisher's exact test was used to calculate statistical significance. For survival analysis, Kaplan-Meier method was used.

Table 1.

Features at diagnosis			
Feature	**value**	**range or %**	**measure**
Age at diagnosis	51	25 - 86	years
Male sex	46/57	81%	rate
WBC	3.28	1.20 - 53.39	x 10^9/L
Hb	12.6	8.7 - 15.7	g/dL
PLT	78	22 - 170	x 10^9/L
ANC	0.98	0.29 - 3.73	x 10^9/L
Features at treatment-1 start			
Feature	**value**	**range or %**	**measure**
Treated patients	50/57	88%	rate
Age	52	25 - 86	years
CIRS	2	0 - 11	score
CIRS ≥ 3	5/45	11%	rate
Spleen size	14.5	8.5 - 29	cm
BM infiltrate	70	2 - 95	%
WBC	3.00	1.20 - 54.39	x 10^9/L
Hb	12	7.5 - 15	g/dL
PLT	72	33 - 134	x 10^9/L
ANC	0.87	0.29 - 3.50	x 10^9/L
Hairy cells on PB	17/27	63%	rate
Treatment-1 criteria			
Anemia	12/50	24%	rate
Thrombocytopenia	32/50	64%	rate
Neutropenia	26/50	52%	rate
Splenomegaly	6/50	12%	rate
Enlarged lymph nodes	0/50	0%	rate
B symptoms	1/50	2%	rate
NA	13/50	26%	rate
First line treatment			
Cladribine	22/50	44%	rate
Pentostatin	15/50	30%	rate
Interferon	11/50	22%	rate
Rituximab	1/50	2%	rate
Chemotherapy	1/50	2%	rate
Response to first line			
CR	19/50	38%	rate
PR	21/50	42%	rate
SD	5/50	10%	rate
NA	5/50	10%	rate
Avail. MRD data in CR	13/19	68%	rate
MRD-negativity rate	11/13	85%	rate
Relapse/progression	24/50	48%	rate
Second line treatment			
Treated patients	19/24	79%	rate
Cladribine	6/19	32%	rate
Pentostatin	4/19	21%	rate
R-pentostatin	2/19	11%	rate
Rituximab	1/19	5%	rate
Interferon	5/19	26%	rate
Splenectomy	1/19	5%	rate
Response to second line			
CR	6/19	32%	rate
PR	12/19	63%	rate
SD	1/19	5%	rate

Results. We identified 57 HCL patients followed at our institution whose characteristics are listed in Table 1. First-line regimens consisted in cladribine (44%), pentostatin (30%), interferon (22%), rituximab (2%), or chemotherapy (2%). Overall response rate (ORR) was 80% (40/50), with complete remission (CR) rate of 38%. CR rate was not significantly associated with baseline cytopenias, age > 65 years or spleen enlargement (> 13 cm). Use of purine analogues was associated with a non-significant trend in higher CR rate (47%

vs 22%, p=0.26). Relapse/progression rate was 24/50 (48%), leading to further treatment in 19/24 (79%) patients. Second line consisted of cladribine (32%) or pentostatin +/- rituximab (32%) and other treatments (Table 1) with a total ORR of 95% (CR in 32%). Estimated 5-year and 10-year progression-free survival after first line were 68% (95%-confidence interval, CI, 56 – 84%) and 62% (CI 49–80%), respectively. Complete remission was associated with significantly longer PFS (p<0.001). Rate of grade > 2 hematological toxicity and infections was 70% (26/37) and 46% (18/39) of evaluable patients while rash was reported in 15/37 (41%) patients. Cladribine courses were associated with higher hematological grade >2 toxicity (in 23/31 courses, 74%) and infections (15/31, 48%) compared to pentostatin (4/7, 57%; 1/7, 14%; respectively) or interferon (2/8, 25%; 2/8, 25%; respectively). Despite a comparable duration of follow-up, patients exposed to pentostatin experienced a higher rate of second tumors compared to unexposed patients (5/19, 26% *vs* 2/40, 5%, respectively; p=0.03). After a median follow-up of 8.3 years only one death was recorded.

Conclusions. HCL frequently requires treatment after diagnosis. Cladribine produces high rates of CR, but may be associated with higher rates of infections and hematological toxicity. CR is associated with longer PFS.

P087

SEROLOGICAL AND CELL-MEDIATED IMMUNE RESPONSE TO COVID-19 VACCINATION IN PATIENTS WITH HEMATOLOGICAL LYMPHOID NEOPLASMS

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The higher mortality and morbidity observed for hematological patients infected with SARS-CoV2 has prompted the use of vaccination strategies to ameliorate the outcome, despite the lack of evidence owing to exclusion of these patients from pivotal clinical trials. Moreover, lymphoid malignancies and anticancer therapies result in a prolonged impairment of humoral responses, as observed for other vaccines. We prospectively analyzed the serological response (SR) for 162 patients with Hodgkin's disease (HD), Non-Hodgkin lymphomas (NHL) and chronic lymphocytic leukemia (CLL) after two mRNA COVID-19 vaccine doses and for 70 patients after the third vaccine dose, from 15/01/2021 to 07/05/2022; the cell-mediated response (CMR) was evaluated for 65 patients after two doses. 85% of patients were on active anticancer treatment. SR was observed in 36% of cases after two doses: 35% for patients with CLL, 42% for aggressive NHL (aNHL), 22% for indolent NHL (iNHL). All HD patients achieved SR. Treatment-naïve patients or treated with brentuximab or PD-1 inhibitors seroconverted in 57% of the cases. SR were lower for patients treated with monoclonal anti-CD20 antibodies within 6 months the vaccination (1.8%) and for patients treated with more than 8 doses of rituximab before vaccination (9%). SR was observed for 37% of patients in treatment with target therapies (ibrutinib, idelalisib, venetoclax). Increasing age, indolent lymphoma, lower IgG levels, absence of circulating B lymphocytes, LDH levels ≥ 480 UI/L, active treatment with immunochemotherapy, number of rituximab doses received (>8) and time from last rituximab were associated with an increased risk of no humoral response (p<0.05). At the multivariate analysis, age ≥60 years, IgG levels <600 mg/dL, absence of B lymphocytes and last rituximab dose within 6 months of the vaccine were significant factors (p<0.05). CMR was observed in 48% of the cases (43% for patients without seroconversion); no correlation between this response and other clinical parameters emerged at the univariable analysis. 26% of patients with no humoral response after two doses obtained the seroconversion after the third dose, but almost none of them was treated with rituximab.

Our study highlights that indolent lymphomas and recent treatment with rituximab severely limit the seroconversion even after the third dose. Cell-mediated response is apparently independent of the therapies received.

P088

TREATMENT SEQUENCING AND OUTCOME OF CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS TREATED AT FONDAZIONE POLICLINICO UNIVERSITARIO AGOSTINO GEMELLI IRCCS: A THIRTY-YEAR SINGLE-CENTER EXPERIENCE.

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Introduction. The introduction of covalent Bruton's Tyrosine Kinase inhibitors (cBTKi), B-Cell Lymphoma-2 inhibitor (BCL2i) into the chronic lymphocytic leukemia (CLL) care pathway has changed the treatment approach over the years. This monocentric retrospective observational study describes the treatment patterns and outcomes of patients (pts) with CLL, to better understand the impact of treatment sequencing in the novel targeted-agents era.

Methods. Adult CLL pts treated between 1992 and 2022 were included. Time-to-event outcomes were evaluated using Kaplan Meier method. Time to next treatment (TTNT) was defined as time from treatment start to the start of subsequent therapy or death. Time to next treatment failure or death (TTNTF) was defined as time from treatment discontinuation to the discontinuation of subsequent therapy or death.

Figure. Patients' characteristics and time to next treatment in BTKi-exposed and BCL2i-exposed patients according to the line of treatment.

Patients' characteristic	n=318
Male/Female	201/117 (63.2%/36.8%)
Median age at first treatment (range)	68 years (61-74)
Median time from diagnosis to first treatment (range)	24 months (7-51)
Del17p (not available = 39)	28/279 (10.0%)
TP53 mut (not available = 86)	42/232 (18.1%)
IGHV unmutated (not available = 63)	137/255 (53.7%)
cBTKi-exposed	157 (49.4%)
BCL2i-exposed	60 (18.9%)
BCL2i-exposed cBTKi- naive	34 (10.7%)
cBTKi- and BCL2i-exposed	26 (8.2%)
CIT-, cBTKi- and BCL2i-exposed	17 (5.3%)
cBTKi- and BCL2i- naive	127 (39.9%)

cBTKi = covalent Bruton's Tyrosine Kinase inhibitors; BCL2i = B-Cell Lymphoma-2 inhibitor; CIT = chemoimmunotherapy

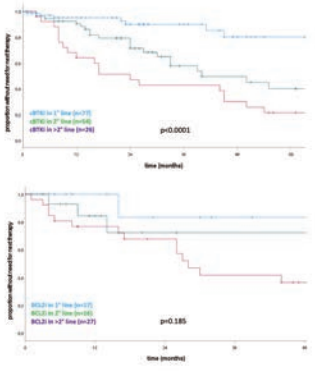

Figura 1.

Results. Of 637 registered pts, 318 (49.9%) received treatment (characteristics in Figure 1). Of 157 cBTKi-exposed pts, 77 (49%) received cBKTi frontline (1L), 55 (35%) in second line (2L), 28 (17.8%) after >2 lines of treatment (>2L). Collectively, the need for subsequent treatment or death was 30.6% (48/157). For the 34 BCL2i-exposed cBTKi-naïve pts, BCL2i was administered 1L in 13

(38.2%), 2L in 12 (35.3%), >2L in 11 (32.3%). Collectively, the need for subsequent treatment or death was 17.6% (6/34). For the 26 double-exposed pts, 96.1% (n=25) received BCL2i after cBTKi. Collectively, the need for subsequent treatment or death was 38.5% (10/26). Five-year TTNT in cBTKi-exposed pts were 80% (median NR), 40% (median 40 months), 21% (median 24 months) months in 1L, 2L and >2L respectively (p<0.0001). Five-year TTNT in BCL2i-exposed pts were 83% (median NR), 72% (median NR), 12% (median 28 months) in 1L, 2L and >2L respectively (p=0.185) (Figure 1). Median TTNTF was 9 months (range 1-87) for all pts who discontinued the cBTKi independently of the line of treatment, and 17 months (range 8-49) for those who discontinued both a cBTKi and BCL2i. TTNTF in double-exposed pts was higher probably because 4 pts in this group underwent allogeneic hematopoietic stem cell transplantation for high-risk CLL features or Richter's transformation.

Conclusions. Despite its limitations, this study shows how anticipating target therapy improved the outcome of CLL pts. Nonetheless, the poor outcomes in advanced lines of therapy also highlight the need for even more effective treatments, especially for younger and high-risk pts.

P089

THE EFFICACY OF VENETOCLAX AND RITUXIMAB COMBINATION IN RELAPSED CLL PATIENTS: FOCUS ON MRD AND IMMUNOLOGICAL ASPECTS

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Venetoclax (Ven), a selective BCL-2 inhibitor, is approved for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in first or further lines, in association with anti-CD20 monoclonal antibodies. Its combination with Rituximab in the Murano trial offered high percentages of responses and MRD negativity. By the immunological point of view, Ven treatment results in loss of naïve but not memory T cells, with increased levels of CD4+ and CD8+ T effector cells.

In the DEDALO protocol 22 relapsed CLL patients received Ven in combination with Rituximab for 2 years. The aim of this no-profit study was to evaluate 1) the ability of Ven to induce MRD negativity in real-life (assessed both by flow cytometry and by advanced ultrasonography) and 2) to investigate the eventual immunological action of Ven/Rituximab. These analyses were performed after 1, 6, 12, 18 months of treatment and at the stop therapy. All patients except one (95%) achieved MRD negativity already after one cycle of Ven and Rituximab; 6 stopped treatment, with 4 of them still being MRD-negative. The patient still MRD-positive at 24 months did never achieved the MRD response. The combined treatment was well tolerated, the most frequent serious adverse reactions being infections and neutropenia, especially after the first Rituximab infusion. No patients discontinued therapy for toxicity. From the immunological point of view, our data suggest that the first infusion of Rituximab induced T and B cell depletion; when Ven were used alone, B lymphocytes remained low, while NK and T naïve cells were stable respect to the first cycle. About TEMRA, data from literature showed their increased number during Ven assumption; in our experience, their number was extremely variable, according to different patients, without any correlation with the response or clinical features.

In conclusion, our study confirms the efficacy and safety of Ven and Rituximab in relapsed CLL patients; the data concerning MRD recapitulate those from literature; the eventual immunomodulating effect exerted by Ven has to been further evaluated in larger series and at further time points.

P090

NEXT GENERATION SEQUENCING (NGS) BASED MULTIGENE SCREENING FOR CHRONIC LYMPHOCYTIC LEUKEMIA: APPLICABILITY FOR DIAGNOSTICS AND PROGNOSIS

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Chronic lymphocytic leukemia (CLL) is characterized by a chronic relapsing course and biological and clinical heterogeneity. Genetic profiling by target NGS or whole genome sequencing (WGS) allows to identify molecular alterations in recurrent genes associated with prognosis and pathogenesis of disease. The significance of the mutational status of the IGHV and TP53 genes is known, but from recent WGS studies somatic variants in other genes have emerged as well as a role of CLL subclonal evolution. Nowadays, the predictive value of these genes is not clearly established, therefore the use in clinical practice of a universal and complete gene panel is a challenge. In our Center a custom panel was designed with 23 genes correlated with haematological-lymphoid disorders (ATM, BCL2, BIRC3, BRAF, BTK, CDKN2A, CDKN2B, CRLF2, CXCR4, EGR2, FBXW7, IKZF1, KRAS, MYC, MYD88, NFKBIE, NOTCH1, PLCG2, POT1, RB1 , SF3B1, TP53, XPO1). 26 patients diagnosed with pretreatment, relapsed, and therapy-resistant CLL were tested. Among these 65% the analysis of the mutational status of the IGHV gene was also performed by NGS. Interpretation of NGS results follows ACMG/AMP guidelines. 88% of samples were carrier of Tier I, Tier II, and Tier III class variants in several genes of the panel. In particular, the most frequently mutated genes were FBXW7, TP53, XPO1, NOTCH1, POT1, ATM and SF3B1. Less variants were found in BIRC3, BRAF, CDKN2A, CXCR4, EGR2, KRAS, MYD88, RB1 genes. The remaining genes showed only benign or likely benign (Tier IV) variants. ATM, NOTCH1 and POT1 genes presented more Tier III variants than other genes, most of which with allele frequencies suggestive of a state of germline heterozygosity. The clinical significance of the identified variants still remains unclearly defined, however not only variants in TP53 but also in NOTCH1, SF3B1 and XPO1 genes seem to be related to cases of refractory to chemotherapy or progressive CLL. Furthermore, Tier I variants correlate with unmutated IGHV. The design of this panel represents a proof of concept study, NGS analysis appears to have a valid approach to study the genetic profile of CLL. The results, although the limited number of patients, suggest the clinical role of our panel, however considering a possible future revision of the genes.

P091

"KINETICS OF LYMPHOCYTOSIS IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS TREATED WITH BTK COVALENT INHIBITORS IN FIRST LINE". AN ITALIAN MULTICENTER EXPERIENCE OF REAL LIFE

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Introduction. The first phase of treatment with covalent Bruton's tyrosine kinase inhibitors (cBTKi) is characterized by an increased absolute lymphocyte count (ALC) in chronic lymphocytic leukemia (CLL). Ibrutinib (IBR) induces lymphocytosis in about 57% of patients (pts) treated in 1st line. This phenomenon is transient in most pts, resolving within 8 months, but can rarely persist over 12 months, without impact on survival. Despite lymphocytosis in IBR has been widely investigated, little is known about the presence and duration of lymphocytosis in pts treated with Acalabrutinib (Acala).

Aims. The main purpose of this study is defining kinetics of drug-induced lymphocytosis during treatment of CLL pts with Acala or IBR, to underline possible differences in terms of entity and duration of the lymphocytosis.

Methods. We retrospectively enrolled 204 pts (127 male and 77 female), treated in first line with cBTKi (136 IBR and 68 Acala), from 16 different Italian centers, with last follow up in April 2023. For each patient we collected data about the burden of disease at baseline, the biological features of the disease and the ALC at the baseline and at well-defined time-points (first two weeks, 1, 2, 3, 6, 9, 12 months) over an observational period of 1 year (Table 1).

Results. We observed a median ALC increase after the beginning of therapy both in the IBR and in the Acala group. Median lymphocytosis was higher than baseline during the first month of treatment in both cohorts. A progressive decrease in median ALC occurred from the second month of treatment in both groups: at this time-point, median lymphocyte count was 62% of baseline in Acala cohort *vs* 84% in IBR cohort (p 0.025). From 6th month to the end of the study, we found differences in the ALC with higher counts in IBR. At 6th month median ALC was 6960/microL in Acala *vs* 11010/microL in IBR group, at 9th 4550/microL *vs* 8230/microL and at 12th 2740/microL *vs* 5520/microL (Table 1).

Conclusions. Acala can determine, like IBR, an increase of ALC immediately after starting therapy. Therefore, lymphocytosis appears as a cBTKi-class effect. Despite this, the kinetics of lymphocytosis are not overlapping when comparing the two drugs. From the 6th month ALC reached almost-normal values in Acala group, with significant statistical differences compared to IBR.

Our results suggest that lymphocytosis seems to be less durable and to resolve faster in pts treated with Acala than in those treated with IBR.

Clinical and Biological features and results

Clinical and Biological characteristics 204 patients (last follow up April 2023)					
		All patients n=204	Ibrutinib arm n=136	Acalabrutinib arm N=68	P-value
Age (163/204)	Median years	72	73	71	0.593
Gender (204/204)	M, n (%) F, n (%)	127 (62) 77 (38)	82 (60) 54 (40)	45 (66) 23 (34)	0.413
Rai Stadium (204/204)	A, n (%) B, n (%) C, n (%)	23 (11) 92 (45) 89 (44)	20 (15) 63 (46) 53 (39)	3 (4) 29 (43) 36 (53)	**0.040**
Lymph nodes (203/204)	Absent < 5 cm 5-10 cm > 10 cm	13 118 46 26	11 80 27 18	2 38 19 8	0.34
Splenomegaly (204/204)	n	138	89	49	0.34
FISH, n	del 17p (198/204) del 11q (199/204) del 13q (198/204) trisomy 12 (198/204)	48 19 63 36	42 6 46 23	6 13 17 13	**0.0007** **0.0005** 0.272 0.591
Molecular Biology, n	TP53 (193/204) NOTCH1 (127/204)	66 14	59 6	7 8	**< 0.001** **0.028**
IgVH mutational status, n	mutated unmutated (168/204)	65 93	44 64	21 29	0.464

Figura 1.

Acute leukemias

P092

FEASIBILITY AND EFFICACY OF PEG-ASPARAGINASE-BASED TREATMENT IN ELDERLY PHILADELPHIA NEGATIVE ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS

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Treatment of elderly Acute Lymphoblastic Leukemia (ALL) is a major clinical challenge due to the low intensive chemotherapy tolerability and high therapy-related mortality. To limit toxicity, elderly patients are treated with reduced-intensity protocols that however fail to provide adequate efficacy. The use of high-dose PEG-asparaginase (PEGASP) in older patients is debated, due to perceived risk of toxicity. We explored the feasibility and efficacy of reduced toxicity induction chemotherapy combined with early and intensive PEGASP administration in elderly patients (>60 yy) with Philadelphia negative ALL. Patients received reduced induction chemotherapy with PEGASP administration at 2000 UI/sqm on day 10 and 24 (with further doses adjustment according to age) followed by 8 consolidation cycles, 4 of them including PEG-ASP in association with high-dose methotrexate. Minimal residual disease (MRD) was measured by flow cytometry (MFC) and RT-PCR for JH rearrangements (MOL), after induction (TP1) and before each consolidation cycle.

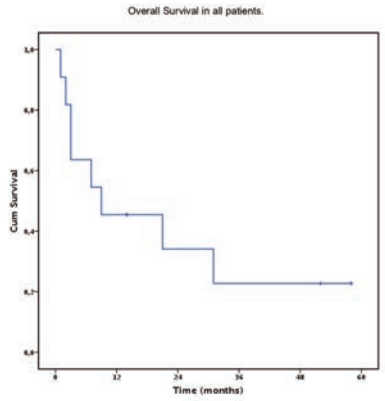

Figura 1.

Eleven patients have been enrolled so far, 9 B-ALL and 2 T-ALL. Median age was 65 years. Ten out of 11 were defined unfit as per SIE-SIES-GITMO criteria. Two patients died due to infections before response assessment. Complete remission (CR) rate at TP1 was 72%. MFC was negative at TP1 in 6/8 (75%) responding patients, whereas MOL was negative in 4/8 patients (50%). All except one patient were able to achieve MOL and MFC MRD negative during consolidation phases. Most responding patients were able to proceed with all the planned consolidation courses. Patients received a median cumulative dose of 6300 UI/sqm of PEG-ASP, with a median of 4 administrations. Overall, PEG-ASP related toxicity was acceptable, and was mostly asymptomatic increase in bilirubin or liver enzymes. After a median follow up of 39 months (CI 95%: 23.4-46.1), 1 patient relapsed and died, 4 patients died while in MRD negative remission due to infections. All other patients are alive and in a MRD negative status. 3-year OS was 38% (median 21 months). Our real-life data demonstrate the feasibility of the intensive and early use of PEG-ASP associated to antimetabolic therapy in elderly ALL patients with encouraging CR and MRD negativity rate at the end of induction phase. Infections represent the leading cause of death. In this view the incorporation of novel targeted drugs may further improve the outcome.

P093

FULL PEDIATRIC INDUCTION ACCORDING TO AIEOP-BFM LAL 2009 IN ADULTS WITH PHILADELPHIA-NEGATIVE ACUTE LYMPHOBLASTIC LEUKEMIA: A FEASIBLE AND EFFECTIVE THERAPEUTIC STRATEGY

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Historically, treatment of acute lymphoblastic leukemia in adults showed unsatisfactory outcomes, if compared to the outstanding results obtained in pediatric patients. Pediatric protocols rely on increased drug intensity and on a tighter evaluation of minimal residual disease (MRD) for early intensification. Pediatric-inspired protocols have been established as the standard of care for adolescents and young adult patients (AYA) but their feasibility in older patients is still matter of debate. The aim of our study was to evaluate the feasibility and efficacy of the full pediatric AIEOP-BFM LAL 2009 protocol in a cohort of adult patients up to 55 years. Since May 2013, 28 consecutive adults diagnosed with Ph-neg ALL received first line therapy according to AIEOP-BFM-ALL 2009 protocol, which includes high PEG-asparaginase (PEGASP) doses. Fifteen patients had B-ALL, 13 T-ALL/T including 5 Early-T phenotype. Dose intensification and stem cell transplantation were scheduled according to baseline and MRD-driven risk assessment. All patients achieved complete hematological remission after first Induction course (100%). One patient died during induction due to infection by multidrug resistant P. aeruginosa. Eight patient had G3-4 infections during induction.

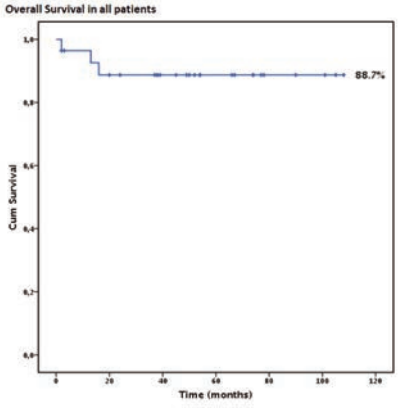

Figura 1.

In general, therapy was well tolerated. Remarkably, patients in this study received high dose of PEGASP (median 10000 UI/sqm, equal to 4 administrations at 2500 UI/sqm each) without experimenting life threatening toxicities, which mostly consisted in asymptomatic elevation of transaminase (7 patients G3, 1 G4) and/or bilirubin (9 patients G3, 1 G4) requiring supportive therapy. No major bleeding or thrombotic events o other >G2 toxicities were observed.

After a median follow up of 54 months (CI 95% 33.85-74.15), median survival was not reached, 5-years OS was 88.7% (Figure 1). One patient died due to progressive transverse myelitis after isolated CNS relapse and 1 patient died due to sudden cardiac arrest while in complete MRD negative remission. All other 25 patients are alive and in complete MRD negative remission. The application of a full pediatric induction regimen in a cohort of adult ALL patients with a median age of 45 years proved to be feasible, with mild toxicities. Specifically, we didn't observe major toxicities during the intensified PEGASP administration, and all patients were able to receive the planned PEGASP doses. This translated in very high MRD negativity rate and promising OS.

P094

ABSTRACT WITHDRAWN

P095

LOW RATE OF INFECTIOUS COMPLICATIONS AFTER INTENSIVE PEDIATRIC-LIKE CHEMOTHERAPY (INDUCTION VS CONSOLIDATION) IN ACUTE LYMPHOBLASTIC LEUKEMIA, OMITTING ANTIBACTERIAL PROPHYLAXIS

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Data about infections after intensive chemotherapy (cht) for Acute Lymphoblastic Leukemia (ALL) are limited. Fluoroquinolone (FCQ) prophylaxis in severe neutropenia is used as standard care because it reduces fever episodes, infections and mortality. Considering the high local FCQ resistant strains and to reduce the incidence of multidrug resistant bacteria, our center started to omit antibacterial prophylaxis. We report a real-life experience of 75 hospitalization for prolonged neutropenia (≥7 days) after intensive cht according to pediatric-like protocols (NILG10/07, GIMEMA LAL1913 and GIMEMA LAL2317) in 41 ALL patients (pts) treated from January 2015 to December 2022. The median age was 48 years (17-75), 23/41 were male and 18/41 female. 33/41 had a B-ALL, while 8/41 had a T-ALL. Our population received antifungal prophylaxis (liposomal amphotericin b 50mg/2 days), without receiving FCQ prophylaxis. All pts characteristics are summarized in Table 1. Fever, defined as a single temperature (T) measurement of ≥38.5°C or a T of ≥38.0 °C in two consecutive detections over a 1-hour period, occurred in 51/75 cycles: induction (41 events) and consolidation (34 events). In induction cycles we registered 11/41 fever of unknown origin (FUO) and we observed 15/41 microbiologically documented infections: 14/41 bacterial infections (70% gram negative, 30% gram positive), 7/41 fungal and 2/41 viral ones. Additionally, we recorded 8/41 radiologically documented infections: 4/41 were fungal, 3/41 were bacterial while 1/41 was viral; septic shock occurred in 5/41 pts. Considering consolidation cycles we registered 10/34 FUO and 11/34 microbiologically documented infections: 11/34 were bacterial (73% gram negative, 27% gram positive) and 3/34 were fungal. Finally, we recorded 5/34 radiologically documented infections: 3/34 were fungal and 2/34 bacterial. Septic shock occurred in 2/34 pts. Overall mortality was 4/41 (9,8%): two for progressive disease, one treatment related and one for an aspergillus pneumonia, thus the infection related mortality was 1/41 (2,4%), lower than data reported in comparable setting. With the limitations of a small population, our results support the safety of avoiding FCQ prophylaxis in ALL pts with benefits in containing the risk of multi-resistant infections, although we think it is mandatory to have an efficient protocol for prompt treatment of neutropenic fever.

Table 1. Baseline, treatment characteristics and infection events.

Baseline characteristics	**ALL pts (n=41)**	
Median Age (years) (range)	48,5 (17-75)	
Sex		
male	23 (56%)	
female	18 (44%)	
B-ALL	33 (80%)	
T-ALL	8 (20%)	
Risk classification (according to NILG)		
very high risk	25 (61%)	
high risk	2 (5%)	
standard risk	14 (34%)	
Censor reason		
next treatment	37 (90%)	
death	4 (10%)	
infectious related death	1 (0,5%)	
Treatment characteristics	**Induction cycles (n=41)**	**Consolidation cycles (n=34)**
Baseline ANC count		
< 500/mmc	8 (20%)	1 (3%)
≥ 500/mmc	33 (80%)	33 (97%)
Median days at risk (ANC < 500/mmc) (range)	12 (7-38)	12 (7-22)
Median days at risk (ANC < 100/mmc) (range)	8 (3-37)	8 (3-12)
Median hospitalization time (days) (range)	20 (14-45)	20 (8-25)
Infection events	**Induction cycles (n=41)**	**Consolidation cycles (n=34)**
Fever		
yes	31 (76%)	20 (59%)
no	10 (24%)	14 (41%)
FUO		
yes	11/31 (35%)	10/20 (50%)
no	20/31 (65%)	10/20 (50%)
Microbiologically documented infections	15 (37%)	11 (32%)
bacterial	15 (37%)	11 (32%)
gram negative	10 (24%)	8 (24%)
gram positive	5 (12%)	3 (9%)
virus	2 (5%)	0
fungal	7 (17%)	3 (9%)
Radiologically documented infections	8 (20%)	5 (15%)
bacterial	3 (7%)	2 (6%)
virus	1 (2%)	0
fungal	4 (10%)	3 (9%)
radiologically documented only	3 (7%)	1 (3%)
Site of infection		
bloodstream	13 (32%)	8 (24%)
upper respiratory tract	0	0
lower respiratory tract	2 (5%)	2 (6%)
gastrointestinal	3 (7%)	1 (3%)
skin	0	0
central nervous system	0	0
genito-urinary	1 (2%)	1 (3%)
Treatment related ICU admission (VOD)	1 (2%)	0

ALL: acute lymphoblastic leukemia, pts: patients, NILG: Northern Italy Leukemia Group, ANC: absolute neutrophil count, FUO: fever of unknown origin, ICU: intensive care unit, VOD: veno-occlusive disease

P096

ABSTRACT NOT PUBLISHABLE

P097

IMPACT OF NGS ANALYSIS ON THE CHARACTERIZATION, DIAGNOSTIC CLASSIFICATION AND PROGNOSTIC STRATIFICATION OF ACUTE MYELOID LEUKEMIA

S. Martinelli[1], A. Paolini[1], R. Maffei[1], B. Conte[1], F. Giacobbi[1], G. Corradini[1], F. Pilato[1], D. Bernabei[1], G. Riva[1], V. Nasillo[1], F. Forghieri[2], A. Candoni[2], M. Morselli[2], L. Potenza[2], D. Giusti[2], E. Colaci[2], F. Bettelli[2], P. Bresciani[2], A. Cuoghi[2], A. Gilioli[2], A. Messerotti[2], V. Pioli[2], M. Maccaferri[2], G. Leonardi[2], R. Marasca[2], M. Luppi[2], T. Trenti[1], E. Tagliafico[1]

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A retrospective study based on Next Generation Sequencing

(NGS) analysis of samples collected from 69 patients with acute myeloid leukemia (AML) at diagnosis, mainly 'de novo' and with normal karyotype, was performed with the main aim of redefining the diagnosis and prognosis according to World Health Organization (WHO), International Consensus Classification (ICC) and European Leukemia Net (ELN) 2022 guidelines, in comparison to the previous ones. We therefore evaluated the presence of gene mutations, in relation to these classifications (Table 1) and to clinical outcomes such as RFS (relapse-free survival) and OS (overall survival).

Table 1. Diagnostic classification and prognostic stratification of 69 AML cases according to old and new guidelines

	ELN 2017 PROGNOSTIC STRATIFICATION					
	F RISK		I RISK		A RISK	
DIAGNOSTIC CLASSIFICATION	N° cases	% cases	N° cases	% cases	N° cases	% cases
WHO 2016						
AML-NOS (n=25)	0/25	0%	24/25	96%	1/25	4%
AML-RGA (n=38)	22/38	57.9%	16/38	42.1%	0/38	0%
AML-MRC (n=5)	0/5	0%	5/5	100%	0/5	0%
AML-THER (n=1)	0/1	0%	0/1	0%	1/1	100%
	ELN 2022 PROGNOSTIC STRATIFICATION					
	F RISK		I RISK		A RISK	
DIAGNOSTIC CLASSIFICATION	N° cases	% cases	N° cases	% cases	N° cases	% cases
WHO 2022						
AML-DBD (n=14)	0/14	0%	9/14	64.3%	5/14	35.7%
AML-DGA (n=55)	24/55	43.6%	14/55	25.5%	17/55	30.9%
ICC 2022						
AML-NOS (n=9)	0/9	0%	9/9	100%	0/9	0%
AML-RGA (n=40)	24/40	60%	14/40	35%	2/40	5%
AML-MRCgen (n=20)	0/20	0%	0/20	0%	20/20	100%

Legend: ELN=European Leukemia Net; F=favourable; I=intermediate A=adverse; WHO=World Health Organization; NOS=not otherwise specified; RGA=recurrent genetic abnormalities; MRC=myelodysplasia related changes; THER= therapy related; ICC=International Consensus Classification; MRCgen=myelodysplasia related genetic changes; DBD=defined by differentiation; DGA=defining genetic abnormalities

All patients had at least 1 mutated gene and 82.6% at least 2, with a higher frequency of mutations in NPM1 and DNMT3A genes. We found positive correlations between the variant allele frequencies (VAFs) of NPM1, DNMT3A and TET2 genes (all $p<0.005$) and positive associations between NPM1 and PTPN11 mutations ($p=0.005$), between KIT and NRAS mutations ($p=0.013$) or CSF3R mutations ($p=0.037$), between SF3B1 and RUNX1 mutations ($p<0.001$). Conversely, we observed that NPM1 mutations were mutually exclusive with CEBPA mutations ($p=0.027$) or RUNX1 mutations ($p=0.014$). Genes showing multiple variants in a same patient were TET2, CEBPA, FLT3, DNMT3A, RUNX1, WT1 and KIT. Re-stratifying the risk of AML cases, the adverse-risk group increased from 2.9% (according to ELN 2017) to 31.9% (according to ELN 2022), the intermediate-risk one decreased from 65.2 % (ELN 2017) to 33.3% (ELN 2022), whereas the favorable-risk group remained quite constant. ELN 2022 guidelines enabled to separate patients with significantly different OS ($p=0.016$) better than ELN 2017 recommendations (p=n.s). Furthermore, the presence of CSF3R or ZRSR2 mutations could stratify patients with different RFS, with the mutated cases relapsing earlier than non-mutated ones ($p=0.016$ and $p=0.031$, respectively). Mutated CSF3R gene was also associated with AML cases having shorter OS, as well as mutated SRSF2 gene ($p=0.047$ e and $p=0.027$, respectively), even in the favorable-risk ELN group. Our data confirmed a better stratification by ELN 2022 guidelines in identifying the adverse-risk patients at diagnosis, thus allowing an optimization in transplant procedures timing. Of note, although deserving further confirmation in larger case series, our data may suggest a possible inclusion of CSF3R mutations in the future diagnostic and prognostic AML classifications.

P098

NPM1-MUTATION TRANSCRIPT MONITORING DURING GILTERITINIB TREATMENT IDENTIFIES DIFFERENT DYNAMICAL PATTERNS IN RESPONSIVE PATIENTS

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Background. Gilteritinib (Gilt) is a potent FLT3-inhibitor approved for relapsed/refractory (R/R) *FLT3*-positive (*FLT3*+) acute myeloid leukemia (AML). 45% of *FLT3*+ AML harbor concomitant *NPM1* mutations (*NPM1*m) that allow minimal residual disease (MRD) monitoring via *NPM1*m-specific qRT-PCR assay. The *NPM1*m transcript course under treatment with Gilt is currently unknown.

Aims. To explore the dynamics of *NPM1*m transcript in disease monitoring in *FLT3*+*NPM1*m AML patients (pts) treated with Gilt.

Materials and Methods. R/R *FLT3*+*NPM1*m AML pts responsive to Gilt were retrospectively evaluated. Inclusion criteria: 1) achievement of at least morphological leukemia free state (MLFS); 2) availability of ≥2 on-Gilt time-points for *NPM1*m analysis (relapse and post transplantation excluded). Disease was assessed on bone marrow (BM), results are reported as *NPM1*m copy number/*ABL* copy number x 100. Significant increase/decrease between samples was defined as a variation >1 logarithm (log).

Results. 12 pts (median age, 57 ys; range 32-71 ys) treated with Gilt were analyzed; 8 of 12 (67%) were treated at salvage 1 (S1), 3 (25%) at S2, 1 (8%) at S3. At Gilt treatment, 10 (83%) pts had *FLT3*-ITD (7 ARhigh, 2 ARlow, 1 unknown), 2 *FLT3*-TKD. The most frequent comutation at diagnosis was *DNMT3A* in 8 of 9 (89%) pts. Median *NPM1*m transcript at Gilt treatment was 69,65% (range, 0,53-245). Median BM blast count was 20% (range, 5-90).

Median n of Gilt cycles (post-transplant cycles excluded) was 5 (range 3-13). BM response (CR/CRh/CRi) was achieved after a median of 2 cycles (range, 1-5); 1 patient achieved MLFS. Three trends for *NPM1*m transcript were observed: 1) log reduction>1 (n=3); 2) log increase>1 (n=4); 3) stable values (n=5). Paired *NPM1*m and *FLT3*-ITD AR evaluation was available for the 10 *FLT3*-ITD pts. In pts experiencing *NPM1*m reduction, *FLT3*-ITD AR decreased in concordance with *NPM1*m transcript (3/3 pts); in patients experiencing increase, *FLT3*-ITD AR was stable in 2/3 pts, 1 became *FLT3*neg; in patients with stable *NPM1*m levels *FLT3*-ITD AR was stable (3/4), 1 became *FLT3*neg. Median follow-up is 13.4 mo (range, 5.6-52.0). 8 pts proceeded to HSCT, 2 died from NRM, and 6 are alive in CR. The 4 (33%) pts who did not undergo HSCT relapsed; in all cases *NPM1*m transcript increase was observed.

Summary. *NPM1*m monitoring in Gilt sensitive pts may follow different dynamical patterns, maybe reflecting drug-induced differentiation and not necessarily correlating with disease burden.

P099

APPLICABILITY OF SIE/SIES/GITMO FITNESS CRITERIA TO THERAPY-RELATED AND AML-MRC RECEIVING CPX-351: A RETROSPECTIVE, MULTICENTRIC, OBSERVATIONAL STUDY

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Treatment of therapy-related (t-AML) and AML evolving from an antecedent myelodysplastic syndrome (AML-MRC) represent a clinical unmet need being characterized by an unfavorable outcome. Among the emerging treatment options, CPX-351 has been approved by EMA and FDA for the treatment of fit patients (pts) affected by these AML sub-types. Although patented for the treatment of pts fit for intensive chemotherapy, in real-life CPX-351 is also administered to unfit ones, raising the case of tolerability in these categories. Among scores for fitness definition, SIE/SIES/GITMO criteria were extensively validated in large cohorts of AML pts receiving intensive chemotherapy and are now firmly incorporated into clinical trials. However, since these criteria have not been tested yet in the subset of t-AML and AML-MRC, we investigated their applicability in pts with these diseases and that received CPX-351. This retrospective study includes 281 pts with t-AML or AML-MRC enrolled from 19 Italian Institutions between 2018 and 2023. Median age was 65 years (range 32-79), with a slight male prevalence (54.8%). According to SIE/SIES/GITMO criteria, 225 (80%) pts qualified as fit and 56 (20%) as unfit. After 1-2 induction courses, 138 of 225 (61.3%) fit and 36 of 56 (64.3%) unfit achieved a complete remission (CR), for a total of 174 (61.9%) pts entering CR. From CPX-351 start, 11 and 42 deaths at day 28 and 100 occurred, respectively. Death rate at 28 days did not differ between the two groups (2.7% *vs* 9.1% for fit and unfit respectively; p=0.06). Conversely, a significantly higher mortality rate at 100 days was observed among unfit as compared to fit pts (13.6% *vs* 28%, respectively; p<0.01). Accordingly, unfit pts were characterized by a significantly shorter survival as compared to fit ones (median overall survival of 9 months [CI 95%: 4.089-13.911] and of 19 months [CI 95%: 15.3-22.7] for unfit and fit pts, respectively; p<0.01) [Figure 1]. Competitive risk analyses showed no differences in terms of early death by relapse between the two groups. In this retrospective analysis, we demonstrated the applicability of the SIE/SIES/GITMO criteria in pts with t-AML and AML-MRC submitted to CPX-351. As unfit patients were more likely to experience early death and shorted survival, these findings may help optimize the use of CPX-351 in this specific AML category. In this view, an optimization strategy may be the delivery of attenuated doses in unfit pts.

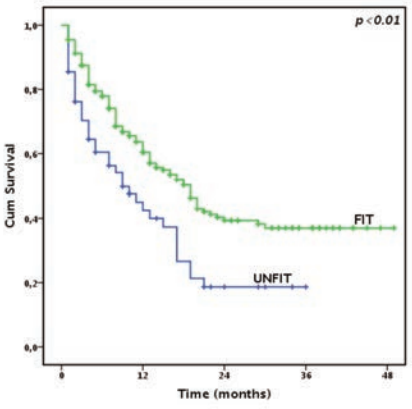

Figura 1. Median OS of the whole study group, stratified according to fitness status. Unfit patients were characterized by a significantly shorter survival as compared to fit ones (Median overall survival of 9 months [CI 95%: 4.089-13.911] and of 19 months [CI 95%: 15.3-22.7] for unfit and fit patients, respectively; p<0.01).

P100

REAL WORLD EXPERIENCE OF CPX-351 IN PATIENTS WITH HIGH-RISK ACUTE MYELOID LEUKEMIA (AML): THE MULTICENTER COHORT OF "ITALIAN TRIVENETO REGISTRY"

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Background. CPX-351, a liposomal encapsulation of cytarabine and daunorubicin, has been approved for the treatment of patients with newly diagnosed therapy-related Acute Myeloid Leukemia (t-AML) or AML with myelodisplasia-related changes (MRC-AML), improving survival probabilities in comparison with standard chemotherapy. To provide more clinical data we describe the Italian experience with CPX-351 as first-line therapy in a real world setting, outside of clinical trials or compassionate use program.

Patients and Methods. We retrospectively analyzed a cohort of 103 newly diagnosed AML pts treated in-label with CPX-351 in 11 Italian Hematological Centers from August 2019 to August 2022. Median age at diagnosis was 65 yrs (range 34-83). Sixty-two pts (60%) were diagnosed with secondary AML (sAML) evolving from myelodisplastic syndrome, 21 pts with MRC-AML (20%) and 20 patients with t-AML (19%). The cytogenetic risk (according to ELN

2017) was adverse in 48/103 pts (46.6%). A total of 31 pts (30%) had been treated previously with hypomethylating agents (azacitidine). All pts received the induction cycle at a standard dose. 55/103 pts (53,3%) received at least 2 courses of CPX-351 and 46/103 pts (44.6%) proceeded to allogeneic hematopoietic stem cells transplant (HSCT).

Results. In 97 evaluable pts the Overall Response Rate (ORR=CR+CRi) after the induction course was obtained in 76 pts (73.7%) with a median of 38 days from start of therapy. After a median follow up of 9.5 months (range 0.23-35.5) we observed a median response duration of 8 months (range 0.5-32). At last follow-up, 60/103 pts (58%) were still alive while the main cause of death was disease progression (in 30 out of 43 deceased pts, 69.7%). Twelve-months overall survival was 68.4%, while in the subset of patients that underwent HSCT the observed twelve-months OS was 91.5%. Multivariate analysis of factors affecting response showed no statistically significant predictors of a lower response. CPX-351 was generally well tolerated without onset of severe mucositis. The most common toxicities were myelosuppression and infective complications.

Conclusions. These data confirm the efficacy and the emerging role of CPX-351 in the real word management of high risk AML, as well as the importance of HSCT consolidation in this particular subset of AML pts. Future directions include determining dose optimization with CPX-351 to induce an MRD-negative at transplant and studying new combination with target therapies.

P101

ABSTRACT NOT PUBLISHABLE

P102

REPURPOSING OF ANTIBIOTICS INHIBITING MITOCHONDRIAL TRANSLATION IN COMBINATION WITH VENETOCLAX IN ACUTE MYELOID LEUKEMIA: PRELIMINARY RESULTS FROM A ACC-HEMA NETWORK MULTICENTER STUDY

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Venetoclax (VEN) resistance is an unmet clinical need in acute myeloid leukemia (AML). Pharmacological disruption of mitochondrial respiratory chain is a promising strategy to circumvent VEN resistance. We previously confirmed that Tigecycline (Tig) and Linezolid (Lin), two antibiotics largely used in AML patients (pts), inhibit mitochondrial respiration in preclinical AML models, demonstrating acceptable safety and promising efficacy in a small cohort of patients with AML receiving Tig and Lin combination with VEN-based regimens. To extend our observations and increase the sample size, we retrospectively reviewed a multicentric cohort of all AML pts treated with VEN between 2018 and 2023 within the Hematology Working Group of Alliance against Cancer (ACC-Hema) Network, focusing on pts receiving VEN and concomitant antibiotic therapy with Lin or Tig for at least 7 days in the context of infectious complications during the normal clinical practice. We analyzed clinical data of 13 AML pts treated with Lin 600 mg bid (n=9) or Tig 50 mg bid (n=4) during VEN-based regimens at 5 ACC-Hema Centers. VEN-based regimens included hypomethylating agents (HMA) in 12 cases, cytarabine (AraC) in 1 patient. Median age was 51 y.o. (35-76), median time of exposure to combination treatment was 9 days (7-24). Two heavily pretreated pts died of sepsis shortly after treatment (unrelated to Lin), without response evaluation. Notably, in the remaining pts (n=11) we did not observe any extrahematologic toxicity or delayed hematologic recovery. Three pts died of disease progression: 1 treated in first-line, 2 in second line. Overall, 11 pts were evaluable for response. Complete remission (CR) was observed in 6 pts (54%): 4 first-line pts achieved CR [3 with decitabine (DEC)-VEN-Lin and 1 with azacytidine (AZA)-VEN-Tig]. The remaining 2 pts achieving CR were treated for their second AML recurrence with AZA-VEN-Tig and AraC-VEN-Lin. Notably, 4 of the pts achieving CR had high risk AML, 2 had intermediate risk. The CR rate in first-line was 80%. Partial remission was achieved in 2 pts treated with AZA-VEN-Tig and DEC-VEN-Lin in the relapse/refractory setting. The overall response rate (ORR) in the whole cohort was 73%. In conclusion, mitochondrial translation inhibitors such as Lin or Tig are confirming preliminary signals of efficacy and favorable safety profile in combination with VEN-based therapy in AML. Enrollment is ongoing and updated results will be presented at the meeting.

P103

DISTINCT MUTATIONAL AND MORPHOLOGICAL PROFILE CHARACTERIZES PATIENTS WITH MYELOID NEOPLASMS HARBORING SRSF2-IDH1/2 DOUBLE MUTATIONS

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A prospectively collected cohort of 266 patients with myeloid neoplasms underwent evaluation for myeloid-related gene mutational status by targeted next-generation sequencing in peripheral blood or bone marrow diagnostic samples. We identified 17 (6.4%) patients harboring concomitant mutations in SRSF2 and IDH1 or IDH2 genes, defined as SRSF2/IDH-double mutant (DM) subset. A linear correlation was detected between variant allelic frequencies identified in SRSF2 and in IDH1/2 genes (p=0.02). Only 2 out of 17 cases showed subclonal IDH1/2 mutations (VAF=2.5% and 5.1%). We evaluated the mutational pattern, morphology and clinical outcome of this genetic subset as compared to patients harboring SRSF2-only (n=17, 6.4%) or IDH1/2-only (n=21, 7.9%) mutated genes. Lack of TET2 mutations was observed in SRSF2/IDH-DM subset (0% *vs* 14% and 53% in SRSF2/IDH-DM *vs* SRSF2-only and IDH-only subsets, p<0.001). Mutations in ASXL1 and DNMT3A were mutually exclusive in SRSF2/IDH-DM subsets, whereas multiple mutations of TET2 and DNMT3A were observed in SRSF2-only subset. Overall, DTA genes (DNMT3A, TET2 and ASXL1) were mutated in 88% of SRSF2-only subset and in 65% of cases in the other subsets.

SRSF2/IDH-DM cases showed higher frequencies in CEBPA mutations (p=0.033, compared to SRSF2-only subset) and in mutations affecting RUNX1, JAK2 and CSF3R (p<0.05, compared to IDH-only subset). Two patients displayed concomitant mutations in splicing factors i.e., SRSF2 and SF3B1. Other genes involved in splicing regulation such as U2AF1 and ZRSR2 were exclusively present in IDH-only subset. In AML cases, single- or multilineage morphological dysplasia was seen more frequently in SRSF2-only as compared to SRSF2/IDH-DM and IDH-only subsets (38.5% *vs* 12% and 0%, p=0.02). The median percentage of blast cells in bone marrow samples was 53% in IDH-only cases, 36% in SRSF2/IDH-DM and 24% in SRSF2-only subsets (p<0.05). We did not observe any differences in overall survival (OS) between SRSF2/IDH-DM and other subsets. Nevertheless, the presence of mutations in ASXL1 and JAK2 genes, age >65 years and the presence of fibrosis were associated with reduced OS (p<0.05, Kaplan-Meier), whereas NPM1-mutated gene characterized patients with better outcome. Overall, a typical mutational pattern and distinct morphological features defined patients affected by myeloid neoplasms with concomitant mutations in SRSF2 and IDH1/2.

P104

NUTRITIONAL ASSESSMENT VIA BIOELECTRICAL IMPEDANCE ANALYSIS IN PATIENTS UNDERGOING INTENSIVE CHEMOTHERAPY FOR ACUTE MYELOID LEUKEMIA

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Fit patients (pts) with acute myeloid leukemia (AML) are conventionally administered repeated cycles of intensive chemotherapy (CHT), often followed by allogeneic hematopoietic stem cell transplant. Pts need to be hospitalized in a protected setting, they are often prescribed a neutropenic diet, and chemotherapy-induced gastro-intestinal toxicity is common. As a result, nutritional imbalance is frequently observed.

Aim of this study was to systematically assess the nutritional status of pts undergoing treatment for AML and to explore early predictors and associations with known nutritional risk scores and relevant clinical outcomes. Monitoring included a bioelectrical impedance analysis (BIA) performed by a dietitian to assess fat mass (FM), fat-free mass (FFM), body cell mass (BCM) and the phase angle (PhA) together with standard measures (body weight, BW; body mass index, BMI). Variations in nutritional parameters at day 7 (dif7) and day 14 (dif14) after admission were calculated and tested for correlation with variations of the same parameter at discharge from the same cycle (dif30) or at discharge after the first consolidation cycle (dif60). From March 2021 to March 2023, 26 pts with newly diagnosed AML (median age 55y, range 21-74) were monitored during a total of 61 cycles of intensive CHT (35 induction cycles, 26 consolidation cycles). Median Nutritional Risk Score 2002 (NRS) at enrolment was 3 (range 2-6). Median follow up for surviving pts is 300 days.

We observed a significant reduction in FFM and BCM during induction cycles. These trends were observed irrespectively of baseline NRS, disease response, or fever lasting more or less than 7 days. NRS was not significantly associated with any nutritional parameter variation. Variations in BCM and PhA (but not in BW or BMI) at day 7 correlated with total variation between time of diagnosis and time of discharge after induction CHT (dif30) and after the first consolidation cycle of CHT (dif60). Interestingly, variations in BCM (but not in BW) at day 7 of induction CHT correlated with total weight loss at time of discharge after the first consolidation cycle.

No relevant correlation was found between nutritional status and length of stay or disease response to treatment.

Preliminary results from this study show that BIA could reveal a nutritional deterioration as early as 7 days from admission, before BW changes become informative, and could trigger earlier and more effective support measures.

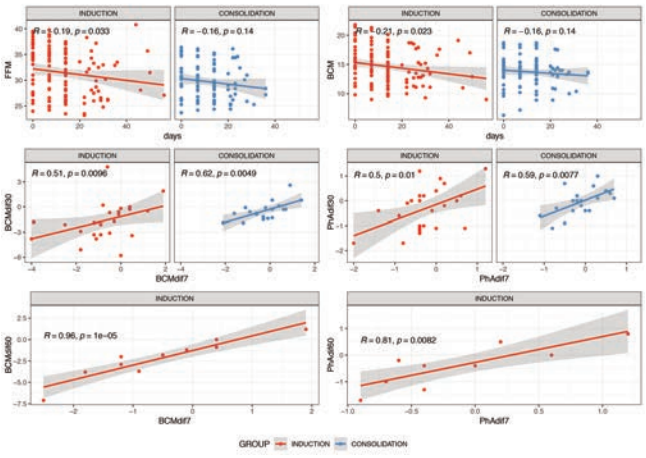

Figura 1.

P105

TREATMENT OF ACUTE MYELOID LEUKEMIA WITH HMA OR HMA+VENETOCLAX IN OCTOGENARIANS: A MULTICENTER EXPERIENCE ON 66 PATIENTS

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According to SIE/SIES/GITMO criteria, non-frail patients (pts) with Acute Myeloid Leukemia (AML) aged >75 years (y) should receive non-intensive treatment. The recently available more effective addition of Venetoclax to standard HMA has a different toxicity profile which makes its choice questionable in pts aged >80 y. We have retrospectively evaluated the outcome of 66 octogenarians with AML diagnosed from 2018 to 2023 in 4 Hematology Unit of Northern Italy (Brescia, Padova, Torino), according to clinical and biological features and treatment. Median age was 82 y (range 80-88). AML was de-novo in 31, secondary to MDS/MPN in 35 pts. Median WBC at diagnosis was $2.7x10^9$/L (1-290). Karyotype (k) was adverse in 19 pts (31%), NPM1-A mutated in 10 (19%), FLT3-ITD in 6 (11.5%). Pts were treated according to clinical choice, 48 received HMA single agent (HMA) (median cycles 5, range 1-44) and 18 (27%) Venetoclax+HMA (VEN-HMA) (median cycles 4, range 1-12). Characteristics of the 2 groups were similar (Table 1), except for differences in median age (83 *vs* 81y; p 0.0017), rate of NPM1 mutation (8.3% *vs* 33.3%; p 0.02), and antifungal prophylaxis (29.2% *vs* 94.4%; p<0.0001) in HMA *vs* VEN-HMA, respectively.

Overall response rate (ORR) [78% *vs* 44% (p 0.048)] and complete remission (CR) [72% *vs* 19% (p 0.0001)] were significantly higher in VEN-HMA than in HMA. Sixty-day mortality was 6% without difference in 2 groups. In whole population, OS was 47.5% at 1-y and 30% at 2-y. Cause of death was disease progression in all pts.

Age (≥/< 85 y), de novo *vs* secondary AML and treatment (HMA *vs* VEN-HMA) did not impact on survival. Adverse K had a worse outcome compared to not adverse (median OS: 9.7 *vs* 15.8 months, respectively; p 0.032) regardless of treatment received. Pts responsive to HMA and VEN-HMA survived longer than not responder (NR) (p 0.0071 and p 0.003). Survival was longer in NR pts receiving HMA compared to VEN-HMA (p.0.018) and HMA had received significantly more cycles [5 (1-35) *vs* 2 (2-4); p 0.006 according to F-test]. With limitations regarding the number of pts, treating very older pts with HMA+VEN is feasible and safe and performs better than best supportive care which offers a reported median survival of about 3 m. Cytogenetic risk and response impact on survival of whole population. With limitations of shorter median follow up of VEN-HMA, type of therapy did not impact on OS, whereas prolonged HMA treatment seems to offer a survival advantage in NR pts.

Table 1.

	Total n 66	HMA n 48	VEN-HMA n 18
Year of diagnosis (> 2020)	42/66 (64%)	24 (50%)	18 (100%)
Median age	82 y (80-88)	83 y (80-88)	81 y (80-85)
WBC at diagnosis Median (range)	2.74 x10^9/L (1- 290)	2.67x10^9/L (1.08-290)	3.1x10^9/L (1-134.94)
K adverse	19/62 (31%)	14/45 (31%)	5/17 (29%)
K not adverse	43/62 (69%)	31/45 (69%)	12/17 (71%)
NPM1-mutated	10/52 (19%)	4/41 (10%)	6/11 (55%)
FLT3-ITD mutated	6/52 (12%)	3/41 (7%)	3/11 (27%)
De novo AML	31/66 (47%)	20/48 (42%)	11/18 (61%)
Secondary AML	35/66 (53%)	28/48 (58%)	7/18 (39%)
Antifungal prophylaxis	31/66 (47%)	14/48 (29%)	17/18 (94%)
Median dose VEN (cycle 1)	-	-	1380 mg (0-7400)
Median n of cycles	4 (1-44)	5 (1-44)	4 (1-12)
ORR	35/66 (53%)	21/48 (44%)	14/18 (78%)
CR	22/66 (33%)	9/48 (19%)	13/18 (72%)
Early death (<60 days)	4/66 (6%)	4/48 (8%)	0/18
Median survival	11 months	12.1 months	9.8 months

P106

PROGNOSIS AND TREATMENT OF FLT3 MUTATED MYELOID SARCOMA IN THE ERA OF FLT3 INHIBITORS: RETROSPECTIVE EVALUATION IN 5 ITALIAN CENTERS.

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Myeloid sarcoma is a rare neoplastic condition, whose clinical characteristics and optimal treatment are not well defined, especially in relapsed setting. Although FLT3 ITD or TKD mutations have been described in 6-17% of patients, little is known of the activity of FLT3 inhibitors in this setting. We reviewed clinical records of 16 FLT3 mutated patients (median age 60 years; range, 30-71) with myeloid sarcoma, diagnosed in five Italian centers between 2011 and 2022. At diagnosis median WBC was 86,5x10^9/L (range 262-3,4);10 (62,5%) patients were FLT3 ITD+, 25% were FLT3 TKD+ and 12,5% were FLT3 wild type. These latter gained FLT3 at first relapse, one ITD and one TKD. Eleven patients (68,8%) co-harbored NPM1 mutation at diagnosis. Myeloid sarcoma was diagnosed in skin (n=9), in CNS (n=5), in lymph nodes (n=2), in colorectal (n=1), in breast (n=1) and ovarian (n=1). In 13 patients (81%) myeloid sarcoma were present at diagnosis, while 3 patients developed it at first relapse of AML. First line therapy was 3+7 or analogues in 81,3% of patients, CPX-351 in one patient, HMA plus venetoclax in one patient. Only one patient underwent radiotherapy during induction or salvage chemotherapy. Five (31,3%) patients received midostaurin as part of their induction regimen. Allo-HCT was performed in 6 patients, 3 in first CR and 3 in second CR. Median OS of the entire cohort was 19.9 months. In patients treated with midostaurin as a part of their induction regimen CR rate was 60%, median OS was 18.5 months, and median EFS was 16.7 months. One of these patients was refractory only because of myeloid sarcoma persistence. Nine patients (56%) received gilteritinib at first or subsequent relapses. CR rate was 55.6%. Median number of cycles was 4, and median number of cycles before achieving best response was 2. Notably, two out of the three patients with CNS involvement treated with gilteritinib achieved CR. Extra hematological toxicities were mild (CTCAE 1-2) and only in 2 cases led to dosage reduction. Gilteritinib was bridge to allo-HCT in 22.2% of patients. OS from initiation of gilteritinib was 9.6 months, with 50.5% of patients alive at 12 months.

The prognosis of FLT3 mutated AML with associated myeloid sarcoma remains dismal. Gilteritinib could play a role in relapsed setting, and in our series demonstrated activity in CNS disease; this positive effect needs to be validated in a larger series of patients.

P107

PREDICTIVE ROLE OF PLATELETS RECOVERY IN THE SETTING OF ACUTE MYELOID LEUKEMIA PATIENTS TREATED WITH AZACYTIDINE-VENETOCLAX

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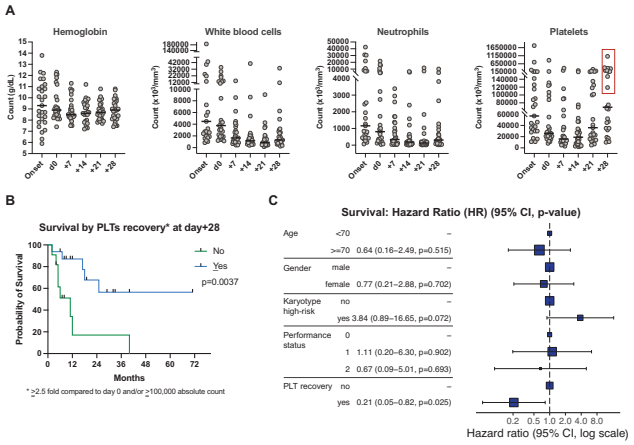
Background. Patients with de novo acute myeloid leukemia (AML) unfit for intensive CHT have a dismal prognosis. Combination therapy of azacytidine (hypomethylating agent) and venetoclax (BCL2 inhibitor) (aza-ven) has improved overall survival (OS) for this subgroup of previously untreated patients.

Aim. To investigate clinical factors with a predictive role on prognosis in AML patients treated with aza-ven.

Results. We retrospectively collected 27 patients affected by AML (n=21 de novo and n=6 secondary/transformed AML) treated at our Institution with aza-ven. The median age was 73 years (range 53-79), median follow-up was 10.5 months (2-71). In 24/27 patients (89%) with evaluable cytogenetics, 8 (33%) had high-risk karyotype aberrations according to the ELN 2022 classification. The most common genetic aberrations were found in: NPM1 (22%), IDH1 (11%), IDH2 (6%), FLT3-ITD (5%), CBFb/MYH11 (10%). Based on physician decision, 11/27 patients (41%) had received pre-treatment with hydroxyurea; additionally, 12/27 (44%) had been administered azacytidine only for one or more cycles (median: 3, 1-37). Patients received a median of 3 cycles of aza-ven (1-28), with a median interval of 41 days between each cycle (28-64), due to prolonged cytopenias. After the first cycle, 16/27 (59%) patients obtained a complete response (based on bone marrow blast count by cytomorphology), 8/27 (30%) a partial response, and 3/27 (11%) were refractory. The median OS of the entire cohort was 18 months. Transfusion dependency was higher during the first cycle, with 23/27 patients (85%) receiving at least 1 blood and/or PLT unit *vs* 15/27 (55%) from C2 onwards (p=0.03). Predictors of survival and response to Aza/Ven were analyzed, so several variables were considered (Figure 1). We found that patients achieving a significant increase in PLTs count at day+28 (>2.5 times and/or >100x10^3/mm^3) of the first cycle had a significantly better OS compared to those who did not (p=0.0037). These data held true by multivariate analysis including known risk factors such as: age, gender, karyotype, and performance status. Ultimately, this same finding was maintained and even improved at the begin-

ning of the 2 nd cycle (p<0.0001) (Figure 1).

Conclusions. Our data indicate that PLTs recovery can be utilized as a simple, yet effective, predictor of OS in the setting of AML patients, treated with aza/ven combination.



(A) Blood count levels at disease onset, before and during the first cycle of azacytidine-venetoclax (aza-ven). At day +28, hemoglobin levels tended to rise, white-blood cells and neutrophils decreased, while platelets count increased in a proportion of patients (red square). **(B)** Kaplan-Meier survival plot comparing overall survival of AML patients with platelets recovery (≥2.5 fold compared to day 0 and/or ≥100,000 absolute count) at the end of 1° cycle vs those with no recovery. P-value was calculated with log-rank test. **(C)** Multivariate Cox regression analysis estimating overall survival hazard ratios (HR) of platelets recovery combined with known risk factors including age, gender, karyotype and performance status.

Figura 1.

P108

RETROSPECTIVE ANALYSIS OF CPX-351 VS FLUDARABINE-CONTAINING REGIMENS AS INDUCTION THERAPY IN SECONDARY ACUTE MYELOID LEUKEMIA

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Background. Liposomal daunorubicin and cytarabine (CPX-351) has been approved for the treatment of adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC), with established improved survival compared to 3+7 chemotherapy. Fludarabine-containing regimens are often preferred as induction chemotherapy in the setting of high risk and secondary leukemia. Comparative data for CPX-351 *vs* intensive regimens containing fludarabine is lacking, above all in the setting of young patients with secondary AML and allo-HSCT program.

Aims and Methods. We conducted a retrospective analysis restricted to cases with t-AML and AML-MRC treated with either CPX-351 or Fludarabine-based induction therapy (F-Ind). The primary outcome was OS, secondary outcomes were CR, EFS and allo-HSCT access rate.

Results. A total of 44 patients (pts)(from 2 Institutions, treated from 2008 to 2022) received F-Ind and 56 received CPX-351 (from 4 Institution, treated 2019-2023). Median follow-up time was 11 months for CPX-351 and 12.5 months for F-Ind (p<0.05), with 29 deaths in the CPX-351 group (51,8%) and 30 deaths in the F-Ind group (73,2%). Patient characteristics (including ELN cytogenetic risk groups, mutational status-TP53, FLT3, IDH, NPM1-, AML subtype according to WHO2022) were similar between groups, except for age. Pts receiving CPX-351 were older (mean age, 61 *vs* 57 years; P< 0.05). In the group of CPX-351 8 pts out of 56 had therapy related AML (14%), whereas 26/56 progressed from MDS (46%). In the group of F-Ind t-AML were 6.8% and 65.9% progressed from MDS. Adverse cytogenetic was detected overall in 41.5 % (53.5% for F-Ind and 31.4% for CPX-351, P 0.05). Median OS was 14.9 months for all pts and 18.3 months for CPX-351 *vs* 14.0 months for F-Ind. Estimated one-year OS was 64% *vs* 54% for CPX-351 and F-Ind, respectively. Seventy percent of pts undergoing F-Ind had a CR or CRi, and 57.1% undergoing CPX-351 had CR or CRi (P 0.248). MRD (quantitative WT1 or IF) negativity was achieved in 8/26 cases (30%) treated with F-Ind and in 22/32 (69%), in the CPX-351 group. No early deaths were recorded with F-Ind, whereas with CPX-351 were 5% (D30) and 11% (D60). Median EFS was 7.6 months, 5.3 for CPX-351 and 9.4 months for F-ind. There were no differences in the rate of access to allo-HSCT (59.1% for F-Ind and 50.9% for CPX-351, P 0.54).

Conclusions. In this setting of secondary AML, induction treatment with CPX-351 or F-Ind resulted in similar OS. The limited number of pts and the high numbers of bias due to the different treatment times of the two groups and the different follow-up may influence the results. Prospective studies are needed to fully address a real comparation between these regimens.

P109

REAL-WORLD EFFICACY AND SAFETY OF GEMTUZUMAB OZOGAMYCIN (GO) AND 3+7 REGIMEN IN FIT NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA (AML) PATIENTS. A RETROSPECTIVE MULTICENTER STUDY OF "RETE EMATOLOGICA PUGLIESE" (REP)

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Background. Gemtuzumab Ozogamicin (GO), a monoclonal antibody targeting CD33, linked to calicheamicin, is approved in combination with daunorubicin and cytarabine (3+7) for the treatment of patients with previously untreated, de novo CD33-positive non promyelocytic AML. The aim of this study was to evaluate the outcome of patients with untreated CD 33+ AML receiving 3+7 plus GO as front-line therapy outside clinical trials.

Methods. Between January 2020 and December 2022, 34 consecutive fit CD33+ AML patients, 17 male and 17 female, median age 54.5 years (range, 25-75) were treated. 32% (11/34) of patients were older than 60 years. GO was administered in combination with 3+7 at standard dose of 3 mg/m^2 on days 1, 4, 7 of induction therapy and on day 1 of the two consolidation therapy. According to European

LeukemiaNet (ELN) 2017, risk stratification was 29.4% (n=10) high, 41.2% (n=14) intermediate and 29.4% low.

Results. Overall, Complete Remission + Complete Remission with Incomplete Count Recovery (CRi) rate was 79.4% (n=27) after induction therapy, including 23.5% of CRi (n=8). After one (n=12) or two (n=14) consolidation courses , 35% of patients (n=12/34) resulted MRD negative and 47% (n=16/34) underwent to allogenic stem cell transplantation. After a median follow-up of 13 months, overall survival was 79.4% (Figure 1) with no statistically significant differences between transplanted and non-transplanted patients (p=0.4). A trend for better survival was observed for low-risk (p=0.08) and NPM1 mutated patients (p=0.07). There were 2 induction deaths (one cerebral hemorrhage and one Pseudomonas A. sepsis), additional 2 patients died afterwards by infections (COVID-19 pneumonia and Pseudomonas A. sepsis) and 3 patients due to recurrence of disease. Any grade hematologic and non-hematologic toxicity was 73.5% and 76.5% respectively. The most common grade 3-4 non-hematologic AEs were sepsis (70%) and COVID-19 Pneumonia (25%). In allo-transplanted patients two cases of grade 2 veno-occlusive disease (VOD) were observed (5.8%). Grade 3-4 hematological toxicity was as expected.

Conclusion. This study, although carried out on a limited number of patients, confirms in real life setting the efficacy and toxicity data reported in clinical trials. GO + 3+7 is effective and well tolerated and should be offered to patients with CD33+ AML with some caution for patients older than 60 years.

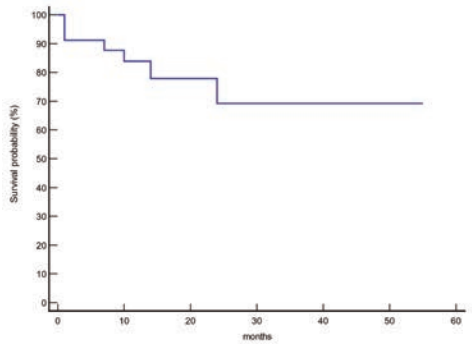

Figura 1. Overall survival of the whole population (34 cases) from the diagnosis.

P110

LATE HEMATOLOGIC RECOVERY AFTER CPX-351 INDUCTION CHEMOTHERAPY IN AML: PREDICTIVE DISEASE AND PATIENT'S FACTORS AND THEIR IMPACT ON SURVIVAL

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Background. The use of CPX-351 in the treatment of high-risk AML has entered clinical practice, with good efficacy and tolerability data. Longer time for haematologic recovery (HR) after induction cycle (IC) is reported.

Aims and Methods. We investigated several disease or patients(pts)-specific factors that may affect the late HR and the outcome of the therapeutic program for these pts, collecting retrospective data from 59 pts with newly diagnosed AML who received 1 or 2 cycles of CPX-351. Pts were treated according to the EMA–approved dosing and schedule of CPX-351. M/F 19/37 median age 61 years (r: 32-74. The AML subtypes (WHO2022) were AML-MR (64%), with cytogenetic abnormalities (CA)(32%) or with only genetic abnormalities (29%). Twenty pts had AML-NOS. 8/56 were therapy related (14%), 26/56 progressed from MDS (46%). 26/59 pts received a second course of CPX-351 after IC, the ORR was 54%, and 59% after 2 courses. 28/30 pts who achieved CR/CRi were evaluable for MRD and among them 22 (73%) had reached negativity. We recorded all the adverse events (AE). Median time to neutrophil (PMN) >0.5×10^9/L and platelet (PLT)>20×10^9/L recovery was 30 (r:18-45) and 30 (r:10-89) days, respectively, in pts that reached CR/CRi. Four pts didn't achieve PMN or PLT recovery even if in CRi. Twenty-eight pts underwent ASCT (50%), with a median time to transplant of 186 days (range 88-638); 7 pts went to ASCT after a second line of therapy. The median OS was 18 months 95% CI (14.2-19.8).

Results. In univariate analysis no correlation between patient's characteristics (sex, age), disease characteristics at diagnosis (cytogenetic risk, AML subtypes, diagnostic qualifiers, molecular profiles) or AE (bleeding, FUO, sepsis) and late HR was detected. A restricted group of late-recovering pts (8 pts, showing a time to PMN >500 recovery > 35 days and/or PLT>20.000 > 40 days). They reached CR (100%), and MRD negativity in 7/8 cases. Low bone marrow cellularity at diagnosis was correlated with late HR ($p<0.05$); 75% had no CA (75%) or int-risk CA (25%); time to CR and to allo-HSCT were longer, but comparison of this group with the other pts that reached CR after IC showed no difference in OS and EFS rate.

Conclusions. pts with late HR seems to identify AML pts progressing from MDS with low cellularity, having no adverse cytogenetic risk (hypoplastic/aplastic MDS) and showing a good response and a better outcome after therapy. These results need to be confirmed in a large cohort of patients.

P111

IMPACT OF OUTPATIENT VS INPATIENT MANAGEMENT OF HMA-VEN TREATED PATIENTS: HOSPITALIZATION DURING THE FIRST CYCLE IS REALLY NEEDED? A RETROSPECTIVE, SINGLE CENTER EXPERIENCE

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The combined therapy of hypomethylating agents (HMA) and venetoclax (VEN) has become the standard of care for chemotherapy-ineligible acute myeloid leukemia (AML) patients. Despite the lack of guidelines, hospitalization is recommended for at least the first cycle of therapy. This retrospective, single center study aims at evaluating the difference between outpatient and inpatient management during induction, in terms of cumulative infection (cIR), rehospitalization rates in subsequent cycles (sHR) and overall survival (OS). We report on 47 patients, treated frontline (FL,n=26) or at relapse (RR, n=21) with HMA-VEN, who completed at least one cycle of therapy. The median follow-up was 8.3 months (range 1.5-26). Twenty-one patients (45%) received induction as inpatient (IN) whereas 26 (55%) were treated outpatient (OUT). Patients'clinical characteristics and outcome are resumed in Table 1. Due to our local epidemiological issues, none of these patients had received antibiotic

prophylaxis. During the first cycle 5 out of 26 patients (19%) of the OUT group required hospitalization for complications. None of these patients had fatal outcomes and all of them continued with the treatment for at least another cycle. Despite a similar median OS (8.9 *vs* 11 months, p=0.6), univariate analysis showed a significant difference in terms of cIR [90% (19/21) *vs* 42% (11/26); p=0.0008] and sHR [57% (12/21) *vs* 15% (4/26), p=0.004] for IN and OUT group, respectively. In the IN group 5 out of 12 (42%) patients required readmission for septic shock that was fatal in all but one. In the OUT group, 4 patients were hospitalized in subsequent cycles and one of them died for septic shock. Non-relapse-mortality (NRM) rate was not significantly different [IN, 19% (4/21) *vs* OUT 3,8% (1/26); p=0.09]. These differences may partially be explained by the worse performance status (PS) of IN patients (p=0.0005). Moreover, patients with ECOG higher than 1 at diagnosis had an increased risk of subsequent hospitalization (p=0.0003). No significant correlation was found between ECOG and risk of death for complications (p=0.6). As reported in other studies1,2, these data highlight the safety of an outpatient management in patient receiving HMA-VEN therapy. The worst outcomes in the IN group (especially high NRM) may also depend on factors other than PS, such as local epidemiology and prevalence of multidrug-resistant infections.

Table 1.

Table 1. Patients' baseline clinical characteristics

Parameter	INPATIENTS, n=21 (45%)	OUTPATIENTS, n=26 (55%)	P value
M/F	12/9 (1.3/1)	18/8 (2.2/1)	0.5
Age, years (range)	64 (40-80)	69 (22-79)	0.3
PS-ECOG, n (%)			**0.0005**
• 0-1	5(24)	17(65)	
• 2	5(24)	6(23)	
• 3-4	11(52)	3(12)	
N° of cycles (mean)	4.8(1-14)	5.1(1-23)	0.17
Line of therapy, n (%)			**0.03**
• First line (FL)	17 (81)	12(46)	
• Relapsed/Refractory (RR)	4 (19)	13(54)	
AML WHO type, n (%)			0.7
• *De novo*	9(43)	13(50)	
• Secondary (MDS or MPN)	12(57)	13(50)	
ELN 2017 risk group, n (%)			
• Favorable	8(38)	7(27)	
• Intermediate	6(28)	4(15)	
• Adverse	3(14)	6(23)	
• Not available	4(19)	9(34)	
cIR, n (%)	19(90)	11(42)	**0.0008**
sHR, n (%)	12 (57)	4(15)	**0.004**
Disease status at subsequent hospitalization, n (%)			
• CR	6(50)	2(50)	
• PR	3(25)	2(50)	
• SD	2(16)	0	
• PD	1(8)	0	
NRM rate, n (%)	4 (19)	1(3.8)	0.09
Median OS, months (95% CI)	8.9 (1.5-23.7)	11 (1.4-25.9)	0.2

PS-ECOG: Performance Status-Eastern Cooperative Oncology Group; cIR:cumulative infection rate; sHR: hospitalization in subsequent cycles; CR:complete remission, PR:partial remission, SD:stable disease; PD:progressive disease; NRM:non-relapse mortality

P112

INTENSIVE CHEMOTHERAPY FOR THE TREATMENT OF NPM1-MUTATED ACUTE MYELOID LEUKEMIA, A RETROSPECTIVE COMPARISON OF NEW COMBINATION REGIMENS *VS* FLAI IN A REAL-LIFE SETTING

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Introduction. Normal karyotype (NK) NPM1-mutated AML represents a subset of AML with a favorable (fav) or intermediate (int) prognosis depending on the presence of FLT3 mutations. The introduction of midostaurin and gentuzumab ozogamicin (GO) changed therapeutic strategies. In this retrospective study we compared new regimens versus a historical cohort of patients (pts) treated with FLAI.

Patients and Results. 67 pts with NK NPM1-mutated AML, 52 treated with FLAI, 6 with 3+7+GO and 9 with 3+7+midostaurin between 2010 and 2022 were included. Endpoints were OS, overall response rate and tolerability. Median age was 60 years, 25% of pts were ≥65 years; 58% (39/67) were at fav risk. CR rate after induction was 74% (48/65), ORR was 84% (57/65) with 2 deaths during induction. Among 41 evaluable pts, MRD negativity rate was 88%. CR rates were similar for the 3 inductions. Concerning tolerability, cardiac complications were more frequent for 3+7+GO than FLAI group (33% *vs* 8%, P=0.07), while bacterial infections were more frequent in FLAI group (p=0.07). Platelet recovery was delayed in 3+7+GO group than in FLAI (28.5 *vs* 22 days, P=0.06). Overall, 26/65 pts (40%) underwent HSCT, 77% (20/26) in first line. Main reasons for HSCT in first line for int risk were clinical high-risk at onset (hyperleukocytosis or CR after second cycle, 50%, 10/20), and MRD positivity (25%, 5/20). OS rates at 2 and 5-year were 58% and 51%, respectively without differences according to induction. Factors associated with better 2-yeas OS were age ≤65 (70% *vs* 22%, P=0.0004) and HSCT (69% *vs* 51%, P=0.0277), while risk did not influence OS. Age influenced survival in both fav and int risk group, HSCT only in the int risk (2-year OS 73% *vs* 26%, P=0.0067).

Conclusions. our data outline that new regimens share the same ORR, molecular CR rate and OS than FLAI in NK NPM1-mutated AML. For older pts prognosis remains unfavorable, and the tolerability of the new regimens remains to be explored in real life. Finally, int risk patients fared better when referred to HSCT, especially in presence of clinical high-risk features. Prospective studies are needed to determine if MRD monitoring is sufficient to guide therapeutic decisions in this risk category.

P113

CASE REPORT: NGS-BASED DONOR SEARCH FOR AML/MDS PATIENTS WITH DDX41 MUTATION

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This clinical case illustrates how NGS techniques can detect germline mutations in genes such as DDX41 in patients with acute myeloid leukemia and a positive family history of hemopathies, with important implications for management and therapy. Studies have shown that mutations in the DEAD-Box RNA-helicase 41gene, located at 5q35.3, are present in 1.5-3.8% of patients with AML/MDS and acute erythroid leukemia. For this case,the Lympholyte kit was utilized for the isolation of viable granulocytes and peripheral blood mononuclear cells (PBMCs), such as monocytes and lymphocytes, from human peripheral blood and bone marrow. The germ-line mutation was studied on a saliva sample,that was collected in a Oragene DNA Saliva collection tubes and mixed with the homonymous solution. The case concerns a 60-year-old woman with AML, presenting with trilinear cytopenia with a family history of hemopathy. NGS revealed a missense mutation in Exon 15/17 Arg525His (VAF: 0.15) and Exon 8/17 Gly218Asp (VAF 0.51) in heterozygous form in the bone marrow blood sample. The presence of two DDX41 pathogenic variants in malignant myeloid cells, particularly if one variant allele frequency (VAF) exceeds 0.4, strongly suggests the presence of the

variant in the germline. It was also assessed a somatic mutation was also found in the SRSF2 gene: Pro95His with VAF 0.15; this mutation is suggestive of a secondary form. Treatment with Daunorubicin-Cytarabine was initiated, and due to the high-risk nature of the patient's condition, a HSCT from a related donor was considered. However, no suitable donors were found, and the patient underwent a MUD 7/8 transplant. Screening family members for the same mutation when searching for a donor for HSCT can improve the chances of successful transplantation, but raises ethical and counselling considerations.This highlights the importance of reporting mutations that are classified as variants of uncertain significance (VUS) in the literature, as this can aid in identifying new pathogenic mutations in future studies The discovery of germline mutations in genes, including DDX1, that predispose individuals to hereditary hematological malignancies is crucial in allogeneic transplantation management, especially for younger and healthier patients.

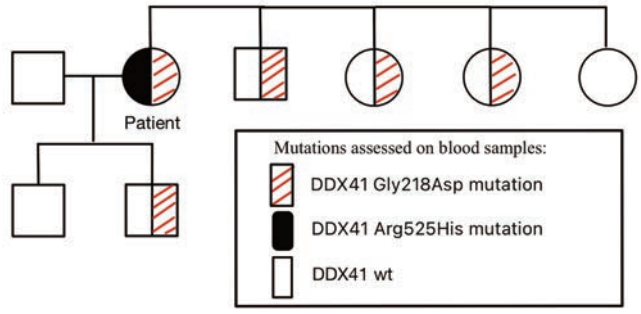

Figure 1.

P114

BREAST TUMOR CHARACTERIZED BY THE PRESENCE OF TUMOR CELLS IN PERIPHERAL BLOOD MIMICKING MYELOID ACUTE LEUKEMIA: A CASE REPORT

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75-year-old woman with a history of breast lobular adenocarcinoma (ER-positive, PgR-positive, HER2-negative) treated with mastectomy and radiotherapy in 2021 and taking hormone therapy, presented with asthenia and tremors. Laboratory tests showed leucocytosis 23.4x10^3/microl, anemia Hb 72 g/l, platelets count 138x10^3/microl, calcium level 13 mg/dl, LDH 600 UI, indirect bilirubin 5 mg/dl, aptoglobin 0.1 g/l and reticulocytes 11%. No coagulation abnormalities were documented, direct Coombs test was negative and renal function was normal. Peripheral blood smear showed marked red cell anisocytosis, a remarkable proportion of schistocytes (15% of erythrocytes, arrows in the figure), erythroblasts (3% of nucleated cells) and immature granulocytes (promyelocytes, myelocytes and metamyelocytes, hashtag in the Figure 1). Furthermore, a significant number of cells of unclear lineage (15% of nucleated cells, asterisk in the figure) was also detectable. Therefore, in the hypothesis of a macroangiopathic hemolytic anemia (MAHA) related to cancer recurrence, total body CT and 18F-FDG PET/CT were planned. The first examination resulted negative, whereas the second one showed only a slight FDG uptake in the spine, ascribed to increased bone marrow activity due to MAHA. Then, to exclude the diagnosis of acute leukemia due to the presence of circulating suspected abnormal cells, bone marrow aspirate and trephine biopsy were performed, along with an immunophenotyping. The first myeloid flow cytometric panel evidenced a CD45+, CD34-, CD117+ population (20%), with high FSC and SSC. All myeloid markers were negative. A more extensive panel was performed, including plasma cell and erythroid markers. Interestingly, this population resulted positive for CD138 and CD71 with negativity for CD38. A recent study reported that in addition to CD45 negativity, non-hematological neoplasms frequently express CD56, CD117 or CD138. Therefore, a further panel for non-hematological markers included EpCAM (epithelial cell adhesion molecule) was carried out. This population resulted EpCAM+ and CD9+, a marker typically expressed on breast neoplastic cells. The flow cytometric analysis allowed to discover the non-hematological nature of this population, circulating at high level in peripheral blood. Aspirate smears revealed the presence of the same cells, and immunohistochemistry on bone marrow confirmed the massive infiltration of breast cancer cells, allowing to diagnose bone marrow metastases.

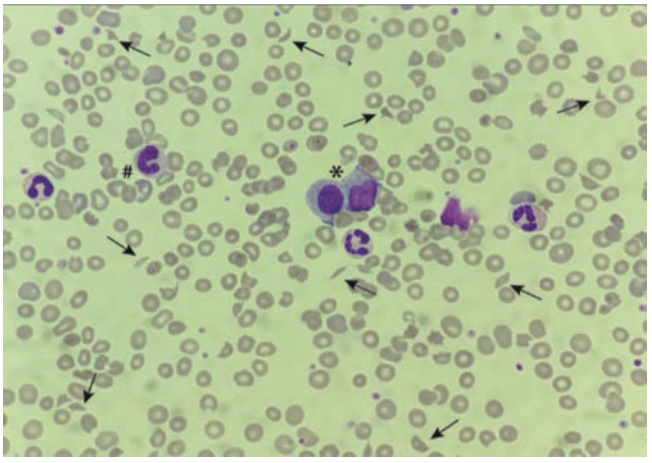

Figure 1.

P115

AML WITH FLT3-ITD MUTATION: DOES THE ALLELIC-RATIO REALLY MATTER?

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The role of FLT3-ITD allelic ratio (AR) has been questioned and removed from the 2022 ELN risk classification. The aim of this study is to explore the impact of FLT3-ITD AR in AML patients (pts) receiving intensive chemotherapy with 7+3 with or without midostaurin (mido). We retrospectively analysed 37 cases with FLT3-ITD. 15 pts underwent 7+3 (from 2013 to 2018) and 22 pts received 7+3 and mido (from 2019 to 2023). Table 1 summarizes clinical features. The overall response rate after the induction treatment, including CR and CRi, was 68% (25 pts out of 37) and did not differ based on FLT3-

ITD AR (16/24, 67% *vs* 9/13, 69%, for low and high AR groups, p=0.8), on NPM1 mut (6/12, 50%, for NPM1 wild type (w.t.) and 19/25, 76%, for NPM1 mut, p=0.1), or on associated mido treatment (9/15, 60%, for pts not treated with mido *vs* 16/22, 73%, for mido based treatment, p=0.4). Measurable residual disease (MRD) was evaluated after induction in 19/25 responding pts, resulting positive in 4 of them and persisting after 1st consolidation. Bone marrow transplantation (BMT) was performed in 1st CR in 11 pts out of 25 (44%). The rate of BMT did not differ between high and low FLT3-ITD AR. At a median follow-up of 37.5 months (mo), 15 pts relapsed. Overall disease-free survival (DFS) was 7.9 mo and did not differ according to FLT3-ITD AR (6.8 mo *vs* 15.2 mo for low and high AR groups, p=0.2) and treatment with mido (5.3 mo *vs* 7.9 for pts treated without and with mido, p=0.3). Pts with NPM1 mut had a DFS higher than NPM1 w.t. (10.3 mo for NPM1 mut *vs* 3 mo in w.t. cases, p=0.02). Pts with positive MRD had a trend of DFS lower than MRD-negative patients (5.3 *vs* 10.3 mo, p=0.06). Transplanted pts had a DFS higher than non-transplanted pts (not reached median *vs* 3 mo, respectively, p=0.01). FLT3-ITD was retested at relapse in 11 out of 15 relapsed pts and was found in 6 cases (55%). Median overall survival (OS) was 13.9 mo. Pts responding to induction treatment had an OS higher than refractory pts (16.5 mo *vs* 10.8 mo, respectively, p=0.049). OS was not influenced by FLT3-ITD AR, NPM1 mut, MRD positivity, and type of treatment (high-dose chemotherapy alone, use of mido, or BMT). In conclusion, we found that pts with FLT3-ITD showed a comparable survival independently from AR, corroborating what was stated in the updated 2022 ELN classification. Mido-based treatment increased the percentage of CR and OS, although not statistically significant, probably due to the limited sample size.

Table 1. Disease characteristics.

Characteristic	No mido (N=15)	Mido (N=22)	Total (N=37)
Sex — no. (%)			
• Male	6 (40)	8 (36)	14 (38)
• Female	9 (60)	14 (57)	23 (62)
Median age (range)	54.1 (31.8-65)	51.2 (31.4-66.2)	52.1 (31.4-66.2)
Allelic ratio			
• High	2	11	13
• Low	13	11	24
NPM1			
• Mut	10	16	26
• w.t.	5	6	11
Cytogenetic risk			
• low	0	1 (5%)	1(3%)
• intermediate	11 (73%)	21 (95%)	32 (86%)
• high	1 (7%)	0	1 (3%)
• failed	3 (20%)	0	3 (8%)
ORR	9/ 15 (60%)	16/22 (73%)	25/37 (68%)
Number of consolidation cycles (calculated on responding patients)			
• 1-2	7/9 (78%)	6/16 (38%)	13/25 (52%)
• 3-4	2/9 (22%)	10/16 (63%)	12/25 (48%)

P116

LATE HEMATOLOGIC RECOVERY AFTER CPX-351 INDUCTION: PREDICTIVE DISEASE AND PATIENT'S FACTORS AND ITS IMPACT ON SURVIVAL

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Background. The use of CPX-351 in the treatment of high-risk AML has entered clinical practice, with good efficacy and tolerability data. Longer time for haematologic recovery (HR) after induction cycle (IC) is reported.

Aim and Methods. We investigated several disease or patients(pts)-specific factors that may affect the late HR and the outcome of the therapeutic program for these pts, collecting retrospective data from 59 pts with newly diagnosed AML who received 1 or 2 cycles of CPX-351. Pts were treated according to the EMA–approved dosing and schedule of CPX-351. M/F 19/37 median age 61 years (r: 32-74. The AML subtypes (WHO2022) were AML-MR (64%), with cytogenetic abnormalities (CA)(32%) or with only genetic abnormalities (29%). Twenty pts had AML-NOS. 8/56 were therapy related (14%), 26/56 progressed from MDS (46%). 26/59 pts received a second course of CPX-351 after IC, the ORR was 54%, and 59% after 2 courses. 28/30 pts who achieved CR/CRi were evaluable for MRD and among them 22 (73%) had reached negativity. We recorded all the adverse events (AE). Median time to neutrophil (PMN) >0.5×10^9/L and platelet (PLT)>20×10^9/L recovery was 30 (r:18-45) and 30 (r:10-89) days, respectively, in pts that reached CR/CRi. Four pts didn't achieve PMN or PLT recovery even if in CRi. Twenty-eight pts underwent ASCT (50%), with a median time to transplant of 186 days (range 88-638); 7 pts went to ASCT after a second line of therapy. The median OS was 18 months 95% CI (14.2-19.8).

Results. In univariate analysis no correlation between patient's characteristics (sex, age), disease characteristics at diagnosis (cytogenetic risk, AML subtypes, diagnostic qualifiers, molecular profiles) or AE (bleeding, FUO, sepsis) and late HR was detected. A restricted group of late-recovering pts (8 pts, showing a time to PMN >500 recovery > 35 days and/or PLT>20.000 > 40 days) was identified. They all reached CR (100%), and MRD negativity in 7/8 cases. In this group low bone marrow cellularity at diagnosis was correlated with late HR (p<0.05); 75% had no CA (75%) or int-risk CA (25%); time to CR and to allo-HSCT were longer, but comparison of this group with the other pts that reached CR after IC showed no difference in OS and EFS rate.

Conclusions. pts with late HR seems to identify AML pts progressing from MDS with low cellularity, having no adverse cytogenetic risk (hypoplastic/aplastic MDS) and showing a good response and a better outcome after therapy. These results need to be confirmed in a large cohort of patients.

Anemias, myelodysplastic syndromes and chronic myeloid leukemia

P117

ABSTRACT NOT PUBLISHABLE

P118

APLASTIC ANEMIA AFTER SARS-COV-2 VACCINES: A SINGLE CENTER EXPERIENCE

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Exacerbations of autoimmune cytopenias secondary to COVID-19 vaccines have been frequently reported, whilst the association with aplastic anemia (AA) is rarer. We conducted a single center case series and laboratory study about AA after SARS-CoV-2 vaccines. We focused on features of immune activation and Spike protein integration in the bone marrow (BM) by immune-histochemistry. Eight patients diagnosed with AA at a single in Milan, Italy from March 2020 to March 2022 were included: 6 severe (SAA) and 2 non severe (NSAA), with a median age of 61.75 years (range 40-83), 5 males and 3 females (Figure 1).

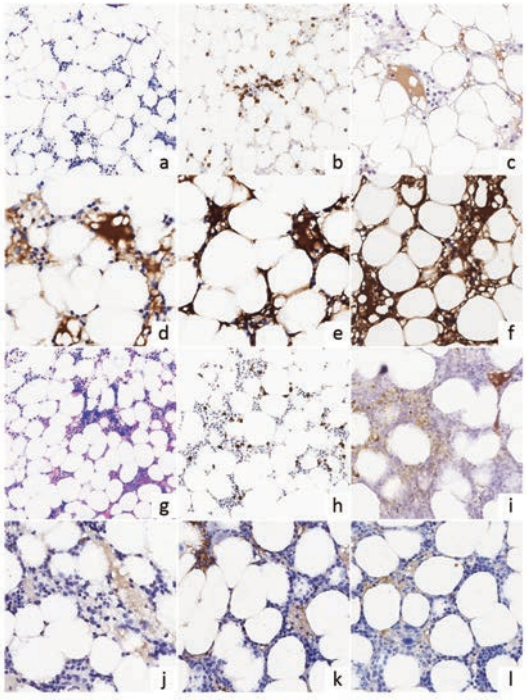

Figure 1. Immune-histochemistry studies on bone marrow samples of aplastic anemia cases. Representative panel (a-f) of a post-vaccine aplastic anemia (AA) case, depicting a severely hypocellular bone marrow (BM, a. Giemsa, 200x) with a CD8+ T-cell infiltrate (b. 200x), a moderate-high burden of serous C3 (c. 400x) and C4d (d. 400x) deposits as well as intense extracellular deposits of IgM (e. 400x) and IgG (f. 400x). Panel g-l depicts a control case with BM hypoplasia (g. Giemsa, 200x) and a moderate amount of CD8+ T-cells (h. 200x); complement fractions C3 (i. 400x) and C4d (j. 400x) feature a lower burden of reactivity, in a serous pattern, but with enhancement on the RBC membranes; a similar profile is observed for IgM (k. 400x) and IgG (l. 400x), the former featuring a more intense reactivity.

All cases were diagnosed de novo after a median of 2.29 months from the last vaccine dose (3 patients were diagnosed after the 1st dose, 3 after the 2nd, and 2 after the 3rd one); one patient had also experienced SARS-CoV-2 infection before vaccination. All received immunosuppressive treatment: anti-thymocyte globulin (ATG) plus cyclosporine (CYA) in 4 cases (all SAA), CYA alone in 3 cases (2 SAA and 1 NSAA), and CYA plus eltrombopag (EPAG) in 1 case (NSAA). At 6 months response rates were: 75% with ATG plus CYA, and 66% with CYA alone. The addition of EPAG induced an improvement in all the 4 non-responding patients. At the last follow up, 4 patients were on stable hematological response, 3 patients had required a further therapy line (HSCT, EPAG, Danazol), and 2 had died. BM trephine evaluation showed hypoplasia/aplasia, with an accompanying infiltrate of (mostly CD8+) T-cells (Table 1). Immunehistochemistry showed an abundant anti-IgM and anti-IgG immunoreactivity in the serous spaces and on myeloid precursors. A serous pattern of immunoreactivity was detected also for C3 and C4d, whilst no Spike protein integration was observed. A group of 6 patients with AA diagnosed before Covid-19 pandemic was used as control and globally showed lower intensity and distribution of IgG/IgM/C3/C4 deposition. In conclusion, AA post-SARS-CoV2 vaccine showed similar severity and response patterns as idiopathic AA. It is not possible to establish a definite causative link between SARS-CoV-2 vaccines and AA development, although temporal association and the broader humoral and complement immune activation in the BM may suggest a relationship.

Table 1. Aplastic anemia developing after SARS-CoV-2 vaccination.

Case	AA grade	Date of diagnosis	Age year-old	Sex	Hb g/l	PLT x 10⁹/l	PLT x 10⁹/	Hb U/l	PLT x 10⁹/l	Cytogenetic	Vaccine/Infection	Day between infection/vaccination and AA	AA treatment Outcome
1	SAA	21st September 2021	40	F	47	40	0.89	1052	10.4	Normal	Vaccine (Moderna) 2nd in August 2021	10 days after 2nd dose	Steroid → PR CYA and EPAG → CR Alive
2	SAA	5th April 2021	72	F	103	68	0.46	408	4.4	Normal	Vaccine (NA type) 1st dose in February 2021	60 days	Steroid (STOP) → NR CYA → NR Alive
3	NSAA	6th October 2021	43	M	95	17	1.4	543	8	Trisomy of chromosome 6 (1 metaphase) and Y deletion (1 metaphase)	Infection in November 2020 Vaccine (Pfizer) 1st dose in April 2021	210 days after infection 60 days after 1st dose	Steroid and CYA → NR EPAG → PR Alive
4	NSAA	2nd March 2022	83	M	85	5	0.98	NA	4.3	Normal	Vaccine (Pfizer) 2 doses in April 2021, 3rd dose in November 2021	150 days after 2nd dose	Steroid, CYA and EPAG (+ EPO by nephrologist) → NR Alive (Danazol is under evaluation)
5	SAA	24th February 2022	72	M	91	6	1.1	571	150	Normal	Vaccine (Moderna) 3rd dose in December 2021	90 days after 3rd dose	Steroid, CYA and rATG → NR EPAG → NR Death for complications
6	SAA	12th April 2021	77	M	112	3	0.49	NA	NA	Normal	Vaccine (Pfizer) 1st and 2nd dose in February/March 2021	Some months	CYA and rATG → PR Alive
7	SAA	12th November 2021	49	M	116	3	1.9	NA	NA	NA	Vaccine (Pfizer) 1st and 2nd dose in February/March 2021	Some months	CYA and rATG → CR Alive
8	SAA	08th November 2021	58	F	99	0	0.37	771	2.9	Normal	Vaccine (NA type) 2nd dose in June 2021	Concomitant	CYA and rATG → NR EPAG → NR Danazol ongoing HSCT is under evaluation Alive

P119

INCREASE OF SERUM PENTRAXINE 3 (PTX3) AS A POSSIBLE BIOMARKER OF BONE REMODELLING IN PATIENTS WITH TRANSFUSION DEPENDENT THALASSEMIA TREATED WITH LUSPATERCEPT: PRELIMINARY DATA

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Introduction. The prevalence of fractures in patients with transfusion-dependent beta-thalassemia (TDT) ranges from 16 to 49%. The causes of this severe complication depend upon various factors, mainly including iron-chelating therapy, growth hormone reduction and ineffective erythropoiesis. It has been reported that administration of Luspatercept (a TGF-beta ligand that stimulates erythropoiesis) in animal models with myelodysplastic syndrome induces an increase in bone mass. The aim of our study was to evaluate some

parameters of bone metabolism in patients affected by TDT treated with Luspatercept.

Materials and Methods. 53 patients (27F/26M) with TDT, aged 21-57 yrs, were enrolled for the study at the Thalassaemia Regional Center, University of Bari. Fifteen patients treated with Luspatercept (group1) and 38 untreated (group2) were examined. The drug was administered every 21 days, when hemoglobin value was ≤11.5g/dl, at a concentration of 1 mg/kg/day, adjusted to a dosage of 1.25 mg/kg/day based on the patient's clinical response. In each group we evaluated serum levels of ionized calcium; total calcium; total proteins; complement C3;C4; C1 inh; IL-6; IL-1β; S100 calcium-binding B ; calcitonin; FGF23;osteoprotegerin; osteocalcin; vitamin D; pentraxin 3 (PTX3) and Rank-L.

Results. A significant increase of PTX3 in group1 (6,758±2,078 *vs* 4,453±1,785 pg/ml, Pv 0.0006) was observed, while no significant differences between the two groups were found regarding other parameters (Figure 1).

Discussion. PTX3 is a prototypic humoral pattern recognition molecule also involved in tissue repair and regulation of cancer-related inflammation. It has been reported that femoral bone in PTX3 KO mouse (ptx3−/−), analyzed by micro-computed tomography and immunohistochemistry of biopsied tissue, have less trabecular bone formation compared to the wild-type (ptx3+/+) animals. Furthermore, an inverse correlation between TGF β1 and PTX3 expression in fibroblasts has been demonstrated. In our still preliminary experience, PTX3 was found significantly increased in TDT patients treated with Luspatercept compared to the untreated ones. We hypothesize that such an increase could be related to the inhibition of TGF β by luspatercept. We are now evaluating dual-energy X-ray absorptiometry (DEXA) in our patients to correlate these finding with the possible clinical effects of Luspatercept on bone remodelling. Preliminary data support this hypothesis, that is currently evaluated in a multicenter clinical trial.

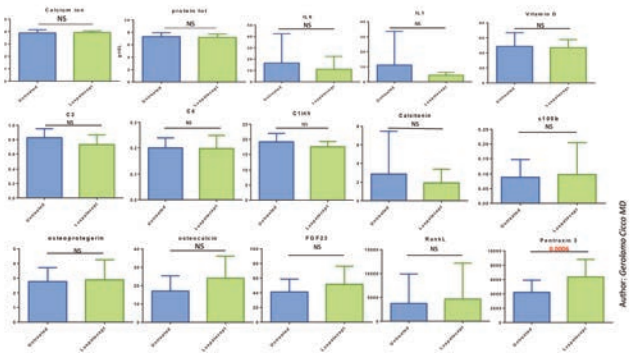

Figure 1.

P120

PROLONGED ELTROMBOPAG TREATMENT FOR APLASTICA ANEMIA REFRACTORY OR RELAPSED AFTER IMMUNOSUPPRESSIVE TREATMENT: MULTICENTER RETROSPECTIVE STUDY OF 22 PATIENTS FROM 4 ITALIAN HAEMATOLOGICAL CENTERS

C. Finelli[1], I. Capodanno[2] , C. Bosi[3], M.B. Giannini[4], S. Paolini[1], S. Parisi[1], L. Zannoni[1], G. Cristiano[1], C. Sartor[1], M. Fogli[1], A. De Vivo[1], F. Bonifazi[1], C. Di Giovanni Bezzi[1], M. Fiacchini[1], A. Curti[1], M. Cavo[1]

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Introduction. Eltrombopag (ELT) has shown efficacy in acquired severe Aplastic Anemia (SAA) either in the refractory setting or in the first-line therapy, in addition to standard immunosuppressive treatment (IST). However the therapeutic efficacy and safety of ELT for AA in the real-world setting still need to be explored. Therefore we retrospectively analyzed our multicenter experience on ELT treatment in AA patients either refractory or relapsed (RRAA) after IST.

Methods. From January 2014, 22 pts (10 males), median age: 68.5 (27-85) yrs, from 4 Italian Centers, were treated with ELT because of a diagnosis of RRAA. The following response criteria were used: complete response (CR): Hb >10 g/dL, neutrophil count >1.5x10^6/ml and platelet count >100x10^6/ml; partial response (PR): transfusion-independence; minimal response (MR): improvement in one or more lineage not fulfilling the criteria of PR.

Results. At the start of ELT, 14 pts showed severe AA, 2 pts very severe AA, and 6 pts non severe AA. Previous IST treatment was: ATG + cyclosporine (CYA) + prednisone (MP): 7 pts; CYA ± MP: 14 pts; MP alone: 1 pt. 15 pts were treated with ELT + CYA, and 7 pts with ELT alone. Maximum daily dose of ELT: 150 mg (18 pts), 175 mg (1 pt), 100 mg (1 pt), 75 mg (1 pt), 50 mg (1 pt). Median duration of treatment: 8 (1-59) months. 15/22 pts showed a clinically significant response to ELT (ORR: 68.2%). Best response to ELT: CR in 3 pts (13.6%), PR in 9 pts (40.9%), MR in 3 pts (13.6%). Median time to first response: 4 (1-17) months (> 6 months in 3 pts); median time to best response: 11 (1-50) months (> 6 months in 8 pts). Median duration of response (DOR): 25 (2-101) months (> 24 months in 7/15 pts). 7/15 responders maintained response after ELT discontinuation, 4 under CYA alone and 3 without CYA, with a median DOR of 50 (6-101) months. 5/13 responders are still maintaining response under ELT, median DOR: 4 (2-27) months. A transient liver toxicity possibly related to ELT was observed in 8 pts (36.4%) (grade > 2 in 2 pts, 9.1%). With a median follow up of 22 (2-104) months, 7 pts died; median OS not reached. Only 1 pt showed a clonal evolution into chronic myelomonocytic leukemia (CMML) under CYA alone, 41 months after ELT discontinuation.

Conclusions. ELT confirmed to be effective and safe in RRAA, and a prolonged treatment showed a relevant portion of late responses, with a low incidence (4.5%) of clonal evolution.

P121

RECOMBINANT ERYTHROPOIETIN IN AUTOIMMUNE HEMOLYTIC ANEMIA WITH INADEQUATE RETICULOCYTOSIS: A SINGLE CENTER PROSPECTIVE STUDY

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Autoimmune hemolytic anemia (AIHA) is a rare hemolytic disorder mediated by autoantibodies with or without complement activation. Bone marrow (BM) response may be insufficient to compensate hemolysis as demonstrated by inadequate reticulocytosis or inappropriately low endogenous erythropoietin (EPO). To evaluate the efficacy and safety of recombinant (r)EPO in AIHA, we prospectively studied 47 patients with Hb ≤ 100 g/L and bone marrow responsiveness index (BMRI) < 121, evaluated at a single center in Milan, Italy, from January 2019. Subcutaneous epoetin alpha 40,000 U/week was administered in addition to standard of care. AIHA type (warm, cold, mixed and atypical), hematologic parameters and transfusion need were recorded. Responses were evaluated at 15, 30, 90, 180 and 360 days from rEPO start and were classified as partial (PR, for Hb increase ≥ 20 g/L or Hb ≥ 100 g/L) or complete (CR, for Hb ≥ 120 g/L). Adverse events were recorded according to CTCAE v. 5. Furthermore, we compared the cohort with a sex and aged matched control group of 43 AIHAs with BMRI < 121 not receiving rEPO evaluated in the same time period. Overall, 47 AIHA patients were included: 22 warm, 19 cold and 6 mixed or atypical. At baseline, the median time from diagnosis was 16 months (range 0;346 months) and 91% of patients had been already treated, with a median of 2 therapy lines (0;6). Median Hb at rEPO start was 76 g/L (32;100), median BMRI 76 (3;120) and median EPO serum levels 56 IU/L (11;457). 44 received concomitant treatment with steroids (40), rituximab (16), IVIG (8), or other immunosuppressants (5). As shown in Figure 1, response rates were 55%, 74%, 73%, 78% and 91% at the various time points. Consistently, transfusion need progressively decreased from 30% at day 0 to 9% at +15, 7% at +30, 4% at +90, 8% at +180 and 3% at day 360. Overall, 12 (26%) relapsed, of whom 5 at day +90, 5 at +180 and 2 at +360. At day 360, 35 (74%) had discontinued rEPO (median time on rEPO of 120 days, 1-1773) mainly due to persistent response in 30 (64%). Only 1 patient experienced a G3 pulmonary embolism during admission for severe pneumonia and AIHA relapse. Patients treated with rEPO showed higher median Hb levels compared to the control group at day +15 (94 *vs* 86 g/L, p=0.04) and at +30 (105 *vs* 95 g/L, p=0.05). We show rEPO efficacy in more than 90% AIHA with inadequate BM compensation with transfusion reduction and significant Hb increase compared to controls at 15 and 30 days.

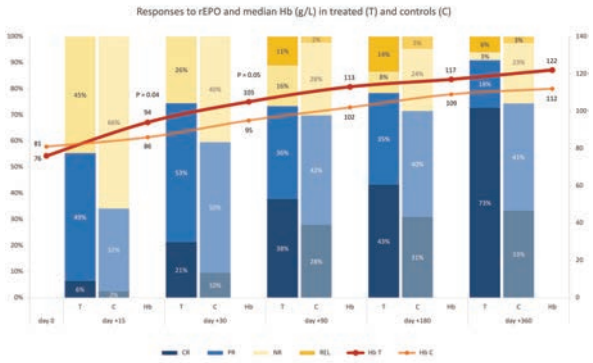

Figure 1.

P122

ANTI C5 THERAPY WITH CYCLOSPORINE +/- ELTROMBOPAG IN THE TREATMENT OF HYPOPLASTIC/HYPOCELLULAR PNH PATIENTS: RESULTS OF A REAL-LIFE EXPERIENCE

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease characterized by chronic hemolysis, increased risk of thrombosis and the association with bone marrow failure (BM) syndromes. Some PNH patients show an hypocellular/aplastic bone marrow. The aim of this study is to evaluate safety and efficacy of the association of anti C5 therapy with cyclosporine A (CYA) with or without Eltrombopag (ELT) in this subgroup of hypoplastic/aplastic BM PNH patients. We collected retrospective data of patients from six Northern Italy Hematology Centers.

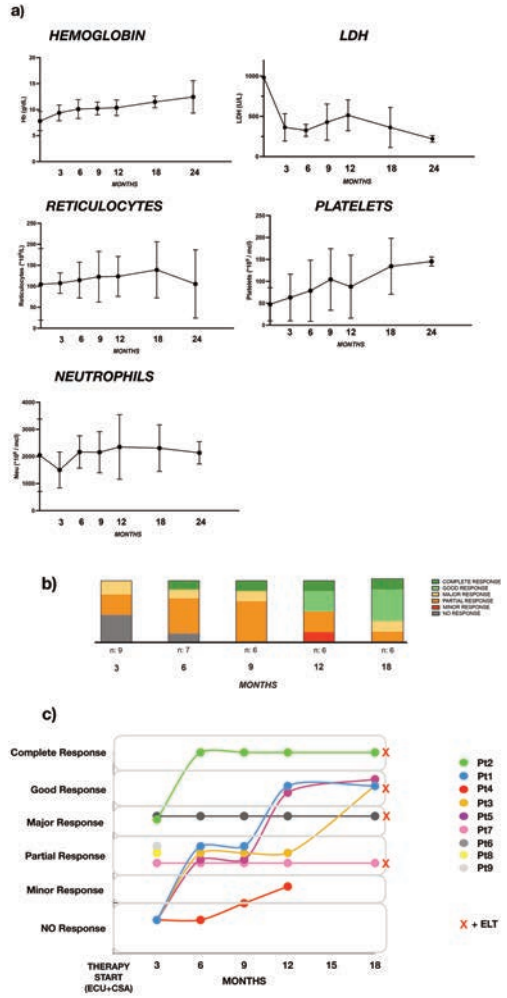

Figure 1. Levels of hemoglobin, lactate dehydrogenase (LDH), reticulocytes, plateletes and neutrophils in enrolled patients after the treatment was started. Data are shown as means with standard deviation (a). Hematological responses (Risitano AM *et al.*, Front Immunol 2019; Risitano AM *et al.*, BJH 2022) (b,c).

Responses were evaluated using criteria previously described (Risitano AM *et al.*, Front Immunol 2019; Risitano AM et al, BJH 2022). Nine patients were enrolled. Median age was 55 years old; males were 6/9 (66%). One patient had a diagnosis of classical PNH, while 8 displayed a PNH with hypoplastic/aplastic bone marrow (AA-PNH). At the time of diagnosis, median hemoglobin level was 8 g/dl in AA-PNH and 3,5 g/dl in the classical PNH patient, respectively. Blood transfusions were recorded in 7/9 patients (1-4 units/month) in the 2 months before therapy start. Three patients were treated with eculizumab (ECU) and 4 with ravulizumab (RAVU); 2 patients started with ECU and continued with RAVU. CYA was initiated before anti C5 therapy in 5 patients (3-102 months, median 60) and after in 4 patients (2-6 months, median 5). Four patients received also ELT. Hematological responses were recorded at different timepoints: at 3 months, 2 patients were in major response (MR), 3 in partial response (PR), 4 in no response (NR); at 6 months 1 patient was in complete response (CR), 1 in MR, 4 in PR and 1 NR; at 9 months 1 was in CR, 1 in MR, 4 in PR; at 12 months 1 in CR, 2 in good response (GR), 2 in PR and 1 in minor response (mR); at 18 months, 1 was in CR, 3 in GR, 1 in MR and 1 in mR (Figure 1). Platelets and neutrophil levels globally increased (PR). Median follow up was 21 months. One patient died after allogeneic bone marrow transplantation due to invasive aspergillosis 14 months after the diagnosis. At the last follow up, all alive patients maintained their best response achieved. No severe adverse events were recorded. Just one episode of breakthrough hemolysis was described in one patient after Covid19 infection.

In conclusion, we showed that the association of anti C5 therapy with CYA with or without ELT is safe and effective both on PNH-hemolysis and BM failure.

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EFFICACY OF FRONTLINE TREATMENT WITH INITIAL LOW-DOSE TYROSINE-KINASE INHIBITORS IN ELDERLY PATIENTS WITH CHRONIC MYELOID LEUKEMIA: A "CAMPUS CML" STUDY

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Introduction. Three TKIs, imatinib (IM), dasatinib (DAS) and nilotinib (NIL), are approved for frontline therapy in Italy. Choice of frontline TKI is based mainly on evaluation of patient's characteristics and clinical expectations. To avoid long term adverse events or drug interactions, elderly patients may start CML treatment with a frontline reduced dose of TKI (RD-TKI).

Aims. To analyse outcome of CP-CML patients aged over 65 years in a large and unselected cohort treated with RD-TKI.

Methods. We retrospectively evaluated 747 patients from 1/2012 to 12/2019 at 36 Hematology Centres participating at the "Campus CML" project.

Table 1. Clinical features of the whole cohort and according to frontline TKI initial dose.

	All patients (747)	Standard dose (605)	Reduced dose (142)	p
Gender, M/F (%)	445/302 (59.6 – 40.4)	367/238 (60.7– 39.3)	78/64 (54.9 – 45.1)	0.210
Median age (years) (IQR)	73.9 (69.3 – 78.9)	72.8 (68.7 – 77.6)	78.8 (74.3 – 82.4)	**<0.001**
Hb, g/dl (IQR)	12.8 (11.2 – 14.1)	12.9 (11.2 – 14.1)	12.7 (11.1 – 14.2)	0.417
WBC, x 10⁹/l (IQR)	48.0 (26.7 – 91.8)	48.4 (26.4 – 94.4)	43.3 (26.8 – 81.0)	0.721
PLTS, x 10⁹/l (IQR)	370 (245 – 593)	378 (251 – 616)	330 (219 – 550)	0.117
Spleen, n° evaluable (%): Not palpable < 5 cm below costal margin ≥ 5 cm below costal margin	732 450 (61.5) 214 (29.2) 68 (9.3)	592 357 (60.3) 172 (29.1) 63 (10.6)	140 93 (66.4) 42 (30.0) 5 (3.6)	0.033
Sokal score, n° evaluable (%): Low Intermediate High	722 74 (10.2) 492 (68.2) 156 (21.6)	587 65 (11.1) 396 (67.5) 126 (21.4)	135 9 (6.7) 96 (71.1) 30 (22.2)	0.313
Frontline TKI, n° (%): Imatinib Dasatinib Nilotinib	579 (78.8) 78 (10.4) 80 (10.8)	467 (77.2) 64 (10.6) 74 (12.2)	122 (85.9) 14 (9.9) 6 (4.2)	**0.018**
Arterial hypertension, n° (%)	473 (63.3)	374 (61.9)	99 (70.2)	0.066
Diabetes, n° (%)	135 (18.1)	98 (16.2)	37 (26.2)	**0.005**
Previous neoplasm, n° (%)	167 (22.4)	133 (22.0)	34 (24.1)	0.591
COPD, n° (%)	112 (15.0)	90 (14.9)	22 (15.7)	0.808
Ischemic heart disease, n° (%)	98 (13.1)	72 (11.9)	26 (18.4)	**0.039**
Cerebrovascular events, n° (%)	41 (5.5)	29 (4.8)	12 (8.5)	0.082
Concomitant drugs, n° evaluable (%): 0 - 2 3 – 5 > 5	739 277 (37.5) 265 (36.8) 197 (26.7)	598 243 (40.6) 216 (36.1) 139 (23.2)	141 34 (24.1) 49 (34.8) 58 (41.1)	**<0.001**

Results. Clinical features for the whole cohort according to frontline TKI initial dose are reported in Table 1. Among all patients, 605

(81%) were treated with standard dose (SD) while the remaining 142 (19%) with reduced dose (RD). As to frontline TKI, 579 patients (77%) received IM and 158 (23%) a 2G-TKI (DAS n=78, 49%; NIL n=80, 51%). Of the 142 RD-TKI, 122 (85.9%) started with IM, 14 (9.9%) with DAS and 6 (4.2%) with NIL. Median RD was 100 mg for IM (range 100-300), 20 mg for DAS (range 20-50) and 250 mg for NIL (range 150-300). RD-TKI was mainly reported in IM treated patients (p=0.018), in elderly (p<0.001) and in patients with comorbidities, in particular diabetes (p=0.005) and ischemic heart disease (p=0.039). Number of concomitant drugs was also significantly associated with RD-TKI (p<0.001) probably to avoid drug interactions and subsequent toxicity. Sokal score did not impact on TKI starting dose. TKI frontline dose was not associated with difference in resistance, nor primary neither secondary resistance. Progression to blastic phase was reported in 1.2% of the whole population, none of which in RD-TKI. At 12 months no differences were noted in terms of achievement of major molecular response (MMR), while RD-TKI had inferior probability of deep molecular response (DMR) achievement (p=0.003). No differences were reported in 12-months cumulative rate of permanent discontinuation for any cause and for primary resistance between SD-TKI and RD-TKI.

Conclusions. RD-TKI was a frontline treatment strategy used mainly in frail elderly patients, with more comorbidities and concomitant therapies. RD-TKI did not impact on primary resistance leading to TKI switch. While no differences were reported in the rate of MMR, the rate of 12-months DMR achievement was inferior in RD-TKI, but this result need to be confirmed with longer follow-up.

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EXPERIENCE OF FOUR LABORATORIES OF THE ITALIAN CML LABNET NETWORK IN THE USE OF THE CEPHEID CARTRIDGE SYSTEM

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Chronic myeloid leukemia is characterized by rearrangement of the BCR::ABL1 oncogene resulting in the production of p210 and p190 fusion proteins with deregulated tyrosine kinase activity. Monitoring BCR::ABL1 transcript levels in PB of patients on TKI therapy using RT-qPCR is the gold standard for management of chronic myeloid leukemia (CML). Xpert® BCR-ABL Ultra p210, is a cartridge-based assay that automates all quantitative process integrating all steps directly from clinical samples in less than 3 hours. The aim of the study was to compare two different methodological approaches through the measure of the concordance between the quantitative values obtained by the analysis of PB CML patients samples. These analysis were performed in parallel with the use of Cepheid cartridge and with the assay used in 4 reference laboratories of the Italian Labnet network. The comparison of methodological approach also occurred through the use of a reference material such as the ACROMETRIX BCR::ABL1 Reference Panel and the analysis of two samples received from the UK NEQAS Control Panel. 25-30 CML peripheral blood samples were evaluated in triplicate using the Xpert BCR-ABL Ultra test and each of the 4 comparator assays of 4 study sites. The analysis included 193 measurements, quantified by both the Cepheid and the Standard in-house method.The measurements were divided by level of disease, with 31 for MR1, 36 for MR2, 54 for MR3, 26 for MR4, 28 for MR4.5, and 18 for MR5. Finally, we evaluated the agreement between the reference and Cepheid results according to Branford *et al.* (Blood 2008; 112: 3330–3338) by applying three criteria. The first criterion required that the ratio of the reference result to the Cepheid results fell between 0.5 and 2.0 in at least 50% of the patient samples. The second criterion required the ratio to fall between 0.33 and 3.0 in at least 75% of the patient samples. Finally, the third criterion required the ratio to fall between 0.2 and 5.0 in at least 90% of the patient samples. By meeting two out of these three criteria, we determined the level of agreement between the two methods (Table 1).

Statistical analysis of the data obtained with the two systems and on the three different types of material demonstrated a good correlation at all different levels of disease. The CEPHEID cartridge system could therefore be considered as an alternative to the analysis systems currently validated within the Italian network CML LabNet.

Table 1.

Eutos Criteria	≥ 50% between 0.5 and 2.0 fold	≥ 75% between 0.33 and 3.0 fold	≥ 90% between 0.2 and 5.0 fold
Overall N= 193	109 (56.5 %)	155 (80.3%)	182 (94.3%)

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HETEROGENEITY OF CYTOPENIAS IN VEXAS SYNDROME: A SINGLE CENTRE EXPERIENCE

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VEXAS syndrome is an autoinflammatory X-linked disorder characterized by acquired UBA1 gene mutation, usually arising in adult men, with variable autoinflammatory manifestations and potential aggressive behavior. Hematological alterations are frequent, with macrocytic anemia and vacuolization in erythroid and myeloid progenitors being the most frequent ones. Cytopenias are common and myelodysplastic syndromes (MDS) are diagnosed in about 40% of patients. Due to the presence of dysematopoiesis and vacuolization, it is not easy to correctly classify cytopenias. We retrospectively analyzed bone marrow samples from 7 patients diagnosed with VEXAS syndrome at our centre between 2021 and 2022. Aspirates and trephine biopsies were performed at diagnosis and repeated at follow up in case of change in blood counts. Morphological, cytogenetic and molecular testing by NGS were exploited. MDS, CCUS (clonal cytopenia of uncertain significance) and ICUS (idiopathic cytopenia of uncertain significance) were defined according to WHO 2022 criteria. All patients were men older than 60 years at diagnosis; two patients (28.5%) were diagnosed with low/intermediate risk MDS according to IPSS-R, without cytogenetic abnormalities or somatic

mutations. Three (43%) patients who did fulfill criteria for MDS, and did not harbor somatic mutations or cytogenetic abnormalities, were diagnosed with ICUS. Two (28.5%) patients who did not fulfill criteria for MDS but with somatic mutations consistent with clonal hematopoiesis were diagnosed with CCUS. During follow up, patients with ICUS did not show significant changes in blood counts; a second NGS performed on peripheral blood in patient 6 was negative 12 months after diagnosis. Patients with MDS had worsening cytopenias without clonal evolution or leukemic transformation and were treated with erythropoiesis stimulating agents or hypomethylating agents. One patient with CCUS progressed to low risk MDS, while the other acquired a further somatic mutation without evolving to MDS, after a 6-month follow up.

In conclusion, our case series shows that cytopenias in VEXAS syndrome are heterogeneous and might be clustered into three groups: 1) NGS-negative cytopenias, probably related to the inflammatory status ("VEXAS-associated cytopenia"); 2) CCUS at high risk of clonal evolution; 3) MDS with no leukemic evolution but progressive bone marrow failure. Further studies are warranted to better characterize myeloid alterations in VEXAS patients.

Table 1. Classification of Cytopenias in VEXAS syndrome. ICUS = idiopathic cytopenia of undetermined significance; CCUS = clonal cytopenia of undetermined significance; MDS = myelodysplastic neoplasia. * only oncogenic and potentially oncogenic variants are reported; § a second NGS testing performed during follow up on peripheral blood was negative.

	Timing of bone marrow evaluation	Classification WHO 2022	IPSS-R	NGS (VAF %)*	Karyotype
PT1	Diagnosis	CCUS		ZRSR2 (3.79%) DNMT3A (38%)	46, XY [23]
	Follow up	CCUS		ZRSR2 (3.47%) DNMT3A (37%) ASXL1 (2.12%)	46, XY [20]
PT2	Diagnosis	CCUS		DNMT3A (39%)	46, XY [19]
	Follow up	MDS-LB	Low	DNMT3A (40%)	46, XY [21]
PT3	Diagnosis	ICUS	/	Negative	46, XY [28]
PT4	Diagnosis	MDS-LB	Low	Negative	46, XY [24]
	Follow up	MDS-LB	Intermediate	Negative	46, XY [20]
PT5	Diagnosis	MDS-LB	Very low	Negative	46, XY [18]
	Follow up	MDS-LB	Low	Negative	46, XY [28]
PT6 §	Diagnosis	ICUS		Negative	46, XY [22]
PT7	Diagnosis	ICUS		Negative	46, XY [20]

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CD4+ CD25HIGH REGULATORY T CELLS IN CHRONIC MYELOMONOCYTIC LEUKEMIA

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Chronic myelomonocytic leukemia (CMML) is a myeloid neoplasm characterized by dysplasia, abnormal production of monocytes, and an increased risk of leukemic evolution. According to WHO, CMML patients show a persistent (≥3 months) absolute PB Monocytosis (≥1×10^9/L) and relative Monocytosis (≥10% of PB leukocytes), with the exclusion of Chronic Myeloid Leukemia (CML), Myeloproliferative Neoplasms. This study aims to explore the different immune T-cell responses in CMML patients and identify correlations and changes in T cells population with clinical features. Flow cytometry was performed by DxFLEX (Beckman Coulter), and data were analyzed on KALUZA software. Statistical Analyses were performed using JMP pro 13.0. The nonpaired t-test and Mann-Whitney U test were used to compare low- and high-risk groups, and significance was set at a P value less than .05. We analyzed the number of CD4+ and CD8+, and CD4+CD25high T regulatory cells in the peripheral blood (PB) and bone marrow (BM) of 21 CMML patients, with a median age at diagnosis of 78 (range 49-87 years). According to WHO classification, 13 (61,9%) patients had CMML-0; 5 (23,8%) had CMML-1, and 3 (14,3%) had CMML-2. According to the FAB classification, 18 patients (85,7%) were diagnosed with CMML-Myelodisplastic (MD), and 3 patients (14,3%) with CMML-Myeloproliferative (MP). Transfusion-dependent anemia was present in 23.8% of patients. Cytogenetics were normal in 76.2 % of patients, and single stable abnormalities were present in 19.0 %. Only in 13 patients was molecular analysis performed in NGS. These patients were treated with a different therapeutic approach: 7 (33,3%) patients did not receive any treatment; among the other patients, 23,8% received HMA, 19% EPO, and 19% HU. Moreover, one patient underwent allogeneic hematopoietic stem cell transplantation (HSCT). Median CD4+ CD25+high Tregs were significantly higher in patients with MP features than MD features (15% *vs* 6.5%, p=0.035). Median CD4+CD25+high Tregs was significantly lower in patients with CMML-2 compared with CMML-0 and CMML-1 (3% *vs* 7.5% *vs* 8.5%, respectively; P=0.03) and median CD45RA+ on Tregs was higher in CMML-2 compared to other WHO categories (p=0.04). Our preliminary data showed that T cell subpopulations are distributed differently according to WHO and FAB classification in CMML. Larger cohorts of patients are needed to validate these results.

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SHORTER TIME FROM DIAGNOSIS TO LUSPATERCEPT TREATMENT IMPROVES OUTCOMES IN A SINGLE-CENTER SERIES OF MYELODYSPLASTIC NEOPLASMS WITH RING SIDEROBLASTS

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Patients with myelodysplastic neoplasms with ring sideroblasts are characterized by severe anemia, transfusion dependence, and somatic mutation of SF3B1 in the majority of patients (MDS-SF3B1). For those not candidate to or failing erythropoiesis stimulating agents (ESAs), luspatercept is an effective option. We studied a single-center series of 19 MDS-SF3B1 patients treated with luspatercept from January 2021 until March 2023, to evaluate efficacy and safety and unravel predictors of response. Clinical and laboratory features, number of red blood cell (RBC) transfusions pre and post therapy and adverse events were retrospectively registered. Patients were divided in two groups A) luspatercept in compassionate use vs B) reimbursement phase. As showed in Table 1, a total of 19 patients were treated, 9 in group A and 10 in group B. Overall, patients were mainly elderly [median age 79 years (70-89)] with a male to female ratio of 8.5, and belonged to either very low, low or intermediate IPSS-R risk category. All subjects had been previously treated with ESAs and median time from diagnosis to luspatercept start was shorter for patients treated in group B [2.6 years (0.7-6.8)] versus those treated in the compassionate program [4.3 (2.8-19.6); p=0.03]. The latter (group A) included a higher proportion of patients classified as having "high transfusion burden" (67% versus 40% in group B), with a median of 6 (4-8) RBC-U over a 8 week period before luspatercept. After a median follow up of 11 months (2-25), a total of 10 patients obtained a hematologic improvement (according to IWG 2018 criteria): 8 became transfusion independent and 2 subjects displayed a reduction >33% of transfusion need. Interestingly, the rate of response was higher in group B (50% *vs* 33%). Additionally, in group A all patients except for one required dose titration to 1.75 mg/kg/3 weeks, while 5 patients in group B achieved a response with lower doses (2 at 1

mg/kg and 3 at 1.33 mg/kg). Rate of discontinuation was 47%, similar for the two groups. One non-responder eventually evolved to acute myeloid leukemia and died. Three patients experienced a grade 2 adverse event (AE), including dizziness (2), and facial eczema (1), not related to dose-increase.

These data show that, along with low transfusion burden at baseline, earlier access to luspatercept in the reimbursement phase led to increased rate of transfusion independence.

Table 1.

N=19	Compassionate use (9)	Reimbursement phase (10)
Median Age, years (range)	78 (73-89)	79 (70-87)
M/F	7/2	10/0
IPSS-R VL/L/I	3/5/1	4/3/3
Median time from diagnosis, years (range)*	**4.3 (2.8-19.6)**	**2.6 (0.7-6.8)**
HTB	6 (67%)	4 (40%)
LTB	3 (33%)	6 (60%)
Median N. RBC/8 weeks	6 (4-8)	4 (2-8)
Median N. RBC/16 weeks	12 (8-17)	8 (4-17)
RBC-U reduction ≥33%	1 (11%)	1 (10%)
RBC TI	**3 (33%)**	**5 (50%)**
NR	5 (56%)	4 (40%)
Last LUSPA dosing		
- 1 mg/Kg	0	2 (20%)
- 1.33 mg/Kg	1 (10%)	3 (30%)
- 1.75 mg/Kg	8 (80%)	5 (50%)
Possibly related AEs	3 (33%) – 2 dizziness 1 eczema	0
Dose reduction	1 (11%) – eczema	0
Discontinuation	5 (56%)	4 (40%)
- NR	3 (33%)	4 (40%)
- NR and AEs	2 (22%)	0

HTB, high transfusion burden; LTB, low transfusion burden; RBC, red blood cell; RBC-U, red blood cell-unit; RBC TI, red blood cell transfusion independence; NR non responders; AEs, adverse events; *p=0.03

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COULD AN UP TO DATE SINGLE-CENTER SERIES TELL US SOMETHING ELSE ABOUT LUSPATERCEPT?

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Background. Luspatercept is a TGF-β pathway inhibitor, acting as an antagonist of ineffective erythropoiesis and promoting late-phase erythroid differentiation. It has been approved for MDS-SF3B1 patients who fail ESAs treatment and become transfusion-dependent. Here we report, retrospectively, the data on the trend of patients affected by MDS-SF3B1 and refractory to ESA treated with Luspatercept at our center since the opening of the Early Access Program (EAP).

Materials and Methods. We retrospectively evaluated data from all patients (pts) with an IPSS-R very low, low and intermediate risk MDS-SF3B1 treated with Luspatercept at our center. Statistical analyzes were performed using «IBM SPSS ver.26» software. The Kaplan- Meier method was used for Overall Survival (OS) and Progression -free Survival (PFS) curves. A significant p-value was expressed as <0.05.

Results. We treated 13 pts from January 2021 to April 2023 whose characteristics are summarized in Figure 1A. Considering all the pts, 7 (54%) reached transfusion independence (TI), of these 4 (31%) before and 3 (23%) after the first 24 weeks (w) of therapy. One case after an initial Hematological Improvement (HI), reached TI at 87th w (Figure 1B). Interestingly, in our series, the presence of SF3B1 mutation on exon 14 compared to exon 15 correlated with earlier achievement of TI, respectively at the evaluation after the first 8w: 75% *vs* 0% (p 0.003) and within 24w: 75% *vs* 11%, respectively (p 0.021) (Figure 1C). Whereas no difference was found considering other covariants. Median follow-up (FU) was 23.6 months from the start of therapy (range 0.7-25.4), while median for both PFS and OS (Figure 1-D) was not reached. Safety was recorded but no events of Severe Adverse Events (SAEs) needing a discontinuation or reduction of treatment happened.

Conclusions. In our "real world" setting, the response rates of the registration studies appear to have been reproduced on a small scale. Furthermore, the failure to achieve a TI in 24w does not seem to preclude the possibility of achieving it even some time after the start of treatment. The SF3B1 mutation on exon 14, on the other hand, seems to identify a group of "early responders" pts, characterized by the achievement of TI already after the first 8 w of treatment. On the contrary, given the small number of cases, it is not possible to identify characteristics of the «late responders».

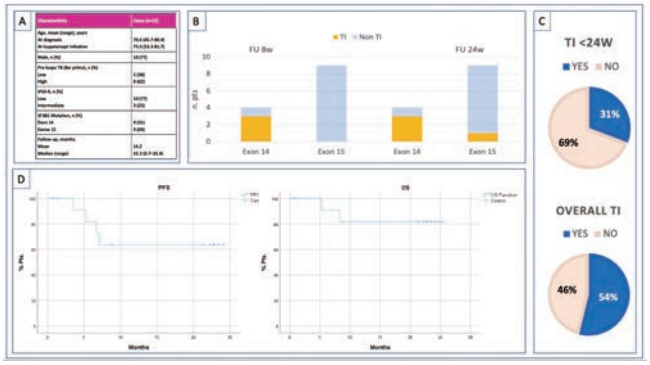

Figure 1.

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DOES TAILORING OF LENALIDOMIDE DOSAGE IN ELDERLY MDS DEL(5Q) MAINTAIN EFFICACY WITH GOOD TOLERABILITY? A SINGLE-CENTER EXPERIENCE

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Background. Myelodysplastic syndrome with isolated deletion of chromosome 5q (MDS Del(5q)) is the only cytogenetically defined subtype currently recognized by WHO and ICC. Lenalidomide is an immunomodulatory agent that selectively suppresses the Del(5q) clone.

Materials and Methods. We retrospectively collected data from all MDS Del(5q) patients treated with Lenalidomide at our center from 2010. We considered both hematological (HeR), as transfusion independence, and cytogenetic (CyR) response. The curves of Overall Survival (OS) and Progression-free Survival (PFS) were obtained using the Kaplan-Meier method. A significant p-value was expressed as <0.05.

Results. We considered 19 pts with a median age of 69.4 years (range 42.8-90.4) at diagnosis and of 70.8 (range 43.4-90.9) at the start of lenalidomide. All other clinical features are summarized in Figure 1A. Pathognomonic alteration was present in all pts at diagnosis, with the widest region involved (q13q33), present in 6/19 (31.5%) cases. It was the sole cytogenetic abnormality in 15/19 (78.9%). Dose reduction until cycle 6 was chosen in 7 pts (36.8%): 4 (21%) started already at a lower dose due to age and reduced renal function, while in 3 (16%) was reduced later due to hematological toxicity. Among these patients, the most common regimen was 10 mg every other day. Rate of response was 16/19 (84.2%) and 9/19

(47.3%) for HeR and CyR, respectively. Interestingly, rate did not vary between group univariate analysis for dose, age, or risk group. Median follow-up was 67.7 (range 16.8-143.6) months from diagnosis and 46.6 (range 8.1–97.3) since Lenalidomide start. Five-year OS (Figure 1B) and PFS (Figure 1C) were 93.8% and 55.9%, respectively; with only one case (0.5%) of progression to acute myeloid leukemia after 54 months of therapy. Neither dose reduction nor age at lenalidomide start impacted OS and PFS, while HeR and CyR are related to a better outcome in terms of life free from progression ($p<0.05$).

Conclusions. In this experience, lenalidomide proved feasible and effective even in elderly (usually excluded from clinical trials or by stringent criteria for standard therapy) with dose reduction due to age, renal dysfunction, or other comorbidities. As highlighted, a dose reduction tailored on patients' features did not affect the response rates with excellent tolerability, showing, albeit on a small cohort, that it is possible to expand the pool of patients who can benefit from this treatment.

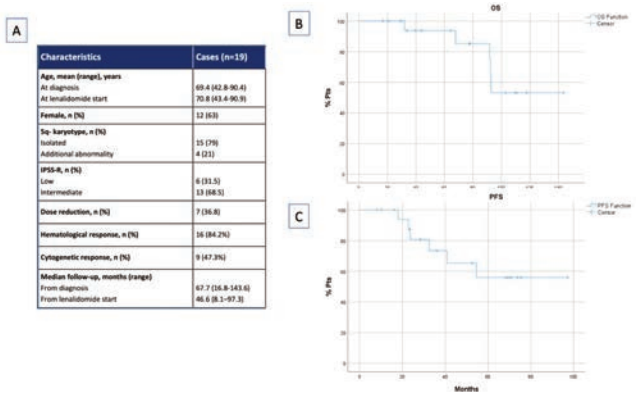

Figure 1.

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LUSPATERCEPT IN PATIENTS WITH MYELODYSPLASTIC SYNDROME WITH RING SIDEROBLASTS: REAL-LIFE EXPERIENCE IN TURIN

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Myelodysplastic syndromes with ring sideroblasts (MDS-RS) are a subgroup of MDS characterized by iron overload in erythroblasts and transfusion-dependent anaemia. The use of agents like erythropoietin (EPO) and luspatercept improves erythropoiesis and reduces the transfusion burden. Nowadays, real-life data of luspatercept are still limited. We analysed a cohort of adult patients with very low, low and intermediate R-IPSS risk MDS-RS, treated with luspatercept in the Hematology Department of Città della Salute e della Scienza of Turin. All patients had a transfusion-dependent anaemia, with inadequate response, or ineligible to, EPO. Pre-luspatercept transfusion burden and response to treatment were assessed according to the IWG 2018 HI-E criteria. The cohort includes 17 patients, 76% male, with a median age at diagnosis of 74 years, treated with luspatercept from March 2021 until nowadays, after a first line treatment with EPO (in 100% of patients, median duration 30 months). A total of 10 patients (59%), with a median ferritin level of 2348, received iron chelation. Luspatercept was initiated starting from a High Transfusion Burden (HTB) in 82% of cases and from a Low Transfusion Burden (LTB) in 18%. Maximum luspatercept dosage was 1, 1.33 and 1.75 mg/kg in 12%, 18% and 70% of patients, respectively. In weeks 1-48 from treatment start, 12 patients (71%) obtained a haematological improvement-erythroid (HI-E); 50% of responders achieved a transfusion independence (TI) > 8 weeks. A total of 5 patients (29%) did not respond and were therefore discontinued. Therapy was well tolerated, without significant toxicity (no toxicity grade > 1 according to CTCAE). With a median FU of 33 weeks from luspatercept start, 16 patients are alive (94%). Of note, two HTB patients achieved major HE-I response in 8 weeks at a maximum dose of 1 mg/kg. In conclusion, in our cohort, luspatercept confirmed its efficacy, with responses comparable to published data (TI > 8 weeks in weeks 1-48, in 36%, *vs* 45.1% of the long-term benefit study). Considering the pre-luspatercept transfusion burden, 83% of responders had a HTB before treatment. No correlation was observed between iron chelation therapy and response to luspatercept; the absence of iron-chelation treatment does not appear to affect response to luspatercept. Given the efficacy with an excellent safety profile, luspatercept confirms his promising role; further larger real-life studies are needed to confirm local data.

Allogeneic and autologous transplant

P131

THE IMPACT OF CARBAPENEMIC RESISTANT ENTEROBACTERIACEAE COLONIZATION IN ALLOGENEIC STEM CELL TRANSPLANT SETTING: A RETROSPECTIVE SINGLE CENTRE EXPERIENCE IN THE ERA OF NEW AGENTS AND SARS-COVID19 PANDEMIC

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Backgrounds. The progressive raise of Carbapenemic Resistant Enterobacteriaceae (CRE) infections correlates with increased morbidity and mortality in allogeneic stem cell transplantation (HSCT). Our primary aims were to analyze the impact of SARS-COVID19 (COV 19) pandemic on CRE colonization and the efficacy of new antibiotics on the 100 days and 1-yr TRM in both CRE colonized and non-colonized patients (pz). The secondary aims were to compare the two cohorts in terms of hospitalization's duration, aGVHD occurrence and PMN and PLTS engraftment.

Methods. From July 2019 to November 2022, 83 pz (median age of 48 years) underwent first HSCT at Cardarelli Transplant Program(PT) in Naples. Fifty-nine (71%) pz were affected by high risk Acute Leukemia (AML 52%, ALL19%) and 34 (41%) received HSCT from a HLA-identical sibling donor (see Table 1). Conditioning regimen was TBI based or Valencia schedule (TBF) in almost all ALL (75%) and AML (82%), respectively, and MAC or RIC according to the patient's age and comorbidities. GVHD prophylaxis consisted of CSA+MTX, CSA+MTX+ATG or PT-CY+CSA+MMF association according to the stem cell source and type of donor. Pz were divided in 2 groups and 2 subsets according to the CRE colonization (35 *vs* 48) and the period of COV 19 associated restrictions (36 *vs* 47). CRE colonized pz with fever received empirical antibiotic treatment based on novel anti-MDR antibiotics.

Results. Overall, 35 out of 83 (42%) pz were colonized by CRE. Median follow up was 10 months (range 1-42), significantly longer in non colonized group (512 *vs* 274 days, p<0.001). No other significant difference was observed between the 2 groups. CRE colonization rate at our PT was 61% and 19%, respectively before and after COV 19 associated restriction were adopted (29/47 *vs* 7/36 colonized pz; p<0.0001). However, 100 days and 1 yr-TRM were similar in the 2 groups of CRE colonized and not colonized: 0.6% *vs* 1.5% (p= ns) and 1.3% *vs* 5.5% (p=ns). Moreover, there were no significant differences in terms of aGVHD occurrence, median hospitalization duration and median time to PMN and PLTS recovery with 4.32 *vs* 9.5 % (p=ns), 39 (20-75) *vs* 43 (25-109) (p=ns), 21 (8-97) *vs* 21(6-53) (p=ns) and 18 (11-25) *vs* 17 (10-27) days (p=ns) in colonized and non colonized pz.

Conclusions. COV 19 associated restrictions reduced the CRE colonization rate at our PT. In our case-series, empirical therapy with novel anti-MDR antibiotics for febrile cases allowed the disappearence of the difference in terms of poor outcome in the two cohorts analyzed.

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STUDY OF THE INFORMATIVE MARKERS IN THE CHIMERISM ANALYSIS OF RECIPIENT/DONORS PAIRS FROM CAMPANIA

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Chimerism analysis is sensitive and informative method to evaluate the graft status of the Hematopoietic Stem Cell Transplantation (HSCT). The chimerism test is based on the differences in biallelic insertion/deletion (In/del) polymorphisms markers between patient and donor in order to identify the informative markers in the recipients. The aim of this study was to evaluate the prevalence, of the informative markers in Campanian recipient/donor pairs. Between 2019-2022, 83 first allogeneic HSCT were performed at AORN Cardarelli Transplant Program in Naples, 52 males and 31 females with a median age of 48 years (range 20-69). About this 59 of 83 (71%) were affected by Acute Leukemia. Most of them (65%) received PBSC, as stem cell source, from HLA-identical sibling, unrelated or haploidentical donor in 43, 32 and 25% of cases, respectively. Genomic DNA was extraction, using a commercial kit (QIAamp® Blood Mini kit Qiagen), from 83 pairs at baseline. All pairs were genotyped using KMRtype Extended Genotyping kit (GenDx) which includes 39 In/del polymorphisms markers on different chromosomal location and analysis was performed using relative software. qPCR was carried out using Applied Biosystems® 7500 (Thermo Fisher Scientific). Informatives markers were selected occuring sex and karyotype pre allo-HSCT. We defined as prevalent informative markers those which occurred > 15% of recipients. In our population, the median of informative markers for every patient resulted 5 (range 2-10) and the prevalence is detailed in Table 1.

Table 1. Informative markers prevalence in recipient and donor pairs.

MARKERS	LOCUS	%RECIPIENTS	%DONORS
KMR016	17q	23	11
KMR010	5q	22	18
KMR050	1p	22	17
KMR030	9p	20	8
KMR043	1p	20	22
KMR048	14q	20	14
KMR052	10q	19	5
KMR014	12q	18	11
KMR028	20q	18	18
KMR039	17p	18	11
KMR047	18q	17	22
KMR056	1p	17	7
KMR034	1p	16	13
KMR009	17p	10	18
KMR004	18q	11	17
KMR051	4q	14	16
KMR019	20q	12	16

According to diagnosis, we identified KMR41 and 42 as informative markers only in AML setting (9,5%) while KMR10 and 16 were more present respect to KMR41 and 42 (23% *vs* 9.5%) but not specific for AML. On the other hand, KMR38 and 52, KMR28 and 31, KMR48 and 50 were observed in 31% of ALL, in 50% of MDS, in 58% and 67% of HD, respectively. Moreover, KMR29-35-37-55-57 were never observed in female Campanian recipients, while, KMR41and 49 were identified as informative markers in unrelated donors with non-Campanian origin. This analysis on Campanian pairs represents a useful tool for the laboratory management for the acquisition of single markers instead of kits for monitoring the chimerism in allogeneic HSCT. Our preliminary data shows that KMR016 on CHR17q locus seems to represent the informative marker with higher prevalence (23%) markers in Campanian recipient setting. Further investigation is necessary to understand this preliminary data.

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IMPACT OF BUSULFAN DOSE-FRACTIONING AND CUMULATIVE DOSE ON POST-TRANSPLANT TOXICITIES IN PATIENTS UNDERGOING DUAL ALKYLATING REDUCED-INTENSITY CONDITIONING REGIMEN

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Introduction. Conditioning regimens are responsible for major toxicities in the immediate post-transplant setting. Busulfan is a widely used alkylating agent thought to be responsible for pulmonary, neurological and mucosal toxicity. Double alkylating regimen with Thiotepa, Busulfan and Fludarabine (TBF) is feasible conditioning approach, where busulfan can be administered at a daily dose of 3.2 mg/kg for 1 (TBF1), 2 (TBF2) or 3 (TBF3) days, according to performance status and comorbidities. TBF1 and TBF2 are considered Reduced Intensity conditioning (RIC) regimens. Busulfan was administered as a single daily dose up to October 2021, thereafter it was administered in 4 doses/day of 0.8 mg/kg every 6 hours. We aimed to evaluate the impact of different schedules of busulfan (TBF1 *vs* TBF2 and Bu^4 *vs* Bu^1) on organ toxicities occurred after HSCT conditioned with RIC regimens.

Patients and Methods. We retrospectively included 115 recipients affected by hematologic malignancies receiving HSCT from november 2019 to november 2022, with a median age of 60 years. Thirty-one patients received TBF1 and 84 TBF2, among them, busulfan was administered in 4 doses in 32 patients. There were no significant differences between Bu^4 and Bu^1 with regards to HLA matching, main diagnosis, demographic characteristics, or disease status at transplantation. Toxicities were graded according to CTCAE criteria.

Results. Any-grade pulmonary toxicity of any grade was independently associated with older age (p=0.097) and Bu^1 (p=0.071), while a HCT-CI ≥2 predicted severe (G3-4) lung toxicity (OR 4.07, p=0.081). The cumulative dose of busulfan (TBF2 *vs* TBF1) conferred an increased risk of mucositis (OR 3.26, p=0.008), while a trend for G3-G4 mucositis was observed in patients receiving busulfan with Bu^1 schedule (OR 2.84, p=0.074). A strong risk factor for hepatic toxicity was an HCT-CI ≥2 (OR 11.75, p=0.020), while older patients were at higher risk of severe cardiac toxicity (p=0.075).

Conclusions. In the setting of dual alkylating RIC regimens receiving triple PTCy-based prophylaxis, the cumulative dose of busulfan impacts on mild-to-moderate mucositis, whereas fractioned-dose strategy appears to protect against severe mucositis and the onset of pulmonary toxicity. Pre-transplant age and comorbidities confirm an important role as risk factors for cardiac, pulmonary, and hepatic toxicity, while the male population may be at increased risk for bladder toxicity.

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HEMATOGONE EXPANSION AS A SENSIBLE AND EARLY BIOMARKER OF ALLOGENEIC STEM CELL TRANSPLANTATION OUTCOME: A REAL-LIFE SINGLE-CENTER EXPERIENCE

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Hematogones repopulate the bone marrow after cell-depleting events, such as conditioning regimens for hematopoietic stem cells transplantation (HSCT) preparation, and have been proposed as a candidate prognostic biomarker of clinical outcomes after allogeneic HSCT. In this retrospective real-life monocentric study, we studied the prognostic role of hematogones in transplanted patients, and their association with other clinical, biological, and molecular features. A total of 60 consecutive patients who underwent allogeneic HSCT from 2016 to December 2022 were included in this study. Evaluated parameters were divided in three groups: patients' related factors, including percentage of hematogones after HSCT, age, sex, cytomegalovirus (CMV) positivity, type of disease, comorbidities, cytogenetic abnormalities, clinical and molecular biology; donor's related factors, such as age, sex, and CMV positivity; and transplant procedure-related factors, including source of stem cells, HLA-matching, homogroup, and the number of infused CD34+ cells. Increased percentage of hematogones at first re-evaluation (median, 104 days) correlated with early engraftment, and hematogones levels at most-recent re-evaluation post-transplant (median, 522 days) were associated with a higher overall survival (OS) and relapse-free survival (RFS). Interestingly, percentage of B cell precursors were significantly higher in female recipients than in males and at most recent re-evaluation ($p<0.05$ and $p<0.01$, respectively). No associations were described between hematogones appearance and other factors, such as recipient and donor age, CMV positivity, or probability to develop acute or chronic GvHD or cGvHD. Our results confirmed that hematogones evaluated by flow cytometry immunophenotyping could be a useful valid prognostic marker of engraftment efficiency and HSCT outcomes even in a real-life setting. Moreover, the evidence of B cell precursors expansion as a sex-related factor poses further questions on molecular microenvironment favoring this increase and potential pharmacological perspectives.

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USE OF DARATUMUMAB IN REFRACTORY RED CELL APLASIA AND REFRACTORY HEMOLYTIC ANEMIA AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Pure red cell aplasia (PRCA) is a complication secondary to ABO mismatched allogeneic stem-cell transplantation(HSCT)and the incidence varies between 1 to 50% of all ABO mismatched HSCT. Autoimmune hemolytic anemia (AIHA) accounts for most cases of post-HSCT autoimmune cytopenia (AIC), with a variable incidence from 0.7% to 5.6%, occurring at average 5-10 months post-HSCT. Daratumumab is a humanized IgG1-kappa monoclonal antibody directed against CD38, widely expressed on plasma cells and it could target the plasma cell clone determining the delayed erythroid engraftment. From 2022 to date, we treated 4 patients with daratumumab after HSCT, 3 affected by PRCA and 1 affected by AIHA.Their baseline characteristics are listed in Table 1.

Table 1.

Total patients number	**4**
Evaluable	**3**
Gender n (%)	Male 3 (75 %)
	Female 1(25 %)
Median age at transplant	
Years (range)	65 years (56-70)
Hematological disease n (%)	
AML	2 (50%)
MDS	1 (25 %)
AA	1 (25 %)
Conditioning n (%)	
TBF2	1 (25 %)
TBF1	2 (50 %)
Baltimore	1 (25 %)
Median Hb value pre-daratumumab (range, g/dl)	7 (6.5-7.4)
Median reticulocytes value pre-daratumumab (range, %)	0.2 (0 – 0.5)
Median Hb value post-daratumumab (range, g/dl)	10.2 (9.3 – 10.8)
Median reticulocytes value post-daratumumab (range, %)	4.9 (1.9 – 6.4)

Three patients underwent thiotepa-busulfan-fludarabine (TBF). One patient underwent "Baltimore" regimen.Two patients underwent plasma exchange (PE) before stem cell infusion.Three patients were AB0-mismatched and one patient Rh-mismatched. Three patients received matched unrelated donor(MUD), two of them mismatched at one allele (UD) and one patient received sibling donor.Graft-vs-host disease (GVHD) prophylaxis consisted of post-transplant cyclophosphamide, cyclosporine and mycophenolate mofetil and thymoglobulin therapy in 2 out of 4 patients. All obtained white blood cells and platelets engraftment with a median of 26 days and median chimerism was 98% (range 96-99%).Median hemoglobin was 7 g/dl (range 6.5-7.4) and median reticulocytes count was 0.2% (range 0-0.5%) and patient affected by AIHA was positive to direct and indirect Coombs test. Two patients underwent PE and rituximab, one patient only rituximab. After a median of 5 months,compassionate use or off label daratumumab 16 mg/kg weekly was administered. Two patients received 8 doses of daratumumab,1 patient 4 doses, 1 patient 2 doses respectively. After daratumumab, median hemoglobin level was 10.2 g/dl (range 9.3-10.8) and median reticulocytes level was 4.9% (range 1.9-6.4%). All but one patients became transfusion independent, 1 patient died from septic shock unrelated to daratumumab and was not evaluable for response.We report the successful use of daratumumab in post-HSCT immune-mediated anemia. Despite the limitation of our small cohort, in accordance to literature,our real life experience suggest that daratumumab may represent an effective and rapid alternative to conventional immunosuppressive drugs, PE and erythropoietin and its use in refractory post-HSCT immune-mediated anemia is emerging as a treatment of choice.

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PRE-EXPOSURE PROPHYLACTIC ADMINISTRATION OF TIXAGEVIMAB/CILGAVIMAB AND SARS-COV-2 INFECTION IN ALLOGENEIC STEM CELL TRANSPLANTATION RECIPIENTS

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Despite strengthened vaccination programs, patients (pts) with hematologic malignancies undergoing allogeneic stem cell transplantation (alloSCT) are at increased risk of SARS-CoV-2 infection and severe forms of COVID-19. For these vulnerable pts pre-exposure prophylaxis (PrEP) with anti-SARS-CoV-2 antibodies tixagevimab/cilgavimab (Evusheld, AZD7442) is indicated. Few studies evaluate the efficacy of Evusheld PrEP among alloSCT recipients, especially since January 2022, when Omicron variants with reduced sensitivities to adoptive antibody therapy have emerged.Here we report on the frequency and clinical outcome of SARS-CoV-2 infections among newly transplanted alloSCT pts who received Evusheld for PrEP. Between May 2022 and January 2023, 62 consecutive alloSCT pts were treated with a single 150/150 mg dose of Evusheld, without reporting any major adverse event. Among the pts included, 30 (48%) received PrEP at a median time of 90 days (range 20-210) after alloSCT and 32 (52%) at a median time of 10 days (range 1-120) before transplant.During 3-12-month follow-up, occurrence of infections and SARS-CoV-2 immunoglobulin G (IgG) titer were routinely tested. At a median of 120 days (range 30-170) after the injection of Evusheld, 12 (19%) pts developed COVID-19. Among infected pts, 9 (75%) were within 6 months of alloSCT and 5 (56%) of them were still undergoing immunosuppressive treatment. Moreover, 10 (83%) pts had previously received at least 3 doses of COVID-19 vaccination with a median pre-Evusheld IgG titer of 2500 U/ml (range 1-2500). Interestingly, pts w/o previous SARS-CoV-2 infection had a significant higher risk to be infected after Evusheld (P=0.024), while no other patient or transplant feature had a significantly different distribution between infected and uninfected pts. SARS-CoV-2 IgG titer either before or after PrEP was similar in the 2 groups (Table 1). No severe form of disease occurred, with the exception of one case that required hospitalization in intensive care unit and no patient died from SARS-CoV-2 infection. Our data show that

a substantial number of alloSCT recipients become infected despite PrEP and sustained antibody titers. Indeed, only previous SARS-CoV-2 infection and not previous COVID-19 vaccination or specific antibody level either before or after PrEP were predictive factors of SARS-CoV-2 infection. Nevertheless, Evusheld treatment may have contributed, together with the lower virulence of Omicron, to the mild course of disease.

Table 1. Baseline characteristics and antibody titers of alloSCT patients who received Tixagevimab/Cilgavimab.

Patient characteristics	SARS-CoV-2 uninfected (n = 50)	SARS-CoV-2 infected (n = 12)	P value*
Median age, y (range)	60 (23-76)	54 (22-74)	0.476
≥65 y, n (%)	17 (34)	3 (25)	0.735
≥60 y, n (%)	26 (52)	5 (42)	0.561
Sex, n (%)			0.388
Male	28 (56)	8 (67)	
Female	22 (44)	4 (33)	
Transplant indication, n (%)			0.283
AL/MDS	38 (76)	7 (58)	
Other	12 (24)	5 (42)	
Median previous lines of therapy (range)	2 (1-6)	3 (1-5)	0.076
Type of donor, n (%)			0.704
Matched unrelated	21 (42)	5 (42)	
Mismatched unrelated	10 (20)	1 (8)	
Matched related	5 (10)	1 (8)	
Haploidentical	11 (22)	3 (25)	
Other	3 (6)	2 (17)	
GvHD prophylaxis			0.283
ATG	26 (52)	6 (50)	
EDX	22 (44)	4 (33)	
Other	2 (4)	2 (17)	
Grade II-IV acute GvHD			0.461
Treated	11 (22)	4 (33)	
Not treated	39 (78)	8 (67)	
Previous SARS-CoV-2 infection, n (%)	22 (44)	1 (8)	**0.024**
Median previous SARS-CoV-2 vaccine doses, n (range)	3 (0-5)	3 (2-4)	0.710
SARS-CoV-2 IgG titer before Evusheld, U/ml			0.107
Median (range)	1771 (0-2500)	2500 (1-2500)	
SARS-CoV-2 IgG titer at 5-8 months after Evusheld, U/ml			0.650
Median (range)	1196 (192-2500)	1367 (208-2500)	

AL: acute leukemia; MDS: myelodyslastic syndrome; other: lymphoma, myeloproliferative neoplasms, multiple myeloma; GvHD: graft versus host disease; ATG: anti-thymocyte globulin; EDX: cyclophosphamide

*comparisons were made using the Pearson chi-square test or the Fisher exact test for categorical variables and the T test or the Mann-Whitney U test for continuous variables. Differences were considered significant with P <0.05

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NGS HEMATOPOIETIC CHIMERISM MONITORING IN ACUTE MYELOID LEUKEMIA PATIENTS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION: A PROMISING METHOD FOR PATIENTS LACKING SPECIFIC MOLECULAR MARKERS

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Background. Hematopoietic Chimerism (HC) is not currently considered a marker of MRD not only due to lack disease specificity, but also due to the scarce sensitivity of Short Tandem Repeat (STR) approach used (around 5% of recipient cells). Recently, with Next Generation Sequencing (NGS), the sensitivity of HC monitoring could reach a sensitivity of 0,05% of recipient cells. In Acute Myeloid Leukemia (AML), only 40% of cases is positive for sensitive Minimal Residual Disease (MRD) markers. In all other cases, the expression of the Wilm's tumor gene (WT1) can also be used as MRD marker, although low sensitivity.

Aim. First, we searched the alignment between STR and NGS methods on AML bone marrow samples. Second, we investigated the prognostic value of mixed HC, in comparison with a specific MRD marker such as NPM1 type A mutation or WT1 expression.

Materials and Methods. Retrospectively, we consider 20 consecutive AML patients undergoing hematopoietic stem cell transplantation at our Transplant Unit between 2019 and 2022 with almost 3 HC assessment within the first year. 82 bone marrow samples were analyzed by our standardized STR approach on 16 loci and by NGS approach, based on 21 indel loci. As MRD marker, 4 patients presented NPM1 type A, 15 only WT1 expression and 1 had no markers. 13 (65%) had a hematological relapse at median time of 4,5 months after transplantation.

Results. The alignment between the two methods gave overlapping values, with a Pearson coefficient r equal to 0,9942. As clinical cut-off for mixed HC in NGS, we chose the median value among all monitoring samples of no relapsed patients in any time point, equal to 99,5% donor level. In 9 out 13 relapsed patients (69%), NGS chimerism decreased below 99,5% at least one month before the clinical relapse. NPM1 type A has always changed earlier than chimerism. About WT1 expressing patients, in 4 cases NGS chimerism decreased earlier then WT1 raising. In no case did the increase in WT1 anticipate the decline in NGS chimerism. Even in the patient without MRD markers, NGS chimerism dropped below the threshold 2 months before cytological relapse.

Conclusions. NGS chimerism supply a HC assessment aligned to STR in AML diagnostic specimens. NGS chimerism on bone marrow samples could provide early information on disease recurrence in AML patients. NGS HC seems to be more sensitive then WT1 and could be useful in patients lacking specific and sensitive MRD markers, alone or combined with WT1 expression.

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ALOGENEIC TRANSPLANT IN NEWLY DIAGNOSED SECONDARY ACUTE MYELOID LEUKEMIA: IMPACT OF CPX-351 INDUCTION *VS* OTHER INDUCTION REGIMENS

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Background. Allogeneic transplant (HSCT) remains the only potentially curative therapy for secondary acute myeloid leukemia (sAML). There are many evidence that CPX-351 has increased HSCT rate but less is known regarding the impact on post-HSCT outcome.

Methods. in this study we evaluate all 53 patients (pts) with newly diagnosis of sAML underwent HSCT at our Center between January 2016 and June 2022. We compared outcome of 26 pts with diagnosis of sAML (classified according to WHO 2016) underwent HSCT after CPX-351 induction with 27 pts receiving other induction regimen (no-CPX cohort).

Results. Median age at transplant was 63(23-74) years. No-CPX cohort included:12/27 fludarabine based regimen, 7/27 HMAs±venetoclax, 6/27 "3+7", 1/27 other regimens. Most pts received graft from an unrelated donor (58%) following a myeloablative conditioning (58%). Pts and transplant characteristics were well balanced between two cohorts except for higher proportion of HCT-CI>2 (p=0,0254) and higher median CD3+ infused cells from no-CPX cohort (p=0,0122). A larger number of patients treated with CPX-351 induction achieved a complete remission before HSCT (65% *vs* 44%) (p=0,1704). Median follow-up was 11 months for the CPX-351 cohort and 23 months for no-CPX cohort. Median OS since transplant was not reached in the CPX-351 group while it was 16 months in the

no-CPX cohort (p=0,11, HR 2.052, 95% CI 0.8685-4.846). The 2-year-OS was 73% *vs* 44% (p=0,1152), respectively while it was 54% globally Figure 1. There are no differences in terms of 2-years-PFS (51% *vs* 35%; p=0,2274), 2-years-TRM (19% *vs* 16%, p=0,9140), cumulative incidence of acute GVHD (54% *vs* 61%, p=0,6967) and relapse rate (31% *vs* 55%, p=0,1621). The most common causes of death were disease relapse (CPX-351 4% *vs* 44% no-CPX) and GVHD complications (15% *vs* 11%). Age >65 years, hyperleukocytosis at diagnosis and disease status prior to HSCT were the factors that influence 2-yr-OS in univariate analysis. In multivariate analysis only age and disease status impact on 2yrOS.

Conclusions. in our real-life experience, we observed a longer OS and PFS after HSCT for sAML patients treated with CPX in comparison with no-CPX cohort (2yrOS 73% *vs* 43%; 2yrPFS 51% *vs* 35%), although these differences are no statistically significant probably due the small number of patients, without differences in terms of toxicity and GVHD. We confirm that age and pre-transplant disease status are the main factors that impact on survival after HSCT in sAML.

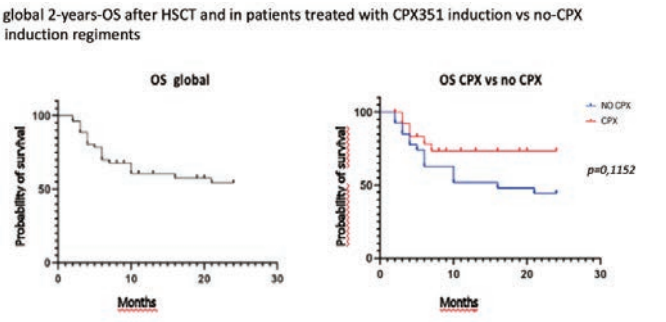

Figure 1.

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DONOR DERIVED NK CELLS INFUSION FOLLOWING HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANT IN PEDIATRIC HIGH-RISK B CELLS ACUTE LYMPHOBLASTIC LEUKEMIA (B-ALL)

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Background. Natural killer lymphocytes (NKs) are cells of innate immunity that recognize self and non-self HLA class I ligands. Killer-cell Immunoglobulin-like Receptors (KIRs) are inhibitory molecules expressed on NK surface. They act "educating" NKs in effective defense against unhealthy self/non-self cells and tolerance towards healthy self cells. In B-/T-cell alpha/beta depleted haplo-HSCT, donor-versus-recipient alloreactive NKs exert an efficient graft versus leukemia (GvL) effect, mediated by inhibitory KIRs. We evaluated the alloreactive effect of donor-derived NKs in 3 pediatric high-risk B-ALL who underwent B-/T-cell alpha/beta depleted haplo-HSCT followed by donor NK infusion.

Methods. Median age was 13 months. Patients 1 and 2 had infant ALL, patient 3 had refractory-relapsed (r/r) ALL. All patients received a median of 3 lines chemotherapy. Patient 1 received a prior allo-HSCT. Two patients received chemo-based conditioning regimens. Patient 3 received Total Body Irradiation (TBI)-based conditioning regiment plus chemotherapy. All patients received rituximab and letermovir for EBV and CMV prophylaxis, respectively. Mother was Donor for all patients. NKs alloreactivity was tested by evaluating KIR genotyping and KIR/KIR-ligand mismatch in graft-versus-host direction. All three patients present KIR/KIR-ligand mismatch. NK reconstitution was analyzed in all three transplanted patients.

Results. All three patients showed a fast reconstitution of NKs at day +14. Patients received NKs infusion at median day +36. No infusion reactions were observed. Median NK infused were $256x10^6$/kg. None of the patients developed EBV reactivation. Patient 1 developed CMV and ADV reactivation at day +19 and +288, respectively, without needing to treat. Patient 2 developed Grade 2 acute GvHD (skin) at day +48, treated by steroid, and Score 3 chronic GvHD (skin) 5 months after transplantation, resolved with ciclosporine treatment. No Grade GvHD 3-4 was observed. Currently all patients are in CR with full donor chimerism.

Conclusions. Alloreactive NKs add-back infusion after B-/T-cell alpha/beta depleted haplo-HSCT could represent an effective option to improve transplant outcome. NKs may improve efficacy by enhancing GvL and contribute to maintain "disease control" through immunologic surveillance in high-risk ALL. Infusion of phenotypic mature NKs could be more useful to maintain the immunologic control of MRD and virus reactivation, without increase GvHD incidence.

Myeloma and monoclonal gammopathies

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OUTCOME PROGNOSTICATION OF RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS ACCORDING TO PRIOR LINES OF THERAPY OR TO REFRACTORINESS STATUS: AN ISSUE STILL TO BE SOLVED

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Background. Moving upfront all classes of drugs in all multiple myeloma patients, the triple-refractory patients rate is rapidly increasing, also after 1-2 prior lines of therapy (LOTs). Their outcome is very dismal since no effective therapies are currently available, being CAR T cells and bispecific mAbs approved for triple-exposed patients with ≥3 prior LOTs.

Methods. We analyzed data from relapsed/refractory MM (RRMM) patients treated at a single tertiary center, to evaluate the relationship between prior LOTs/refractoriness status (RS) and PFS/OS. Each second and subsequent regimen started at relapse was considered as index (IR) and for each one, LOTs and RS were classified as per IMWG criteria. PFS and OS were analysed as per Kaplan-Meier methods and compared by log-rank test. The relationship between LOTs-RS and PFS was analysed by univariate and multivariate Cox regression methods.

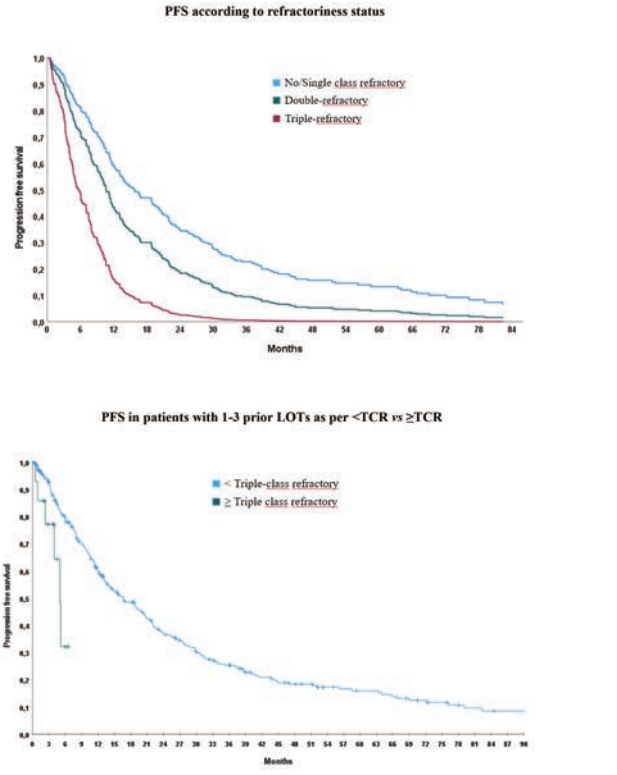

Figure 1.

Results. From 2011 to 2022, 200 RRMM patients received 387 regimens. Median age was 67 years, ECOG PS ≥2 in 25.5%, R-ISS stage II/III in 75% and renal failure in 19.5% of them. As per RS, PFS was 16.9 months in 309 IR administered to no/single class refractory (N/SCR) patients, 7.9 months in 58 IR to double class refractory (DCR) and 5 months in 20 IR to triple class refractory (TCR) (p<0.001). Considering prior LOTs, PFS was 18.8, 10.5 and 7.5 months in 208, 151 and 28 IR given in 1, 2-3 or ≥3 prior LOTs (p< 0.001). Focusing on 1-3 prior lines setting, the typical of clinical trials, PFS was 16.5 months in <TCR *vs* 5 months in ≥TCR (p<0.001) whereas OS was 26.5 *vs* 10.6 months, respectively (p<0.001). After the third line, PFS was 7.5 and 3.7 months in <TCR and ≥TCR, respectively (p=0.032), being OS 9.5 *vs* 5.3 months (p=0.029), respectively. [b]Among factors considered in univariate analysis (age, PS, R-ISS, time from diagnosis, RS and LOTs), the multivariate one selected both RS (p<0.001) and LOTs (p=0.003) as factors affecting PFS. However, HR for PFS was 2.96 (CI95%: 1.5-6.0, p<0.001) for TCR *vs* <TCR whereas it was 1.93 (CI95%: 1.6-2.3, p<0.001) for >3 LOTs *vs* ≤ 3 LOTs.

Conclusions. Our study suggests that in RRMM, RS should be the most powerful factor to consider in early relapse to better prognosticate patient outcome whereas the RS value seems to be lower in >3 prior LOTs setting. We claim the need for new inclusion criteria to design early RRMM clinical trials and a new modality of drugs approval both based on RS to have effective regimens even in very early relapse.

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MM-UMA PANEL, AN NGS APPROACH TO DEFINE THE MOLECULAR PROFILE OF MM PATIENTS: INTRA AND INTER LABORATORY VALIDATIONS' RESULTS

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Introduction. Next-generation sequencing (NGS) technologies have proven useful in identifying Multiple Myeloma (MM) patients (pts) genomic abnormalities, such as mutations, copy number alterations (CNAs) and IgH translocations (t-IgH), resulting in pts' genomic profiles wider than conventional methods. To identify all these MM's genomic abnormalities in a single assay, we set up the MM-UMA panel (Multiple Myeloma-Unique Molecular Assay).

Methods. A cohort of 108 newly diagnosed MM pts with fluorescence in situ hybridization (FISH) data available were profiled by MM-UMA panel on a MiSeq platform (Illumina). Additional 50 pts were analyzed to validate the panel, both internally and with an external laboratory (University of Milan). Raw sequencing data were analyzed by diverse bioinformatics tools to reach the optimal aberrations call's concordance: Delly and Manta for t-IgH; Varscan, Mutect and Freebayes tools for SNVs (Single Nucleotide Variants); CNVkit and CopywriteR for CNAs.

Results. The intra-laboratory validation tests allowed the optimization of several technical NGS parameters: a median of 4,3 million (M) reads (range: 3,8-4,9M) was estimated adequate to confidently call both t-IgH and SNVs. Moreover, a 60% off-target threshold and a 0,15 MAD (Mean Absolute Deviation) cut-off have been defined optimal to call CNAs. The inclusion of intra- and inter-run replicates highlighted a high reproducibility across experiments (correlation parameters between intra- and inter run SNVs variant allele frequency = R>0.95, p<0.001). A good concordance was reached

(95,5%, range: 88,7%-100%) by comparing t-IgH (*i.e.* t(4;14), t(11;14), t(14;16) and t(14;20)) and CNAs pts' profiles, as obtained by NGS and FISH. Finally, a total of 500 SNVs were identified, with the most mutated genes being KRAS, NRAS, ATM, TP53 and BRAF. The inter-laboratory validation experiments were carried out by comparing run quality parameters (i.e. total reads, off- and on-target, coverage and MAD) and call alterations (i.e. SNVs). Overall, results showed a concordance of 94,7% for CNAs, of 93,1% for t-IgH and of 83,3% for SNVs; quality parameters resulted concordant as well.

Conclusions. A novel NGS targeted panel was designed and successfully validated, whose main novelty resides in the possibility to call CNAs from off-target reads, that can be used to define MM pts' genomic risk factors, possibly required in the daily clinical practice.

Thanks to AIRC IG2018-22059, AILBolognaODV.

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AUTOLOGOUS STEM CELL COLLECTION AFTER DARATUMUMAB, BORTEZOMIB, THALIDOMIDE AND DEXAMETHASONE VERSUS BORTEZOMIB, THALIDOMIDE AND DEXAMETHASONE IN NEWLY DIAGNOSED MULTIPLE MYELOMA: A REAL-LIFE MONOCENTRIC ITALIAN EXPERIENCE

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In newly diagnosed multiple myeloma (NDMM) patients (pts), induction followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) is the standard of care. The addition of an anti-CD38 antibody, daratumumab, to an established frontline protocol based on bortezomib, thalidomide and dexamethasone (D-VTd), improves efficacy but could hamper peripheral blood stem cell collection (PBCS).[1] The aim of our study is to evaluate the possible impact of daratumumab on PBCS. We hereby, report a monocentric Italian experience in 55 pts with NDMM who underwent induction therapy with VTd (31) or D-VTd (24), managed at the Hematology Department of Sapienza in Rome. Patient baseline characteristics were equally distributed among groups, as summarized in Table 1. A combination of cyclophosphamide with granulocyte colony stimulating factor (G-CSF) was used as the first mobilizing regimen attempt in both groups. The median time between the last day of induction therapy and the first day of mobilization therapy was 30 days for D-VTd groups and 22 days for VTD groups (p=0.059). Overall, 94% of pts treated with VTd met the desired collection goal after first mobilization therapy, compared to 63% of pts treated with D-VTd (p=0.013). In the VTd arm, 2 pts required a third mobilization attempt. In the D-VTd arm, 4 pts required a second mobilization attempt, and 2 pts also required a further one. Overall, 3 pts did not meet the collection goal. In pts with impaired mobilization, plerixafor was used. In the VTd arm 12% of pts received plerixafor, compared to 33% of pts treated with D-VTd (p=0.101). The median PBSC collection was $9x10^6$ $CD34^+$ cells/Kg in the whole cohort, with no significant difference in the two groups. A lower pre-mobilization therapy level of neutrophils and platelets was observed in the D-VTd arm compared to the VTd arm, possibly reflecting prolonged hematological toxicity. No significant difference was observed in the leucocyte (WBC) azimuth value in the 2 arms. However, the 2 arms reached this value on 2 different days. In the VTd arm the median day was 8, and in the D-VTd arm it was 11 (p=0.010). The use of G-CSF for more days did not result in an increase in $CD34^+$. The median azimuth value was significantly lower in the D-VTd group than in the VTD group (p<0.001). Daratumumab can impair PBSC collection, which can be overcome with plerixafor, so new mobilization strategies should be investigated.

Table 1. Baseline patient's clinical characteristics and the frontline induction therapy.

Characteristics	Patients (N= 55)		%	
	D-VTD = 24	VTD = 31	D-VTD	VTD
Gender				
Male	17	19	71	61
Female	7	12	29	39
Age (years)				
Median (range)	61 (58-66)	60 (54-64)		
Type of Heavy chain				
G	16	16	67	52
A	4	8	17	26
D	0	1	0	3
Absent	4	6	17	19
Type of Light chain type				
κ	16	18	67	57
λ	8	13	33	43
ISS				
I	10	9	43	31
II	7	10	30	34
III	6	10	26	34
NA	1	2	1	1
Cytogenetic abnormalities, n (%)				
High risk	14	12	67	50
Standard risk	7	11	21	24
NA	3	8	12	26
CRAB				
Hypercalcemia	5	5	21	16
Renal insufficiency	4	5	17	17
Anemia	11	14	46	45
Osteolytic bone lesions	22	28	92	90
R-ISS				
I	7	3	30	10
II	8	16	33	52
III	5	5	21	16
NA	4	7	16	22
Total dose of CTX (gr),				
median (range)	4.5 (2.0-6.0)	4.2 (3.5-5.2)		
Mobilization protocol				
First attempt	CTX + G-CSF	CTX + G-CSF		
Second attempt	G-CSF	G-CSF		
Third attempt	CTX + G-CSF	G-CSF		
Number of plerixafor dose, n (%)				
1	1	2	4	6
2	1	0	4	0
Response after induction therapy				
CR	5	13	21	42
VGPR	16	14	67	45
PR	3	4	12	13
Bone marrow plasma cell infiltration				
Median (range)	51 (11-90)	40 (10-84)		
Bone marrow function pre-mobilization, median (range)				
Hb, g/dl	13.4 (12.5-14.4)	13.8 (11.8-14.5)		
Platelets, mm^3	206 (168-324)	279 (224-328)		
Neutrophils, mm^3	2250 (1760-3340)	3400 (2640-4190)		

Reference

1. Hulin C. et al. Haematologica 2021

P143

HIGH-DOSE CYCLOPHOSPHAMIDE 4 G/M2 GRANTS OPTIMAL STEM-CELL MOBILIZATION AND COLLECTION AFTER DARATUMUMAB-BASED QUADRUPLET INDUCTION IN NEWLY DIAGNOSED MULTIPLE MYELOMA

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Induction with Daratumumab, Bortezomib, Thalidomide and Dexamethasone (Dara-VTd) has become the standard treatment for transplant-eligible newly diagnosed multiple myeloma (NDMM). Despite improved response rates, concerns with stem-cell mobilization and collection emerged in CASSIOPEIA trial. Following cyclophosphamide 2 to 3 gr/m^2 and G-CSF 10 µg/kg/day, patients (pts) treated with Dara-VTd had greater use of plerixafor, longer leukapheresis (LK) and lower number of collected CD34+cells/Kg. We report a real-life retrospective analysis of NDMM that underwent stem-cell collection after Dara-VTd induction at two Italian centers (IRCCS Ospedale San Raffaele, Milano; Ospedale Civile Santo Spirito, Pescara).

Table 1. Characteristics of patients, stem-cell mobilization and harvesting.

Median age at diagnosis: n (range)	62 years (38-71)
ISS 3 at diagnosis: n (%)	13 (28%)
R ISS 3 at diagnosis: n (%)	5 (11%)
High risk cytogenetics*: n (%)	17 (36%)
Dose reduction in Dara-VTd induction: n (%) – Thalidomide – Bortezomib – Daratumumab	 36 (76%) 12 (25%) 2 (4%)
Days from start of induction to HD-CTX: median (range)	133 (113-232)
Days from last Daratumumab to HD-CTX: median (range)	32 (16-93)
Grade III – IV adverse events of HD-CTX: – Febrile neutropenia – Infection	5 (11%) 4 (9%) 1 (2%)
Days from HD-CTX to first day of leukapheresis: mean [SD] (range)	11.6 [1.65] (9-16),
Total G-CSF (µg/kg) administered per patient: mean [SD] (range)	440 [128] (240-768)
Peripheral white blood cells/µl on first day of leukapheresis: median (range)	13.400 (1.600 -67.000)
Peripheral CD34+cells/µl on first day of leukapheresis: median (range)	57 (20-226)
Number of days of leukapheresis: – 1 – 2	 15/43 (35%) 28/43 (65%)
Total number of leukapheresis days: mean [SD] (range)	1.7 [0.48] (1-2)
Plerixafor use: number (%) – Indication <20 CD34+cells/µl – Other	21/43 (49%) 14/21 (66%) 7/21 (34%)
Amount of CD34+cells x10^6/kg collected per patient: mean [SD] (range) – Day 1 – Day 2 – Total	 6,98 (1,4-17,6) 5,77 (3,2-12,6) 10,68 [2.54] (4,94-18,8)
Collection efficiency: mean [SD] (range) – Day 1 – Day 2	 64% [17] (18-99) 71% [19] (26-100)
Total blood volume processed (liter): mean [SD] (range)	4.58 [2] (1,6-9,6)

HD-CTX: high-dose cyclophosphamide. SD: standard deviation. G-CSF: granulocyte colony-stimulating factor.

** High-risk cytogenetic abnormalities defined as del17p13, t(4;14) and t(14;16).*

Pts received high-dose cyclophosphamide (HD-CTX) 4 g/m^2 and were monitored out-patient. G-CSF 5 µg/kg/day was administered from day 3 to 5 after HD-CTX. Plerixafor was administered on demand either in pts with <20 CD34+cells/µl or in those predicted to be poor mobilizer according to: 1) white blood cells count > 10x10^9/L together with CD34+ count <15/µL; 2) ratio of pts body weight (kg) and CD34+/µL > 2; 3) yield < 25% of total CD34+ target dose on first day of LK. Pre-planned total target dose was 10 x10^6 CD34+cells/Kg to allow for multiple ASCT. From December 1st, 2021 to February 28th, 2023, 47 NDMM completed induction at our institutions. After a median of 4 Dara-VTd cycle (range: 4-6), overall response was 98%. 46 pts received HD-CTX 4 g/m^2. 5 pts had grade 3 adverse events (11%). After a median of 11 days (range: 9-16), 43/46 pts (93%) underwent LK; 21 (49%) received Plerixafor. All pts undergoing LK completed stem-cell collection, harvesting a mean total amount of 10.68x10^6 CD34+cells/kg (SD 2.54) (range: 4.92-18.8). Three pts who received HD-CTX 4 g/m^2 did not undergo stem-cell collection. After a median of 195 days from induction (range: 164-283), 35/43 (81%) pts who completed LK already underwent ASCT. Mean number of infused CD34+cells per pts was 4.84 x10^6/kg (SD 1.20) (range: 2.96-9.86). Neutrophils and platelets engraftments were obtained after a median of 12 days (range: 9-14) and 16 days (range: 10-25), respectively. High-dose CTX 4 g/m^2 and G-CSF after Dara-VTd induction in NDMM proved feasible and effective in terms of stem-cells mobilization. Increased dose of CTX together with on-demand plerixafor allowed high collection numbers of CD34+cells per pts, ensuring sufficient cells for multiple ASCT and favorable transplantation outcomes.

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THE MANAGEMENT OF CAST NEPHROPATHY IN NEWLY DIAGNOSED MULTIPLE MYLEOMA IN THE REAL-LIFE: 15 YEARS EXPERIENCE OF THE CAGLIARI'S DEPARTMENT OF HAEMATOLOGY

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Background. Cast nephropathy (CN) represents an emergency in the management of multiple myeloma, caused by acute obstruction of the distal renal tubules by deposits of monoclonal free light chains (FLCs). This medical complication requires rapid specific therapy against multiple myeloma and aggressive supportive care to restore renal function and avoid chronic dialysis.

Methods and Results. In this report, we describe the outcome of 45 newly diagnosed multiple myeloma (NDMM) patients with a CN at baseline. Disease diagnosis was made by renal biopsy, which showed the presence of casts. Biopsy was avoided in the presence of acute renal insufficiency (AKI) and concomitant high monoclonal FLC levels (> 500 mg/dl).

Results. From November 2008 to August 2022, 45 NDMM patients with AKI due to cast nephropathy were treated in our center. Of these, 31 were male and 14 were female. The median age was 68 years (26-85). Twenty-two patients (48.88%) had micromolecular multiple myeloma. The ISS stage of all subjects was 3. Median serum creatinine was 13 mg/dl (1.6-26) and estimated glomerular filtration rate (MDRD equation), was 10.4 ml/min/1.73m^2 (1.5-39). At diagnosis, the median FLCs value was 6059 mg/l (754.61-65284) and 3063 (88.65-33699) for kappa and lambda respectively. Renal biopsy was performed in 33 (73%) of patients. Thirty (66.6%) patients were not on dialysis at the time of diagnosis, and 13 (29%) underwent plasmapheresis. Forty-one (95.3%) of the 43 patients were treated with a bortezomib-based regimen. One (2.3%) patient performed therapy with daratumumab-lenalidomide-dexamethasone and 1

(2.3%) melphalan-prednisone-thalidomide. Five patients (11.1%) received a single and 9 (20%) a double autologous hematopoietic peripheral stem cell transplantation (AHSCT). Of the 14 patients who required dialysis at diagnosis, only 6 (43%) failed to reverse this condition. Table 1 shows the hematologic response at first-line treatment in 41 patients (2 died before specific treatment and 2 lost to follow-up). Twenty-four patients underwent a second line of therapy, and only 4 were treated with more than four lines of therapy. Median global progression-free survival was 32 months (range 2-91) and median overall survival was 48 months (range 2-161).

Conclusions. These data provide confirmation of the efficacy of bortezomib-based therapeutic regimens in the treatment of multiple myeloma with CN, as well as the feasibility of AHSCT even in the setting of dialysis treatment.

Table 1.

Hematologic Response after first AHSCT	**N =14**
Stringent complete response (sCR)	**2 (14%)**
Complete response (CR)	**3 (21,4%)**
Very good partial response (VGPR)	**6 (43%)**
Partial response (PR)	**3 (21,4%)**
Hematologic Response after double AHSCT	**N = 9**
Stringent complete response (sCR)	**3 (33,3%)**
Complete response (CR)	**4 (44,4%)**
Very good partial response (VGPR)	**2 (22,2%)**
Partial response (PR)	**0**
Hematologic Response in non-transplant population*	**16**
Stringent complete response (sCR)	**1 (6,2%)**
Complete response (CR)	**0**
Very good partial response (VGPR)	**4 (25%)**
Partial response (PR)	**6 (37,5%)**
Minimal response (MR)	**1 (6,25%)**
Progressive disease (PD)	**4 (25%)**

***after indution therapy and non-transplant population**

P145

CIRCULATING CLONAL PLASMA CELLS AT START OF SALVAGE REGIMEN PROVIDE POWERFUL PROGNOSTICATION BIOMARKER IN MULTIPLE MYELOMA PATIENTS AT FIRST RELAPSE

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Introduction. There is a growing interest in investigating the clinical impact of circulating clonal plasma cells (CCPC) quantitation reflecting the tumor burden in multiple myeloma (MM), due to its easy access and non-invasive nature. Recent studies have highlighted the value of quantification of CCPC at diagnosis for risk stratification of transplant eligible and not MM. However, prospective data on the real-world utility of CCPC quantitation in relapsed-refractory patients (RRMM) treated with novel immunotherapies are extremely scarce.

Aims. To investigate the prognostic value of CCPC quantitation in treated with novel immunotherapies using high-sensitivity multicolor-flowcytometry (HS-MFC) and the relevance of their assessment in predicting overall survival (OS).

Methods. We prospectively evaluated 44 consecutive MM patients requiring the first salvage regimen containing daratumumab from July 2018 through July 2021 (age: median-65 years; range 44-81 years; M/F-30/14). CCPC levels were studied using 10-13 color HS-MFC (sensitivity- 0.0001% or $1x10^{-6}$) at the start of the salvage regimen. CCPC levels were calculated as CCPC percentages in total WBCs (%CCPC/WBC). The cut-off value was identified using ROC analysis against OS. Initial therapeutic response (ITR) was monitored at the end of the second cycle of treatment.

Results. The median follow-up was 46 months (range 1-51 months). ITR included CR-VGPR 6.5%, VGPR/PR-63.0%, SD-21.7%, and 4 (8.7%) patients who died during initial therapy. CCPCs were detected in all patients. The median %CCPC/WBC was 0.41% (range, 0.004-6%). CCPCs from patients with higher LDH and extramedullary disease carried significantly lower amounts of CD27 and CD81 and higher amounts of CD200 although no difference in the percentage of CCPCs was recorded. %CCPC/WBC≥0.4% was strongly associated with OS (27.1 months *vs* 48.5; HR-2.5; p=0.04).

Conclusions. This prospective study showed that CCPC quantification (≥0.4% of WBC) at the start of a daratumumab-based salvage regimen in RRMM patients treated at the first relapse provides a powerful independent biomarker for the prediction of OS. Such assessment is more convenient for routine clinical practice and should be confirmed in larger studies.

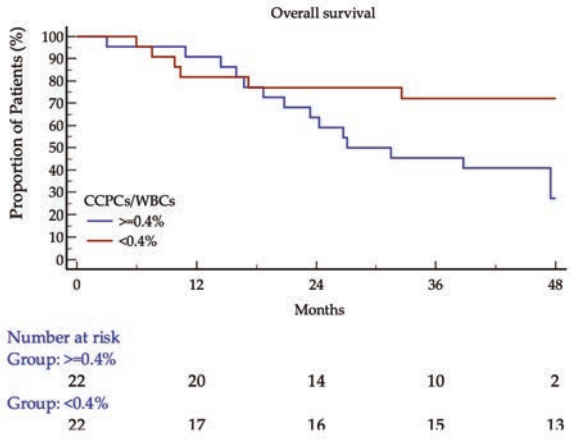

Figure 1.

P146

SOLUBLE B-CELL MATURATION ANTIGEN: ROLE IN SHORT-TERM MONITORING OF DIFFERENTLY TREATED MULTIPLE MYELOMA PATIENTS

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Background. Multiple Myeloma remains incurable and there is a need for new therapeutic targets and more accurate ways to assess disease status. Although laboratory biomarkers are inexpensive and easy to obtain, they may have limitations: M protein may be a poor indicator of disease status due to the long half-life of Ig and the low sensitivity of the techniques used; FLC may be affected by renal function and cannot be used in non-secretory MM; furthermore, different tests on the same sample may give discordant results; MRD requires bone marrow blood samples and is costly and not routinely performed.

Aims. Soluble BCMA is released into the serum by γ-secretase, with a half-life of 24-36 h independent of renal function. Its levels correlate with the percentage of plasma cells in the BM; higher levels

appear to predict a shorter PFS. Lower levels of sBCMA have been found in patients with a better response to therapy, as well as in SMM and MGUS. It also allows monitoring of non-secretory MM. In addition, high levels may interfere with the binding of BAFF to BCMA, thereby affecting the production of polyclonal Ab, and may interfere with the efficacy of the newer targeted therapies against BCMA; furthermore, sBCMA, reflecting the action of γ-secretase, reduces the amount of membrane BCMA, thereby depriving these therapies of their target.

Methods. This study focus on the role of sBCMA in 100 patients undergoing different therapies (20 at diagnosis, 20 at 1st, 30 at 2nd and 30 at 3rd or higher relapse). Disease assessment has been done at the beginning of the treatment, after 1 and 6 months, by collecting peripheral blood samples on which we measured serum levels of sBCMA using commercial ELISA, although there is no BCMA ELISA kit for human use (only research kits are available).

Expected Results. Our goal will be to identify a possible role for sBCMA, either alone or in combination with other parameters, as a predictive factor and potential tool for treatment indications. ELISA proved to be a simple and rapid method to measure serum levels of sBCMA, and it was found to be feasible in all patients. We have currently enrolled 74 patients, of which we have currently collected the 3 samples scheduled for analysis in 36 patients. Although the number of patients can be considered small, we believe that some interesting results have already been obtained, which can be expanded in the future and may already provide interesting insights into the management of MM.

P147

FERRITIN METABOLISM REFLECTS MULTIPLE MYELOMA MICROENVIRONMENT AND PREDICTS PATIENT OUTCOME

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Multiple myeloma (MM) is a hematologic malignancy with a multistep evolutionary pattern, in which the pro-inflammatory and immunosuppressive microenvironment and genomic instability drive tumor evolution. MM microenvironment is rich in iron, released by pro-inflammatory cells from ferritin macromolecules, which contributes to ROS production and cellular damage. In this study, we showed that ferritin increases from indolent to active gammopathies and that patients with low serum ferritin had longer first line PFS (42.6 *vs* 20.7 months respectively, p=0.047) and OS (NR *vs* 75.1 months respectively, p=0.029). Moreover, ferritin levels correlated with systemic inflammation markers and with the presence of a specific bone marrow cell microenvironment. The results demonstrated that HF MM patients presented an increase in systemic inflammatory markers as well as in BM PCs, while other normal subpopulation such as neutrophils and CD38dim NK are significantly reduced. Finally, we verified by bioinformatic approaches in large transcriptomic and single cell datasets that FHT1 and FTL genes increased significantly from MGUS to MM patients. Then, we correlated the distribution of the different immune subpopulations with the presence of high or low levels of FTH1 and FTL and we confirmed the decrease of NK cells (as seen in the flow cytometry analysis), the increase of monocytes (as reported by laboratory variables) and the decrease of B naïve cells (as observed as a trend in the PCD tube analysis) in patients with high FTH1 or FTL1 levels. So, we identify a gene expression signature associated with ferritin biosynthesis correlated with worse outcome, MM cell proliferation and specific immune cell profiles. Overall, we provide here evidence of the role of ferritin as a predictive/prognostic factor in MM, setting the stage for future translational studies investigating ferritin and iron chelation as new targets for improving MM patient outcome.

P148

SAFETY AND EFFICACY OF NEW DRUGS COMBINATIONS IN NEWLY DIAGNOSED MULTIPLE MYELOMA WITH RENAL FAILURE AT ONSET: A RETROSPECTIVE STUDY

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Renal injury at onset of newly diagnosed multiple myeloma (NDMM) is associated with poor outcome. Patients with severe renal failure due to MM are excluded from clinical trials with new drugs. The aim of this retrospective study was to describe the clinical characteristics, the treatment choices, the efficacy and the incidence of treatment-related toxicities of NDMM patients with renal insufficiency. We enrolled all NDMM patients with renal failure due to the disease treated at our Centers from 2012 to present. Forty-four patients with a median age of 75 years were included; 77% had an International Staging System (ISS) of 3; 72% had anemia, 72% bone lesions and 25% had hypercalcemia; 27% had micromolecular myeloma. Thirty two percent of patients had severe renal failure requiring dialysis treatment. Forty-one percent of patients received treatment according to a VMP (Bortezomib, Melphalan and Prednisone) scheme, 23% received a triplet including Bortezomib and an immunomodulatory drugs (IMIDs) and 23% received a regimen including Daratumumab. The remaining 13% received a douplet (lenalidomide-dexamethasone or melphalan- prednisone). Twenty-seven percent of patients underwent an autograft procedure. Overall response rate (ORR) was 93% with an complete response (CR) rate of 18%. In terms of recovery of renal function, 45% achieved at least minimal renal response according to IMWG criteria, with 32% obtain a complete recovery of renal function. Patients who received more innovative treatment (regimens containing Daratumumab or Bortezomib in combination with IMIDs) achieved a response rate superior than very good partial response (≥ VGPR) of 65% with hematologic, neurologic, and infectious toxicities grade ≥3 of 10%, 10%, and 35%, respectively. Patients who received therapy with VMP or douplet had response rates ≥ VGPR of 25% with hematologic, neurologic, and infectious toxicity grade ≥ 3 rates of 29%, 4%, and 21%, respectively. Complete renal response rates in these two groups of patients were 45% and 20%, respectively (p<0,05). No death due to toxicity was registered. Patients with NDMM with renal failure at onset had a high burden of disease with unfavorable prognostic features. Although the small numbers of the cohort and the retrospective nature of this study it can be concluded that these patients can received new drugs combinations treatments with excellent response rates and without increased toxicity.

P149

MEASURABLE THERAPEUTIC ANTIBODY IN SERUM AS A POTENTIAL PREDICTIVE FACTOR FOR RESPONSE TO ANTI-CD38 THERAPY IN NON-IGGK MYELOMA PATIENTS

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Multiple myeloma (MM) is a hematologic malignancy characterized by the proliferation of abnormal plasma cells within the bone marrow. While monoclonal antibodies targeting the CD38 protein, such as daratumumab and isatuximab, have shown significant efficacy in improving survival for MM patients, there are currently no predictive factors for response to anti-CD38 therapy. We conducted a retrospective study to evaluate the association between the appearance of positive IgGk (*i.e.* the therapeutic antibody) immunofixation (IF, despite of persistence of the original paraprotein) and response rates in 77 non-IgGk MM patients treated with daratumumab or isatuximab in three different hematology centers (Figure 1A).

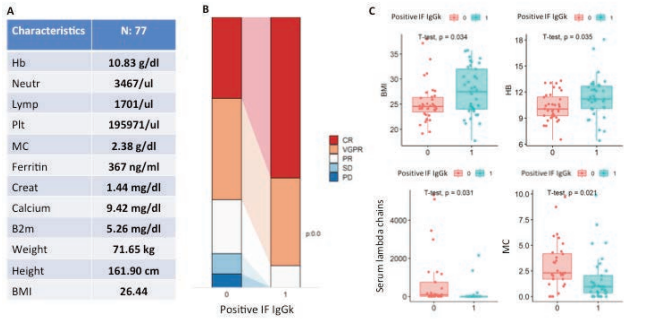

Figure 1.

The patients included 30 IgA (20 kappa and 10 lambda), 33 IgG lambda, 1 IgD, 1 IgM, 8 light chains, and 1 non-secreting MM. Patients were treated as follows: 43 with DaraRD, 17 with DaraVTD, 7 with DaraVMP, 7 with DaraVD, and 3 with IsaKD. 46 patients were in the first line setting. Positive IF was observed in 37 out of 77 evaluable patients, and the appearance of positive IF was observed at the third cycle (median value). Our results showed that the presence of positive IF was significantly associated with a higher rate of response to anti-CD38 therapy in non-IgGk myeloma patients. Among the IF-positive patients, we recorded 22 complete responses (CR), 12 very good partial responses (VGPR), and 3 partial responses (PR). Among the IF-negative patients, we registered 12 CR, 15 VGPR, 8 PR, 3 stable disease, and 2 progressive disease (chi-square p=0.033) (Figure 1B). Moreover, we identified several clinical and laboratory parameters significantly associated with the appearance of positive IF, including a high BMI (p=0.02), higher levels of hemoglobin (p=0.004), lower levels of lambda light chains (p=0.01), and lower levels of monoclonal component (p=0.02) (Figure 1C). Our findings suggest that monitoring these parameters may be important for predicting response to anti-CD38 therapy and optimizing treatment strategies for MM patients.

In conclusion, our study provides evidence that the appearance of "measurable" therapeutic antibody in serum is a potential predictive factor for response to anti-CD38 therapy in non-IgGk myeloma patients. However, further research is needed to validate these findings and identify additional predictive factors to improve patient outcomes in the view of a cost-effective personalized medicine.

P150

POTENTIAL CLINICAL RELEVANCE OF UPAR BLOCKADE IN MULTIPLE MYELOMA

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In multiple myeloma (MM), neoplastic plasma cell survival strongly relies on microenvironment stimuli and complex cross-talks between stromal cells and neoplastic clones, as microenvironment can modulate immune surveillance against tumor cells, facilitate tumor growth, angiogenesis, and drug resistance. Mesenchymal stromal cells and macrophages are essential for MM development and progression, and MM-associated macrophages also release urokinase-type plasminogen activator (uPA), promoting tumor progression. Therefore, targeting uPAR could reduce malignant plasma cell survival, diffusion, and osteolytic lesion. To preliminarily investigate potential anti-cancer effects in MM of uPAR inhibitors, first, BM specimens were collected from MM patients and healthy controls, and then adherent cells were cultured for 21 days. Mesenchymal phenotype was confirmed according to the International Society of Cellular Therapy guidelines. However, at light microscopy examination, diffuse monocyte-like cells were also observed (0.2-2.6% of total nucleated cells by flow cytometry) showing an M2-macrophage-like phenotype with positivity for CD163 and CD206. Next, a minimum of 4×10^3 cells were treated with C6 or C37 at a final concentration of 50 μM for 1 hour, culture media were collected before and after uPAR inhibitor treatment, and cytokine levels measured by bead-based multiplex custom immunoassay (9-plex LEGENDplexTM Custom Panel; BioLegend, San Diego, CA, USA) for IL-1, IL-6, TNF-α, HGF, IL-15, IL-10, macrophage inflammatory protein-1α and 1β, and Dickkopf-related protein 1 (DKK1) assessment. All compounds induced a significant decreased in IL-6 and DKK-1 levels (all $P<0.05$ by uncorrected Fisher's LSD test), more markedly after C6 treatment. Indeed, after C6 treatment, IL-6 (mean+SD, 8734.95+4169.2 pg/mL *vs* 359.26+393.8 pg/mL, pre- *vs* post-treatment; $P = 0.0012$), and DKK-1 levels (mean+SD, 7005.41+6393.4 pg/mL *vs* 61.74+55.2 pg/mL, pre- *vs* post-treatment; $P=0.0043$) were almost completely abolished. Our preliminary results support further investigation of uPAR inhibition as a therapeutic strategy for MM treatment, as uPAR inhibitors could exert both an anti-inflammatory and a pro-immunosurveillance activities. However, our preliminary results need further validation in additional *in vitro* and *in vivo* studies.

P151

CHEMO-FREE MOBILIZATION WITH G-CSF AND PLERIXAFOR ON DEMAND: RETROSPECTIVE MULTICENTER EXPERIENCE IN PATIENTS WITH MULTIPLE MYELOMA ELIGIBLE FOR AUTOLOGOUS TRANSPLANT

A. Mele[1], B. Rossini[2], C.R. Germano[3], A. Ostuni[4], E. Prete[1], S. Citiso[1], R. De Francesco[1], M. Caputo[1], M.R. Morciano[1], G. Rizzo[1], E. Turco[1], A. Orlando[1], L. Abbruzzese[1], A. Quinto[2], G. Lerario[3], F. Clemente[2], F.A. Ciardo De Marti[1], A. Guarini[2], G. Tarantini[3], V. Pavone[1]

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Background. Novel induction agents markedly improve remission rate in Multiple Myeloma (MM) and the use of chemotherapy for CD34+ stem cell mobilization has been questioned. We evaluated the efficacy of chemo-free mobilization with G-CSF alone and Plerixafor (PLX) on demand for transplanted eligible MM patients.

Methods. We reviewed 83 MM patients (aged 34 to 72 years) mobilized in three hematology centers from January 2017 to January 2023. Per institutional guidelines, the goal for mobilization was to collect CD34+ cells for two transplants with the minimum collection of 4x10^6/Kg cells (primary end-point). All patients received 10 mcg/Kg/day G-CSF until the first planned day of apheresis. PLX was added on demand when the peripheral CD34+ cell count was 2-15/μL on night 4 of G-CSF use.

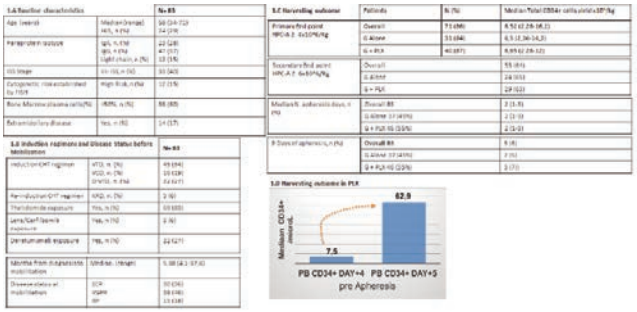

Figure 1.

Results. Figure 1 showed the baseline characteristics patients. Primary end-point (4x10^6/Kg) was reached in 71 patients (86%) and 31 of them (84%) with G-CSF alone. The median total CD34+ cells yeld was 6,42x10^6/Kg (range 2,28-16,2). Forty-six patient (55%) required PLX and median dose of injections was 1 (range 1-2). In plerixafor mobilizing patient first apheresis (at day +5) was observed in 36 patients (78%) with a median of 4,58x10^6/Kg (range 1,42-12,1). Use of PLX resulted in a nearly significant higher peripheral blood peak median on day +5 (62,9/μL *vs* 7,5; P 0,0001). In multivariate analysis, factors predicting PLX use were III-ISS (p 0,0001), prior lenalidomide (p 0,007) or daratumumab (p 0,005). Twenty-two patients (26%) used D-VTD as induction regimen, obtaining more CR rates (59% in D-VTD *vs* 28% with other inductions, p 0,003). Patients treated with D-VTD collected adequate number of CD34+ as thpse treated without daratumumab regimens (≥4x10^6/Kg: 86% *vs* 85%; P NS; ≥6x10^6/Kg: 77% *vs* 59%; P NS). No differences were observed in terms of days of apheresis (≥2 days: 50% *vs* 57%; P NS). More D-VTD patients required PLX (77% *vs* 48%; P 0,01) and 88% needed of 1 PLX injection. Median of CD34+ cells was similar in the two group of patients (6,29 with range 2,2-16,2).

Conclusions. Our experience demonstrated than a chemo-free mobilization with G-CSF and PLX on demand was associated with efficacy in CD34+ cells collection and optimal safety. Daratumumab increased CR rates and requirement for PLX without impact of successful CD34+ harvest.

P152

MITOCHONDRIAL EVENT AS AN ULTIMATE STEP IN FERROPTOSIS INDUCED BY TARGETING BCMA IN MULTIPLE MYELOMA CELL LINES

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Background. Belantamab Mafodotin (BeMa) is an anti-BCMA antibody-drug conjugate licensed for treatment of relapsed-refractory Multiple Myeloma (MM) patients.

Methods. To investigate the molecular machinery involved in resistance to BeMa, RNAseq, lipidomics and proteomic assays were performed in three different human MM cell lines (U266, H929 and OPM2) treated for different timepoints with increasing concentrations of BeMa.

Results. RNAseq analysis revealed activation of various metabolic pathways involved in BeMa resistance or susceptibility. Overall, 66 genes resulted significantly differentially expressed and among these, based on Log2FC, the 50 top variable genes ($p<0.5$) highlighted a significant activation of senescence and cell cycle arrest pathways in U266 and NCI-H929, while in OPM2 the glycolysis activation was required to overcome BeMa-induced stress. To further investigate how BeMa resistance is associated to increased glycolytic flux, mitochondrial activity in sensitive cytotypes was investigated. BeMa increased mitochondrial ROS amount in sensitive U266 and NCI-H929,leading to increased lipid peroxides formation, hallmark of ferroptosis. While the oxidation of polyunsaturated fatty acids (PUFA) is pro-ferroptosis, the MUFA activation promotes a ferroptosis-resistant cell state. Interestingly, palmitic acid (MUFA) supplementation induced a ferroptosis-resistant cell phenotype in BeMa sensitive cells. In accordance, lipidomics demonstrated higher levels of MUFA than PUFA in BeMa resistant OPM2, and an increase of Stearoyl CoA desaturase 1 (SCD1) that catalyzes the rate-limiting step in the production of MUFA. Moreover, we also found a downregulation of acyl-CoA synthetase long-chain family member 4 (ACSL4). Accordingly, combination of GPX4 inhibitor with BeMa induced cell death in BeMa resistant OPM2. Treating the same cell lines with Elrnatamab (a bi-specific a-BCMA antibody), in presence of T cells for 4- 24 h at an E:T ratio of 1:5 and 1:10, we found that cytoplasmatic LDs decreased in U266-S compared to OPM2-R, associated in U266 to increased levels of LOOH, GPX4 and SLC7A11 confirming a ferroptosis-primed resistant phenotype when BCMA is targeted also by Elranatamab.

Conclusions. In this study, for the first time, we defined ferroptosis as novel mechanism of action of BeMa, addressing the role of ferroptosis inducers as an emerging class of agents to get combined for next generation immunotherapy.

P153

MRD ASSESSMENT IN MULTIPLE MYELOMA USING FLOW CYTOMETRY: A REAL-WORLD MONO-INSTITUTIONAL EXPERIENCE

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Multiple myeloma (MM) is a hematologic malignancy characterized by the presence of at least 10% of clonal plasma cells in bone marrow (BM). Many studies in recent years established the importance of minimal residual disease (MRD) assessment by flow cytometry as a predictor of improved progression free survival and overall survival in both newly diagnosed and relapsed/refractory MM patients. Based on International Myeloma Working Group (IMWG) guidelines, MRD evaluation should be performed through Euroflow protocol (currently not feasible in the real-world clinical practice outside of clinical trials due to administrative constrains) or other standardized methods to reach a minimum sensitivity of 10^{-5}. To overcome this limitation, we evaluated the feasibility of using 2 different CE IVD commercial tubes in routine clinical setting to fulfil IMWG requirement.

Table 1.

Patient's demographic and characteristics	Number of patients
Sex:	
- Male	30/49 (61)
- Female	19/49 (39)
Timepoint:	
- Induction	17/49 (35)
- ASCT	10/49 (20)
- Not transplant eligible or beyond 12 months from ASCT	18/49 (37)
- Unknown	4/49 (8)
Treatment:	
- Isa-Kd	1/49 (2)
- Daratumumab	2/49 (4)
- Dara-VTd	13/49 (27)
- VTd	7/49 (14)
- Dara-Rd	10/49 (20)
- VRd	1/49 (2)
- KRd	2/49 (4)
- VCd	1/49 (2)
- Rd	1/49 (2)
- Kd	1/49 (2)
- Dara-Vd	2/49 (4)
- Vd	1/49 (2)
- Dara-VRd	1/49 (2)
- Unknown	6/49 (12)
Status:	
- Alive	48/49 (98)
- Dead	1/49 (2)
MRD status:	
- Positive	33/54 (61)
- Negative	21/54 (39)
Disease status:	
- Relapsed	6/49 (12)
- No relapse	43/49 (88)
MRD+ disease status	
- Relapsed	6/33 (18)
- No relapse	27/33 (82)
MRD- disease status	
- Relapsed	0/21 (0)
- No relapse	21/21 (100)

Accordingly, BM samples from patients with MM at specific timepoints (post induction, post autologous stem cell transplant (ASCT) and every 12 months if on maintenance or transplant ineligible) were collected in EDTA tubes and filtered with a 40 um cell strainer, then assessment of nucleated cell number was performed. Next, two to four million cells were stained with lyophilized antibodies contained in the 2 standardized tubes which include common surface antigens CD45, CD19, CD38, CD138 (used as backbone markers) and tube specific antigens (CD28, CD27, CD81, CD117, CD56, β2-microglobulin, κ and λ chains). With this protocol we aim to achieve a minimum number of 10^6 cells from each tube, leading to a total of $2x10^6$ events. Here we report the results of 49 MM patients evaluated between March 2022-April 2023. Of the MRD samples analysed, the average number of events collected was $1,55x10^6$ ($\pm 1.03x10^6$), with an average limit of detection (LOD) of $1.4x10^5$ cells. Since the adoption of the method, LODs and the number of events acquired has been gradually improving. Of the 49 patients examined (54 total MRD assesment), 33 patients were MRD+. Of them, at the time of analysis, and with a median follow up of 11 months, 6 patients relapsed and 1 of them died for progression. Of the MRD- patients, currently none is in relapse, and a 12-months MRD surveillance program is ongoing to assess the "sustained" MRD negativity. These data support the relevance and feasibility of MRD assessment by flow cytometry in common clinical practice to support the clinicians in the prognostication and follow-up of patients with MM.

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ARGININE DEPRIVATION INDUCES ACQUISITION OF A SENESCENT PHENOTYPE CONFERRING RESISTANCE TO PROTEASOME INHIBITORS IN MULTIPLE MYELOMA

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Background. Multiple myeloma (MM) originates from a neoplastic clone of plasma cells which establish vicious interactions with the multicellular microenvironment, including myeloid derived suppressor cells (MDSCs) that produce arginase-1 (ARG-1) leading to arginine (Arg) deprivation. Our previous study demonstrated that treatment with CB1158, an inhibitor of the Arg-1 enzyme, can reverse the level of Arg in serum of patients and decrease MM growth, without affecting the infiltration of myeloid cells. Additionally, we observed that U266 cells cultured with sera of MM patients were resistant to treatment with BTZ in an Arg-1 dependent manner.

Aims. We aimed to investigate the effect of Arg deprivation in promoting MM progression and drug resistance.

Materials and Methods. To assess the impact of arg concentration *in vitro*, we cultured two human myeloma cell lines (U266, NCI-H929) for both short- (48h) and long-term (10 days) in a medium containing either 200 μg/mL or 50 μg/mL of Arg, 20% dialyzed FBS and 1% P/S. Specifically, 200 μg/mL corresponds to the arg concentration found in healthy or MGUS subjects, while 50 μg/mL matches the concentration in the BM of MM patients. To study the cells sensitivity to drug treatments, we administered 10nM BTZ or 8nM CFZ after 24h of deprivation.

Results. Progressive Arg deprivation did not affect cell viability but led to a slowdown in proliferation and cell cycle arrest in the G0-G1 phase. To adapt to Arg starvation, NCI-H929 cells activated the unfolded protein response (UPR) system, as demonstrated by the overexpression of PERK protein, while the GCN2 pathway was activated in U266 cells. Neither of two cell lines activated autophagy to recover the starved amino acids. This resulted in increasing cellular stress that led to alteration of mitochondrial activity and metabolism. Specifically, U266 cells showed a reduction in mitochondrial polarization and downregulation of protein involved in oxidative phosphorylation, indicating a low-energy metabolic state associated with the acquisition of a senescence-associated secretory phenotype (SASP). Finally, the overexpression and nuclear translocation of heme-oxygenase 1, an anti-oxidant protein involved in resistance, promoted a reduction in sensitivity to treatment with BTZ and CFZ.

Conclusions. Taken together, our findings suggest that arginine deprivation, conveys a complex adaptive response which causes that leads to the acquisition of SASP and promotes drug resistance.

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CLINICAL FEATURES IN PATIENTS WITH MULTIPLE MYELOMA WITH CD20 EXPRESSION: REAL-LIFE EXPERIENCE OF THE GIMEMA MULTIPLE MYELOMA MACROREGION CENTRO-ITALY DISTRICT

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Background. CD20 antigen is usually negative in the immunounophenotypic pattern of Multiple Myeloma (MM) plasmacells (Pls). However, a small number of MM displays various degrees of CD20 expression on neoplastic Pls: CD20+ is described in about 15-20% of patients (pts), often associated with some morphological and clinical features. However, the clinical and prognostic significance of this CD20 expression is still a matter of debate.

Methods. To highlight the clinical features in this subset, we collected data on 92 CD 20+ MM pts [52M, 40F), median age 68 (IQR 58, 76 years) diagnosed and followed in 7 Hematologic Centres in Italy from 01/2015 to 06/2022 (12.2% of the overall MM followed in the same period). MGUS was present before the diagnosis of MM in 25/92 pts (27%), MM-associated AL amyloidosis in 2/66 pts (3%) and renal insufficiency in 15 (16%). CD20 expression was evaluated with immunohistochemistry performed on bone marrow (BM) biopsy specimen or/and flow-cytometry analysis on BM aspirate. Conventional karyotype/FISH on BM Pls were performed in 82/92 patients: high-risk karyotype was considered in cases with 1q deletion/gain or 17p/p53 or t(4;14) or t(14;16) or > 3 aberrations (complex karyotype).

Results. Clinical features at diagnosis and response to 1st line therapy are reported in the Table 1. Karyotype was normal in 16/82 (19.5%): among the remaining 66 pts with altered karyotypes, a t(11;14) and/or the amplification of the CCND1 gene (located on the long arm of chromosome 11–band 11q13) were reported in 34 pts (41.5% of the entire cohort evaluable for karyotype, 51.5% of patients with altered karyotype; 8/38 (21%) of the pts at high cytogenetic risk). 19/92 pts (20.7%) were asymptomatic (without SLIM-CRAB criteria) and did not receive any treatment up to now, while the remaining pts (78.6% of the entire cohort) were symptomatic and received 1st line treatment as reported in the Table. Among these 73 treated pts, 63 were already evaluable for response: of them, 35 pts (55.6%) had >VGPR, 14 (22.2%) PR and 14 (22.2%) SD or PD. At the last follow-up, 4 pts died: 1 from acute myocardial infarction during Covid-19 infection and 3 for progression.

Conclusions. In this multicentric real-life cohort of patients with MM and CD20+, high rates of t(11-14)/CCND1 gene alterations were reported (12.2%). However, large comparative prospective study must be due to better understand the clinical and prognostic impact of CD20 expression.

Table 1. Clinical features, 1st line treatment and response in MM patients with CD20 expression.

Characteristics		Characteristics		Therapy, n° (%)		Response, n° (%)	
ALL	92	Male/Female, n° (%)	52/40 (56.5/43.5)	No Treatment	19 (20.7)	NE	10 (13.7)
		Smouldering MM, n° (%)	19 (20.7)	D-RD	11 (12.0)	Evaluable	
				D-VTD	2 (2.2)	PD	6 (8.2)
Median age, yrs (IQR)	68 (58-76)	Cytogenetics, n° (%):	82 (100)	D-VRD	2 (2.2)	SD	8 (11.0)
		Normal	16 (19.5)	VMP/VMD	12 (13.0)	PR	14 (19.2)
Previous MGUS, n° (%)	38 (41.3)	t(11-14)/CCND1	34 (41.5)	RD	4 (4.3)	VGPR	16 (21.9)
		High Risk [1q-, t(4-14), t(14-16), Complex]	26 (31.7)	VTD/VCD	37 (40.1)	CR	16 (21.9)
				VRD	3 (3.3)	sCR	3 (4.1)
BM PLASMA cell, % (IQR)	60 (30-80)	Del 13q	1 (1.2)	Others	2 (2.2)		
IgG, n° (%)	58 (63.0)	Others	3 (4.0)				
		Not done	10				
IgA, n° (%)	14 (15.2)	NE= Still not evaluable; PD= Progressive Disease; SD= Stable Disease; PR= Partial Remission; VGPR= Very Good Partial Remission; CR= Complete Remission; sCR= Stringent Complete Remission					
LC(K or λ), n° (%)	14 (15.2)						
Others, n° (%)	6 (6.6)						

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DOUBLE VERSUS SINGLE AUTOLOGOUS STEM CELL TRANSPLANTATION IN ELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: A REAL-LIFE MULTI-CENTER REPORT

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Introduction. High dose melphalan followed by autologous stem cell transplantation (ASCT) remains the key treatment for eligible patients with newly diagnosed (ND) multiple myeloma (MM); however, two consecutive ASCTs show controversial results, and current guidelines recommend their use only in high-risk MM. In this retrospective multi-center experience, we evaluated outcomes of one *vs* two ASCTs in eligible patients with ND-MM regardless risk stratification.

Materials and Methods. A total of 65 ND-MM patients who received high dose melphalan and ASCT were enrolled since January 2016 and divided in two cohorts: single and double ASCT. Primary endpoint was progression free survival (PFS). Secondary endpoint was overall survival (OS).

Results. Patients' characteristics are summarized in Table 1. In double ASCT cohort, patients were younger (median age, 54 *vs* 62 years; P=0.003) and with a higher prevalence of high-risk MM (36%

vs 12%; P= 0.02). As induction therapy, bortezomib-thalidomide-dexamethasone (VTD) and bortezomib-cyclophosphamide-dexamethasone (VCD) were more frequently applied to double and single ASCT groups, respectively (P=0.02). No difference was observed in hematological responses before ASCT (P=0.94) and maintenance with lenalidomide was started after ASCT in 63% and 82% of patients in single and double ASCT cohorts (P=0.11), respectively. Median PFS was 60 *vs* 70 months in single *vs* double ASCT (P=0.38), lower (42 *vs* 70 months; P=0.79) when population was stratified for high-risk MM. Furthermore, median PFS was similar (62 *vs* 65 months; P=0.57) for the group who started lenalidomide maintenance. Median OS was not reached, while 5-year OS was 92% *vs* 86% in single and double ASCT group, respectively (P=0.32).

Discussion. In our multicenter real-life study, we showed that single or double ASCT had similar outcomes, regardless the type of induction therapy. When maintenance with lenalidomide was introduced, the difference in outcomes between the two cohorts decreased. Furthermore, our study confirmed current recommendations on double ASCT for patients with high-risk MM. Further validation on larger and prospective clinical studies are needed.

Table 1. Patient's and disease features.

Characteristics	Single ASCT cohort N = 43	Double ASCT cohort N= 22	P value
Median age, years (range)	62 (41-69)	54 (39-71)	**0.003**
Gender, n (%)			
Male	24 (56)	13 (59)	0.8
Female	19 (44)	9 (41)	
M-protein type, n (%)			
IgG	31 (72)	16 (72)	0.48
IgA	5 (12)	1 (4)	
Micromolecular	7 (16)	5 (22)	
Light chain type, n (%)			
Kappa	34 (79)	17 (77)	0.86
Lambda	9 (21)	5 (23)	
High genetic risk multiple myeloma, n (%)	5 (12)	8 (36)	**0.02**
Extramedullary disease, n (%)	7 (16)	5 (23)	0.52
R-ISS, n (%)			
I	8 (19)	7 (32)	
II	17 (39)	6 (27)	0.06
III	17 (39)	9 (41)	
Free light chain ratio, median (range)	234 (1824-2)	135 (18-4817)	0.74
β2 microglobulin mg/dl, median (range)	3.2 (1-92)	3.5 (1-24)	0.29
LDH U/l, median (range)	253 (94-2247)	207 (108-838)	0.6
Albumin gr/dl, median (range)	3.6 (1.8-4.9)	3.7 (1.8-4.6)	0.62
GFR< 40 ml/min, n (%)	5 (12)	2 (9)	0.8
Therapy setting, n (%)			
Bortezomib-lenalidomide-dexamethasone	11 (26)	6 (27)	
Bortezomib-thalidomide- dexamethasone	9 (21)	12 (55)	**0.02**
Daratumumab-bortezomib-thalidomide- dexamethasone	5 (12)	-	
Bortezomib-cyclophosphamide-dexamethasone	18 (42)	4 (18)	
Response before first ASCT, n(%)			
CR	12 (28)	7 (32)	
VGPR	25(58)	12 (55)	0.94
PR	6 (14)	3 (13)	
Time to second ASCT, median, days (range)	-	120 (93-192)	
Full-dose conditioning with melphalan 200 mg/m2, n (%)	38 (88)	22 (100)	0.15
Lenalidomide maintenance, n (%)	27 (63)	18 (82)	0.11
Progression free survival, median, months (95%-CI)	60 (50.2-69.7)	70 (50.6-93.3)	0.38
PFS in high-risk MM, median, months (95%-CI)	42 (32-50)	72 (46-87)	0.79
PFS in lenalidomide maintenance, median, months (95%-CI)	62 (55.5-68.4)	65 (46.1-83.8)	0.5
Overall survival, median, months (range)	NR (7-115)	NR (18-115)	0.57
5 year-OS, %	92	86	0.32

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DARA-RD COMBINATION IN FIRST LINE TREATMENT IN PATIENTS WITH NEWNLY DIAGNOSED MULTIPLE MYELOMA INELIGIBLE FOR ASCT: A REAL-LIFE EXPERIENCE

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Background. The introduction of daratumumab represented a significant breakthrough in the myeloma therapy scenario, especially in first line treatment. The combination daratumumab-lenalidomide-dexamethasone (Dara-Rd) has shown excellent results in the treatment of newly diagnosed multiple myeloma patients (NDMM) ineligible for autologous steam cell transplant (ASCT) in the MAIA trial.

Aim of the study. We retrospectively evaluated the safety and efficacy of Dara-Rd combination in a cohort of elderly patients in a real-life setting.

Methods. We evaluated patients with NDMM ineligible for ASCT, treated with Dara-Rd between March 2021 and March 2023, at AOU Careggi Hospital. For all patients we collected baseline data at diagnosis and after each cycle. Patients received therapy according to MAIA schedule; the lenalidomide starting dose was 25 mg in patients with a normal renal function and the dose of oral dexamethasone was reduced in patients with age ≥75 or amyloidotic involvement.

Results. Our observational retrospective study included 38 consecutive patients, M/F=25/26, median age 73 (range 62-83), ECOG performance status ≥2 in 47%, score 29% were intermediate-fit and 5% frail, according to IMWG. High-risk cytogenetic features were identified in 8%, amyloidotic involvement in 13%, renal impairment in 10,5%. After a median follow up of 9,3 months, the overall response rate was 92%, with high-quality response (≥VGPR) in 73,7% of the patients. Three pts (8%) were primary refractory. The median number of treatment cycles was 8,5 (range 2-23) and the best response was achieved after a median of 4 cycles. The median PFS and OS were not reached; the estimated OS after 24 months was 65%. At the time of data cut-off in 87% of patients therapy was still ongoing. The most common adverse events were hematological ones: anemia (55%), neutropenia (68%; G3-4 50%) and thrombocytopenia (24%). The incidence of infections of any grade was 18%; in particular pneumonia occurred in 8% of pts. The percentage of patients who reduced lenalidomide due to hematological toxicity or worsening renal function was 44,7% and three patients discontinued lenalidomide permanently.

Conclusions. In conclusion, even in real-life, Dara-Rd combination is an effective and well-tolerated treatment, even by elderly patients with comorbidities.

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DARATUMUMAB-BORTEZOMIB-THALIDOMIDE-DEXAMETHASONE (D-VTD) IN TE-NDMM PATIENTS: A SINGLE-CENTER RETROSPECTIVE EXPERIENCE

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The CASSIOPEIA study showed the clinical benefit, in terms of depth and duration of response, of combining daratumumab to the standard of care (D-VTD) in transplant-eligible newly diagnosed multiple myeloma (TE-NDMM) patients. Here we report a single-center retrospective observational study of 35 patients treated in a real setting with D-VTD, according to the standard practice, with the aim of evaluating response and safety. For risk stratification, we used the International Staging System (ISS) and Revised-ISS; high-risk FISH was defined when ≥1 abnormality among del(17/17p), t(4;14), t(14;16) and gain/amp(1q) occurred. Minimal residual disease (MRD) was assessed by multiparametric flow cytometry (sensitivity 10^{-5}) before and after ASCT. From 23 December 2021 to 15 April 2023, 35 TE-NDMM patients were treated at the Hematology Unit of Careggi Hospital. The median age was 56 years (range: 39-69 years); 60% were males. High-risk cytogenetics were found in 13 (37%); 26% and 28% were ISS-2 and ISS-3, while 43% and 14% were R-ISS 2 and R-ISS 3 respectively. After a median follow-up of 8,7 months (range: 1-14,5 months), 29 patients (83%) completed induction phase (4 D-VTD cycles). CD34+ stem cells (SC) mobilization was performed with cyclophosphamide (2-4 g/smq) and G-CSF in 26 patients (74%) after a median time of 28 days (range: 13-50

days) from the end of induction; 3 (11%) patients were mobilized only with G-CSF. Plerixafor on demand was administered in 13 pts (50%) failing to achieve the desired collection target. The median number of CD34+ harvested was 9,46x10^6 cells/Kg (range: 4-16x10^6 cells/Kg). One patient required a second mobilization attempt, despite failing SC collection. Nineteen patients (54%) underwent ASCT; 17 (49%) completed the consolidation phase (D-VTD cycle 5 and 6) while maintenance therapy was initiated in 7 patients (20%). The median PFS and OS were NR. Responses and MRD rates are reported in Figure 1. Hematological toxicity was the most common adverse event (50%; G≥3 anemia, neutropenia, thrombocytopenia occurred in 8%, 17% and 8% respectively), followed by infections (33%) and PNP (25%). In our real-life experience, D-VTD regimen was proven effective and well tolerated in TE-NDMM patients.

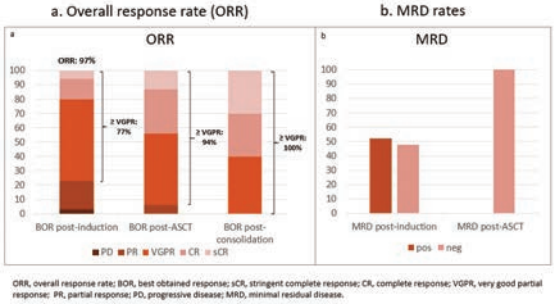

Figure 1.

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DOES SARCOPENIA IMPACT THE OUTCOME OF AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH MULTIPLE MYELOMA?

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Sarcopenia is defined as an age-associated loss of skeletal muscle function and mass and it has been associated with chronic diseases, such as chronic obstructive pulmonary disease and cancer. An increasing interest regarding this alteration in oncology, in the last years, is due to its high prevalence and association with adverse outcomes. For this reason, a single-center retrospective study was conducted to evaluate the incidence and prevalence of sarcopenia in patients with Multiple Myeloma (MM) undergoing autologous hematopoietic stem cell transplantation (auto-HSCT), and its impact on overall survival and progression-free survival data. L3-SMI was quantified in 68 eligible patients, based on measurement of skeletal muscle area (cm^2) on computed tomography (CT) scans at the level of the L3 vertebra. 37 (54%) patients with L3-SMI values <52.4 cm^2/m^2 for men and 38.9 cm^2/m^2 for women were categorized as sarcopenic. The majority of sarcopenic patients included were 26 (60%) males (p=0.02), older than 60 years old (69%, p=0.0005), and with BMI <25 (75%; p= 0.0000). A significant association was found between sarcopenia and Sorror score value > 1, finding that 10 (66%) patients with higher risk class were sarcopenic (p=0.02). The Kaplan Meyer curve showed a median OS of 73.5 months for non-sarcopenic patients *vs* 86.5 months for sarcopenic patients, suggesting that sarcopenia is not an independent prognostic factor in our cohort of patients with Multiple Myeloma undergoing autoHSCT

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IRE1A-INDUCED FLNA PHOSPHORYLATION ENHANCES MIGRATION OF MSC DERIVED FROM MULTIPLE MYELOMA PATIENTS

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Multiple myeloma (MM) is an aggressive malignancy that shapes, during its progression, a pro-tumor microenvironment characterized by altered protein secretion, gene expression and behavior of different cell type as mesenchymal stem cells (MSC). MSC from MM patients display various alterations that range from high pro-tumor to weak immunosuppressive behavior, comprising osteogenic differentiation impairment. Here we show for the first time a greater mobility and activation of FilaminA (FLNA) in MM-derived compared to healthy donor (HD)-derived MSC. Moreover we demonstrate an involvement of IRE1a-FLNA axis in the control of MSC migration process. Notably IRE1a is a good candidate as new target of wide anti-MM therapy, considering its role as pro-survival, pro-osteoclast and chemioresistance agent in MM microenvironment. Our results highlight as anti-IRE1a approach could interfere also with the response of MSC to MM stimuli and possibly impact on cell mediated drug resistance (CMDR). In addiction the observed mechanism of IRE1a-FLNA role in migration could pave the way for further improvement of efficacy in homing process of MSC-based cell therapy.

Infections, cytogenetic and quality of life

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SIMILAR PATTERN OF SOMATIC MUTATIONS IN T-MDS/AML PATIENTS TREATED WITH PARP-INHIBITORS FOR OVARIAN CANCER

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Poly ADP-ribose polymerases (PARP) are crucial in maintaining genomic stability, involved in many DNA-repair pathways and apoptosis. They act through covalent ADP-ribosylation of polypeptides that, once enabled by this process, can take part to DNA repair process. BRCA 1 /2 mutated cells lack in HRR mechanism, becoming strongly dependent on PARPs activity for survival; this synthetic lethality rationale led to the development of PARP-inhibitors (PARP-i), proteins designed to compete with NAD+ site on PARPs, for maintenance therapy of recurrent platinum sensitive BRCA-mutated ovarian cancer (OC), resulting in a significant improvement in progression free survival. Prior exposure to PARP-i correlates with increased risk of development of myeloid neoplasm and is now included as a qualifying criterion for post cytotoxic therapy (MN-pCT). We studied 17 consecutive patients with MN-pCT undergoing maintenance treatment with PARP-i for BRCA-mutated OC. The median age at the time of diagnosis was 50 years (range 45-73), all patients underwent a minimum of 2 lines of standard chemotherapy (including at least 1 platinum-based regimen) before PARP-i oral maintenance; 10 patients (58%) had been exposed to Olaparib, 5 (29.5%) to Niraparib and 2 (11.5%) to Rocuraparib. The hematological diagnosis (median time from PARP-i first exposure 12 months, range 3-28) was MDS in 12 patients (70.6%) and AML in 5 patients (29.4%); 16 out of 17 patients were in complete remission for the OC. Bone marrow evaluation at diagnosis showed cytogenetic abnormalities, both from conventional karyotype analyses and FISH, in 15 patient (88%), with only 1 patient having normal karyotype (and absence of metaphases in 1 case); in particular, 5 (29.4%) patients had complex karyotype, 5 (29.4%) showed a hypodiploid pattern, 2 (11.7%) a hypodiploid pattern and del5q and 5q-/-7 were found in 1 (5.8%) patient each. After performing NGS analysis for pathogenic mutations we found TP53 mutated in 16 (94%) patients. Other NGS-detectable alterations were TET2 and DNMT3A, both found in 5 patients (29.4%), EZH2 and RUNX1 were mutated in 2 patients (11.7%) and IKZF1, CSF3R, IDH1 and KIT were all mutated in 1 patient (5.8%) each. Recurrent molecular alterations were not found in our patients. Our data show how MN-pCT occurring after the combination of platinum-based chemotherapy and PARP-i oral maintenance share common cytogenetic alterations, mostly involving chromosome 5 and 7, and NGS-detectable mutations.

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HOW MEASURE OF PONATINIB PLASMA LEVELS COULD HELP TO DO A PATIENT-TAILORED THERAPY IN CHRONIC MYELOID LEUKEMIA

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Ponatinib (PON) is also effective in BCR::ABL1-mutated patients. Because arterial occlusive events occurrence reduces of 33% for each 15 mg decrease in daily dose, different algorithms for adjusting dose have been proposed. In this work, we measured the PON plasma concentrations in 32 CML patients in chronic phase to define the plasma levels reached according to the different delivered doses and if different plasma concentrations might condition different the molecular response or the adverse events occurrence. PON plasma concentrations were determined by High Performance Liquid Chromatography-High Resolution Mass Spectrometry. Seventeen patients received PON as second line, 11 as third line, 3 as fourth line, and one as sixth line. Overall, 18 received PON because of failure and 14 for intolerance to a previous TKI. With a median follow-up of 27 months, all patients were alive and in treatment with different PON doses (in 9 occasions PON was administered at 45 mg/day, in 17 at 30 mg/day, in 12 at 15 mg/day). Molecular response of 3 logs (MR3) was achieved at 25/38 timepoints (65.7%), and deep molecular response (DMR) in 15/38 cases (39.5%). In the whole series, the mean PON plasma concentration was 30.19±18.55 ng/mL, and the median value 27.13 ng/mL (range, 3.16-72.7 ng/mL). In the cohort receiving 45 mg/day, the mean value was 41.99±23.77 ng/mL; in that at 30 mg, 34.27±15.19 ng/mL; in the subgroup receiving 15 mg/day, the mean PON plasma level was 15.25 ± 8.56 ng/mL. These differences were significant between the group 1 (at 45 mg/day) or group 2 (at 30 mg/day) and group 3 (at 15 mg/day) ($p=0.003$ between group 1 and 3, and $p=0.001$ between group 2 and 3), but not between group 1 and 2 ($p=0.322$). A concentration ≥20 nM was reached by 8/9 patients treated with 45 mg/day (89%), by all patients receiving 30 mg/day, and by 8/12 patients receiving 15 mg/day (66.7%) ($p=0.032$). Moreover, the optimal target concentration of 40 nM was reached by 8/9 patients receiving 45 mg/day (89%), by 14/17 (82.4%) in the group receiving 30 mg/day and by 5/12 (31.6%) subjects treated at 15 mg/day ($p=0.024$). In conclusion, a significant lower probability of achieving the optimal plasma levels was observed in patients receiving 15 mg/day; nevertheless, 67% of them achieved 20 nM and 32% 40 nM, so explaining why PON is efficacious even at lower doses. To our cohort PON offered 65.7% of MR3 and 39.5% of DMR, and PON daily dose did not condition the quality of MR.

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"INTEGRATED DIAGNOSTIC REPORT" FOR MYELOID NEOPLASMS: A MORPHOLOGY-DRIVEN DIAGNOSTIC ALGORITHM

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To uniform diagnostic procedures for the diagnosis of myeloid neoplasms in patients referred to the Departments of AOU and AUSL of the Province of Modena, especially for acute myeloid leukemia and myelodysplastic syndromes/neoplasms, we designed a diagnostic algorithm in which a preliminary diagnosis, established by a skilled morphologist, defines, in the presence of cytopenia(s), cytosis and/or organomegaly (particularly splenomegaly), and after the immunophenotypic characterization, the appropriateness and priority of further investigations leading to a definite diagnosis and preventing unnecessary investigations.

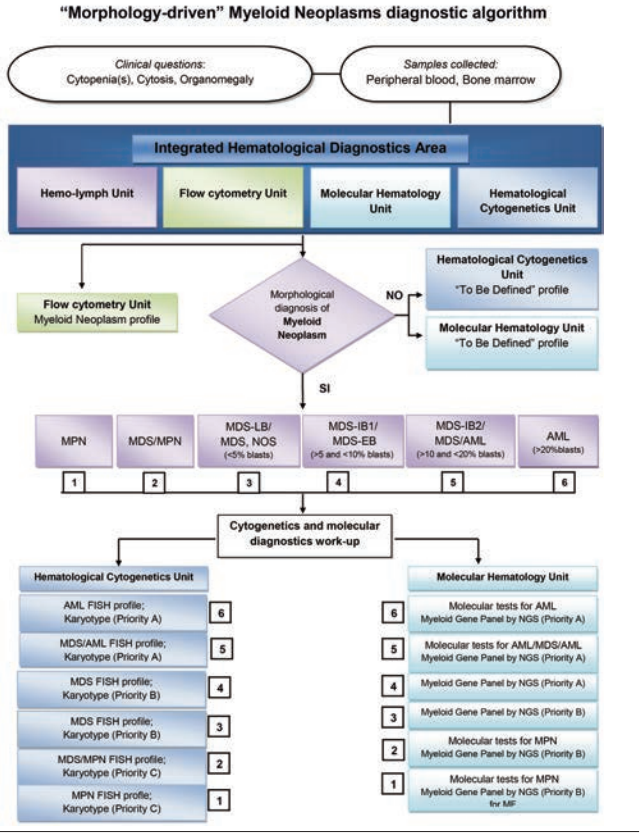

Figure 1.

Based on preliminary diagnosis of myeloid neoplasm, mainly defined by cytomorphologic findings, the cytogenetics, molecular diagnostics and genomic tests are scheduled in terms of priority and panels of execution, according to the algorithm showed in Figure 1. Upon completion of each cytogenetic (by Fluorescence in situ Hybridization and karyotype) and molecular (by targeted PCR and next-generation sequencing) investigation, individual reports will be formulated signed and released by the professionals responsible. Once all the aforementioned data have been obtained, the results will be presented and reviewed during meetings of the staff involved in the Integrated Hematological Diagnostics Area of Diagnostic Hematology and Clinical Genomics Section and a summary report (called "Integrated Diagnostic Report") including morphological (cyto-histological), immunophenotypic, cytogenetic and molecular data will be provided and signed as a consultancy by the morphologist of the Hemo-lymphopathology Unit. The "Integrated Diagnostic Reports" will provide a detailed and definitive diagnosis according to both the Fifth Edition of the World Health Organization (WHO 5th) and the International Consensus Classifications (ICC) of Myeloid Neoplasms. This final "Integrated Diagnostic Report" will be released and, if necessary, it will be further discussed during periodic meetings with the clinicians, also to help with the divergences between WHO 5th edition and ICC. This integrated reporting has been successfully employed for the diagnosis of 92 cases of myeloid neoplasms out of 1300 bone marrow aspirates, in the last 12 months.

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IMPACT OF SARS-COV-2 PROPHYLAXIS WITH TIXAGEVIMAB-CILGAVIMAB IN HIGH-RISK PATIENTS WITH B-CELL MALIGNANCIES: A SINGLE-CENTER RETROSPECTIVE STUDY

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Background. Pre-exposure prophylaxis with tixagevimab-cilgavimab, a combination of two monoclonal antibodies (MoAb) binding SARS-CoV-2 spike protein, is an additional strategy to decrease the morbidity and mortality of COVID19 for patients with B-cell malignancies. In the setting of hematology real-life, data are still lacking.

Aims. To evaluate the clinical benefit and the safety of this strategy at our center.

Methods. We retrospectively collected data of patients affected by B-cell malignancies who received tixagevimab-cilgavimab (150+150 mg) as pre-exposure prophylaxis, between February 2022 and February 2023.

Results. A total of 106 patients received prophylaxis, median age at infusion was 64 years (range 30-83), the majority was affected by non-Hodgkin lymphoma (65%, 69/106). 9.4% received the MoAb before, 39.6% within 6 months, and 50.9% within 1 year from hematologic treatment start (Table 1). Median follow-up was 124 days (25-380). No serious adverse events were related to MoAb administration. Out of 106 patients, 18 developed COVID19 (17%), after a median of 85 days (range 35-222) from MoAb infusion, 83.3% (15/18) developed symptoms and fever, 44.4% (8/18) required hospitalization and 16.7% (3/18) required oxygen support. Antiviral treatment was administered in 44.5% (8/18) patients. Comparing patients who developed COVID19 to the non-infected group, we observed a significantly higher frequency of at least 1 comorbidity among the former (77.8% *vs* 52.3%, p=0.047). Overall, the death rate was 6.8% (6/88) in the non-infected group (due to hematologic disease progression in all cases), and 22.2% (4/18) in the infected group (p=0.04), 3 cases for COVID19 (16.7%, 3/18) and 1 for hematologic disease progression. SARS-CoV-2 breakthrough infection was not related to aggressive hematologic disease. For patients developing COVID19, hospitalization (3/4, p=0.02) and oxygen therapy require-

ment (3/4, p=0.006) were the only significant death-related risk factors. Anti-spike antibodies were tested before MoAb in 9 of 18 infected patients, 6 (66%) had a negative and 3 (33%) a positive titer.

Conclusions. In our high-risk patients, tixagevimab-cilgavimab prophylaxis was safe and could be associated with a reduction in incidence of COVID19 breakthrough infection and in oxygen therapy. Larger studies are needed to assess the additional benefit of this strategy.

Table 1. Characteristics of hematologic patients who received SARS-CoV-2 prophylaxis with tixagevimab-cilgavimab.

		Patients who did not develop SARS-CoV-2 infection		Patients who developed SARS-CoV-2 infection		Whole Cohort		
		N (88)	%	N (18)	%	N 106	%	p
Sex	Male	53	60.2%	7	38.9%	60	56.6%	0.09
	Female	35	39.8%	11	61.1%	46	43.4%	
Age	>65years	37	44%	10	55.6%	47	46.1%	0.37
	<=65years	47	55%	8	44.4%	55	53.9%	
Diagnosis	B-Cell NHL	53	60.2%	16	88.9%	69	65.1%	0.09
	HL	10	11.4%	0	0.0%	10	9.4%	
	MM	22	25%	1	5.6%	23	21.7%	
	CLL/SLL	3	3.4%	1	5.6%	4	3.8%	
Comorbidities	None	41	47.7%	4	22.2%	45	43.3%	0.047
	At least 1	45	52.3%	14	77.8%	59	56.7%	
ECOG (PS)	0-1	80	95.9%	18	100%	98	97%	0.43
	2	3	4.2%	0	0.0%	3	3%	
Disease Stage	Early	20	23.5%	4	22.2%	24	23.3%	0.9
	Advanced	65	76.5%	14	77.8%	79	76.7%	
Risk stratification according to disease	Low	7	9.2%	0	0.0%	7	7.4%	0.36
	Intermediate	19	25.0%	6	33.3%	25	26.6%	
	High	50	65.8%	12	66.7%	62	66%	
Active Hematologic Disease	No	52	60.5%	9	50.0%	61	58.7%	0.41
	Yes	34	39.5%	9	50.0%	43	41.3%	
Number of prior lines of therapy	0	61	72.6%	11	61.1%	72	70.6%	0.87
	1	13	15.5%	4	22.2%	17	16.7%	
	2	3	3.6%	1	5.6%	4	3.9%	
	≥3	7	8.4%	2	11.1%	9	8.9%	
Ongoing Treatment at time of infection	No	37	44.6%	7	41.2%	44	44%	0.72
	Yes	46	55.4%	10	58.8%	56	56%	
Last Treatment regimen or planned at infusion	Chemotherapy	5	5.7%	3	17%	8	7.5%	/
	Immuno-Chemotherapy	39	44.3%	11	61.1%	50	47.1%	
	Immune-modulators	6	8%	4	22.2%	10	9.4%	
	Immuno-Chemotherapy + ASCT	20	26.7%	1	5.6%	21	19.8%	
	CAR-T cells	5	6.7%	0	0.0%	5	4.7%	
	Others	13	14.7%	0	0.0%	13	13%	
Anti-CD38 MoAbs	No	70	83.3%	17	94.4%	87	85.3%	0.22
	Yes	14	16.7%	1	5.6%	15	14.7%	
Anti-CD20 MoAbs	No	29	34.5%	3	16.7%	32	31.4%	0.13
	Yes	55	65.5%	15	83.3%	70	68.6%	
Bendamustine Exposed	No	63	76.8%	13	72.2%	76	76.0%	0.67
	Yes	19	23.2%	5	27.8%	24	24.0%	
Number of vaccine doses received	0	2	3.8%	0	0.0%	2	3.2%	0.74
	2	4	7.5%	1	10.0%	5	7.9%	
	≥3	53	88.7%	9	90.0%	63	88.9%	
Previous COVID19	No	56	63.6%	14	87.8%	70	67%	0.13
	Yes	32	36.4%	4	22.2%	36	33%	

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THE CLINICAL SPECTRUM OF LARGE GRANULAR LYMPHOCYTE (LGL) DISORDERS: A SINGLE CENTER ANALYSIS

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Large Granular Lymphocytes (LGL) are a lymphoid subtype originating from mature T-cells or natural killer (NK) cells. Their expansion can be monoclonal or polyclonal and can be associated with autoimmune, infectious or neoplastic diseases that may, in turn, jeopardize the diagnosis. To assess the clinical presentation and course of patients with LGL expansion a retrospective cohort study was conducted on 89 patients at a single center from 1997 to 2022. Patients were divided in 3 groups: T-LGL leukemia (T-LGLL, clonal T-cells),T-LGL (unknown clonality/polyclonal T-cells) and NK-LGL. Clinical and laboratory findings as well as bone marrow (BM) features were retrospectively registered. Complications were recorded and graded according to CTCAE v5.0. As shown in Table 1, a total of 89 patients (57% females, median age 59 years, 23-83) were included.

Table 1. Values are expressed as median (range) if not otherwise specified.

	All (N=89)	T-LGLL (N=35)	T-LGL (N=38)	NK-LGL (N=16)
Sex, N (%)	M 38 (43%) F 51 (57%)	M 15 (43%) F 20 (57%)	M 17 (45%) F 21 (55%)	M 6 (38%) F 10 (63%)
Median age at diagnosis, years	59 (23-83)	58 (23-83)	60 (23-82)	60 (31-82)
Hb, g/dL	13.1 (6.7-17.8)	12,6 (6.7-17.3)	13.5 (9.2-17.8)	13.1 (9.2-15.8)
Anemia, N (%)	24 (27%)	13 (37%)	8 (21%)	3 (19%)
PLT count, cellsx10^9/mm3	208 (57-485)	197 (57-343)	218 (124-485)	210 (57-331)
Thrombocytopenia, N (%)	9 (10%)	7 (20%)	0 (0%)	2 (13%)
ANC, cellsx10^9/mm3	2.25 (0.02-13)	2.15 (0.02-13)	2.63 (0.2-7.7)	1.6 (0.72-4)
Neutropenia, N (%)	53 (60%)	23 (66%)	18 (47%)	12 (75%)
ALC, cellsx10^9/mm3	3.9 (0.45-13.2)	4.4 (0.7-12)	3.5 (0.7-11)	3.7 (0.45-13)
Lymphocytosis, N (%)	35 (39%)	17 (49%)	14 (37%)	4 (25%)
Splenomegaly, N (%)	19 (21%)	11 (31%)	5 (13%)	3 (19%)
Lymphadenopathy, N (%)	12(13%)	6 (17%)	3 (8%)	3 (19%)
LDH, U/L	230 (112-621)	240 (112-561)	205 (115-401)	269 (158-621)
Beta-2 microglobulin (b2m), mg/L	3.0 (0.8-10.7)	3.2 (1.3-7.7)	3 (0.8-10.7)	2.5 (1.4-4.9)
Autoimmune disorders, N (%)	35 (39%)	15 (43%)	11 (29%)	9 (56%)
Solid Tumors, N (%)	18 (20%)	10 (29%)	6 (16%)	2 (13%)
MGUS, N (%)	8 (9%)	3 (9%)	4 (11%)	1 (6%)
Hypocellular, N (%)	24 (27%)	8 (23%)	10 (26%)	6 (38%)
BM Fibrosis, N (%)	8 (9%)	7 (20%)	0 (0%)	1 (6%)
BM Dysplasia, N (%)	38 (43%)	16 (46%)	16 (42%)	8 (50%)
T-cell BM Infiltrate, %	10 (2-30)	13 (5-30)	8 (2-30)	6 (2-10)
Complications, N (%)	29 (33%)	17 (49%)	8 (21%)	4 (25%)
G1-2 Complications, N (%)	13 (15%)	8 (23%)	3 (8%)	2 (13%)
G3-4 Complications, N (%)	13 (15%)	7 (20%)	5 (13%)	1 (6%)
G5 Complications, N (%)	3 (3%)	2 (6%)	0 (0%)	1 (6%)
Therapy, N (%)	11 (12%)	10 (29%)	0 (0%)	1 (6%)

Neutropenia was the most frequent presentation (53%), followed by lymphocytosis (35%), anemia (27%), and thrombocytopenia (10%); splenomegaly and lymphadenopathies were present in 21 and 13% of cases, respectively. T-LGLL patients had higher prevalence of thrombocytopenia (p=0.02), anemia and neutropenia as compared to T-LGL and NK-LGL. The most frequently associated conditions were autoimmune disorders (39%), solid tumors (20%) and MGUS (9%). At BM evaluation, median T-cell infiltrate was 10% (2-30), 27% of patients had hypocellularity, 43% dysplastic features and 9% reticulin fibrosis. T-LGLL patients had significantly higher T-cell infiltrate and frequency of fibrosis compared to the other groups (both p<0.0001). During a median follow up of 44 months (1-304), immunosuppressive therapy (cyclosporine, methotrexate, and cyclophosphamide) was required in 12% of patients due to cytopenias (10 T-LGLL and 1 NK-LGL) and 54% responded. Finally, 33% of patients experienced an infectious complication, which resulted in 3 deaths (3%). Infections were associated with T-LGLL (p=0.001), higher beta-2 microglobulin (p=0.006), BM fibrosis (p=0.04), dysplasia (p=0.03) and T-cell infiltrate (p=0.002), while neutropenia degree did not impact infection rates. In conclusion, cytopenias are the main clinical presentation of LGL disorders. T-LGLL patients are gen-

erally more cytopenic and exhibit higher BM T-cell infiltrate, reticulin fibrosis, and occurrence of infectious complications, pinpointing the importance of TCR clonality evaluation to tailor follow up. The degree of neutropenia is not associated with infectious complications.

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NEUTRALIZING ANTIBODIES AGAINST SARS-COV-2 AND ITS OMICRON BA.1 VARIANT IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES: A SINGLE-CENTER REAL-WORLD EXPERIENCE

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Introduction. SARS-CoV-2 and its variants are the etiological agents of pandemic coronavirus-19 disease (COVID-19). Hematological patients are at higher risk of severe COVID-19 because of their immunosuppression status. Anti-SARS-CoV-2 neutralizing antibodies effectively protect against severe COVID-19; however, seropositivity conversion rates are variable in general population and in hematological patients. In this real-life retrospective study, prevalence of neutralizing antibodies in immunocompromised hematological patients was assessed.

Table 1. Patients' characteristics.

Characteristics	N = 106
Median age, years (range)	65 (18-98)
Male, n (%)	65 (61)
Hematological malignancy, n (%)	
-Multiple Myeloma	24 (22)
-Myelodysplastic syndrome	14 (13)
-Acute leukemias	22 (21)
-Non-Hodgkin / Hodgkin Lymphomas	29 (28)
-Chronic leukemias	7 (7)
-Others	10 (9)
Number of vaccine doses, n (%)	
1 / 2	3 (3) / 13 (12)
3 / 4	63 (61) / 13 (12)
Type of vaccine, n (%)	
- Messenger RNA	82 (77)
- Mixed	7 (7)
- Not available	5 (5)
Prior natural SARS-CoV-2 infection, n (%)	36 (33)
Number of SARS-CoV-2 infection, n (%)	
1	34 (32)
2	2 (2)
Specific treatment in the last 12 months, n (%)	
-Anti-CD20 monoclonal antibodies	22 (21)
-Anti-CD38 monoclonal antibodies	14 (13)
-Azacytidine	23 (22)
-Immunosuppressive agents	6 (6)
-High-dose chemotherapy	26 (25)
Anti-SARS-CoV-2 neutralizing antibody response, n (%)	
-Wuhan virus	75 (71)
- Omicron BA.1 virus	87 (82)
-Not available	6 (6)
Anti-Wuhan neutralizing antibody titer, n (%)	
<1:10	25 (24)
1:10	20 (19)
1:40	29 (27)
1:160	15 (14)
1:640	11 (10)
Anti-Omicron BA.1 neutralizing antibody titer, n (%)	
<1:10	13 (12)
1:10	34 (32)
1:40	26 (25)
1:160	25 (24)
1:640	2 (2)

Patients and Methods. A total of 106 consecutive patients with different hematologic malignancies was enrolled between May and June 2022 at the Hematology and Transplant Center, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy (Table 1). Serum samples were collected for neutralizing antibody dosage. Primary endpoint was anti-SARS-CoV-2 antibody response against Wuhan and Omicron BA.1 virus, defined as a neutralizing antibody titer > 1:10.

Results. Almost all patients (95%) received anti-SARS-CoV-2 vaccination, as mRNA-based or both viral-vector-based (first dose) + mRNA formulations, and the majority of subjects (73%) were fully vaccinated with three or more doses. Adequate neutralizing antibody response was observed in 75 (71%) and 87 (82%) patients against the original Wuhan virus and its Omicron BA.1 variant, respectively. In the prior 12 months, 21% and 13% received anti-CD20 or anti-CD38 monoclonal antibodies (moAb), while azacytidine, high-dose chemotherapy, and immunosuppressive agents were used in 22%, 25%, and 6% of cases, respectively. However, only patients treated with anti-CD20 moAb had lower seropositivity conversion especially against Omicron BA.1 variant (73% *vs* 91%, anti-CD20 moAb *vs* others; P = 0.02), also confirmed by multivariate logistic regression (OR, 0.23; 95%CI, 0.05-0.98; P=0.04).

Discussion. Our real-life experience confirmed that full vaccination against SARS-CoV-2 induce adequate neutralizing antibody protection for both original Wuhan virus and its variants, even in hematological frail patients. However, protective measures should be maintained in those subjects treated with anti-CD20 moAb, because of reduced neutralizing antibody production.

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HIGH HUMORAL AND LOW T-CELL RESPONSE AFTER THIRD DOSE OF COVID-19 MRNA VACCINE: A MONOCENTRIC REAL-LIFE EXPERIENCE

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Background. Vaccine efficacy is often reduced in patients affected by hematological malignancies, which are immunosuppressed and vulnerable to severe COVID-19 infections. Several studies have documented a failing humoral response, with some improvement after the third dose of vaccine; moreover, few data are reported regarding T-cell response after booster dose and most of them derives from small groups of patients. Aim of our study was to evaluate humoral and T-cell response after third mRNA vaccine dose or after two doses and a previous SARS-CoV2 infection in a large cohort of hematological patients (HPs), defining the correlations with the different type of disease and treatment.

Methods. All consecutive HPs in active treatment in our Hematology Unit from March to July 2022 were analyzed. Humoral response and CD4 and CD4-CD8 T-cell mediated immune response were evaluated by detecting anti-spike antibodies, and by interferon-gamma release assay (quantiferon) respectively. Correlations with clinical and therapeutic features were studied by a univariate analysis (Fisher Exact test).

Results. We evaluated 232 patients. Median age was 66 (range 22-91), 14% were affected by myeloproliferative disease (acute myeloid leukemia, myelodysplastic syndrome and myelofibrosis) and 86% by lymphoproliferative disease (12% myeloma, 37% aggressive lymphoma, 11% B-cell chronic lymphocytic leukemia, 25% indolent lymphoma); 70% were in their first line of therapy, and median time from the last dose of vaccine was 4 months. Anti-spike antibodies

were detected with a positive titer in 90% of population; quantiferon was positive in 31% of cases, negative in 57% and indeterminate in 11%. Among each subgroup analyzed (see table) no significant differences were found neither in serological nor in T-cell response; a trend for a less seroconversion in patients with B lymphoproliferative syndrome and in those treated with anti-CD20 was observed.

Conclusions. The high rate of seropositive patients in our cohort supports the importance of booster dose, which increases seroconversion in HP, and of completing the vaccination cycle before starting treatment. The lower rate of T-cell response compared to literature data can be explained by the delayed time-point of our detection (median of 4 months *vs* few days after third dose). Only a longitudinal study could clarify discordant humoral and cellular response already reported in different studies involving immunocompromised patients.

Table 1.

	Ab anti spike+	Ab anti spike-	tot	Fisher	Reactive	No reactrive	Indeterminate	tot	Fisher
Anti-CD20	77 (86,5%)	12 (13,5%)	89	p=0,0769	32 (28,6%)	67 (59,8%)	13 (11,6%)	112	P=0,4571
No anti-CD20	87 (94,5%)	5 (6,5%)	92		36 (33,3%)	60 (55,5%)	12 (11,1%)	108	
Rituximab/Obinotuzumab-Bendamustine	36 (83,7%)	7 (16,3%)	43	p=0,1291	13 (25%)	35 (67,3%)	4 (7,7%)	52	P=0,2243
no Rituximab/Obinotuzumab-Bendamustine	128 (92,8%)	10 (7,2%)	138		55 (32,7%)	92 (54,8%)	21 (12,5%)	168	
Ibrutinib	12 (80%)	3 (20%)	15	p=0,1536	9 (47,4%)	9 (47,4%)	1 (5,2%)	19	P=0,1953
No Ibrutinib	152 (91,6%)	14 (8,4%)	166		59 (29,4%)	118 (58,7%)	24 (11,9%)	201	
Venetoclax	14 (100%)	0 (0%)	14	p=0,3684	7 (38,9%)	9 (50%)	2 (11,1%)	18	P=0,4271
No Venetoclax	150 (89,8%)	17 (10,1%)	167		61 (30,2%)	118 (58,4%)	23 (11,4%)	202	
One line therapy	109 (91,6%)	10 (8,4%)	119	p=0,5942	52 (34,2%)	84 (55,3%)	16 (10,5%)	152	P=0,1447
> one line therapy	55 (88,7%)	7 (11,3%)	62		16 (23,5%)	43 (63,2%)	9 (13,2%)	68	
Myeloproliferative diseases	32 (100%)	0 (0%)	32	p= 0,084	10 (31,2%)	18 (56,3%)	4 (12,5%)	32	P= 1
Lymphoproliferative diseases	diseases 178 (89,9%)	20 (10,1%)	198		62 (31,3%)	114 (57,6%)	22 (11,1%)	198	
>65 yrs	130 (89,1%)	16 (10,9%)	146	p= 0,1453	45 (30,7%)	89 (60,5%)	13 (8,8%)	147	P=0,5378
<65 yrs	80 (95,2%)	4 (4,8%)	84		27 (32,5%)	43 (51,8%)	13 (15,7%)	83	
Previous COVID-19+	45 (91,8%)	4 (8,1%)	49	p= 1	58 (32%)	103 (56,9%)	20 (11,1%)	181	P=0,7225
No previous COVID-19-	165 (91,2%)	16 (8,8%)	181		14 (28,6%)	29 (59,2%)	6 (12,2%)	49	

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SINGLE CENTER EXPERIENCE WITH TIXAGEVIMAB/CILGAVIMAB AS PRE-EXPOSURE PROPHYLAXIS AGAINST SARS-COV-2 IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

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Background. Tixagevimab/Cilgavimab (T/C) is a combination of two monoclonal antibodies against SARS-CoV-2 that was approved in 2022 for pre-exposure prophylaxis in patients at increased risk of infection. The emergence of newer SARS-CoV-2 variants has, however, quickly outrun the drug's efficacy which was retired by the FDA in January 2023. In this study we report our experience with T/C in patients with hematological malignancies during the omicron wave, with the hope that it could prove valuable for the future design of other monoclonal antibodies and preventions strategies.

Methods. 35 patients with hematological malignancies and suboptimal response to SARS-CoV-2 vaccinations (defined by a serum anti-SARS-CoV-2 spike protein IgG titer ≤53.0 kBAU/L) were treated with T/C. This cohort was compared with another one of 68 patients with hematological malignancies but adequate response to a full vaccination course (IgG titer >53.0 kBAU/L) that underwent observation or a fourth mRNA-based vaccine dose. The primary outcome was the cumulative incidence (CI) of SARS-CoV-2 infection at 3-months. The cumulative incidence of infection was estimated by the cumulative incidence function, treating death as a competing factor and compared with Gray's test.

Results. Patients in the T/C group were at a higher risk for SARS-CoV-2 infection due to inadequate response to vaccination but also due to older age (mean age 74.1 *vs* 63.5 years, p<0.001) and a higher proportion of patients on active therapy (71% *vs* 44%, p=0.01). With a median follow-up of 4.24 months, 8 patients (23%) in the T/C group contracted SARS-CoV-2 infection *vs* 15 (22%) in the observation-only group. The CI of infection at 3 months was 20% (95% CI: 7.8-36%) in the T/C group versus 12% (95% CI: 5.6-21%) in the observation only group (HR 1.57; 95% CI: 0.65-3. 56; p = 0.34) (Figure 1).

Conclusion. The administration of T/C to high-risk patients with hematological malignancies resulted in an incidence of infection that was comparable to that observed in an untreated population that responded to previous vaccinations. Although it is possible that T/C provided some degree of protection to this high-risk population, most of its efficacy was likely superseded by the emergence of newer, resistant, variants. In light of SARS-CoV-2's and other viral agents' ability to evade the neutralizing ability of monoclonal antibodies, new antibody designs with different mechanisms of action will be needed in future pandemics.

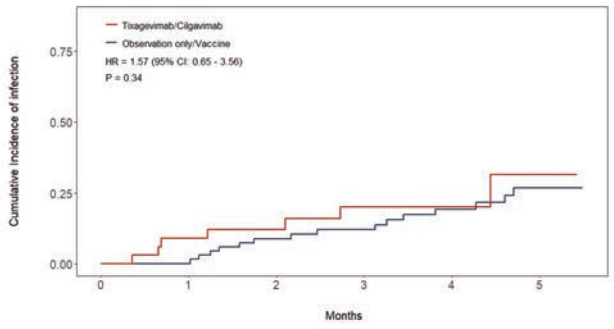

Figure 1.

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REAL-WORLD EVALUATION OF TIXAGEVIMAB-CILGAVIMAB AS PRE-EXPOSURE PROPHYLAXIS IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES IN THE ERA OF COVID19: A MONOCENTRIC EXPERIENCE

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Background. The COVID-19 pandemic has posed a challenge for healthcare systems worldwide, especially for vulnerable populations like haematological patients. Delayed treatment due to prolonged COVID-19 infection highlights the need for supplementary prophylactic measures, in addition to vaccines. Tixagevimab-Cilgavimab (Evusheld) is a combination of monoclonal antibodies that had been authorized by the FDA as pre-exposure prophylaxis of COVID-19 in patients who are at high risk of developing severe illness. However, its efficacy in haematological patients is not yet established.

Methods. We started a retrospective study, enrolling 41 haematological patients (15 females, 26 males) with a median age of 61 years (range 23-82) who received Tixagevimab-Cilgavimab pre-exposure prophylaxis for COVID-19 between July 1st 2022 and January 1st 2023 prior to and during treatment for their haematological disease. Patients were grouped by age, haematological disease, therapies received after prophylaxis, vaccination status, and comorbidities. The study aimed to determine the incidence, severity, and duration of SARs-CoV-2 infection at 6-month follow-up, as well as the relationship between the specific haematological therapy and the primary outcomes.

Results. Among the 41 haematology patients receiving Evusheld prophylaxis, 63.4% (26/41) were not SARS-CoV-2 affected at 6-month, whereas the 36.6% (15/41) were infected. Among these the median duration for positivity was 11 days (range 9-36) and 93.3% of these patients experienced only mild symptoms without developing pneumonia. No patient required intensive support therapy for COVID-19 and there were no COVID-19-related deaths. Interestingly, even in the subgroup of patients treated with chemotherapy and immunotherapy the positivity rate for Sars-CoV-2 infection at 6 months was still less then 20%.

Conclusions. Our preliminary results suggest that Tixagevimab-Cilgavimab prophylaxis is a safe and represents an effective measure in reducing the incidence and severity of COVID-19 in haematological patients. However, its use should not be considered as a substitute for preventive measures such as vaccination or social distancing, but as an additional tool to reduce the risk of COVID-19 in vulnerable patients. An extended follow up and larger series are necessary to assess the effectiveness of this prophylactic measure.

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ACUTE LEUKEMIA AND LATENT TUBERCOLOSIS INFECTION IN ITALY: QUANTIFERON-TB TEST IN A LOW TUBERCOLOSIS INCIDENCE COUNTRY

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Latent tuberculosis infection (LTBI) is defined as the presence of M. tuberculosis in individuals without any symptoms or signs of active disease. Contact investigation to identify these cases is a critical step of tuberculosis (TB) surveillance, especially in low incidence countries - such as Italy - and it should be limited to situations with a clear likelihood of transmission or with a higher probability of developing active TB, such as immunodepression. Patients (pts) with hematologic malignancies have a 2-40 times higher risk of progression from LTBI. According to current guidelines, in TB non-endemic countries no clear TB screening program is established at diagnosis for pts with acute leukemia (AL) while it is used prior to hematopoietic stem cells transplantation. We recently started performing QuantiFERON (QFT)-TB screening, in pts with AL (myeloid, lymphoblastic, promyelocytic), before induction or consolidation or during follow-up. From October 2019 to April 2023, we analyzed a total of 45 pts, with 7 (15,5%) testing positive, 6 (13,3%) before induction chemotherapy and 1 (2,2%) before first consolidation, without any symptoms or signs of active TB, and 2 (4,4%) resulting indeterminate. No differences were observed in examined variables (Table 1).

Table 1.

		Quantiferon + (n=7)	Quantiferon – (n=38)	p
Age	Median (range)	61 (50-82)	59.5 (18-82)	0.3
Sex	Male, n (%)	3 (43)	20 (53)	0.6
	Female, n (%)	4 (57)	18 (47)	
Foreign born	n (%)	1 (14)	5 (13)	0.9
Smoking habit	n (%)	4 (57)	17 (45)	0.4
Diagnosis	AML, n (%)	6 (86)	30 (79)	0.7
	ALL ph+, n (%)	0	2 (5)	
	ALL, ph-, n (%)	1 (14)	3 (8)	
	APL, n (%)	0	3 (7)	
Intensive treatment*	n (%)	4 (57)	21 (58)	1
Treatment phase	Induction, n (%)	6 (86)	32 (84)	0.6
	Consolidation, n (%)	1 (14)	1 (3)	
	Salvage therapy, n (%)	0	3 (8)	
	Post-transplant, n (%)	0	2 (5)	
Neutrophils**	Median (range)	950 (320-3.440)	750 (20-23.600)	0.5
Lymphocytes**	Median (range)	1.480 (740-7.430)	880 (160-145.750)	0.2
Monocytes**	Median (range)	880 (250-5.620)	270 (0-51.070)	0.1
Bronchoalveolar lavage (BAL) positivity***	n (%)	2 (40)	3 (12)	0.1
	Not performed, n (%)	2 (28.5)	13 (34)	
Pulmunary lesion at RX	n (%)	3 (100)	11 (48)	0.2
	Not performed, n (%)	4 (57)	15 (39)	
Pneumonia of other origin	n (%)	4 (57)	20 (53)	0.8

Table no. 1
* Two patients (in Quantiferon – group) were tested in off-treatment setting (post-transplant).
** Blood test performed at the time of Quantiferon.
*** BAL was performed in order to investigate the direct or indirect presence of bacterial or fungal infection. The two Quantiferon + patients resulted also positive for Pneumocistis Jirovecii and Enterococcus Faecalis in BAL. Among the 3 Quantiferon – patients, one resulted positive for Pneumocistis Jirovecii and two for Galattomannan.

AML: Acute Myeloid Leukemia; ALL: Acute Lymphoblastic Leukemia; APL: Acute Promyelocytic Leukemia.

One pt had occupational related risk; 21 (46,6%) pts had smoking habit. All positive pts started prophylaxis with isoniazid 300 mg/die combined with pyridoxine supplementation, without any side effect; 57% of them underwent intensive chemotherapy. Indeterminate pts did not receive any prophylaxis. Pts with febrile neutropenia underwent chest computed tomography scan and bronchoalveolar lavage (BAL), if lung infiltration was detected. Active TB was excluded by imaging, as well as microscopic, cultural, and molecular examination

on BAL. During the 42-month period of observation none of the pts developed TB reactivation, while data collection is still ongoing. Although our data are preliminary and collected on a small sample of pts, we conclude that LTBI is not uncommon as expected. Thus, considering the growing globalization, immigration – also from TB-endemic countries – and the median age at diagnosis of pts with AL, it seems necessary to implement TB screening in pre-treatment setting. Such a strategy appears even more desirable in a time when more numerous active treatments are becoming available also for pts ineligible to intensive chemotherapy.

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ANTIVIRAL PROPHYLAXIS TO HERPES SIMPLEX VIRUS AND VARICELLA ZOSTER VIRUS IN ADULTS WITH NEWLY DIAGNOSED ACUTE LEUKEMIA: RESULTS OF A SURVEY SUBMITTED TO CENTERS BELONGING TO SEIFEM (SORVEGLIANZA EPIDEMIOLOGICA INFEZIONI NELLE EMOPATIE) GROUP

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Reactivation of HSV, commonly with ulcerative stomatitis, has been reported to occur in 60% to 80% of acute leukemia (AL) patients (pts) receiving intensive chemotherapy without adequate prophylaxis, while epidemiological data on VZV reactivation in this clinical setting are more limited. Based upon the results of former randomized clinical trials carried out some decades ago on limited number of pts, but showing significantly lower rates of symptomatic HSV reactivation with acyclovir compared to placebo, antiviral prophylaxis is recommended in patients with AL receiving intensive chemotherapy, at least during neutropenic phase following remission induction regimen. To investigate the adherence to these recommendations in clinical practice, we submitted a dedicated survey to the Hematology centers belonging to SEIFEM group. Among the 30 responders, 18 (60%) and 5 (16.7%) centers prescribe antiviral prophylaxis to AML/ALL cases or to ALL patients only, respectively, while receiving intensive induction and consolidation courses. Prophylaxis, mainly based on oral aciclovir (82.6% of cases), is continuously administered since induction chemotherapy to the completion of intensive treatments by most physicians (78.2%), whereas 13% prescribe intermittent antivirals only during neutropenic periods. Of interest, being the seroprevalence of HSV-1 and VZV about 90% in adults, 17 (56.7%) and 21 (70%) centers do not perform serological testing to detect previous HSV-1 and VZV infections, respectively. Therefore, 10 centers follow a universal prophylactic strategy for all AL pts at risk of viral reactivations, irrespective of serology data. While clinical reactivations are monitored by physical examination alone or combined with molecular assays in 40% and 56.7% of centers, respectively, epidemiological data are available from a minority of physicians (36.7%). Among 11 centers reporting data, 100 cases of HSV/VZV reactivation were observed over a 5-year observation (2018-2022) in 1310 intensively-treated AL pts, resulting in an estimated 7.6% cumulative incidence. Our questionnaire shows a rather heterogeneous scenario in antiviral prophylaxis policies in non-transplant AL patients from different Italian Hematology units, warranting prospective studies to further investigate clinical efficacy of aciclovir/valaciclovir prophylaxis in different treatment phases. A more widespread use of serological testing may spare drug exposure and potential toxicity in nearly 10% of pts.

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MANAGEMENT OF LATENT TUBERCULOSIS INFECTION (LTBI) IN NEWLY DIAGNOSED ACUTE LEUKEMIA ADULT PATIENTS: RESULTS FROM A NATIONAL SURVEY SUBMITTED TO CENTERS BELONGING TO SEIFEM (SORVEGLIANZA EPIDEMIOLOGICA INFEZIONI NELLE EMOPATIE) GROUP

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The prevalence of LTBI in patients (pts) with hematologic malignancies is closely related to the overall TB epidemiology of different regions, but with higher risk of progression to active TB compared to general population. However, preventive treatment of LTBI did not significantly decrease the development of overt TB in most studies focused on HSCT setting. Information on management of LTBI in pts with newly diagnosed acute leukemia (AL) is so far limited, especially in low-endemic countries. To investigate this controversial issue, we submitted a survey to the Centers belonging to SEIFEM group. Among the 30 responders, 24 (80%) globally perform LTBI screening, in all (16.7%) or selected (63.3%) AL pts at diagnosis, mainly using Interferon-gamma release assay Quantiferon-TB in 96.3% of cases. Of note, 14 (46.7%) centers perform LTBI screening only in at-risk pts from high endemicity countries or with previous TB exposure or showing chest imaging abnormalities suggestive of LTBI. Some epidemiological data are available from 15 centers, with 67 LTBI cases observed over a 5-year period (2018-2022) among 2111 (3.2%) AL pts. However, these data are underestimated since most centers investigate LTBI only in selected instances, while precise prevalence of LTBI was available from only 4 Institutions, with 30 cases overall documented among 546 (5.5%) AL pts. Active TB was extremely rare with only 2 cases occurred over 5 years in 20 centers with available information, resulting in estimated cumulative incidence 0.09%. Once positivity of Quantiferon-TB is found, after exclusion of active TB, AL pts receive treatment of LTBI either irrespective of the cytoreductive program or only in selected cases candidate to moderate to intensive chemotherapeutic approaches in 43.3% and 53.3% of centers, respectively. Most clinicians (86.6%) start LTBI treatment concurrently with first-line chemotherapy, mainly with a long-course (at least 6-9 months) isoniazid monotherapy (76.7% of cases), whereas a rifampicin-based approach is considered by only 16.6% of centers. This multicenter survey from different Italian Leukemia units documents a rather heterogeneous picture in management of LTBI in AL pts, warranting further prospective investigations. It could currently be suggested that LTBI screening and treatment may be reserved to pts candidate to potentially curative therapeutic approaches, carefully balancing the risk of TB reactivation and possible drug toxicity with prophylaxis.

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SARS-COV-2 SCREENING POLICIES IN HOSPITALIZED ONCO-HEMATOLOGIC PATIENTS: RESULTS FROM A NATIONAL SURVEY SUBMITTED TO CENTERS BELONGING TO SEIFEM (SORVEGLIANZA EPIDEMIOLOGICA INFEZIONI NELLE EMOPATIE) GROUP

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During COVID-19 pandemic multiple aspects of healthcare system has been profoundly affected, involving patients, physicians, and more generally public health policies and hospital organization in particular in terms of clinical risk management. Oncohematologic patients are severely immunosuppressed and therefore special attention has been dedicated to prevent SARS-CoV-2 infections especially during hospitalization for therapeutic purposes. Common strategies for COVID-19 nosocomial spreading prevention may include reducing visits, strict compliance to reverse isolation policies, and screening for SARS-CoV-2 of asymptomatic patients 48-72 hours before admission with a nasopharyngeal swab (NPhS). Nucleic Acid Amplification Test (NAAT) still represents the golden standard in terms of sensitivity and specificity, but antigen tests have been also adopted for its easy, rapidity and reduced costs, even if has a sensitivity of 63% in asymptomatic individuals, notwithstanding a specificity of 99%. To investigate the SARS-CoV-2 screening policies in clinical practice for hematologic patients admitted to Italian Hematology Units, we submitted a dedicated survey to the hematology centers belonging to SEIFEM (Sorveglianza Epidemiologica InFezioni nelle Emopatie) group. We asked if they perform SARS-CoV-2 screening at admission, with which technique (NAAT or antigenic NPhS), and if they perform sequential testing during hospitalization and with what frequency. Among 13 responders, all centres perform a screening at admission with NPhS, 6 with antigenic NPhS, 8 with NAAT NPhS (1 centre with both). All centres has a policy of sequential testing (Figure 1), 6 centres with antigenic and 6 centres with NAAT NPhS. Two centres repeat the test only in case of COVID-19 suggestive symptoms appearance. Seven centres once a week and 4 centres twice a week in asymptomatic patients. No differences were reported in the hematology and in the hematopoietic stem cell transplant wards. This multicenter survey in 13 Italian Hematology Units, documents a heterogeneous picture in the policies of SARS-CoV2 screening in hospitalized oncohematologic patients, and warrants further studies to investigate the efficacy of the different screening policies adopted in clinical practice in terms of identification of asymptomatic carriers before and during hospitalization and in preventing COVID19 clusters occurrence.

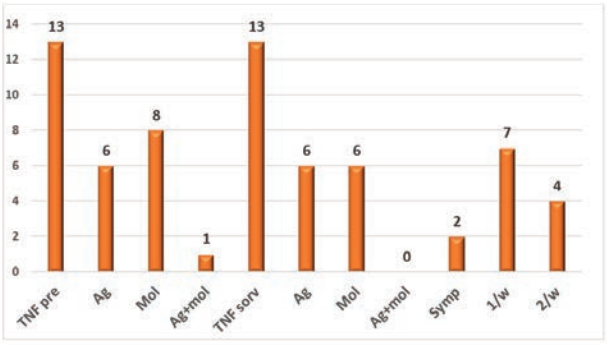

Figure 1.

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RELATIONSHIP BETWEEN LEUKOCYTE COUNT AND BACTERIAL INFECTION DIAGNOSIS IN THE CEREBROSPINAL FLUID. A CASE REPORT

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The leukocyte count of the cerebrospinal fluid (CSF) is the preliminary test to diagnose an infectious disease. The aim of this work was to highlight the relationship between a high number of neutrophils and a positive culture for bacteria Gram negative. We have described the case of a patient who arrived in the Intensive Care Unit of a hospital of the ASL BT for head trauma secondary to a road accident. The patient was placed a ventriculo-peritoneal shunt (DVP). A biochemical and microbiological examination of the CSF was performed at the appearance of turbidity in DVP and hyperpyrexia. The CSF was examined on Body Fluid channel (Yumizen H2500 HORIBA) for total leukocyte count and differential count of polymorphonuclear (PN) and mononuclear (MN) cells. Two smears were performed: one stained with May-Grunwald Giemsa on Yumizen SPS to confirm differential count, either stained with Gram on AEROSPRAY® Delcon for bacterioscopic examination. Culture was performed on selective Becton Dickinson plates for Gram positive, Gram negative, difficult bacteria and fungi, incubated at 37°C for 5 days. Identification and susceptibility antimicrobial were performed on bioMeriéux Vitek 2 system and manual methods for colistin, phosphomycin and aztreonam, according to EUCAST. 21 CSF samples were examined. 4 samples were analyzed only biochemical examination: in one case leucocyte count not was evaluated, in the remaining 3 cases 407, 1435, 2424 elements/µl were counted with a higher PN percentage. 5 samples were processed only for the culture test which has a negative result. 3 samples were examined for count and culture: the leucocyte count was not performed due to the presence of macroclots and frustules, the culture resulted negative in one sample, positive in the remaining two. In 6 samples 5, 6, 8, 11, 40 and 103 elements/µl were counted with MN prevalence and the culture was negative; 3 samples had leukocytes 5037 (PN 66%), 9569 (PN 90%), 392.296 (PN 90%), bacterioscopic examination positive for Gram negative bacilli and culture positive. Antibiotic-sensitive K. pneumoniae tested by automated and manual methods was detected in all cultures. Data analysis allows to observe the direct relationship between high leukocyte count with polymorphonuclear prevalence and positive culture. Our working method has provided indications to the clinician to establish an empirical therapy for the containment of the infection up to the final antibiogram.

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LONG-TERM NEUROLOGICAL AND PSYCHOLOGICAL IMPAIRMENTS IN PATIENTS WITH IMMUNE_MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA

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Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare, life-threatening blood disorder. In iTTP, blood clots are formed throughout the body, including the central nervous system, where they may lead to neurological disorders. If iTTP is not recognized in time, it can result in serious complications, which can have psychological, emotional, and neurological implications. The presence of neurological symptoms during an acute episode of iTTP is associated with an increased likelihood of abnormal cerebral MRI scans, which are then associated with cognitive impairment.[1] Anxiety and depression are also common findings regardless of neurological involvement. Patient self-report questionnaires, respectively, Cognitive Function Test (FACT-Cog)[2] and Hospital Anxiety and Depression Scale (HADS)[3] were used to assess neurological and psychological complications in patients with iTTP. The HADS consists of 14 items and is divided into anxiety and depression subclasses. HADS is considered a reliable measure of mood changes. The FACT-Cog test is made up of four subscales: perceived cognitive impairments (PCI); perceived cognitive abilities (PCA); the impact of perceived cognitive impairment on quality of life (QoL); and comments from others on cognitive function (CoO). This 37-item instrument allows patients to assess their memory, attention, concentration, language, and thinking abilities. A preliminary cohort of 34 patients with iTTP who had first-onset or relapsed (FOG or RG) were recruited at Hematology Department, Hospital Businco, Cagliari, Italy. The median follow-up from the last iTTP episode was 10.8 years. The majority of iTTP patients reported abnormal or borderline levels of anxiety and depression. In comparison to the FGO group, the RG group showed an overall lower level of anxiety and depression, although these differences were not statistically significant (Figure 1). PCI, as measured by the FACT-Cog test, did not differ between groups; however, a significant cognitive impairment emerged based on other comments ($P<0.05$) (Figure 2). In conclusion, preliminary outcomes indicate that iTTP patients present at long-term follow-up abnormal or borderline levels of anxiety and depression; in addition, relapse seems associated with a worst cognitive impairment primarily identified by others.

References

1. DOI: 10.1111/bjh.17126
2. DOI: 10.1016/j.jpainsymman.2017.12.486.
3. DOI: 10.1007/s00520-019-05244-8.

Fig. 1 *Hospital Anxiety and Depression Scale* (***HADS***)

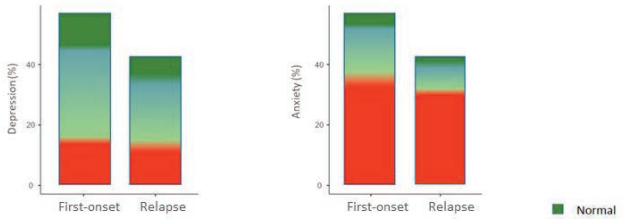

Fig. 2 *Cognitive function issues* (***FACT-Cog***)

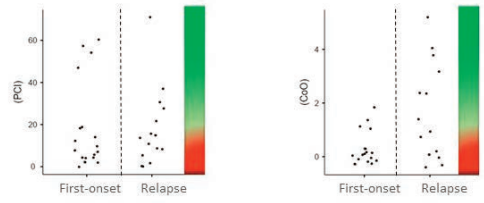

Fig.1 Hospital Anxiety and Depression Scale (HADS): χ2 test, frequency distribution of the variables; Fig. 2 Cognitive function (FACT-Cog) Test: range defined as normal, borderline and abnormal; T-test. Comparison between First-onset (FGO) and Relapse (RG) groups.

Figures 1 and 2.

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PALLIATIVE CARE IN HEMATOLOGICAL PATIENTS IS RELATED TO LESS AGGRESSIVE TREATMENT IN THE END-OF-LIFE, A RETROSPECTIVE STUDY

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Introduction. Patients with blood cancers experience high-intensity medical care near the end of life (EOL), have low rates of hospice and palliative care (PC), and are more likely to die in a hospital. Offering PC to hematological patients regardless of diagnosis and prognosis is a concept emphasized by recent reports from the European Hematology Association and the World Health Association. The goals of care (GOC) in the treatment of terminal cancer patients include low chemotherapy use, low access to the emergency room (ER) or intensive care unit (ICU), and a low rate of hospital deaths. However, scanty information about the rate of this GOC in hematological patients is available.

A

	Group 1	Group 2
Patients number	57	87
chemotherapy lines (range)	1.75 (0-7)	1.89 (0-8)
sex, male	34 (59.6%)	51 (58.6%)
mean age (range)	75.6 (42-86)	73.2 (34-92)
Disease		
AL	11 (19.3%)	21 (24.1%)
DLBCL	11 (19.3%)	25 (28.7%)
MM	9 (15.8%)	12 (13.8%)
MDS	8 (14%)	10 (11.5%)
other	18 (31.6%)	19 (21.9%)

B

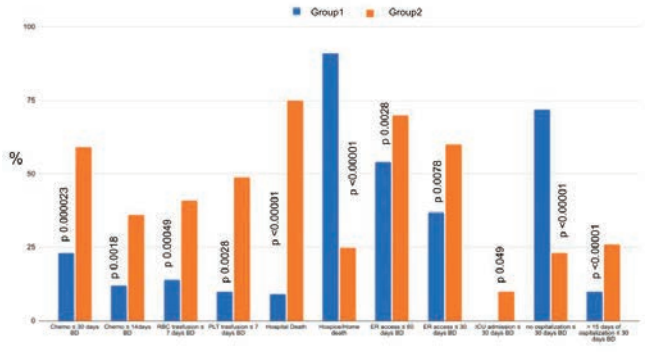

Figure 1.

Purpose. This retrospective observational study aimed to evaluate the achievement of these quality indicators in patients followed by the hematologist with or without the palliativist.

Methods. We evaluated a cohort of consecutive patients with hematologic diseases followed at our institution who died between January 2021 and December 2022. The quality indicators evaluated were: the use of antineoplastic therapy in EOL, place of death, transfusions, ER access, ICU access, and days of hospitalization in the last month of life.

Results. 144 patients were enrolled. 57 (39.6%) were offered PC (Group 1), and 87 (60.4%) were cared by the hematologist alone (Group 2). Mean age, gender, lines of therapy, and diagnoses were comparable in the two groups (Figure 1A). Patients referred to PC were followed for an average of 94 days, range 1-1249 days. We found a statistically significant difference for each GOC in favor of Group 1 compared to Group 2. Patients of Group 1 underwent less aggressive treatment in EOL; none of them was intubated or admitted to ICU in the last month of life. Furthermore, the rate of transfusion or chemotherapy in Group 1 was less than half that of Group 2, as was the number of hospitalization days. Finally, 91.2% of Group 1 patients died at home or in hospice, while 74.7% of Group 2 patients died in a hospital (four of them in the ER [Figure 1B]).

Conclusions. Many patients who died from hematological malignancies received intensive treatment near the EOL. Our data show that this rate is significantly lower when a PC team follows patients. Improved and earlier integration of the PC approach should be a goal of the practice of hematology patients with malignancy.

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MULTIFACTORIAL EVALUATION OF SEXUALITY ALTERATIONS IN PATIENTS TREATED FOR LYMPHOMA

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Introduction. The WHO establishes sexual and reproductive health as an integral part of a person's psycho-physical health. Few studies show the existence of sexual disorders in the 10-65% of lymphoma patients but the methodological approach is often non homogeneous. Sexuality changes in lymphoma patients are not typically considered in the QoL assessment.

Aim. The aim of the present study was to analyze the sexual sphere in the context of QoL assessment in lymphoma survivors and possible advantages of rehabilitation on the subject within survivorship follow-up programs.

Methods. This is a single-center, prospective observational study. Patients diagnosed with HL, DLBCL, PMBCL and FL were enrolled from 1 to 10 years after lymphoma treatment. Patients answered a series of self-administered questionnaires: SF-12, HADs, DAS and EORTC SHQ-C22. The study was approved by the local EC.

Results. Sixty-five patients were enrolled from January 2022 till April 2023 during follow-up visits. The median age was 39.5 years (range, 19-70 years), with a slight male predominance - 41 men (63%) and 24 women (37%). The 39% pts were in remission from 1 to 3 years *vs* 61% from 3 to 10 years. Out of enrolled patients, 36 (60%) had a diagnosis of HL, 15 (25%) of DLBCL, 5 (8%) of PMBCL and 4 (7%) of FL. Stage III-IV disease were present in 58% of patients. With respect to physical activity, 61% of patients were physically active (full or partially). Presence of partner was commonly reported by all survivors (88% woman and 94% men). To what regards sexual well-being, 83% of patients reported as quite a bit/very much important having an active sexual life; 16% of patients has had quite a bit/very much decrease in libido. Sexual satisfaction rates were 37.84 (SD 22,7, range 0-100), Sexual Pain was quite low 8.01 (SD 19,1, range 0-100). Dyspareunia was registered in 38% of the female population and in none of men. Interestingly, all patients have not been satisfied regarding communication on sexual issues

with health professionals. The correlation with psychological and QoL features is ongoing.

Conclusions. Our analyses show that sexual alterations could emerge after lymphoma treatments and probably affect QoL. Unsatisfaction on communication with health professionals on sexual issues confirm that counseling is an important consideration due to young age and high cure rate of patients with lymphoma. Multi-disciplinarity might be the best approach for the most comprehensive care.

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SUBCUTANEUS DARATUMUMAB AT HOME IS A SAFE AND EFFECTIVE PROCEDURE FOR FRAIL PATIENTS WITH MULTIPLE MYELOMA

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Background. Treatment of multiple myeloma (MM) is often difficult due to patient (pts) frailty, bone lesions/fractures that can hinder transport or long distance from the hospital. The availability in the Viterbo province of a Domiciliary Hematologic Care Unit (DHCU) allowed to overcome these difficulties: herein, the experience in 14 patients with MM treated as outpatients [9 at home (HC) and 5 in a long term residential accomodation (LTRA)] with subcutaneous (sc) daratumumab (dara) is reported.

Table 1. Main clinical features at dara start.

Number of pts	14		
Median Age, years (range)	69 (58 – 84)	Reason for home treatment, n° (%)	Long distance and/or social condition 4 (27) Illness 7 (50) Age > 80 yrs 3 (23)
Gender (M/F)	7/7		
Type of MM, n° (%)	IgG(K) 5 (37) IgG(λ) 2 (14) IgA(K) 1 (7) IgA(λ) 2 (14) LC (K) 2 (14) LC (λ) 2 (14)	Treatment schedule, n° (%)	DRD 6 (43) D-VTD 4 (27) D-d 1 (7) D-VD 1 (7) D-VMP 2 (14)
		Phase of disease, n° (%)	1st line treatment 6 (43) 2nd line 7 (50) >2nd line 1 (7)

Patients and Methods. The main clinical features of pts are shown in the Table 1. The initial 2 dara administrations, either intravenous or sc, were given in hospital to prevent side effects, while subsequent administrations were done as outpatients: the first dara administration as outpatient was done by nurse and physician, while subsequent ones by nurse only.

Results. Different reasons for outpatient management were: advanced age (> 80 yrs) in 3 pts, illness related symptoms in 7 pts, social conditions and/or long distance in 4 pts. Distance from DHCU to pts home was < 20 Km in 4 cases (29%), ≥ 20 < 40 Km in 9 (64%) and ≥40 Km in 1 (7%). Different lines of treatment and different schemes are reported in the Table: among 6 pts treated in 1st line, 3 were transplant eligible and 3 transplant ineligible. On the whole, 87 administrations of sc-dara were performed as outpatient: no adverse event was observed during and immediately after the administration. Main adverse events during domiciliary treatment were infections (pneumonia in 4 pts, sepsis in 2, cystitis in 1) and deep vein thrombosis in 1 pts. Moreover, 4/5 patients (80%) in LTRA had infections and 2 of them died compared to 3/9 pts (33%) in HC with only 1 related death. Two pts were not yet evaluable for response: among the evaluable 12 pts, 1 achieved a stringent complete remission and 4 a very good partial remission, with an overall response rate of 42%, 5 pts had a stable disease and 2 pts a disease progression. At the last follow-up, 7 pts are alive (1 waiting for transplant procedure) and 7 pts died (3 from disease progression, 3 from infective complications and 1 from heart disease).

Conclusions. Treatment at home with sc-dara in frail pts with MM is feasible and safe with improved quality of life, making possible a curative approach also in subjects otherwise excluded by best available therapies or forced to long periods of hospitalization.

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DISTRESS AND PSYCHOLOGICAL IMPACT OF THE EVENT IN PATIENTS WITH NEWLY DIAGNOSED ACUTE LEUKEMIA AND LYMPHOMA. WHICH RISK AND PROTECTIVE FACTORS?

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Introduction. The diagnosis of cancer, antineoplastic treatments and related side effects are stressful and potentially traumatic events for cancer patients. The disease represents a threat of death, can be associated with serious physical injury and evokes psychological reactions such as intrusiveness, avoidance or hyperarousal. Post-traumatic stress symptoms can be more common in patients with acute disease onset, such as hematological malignancies.

Table 1.

	N	%
Gender		
Female	17	40,48
Male	25	59,52
Age		
< 25	5	11,90
25-39	10	23,81
40-55	9	21,43
> 55	18	42,86
Marital status		
Single	6	14,29
Stable relation	33	78,57
Other	3	7,14
Children		
With children	26	61,90
With minor children	10	23,81
Instruction		
Primary School	12	28,57
High School	20	47,62
Degree	10	23,81
Employment		
Unemployed	3	7,14
Employed	27	64,29
Retired	10	23,81
Student	2	4,76

In our study, we aimed to detect the presence of post-traumatic stress symptoms (PTSS) and distress in patients with newly diagnosed acute leukemia (AL) or lymphoma and identify risk and protective factors related to PTSS throughout the treatment course.

Methods. Pts aged 18-70 receiving diagnosis of AL or lymphoma are asked to fill in a multi-point anonymous questionnaire including: a socio-demographic and perceived support questionnaire, the Impact of Event Scale–Revised, the NCCN Distress Thermometer and Problem List. In the second part of the study questionnaires are reproposed at different time-points in order to evaluate the evolution or the onset of distress or PTSS during the period of cancer treatment and follow up.

Results. Here we report the early results of the analysis on 42 consecutive patients who agreed to participate the study and filled in the questionnaire at the time of cancer diagnosis. Five patients were diagnosed with ALL, 17 with AML, 3 with APL, 4 with HL, 13 with NHL (Table 1 for demographics). High level of satisfaction about physician-patient communication was noted. Distress ≥ 5 was present in 63,1% of the sample. The most reported emotional problems were: worries (70% of the sample), fears (43%), sadness (36%). With regard to physical problems, 43% of the sample reported fatigue and 36% sleep problems. The psychological impact of the disease, measured using the IES-R scale, revealed an average total score of 23,9. Of the participants, 36,6% reached a total IES-R score > 32 (9,8% moderate and 26,8% severe). Avoidance and intrusion subscales achieved higher partial scores (8,5% and 9%, respectively) than the hyperarousal subscale (6,5%).

Conclusions. It is important that psychological issues are detected in order to implement appropriate short and long-term health policies in cancer patients. Early identification of patients at increased risk of developing distress and PTSS enables activation of specialized psychological and psychiatric support.

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DRUG DEPRESCRIPTION AND END-OF-LIFE MANAGEMENT IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

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Patients with haematologic neoplasms are entrusted to Palliative Care Services (PCS) in a less percentage compared to patients with solid tumours and in a more advanced stage of disease. There are many reasons: the unpredictability of the trajectory of the disease, the big number of therapies, that often can give real opportunities of healing, but also the reticence of the Haematologists to stop treatments.

In our Hospice, dedicated to the care of cancer patients only, in the first 27 months of opening, among 289 patients 34 had an haematologic tumour. The percentage 11,7% is higher if compared with other hospices. Among these 21 were men and 13 women. The mean age was 75,9 ys (range 53 to 100). Considering the pathologies:

- 11 Myeloid Acute Leukemia
- 10 non-Hodgkin Lymphoma (4 with encephalic involvement)
- 8 Multiple Myeloma
- 2 Lymphatic Acute Leukemia
- 1 Hodgkin Lymphoma
- 1 Polycythemia
- 1 Lymphatic Chronic Leukemia

Many of our patients had important comorbidities expecially involving cardiovascular system; all those affected by Multiple Myeloma had renal compromission of different level; 1 had a cardiac amyloidosis.

Considering the provenience:

- 20 came from Haematologic Divisions
- 10 from other hospital wards (General Medicine, Nephrology, Oncology and Geriatrics)
- 4 from house sent by Home Palliative Care Services.

The mean days of hospitalization was 13,8 days (range 1 to 59); for 7 patients less than 3 days (about 20%).

Altough all the patients with Acute Leukemia presented severe pancytopenia only 2 of them was supported with blood transfusions and none with platelet transfusions. 11 of them were support with blood substitutes (iron and folic acid) and 4 with antifibrinolytic acid and vitamin K to control the bleeding. Only 5 patients continue the antibiotic treatment already present at the admission. Asthenia and fever, the most frequent symptoms, were well controlled with steroid therapy. 5 of 34 patients (14,7%) could come back home; 2 of them returned in Hospice at the end of life.

29 patients died (85%); for 18 (62%) a terminal palliative sedation was necessary, included the 4 with encephalic involvement.

Our experience reflects what literature reports:

1) patients with haematologic tumours have access to PCS only if age or comordities exclude a treatment
2) the high percentage of patients dying into 3 days confirm that they are entrusted to PCS only in the end of life
3) it's possible to do a drug deprescription avoiding unnecessary therapies.

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A NATIONAL BASED REAL-WORLD GIMEMA STUDY ON HEALTH-RELATED QUALITY OF LIFE OF PATIENTS WITH LYMPHOMA TREATED WITH CAR T-CELL THERAPY

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Background. Real-world data (RWD) are critical to better understand the health-related quality of life (HRQoL) impact of novel therapies on patients with hematologic malignancies. However, activation of multicenter real-world studies may face several administrative and implementation challenges.

Objective. We aimed to document the setting-up and implementation of a large national-based real-world study by the GIMEMA in collaboration with the SIE, to assess HRQoL in adult patients with aggressive B cell NHL treated with CAR T-cell therapy.

Methods. All centers participating in an ongoing SIE observational study on patients with aggressive B cell NHL treated with CAR T-cell therapy were invited to join a new HRQoL study. The GIMEMA coordinated start-up study activation procedures. The protocol was written involving key Investigators of the companion SIE

clinical study protocol to ensure alignment on the inclusion of complementary objectives of the two studies. The target accrual is 150 patients and follow-up is planned for two years. Patients can complete HRQoL assessment either in a standard paper-copy format, or via-web to maximize data capture. HRQoL is evaluated at the following timepoints: just before CAR T-cell infusion, at day +10 and 1st, 3rd, 6th, 9th, 12th, 18th and at 24th month. The following validated HRQoL questionnaires are used: EORTC QLQ-C30, EORTC QLQ-NHL-HG29, PROMIS Fatigue, PROMIS Cognitive Function, PROMIS Ability to Participate in Social Roles and Activities.

Results. The study protocol was finalized in December 2021. Of the 18 initially invited Italian centers, 15 accepted to participate. Mean time for obtaining all ethical committee approval and hospital authorization was 5 months. Out of the 11 centers open to enrollment, 10 have enrolled at least 1 patient. The first patient was enrolled in June 2022 and, as of April 2023, we have a total of 50 patients enrolled in this study, with a median age of 59 years (range: 28 - 77), of whom 67%, and 33%, males and females, respectively. Compliance with HRQoL assessment is optimal regardless of mode of administration. Initial HRQoL results will be available soon.

Conclusions. Substantial administrative and logistic efforts are needed for the conduct of large HRQoL real-world studies. However, RWD generated from this GIMEMA-SIE project will provide unprecedented insights on the value of CAR T-cell therapy from the patients' standpoint.

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REAL-WORLD OBSERVATIONAL STUDY OF MOGAMULIZUMAB IN ADULT PATIENTS WITH MYCOSIS FUNGOIDES AND SÉZARY SYNDROME (PROSPER)

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Objectives. Mycosis fungoides (MF) and Sézary syndrome (SS) are cutaneous T-cell lymphomas associated with a wide range of symptoms, including severe pruritis and other morbidities. In the phase 3 MAVORIC trial (NCT01728805), mogamulizumab, a first-in-class defucosylated humanized IgG1-kappa monoclonal antibody that selectively binds to C-C chemokine receptor 4, significantly improved progression-free survival compared to vorinostat in patients with relapsed or refractory MF or SS and health-related quality of life (HRQoL). The objectives of the PROSPER study (NCT05455931) are to evaluate patient-reported changes in key patient-report symptoms of disease, fatigue, and HRQoL following initiation of mogamulizumab treatment. Changes in caregiver HRQoL, real-world treatment patterns will also be assessed.

Methods. PROSPER is an international, observational, prospective, mixed methods multi-centre study recruiting 80 patients aged ≥18 years with a confirmed diagnosis of MF or SS who are scheduled to start mogamulizumab. Up to 25 primary caregivers of patients will also be invited to participate. All patients will complete a bespoke symptom diary as well as the Brief Fatigue Inventory (BFI) and MF/SS CTCL QoL questionnaires, with voluntary participation in one-on-one interviews and photographs of significant lesions prior to mogamulizumab initiation and at regular intervals throughout the study for a follow-up period of up to 50 weeks. Patient medical data will be entered into an electronic data capture system. Caregivers will complete the CareGiver Oncology Quality of Life questionnaire (CarGoQoL). The study period is from November 2022 to end of 2024.

Results. As a trial-in-progress, data are not yet available. In Italy, it was scheduled to open 6 centers. Patient enrollment is ongoing.

Conclusions. The PROSPER study will provide novel patient insights into the impact of mogamulizumab treatment on symptoms and HRQoL of patients with MF and SS as well as their caregivers in the real-world clinical practice setting.

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NARRATIVE-BASED MEDICINE ASSESSMENT DURING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: A TOOL TO PROMOTE PSYCHOLOGICAL HEALTH?

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Psychological impact of allogeneic hematopoietic stem cell transplantation (allo-HSCT) can cause prolonged psychological distress. Therefore, psychological assessment and interventions have a high priority in preventing psychosomatic implications related to allo-HSCT. Narrative-based medicine (NBM) approach offers an opportunity for deeper understanding of the patient's emotions and psychological dynamics and can help guide interventions to promote psychological health. Patients undergoing allo-HSCT from July 2020 to July 2022 in our Unit were recruited. Psychological interview was carried out at least 3 times a week and was accompanied by collage technique on the disease and writing sessions, spaced one week apart. A final follow-up interview 3 months after the last writing session was held. Each writing session focused on a specific transplant phase (before, during and after hospitalization) and the associated feelings. Patients with severe psychiatric comorbidities were excluded. A preliminary analysis of these narratives shows that there is not a unique behavioural pattern, thus determining a personalized approach with every patient. The moment of hospitalization marks the transition to an environment where time seems to stop abruptly. Hospital room is a "place full of emotions, encounters, disappointments, efforts, hopes and dreams", where there is "absence of time and air", but also "a place devoid of space, where the windows are small and sealed and the day to day is locked outside the door". The beginning of conditioning therapy marks the relief from anxieties and second thoughts, but it is also the moment when "the train has already left the station". Narrative analyses show that the most frequently used words are "isolation" and "loneliness". Patients in their narratives describe the allo-HSCT as a "lack of protection/safety since the main substances of the organism will be provided by another person outside of themselves". This metamorphosis impacts not only hematopoiesis changings but also psychological behavior with patients reporting "modifications in their physical, cognitive, sexual, and interpersonal functioning". A high level of expectations prior to allo-HSCT was associated with high psychological distress. NBM approach represents a valid tool to explore the subjective experience of patients undergoing allo-HSCT and may help in interpreting patients' emotions, feelings and reactions during the different phases of this difficult path.

Hemostasis, thrombosis, thrombocytopenia and platelet diseases

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REAL-LIFE DATA ON THE MANAGEMENT OF BLEEDING COMPLICATIONS IN PATIENTS WITH MYELODYSPLASTIC SYNDROME AND SEVERE THROMBOCYTOPENIA

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Myelodysplastic syndromes (MDS) are hematological malignancies characterized by unilineage/multilineage cytopenia(s), often treated with hypomethylating agents (HMA). Persistently low platelet (PLT) counts are a common manifestation of MDS and they can lead to an increased bleeding risk, moreover HMA may induce or worsen thrombocytopenia, thus requiring more platelet transfusions with a secondary risk of refractoriness over time. This retrospective, observational study on patients affected by MDS describes the clinical manifestations of persistent thrombocytopenia, in terms of hemorrhagic complications, morbidity and mortality related to bleeding and their management.

Table 1.

Table.1: Bleeding symptoms of patients with MDS and thrombocytopenia

RISK	
IPSS-R very low risk	1.5%
IPSS-R low risk	62.5%
IPSS-R high risk	19%
IPSS-R very high risk	17%
On treatment (HMA)	32.5%
TYPE OF DYSPLASIA	
Unilinear dysplasia (PLT)	35%
Multilinear dysplasia	65%
PLT	
Mean PLT at diagnosis of MDS (cells/microL)	60000
Mean PLT at PLT nadir (cells/microL)	34000
Hospitalization due to MDS	52% (21)
Dead at the time of data collection	60% (24)
Deaths related to hemorrhages	8% (2)
Positive bleeding history	35% (14)
TYPE OF BLEEDING	
Mucosal bleeding	43% (6)
Skin bleeding	57% (8)
Organ bleeding	14% (2)
THERAPY	
Therapy not needed	29% (4)
Tranexamic acid (local)	21% (3)
Tranexamic acid (systemic)	36% (5)
Surgery	14% (2)
TPO-RAs	7% (1)

Legend: Percentages refers to the total cohort (40 patients).

The study included 60 consecutive patients (M:F ratio 1.7:1, median age 76.5 years, range 55-92), diagnosed with MDS and thrombocytopenia (PLT < 50000/μL) in the last ten years (between December 2012 and December 2022) at our Hematology Unit. Informed consent was signed by each participant, the study was approved by the IRB of the University Hospital "P, Giaccone". The patient sample did not include 5q- MDS. The following data were collected and analyzed: MDS staging according to International Prognostic Staging System, median PLT count at diagnosis, median PLT nadir, exposure to HMA, occurrence of bleeding events, management of bleeding, administration of thrombopoietin receptor agonists (TPO-RAs), transfusion requirements, hospitalization. MDS staging, characteristics and management of bleeding of the analyzed cohort are reported in Table 1.

All the enrolled patients had a personal negative bleeding history before the diagnosis of MDS. Our results show a relative low morbidity and mortality directly related to thrombocytopenia in MDS. We found that petechiae and sub-cutaneous hematomas were the most common bleeding manifestations, followed by mucosal bleeding, organ and life-threatening bleedings were the rarest. Tranexamic acid was the most employed anti-hemorragic therapy. Surgery was reserved to severe bleeding, occurred in 2 cases. Severe thrombocytopenia in MDS is a challenging scenario due to the lack of effective specific therapeutic options. The current analysis shows that different therapeutic options, with either symptom controlling or curative intent, including TPO-RAS in low risk MDS, are adopted in common clinical practice to face bleeding in patients affected by MDS, robust evidences on a common and shared approach of bleeding in patients affected by MDS are still lacking.

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SIX CASES OF INTRCRANIAL HEMORRHAGE IN PATIENTS WITH FLT3-AML TREATED WITH GILTERITINB

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We retrospectivelly collected five cases of intracranial hemorrhage (ICH) in patients with Acute myeloid leukemia (AML) who received gilteritinib, a FLT3-inhibitor drug approved for relapsed or refractory FLT3-mutated AML. FLT3 mutations are present in 25-30% of AML patients and activate the PI3K and RAS pathways, leading to cell proliferation and inhibiting apoptosis. The ADMIRAL study showed that gilteritinib extended overall survival in patients compared to those receiving chemotherapy. However, the drug has been associated with adverse events such as febrile neutropenia, anemia, and thrombocytopenia. A post-marketing surveillance program study showed that 9.3% of patients had hemorrhagic complications, with 7% of patients experiencing grade ≥3 bleeding events. One patient had an intracranial hemorrhage after exposure to a subtherapeutic dose of gilteritinib during the phase I/II trial, but ICH was never reported neither in real-world studies. However, we described clinical histories of six patients from three Italian Institutions who developed ICH shortly after receiving gilteritinib. In the 3 centers a total of 25 patients had been treated with gilteritinib, in the last two years. The ICHs occurred within days to weeks of starting gilteritinib, and in most cases, the patients had normal conventional coagulation tests and PLTs before the start of the treatment. Two of the six patients died of ICHs and its complications, four had full recovery without neurological sequelae. Three ICH were subdural, two of the brain's parenchima and one of both (The Patients' characteristics are summarized in the TABLE). Even if the mechanism of action that could explain ICH is mainly unknown, we speculated that the occurrence of ICH may indicate a possible adverse event associated with gilter-

itinib therapy, and physicians should monitor patients carefully for signs of bleeding, even in the absence of coagulation abnormalities. We also highlight the need for further studies to determine the exact incidence and risk factors for ICH in patients receiving FLT3-inhibitors.

Table 1.

	Age	Sex	Genetics	1st line therapy	2nd line therapy	Day of ICH	Site	Outcome
#1	51	M	NPM1+ FLT3TKD	3+7+mido		10	Subdural	Recover
#2	67	M	Rel FLT3-TKD	2+5	Aza/ven	19	Subdural	Recover
#3	29	F	FLT-ITD low	7+3	Aza/ven	12	Parenchymal	Death
#4	67	M	IDH1, Rel FLT3-ITD	Deci/ven		40	Parenchymal	Death
#5	37	F	Rel FLT3-ITD low	CPX-351	Allo-SCT	14	Parenchymal	Recover
#6	78	F	NPM1+ FLT3TKD	Aza		12	Subdural	Recover

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ACQUIRED AMEGAKARYOCYTIC THROMBOCYTOPENIA (AAMT) DIAGNOSIS AND TREATMENT: A SINGLE CENTRE EXPERIENCE

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Introduction. Acquired Amegakaryocytic Thrombocytopenia (AAMT) is a rare condition characterized by severe thrombocytopenia, aplastic or hypoplastic megakaryocytic lineage, and preserved erythroid and granular lineage. The pathophysiology is poorly understood, so there is no consensus on therapy. Approaches usually adopted for Aplastic Anemia (AA) have shown promising results; recently Thrombopoietin receptor agonists (TPO-RAs) have been proposed.

Methods. We describe 4 cases of AAMT diagnosed in our Centre between 2017 and 2022. For each patient (pt), data on treatment and response according to immune thrombocytopenia (ITP) guidelines were collected.

Results. 3/4 of pts showed platelet count below $20x10^9$/L and bruising, while all of them have anemia, normal absolute neutrophilic count, and no history of autoimmunity. Bone Marrow (BM) evaluation showed reduced cellularity only in 2/4. Paroxysmal Nocturnal Hemoglobinuria (PNH) clone was significant only in pt#2. NGS analysis was performed in all pts at different time points. Interestingly, pt#1 showed JAK2 CNV with deletion of exons 7-13; pt#2 showed U2AF1 mutation. Complete characterization is shown in Table 1. Pt#2 and pt#4 were first treated with steroids because of misdiagnosed ITP, without response. Then they were treated with Cyclosporin A (CyA) and achieved Response (R) or Complete Response (CR). Pt#1 and pt#3 received CyA as first-line, but only pt#1 achieved R. For the 3 pts who responded to CyA, the median Time To Response (TTR) was 3 months (range 1-20), but all of them developed intolerance. All pts received TPO-RA Eltrombopag as second or further-line therapy. Pt#3 and pt#4 achieved at least R, and the median TTR was 2.5 months (range 1-4). Pt#1 and #2 were no responders, so CyA was reintroduced as rescue therapy. Only pt#3 showed increased BM cellularity during TPO-RA treatment. Pt#2 showed stable BM cellularity with dysplastic signs of new onset. Pt#1 and #4 showed a decrease in BM cellularity during treatment.

Conclusions. Two different mechanisms may explain our limited cohort's lack of response to TPO-ARs. In pt#1, the deletion of JAK2 involving FERM and SH2 domains likely alters the binding of JAK2 to TPO-R, resulting in the lack of TPO response, and in pt#2, the U2AF1 mutation, which suggests a transition toward Myelodysplastic Neoplasm. Our data highlight the need for a careful differential diagnosis and the integration of new techniques for choosing the most appropriate therapy for AAMT.

Table 1. Patients' characteristics. Dx= diagnosis, PLT= platelets, Hb= hemoglobin, ANC= absolute neutrophilic count, BM= bone marrow, PNH= Paroxysmal Nocturnal Hemoglobinuria, CG= cytogenetic, FISH= Fluorescent in situ hybridization, NGS= Next. Generation Sequencing, TTR= Time To Response, FU= Follow Up; F= female, M= male, MK= megakaryocytic, CNV= Copy Number Variation, mo/s= month/s, AA= Aplastic Anemia. CyA= Cyclosporin A, TPO-AR= Thrombopoietin receptor agonist (Eltrombopag), PDN= Prednisone. Type of response according to ITP guidelines: R (Response), CR (Complete Response), NR (No Response). * (A)= pathogenic mutation ** (B)= probably pathogenic mutation.

							Erythroid normal Granulocitic normal		(del ex 7-14)			Iso-Ab	TPO-AR 50-150 mg/die Danazol + PDN CyA 2 mg/Kg + TPO-AR 150 mg/die + PDN (tapering to stop)	NR (14 mos) NR (6 mos) R (6 mos)	NA NA 4 mos				[April 2023]
M	27/02/19	47	1	110	3.0	60%	MK absent Erythroid hypoplastic Granulocitic hyperplastic	10%	46, XY	U2AF1 (A)** CSF3R (B)**	Neg	Neg	Neg	PDN 1 mg/Kg CyA 2 mg/Kg CyA (tapering) + TPO-AR 50-150 mg/die CyA 2 mg/Kg	NR (1 mos) CR (46 mos) NR (3 mos) R (1 mos)	NA R: 1 mo CR: 2 mos NA R: 1 mo	60%	MK hypoplastic/displastic Erythroid normal Granulocitic hyperplastic	R [April 2023]
M	27/04/20	73	12	100	2.0	20%	MK reduced Erythroid hyperplastic/distrofic Reactive T-Lyphoid infiltrate	0.1%	46, XY	TET2 (B)**	Neg	Neg	Neg	PDN 1 mg/Kg + CSA 4 mg/Kg TPO-RA 50-100 mg/die	NR (6 mos) CR (29 mos)	NA R: 4 mos CR: 12 mos	30%	MK minimally reduced Erythroid hyperplastic Granulocitic normal	CR [March 2023]
F	19/10/21	26	18	70	1.3	60%	MK hypoplasia Erythroid hyperplastic/distrofic	0.9%	46, XX	Neg	Neg	Neg	Auto-Ab (low signal)	PDN 1 mg/kg CyA 5 mg/Kg CyA 5 mg/Kg (tapering to stop) + TPO-RA 50-150 mg/die	NR (1 mos) R (5 mos) R (10 mos)	NA R: 3 mos R: 1 mos	15%	MK hypoplastic Erythroid hyperplastic Granulocitic reduced	R - Exekatio to AAT [April 2023]

ab1: Patients' characteristics. Dx= diagnosis, PLT= platelets, Hb= hemoglobin, ANC= absolute neutrophilic count, BM= bone marrow, PNH= Paroxysmal Nocturnal Hemoglobinuria, CG= cytogenetic, FISH= Fluorescent in situ hybridization, NGS= Next. Generation Sequencing, TTR= Time To Response, FU= Follow Up; F= female, M= male, MK= megakaryocytic, CNV= Copy Number Variation, mo/s= month/s, AA= Aplastic Anemia. cA= Cyclosporin A, TPO-AR= Thrombopoietin receptor agonist (Eltrombopag), PDN= Prednisone.

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IDIOPATHIC THROMBOCYTOPENIC PURPURA AND PREGNANCY: MONOCENTRIC REAL LIFE COMPARISON BETWEEN CHRONICALLY TREATED PATIENTS AND NOT

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Backgroud. Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease; TPO receptor agonists (TPOras) treatment allows pts reaching platelet(plt) count stability. In pts searching for pregnancy,therapy is a challenge due to limited choices: TPOras aren't recommended due to risk of placenta crossing so,at the start of pregnancy,discontinuation is recommended with consequent flare-up risk. Though case reports on their use during pregnancy are found in literature, follow up time is too short to provide data on long term security.

Aims. Evaluate any differences in plt mean value and in ITP flare-up over trimesters and delivery time between patients who stopped chronic therapy and those not in active treatment.

Materials and Methods. Our cohort consisted of 23 women diagnosed with ITP: median plt count (mpc) at diagnosis was 50.000(1-100), median age at the start of pregnancy was 31 yo(24-40).Before pregnancy mpc was 80.000 (200-18). 10 pts were in their second pregnancy and 8 already experienced ITP in a previous uncomplicated pregnancy. Out of total 3 pts were in active treatment at conception time, 11 pts were in therapy before, 9 pts never required therapy; ongoing treatment was with TPOras (1 romiplostim, 2 eltrombopag) thus stopped and shifted to steroid.We divided pts in 2 groups: GROUP1(3pts) in active therapy at conception time; GROUP2(20pts) all others. Data set was closed on April23.

Results. Mpc through trimesters are listed in table1; we didn't experience any statistically significant variation between groups in any of the trimesters, respectively: p(I)=0.079, p(II)=0.0721, p(III) =0.0279. Out of total 7 pts (16%) had ITP flare up necessitating res-

cue therapy in gestation time: just 2 of them were in group 1; no statistical difference was seen between groups in flare up outbreak(p= 0.138). To experience delivery in security 12 pts (52%) needed a short-term low dose steroid treatment, among them 2 pts (9%) required rescue therapy: both didn't need any therapy before.A 65%(15) of pts reached delivery time with a safe plt level (>70.000) with 11(60%) not requiring any treatment.

Conclusions. Our limited data didn't show any significant difference in flareup incidence and in mpc variation regardless of concomitant therapy: this is in line with literature findings that shows ITP biology is not noticeably modified by pregnancy. Anyway, to face peripartum procedures in security, on demand treatment must be available: in our group low dose steroid proved its efficacy and safety.

Table 1.

Median Platelet count through trimesters

	I trimester	II trimester	III trimester
Median Platelet Count in Group1	84 (353-45)	125 (72-136)	51 (38-64)
Median Platelet Count in Group2	80 (162-40)	80 (1-397)	82 (23-397)

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SURGERY AND PROPHYLAXIS WITH SUSOCTOCOG-ALFA IN ACQUIRED HEMOPHILIA: A CASE SERIES

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Background. Acquired hemophilia A (AHA) is a rare bleeding disease due to autoantibodies against clotting factor VIII (FVIII). It is frequently caused by underlying conditions such as systemic rheumatic disease, malignancy, drugs or postpartum. Treatment consists of inhibitor eradication with immunosuppressive therapy (IST) and prompt bleeding control with bypassing agents (BPA) or recombinant porcine factor VIII (rpFVIII). The latter has recently been licensed for management of acute bleeding in AHA. Unlike BPA, the hemostatic effect of rpFVIII can effectively be monitored without risk of overtreatment. This advantage is important in patients with high thrombotic risk or those who undergo surgery. However, in patients with high haemorrhagic risk, after resolution of acute bleeding, prophylaxis with rpFVIII is reasonable. Here, we report three cases in whom rpFVIII was used with an unconventional schedule despite the presence of rpFVIII inhibitors.

Case 1. A 70-year-old woman with myasthenia gravis and Hashimoto thyroiditis was hospitalized for upper right limb hematoma. She was initially treated with steroids, and then with cyclophosphamide. During hospitalization she underwent surgery for diverticular perforation while on recombinant factor VIIa (rFVIIa). In the post-operative period, given her elevated rFVIIa dependency, rpFVIII was administered without complications.

Case 2. A 79-year-old man with a history of stomach carcinoma, suspected urothelial neoplasia and polymyalgia rheumatica presented with haematuria and diffuse hematomas. He was treated with rFVIIa. However, given the inadequate response, rFVIIa was replaced with rpFVIII. He underwent ureteroscopy with biopsy and laser ablation in the nearby neoplastic lesion while on rpFVIII coverage without complications. In the meanwhile, he received four lines of IST for persistently high inhibitor titres.

Case 3. A 31-year-old woman was admitted for anemia and lower right limb hematoma 60 days after delivery.

rFVIIa and steroids were started with immediate response. She was discharged 8 days later. However, she was readmitted 5 days later for new onset of bleeding. rFVIIa was replaced with rpFVIII, continued as outpatient at prophylactic dosage. She had no AHA relapse.

Conclusions. rpFVIII demonstrates safety and efficacy both in the presence of rpFVIII inhibitors and in unconventional settings. Outpatient management represents a favourable cost-efficacy alternative for patients with high risk of re-bleeding.

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EFFECTIVENESS AND SAFETY OF ELIGLUSTAT TREATMENT IN GAUCHER DISEASE: REAL-LIFE UNICENTRIC EXPERIENCE

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Introduction. The therapy and management of Gaucher's disease (GD) has radically changed with the use of substrate reduction therapy (SRT), of which eliglustat is the most widely known drug, allowing it to overcome what used to be the limits of replacement therapy. The rarity of GD and the still limited use of eliglustat requires adequate studying of the strengths and weaknesses of this drug.

Aim and study design. This retrospective unicentric study included 12 (6 males and 6 females) adults affected by GD and treated for at least 12 months with eliglustat in our Center between 2019 and 2022. Our aim was to evaluate the differences in terms of serological tests, blood count, and feature primary characteristics of GD after one year of treatment. We assessed the ratios between the values at the start of eliglustat treatment (T0) and the follow-up (T1) to consider the reduction in Gaucher disease markers. We evaluated possible differences by dividing the patients based on age (median threshold of 53 years), sex, and previous enzyme replacement therapy (ERT).

Results. The differences in hemoglobin (p=0.451) and platelets (p=0.128) value were not statistically significant. We reported a reduction in ferritin values (340 *vs* 259 ng/mL, p=0.043), while the results concerning transferrin saturation, creatinine, ALT/AST, and total cholesterol (all with p>0.6) did not. Moreover, a significant reduction in chitotriosidase (394.3 *vs* 181.1 nmol/h/mL, p=0.027) and Lyso-Gb1 (45.1 *vs* 18.9 ng/mL, p<0.001) compared to baseline was noted, confirming the efficacy of eliglustat therapy. Considering the ratios between T1 and T0, the median reduction was 41% for chitotriosidase (albeit with an increase reported in two cases - 19% and 87%) and 45% for lyso-Gb1. Dividing patients according to age, sex, and experience of previous therapies, we found that, considering chitotriosidase (median reduction of 41%), patients <53 years have a higher rate reduction (73% *vs* 18%) compared to baseline (p=0.002). The same values were not found for the other variables (sex and number of previous treatment lines) and for lysoGb1, where all patients experienced a significant reduction, despite prior ERT. All data are reported in Table 1. No adverse events were reported.

Conclusions. Despite the critical limitations of our report due to the small cohort, these data confirmed how eliglustat could significantly improve the outcome of patients suffering from GD, also in patients treated with ERT.

Table 1.

Median Platelet count through trimesters

	I trimester	II trimester	III trimester
Median Platelet Count in Group1	84 (353-45)	125 (72-136)	51 (38-64)
Median Platelet Count in Group2	80 (162-40)	80 (1-397)	82 (23-397)

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CYCLIC THROMBOCYTOPENIA AND IMMUNE THROMBOCYTOPENIA: OUR STRATEGY TO IMPROVE DIFFERENTIAL DIAGNOSIS

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Introduction. Cyclic thrombocytopenia (CTP) is a rare blood disorder where platelet counts fluctuate. Diagnosis requires a long observation period with frequent complete blood cell counts to confirm cyclicity. It may frequently be misdiagnosed as immune thrombocytopenia (ITP) that results in inconsistent or even absent response to therapy. Here we report a case of a woman who, after being unsuccessfully treated for a misdiagnosed ITP for years, was eventually diagnosed with CTP in the light of laboratory data and histology studies.

Case Report. A 51-year-old woman with a previous history of thymoma, presented with petechiae and isolated thrombocytopenia (38.000/uL). In suspicion of ITP, steroids were started and complete response was achieved. The disease soon recurred and a thrombopoietin-receptor agonist (TPOra - Eltrombopag) was started as second line with short-lived benefit. A second TPOra (Romiplostim) was started upon the second recurrence. A peculiar trend of platelet counts which alternated between thrombocytopenia and thrombocytosis in monthly cycles was noticed. This cyclicity persisted despite treatment and only a monthly low dose of TPOra was administered to maintain platelet counts within a safe range. The disease remained refractory and CTP was then considered in the differential diagnosis. To better characterized this platelet disorder, we scheduled 2 bone marrow biopsies 8 weeks apart. The first one, when platelet counts were decreasing, showed a profound isolated megakaryocyte hypoplasia which was not suggestive of ITP. By contrast, the second one, when platelet counts were increasing, showed megakaryocyte hyperplasia with aggregates, remarkably more pronounced than in a typical ITP setting, accompanied by a T-lymphocyte infiltrate. TPO levels, evaluated during 2 monthly cycles, were consistently specular to platelet counts with levels (range: 7-1756 pg/mL) even higher than what usually seen in aplastic anemia. Overall, marrow biopsies and TPO levels ruled out ITP and confirmed CTP. Therapy with Romiplostim was stopped and Cyclosporine plus Avatrombopag were started.

Conclusions. There is still little evidence about the biological characterization of CTP and no consensus on diagnosis and treatment. Various treatments including, among others, Cyclosporine and Danazol have been employed though responses greatly varied, from refractoriness to spontaneous resolution. Reports like ours may help to define a better diagnostic algorithm.

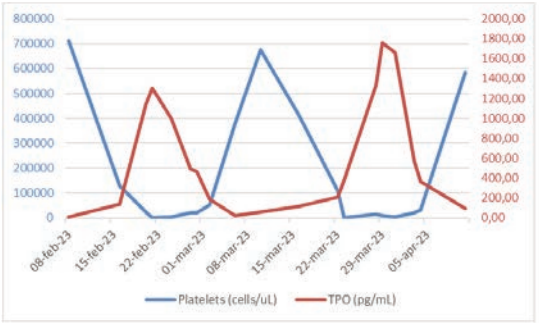

Figure 1. Specular trends of platelets and thrombopoietin along two monthly cycles.

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BEYOND PLATELETS COUNT: IS THERE ANY ROLE FOR THROMBOELASTOMETRY IN EVALUATING THE BLEEDING RISK OF PATIENTS WITH IMMUNE THROMBOCYTOPENIA?

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To date, beyond platelets count there are no standardized methods to assess the bleeding risk to patients with immune thrombocytopenia (ITP). Bleeding tendency can however vary significantly among patients with a similar platelet count and even thrombotic events may occur in spite of severe thrombocytopenia. Thromboelastometry is the only global assay validated to guide clinical decisions, at least in the emergency setting. We here report the preliminary results of an observational prospective study started at our Center in May 2022, with the primary aim to explore the potential role of thromboelastometry (performed by TEG®) in evaluating the hemostatic balance of patients with ITP, at first evaluation and during regular follow-up (6-12 months after the baseline analysis, or earlier in case of new bleeding or thrombosis onset). The study is enrolling all the patients diagnosed with primary ITP and treated at our Centre, patients affected by comorbidities that could contribute to a higher hemorrhagic risk are excluded. TEG analysis is performed to evaluate correlations, if any, between the hemorrhagic phenotype of the enrolled patients and thromboelastometric parameters. Our population consisted of 13 patients (4 males and 9 females of median age 67 years), diagnosed with ITP and currently followed up at our Hemostasis and Thrombosis Unit. The baseline TEG analysis was performed within three months from enrollment, a complete blood cells count and standard coagulation assays were performed on the same day of TEG. At the time of enrollment, 12 patients had chronic ITP and one patient had newly diagnosed ITP. Among the enrolled patients, 11 were on active treatment while 2 were off-therapy. TEG parameters and characteristics of the population are listed in Table 1. Most common TEG alterations were reduction of R-time and maximum amplitude (MA). Follow-up TEG was available only for one patient at the time of the current analysis. This patient's platelet count at the time of TEG was 5000/mi-

croliter, she was treated with fostamatinib and eltrombopag, and the analysis showed a reduction in R-time (8.8 min) and MA (12.6 mm). Our findings indicate a reduction of the latency before the start of clot formation, associated with a reduction in the clot size and its overall strength, this was confirmed also at follow-up TEG. Preliminary results of the ongoing prospective study show a homogenous trend of thromboelastometric alterations in patients affected by ITP.

Table 1. ITP characteristics and thromboelastography profile of the enrolled patients.

Study population (n)	13
Baseline TEG (n)	13
Follow-up TEG (n)	1
Baseline TEG	
Newly diagnosed ITP (n)	1
Chronic ITP (n)	12
Median PLT (cells/microL)	51000 (4000 - 281000)
Under active treatment (n)	11
• Oral prednisone (n)	4
• TPO-RAs (n)	6
• Fostamatinib (n)	1
Normal range TEG parameter	
R-time (mm)	9-27
MA (mm)	44-64
Alpha-angle (degrees)	22-58
Patients with TEG alterations (n)	4 of 13
• **R-time alterations (n)**	3 of 13
• **MA alterations (n)**	4 of 13
• **Alpha-angle alterations (n)**	1 of 13
Mean and std.dev. R-time for all patients (min)	11.2 (2.9) (range: 7.4-16.8)
Mean and std.dev. R-time for patients with alterations (min)	7.6 (0.2) (range: 7.4- 7.8)
Mean and std.dev. MA for all patients (mm)	48.6 (14.7) (range: 17.1- 66.6)
Mean and std.dev. MA for patients with alterations (mm)	36.1 (21.3) (range: 17.1 - 66.6)
Alpha-angle value for all patients (degrees)	39.3 (11) (range: 18.1 - 54.3)
Alpha-angle value for the patient with alterations (degrees)	18.1

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TPO-RA USE FOR THE TREATEMENT OF CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA

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Introduction. Chemotherapy-induced thrombocytopenia (CIT) leads to delay/reduction of cancer treatment, affecting progression-free and overall survival. There are no approved treatments for CIT, it remains an unmet clinical need. Small studies demonstrated that Romiplostim administered before or after chemotherapy is effective in improving platelet counts. A prospective study (J Clin Oncol, 2019) confirmed that thrombopoietin receptor agonists (TPO-Ra) are effective in normalizing CIT. Kuter retrospectively evaluated 173 patients with CIT treated with Romiplostim demonstrating its safety and efficacy in this setting. We describe use of TPO-Ra to achieve platelet counts compatible with standard dose chemotherapy in 3 cancer patients.

Case Reports. 1. A 49 y/o woman with breast cancer diagnosed in 2017 was treated with Docetaxel/Pertuzumab/Trastuzumab followed by surgery, radiotherapy (RT) and maintenance with Pertuzumab/Trastuzumab. Baseline platelet count 180.000/mmc. In 2020, disease recurrence was treated with Trastuzumab; after 4 months, platelet count dropped to lower than 70.000/mmc. 25% dose reduction was instituted and Trastuzumab was schedules every 4 weeks instead of 3. In February 2023, she started Romiplostim 3 mcg/kg and, after 3 weekly doses, platelet counts raised to 100.000/mmc. Up to now, Trastuzumab has been administered at the scheduled dose every 3 weeks with Romiplostim 3 mcg/Kg/week. 2. A 61 y/o woman with pancreatic adenocarcinoma and portal vein thrombosis diagnosed in May 2022 was treated with Capecitabine/Gemcitabine. Baseline platelet count was 171,000/mmc. IV cycle was not administered because platelet count of 77.000/mmc. In December 2022, weekly Romiplostim 1 mcg/Kg was started and after 2 weeks platelet count reached the target level of 100.000/mmc. Full dose chemotherapy and anticoagulant treatment were safely continued. 3. A 69 y/o woman with oropharyngeal carcinoma diagnosed in August 2021 was treated with Cisplatin/5-Fluorouracil. Baseline platelet count was 71.000/mmc because of concomitant liver cirrhosis; after chemotherapy platelet count was 41.000/mmc. In December 2022 RT was considered if a platelet count of at least 70.000/mmc was reached. In January 2023, Lusutrombopag was started at a dose of 3 mg/day for 7 days. Platelet count was 72.000/mmc and remained stable for the entire course of RT.

Conclusions. TPO-Ra is safe and effective to treat CIT. Moreover, it allows to avoid dose reductions of chemo- and radiation therapies.

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ACQUIRED HEMOPHILIA AS EARLY MANIFESTATION OF MALIGNANCIES: A RETROSPECTIVE ANALYSIS FROM A REFERENCE REGIONAL CENTER

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Acquired hemophilia A (AHA) is a rare bleeding disorder caused by autoantibodies (inhibitors) against coagulation factor VIII (FVIII), leading to severe hemorrhages. It is associated in 10-15% of cases with neoplasm and suspected when a patient with cancer or autoimmune disease has bleeding. Causes leading to FVIII inhibitor are unclear. According to available data, cancer resolution leads to inhibitor eradication whereas non-responders to AHA treatment may have advanced or metastatic cancer. We have retrospectively evaluated, after approval by our IRB, 18 cases of AHA, managed at our Center in the last 10 years and we report on 2 cases where AHA occurred early before cancer diagnosis, in one case it relapsed early before cancer relapse (Table 1).

Case 1. In 2013 a 59-year-women presented with subcutaneous haematomas of the legs and was diagnosed with AHA and treated with corticosteroids and activated prothrombin complex concentrate (APCC) until remission. In 2014, IgG lambda monoclonal gammopathy was detected and follow-up was started. In 2015, multiple myeloma (MM) was diagnosed, the patient was treated with borte-

zomib, melphalan and prednisone reaching a complete remission. In 2016, a routinary blood test showed prolonged aPTT, with a high titre of FVIII-inhibitor. In the same year, the patient had a MM relapse, treated with bortezomib and prednisone until complete remission. In 2020 a second relapse of MM was associated with a relapse of AHA and managed with lenalidomide, prednisone and APCC.

Case 2. in 2019, a 68-year-women was admitted to the ER due to spontaneous ecchymoses and leg pain. aPTT was 160 sec. After diagnosis of AHA was made in our Center, steroids and APCC were started. Laboratory tests and imaging ruled out autoimmune disease and cancer. In 2020, the patient experienced an AHA relapse, treated with recombinant activated Factor VII, APCC and anti-CD20. A complete remission was reached. In 2021, a breast lump was found at a mammogram, a biopsy showed an invasive ductal carcinoma. Cancer was treated with quadrantectomy.

These cases, representing a proportion of subjects followed at our Center in the last ten years, show that AHA may be an early manifestation of cancer and highlight the need of regular follow-up in newly diagnosed AHA, not only for the bleeding risks but also for the risk of developing a malignancy. Surveillance for underlying cancer and autoimmunity should be strict because of the subtlety of this clinical presentation.

Table 1.

Characteristics of patients with Acquired haemophilia A (AHA) as early manifestation of cancer

Patients with AHA (Jan 2013 -Jan 2023)	18	
	CASE 1	CASE 2
AGE AT DIAGNOSIS	68	59
COMORBIDITY	none	Hypertension Dyslipidemia Hyperthyroidism
FVIII:C AT DIAGNOSIS	6.3 %	1 %
FVIII-INHIBITOR AT DIAGNOSIS	34.6 U.B./mL	136 U.B./mL
TIME TO INHIBITOR ERADICATION	7 months	1 month
IMMUNOSUPPRESSIVE THERAPY	oral prednisone	cyclophosphamide
BYPASSING THERAPY	APCC	APCC
AGE AT FIRST RELAPSE	70	60
MEAN FVIII:C AT RELAPSES	8.2%	2.2 %
MEAN FVIII-INHIBITOR AT RELAPSES	22.3 U.B./mL	56.7 U.B./mL
MEAN TIME TO INHIBITOR ERADICATION AT RELAPSES	7 months	3 months
IMMUNOSUPPRESSIVE THERAPIES AT RELAPSES	oral prednisone	rituximab
BYPASSING THERAPY AT RELAPSE	APCC	APCC
UNDERLYING CANCER	multiple myeloma	breast cancer
TIME FROM DIAGNOSIS OF AHA TO CANCER	2 years	2 years
NUMBER OF RELAPSES OF AHA	3	1
NUMBER OF RELAPSES OF CANCER	2	0
TREATMENT FOR CANCER	chemotherapy	surgery

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IDIOPATHIC THROMBOCYTOPENIC PURPURA AND AVATROMBOPAG: A REAL-LIFE MONOCENTRIC EXPERIENCE

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Background. The thrombopoietin receptor agonists (TPOra) represent the second line in the management of chronic idiopathic thrombocytopenic purpura (ITP). Avatrombopag is a new member of this group and constitutes a second generation TPOra. The mechanism of action consists in acting on thrombopoietin receptor and stimulating platelet (plt) production, without determining hepatotoxicity or without the necessity of food restrictions. The pivotal phase III study demonstrated its durable and meaningful response in ITP patients (pts) and seems to facilitate the corticosteroid tapering.

Aims. We evaluated the efficacy and safety of avatrombopag in a real-life setting of ITP pts followed in our center.

Materials and Methods. We retrospectively collected data about a monocentric cohort of 11 ITP pts (7 women, 4 men) with a median age of 62 years (24-89) at the time of avatrombopag start. All pts were on chronic ITP phase. The median plt value at the beginning was 36000/μL (1000-146000). To evaluate the response after the start of therapy we collected blood samples every week in the first month and then once a month, from August 2022 to March 2023.

Results. After two weeks of treatment the median plt count in all pts was 307000/μL (22000-632000). Of these, 8 pts (73%) obtained a response defined as a plt counts >50000/μL at the 2-weeks timepoint. Only 1 pts never reached a plt counts >50000/μL. The starting dose of avatrombopag was 20 mg/die, an increasing dose was needed only in two pts (18%). At the 2-weeks timepoint, only 3 pts (27%) were still receiving a concomitant therapy with corticosteroids. The number of past therapies did not have an impact of avatrombopag response, in particular comparing pts who had received more or less than three lines previously (p=0.241). The treatment has been definitely suspended in 3 pts (27%) for different reasons: 2 (18%) failures (no responders) and 1 (9%) for fluctuation of plt values. All these 3 pts have been subjected to splenectomy in their ITP history. Moreover, 1 pts (9%) needed a temporary suspension for thrombocytosis. In 4 pts (36%) the dosage was definitely reduced for plts above 150000/μL in a median time of 9 days (7-20). No adverse events (AEs) were reported.

Conclusions. In our limited case studies, we observed an adequate platelet count and a durable response to avatrombopag, despite the multiple lines of therapy carried out by our cohort of ITP patients. Moreover, the absence of AEs confirms the safety profile of the drug.

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CAPLACIZUMAB-RELATED BLEEDING IN A PATIENT AFFECTED BY THROMBOTIC THROMBOCYTOPENIC PURPURA: A CASE REPORT

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Introduction. Caplacizumab is a monoclonal antibody approved in 2018 as first line treatment for acquired thrombotic thrombocytopenic purpura (aTTP). It prevents the excessive platelet consumption by blocking the Von Willebrand factor (vWF) and allows a faster complete response. Given its mechanism of action, the principal adverse event is an increased bleeding risk though mostly mild. Nevertheless, some life-threatening bleedings have been described, but the best treatment strategy for such cases is still uncertain. Here, we report a case of abdominal bleeding during Caplacizumab and how we managed it.

Case Report. In September 2021, we admitted a 58-year-old man with newly diagnosed aTTP. The patient presented with an upper limb motor clumsiness and severe thrombocytopenia (5.000/uL) accompanied by a non-immune hemolytic anemia with schistocytes at 7%. ADAMTS13 activity resulted 0,007 IU/mL (0,7%) with high inhibitor titers (89,2 UB/mL). aTTP was confirmed and corticosteroid treatment was started along with daily plasmaphereses and Caplacizumab. After an initial improvement, he then developed deep asthenia and referred an episode of melena. Complete blood counts showed low levels of hemoglobin (5.3 g/dL) without signs of hemolysis, reduced platelet count (76.000/uL) and a positive faecal occult blood test. Caplacizumab was immediately interrupted and a whole-body CT scan was performed. Because of the suspicion of a hemorrhagic spot in the jejunum, an arteriography was performed, but no bleedings requiring embolization were observed. Therefore, we administered Von Willebrand factor/factor VIII (vWF/FVIII) concentrate at 40 U/Kg to counterbalance Caplacizumab. Immediate clinical and laboratory benefits were observed with progressive improvement of platelet counts, ADAMTS13 activity and simultaneous decrease of inhibitors. We eventually discontinued Caplacizumab ahead of time.

Conclusions. Management of major bleeding episodes during treatment with Caplacizumab is mostly reported in the context of clinical trials. Real life experience is rarely reported and there is no general consensus on treatment. Drug discontinuation may be effective though deaths despite the use of a vWF/FVIII concentrate rescue have been reported. To our knowledge, this is the first report of a major bleeding episode during treatment with Caplacizumab successfully treated with anti-haemorrhagic rescue in the real-life setting.

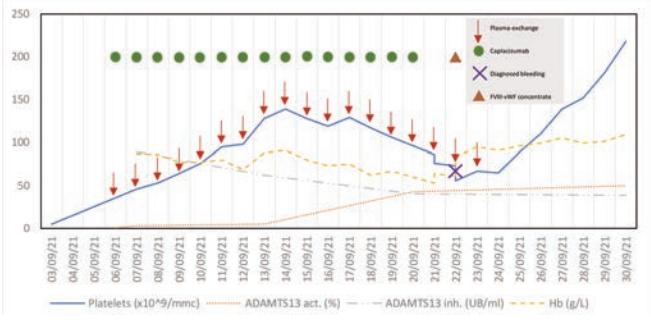

Figure 1. Clinical management of TTP and bleeding. Corticosteroid treatment was continued throughout all the period.

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EFFICACY OF THROMBOPOIETIN RECEPTOR AGONISTS FOR THE TREATMENT OF A PATIENT WITH IMMUNE THROMBOCYTOPENIA AFTER CAR T-CELL THERAPY FOR PLURIREFRACTARY MEDIASTINAL LARGE B-CELL LYMPHOMA

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Introduction. Chimeric antigen receptor T (CAR T) cell therapy represents an innovative treatment for patients with numerous relapsed or refractory hematological malignancies. It often causes hematologic toxicity, including thrombocytopenia, more and more often managed with thrombopoietin receptor agonists (TPO-RAs).

Methods. We describe the case of a 44-year-old woman diagnosed in June 2018 with primary mediastinal large B-cell lymphoma (PMBCL) and treated with seven lines of numerous chemo-immunotherapy treatment, including autologous stem cell transplantation and, at last, immune checkpoint inhibitor nivolumab in combination with anti-CD30 Brentuximab off label as bridge to CAR T-cell therapy. In July 2021 she was treated with axicabtagene ciloleucel, obtaining a complete remission with full hematological recovery within 3 months. Bone marrow biopsy confirmed absence of signs of dysplasia and patient undertook follow up. In May 2022, ten months away from CAR T-cell therapy, she went to the emergency room for metrorrhagia, and bruising spread due to severe thrombocytopenia (platelets 2.000/mmc), without additional alterations of the blood count. She practiced treatment with high dose steroids and intravenous immunoglobulins, obtaining a poor response. So, a marrow aspiration was done confirming the diagnosis of ITP. Therefore, we decided to start early treatment with the oral TPO-RA Eltrombopag, at full dose of 75 mg once a day, achieving a complete but short-lived response. Thus, she was switched with subcutaneous TPO-RA Romiplostim at the starting dose of 3 mcg/kg/week.

Results. After only one administration of Romiplostim, the patient showed rapid response, with the development of thrombocytosis after the second administration and subsequent temporary discontinuation for 3 weeks. Then the treatment was resumed at the minimum dose of 1 mcg/kg/week, which the patient continues to date without complications and maintaining a platelet count constantly higher than 100,000/mmc, compatible with a complete response, that meet the criteria for starting taper in order to pursue a free treatment remission.

Conclusions. The dysimmune complications of CAR T-cell therapy may also include immune thrombocytopenia, which, like primary forms, responds well to TPO-receptor agonists. They are also used in the management of the early stage of the hematological toxicity of the cellular therapy, showing high efficacy and good safety profile.

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CORRELATION BETWEEN HIGH D-DIMER VALUES AND SARS-COV-2 POSITIVITY

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The initial stage of COVID-19 disease may be associated with alteration of coagulation parameters including D-Dimer (D-D). A retrospective study was carried out to evaluate the concentration of D-D in Sars-CoV-2 positive patients during 2022, that were symptomatic for respiratory disease and were admitted to the infectious diseases department of the ASL BT, in order to identify the possible relationship between D-D dosage and the Sars-CoV-2 positivity. There were 94 patients, 56 (57%) males and 38 (43%) females divided into three age groups: 0-30, 30-60, >60. 8 (14%) of the 56 positive males were in the 30-60 age group and 48 (86%) in the >60 age group. Only one patient (3%) of the 38 positive females was observed in the age group 0-30, 6 (16%) in the 30-60 group and 31 (81%) in the >60 group. We have considered the subjects with D-D value greater than the 500 ng/mL cut-off, adjusted for age after 50 years. In male subjects, D-D values between 191 ng/mL and 8191 ng/mL were detected; the concentration of D-D was higher than the cut-off in all subjects aged 30 to 60 years (8 males) and in 34 of 48 (70.9%) males over 60. D-D values between 247 ng/mL and 8747 ng/mL were detected in females; values above cut-off were measured in 3 of 6 (50%) females aged 30 to 60 years and in 20 of 31 (64.5%) females >60. High values of D-D were highlighted in 65 (69%) of total patients, confirming, in line with literature data, a correlation with SARS-CoV-2 positivity. The proportion of subjects with elevated D-D is higher in males (75%) than in females (60.5%). It is observed that 100% of males 30-60 have a D-D higher than the cut-off: this data allows us to recognize the usefulness of this dosage in younger subjects for an assessment of the thrombotic risk associated with the action of Coronavirus. It is evident that in the over 60s an increased of D-D in COVID-19 must take into account several factors that determine the increase in D-D also linked to sex, age and the relative. The clinical and prognostic significance of the increase in D-D requires further study and above all prospective analysis associated with evaluation of symptoms and disease course.

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IS THERE A CORRELATION BETWEEN ITP AND IGG4-RD? A CASE REPORT

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Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition associated with single or multi-organ swelling and subsequent fibrosis affecting multiple organs. In some rare cases it is seen association of IgG4-RD and Primary immune thrombocytopenia (ITP) with IgG4-anti platelet. ITP is an acquired immune mediated disorder characterized by isolated thrombocytopenia, defined as a platelet count (PLT) <100.000/uL, and the absence of any underlying cause of the thrombocytopenia.

A 56 years old woman was admitted in Our Clinic in 2005 for PLT of 1.000/uL and petechial rash, infective causes were excluded. ANA, ENA, ANCA, anti-phospholipid antibodies were negative. A bone marrow evaluation excluded malignancy and showed adeguate megacariocytes. Considering it as an ITP the patient was put on Dexamethasone 40 mg for 4 days + IgIv 2 g/kg with a complete platelet recovery (CR). In 2011, the patient had jaundice and initial diabetes requiring insulin, an abdomen CT (a-CT) scan showed a 10 cm mesenterial lesion and a swelling of the pancreas. The patient underwent an agoaspirate of pancreas and a Whipple precedure. Histopathology was negative for malignancy, instead showing IgG4 autoimmune disease with an infiltration of IgG4 secreting plasmacells with the serum IgG4 being > 250 mg/ml, so the patient initiated a first line therapy with steroids with a prompt serum response. An a-CT control in 2014 the pancreatic pseudotumor persisted, so Azathioprine was initiated for 1 year in the attempt to reduce the mass, with a little to no response.

On the first (2013) and second relapse (2018) of ITP a round of Prednisone (PDN) 1 mg/kg + IgIv was done attaining a CR. At the third relapse (2019), we went for Rituximab 375 mg/mq/wk x 4 with a CR for another year. So, the patient started a TPO-RA therapy with Eltrombopag then switched to Romiplostim, with partial response. On January 2022, PLT was 0/uL and Fostamatinib was seen as a good option, indeed the patient obtained a CR for a year, followed by a progressive reduction on the PLT, till reaching 8000/uL on April 2023, so we decided to try an association of small doses of PDN with Mycophenolate. Two weeks apart now we see an initial response with a PLT of 34.000/uL.

To date, there are ten reports of IgG4-RD and ITP occurring in the same patient, but there is still not known the physiopathological correlation among them.

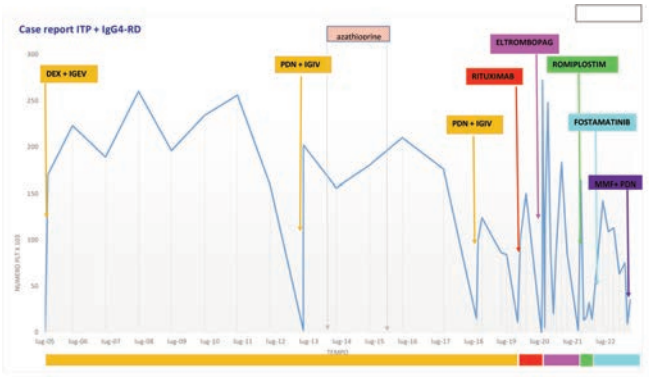

Figure 1.

PUBLISHED ONLY

SP01

IDIOPATHIC ERYTHROCYTOSIS AND THE PRESENCE OF MULTIPLE ALTERED GENES

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Background. Absolute erythrocytosis is characterized by persistently raised haemoglobin and haematocrit levels. Primary acquired erythrocytosis referred to Polycythaemia vera and secondary form happens when erythropoietin is generated either appropriate or inappropriate. Rare congenital erythrocytosis occur in molecular alteration of erythropoietin receptor gene (*EPOR*) or in genes involved in the oxygen sensing pathway. Idiopathic erythrocytosis (IE), 70% of patients, has no recognized cause.

Methods. An ad hoc Next Generation Sequencing (NGS) panel including genes known to induce erythrocytosis (*EGLN1*, *EPAS1*, *VHL*, *EPOR* and *JAK2*) has been used in a large group of patients with sporadic clinically diagnosed IE. Multiplexing PCR was the method used for libraries preparation and data were analysed using bioinformatics tools. Sanger sequencing was used to validate NGS data. The clinical significance of variants was inferred using ACMG classification.

Results. While in 29 (24.5%) patients out of the 118 (M/F =101/17; mean age 53.7±17.2 years) evaluated, 1 gene alteration was detected, while in 8 (6.8 %) patients we found germline variants in 2 evaluated genes. *EGLN1*C127S, *EGLN1*Q157H, *EPAS1*F374Y and *EPOR*N487S but not the other alterations have been jet observed in erythrocytosis. 11 (55%) out of the 20 different alterations encountered were in exons different than those usually studied (Table 1).

Conclusions. In our study, the use of NGS allowed the identification of a number of molecular variants in genes known to be altered in erythrocytosis, not detected with usual methods being in exons not previously analysed. Interestingly, all our patients were clinically classified as IE while NGS data suggest the existence of a hereditary disease. Unfortunately, most of these variants are considered benign or likely benign in the international classifications but no biological functions are reported and their role has to be clarified.

Table 1.

Variants found in our 37 IE patients

Variant	N° of pats	Exon	ACMG classification
*EGLN1*C127S	6	1	Benign
*EGLN1*Q157H	5	1	Benign
*EGLN1*I269T	1	1	Uncertainly
*EPAS1*R550W	1	12	Likely benign
*EPAS1*F374Y	1	9	Benign
*VHL*P25L	2	1	Benign
*EPOR*E181D	1	4	Likely benign
*EPOR*G46E	1	2	Benign
EPORD398E	1	8	Likely benign
*EPOR*N487S	3	8	Benign
*JAK2*L393V	1	9	Likely benign
*JAK2*N1108S	1	25	Benign
*JAK2*L113V	1	4	Benign
*JAK2*T78I	1	4	Uncertainly
*JAK2*R923C	1	21	Uncertainly
*JAK2*G571S	2	13	Uncertainly
TOTAL	29		

				Associated variant	Exon	ACMG classification
*EGLN1*C127S	5	1	Benign	*JAK2*L393V	9	Likely benign
				*EGLN1*R370G	*3*	Uncertainly
				*EPAS1*T766P	15	Benign
				*EPAS1*F374Y	9	Benign
				*VHL*P25L	1	Benign
*EGLN1*Q157H	1	1	Benign	*EPOR*A99V	3	Benign
*EPAS1*F374Y	2	9	Benign	*JAK2*G48E	3	Benign
				*EPOR*N487S	8	Benign
TOTAL	8					

SP02

LACTOFERRIN EFFICACY IN TREATING PATIENTS WITH HAEMOCHROMATOSIS

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Haemochromatosis, a systemic iron overload, is a genetic disease caused by hepcidin deficiency or hepcidin-ferroportin binding reduction. Hepcidin regulates the activity of ferroportin, the iron exporter of enterocytes, hepatocytes, macrophages and placental cells. The most common form of haemochromatosis is due to mutations in HFE which leads to a decrease in hepcidin and an increase in ferroportin. Haemochromatosis is also due to mutations in SLC40A1 ferroportin gene that prevent hepcidin-ferroportin binding. Non-HFE forms of haemochromatosis, including hemojuvelin (Hjv), hepcidin (HAMP) and transferrin receptor 2 (TfR2) mutations, are much rarer. In patients with hemochromatosis, the plasma iron increase mainly depends on an excessive iron release from ferroportin of enterocytes and macrophages which are able to recycle more iron from senescent erythrocytes with respect to healthy subjects. The plasma iron overload leads to its accumulation in the parenchymal cells of various organs, resulting in several pathologies. Iron chelators can be administered to some of these patients even if they exert side effects. Therefore, the best current therapy is phlebotomy. Here, we report a retrospective study carried out on 23 patients suffering from hemochromatosis, treated with lactoferrin (Lf) (200mg one or two times a day). Among these two patients were previously treated with one phlebotomy. Lf, an iron-binding cationic multifunctional glycoprotein, is able to inhibit reactive oxygen species formation, oxidative stress, cell damage, infections and iron-induced inflammation. Remarkably, the Lf-treated patients showed a significant reduction of serum ferritin (sFtn) levels (-45%, P<0.001), a trend in reducing D-dimers (-6.67%, P=0.06); and a significant increase of red blood cells (+2.74%, P<0.001). The median values of hemoglobin and hematocrit are identical before and after Lf treatment, even if the intraindividual variations resulted as statistically significant (P<0.001 and P=0.024). The reduction of sFtn was less marked in patients with comorbidity (median: 330 ng/mL, IQR: 244-417) with respect to those without such complications (median: 515 ng/ml, IQR: 374-702) (P=0.023).

Even if a larger number of Lf-treated patients is required, this is the first retrospective study on patients suffering from hemochromatosis, suggesting Lf as an innovative future approach in treating this important iron homeostasis disorder.

SP03

LACTOFERRIN EFFICACY IN TREATING PATIENTS WITH HYPERFERRITINEMIA

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Ferritin (Ftn), a globular protein able to sequester 4,500 atoms of iron per molecule, is an acute-phase reactant. It consists of two types of subunits, H (heavy) and L (light). Ftn is elevated in inflammatory conditions, including rheumatic, hematologic, and infectious diseases and alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), and viral hepatitis. The mainstay of the treatment of hyperferritinemia is phlebotomy. Iron depletion by phlebotomy, together with the modification of diet and life-style habits, represents the therapeutic approach to decrease metabolic alterations. Conversely, phlebotomy is not recommended for isolated hyperferritinemia without further evaluation. In iron overload conditions, patients with anemia are intolerant to phlebotomy while an iron chelating approach represents the primary therapy. Here, we report a retrospective study carried out on 17 patients, suffering from several pathologies unrelated to hemochromatosis, treated with lactoferrin (Lf) (200 mg one or two times a day). Lf, a cationic multifunctional glycoprotein synthesized by exocrine glands and neutrophils, is able to chelate two ferric ions per molecule, thus inhibiting reactive oxygen species formation, oxidative stress, cell damage, bacterial and viral replication and iron-induced inflammation. Remarkably, the Lf-treated patients showed a significant reduction of serum Ftn (sFtn) levels (-54%, P<0.001), CRP (-86.0%, P<0.001) and D-dimers (-18.0 P<0.001) and a significant increase of hemoglobin (+5.0%, P<0.001), red blood cells (+8.0%, P<0.001), and hematocrit (+7.0%, P=0.002). The reduction of sFtn due to Lf treatment was largely independent of gender (P=0.78), age (P=0.66), baseline symptoms (P=0.20), and concomitant active (P=0.34) and chronic infections (P=0.53). Our clinical experience shows that lactoferrin can be a valid treatment in restoring iron homeostasis, curing anemia and reducing the inflammatory state. Even if a larger number of Lf-treated patients is required to confirm these preliminary observations, this is the first retrospective study on patients suffering from hyperferritinemia unrelated to hemochromatosis and treated with Lf whose supplementation might be an innovative future approach in treating this important iron homeostasis disorder.

SP04

ECULIZUMAB IMPROVES SEVERE ACROCYANOSIS IN COLD AGGLUTININ DISEASE: A CASE REPORT

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[1]Department of Medicine and Surgery, University of Milano-Bicocca; [2]Hematology Division and Bone Marrow Unit, Fondazione IRCCS San Gerardo dei Tintori; [3]Department of Oncology and Onco-hematology, University of Milan; [4]Hematology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy

Cold agglutinin disease (CAD) is a subtype of AIHA in which monoclonal IgM autoantibodies (AAbs) bind to erythrocyte at temperatures below 37°C leading to red blood cells agglutination and a

complement-mediated hemolysis. Patients typically present with moderate or severe anemia and ischemic symptoms such as acrocyanosis. Despite cold avoidance, about 70% of patients require pharmacological treatment. Corticosteroids are widely employed but effective only at high doses, so that current treatment consists in anti-B-cell agents to reduce AAbs production, especially rituximab-based regimens. Recently, complement inhibitors, including the anti-C5 eculizumab, have been employed with efficacy on hemolysis but not on circulatory symptoms. A 75-year-old woman was admitted to our emergency department (ED) with acrocyanosis on fingers and toes, complaining hypoesthesia and pain in hands and feet. Her past medical history included CAD for 20 years and a more recent low-grade lymphoma treated with a rituximab-based therapy up to 10 days before the admission. In ED, hemoglobin level was 9 g/dL and blood tests showed positive direct antiglobulin test, undetectable haptoglobin, elevated lactate dehydrogenase, unconjugated hyperbilirubinemia, complement consumption and IgM 526 mg/dl; serum protein electrophoresis demonstrated monoclonal IgMκ of 0.75 g/dL, increased during rituximab. The patient was refractory to steroids and quickly developed necrosis in the area of demarcation of the fingers and toes of the left hand and foot. Eculizumab 900 mg iv was administered and bortezomib 1.3 mg/sm was started on the next day as to target the B-cell clone. After few hours from eculizumab's infusion the ischemic lesions on feet and right hand disappeared; acral fingers necrosis remained on left hand but reduced in size. The 5th day after admission she underwent partial surgical amputation of involved fingers. A 2nd and a 3rd dose of eculizumab were administered since acrocyanosis on feet reappeared when the heated blanket was removed. A 2nd cycle of bortezomib was also administered. During the following days, hemoglobin progressively increased and hemolysis decreased together with IgM levels. This experience suggests that complement inhibitors may be effective in severe cases and acute exacerbations of CAD, possibly providing a bridge for anti-B-cell agents. Interestingly, an effect on circulatory symptoms besides hemolysis may also be observed.

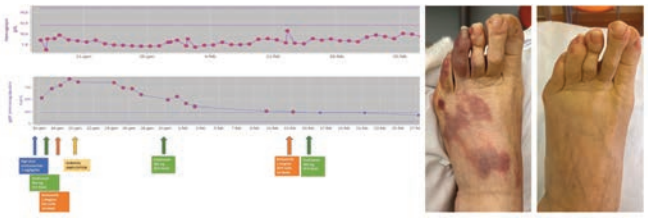

Figure 1.

SP05

ADVERSE OUTCOMES IN PREGNANT WOMEN WITH SICKLE CELL TRAIT (SCT)

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Background. Sickle cell disease (SCD) is a severe and complex inherited genetic disorder and the most common hemoglobinopathy worldwide. Individuals with 1 abnormal allele of the hemoglobin gene (HbS, heterozygous) have sickle cell trait (SCT), whereas those with 2 abnormal alleles have SCD. SCT is more prevalent in people of African-descent from tropical and sub-tropical regions where malaria is endemic. Migration of people from areas of high prevalence of SCD, the incidence of SCT and SCD is increasing in the Western part of the world. The province of Modena in Northern Italy, with a total population of 700,914 inhabitants, accounts for approximately 92,400 (13.2%) immigrants, mainly from sub-Saharan countries (Ghana, Nigeria, Senegal) in which SCD is endemic.

Aims. The aim of this study was to identify SCT pregnant women and to asses their risk of developing pregnancy related complication.

Methods. This retrospective case control cohort study included data on SCT pregnant women and newmothers between January 1, 2015, and november 15, 2020 followed at Mother and Infant department unit of the University Hospital of Modena. Case control rate 1:2. High Liquid performance Chromatography (HPLC) Hemoglobin profile is offered since 2013 to all pregnant women and new mother of the province of Modena through a screening program coordinated at Trasfusion Medicine Department of the Hospital. Socio-demographic parameter (age, education, emploiment, race, BMI), reproductive history and obstetric parameter where examined. Logistic regression analisys was also performed.

Results. We analyzed 242 SCT pregnant women and newmother and 490 controls with normal hemoglobin profile. SCT patients are younger than controls, more frequent unemployed, less educated, non caucasian, higher BMI and multiparous. SCT pregnant women show less gestational weight gain than normal controls, higher Caesarean-section rate and lower levels of hemoglobin and Hematocrit during I, II e III trimester. Newborn of SCT mothers showed higher rate of adverse outcomes.

Conclusions. Our study shows that the SCT rapreset an indipendent risk factor for adverse outomes during pregnancy. Thus, the delivery of SCT pregnant women should be considered at higher risk, comnpared to those of non-SCT women. Multidisciplinary teams with expert in obstetrics, perinatal medicine, hematology adn transfusion medicine should provide the optimal care to SCT women during pregnancy and delivery.

SP06

THE STRANGE CASE OF PERNICIOUS ANEMIA AND THE HIDDEN ARCUATE LIGAMENT SYNDROME

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[1]ASST Melegnano e della Martesana Dipartimento della Medicina Diagnostica e dei servizi Servizio di Immunoematologia e Medicina Trasfusionale, Italy

A 68 year-old woman presented for moderate megaloblastic anemia, unexplained weight loss, proxymal sarcopenia and marked fatigue. She was admitted to hospital about 10 years before this presentation because of an episode of major depression due to a family mourning; now she is stable in bland antidepressant therapy. The patient reported that in the past all her physical disturbancies had been attributed to the mood disorder. She reported also to have abdominal discomfort occurring after meals. At presentation (03/2023): Hb 8.1 g/dL; MCV 126 fL; WBC 4280/mcl; PMN 1580/mcl; Ly 2230/mcl; LDH 564 U/L (> 2.5 ULN); Iron 143 mcg/dL; Ferritin 116 ng/mL; FOB on 3 specimens: negative 3/3; Vit B12 123 pg/mL (< LLN). Folate 4.5 ng/mL. PE: ABP 115/70 mmHg HR 98 bpm. Heart: normal tones, no murmurs. Thorax: normal. Abdomen: treatable, no pain to palpation, no splenomegaly or enlarged lymphnodes. BMI 16. Presence of an upper abdominal murmur 4/6. We started therapy and work up as follows: 5000 UI VitB12 i.m/weekly for 5 weeks, then every 2 months, folic acid 5 mg/day/p.o, upper endoscopy and abdominal doppler ultrasound of large vessels (the latter to identify the origin of the murmur). Blood tests (after 2 weeks of supplementations) showed an optimal response Hb 11,6 g/dL; MCV 105 fL; WBC 5620/mcl; PMN 2470/mcl; LDH 328 U/L; B12 458 pg/mL;

folic 12.3 ng/mL. Anti parietal gastric cells Antibodies were negative. Doppler US of abdominal vessels demonstrated a critical stenosis of superior mesenteric artery, with flow acceleration and a thin inferior mesenteric artery. Subsequently, an abdominal contrast CT was prescribed. It confirmed the stenosis of superior mesenteric artery mediated both by arcuate ligament syndrome (with atherosclerotic plaques worsening the situation) and a markedly hypoplastic inferior mesenteric artery. Upper intestinal endoscopy showed hypotrophic gastroduodenal mucosa without H. pylori infection. This patient now is under evaluation to have vascular surgery. She feels better, with no more fatigue and collateral amelioration of her mood disorder.

Conclusions. This clinical case of pernicious anemia due to chronic severe hypoperfusion shows clearly that clinical cases are not always what they seem: laboratory data and clinical assessment must be kept together to achieve the aim of patients' physical and mental health.

SP07

THE IMPORTANCE OF AN INTEGRATED VIEW OF LABORATORY DATA FOR A CORRECT DIAGNOSTIC PATH: SYNERGY BETWEEN CLINICAL CHEMISTRY AND HEMATOLOGY. A CASE REPORT

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Clinical Pathology and Microbiology Unit, PO Bonomo, Italy

New methodologies for cellular analysis allowed the creation of hemocytometers with great sensitivity in detecting cellular abnormalities. However, morphological examination of peripheral blood smear remains the gold standard for detecting alterations that may escape analyzers, especially in hematological emergencies such as thrombotic thrombocytopenic purpura (TTP). TTP recognition is based on timely microscopic detection of schistocytes, a pathognomonic laboratory sign of intravascular mechanical hemolysis. The new analyzers are capable of producing automatic alarms in the presence of schistocytes, but sometimes these reports can be deficient. The aim of this work is to highlight that the diagnosis of intravascular hemolysis requires an evaluation of the blood count integrated with other parameters, such as very high levels of LDH and indirect bilirubin and reduction of haptoglobin, up to undetectable levels: observing these data it is recommended to resort to microscopic examination of a peripheral blood smear. We report the case of a female patient, 40 years old, who arrived at the Andria Hospital in a state of coma. The blood samples, after centrifugation, are strongly hemolyzed. We found anaemia (Hb: 5.2 g/dl), thrombocytopenia (PLT: $8*10^3/\mu L$), platelet anisopoikilocytosis, evidenced by PLT scattergram and platelet interference alarm. There is no instrumental signaling for the presence of schistocytes. Serological tests show elevated LDH (4268 IU/L), increased indirect bilirubin (3.3 mg/dl) and severe decreased haptoglobin (3 mg/dl). A peripheral blood smear is performed and the presence of schistocytes is detected (count >5 schistocytes/100 erythrocytes /field). We immediately contact the patient's department of origin, which confirms the diagnosis of Moschowitz Syndrome (PTT). The technological evolution of haematological diagnostics cannot be separated from the global evaluation of each patient, from the morphological cellular examination and from communication with clinicians. In our experience, the contribution to the diagnostic-therapeutic path was effective: after the coma state, the patient was transferred to a hematology unit with stabilization of all blood count and chemical-clinical parameters.

SP08

ERYTHROBLAST COUNT: ROLE IN THE TIMELY DIAGNOSIS OF THE NEWBORN HYPOXIA. CASE REPORT

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In healthy newborns, NRBC count is reduced by half 12 hours after birth, and there are only 20–30 NRBCs/m^3 48 hours after birth. Although on the third or fourth day of birth, NRBCs are not seen in the blood circulation, but in preterm newborns, small amounts of NRBCs may be seen in the first week of life. The increase in newborns NRBC count can be considered a sign of birth hypoxia. Hypoxia may have serious effects on many vital organs of neonates such as: respiratory distress syndrome, myocardial ischemia, adrenal hemorrhage, metabolic complications, acute tubular necrosis, neurological complications. This condition is the cause of about one-fifth of neonatal deaths and the second leading cause of neonatal mortality after severe prematurity. So, predicting the newborn hypoxia is really important for complications prevention and timely targeted treatment. We report the case of a 24 hours old full-term female newborn, hospitalized at the Pediatric Department with fever. Routine laboratory tests are requested for suspicion of a septic condition: C-Reactive Protein and electrolytes are found to be normal. Leukocytosis, mild plateletopenia and instrumental reporting of a NRBC population of 55% of total nucleated cells, associated with alert of presence of platelet aggregates are observed on complete blood count examination. Aggregates could interfere with the instrumental NRBC count and result in an overestimation of erythroblasts, for this reason a peripheral smear is performed to confirm the percentage of NRBCs reported by the instrument. The microscopic count confirms the presence of Erythroblasts in a percentage corresponding to the instrumental one. We promptly contact the home department, communicating the finding to the clinician: the NRBC value and the finding on objective examination of mild tachypnea and respiratory noises directs the diagnosis toward respiratory distress, necessitating admission to the neonatal intensive care unit. The high number of NRBCs in perinatal age results to be a key marker in the early detection of the condition of neonatal hypoxia/asphyxia, and the timely communication of the laboratory data to the ward physician can play a decisive role in the diagnosis and a rapid targeted therapeutic intervention.

SP09

FLOW CYTOMETRIC ANALYSIS OF PERITONEAL FLUID: EXPERIENCE ON AUTOMATION AND MICROSCOPY COMPARED. DIAGNOSTIC ALGORITHM PROPOSAL

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Cytometric analysis of liquids can be performed in automation and microscopy. The aim of this work was to highlight when the instrumental and microscopic cellular evaluation of peritoneal fluid could be useful for the diagnosis and therapy. The automated analysis was performed on an EDTA test tube sample, using the Body Fluid application of Yumizen 2500 (HORIBA) which counted total leukocytes (BF-WBC), red blood cells (BF-RBC), polymorphonuclear cells (BF-PN) and mononuclear cells (BF-MN). The microscopic analysis was carried out on May-Grumwald Giemsa smears set up and was colored by Yumizen SPS, after centrifugation of the sample at 2000 rpm for 5 minutes. We selected 4 cases of leukocyte counts

on peritoneal fluid. Case 1: 403 leukocytes/µL with 66% PN and 34% MN, under the microscope 52% PN and 48% MN of which 20% lymphocytes, 28% cells with nucleocytoplasmic ratio in favor of cytoplasm, probably of mesothelial origin. Case 2: 1017 leukocytes with 5% PN and 95% MN, under the microscope 3% PN and 97% MN of which 67% lymphocytes, 30% cells surrounded by lymphocytes. Case 3: 4129 leukocytes with 26% PN and 74% MN, under the microscope 1% PN and 99% MN, of which 9% lymphocytes and 90% voluminous mononuclear cells with nucleocytoplasmic ratio in favor of the nucleus, nucleolate, chromatin in large plates and basophilic and vacuolate cytoplasm. Case 4: 69 leukocytes differentiated into PN 4% and MN 96%, differential evaluation was not executable on microscopy due to the scarcity of the elements available. An algorithm was developed to standardize the diagnostic pathway on the peritoneal fluid: in the case of a cell count <100 we reported only the absolute value of the determined elements; for counts with elements >=100 we reported the absolute value with the instrumental differentiation in PN and MN expressed in terms of percentage and note relating to the interference on MN of mononuclear elements of probable mesothelial origin; we performed the smear to confirm instrumental data and communicate microscopic evaluation to clinician.

The cut-off 100 was decided empirically, the Case 4 showed how cellular elements <100 were few for an effective microscopic evaluation. In our opinion a cut-off of 100 may be the most appropriate number to perform a differential cell evaluation useful to the diagnostic path; however, additional verification is necessary on a more significant number of cases.

We also believe that this algorithm can be applied to other fluids but not CSF.

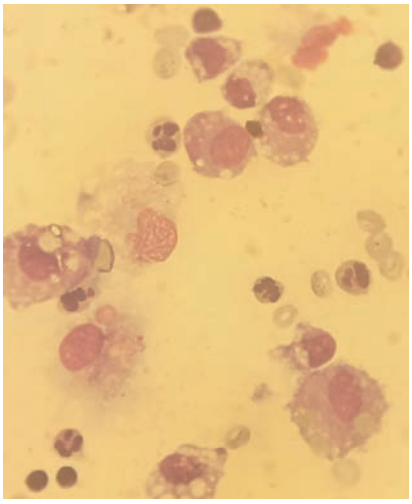

Figure 1.

SP10

ACUTE MYELOID LEUKEMIA WITH BCR::ABL1 FUSION PRESENTING WITH ERYTHROID LINEAGE FEATURES AND TRILINEAGE DYSPLASIA: A CASE REPORT AND LITERATURE REVIEW

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Introduction. According to the latest WHO classification, acute myeloid leukemia (AML) with BCR::ABL1 fusion constitutes a rare novel entity, accounting for 1.5% of de novo AML. Moreover, differential diagnosis between this entity and a chronic myeloid leukemia (CML) in blast phase (BP) can be challenging. The prognostic impact of BCR::ABL1 is retained adverse, considering that these patients are often chemotherapy-refractory and the tyrosine-kinase inhibitors (TKI) responses are poor. Few cases have been reported in literature with a detailed morphologic description.

Case presentation: A 70-year-old female attended our hospital with normocytic anemia (Hb 9.5 g/dL), thrombocytopenia (Plt $16x10^9$ /l), increased white blood cell count (WBC $25x10^9$ /l) with 23% of immature granulocytes and 3% of blasts. Dysplastic neutrophils, erythroblasts and RBC abnormalities were reported too in peripheral blood (Figure 1 PB, A-C), while reticulocyte count, vitamin B12 and folate were normal.

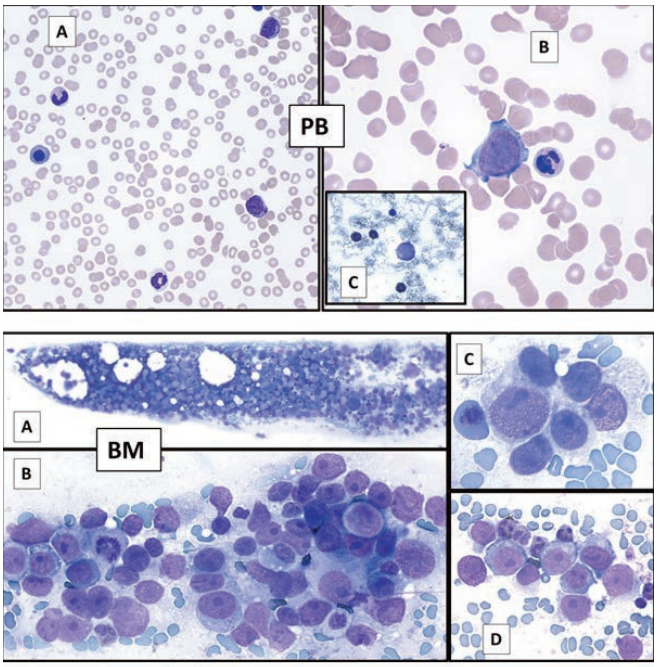

Fig.1PB Images from peripheral blood smears at presentation

A: May-Grünwald Giemsa, x50: One nucleated red blood cell (left), two granulocytic precursors (right), and two hypogranulated neutrophils
B: May-Grünwald Giemsa, x100: One large blast with round nucleus and prominent nucleoli (left) and one neutrophil
C: Myeloperoxidase (MPX) Stain x100: One MPX-negative large blast, one small lymphocyte (upper side), three MPX-positive neutrophils.

Fig.1BM Images from bone marrow aspirate smears at presentation

A: May-Grünwald Giemsa, x10: Hypercellular bone marrow particle with monomorphic cell features
B: May-Grünwald Giemsa, x100: Large blasts with round nuclei and prominent nucleoli, often vacuolated basophilic cytoplasms and high N/C ratio
C: May-Grünwald Giemsa, x100: One dysplastic intermediate erythroblast on the left side of a large blast cluster
D: Myeloperoxidase (MPX) Stain x100: MPX-negative large blasts and four MPX-positive neutrophils (upper side).

Figure 1.

Methods. Bone marrow smear showed markedly increased cellularity with 65% of large myeloperoxidase negative blasts with a high mitotic rate, suggestive of erythroid lineage (round nuclei, finely granular chromatin, prominent nucleoli, intensely basophilic cytoplasm, sometimes with vacuoles and blebs) (Figure 1 BM, A-C). Trilineage dysplasia was also detected. At flow cytometry analysis these blasts showed co-expression of CD34, CD71 (bright), CD105, CD43, CD99 while HLA-DR, CD13, CD123 and CD117 were negative.

Results. CML was excluded for lack of splenomegaly, basophilia and presence of trilineage dysplasia. At this point, the proposed di-

agnosis was AML NOS with erythroid differentiation according to WHO 4th edition, although CD34+ is reported as uncommon in acute erythroid leukemia (AEL). Later, molecular biology testing found a BCR::ABL1 mutation (p210 transcript), leading to add treatment with TKI (imatinib – 600 mg/day) other than hydroxyurea-based cytoreductive therapy, and setting the final diagnosis as AML with BCR::ABL1 fusion. Next generation sequencing (NGS) is ongoing. The patient condition suddenly worsened, developing a septic shock and later decease.

Conclusions. AEL represents an AML subtype with erythroid differentiation lacking defining genetic abnormalities. In this case, the most suitable diagnosis was AML with BCR::ABL1 fusion presenting with erythroid lineage features and trilineage dysplasia, demonstrating how an accurate molecular biology testing is mandatory.

SP11

INTERPRETATION AND REPORTING OF COMPLEX CLONALITY CASES

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Clonality tests on B cells have high sensitivity and may be decisive in the diagnosis of suspected lymphoproliferations for which histological and immunohistochemical data may be not sufficient. These tests are based on the amplification of specific regions, included between the variable region (Vh) and the joint region (Jh). These regions are subject to recombination events so that each cell clone produces unique antigen receptors in terms of length and or sequence. The high sequence variability of these regions can make the interpretation of the results difficult, due to amplicons that deviate from the expected size results. Here we focused on two cases that required further investigation for the interpretation test results. In particular, we performed a Sanger sequencing of the amplified region, and we aligned the sequences by using the IMGT/V-QUEST tool, which allows us to compare sequences of the patient with the immunoglobulin sequences of the variable regions and domains contained in the IMGT/V-QUEST reference directory sets. In one patient, with suspected cutaneous lymphoma, we analyzed a sample with 90% of tumoral cells. The test we performed is based on the use of 3 different combinations of primers which recognize different framework regions (FR) in Vh region. These primers can amplify these variable regions, exploiting conserved nucleotides in specific positions. We detected a clonal population in 2 of the 3 mixes used (FR1 and FR2), but we didn't observe any clonal peak or a reproducible polyclonal pattern in FR3. The sizes obtained for FR1 and FR2 mixes were 10-15 base pairs smaller than the minimum limit for the amplification range recommended by the kit. In the other patient with a suspected gastric lymphoma, we analyzed a sample with about 70% of tumoral cells and we detected a clonal peak in all mix used (FR1, FR2, FR3) and another peak out of the valid range size recommended by the kit. In both cases, the sequencing allowed us to characterize the clonal population and interpret test results properly. Our data suggest the complexity of developing a CE-IVD test on such a variable genomic target and that, in some cases, sequencing is crucial for correct reporting. It is reasonable to think, also considering the most recent evidence in the literature, that a test that combines the two analytical approaches, such as a custom NGS panel, could guarantee optimal detection performance and hopefully a reduction in interpretations and reporting times.

SP12

NEXT-GENERATION SEQUENCING (NGS) ANALYSIS REPORT, DOES A CONSENSUS EXIST?

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Widespread diffusion of NGS technologies in Oncology and Haematology requires standardization and harmonization in report. In a highly heterogeneous panorama of instrument platforms, multigenic panels (physical or in silico), chemistries and analysis algorithms, the need for greater standardization has been pointed out for NGS reports that are increasingly getting in clinical-diagnostic routine. Moreover, considering that reports such as patients can move from Center to Center, this makes it necessary to have a clearer and easier understanding of these analysis. General indications such as personal data, type and traceability of the sample are not comprehensive a complete NGS report, which should also follow requirements more suitable in Medical Genetics (*e.g.* clinical question, method, interpretation, limits of the analysis) useful for a better result interpretation in the clinical context. It is ever more important to provide with a "spoken report" showing a brief interpretation, which can support clinical/diagnostic decisions, as well as the list of identified variants. To define all the necessary requirements for a useful and complete report, it should be considered that NGS analysis is requested at the onset, at follow-up and on different tissues; recent scientific studies about oncological genetic profiling continuously increases the lists of pathology-related gene. Furthermore, whole genome and/or target sequencing instead of hot-spot regions makes more frequent the detection of variants of difficult interpretation. Information such as tissue, clinical context, reason for testing and time point allows to provide a correct classification of the reported variants (by categorization by Tier-ACMG\AMP guidelines) to better answer the main questions of prognosis, response to therapy and diagnosis. These data are useful to define a cut-off for the frequency of variant (VAF) depending on the clinical context. Finally, in addition to biological and clinical aspects, NGS report should be integrated with qualitative report demonstrating the reliability of the result, such as the list of sequenced genes, read depth, coverage of the regions of interest (ROI), type of detected variants and limitations of method. Last but not least, in NGS analysis it is necessary to find out the risk to identify germinal variants and recommending patients to genetic counselling, especially in relation to pathologies well-known for presenting a hereditary genetic susceptibility.

SP13

A DEFINITION OF A TIMELY DIFFERENTIAL DIAGNOSIS: THE KEY ROLE OF RELATIONSHIP BETWEEN LABORATORY AND CLINICIAN. WE BELIEVE IN IT AND WHAT ABOUT YOU?

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Golimumab is FDA approved for the treatment of moderate to severe rheumatoid arthritis (RA), and other autoimmune diseases. It is a human monoclonal antibody against tumour necrosis factor-alpha (TNFα). The aim of this work was to describe the interactions between our Clinical Pathology Unit with Clinical of our hospital and

Clinical Hematology of ASL BT for a timely differential diagnosis. A 78-year-old men arrived at the emergency room of the Andria PO. The patient presented a normal blood count, routine laboratory tests were requested for suspicion of a septic condition: electrolytes and procalcitonin were normal, while C-Reactive Protein was 214.6 mg/L. The patient was admitted to the internal medicine department of our hospital, blood counted, routine clinical chemistry and virology tests carried out. The blood counts and blood smear were performed on Yumizen H2500/Yumizen SPS-Horiba, the blood chemistry tests on the Beckman Coulter DXC 880i platform and the indirect virology tests on the Liaison XL analyzer. 4 days later, the routine laboratory tests presented an increase of creatinine, urea and bilirubin; a septic conndition was found: procalcitonin 24.9 ng/ml and C-Reactive Protein > 500 mg/L. But this time the blood count showed: Hb 16.3 g/dL, leukocytes 930/mmc with neutrophils 5.9%, lymphocytes 59.6%, monocytes 25.8%, and large immature cells (LIC) 23.1%. In a peripheral blood smear, we reported the presence of immature and atypical lymphocytes. HBsAg, anti-HBc, anti-HBs and anti-HCV were negative and HSV IgM, Toxoplasma IgM, Cytomegalovirus IgM and Parvovirus IgG/IgM were absent. Days later, we observed also anemia (Hb: 11.3 g/dl) and thrombocytopenia (PLT: 22 10^3/μL), hematological consultation was requested to the Hematology Unit of ASL BT. Clinicians collected the medical history information of the patient, he was affected by RA and had received a recent new treatment with Golimumab injection. For hematology, no diagnosis of hematologic disorder was made, the singular condition of the patient was probably secondary events that was attribuited to treatment anti-TNFα riceived. Although generally Golimumab was well tolerated, we observed the symptoms disappear after the complete discontinuation of the drug. We believe in the power of the professional relationship between laboratory and clinician, it was useful for discover timely hematological disorders, differential diagnosis with autoimmune diseses and the correct therapeutic approaches.

SP14

HUMORAL AND CELL-MEDIATED RESPONSES TO SARS COV 2 VACCINATION IN A COHORT OF IMMUNODEFICIENT PATIENTS

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Patients with primary and secondary immunodeficiency highly benefit from Covid-19 vaccination as the only currently available treatment to prevent the severe form of the disease. It is known that in addition to antibody production, T cell-mediated immune responses are a useful tool to evaluate vaccine-induced protective responses, as they play a very important role in preventing the severe form of the SARS-CoV-2 virus. In this study, we have evaluated quantitative and qualitative CD4 and CD8 T lymphocyte responses, as well as antibody responses, in patients with several clinical forms of immunodeficiencies. As expected, XLA patients do not produce antibodies after the two doses of vaccine, but have a good T-cell-mediated response that is superior to that of CVI and CI patients. In CI patients, the antibody response was lower than that of CVI patients, and in these latter patients, defects are present not only in B lymphocytes but also in other immune cells involved in generating an effective humoral response, including antigen-presenting cells and Th cells, thus worsening the B-cell defect as a consequence of B-T cooperation failure. However, the intact CD4 T-cell response characterized by IFN-γ and IL-2 production after stimulation with S protein underscores how the vaccine elicits a cell-mediated response, likely to protect against the virus. In fact, only two patients with CVI contracted SARS-CoV-2 with almost no symptoms. Finally, one of the criteria for the diagnosis of CVI is poor antibody response to vaccines. However, the high proportion of immunodeficiency patients who responded to the vaccine, including patients diagnosed with CVI, suggests that the vaccine response should be interpreted with caution and that a positive antibody response does not exclude a clinically significant antibody deficiency. Through a simple assay, we therefore demonstrate how vaccine-induced specific CD4 and CD8 T cells can be detected and quantified, thus monitoring the vaccine response, thus highlighting that even in the absence of a humoral response, the T-cell response is often preserved. In conclusion, our study shows that vaccination with mRNA vaccines induces a specific T-cell-mediated immune response against SARS-CoV-2, independent of the B-cell response.

SP15

NELARABINE, ETOPOSIDE AND CYCLOPHOSPHAMIDE FOR ADULT T CELL ACUTE LYMPHOBLASTIC LEUKEMIA/ LYMPHOMA RELAPSING AFTER PEDIATRIC-INSPIRED FRONTLINE APPROACHES: REPORT OF 3 CASES FROM A REAL-LIFE SETTING

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[1]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [2]CRIMM, Center for Research and Innovation of Myeloproliferative Neoplasms, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; [3]Hematology Department, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; [4]Hematology and Bone Marrow Transplantation Unit, Laboratory of Molecular Medicine (CREO), Department of Medicine and Surgery, University of Perugia, Italy

Background. The outcome of adult patients with relapsed/refractory (R/R) T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL) is particularly poor. Nelarabine is the only agent approved for R/R T-ALL/LBL in Europe. Its safety profile and efficacy have been explored in combination regimens with cyclophosphamide and etoposide (NCE) in children. Less defined is its role in adults. Here we describe the outcome of 3 adult patients treated with NCE with an intention-to-transplant.

Clinical Cases. Patient 1 was a 22 year old female patient diagnosed with a cortical T-ALL with inv(7)(p15q34;TCRB::HOXA) and delCDKN2AB/9p21. She experienced an early relapse after the frontline treatment according to the NILG ALL 10/07 protocol. Salvage therapy with Venetoclax-Decitabine was administered with a transient CR before a second hematological and extramedullary relapse occurred. At this time, she was treated with NCE regimen achieving MRD negative CR and complete resolution of extramedullary disease; she proceeded with HSCT but died before engraftment due to septic shock. Patient 2 was a 36 year old male patient with a cortical T-ALL with TRB::TLX1 rearrangement, delCDKN2AB/9p21 and TP53/17p13. The patient was treated according to the NILG ALL 10/07 protocol and relapsed 3 years after HSCT with BM and mediastinal involvement. NCE regimen was administered obtaining MRD negative CR along with a reduction of the mediastinal mass. The patient proceeded to a second HSCT but died due to a post-transplant disease relapse. Patient 3 was a 35-year-old female with a mediastinal T-LBL. She experienced an isolated CNS relapse before the initiation of maintenance; thus we performed biweekly triple intrathecal therapy administrations followed by high-

dose cytosine arabinoside and mitoxantrone (HAM) regimen, obtaining CNS1. Soon after, the patient experienced a leukemic relapse with a concomitant mammary mass. A new salvage attempt with NCE regimen was offered with only a transient peripheral blast clearance and partial reduction of the extramedullary disease.

Discussion. Although limited, our experience is confirmatory of the clinical activity of NCE in adult patients with R/R T-ALL/LBL. Remission is expected to be short-lived and the pursuit of disease eradication mandates prompt HSCT bridging. The NCE regimen was generally safe and manageable. None of the patients experienced neurotoxicity events; intrathecal prophylaxis was delayed in order to mitigate this risk.

SP16

MOLECULAR MINIMAL RESIDUAL DISEASE (MRD) PREDICTS RELAPSE IN ACUTE MYELOID LEUKEMIA (AML): A CASE REPORT

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The main cause of treatment failure after allogeneic stem cell transplantation (al-HSCT) is due to relapse of disease. Molecular MRD detection in AML is based on PCR amplification of leukemia-associated targets, hematopoietic chimerism analysis and LAIP flow cytometry detection. We present the case of a 53-year-old female patient diagnosed with AML NPM1+ and FLT3+ who underwent a 9/10 allogeneic bone marrow transplant and then DLI. The patient was initially characterized by molecular analysis for variants in NPM1 and FLT3 genes, resulting in positive type A variant in exon 12 of NPM1 and ITD variant in FLT3. The patient was monitored during the induction and consolidation therapy and at the first evaluation only FLT3 was negative but later also NPM1. Post-transplant MRD consists of chimerism analysis performed on whole blood and CD3+ cellular lineage (LoD 10-1), quantitative NPM1 (LoD 10-4) and FLT3 analysis (LoD 10-1). Follow-up was performed on bone marrow samples at +30d, 60d, 90d, 1y, 2y with complete chimerism, NPM1 and FLT3 negative. After 36 months a molecular relapse for NPM1 was observed (ratio 0.8%=0.008) which was confirmed at 3 months with a rising log (ratio 2.9% =0.029) and 99% chimerism on CD3+. These results were confirmed by flow cytometry analysis, so the patient underwent a DLI therapeutic procedure. Prior to DLI, molecular investigations were carried out for recurrent chromosomal rearrangements, FLT3 gene and NGS panel related to myeloid disorders, all of which were negative. After 2 years, MRD analysis is negative for NPM1. This case demonstrates the predictive role of molecular MRD evaluation in pre and post-transplantation to better define the outcome. The patient showed in fact molecular relapse reported only chronic GVHD (ocular, hepatic and oral cavity). Moreover, the molecular evaluation over time shows the FLT3 unfitness as a single marker in follow-up, better to be evaluated with other targets. Finally, this case is an example of the evolution and deployment of molecular biology techniques useful for the genetic characterization of patients as a result of a better clinical/therapeutic management.

SP17

LONG TERM MOLECULAR REMISSION AFTER DASATINIB DISCONTINUATION IN PHILADELPHIA POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA PATIENT

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Introduction. The Philadelphia cromosome (Ph+) is the most common chromosomal abnormality in adult acute lymphoblastic leukemia (ALL) [1] and its incidence increases with age, reaching 50% in patients older than 60 years [2]. With the successful use of tyrosine kinase inhibitors regimen (TKI), remissions occur more frequently and patients live longer. Despite the significant progresses that have been made, frequent relapses remain a challenge [3-4].

Methods. It's here reported the case of a ph+ ALL patient treated with dasatinib who maintained a deep molecular remission despite TKI discontinuation of 29 months. A 64 year old caucasian woman has been admitted to hematology unit in April 2017. The blood count showed hemoglobin of 9,7 gr/dl, white blood cell count of 6100x10^9/l with 56% of blasts and 89000x10^9/l platelets. Bone marrow examination showed 82% lymphoid blasts with immunophenotype CD34+, CD19-10+, CD9 19+, CD79a+, TdT 55% CD19 68%, CD22 63%. The BCR ABL 1 rearrangement was identified with RT-PCR techniques (PCR-RT), with the presence of p190 transcript. The patient underwent induction treatment with dasatinib, steroid and intratechal therapy obtaining molecular response (day+30). During dasatinib treatment, the minimal residual disease (MRD) remained persistently negative. In 2020, the patient interrupted the treatment on his own. Blood count and MRD were carefully monitored every two months revealing a persistent deep molecular response (deep molecular remission after 29 months).

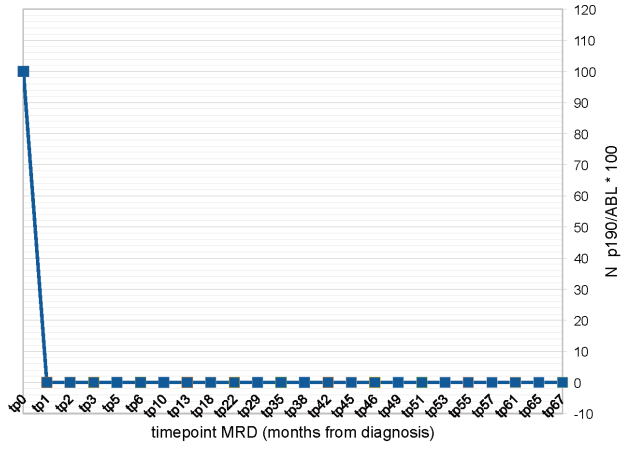

Figure 1.

Results and Discussion. A seminal study demonstrated that imatinib discontinuation could be safely attempted in CML patients and showed a durable complete molecular remission (CMR) [7-8]. Several studies demonstrated the exsistence of anti BCR ABL1 specific T lymphocites which persist after TKI discontinuation [5]. Many reports showed a correlation between bone marrow T cytotoxic lymphocytes (CTLs) and MRD in PH+patients during TKI treatment [6]. Some authors showed that the development of large granular lymphocyte lymphocytosis in patients treated with TKI, was significantly associated with an improved molecular response [6]. As long as this cases remains anecdotal, TKI discontinuation is strongly not recommended outside formal clinical trial, because no extensive data is available.

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SP18

PREVENTION OF INFUSION REACTIONS IN PATIENTS WITH CHRONIC LYMPHATIC LEUKEMIA TREATED IN FIRST LINE WITH VENETOCLAX-OBINUTUZUMAB: CLINICAL EXPERIENCE

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In the last few years, Chronic Lymphatic Leukaemia (CLL) has undergone a real scientific revolution with an impact on prognostic definition with the availability of new therapeutic options, such as BTK and Bcl-2 inhibitors, which have given excellent responses in terms of PFS. Today, it is possible to treat first-line patients with a fixed duration chemo-free protocol using Venetoclax, a Bcl-2 inhibitor in combination with Obinutuzumab, a monoclonal anti-CD20 antibody, and to abandon conventional chemotherapy. The most feared complications of this protocol are the infusion reactions to anti-CD20 and the risk of TLS, correlating with disease burden. The incidence of TLS, which is higher in the Murano study where Venetoclax is added at day 1 when a high disease burden is present, is reduced in the CCL-13 and CLL-14 studies, where Venetoclax is introduced only at day 22 when most of the disease has been significantly reduced by Obinutuzumab. In addition, the CLL-14 protocol provides a premedication with corticosteroid, antihistamines and analgesics at day 1. In our division, from May 2022 to date, 18 patients with CLL have been treated with Obinutuzumab-Venetoclax in I line. Our therapy provides for 3 days prior to Obinotuzumab administration (day1), premedication with Prednisone (25mg 1 cpr twice a day) and Cetirizine (10mg 1 cpr twice a day); on the previous day, 500ml saline solution, Rasburicase 2 fl and 250cc bicarbonate solution in DH; from day -3 to day +10 home hydration with 500ml saline solution twice a day; on day1 premedication with oral paracetamol and antihistamine and iv corticosteroids 30-60 minutes before administration. During the first 10 days of therapy, patients visited the DH every other day for evaluation of blood count and liver/renal function. No patient required hospitalization. One patient needed weekly transfusion support for 20 days, six patients required support with G-CSF for neutropenia without fever. A grade I infusion reaction resolved with corticosteroids and the patient re-started treatment after 30 minutes. By day 22, all patients had disappeared leukocytosis, reduced splenomegaly by 30% and reduced lymph node swelling by 50% with a clear reduction of the risk of TLS, which did not occur in any of our patients after the addition of Venetoclax. The Obinutuzumab-Venetoclax combination is the first fixed duration chemo-free protocol used in first line CLL. In our scheme, premedication significantly reduced the risk of infusion reactions. The debulking action performed by Obinutuzumab in the first 22 days lowered the risk of TLS following Venetoclax administration, which is important for the depth of response.

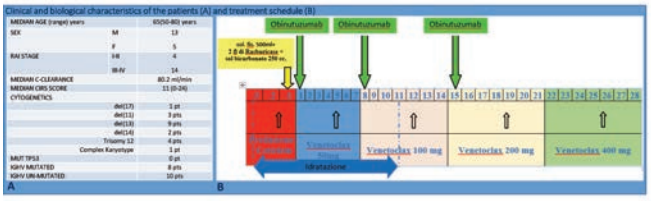

Figure 1.

SP19

ITALIAN MULTICENTRIC OBSERVATIONAL SECONDARY DATA COLLECTION STUDY OF ACALABRUTINIB IN THE TREATMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (ARISE)

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Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults in Western countries. The annual incidence of CLL in Italy is approximately 5 cases per 100,000 inhabitants, most of which occur in men with a median age of 70 years at diagnosis. (I numeri del Cancro 2021, AIOM). The efficacy and safety of acalabrutinib, a selective next-generation Bruton Tyrosine Kinase (BTK) inhibitor, have been assessed in three phase III clinical trials, ELEVATE-TN (treatment-naïve CLL), ASCEND and ELEVATE-RR (relapsed and refractory CLL). These pivotal randomized clinical trials established the efficacy and safety of acalabrutinib in CLL patients; however, further data are required to evaluate its use in the real-life setting. ARISE is an Italian non-interventional/observational, multicentre, longitudinal secondary data usage study, based on a retrospective cohort of patients with CLL who initiated treatment with acalabrutinib according to Italian legislation dlg 219/2006 art.125 between 1st May 2021 and 30th April 2022 (index date). Data will be collected from medical records at several time points covering a period of at least 5 years after first acalabrutinib dose. All consecutive CLL patients who received acalabrutinib within the index date are eligible for enrolment. The primary endpoint of the ARISE trial is to evaluate the time to treatment discontinuation for acalabrutinib in a real-world setting. Secondary endpoints include analysis of patients demographics and clinical characteristics; and acalabrutinib treatment patterns (e.g. dose modification and, temporary or permanent

discontinuation and their reasons). The study will also describe acalabrutinib effectiveness in terms of Progression Free Survival (PFS); Overall Survival (OS); Overall Response Rate (ORR – categorization according to the iwCLL) and Time To Next Treatment (TTNT). The study aims to include around 200 patients treated in about 45 Italian sites. Retrospective data collection will start in Q3 2023 and five data extractions are planned (one each year) to generate evidence for the whole study duration. This study will provide the first real-world data on the use of acalabrutinib in treating CLL in Italy.

SP20

BRUIN CLL-322: A PHASE 3 OPEN-LABEL, RANDOMIZED STUDY OF FIXED DURATION PIRTOBRUTINIB PLUS VENETOCLAX AND RITUXIMAB VERSUS VENETOCLAX AND RITUXIMAB IN PREVIOUSLY TREATED CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (TRIAL IN PROGRESS)

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Background. The MURANO study established 2-year fixed duration venetoclax+rituximab as a standard of care regimen for patients with relapsed/refractory CLL/SLL, though its efficacy has not been formally assessed in CLL/SLL patients treated with a covalent Bruton tyrosine kinase inhibitor (cBTKi). Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi, inhibits wildtype and C481-mutant BTK with equal low nM potency and has favorable oral pharmacology that enables continuous BTK inhibition throughout dosing interval regardless of intrinsic rate of BTK turnover. In phase 1/2 BRUIN, pirtobrutinib demonstrated promising durable overall response rates (ORR) and was well tolerated in patients with pretreated CLL/SLL regardless of prior therapy (including cBTKi), number of prior lines of therapy, BTK C481 mutation status, or reason for prior cBTKi discontinuation. The objective is to assess the superiority of adding time-limited pirtobrutinib to the MURANO regimen, hypothesized to prolong disease control in a largely BTKi-pretreated population.

Methods. BRUIN CLL-322 (NCT04965493) is a randomized, open-label, global, phase 3 study comparing time-limited pirtobrutinib (200 mg QD)+venetoclax and rituximab *vs* venetoclax and rituximab in previously treated CLL/SLL patients. Approximately 600 patients, 80% who have been previously treated with cBTKi, will be randomized 1:1 and stratified by del(17p) status (yes/no) and prior BTKi experience (discontinuation due to progressive disease *vs* due to other reasons *vs* no prior BTKi exposure). Eligible patients are adults diagnosed with CLL/SLL and require therapy per iwCLL 2018 criteria who have received prior therapy that may/may not include a cBTKi. There are no restrictions on the number of lines of prior therapy. Key exclusion criteria include CNS involvement by CLL/SLL, Richter transformation at any time, prior BCL2 inhibitor/non-covalent BTK inhibitor, or a history of allogeneic or autologous stem cell transplant, or chimeric antigen receptor T-cell therapy within 60 days prior to randomization.

The primary endpoint is progression-free survival (PFS) per iwCLL criteria assessed by an independent review committee. Secondary endpoints include investigator-assessed PFS, ORR, overall survival, time to next treatment, event-free survival, safety and tolerability, and patient-reported outcomes. Enrollment is ongoing for patients previously treated with BTKi and completed for BTKi-naïve patients.

SP21

TRANSCRIPTOMIC SIGNATURE OF A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA WITH DEEP FLUCTUATIONS OF LYMPHOCYTOSIS IN NUTRITION AND PROLONGED FASTING PERIODS

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We aimed to investigate the causes of deep fluctuations of lymphocytosis in an untreated patient with Chronic Lymphocytic Leukemia (CLL) with good prognosis since the time of diagnosis. So far, the patient voluntary decided to follow a mainly vegetarian and fruitarian diet, with a periodical prolonged fasting (from 4 to 39 days) every year. To this end, we performed a gene expression profiling analysis of peripheral blood (PB) CD19+ cells of this patient (#1) at different time points with respect to the same cells in 5 untreated patients with CLL who eated a various diet. Therefore, CLL patients were divided in two cohorts: the 1st group composed of patient #1 at 20 time points (16 time points during nutrition and 4 time points during fasting), and the 2nd group consisted of one time point for each patient (#2, #3, #4, #5, and #6) because they followed a varied diet. Gene expression experiments were carried out using Affymetrix Human Clariom D Pico Assay.

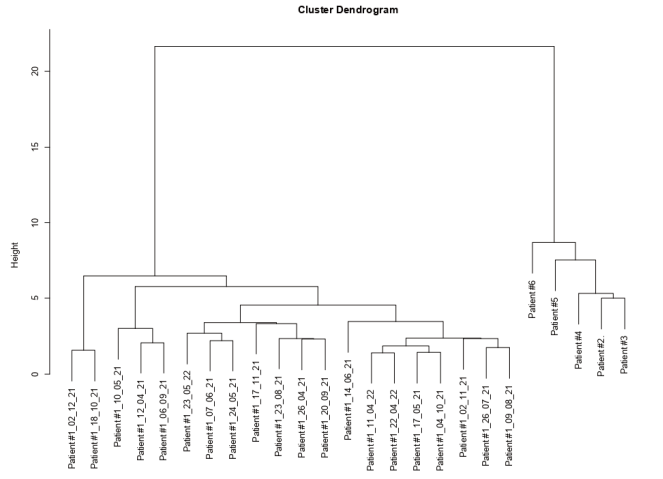

Figure 1. Clustering results. The figure illustrates the outcomes of clustering (hierarchical agglomerative clustering) achieved by grouping samples according to the similarities in gene expression of the differentially expressed genes.

A statistical analysis was conducted to select differentially expressed genes and perform the clustering of samples. Lymphocytosis pattern of patient #1 showed recurrent deep fluctuations since diagnosis, and interestingly, we noticed that approximately 4-6 weeks after the end of fasting the absolute number of lymphocytes was about halved. The results of gene expression profiling showed that 9 genes were statistically differential expressed between the 1st and 2nd groups. IGLC3, RPS26, CHPT1, and PCDH9 were under expressed, whereas IGHV3-43, IGKV3D-20, PLEKHA1, CYBB, and GABRB2 were over expressed in the 1st group *vs* the 2nd group of CLL patients, respectively. Additionally, cluster analysis confirmed that all samples from patient #1 were grouped relative to samples from other CLL patients (Figure 1).

In conclusion, our transcriptomic study showed a small set of nine genes which characterized an untreated CLL patient, who followed a prolonged fasting period and maintained a slow-growing tendency of lymphocytosis, compared to 5 untreated CLL patients with a varied diet. Future investigations of patient #1 could demonstrate the potential role of prolonged periodic fasting and the involving of the nine genes in maintaining the trend of lymphocytosis and the benign course of the disease.

SP22

OBINUTUZUMAB/VENETOCLAX (VEN-O) FIRST LINE TREATMENT IN CLL, SINGLE CENTER EXPERIENCE

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Chronic Lymphocytic Leukemia (CLL) is the most prevalent form of leukemia in the western world. Current first line treatment options include time limited Venetoclax plus Obinutuzumab (VenO), approved for unfit CLL patients (pts) according to CLL14 study. Here we report our center experience with 8 pts affected from CLL, treated in AOU Policlinico of Naples Hematology Unit between September 2022 and May 2023 and receiving at least one cycle of first line treatment with VenO. Median age at diagnosis was 59 yo (range 41-64). Median interval from diagnosis to treatment was 48 mo (IQR 3-81). All pts were p53 wild-type. IgHV status was unmutated in 63%. 38% had NGS adverse mutations. Pretreatment assessment comprehended: Binet and Rai stage (median was C and IV, respectively), comorbidity evaluation (median CIRS score 2,5), PS rating (all pts had ECOG 0) and Tumor Lysis Syndrome (TLS) risk score appraisal (high risk in 38%). At clinical exam/ultrasonography before therapy all pts had splenic enlargement and enlarged lymph nodes. 50% pts completed 6 obinutuzumab cycles; 75% reached Venetoclax dose of 400 mg die; 25% are currently completing the ramp-up. Median duration of the escalation was 35 days (range 35-44). 1 pt suspended Venetoclax for thrombocytopenia. Median dose intensity was 100% (range 80-100) Table 1.

Table 1. Dose modifications and discontinuations due to adverse events. Abbrev: AE, Adverse Events; VenO, Obinutuzumab/Venetoclax.

PATIENTS (n=6)	
Dose reduction due to AE, n (%)	1 (17%)
Treatment emergent (VenO) AE leading to treatment discontinuation, n (%)	1 (17%)
Treatment discontinuation due to any AE, n (%)	0
Median dose intensity, % (range)	100 % (80-103)

TLS prophylaxis consisted of oral hydration and oral uricosuric drugs for all pts, 38% received in addition EV hydration and 38% rasburicase, respectively, according to TLS risk score assessment. All pts received anti-infective prophylaxis with Acyclovir 400 mg BID, Trimetoprim/sulfametoxazol 2 cp twice weekly, Lamivudine 100 mg once daily (only if HBsAg neg, HBcAb pos). 38% received Covid19 infection prophylaxis with tixagevimab/cilgavimab within the 3 weeks before the treatment was started. Subcutaneous filgrastim was given as prophylaxis of neutropenia in 6/8 pts (median injections of 3 for the first cycle, 5 for the 2nd, 4 for the 3rd, 3 for the 4th, 2 for the 5th and 4 for the 6th). Further supportive care consisted of subcutaneous erythropoietin for Hb values of <10 and blood transfusions in 2 pts for hb mean value of 7 g/dL. Infusion reaction to first Obinutuzumab administration (grade 2 to 3) was observed in 4/8. 1 pt developed lab TLS according to Cairo-Bishop criteria. Only 1 pt developed symptomatic Covid19 infection and 1 pt labial herpes during VenO treatment. After the first cycle of treatment, response was evaluated with blood count, clinical examination and Cytofluorimetric exam on peripheral blood sample, achieving complete response in all pts.

SP23

EFFICACY AND SAFETY OF THE COMBINATION OF VENETOCLAX AND RITUXIMAB FOR THE TREATMENT OF A DIALYSIS PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction. The BCL-2 inhibitor Venetoclax has shown high efficacy in patients with newly diagnosed or previously treated chronic lymphocytic leukemia, changing the standard of care, and replacing chemo-immunotherapy regimens. We have shown the safety and the efficacy of the combination of venetoclax with rituximab in a patient with terminal renal failure in three weekly hemodialysis.

Patient characteristics and Methods. We describe the case of a 62-year-old patient diagnosed in 2003 with CLL, previously treated with Chlorambucil, and chemo-immunotherapy with R-CVP regimen. In February 2021 he developed moderate thrombocytopenia and anemia, enlarged spleen (22 cm) and multiple lymph nodes (maximum 4 cm). Bone marrow biopsy confirmed clonal B infiltrate with hemopoiesis reduction, while biological study didn't document high-risk mutations, and the IgHV mutational status was favorably mutated. However, the patient presented with renal failure not CLL-related and anti-CLL treatment was delayed. The high hemorrhagic risk of the patient, burdened by the anticoagulant therapy necessary for the future hemodialysis, together with the non-adverse biological risk, didn't favor a treatment with Bruton tyrosine kinase inhibitors. On the other hand, the well-known risk of Tumor Lysis Syndrome related to venetoclax contraindicated to start treatment before the patient undertook dialysis. So, we decided at first to start dialysis followed, after a week, by the ramp-up of venetoclax, taken after the hemodialysis session, prolonging the dose-escalation phase to 10 weeks, with dose increments every 2 weeks.

Results. The patient completed the 10-week ramp up phase reaching venetoclax full dose of 400 mg once a day, and the six infusions of monthly Rituximab were carried out, followed by venetoclax alone for 24 months. In April 2023, at the end of the treatment the patient has not reported extra-hematological and hematological toxicities, and instrumental re-evaluations of the disease showed disappearance of lymph nodes and normalization of splenic dimensions, while the cytofluorimetric assessment of Minimal Residual Disease on peripheral blood has shown a complete response with incomplete hematological recovery.

Conclusions. The fixed-duration treatment with Ven-R showed

high efficacy and feasibility even in patients with renal failure on dialysis and with high hemorrhagic risk, for which BTK-inhibitors may not represent a safe therapeutic alternative.

SP24

DURATION OF RESPONSE ACCORDING TO MEDIAN RECYCLING DELAY IN AML PATIENTS TREATED FRONTLINE OR AT RELAPSE WITH HYPOMETHYLATING AGENTS AND VENETOCLAX

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The combined of hypomethylating agents (HMA) and venetoclax (VEN) has been recently approved for treatment of unfit acute myeloid leukemia (AML) patients. After achieving complete remission, treatment should be continued until disease progression but is often associated with prolonged cytopenia leading to a delay among subsequent cycles. Current expert opinions suggest to postponing upcoming post-remission cycles for up to 14 days.

Table 1.

Table 1. Patients' baseline clinical characteristics according to median delay between cycles

Parameter	<10 days, n=12 (54%)	>10 days n=10(46%)	p-value	<14 days n=14(63%)	>14 days n=8(37%)	p-value
M/F	3/9 (1/3)	8/2 (2/1)	p=0.03	3/11 (1/3.6)	8/0	**p=0.001**
Age, years (range)	73,1 (61-80)	69,3 (52-78)	p=0.08	73.5 (61-80)	67.5 (52-75)	**p=0.01**
N° of cycles (range)	10,2(3-23)	5.8(3-14)	p=0.01	10.5(3-23)	4.1(3-7)	**p=0.0006**
Line of therapy, n (%)			p=0.6			p=0.3
• First line (FL)	9 (75)	6(60)		11(78.5)	4(50)	
• Relapsed/Refractory (RR)	3(25)	4(40)		3(21.5)	4(50)	
AML WHO type, n (%)			p=0.6			p=0.3
• *De novo*	9(75)	6(60)		11(78.5)	4(50)	
• Secondary (MDS or MPN)	3(25)	4(40)		3(21.5)	4(50)	
ELN 2017 risk group in FL, n (%)			p=0.2			p=0.4
• Favorable	4(44)	1(17)		1(9)	1(25)	
• Intermediate	2(22)	2(33)		4(36)	0	
• Adverse	1(11)	1(17)		4(36)	1(25)	
• Not available	2(22)	2(33)		2(19)	2(50)	
Medium re-cycling delay, days (range)	5.8 (0-9.6)	18.8 (10.7-39)	p=0.0001	6.5 (0-12.2)	20.7 (14-39)	**p=<0.0001**
Median DOR, months (95% CI)	NR	9.6 (2.8-16.6)	p=0.06	13.4(6.5-25)	7(2.8-9.6)	**p=0.0007**
Median OS, months (95% CI)	16.4 (3.9-25.9)	16.3 (4.1-17.6)	p=0.9	18.8(3.9-25)	12.5(4-17)	p=0.1

DOR, Duration of response; OS, Overall Survival; ELN,European Leukemia Net

This retrospective, single center analysis aims to evaluate the impact of re-cycling delay on treatment outcome and response duration, in patients achieving complete remission. We analyzed data of 22 patients (11 males and 11 females), treated frontline (FL, n=15) or at relapse (RR, n=7) with HMA-VEN who received at least two post-remission cycles of therapy. In the entire cohort the median age at diagnosis was 71 years (range 52-80) and the median number of cycles was 8.4 (range 3-23). FL patients had a median age of 72 years (range 52-80) *vs* 68.9 years (range 66-75) of RR patients. The median number of cycles received was 7.8 (range 3-16) for FL patients *vs* 9.7 for RR patients (range 3-23). The median delay of upcoming cycles was 9.4 (range 0-26) and 15.3 days (range 4-39) for FL and RR patients, respectively (p=0,365). We compared the outcome of the entire cohort by dividing patients according to the median delay between cycles [< 10 days, n=12 (54%) and > 10 days, n= 10 (46%); <14 days, n=14 (63%) and > 14 days, n=8 (37%)]. Patient' characteristics are summarized in Table 1. With a median follow up of 11 months (range 3-22), univariate analysis demonstrated that patients in the <10 days group had a longer duration of response (DOR) than >10 days patients (not reached *vs* 9.6 months, respectively; p= 0.06). Interestingly, DOR was significant different between patients in the < 14 days group than those in the > 14 days (13,4 *vs* 7 months, respectively; p=0.0007). In our small cohort these differences did not translate into a significant survival improvement (OS 18,8 *vs* 12,5 months, respectively for < 14 days and > 14 days group; p= 0,160). Despite the limited number of patients, these data suggest the importance of a correct adherence to treatment schedule in patients with post-remission cytopenia, by avoiding delay of more than 14 days between cycles re-initiation. Further studies are needed to confirm our results also considering the impact of reducing Ven dosing days.

SP25

EFFICACY AND SAFETY OF CHEMOTHERAPY PLUS GEMTUZUMAB OZOGAMYCIN IN FIT PATIENTS DIAGNOSED WITH UNTREATED ACUTE MYELOID LEUKEMIA: A REGIONAL MULTICENTRIC REAL LIFE EXPERIENCE

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Introduction. Gemtuzumab-ozogamycin (GO) is approved in combination with high-dose chemotherapy for treatment-naïve low and intermediate risk acute myeloid leukemia (AML). In this retrospective real-life multicenter study, we reported efficacy and safety of GO plus high-dose chemotherapy in newly diagnosed AML patients.

Patients and Methods. A total of 31 fit low and intermediate risk AML patients were retrospectively included in this real-life multicenter study between January 2020 and January 2023 (Table 1). GO was administered in combination with daunorubicin and cytarabine (3+7, N = 30; or 2+5, N = 1) at standard dose on days 1, 4, 7 of induction, and on day 1 of consolidation for up to two cycles. Primary endpoint was complete remission (CR) rate. Secondary endpoints were overall survival (OS), minimal residual disease (MRD) negativity, and safety.

Results. In our cohort, CR rate after induction was 77%. Most responders (45%) received two GO-based consolidation, and MRD negativity was observed in 11 cases (35%) after the end of consolidation. Nine patients intensified therapy with autologous (N = 1, 3%) or allogenic (N = 8, 26%) stem cell transplantation. The 1-year OS was 77%. Low genetic risk was associated with increased CR rate compared to intermediate risk AML (88% *vs* 33%, respectively; P < 0.001), as well as prolonged OS (hazard ratio [HR], 0.16; 95% confidential interval [CI], 0.02-0.89; P < 0.001). NPM1 mutation was not correlated with better outcome (P = 0.94), while core binding factor (CBF) could influence AML prognosis (HR, 0.03; 95%CI, 0-87; P = 0.39), although not significant, likely because of the small number of subjects included in this group. Regarding safety profile, GO-treated patients commonly experienced fever of unknown origin (42% of cases) and sepsis (36%), with one death during induction due to septic shock. No cases of veno-occlusive disease after allogeneic transplantation were observed.

Discussion. Our real-life multicenter study confirmed GO-based treatment efficacy with high MRD negativity rates in fit newly diagnosed AML patients, especially in those with low genetic risk, while no significant benefits were observed in intermediate risk AML. Moreover, CBF AML subjects could greatly benefit from GO-based treatments. However, further validation on larger prospective cohorts is required.

Table 1. Patients' characteristics.

Characteristics	N = 31
Median age, years (range)	50 (19-68)
Gender, n (%)	
Male	13 (42)
Female	18 (58)
ELN risk stratification, n (%)	
Low	22 (71)
Intermediate	9 (29)
AML type, n (%)	
NPM1-mutated	15 (48)
FLT3-mutated	2 (6)
INV-16	4 (12)
t (8;21)	1 (3)
Bone marrow blasts, % (range)	58 (17-90)
Induction with GO, n (%)	
3+7	30 (97)
2+5	1 (3)
Complete response after GO-based induction, n (%)	
Yes	24 (77)
Number of consolidation courses, n (%)	
1	6 (20)
2 but only one with GO	4 (13)
2 with GO	14 (45)
MRD status after consolidation, n(%)	
Negative	11 (35)
Positive	7 (23)
Not available	6 (20)
Allogenic stem cell transplant, n (%)	8 (26)
Autologous stem cell transplant, n (%)	1 (3)
Refractory or relapsed AML, n (%)	11 (35)
Overall survival, median, months (range)	Not reached (1-32)
12-month overall survival, %	77
Safety, n (%)	
Neutropenia with FUO	13 (42)
Sepsis	11 (36)
Pneumonia	1 (3)
Typhlitis	1 (3)
Persistent thrombocytopenia	1 (3)
Death by toxicity	1 (3)

Abbreviations. Ig, immunoglobulin; IRR, infusion-related reaction; SC, subcutaneous. FUO, fever of unknown origin

SP26

CORRELATION OF FLT3/ITD-TKD AND NMP1 GENES WITH CD7 EXPRESSION IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML)

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AML represents a heterogeneous constellation of different immunophenotipic, cytogenetic and molecular subentities. The most frequent mutations in AML– FLT3-ITD and NPM1– are associated with a specific immunophenotipic. We evaluated the levels of surface antigens CD7+in AML patient population according to the combination of FLT3-ITD and TKD/NPM1 mutations. Mutations of the FLT3 gene occur in approximately 30% of all AML cases, with the internal tandem duplication (ITD) representing the most common subtype; approximately 25% of all AML cases). The prognostic value of a FLT3 mutation in the tyrosine kinase domain (FLT3-TKD, approximately 7-10% of all AML cases) is uncertain. NPM1 is a ubiquitously expressed nucleocytoplasmic shuttling protein that plays an active role in ribosomal protein assembly, chromatin remodeling, and DNA repair, replication, and transcription. Mutations in the NPM1 gene are note in□35% of AML cases. CD7 is a Tcell associated antigen expressed by the majority of mature Tcells. It is a member of immunoglobulin super family encoded by the CD7 gene mapping to chromosome 17q25.2-25.3, it is present in 30% of AML case and linked with poor prognosis.

Aim of this study was to evaluate the association of aberrant CD7 expression in AML patients with FLT3 and NPM1 mutation. We retrospectively analyzed 206 AML patient diagnosed to Hematology Unit of Cardarelli Hospital (Naples) 2018-2022. In our cohort, 91 were find to be positive for FLT3 (70 ITD positive, 17 TKD positive and 4 positive for both). CD7 was positive in 30 of the 91 FLT3 positive cases (33%). Of the 70 ITD positive cases, 26 were positive for CD7 (37%). Of the 17 FLT3-TKD positive cases, 2 were positive for CD7 (12%). The association CD7 positivity and FLT3 positivity was found to be significant using Pearson χ^2 is 9.94 (P=0.019). If analyzed the individual type of FLT3 mutation there was a statistically significant positive association of CD7 positivity with ITD mutation $\chi 2$ is 7.80 (P= 0.0061) but not with FLT3-TKD mutation $\chi 2$ is 2.8 (P= 0.0942). We also analyzed CD7 positivity cases with NPM1 positivity linked to FLT3 mutation. We found 86 cases positive for NPM1 and 25 also were positive for CD7 and ITD mutation (29%) χ^2 is 14.22 (P=0.002).

We can conclude that the expression of CD7 is statistically significative in association with FLT3-ITD but not association with FLT3-TKD, further the association with FLT3 ITD/NPM1 mutation was relevant and this is helpful to monitoring treatment.

SP27

EFFICACY AND SAFETY OF CPX-351 COMPARED TO STANDARD OF CARE CHEMOTHERAPY IN A REAL-LIFE STUDY: CONFIRMING PREVIOUS EVIDENCE AND FACING NEW CHALLENGES

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Background. Acute myeloid leukemia "myelodysplasia-related" and "post-cytotoxic therapies", as defined by 2022 WHO classification, represent very high-risk AML subgroups with adverse biological features; since 2017, CPX-351 has been approved as 1st line treatment in this setting. Currently, real-world experience is providing crucial data confirmation. Moreover, increasing knowledge in disease biology led to relevant changes in the diagnostic criteria of MR-AML.

Aim of this study is to compare CPX-351 and SOC chemotherapy in the treatment of AML-MRC and t-AML, in the real-world setting of S. Gerardo Hospital in Monza (IT).

Methods. This is a monocentric, observational, retrospective-prospective study with a historical comparison cohort: it enrolled 24 pts with newly diagnosed AML-MRC or t-AML in 2015-2022, 13 in CPX-351 and 11 in SOC cohort. Primary endpoint was OS; secondary endpoints explored efficacy, safety and HSCT outcomes. Diagnoses were based on 2016 WHO criteria.

Results. With a median follow up of 21.2 months, CPX-351 showed a trend towards better OS (NR *vs* 15.4 months, p = 0.6) and lower disease-related mortality (25% *vs* 83%), compared to SOC. CPX-351 was associated to slower hematologic recovery (median ANC recovery 35 *vs* 23 days). Higher rates of AEs in CPX-351 arm were reported (69% *vs* 30%), without a significant increase in severe infections and early mortality. CPX-351 showed a trend towards

higher CR/CRi rates at end of treatment, lower relapse rates and higher rates of HSCT in CR/CRi. In CPX-351 cohort, 7/13 pts underwent MRD monitoring with WT-1: MRD negativity was obtained after 1st induction in 6/7 pts and after HSCT in 1/7.

MRC-AML diagnoses were reviewed: 3/24 pts, showing only morphologic dysplasia, wouldn't meet 2022 WHO criteria. Considering new MR-AML-defining somatic mutations, we observed 1 mutation in U2AF1 and 3 in ASXL1; 1 patient was TP53+.

Conclusions. Our study confirms safety and efficacy of CPX-351 in MRC-AML and t-AML. Prolonged neutropenia without severe infections excess suggests that liposomal formulation leads to selective marrow toxicity with low mucosal damage. MRD monitoring is crucial in high-risk AML: WT-1, together with flow-cytometry, is a promising tool in the absence of more reliable markers. New WHO criteria outline the role of molecular biology in defining MR-AML: further research is needed to identify subgroups that would benefit from CPX-351 and selected pts, such as TP53+, eligible to biological therapies.

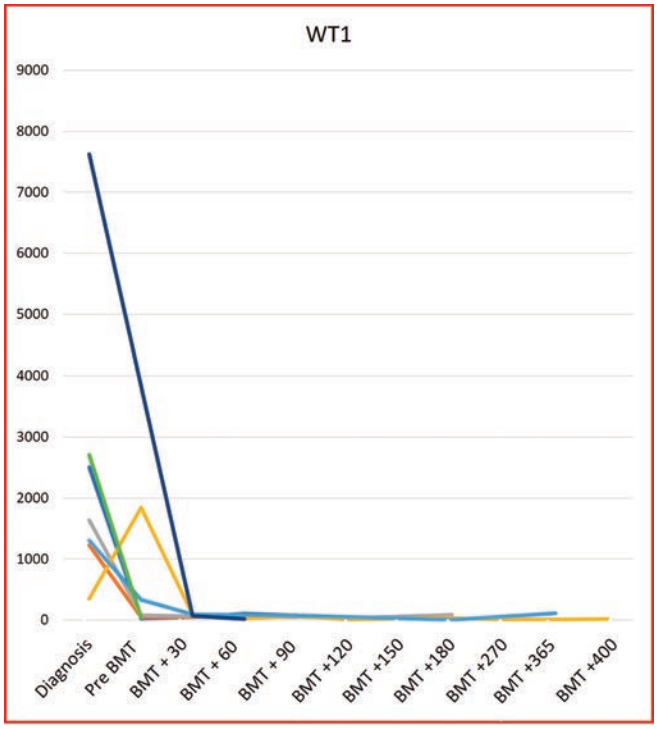

Figure 1.

SP28

APL-LIKE ACUTE MYELOID LEUKEMIA WITH A RARE CPSF6-RARG FUSION GENE: A CASE REPORT

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Acute Promyelocytic Leukaemia (APL) is a subtype of Acute Myeloid Leukaemia (AML) caused by a specific somatic chromosomal 15;17 translocation, which encodes for the PML-RARA oncogene. Less than 2% of APL cases can involve variant translocations that typically involve RARA. In addition, rare cases have been reported where other retinoic acid receptors (RARB and RARG) were involved in AML with promyelocytic features. We now report on a case of a patient who presented with typical APL clinical and laboratory signs but was diagnosed with APL-like AML with an extremely rare RARG fusion. The patient was a 53-year-old white man with a one-week history of fatigue and bruises on the entire body surface. Blood tests showed trilinear cytopenia and coagulopathy with low FBG level and high dimer levels. The bone marrow aspirate showed massive infiltration of blasts with appearance of promyelocytes and numerous Auer rods. Since the clinical presentation and the morphologic and immunophenotypic analysis of the bone marrow were highly suggestive for APL, ATRA+ATO was initiated even before the presence of PML-RARA fusion was confirmed. Two days later results showed that the karyotype was normal and both PCR and FISH for PML-RARA were negative. Later, a FISH RARA break-apart probe failed to show a rupture of the RARA gene. A RNA-Seq analysis identified the presence of CPSF6-RARG fusion gene, which has been previously described in 8 cases of APL-like AML, characterized by a lack of response to ATRA+ATO and a grim prognosis. Given these molecular data, the absence of clinical improvement, the persistent coagulopathy and the lack of differentiation signs induced by the treatment, we interrupted ATRA+ATO and started 3+7 chemotherapy regimen with idarubicin and cytarabine. During the chemotherapy administration we observed a transient clinical and laboratory improvement of coagulopathy, but without normalization of the values. A bone marrow aspirate on day +15 evidenced persistence of disease. Shortly after, our patient experienced a septic shock for which he started antibiotic therapy with clinical benefit. Unfortunately, before we could begin a second line salvage treatment, he died after 28 days of hospitalization due to a brain haemorrhage. In conclusion, we describe the diagnostic process and clinical course of a case of APL-like AML with CPSF6-RARG fusion gene, and report the correlation of this rearrangement with a lack of response to ATRA+ATO and a negative prognosis.

SP29

ACUTE MYELOID LEUKEMIA IN PREGNANCY: CASE REPORT OF A YOUNG WOMAN TREATED WITH AZA-VENETOCLAX IN THE IMMEDIATE POST- PARTUM

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To date, the management of the pregnant patient with acute myeloid leukemia remains a challenge. The severity of the disease requires the immediate start of intensive chemotherapy, but it should be considered that antileukemic treatment may be associated with serious adverse events for the fetus, especially in the first two trimesters of pregnancy. The outcomes in these patients have not been systematically studied and have been limited to case reports. Based on available data, standard high-dose chemotherapy regimen should be considered at a late stage of pregnancy. However, only a few small trans-placental studies have been conducted to evaluate drug concentrations in amniotic fluid and fetal tissues. In this report we discuss the case of a 36-years-old woman with acute myeloid leukemia diagnosed at 25th week of gestation and managed by a multidisplinary team of hematologists, gynecologists and neonatologists; she presented with mild symptoms mainly characterized by monocytosis, anemia, thrombocytopenia and severe gingival hyperplasia. The blast population was up to 14%; Next Generation Sequencing (NGS) evidenced NPM1, FLT3 and DNMT3A mutations. Based on clinical presentation and laboratory data, the patient was kept in fol-

low-up, monitoring the blastic quote every week in order to start the treatment as late as possible. Because of the stability of symptoms and blastic cells count that remained under 10% for the subsequent weeks, the delivery was planned and done at 32 weeks; no adverse events for both mother and newborn were observed. Soon after the delivery, bone marrow re-evaluation showed increase in the blast population (90%) and an appropriate treatment was planned. Although the patient was eligible to standard high-dose chemotherapy in the ordinary inpatient setting, in order to fulfill the patient's wish to nurse the new born an out-patients treatment, consisting of hypomethylating agents with Azacytidine plus antiBcl2 (Venetoclax), was started. The follow-up was free for any adverse events and a complete haematological response was obtained after the fourth cycle; the bone marrow aspirate confirmed complete leukemia remission and the patient is now candidate to allogenic bone transplantation. Our case highlights the complexities of AML management in pregnancy; accordingly to recently published data, late onset of antileukemic therapy may be considered in special population.

SP30

ARSENIC TRIOXIDE NEUROTOXICITY IN ACUTE PROMYELOCYTIC LEUKEMIA PATIENTS: SINGLE CENTER EXPERIENCE WITH LITERARATURE REVIEW

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Combination of arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) is the standard of care in patients with low/intermediate risk acute promyelocytic leukemia (APL). Neurological toxicity including peripheral neuropathy and cerebellar disfunction are known signs of arsenic poisoning, but evidence of neurologic adverse events (AEs) in APL patients treated with ATO are limited to few case reports. Further, the association between ATO and the development of neurologic AEs was not clearly established. The Eudravigilance database (European database of suspected AEs reports) shows 115 cases of suspected neurological AEs to ATO: 41 in APL patients. Here we present three cases of neurotoxicity secondary to ATO exposition occurred in our Hematology Department in the last five years; the correlation between symptoms and ATO was estimated with the Naranjo algorithm. Case 1: A 59-year-old woman with an intermediate risk APL treated with ATO plus ATRA, developed incoercible vomiting and paralytic ileus, followed by hyporeactivity and paraesthesia of limbs at the end of induction phase. Neurologic examination showed weakness of limbs, muscle atrophy of extremities and absence of tendon reflexes. Electromyography showed axonal sensorimotor polyneuropathy and neuro counselling suggested Guillan-Barré syndrome or pharmacological neurotoxicity. With thiamine and cobalamin supplement and physiotherapy, her neurological signs and symptoms gradually improved until complete regression. Naranjo algorithm showed a probable association. Case 2: A 52-year-old woman relapsed after 10 years from treatment with ATRA plus chemotherapy and was started on ATO plus ATRA. During the induction phase, she developed paraesthesia and peripheral neuropathy in the limbs, with fingers and toes tremors. Brain MRI was negative. AEs were managed with clonazepam and ATO dose reduction. The association with Naranjo algorithm was probable. Case 3: A 55-year-old female with a diagnosis of low-risk APL, treated with ATO plus ATRA, developed paraesthesia in the feet in the first consolidation course, with extension to the hands and lower limbs in the subsequent courses. No ATO dose reduction was applied; mild symptoms are still present after 3 years from the end of treatment. Naranjo algorithm showed a probable association. Finally, early recognition and prompt management of neurological AEs is crucial in a disease nowadays highly curable such us low/intermediate risk APL.

SP31

EARLY RENAL SUPPORT IN THE TREATMENT OF ACUTE MYELOID LEUKEMIA WITH ACUTE KIDNEY INJURY (AKI)

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The onset of AKI is an important negative prognostic factor in Acute Myeloid Leukemia (AML). Whether or not to provide kidney replacement therapies, and when to start, are fundamental issues in severe AKI. In some cases, renal support by hemodialysis can be used to enhance kidney function, modify fluid balance, and administer drugs without concerns about drugs and fluid accumulation.

Case 1. A 56yo man had a diagnosis of NPM1 mutated, FLT3-ITD mutated AML. Blood tests revealed creatinine 2.98mg/dL, uric acid 10.5mg/dL, K 2.7mg/dL, Ca 8.7mg/dL, Mg 1.58mg/dL, P 4.9mg/dL, LDH 515Ui/L, WBC 100'600/uL. Renal ultrasound was compatible with acute damage. To safeguard renal function and prevent tumor lysis syndrome related AKI (TLS-AKI) he started chemotherapy followed, each day, by dialysis in the next morning: Fludarabine 30mg/sqm 75% (5 days); Cytarabine 1500mg/sqm 66% (5 days); Idarubicin 6mg/sqm 75% (day 3-4); associated with G-CSF 30MUi (6 days), and Venetoclax (14 consecutive days) according to scheme. The patient performed a total of five 4 hours dialysis, well tolerated and was finally discharged (+36 days from the end of chemotherapy) in good condition with neutrophils >500/uL and creatinine 0.94 mg/dL.

Case 2. A 71yo woman had a diagnosis of NPM1 mutated, FLT3 wild-type AML. Blood tests revealed creatinine 2.67mg/dL despite adequate hydration, uric acid 6.3mg/dL, K 4.4mg/dL, Ca 8.6mg/dL, Mg 1.77mg/dL, P 4.1mg/dL, LDH 2544Ui/L, WBC 24'600/uL. Renal ultrasound was compatible with acute damage. To safeguard renal function and prevent TLS-AKI, she started chemotherapy followed by dialysis in the next morning: Fludarabine 20mg/sqm 80% (5 days); Cytarabine 1600mg/sqm 63% (5 days); Idarubicin 5mg/sqm 50% (day 1-3-5). The patient performed a total of five 4 hours dialysis sessions, which were well tolerated, serum creatinine settled around 1.56-1.7mg/dL and the patient was discharged (+17 days from the end of chemotherapy) in fair general condition with neutrophils >500/uL. During the cytopenic phase both patients had infectious complications treated with nephrotoxic antibiotic therapy, without further renal toxicity.

Conclusions. Renal impairment is an exclusion criteria for high intensity chemotherapy, in our two AML patients renal support by hemodialysis allowed potentially curative treatment without worsening of renal function. Both patients achieved complete remission and underwent consolidation with high dose cytarabine.

SP32

EARLY ONSET OF INFECTIOUS COMPLICATIONS IN AML PATIENTS TREATED WITH HYPOMETHYLATING AGENTS AND VENETOCLAX: A SINGLE CENTRE EXPERIENCE

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The combination of venetoclax (VEN) and hypomethylating agents (HMA; either azacitidine or decitabine) significantly improved outcomes and became the standard of-care treatment for newly diagnosed acute myeloid leukemia (NDAML) patients ineligible to intensive chemotherapy. Despite evidence of benefit, VEN-HMA therapy is commonly complicated by prolonged and profound neutropenia, exposing patients to an increased risk of infections throughout the course of therapy. We retrospectively investigated the incidence and timing of infectious complications in 13 patients who received at least one cycle of venetoclax in combination with azacitidine or decitabine between October 2020 and March 2023. Median patients' age was 74 years. Patients were hospitalized from the beginning of the first cycle of therapy until they recovered from severe neutropenia (i.e. neutrophil count $\geq 0.5x10^9$/L). They received antifungal prophylaxis with posaconazole but no antimicrobial prophylaxis. Of the 13 patients, 6 (46%) experienced infectious complications during the observation period. A total of 9 infectious events were observed, 7 (78%) ≥ grade 3 and 2 (22%) ≤ grade 2. Most of the infectious complications were pneumonia and occurred during the first cycle of therapy and none of them were lethal. Every patient was in neutropenia at the onset of infectious complications, which occurred after a median of 12 days. The median onset time of grade 3 infectious complications was 12 days.

In conclusion, we confirm the high risk of infections related to the adoption of the combination VEN-HMA in AML patients ineligible to intensive chemotherapy. However, in our experience the infections mainly occur early after the start of first cycle while the incidence is drastically reduced thereafter in spite of the typical prolonged neutropenia and in the subsequent cycles. These findings could help physicians in defining the right time for a safe discharge.

SP33

GILTERITINIB MONOTHERAPY AS A TRANSPLANT BRIDGING OPTION FOR HIGH RISK FLT3-MUTATED NPM1 MUTATED AML IN MORPHOLOGICAL BUT NOT MOLECULAR REMISSION FOLLOWING STANDARD INDUCTION AND SAVAGE THERAPY

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The presence of internal tandem duplications (ITD) of the related-receptor-tyrosine kinase 3 (FLT3) gene is a poor prognostic marker at diagnosis and in refractory or relapsed cases of Acute Myeloid Leukemia (AML). Currently, new target therapies are available for these patients, such as the oral selective FLT3 inhibitor Gilteritinib

Case Report: On February 2022, a 54 years old female patient, came to our observation for leukocytosis, anemia, thrombocytopenia in addition to right apical bronchopneumonic outbreak and SARS COV2 infection. She received diagnosis of chronic myelomonocytic leukemia. The patient started cytoreductive therapy with hydroxyurea but after recovery from the SARS COV2 infection, presented cutaneous nodularities, jet vomiting, eyelid ptosis and decreased visual acuity. Histological analysis of skin lesions was consistent with infiltration by leukemic disease, and examination of CSF showed leukemic meningosis. She started induction chemotherapy 3+7 regimen plus anti-CD33 gemtuzumab-ozogamicin therapy and medicated lumbar punctures with cytarabine. There was neutrophil and platelet recovery and bone marrow examination showed complete remission. HLA typing was started. The re-evaluation of the disease showed a picture of acute monoblastic myeloid leukemia positive for NPM1 and FLT3-ITD mutations. She was initiated into salvage therapy according to IDA-FLAG scheme and, because of not hematologic recovery, she started gilteritinib at dose of 120 mg/day monotherapy as a transplant to bridge option. Central nervous system involvement was excluded. After six weeks, repeated bone marrow examination demonstrated morphological complete remission but the persistence of 3.3% NPM1 mutation. The patient was started to pre-transplantation work up but unfortunately a cytomegalic infection complicated by acute heart failure led to the death of the patient. In conclusion, this case report points out some effects of Gilteritinib: the potential utility of FLT3 inhibitors in relapsed AML patients, the safe administration, the efficacy of gilteritinib monotherapy also as a bridge to transplantation, the ability to clearance blast percentage in a short period of time.

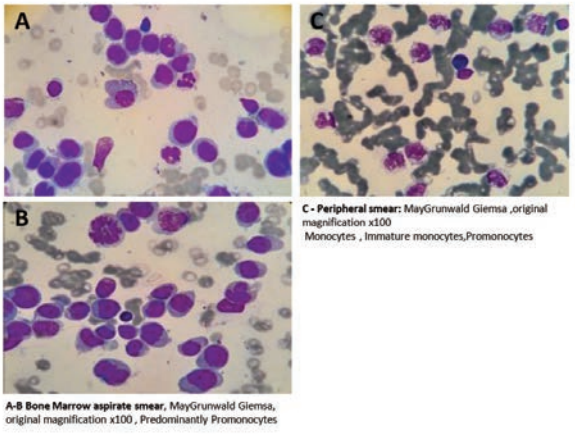

Figure 1.

SP34

PERMANENT DISCONTINUATION OF TYROSINE KINASE INHIBITOR FRONTLINE THERAPY IN PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA DURING THE FIRST 2 YEARS OF TREATMENT: A "CAMPUS CML" STUDY

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Background. The first years of tyrosine kinase inhibitors (TKIs) therapy are crucial to achieve optimal response in chronic phase (CP) chronic myeloid leukemia (CML) patients (pts); however, in this early period, toxicities or suboptimal response/resistance may occur, leading to permanent discontinuation of frontline TKI a need for a second-line treatment.

Methods. To evaluate in a large real-life cohort of CML pts the incidence and pattern of events leading to permanent discontinuation of frontline TKI during the first 2 years of therapy we retrospectively analysed 1459 pts diagnosed from 2012 to 2019 and treated with imatinib (IM) or second-generation (2G) TKIs dasatinib or nilotinib.

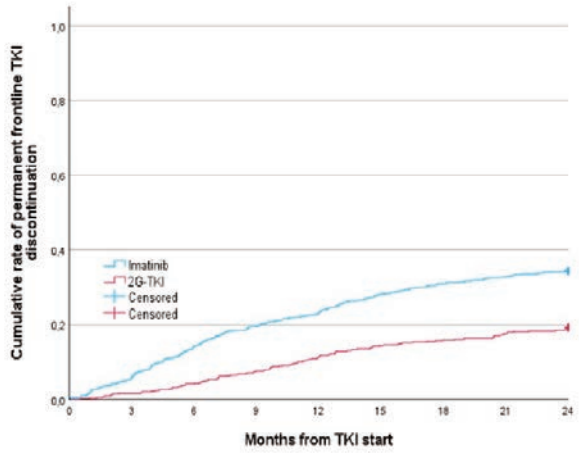

Figure 1.

Results. Frontline TKI was IM in 890 (61.0%) and 2G-TKIs in 569 (39.0%) cases; IM-treated pts were older (p<0.001) and had more comorbidities (p<0.001). Cumulative incidence of permanent TKI discontinuation was 19.7% [95% confidence interval (CI) 17.7-21.6] at 12 months and 28.1% (95%CI 25.8-30.4) at 24 months: cumulative incidence of discontinuation was significantly higher with IM compared to 2G-TKI at any time-point (p<0.001 - Figure 1). Among the 432 pts discontinuing therapy within 24 months, cause was hematologic toxicity in 33 (7.6%), extra-hematologic toxicity in 122 (28.2%), primary resistance in 185 (42.8%), secondary resistance in 17 (3.9%), evolution in blast phase in 19 (4.3%), unrelated deaths in 25 (5.8%) and other in 31 (7.4%). At univariate analysis, in addition to IM therapy, factors predictive for a higher rate of TKI discontinuation were age >65 years (p=0.001), WBC≥100x10^9/L (p<0.001), Hb <10 g/dL (p<0.001), spleen ≥5 cm below costal margin (p<0.001) and high Sokal score (p<0.001). At multivariate analysis, frontline IM (HR 3.22; 95%CI 2.34-4.42, p<0.001), WBC ≥100x109/L (HR 2.18; 95%CI 1.57-3.02, p<0.001), splenomegaly (HR 1.91; 95%CI 1.22-3.00, p=0.005) and high Sokal (HR 1.78; 95%CI 1.16-2.72, p=0.007) retained significance for TKI discontinuation.

Conclusions. This real-world study on over 1450 cases reveals that about 30% of newly diagnosed CML pts discontinued frontline TKI during the first 2 years of therapy, mostly for primary resistance or toxicity. Discontinuation rates were higher with IM compared to 2G-TKIs at any time-point: however, the role of elderly age, higher risk and more comorbidities in the IM cohort should be considered. Other factors seemed to affect the risk of frontline TKI discontinuation, but their role needs further investigations.

SP35

LONG-TERM SURVIVAL OF PATIENTS WITH MANTLE CELL LYMPHOMA: A SINGLE-CENTER, RETROSPECTIVE, 15-YEAR REAL-LIFE EXPERIENCE

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Introduction. Mantle-cell lymphoma (MCL) prognosis significantly improved since the introduction of rituximab and high-dose cytarabine-based first-line regimens, followed by autologous stem-cell transplantation. Ibrutinib represents an effective regimen for relapsed/refractory (R/R) disease. However, MCL is characterized by multiple relapses and the possible survival benefit of new therapies in last years should be evaluated, especially for elderly patients.

Methods. We would like to report our 15-year real-life experience, in which we investigated 73 consecutive MCL patients managed at our Institution from 2006 to 2020. Progression-free survival (PFS) was our first end-point. Survival analysis were performed using Kaplan and Meier method and our results were reported as a hazard ratio (HR), with its 95% confidence interval (CI).

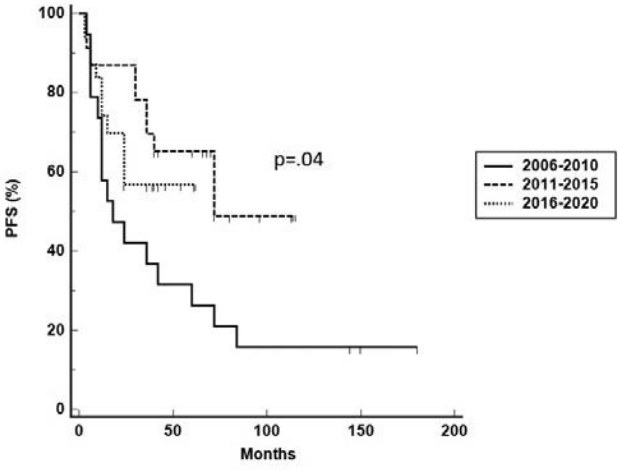

Figure 1.

Results. For younger patients <65 years old, median PFS was 72 months and we report a 2-year, 5-year and 10-year PFS of 73%, 62% and 41%; median OS was not reached and we report a 2-year, 5-year and 10-year OS of 88%, 82% and 66%. For patients aged between 65 and 74 years, median PFS was 36 months and we report a 2-year, 5-year and 10-year PFS of 64%, 47% and 23%, respectively; median OS was 84 months and we report a 2-year, 5-year and 10-year OS of 79%, 52% and 34%, respectively. For patients aged 75 years or older, median PFS was 36 months and we report a 2-year, 5-year and 10-year PFS of 52%, 37% and 37%, respectively; median OS was not reached and we report a 2-year, 5-year and 10-year OS of 72%, 55% and 55%, respectively. According to specified treatment periods (2006-2010, 2011-2015, 2016-2020), median PFS was 18 months, 72 months and not reached, respectively. Median PFS was significantly reduced for patients treated between 2006-2010 if compared to patients treated between 2011-2015 (HR 2.5716, 95% CI 1.15-5.7) and between 2016-2020 (HR 1.6803, 95% CI 0.72-3.88) (p=.04, Figure 1). Interestingly, there was a trend towards an improved OS for patients treated between 2016-2020 compared to 2006-2010 and 2011-2015 (5-year OS was 91%, 44% and 33%, respectively).

Conclusions. We observed a PFS improvement for MCL patients treated after 2010. This finding could be due to the introduction of BR as 1st line regimen for elderly patients, which demonstrated sustained efficacy. Furthermore, the abovementioned OS benefit during last 5 years for elderly patients could be due to the introduction of ibrutinib as ≥2nd line regimen in Italy.

SP36

EIGHT YEARS REAL LIFE MONOCENTRIC EXPERIENCE OF OUTPATIENTS R-DAEPOCH REGIMEN IN PMBCL

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Introduction. Primary Mediastinal B-Cell Lymphoma (PMBCL) represents about 2-7 % of all DLBCL and is most common in young female population (diagnosis median age 35 yo). Even if most patients (pts) can recover with first line therapy (thp), there is no consensus regarding standardized first line immunochemotherapy (IC) for PMBCL. We surely know that R-CHOP21 is a suboptimal thp; regarding the other available treatment options (R CHOP 14, R-VACOP B and R DAEPOCH) they all seem to be equally effective. Radiotherapy (RT) consolidation, previously largely used, is still a theme of discussion in complete remission (CR) pts. Here we show our center eight years long experience with outpatient administration of R DAEPOCH scheme.

Methods. 19 pts (17 pts with PMBCL and 2 pts with unclassficable features intermediate between DLBCL and classical Hodgkin lymphoma) diagnosed at our center from 2015 and 2022 were enrolled and clinical characteristics collected. All pts received 6 R DAEPOCH of outpatient treatment with the exception of the first cycle that often requested hospitalization for clinical presentation with mediastinal syndrome. Our aim is to evaluate OS, PFS, Response Rates and immediate and late toxicities (cardiological events and second malignancies).

Results. Median age was 41 yo at the diagnosis. 16/19 were stage I-II; 3/19 stage III-IV; everyone completed 6 cycles of R DAEPOCH; only 3 of them received RT. 16 obtained CR (84.2%) and 3 Partial Remission (15.8%). Median PFS was 60,7 mo, and OS 60,7 mo. 2/3 PR pts received RT consolidation and one second line thp. 79% (15/19) of patients were still alive with a median follow up of 60,7 mo. Adverse events were G4 Thrombocitopenyas (2/19), G4 Neutropenia (19/19), febrile Neutropenia (6/19) with 1/19 sepsys and 1/19 pneumonia. 5/19 paresthesia G2 with necessity of vincristine reduction. 4 pts died: 3 for relapse, 1 for COVID19 infection 7 mo after thp in CR. Only 1 pt had second malignancy (breast cancer) and 1 had a sequential Hodgkin lymphoma. No toxic cardiac events were seen.

Conclusions. In our experience outpatient R DAEPOCH scheme is an effective and safe therapy for PMBCL with an high rate of CR (84%) and both immediate and late toxicities. OS and PFS were comparable to literature data. In our center the use of a temporary pump for the infusion which was easily changed weekly made possible the somministration in a Day Hospital regimen improving quality of life of pts.

SP37

CLINICAL EFFICACY OF MAINTENANCE THERAPY WITH RITUXIMAB IN DIFFUSE LARGE B CELL LYMPHOMA PATIENTS IN PARTIAL REMISSION AFTER STANDARD CHEMOTHERAPY

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Diffuse large B-cell lymphoma (DLBCL), an aggressive B-cell non-Hodgkin lymphoma (NHL), is currently treated with rituximab-based high-dose chemotherapy as first-line therapy; however, 30-40% of subjects relapsed or are refractory and have a high risk of morbidity and mortality. Maintenance therapy with rituximab has demonstrated clinical efficacy in indolent NHL, while no conclusive or unsatisfactory data are reported for aggressive lymphomas with high rate of adverse events. In this real-life single-center experience, we investigated efficacy of maintenance therapy with rituximab in DLBCL patients in partial remission after standard chemotherapy with R-CHOP or R-COMP regimens. A total of 143 consecutive DLBCL patients were included in this study, from 2009 to 2022, and 18 of them (12.5%) were in partial remission after R-CHOP/R-COMP therapy evaluated by PET analysis. These subjects had a median age of 63 years old, and were mostly males (M/F, 13/5). Rituximab was given as maintenance therapy at 375 mg/m^2 with the following schedule: weekly for 4 weeks, and subsequently, every two months for 12 total administrations. At the end of treatment, a PET scan was performed to assess disease status. Primary endpoints were event-free survival (EFS), progression-free survival (PFS), and overall survival (OS). Most patients (55%) received R-CHOP, while the remaining 45% of subjects were treated with R-COMP because of advanced age and cardiovascular comorbidities. After standard chemotherapy, all patients displayed a partial remission at PET evaluation with a Deuville Score of 4-5. Seven patients (38.8%) received a second-line therapy before maintenance with rituximab. Median follow-up was 53 months, PFS and EFS were 53 months, and OS 60 months, and 77.7% of patients achieved a complete remission at the end of maintenance, while 16.6% of cases showed a partial remission. Toxicity was reported in 11.1% of cases with grade III liver toxicity and cytomegalovirus reactivation. Only one subject died for disease progression. In our real-life experience, maintenance therapy with rituximab was administered only in those DLBCL patients showing a partial remission at the end of standard chemotherapy with R-CHOP/R-COMP. This therapeutic strategy showed clinical efficacy with better outcomes and a safety toxicity profile. However, further validation in larger prospective randomized cohorts is required.

SP38

PRIMARY MEDIASTINAL B-CELL LYMPOMA: A MONOCENTRIC, RETROSPECTIVE EXPERIENCE

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Introduction. Primary mediastinal large B-cell lymphoma (PMBCL) is an aggressive lymphoma entity whose outcome has improved in recent years. However the chemotherapy (CHT) of choice and the role of radiotherapy (RT) are currently under discussion. The aim of this study was to evaluate the outcome of PMBCL pts in a monocentric, real-life setting.

Table 1. Patients clinical characteristic.

CHARACTERISTICS	N PATIENTS (%)
SEX male female	 16 (37,2%) 27 (62,8%)
ECOG PERFORMANCE STATUS (data available for 41 pts) 0-1 >2	 41 1
STAGE I/II III/IV	 31 (72,1%) 12 (27,9%)
HIV (data available for 31 pts) negative positive	 31 0
B SYMPTOMS absent present	 30 (69,8%) 13 (30,2%)
MEDIASTINAL BULKY absent present	 18 (41,9%) 25 (58,1%)
SUPERIOR VENA CAVA SYNDROME absent present	 24 (55,8%) 19 (44,2%)
PERICARDIAL EFFUSION absent present	 25 (58,1%) 18 (41,9%)
PLEURAL EFFUSION (data available for 40 pts) absent present	 19 21
LDH (data available for 40 pts) normal abnormal	 13 27
IPI SCORE (data available for 39 pts) 0-1 >2	 31 8
R-IPI SCORE (data available for 39 pts) 0 1-2	 8 31
THERAPY R-CHOP R-DA EPOCH R-MACOP-B	 30 (69,8%) 9 (20,9%) 4 (9,3%)
RADIOTHERAPY (data available for 41 pts) yes not	 30 11

Methods. We retrospectively collected clinical data of 43 consecutive PMBCL patients (pts) treated in our Institution from 2007 to 2019. Survival analysis was performed using Kaplan-Meier method, different groups were compared by log-rank test. Multivariate analysis was estimated by Cox's proportional risk regression and was expressed as a hazard ratio with 95% confidence interval. All statistical tests are two-tailed, and was considered the conventional cut-off of 5% as the threshold of significance. The statistical analysis was performed through the SPSS software.

Results. Clinical characteristics are summarized in Table 1. All pts received a rituximab-based CHT, in particular, 30 pts (69.8%) received R-CHOP14 (27 early stage and three advanced stage), nine pts (20.9%), all in advanced stage, were treated with R-DA-EPOCH; four pts, all in early stage, received R-MACOP-B. At restaging, 20 pts treated with R-CHOP14 obtained a complete remission (CR), nine a partial response (PR), one was in progressive disease (PD) and received second line treatment with stem cell transplant and is currently in second CR. 26 pts received consolidation RT (17 CR, 9 PR). Among pts treated with R-DA-EPOCH, we observed six CR and PR, one patient rapidly progressed and died. Of the 2 PR pts, only one received RT after R-DA-EPOCH: both did not relapse during follow-up. All pts treated with R-MACOP-B obtained a CR, three of them received RT. RT was performed in 30 pts (73% of CR/PR patients after CHT). Overall, at the end of induction therapy, 30 pts obtained a CR (69.7%) and 11 pts a PR (26.7%), with a 95.3% overall response rate. Survival analysis after a median follow-up of 68 months showed 97.6% overall survival and 95.2% event free survival at 6 years.

Conclusions. With the limitations of a monocentric, retrospective analysis, the data showed a good prognosis in patients treated with a modern approach and seem to support the possibility to skip RT in CR patients after R-CHOP14. The small number of events did not permit the evaluation of prognostic factors. Larger, multicentric cohorts are warranted to evaluate prognostic factors.

SP39

A MONOCENTRIC EXPERIENCE ON HEMATOPOIETIC STEM CELL MOBILIZATION IN PATIENTS WITH MANTLE CELL LYMPHOMA

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High-dose (HD)-cytarabine-containing immunochemotherapy followed by autologous stem cell transplantation (ASCT) is considered the standard of care for younger patients (pts) with mantle cell lymphoma (MCL). In the BTKi era, the benefit of ASCT is under debate, induction and mobilization strategies are not standardized and poor mobilization might lead to postponing or even abandoning a transplant strategy. We present a monocentric experience of treatment outcomes with the actual standard of care for younger patients with MCL. From January 2018 to March 2023, we collected 27 pts with a median age of 57 years (range 40-68), who started first line treatment with induction chemotherapy consisting of an alternation of 3 cycles R-CHOP with 3 cycles of an R-DHAP-like regimen that consisted of rituximab, mitoxantrone, carboplatin and cytarabin (R-MICMA). The last cycle was used for hematopoietic stem cell (HSC) mobilization; 3 (7%) pts did not complete the induction therapy (1 for progression, 1 for G4 transaminitis, 1 for sepsis) and in 24 (89%) pts HSC mobilization was attempted. In 15 of 24 (62%) pts, a sufficient HSC product (>2.5x10^6 $CD34^+$ cells/kg) was harvested after the last cycle of induction, in 4 (27%) pts plerixafor was administered. In 9 (37%) pts, HSC mobilization failed: 3 pts started Ritux-

imab (RTX) maintenance, while in 6 pts a second HSC mobilization attempt using R-HD-cytarabine (4 doses of 2g/m^2) was undertaken. HSC harvesting was successful in 5 of 6 (83%) pts, plerixafor was administered in 4 pts, while 1 pt failed and started RTX maintenance. In total, 20 of 24 (83%) pts succeeded in harvesting HSC. We analyzed parameters characterizing mobilization failure: in univariate and multivariate analysis, age>60 years and the need for platelet transfusion during induction were statistically significant predictors for HSC mobilization failure (odds ratio 1.15 range 1.06-1.30, p=0.04), while other parameters, such as leukemic presentation, pre-mobilization hemoglobin, platelet and leukocyte counts, were not predictive. In conclusion, the efficacy of our induction chemotherapy appears similar to data reported by the MCL Younger trial (Hermine O. *et al,* 2016) (62% and 66%, respectively). R-HD-cytarabine showed a high efficacy as second line mobilization regimen. It has to be explored whether replacing the last cycle of the induction regimen with HD-cytarabine could reduce the risk for HSC mobilization failure in patients at risk.

SP40

MOGAMULIZUMAB IN MYCOSIS FUNGOIDES AND SÈZARY SYNDROME: AN ITALIAN SINGLE CENTER EXPERIENCE

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Background. Mycosis fungoides (MF) and Sèzary Syndrome (SS) are the most studied subtypes of Cutaneous T-Cell Lymphomas (CTCLs). MF is the most common disease and is mainly indolent, whereas SS is a rare condition with more aggressive behaviour. Both are characterized by heterogeneous clinical presentation and response to treatment and are generally incurable. The aim of therapy is to control symptoms and extension of cutaneous lesions and avoid disease progression. Recently, new drugs are available for the management of these diseases: one is Mogamulizumab, a first-in-class defucosylated humanized IgG1 κ monoclonal antibody approved by FDA and EMA in 2018 for the treatment of adult patients with relapsed or refractory (R/R) MF or SS after at least one prior systemic therapy.

Aims. In this report we show the results of the analysis of nine patients with MF and SS R/R treated with Mogamulizumab at our Institution.

Methods. We have collected and analised data of patients from medical records. Response was graded according to ISCT/USCLC/EORTC consensus guidelines.

Results. Nine patients (3 F and 6 M) have received Mogamulizumab in our Department; three of them was affected by MF and 6 by SS; median age at diagnosis was 70 years (range 47-77) , at mogamulizumab start was 71 (range 51-83) (Table 1). Median number of previous treatment was 3 (range 1-4); all of them but one had bexarotene, 7 had steroids, 4 interferon alpha, 3 monochemotherapy with Gemcitabine and 2 polichemotherapy (CHOP/CHOEP), 3 Psoralene Ultra-Violet A (PUVA), 1 radiotherapy and 2 photopheresis. The reason to start Mogamulizumab was progressive disease (PD) in 6 cases, the other patients had no response (stable disease, SD) to previous approaches. Median number of cycles of Mogamulizumab was 12 (range 3-25). Seven out of 9 received concomitant medication (5 bexarotene , 1 PUVA, 2 steroid, 1 clormetine gel). Best response achieved was as follow: skin response was complete (CR) in 1 patient, partial (PR) in 4 and SD in 4; lymphonodes response was: 2 PR , not evaluated (NE) in 2 and not applicable in 5(NA); blood response was assessed in SS: 4 CR, 1 PR and 1 SD; global response was: 1 CR (patient with MF), 5 PR (4 SS, 1 MF), 3 SD (2 SS, 1 MF). All patient complained pruritus that resolved in all of them with mogamulizumab alone or in combination therapy. Response in blood occured after 1 week in 4 patients and 4 weeks in 1; skin response was slower: occured in median 3 weeks (range 1-6). Median progression free survival was 11 months (range 2-24 months). Regarding side effect, we observed new skin lesions in 3 patients (grade 1), no biopsies was performed and local steroids were effective. Mogamulizumab was definitely stopped in 3 patients for progressive disease (PD) in 2 of them and for ulceration and infection of cutaneous nodules in the other one.

Conclusions. In our experience Mogamulizumab alone or in combination show good response and disease control in R/R patients with MF and SS. The treatment was well tolerated and no safety concern was noticed.

SP41

AN ATYPICAL NON LEUKEMIC PRESENTATION OF HAIRY CELL LYMPHOMA WITH A BULKY MEDIASTINAL MASS

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Hairy cell leukemia (HCL) is an indolent chronic lymphoid neoplasm originating from mature B lymphocytes. Patients more commonly present with splenomegaly and bone marrow infiltration which causes variable cytopenias; lymphadenopathies are generally absent to minimal. Diagnosis is based on morphology, immunophenotype and corroborated by the detection of BRAFV600E somatic mutation. Anecdotal cases of HCL with atypical presentations have been reported with variable involvement of bone, breast, CNS and serous cavities. Many of these cases lack splenomegaly and/or the typical bone marrow infiltration.

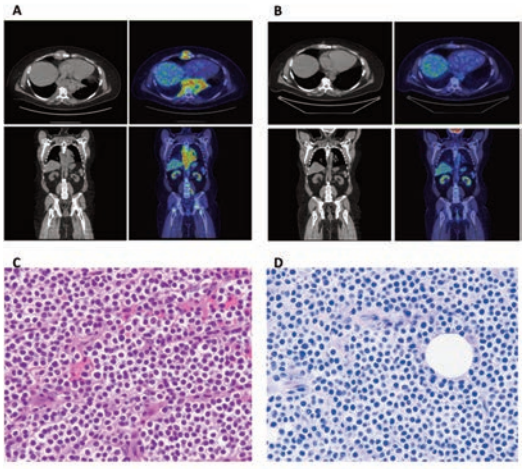

Figure 1. PET/CT scan at baseline (A): CT scan shows an anterior mediastinal mass extending to the periesophageal soft tissue and posterior mediastinum. PET scan shows increased FDG uptake within the anterior mediastinal mass, extending to the para-cardiac region and to the posterior mediastinum, surrounding the trachea, oesophagus and aorta, up to the diaphragm and in close proximity of the left psoas muscle and within the head of the left femur and acetabulum. PET/CT scans 6 months after treatment (B): CT scan shows complete remission with no measurable residual mass. PET scan shows complete metabolic response. Histologic findings (C-D): H&E (C), Giemsa Stain (D). There is a monotonous proliferation with a diffuse pattern of growth (D), composed of small lymphocytes with mature chromatin, incospicuous nucleoli and an abundant pale cytoplasm imparting a "fried-egg" appearance.

We report the case of a 56 years old Caucasian male presenting with a bulky palpable mediastinal mass causing shortness of breath and dysphagia. Complete blood counts and biochemistry were all within normal limits. A CT scan showed an anterior mediastinal mass (20x9 cm) extending to the periesophageal soft tissue and posterior mediastinum and a solid mass (5x5cm) at the chondrosternal level involving the surrounding ribs and sternum. Neither lymphadenopathies nor hepatosplenomegaly were described. An FDG-PET scan showed increased FDG uptake within the described lesions (SUV max of 8.4). An incisional biopsy of the anterior mediastinal mass was performed, showing monomorphic proliferation of small mature lymphocytes with clumped chromatin, inconspicuous nucleoli and an ample cytoplasm. Immunohistochemistry showed positivity for CD20 and HCL-associated markers, including Annexin-1, CD25, TRAP, DBA.44, CD123, TBET and BRAF V600E, weak reactivity for Cyclin D1and negative stain for CD5, SOX11, CD23, and CD138. Next-generation sequencing on formalin-fixed paraffin embedded tissue identified the BRAFV600E mutation (variant allele frequency 47%). Bone marrow biopsy couldn't be performed, but there was no evidence of hairy cells at the peripheral blood smear. Giving the overall microscopic and molecular findings, a diagnosis of HCL with an atypical "lymphoma-like", non-leukemic presentation was performed. The patient was treated with a single cycle of cladribine as per standard HCL protocols. A 6 month follow up PET-CT scan showed a complete metabolic response (Deauville Score 1) with no measurable residual mass. This case underlines the existence of "non- leukemic, non- splenic" HCL with atypical clinical features. A diagnosis of HCL should not be discarded if the overall morphologic, immunophenotypic and molecular findings are consistent with such a diagnosis.

SP42

SEQUENTIAL DLBCL AND CLASSICAL HODGKIN LYMPHOMA: REPORT OF TWO CASES WITH EMPHASIS ON MOLECULAR CHARACTERIZATION

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The term "sequential lymphoma" (SL) describes cases of classical Hodgkin lymphoma (cHL) followed by non Hodgkin lymphoma (NHL), mostly diffuse large B cell lymphoma (DLBCL), or vice versa. The underling molecular aspects of SL are not fully understood. However, clonally unrelated SL are regarded to have a worse prognosis compared to their de novo counterpart. We describe two cases of SL treated at our Institution reporting on presentation, histologic and molecular findings, treatment and outcome.

Patient 1: In May 2021 a 29 years old female presented with DLBCL, non Germinal Center (non-GC) type, Ann Arbour stage IV, IPI score 3, CNS IPI score 4. She received R-CHOPx6 followed by 3 cycles of HD-MTX, achieving a complete metabolic response (CR). A CT scan performed in June 2022 for follow up (FU) revealed a 35 mm abdominal nodule suspicious for relapse, confirmed by a subsequent PET scan. The biopsy performed at this time showed findings of cHL, mixed cellularity. We performed NGS on the first sample (DLBCL) and on sample at relapse (cHL). The first showed pathogenic mutations of IRF4 (variant allele frequency- VAF 32.1%), SOCS1 (VAF 40.6 %) and IKBKB (VAF 53.1%). The second showed SOCS1 (VAF 1.4%) and IKBKB (VAF 1.0%). We also performed IGH clonality studies (EuroClonality/BIOMED-2 protocol). The first sample showed no evidence of clonality; the second was inadequate for analysis.

Patient 2: In May 2019 a 38 years old female presented with DLBCL non-GC, Ann Arbour stage IV, IPI score 2, CNS IPI score 1. She received R-DA-EPOCHx6 and radiation therapy, achieving a CR. In September 2021 a CT scan performed during fu showed an FDG avid lung mass of 30 mm. A lung resection showed findings of cHL, mixed cellularity. For this case we could perform NGS only on the relapse sample (cHL). This showed a somatic mutation in KMT2C (VAF of 5.7%). As salvage chemotherapy, both patients received BeGEVx2 achieving a CR followed by consolidation with autologous stem cell transplant. At the last fu (February 2023), the patients are still in CR.

In the setting of other transformed B cell lymphoma (e.g. CLL and Richter's transformation), information on the clonal relationship between diseases has relevant prognostic implications. This concept is not so fully validated in SL, possibly due to the paucity of literature available on the topic. IGH analysis and NGS need to be used to establish the clonal relationship between SL, thus providing useful clinical information.

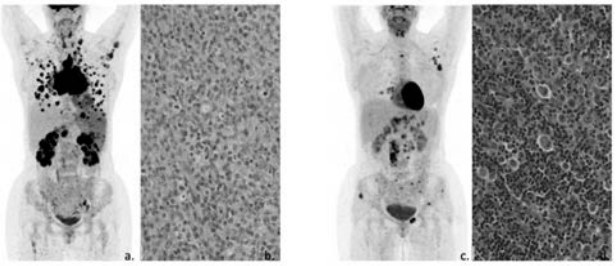

Figure 1. Patient 1- PET and histologic findings at first diagnosis and relapse. Onset: a) Maximum intensity projection (MIP) PET image: Supra and sub-diaphragmatic lymphadenopathic findings sites and high metabolic parenchymal areas of the lungs, spleen, stomach, and kidneys. b) Hematoxylin and Eosin (HE) staining of the anterior mediastinal mass showing a diffuse proliferation of medium size centroblasts. Relapse: c) MIP PET image: High metabolic lymphadenopathic (above and below diaphragm), medullary, splenic and pleuric findings. d) HE staining of the left axillary lymph node showing scattered Hodgkin and Sternberg cells dispersed in a mixed inflammatory background.

SP43

MOGAMULIZUMAB TREATMENT IN AGGRESSIVE/REFRACTORY SÉZARY SYNDROME AND MYCOSIS FUNGOIDES: REAL LIFE DATA FROM A MONOCENTRIC CASE SERIES

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Sézary syndrome (SS) and mycosis fungoides (MF) are forms of cutaneous T-cell lymphoma (CTCL) characterized by poor prognosis. Mogamulizumab is a defucosylated humanized monoclonal antibody that selectively binds to CCR4, highly expressed on malignant T cells in MF skin lesions and on circulating malignant T cells in patients with SS, therefore being an ideal molecule for targeted therapy. In this single center retrospective case series study, we report the efficacy and safety outcomes of 6 patients treated in the Hematology

Department of Federico II University of Naples. Our small sample consisted in 5 males and 1 female patients, with mean age at diagnosis of 64,1 years (range 46-71); 4 of them were diagnosed with MF and the remaining 2 with SS. All patients had an aggressive/refractory advanced stage CTCL and received a median of 2,3 (range 2-4) skin-directed and/or systemic treatments before mogamulizumab. They received intravenous infusions of mogamulizumab at a dose of 1.0 mg/kg on the standard 28-day cycle schedule, with administrations on days 1, 8, 15 and 22 in the first cycle and on days 1 and 15 in the subsequent cycles. SS patients presented with hitchy skin lesions and erythroderma, and skin biopsies showed a dermal lymphocytic infiltrate with an aberrant phenotype. MF patients, instead, arised with localized patches, plaques and tumors, mostly on legs; particularly one of them had a complex ulcerated lesion on the zygomatic region. SS patients achieved a complete remission in the blood compartment since the 3rd infusion of mogamulizumab and a partial response in the skin since the 6th infusion. Treatment is still ongoing for one of them, while the other one relapsed after 10 cycles and was subsequently treated with Alemtuzumab and then with Pembrolizumab. Regarding MF patients, 2 of them are still under treatment, while the other 2 had a disease progression after the 2nd and 3rd cycle, and respectively received RT palliation and Brentuximab. All adverse events were evaluated according to the CTCAE v.5 criteria: no patients recorded mogamulizumab-associated rash (MAR) and no treatment discontinuation was required. In our small but with a quite long follow-up case series, we confirm the hypothesis that patients with SS may achieve a longer response than MF ones, since mogamulizumab was employed for a mean number of 14 cycles in SS against 4 cycles in MF. In conclusion, mogamulizumab represents a valuable therapy for advanced SS/MF as it can produce prolonged responses in pluryrefractory patients.

SP44

SECONDARY MYELOID NEOPLASM (SMN) IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) SURVIVORS, A SINGLE CENTER RECENT EXPERIENCE

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Survivors of DLBCL have an increased risk of secondary primary malignancies; previous studies found that incidence of acute myeloid leukaemia (AML) nearly doubled in the post rituximab era. Here we report two cases of SMN arising in DLBCL survivors, both diagnosed recently in our center.

In October 2021, a 67 years old man was diagnosed with a IV stage DLBCL and poor R-IPI score. Due to a retrorbitary localization and middle spine pathological tissue, R-CHOP intensified with high dose methotrexate was started. Lumbar puncture was negative. In April 2022, despite the interim PET-TC scan good result, progressive disease emerged. Due to severe chronic obstructive pulmonary disease, autologous transplant was excluded, thus request for Tafasitamab-lenalidomide under an extended access program was sent and approved in July 2022. After two cycles, lenalidomide was reduced because of grade 3-4 neutropenia poorly responsive to G-CSF. Although immunomodulant was definitively stopped after 3 cycles, neutropenia persisted and worsening anemia appeared. Bone marrow analysis showed 75% of myeloid blasts: according to ELN risk stratification, AML with adverse risk was diagnosed. Patient started decitabine plus venetoclax protocol that is still ongoing. Of note, both NGS and cytogenetics found ETV6 delection in the 90% of the nuclei, a germline predisposing abnormality.

The second patient was diagnosed in 2019, at the age of 58. Diagnosis was IV stage DLBCL with a poor R-IPI score too, characterized by pleural and Waldayer's ring involvement. He underwent R-CODOX- M/IVAC chemotherapy, obtaining a complete response. In Novemeber 2022, mild thrombocytopenia and anemia appeared, bone marrow investigations were diagnostic for a very high risk myelodisplastic syndrome according to the IPSS-R. Citogenetics evidenced the typical deletion of chromosome 7q in the 80% of the nuclei. Patient has been candidated to allogenic transplant and azacitidine is now ongoing. In our hand DLBCL survivors have a substantial risk of developing SMN. Retrospective studies described unique risk SPM patterns, moreover evidenced that patients aged 60–74 years and advanced stage are more prone to secondary AML. Compared with their "de novo" counterparts, they have a worse prognosis. Recently, the risk of SMN is also of particular concern in the CAR-T receivers. In conclusion a better comprehension of SPM/SMN pathology in DLBCL survivors is needed in order to guide the best "tailored" surveillance.

SP45

AN UNUSUAL CASE OF INTRAVASCULAR LARGE B-CELL LYMPHOMA AND LEISHMANIOSIS

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Background. Intravascular Large B-cell lymphoma (IVLBCL) is an aggressive, rare and distinct subtype of non-Hodgkin lymphoma, characterised by selective grouth of tumor cells in the lumina of small vessels of various organs. IVLBCL diagnosis is difficult because no pathognomonic signs and symptoms exist. R-CHOP chemotherapy has significantly improved the previously dismal prognosis of IVLBCL. Herein we present a case of patient diagnosed simultaneously with IVLBCL and Leishmaniasis.

Case presentation. We report a case of a 56-years-old Italian man who was admitted to the Department of Internal Medicine for fever, associated with B symptoms and diffuse arthralgias, wich started about 2 months before. Previously in good health, he had no past or family history of malignant tumors. He lives in countryside, with no pets and works as welder. He had not travelled outside Sardinia in the last period. On admission, he presented markedly poor general clinical condition, PS ECOG 2; physical examination showed diffuse jaundice, sacral and lower limb edema and hepatosplenomegaly; regional lymphonodes was not enlarged. Abnormal laboratory tests findigs were detected: anemia, thrombocytopenia, hyperbilirubinemia (predominantly direct), incresed livers enzymes with hypoalbuminemia, increased PCR, procalcitonine, LDH and ALP. Among the investigations performed, CT and total-body PET scans showed hepatosplenomegaly, with hepatic, splenic and bone marrow uptake. Aspirate and bone marrow biopsy were therefore performed. At histological examination were found abundant atypical lymphoid cells, with sinusoidal involvement, the tumor cells were large and had rough and deep-staining chromatin in irregular shaped nuclei, nuclear vacuoles and prominent nucleoli; interestingly, there were scattered non neoplastic hemophagocytic histiocytes and Leishmania. Immunohistochemistry results showed that the tumor cells were positive for CD20, CD79a, PAX5, CD10, BCL2, BCL6, CD45, MUM1 and negative for CD23, CD3, Cicline D1, CD5, CD30, TdT, CD1a, CD138, MPO, CD33, CD117, CD34; Ki67 staining was about 90%. A diagnosis of IVLBCL (stage IVB, SNC IPI 3) associated with Leishmania infection was made. The patient was promptly started on antinfective therapy with Amphotericin-B and chemo-immunotherapy according to R-CHOP scheme with intrathecal CNS prophylaxis, with marked improvement of general clinical condition, symptomatology, laboratory values and blood counts. To date, the patient has undergone 6 total cycle of R-CHOP

plus 2 Rituximab and 4 medicated lumbar punctures. Post treatment CT and PET scans showed complete response to therapy.

SP46

FLOW CYTOMETRIC DETECTION OF A SMALL CIRCULATING POPULATION OF ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA CELLS: A CASE REPORT

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Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive neoplasm of mature T follicular helper cells, that accounts for 1-2% of all non-Hodgkin lymphomas. AILT is characterized by some peculiar laboratory features, including polyclonal hypergammaglobulinemia, hemolytic anemia, circulating immune complexes and cold agglutinins. AITL is also often associated with B-cell or plasma cell expansion, mimicking B cell lymphomas or plasma cell neoplasms. Therefore, the diagnosis of AITL can sometimes be challenging and requires a complete immunophenotypic and molecular workup. However, the peripheral blood involvement in AITL seems rare and has not been frequently addressed in the literature.

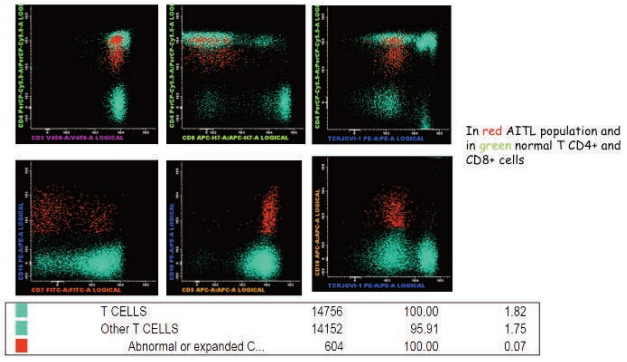

Figure 1.

We report the case of 54 years old man with multiple lymphadenopathies, hepatosplenomegaly and skin rash, complaining of asthenia. Laboratory tests showed anemia grade 3 (Hb 67 g/l), lymphopenia (Lymphocytes 2.7%, 0.3x10^9/l), preserved haptoglobin, LDH 495 UI and hypergammaglobulinemia. Direct Coombs test was positive for IgG and C3. Peripheral blood smear showed plasmacytoid cells and red cell rouleaux. A first flow cytometry screening panel of peripheral blood disclosed marked polyclonal plasmacytosis (12%). No mature B lymphocytes were detectable. In the suspicion of an AITL lymphoma, another flow cytometric panel was performed, including CD2, CD3, CD4, CD5, CD7, CD8 and CD10. The analysis disclosed a small circulating population of atypical T cells (0.07% out of 793,000 CD45+ white cells) expressing CD2+, CD4+, CD3+, CD10+, partially CD7+, and negative for CD8 (Figure 1). Moreover, the anti-TRBC1 antibody JOVI-1, recently identified as a marker able to identify T cell clonality, was used, confirming the T cell clonal restriction of this abnormal AITL population. Immunohistochemistry on excised lymph node sections was carried out. The analysis confirmed the presence of an atypical T cell population expressing CD3+ CD4+ CD7+ CD2+ PD1+ CD10+ Granzyme+, while the T cell Receptor Gene rearrangement was detected by a molecular analysis. In this case, the unexpected detection of a small circulating population of AITL cells by high-resolution flow cytometry has prompted an extensive diagnostic workup leading rapidly to the correct diagnosis. Therefore, an integrated approach, including clinical data, histologic and molecular findings and an appropriate high-resolution immunophenotypic analysis is essential to reach an accurate diagnosis of AITL.

SP47

CLINICAL EFFICACY OF DARATUMUMAB PLUS BORTEZOMIB-THALIDOMIDE-DEXHAMETASONE IN UNTREATED MULTIPLE MYELOMA PATIENTS: A REAL-LIFE MULTICENTER EXPERIENCE

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Introduction. Daratumumab, an anti-CD38 monoclonal antibody, can be associated with the standard triplet bortezomib-thalidomide-dexamethasone (dara-VTD) regimen as first line therapy of newly diagnosed multiple myeloma (ND-MM) who are eligible to autologous stem cell transplantation (ASCT). To date, real-life data on clinical efficacy of dara-VTD in MM treatment are still few. In this multicenter retrospective study, we report preliminary results of our real-life experience on dara-VTD as induction treatment for ND- MM.

Table 1.

Characteristics	Dara-VTD cohort N = 30
Median age, years (range)	58 (44-69)
< 50 years, n (%)	5 (17)
Gender, n (%)	
Male	17 (57)
ECOG scale, n (%)	
0-1	29 (97)
≥ 2	1 (3)
M-protein type, n (%)	
IgG	22 (73)
IgA	6 (20)
Micromolecular	2 (7)
Light chain type, n (%)	
Kappa	15 (50)
Lambda	15 (50)
Median glomerular filtration rate, ml/min (range)	96 (26-120)
Glomerular filtration rate < 40 ml/min, n (%)	3 (10)
β2 microglobulin mg/dl, median (range)	3 (1.5-9.4)
LDH U/l, median (range)	230 (117-1021)
Albumin gr/dl, median (range)	3.7 (2.7-4.6)
Body weight, median, kg(range)	70 (51-120)
M-protein, median, gr/dl (range)	2.5 (0.1-8.4)
Free-light chain ratio, median (range)	18.5 (2-512)
High genetic risk MM, n (%)	7 (23)
Extramedullary disease, n (%)	4 (13)
Revised international staging system, n (%)	
I	12 (40)
II	7 (23)
III	10 (33)
Response after one cycle, n (%)*	
Complete response	-
Very good partial response	11 (41)
Partial response	11 (41)
Stable disease	5 (18)
Progression	-
Not available	2
Response after 4 cycles, n (%)*	
Complete response	4 (17)
Very good partial response	14 (61)
Partial response	2 (9)
Stable disease	-
Progression	3 (13)
Not available	7
Autologous stem cell transplantation, n (%)	7 (23)
Time to ASCT, median, months (range)	6 (5-8)
Maintenance with lenalidomide, n (%)	6 (20)
Progression free survival, median, months (range)	NR (1-16)
One-year PFS, %	74
Overall survival, median, months (range)	NR (1-18)
One-year OS, %	97
Peripheral neuropathy, n (%)	
Grade I-II	5 (17)
Grade III-IV	1 (3)
Pneumonia, n (%)	5 (17)

*% calculated on available data

Material and Methods. A total of 30 consecutive ND-MM patients who started dara-VTD outside clinical trials were enrolled since January 2022. Primary endpoint was overall response rate (ORR) after one and four dara-VTD cycles. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety.

Results. Patients' characteristics are summarized in Table 1. Median age was 58 years and 17% were younger than 50 years. Of total subjects, 23% had high-risk MM and 13% presented with extramedullary disease at diagnosis. Revised international staging system (R-ISS) was I, II, and III in 40%, 23%, and 33% of subjects, respectively. Only 10% of cases had severe renal dysfunction with a glomerular filtration rate < 40 ml/min. In our cohort, ORR was 82% and 87% after one and four cycles, respectively. Seven patients (23%) received ASCT, with a median time to transplant of 6 months, and six subjects (20%) started maintenance with lenalidomide. However, five patients (17%) experienced disease refractoriness or relapse, and an overall 1-year PFS of 74%. Median OS was not reached and 97% of patients was alive at one year of follow-up. Finally, dara-VTD was well tolerated, with only one case (3%) of reversible grade III peripheral neuropathy leading to thalidomide discontinuation and bortezomib dose reduction, and 17% of cases of pneumonia.

Discussion. Our preliminary real-life results on dara-VTD regimen, just only recently introduced in clinical practice, showed an excellent ORR, similar to that of phase III CASSIOPEIA trial (92.6%). However, a longer follow-up period is required, as some patients has not yet completed induction, received ASCT, and started lenalidomide maintenance at the time of writing.

SP48

COMPARING THE EFFICACY OF SINGLE VERSUS TANDEM AUTOLOGOUS TRANSPLANT IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: A REAL-WORLD ANALYSIS

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Background. Autologous stem cell transplantation (ASCT) is an effective treatment option for patients with multiple myeloma (MM), but the efficacy of single transplantation (ST) versus tandem transplantation (TT) is debated, especially after introduction of new drugs available in newly diagnosed (NDMM) and relapsed/refractory multiple myeloma (RRMM). The aim of this retrospective analysis is to compare the progression-free survival (PFS) of ST versus TT in patients with NDMM.

Methods. Data from 53 patients with NDMM who underwent ASCT after induction treatment with VTD at a single center from 2018 to 2022 were analyzed. Patients referred to other centers, those with follow-up shorter than 24 months, and those treated with lenalidomide maintenance were excluded. Among the remaining 20 patients, 14 underwent ST and 6 underwent TT. The PFS of the two groups was compared using Kaplan-Meier analysis.

Results. We analyzed the data of 20 patients with a median age of 57 years (35-66). All patients received conditioning regimen MEL200 and all except 1, who relapsed shortly after transplant, obtained at least VGPR. The median PFS of the ST group was 36.5 months, while that of the TT group was 39.5 months with a p value of 0.89 thus not maturing a statistic significance.

Discussion. ASCT is a fundamental aspect of the therapy in MM, despite the introduction of numerous innovative drugs. Indeed, the use of Daratumumab associated with VTD as induction treatment in NDMM or as salvage treatment in RRMM has showed deeper and longer response rates. Numerous studies demonstrated that TT did not significantly improve PFS. Considering the potential risks associated with myeloablative chemotherapy used in these patients and the potential benefit of salvage ASCT in RRMM the question of whether there is still a need for TT in patients with MM remains open until today.

Conclusions. This retrospective and preliminary analysis suggests that there is no significant difference in PFS between ST and TT in patients with NDMM. Despite the small sample size and the retrospective nature of the data, these findings are consistent with previous studies and provide further evidence that TT does not confer a significant advantage over ST in terms of PFS. However, additional studies, incorporating other data such as molecular and cytogenetic analysis and considering patients treated with newer induction regimens, are needed to identify patient populations that may benefit from TT over ST.

SP49

EFFECTS OF LENALIDOMIDE ON PERIPHERAL BLOOD STEM CELL COLLECTION IN PATIENTS AFFECTED BY MULTIPLE MYELOMA: A REAL-LIFE RETROSPECTIVE BI-CENTER EXPERIENCE

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Background. Lenalidomide, a milestone in multiple myeloma (MM) treatment, can variously impact on peripheral blood stem cell collection (PBScC); however, controversial outcomes are reported. In this retrospective two-arms bi-center experience, we investigated PBScC efficiency and autologous stem cell transplant (ASCT) engraftment in MM subjects following lenalidomide-based regimens, and results were compared to thalidomide-treated control population.

Methods. A total of 34 treatment naïve or relapsed/refractory MM patients who underwent PBScC were retrospectively included in this study and were divided in two groups: lenalidomide-treated (LT; N=22) and thalidomide-treated (TT; N=12) patients. PBSC mobilization was performed using G-CSF, plerixafor or intravenous cyclophosphamide 3gr/m^2. PBScC failure was defined as a CD34+ cell count < 2 x 10^6/kg.

Results. Patients' and treatment features are resumed in Table 1.

No differences in median harvested CD34+ cells were described (6.4 versus 7.9 x 10^6/kg), while CD34+ cells x 10^6/kg collected on day-1 were significantly higher in the TT arm (3.1 versus 5.1 x 10^6/kg; P= 0.01), as well as delayed mobilization (77% versus 42%, LT *vs* TT; P=0.02). No significant differences in collection failure rate and neutrophil/platelet engraftment were described in both arms; however, one patient in the LT arm failed PBScC with G-CSF plus plerixafor, and cyclophosphamide was used collection. Use of lenalidomide (odds ratio [OR], 7.4; 95%CI, 1.4-38.4; P=0.017) and of cyclophosphamide for mobilization (OR, 0.08; 95%CI, 0.01-0.5; P=0.008) were inversely associated with a delayed mobilization risk for the entire population by univariate logistic regression.

Discussion. Previous reports have demonstrated a negative effect of lenalidomide on PBScC due to its impact on bone marrow microenvironment, despite its high efficacy as anti-MM agent. In our real-life retrospective experience, we showed that lenalidomide exposure could only delay PBScC in MM patients, while not affecting collection efficiency, median harvested CD34+ stem cells, or neutrophil/platelet recovery after transplantation. Our two cohorts

showed significant baseline differences including mobilization protocol or hematological response that might also have influenced our results. However, only lenalidomide and mobilizing cyclophosphamide were associated to delayed mobilization. Our preliminary results need further validation in larger prospective studies.

Table 1.

Characteristics	Lena-treated cohort N = 22	Thali-treated cohort N=12	P value
Median age at PBScC, years (range)	62 (40-70)	57 (44-65)	§NS
Gender, n (%) -Male -Female	 10 (45) 12 (55)	 7 (58) 5 (42)	NS
M-protein type, n (%) -IgG -IgA -Micromolecular -Not secernent	 14 (64) 10 (22) 2 (9) 1 (5)	 11(92) - 1 (8) -	NS
Light chain type, n (%) - Kappa - Lambda	 15 (68) 7 (32)	 11 (92) 1 (8)	NS
Body weight, n (%) - ≤ 65 kg - > 65 kg Median body weight, kg, (range)	 5 (23) 17 (77) 76 (49-96)	 2 (17) 10 (83) 70(49-94)	NS
Previous treatment, n (%) -Yes -Not *Median treatment, n (range)	 5 (23) 17 (77) 1 (1-3)	 - 12 (100) 1 (1-1)	NS
What lenalidomide/thalidomide-based treatment, n (%) -Bortezomib-lenalidomide-dexamethasone (VRD) -Carfilzomib-lenalidomide-dexamethasone (KRD) - Bortezomib-thalidomide-dexamethasone (VTD)	 18 (82) 4 (18) -	 - - 12 (100)	-
Number of cycles before PBScC, median (range)	5 (2-26)	3.5 (3-4)	NS
Radiotherapy before PBScC, n (%)	1 (5)	-	NS
Prior ASCT, n (%)	1 (5)	-	NS
PBSC after 12 months from MM diagnosis, n (%)	9 (41)	2 (17)	**<0.005**
#Type of hematological response before PBSC, n (%) -Complete response -Very good partial response -Partial response	 11(50) 8 (36) 3 (14)	 1 (8) 9 (75) 2 (17)	**0.04**
Days ≥ 2 to collect stem cells, n (%)	17 (77)	5 (42)	**0.02**
G-CSF before PBScC, n (%)	21 (95)	2 (17)	**<0.005**
Plerixafor before PBScC, n (%)	9 (41)	-	**<0.005**
Cyclophosphamide 3 gr/m² before PBCcS, n (%)	5 (23)	12 (100)	**<0.005**
CD 34 x 10^6/kg collected, median (range)	6.4 (3-22)	7.9 (4.7-18)	NS
CD 34 x 10^6/kg collected on day 1, median (range)	3.1 (1.5-13.3)	5.1 (2.7-18)	**0.01**
CD 34 < 2 x 10^6/kg, n (%)	1 (5)	-	NS
Autologous stem cell transplant, n (%)	20 (91)	12 (100)	NS
Neutrophil engraftment, days after ASCT, median (range)	11 (9-19)	12 (9-14)	NS
Platelet engraftment, days after ASCT, median (range)	14 (11-30)	14 (10-17)	NS

* Current therapy included # According to IMWG response criteria; § Not significant

SP50

CHOICE OF MULTIPLE MYELOMA TREATMENT SEQUENCES: AN EMN ITALY DELPHI PANEL STUDY

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Multiple Myeloma (MM) is still an uncurable malignancy and its management is based on sequential lines of therapy. International guidelines recommend to switch drug combination according to previous therapy. Rarely, patient's characteristics are taken into account in the therapeutic decision. Objective of this study was to understand the factors (previous therapies, clinical characteristics, frailty/fitness, supposed drug efficacy, route of administration) that influence the treatment choice at first relapse in Italy, in 2023. The Delphi Panel survey method was applied using a questionnaire administered anonymously to European Myeloma Network (EMN) Italy centres. Treatments were identified using all available web-based information sources, including treatments most likely to be approved and commercialised in Italy during 2023. Participants were asked to report on the likelihood of treatment prescription in first relapse MM patients, including transplant eligible (TE) following VTd+R (bortezomib-thalidomide-dex followed by lenalidomide maintenance), and transplant ineligible (TI) following either VMP (bortezomib-melphalan-prednisone) or Rd/VRd (lenalidomide-dex/ bortezomib-lenalidomide-dex). Across 15 participating centres, the sequences that appear most opted for are: IsaKd (isatuximab-carfilzomib-dex) 52% in TE after VTd+R and 25% in TI after Rd/VRd; DPd (daratumumab-pomalidomide-dex) 29% in TE after VTd-R and 38% in TI after Rd/VRd; DRd (daratumumab-lenalidomide-dex) is largely preferred (72%) in TE after VMP, followed by IsaKd and KRd (carfilzomib-lenalidomide-dex) [Figure 1].

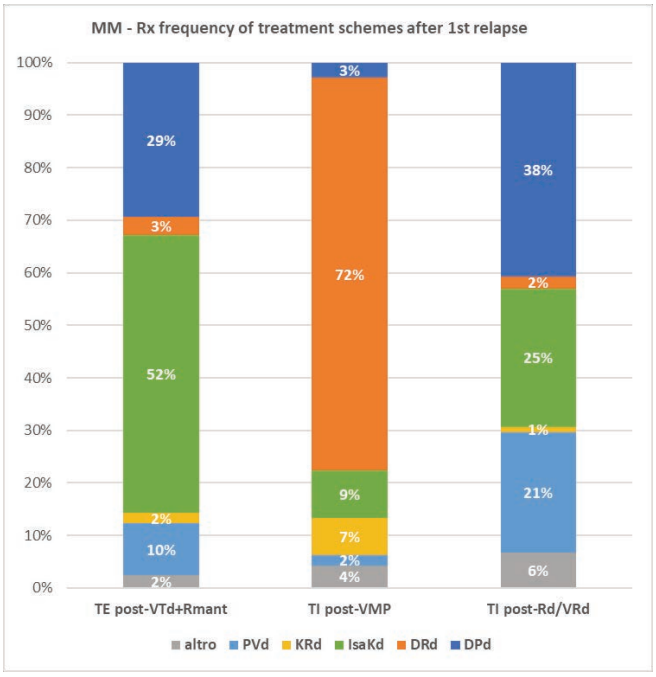

Figure 1.

Quite independently from previous treatment, IsaKd appears mostly opted for treatment scheme efficacy, in FIT patients (IMWG 0), in patients with high cytogenetic risk and with reduced renal function (ClCr <30). DPd appears mostly prescribed in the elderly (age>70), for ease of administration schedule, scheme efficacy and in patients with reduced renal function (ClCr <30). DRd seems mostly prescribed due to scheme efficacy, in FIT and FRAIL patients

and in the elderly. The EMN Expert Panel agrees that in 2023, IsaKd, DRd and DPd will represent the most likely adopted approach for TE and TI MM patients at first relapse. Clinicians differentiate prescription of treatments schemes after first relapse considering: frailty/fitness, age, renal function and treatment efficacy. IsaKd and DRd are mostly selected for efficacy and DPd for ease of use. The study was funded by Sanofi.

SP51

SEE CLEARLY ABOUT BELANTAMAB MAFODOTIN IN MYELOMA PATIENTS WITH BASELINE KERATHOPATY: A CASE REPORT

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Novel agents in Multiple Myeloma (MM) changed both treatment strategies and new side effects management. Belantamb mafodotin (Belamaf) is an anti-BCMA moAb linked to the microtubule disruping-agent auristatin F, approved for relapsed or refractory MM (RRMM) treated with ≥4 prior therapies. Its use is characterized by keratopathy in up to 70% of patients but only a post hoc analisys included informations on baseline ocular conditions, moreover corneal transplant is not frequent and would be a controindication for drugs with corneal iatrogenicity. Here we report the case of a 73-years old man affected by RRMM and a clinical history of left keratoconus treated with corneal transplant. In 2013, at diagnosis, he underwent double autologous stem cells transplant after VTD induction. At first relapse, in 2016, patient started lenalidomide-dex which was stopped in 2019 for H1N1 pneumonia complicated by Aspergillosis. In december 2020, DVd regimen was given as third line therapy but early stopped for a serious pneumonia that required home oxygen-therapy that is actually ongoing. In november 2021, at third relapse, patient underwent local radiotherapy for a huge right homeral osteolysis and started Pomalidomide-Vd. Triplet was continued until the 10th cycle when bone progression occured again. An echocardiography and an eye examination including assessment of the cornea with slit lamp and measurement of visual acuity were done. Due to the corneal transplant, our ophtalmologist advised against belamaf but patient refused carfilzomib based strategies. Belamaf was given by intravenous infusion at the standard dose of 2,5 mg/kg every 3 weeks; patient self-administered preservative-free lubricant eye drops 4 times daily in both eyes, starting 24 hours pre-belamaf. Eye examinations were scheduled before the subsequent 3 cycles and then carefully continued every month. A mild keratopathy was described before cycle 3 and fluorometholone drops were prescribed achieving an improvement during subsequent eye controls. Patient is asymptomatic, in VGPR and is continuing treatment. In conclusion belamaf was effective and safe also in case of prior corneal disease requiring transplant. Close collaboration with ophtalomologists revealed to be precious to allow treatment. Although a limited experience, it suggests to deepen the role of pre-existent keratopathy and corneal transplant too in order to ensure therapeutic chances to all advanced RRMM patients, regardless comorbidities.

SP52

ISATUXIMAB, POMALIDOMIDE AND DEXAMETHASONE TREATMENT IN A PATIENT WITH RELAPSED-REFRACTORY AL AMYLOIDOSIS AND SEVERE RESPIRATORY DISEASE: A CASE REPORT

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Amyloid light-chain (AL) amyloidosis is a multi-system disease that arises from clonal expansion of plasma cells that produce toxic immunoglobulin light chains, whose deposition can cause rapidly progressive multi-organ dysfunction and death. Current treatments for AL amyloidosis involve the use of multiple myeloma–derived therapies that directly target the plasma cell clone. Daratumumab, an anti-CD38 monoclonal antibody (moAb), has recently become the first treatment to receive regulatory approval in the history of the disease, in combination with bortezomib, cyclophosphamide and dexamethasone (CyBorD). Here, we report the case of a 64-year-old male with relapsed-refractory (RR) AL amyloidosis, who was successfully treated with the novel anti-CD38 moAb, isatuximab. The patient was diagnosed with AL amyloidosis in November 2020 and had a history of severe chronic obstructive pulmonary disease. He presented with cardiac stage II, renal stage II (proteinuria), revised Mayo Clinic staging system I. Fluorescence in situ hybridization tested positive for t(11;14). He received first-line treatment with CyBorD and second-line treatment with melphalan and dexamethasone, both rapidly suspended due to hematologic and organ progression, with severe renal insufficiency and the need to start hemodialysis. He could not be enrolled in a clinical trial on daratumumab, pomalidomide and dexamethasone due to his respiratory disease. Basing on data on multiple myeloma and on the results of the phase II study SWOG S1702 (Parker TL et al, *Blood*, 2020) we decided to treat the patient with isatuximab, pomalidomide and dexamethasone (IsaPd). Isatuximab is a novel anti-CD38 moAb that binds to a different epitope compared to daratumumab and the two drugs have biological as well as safety differences, which make isatuximab a better option for patients with pre-existing respiratory conditions. The patient started treatment with IsaPd on January 2022. He had no infusion-related reactions and rapidly achieved a hematologic very good partial response (VGPR), that is still maintained after 15 courses of therapy; he is still receiving hemodialysis three times per week and is a possible candidate for renal transplantation.

In conclusion, isatuximab proved to be a safe and effective treatment option in a patient with RR AL amyloidosis and severe respiratory disease.

SP53

EFFICACY OF DARATUMUMAB-BASED REGIMEN AS SECOND LINE TREATMENT IN A CASE OF REFRACTORY PLASMA CELL LEUKEMIA NOT ELIGIBLE FOR CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION

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Background. Plasma cell leukemia (PCL) is an aggressive and rare plasma cell dyscrasia. Currently, there is no standard of care for PCL, but the novel targeted therapies approved for multiple myeloma have been tested with improved survival outcomes in this setting.

Clinical case. We report a case of a 61-year-old woman presented to the emergency room with a 5-month history of asthenia, weight loss and dyspnea. Clinical history was positive for actinic cardiomyopathy that developed after radiotherapy performed for mammary adenocarcinoma. Laboratory tests revealed severe leukocytosis, anemia and stage 2 acute kidney injury (AKI). Serum electrophoresis showed a monoclonal component composed of κ free light chains (FLC) of 2.468 mg/L and FLC ratio >100. Peripheral blood (PB) and bone marrow (BM) investigations confirmed the presence of κ-light-chain-restricted clonal plasma cells (75% in PB). FISH detected t(11;14) and deletion of 16q23 locus/monosomy of chromosome 16. Taken together, these features were consistent with a diagnosis of PCL. Considering anemia and renal dysfunction, the patient initially received 2 cycles of a bortezomib-dexamethasone regimen, resulting in refractory disease.

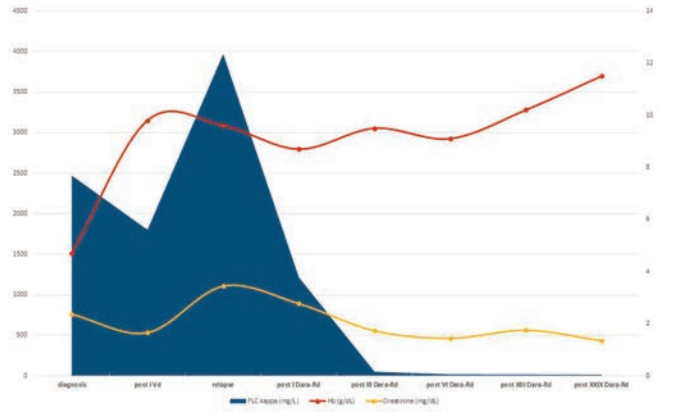

Figure 1.

Despite renal impairment, daratumumab-based regimen in combination with dose-adjusted lenalidomide and dexamethasone was chosen as second-line therapy, leading to a remarkable improvement in patient's health conditions and blood tests after the first cycle. Evidence of undetectable serum and urinary immunofixation confirmed complete remission (CR) achievement after 3 cycles. BM revaluation after 13 cycles was consistent with CR status, showing clearance of clonal plasma cells on the BM smear and 0,01% of measurable residual disease (MRD) by multiparametric flow cytometry (MFC). The patient is currently in good health conditions and in long-lasting CR after 29 months of treatment.

Discussion. Although in recent years there has been an outstanding improvement in survival outcomes for PCL patients, prognosis remains poor for those who are refractory to first-line treatment. In our case, clinical choice of a daratumumab-based salvage therapy was guided by multiple factors: actinic cardiomyopathy, AKI and bortezomib refractoriness. As supported by the most recent data, our experience suggests that daratumumab-based regimens can significantly improve outcomes in PCL patients, even if they present comorbidities that may preclude the use of chemotherapy and transplant eligibility.

SP54

IMPORTANCE OF SYNERGISTIC CLINICAL-LABORATORY EVALUATION OF WALDENSTROM'S MACROGLOBULINEMIA FOR AN CORRECT ANALYTICAL PATHWAY: CASE REPORT

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Waldenstrom Macroglobulinemia (WM) is characterized by the presence of monoclonal IgM component and at least 10% plasma cell infiltration of the bone marrow. Quantitative determination of IgM immunoglobulins is important for follow-up investigations. WM-related clinical manifestations are triggered by both of the deposition of the paraprotein and the autoantibody activity. Epiphenomenon of the WM can be Cold Agglutinin Disease (CAD): in this case, the sample used for the paraprotein assay must be incubated at 37°C from the time the sample is taken until the analytical step. In this paper, we describe the case of a 57-year-old male patient admitted on Day Service at the Oncohematology Unit of ASL BT, with a diagnosis of WM. Laboratory tests performed in February 2023 showed anemia (Hb: 12.7 g/dl), proteinuria of 275 mg/24h, increased total IgM on nephelometer (664 mg/dl), increased total serum protein (9.7 g/dl); on electrophoretic tracing we find the presence of a IgM-Kappa type monoclonal component in the gamma zone (0.86 g/dl) and Bence Jones Kappa type proteinuria. The clinician reported us crucial information: IgM assay was reduced from the previous one, 1800 mg/dL, from September 2022, in a patient that had not received any therapy. This conditions could have had account for the reduction detected. These reports led us to hypothesize that the assays obtained at the two different periods of the year may had been influenced by the different environmental temperatures to which the sample had been exposed; in particular, we considered that the outdoor temperature in February was resulted in the precipitation of cold agglutinins and the consequent underestimation in the assay. We decided to incubate the February 2023 serum at 37°C for 30 min, to excluded interference on serum electrophoresis and IgM assay of cold agglutinins or cryoglobulins related to the patient's underlying pathology. After incubation at 37°C, electrophoretic tracing showed monoclonal component of 2.09 g/dL and nephelometric examination showed IgM assay of 4820 mg/dL. The interaction with the clinician is helpful in implementing laboratory procedures for sample processing, aimed at providing correct data useful for disease monitoring and appropriate therapeutic treatment for the patient.

SP55

EVALUATION OF HEALTH RELATED QUALITY OF LIFE AND FATIGUE BEFORE AUTOLOGOUS STEM CELL TRANSPLANTATION AND AT EARLY FOLLOW UP

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Between April 2022 and April 2023 we investigated the health status and fatigue before autologous Stem Cell Trasplantation (autoSCT) and at early follow up as perceived by patients who received autoSCT in our centre. Two self-administered questionnaires were used and administered before conditioning regimen (T1) and at 4 months, median, (range 4-6) from autoSCT (T2). SF-36 questionnaire (Short Form Health Survey- Form-36) consists of eight health sections: physical functioning (10 items), pain (2 items), role limitation due to physical health(4 items), role limitation due to emotional problems (3 items), energy/fatigue (4 items), emotional well-being (5 items), social functioning (2 items), general health (5 items). For each sections the scores range from 0 to 100, with a higher score defining a more favorable health state. Piper fatigue scale consists of 22 items measured from 0 to 10 and evaluating four subjective measurements of fatigue. 13 of out 22 patients were willing to partecipate in the study, overall the questionnaires were administered in 14 before autoSCT (two auto in one patient), 10 patients completed questionnaries at follow up. The diagnosis were: multiple myeloma 8 , non hodgkin lymphoma 2 , hodgkin lymphoma 2, acute myeloid leukemia 1. the patients were 2 females and 11 males, median age was 59 years (range 31-67). At T1 patients reported fatigue as light (7), moderate (4), severe (1). At T2 patients reported fatigue as light (5), moderate (4) , severe (1). At T1 and at T2 the SF-36 median scores were : physical functioning: 65 and 80, pain: 75 and 60, role limitation due to physical health: 25 and 0, role limitation due to emotional problems: 66 and 83.5, energy/fatigue: 65 and 55, emotional well-being: 62 and 76, social functioning: 50 and 43, general health: 55 and 55, respectively. these results show a stable self-perceived fatigue at T1 and T2. SF-36 at T2 scores show a scores worsening in sections limitation of physical health and physical functioning, whereas the scores of sections of emotional status improve and perception of general health remains stable. the worsening of physical health could be due to toxicity of conditioning regimens whereas the improvement of emotional status could be due to favorable effect of overcoming the autoSCT and to the associated hope of cure. Questionnaires will be administrated to evaluate late toxicities and health related quality of life after a longer follow up.

SP56

ASSESSING HEALTH-RELATED QUALITY OF LIFE (HRQL) IN HEMATOLOGICAL PATIENTS WITH HODGKIN LYMPHOMA UNDERGOING RAFTING PROTOCOL

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Standard chemotherapy treatment for Hodgkin lymphoma (HL) is ABVD protocol (doxorubicin, bleomycin, vinblastine, dacarbazine) and involved-site radiotherapy (IS-RT). Risk-adapted chemotherapy and RT usually lead to cure. High rate of complete remission (CR) is being obtained at the cost of significant toxicity and death related to treatment. Finding ways to reduce morbidity and mortality related to treatment is one of the main objectives of the RAFTING protocol. This study aims to assess the efficacy of a risk/response adapted strategy with ABVD alone in early stage non-bulky HL, with low metabolic tumor value (MTV) and a negative interim PET; assess the efficacy of combined treatment (chemotherapy + IS-RT), followed by Nivolumab maintenance in high risk e-HL and evaluate the rate of HL relapses that could be salvaged with IS-RT followed by Nivolumab. Considering that RAFTING is a personalized medicine trial, we have given all patients enrolled in the study and treated with Nivolumab questionnaires to evaluate psychological impact and health-related quality of life (HRQL). Patients undergoing Nivolumab (from April 2022 to March 2023) in the Hematology Unit of University Federico II of Naples were recruited. Psychological impact and HRQL were assessed using: Hospital Anxiety and Depression Scale (HADS), a self-report questionnaire designed to assess anxious and depressive states; Psychological Distress Inventory (PDI) to measure the level of distress caused by hematological cancer and Functional Assessment of Chronic Illness Therapy-Lymphoma (FACT-Lym) to assess HRQL in this patients. Six patients were enrolled. Psychological and HRQL questionnaires have been completed by participants beginning at Day 1 of ABVD, after interim PET, finish ABVD cycles and at cycle 1 and 8 of Nivolumab; patients will also complete questionnaires at cycle 16 and 24 of Nivolumab. Patients with severe psychiatric comorbidities and who did not speak Italian or English were excluded. The preliminary analysis of questionnaires did not found differences in terms of HRQL and psychological impact (distress, depression and anxiety) in patients between ABVD therapy and subsequent maintenance with Nivolumab (Table 1). Our exploraty study shows that both the burden of the disease and the prolonged time of therapy don't affect any aspect of the life of our patients. These are, however, preliminary findings of an ongoing protocol.

Table 1. Comparison of ABVD vs I Nivolumab, VIII ABVD vs I Nivolumab, VIII ABVD vs VIII Nivolumab questionnaire results.

p-value I ABVD vs I Nivolumab	0,24	0,39	0,14	0,59	0,28
Mediana I ABVD	77,5	69	97,75	22,5	8,5
Min ABVD	63	39	80	16	6
Max ABVD	103	101	158	30	10
Mediana I Nivolumab	85	71,5	121	24	9
Min I Nivolumab	80,0	66,3	112,3	18,0	5,0
Max I Nivolumab	108,0	103,0	159,0	38,0	30,0
p-value VIII ABVD vs I Nivolumab	0,33	0,37	0,39	0,58	0,40
Mediana VIII ABVD	81,5	65,5	113,5	24	9
Min ABVD	59	47,5	86	18	5
Max ABVD	104	103	157	28	15
Mediana I Nivolumab	85	71,5	121	24	9
Min I Nivolumab	80,0	66,3	112,3	18,0	5,0
Max I Nivolumab	108,0	103,0	159,0	38,0	30,0
p-value VIII ABVD vs VIII Nivolumab	0,39	0,45	0,42	0,63	0,97
Mediana VIII ABVD	81,5	65,5	113,5	24	9
Min ABVD	59	47,5	86	18	5
Max ABVD	104	103	157	28	15
Mediana VIII Nivolumab	76	58,5	104	28	15,5
Min VIII Nivolumab	71	48,625	92,375	24	9
Max VIII Nivolumab	103,8333	97,83333	153,8333	38	27

SP57

SUPPORTIVE CARE TO PATIENTS WITH NON-HEMATOLOGICAL COMPLICATIONS IN INTERNAL MEDICINE DEPARTMENT WITH HEMATOLOGICAL SKILLS

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Due to the availability of the great number of new biological therapies, outpatient/DH treatment of most hematological patients is becoming the standard of cure regimen. Actually, Hematology wards H24 beds are almost exclusively reserved for patients (pts) who need of intensive and high-dose or biological therapies that cannot be administrated without strict, continuous skillful supervision.

Often, these pts are admitted in general medical ward or, frequently, in emergency department with physicians who take care of them not trained to face to hematological problems. For this reason, we proposed to activate a section inside the Internal Medicine ward of Villa Betania Hospital in Rome where hematologist and hospitalist took care together of frail pts with hematologic diseases, with comorbidity or complications of hematologic therapy.

Table 1.

Hematological Diagnosis	Number of Pts	%	Medical Complicance	Number of Pts	%
Multiple Myeloma	16	26%	INFECTION	16	26%
Chronic Lymphocitic Leukemia	12	19%	HEART DISEASE	9	15%
Myelodisplasia	9	15%	PAIN	8	13%
Acute Leukemia	2	3%	DIABETES	5	8%
Non-Hodgkin Lymphoma	3	5%	ORTHOPEDICS	5	8%
Myelofibrosis (MF)	7	11%	RESPIRATORY DISEASE	5	8%
MPN other than MF	4	6%	HEMORRAGY	4	6%
Others	9	15%	ELECTOLYTE IMBALANCE	3	5%
Total	62	100	BLOOD DISORDERS	3	5%
Median Age	77 (41-96)		KIDNEY DISEASE	2	3%
Male	31 (50%)		ANEMIA	2	3%
Female	31(50%)		SOLID NEOPLASM	1	2%

Patients and Methods. In 1 year, 62 pts (31 M, 31 F, median age 77 years) were admitted to our ward, forwarded by various Hematology Department (Dp) or by the Emergency Departments (EDs) of general hospitals of Roma: Umberto I, S. Filippo Neri, S. Spirito, S. Giovanni and Cristo Re. The admittance procedure provided the patient admission in our ward in 24-72 h since the request forwarding by the proposing hospital.

Patient typology: during the study period, our hospital received by mail 62 requests for admitting pts affected by hematologic disease or complications of hematologic therapy. The patient characteristics are shown in Table 1. All admitted patients were assisted with specific therapies according to the specific complications or complaints (supportive treatment, antibiotics, hydration, etc.) and 47 out of 62 were referred back to their hematologists; 4 patients were followed after discharge at least once before referring back to sending hematologists, 8 were sent to long-term or motor rehabilitation hospitalization, and 2 pts died for complications.

Conclusions. In our opinion, this new specific regimen of assistance has achieved its expected goal in taking cure of comorbid, frail pts with complication of hematological disease or therapy. An internal medicine Dp where hematologist with knowledge of hematological protocols and of side effects of the news molecules work together with the hospitalist and can improve the assistance and the outcome in this specific field. Moreover, to our knowledge, our initiative is the first operating in our town and it has been very welcome by Hematological Dp cooperating.

SP58

IMPACT OF EMDR PSYCOTHERAPY COMBINED WITH EARLY ANALGESIC THERAPY ON THE QUALITY OF LIFE IN THE ONCOHAEMATOLOGICAL PATIENTS WITH PAIN:PROJECT IN A SINGLE HEMATOLOGICAL INSTITUTE

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The haematological patient experiences “pain” frequently,infact approximately 86% of patients with multiple myeloma (mainly bone and neuropathic) and about 83% of patients with lymphoma (43% mainly visceral) report this disabling symptom in the course of the disease.Clinical studies show that the use of pain therapy improves the patient’s quality of life.Much progress has been made moving from a traditional approach with a passive role of the patient,to a biopsychocial approach that places pain among experiences of the individual.Recent studies conducted with Functional Magnetic Resonance evaluated brain activation in relation to the expected pain intensity, highlighting that the expectation of a high pain is associated with a more intense activation of the thalamus, the insular regions, the prefrontal cortex and anterior cingulate.EMDR (Eye Movement Desensitization and Reprocessing) treatment can modify the sensory and emotional dimensions of PTDS (Post traumatic stress disorder) and pain, favoring the reduction of physiological arousal and emotional discomfort, increasing relaxation and leading to a detachment from the problem. The aim of our project, undertaken in our institute about 1 month ago (with the help and guidance of our department psychologist) in patients suffering from pain with multiple myeloma and non-Hodgkin’s lymphoma, is the evaluation of improvement of the quality of life with early analgesic therapy and psychotherapeutic support through an EMDR protocol, using ongoing evaluation scales (Oswestry Disability Index ODI,Numerical rating scale -NRS 0-10,verbal number scale VNS and Brief Pain Inventory BPI) during the following 6 months.The EMDR protocol for pain management, is an 8-step process :History Gathering,Preparation Assessment, Desensitization,Installation, Body Scan Closure and Reassessment. Considering the impact that past trauma and the effects of pain have on identity, it is necessary to deal with 7 key tasks:contain the pain, reworking the traumas, regulate emotions,discover the meaning of one’s pain,coping with other stressors, promote self-care,promote reintegration.There are currently no studies in progress regarding the application of EMDR protocols for management of pain in haematological diseases.Our preliminary project, which will be concluded in the coming months, aims to investigate this aspect of the quality of life in haematological patients suffering from pain, never analyzed so far.

SP59

MYELODYSPLASTIC SYNDROMES WITH TRISOMY 8 ISOLATED OR ASSOCIATED WITH OTHER CYTOGENETIC ABNORMALITIES: A RETROSPECTIVE MULTICENTRIC ANALYSIS ON BEHALF GROM-L

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Background. Myelodysplastic Syndromes (MDS) are a heterogeneous group of myeloid neoplasms caused by clonal proliferation of the hematopoietic stem cell. Diagnosis is still challenging, and cytogenetic analysis is fundamental both for the diagnosis and for prognostic scoring systems (IPSS and IPSS-R). Trisomy 8 is the most common chromosomal gain in MDS however little is known about the features of MDS patients either with Trisomy 8 isolated or in addition to other aberrations.

Methods. We retrospectively evaluated clinical and biological data of 71 patients with MDS characterized by Trisomy 8, isolated or associated to other abnormalities, referred to eight hematological centers of the GROM-Lazio, between 2003 and 2022. Both response to conventional MDS therapies and evolution to AML were analyzed.

Results. We subdivided the patients in two groups: group A characterized by isolated Trisomy 8 (51) and group B with Trisomy 8 associated with other chromosomal abnormalities (20). There were no differences according to gender, while patients in group A were older (median age: 75 *vs* 68 yrs). According to the IPSS-R, evaluable patients in group A included 13 low risk, 15 intermediate, 13 high and 6 very high risk. Group B included 2, 1, 3, 6 and 8 patients, respectively. Therapy response was evaluated according to the International Working Group criteria. 36/51 patients in group A were treated with Erythropoietin (58.5%), Azacitidine (19.5%) or both (22%). Of the 33 evaluable patients, 5 (14%) cases progressed to higher risk MDS, whereas 6 (22%) cases developed an overt AML. In group B, 16/20 patients were treated with Erythropoietin (31.5%), Azacitidine (56%) or both (12.5%). A Higher progression rate was observed in this group, since evolution in AML occurred in 7/13 (44%) evaluable patients. Response to therapy was poor in both groups of patients suggesting that Trisomy 8 plays a major prognostic role.

Conclusions. Trisomy 8 is associated with poor prognosis in MDS, either isolated or associated with other cytogenetic aberrations. We aim to confirm these results on larger patient population, evaluating in addition the specific prognostic role of additional abnormalities.

SP60

REFINED PROGNOSTICATION USING IPSS-M SCORE SYSTEM IN A MDS REAL-LIFE COHORT: A SINGLE CENTER EXPERIENCE

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Background. The Revised International Prognostic Scoring System (IPSS-R) allows to predict the risk of the course of MDS and guides the clinician in the choice of the most appropriate treatment. The Molecular International Prognostic Scoring System (IPSS-M) combines the genomic mutations in MDS relates genes with haematological parameters and cytogenetic abnormalities providing a more precise characterization of the myelodysplastic patient, contributing to a more personalized therapeutic approach.

Aims. To evaluate the application of the IPSS-M scoring system in 30 MDS patients in a real life context.

Methods. Thirty MDS patients newly diagnosed from October 2021 to December 2022 were retrospectively evaluated and stratified by risk according to IPSS-R and IPSS-M. Demographic and clinical data, cytogenetic and molecular characteristics at diagnosis were availables. Molecular data of MDS-related genes were obtained by next generation sequencing on peripheral blood specimens at time of diagnosis from the from FISiM MDS NGS Study or in-house NGS reports.

Results. The IPSS-M score was calculated according to clinical and molecular features collected at diagnosis and allowed to classify 11/30 (37%) as low, 5/30 (16%) moderate-low, 3/30 (10%) moderate-high, 9/30 high and 2 very-high. With respect to IPSS-R, 15 patients were ri-assigned to a different risk group: 2 subjects were downstaged and 13 were upstaged.

Conclusions. NGS study is a useful technology in daily practice to detect clonal disease markers critical for accurate assessment at onset of myelodysplastic disease, guide for rigorous follow-up and early treatment and a more effective selection of candidates to HSCT.

SP61

LUSPATERCEPT IN LOW-RISK MYELODYSPLASTIC SYNDROME: A REAL-LIFE SINGLE INSTITUTION EXPERIENCE

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Introduction. The frontline treatment in anemic low-risk MDS patients are erythropoiesis stimulating agents (ESAs). Luspatercept is a recombinant fusion protein, recently approved for patients refractory or ineligible for ESAs therapy, that binds transforming growth factor-beta ligands to reduce SMAD2 and SMAD3 signaling, allowing erythroid maturation and erythroblastic differentiation.

Methods. We collected data of 15 patients treated with Luspatercept in our Institution from January 2021 to date as shown in Table 1. Patients were diagnosed with MDS with low blast count and SF3B1 mutation and/or ring sideroblasts (WHO 2022) and had ESA-refractory transfusion anaemia. Both Revised International Prognostic Score (IPSS R) and the Molecular International Prognostic Score (IPSS M) were calculated at diagnosis. Treatment response was eval-

uated 24 weeks after the start of Luspatercept using haematological response criteria proposed by the International Working Group 2018. Statistical analysis was performed with GraphPad Prism 8.4.

Results. One patient discontinued treatment after 3 doses due to non-compliance. Fourteen patients underwent therapy for 24 weeks without evidence of side effects. At 24 weeks 10 patients (71%) achieved Hematological Improvement (HI) while 4 (29%) patients did not respond. All non responders reached the maximum Luspatercept dose (1.75 mg/kg) and continued treatment up to 24 weeks, considering the reduction of Trasfusion Burden (TB), although they did not meet 2018 IWG HI criteria. Twelve patients are still in treatment, 2 stopped Luspatercept after 24 weeks due to loss of response. Applying Fisher's exact test, neither TB nor patient classification (IPSS R and IPSS M) had a statistically significant impact on treatment response. There was no difference between the responder group and the non-responder group in terms of size of SF3B1 clone (VAF), nor regarding number and type of additional mutations assessed by NGS.

Conclusions. Most patients took advantage from treatment with Luspatercept in our small series, achieving haematological improvement with no evidence of side effects. TB did not show a statistically significant impact on response, although Low TB group reported a better response compared to the High TB group. No other characteristics appeared to have a significant impact on transfusion dependence response. To better assess predictive factors of response to Luspatercept a larger number of patients need to be included.

Table 1.

Total number of MDS-RS patients treated with Luspatercept	15
Age	
years, median (range)	74 (52-83)
Sex, n (%)	
Male	10 (67)
Female	5 (33)
Cytogenetic, n	
Normal	11
8	1
Y	1
del 11q	1
del 20q	1
IPSS-R Classification, n (%)	
Very Low Risk	1 (15)
Low Risk	7 (47)
Intermediate Risk	6 (38)
Mutation status, detected by NGS	
SF3B1, n (%)	14 (92)
Vaf , %, median (range)	39 (21,4-46,3)
Patients with others concomitant mutations	11 (73%)
IPSS M Classification, n (%)	
Very Low Risk	2 (13)
Low Risk	8 (54)
Moderatly Low Risk	4 (26)
Intermediate Risk	1 (7)
Duration of EPO traitment before Luspatercept	
Months, median, range	21, 6-104
Transfusion burden sec. IWG 2018	
Low Trasfusion Burden, n (%)	7 (46)
High transfusion burden , n (%)	8 (54)

SP62

LATE RESPONSE TO LUSPATERCEPT IN A CASE OF MDS-RS-T

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G.F. a young woman aged 21 in August 2011 was hospitalized in our Haematology for a flu-like episode and severe anemia. Onset exams (Hb 6.8 g/dl), MCV 96; PLT 608,000; GB 9250 (N 7330; L 1420; Monocytes 459) serum iron 149; Ferritin 342; creatinine 0.67; LDH 381.SOF neg. Excluding causes of deficiency or haematic losses, she was subjected to a osteomedullary biopsy which concluded for Myelodysplastic/myeloproliferative process with uncertain nosological classification (MDS-U). Blasts (CD34+) <5% of the nucleated population. Cytogenetic study 46 XX. Molecular study revealed no mutations in BCR-ABL1, JAK2 negative, EXON 12 and EXON 10 absent MPL, no PNH clones. She has carried out 11 transfusions since the beginning of the disease (last transfusion on 02/14/2012) and subsequently remained under observation. From 14 February 2012 no more transfusions until 10.2019 when transfusions resume (10 U EC until 12/2019). In october 2019 repeat biopsy which results MDS/MPN-RS-T(10/2019) sec WHO 2016 R-IPSS Low risk. The marrow aspirate shows: shift to the left of the maturation curve with prevalence of proerythroblasts, ring sideroblasts about 20%, blasts 1-2% normal cytogenetics. Perls + SF3B1 NEG. Transfusional burden pre-reblozyl (5 UGR/8 weeks in the previous 16 weeks). Previous treatment with ESA Dosage 40000/week of duration of 2 months (10/19-1/20) was stopped cause NR. Iron chelation therapy : Exjade from 2019 to 2022, now suspended. The patient started Reblozyl with EAP on 3/24/21 Reblozyl at the initial dose 1.0 mg/Kg. In the previous 16 weeks she had transfused 10 units of packed red blood cells (5 U GR/8 wk). She continued to transfuse until the 30th week (10/29/21) of treatment despite a maximum dose of 1.75 mg/kg. Since the 31st week she never transfused again, however the increase in Hb values gradually took place between the 31st and 41st weeks. On 12.1.22 she administered the last reblozyl with a starting value of Hb 11 achieving also haemoglobin values of 15 gr/dL. The patient thus met the secondary endpoint of RBC-TI greater than 12 wk by 48 week as occurred in 33.3% of patients in the Medalist protocol. The patient is still independent of transfusions and maintains an Hb value of 12 g/dL.

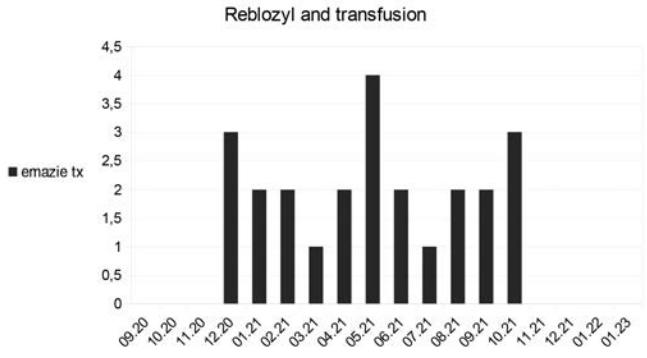

Figure 1.

SP63

A CASE REPORT OF SYSTEMIC MASTOCYTOSIS WITH AN ASSOCIATED HEMATOLOGICAL NEOPLASM (SM-AHN)

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Mastocytosis is a rare hematological neoplasm characterized by heterogeneous clinical manifestations due to the proliferation of abnormal clonal mast cells in cutaneous and extracutaneous sites. Diagnosis of SM is based on major and minor criteria including the pathognomonic dense infiltrate of MCs detected in bone marrow, serum tryptase level, abnormal MCs CD25 expression and the identification of KITD816V mutation. SM with an Associated Hematological Neoplasm (SM-AHN)displays a more aggressive clinical course versus the other variants. In August 2020, a 71-years old man came to our center for abdominal pain, splenomegaly, asthenia, anemia,increased LDH value, leukocytosis with monocytosis.Bone marrow biopsy demonstrated the presence of mature MCs dispersed in the interstitial site and a single micro-aggregate in a LMMC I setting. Negative cytogenetic and molecular biology tests. Tryptase value < 15ng/ml, REMA score equal to +1. The patient started hematological follow up, treatment with hydroxyurea and transfusion support for LMMC diagnosis. In July 2021, despite the stability of the clinical data,the patient's history was complicated by spleen rupture and right portal vein thrombosis. In April 2022 the patient underwent disease re-evaluation for worsening of leukocytosis,anemia,greater transfusion dependence,dyspnea, dependent edema with increased triptase value (132 ng/ml), detection of c-KIT gene mutation.The bone marrow biopsy showed the presence of two associated myeloid neoplasms: mastocytosis occupied 8% of cellularity (>15 MCs in aggregates) and myeloid neoplasm with sever fibrosis with blast rate equal to 8%. CT scan revealed the presence of multiple vertebral fractures, mesentery lymphonodes increased in volume, pleural effusion and pulmonary parenchymal consolidations in absence of hyperpyrexia and positive culture tests.We are therefore faced with a diagnosis of evolution in aggressive SM-AHN due to presence of the major criterion, two minor criteria and C-findings presence according to WHO 2016. The patient started treatment with Midostaurin with improvement of dependent edemas, breathing and restoration of leukocite count to normal values.Transfusion support is still needed. Midostaurin is a TKI effective against KITD816V with an ORR of 60% in aggressive SM. Although midostaurin represents the most potent agent available for SM patients, other medications are under investigation to overcome resistance due to D816V-mutated variant of KIT.

SP64

A BRILLIANT CASE OF ERYTHROID RESPONSE TO LUSPATERCEPT THERAPY IN A LONG-TERM HEAVY TRANSFUSED AND IRON OVERLOADED MYELODYSPLASTIC PATIENT

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Introduction. Luspatercept is a recombinant fusion protein approved for the treatment of Myelodysplasia with SF3B1 rearrangement. It binds TGF-beta superfamily ligands in order to reduce hyper expression of SMAD signal so that ameliorate erythroid maturation. The MEDALIST trial demonstrated in this population how the heavy transfusional burden has negatively correlate with erythroid response to luspatercept. Here we describe a case of brilliant erythroid response in a long-term heavy transfused iron overloaded patient affected by MDS with SF3B1-rearrangement after the introduction of luspatercept.

Patient, **Material and Methods.** A 71years old male, diagnosed in 2005 in our institution, of LR-MDS with ringed sideroblasts SF3B1+ that has no beneficial from previous therapies (ESA) or investigational studies for erythroid response (Hydrossiurea, Lenalidomide) and iron-chelation therapy (MDS0306, TELESTO) was enrolled in October 2022 in our prospective pilot study on the usefulness of peripheral blood immunophenotyping as erythroid response marker during luspatercept treatment in SF3B1+ myelodysplastic syndrome. Patient characteristics at baseline are showed in TAB 1. Criteria for hematological response and luspatercept's dose escalation are considered as for MEDALIST study as well adverse events. Peripheral blood immunophenotyping are tested by 8-color Euro-Flow antibody panels define progressive terminal stages of erythroids' maturation.

Results. Patient reached transfusion independence in 3 months of luspatercept therapy (before V doses). The progressive increase of the hemoglobin value and the transfusion independency have been associated to an ameliorate of late stage erythroid maturation reveal by peripheral blood immunophenotyping (in particular Pro-erythroblasts and orthochromatic) as showed in Table 1. We observed also the reduction of Ferritin till the needed of interruption of iron chelation therapy at 6 months. Furthermore, during the follow up, the hemoglobin subtype has been analyzed, highlighted an impressive increase in the fetal hemoglobin expression (24%).

Conclusions. In this case of a long-term heavy transfused and iron overloaded patient, luspatercept has successed were other drugs have failed despite to the low expectation based on the MEDALIST sub analysis in this population. This patient showed at 6 month an impressive ameliorate peripheral blood maturation started by Pro-erythroblasts. Of course, more studies are needed to evaluate response markers and its correlation with the increase of fetal hemoglobin levels.

Table 1. Patient's characteristic and erythroid response.

	Baseline	3rd month	6th month
Hb	8,1g/dl	9.3g/dl	10.4g/dl
Ferritin	810ug/L	220ug/L	70ug/L
EPO	51.2mUI/ml	88mUI/ml	28.2 mUI/ml
ET rate in 12W	8U	0	0
Pro-erythroblasts	67	184	4991
Basophilic erythrob.	11	42	7
Polychromatic erythrob.	55	975	27
Orthochromatic erythrob.	169	1472	810
Reticulocytes	$8x10^9$/L	$43x10^9$/L	$53x10^9$/L

SP65

FEDRATINIB MAY BE THE FIRST CHOICE FOR PATIENTS AFFECTED BY MYELOFIBROSIS AND CONCURRENT LYMPHOPROLIFERATIVE DISORDER OR DEVELOPED AFTER ANOTHER JAK INHIBITOR THERAPY

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The simultaneous presence of myeloproliferative diseases, specifically myelofibrosis (MF) and lymphoproliferative disorders (LPD), has been reported. The first-in-class JAK inhibitor ruxolitinib (RUX) can control the disease, splenomegaly, and systemic symptoms. The inhibition of the JAK-STAT pathway leads to a state of immunosuppression, with an increased risk of infections or growth of pre-existing lymphoid clones, resulting in LPD. We reported two interesting cases of patients who could control the LPD developed under RUX treatment through shifting treatment to fedratinib (FED). The first is a case of a 65-year-old woman affected by JAK2 mutated polycythemia vera (PV) progressed in MF after 4 years. We treated the patient with RUX based on the prognosis and worsening symptom burden. After about 12 months of treatment, she reported a new worsening of symptoms (night sweating) associated with the finding of two cutaneous lesions in the scapular region, diagnostic for cutaneous marginal zone lymphoma (MZL). Considering the relationship between LPD and RUX treatment, we discontinued RUX administration. We started therapy with FED at the standard dose of 400 mg daily, with the progressive disappearance of the lesions in about two months and reasonable control of the underlined MF. A second case is a man affected by CALR-mutated secondary myelofibrosis to essential thrombocythemia (PET-MF).

Table 1. Brief description of the two cases mentioned in the text. PPV-MF: post-polycythaemia vera myelofibrosis; PET-MF: post-essential thrombocythaemia myelofibrosis; MPN: myeloproliferative disorder; RUX: ruxolitinib; FED: fedratinib

Case	Diagnosis	Prior treatment for MPN	Lymphoproliferative disorder	Months from RUX	Outcome
Female, 65 years	Int-1 PPV-MF, JAK2 mut, arose 4 years after the PV diagnosis	HU for about 3 years for PV, RUX as first-treatment choice for MF	New appearance of different skin lesions in the trunk, diagnostic for cutaneous marginal zone lymphoma (B-component CD20+, CD19+, CD43+, and CD10-, T-component CD3+, CD43+, CD5+, CD4+>CD8+ and CD30-)	12	Disappearance of lesions in about 2 months from FED therapy shift, with well-control of MPN-related symptoms
Male, 75 years	Int-1 PET-MF, CALR mut, arose 17 years after the ET diagnosis	Anagrelide for PLT control in ET, RUX as first-treatment choice for MF	New lymphocytosis (>8000/mmc), diagnostic for chronic lymphocytic leukemia (monoclonal B-lymphocytes CD19+, CD20+, CD5+, CD23+, CD200+)	5	Normalisation of lymphocyte value after about 3 months from FED therapy shift, with well-control of MPN-related symptoms

Faced with a symptomatic secondary MF, he started RUX. During the follow-up, after 5 months of RUX, lymphocyte count was increased, with immunophenotype diagnostic for chronic lymphocytic leukemia (CLL). After the LPD diagnosis, we decided to withdraw RUX and treat the patient with FED without accessory treatment for the indolent CLL. Immediately after the RUX discontinuation, we witnessed a progressive decrease in lymphocyte count, reaching values around the upper threshold limit. From a clinical point of view, our limited series suggests carefully evaluating patients affected by MPN and treated with JAKi. It may be appropriate to try to detect a subclinical lymphoid clone before initiating JAKi treatment. The data presented in this report allows us to suggest FED in the first line for patients harboring indolent lymphoid clones, closely monitoring potential progressions, and as a second line JAKi in case of the development of LPD during RUX therapy. Understanding the underlying biological processes could help treat these patients at best in the future.

SP66

ATYPICAL CHRONIC MYELOID LEUKEMIA (ACML) AND AUTOIMMUNE DISEASE: REPORT OF TWO CASES

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According to the new International Consensus Classification, atypical chronic myeloid leukemia (aCML) is characterized by dysplastic neutrophilia, with monocytes and eosinophils each comprising <10% of the white blood cell count (WBC). It carries a poor prognosis, for the high rate of leukemic transformation and no standard treatment. Autoimmune disorders (AD) increase the risk of developing myeloid diseases. We report two cases of aCML associated with previous diagnosis of AD.

Case 1 is a 56years old woman, with methotrexate(MTX)-treated rheumatoid arthritis. She presented with fatigue, 12.8cm spleen, hyperleukocytosis (WBC 43.000/L) and anemia (Hemoglobin (Hb) 85g/L). On manual blood cell count, increased immature myeloid cells (IMC) and 2% blasts were identified. Bone Marrow Aspirate (BMA) showed hypercellularity, with myeloid hyperplasia, trilineage dysplasia, and 5% blasts. Bone marrow (BM) biopsy was hypercellular with MF1 fibrosis, and cytogenetic normal 46 XY. On account of negative PCR for BCR-ABL1 and JAK2, Next Generation Sequencing (NGS) revealed mutated SRSF2(VAF40%), ASXL1(VAF47%), and RUNX1(VAF46%). The diagnosis of aCML was made and low dose Hydroxyurea (HU) started. Currently, she has monthly transfusion needs and her blood count is Hb 94 g/L, WBC 14.600/L, PLT 146.000/L. A haploidentical HLA donor has been found.

Case 2 is a 72years old man, with MTX-treated psoriatric arthritis, presenting with 13cm spleen, anemia (Hb 87g/L) and hyperleukocytosis (WBC 22.300/L). On blood smear, hyperleukocytosis was confirmed along with IMC, dysgranulopoiesis, and 5% blasts, whereas BMA showed hypercellularity with marked trilineage dysplasia, erythroblastic hypoplasia, and 1% blasts. BM biopsy reported MF1 and karyotype was normal. Unlike BCR-ABL1 and JAK2, FLT3 was mutated. NGS showed ASXL1(VAF48%), CUX1(VAF49%), FLT3(VAF7%), SETBP1(VAF47%), SRSF2(VAF 48%). The transfusion needs were enhanced by the patient's small bowel angiodysplasia. Low dose HU treatment was started and his current blood count is Hb 85 g/L, WBC 22.300/L, PLT 38.000/L. FLT-3 inhibitor treatment is under evaluation. Both patients were diagnosed with SRSF2-mutated aCML, have received low dose HU and had been previously treated with MTX for AD. aCML is a rare disease whose diagnosis has become easier through NGS, which may also allow to detect actionable mutations. Immune driven tumorigenesis as well as AD treatments might play a role in the development of myeloproliferative neoplasms.

SP67

AN UNUSUAL CASE OF HYPEREOSINOPHILIA

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A 73-year-old female was admitted on August 11, 2021, for fever and weight loss. Blood tests showed a white blood cell (WBC) count of $97x10^9$/L with an absolute eosinophil count (AEC) of $25,33x\ 10^9$/L hemoglobin level of 9.5 g/dl and a normal platelet count of $220x10^9$/L. A computered tomography (CT) of abdomen revealed splenomegaly with a lower hyperdense lesion, compatible with splenic spontaneous hematoma. The patient didn't refer pruritus nor rash. There were no clinical or serologic evidences of secondary (reactive) cause of eosinophilia, Strogyloides infection was excluded, while FIPL1-PDGFRA and BRC/ABL transcript fusions were not detected by polymerase chain reaction (PCR) on bone marrow aspirate. Moreover, JAK2 V617F was not detected and no abnormalities were revealed by conventional cytogenetics. The bone marrow morphology and histological features were compatible with myeloproliferative neoplasm NOS and cytoreduction with hydroxyurea was started. In order to exclude an Interleukin-5 pathogenic involvement and allow beginning of Mepolizumab treatment, a whole cytokines panel was performed (IL-1b; Il1-ra; IL2; IL4; IL5; IL7; IL8; IL9; IL10; IL12; IL13; IL15; IL17; Eotaxina; FBF; GM-CSF; IP10; IFNgamma; MCP-1; MIP1PDGF; MIP; Rantes; TNF-alfa; VEGF), but only over range value of G-CSF was found. A CT abdomen performed three months later showed enlargement of spleen lesion and splenectomy was performed on October 19, 2021, revealing pleomorphic sarcoma NOS. Post splenectomy WBC increasing with worsening anemia and progressive thrombocytopenia led to exitus three months later. Detection of hypereosinophilia (HE) in solid tumors is a rare phenomenon and is mainly associated with carcinomas arising from the mucin-secreting epithelium (e.g. bronchus, gastrointestinal tract). The prognostic impact of paraneoplastic HE in solid tumors is just reported in the literature were mortality rate at 1 year from diagnosis is 77%. To date, the association of HE with mesenchymal tissue tumor is reported in nearly 12 cases and no case of spleen deriving soft tissue neoplasm was described.[1]

Reference

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SP68

ERDHEIM-CHESTER DISEASE LIMITED TO CENTRAL NERVOUS SYSTEM: A CASE REPORT

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Erdheim-Chester disease (ECD) is a rare histiocytic disorder characterized by the accumulation of cells with a macrophage or dendritic phenotype at a systemic level. (McClain KL et al. Nat Rev Dis Primers 2021) Here, we present a case with unusual, exclusive involvement of CNS and peculiar radiological findings. A 41-year-old man with no significant comorbidities presented to the ER with a 4-month history of worsening, debilitating neurological symptoms: cervico-nuchal headache, diplopia, photo- and phonophobia, face and lower limbs paresthesias, dizziness, tremors, confusion and postural instability. He also reported weight loss, weakness, nausea and vomiting, distimia, low-grade evening fever and voiding disorders. The neurological examination detected horizontal nystagmus, conjugate eye movement disorder, positive Romberg test and unsteady gait. A lumbar puncture showed abnormal levels of glucose (1 mg/dL, rr 40-70 mg/dL), proteins (246 mg/dL, rr 15-45 mg/dL) and leucocytes (285/mmc, rr 0-5/mmc) in the CSF. Flow cytometry and microbial cultures were negative. Head CT showed a hypodense 25mm area in the cerebellum, while the MRI showed abnormal contrast uptake of the leptomeninges along the cranial nerves (especially III, V, VII, VIII) and the spinal cord in T1 sequences, and multiple diffuse nodular lesions located in the cerebellum, the pons and the mid-brain, characterized by hyperintensity in FLAIR sequences (Figure 1). Total body CT scan was unremarkable. PET scan showed strong uptake in the previously described lesions with SUVmax values up to 35.1; no lesions were identified outside the CNS. A biopsy of one of the nodules showed a diffuse histiocytic infiltrate positive for CD68, CD14, CD33 and CD163, negative for CD207, with a low Ki67 proliferative index (8-10%). The findings were suggestive of ECD. The search for the BRAF V600E mutation resulted negative, as well as that of other genetic variants along the MAPK-ERK and the PI3K pathway; however, due to the limited size of the biopsy sample, it was not possible to test all genes involved* .(Goyal *et al.*, Blood 2020; Diamond *et al.*, Nature 2019). Based on literature data available treatment was started with the MEK inhibitor trametinib with a rapid improvement of the patient's symptoms; no side effects have been reported up to date (1 month of treatment exposure).(Janku *et al.*, Blood 2019)

* Tested: ALK, BRAF, EGFR, POLE; ERBB2, KIT, FGFR3, IDH1, IDH2 MET, NRAS, KRAS, HRAS, PI3KCA, PDGFRA, RET, ROS1.

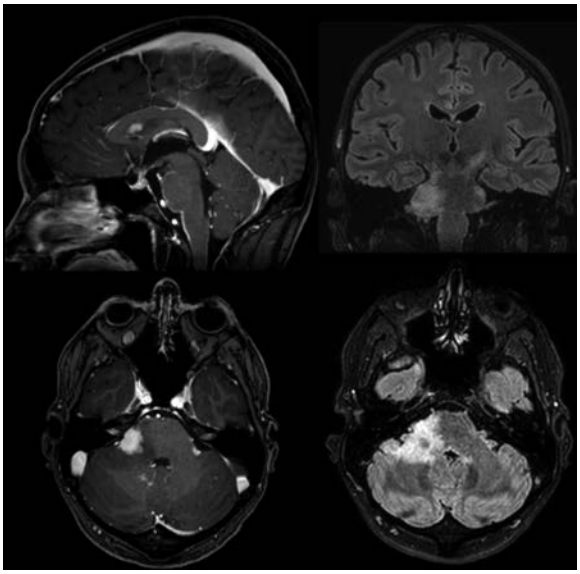

Figure 1.

SP69

COMPARISON BETWEEN SYSMEX XN-1000 HEMATOLOGY ANALYZER AND FLOW CYTOMETRY IN HEMATOPOIETIC PROGENITOR CELL COUNT FOR MANAGEMENT OF PERIPHERAL BLOOD HEMATOPOIETIC STEM CELLS APHERESIS HPCA IN MULTIPLE MYELOMA PATIENTS

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Introduction. Effective bone marrow transplantation relies on the enough numbers of peripheral blood stem cells. White blood cell (TLC) and CD34 cell count in peripheral blood predict the timing of CD34 cells harvest. The fully automated Sysmex XN hematology analyzer (XN-HPCs) has been used with FACS Canto II Flow Cytometry at the cellular therapy laboratory (CTL) of Hamad Medical Corporation (HMC), Doha, Qatar to monitor the timing of stem cells harvest and for cell product quality control. WBC and CD34 cells count reports are obtained within 4 minutes using Sysmex XN 1000, where the CD34 results are expressed as hematopoietic progenitor cells (HPC) absolute count and percentage of the total WBC cells.

Aim of study. Multiple Myeloma patients are the most HPCA collections for autologous transplant in CTL laboratory. The aim of our work is to highlight the predictability of CD34 count for apheresis timing after mobilization, and the correlation between CD34 cells count of MM patients obtained from Sysmex XN-1000 hematology analyzer with FACS CantoII Flow Cytometry.

Materials and Methods. A retrospective data of CD34 cells count of 36 peripheral blood and 101 apheresis samples, 87% of them were MM and 12.5% were NHL collected from January 2023 to April 2023 has been included in this study. CD34 cell enumeration was performed using BD Stem Cell enumeration kit on FACS Canto II flow Cytometry. HPC absolute count and percentage were obtained from Sysmex XN 1000.

Results. In this study, there was a significant difference between Sysmex XN-1000 HPC count and Flow cytometry CD34 count of samples collected from MM and NHL. CD34 Count > $20x10^6$/L was used as a cut off value to start the collection; for MM patients' group, the minimum value of CD34 count before staring the apheresis was $23x10^6$/L. The HPC count of apheresis samples using XN-1000 Sysmex were 1,65 times more in MM samples and 0.9 times more in NHL comparing with Flow cytometry CD34/L counts.

Conclusions. The HPCs count using XN-1000 Sysmex hematology analyzer is a time- saving and cost effective that can be performed with minimum operator skill. However, its used as a replacement for Flow cytometry is not recommended, especially for MM patients where there was an overestimation of CD34 cell count reflecting the possible role of heterogeneity of sample type.

SP70

THE IMPACT OF ATG REAL-DOSE (RD) /THERORETICAL-ALC-BASED-DOSE (TD) RATIO ON OUTCOME IN ADULT PATIENTS UNDERWENT ALLOGENEIC-STEM-CELL TRANSPLANT AFTER MYELOABLATIVE CONDITIONING FOR MYELOID MALIGNANCIES: A RETROSPECTIVE-SINGLE-CENTER ANALYSIS

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Background. Rabbit polyclonal anti-thymocyte globulin (ATG) is extensively used as graft versus host disease prophylaxis both after matched related(MRD) and unrelated donor (UD) allogeneic stem cell transplantation (allo-SCT). Optimal ATG dosage is crucial to obtain the higher clinical benefit. Absolute lymphocyte count (ALC)-based ATG dosing had more chance to predict the optimum exposure than fixed dose weight-based.

Methods. We analyzed retrospectively data from patients undergoing allo-SCT from matched UD (MUD) after MAC conditioning regimen. The principal aim of this study was to evaluate if the weight-based ATG dosing had an impact on main outcomes normalized by theoretical ALC-based dose. We calculated retrospectively a ratio between the real cumulative dose (RD) administered and theoretical (TD) ALC-based dose as proposed by Admiral et al. The hypothesis was that patients with ratio <1 (under-dosage) could have more alloreactivity, and patients with ratio>1 (over-dosage), more toxicities. MAC regimen between 2005 and 2021 for AML (n=60), ALL (n=28) and MDS (n=12). Only 3 patients with AML and 1 patient with ALL had active disease at transplant. Median age was 46 y (13.7-69). Stem cell source was PBSC in 88%. ATG was administered at day -2 and -1 before allo-SCT. Median ATG/Kg dose was 7 mg/Kg. Median ATG cumulative dose was 460 mg (212-980). Median ALC at first day of ATG infusion day was 320/microliter (1-5410).

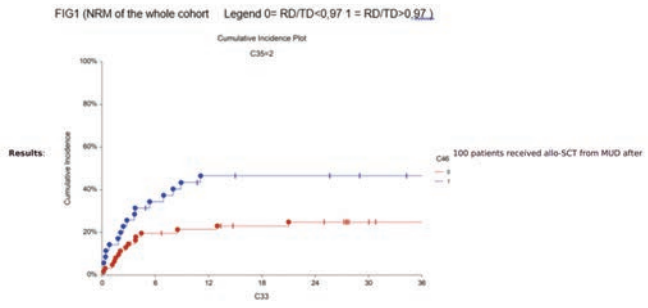

Figure 1.

After a median follow up of 14.8 months, median OS was 30 months, the 2-y OS was 53 %, median PFS was 21 months and 2-year PFS was 50%, 1-year NRM was 31%. The cumulative incidence (CI) of grade 2-4 was 28% and 3-4 aGVHD was 10%. The RD/TD was 0.85 (0.24-1.90). We used this ratio to perform ROC analysis. For OS of the whole cohort, the best cut off was 1.08 and 1-year CI of OS above *vs* under cut off was 52% *vs* 64% respectively (p = 0.18). For NRM the best cut off was 0.97. Using this cut-off, 1-year CI of NRM above *vs* under cut off was 47% *vs* 25% respectively (p = 0.02), (Figure 1). Using the same cut off, we showed no difference in term of grade 3-4 and 2-4 aGVHD. The analysis was restricted to AML cohort (N=60) but we did not found difference in terms of OS (63% *vs* 68%), NRM (33% *vs* 14%, p= 0.2).

Conclusions. We found no difference in overall survival, aGVHD 2-4 and 3-4 incidence, in patients receiving allo-SCT from MUD, having lower or higher exposure to ATG. NRM was higher for patients with higher ATG/ALC ratio. This higher NRM probably due to higher incidence of infections.

SP71

MACROPHAGE ACTIVATION SYNDROME AND TRANSPLANT-ASSOCIATED THROMBOTIC MICROANGIOPATHY: A RETROSPECTIVE/PROSPECTIVE SINGLE CENTER STUDY

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Introduction. Transplant-associated thrombotic microangiopathy (TA-TMA) can associated to high mortality after allogeneic stem cell transplantation (allo-SCT). TA-TMA is characterized by non-immune hemolytic anemia, platelet consumption, and mainly by multi-organ damage due to microvascular occlusion. Macrophage Activation Syndrome (MAS) is another life-threatening syndrome, associated or not to infections or graft versus host disease (GVHD). Diagnosis is difficult leading to variable incidence.The first aim of this study was to determine the incidence and their outcome of these 2 post-allo-SCT complications.

Patients and Methods. All consecutive patients receiving an allo-SCT since September 2021 were included. Even if this is a retrospective study, clinical and biological variables were collected prospectively. Patients were monitored every day for hypertension detection, and one time per week LDH, proteinuria as measured by routine dipstick, and ferritin levels. Renal function was controlled every day starting from day 0. Abnormal values were monitored more frequently. Diagnostic criteria used for TA-TMA were those proposed by Jodele et al. (except for sC5b-9) complex including LDH above normal, presence of schistocytes, thrombocytopenia, anemia, hypertension, proteinuria above 30mg/dL. Every patient with probable TA-MAT was screened for direct Coombs test. Diagnostic criteria for MAS were ferritin >10.000 ng/ml and at least one other criterion such as fever, cytopenia, LDH levels, evidence of hemophagocytosis in bone marrow, triglycerides.

Results. Since September 2021 to October 2022, 43 patients received first allo-SCT. The median follow-up was 3.3 months (0.2-10.8). Patient and transplant characteristics were reported in Table. Median age was 50 years (range 19-71). For the whole population, the cumulative incidence (CI) of grade 2-4 acute graft versus host disease (aGVHD) was 14%, CI NRM at 3 months was 10%. The CI of relapse at 3 months was 7%. Overall, 100-day CI of TA-MAT and MAS was 25%. 100-day CI TA-MAT was 11% (4/36). The median time to diagnosis was 21 (range 16-25). In these patients, TA-MAT was considered primary in 1 patient and secondary to active infections in 3 patients. 2 patients were treated with Eculizumab with complete regression. No patients died from TA-MAT. 100-day CI of MAS was 14% (5/36). The median time to diagnosis was 17.6 days (range 14-22 days). The median ferritin levels were 22.390 ng/ml (8.898- >33.510 ng/ml). Other symptoms/signs associated to hyperferritin were fever, diarrhea, increase bilirubin, and triglycerides increase. 2 patients were treated with steroids and iv immunoglobulins, achieving a complete response. No patients died from MAS.

Conclusions. In this retrospective single center analysis, the CI of TA-MAT and MAS was 11% and 14% respectively. Overall, 44% of these patients were treated. Although the incidence can be considered similar to that reported in other studies, the impact on early outcome of TA-MAT and MAS in our cohort was null. It can hypothezed that systematic prospective monitoring for these 2 complications could lead to early identification and treatment initiation. Furthermore, in this cohort, the good prognosis could be related to fact that no patients had concomitant GVHD diagnosis.

SP72

EFFICACY AND SAFETY OF SORAFENIB TREATMENT IN FLT3-ITD MUTATED AML AFTER ALLOGENEIC STEM CELL TRANSPLANTATION: A REAL-LIFE EXPERIENCE

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FLT3-ITD mutated acute myeloid leukemia (FLT3-ITD+ AML) is still one of the greatest hematological challenges due to its poor prognosis despite allogeneic hematopoietic stem cell transplantation (HCT). FLT3 inhibitors, such as the multi-targeted tyrosine kinase inhibitor sorafenib, have proved their efficacy in both induction and salvage treatment. Although the use of FLT3-inhibitors after HCT is still off-label, sorafenib maintenance is recommended by the Acute Leukemia Working Party - European Society for Blood and Marrow Transplantation, as it demonstrated safety and efficacy in reducing relapse and improving survival in the SORMAIN trial. The aim of our study is to evaluate the safety and efficacy of post HCT treatment with sorafenib in FLT3-ITD+ AML. We report data from 20 adult patients with FLT3-ITD+ AML receiving sorafenib after HCT between Feb-2017 and Feb-2023, with different indications: 1) maintenance, if disease in complete remission (CR); 2) pre-emptive, in case of molecular relapse (measurable MRD in NPM1 mutated patients); 3) treatment, in case of hematologic relapse.

Table 1. Patients features. CR = complete remission, MRD = measurable residual disease, MAC = myeloablative conditioning, RIC = reduced intensity conditioning, PTCy = post transplat cyclophosphamide, GvHD = graft versus host disease

	20 patients
Sex (M/F)	10 / 10
Median age at HCT– years (range)	51 (41-75)
Mutational status at diagnosis	
NPM1+/FLT3-ITD+	12
FLT3-ITD+	20
Disease status at transplant	
CR1	9
CR2	3
CR MRD+	4
Advanced disease	4
Conditioning	
Treosulfan MAC	15
Treosulfan RIC	5
GvHD prophylaxis	
PTCy + Rapamycin based	20
Donor	
Matched related donor	5
Mismatched related donor	5
Matched unrelated donor	7
Cord Blood	3

Patient characteristics are reported in Table 1.14 patients received sorafenib as post HCT maintenance, 5 patients as pre-emptive therapy and 1 patient for hematologic relapse. The median time of sorafenib initiation from HCT was 118 days (range 49-904) and median

treatment duration was 698 days (range 3-1431). The median follow-up was 1414 days (range 180-2252). 8/14 patients completed the 2-years maintenance (6 are still on treatment). 7/8 of patients (88%) maintained MRD negativity after maintenance completion, while 1 patient restarted sorafenib due to early MRD detection, re-obtaining MRD negativity. Overall, the 2-year overall survival was 87.5% with a 2-year progression-free survival of 80%. Sorafenib was introduced at a minimum dosage of 200 mg daily to reduce the drug-drug-interaction (maximum 800 mg daily). 6 patients required a reduction to 200 mg every-other-day due to gastrointestinal intolerance. Discontinuation occurred in 20% of patients (4/20), in 50% of cases due to grade 3 CTCAE toxicity (1 for diarrhea,1for QTc prolongation) and in 50% of cases due to disease progression. Our real-life practice confirms that sorafenib is well-tolerated and contributes to sustained long-lasting CR of FLT3-ITD+ AML after allogeneic HCT. In particular, sorafenib should be considered a feasible and effective therapeutic option as maintenance drug in the post-transplant setting.

SP73

POST TRANSPLANTATION CYCLOPHOSPHAMIDE FOR PREVENTION OF GRAFT VERSUS HOST DISESE IN PATIENTS WITH ACUTE LEUKEMIA RECEIVING ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION WITH PERIPHERAL GRAFT: A SINGLE CENTER EXPERIENCE

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Background. Post-transplant cyclophosphamide (PTCY) has become widely used for preventing graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplantation (allo-HCT). Although CY is believed to act by selective elimination of alloreactive T cells and induction of suppressor T cells, the exact mechanism of action is not yet fully elucidated. However, PTCY has shown to significantly reduce acute and chronic GVHD rates without the need of T-cell depletion. We report the single-centre experience of patients with intermediate/high-risk acute leukaemia (AL) received PTCY as GVHD prevention after allo-HCT with progenitor cells collected by peripheral blood.

Methods. Between February 2019 and November 2022, 41 AL patients, median age: 53 years (range: 26 to 74) underwent to allo-HSC, 34 AML and 7 ALL; 31 patients (76%) received allo-HSC in 1st and 10 (24%) in ≥ 2nd complete remission (CR) respectively. Haplo-HSC peripheral graft was offered to 32 (78%) patients and a full matched related peripheral graft to 9 (22%). Conditioning regimen was myeloablative in 78% (n=32) of cases and reduced intensity in the remaining 9 patients (22%). All patients received PTCY 50 mg/Kg on day+3 and day+5 combined with CSA+MMF.

Results. The median number of CD34+ cells infused was 5.62 x 10^6/Kg (range 4.27-8.6). The median time to ANC >0.5x10^9/l and platelets >20x10^9/l was 14 (range 12-18) and 15 days (range 11-42) respectively. All but two (95%) patients achieved full engraftment. Failure engraftment was observed in one patient with refractory AML in CR2 while another one with relapse ALL in CR2 showed autologous reconstitution. Acute GVHD evaluated in all patients was 26% with 5% of grade III-IV while chronic GVHD (evaluated in 37 patients) was 61% with 16% of grade III-IV. Nine patients (21%) with acute and chronic grade II-IV steroid refractory GVHD responded to ruxolitinib combined to extracorporeal photophoresis. After a median follow-up of 22 months (range: 2-49) 70% of patients are alive and in continuous CR and MRD negative. Seven patients (17%) died of progressive disease. The transplant-related mortality (TRM) was 7% and 13% at day 100 and 1-year respectively (Figure 1).

Conclusions. Our results confirm, although on small series of patients, the efficacy of PTCY as GVHD prophylaxis. The use of mobilized peripheral graft showed also in our series rapid engraftment, optimal control of leukemia with low rates of both chronic and acute extensive GvHD.

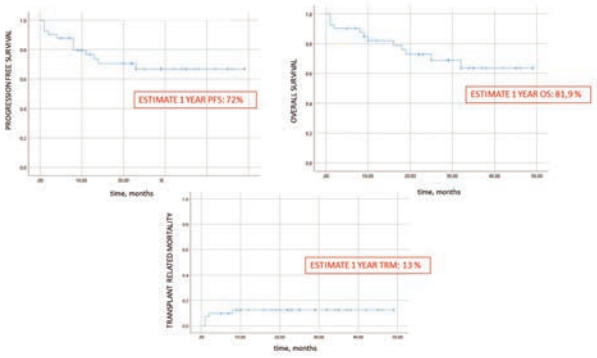

Figure 1.

SP74

UNCHANGED TRANSPLANT ACTIVITY AND PATIENTS' OUTCOME DURING COVID-19 PANDEMIC: A SINGLE CENTER COMPARISON WITH PRE-PANDEMIC

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The first Italian patient affected by COVID-19 was identified on 21st February 2020 and more than 25.500.000 cases have been reported in Italy so far. In the first months of the pandemic, patients with haematological malignancies had worse outcomes than the general population with COVID-19. Subsequently, the mortality rate significantly decreased. Combination of prophylactic and therapeutic strategies and individual-level prevention steps have been developed against SARS-CoV-2 leading to improved prognosis in high-risk patients. Tailored hospital organization and a redefinition of patient's journey towards transplant unit were fostered through a task force promoted by the haematological societies. Recommendation to reduce the risk for patients and healthcare workers, as well as *vademecum* for caregivers and donors were of paramount importance to overcome the pandemic phase. The aim of our study was to retrospectively compare transplant activity in the pre-pandemic phase (2018-2019) and during the pandemic phase (2020-2021) in our Institute. All consecutive patients who received allogeneic transplant were evaluated for major outcomes. Overall, 157 patients received an allogeneic transplant in the pre-pandemic phase (median follow-up 4 years) and 159 in the pandemic phase (median follow-up 2.3 years). Median age, gender, diagnosis and disease status at transplant were superimposable between the two cohorts (p ns). Overall in the pre-pandemic cohort 28 patients received a transplant from a matched related donor (MRD), 45 from a mismatched related donor (MMRD), 72 from a matched unrelated donor (MUD) and 12 re-

ceived a cord blood (CB) transplant. Similarly, in the pandemic cohort 23 patients received a transplant from a MRD, 34 from a MMRD, 87 from a MUD and 12 received a CB transplant. Despite the slightly increase in number of unrelated donor (both MUD + CB) and the decreasing number of related donor (both MRD + MMRD) the trend was not statistically significant (p 0.0672). The 2-years overall survival in the pre- and pandemic cohort was 62.92% (CI 95% 54.27-70.38%) and 72.34% (CI 95% 64.62-78.65%) respectively – p ns. Accordingly, the 2-years event free survival in the pre- and pandemic cohort was 60% (CI 95% 67.46%-51.54%) and 68.27% (CI 95% 60.21%-75.04%) respectively – p ns.

The integration of strategies for environment and patients' protection during the pandemic translated into an unchanged transplant activity and patients' outcomes.

SP75

EFFICACY AND SAFETY OF BIOSIMILAR PEGFILGRASTIM AFTER AUTOLOGOUS STEM CELL TRANSPLANT: A COMPARATIVE STUDY WITH BIOSIMILAR FILGRASTIM, LENOGRASTIM AND ORIGINATOR PEGFILGRASTIM

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Biosimilar Pegfilgrastim has been approved for prophylaxis of severe neutropenia duration and febrile neutropenia in cancer patients, including hematologic malignancies. However, poor data have been so far published among patients undergoing both allogeneic and autologous transplant. From Jun-2021 to Dec-2022, 53 consecutive adult patients with hematologic malignancies (Plasma cell disorders 38; Lymphomas 15) underwent autologous transplant (ASCT) in our Institution. Biosimilar pegfilgrastim was given at the dosage of 6 mg single dose at day 3 after infusion of stem cells, with the aim to evaluate its efficacy and the safety. This cohort of patients was compared with three historical cohorts: a) 392 consecutive adult patients treated with biosimilar Filgrastim at dosage of 5 mcg/Kg daily given from day 3 after infusion from Mar-2013 to May-2021; b) 99 consecutive adult patients treated with Lenograstim at dosage of 5 mcg/Kg daily given from day 3 after infusion from Jan-2009 to Feb-2013; c) 60 consecutive adult patients treated with originator peg-filgrastim at dosage of 6 mg single dose at day 3 after infusion from Mar-2006 to Dec-2008. The four patient cohorts were similar for all baseline features analyzed, even if patients treated with biosimilar pegfilgrastim were older, more frequently diagnosed as myeloma and received a significant lower number of CD34+/Kg cells.

Table 1. Clinical results of patients, according to the received G-CSF formulation.

Results	Biosimilar pegfilgrastim N=53	Lenograstim N=99	Pegfilgrastim N=60	Biosimilar filgrastim N=392	P
Haematologic recovery, days (range)					
ANC > 500/mcL	10 (9-12)	11 (9-29)	10 (8-18)	11 (7-30)	< 0.001
PLTs > 20.000/mcL	11 (9-16)	14 (10-35)	12 (9-23)	13 (8-120)	< 0.001
Median G-CSF injections, days (range)		9 (4-26)		8 (4-26)	< 0.001
FUO in neutropenia episodes (%)	14 (26.4%)	10 (10.1%)	13 (21.7%)	58 (14.8%)	0.055
Microbiologically documented infections (%)	18 (34%)	43 (43.4%)	19 (31.7%)	151 (38.2%)	0.607
Intravenous antibiotics needing (%)	32 (60.4%)	53 (53.5%)	32 (53.3%)	209 (53.3%)	0.778
RBC transfusions (Mean ± SD)	0.3 ± 0.742	0.78 ± 1.475	0.44 ± 0.952	0.64 ± 1.212	< 0.001
Median PLT transfusions (range)	1 (0-15)	2 (0-12)	1 (0-6)	2 (0-18)	< 0.001
Median hospitalization duration, days (range)	19 (14-59)	24 (15-68)	21 (6-29)	20 (13-66)	< 0.001
TRM (%)	1.9%	2%	1.7%	2%	0.683

RBC: Red Blood Cells; PLT: Platelets; ANC: Absolute Neutrophilis Count; FUO: fever of unknown origin; TRM: Transplant-Related Mortality; SD: Standard Deviation.

The results of the study show a significantly shorter time to neutrophilis and platelet recovery (P<0.001) in the cohort of patients treated with both biosimilar and originator Pegfilgrastim, whereas no difference was observed among the other two groups. Moreover, patients treated with biosimilar Pefilgrastim showed a shorter hospitalization time (P<0.001) and a lower transfusion need (P<0.001) compared with other groups of patients. As for the other analyzed parameters, we did observe a similar incidence of febrile episodes (P=0.055), microbiologically documented infections (P=0.607), needing of intravenous antibiotics (P=0.778), and transplant-related mortality (P=0.683). No difference in terms of drug-related adverse events was observed. Similar results were obtained performing two separate sub-analysis only for lymphoma or myeloma patients. From our data biosimilar Pegfilgrastim seems to be substantially equivalent in terms of efficacy to the originator one and superior than Lenograstim and biosimilar Filgrastim in terms of hematologic recovery, when used in this setting.

SP76

TREOSULFAN PLUS FLUDARABINE AS CONDITIONING TREATMENT BEFORE UNMANIPULATED HAPLOIDENTICAL TRANSPLANTATION FOR ACUTE LEUKEMIA PATIENTS OLDER THAN 65 YEARS

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Background. Allogenic stem cell transplantation (allo-HSCT) is the only curative option for intermediate and high-risk adult acute leukemia (AL). The majority of patients (pts) older than 65y had been excluded from this potentially curative option for decreasing allo-HSCT tolerance, for toxicity related to myeloablative conditioning and for a low probability of finding a HLA-identical donor. We report here the outcome of AL pts with older than 65y who underwent unmanipulated haploidentical transplantation (aplo-HSC) received intravenous 10 g/m² treosulfan daily, for 3 days (days –4 to –2) plus 30 mg/m² intravenous fludarabine daily for 5 days (days –6 to –2) with encouraging results in terms of survival, transplant related mortality (TRM), relapse, engraftment and graft-versus-host disase (GvHD) incidence.

Methods. Between Jun 2019 and December 2022, 20 consecutive adult pts aged ≥65y received an aplo-HSCT for AL in three Hematology Transplant Unit. Patients' median age was 69y (range 65–74). Fourteen pts (70%) and 6 experienced this in 1° complete remission (CR) and in ≥ 2° CR respectively. All patients received post-transplant cyclophosphamide (PT-CY) and peripheral blood stem cells as sours of graft (PBSC), (Figure 1).

Results. The median time to neutrophil engraftment>0.5x10^9/l and platelet>20x10^9/l was 14 days (range 13-21) and 22 days (range 13-48) respectively. All pts achieved full engraftment. One patient with relapse AL in CR2 had autologous reconstitution. Among the 19 pts alive at day 100, chimerism was full donor in 18 (94%). The cumulative incidence of acute GvHD was 25% (grade I-II and III-IV was 10% and 15% respectively) and cumulative incidence chronic GvHD (evaluated in 19 patients) was 35% (grade I-II and III-IV was 20% and 15% respectively). After a median follow-up of 15 months (range 2-46); 13 (65%) pts are alive and maintained CR with MRD negativity and 7 pts died. Three pts (15%) died of progressive disease and

4 (20%) from transplant related causes (1 pts from infection, 2 pts from GvHD, and 1 pts from cachesia). The TRM was 5% and 15% at day 100 and 1-year respectively. The estimate 1-year median progression free survival an 1-year overall survival were 63% and 69% respectively (Figure 1).

Conclusions. In our experience Treosulfan plus Fludarabine as conditioning treatment before aplo-HSCT for older acute leukaemia pts with the exclusive use of PBSC did not increase the incidence of GvHD II–IV with NRM rates acceptable.

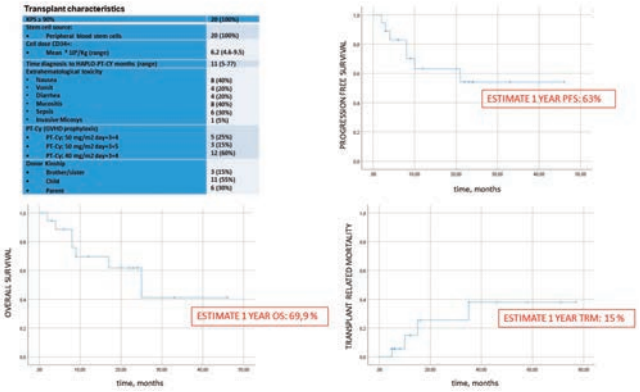

Figure 1.

SP77

IMPACT OF PHOTOBIOMODULATION IN THE DEVELOPMENT OF ORAL MUCOSITIS IN MULTIPLE MYELOMA PATIENTS UNDERGOING AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background. Oral mucositis (OM) represents an extremely common complication in patients undergoing autologous stem cell transplantation (ASCT): in this cohort of patients, the incidence of OM reaches up to 80%. This complication strongly affects the quality of life (QoL): it impairs oral function, leads to increased pain and the need for pain medication use, increased infection risk and prolonged hospitalization with consequent economic impact. For the prevention of OM, the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) guidelines recommend several options, including photobiomodulation (PBM).

Methods. We aimed to evaluate the impact of preventive PMB in OM in multiple myeloma (MM) patients undergoing ASCT in our Institution. According to MASCC/ISOO guidelines, daily PBM sessions were scheduled at the patient's bed from the day of the start of conditioning regimens to day +2 post-transplantation. OM was graded according to WHO classification and assessed at T0 (start of conditioning regimen), T7 (+7 post-transplant) and T14 (+14 post-transplant); in addition, the need for pain medication and therapeutic further PBM, as well as the occurrence of gastric and intestinal mucositis and febrile neutropenia were evaluated.

Results. 22 transplant procedures were analyzed. Males were 14 (64%), median age at transplant was 64 years (range 45-70). 15 procedures (68%) were first ASCT. Conditioning regimen was Mel 200 mg/mq and Mel 140 mg in 17 (77%) and 5 cases (23%), respectively. Engraftment was observed in all patients. In 9 patients, no OM was observed. WHO grade 1 and 2 OM occurred in 9 (41%) and 4 (18%) patients, respectively. No patient experienced WHO grade 3-4 OM. Patients with no occurrence of OM (WHO 0) experienced WHO grade 0, 1, 2, 3 gastric mucositis in 27%, 5%, 9% and intestinal mucositis in 13%, 13%, 9% and 5%, respectively. 6 patients (27%) developed febrile neutropenia, 4 of whom had WHO grade 1-2 OM. All results are shown in Table 1.

Conclusions. In MM patients undergoing ASCT, preventive PBM is a non-invasive, painless, easy and safe procedure that significantly reduces the occurrence of severe OM and the need of pain medication.

Table 1. Characteristics and outcome of patients according to WHO OM grading.

	WHO OM GRADING			
	0	1	2	Total
N° ASCT procedure, n (%)	9 (41)	9 (41)	4 (18)	22 (100)
Median age, n [range]	56 [45-68]	64 [61-70]	67 [65-67]	64 [45-70]
Age≥ 65 years	2 (9)	4 (18)	4 (18)	10 (45)
Male gender, n (%)	5 (23)	6 (27)	3 (13)	14 (64)
Female gender, n (%)	4 (18)	3 (13)	1 (5)	8 (36)
I ASCT	7 (32)	5 (23)	3 (13)	15 (68)
II ASCT	2 (9)	4 (18)	1 (5)	7 (32)
Conditioning regimen:				
Mel200	7 (32)	7 (32)	3 (13)	17 (77)
Mel140	2 (9)	2 (9)	1 (5)	5 (23)
Hematological Recovery:				
Neutrophils > 1 x 10^9/L	+11 [9-13]	+10 [9-11]	+10 [10]	+10 [9-13]
Platelets > 20 x 10^9/L	+20 [12-24]	+13 [11-20]	+ 13 [13-20]	+14 [11-24]
Febrile neutropenia, n (%)	2 (9)	1 (5)	3 (13)	6 (27)
WHO Gastric Mucositis Grading, n (%)				
0	6 (27)	3 (13)	/	9 (41)
1	1 (5)	1 (5)	/	2 (9)
2	2 (9)	5 (23)	4 (18)	11 (50)
≥3	/	/	/	/
WHO Intestinal Mucositis Grading, n (%)				
0	3 (13)	3 (13)	/	6 (27)
1	3 (13)	3 (13)	/	6 (27)
2	2 (9)	3 (13)	4 (18)	9 (41)
3	1 (5)	/	/	1 (5)
4	/	/	/	/
Need for pain medications, n (%)	/	1 (5)	2 (9)	3 (13)
Therapeutic PBM, n (%)	/	1 (5)	2 (9)	3 (13)

SP78

MANAGEMENT OF CINV IN PATIENTS WITH MULTIPLE MYELOMA OR LYMPHOMA UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION: NEPA VERSUS TROPISETRON. A MONOCENTRIC REAL-LIFE EXPERIENCE

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Introduction. Chemotherapy-induced nausea and vomiting (CINV) observed during autologous hematopoietic stem cell transplantation (ASCT) in patients (pts) with lymphoma and multiple myeloma (MM) have an important impact on the quality of life and

treatment compliance. Netupitant-Palonosetron (NEPA) has been approved as prophylaxis of CINV but its experience is limited.

Aims. We compared the efficacy of Tropisetron and NEPA in terms of reduction of CINV in pts undergone to ASCT for lymphoma or MM. The secondary aim included comparing the duration of CINV, based on the use of Tropisetron or NEPA, and their safety profile in terms of reduction of extrahaematological toxicity.

Methods. In this retrospective monocentric study, we enrolled 76 pts who underwent ASCT between March 2021 and March 2022. Patients' characteristics are in Table 1. The Likert scale was used to measure the effectiveness of antiemetics.

Table 1 and Figure 1.

Table 1. Patients' characteristics.

Overall, 76 patients		Multiple Myeloma	Lymphoma
Number of patients		48	28
Median age, years		61	61
Conditioning Regimen		Alkeran	FEAM
Type of antiemetic received	NEPA*, n	33	21
	Tropisetron**, n	15	7

*in multiple myeloma one shot the day of conditioning, in lymphoma every 72 hours during conditioning;
**twice daily during conditioning in both multiple myeloma and lymphoma.

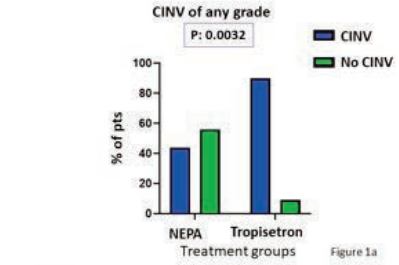

Figure 1a

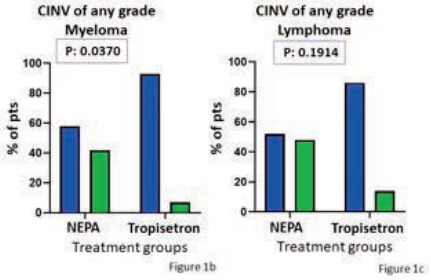

Figure 1b

Figure 1c

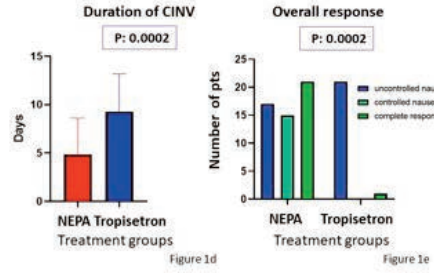

Figure 1d

Figure 1e

Results. Fifty patients (65%) reported CINV of any grade. In particular, about half of pts treated with NEPA (56%) and almost all those treated with Tropisetron (91%) reported CINV. Among pts who didn't report CINV (35%), the majority received NEPA (92%) (P = 0.0032) (Figure 1a). Focusing on pts with MM, 59% of those treated with NEPA and 93% of those treated with Tropisetron reported CINV. Fifteen patients did not experience CINV (32%) and almost all (93%) had been treated with NEPA (P = 0.037) (Figure 1b). Sixty-one percent of the patients with lymphoma reported CINV (Figure 1c). Mean duration of CINV was significantly shorter for pts treated with NEPA than for those treated with Tropisetron (4.8 days *vs* 9.2 days) (P=0.002) (Figure 1d). We didn't find any significant difference of extraematological toxicity of chemotherapy between the two groups of patients. Regarding the outcome, 37% of pts had complete response to NEPA, 28% had controlled nausea and 31% had uncontrolled nausea. Only 5% of patients had complete response and 95% had uncontrolled nausea in the Tropisetron group (Figure 1e).

Conclusions. In our experience, NEPA showed superiority in the prevention of CINV in highly emetogenic regimens in both patients with myeloma or lymphoma, with advantages on the severity and the duration of CINV. Given the high burden of CINV in the whole population analyzed in the study, regardless of the antiemetic used, it would be useful to identify patients at greatest risk and standardize CINV prophylaxis and treatment protocols depending on the different chemotherapy regimens and their emetogenic risk.

SP79

THE POLICLINIC OF BARI UNIVERSITY HOSPITAL EXPERIENCE IN TREATING ACUTE LYMPHOBLASTIC LEUKEMIA WITH ALLOTRANSPLANTATION: THE IMPACT OF TOTAL BODY IRRADIATION-BASED CONDITIONING REGIMEN ON POST-ALLOTRANSPLANT OUTCOMES

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The outcome of acute lymphoblastic leukemia (ALL) is associated with diagnostic prognostic factors in addition to the pediatric-like therapeutic approaches in association to the monitoring of minimal residual disease (MRD) in order to define the allotransplant indication. Moreover, allotransplant procedures in ALL reflect the center experience, although the total body irradiation (TBI)-based myeloablative conditioning regimen seems to determine the best post-transplant outcome in terms of overall survival (OS), disease free survival (DFS) and acceptable cumulative incidence (CI) rates of non-relapse mortality (NRM) and Relapse (R).

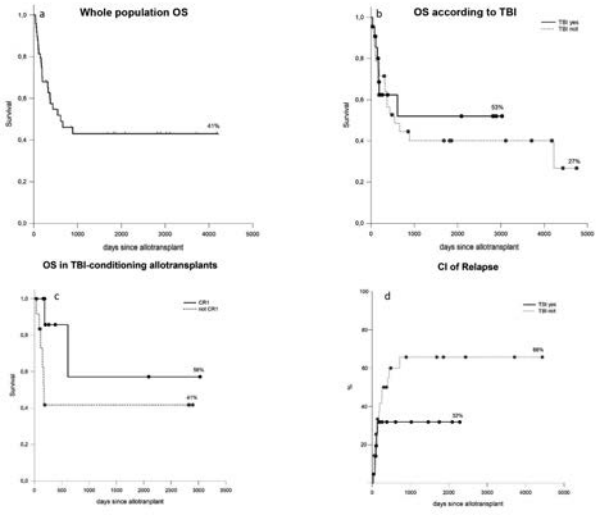

Figure 1.

In this study we retrospectively analyzed the ALL-patients undergoing allotransplantation in the last ten years with the aim to appre-

ciate how the firm introduction of GIMEMA protocols may have impact the post-transplant survival outcomes (OS, DFS) together with the NRM and R analysis. Briefly, fifty allotransplants were performed in ALL-patients (median age, 32 years, r 17-64); Male sex in 60% (n=30) with at allotransplant CR1 and TBI-based myeloablative conditioning in 42% (n=21) and 44% (n=22), respectively. B, T and mixed lineage was described in 66% (n=33, PH-positive in 16 cases), 30% (n=15) and 4% (n=2), respectively. According to disease status (first complete remission (CR1) *vs* not CR1), the median OS was not reached (NR) and of 194 days (d) in CR1- and not CR1-allotransplants (p=0.006), respectively. The patients undergoing TBI-based conditioning shew a trend in favor of better median OS if compared with those who did not receive TBI (NR *vs* 543 d), although at 5 years it's possible to appreciate a clear benefit by TBI-based conditioning (Figure 1b). In particular, when analyzing TBI-conditioning allotransplants, a better median OS was documented (NR and 194 d in CR1- and not-CR1-patients, respectively, p=0.05, Figure 1c). Accordingly, the 3-year CI of relapse (CIR) in TBI- and not TBI-allotransplanted patients was of 32% and 66% (HR=0.51; IC95%: 0.21-1.320, p=0.16, Figure 1d), respectively. As expected, the 3-year CIR in CR1- and not CR1- patients was of 34% and 70% (p=0.025), respectively and the 5-year TRM in CR1- was better if compared with not CR1-patients (HR=0.51; IC95%: 0.225-1.173, p=0.102). ALL outcomes seem to benefit by the pediatric-like inspired approaches given the already demonstrated impact on pre-transplant CR which seems to be boosted by the right conditioning pre-allotransplant regimen.

SP80

PROSPECTIVE AND RETROSPECTIVE VALIDATION OF AUTOMATED GMP CLOSED SYSTEM RBCS DEPLETION FOR ABO-MISMATCHED IN HPCM TRANSPLANT. A COMPARISON STUDY WITH HMC OF DOHA (QATAR)

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Introduction. Despite the worldwide use of peripheral blood as a source of stem cells, bone marrow (BM) derived stem cells still account for about 25% of all allogenic transplant in USA, and South Europe. BM is still the stem cell source of choice especially for young age patients because of a decreased risk of graft-versus-host disease compared with allogenic apheresis hematopoietic stem cells (HPCA) transplants. The insignificant incidents of GVHD resulted in the reduction of the hospitalisation time, minimizing the life-threatening complications of chronic or acute GVHD. For allogeneic transplants, processing of bone marrow requires the depletion of ABO-mismatched red blood cells (RBCs) to avoid transfusion reactions.

Aim of study. to optimize the fully automated close system RBC depletion procedure of Sepax-2 device using Smart Redux software.

Materials and Methods. As bone marrow is difficult to be obtained for optimization purposes, we attempted to simulate the bone marrow harvest using either buffy coat (kindly provided by Blood bank) or cryopreserved peripheral blood stem cells that were thawed and washed before mixing with RBCs and supplemented with Plasma-Lyte A and 5% human serum albumin to obtain initial products close to BM characteristics for transplantation (high quantities of white blood cells (WBC) and packed RBC resulting in hematocrit (Hct) between 35% to 50%). Ten 10x reduction fold was tested on eight procedures of 600 ml each bag of BM like products processed on Sepax-2 device using Smart Redux software.

Results. The median RBCs reduction was 95.36% (range from 92.02 to 96.87%), using 10X reduction fold. The median RBCs volume in the final bag was 9.3ml (range from 5 to 20 ml). In the plasma, the median percentage of residual Total Nucleated Cells was 0.3% (range from 0% to 0.5%), while residual RBCs was 0.031%(range from 0% to 0.1%). The result was comparable with the retrospective validation using 2 true Bone Marrow Hematopoietic Stem Cells (HPCM) where the median of RBCs reduction was 94.76 and the median reduction of RBCs volume was 7.4 ml. In plasma the TNC residual was 0.12% and RBCs residual was 0.04%. However, the TNC recovery was lower in bone marrow like product comparing with the true HPCM.

Conclusions. The results of RBCs reduction rate of bone marrow like product showed a comparable result with the real bone marrow using 10x reduction fold. However, TNC recovery was lower when the thawed washed peripheral blood cells were used in preparation of the bone marrow like product. Given data from our prospective optimization and the data of previous retrospective study, HPCM RBCs depletion procedure using closed automated system is validated on 10x reduction fold to be used for HPCM-RBCs depletion.

SP81

EFFICACY AND FEASIBILITY OF LETERMOVIR PROPHYLAXIS IN CMV SEROPOSITIVE PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELLS TRANSPLANTATION: A MONOCENTRIC EXPERIENCE

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Cytomegalovirus (CMV) infection is a serious complication occurring after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Letermovir (LET) has resulted in low risk of CMV infection and reactivation when administered during the first 100 days after transplant with little toxicity. We report 23 CMV seropositive patients (7 males, 16 females) undergoing allo-HSCT in the Transplant Unit of Federico II University of Naples from July 2020 to March 2023 and receiving 240 mg daily LET prophylaxis from day 1 to day 100 after allo-HSCT. Median age at transplant was 55 (range 30-69) years. The main diagnosis for transplant were AML (n=15), ALL (n=4), BP-CML (n=2), MDS (n=1), MDS/MPN (n=1). Fifteen patients were transplanted in CR, while 3 and 5 with MRD+ or with active disease, respectively. Sorror score was >2 in 4 patients. Stem cell source was peripheral blood for 13, bone marrow for 10 patients. Donors were HLA identical siblings for 8, matched unrelated for 9 (10/10 n=8; 9/10 n=1), haploidentical for 6 patients. Conditioning regimen was myeloablative in 8, reduced-intensity in 10, sequential in 5 patients. Graft versus host disease (GVHD) prevention consisted of cyclosporine (n=1) with either methotrexate (n=8) or mycophenolate mofetil (n=14). Antityhmocyte globulin (n=15) or post-transplant cyclophosphamide (n=8) were also associated. No toxicity with LET was observed. Biweekly monitoring of CMV-DNA in peripheral blood was performed in all patients. CMV-DNA was detected in 3 patients (2 at high risk, 1 at low risk) on LET before day 100 with only one needing treatment with valganciclovir. Despite steroid treatment in 6 patients being on LET, CMV-DNA detection was observed in only one. After LET withdrawal, 5 patients (4 at high risk, 1 at low risk) experienced detectable CMV-DNA, including 2 on steroids. Two needed treatment with valganciclovir. No CMV disease was observed. Six patients experienced acute GVHD. With a median follow-up of 16 (range 5-34) months, 1-year OS, PFS and GRFS were

82±8%, 76±9% and 66±10%, respectively. Six patients needed additional treatments after HSCT for prophylaxis (n=1), molecular (n=4), or hematological (n=1) relapse. Four patients died, 2 due to GVHD and 2 due to disease relapse. In our experience, LET prophylaxis is confirmed to be a valid strategy to prevent CMV infection during the first 100 days after allo-HSCT. Clinical trials to assess use of LET beyond day 100 are awaited.

SP82

HAPLOIDENTICAL ALLOGENIC TRANSPLANTATION IN HL R/R: EXPIRIENCE OF ONE SINGLE CENTER WITH T CELL DEPLETED TRANSPLANT

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Hodgkin's lymphoma (HL) is one of the most frequent lymphoproliferative disorders in young adults, with peak incidence between 15-30 years of age. Even if most patients respond to chemo-immune therapy, some of theme need an intensive treatment. Due to the graft versus leukemia (GVL) effect, allogenic transplantation (HSCT) is an effective and curative approach in patients with relapsed/refractory disease (R/R) after chemoimmunotherapy. From 2016 to 2023, 9 patients (median age 28 years old) heavly pretreated received HSCT from haploidentical donors with abT cell depletion at our Centre. All patients had received at least three therapeutic lines: all of them previous autologous transplant and one patient received previous HSCT from MUD.

Table 1. Characteristics of the analyzed population.

	DOB	Previous treatment	Nivolumab	Conditioning regimen	GVHD prophylaxis	Infection	GVHD	OUTCOME
F	8/1/92	3		TTF	ATG+ T CELL DEPL	CMV/EBV		Alive
F	9/14/88	5	YES	TTF	ATG+ T CELL DEPL	CMV	aGVHD II	Death: TMA
F	3/29/88	4		TTF	ATG+ T CELL DEPL	CMV		Alive
F	31/07/1985	4		TTF	ATG+T CELL DEPL			Lost FU
F	12/27/82	6	YES	TTF	ATG+T CELL DEPL		AGVHD III	Death: GVHD
M	7/23/90	9	YES	TTF	ATG+T CELL DEPL	CMV/influenza A/BK urine		Alive
M	10/12/94	4		TTF	ATG+T CELL DEPL	EBV		Alive
F	4/30/96	8		TTF	ATG+T CELL DEPL	BK urine/CMV/PARVOVIRUS		Alive
M	10/14/77	8	YES	TTF	ATG+T CELL DEPL			Alive

Methods. Conditioning consisted of ATG 1,5 mg/kg from day -13 to day -10, Treosulfan 12gr/sqm from -9 to –7, Fludarabine 30 mg/sqm from -6 to -2 and Thiotepa 5 mg/Kg on days -5 and -4. CMV IgG positive patients received prophylaxis with Ganciclovir during conditioning. All patients received Ambisome for fungal prophylaxis. TCRalfabeta/CD19+ depletion was the only GVHD prophylaxis.

Results. Grafts contained median number of $9x10^6$/Kg CD34 and abT cell cut off was $<1x10^5$/Kg. All patients achieved rapid full donor engraftment. Median day to reach 500 neutrophils and 50,000 platelets was 13 (range 9-18) and 11 days (range 9-13), respectively. A sustained remission at a median follow up (FU) of 48 months was seen in all patients. One patient was lost to FU; two patients died due to transplant related complications (one to GVHD and one to TMA). The major infective complications were viral reactivations. CMV reactivation was seen in 55% of patients. No fungal infections occured. Three patients required donor lymphocite infusion (DLI) to anti infective purposes; only two patients (25%) developed GVHD, one after DLI and one during CMV reactivation (CMV-negative donor/CMV-positive recipient).

Conclusions. The infusion of abT/CD19-depleted graft is a sure and effective option for heavely pretreated patients affected by HL R/R resulting into rapid donor hematopoietic engraftment and early expansion of donor-derived γδT lymphocytes, without life-threatening infectious complications and very low incidence of GVHD.

SP83

THE IMPACT OF ONLINE TEAM MEETINGS ON CLINICAL PRACTICE, QUALITY OF CARE AND TEAMWORK IN THE TRASPLANT UNIT: A MONOCENTRIC EXPERIENCE

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Taking care of patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) requires major expertise from all the involved healthcare workers (HCW, i.e., nurses, doctors, residents, psychologist), since peculiar complications may occur and rapid interventions are crucial. Continuous communication among HCW involved in patients care is very important to spread awareness and may guide not only clinical but also relational approaches depending on patient history and psychological issues. Since July 2020, when the Transplant Director (TD) in our Center changed, periodical meetings involving HCW have been introduced to discuss hospitalized patients undergoing allo-HSCT. Meetings were held online by using video conferencing platform, especially during COVID-19 pandemic. Meetings were held by residents (supervised by the TD) through Power Point presentations and consisted of a first part focusing on the clinical history of the patient and transplant program and a second theoretical part to spread knowledge about specific transplant complications. Discussion also focused on patient specific psychological issues and on how to implement HCW/patient relationship. Periodic meeting updates were held whenever needed. Several results have been obtained through these meetings: fellows gained abilities in the use of Power Point, oral presentations and clinical and theoretical knowledge; nurses theoretical knowledge was implemented and also their capability to alert doctors in a timely manner through the early recognition of transplant complications; a uniform approach from all the HCW was offered to the patient, with particular attention on the psychological/relational aspect. Meeting also reinforced relationship between HCW, favored HCW motivation in doing their job, raised their sense of responsibility and the importance of their role, highlighting that the final outcomes resulted from a teamwork activity. The final result was the better quality of care and better organizational skills of the Transplant Unit. The major involvement of nurses also favored interest in research activities. Periodic meetings involving all the HCW allow spreading knowledge, reinforce teamwork and its importance, and also help in focusing on the specific patient needs and promote early interventions in order to provide high quality of care without forgetting patient psychological needs, favoring a personalized and uniform relationship according to each patient.

SP84

MYCOPHENOLATE-MOFETIL PLUS HIGH DOSE STEROID ARE USEFUL IN ACUTE KIDNEY DAMAGE (AKI) AFTER ALLOGENIC HSCT

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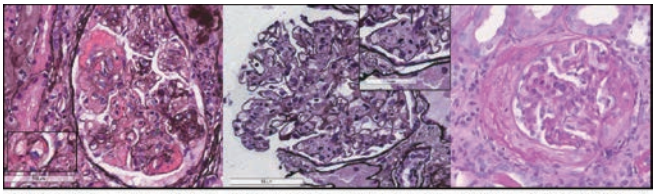
Acute Kidney Injury (AKI) is a common complication after hematopoietic stem cell transplantation (HSCT) with various causes, such as thrombotic microangiopathy (TMA), infections, Graft versus Host Disease (GvHD) and it can show glomerular and/or tubulointerstitial damage. Here we describe 3 cases of late onset AKI.

Case 1: a 69 years old (yo) male underwent haploidentical HSCT for myelodysplastic syndrome. Chronic cutaneous and pulmonary GvHD and multiple cytomegalovirus (CMV) reactivations occurred during post-transplant phase. At 2 years post HSCT, nephrotic syndrome and haematuria appeared, with ANA, ENA and anti-SSA-Ro52 positivity on peripheral blood; furthermore, there was evidence of TMA at the kidney biopsy. Due to the immunological pathogenic mechanism, he was treated with high dose steroid and mycophenolate mofetil (MMF), gaining a reduction of the proteinuria and a stabilization of the renal function at stage IV.

Case 2: a 67 yo male underwent sibling HSCT for acute myeloid leukaemia (AML). To note: the patient was solitary kidney with chronic renal disease stage II for a previous renal tuberculosis. One year after HSCT he developed AKI with histological evidence of membranous-proliferative glomerulonephritis ANCA associated and glomerular mesangiolysis, compatible with chronic microangiopathic damage by calcineurin inhibitor which he had continued for a previous late onset GvHD. So he stopped cyclosporin and started MMF associated to high dose steroid. After 15 months of therapy, renal impairment remained stable at a stage IV.

Case 3: a 65 yo male received a MUD-HSCT for AML. The post transplantation course was complicated by prolonged pancytopenia, multiple infections and a loss of chimerism 2 years after HSCT, so he received DLI infusions (4 increasing doses starting from $1x10^6$ CD3+/kg). After few weeks, severe proteinuria with anasarca blew up. Histological evidence of focal segmental glomerulosclerosis was found. Even so, we used high dose steroid and MMF with an improvement of the renal function. This treatment is still ongoing.

In conclusion, in our small series, AKI plays a crucial role in patients' outcome, with a negative impact on survival. Recognition of a dis-immune cause of the renal impairment is challenging and usually the effectors are multiple, but kidney-specific GvHD seems to have a key-role. In fact, MMF associated to high dose steroid appears to be effective in the disease control. Further data need to confirm our hypothesis.



1) Global mesangiolysis, segmental formation of double contour in capillary loops, and red blood cell fragments in the thickness of capillary walls (bottom left detail, Jones, x40)

2) Global mesangiolysis with reduction of mesangial matrix and mesangial cellularity (Jones, x20), with a detail (upper right, Jones x40) showing dissolution of matrix

3) A glomerulus with periglomerular fibrosis and segmental obliteration of capillary loops with increase in collagen matrix in perihilar region, compatible with segmental sclerosis, perihilar variant (PAS, x20)

Figure 1.

Main program

CAR-T: PRESENT AND FUTURE

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Conventional therapy yields unsatisfactory results in patients with refractory triple-class (IMiDs, PIs, anti-CD38 mAbs) and penta-drug (lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab) multiple myeloma (R/R MM)[1]. The introduction of chimeric antigen receptor (CAR) T cell therapies targeting BCMA has resulted in impressive responses. Two BCMA-directed CAR-T products, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), have been approved by the FDA and EMA for patients with R/R MM after at least four prior lines of therapy.[2]

In the phase 2 KarMMA trial, 128 R/R MM infused with ide-cel obtained complete response (CR) in 33% of patients and a median progression-free survival (PFS) of 8.8 months. Circulating CAR-T cells were detected in 59% of patients at 6 months and 36% at 12 months post-infusion.[3] In the phase 3 randomized trial KarMMA-3, ide-cel significantly prolonged PFS and improved response as compared with standard of care (SoC). All grade cytokine release syndrome (CRS) and neurotoxic effects occurred in 88% and 15% of the patients infused with ide-cel, respectively[4] (Table 1).

In the phase 1b/2 CARTITUDE-1 trial, median PFS was 34.9 months in 97 R/R MM infused with cilta-cel.[5,6] In the phase 3 trial CARTITUDE-4, 419 lenalidomide-refractory MM were randomized to receive cilta-cel or SoC: at a median follow-up of 15.9 months, both median PFS and overall response were superior in cilta-cel compared to SoC; MRD-negative was obtained in 73.1% of cilta-cel group and in 15.6% of SoC group. All grade CRS and neurotoxic events were observed in 76.1% and 4.5% of the patients infused with cilta—cel, respectively.[7] (Table 1)

Those impressive results on PFS and CR were confirmed also in real-life experiences.[8-10]

Novel CAR-T products are under investigations: PHE885 CAR-T cells, based on T-Charge, a rapid manufacturing platform for BCMA-targeted CAR-T cells (phase 1 trial NCT04318327), and experimental CAR-T products targeting GPRC5D and CD38.

In conclusion, anti-BCMA CAR-T offer a significant opportunity for potential cure, delivering responses previously unattainable with standard treatments for heavily treated R/R MM patients. The optimal sequencing of novel agents, including CAR-T and T-cell redirecting bispecific antibodies, as well as strategies to limit CRS, neurotoxicity and infections remains a matter of debate.

Table 1.

Therapy	Trial	Patients (N)	Triple class refractory, %	Penta-drug refractory, %	Cytogenetic abnormalities, High-risk %	ORR %	≥ CR %	PFS Median (months)	OS Median (months)	CRS (all grade/ >=3) %	Neurotoxicity (all grade/ >=3) %
Ide-cel	KarMMA[3] Phase 2	128	84	26	35	73	33	8.8	19.4	84/5	18/3
Cilta-cel	CARTITUDE-1[5,6] Phase 1b/2	97	88	42	24	98	82.5	34.9	Not reached	95/5	22/12
Ide-cel	KarMMA-3[4] Phase 3	254	65	6	42	71	39	13.3	N/E	88/5	15/3
SoC	KarMMA-3[4] Phase 3	132	67	4	46	42	5	4.4	N/E	N/A	N/A
Cilta-cel	CARTITUDE-4[7] Phase 3	208	14	1	59	85	73	Not reached	N/E	76/1	20/3
SoC	CARTITUDE-4[7] Phase 3	211	16	0.5	63	67	22	11.8	N/E	N/A	N/A

Ide-cel: Idecabtagene Vicleucel; Cilta-cel: ciltacabtagene autoleucel; Triple-refractory disease was refractory to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Penta-refractory disease was refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab. High-risk cytogenetic abnormalities included the following: del(17p), t(4;14), and t(14;16); N: number; ORR: overall response rate; CR: complete response; PFS: progression free survival; OS: overall survival; CRS: cytokine release syndrome; Neurotoxicity: includes ICANS (immune effector cell–associated neurotoxicity syndrome) and other neurotoxicities; N/E not evaluable; N/A: not applicable.

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BISPECIFIC ANTIBODIES: PRESENT AND FUTURE

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Relapsed/refractory (RR) multiple myeloma (MM) patients already exposed to proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies (mAbs) (triple-class exposed, TCE) have a very poor clinical outcome, stressing the need for treatments with novel mechanisms of action.

Bispecific antibodies (BsAbs) are artificially engineered Abs that can bind simultaneously to the CD3 subunit within the T-cell receptor complex and an antigen on tumor cells, leading to T-cell activation and tumor cell killing. BsAbs against B-cell maturation antigen (BCMA) or G-protein-coupled receptor family C group 5 member D (GPRC5D) have shown impressive clinical activity in heavily pretreated RRMM, and the results of early-phase clinical trials targeting Fc receptor-homolog 5 (FcRH5) are also promising.

Teclistamab is a humanized IgG-like anti-BCMA BsAb that has been approved by EMA and FDA for clinical use in TCE RRMM, based on the results of the phase 1/2 MajesTEC-1 study showing an overall response rate of 63%, with 45.5% of at least complete response, and a median progression-free survival of 11.3 months.[1] Similarly, deep and durable response have been reported in extensively pretreated RRMM patients, with the anti-BCMA BsAb Elranatamab,[2] as well as with the anti-GPRC5D BsAb Talquetamab,[3] leading to filing requests for approval. Several other BsAbs are also in clinical development, with some differences in terms of target, construct, binding affinity, administration route, schedule and step-up dosing requirements[4-8] (Table 1). Main toxicities include cytokine release syndrome, neurotoxicity, cytopenias, hypogammaglobulinaemia, and infections.[1-8] On-target off-tumor adverse events with anti-GPRC5D BsAbs may also include skin, mucosal, hair and nail toxicities.[3,7]

To further optimize BsAbs treatment, novel strategies to augment their potency are under investigation. Early phase trials investigating combinations of a BsAb with an IMiD and/or an anti-CD38 mAb to induce potentially synergistic anti-MM effects and overcome the immunosuppressive bone marrow microenvironment, as well as combinations of BsAbs targeting different MM antigens to reduce the risk of antigen loss–related relapse, have already demonstrated considerable efficacy.[9-10] Finally, the use of BsAbs in earlier lines of therapy,[9] when MM patients may have a more favorable immune profile and a lower risk for T-cell exhaustion, is expected to enhance efficacy.

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Table 1. Results of selected studies with bispecific antibodies in relapsed/refractory Multiple Myeloma patients. ORR: overall response rate; CR: complete response; DOR: duration of response; PFS: progression free survival; pts: patients; BsAbs: bispecific antibodies; BCMA: B-cell maturation antigen; QW: weekly; SC: subcutaneous; Q2W: every other week; mo: months; IV: intravenous; NR: not reached; Q4W: every four weeks; Q3W: every three weeks; GPRC5D: G-protein-coupled receptor family C group 5 member D, FcRH5: Fc receptor-homolog 5.

	Target	Construct	Trial phase	Median prior lines, n°	ORR	CR	DOR	PFS
Anti-BCMA BsAbs								
Teclistamab [1] n° pts= 165, 1.5 mg/kg QW, SC	BCMA	IgG-like	1/2	5	63%	45.5%	21.6 mo, median	11.3 mo, median
Elranatamab [2] n° pts= 123, 76 mg QW→Q2W, SC (Cohort A: BCMA-naïve)	BCMA	IgG-like	2	5	61%	27.6%	71.6% at 12 mo	58.8% at 12 mo
Alnuctamab [4] n° pts= 68, 10→60 mg, QW→Q2W→Q4W, SC	BCMA	2+1 configuration	1	4	53%	23%	NR	NR
ABBV-383 [5] n° pts= 6@40mg, 58@60mg, Q3W, IV	BCMA	Triple chain: 2 BCMA	1	4/5	83% @40 60% @60	67% @40 29% @60	NR	NR
Linvoseltamab [6] REGN5458 n° pts=104@50mg, 117@200mg, QW→Q2W→Q4W, IV	BCMA	Veloci-Bi Fc	2	6/5	50% @50 71% @200	21% @50 30% @200	NR	54.6% @50 72.7% @200 at 6 mo
	Target	**Construct**	**Trial phase**	**Median prior lines, n°**	**ORR**	**CR**	**DOR**	**PFS**
Non-BCMA BsAbs								
Talquetamab [3] n° pts= 143@0.4mg/kg QW, 145@0.8mg/kg Q2W, SC	GPRC5D	IgG-like	1/2	5	74.1% @0.4 71.7% @0.8	33.6% @0.4 38.7% @0.8	9.5 mo @0.4, median NR @0.8	34.9% @0.4 54.4% @0.8 at 12 mo
Forimtamig [7] n° pts= 51@6→10000µg IV, 57@ 30-7200µg SC, Q2W	GPRC5D	2+1 configuration	1/2	5	71.4% @IV 63.6% @SC	34.7% @IV 25.5% @SC	NR	NR
Cevostamab [8] n° pts= 161, 0.15→198mg, Q3W, IV	FcRH5	IgG-like	1	6	56.7%	8.4%	11.5 mo, median	NR

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PREVENTION AND MANAGEMENT OF ADVERSE EVENTS DURING TREATMENT WITH CAR-T CELLS AND BISPECIFIC ANTIBODIES IN MULTIPLE MYELOMA

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Chimeric antigen receptor T cells (CAR-T) and T-cell redirecting bispecific antibodies (BsAbs), targeting B-cell maturating antigen (BCMA), G protein-coupled receptor class C group member D (GPRC5D) and Fc receptor-homolog 5 (FcRH5), have been revolutionizing multiple myeloma (MM) therapy. Efficacy results are impressive, but early and late adverse events (AEs) should be kept in mind for appropriate prevention and management (Table 1).

Early AEs are caused by cytokine storm (especially IL-6) combined with macrophage and T-lymphocytes activation.[1] Cytokine release syndrome (CRS), mostly grade (G) 1 or 2, occurs within the first week after CAR-T infusion or during BsAbs step-up dosing. The management of CRS includes antipyretics, tocilizumab (anti IL-6), or corticosteroids, according to severity (*i.e.* isolated fever, hypotension, hypoxia or organ disfunction), and may require intensive care unit admission[2]. Neurotoxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), occurs mainly after CRS resolution and it should be managed with antiepileptics or antipsychotic and high-dose corticosteroids; tocilizumab (in case of concomitant CRS) or anakinra (anti IL-1) can be needed in refractory cases.[2] Furthermore, some patients might develop late Parkinson's disease-like movement disorders as reported in CARTITUDE-1 trial.[3] Macrophage activated syndrome (MAS) is rare but potentially life-threatening condition; corticosteroids, tocilizumab and anakinra are crucial for event control.[2] Both BsAbs and CAR-T are associated to a high risk of infection or viral reactivation because of neutropenia, lymphopenia and hypogammaglobulinemia.

Periodically granulocyte colony-stimulating factor (G-CSF) could be useful in patients with G ≥3 neutropenia, although it may be ineffective due to underlying pathogenesis (*e.g.* low bone marrow reserve rather than inflammation)[4].

Prophylactic administration of immunoglobulin is recommended in patients with hypogammaglobulinemia (<400 mg/dL) or recurrent bacterial infections.[4] Antiviral or antibacterial prophylaxis should be considered as well.[4] Efforts to enhance patients' protection with vaccination seem pointless until lymphopenia recovery.[5]

Off-target anti-GPRC5D effects related to the presence of GPRC5D on keratin-expressing cells include skin or nail changes and dysgeusia reported mostly after BsAbs administration,[6] while cerebellar neurotoxicity was solely noted after anti-GPRC5D CAR-T infusion.[7]

Table 1. Selected studies on CAR-T and BsAbs and their relative AEs. BCMA, B-cell maturating antigen; GPRC5D, G protein-coupled receptor class C group member D; FcRH5, Fc receptor-homolog; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; MAS, macrophage associated syndrome; AE, adverse events; G, grade; sc, subcutaneous; IV, intravenous.

	Idecabtagene vicleucel (KarMMa)[8]	Ciltacabtagene autoleucel (CARTITUDE-1)[9]	MCARH109 (NCT04555551)[7]	Teclistamab (MajesTEC-1)[10]	Talquetamab (MonumenTAL-1)[6]	Cevostamab (NCT03275103)[11]
Target structure	BCMA	BCMA	GPRC5D	BCMA/CD3	GPRC5D/CD3	FcRH5/CD3
Number of patients	128	97	17	165	232	160
Phase study	2	1B/2	1	1/2	1	1
CRS	84% (G≥3: 5%)	95% (G≥3: 4%)	88% (G≥3: 6%)	72% (G≥3: 1%)	405 µg sc: 77% (G≥3: 3%) 800 µg sc: 80% (G≥3: 0) IV infusion: 49% (G≥3: 5%)	80% (G≥3: 1.3%)
Neurotoxicity	18% (G≥3: 3%)	21.6% (G≥3: 12.3%) Parkinsonism: 6%	ICANS G≥3: 6% Cerebellar disorders: G≥3: 12%	Neurotoxicity 14.5% ICANS 3% (G≥3: 0)	405 µg sc: 10% 800 µg sc: 5% With IV infusion: G≥3: 3%	ICANS associated with CRS: 13.1%
MAS	-	-	G≥3: 6%	-	-	-
Infection	88% (G≥3: 22%)	58% (G≥3: 20%)	18% (G≥3: 12%)	76.4% (G≥3: 45%)	405 µg sc: 47% (G≥3: 3%) 800 µg sc: 34% (G≥3: 7%)	42.5% (G≥3: 19%)
Cytopenia	Neutropenia 91% (G≥3: 89%)	Neutropenia 96% (G≥3: 95%)	Neutropenia 100% (G≥3: 95%)	Neutropenia 71% (G≥3: 64%)	405 µg sc: 37% (G≥3: 23%) 800 µg sc: 23% (G≥3: 11%)	Neutropenia 18% (G≥3: 16%)
	Thrombocytopenia 63% (G≥3: 52%)	Thrombocytopenia (G≥3: 60%)	Thrombocytopenia 88% (G≥3: 65%)	Thrombocytopenia 40% (G≥3: 64%)	405 µg sc: 47% (G≥3: 3%) 800 µg sc: 34% (G≥3: 7%)	Thrombocytopenia 10% (G≥3: 6%)
	Anemia 70% (G≥3: 60%)	Anemia 81% (G≥3: 68%)	Anemia 88% (G≥3: 65%)	Anemia 52% (G≥3: 37%)	405 µg sc: 60% (G≥3: 30%) 800 µg sc: 43% (G≥3: 23%)	Anemia 40% (G≥3: 22%)
Hypogammaglobulinemia	21%	-	-	75%	405 µg sc: 87% 800 µg sc: 71%	-
Others	-	-	Nail loss 65% Rash 18% Dysgeusia/dry mouth 12%	-	Nail-related AE 405 µg sc: 57% 800 µg sc: 27% (G≥3: 2%) Rash-related AE 405 µg sc: 47% 800 µg sc: 30% (G≥3: 16%) Dysgeusia: 405 µg sc: 63% 800 µg sc: 57%	-

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TREATMENT OF FOLLICULAR LYMPHOMA IN FIRST RELAPSE

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Follicular lymphoma (FL), most common indolent NHL with favorable outcome is characterized by variable clinical relapsing/remitting course with progressively shorter response after subsequent lines.

Early progression within 24 months of frontline therapy (POD24) occurring in 20% of cases, is associated with inferior overall survival (5-yrs OS 50%vs90%). 70% of POD24 are histologic transformation to aggressive lymphoma. Biopsy is needed to rule out tFL. Although clinical/biologic risk models have been developed, the early identification of risk patients remains challenging (unmet medical needs).

Asymptomatic patients in late relapse do not need immediate treatment and should be monitored. Chemoimmunotherapy (BR,R-CHOP,R-CVP), +/- Rituximab maintenance, classically was an option, although isn't likely to result in long-term survival in early relapse. Obinutuzumab-bendamustine may overcoming rituximab refractoriness in early failure. Autologous SC-transplantat followed first salvage, improve long-term survival (5-yr OS 77%) but its use is reduced in modern era considering late toxicity.

Radioimmunotherapy, consolidation therapy in relapsed FL, no longer used for vary logistic reasons.

Lenalidomide in combination with Rituximab (R2), becomes a standard treatment option for relapsed FL based on AUGMENT study demonstrated a progression-free survival advantage (mPFS 39vs14mo). Combination with novel agents are being evaluated for improving efficacy of R2 (35%CR rate): BTKi, Tafasitamab, Polatuzumab.

Zanubrutinb is promising in combination with obinutuzumab (ORR 68%,CR 37%,mPFS 27mo).

Other therapeutic options are typically available after 2 or more lines of therapy.

PI3Ki (idelalisib, copanlisib, duvelisib, umbralisib) are active but some of these drugs have been US withdraw from the market for safety reasons.

Tazemetostat, EZH2 inhibitor, showed higher response (ORR 69%,13%CR) with a favorable toxicity profile. Also approved for RR FL without EZH2 mutations (PFS 13.8vs11mo).

Significant survival improvement in heavily treated patients with CAR-T cell therapy. Bispecific antibodies also shown promising results with lower toxicity. These positive data support evaluation in earlier lines of therapies.

Many emerging drugs are available and novel combinations are on the venue. The best choice and optimal sequencing for relapse FL remains challenging. New models predicting poor outcomes prior to treatment failure are needed to personalize treatment approaches.

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BISPECIFIC ANTIBODIES AND CAR T-CELL THERAPY IN THE TREATMENT OF RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

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Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL). Although historically considered an incurable disease due to its tendency to relapse, the median overall survival of patients diagnosed with FL has improved significantly in the past two decades thanks to advances in understanding the biology along with novel treatment approaches for both new diagnosed and relapsed/refractory (R/R) disease. Chimeric antigen receptor (CAR) T-cells are autologous T-cells genetically modified to target a specific antigen in an HLA independent way. Over the past 3 years, three phase 2 studies has been conducted to evaluate the efficacy and safety of CAR T-cells in patients with R/R FL, specifically axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel) and lisocabtagene maraleucel (liso-cel).[1-5] Although it's not possible to make a direct comparison among these three studies because of different design and population, all of them demonstrated high efficacy with an overall response rates (ORR) ranging from 86-94%, even in patients with high risk disease. Moreover, CAR T-cell therapies showed a durable response, with nearly 60% of patients free of a disease progression at 2 years (PFS). In all the three studies, the most common grade ≥3 adverse events (AEs) were cytopenia and infections, although with different incidences. The use of Axi-cel compared with others was associated with an increased risk of both mild and severe cytokine release syndrome (CRS) and neurological events (ICANS) (Table 1). Bispecific monoclonal antibodies (BiTEs), by simultaneously targeting CD3 and a lymphocyte B surface antigen, usually CD20, redirect cytotoxic T cells against malignant B cells, resulting in their elimination. Several BITEs were studied in R/R FL with promising results[6-9] (Table 1). In particular, the ORR ranged from 70 to 90%, with a median PFS between 12 and 24 months. The incidence of CRS and ICANS was numerically lower than CAR T-cell therapy with predominantly grade 1-2 events. In conclusion, both CAR T-cell treatment and BiTEs show promise in R/R FL, with high response rates and deep and durable responses also in high-risk patients. The safety profile seems to be slightly better with BiTEs than with CAR T-cells, especially compared to axi-cel. The debate about how to sequence CARs versus BiTEs is still being defined, and numerous questions are open about the right setting in which to prefer one therapy over the other.

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Table 1. Results from CAR T-cells and bispecific antibody main studies.

	Axi-cel[1,2]	Tisa-cel[3,4]	Liso-cel[5]	Axi-cel real world[10]	Mosunetuzumab[6]	Odronextamab[9]
Trial	ZUMA-5	ELARA	TRANSFORM	CIBMTR	GO29781	ELM-2
Status	Phase 2	Phase 2	Phase 2	Retrospective	Phase 2	Phase 2
FL patients, n	124	97	130	151	90	131
Median prior therapies	3	3	3	4	3	3
POD24 (%)	55	63	43	****	52	48.1
ORR (%)	94	86	97	93	78	81.8
CR (%)	79	68	94	84	60	75.2
Median follow-up (months)	40.5	29	17.5	6 months	18.3	22.4
Median PFS (months)	40.2	NR	NR	NR	24	20.2
Median OS	NR	NR	NA	NA	NR	NR
Any grade CRS/ICANS (%)	78/56	49/4	58/15	73/39	44/4.4	56.4/0.8
Grade ≥ 3 CRS/ICANS (%)	6/5	0/1	1/2	2/12	2/0	3.8/0
Grade ≥ 3 cytopenia (neutropenia, anemia, thrombocytopenia)	60% N, 23% A, 23% T	24% N , 7% A, 5% T	65%	NA	29% N, 13% A, 10% T	32.1%, 17.6% A, 13% T
Infections Any grade / grade 3-4 (%)	NA/18	17/9	NA/5	34/NA	20/14.4	65.6/32

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MANAGEMENT OF RELAPSED/REFRACTORY MARGINAL-ZONE LYMPHOMA

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Marginal zone lymphomas (MZL) account for approximately 5%–17% of all non-Hodgkin's lymphoma (NHL) and represent the second most common indolent NHL. The course of MZL is generally indolent, particularly in patients with primary extranodal disease.[1] Progression of disease within 2 years after initial treatment is the strongest prognostic biomarker of reduced survival.[2] No standard therapy has been defined so far for these entities, particularly in the setting of relapsed/refractory disease, in whom no randomized trial was never specifically performed yet. The rarity of MZL historically limited preclinical and clinical research to these entities. In the past MZL entities were often incorporated, and thus underrepresented, into larger trials designed for a biologically similar indolent disease, in particular follicular lymphoma. Therefore, only a small number of clinical trials were specifically developed in this setting. Nevertheless, improved understanding of the disease biology, including characterization of molecular pathogenesis and microenvironment, altered the therapeutic landscape of MZL. Targeted therapies focusing on intracellular signaling pathways, such as the B-cell receptor-signaling pathway, resulted in improved efficacy and tolerable toxicity profiles over chemotherapy-based approaches. Increasing amount of data were reported with Bruton's tyrosine kinase (BTK) inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors and immunomodulatory agents,[3-7] but in some cases, substantial toxicity limited the further development of these drugs. While these new therapeutic agents are providing additional options for patients with R/R MZL, there remains an unmet need for effective, tolerable therapies to improve long-term outcomes in these indolent entities.[8]

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LIVER HEALTH AND GENE THERAPY

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Persons with hemophilia (PWH) have long been exposed to the risk of HBV/HCV infections due to the treatment with plasma-derived products. As a consequence, for decades, the main goal of liver health has been the management of chronic hepatitis virus infections in order to reduce the risk of complications due to portal hypertension (e.g., ascites, acute gastro-intestinal bleeding, hepatic encephalopathy) and hepato-cellular carcinoma (HCC). At today the progress in the pharmacology of hemophilia, the development of successful antiviral therapies against HBV/HCV, the efficacy of HBV vaccine have sensibly reduced the rate of new infections and ameliorated the risk of hepatic complications but liver health is still matter of debate in this clinical setting. In particular, the introduction of hepatocyte-targeted gene-therapies based on adeno-associated virus 5 (AAV5) vectors have renewed the alliance between hepatologists and hemophilia treaters in order to optimize the benefit/risk ratio of this innovative therapy. Indeed, while clinical trials have demonstrated long-term benefits with sustained factor activity levels after a single administration of AAV5-gene therapies, the immunological and cellular response against transfected hepatocytes may cause hepatoxicity as demonstrated by acute increase of liver enzymes thus giving rise to concerns for liver health. Furthermore, although experts assume that AAV5 genome remains episomal after transduction, the potential integration of the vector into the host genome may be matter of genotoxicity and, finally, risk of liver carcinogenesis.

This biological scenario has important clinical consequences and the key-strategy to minimize the risk for liver health in candidates to gene therapy is represented by the exclusion of advanced fibrosis/cirrhosis. This goal is warranted by taking into account several aspects, among them, the influence of successful antiviral therapies on the accuracy of Fibroscan and other non-invasive tests to detect an advanced chronic liver disease, the prevalence and incidence of risk factors of chronic liver damage other than viral hepatitis (e.g.; metabolic syndrome), the underestimated risk represented by alcohol exposure that advocates for important educational health programs particularly among young people.

All these issues will be discussed into details during this meeting to offer a guide for physicians based on the most updated approach for liver health in PWH who are candidate to gene therapy.

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TERAPIA GENICA. AGGIORNAMENTO STUDI NELL'AMBITO DEL MEETING EDUCAZIONALE LA TERAPIA GENICA IN EMATOLOGIA"

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The concept that the introduction of exogenous DNA into a diseased cell might be a therapeutic strategy has been postulated several decades ago. Over years the advent of recombinant DNA technologies combined with the knowledge of viruses enabled researches to manipulate the genome of a virus, removing all the unnecessary genes, and equip it with a therapeutic gene. In this way, the recombinant virus ("viral vector") can deliver the correct copy of a gene of interest into a living organism, infect target cells, and drive the continuous expression of the missing/defective protein, thus rescuing the physiological function with a therapeutic effect ("gene therapy"; GT).

GT has been explored for many human genetic disorders, and the deficiencies of coagulation factor VIII (hemophilia A, HA) or IX (hemophilia B, HB) have represented pioneer diseases and paradigmatic examples of success, as demonstrated by two GTs that received authorization by FDA (for HB) and EMA (for HB and HA), and several other showing promising results in clinical trials.

For both disorders the authorized GTs consists of a adeno-associated virus with serotype 5 (AAV5), chosen for its ability to target and infect human hepatocytes and then persisting in a episomal state, delivering the coding sequence of a B-domain deleted FVIII variant (AAV5-BDD-FVIII) or of the hyperactive FIX Padua variant (AAV5-FIX_{Padua}).

In Phase III clinical trials a single injection of AAV5-BDD-FVIII in severe HA patients or of AAV5-FIX_{Padua} in severe HB patients resulted in the years after treatment in therapeutic FVIII/FIX levels in plasma with remarkable reduction of the annualized bleeding ratio and need for FVIII/FIX concentrate.

Notwithstanding there are still open issues regarding durability of the effect and safety aspects that require further investigation and optimization. In this lecture on GT for Hemophilia we will discuss the rationale behind the choice of the AAV vector, the design of the therapeutic gene and the main results obtained in clinical trials, which eventually led to the authorization by regulatory agencies, together with the open issues and current limitations.

OPTIMIZING ANTI-COMPLEMENT THERAPIES FOR THE TREATMENT OF PNH

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease characterized by complement-mediated intravascular hemolysis (IVH), severe thrombophilia and bone marrow failure.[1] Continuous IVH, with possible exacerbations (paroxysms) is due to impaired regulation of the complement Alternative Pathway (AP) resulting from the lack of the two endogenous complement inhibitors CD55 and CD59 on affected erythrocytes surface.

The first anti-complement treatment for PNH became available in 2007, when the humanized anti-C5 mAb eculizumab was demonstrated effective in controlling MAC-mediated IVH, leading reduced transfusion need, hemoglobin stabilization and prevention of thrombosi.[2] While this effect on IVH and thrombosis significantly improve survival, up to two-thirds of patients remain anemic, as shown by remarkable reticulocytosis, largely because of emerging extravascular hemolysis (EVH). Indeed, when anti-C5 treatment inhibits the terminal complement pathway, surviving PNH erythrocytes are protected from lysis but remain unable to control surface C3 activation, which rises accumulation of C3 split fragments eventually leading to C3-mediated EVH.

In the recent years' novel strategies of therapeutic complement inhibition have been developed to improve different aspects of current PNH treatment. Long-lasting monoclonal anti-C5 mAb, such as ravulizumab and crovalimab, have improved patients' convenience due to longer interval of (possibly subcutaneous) administration.[3-5] Moreover, a new class of agents targeting early phases of complement activation has been developed to address C3-mediated EVH of hemolysis. These "proximal complement inhibitors" aim to prevent C3 activation (and thus C3-mediated EVH), while also disabling the terminal complement pathway (thereby avoiding MAC-mediated IVH). Mature clinical data are already are available for inhibitors targeting C3 (pegcetacoplan[6]), Factor D (danicopan[7,8] and vemircopan) and Factor B (iptacopan[9,10]), either used in combination with anti-C5 mAb or in monotherapy.

With all these agents, concomitant inhibition of IVH and prevention of C3-mediated EVH resulted in meaningful improvement of anemia and of QoL measurements, apparently with no safety concerns (infections and autoimmune diseases). We are now at the corner of defining the best use of these potentially more effective agents (*e.g.* mono- *vs* combined therapy), as well as the optimal PNH treatment for each specific patient.

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THERAPEUTIC OPTIONS FOR TRIPLE REFRACTORY HODGKIN LYMPHOMA PATIENTS

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The treatment landscape of relapsed/refractory (R/R) classic Hodgkin lymphoma (cHL) has evolved significantly over the past decade after the approval of brentuximab vedotin (BV) and the programmed death-1 (PD-1) inhibitors. The availability of novel agents and improved salvage therapy before autologous hematopoietic cell transplantation (AHCT) has changed outcomes and therapeutic patterns for patients with R/R cHL who underwent AHCT. A recent single-center retrospective study conducted at Stanford has shown that overall survival (OS) was significantly superior for patients autografted in the modern era (2011-2020) compared with those autografted from 2001 to 2010.[1] Additionally, among patients who progressed after AHCT, 4-year post-progression survival increased from 43% to 71% in the modern era, reflecting the increasing use of BV and PD-1 inhibitors. A retrospective study in four academic centers in the United States reported improved survival after relapse post-AHCT for patients autografted between 2011 and 2016 compared to patients autografted between 2005 and 2010.[2] An EBMT retrospective study analyzed 1781 adult cHL who relapsed between 2006 and 2017 after a first AHCT.[3] The 4-year OS after relapse continuously increased from 32% for patients relapsing in 2006-2008 to 63% for patients relapsing in 2015-2017. While the use of BV and PD-1 inhibitors has improved the outcome of R/R cHL who were autografted and of those who relapsed after AHCT, this selective pressure has generated a new challenging unmet medical need, the *triple refractory* cHL, defined as cHL who have failed AHCT, BV, and PD-1 inhibitors. These patients account for nearly 20% of R/R cHL. Provided they can be re-induced in complete remission (CR) by retreatment with PD-1 inhibitors, Allo-HCT is their only potentially curative treatment.[4] Alternatively, if triple refractory patients do not respond to PD-1 inhibitors, they can be addressed with a sequence of PD-1 inhibitors followed by chemotherapy. The rationale for this therapeutic approach relies on PD-1 inhibitors-induced chemosensitization, a phenomenon that has been shown to induce CR rates ranging from 32% to 82% (Table 1).[5-8] Cutting-edge therapeutic strategies for triple refractory cHL also include bispecific antibodies and CAR-T cells. These advanced immunotherapies are at an early stage of development, and preliminary results will be discussed at the meeting.

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Table 1. Studies supporting PD-1 inhibitors-induced chemosensitization.

	Number of patients	Median number of prior therapies	ORR (%)	CR (%)
Rossi *et al*., 2018	17	6	59%	41%
Carreau *et al*., 2020	81	4	62%	42%
Casadei *et al*., 2020	25	4	60%	32%
Calabretta *et al*. 2022	28	4	93%	82%

MANAGEMENT OF OLDER PATIENTS WITH HODGKIN LYMPHOMA

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Survival of Hodgkin Lymphoma (HL) patients has significantly improved over the past several decades. However, the outcome of elderly patients (commonly defined as ≥60 years of age) is markedly worse compared with younger patients or age- and sex-matched controls.[1]

Inferior outcome of older patients has been attributed to a variety of factors, including presence of comorbidities, frailty, histologic and biologic differences (*i.e.* advanced stage, increased mixed cellularity, Epstein-Barr virus related), inability to tolerate chemotherapy at full dose and schedule, and increased treatment-related toxicity and mortality.[2-3]

As far as the toxicity, it is well demonstrated that the bleomycin related lung toxicity represents a real problem in these patients. In particular, the study E2496 comparing ABVD vs Stanford V reported a grade 3-4 lung toxicity of 26% with an overall treatment-related mortality of 9.3% (*vs* 0.3% <60 years, p<0.001).[4]

The impact of geriatric assessment (GA) in these patients has been well studied and it must be used to guide the treatment options. All items included in GA (i.e. ADL, IADL, comorbidities, nutrition, ecc) are predictive of outcome.[5-6]

The introduction of target therapy and/or immunotherapy seems to give the opportunity to improve the approach to elderly HL patients. Generally, fit patients should be treated with curative intent using anthracycline-based chemotherapy similarly to those used for younger patients. The addition of Brentuximab Vedotin (BV) with AVD represent the best-reported outcome to date with a 2yr- and 5yr-PFS of 70.3% and 67.1%, respectively.[7] Therapy for unfit and frail patients is less clear and should be individualized. Lower dose chemotherapy or a combination of BV and dacarbazine may be a good option. A prospective phase 2 trial demonstrated a CR rate of 66% with a median duration of response of 45.4 months (range 0-67.3 mo).[8]

Finally, the introduction of checkpoint inhibitors may improve these results. Recently the combination of brentuximab and nivolumab as frontline treatment for unfit patients showed a 48% of metabolic CR rate and a median PFS of 18.3 months with an acceptable toxicity profile.[9]

In conclusion, Concerted efforts should be made to continue to prospectively tailor therapy based upon a GA prior to therapy and concurrently incorporate response-adapted concepts into treatment paradigms.

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VIRTUAL CLINICAL TRIALS: NEW TECHNOLOGIES TO ACCELERATE THE DEVELOPMENT OF INNOVATIVE TREATMENTS IN HEMATOLOGY

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Randomized Controlled Trials (RCTs) are considered the gold standard in clinical research for evaluating new medical treatments. However, traditional RCTs have fixed designs, which can be time-consuming and costly. Adaptive RCTs – actively explored by The European Medicines Agency - have gained interest, allowing modifications in trial design.

When RCTs are not feasible, alternative methods like Propensity Score Matching, weighting, or Matching Adjusted Indirect Comparison (MAIC) can evaluate treatment effectiveness. These methods reduce bias by creating comparable control groups based on observed characteristics or propensity scores to estimate treatment effects indirectly.

Another option is offered by the exponential growth of artificial intelligence (AI) that allows the generation of synthetic patients' cohorts. These simulated populations replicate real patients' characteristics and can be employed in virtual trials, allowing researchers to simulate treatment scenarios and assess interventions in controlled environments. This approach offers advantages such as exploring diverse treatments, reducing costs, and accelerating evaluation.

Synthetic data enables virtual randomized trials, comparing patient responses between active therapy and synthetic control groups. This optimizes resource allocation by enrolling more patients in active therapy arms. Synthetic cohorts can be generated using methodologies like generative adversarial networks (GANs), decision trees, and parametric methods.

GIMEMA Foundation conducted an initial study applying synthetic patient cohorts to data from the AML1310 study for newly diagnosed patients affected by acute myeloid leukemia (AML). The virtual cohort of 890 patients accurately replicated covariate distributions and exhibited similar characteristics to the original population. Furthermore, survival patterns in the synthetic data closely resembled those in the original data.

This groundbreaking study represents, to the best of our knowledge, the first concrete example of implementation of AI into clinical trial design for AML. In particular, we demonstrated the feasibility and the potential of generating a virtual cohort of patients from real patients' data in the setting of AML. This strategy could be extended also to other diseases to improve the prognosis and the management of clinical trials. Indeed, while RCTs remain the gold standard, the use of AI techniques may lead to remarkable advancements in clinical research.

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HEALTH DIGITAL TWINS. L'INTELLIGENZA ARTIFICIALE A SUPPORTO DEL PROCESSO CLINICO DECISIONALE IN EMATOLOGIA

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Rare diseases are life-threatening or chronically debilitating diseases which affect fewer than 5 in every 10 000 people in the EU. Most rare diseases lack effective treatments representing an enormous unmet medical need. The major challenge is to understand rare-disease mechanisms better and ensure that research and innovation are effectively translated into new diagnostics and treatments. Personalized or precision medicine combines established clinical-pathological parameters with advanced profiling to create innovative diagnostic, prognostic, and therapeutic strategies. This approach is relevant in the context of rare hematologic diseases, where additional information from transcriptomics (and other omic features), as well as from digitized images, may improve the clinical decision-making process and the choice of optimal therapy or treatment.

Health digital twins are virtual representations of patients generated from historical multimodal patient data, as clinical, genomics, physiology, images, treatment, outcomes, physics, quality of life (QOL) and wearables. They can improve diagnosis and prognosis, predict treatment in a specific patient population and create virtual scenarios to support clinical decision-making. Health digital twins implement data-driven Artificial Intelligence (AI) and Machine Learning (ML) methods, trained on patients' longitudinal data, to build robust predictive models that integrate multiple information to address unmet clinical needs. AI-based models integrate multi-layer information and simulate the behavior and prognosis of the disease in the individual patient, allowing a detailed understanding of the disease and treatment effects, and defining the patient's individual risk.

The impact of health digital twins can be evaluated in several areas: 1) improve patient outcomes by using specific patient information to identify the most appropriate treatment; 2) reduce healthcare costs with more targeted and effective therapies; 3) accelerate clinical and pharmaceutical research; 4) deal with ethical and privacy issues, detaching the link between people and the value of data. Despite innovative AI technology being extensively applied to different medical fields, health digital twins represent a novel and innovative approach that will pave the way for effective personalized medicine. The exploitation of this technology will enable the creation of high performance predictive models, supporting clinical research and decision making.

MEET THE EXPERT - BLASTIC PLASMACYTIC DENDRITIC CELL NEOPLASMS

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Blastic Plasmacytoid dendritic cell neoplasms (BPDCNs) are hematological malignancies characterized by an aggressive clinical course with a poor long-term outcome of roughly 12-18 months.[1] The 5th edition of the WHO classification reclassified BPDCN as a discrete entity among histiocytic and dendritic cell neoplasms (HDCN).[2] On the other hand, in the International Consensus Conference (ICC) classification BPDCN was not included in the chapter of HDCN, as it derives from a precursor of plasmacytoid dendritic cells.[3,4]

The overall incidence is low, accounting for 0.44% of hematological malignancies and 0.7 of cutaneous lymphomas. There is a prevalence in males (4:1 M:F ratio) with a median age at diagnosis of 65 years.[5] The diagnostic approach to BPDCN should necessarily include a multidisciplinary team.

The pathway generating plasmacytoid dendritic cell (pDC) is summarized in Figure 1.[6]

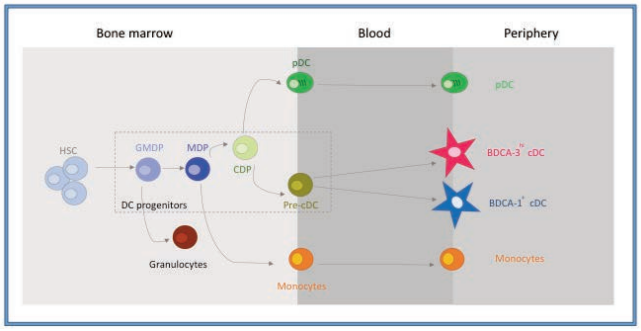

Figure 1. A common monocyte/dendritic cells ancestor (MDPs) give rise to monocytes and a common DC progenitor (CDP). CDPs give rise to plasmacytoid DCs (pDCs), as well as a circulating cDC precursor (pre-cDC).

The key marker to be demonstrated by flow-cytometry and/or immunohistochemistry on BPDCN is CD123. Additional markers are CD4 and CD56 and TCL-1, TCF4 and CD303.[1] Roughly 50% of the cases present an isolated cutaneous involvement but BM involvement or central nervous system (CNS) infiltration is common and needs to be systematically excluded and, if detected, eradicated. Notably, 20% of patients have a prior or concomitant myeloid malignancy (myelodysplasia or chronic myelomonocytic leukemia).

The curative approach to BPDCN for fit patients relies on systemic treatment also for those patients with limited organ involvement (e.g. skin only). Localized therapy should be limited to specific situations because aggressive disease recurrences may occur. Monotherapy with Tagraxofusp (TAG) has notably improved the outcome of these patients with an overall response rate (ORR) of 90% and a median 2-year survival still not reached, particularly for responding patients addressed to allogeneic stem cell transplant (ASCT).[7] Further anti-CD123 therapies (IMGN632) are under active development.[8] Intensive chemotherapy, with or without ASCT, was largely employed before the advent of TAG, and still has a role in BPDCN treatment, alone or in combination. Conventional chemotherapy, both AML-like and ALL-like, has the further advantage of being adaptable in terms of dosage and schedule to unfit/older patients.

In this session, the main diagnostic and prognostic criteria, along with current treatments, will be addressed highlighting certainties and unmet needs in the management of this poor-risk disease.

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PRIMARY CUTANEOUS T-CELL LYMPHOMAS

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Primary cutaneous T-cell lymphomas (PCTCLs) are a heterogeneous group of extranodal NHLs originating in the skin, with no evidence of extra-cutaneous spread for at least six months after initial diagnosis. The incidence of PCTCL has been increasing and is currently 6.4 per million persons, based on surveillance, epidemiology, and end results (SEER) registry data[1] Notably PCTCLs also represent the most frequent cutaneous lymphomas in children and adolescents.[2]

According to the 2022 upgrade of the WHO lymphoma classification,[3] mycosis fungoides (MF) and the Sézary syndrome (SS) are the most frequent subtypes (50-55%) of PCTCL; they are followed by the spectrum of primary cutaneous CD30+ T-cell lymphoproliferative disorders (20-25% of all PCTL) that include lymphomatoid papulosis (LyP), anaplastic large cell lymphoma (ALCL), and borderline cases which show clinical-pathologic features in between LyP and ALCL.

MF and SS are classified as distinct entities, despite closely related to MF, SS is now included among the "mature T and NK-cell leukemias", to highlight its primary site of presentation and consideration in differential diagnosis of mature T-cell leukemias.

Other PCTCL subtypes are subcutaneous panniculitis-like T-cell lymphoma, and a group of very rare entities including respectively PC gamma/delta T-cell lymphoma, PC aggressive epidermotropic CD8+ T-cell lymphoma, primary cutaneous acral CD8+ T-cell lymphoma, and primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder. The 2022 WHO lymphoma up-grade, also introduced the category of primary cutaneous peripheral T-cell lymphoma NOS, including cases that do not fit into one of the well-defined subtypes of CTCL.

In PCTCL, the clinical-pathological correlation is crucial to achieve final diagnosis and precise subtyping, the clinical information influencing the histopathological diagnosis.

With reference to recent molecular diagnostic methods,[4] improvement in assays to assess T-cell clonality including PCTCLs, and particularly the early stage of MF, is been achieved based on next-generation high-throughput sequencing (NGS) technologies.[5] Indeed, NGS search for malignant T-cell clones in skin and blood would strongly corroborate the basic histomorphologic diagnosis.

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RISK ASSESSMENT MODELS FOR VENOUS THROMBOEMBOLISM IN MULTIPLE MYELOMA

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The incidence of VTE in patients with multiple myeloma (MM) is more than 10%.[1] In particular, the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide increase the risk of thrombosis, especially when combined with high-dose steroids and other chemotherapy.[1]

In 2008, the International Myeloma Working Group (IMWG) developed a risk assessment model (RAM) based on individual-, disease- and therapy-related risk factors.[2] However, in the Myeloma XI trial the IMWG RAM did not predict the risk of thrombosis efficiently: 45.3% of thrombosis occurred in the low-risk group.[3] The IMPEDE-VTE RAM is based on data from 4446 patients in the Veterans Administration Central Cancer Registry[4] (Table 1). The respective six-month cumulative incidence of VTE following treatment initiation was 3.3% for the low-risk group (scores <3), 8.3% for the intermediate-risk group (score of 4-7), and 15.2% for the high-risk group (>8 score).[4] A second RAM for MM patients receiving IMiD-based regimens used the SEER-Medicare database to extract data on 2397 patients with MM[5] (Table 2). Patients were grouped into low (score of 0-1) or high risk (score of >2), and the model stratified approximately 30% of patients as high-risk. The IMWG,[2] the American Society of Clinical Oncology,[6] and the American Society of Hematology[7] recommended that all MM patients should be risk assessed and offered thromboprophylaxis. However, there has been little progress regarding VTE prevention. In the Myeloma XI trial the rate of VTE during IMIDs was still as high as 11.8%.[3] In a more recent report on patients treated with lenalidomide with or without Daratumumab VTE occurred in 10.1% of D-RVd patients and 15.7% of RVd patients.[8] The National Comprehensive Cancer Network (NCCN) guidelines recommended the IMPEDE and SAVED RAMs as tools for the VTE risk stratification.[9] The patients with ≤3 points by IMPEDE score or <2 points by SAVED score should receive aspirin at 81 to 325 mg once daily. For those with ≥4 points by IMPEDE score or ≥2 points by SAVED score, the recommendation is enoxaparin (40 mg/d subcutaneously), warfarin (target international normalized ratio, 2.0-3.0), fondaparinux (2.5 mg/d subcutaneously), or a direct oral anticoagulant (DOAC), such as rivaroxaban at 10 mg/d orally or apixaban at 2.5 mg orally twice daily.[9] However, the use of DOACs as antithrombotic prophylaxis in MM is based on small-sized single-arm studies.[10]

Table 1. IMPEDE-VTE Risk Assessment Model.[4]

Predictor	Acronym	Score
Immunomodulatory Drug	**B**	+ 4
Body Mass Index ≥25 kg/m^2	**M**	+ 1
Pelvic, Hip or Femur Fracture	**P**	+ 4
Erythropoiesis-Stimulating Agent	**E**	+ 1
Doxorubicin	**D**	+ 3
Dexamethasone		
High-Dose (>160 mg monthly)		+ 4
Low-Dose (<160 mg monthly)		+ 2
Ethnicity/Race = Asian/Pacific Islander	**E**	− 3
History of Venous Thromboembolism before MM	**V**	+ 5
Tunneled Line/Central Venous Catheter	**T**	+ 2
Existing Thromboprophylaxis: Therapeutic LMWH or Warfarin	**E**	- 4
Existing Thromboprophylaxis: Prophylactic LMWH or Aspirin		- 3

Table 2. SAVED Risk Assessment Model.[5]

Predictor	Acronym	Score
Surgery (within 90 days)	**S**	+ 2
Asian race	**A**	- 3
History of Venous Thromboembolism	**V**	+ 3
Eigthy (age >80 years)	**E**	+ 1
Dexamethasone	**D**	
High-Dose (>160 mg/cycle)		+ 2
Standard Dose (120-160 mg/cycle)		+ 1

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DIAGNOSIS AND TREATMENT OF AUTOIMMUNE HEMOLYTIC ANEMIAS

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Autoimmune hemolytic anemias (AIHAs) are due to autoantibody mediated erythrocyte destruction with or without complement activation.[1] They are classified as warm (wAIHA) or cold (cold agglutinin disease, CAD), basing on the isotype and thermal characteristics of the autoantibody: IgG reacting at 37°C in wAIHA and IgM reacting at lower temperatures ("cold agglutinins") in CAD. Mixed (i.e. concomitant IgG and cold agglutinins) or atypical forms (*i.e.* IgA or "warm" IgM) may also be found.[1-2] The diagnosis is based on the direct antiglobulin test (DAT), to be performed with monospecific anti-sera anti-IgG, IgM, IgA, and complement fractions in order to distinguish the different forms.[3] In about 10% of cases the DAT is negative and more sensitive methods may be employed in reference laboratories. Nevertheless, DAT-negative AIHA diagnosis may be established basing on response to steroids once excluded all other causes of hemolysis (Figure 1).[3]

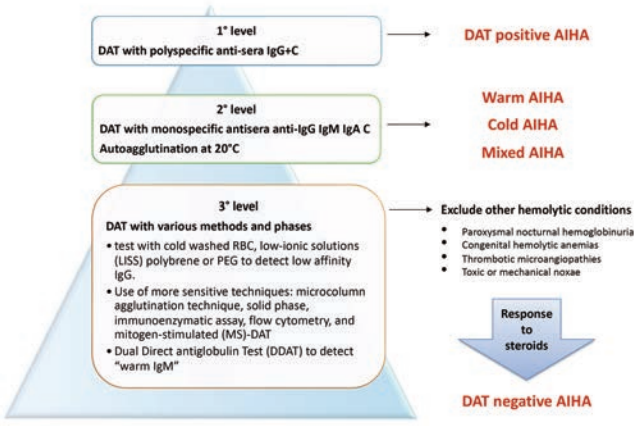

Figure 1. The various levels of direct antiglobulin test (DAT) study. The first level is DAT with polyspecific anti-sera that in the presence of hemolysis and anemia leads to the diagnosis of autoimmune hemolytic anemia (AIHA). The next and fundamental step is DAT with monospecific anti-sera and autoagglutination at 20 °C that allows the distinction of warm (positive for IgG+ or – C at low titer, autoagglutination negative), cold (positive for C and autoagglutination positive), and mixed forms (positive for IgG+C at high titer and autoagglutination positive). For negative cases, it is required to perform the DAT with various methods and phases (3rd level) and exclude all the other causes of hemolysis. Despite all the tests up 5-10% of cases would remain DAT negative.

AIHA treatment has been traditionally based on steroids and splenectomy with satisfactory responses only in wAIHAs (70-80%), but frequent relapses and toxicities.[2] Since the end of 2000s, target therapies directed at the various pathogenic mechanisms (B-cells producing autoantibodies, complement activation, and antibody-dependent cellular cytotoxicity by reticuloendothelial cells) have been introduced (Figure 2). The anti-CD20 rituximab is able to induce 80% of response in wAIHA, being the suggested 2nd line, and 50-60% in CAD, where represents the frontline approach. Median response duration is 18-24 months, shorter in CAD.[4,5]

Other B-cell targeting agents, including BTK inhibitors, anti-BAFF and anti-CD19 agents, are under study to minimize toxicity and improve response duration.[6] The proteasome inhibitor bortezomib and the anti-CD38 MoAbs daratumumab have also been used in several reports to target long-lived plasma-cells responsible of AIHA relapse after rituximab, showing efficacy even in multi-refractory cases.[7,8] The advent of anti-complement therapy is changing the paradigm in CAD, where the anti-C1 sutimlimab rapidly increased Hb and abolished transfusion need in >80% of cases and has been recently FDA and EMA approved.[9] Finally, MoAbs inhibiting the neonatal Fc receptor (FcRn), such as nipocalimab, can reduce the half-life of the pathogenic autoantibodies and represent a promising treatment for wAIHA.[6] In this evolving scenario, combination therapy will have the potential to target the complex landscape of AIHA pathogenesis.

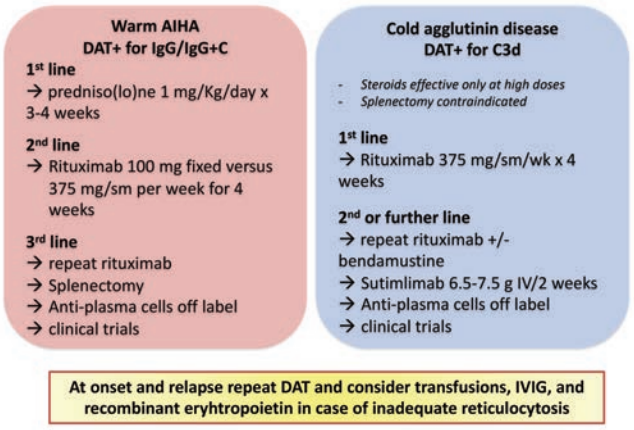

Figure 2. Available therapies for autoimmune hemolytic anemias. Treatment should be clearly differentiated between warm AIHA (wAIHA) and cold agglutinin disease. In wAIHA steroids are the preferred first line with 70-80% response rates. Nearly 2/3 of patients require a 2nd line and rituximab is the preferred choice with >70% responses lasting 18-24 months. We advise 100 mg fixed dose for wAIHA with DAT positive for IgG only, and standard 375 mg/sm dose for IgG+C wAIHA, mixed, and secondary forms. For patients requiring a 3rd line, rituximab may be repeated if a prior response lasting >1 year was observed; splenectomy should be considered in young low-comorbid patients; enrolment in clinical trials should be pursued. In CAD, about 20% of patients may be managed with follow up only, avoidance of low temperatures, and folic acid supplementation. Rituximab at standard dose is advised frontline (steroids may be used during acute severe hemolysis but not long-term). It induces about 50-60% responses, mainly partial, and most patients will relapse. Rituximab may be repeated if a prior response lasting >1 year was observed, with the possible addition of bendamustine; the C1s inhibitor sutimlimab rapidly improves hemolysis in >80% of cases and is given intravenously every 2 weeks; the drug is not active on cold induced peripheral symptoms and has to be administered indefinitely. Enrolment in clinical trials should be discussed after the 1st line. Anti-plasma cells agents off-label can be considered in multi-refractory cases of both wAIHA and CAD. Finally, transfusions, intravenous immunoglobulins, and recombinant erythropoietin are supportive treatment to be evaluated at onset and at each AIHA relapse.

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ADVANCED MOLECULAR PROFILING IN THE CLINICAL MANAGEMENT OF MYELOID NEOPLASMS

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Genomic characterization has become increasingly important for accurate diagnosis, risk assessment, and therapeutic decision making in myeloid neoplasms.[1]

Determining whether persistent unexplained cytopenia reflects a myeloid neoplasm may represent a diagnostic challenge. The absence of driver mutations has high negative predictive value for myeloid neoplasm, while the presence of somatic mutation(s) without a morphologic diagnosis defines clonal cytopenia of undetermined significance (CCUS).[2]

Somatic gene mutations complement morphologic assessment in MDS and MDS/MPN categorization. Both the WHO and ICC classifications recognize genetically defined entities, including MDS del(5q), MDS with mutated *TP53,* MDS with mutated *SF3B1* and MDS/MPN with thrombocytosis and *SF3B1* mutation.[3,4] Somatic mutations may improve risk stratification of patients with MDS or MDS/MPN. Recently, a clinical-molecular IPSS model (IPSS-M) has been developed and validated.[5] In CMML, the integration of somatic mutations in clinical/molecular prognostic systems resulted in more accurate stratification.[6]

Screening for mutations in the known driver genes *JAK2*, *CALR*, and *MPL* is mandatory for establishing MPN diagnosis.[3,4] NGS for variants in other genes, including *ASXL1, EZH2, SRSF2, IDH1, IDH2*, and *U2AF1*, are considered high risk mutations in PMF and are included in current risk assessment schemes.[7] In systemic mastocytosis, the *KIT* p.D816V mutation is identified in >90% of patients, while in advanced SM, prognosis is adversely affected by additional somatic mutations, including *SRSF2*, *ASXL1*, or *RUNX1*.[8]

The diagnostic workup of AML requires integration of cytogenetic and molecular aberrations with morphologic assessment, as the AML defining blast count is lower in the setting of selected genetic abnormalities.[3,4] Complete genomic evaluation including cytogenetics, NGS panel and *FLT3-ITD* testing, should be performed to identify AML subtypes, as well as for abnormalities within the 2022 ELN risk classification to determine prognosis in patients treated with standard intensive therapies.[9]

Individuals with myeloid neoplasms are increasingly recognized as having predisposing germline variants. Current indications for germline genetic testing include younger age, extra-hematologic signs, personal history of multiple tumors or family history of cancer and hypoplastic bone marrow, although recognized that some germline predisposition alleles, such as *DDX41*, may present at older ages.[10]

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