ABSTRACT BOOK

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51° CONGRESSO NAZIONALE SIE
Società Italiana di Ematologia
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BEST ABSTRACTS

B01

PRE-TRANSPLANT INDUCTION AND POST-TRANSPLANT CONSOLIDATION WITH ISATUXIMAB-CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE VS CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS: THE PHASE III RANDOMIZED EMN24 ISKIA TRIAL

S. Oliva[1], F. Gay[2], W. Roeloffzen[3], M.A. Dimopoulos[4], L. Rosiñol[5], M. Van Der Klift[6], S. Bringhen[7], A. Oriol[8], E. Katodritou[9], K.L. Wu[10], P. Rodriguez Otero[11], R. Hájek[12,13], I. Attucci[14], J. Straub[15], M. Van Duin[16], M. D'agostino[2], G. Margiotta Casaluci[17], M. Westerman[18], F. Bassermann[19], M. Offidani[20], P. Musto[21,22], M. Di Ianni[23], G.M. De Sabbata[24], K. S. Jie[25], F. Schjesvold[26,27], J. Bladé[5], H. Einsele[28], P. Sonneveld[16], M. Boccadoro[29], A. Broijl[16]

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The phase III IsKia trial involved transplant-eligible (TE) NDMM patients (pts) aged ≤70 yr randomized to isatuximab-carfilzomib-lenalidomide-dexamethasone (Isa-KRd) *induction, MEL200-ASCT and Isa-KRd consolidation vs.* KRd induction, MEL200-ASCT and KRd consolidation. Post-consolidation MRDneg (NGS; 10^{-5}) was the primary endpoint, evaluated in the ITT population. Key secondary endpoints were post-induction MRDneg (NGS; 10^{-5}) and PFS. Pt characteristics were well balanced between the Isa-KRd and KRd arms (151 *vs* 151 pts): median age 61 *vs* 60 yrs; high risk by IMWG [del(17p) and/or t(4;14) and/or t(14;16)] 18% *vs* 19%; double hit [DH; ≥2 abnormalities among del(17p), t(4;14), t(14;16) and gain/amp(1q)] 9% *vs* 11%. The post-consolidation ITT rates of 10^{-5} MRDneg were 77% *vs* 67% (OR 1.67, p=0.049) and of 10^{-6} MRDneg 67% *vs* 48% (OR 2.29, p<0.001). Consistent MRD results were detected by NGF. The MRDneg advantage (10^{-5}/10^{-6}) was retained in all subgroups (Figure 1) and was similar in standard-risk (SR) and high-risk (HiR) pts. 10^{-5} MRDneg with Isa-KRd was similar in HiR (76%), DH (77%) and SR (79%) pts. In the KRd arm, 10^{-5} MRDneg was 58% in HiR and 53% in DH pts, *vs* 70% in SR pts. 10^{-6} MRDneg with Isa-KRd was 72% in HiR, 77% in DH and 67% in SR pts. Post-induction MRDneg was also significantly higher with Isa-KRd *vs* KRd (10^{-5}: 45% *vs* 26%, OR 2.34, p<0.001; 10^{-6}: 27% *vs* 14%, OR 2.36, p=0.004), with a consistent benefit in all subgroups. Post-induction MRDneg in HiR and DH pts treated with Isa-KRd was: 10^{-5}, HiR 60%, DH 54%; 10^{-6}, HiR 40%, DH 31%. Post-ASCT MRDneg was also significantly better with Isa-KRd *vs* KRd (10^{-5}: 64% *vs* 49%, OR 1.93, p=0.006; 10^{-6}: 52% *vs* 27%, OR 3.01, p<0.001), with a consistent advantage in all subgroups. At the current follow-up (median, 21 months), PFS analysis has not yet been performed. 55% of pts had ≥1 hematologic AEs with Isa-KRd *vs* 44% with KRd; main grade 3–4 hematologic AEs in Isa-KRd *vs* KRd were neutropenia (36% *vs* 22%) and thrombocytopenia (15% *vs* 17%). 41% of pts had ≥3 non-hematologic AEs with Isa-KRd *vs* 37% with KRd. Discontinuation for toxicity was 6% with Isa-KRd *vs* 5% with KRd; treatment-related deaths were 4 with Isa-KRd (1 progressive disease, 3 infection) and 1 with KRd (infection). In TE NDMM pts, Isa-KRd induction and consolidation significantly increased MRDneg in every treatment phase and also in HiR pts, as compared to KRd.

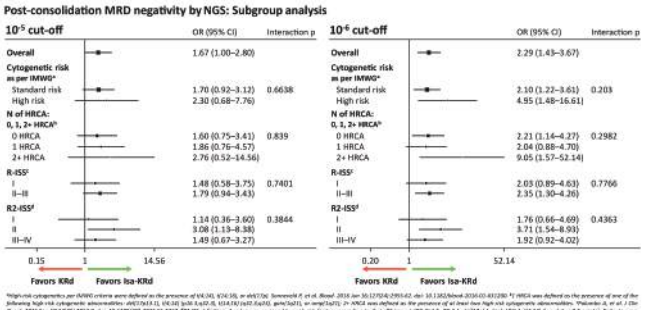

Figure 1.

B02

ELN CRITERIA FOR CYTOREDUCTION START IDENTIFY PATIENTS WITH POLYCYTHEMIA VERA AT HIGHER THROMBOTIC RISK

A. Dedola[1,2], G. Benevolo[3], E.M. Elli[4], R. Latagliata[5], F. Branzanti[2], E. Morsia[6], M. Tiribelli[7], F. Cavazzini[8], A. Tieghi[9], M. Farina[10], A. D'addio[11], E. Abruzzese[12], F. Cavalca[4], M. Venturi[1,2], G. Fontana[1,2], M. Loffredo[1,2], R. Mullai[7], A. Cuneo[8], B. Martino[13], N. Vianelli[1], M. Cavo[1,2], G. Palumbo[14], E. Rossi[15], M. Breccia[16], V. De Stefano[15], F. Palandri[1]

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Recently, the European Leukemia Net (ELN) recommended cytoreduction in patients (pts) with Polycythemia Vera (PV) at low risk (LR) (age<60 yrs and no previous thromboses) but carrying additional criteria for therapy start (CTS). Hydroxyurea (HU) is the most used cytoreductive agent in PV. During HU therapy, we assessed: 1) incidence rate of thrombosis (IR-thro) across risk categories including LR, HR-AGE (age>60 yrs) and HR-THRO pts (previous thrombosis regardless of age); 2) impact of CTS on thrombotic risk. The PV-ARC is a multicenter retrospective study including 1162 PV pts (NCT06134102). Among the 1024 HU-treated pts, we evaluated 739 with available data on CTS. CTS included: persistent/progressive leukocytosis (100% increase if WBC<10 x10^9/L; 50% increase if WBC>10; WBC>15 at diagnosis and HU start); extreme persistent thrombocytosis (>1000x10^9/L PLT at diagnosis and HU start); progressive splenomegaly (increase of >5 cm from diagnosis); inadequate hematocrit (HCT) control (≥6 phlebotomies/yr; HCT≥53% at diagnosis and HU start; PHL intolerance); uncontrolled cardiovascular risk factors (CVRF); itching (≥5/10) at HU start. Overall, 137 (18.5%) pts were at LR and 602 (81.5%) were at HR (HR-AGE, n. 424; HR-THRO, n. 178). During HU, 72 pts had 92 thromboses for an IR-thro of 1.7%p-y. IR-thro was equal in LR and HR-AGE (1.1 *vs* 1.3%p-y, p=0.68), but significantly higher in HR-THRO pts (3.0%p-y) (p=0.006 *vs* LR and p=0.002 *vs* HR-AGE). CTS were present in 445 (60.3%) pts: 95 LR (69.3%), 242 HR-AGE (57.1%) and 109 HR-THRO (61.2%). CTS were associated to significantly increased IR-thro in the total cohort (2.4 *vs* 0.7%p-y, p<0.001), in LR pts (1.6 *vs* 0%p-y, p=0.05), in HR-AGE pts (2.0 *vs* 0.5%p-y, p=0.001) and in HR-THRO pts (4.0 *vs* 1.7%p-y, p=0.04). Thrombosis-free survival (TFS) at 5 yrs was 88.7% and 96.1% in pts with or without CTS (Figure 1a). TFS of LR and HR-AGE pts with CTS were comparable to HR-THRO pts without CTS (Figure 1b). In multivariate Cox analysis considering CTS, age>60 yrs and previous thrombosis, CTS and previous thrombosis remained associated with thrombotic risk (HR: 3.1, p<0.001; HR: 3.2, p<0.001). Albeit retrospective, this study shows for the first time that ELN criteria for therapy start identify an increased risk phenotype either in LR and HR pts treated with HU. These findings call for greater attention to CTS and their integration into prognostic models that go beyond the two categories related only to age and thrombotic history.

Figure 1. Thrombosis-free survival.
TFS was evaluated according to: presence of ELN criteria for therapy start (CTS) at HU start (*fig.1a*, in the overall cohort; *fig.1b*, in the different thrombotic risk categories)

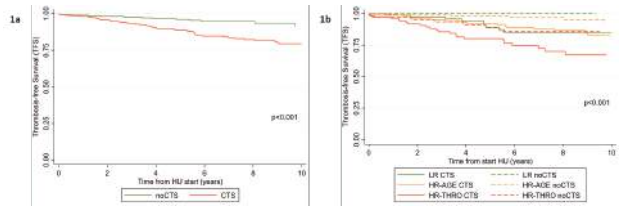

Figure 1.

B03

B04

EXAGAMGLOGENE AUTOTEMCEL FOR TRANSFUSION-DEPENDENT B-THALASSEMIA

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Background. Exagamglogene autotemcel (exa-cel) is a non-viral cell therapy that reactivates fetal hemoglobin (HbF) via ex vivo CRISPR-Cas9 gene-editing of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs).

Methods. CLIMB THAL-111 is a 24-month (mo), phase 3 trial of exa-cel in pts age 12-35y with TDT and a history of ≥100 mL/kg/y or ≥10 U/y packed red blood cell (RBC) transfusions in 2y before screening. Primary endpoint is proportion of pts maintaining a weighted average hemoglobin (Hb) ≥9 g/dL without RBC transfusion for ≥12 consecutive mos (TI12). Evaluable pts had ≥16 mos follow-

up after exa cel infusion. Evaluation started 60 days after last RBC transfusion for post-transplant support or TDT management.

Results. As of 18 September 2023, 54 pts (mean age 21.3 [range 12-35]y; 19 [35.2%] age ≥12 to <18y; 33 [61.1%] with β0/β0 or β0/β0-like genotypes, median annualized transfusion volume 205.7 mL/kg) received exa-cel; median follow-up 28.0 (range 7.3-56.2) mos. All pts engrafted neutrophils and platelets (median 29 and 44 days, respectively). 42/45 pts (93.3%) evaluable achieved primary endpoint (TI12) (95% CI: 82%, 99%; P<0.0001), stopping transfusions 32.3 (SD, 18.1) days after exa-cel infusion and remaining transfusion independent for 27.7 (range, 12.4-53.3) mos (Figure 1). For all pts, mean total Hb was 11.5 g/dL at Month 3 (≥12g/dL Month 6 onward) and HbF was 7.9 g/dL (≥ 11 g/dL Month 6 onward) with pancellular distribution. Proportion of edited BCL11A alleles was stable in bone marrow CD34+ and peripheral blood nucleated cells. Pts not yet evaluable and with sufficient follow-up were also transfusion-free. Quality-of-life (QOL) measures showed clinically significant improvements. All pts had adverse events (AE), most Grade 1 or 2; 48 (88.9%) pts had AEs of Grade 3 or 4 severity. Most common AEs were febrile neutropenia (61.1%), headache (55.6%), and stomatitis (51.9%). As previously reported, 2 pts (3.7%) had SAEs considered related to exa-cel which resolved. There were no deaths, discontinuations, or malignancies.

Conclusions. Exa-cel treatment resulted in early and sustained increases in Hb and HbF, leading to transfusion independence in >90% of pts with TDT and improved QOL which was maintained. Safety profile remains generally consistent with myeloablative busulfan conditioning and autologous transplantation. These results confirm the potential for exa-cel to provide a one-time functional cure to pts with TDT.

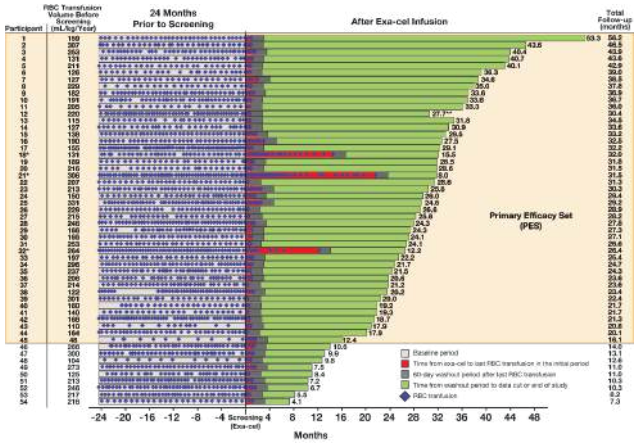

Figure 1. Duration of Period Free from Transfusions after Exa-cel Infusion (Study CLIMB THAL-111 and Study 131). All RBC transfusions that occurred after exa-cel dosing were adjudicated by the Independent Endpoint Adjudication Committee. The washout period refers to the 60 days after the last RBC transfusion for post-transplant support or TDT management. The number to the right of the light green row is the duration of period free from RBC transfusions, starting 60 days after the last RBC transfusion. Participants evaluable for the primary efficacy endpoint shown in tan box (primary efficacy set). *Participants who did not achieve TI12 in CLIMB-THAL-111; of these, participant #18 subsequently achieved TI12 in Study 131. **Indicates patient that decided to withdraw from Study 131 not due to adverse event. Exa-cel: exagamglogene autotemcel; RBC: red blood cell; TDT: transfusion dependent β thalassemia.

B05

QUANTUM-FIRST TRIAL: *FLT3*-ITD–SPECIFIC MEASURABLE RESIDUAL DISEASE (MRD) CLEARANCE ASSESSED THROUGH INDUCTION AND CONSOLIDATION IS ASSOCIATED WITH IMPROVED OVERALL SURVIVAL (OS) IN NEWLY DIAGNOSED (ND) *FLT3*-ITD+ AML PATIENTS (PTS)

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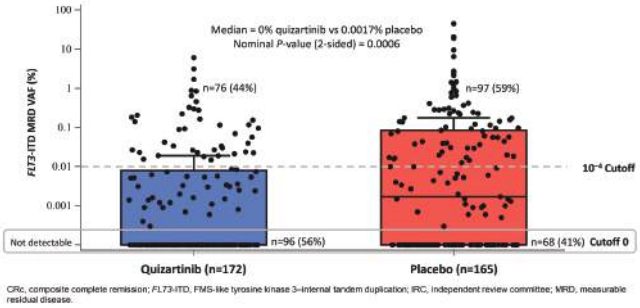
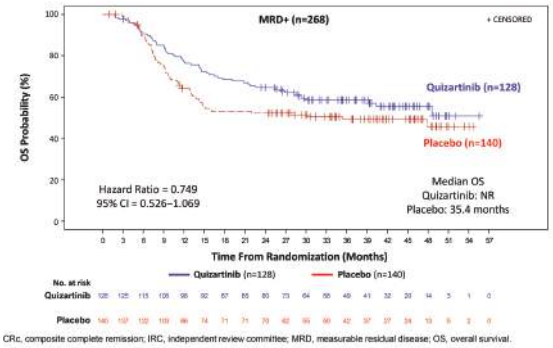
Background. *FLT3*-ITD is among the most common mutations in AML but has not historically been routinely assessed in pts in remission due to limitations of conventional detection methods. In the phase 3 QuANTUM-First (Q-F) trial, quizartinib (Quiz), a type-II FLT3 inhibitor, significantly improved OS *vs* placebo (Pbo) when added to intensive chemotherapy (IC) and as maintenance monotherapy in pts with *FLT3*-ITD+ ND-AML. We analyzed the impact of *FLT3*-ITD–specific MRD on clinical outcomes in Q-F.

Figure 1. *FLT3*-ITD MRD VAF at End of Consolidation by Treatment Arm in Patients Who Achieved CRc per IRC by the End of Induction



CRc, composite complete remission; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; IRC, independent review committee; MRD, measurable residual disease.

Figure 2. OS by *FLT3*-ITD MRD Status (Cutoff 0) in Patients Who Achieved CRc per IRC by the End of Induction With MRD Positivity



CRc, composite complete remission; IRC, independent review committee; MRD, measurable residual disease; OS, overall survival.

Figure 1.

Methods. Genomic DNA from BM or PB in pts with remission after 1-2 courses of induction (IND) and at end of consolidation (CONS; prior to transplant [HCT] or continuation [CONT] for HCT pts and prior to CONT for non-HCT pts) was analyzed with a *FLT3*-ITD PCR-NGS assay. ITD mutations after IND were cross-validated against ITDs at enrollment; ITD variant allele frequencies (VAFs) were calculated with a sensitivity of ~10^{-5} and MRD was classified as undetectable below a 0 cutoff or as MRD– using a predefined 10^{-4} cutoff. Composite CR (CRc; CR+CRi) rates by MRD status during IND were compared between arms by stratified CMH test. ITD VAFs during IND and CONS were compared between arms by Wilcoxon rank sum test. Nominal P-values were not adjusted for multiplicity.

Results. 539 pts were randomized to Quiz (268) or Pbo (271); 368 pts (68.3%) achieved CRc after IND and MRD analysis was performed on 321 (87.2%) of these pts (162 Quiz, 159 Pbo) during IND response assessments. MRD was also assessed in 337 pts (172 Quiz, 165 Pbo) at end of CONS prior to CONT; of these, 166 (87 Quiz, 79 Pbo) received HCT. The % of pts in CRc at end of IND with ITD MRD $<10^{-4}$ was similar between arms (Quiz 25.4% *vs* Pbo 21.8%; *P*=0.3430), but a greater % of pts had CRc with undetectable MRD (0 cutoff) with Quiz *vs* Pbo (12.3% *vs* 7.0%; *P*=0.0403). For pts with CRc at end of IND, the median best ITD VAF by end of CONS was lower with Quiz *vs* Pbo (0% *vs* 0.0017%; *P*=0.0006) (Figure 1A). Using the 0 ITD VAF cutoff at end of IND, a longer OS was observed with Quiz *vs* Pbo regardless of MRD status (HR: 0.79 in MRD−, 0.75 in MRD+; Figure 1B). In MRD+ pts, median OS was not reached with Quiz and 35.4 months with Pbo (Figure 1B). Results were similar using an MRD– cutoff of 10^{-4}.

Conclusions. These findings demonstrate the prognostic utility of ITD–specific MRD measurements in the management of pts with *FLT3*-ITD+ AML, and suggest that long-term OS benefits with Quiz derive in part from a deep and sustained reduction of *FLT3*-ITD.

B06

CAR-HEMATOTOX SCORE PREDICTS OVERALL SURVIVAL IN LARGE B-CELL LYMPHOMAS TREATED WITH ANTI-CD19 CAR T-CELLS: A SUBGROUP ANALYSIS OF CART-SIE

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Background. CAR T-cells have revolutionized the outcomes of relapsed/refractory large B-cell lymphomas. Long-term follow-up highlights the importance of hematological toxicity in the context of a non-relapse mortality primarily driven by infections and has led to the creation of a score that predicts neutropenia: the CAR-HEMATOTOX (HT). Subsequently, the European scientific community (EHA/EBMT) has reached a consensus defining a new entity: immune effector cell–associated hematotoxicity (ICAHT).

Aim. To validate the ability of the HT score to predict ICAHT and survival.

Methods. The CART-SIE is an ongoing multicenter prospective observational study collecting data on patients treated with commercial CAR T-cells.

Figure 1 – Overall survival according to simplified CAR-HEMATOTOX (HT)

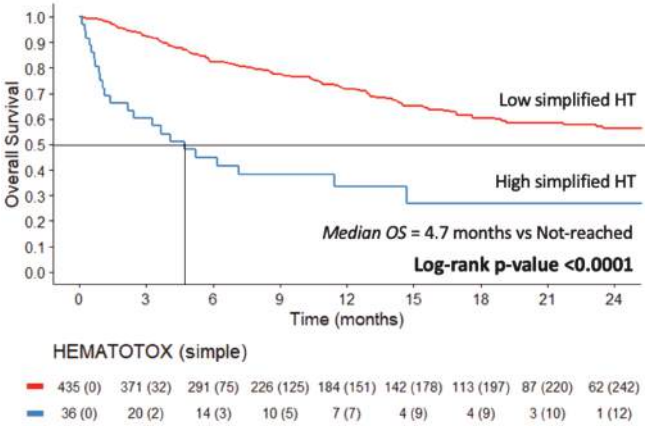

Figure 1.

Results. Since 2019 to 2023, 760 consecutive patients were enrolled. Out of 760, 302 had all the necessary data to calculate the HT score at infusion. Thirty-four percent of the patients were female and median age was 57 years. Patients with high HT score were more frequently had an advanced stage disease (stage III-IV: 80% *vs* 61%, p=0.0007), and had a higher lactate dehydrogenase at the time of infusion (mean 507 *vs* 274mU/ml, p<0.0001). Patients with a high HT score had a 6-fold higher risk of experiencing late ICAHT of grade>2 (OR=5.86, p=0.0042, AUC=71%, sens=69%, spec=72%). Patients with a high HT score also showed lower overall response rates

(ORR) and complete response rates (CRR) at 90 days (ORR: 31% *vs* 59% OR=0.32, p<0.0001; CRR: 24% *vs* 50%, OR=0.33, p=0.0001). Adjusted logistic models confirmed that the effect of HT was independent from baseline characteristics. With a median follow-up of 18 months, patients with a high HT score have lower OS and PFS (1year OS 54% *vs* 80%; 1year PFS 31% *vs* 49%). Patients with a high HT score showed a threefold increased risk of mortality (HR=2.98, 95%CI=1.99-4.45, p<0.0001, Harrell's C=63%). Adjusted Cox models confirmed that HT was an independent prognostic factor for OS. A simplified version of HT, based solely on the platelet count and C-reactive protein at infusion, was calculated for 471 patients and proved capable of predicting both OS and PFS (Figure 1, 1year OS 72% vs 33%, HR 3.65, 95%CI=2.3-5.7, p<0.0001).

Conclusion. For the first time in the context of a prospective real-world study, we validated the ability of the HT score to predict ICAHT and survival. Updated data will be presented at the meeting.

B07

A PHASE I/II TRIAL OF DONOR DERIVED CYTOKINE INDUCED KILLER (CIK) CELLS INFUSION FOR RELAPSED HEMATOLOGIC MALIGNANCY AFTER HAPLOIDENTICAL STEM CELL TRANSPLANTATION: THE HAPLO-CIK STUDY

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Background. Disease relapse is a major cause of mortality following allogeneic hematopoietic stem cell transplantation (alloHSCT) for hematologic malignancies. When alloHSCT fails, donor lymphocyte infusion (DLI) is one of the clinical options, but this treatment is complicated by a high risk of acute graft-versus-host disease (GvHD). Donor's Cytokine Induced Killer (CIK) cells have shown Graft versus Leukemia (GvL) activity with little GvHD and therefore may represent an ideal alternative to treat post-transplant relapse in the setting of HLA disparity.

Table 1. Baseline clinical characteristics of included patients.

	Total N=18
Age, *median (IQR)*	61.5 (47.0-65.0)
Gender, *n (%)*	
Female	11 (61.1)
Male	7 (38.9)
Diagnosis, *n (%)*	
Myeloid neoplasm	17 (94.4)
Myelodysplastic syndromes (MDS)	1
Acute myeloid leukemia (AML)	15
Myelofibrosis	1
Lymphoid neoplasm	1 (5.6)
B-lymphoblastic leukemia/lymphoma	1
Status of disease, *n (%)*	
Hematologic relapse	9 (50.0)
Molecular relapse	4 (22.2)
Immunophenotypic relapse	3 (16.7)
Loss of full donor chimerism	2 (11.1)

Aim. To evaluate the safety and efficacy of donor-derived CIK cells for the treatment of relapse after haploidentical transplantation

Methods. We conducted an academic, phase I/II dose-escalation trial in patients who relapsed after haploidentical alloHSCT (EUDRACT number 2018-000716-24). CIK cells were produced from up to 50 mL of peripheral blood from the previous HSCT donor. For each patient were scheduled three CIK infusions ($5x10^6$, $5x10^6$ and $10x10^6$ cells/kg) every 21 days, followed by restaging at day +100 from the last infusion. The primary objectives were to define safety as the study of treatment-related death or grade ≥III acute GvHD. Secondary objectives included the assessment of the response rate.

Results. Nineteen patients relapsed after haploidentical donor alloHSCT were screened for this study and 18 were enrolled. The clinical characteristics of the enrolled patients are reported in Table 1. Successful production of CIK cells was achieved for all patients. Four patients died before starting therapy, due to disease progression, and 1 patient was withdrawn from the protocol. The remaining 13 patients received at least one CIK administration (6 in the run-in phase cohort and 7 in the expansion phase). None patient developed any grade of acute or chronic GvHD. Complete remission was observed in 8 (62%) patients, stable disease in 1 patient (8%), and progression of disease in 4 patients (31%). Better results were observed for patients enrolled due to MRD/chimerism relapses compared to hematological relapses regarding overall response rate (75% *vs* 40%, respectively).

Conlusions. Our study shows that CIK cells also represent a safe cellular therapy in the context of profound HLA disparity with no reported cases of GvHD. This safety profile represents an important basis for the future development of CIK cells as an ideal platform for developing ready-to-use allogeneic immunotherapies.

B08

PATIENT-REPORTED OUTCOMES (PROS) IN ACUTE MYELOID LEUKEMIA (AML) PATIENTS (PTS) WITH FLT3-ITD MUTATION RECEIVING QUIZARTINIB (QUIZ) AND CHEMOTHERAPY *VS* ONLY INTENSIVE CHEMOTHERAPY: RESULTS FROM THE QUANTUM-FIRST TRIAL

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Introduction. In the phase 3 QuANTUM-First (Q-F) trial (NCT02668653) in pts with *FLT3*-ITD+ ND-AML, quizartinib (Quiz), a type-II FLT3 inhibitor, significantly improved OS *vs* placebo (Pbo) when added to intensive chemotherapy (IC) and as maintenance monotherapy. An exploratory endpoint of the trial was to assess the impact of Quiz on PROs.

Methods. Pts were randomized 1:1 to receive Quiz or Pbo with standard induction (IND) and consolidation (CONS), followed by up to 36 cycles of monotherapy continuation (CONT) for pts achieving remission. The EORTC QLQ-C30 and EuroQol EQ-5D-5L were assessed at baseline (BL; IND cycle [C] 1 day [D] 8), on D28 of IND C1–2, D6 and D28 of CONS C1–4, and D1 of each third C during CONT. A minimal clinically important difference (MCID) score ≥10 points was used for QLQ-C30 domains. A mixed-effect model for repeated measures (MMRM) and time until definitive deterioration (TUDD) assessed longitudinal effects. TUDD was the time to first deterioration of from BL PRO score to beyond the MCID without further improvement of more than one MCID or without any further available score.

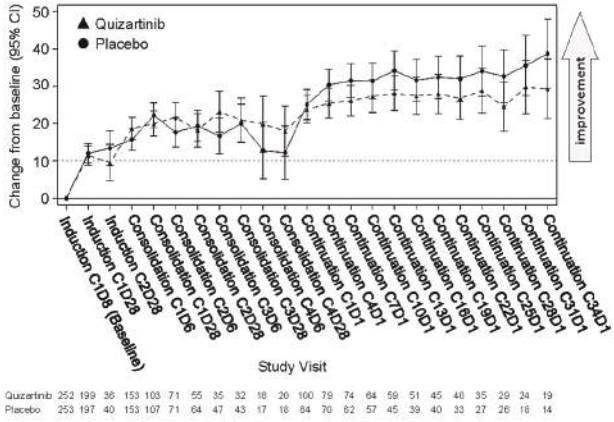
Table 1 and Figure 1.

Table 1. Mean (SD) EORTC QLQ-C30 and EQ-5D-5L Scores at Baseline for Quizartinib vs. Placebo vs. General Population Norm Data for EU and US*

Function Subscale (Higher scores are better)	Quizartinib	Placebo	EU Population Norm	US Population Norm
Physical Function	68.5 (28.2)	68.9 (26.8)	85.1 (18.9)	80.8 (25.2)
Role Function	52.2 (35.1)	49.9 (38.0)	84.3 (24.6)	81.7 (28.2)
Emotional Function	71.7 (24.3)	72.3 (24.3)	74.2 (24.7)	73.3 (28.0)
Cognitive Function	80.4 (22.8)	81.9 (22.6)	84.8 (21.3)	80.9 (25.6)
Social Function	53.5 (34.3)	53.4 (36.1)	86.2 (24.1)	81.6 (29.4)
Symptom Subscale (Lower scores are better)				
Fatigue	51.0 (29.2)	48.0 (29.0)	29.5 (25.5)	31.9 (27.8)
Nausea/vomiting	19.0 (23.7)	19.7 (24.7)	5.9 (16.0)	10.9 (22.6)
Pain	28.6 (29.1)	28.3 (29.8)	23.5 (27.1)	27.5 (30.2)
Dyspnea	23.4 (29.2)	23.8 (29.8)	15.9 (24.6)	19.9 (28.5)
Insomnia	34.8 (31.2)	33.3 (33.3)	26.6 (30.3)	30.8 (33.2)
Appetite loss	45.0 (34.4)	46.5 (35.7)	10.0 (21.6)	14.1 (25.3)
Constipation	18.7 (28.4)	15.8 (25.3)	12.5 (23.3)	18.6 (28.6)
Diarrhea	30.7 (35.2)	25.3 (30.5)	9.5 (20.9)	13.7 (27.1)
Financial difficulties	27.2 (33.0)	25.0 (32.8)	10.6 (23.6)	17.5 (30.8)
GHS/QoL	45.9 (24.4)	48.1 (24.9)	66.1 (21.7)	63.9 (22.9)
EQ-5D-5L (Higher scores are better)				
US index score	0.75 (0.20)	0.77 (0.19)	NA	0.85 (0.22)†
UK index score	0.67 (0.28)	0.70 (0.27)	0.86 (0.23)‡	NA

*Nolte S. et al. Eur J Cancer. 2019;107:153-163
†Jiang R et al. Qual Life Res. 2021;30(3):803-816
‡Kind P et al. Discussion Paper 172, Center for Health Economics, University of York, 1999
EU - Austria, Denmark, France, Germany, Hungary, Italy, The Netherlands, Poland, Spain, Sweden, and United Kingdom (UK)
NA-Not applicable

Figure 1. EORTC QLQ-C30 Global Health Status/QoL Scale Mixed Model with Repeated Measures for Change in Score from Baseline for Quizartinib vs. Placebo



Results. 509/539 pts (254 Quiz, 255 Pbo) were assessed for PROMs. Questionnaire completion compliance at the beginning of each phase was high and similar for both arms and most scales: Global Health Status (GHS) completion rates were 99.2%, 95.3%, and 93.4% at C1 of IND, CONS, and CONT, respectively. BL PRO scores were comparable between arms and were lower than the general population norm QLQ-C30 and EQ-5D-5L scores for EU and US. Per MMRM, there were clinically meaningful improvements from BL in GHS (Figure 1) and fatigue in both arms, but no significant difference between arms for the change from BL score although Pbo had numerically better scores during the maintenance phase (treatment difference [Quiz–Pbo], GHS: –2.0 [95%CI: -4.8, 0.7], p=0.1479; fatigue: 3.0 [95%CI: -0.1, 6.1], p=0.0600). Similar trends were observed in most of the functional and symptom scales of EORTC QLQ-C30 and EQ-5D-5L. By TUDD analysis, Quiz showed slower deterioration in several scales (specifically GHS, cognitive function, appetite loss, and constipation; not statistically significant).

Conclusions. Quiz showed improvement in OS without a detrimental impact on quality of life and symptoms when added to standard chemotherapy followed by maintenance monotherapy in pts with newly diagnosed *FLT3*-ITD AML.

B09

REAL-WORLD OUTCOME OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) TREATED WITH COVALENT BTK INHIBITORS (CBTKI): A SUBGROUP ANALYSIS OF OVER 1200 PATIENTS ENROLLED INTO THE GIMEMA CLL2121 STUDY

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Within the GIMEMA, we have designed the observational CLL2121 study (NCT04867915) with the objective of evaluating the management of CLL in all Italian hematology centers in order to provide a more representative picture of everyday clinics using "real-world" data. This retrospective/prospective Italian multicenter study enrolls pts with CLL/small lymphocytic lymphoma (SLL)/monoclonal B cell lymphocytosis (MBL) diagnosis from 2010. 4598 pts from 82 sites were enrolled into the study at 14 Apr 2024. Within this larger cohort we focused on pts exposed to covalent BTK inhibitors (cBTKi), aiming at defining 1) type of CLL-treatment and response to next-line-treatment after cBTKi discontinuation; 2) overall survival (OS) from cBTKi discontinuation. 1264/2033 treated pts (62%) received ≥1 cBTKi in any line of treatment. The majority were male (794/1261, 63%), 1146 (91%) had a CLL, with only 93 (7%) having SLL and 22 (2%) MBL. The median age at the time of the first BTKi start was 71 years (IQR 63-77). 861 pts received a cBTKi-based therapy in first-line, while the median number of therapies before the first cBTKi in 403 relapsed/refractory pts was 1 (range 1-6). 482/615 with available information (74%) carried unmutated IGHV, and 245/550 (45%) had *TP53* aberrations. 927 pts were treated with ibrutinib-based therapies (583 1L, 344 2+L), 332 with acalabrutinib (259 1L, 73 2+L), 30 with zanubrutinib (19 1L, 11 2+L). After a median follow up of 74 months (range 1-248), the best overall response rate to the first cBTKi among 810 pts was 77%, 24% being complete (CR)/CRi, 46% partial (PR), 7% PR with lymphocytosis, with 13% experiencing progressive disease, 9% stable disease, and <1% death. 33% discontinued their first cBTKi for progression/death, 31% for toxicity, 8% according to the plan, 27% for other reasons, <1% were lost-to follow-up. Next line treatment after BTKi was venetoclax-based (68%), BTKi+/-anti-CD20 (9%), idelalisib+/-rituximab (8%), chemoimmunotherapy (5%), pirtobrutinib (1%), and other (9%). The 12-month OS from the first cBTKi discontinuation was 64.2% (95% CI: 53.2-77.5%) for progressive *vs* 82.9% (95% CI; 72.0-95.4%) for intolerant pts (Figure 1). This real world study on a large cohort of pts with CLL/SLL in Italy shows a high proportion of pts discontinuing BTKi due to toxicity at similar levels compared to clinical progression. Importantly, BTKi discontinuation appears to be a turning point, that portends a short OS, with limited salvage options.

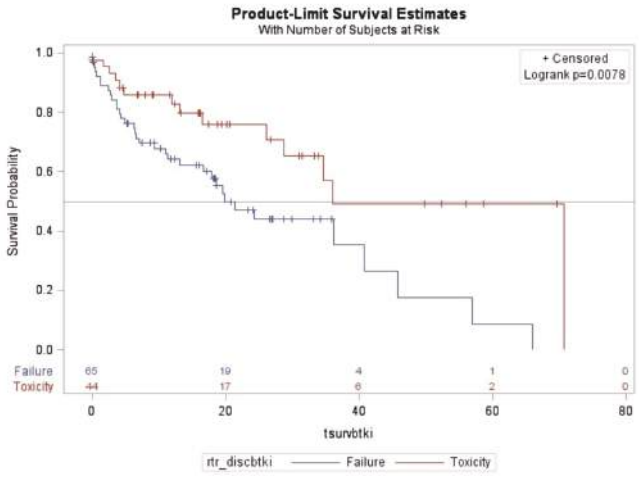

Figure 1.

B10

CARV EPIDEMIOLOGY IN 2023-2024 FALL-WINTER SEASON IN HEMATOLOGIC MALIGNANCY PATIENTS: A REPORT FROM EPIFLUEHA REGISTRY

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The increasing concern regarding the impact of community-acquired respiratory viruses (CARVs) in patients with hematological malignancies (HM) requires proactive measures to mitigate risks and enhance treatment outcomes. This study sought to gather and analyze epidemiological, management, and outcome data from HM patients with CARV collected in the 2023-24 fall-winter season to inform tailored clinical management strategies. Utilizing an online registry, data from of CARV infections in HM patients were collected from September 2023 to March 2024 (period of maximum CARVs spread), spanning 53 sites across 21 countries. We collected 1242 cases of CARV in patients with HM. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) accounted for 599 cases (48%), followed by influenza (n=240, 19%), respiratory syncytial virus (RSV) (n=141, 11%), and rhinovirus (n=134, 11%). The distribution of specific CARVs mirrored the overall prevalence across different malignancies, with 27% in acute leukemias and non-Hodgkin lymphoma each and 22% in multiple myeloma. Prior to CARV infection, 26% of patients had undergone stem cell transplantation or CAR-T therapy, particularly in cases of rhinovirus (46%) and RSV, metapneumovirus, and parainfluenza virus (35%, each). Chronic cardiopathies (43%) were the most common comorbidity across all

CARV cases. Critical illness was more prevalent in patients infected with parainfluenza virus (22%), metapneumovirus (15%) or influenza (12%) compared to RSV or SARS-CoV-2 (6%, each). Invasive mechanical ventilation was more frequent in metapneumovirus and parainfluenza cases (11%, each). Bacterial pathogens (14%) were the primary cause of secondary infections, followed by fungi and viruses (4% each), with consistent distribution across CARV types. Parainfluenza infections had the highest overall mortality rates (19%), surpassing those of influenza (11%) or SARS-CoV-2 (10%). Accordingly, attributable mortality was of 11%, 7% and 5% for parainfluenza, influenza and SARS-CoV-2, respectively. Progression of baseline malignancy contributed to 68% of overall mortalities. Our findings emphasize the profound impact of CARV on patients with HM, notably with SARS-CoV-2 predominance. CARV distribution mirrored malignancy prevalence, with acute leukemias and non-Hodking lymphoma most affected. Additionally, our study highlights the increased severity and mortality rates linked to specific CARV pathogens like parainfluenza and metapneumovirus.

B11

SEVEN-YEAR OVERALL SURVIVAL ANALYSIS FROM THE ECHELON-1 STUDY OF BRENTUXIMAB VEDOTIN PLUS CHEMOTHERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED STAGE III/IV CLASSICAL HODGKIN LYMPHOMA

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Analysis of the 6-year follow-up of the ECHELON-1 (NCT01712490) study demonstrated significant improvements in overall survival (OS) and progression-free survival (PFS) in patients with Stage III/IV classical Hodgkin lymphoma (cHL) treated with A+AVD (brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine) versus ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), with a comparable safety profile. Here, we report OS and PFS data following a 7-year median follow-up. OS and PFS per investigator were analysed in the intent-to-treat (ITT) population (data cut-off March 11, 2023). Patients were randomized 1:1 to receive ≤6 cycles of A+AVD (n=664) or ABVD (n=670) on days 1 and 15, every 28 days. Positron emission tomography scan after cycle 2 (PET2) assessment was compulsory. In the safety population, long-term outcomes included resolution or improvement of peripheral neuropathy (PN), second malignancies, and pregnancies. At a median follow-up of 89.3 months (95% confidence interval [CI]: 87.0–90.2), 7-year OS rates were 93.5% (95% CI: 91.1–95.2) with A+AVD and 88.8% (95% CI: 85.8–91.1) with ABVD; OS favored A+AVD over ABVD (hazard ratio [HR], 0.62; 95% CI: 0.42–0.90; *P*=0.011). Subgroup analyses of OS showed consistent benefit for A+AVD in most subgroups, including age <40 years and Stage IV disease (Table 1). Seven-year PFS rates with A+AVD versus ABVD were 82.3% (95% CI: 79.1–85.0) *vs* 74.5% (95% CI: 70.8–77.7), respectively (HR, 0.68; 95% CI: 0.53–0.86; *P*=0.001). At last follow-up, PN had improved/resolved in most patients (A+AVD: 86.0% [381/443]; ABVD: 87.1% [249/286]). Median (range) time to complete resolution of PN was 16 (0–373) weeks with A+AVD and 10 (0–343) weeks with ABVD; median (range) time to improvement was 42 (2–182) and 19 (15–142) weeks, respectively. PN was ongoing in 27.5% (122/443; 11.7% grade ≥2) and 20.3% (58/286; 7.0% grade ≥2) of patients receiving A+AVD and ABVD, respectively. Livebirths/pregnancies were reported by 84/92 patients and their partners with A+AVD and 59/73 with ABVD; no stillbirths were recorded. Second malignancies were reported in 5.0% (33/662) and 5.9% (39/659) of patients in the A+AVD and ABVD arms, respectively. After a median follow-up of 7 years, patients treated with A+AVD demonstrated sustained OS and PFS benefit versus those treated with ABVD, with PFS rates suggesting potential curability. No new safety signals were reported in patients treated with A+AVD.

Table 1.

Table. 7-year overall survival rates by subgroup (ITT)

Group, % (95% CI)	A+AVD OS rate, % (95% CI) n=664	ABVD OS rate, % (95% CI) n=670	HR (95% CI) *P*-value
All patients	93.5 (91.1–95.2) n=664	88.8 (85.8–91.1) n=670	0.62 (0.42–0.90) 0.011
PET2 negative	95.0 (92.8–96.6) n=588	90.2 (87.2–92.5) n=577	0.57 (0.37–0.87) 0.009
PET2 positive	90.7 (72.3–97.1) n=47	74.0 (59.9–83.8) n=58	0.34 (0.11–1.03) 0.046
Stage III	92.1 (87.6–95.1) n=237	90.3 (85.3–93.7) n=246	1.01 (0.54–1.87) 0.980
Stage IV	94.2 (91.3–96.2) n=425	88.1 (84.3–91.0) n=421	0.49 (0.30–0.79) 0.003
Aged <40 years	98.2 (96.2–99.1) n=396	95.0 (91.9–96.9) n=375	0.39 (0.16–0.95) 0.032
Aged <60 years	96.4 (94.4–97.7) n=580	92.9 (90.3–94.9) n=568	0.49 (0.29–0.83) 0.007
Aged ≥60 years	72.6 (60.6–81.5) n=84	66.7 (55.9–75.5) n=102	1.01 (0.59–1.71) 0.982

B12

OVERALL SURVIVAL, CLINICAL BENEFIT AND DURABLE TRANSFUSION INDEPENDENCE WITH IMETELSTAT IN THE IMERGE PHASE 3 TRIAL OF RED BLOOD CELL-TRANSFUSION DEPENDENT LOWER-RISK MYELODYSPLASTIC SYNDROMES

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In the double-blind, randomized IMerge Ph3 study (NCT02598661), imetelstat, a first-in-class telomerase inhibitor, resulted in significantly higher rates of red blood cell transfusion independence (RBC-TI) for ≥8 weeks, ≥24 weeks, and ≥1 year (39.8%, 28.0%, and 17.8%) than placebo (15.0%, 3.3%, and 1.7%) in patients (pts) with non-del(5q) lower risk-myelodysplastic syndromes that were RBC-transfusion dependent, relapsed/refractory to or ineligible for erythropoiesis-stimulating agents, and naïve to lenalidomide or hypomethylating agents (Platzbecker *et al.* Lancet 2024). Here we report initial assessment of overall survival (OS) and clinical benefit of durable RBC-TI with imetelstat in IMerge. Duration of RBC-TI and OS were calculated by Kaplan-Meier method and compared by stratified log-rank test. Cutoff date was Oct 2022 for primary analysis, Oct 2023 for ≥1-year RBC-TI, and Jan 2024 for OS. Among pts achieving ≥8-week RBC-TI, median duration of TI was 52 weeks with imetelstat (47/118 pts) *vs* 13 weeks with placebo (9/60 pts) (P<.001); median increase from baseline in central hemoglobin (Hb) was 3.6 g/dL *vs* 0.8 g/dL, respectively. Of imetelstat-treated pts in this subset, 70% remained RBC-TI for ≥24 weeks; 64% of ≥24-week responders remained RBC-TI for ≥1 year. Among ≥24-week RBC-TI responders, median duration of TI was 80 weeks with imetelstat (33/118 pts) *vs* 78 weeks with placebo (2/60 pts) (P<.001); median Hb increase was 4.2 g/dL *vs* 1.1 g/dL. In ≥1-year RBC-TI responders, median duration of TI was 132 weeks with imetelstat (21/118 pts) *vs* 131 weeks with placebo (1/60 pts); median Hb increase was 5.2 g/dL *vs* 1.7 g/dL. In a separate assessment, ≥8-week, ≥24-week, and ≥1-year RBC-TI with concurrent Hb rise of ≥1.5 g/dL with imetelstat *vs* placebo occurred in 28% *vs* 2%, 23% *vs* 0%, and 17% *vs* 0% of pts (all P<.001). As of Jan 2024, 55 (47%) and 26 (43%) pts were in follow-up in the imetelstat and placebo groups; median duration of follow-up was 32 and 28 months. Median OS was 40.4 months with imetelstat and not estimable with placebo (HR, 0.98; 95% CI, 0.526-1.823). In the imetelstat group, 2-year OS rate was 78% overall, 81% in ≥8-week TI responders, and 75% in non-responders (Figure 1). In the placebo group, 2-year OS rate was 74%. Results from these updated analyses confirm that achievement of RBC-TI with imetelstat was durable and associated with improvement in Hb level. Additionally, preliminary OS analysis suggests no detriment with imetelstat *vs* placebo.

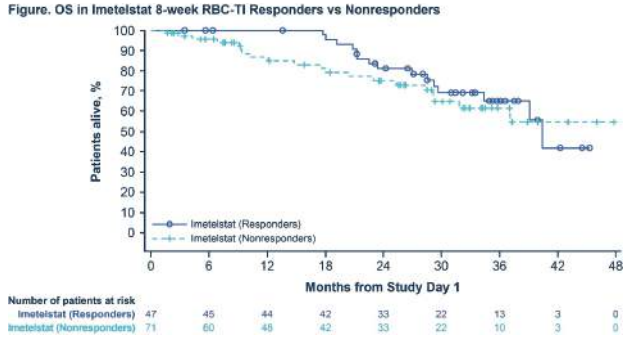

Figure 1.

Myeloma and monoclonal gammopathies I

C001

SAFETY RESULTS FROM THE PHASE 3 MAJESTEC-7 STUDY IN PATIENTS (PTS) WITH TRANSPLANT INELIGIBLE/NOT INTENDED NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM)

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Despite recent advances in the treatment (tx) of transplant ineligible/not intended NDMM, most pts still relapse and require alternative txs, highlighting a need for new frontline tx options. Teclistamab (tec) demonstrated rapid, deep, and durable responses in MajesTEC-1. Preliminary data from MajesTEC-2 demonstrated that tec, daratumumab (dara), and lenalidomide (len) (tec + DR) is tolerable, with promising efficacy in RRMM and NDMM. The phase 3 MajesTEC□7 (NCT05552222) study will compare tec + DR *vs* DR + dexamethasone (dex) in pts with NDMM who are ineligible/not intended for ASCT as initial tx. We report results of the first safety run-in (SRI) from MajesTEC-7. Pts were aged ≥18 y with NDMM and ineligible for ASCT as initial tx, with measurable disease and ECOG PS score 0–2. Pts in the SRI received tec (step-up dose [cycle 1], QW [cycle 2], Q2W [cycle 3–6], and Q4W [cycle 7+]) + DR (as SOC) until progression, unacceptable toxicity, or death. Response assessments were per IMWG. AEs were graded per CTCAE v5.0 (CRS and ICANS per ASTCT). Prophylactic immunoglobulin replacement was highly recommended. As of Nov 27, 2023, 26 pts had received tec + DR (median, 11 cycles; range, 2–14); 24 pts (92.3%) remained on tx. Median follow-up was 10.2 mo (range 2–12). At baseline, median age was 72.5 y; 11.5% had an ECOG PS score of 2; 15.4% had ≥1 soft-tissue plasmacytoma. 4 pts (15.4%) deferred transplant. Treatment-emergent AEs (TEAEs) occurred in 100% of pts (grade [gr] 3/4, 22 pts [84.6%]). Infections occurred in 25 pts (96.2%; gr 3/4, 8 pts [30.8%]). CRS occurred in 16 pts (61.5%; all gr 1). ICANS occurred in 1 pt (gr 1). Gr 3/4 TEAEs occurring in ≥3 pts were neutropenia (13 [50%]), febrile neutropenia (5 [19.2%]), thrombocytopenia (4 [15.4%]), COVID-19 (3 [11.5%]), maculo-papular rash (3 [11.5%]), and hypertension (3 [11.5%]). 1 pt discontinued tec + DR due to withdrawal of consent. 2 discontinued len due to TEAEs (gr 3 maculo-papular rash and gr 4 neutropenia). 1 pt died (due to a TEAE in cycle 3; pneumonia influenza). ORR was 92.3% (≥CR, 73.1%; ≥VGPR, 92.3%). These results from the first SRI of MajesTEC-7 demonstrate a manageable safety profile with early efficacy of tec + DR in NDMM. Two additional SRIs are ongoing investigating tec (less frequent dosing) + DR and talquetamab + DR. This abstract was accepted and previously presented at the 2024 ASCO Annual Meeting.

C002

DARATUMUMAB (DARA) + BORTEZOMIB/LENALIDOMIDE/DEXAMETHASONE (VRD) IN TRANSPLANT-ELIGIBLE (TE) PATIENTS (PTS) WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM): ANALYSIS OF MINIMAL RESIDUAL DISEASE (MRD) IN THE PERSEUS TRIAL

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In the primary analysis of the phase 3 PERSEUS study, subcutaneous DARA (DARA SC) + VRd (D-VRd) induction/consolidation (ind/consol) and D-R maintenance improved PFS and increased depth of response (≥CR and MRD neg) compared to VRd ind/consol and R maintenance for TE NDMM. Here, we report further results on deepening of response and MRD neg during maintenance. TE pts with NDMM were randomized 1:1 to D-VRd or VRd. Pts in both arms received up to six 28-day cycles (4 pre-ASCT ind, 2 post-ASCT consol) of VRd (V 1.3 mg/m^2 SC on Days [D] 1, 4, 8, 11; R 25 mg PO on D 1-21; d 40 mg PO/IV on D 1-4, 9-12) followed by R maintenance (10 mg PO on D 1-28 until progressive disease [PD]). Pts in the D-VRd arm also received DARA SC (DARA 1,800 mg + recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; Halozyme]) QW in Cycles 1-2, Q2W in Cycles 3-6, and Q4W during maintenance until PD. MRD-neg rate (clonoSEQ®) was defined as the proportion of ITT pts who achieved both ≥CR and MRD neg. In the 709 pts randomized (D-VRd, n=355; VRd, n=354), responses deepened over time with D-VRd *vs* VRd, including rates of ≥CR (end of consol: 44.5% *vs* 34.7%; P=0.0078 and overall: 87.9% *vs* 70.1%; P<0.0001). MRD-neg rates increased over time and were higher with D-VRd *vs* VRd at 12, 24, and 36 mo after Cycle 1 Day 1 (all P<0.0001; Table 1). Rates of sustained MRD neg for ≥12 mo were higher for D-VRd *vs* VRd (10^{-5}: 64.8% *vs* 29.7%; P<0.0001; 10^{-6}: 47.3% *vs* 18.6%; P <0.0001); results were consistent across prespecified clinically relevant subgroups. Among pts who were MRD pos at end of consol, significantly higher proportions of pts in the D-VRd group *vs* the VRd group achieved MRD neg during maintenance at 10^{-5} (68.8% *vs* 52.7%; P=0.0330) and 10^{-6} (62.3% *vs* 31.0%; P<0.0001) and sustained MRD neg for ≥12 mo at 10^{-5} (44.2% *vs*

22.6%; P=0.0028) and 10^{-6} (34.4% *vs* 12.7%; P<0.0001). End of consol and overall MRD neg at both 10^{-5} and 10^{-6} were associated with improved PFS. During maintenance, a greater proportion of pts with MRD-pos status achieved MRD neg with D-R *vs* R. The higher rates of deep (10^{-6}) and sustained MRD neg achieved with D-VRd ind/consol and D-R maintenance *vs* VRd ind/consol and R maintenance translated to a clinically meaningful benefit of improved PFS. These data further support D-VRd and D-R maintenance as a new SOC for TE pts with NDMM and highlight the benefit of DARA SC in maintenance.

Table 1.

	10^{-5}			10^{-6}		
	D-VRd (n = 355)	VRd (n = 354)	*P*	D-VRd (n = 355)	VRd (n = 354)	*P*
Rates of MRD neg up to:						
12 mo	65.1%	38.7%	<0.0001	43.9%	20.9%	<0.0001
24 mo	72.1%	44.9%	<0.0001	57.7%	27.4%	<0.0001
36 mo	74.6%	46.9%	<0.0001	63.9%	30.8%	<0.0001

C003

FINAL SURVIVAL ANALYSIS OF DARATUMUMAB PLUS LENALIDOMIDE AND DEXAMETHASONE VERSUS LENALIDOMIDE AND DEXAMETHASONE IN TRANSPLANT-INELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: MAIA STUDY

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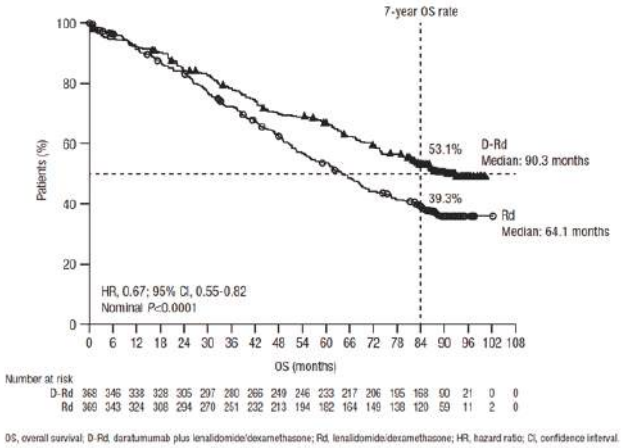
The inclusion of DARA in frontline combination therapy has consistently demonstrated clinical efficacy in pts with NDMM. In the phase 3 MAIA study (NCT02252172), TIE pts with NDMM who were treated with DARA plus D-Rd had superior PFS (median of 61.9 *vs* 34.4 mo.) and OS (median not reached *vs* 65.5 mo.) versus Rd alone. This long-term follow-up analysis of MAIA reports updated OS results for D-Rd versus Rd and new data on subsequent antimyeloma therapies after a median follow-up of 7.5 years. Pts with NDMM ineligible for high-dose chemotherapy and ASCT due to age ≥65 years or comorbidities were randomized 1:1 to receive D-Rd or Rd. All pts received 28-day cycles of Rd with or without DARA until disease progression or unacceptable toxicity. The primary and secondary endpoint of MAIA was PFS and OS, respectively. 737 pts were randomized (D-Rd, n=368; Rd, n=369). Baseline pt characteristics were balanced between groups; median age was 73 years, with 43.6% of pts overall aged ≥75 years. After a median follow-up of 89.3 mo., a 33% reduction in the risk of death was observed with D-Rd *vs* Rd. Median OS was 90.3 mo. in the D-Rd group versus 64.1 mo. in the Rd group (HR, 0.67; 95% CI, 0.55-0.82; nominal P<0.0001; Figure 1). Among those treated, 38.5% pts in the D-Rd group and 55.1% in the Rd group received ≥1 subsequent line of antimyeloma therapy on study, and the median time to subsequent therapy was longer in the D-Rd versus Rd group (not reached *vs* 42.4 mo.; HR, 0.51; 95% CI, 0.41-0.63; nominal P<0.0001). Among pts who received subsequent antimyeloma therapy, the most common antineoplastic agents after D-Rd and Rd, respectively, were bortezomib (27.7% *vs* 41.9%), DARA (6.3% *vs* 28.8%), and carfilzomib (7.7% *vs* 12.3%). Treatment with BCMA- or GPRC5D-targeted therapy was not captured in any patient. Two pts in the D-Rd group and 2 pts in the Rd group received investigational drugs in subsequent therapy lines. Overall, 78.3% and 94.5% pts in the D-Rd and Rd groups, respectively, discontinued study treatment, primarily due to progressive disease. D-Rd continued to demonstrate a clinically significant survival benefit versus Rd in TIE pts with NDMM. Median OS with D-Rd was 7.5 years. Furthermore, subsequent antimyeloma therapy was DARA-based in 28.8% of pts treated with Rd versus 6.3% treated with D-Rd. These data continue to support the use of frontline D-Rd to maximize survival in TIE pts with NDMM.

Figure. OS with D-Rd and Rd.



OS, overall survival; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.

Figure 1.

C004

PROGNOSTIC ROLE OF STANDARDIZED (18)F-FDG-PET/CT IN RELAPSED-REFRACTORY MULTIPLE MYELOMA PATIENTS TREATED WITH ANTI-BCMA CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY

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Background. Anti-BCMA chimeric antigen receptor-T (CAR-T) cells represent a recently approved effective therapy for triple-class exposed (TCE) patients (pts) with relapsed-refractory multiple myeloma. Its use has been related to high rates of hematologic complete response and minimal residual disease negativity by bone marrow techniques; however, prognostic added value of PET/CT (both at baseline and after CAR-T infusion) has not yet been widely evaluated, as well as the use of standardized Deauville scale (DS) in this setting.

Methods. Baseline PET/CT was available in 76 pts enrolled in clinical studies with anti-BCMA CAR-T in Bologna and Pamplona; after CAR-T infusion, PET/CT was evaluated at 1 and 3 months (mos) according to DS (Zamagni et al, JCO 2021) in 68 and 60 pts respectively.

Results. Pts were treated with a median number of 3 prior lines (range:1-10); 64 (84%) were TCE, 49 (64.5%) triple-class refractory, 24 (32%) penta-exposed and 12 (16%) penta-refractory; 30 pts (44%) had high-risk cytogenetics. Median progression-free survival (PFS) in the whole cohort was 12.2 mos. 61 pts (80%) had positive basal PET/CT, a finding associated with a significantly shorter PFS (median 11.5 *vs* 27.5 mos, p=0.015); 33 pts (43%) had paraskeletal disease (PSD; non-significantly associated with PFS: median 8.1 *vs* 16.6 mos, p=0.089) and 13 (17%) had extramedullary disease (EMD; associated with significantly shorter PFS:median 4.6 *vs* 14.5 mos, p=0.013). At 1 mo after CAR-T infusion 43 pts (63%) had positive PET/CT (non-significantly associated with PFS:median 8.2 *vs* 16.6 mos,p=0.237); persistence of PSD (in 18 pts=26.5%) and EMD (in 6 pts=9%) at 1 mo was related to significantly shorter PFS (respectively median 6.9 *vs* 16 mos,p=0.012 and 2.6 *vs* 14.5 mos, p=0.011). 21 pts (35%) had positive PET/CT at 3 mos after infusion (associated with significantly shorter PFS:median 7 *vs* 17.5 mos, p=0.011); persistence of PSD (in 8 pts=13%) and EMD (in 6 pts=10%) at 3 mos was associated with significantly shorter PFS (median 3.7 *vs* 16.6 mos,p<0.001).

Conclusions. Positive baseline PET/CT and presence of EMD (not PSD) are associated with inferior outcome in pts receiving anti-BCMA CAR-T cell therapy. Positive PET/CT at 3 mos is associated with a significantly shorter PFS and could be used as an early time-point to assess metabolic response and predict unfavorable outcome. Early persistence of PSD and particularly of EMD after CAR-T infusion is associated with a dismal clinical outcome.

C005

THE RISING UNMET NEED FOR MULTIPLE MYELOMA PATIENTS AFTER FIRST-LINE TREATMENT WITH DRD: AN EPIDEMIOLOGICAL ESTIMATE IN ITALY BETWEEN 2024-2028

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In Italy, patients with newly diagnosed Multiple Myeloma (NDMM) not eligible for autologous stem cell transplantation (ASCT) recently saw a significant therapeutic advancement with the reimbursement of the combination daratumumab plus lenalidomide and dexamethasone (DRd) as first line (1L) treatment. While the introduction of this triplet in 1L improves early health outcomes, it is also expected to generate a newfound unmet medical need in second line (2L).

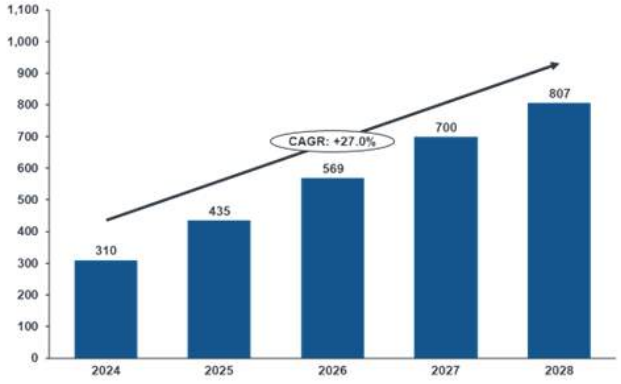

Figure 1. Modelled patients progressing to 2L therapy after receiving DRd in 1L by year. Abbreviations: 2L=Second Line; DRd=daratumumab, lenalidomide, dexamethasone; CAGR=Compound Annual Growth Rate.

This is due to the limited number of treatment options available for a population already characterized by significant frailty and a high humanistic burden, who eventually relapse and become refractory to lenalidomide and daratumumab. EHA-ESMO guidelines recommend only three treatment options for lenalidomide-refractory patients post-DRd currently available at European level: pomalidomide + bortezomib + dexamethasone (PVd), carfilzomib + dexamethasone (Kd) and selinexor + bortezomib + dexamethasone (SVd). The aim of this study is to quantify the unmet medical need in Italy created by the exhaustion of highly effective drugs as early as 1L, by estimating the number of Italian patients progressing to 2L therapy after receiving DRd in 1L over a 5-year time horizon (2024-2028). An epidemiological model was developed with a three-step process: 1) estimation of the number of 1L ASCT patients in treatment with DRd; 2) extrapolation of long-term progression-free survival curves from DRd's MAIA trial; 3) calculation of the number of patients progressing to 2L therapy. Cumulatively between 2024 and 2028, 2,820 ASCT MM patients were estimated to progress to 2L after receiving DRd in 1L. The annual increase was estimated to vary from 310 patients in 2024 to 807 patients in 2028, with a 27% compound annual growth rate (Figure 1). The reliability of the model and robustness

of the results were confirmed by deterministic sensitivity analyses, where the number of patients progressing to 2L in the forecasted period ranged from 2,409 (-14.6%) to 3,384 (+20.0%). This study highlights the increasing unmet medical need developing in the 2L MM setting due to the large number of patients relapsing after 1L therapy with DRd in Italy, for whom available treatment options are very limited thus intensifying their disease burden mainly due to their age, disease severity, cytogenetic profile and the presence of comorbidities.

Non Hodgkin lymphoma I

C006

SECONDARY PRIMARY MALIGNANCIES AFTER CD19-DIRECTED CAR-T CELL THERAPY IN LYMPHOMAS: A REPORT FROM THE ITALIAN CART-SIE STUDY

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Patients (pts) with hematological diseases have a higher risk of both solid and hematological malignancies after chemotherapy (CT), autologous transplant (ASCT) and radiotherapy (RT); secondary primary malignancies (SPMs) have been reported after CD19-directed Chimeric Antigen Receptor (CAR) T-cell therapies in up to 15% of cases. Our aim was to evaluate incidence and identify potential risk factors for occurrence of SPMs in pts enrolled in the Italian CAR-T SIE, a multicenter prospective observational study collecting data

from pts with relapsed/refractory lymphoma treated with axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel) and brexucabtagene autoleucel (brexu-cel) according to AIFA eligibility criteria. Patients with a 30-days minimum follow-up were included. From 2019 to 2023, 651 pts received 48% (312) axi-cel, 39% (253) tisa-cel and 13% (86) brexu-cel, respectively. Median follow-up was 12.2 months (IQR: 6.22-23.29). SPMs were reported in 4.3% (28) pts. Hematological malignancies were seen in 25 (3.8%) pts: 17 myelodysplastic syndromes (MDS), 4 acute myeloid leukemias (AML), 1 Hodgkin lymphoma, 1 EBV-positive lymphoma, 1 T-cell large granular leukemia and 1 T-helper follicular proliferation. Three pts had solid tumors (1 EBV-related nasopharyngeal carcinoma, 1 colorectal cancer and 1 prostate cancer). Focusing on myeloid malignancies (Table 1), median time from CAR-T infusion to diagnosis was 9 months (range 1-39.5); 9/21 pts had complex karyotype and/or TP53 mutation. Univariate analysis showed a higher risk for occurrence of MDS/AML in pts with Ann Arbor Stage III-IV (OR 8.58, p=.04), previous ASCT (OR 3.09, p=.01), high CAR-HEMATOTOX score (OR 3.39, p=.04), platelets <100.000/mmc at day 90 post infusion (OR 9.7, p<.001) and immune effector cell-associated hematotoxicity (OR 5.09, p=.006). No correlation with age, CAR-T product, N of previous lines of therapy, previous RT, development of cytokine release syndrome, immune effector cell-associated neurotoxicity or pre-existing cytopenias was demonstrated. In our large cohort of pts receiving CAR-T cells after ≥ 2 lines of therapy, frequency of SPMs was relatively low, while that of myeloid malignancies was consistent with historical reports after ASCT and/or CT. Our data suggest that late cytopenias should be carefully evaluated to exclude a secondary myeloid neoplasm in heavily pre-treated pts, although longer follow-up is needed to assess the potential causative role of CAR-T cells.

Table 1.

	OVERALL (N=651)	NO MYELOID MALIGNANCY (N=630)	MYELOID MALIGNANCY (N=21)
Age, median [Q1, Q3]	59.0 [49.0, 65.0]	59.0 [48.0, 66.0]	60.0 [52.0, 65.0]
Male sex, n (%)	416 (63.9%)	402 (63.8%)	14 (66.7%)
CAR-T product, n (%)			
Axi-cel	312 (47.9%)	301 (47.8%)	11 (52.4%)
Brexu-cel	86 (13.2%)	84 (13.3%)	2 (9.5%)
Tisa-cel	253 (38.9%)	245 (38.9%)	8 (38.1%)
Histology, n (%)			
DLBCL/HGBL	489 (75.1%)	471 (75.7%)	18 (85.7%)
MCL	84 (12.9%)	82 (13.0%)	2 (9.5%)
PMBCL	76 (11.7%)	75 (11.9%)	1 (4.8%)
Missing	2 (0.3%)	2 (0.3%)	0 (0%)
Disease status, n (%)			
Refractory	442 (67.9%)	428 (67.9%)	14 (66.7%)
Relapse	195 (30.0%)	189 (30.0%)	6 (28.6%)
Missing	14 (2.2%)	13 (2.1%)	1 (4.8%)
Ann Arbor III-IV, n (%)	456 (70.0%)	436 (69.2%)	20 (95.2%)
IPI ≥ 3, n (%)	218 (33.5%)	209 (33.2%)	9 (42.9%)
Extranodal sites, yes, n (%)	342 (52.5%)	329 (52.2%)	13 (61.9%)
Bulky disease, n (%)	224 (34.4%)	215 (34.1%)	9 (42.9%)
Bone marrow involvement, n (%)	80 (12.3%)	75 (11.9%)	5 (23.8%)
N. Previous treatment, median [Q1, Q3]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	3.00 [2.00, 4.00]
Previous ASCT, n (%)	200 (30.7%)	188 (29.8%)	12 (57.1%)
Bridging therapy, n (%)	527 (81.0%)	510 (81.0%)	17 (81.0%)
RT as bridging therapy, n (%)	139 (21.4%)	134 (21.3%)	5 (23.8%)
CAR-HEMATOTOX, n (%)			
Low	119 (18.3%)	111 (17.6%)	8 (38.1%)
High	240 (36.9%)	235 (37.3%)	5 (23.8%)
Missing	292 (44.9%)	284 (45.1%)	8 (38.1%)

C007

PATIENTS WITH RELAPSED/REFRACTORY PRIMARY MEDIASTINAL LYMPHOMA TREATED OFF LABEL WITH PEMBROLIZUMAB OR NIVOLUMAB IN COMBINATION WITH BRENTUXIMAB VEDOTIN IN A REAL-LIFE CONTEXT: ITALIAN MULTICENTER STUDY

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In recent years the use of immune-checkpoint inhibitors (ICIs) has deeply improved the outcome of relapsed or refractory (R/R) primary mediastinal lymphoma (PMBCL) patients, as demonstrated by Company-sponsored trials with ICIs alone (pembrolizumab) or in combination (nivolumab and brentuximab vedotin [BV]). However, real-life data are limited. We report here the results of the PRIMICI trial, a multicenter Italian retrospective observational trial of R/R PML patients treated with ICIs in a real-life (off-label) setting. Forty-one patients (median age 30.2 years; 70.7% female) were enrolled from Nov. 2020 through Nov. 2021 in 16 Centers (Table 1). Patients were treated with pembrolizumab (n=21) or nivolumab-BV (n=20), according to treating physician preferences. The median follow-up for this analysis was 29.8 months. The best overall response and complete response (CR) rates were 65.8% (n=27) and 58.5% (n=24), respectively. Ten out of the 24 patients in CR after ICIs received a consolidation (9 autologous stem cell transplantation [SCT]; 1 allogeneic-SCT); of note, the remaining 14 patients that did not undergo consolidation maintain a CR at the last follow-up. Responses were stable, with the curve showing a plateau and a duration of response (DoR) rate of 89.1% at 3 years, with no difference according to the use or not of consolidation. Grade ≥ 3 hematological and extra-hematological adverse events were reported in 9.7% and 29.2% of patients, respectively. Progression-free survival (PFS) at 1 and 3-years were 81.9% and 62.4%, respectively (median not reached). Overall-survival at 3 years was 89.6% (median not reached). We performed a sub-analysis according to treatment of choice. Overall, no statistically significant differences in safety and efficacy were observed, although in the nivolumab-BV *vs* pembrolizumab group numerically higher rates of CR (65% *vs* 52.4%), 3-year DoR (93.3% *vs* 84.8%) and 3-year PFS (68.6% *vs* 58.1%) were observed. In conclusion, this real-life multicenter retrospective observational study confirmed the safety and efficacy of pembrolizumab or nivolumab-BV as a salvage

therapy in R/R PMBCL patients. The numerically higher rates of CR, DoR and PFS obtained with nivolumab-BV compared to pembrolizumab require confirmation in larger studies. Importantly, the chance to obtain long-lasting responses, regardless of the use of consolidation, indicates that ICIs have a curative potential in a significant subset of patients.

Table 1. Summary of patients' characteristics and outcome.

	Total N = 41	Pembro N = 21	NivoBV N = 20	p
Male, N (%)	12 (29.2)	7 (33.3)	5 (25)	0.558
Refractory to first therapy, %	19 (46.3)	7 (33.3)	12 (60)	0.087
Refractory to last therapy before ICI, N (%)	35 (85.3)	17 (80.9)	18 (90)	0.413
Stage at ICI, N (%)				
I-II	21 (51.2)	11 (52.4)	10 (50)	0.901
III-IV	20 (48.8)	10 (47.6)	10 (50)	0.923
Extranodal involvement, N (%)	22 (53.6)	11 (52.4)	11 (55)	0.867
Bulky, N (%)	33 (80.4)	17 (80.9)	16 (80)	0.939
Previous treatments, N, median (range)	2 (1-5)	2 (2-4)	2 (1-5)	0.869
Previous ASCT, N (%)	8 (19.5)	2 (9.5)	6 (30)	0.098
Age at ICI, years, median (range)	30.2 (18.3-49.9)	29.2 (21.6-48.5)	31.2 (18.3-48.9)	0.099
Extra-hematological AE grade ≥3	12 (29.2)	5 (23.8)	7 (35)	0.431
Hematological AE grade ≥3	4 (9.8)	2 (9.5)	2 (10)	0.959
CRR, N (%)	24 (58.5)	11 (52.4)	13 (65.0)	0.585
ORR, N (%)	27 (65.8)	13 (61.9)	14 (70.0)	0.421
Consolidation after ICIs, N (%)	10 (24.4)	4 (19)	6 (30)	0.484
3-year PFS, %	62.4	58.1	68.7	0.719
3-year OS, %	89.6	90	88.8	0.999
3-year DFS, %	96	91.7	100	0.298
3-year DoR, %	89.1	84.8	93.3	0.577

ICI: immune checkpoint inhibitor; ASCT: autologous stem-cell transplantation; CRR: complete response rate; ORR: overall response rate; PFS: progression-free survival; OS: overall survival; DFS: disease-free survival; DoR: duration of response

C008

CLINICAL OUTCOME AFTER CAR-T CELL THERAPY IN RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA: A REPORT FROM THE ITALIAN CART-SIE PROSPECTIVE OBSERVATIONAL STUDY

A. Chiappella[1], B. Casadei[2], S. Bramanti[3], P. Chiusolo[4], M. Musso[5], S. Ljevar[6], A. Dodero[1], I. Cutini[7], D. Russo[8], A.M. Barbui[9], M. Martino[10], M. Massaia[11], B. Botto[12], J. Olivieri[13], M. Krampera[14], G. Grillo[15], L. Arcaini[16], F. Cavallo[17], A. Di Rocco[18], M.C. Tisi[19], P. Angelillo[20], L. Brunello[21], M. Pennisi[1], P.L. Zinzani[2,22], P. Corradini[1,23]

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Brexucabtagene autoleucel (brexu-cel) is a CD19-targeted chimeric antigen receptor (CAR) T-cell, approved for relapsed/refractory mantle cell lymphoma (R/R MCL) after failure of chemoimmunotherapy and bruton-kinase inhibitors (iBTK). The CART-SIE is an ongoing multicenter observational study collecting data on all consecutive lymphoma patients treated with commercial CAR T-cells in Italy. Since 2019, 865 were enrolled, including 89 MCLs infused. Aim of this analysis was to evaluate disease response and survival outcomes of patients treated with brexu-cel. Clinical characteristics were: median age 63 years (IQR: 55,69), 88% Ann Arbor stage III or IV; median number of prior lines of therapy was 3 (IQR: 2,3), with 51% refractory to last treatment; 57% failed a prior autologous stem cell transplantation, 100% exposed to previous iBTK. Histological subtypes were 71% classic MCL, 17% blastoid and 12% pleomorphic variant. Bridging therapy was performed in 82% of the patients: 50% chemoimmunotherapy, namely bendamustine and citarabine based (RBAC) or bortezomib and anthracycline based (VR-CAP), 10% lenalidomide, 7% radiotherapy, 33% continued iBTK, in 5 cases in combination with venetoclax. Overall response rate (ORR) to bridging was 26%, with 7% of CRs. All received lymphodepletion prior brexu-cel. Any grade cytokine release syndrome (CRS) was reported in 94% of the patients, with 22% severe (grade 3-4) CRS; any grade immune effector cell-associated neurotoxicity syndrome (ICANS) was observed in 47% of the patients, with 21% severe ICANS; tocilizumab and steroids were administered in 82% and 52%, respectively; 20% were admitted in intensive care unit. At day 30 and 90 after infusion, ORR was 73% and day 90 ORR was 72%; CR rate at day 30 was 58% and 63% at day 90. At a median follow-up of 9 months (IQR: 5.10,12.47), 1-year progression free survival (PFS) was 58% (CI: 46-73), with an extimated 2-year PFS of 33% (CI: 15-7); 1-year overall survival was 83% (CI: 74-93). Non-relapse mortality was 8% (one grade 5 CRS, one grade 5 ICANS, 2 multiorgan failure, one gram negative septic shock, one respiratory failures and one unknown). One-year PFS was better in classic MCL (63%, CI: 49-81) compared to blastoid (26%, CI: 6-100) or pleomorphic variant (58%, CI: 33-100), p 0.036. In conclusion, the response rate of R/R MCL treated with brexu-cel in a real-life setting is similar to registration studies, but PFS shows a continuous pattern of relapses without a plateau.

C009

ABSTRACT NOT PUBLISHABLE

C010

ABSTRACT NOT PUBLISHABLE

Acute leukemia I

C011

PRELIMINARY RESULTS OF MYNERVA-GIMEMA AML1919 AMELIORATE TRIAL: FEASIBILITY OF EARLY INTENSIFICATION IN FLT3-MUTATED ACUTE MYELOID LEUKEMIA BASED ON PERIPHERAL BLAST CLEARANCE

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Background. AMELIORATE is a phase 3, randomized, trial aiming to personalization of treatment in FLT3-mutated (mut) AML (EudraCT number 2019-003936-21). The study provides an early appraisal of chemosensitivity based on peripheral blast clearance (PBC) by multi-parameter flow cytometry, from baseline to day 4 of induction. For pts with low PBC (*i.e.* ≤2.0 logs), two adjustments as compared to standard are envisioned in the experimental arm: the immediate switch to intensified induction with high doses cytarabine (HDAC) and the early allocation to high-risk category, further refined later based on post-induction measurable residual disease (MRD).

Aims. The primary aim of the trial is to improve the outcome of FLT3-mut AML. The aim of this preliminary analysis is to verify the feasibility of the PBC-driven approach.

Results. Between April 2020 and March 2024, 28 study sites adhered to the trial; 120 FLT3-mut pts were enrolled. Individual leukemia-associated immuno-phenotypes (LAIPs) identified pretherapy were validated centrally as a pre-requisite for study entry. 16 eligible patients were excluded from PBC study due to lack of suitable LAIP (n=4, 3%), or LAIP+ cell count <100/μL at day 1 (n=12, 10%). A total 99 pts (83%) were assessable for PBC study (Table 1), 83 (84%) with ITD, 18 (19%) with TKD mutation type. Median absolute LAIP count decreased from 4854/μL on day 1 to 36/μL on day 4, resulting in a median PBC of 2.04 log (range 1.38-2.56). By the 2.0 log cut-off, 50 (51%) pts were in a high PBC range (PBChi) and thus proceeded in the standard arm; 49 (49%) were in a low PBC range (≤2.0 log, PBClow) and were randomized between continuing standard induction (n=23, 47%) and switching to HDAC (n=26, 53%). Overall, after induction course, data about 72 pts is available; 61 (85%) pts achieved complete remission, 3 (4%) partial remission, 1 (1%) experienced an early death, and 7 (10%) were non responder.

Median PBC rates in favorable (1.98), intermediate (2.18) and adverse (1.81) ELN 2017 categories did not differ significantly (P=0.2). No relevant safety signals were recorded from the comparison of the two randomization arms in terms of incidence of grade 3-4 adverse events or 30-day mortality.

Conclusions. The AML1919 trial preliminary data demonstrate the feasibility of a real-time assessment of PBC in a prospective and multi-center setting. The early intensification of induction in the experimental arm proved to be safe without any unexpected clinical alert.

Table 1.

Characteristic	N = 99
Age, Median (IQR)	51 (43, 58)
Sex, n (%)	
Male	46 (46%)
Female	53 (54%)
ECOG, n (%)	
0	58 (60%)
1	36 (37%)
2	3 (3.1%)
3	0 (0%)
4	0 (0%)
Unknown	2
Hemoglobin, Median (IQR)	8.80 (8.20, 9.80)
Platelets , Median (IQR)	54 (29, 89)
FLT3-ITD, n (%)	
Negative	16 (16%)
Positive	83 (84%)
FLT3-TKD, n (%)	
Negative	77 (81%)
Positive	18 (19%)
Unknown	4
NPM1, n (%)	
WT	27 (28%)
Positive	71 (72%)
Unknown	1
Risk Category , n (%)	
Favorable	19 (21%)
Intermediate:	54 (60%)
Adverse:	17 (19%)
Unknown	9

C012

EVIDENCE FROM A LARGE REAL-WORLD ITALIAN STUDY ON OPTIMAL DURATION OF CPX-351 TREATMENT AND BEST TIMING FOR CONSOLIDATION WITH ALLOGENEIC STEM CELL TRANSPLANTATION

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CPX-351 has been demonstrated to be superior to conventional 3+7 intensive chemotherapy in patients diagnosed with secondary Acute Myeloid Leukemia (AML) evolving from a previous myelodysplastic syndrome (MRC-AML) or secondary to chemotherapy (t-AML). However, the optimal duration of treatment with CPX-351 and the efficacy among rare s-AML subgroups is still unknown. The aim of this study is to analyze the outcome of CPX-351 treatment in a large cohort of 517 s-AML patient (median age 65.6 years, range 19-79) in order to answer those questions. All patients were allowed to receive up to 2 induction cycles and up to 2 consolidation. Allogeneic stem cell transplantation (HSCT) consolidation was allowed at any time. 108 (21.1%) had t-AML and 405 (78.9%) had MRC-AML. NPM1 and FLT3-ITD mutations were found in 31 (6%) and 24 patients (4.6%), respectively. ELN 2017 score was favorable, intermediate or high in 27 (5.2%), 177 (34.5%) and 309 (60.3%) patients, respectively. Most patients had relevant comorbidities (84%), mainly cardiovascular disease (43%), type II diabetes (39%). 297/513 patients (58%) achieved a complete remission (CR) after cycle 1. CR rate was significantly higher among NPM1 mutated patients ($p<0.05$) and among ELN 2017 favorable risk ($p<0.05$), whereas was not affected by FLT3-ITD mutations. Among responding patients, 118 (34.7%), 137 (40.3%) and 85 (25%) received a total of 1, 2 or 3 CPX-351 courses, respectively. HSCT consolidation was performed in 166/340 responding patients (48.8%). 30 and 60-days mortality were 5.2 and 8.2%, respectively. After a median follow-up of 23.66 months (CI 95% 23.11-26.01), median OS was 16.23

months (CI 95% 13.6-18.9). OS was significantly influenced only by NPM1 mutational status (p<0.05) and ELN 2017 risk score (p<0.05). In a landmark analysis including patients alive and in CR at day 90, HSCT was the strongest predictor of longer survival (p<0.05). In the same model, completion of all allowed CPX-351 treatment was beneficial only in patients not proceeding to HSCT (Figure1A, p<0.05), whereas in patients receiving HSCT consolidation further CPX-351 treatment after cycle 1 did not improve results (Figure 1B, p=n.s.). Our large cohort confirms the efficacy of CPX-351 also in s-AML with NPM1 mutated patients or ELN 2017 favorable risk patients. In eligible patients, HSCT should probably be performed as soon as possible, whereas patients not proceeding to HSCT benefit from completing all available CPX-351 treatment.

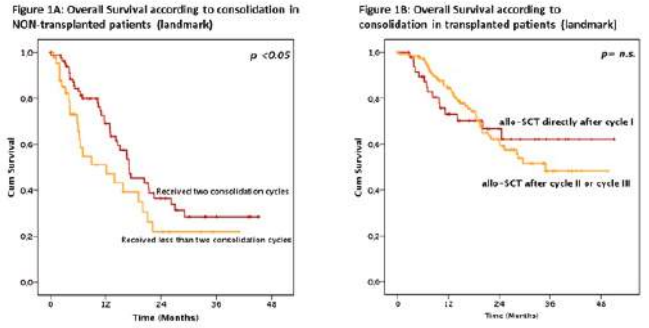

Figure 1.

C013

COMPARING OUTCOMES BETWEEN CPX-351 AND FLUDARABINE-BASED INDUCTION IN SECONDARY ACUTE MYELOID LEUKEMIA: THE PROGNOSTIC RELEVANCE OF MRD

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If treated with conventional 3+7 chemotherapy, patients with secondary Acute Myeloid Leukemia (s-AML) have a poor outcome. Allogeneic hematopoietic stem cell transplantation (HSCT) represents the sole curative option for s-AML, but is effective only if performed in Complete Remission (CR), that is unlikely to achieve with 3+7. Fludarabine combinations (FLAG-IDA) have shown some superiority, but at the price of significant toxicity in older patients. CPX-351 recently showed better results in s-AML, compared to 3+7. In the UK NCRI AML19 trial CPX-351 and FLAG-IDA had similar results in high-risk AML, but subgroup analysis revealed better Overall Survival (OS) with CPX-351 in patients with MDS-related gene mutations. However minimal residual disease (MRD) clearance was not fully evaluated in CPX-351 treated patients and thus remains largely unexplored. The aim of this study was to analyze the CR rate, the rate of multicolor flow cytometry (MFC) MRD negativity and OS a in a cohort of 138 s-AML patients undergoing induction therapy with either CPX-351 (n=82) or a FLAG-IDA age-adjusted regimen (FLAI3, n=101). Median age was 69 years (range 60-77), all patients had s-AML, as defined by WHO 2016 classification. After cycle 1, CR was achieved in 119 patients (65%). CR rate was 64/82 (78%) in patients treated with CPX-351, significantly higher if compared to patients receiving FLAI (55/101, 54.5%, p<0.05). Among CR patients, a total of 65 (54.6%) achieved MFC MRD negativity. MFC MRD negativity probability was higher among patients receiving CPX-351 (MFC MRD negativity rate of 40/64, 62.5% and 25/55, 45% in CR patients receiving CPX-351 or FLAI, respectively, p<0.05 Figure 1). CPX-treated patients had longer OS (p<0.05). Consolidation with allogeneic stem cell transplantation (HSCT) was correlated with higher OS. Notably, 21/64 (32.8%) CR patients treated with CPX 351 underwent HSCT. In multivariate analysis, MRD was the strongest prognostic value for OS in all treatment group (2-year OS of 35% and 79% in patients with or without residual MFC MRD after induction, respectively, p<0.05. The better results observed with CPX-351, that were consistent with the English trial, were explained by a greater anti-leukemic activity, with higher probability of MRD negativity. The likelihood of achieving a good quality CR with CPX-351, alongside with a reduced extra-hematology toxicity, as was recently demonstrated by Renga *et al*. (Blood 2024), enables more patients to undergo HSCT.

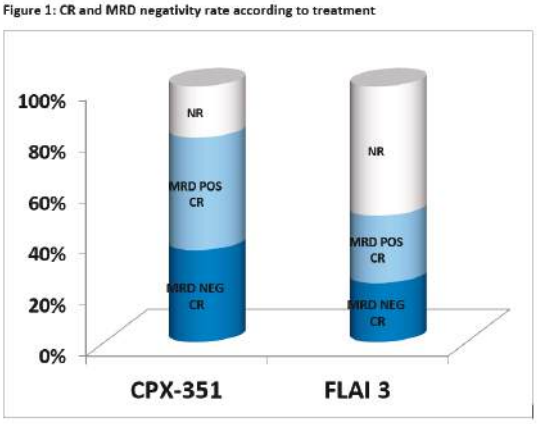

Figure 1.

C014

MUTATIONS IN HIGH RISK GENES DO NOT AFFECT REMISSION RATES AND MRD CLEARANCE IN ELDERLY AML PATIENTS RECEIVING CPX-351 INDUCTION

C. Riva[1], C. Vernarecci[1], M. Chies[1], P. Minetto[2], E. Carminati[1], C. Nurra[1], F. Puglisi[1], S. Rossellini[3], N. Colombo[3], R. Mangerini[3], E. Tedone[3], M. Miglino[1,2], M. Cea[1,2], R.M. Lemoli[1,2], F. Guolo[1,2]

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Mutations in genes such as TP53, ASXL1, SRSF2, RUNX1 have negative prognostic value in acute myeloid leukemia (AML) patients (pts) treated with conventional chemotherapy (3+7). Mutations in TP53, RUNX1, FLT3-ITD, N/KRAS, CBL, and KIT are associated with poor response to hypomethylating agents plus Venetoclax (HMA+VEN). CPX-351 has recently been introduced for the treatment of secondary AML (s-AML), but the prognostic relevance of high-risk mutations in CPX-351-treated pts remains still unexplored. We aimed to explore the prognostic value of specific mutations and mutational burden in a cohort of 80 elderly pts (median age 70, range 60-81) with s-AML treated with CPX-351. NGS analysis encompassing 34 critical gene mutations was conducted (Myeloid Solution panel, SOPHiA Genetics, Illumina MiSeq platform, analyzed with

SOPHiA DDM®). Minimal Residual Disease (MRD) analysis was performed by multicolor flow cytometry. Most frequent mutations involved TET2 (41%), RUNX1 (39%), ASXL1 (29%), DNMT3A (29%), SRSF2 (29%), CBL (27%), TP53 (26%). Median number of mutations per patient (mutational burden) by NGS was 5 (range 2-10); 42 patients had high mutational burden (≥ 4 mutations). Fifty pts (62.5%) and 61 (76%) displayed molecular features related to resistance to VEN or 3+7, respectively. After cycle 1, 64 pts (80%) achieved complete remission (CR) with MFC-MRD negativity in 43/64 responding patients (67%). Four pts died before response assessment. CR probability and MRD negativity rate were not affected by any of the high-risk mutations or by high mutational burden in uni- and multi-variate analysis. After a median follow up of 39.3 months, median OS was 18 months. OS was not affected by any high-risk mutation, high mutational burden, or by the presence of HMA-VEN or 3+7 resistance profile (Median OS 13 *vs* 14 months in patients without resistance profile, p=n.s., Figure 1A). Multivariate OS analysis showed that negative MRD was the strongest independent prognostic factor (p<0.05). In landmark analysis, pts achieving CR and proceeding to allogeneic stem cell transplantation (HSCT) (n=23) within 3 months from CR (N=8) had a significantly better outcome compared to those who did not receive HSCT (n=41) or proceeded later (n=15), <0.03, Figure1B). Our analysis shows that CPX-351 is able to induce MRD negative CR regardless of the presence of high risk mutations or high mutational burden. Early HSCT consolidation is the strongest factor for long term survival.

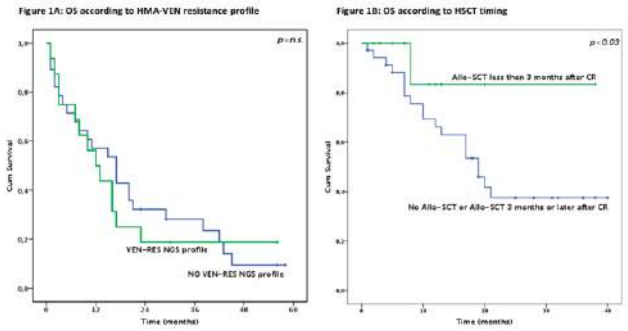

Figure 1.

C015

RETROSPECTIVE COMPARISON OF INTENSIVE CHEMOTHERAPY VERSUS AZACITIDINE PLUS VENETOCLAX IN NPM1-MUTATED ACUTE MYELOID LEUKEMIA PATIENTS AGED ≥ 65 YEARS

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Background. *NPM1*-mutated (*NPM1*m) AML is a recognized WHO2022 AML entity and represents a favorable/intermediate risk AML known to be chemo-sensitive. However, *NPM1*m AML in the elderly/unfit patient is also known to be exquisitely sensitive to bcl2 inhibitor venetoclax (VEN), in association with hypomethylation agents (HMA). Therefore, in the grey patient zone ≥65 years, it is debated whether a non-intensive approach may be superior to chemotherapy.

Aims. To compare a population of *NPM1*m AML patients aged ≥ 65 years treated with intensive chemotherapy (IC) and non-intensive VEN-based approach.

Methods. The study cohort included the molecularly defined AML category of *NPM1*m patients. IC treatment was defined as at least one anthracycline dose in association with intermediate/high-dose cytarabine. Non-intensive cohort received VEN in association with azacitidine or decitabine. Complete remission (CR) was defined as blast cells (BC)<5%; measurable residual disease (MRD) was evaluated either with *WT1* or with *NPM1*m transcript (MRDneg NPM1m/ABL x 100<0.01%).

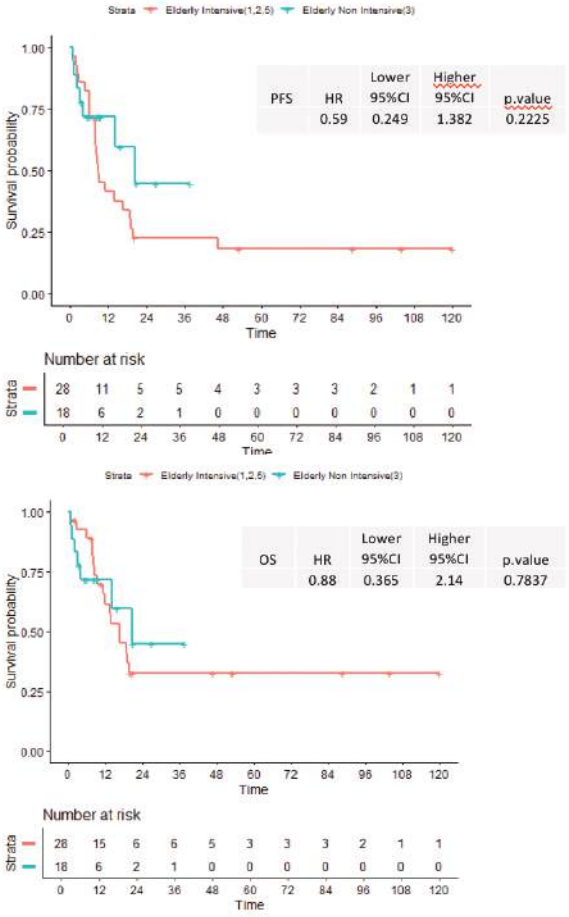

Figure 1. Progression Free Survival (PFS) and Overall Survival (OS). Blu: patients treated with azacitidine and venetoclax; Red: Patients treated with intensive chemotherapy.

Results. From 2014 to 2024, 46 *NPM1*m patients were included in the analysis: 28 patients received IC and 18, elderly/unfit for chemotherapy patients, received VEN-HMA. Patient and disease characteristics were balanced between the 2 cohorts, except median age of 68.0 years (IQR 66.6-70.5) in IC cohort *vs* 72.3 years (69.2-76.4) in VEN-HMA, p .002 (Figure 1). Concerning ELN2022 risk, in IC cohort 1 (3.6%) patient was adverse risk as compared to 2 (11.1%) in AZA-HMA cohort, intermediate risk patients were 9 (32.1%) and 5 (27.8%) respectively. Early death was comparable between the 2 groups, 7.1% in IC group and 11.1% in HMA-VEN, p .37. Response rates were also comparable with a CR rate of 67.9% in IC *vs* 72.2% in HMA-VEN cohort (p 1.0) and a MRDneg rate of 42.9% *vs* 33.3% (p .74). Allogeneic stem cell transplantation (alloSCT) was performed in 5 (17.9%) patients in IC group and 2 (11.1%) in HMA-VEN group. With a median follow-up 27 months (IQR 10.7-53.2), median PFS in IC cohort is 8.7 mo (95%CI 7.7-19)

as compared to 20.4 mo (95%CI 14-NE) in AZA-VEN cohort, p .22, and median OS is 16.5 mo (95%CI 11.3-NE) and 20.7 mo (95%CI 14.1-NE) respectively, p .0.78.

Conclusions. Data from this small retrospective cohort of *NPM1*m AML patients shows no difference in terms of response and survival outcomes between an IC approach as compared to AZA-VEN. This observation requires to be addressed in clinical trials.

Table 1.

Variables		Intensive chemotherapy	VEN-HMA	p
n		28	18	
Age, median [IQR]		67.97 [66.60, 70.53]	72.29 [69.20, 76.35]	0.002
Sex F, n (%)		15 (53.6)	6 (33.3)	0.298
AML type, n (%)	de novo	23 (82.1)	18 (100.0)	0.157
	secondary	5 (17.9)	0 (0.0)	
WBC (median [IQR])		45.78 [26.00, 96.40]	69.09 [48.50, 97.72]	0.257
Hb (median [IQR])		9.20 [7.30, 11.10]	9.20 [7.65, 10.10]	0.834
Plt (median [IQR])		70.00 [39.00, 95.00]	69.50 [34.25, 112.75]	0.777
BM_blast_percentage (median [IQR])		90.00 [82.50, 95.00]	90.00 [70.00, 90.00]	0.584
Karyotype, n° (%)	complex	0 (0.0)	2 (11.1)	0.269
	monosomal	1 (3.6)	0 (0.0)	
	normal	23 (82.1)	13 (72.2)	
	others	4 (14.3)	3 (16.7)	
NPM1m quantitavive, % (median [IQR])		266.50 [151.10, 301.52]	126.06 [89.24, 218.20]	0.160
FLT3 mutational status	mutated	13 (46.4)	7 (38.9)	0.842
FLT3 mutation type, n(%)	ITD	10 (76.9)	3 (42.9)	0.101
	ITD+TKD	0 (0.0)	2 (28.6)	
	TKD	3 (23.1)	2 (28.6)	
DNMT3A mutational status, n (%)	mutated	7 (63.6)	11 (64.7)	1.000
	unmutated	4 (36.4)	6 (35.3)	1.000
IDH1 mutational status, n (%)	mutated	9 (75.0)	17 (94.4)	0.324
	unmutated	3 (25.0)	1 (5.6)	
IDH2 mutational status, n (%)	no	9 (81.8)	13 (72.2)	0.890
	yes	2 (18.2)	5 (27.8)	
Mutations in epigenetic modifiers, n (%)	no	1 (16.7)	8 (47.1)	0.409
	yes	5 (83.3)	9 (52.9)	
Mutations in Ras pathway, n (%)	no	4 (80.0)	8 (47.1)	0.430
	yes	1 (20.0)	9 (52.9)	
Splicing mutations, n (%)	no	4 (80.0)	12 (70.6)	1.000
	yes	1 (20.0)	5 (29.4)	
Secondary AML mutationally defined, n (%)	No	4 (80.0)	11 (64.7)	0.921
	Yes	1 (20.0)	6 (35.3)	
ELN2022 risk category, n (%)	adverse	1 (3.6)	2 (11.1)	0.594
	favorable	18 (64.3)	11 (61.1)	
	intermediate	9 (32.1)	5 (27.8)	
Extramedullary disease (%)	yes	6 (21.4)	3 (16.7)	0.987

Anemias and myelodysplastic syndromes

C016

EXAGAMGLOGENE AUTOTEMCEL FOR SEVERE SICKLE CELL DISEASE

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Background. Exagamglogene autotemcel (exa-cel) is a non-viral cell therapy that reactivates fetal hemoglobin via ex vivo CRISPR-Cas9 gene-editing of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs).

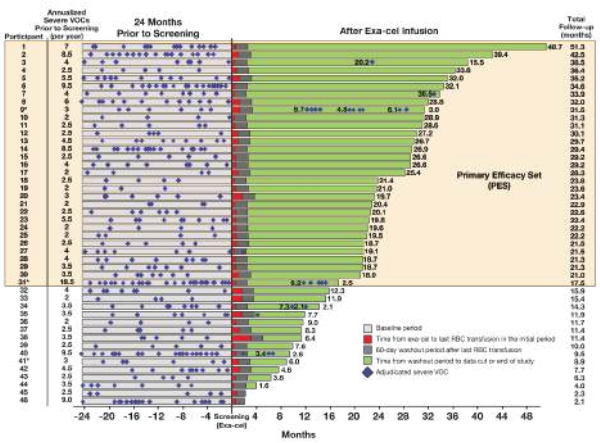
Methods. CLIMB SCD-121 is a 24-month (mo), phase 3 trial of exa-cel in pts age 12-35y with SCD and a history of ≥2 VOCs/y in 2y prior to screening. Primary efficacy endpoint is proportion of pts free of severe VOCs for ≥12 consecutive mos (VF12); key secondary efficacy endpoint is proportion of pts free from inpatient hospitalization for severe VOCs for ≥12 consecutive mos (HF12). Pts evaluable for VF12 and HF12 had ≥16 mos follow-up after exa-cel infusion; evaluation began 60 days after last RBC transfusion for post-transplant support or SCD management.

Results. As of 18 Sept 2023, 46 pts with SCD (age 21.4 [range 12-34]y; 12 [26.1%] age ≥12 to <18y; 4.2 VOCs/y at baseline) received exa-cel; median follow-up 22.3 (range 2.1-51.3) mos. All pts engrafted neutrophils and platelets (median 27 and 34.5 days, respectively). 29/31 (93.5%) pts evaluable were free of VOCs for ≥12 consecutive mos (VF12; 95% CI, 79%-99%; P<0.0001; VOC free duration 25.4 [range 18.0-48.7] mos) and 31/31 (100%) were free from hospitalizations for VOCs for ≥12 consecutive mos (HF12; 95% CI, 89%-100%; P<0.0001) (Figure 1). For all pts, mean total Hb was 11.9 g/dL at Month 3 (≥11.0 g/dL Month 6 onward) and HbF was 37.1% (generally ≥ 40.0% Month 6 onward) with pancellular distribution. Proportion of edited BCL11A alleles was stable in bone marrow CD34+ and peripheral blood nucleated cells. 39/46 pts with ≥60 days follow-up after last RBC transfusion remained VOC free (up to 48.7 mos). Quality-of-life (QOL) measures significantly improved. All pts had adverse events (AEs), most Grade 1 or 2; 46

(100%) pts had AEs of Grade 3 or 4 severity. Most common AEs were nausea (67.4%), stomatitis (63.0%), and vomiting (56.5%). No pts had SAEs considered related to exa-cel. One pt died from respiratory failure due to COVID-19 pneumonia unrelated to exa-cel. There were no discontinuations or malignancies.

Conclusions. Exa-cel treatment led to early and sustained Hb and HbF increases, eliminating VOCs in ~94% of pts and inpatient hospitalization for VOCs in 100% of pts, and improving QOL. Safety profile remains generally consistent with myeloablative busulfan conditioning and autologous transplantation. Results confirm potential for exa-cel to provide a one-time functional cure for severe SCD.

A.



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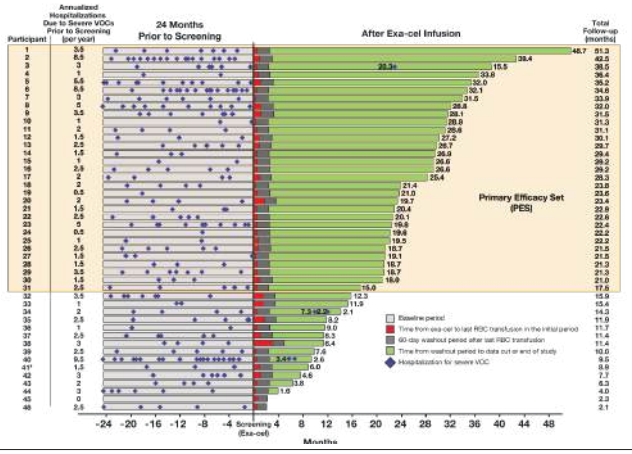

Figure 1. Duration of Period Free From Vaso-Occlusive Crises (A) and Hospitalizations for Vaso-Occlusive Crises (B) (Study CLIMB SCD-121 and Study 131) After Exa-cel Infusion. All VOCs were adjudicated by the Independent Endpoint Adjudication Committee. Participants evaluable for the primary endpoint (VF12) and first key secondary endpoint (HF12) shows in tan box (primary efficacy set). *Participants who did not achieve VF12; #Death from respiratory failure due to COVID-19 infection.

C017

OPTIMIZING ALLOGENIC STEM CELL TRANSPLANTATION FEASIBILITY AFTER ALTERNATIVE BRIDGE THERAPIES IN HIGHER-RISK MYELODYSPLASTIC SYNDROMES: FIRST RESULTS OF THE GIMEMA MD0519 (ACROBAT) TRIAL

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Allogeneic stem cell transplantations (HSCT) remains the only curative option for higher risk myelodysplastic syndromes (MDS). However, the question of the best bridge to transplant remains unsolved, with most recent recommendations leaving open the alternatives of upfront transplant, versus hypomethylating treatment with azacitidine (AZA), or intensive chemotherapy. In this context, we designed the ACROBAT multicenter trial, for transplant eligible patients, aged 18-70 years with intermediate to very-high IPSS-R, de novo or therapy-related MDS. The primary endpoint of this trial is feasibility of HSCT, while complete remission (CR) rate, overall and event-free survival, HCT-CI at enrolment and at HSCT, and quality of life are among secondary endpoints. Regarding the bridge to HSCT therapy, patients with bone marrow (BM) blasts <9% are randomized between transplant upfront and a minimum of 4 AZA cycles. Patients with 10-19% BM-blasts are randomized between conventional chemotherapy (3+7) + one consolidation cycle, versus at least 4 AZA cycles. The study is sponsored by the GIMEMA F. Mandelli foundation and supported by an Investigational grant from AIFA (TRS-2018-00001587). To date, 118 patients have been enrolled from 29 Italian hematology centers, at a median time of 8.1 months from initial MDS diagnosis (range 0.5-39.7). The present analysis includes 107 patients, 59% males and 41% females, of a median age of 62 years (range 27-71). According to IPSS-R, 28% pts had intermediate risk, 42% high and 28% very-high risk MDS. BM blasts were <9% in 57 patients (53%): 30 (53%) started AZA and 27 (47%) were randomized to upfront HSCT, while 50 patients had 10-19% blasts: 25 (50%) received AZA bridge, while 25 (50%) received conventional CHT, including consolidation in 10 cases (Table 1). HSCT was performed in 41 (38%) patients, 20 in the <9% and 21 in

the 10-19% BM-blast groups. Median follow-up for the whole patient groups is 6.1 (0.1-56.9) months, and survival is 70.9 % (57.5-87.3) at 12 months. The preliminary analysis of the ACROBAT trial shows feasibility of HSCT in HR-MDS, independent of the bridge therapy to transplant. Longer follow-up is needed to highlight clinical and molecular prognostic factors predictive for improved survival.

Table 1.

Protocol ARM	Treatment	Patients (n)	CR (%)*	HSCT performed (n)
BM-blasts ≤9%	HSCT upfront	27	0% (0/5)**	10
	AZA	30	43% (6/14)	10
BM-blast 10-19%	3+7	25	57% (9/16)	11
	AZA	25	43% (3/7)	10

* % of evaluable patients
** evaluation before Transplant

C018

FINAL 48-WEEK RESULTS FROM MULTICENTER, PHASE III APPLY-PNH TRIAL-SUSTAINED LONG-TERM EFFICACY AND SAFETY OF FACTOR B INIHIBITOR ORAL IPTACOPAN MONOTHERAPY IN ANTI-C5-TREATED PATIENTS (PTS) WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA AND PERSISTENT ANEMIA

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In the phase 3 APPLY-PNH trial, iptacopan monotherapy was superior *vs* anti-C5 therapy at Week (Wk) 24. We report 24 wks extension period data where all pts received iptacopan monotherapy. Adult PNH pts (mean Hb <10 g/dL, receiving anti-C5 therapy for ≥6 months) were randomized to receive either iptacopan 200 mg twice daily or continue anti-C5 for 24 wks. During extension period, iptacopan arm continued to receive iptacopan for another 24 wks and anti-C5 arm switched to iptacopan monotherapy. In the extension period, 95 pts received iptacopan: 61/62 in iptacopan arm and 34/35 in anti-C5-to-iptacopan arm. Iptacopan showed sustained improvements at 48 wks, with maintenance of increased Hb, normal/near-normal mean Hb levels, improved Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) scores, decreased absolute reticulocyte counts (ARCs) and transfusion avoidance (Table 1).

Table 1.

Table. Summary of efficacy parameters after the entire 48-week treatment period of APPLY-PNH, including comparison of data at Week 48 vs Week 24

Parameter	Arm		
	Iptacopan N=62[a] Anti-C5 to iptacopan N=35[b]	*Adjusted mean change from baseline (95% CI) at Week 48*	*Adjusted mean difference in change from baseline (95% CI): Week 48 vs Week 24*
Change from baseline[c] in Hb level (g/dL)[d]	Iptacopan	**+3.35** (3.03, 3.66)	**−0.41** (−0.80, −0.01)
	Anti-C5 to iptacopan	**+3.36** (2.93, 3.79)	**+3.02** (2.48, 3.56)
Change from baseline[e] in FACIT-F score	Iptacopan	**+9.80** (8.04, 11.56)	**+0.73** (−1.14, 2.60)
	Anti-C5 to iptacopan	**+10.96** (8.58, 13.34)	**+10.79** (8.12, 13.47)
Change from baseline[f] in ARC (10^9/L)	Iptacopan	**−106.26** (−117.57, −94.96)	**+9.92** (−4.40, 24.25)
	Anti-C5 to iptacopan	**−107.95** (−123.18, −92.73)	**−102.29** (−121.57, −83.02)
		Geometric adjusted mean ratio to baseline (95% CI) at Week 48	*Geometric adjusted mean ratio (95% CI): Week 48 vs Week 24*
Ratio to baseline[g] in log-transformed LDH (U/L)	Iptacopan	**1.11** (1.02, 1.22)	**1.12** (1.00, 1.25)
	Anti-C5 to iptacopan	**0.99** (0.88, 1.11)	**0.99** (0.85, 1.15)
		Time period	*Pts not requiring an RBC transfusion since 2 weeks after initiation of iptacopan monotherapy (n [%])*
Transfusion avoidance[h]	Iptacopan	Week 2 to Week 48	**58 (93.5)**
	Anti-C5 to iptacopan	Week 26 to Week 48 (iptacopan)	32 (**94.1**)[i]
		Time period	*n/N[j]*	*Overall adjusted annualized rate of events since initiation of iptacopan monotherapy, including both treatment arms (95% CI)*
Rate of clinical BTH[k]	Iptacopan	Baseline to Week 48	6/62	**0.11** (0.05,0.23)
	Anti-C5 to iptacopan	Week 24 to Week 48 (iptacopan)	1/34	
Rate of MAVEs[l]	Iptacopan	Baseline to Week 48	2/62	**0.04** (0.01, 0.13)
	Anti-C5 to iptacopan	Week 24 to Week 48 (iptacopan)	1/34	

[a]1 pt discontinued due to pregnancy during randomized period. [b]1 pt did not enter the extension period [investigator's decision]. [c]Mean (SD) baseline Hb levels were 8.93 (0.70) and 8.85 (0.90) g/dL in the iptacopan and anti -C5-to-iptacopan arms, respectively. [d]Analysis includes all central lab HB data, including post- transfusion data. [e]Mean (SD) baseline FACIT-F scores were 34.7 (9.8) and 30.8 (11.5) in the iptacopan and anti-C5-to-iptacopan arms, respectively. [f]Mean (SD) baseline ARCs were 193.2 (83.6) and 190.6 (80.9) × 10^9/L in the iptacopan and anti-C5-to-iptacopan arms, respectively. [g]Mean (SD) baseline LDH levels were 269.1 (70.1) and 272.7 (84.8) U/L in the iptacopan and anti-C5-to-iptacopan arms, respectively. [h]Defined as neither receiving to nor meeting the criteria to receive an RBC transfusion. [i]34 of 35 pts in the anti-C5-to-iptacopan arm received iptacopan in the extension period. [j]n=number of pts with event, N=number of pts treated with iptacopan. [k]Events that met the protocol-specified criteria for clinical BTH; [l]Randomized period: 1 serious TIA; extension period: 1 non-serious TIA, 1 serious PVT. The pt with PVT had a history of PVT and discontinued heparin prior to the MAVE.
ARC, absolute reticulocyte count; BTH, breakthrough hemolysis; CI, confidence interval; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; Hb, hemoglobin, LDH, lactate dehydrogenase; MAVE, major adverse vascular event; pt, patient; PVT, portal vein thrombosis; RBC, red blood cell; SD, standard deviation; TIA, transient ischemic attack.

Anti-C5 arm pts who switched to iptacopan had rapid changes in Hb, FACIT-F and ARC, achieving comparable improvements to the iptacopan arm. At 48 wks, both arms, continuous and switched, had mean Hb levels of 12.2 and 12.1 g/dL, respectively. Transfusion avoidance was achieved by 93.5% of pts in the iptacopan arm (Wks 2 to 48) and 94.1% in the anti-C5-to-iptacopan arm (Wks 26 to 48). Mean lactate dehydrogenase levels were generally maintained <1.5 × upper limit of normal in both arms. Breakthrough hemolysis (BTH) was observed in 6/62 pts with continuous iptacopan while 1 pt had BTH after switching which resolved without dose alteration. 3 pts had major adverse vascular events unrelated to iptacopan that resolved without dose changes and were not associated with hemolytic events. Most frequently reported treatment-emergent adverse events (TEAEs) in the iptacopan arm after 48 wks were COVID-19 (29.0% of pts), headache (19.4%), diarrhea (16.1%) and nasopharyngitis (14.5%). There were no deaths, no serious hemolysis TEAEs on iptacopan, no serious infections caused by *N. meningitidis, S. pneumoniae* or *H. influenzae* and no treatment discontinuation due to TEAEs. Iptacopan monotherapy showed sustained improvements in multiple hematological and clinical outcomes over 48 wks which were also seen in anti-C5-to-iptacopan arm, supporting the benefit of switching to iptacopan. The data indicate good control of hemolysis by iptaco-

pan and a similar safety profile at Wk 48 *vs* Wk 24. The findings support oral iptacopan monotherapy as a potential practice-changing treatment for hemolytic PNH.

C019

ORAL IPTACOPAN MONOTHERAPY MAINTAINS EFFICACY AND SAFETY OVER 48 WEEKS IN COMPLEMENT INHIBITOR–NAÏVE PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) IN THE PHASE III APPOINT-PNH TRIAL

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We report 48-week efficacy, safety, and tolerability data from the single-arm, open-label, multicenter, Phase 3 APPOINT-PNH trial (NCT04820530) evaluating iptacopan (first-in-class, oral factor B inhibitor) in complement inhibitor–naïve patients with hemolytic PNH. Forty adults with mean hemoglobin (Hb) <10 g/dL and lactate dehydrogenase (LDH) >1.5 × upper limit of normal (ULN) received iptacopan monotherapy 200 mg twice daily for 48 weeks. At Week 48, 97.4% of patients achieved a Hb increase from baseline of ≥2 g/dL, maintained from Week 24 (94.9%; Table 1). Hb levels ≥12 g/dL were found in 79.5% of patients at Week 48, higher than that at Week 24 (66.7%). The mean Hb level was 13.24 (SD 1.80) g/dL at Week 48 (mean baseline change: +5.09 [SD 2.01] g/dL) and 12.56 (SD 1.49) g/dL at Week 24 (+4.41 [SD 1.40] g/dL). One patient required transfusions, and 97.5% of patients were transfusion-free (95% CI 92.5–100) between Weeks 2 and 48. Mean baseline change in Functional Assessment of Chronic Illness Therapy-Fatigue score was +10.4 (SD 10.14) at Week 48 and +12.1 (SD 9.93) at Week 24. At Week 48, median LDH level was 261.5 (interquartile range [IQR]: 206.0 to 334.0) U/L, and median LDH change from baseline was −1241.5 (IQR: −1795.0 to −925.0) U/L. LDH was ≤1.5 × ULN in 85% of patients at Week 48 *vs* 95% at Week 24. Week 48 mean absolute reticulocyte count (ARC) was 79.51 (SD 42.60) × 10^9/L. Two patients experienced a clinical breakthrough hemolysis (BTH) event; the adjusted annualized rate was 0.05 (95% CI 0.01–0.17). Potential complement-amplifying conditions were identified in both patients; both BTH events resolved without iptacopan discontinuation. No major adverse vascular events were reported. Headache (30.0% of patients), COVID-19 (22.5%), upper respiratory tract infection (17.5%), and diarrhea (15.0%) were the most common treatment-emergent adverse events (TEAEs); eight patients (20.0%) experienced ≥1 serious TEAEs. No treatment discontinuations or deaths occurred. Improvements from the 24-week treatment period were sustained to Week 48, with most patients maintaining clinically meaningful Hb increases from baseline, normal/near-normal Hb levels, good intravascular hemolysis control, transfusion avoidance, and improvements in fatigue and reductions in ARC. Iptacopan was well tolerated, with a consistent safety profile, suggesting that it could become a practice-changing and convenient outpatient treatment for patients with hemolytic PNH.

Table 1.

Table: Summary of efficacy parameters at Weeks 24 and 48 in the APPOINT-PNH trial

	Week 24		Week 48	
Endpoints	**Proportion of patients**	**Summary statistic**	**Proportion of patients**	**Summary statistic**
	*n/M**	*Percentage (%)*	*n/M**	*Percentage (%)*
Hb level increase from baseline of ≥2 g/dL†	37/39	94.9	38/39	97.4
Hb of ≥12 g/dL†	26/39	66.7	31/39	79.5
	n/N‡	*Percentage (%)*	*n/N‡*	*Percentage (%)*
LDH ≤1.5 × ULN	38/40	95.0	34/40	85.0§
	M/N¶	*Change from baseline*	*M/N¶*	*Change from baseline*
Mean (SD) change from baseline¶ in Hb level (g/dL)†	39/40	+4.41 (1.40)	39/40	+5.09 (2.01)
Mean (SD) change from baseline** in FACIT-Fatigue score	37/40	+12.1 (9.93)	39/40	+10.4 (10.14)
Median (IQR) change from baseline†† in LDH level (U/L)	39/40	−1271.0 (−1830.0 to −920.0)	40/40	−1241.5 (−1795.0 to −925.0)§
Mean (SD) change from baseline‡‡ in ARC (10^9/L)	39/40	−87.00 (65.16)	39/40	−76.55 (50.15)
	n/N¶¶	*Adjusted annualized rate (% [95% CI])*	*n/N¶¶*	*Adjusted annualized rate (% [95% CI])*
Rate of clinical BTH***	0/40	0 (0.00–0.17)	2/40	0.05 (0.01–0.17)
Rate of MAVEs	0/40	0 (0.00–0.17)	0/40	0.00 (0.00–0.09)
Transfusion avoidance‡‡	*n/M**	*Estimated proportion§§ (% [95% CI]) from Weeks 2 to 48*		
	39/40	97.5 (92.5–100.0)		

*n=number of patients who met the criteria, M=number of patients with evaluable/non-missing data; †Includes post-transfusion data; ‡n=number of patients, N=total number of patients; §Variability in LDH level at Week 48 was mainly driven by one outlier; ¶M=number of patients with evaluable/non-missing data, N=total number of patients; **Mean (SD) baseline Hb level was 8.16 (1.09) g/dL; **Mean (SD) baseline FACIT-Fatigue score was 32.8 (10.17); ††Median (IQR) baseline LDH level was 1581.5 (1144.5–2054.5) U/L; ‡‡Mean (SD) baseline ARC was 154.33 (63.67) × 10^9/L; ¶¶n=number of patients with at least one event, N=total number of patients; ***Events that met the protocol-specified criteria for clinical BTH; ‡‡Patients not receiving or not requiring transfusions in the specified time period; §§Estimated proportions reflect the probability of meeting the endpoint criteria among the study population. The proportion for Weeks 2–48 was estimated using simple proportion, based on observed data. The 95% CI was obtained using the bootstrap method.
ARC, absolute reticulocyte count; BTH, breakthrough hemolysis; CI, confidence interval; FACIT-Fatigue, Functional

C020

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH SICKLE CELL DISEASE: PRELIMINARY RESULTS OF THE FIRST PATIENTS TRANSPLANTED IN TANZANIA

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Background. Sickle cell disease (SCD) is the most common inherited hemoglobinopathy in Tanzania, with 11,000-14,000 newborns with the disease annually. While life expectancy of SCD patients in high-income settings has improved, the mortality rate is 50-90% in low-income countries. Curative options for SCD (allogeneic hematopoietic stem cell transplantation HSCT, gene therapy,

gene editing) are unavailable in sub-Saharan Africa. Here we present preliminary results of the first SCD patients transplanted in Tanzania.

Methods. Tanzania launched a development program in 2018 to establish HSCT at Benjamin Mkapa Hospital (BMH) in Dodoma. With the support of the Association HELP3-ODV (www.help3.it), starting from 2019 a series of videoconference lectures were done by international HSCT experts to train Tanzanian health professionals. Four nurses, two doctors and two laboratory scientists took part in an observational internship in Italy at different Centers. In January 2023 HSCT program started at BMH with the presence of experienced Italian staff in Tanzania for the first 4 months. Weekly online clinical-logistical round started in March 2023 and are ongoing. Conditioning regimen consisted of Busulfan, Rabbit Antithymocyte Globulin (ATG) and Cyclophosphamide. GVHD Prophylaxis consisted of methotrexate and cyclosporine. Standard Levetiracetam and antimicrobial prophylaxis were used. All patients with symptomatic SCD, received bone marrow stem cells harvested from HLA-identical siblings.

Results. From January 2023 to March 2024 the first 8 HSCT were performed. Six patients were male, two female, median age was 8 (4-11). Median TNC infused was 4.7 x 10 /kg of patient BW (2.6-8.9). Conditioning regimen was well tolerated without grade III-IV adverse events. All patients engrafted with a median ANC and PLT engraftment at day + 28 (19-41) and + 22 (15-35), respectively. All patients experienced febrile neutropenia, responding to broad-spectrum antibiotics. Microbiological findings on blood were P.Falciparum, Coagulase-negative Staphylococci and Gram positive rods, all resolved. Grade II Skin aGVHD was diagnosed on day +21 in one patient, treated with Methylprednisolone and Mycophenolate Mofetil, obtaining complete resolution. At a median follow-up of + 224 (57-421) from HSCT, no other GVHD were diagnosed. One patient was diagnosed with oral HPV lesions, resolved with cryotherapy. One patient was diagnosed with probable Invasive Fungal Disease, treated with Voriconazole. No other long-term complications were diagnosed. All patients remain transfusion free, without SCD events, with blood counts and HbS levels compatible with complete engraftment and chimerism. Four patients stopped immunesuppressants at a median day +292 (265-300), three patients are back to school.

Conclusions. Our preliminary results for the first SCD patients transplanted in Tanzania show that HSCT is feasible in LMICs with comprehensive adjustments on infrastructures and human resources. The first eight patients are now asymptomatic with full chimerism. Of note, half of the patients were transplanted without the Italian staff at BMH and a ninth patient was undergoing HSCT at the time of this submission. Tanzanian government has deliberated to support BMT at BMH Hospital. It'll be fundamental to ensure sustainability of the service considering the immense need of HSCT in Tanzania. Maintaining the cost affordable and creating a reliable supply chain of drugs and consumables will be crucial. Continuous training for health professionals is ongoing and needs to be implemented, ideally to make HSCT feasible also in other disorders.

Allogenic and autologous transplant I

C021

PREVENTION AND TREATMENT OF ACUTE MYELOID LEUKEMIA RELAPSE FOLLOWING ALLOGENEIC STEM CELL TRANSPLANT: A NATIONAL SURVEY BY GITMO (GRUPPO ITALIANO TRAPIANTO MIDOLLO OSSEO)

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Leukemia relapse remains the main cause of treatment failure in patients undergoing allogeneic stem cell transplant (allo-SCT) for acute myeloid leukemia (AML). There is currently no general agreement concerning management of patients at high risk of leukemia recurrence or with overt hematological relapse after allo-SCT. We conducted the present survey with the aim to evaluate the current practice in Italy concerning prevention and treatment of AML relapse after allo-SCT. A questionnaire was sent to GITMO centers including specific questions on three main topic: maintenance, preemptive therapy and treatment of hematological relapse. Most of the agents discussed below currently represent off label prescriptions. In all, 34/60 (57%) of centers performing allo-SCT in Italy completed the questionnaire. 22/34 (65%) routinely employ maintenance strategies (in the absence of measurable residual disease (MRD) or mixed chimerism) after allo-SCT in patients considered at high risk of relapse basing on pre-transplant features (high risk according to ELN 2022 or presence of FLT3-ITD, positive MRD or active disease). Among institutions who deliver maintenance therapy after allo-SCT, in patients harbouring FLT3-ITD 86% administer FLT3 inhibitors (95% Sorafenib, 5% Gilteritinib). In the absence of FLT3-ITD 68% use hypometilating agents (87% azacitidine, 13% decitabine); 2 centers consider addition of venetoclax to hypometilating agents, while one institution prescribes venetoclax as single agent. Interestingly, 26% of institutions administer prophylactic DLI in high risk AML patients, in the absence of MRD relapse or mixed chimerism. With respect to preemptive therapy, the trigger to start treatment is represented by MRD relapse in all centers; 74% of institutions consider mixed chimerism as trigger to start preemptive therapy as well. In patient harbouring FLT3-ITD 82% of centers prescribe FLT3 inhibitors (48% sorafenib +/- azacitidine, 52% gilteritinib). In the absence of FLT3-ITD 62% of institutions use azacitidine (19% with the addition of venetoclax), one institution use venetoclax monotherapy, while 29% use DLI as single approach especially in case of mixed chimerism in the absence

of MRD relapse (Figure 1). Nevertheless, 32/34 (94%) use DLI in addition to pharmacologic preemptive therapy. In patients experiencing haematological relapse after transplant 76% of institutions perform NGS analysis at the time of relapse, while 50% look for HLA loss in case of relapse after haploidentical transplant. In patients harbouring FLT3-ITD 91% of centers treat AML relapse with gilteritinib. In fit patients, in the absence of FLT3-ITD, 44% employ conventional chemotherapy, while 56% consider as first option hypometilating agents (mostly azacitidine) in combination with venetoclax. All institutions consider second allo-SCT after salvage treatment in patients who relapse after first transplant. 62% of centers perform second allo-SCT only in patients achieving CR2, while 38% regardless achievement of response to salvage. Finally, 97% of institutions prefer a different donor for second allo-SCT, if available. Most Italian transplant institutions currently implement strategies to prevent AML relapse after allo-SCT, despite the lack of approved agents in this setting. In patients with haematological relapse a second allo-SCT remains a main option after salvage treatment with standard chemotherapy or hypometilating agents in combination with venetoclax.

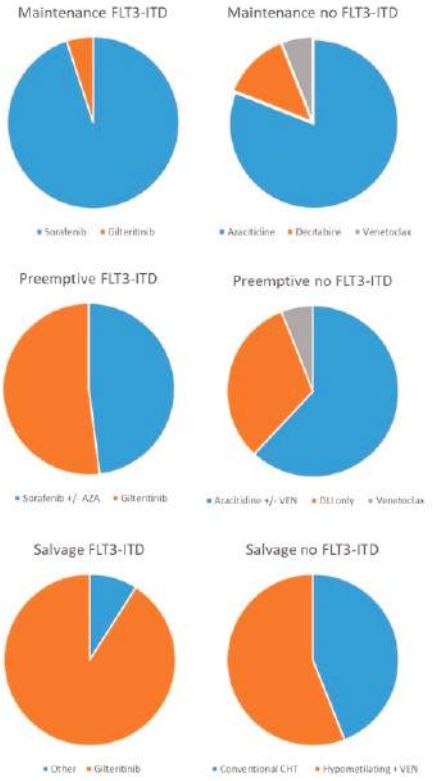

Figure 1.

C022

QUALITY OF ENGRAFTMENT AND INCIDENCE OF ACUTE GVHD GRADE II-IV POST PERIPHERAL HAEMOPOIETIC CELLS CRYOPRESERVATION IN PATIENTS UNDERGOING ALLOGENEIC TRANSPLANTATION FROM HLA IDENTICAL DONORS

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Background. Cryopreservation of allogeneic peripheral blood stem cells (PBSC) was commonly employed during the SARS-CoV-2 pandemic. The purpose of this study was to evaluate hematopoietic reconstitution and acute GvHD incidence in patients transplanted from an HLA-identical related (MRD) or unrelated donor (MUD) donor with cryopreserved PBSC.

Methods. We performed a comparative analysis of 46 patients who underwent an allo-HSCT with cryopreserved (cryo group) and 39 patients with fresh (fresh group) apheresis at our transplant unit. The analysis was retrospective for 61 patients transplanted from January 1, 2016 to May 31, 2022 and prospective for 24 patients transplanted from June 1, 2022 to May 30, 2023. The protocol was approved by the Local Ethics Committee (346/2022). The primary clinical endpoints were time to engraftment, incidence of graft failure (GF) (lack of full donor chimerism), poor graft function (PGF) (severe cytopenia with full donor chimerism) and acute GvHD.

Results. Patient characteristics were comparable between the fresh and cryopreserved group, except for a higher rate of transplants from MUD in the cryo group (p=0.008). One patient who received a fresh graft was not available for engraftment evaluation due to early death. Median time to neutrophil recovery was longer in the cryo group (18 days) (95%CI: 17-18.9) *vs* the fresh group (16 days) (95%CI: 15.3-16.6), (p=0.007), as for platelet recovery: 20 days (95%CI: 17.8-22.1) *vs* 14 days (13.1-14.8) (p≤0.001). For the cryo group GF occurred in 6/46 (13%) patients, while for the fresh group all patients achieved full donor chimerism 1 month after transplant (p=0.03). Among evaluable patients, 100-days incidence of PGF was 12/40 (30%) in the cryo and 1/38 (2,6%) in the fresh group (p=<0.001). The cumulative incidence (CI) of grade II - IV acute GvHD was significantly higher in the cryo group, 36.8% (95%CI: 24.9-54.5) *vs* 10.2% (95%CI: 4.1-25.9) in the fresh group (p=0.002). Similar results were observed when the analysis was limited to the MUD subgroup (37% *vs* 10%) (p=0.05). The CI of grade III-IV was 13.2% (95%CI: 6.2-27.8) in the cryo group *vs* 2.5% (95%CI: 0.3-17.7) in the fresh group (p=0.04). No differences in terms of OS, EFS, RI and NRM were observed.

Conclusions. In our experience PBSC cryopreservation was detrimental for hematological reconstitution and acute GvHD incidence. Further studies are ongoing to confirm and explain our data.

C023

RELEASE OF CD31+ ENDOTHELIAL EXTRACELLULAR VESICLES BY HOST BEFORE HSCT IS ASSOCIATED TO AN INCREASED RISK OF ACUTE GRAFT VERSUS HOST DISEASE

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Acute Graft versus host disease (aGVHD) remains the most important cause of non-relapse mortality of allogenic stem cell transplantation (HSCT). The research of biomarker able to predict the risk of aGVHD is an active field of investigation. The aim of this study was to examine the potential role of endothelial-derived extracellular vesiclesas a potential biomarker of endothelial damage and increased

risk of aGVHD. We collected serum samples at day -6 and -2 before transplantation (before and after conditioning respectively). We used CD31 as endothelium marker and measured CD31+ extracellular vesicles (CD31+ EVs), by multiflow cytometry employing a method implemented in our laboratory (Marchisio 2020). We analyzed 97 patients, who underwent HSCT at IRCCS AOU S. Orsola-Malpighi of Bologna. Median age was 55 years (18-70), 43 were females. The most common disease was Acute Leukemia (n=65), especially Myeloid Acute Leukemia (n=49), other indications for HSCT were Myelodysplastic/Myeloproliferative Neoplasms (n=18), Chronic Myeloid Leukemia (n=5) and lymphomas (n=9). Conditioning regimen was myeloablative in 48 patients (49.5%) and reduced-intensity in the others. All received peripheral blood stem cells (PBSCs) from a sibling HLA-identical (n=7), or from an HLA-matched unrelated 8/8 (n=59) or HLA-mismatched unrelated 7/8 (n=31) donor. GVHD prophylaxis consisted in the combination of Cyclosporine/Tacrolimus (CNI) plus Methotrexate/Mycophenolate plus ATLG. ATLG was administered at a total dose of 30 mg/kg divided in 5 days, from day -6 to day -2 before HSCT. At data cut-off of December 2023, with a median follow-up of 21 months (1-39), 48.5% had developed acute GVHD of any grade (47/97) and 32% of patients had developed grade II-IV a GVHD. Importantly, we found that levels of CD31+ EVs were significantly higher in patients who subsequently developed aGVHD of any grade both at day -6 (median CD31+ EV 372/microL in no aGVHD *vs* 842/microL in aGVHD, p=0.0001) and at day -2 (median CD31+ 387 EV /microL in no aGVHD *vs* 851/microL in aGVHD, p=0.0007). Interestingly, we found that aGVHD occurred earlier in patients with higher levels of endothelial EVs at day -6 and -2 (Spearman r= -0.261, p=0.010 and r=-0.209, p=0.043, respectively). These primary results indicate that, in our cohort, CD31+EVs at day -6 and day -2 before HSCT are predictive of aGVHD occurrence. These findings require further investigations to validate CD31+EVs as an early biomarker of aGVHD.

C024

ASSESSING THE IMPACT OF CONDITIONING INTENSITY ON OUTCOMES OF ALLOGENEIC STEM CELL TRANSPLANTATION: A SINGLE-CENTER STUDY

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Background. The Transplant Conditioning Intensity index(TCI), proposed by EBMT, refines conditioning intensity assessment compared to myeloablative(MAC) and reduced-intensity(RIC) conditioning.

Methods. A retrospective study at Brescia's BMT centre(Mar 2006-Sep 2023) evaluated transplant(HSCT) outcomes: Overall Survival(OS), Non-Relapse Mortality(NRM), GVHD-free Relapse-free Survival(GRFS), and the Cumulative Incidence of Relapse(CIR).

Results. 556 patients underwent HSCT, median age 53 years. Donor categories were match-related(34%), haploidentical(18%), matched unrelated donor(46%) and UCB(2%). MAC and RIC regimens were used in 47% and 53% of cases, respectively. MAC was more prevalent among younger patients with lower comorbidities, higher Karnofsky Performance Status(>80) and diseases not in first remission. TCI scores were distributed as 36% low, 37% intermediate and 22% high. TCI correlated significantly with patient age, comorbidities and performance status. The TCI index provided nuanced stratification, particularly in the 50-70 age group, predicting OS and GRFS. Median OS was 116.8 months versus 27.4 months in MAC and RIC groups(p<0.001). OS rates at 1 and 3 years were significantly higher in MAC compared to RIC. Stratification into Low, Intermediate, and High TCI groups revealed significant differences in median OS(p<0.001) and distinct OS rates at 1 and 3 years within each group(p<0.001). Statistical significance persisted in the 50-70 age group, favoring MAC(p=0.005). GRFS rates at 1 and 3 years also differed significantly between MAC and RIC(p<0.001) and within TCI categories(p=0.02). In the multivariate analysis, significant factors included disease in first complete remission(HR 0.69; 95% CI 0.52-0.90; p=0.006), HCT-CI≥3(HR 1.58, 95% CI 1.22-2.06; p<0.001), KPS≤80(HR 1.69; 95% CI 1.11-2.57; p=0.01) and positive CMV serology(HR 1.85; 95% CI 1.17-2.92; p=0.009). Cumulative incidence of NRM did not significantly differ across TCI categories(p=0.23). CIR showed a significant relationship between MAC and RIC(p<0.001), but not within TCI categories. No association was identified between chronic GVHD(cGVHD) and TCI, but grade II-IV acute GVHD(aGVHD) correlated significantly with high-intensity regimens.

Conclusion. The TCI index is valuable for assessing conditioning regimen impact on transplant outcomes, particularly in patients aged 50-70, predicting OS and GRFS, and associating with aGVHD within nuanced TCI categories.

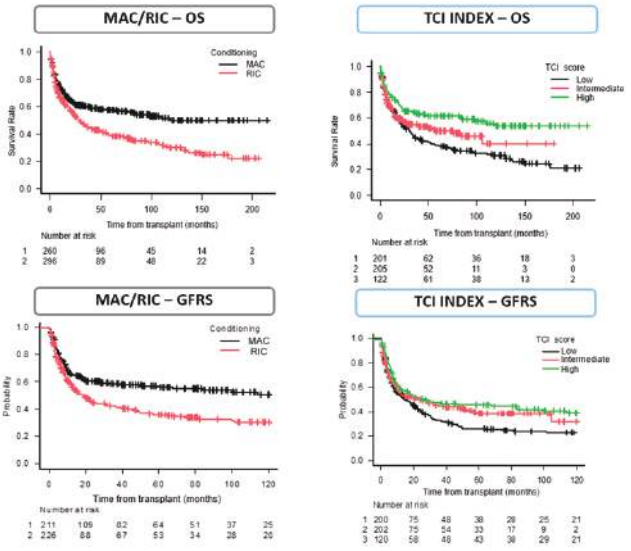

Figure 1.

C025

OUTCOMES OF ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS TREATED WITH THE PEDIATRIC-INSPIRED GIMEMA LAL 1913 PROTOCOL IN REAL-LIFE UNDERGOING ALLOGENEIC TRANSPLANTATION: A MULTICENTER STUDY FROM CAMPUS ALL

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Background. The GIMEMA LAL 1913 is a pediatric-inspired and minimal residual disease (MRD)-oriented chemotherapy protocol that represents the standard treatment for adult Philadelphia-negative acute lymphoblastic leukemia (Ph-ALL) in Italy. The outcome of patients treated with this protocol in the real-life setting and who underwent an allogeneic stem cell transplant (SCT) was the aim of this study.

Methods. Within the framework of the Campus ALL network, we analyzed the post-transplant data of newly diagnosed adult Ph-ALL patients treated according to the LAL 1913 protocol and who underwent a SCT between August 2016 and January 2023 in 35 centers. Patients in 1st remission (CR1) were considered eligible for a SCT based on the joint assessment of the disease risk profile at diagnosis and post-consolidation MRD status. We also included relapsed patients in 2nd CR (CR2). Endpoints were the 2-year overall survival (OS), disease-free survival (DFS), non-relapse mortality (NRM), and cumulative incidence of relapse (CIR). Outcomes were analyzed from the day of SCT.

Results. Among 322 consecutive newly diagnosed Ph-ALL, 201 patients who underwent a SCT were included in this analysis. The median age at diagnosis was 38 years (18-66). The median follow-up was 28 months. Pre-transplant MRD negativity was strongly associated with a superior OS (81% *vs* 50%, p<0.001), DFS (71% *vs* 44%, p=0.003), and CIR (21% *vs* 43%, p=0.006). Patients allografted in CR1 had superior outcomes with regards to CR2 patients, but MRD negativity also impacted favorably on the prognosis of patients transplanted in CR2 in terms of OS and DFS (Figure 1).

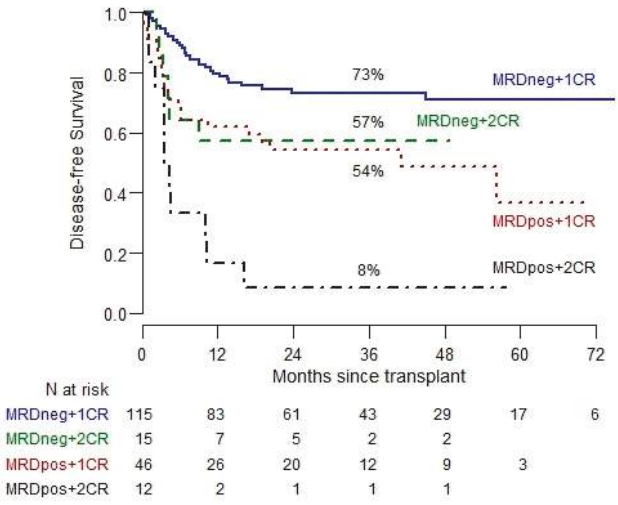

Figure 1.

The outcome was similar between B- and T-lineage ALL, patients' age (< or > 55 years), and baseline risk class. Total-body irradiation (TBI) was adopted in 125 (66%) patients and there was no significant difference when using TBI 800 cGy *vs* TBI 1200 cGy. The 2-year NRM was 11% and it was not significantly affected by pre- and post-transplant factors.

Conclusions. Our study on a series of patients treated with a modern therapeutic strategy confirms the higher risk of relapse in patients with pre-transplant MRD positivity. Given the availability of pre-transplant immunotherapies, all efforts should be made to eradicate MRD before the SCT at least in B precursor ALL. A survival advantage was observed when the transplant was performed in CR1 compared to CR2, highlighting the importance of early identification of patient candidates to SCT.

Hodgkin lymphoma

C026

IMMUNE-RELATED ADVERSE EVENTS IN THE TREATMENT OF HODGKIN LYMPHOMA WITH IMMUNE CHECKPOINT INHIBITORS

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Immune checkpoint inhibitors (ICIs) have recently been found to be effective in Hodgkin lymphoma (HL). However, given the impaired systemic immune response in HL, it is unclear whether immune-related adverse events (irAEs) would manifest differently in this population; data on this topic remains scarce. We conducted an observational retrospective/prospective study on patients with relapsed/refractory HL treated with ICIs to determine the incidence of irAEs assessing the type, severity, and timing of onset, outcome and relationship with study drugs of these events. Within the study period, a total of 78 patients with HL were identified. Among them, 30 (38.5%) patients received nivolumab and 48 (61.5%) received pembrolizumab. The mean age was 37.9 (±14.9) years-old, 43 (55.1%) patients were male, 53 (67.9%) were primary refractory and 59 (75.6%) resulted refractory to the last therapy before ICI with a median of previous therapies of 4 (range 2-10). Twenty patients (25.6%) developed at least one irAE for a total of 21 irAEs. Age at therapy and using ICIs after various previous treatments was not associated with irAEs (Table 1). Among specific irAEs, thyroid dysfunction, skin toxicities, pneumonitis, and colitis occurred in 33.6%, 21.6%, 2.8% and 2.5% of patients, respectively. Median time to presentation of irAEs was 58 days (range 1-97) with a median resolution time of 18 days when applicable. Of note, ICIs were able to be resumed in 82.1% of patients with irAEs. Patients with or without irAE had similar overall survival (OS). Also overall and complete response rates (both final and best) did not differ between patients with and without irAE (Table 1). irAEs were common in patients with HL receiving ICIs. Most patients with irAEs were able to resume ICIs, and the development of irAEs did not affect OS.

Table 1.

Characteristics	irAE, 20(%)	No irAE, 58(%)	p	TOTAL
Age, years	36.8	38.4	0.700	37.9
Gender, F/M	9/11	25/33	>0.999	34/44
Prior BV	15	46	0.7563	61
Prior radiation	4	21	0.2673	25
Prior ASCT	12	31	0.7949	43
Nivolumab	8	22	>0.999	30
Pembrolizumab	12	36	>0.999	48
CR+PR (final), n (%)	10	40	0.1768	50 (64.1)
CR (final), n (%)	6	20	0.7891	26 (33.3)
CR+PR (best), n (%)	14	40	>0.999	54 (69.2)
CR (best), n (%)	6	20	0.7891	26 (33.3)

CR, complete response; irAE, immune-related adverse events; PR, partialresponse.

C027

BRENTUXIMAB-VEDOTIN PLUS AVD CHEMOTHERAPY AS FRONTLINE THERAPY IN PATIENTS WITH STAGE IV CLASSICAL HODGKIN LYMPHOMA: A REAL-WORLD REPORT ON FEASIBILITY, EFFICACY AND INTERIM-PET RESULTS

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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 (cHL) with a manageable increase of toxicity. In Europe, BV-AVD can be offered in label to patients (pts) with stage IV disease; Italian Drug Agency also requires ineligibility to bleomycin for BV-AVD prescription. We retrospectively collected data of 99 cHL pts treated in 15 Italian Centers until May 2023 to describe efficacy and toxicity of BV-AVD and to evaluate the predictive role of interim PET. PET was planned at baseline, after 2 (PET2) and after 6 (PET6) cycles; PET status was assessed according to Deauville Score (DS) obtained from local reports and defined negative with a DS 1-3. Median age was 35 (range 18-81) years; 60/99 pts were male and 11/99 pts had ≥ 65 years. All pts presented with stage IV; B symptoms, bulky disease and skeletal involvement were reported in 72, 28 and 66 out of 99 pts. All pts started BV-AVD frontline: 86/99 pts completed all 6 cycles, while 11 interruptions were due to toxicity and 2 to progressive disease (PD). Forty-four pts had at least one grade ≥ 3 extra-haematological adverse event for a total of 60 events (most common being infections=19, peripheral neuropathy=13 and transaminitis=10). Four pts have died so far, all ≥ 65 years: 1 pt due to PD, 1 pt due to COVID-19, and 2 pts due to sudden death in pre-existing ischemic cardiopathy. All 99 pts underwent PET2; 13 pts had a positive PET2, for which a 94% reduction in the probability to achieve complete remission compared to PET2 negative pts was demonstrated (Odds ratio 0.06, p<.001). PET6 was negative in 83% pts. At a median follow-up of 14.4 months, 1-year progression-free survival (PFS) and overall survival (OS) for all pts were 84.1% (CI 95%: 77-91.9) and 96.9% (CI 95%: 93.6-100). PET2 negative pts had superior 1-year PFS compared to PET2 positive pts: 90.0% (CI 95%: 83.6-96.9) *vs* 46.2% (CI 95%: 25.7-83.0) (p <.001) (Figure 1). PET2 positivity confirmed to predict for lower PFS at multivariate

analysis (HR 4.7, 95% CI: 1.4-15.2, p=.009). BV-AVD confirmed to be effective in this real-world report; PFS was lower than in the ECHELON-1 trial, as expected in an unselected population of stage IV pts. We hypothesize that pts treated with BV-AVD frontline could benefit from a PET-driven approach, considering the predictive role of PET2 status shown in the present study.

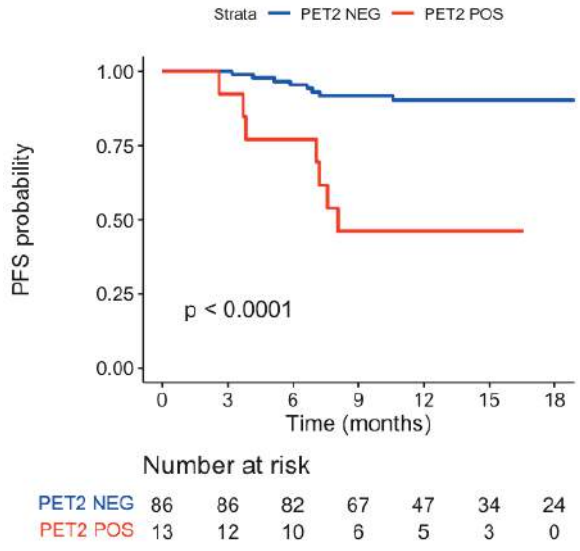

Figure 1.

C028

BRENTUXIMAB VEDOTIN (BV)+AVD IN PREVIOUSLY UNTREATED PATIENTS WITH ADVANCED CLASSICAL HODGKIN LYMPHOMA: AN ITALIAN REAL-LIFE MULTICENTRIC STUDY

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Introduction. In Italy, Brentuximab vedotin (Bv) with AVD (adriamycin, vinblastine, dacarbazine) received approval for the first-line treatment of stage IV classical Hodgkin lymphoma (cHL) since September 2021, after the positive results of the ECHELON-1 study.

Aims. To analyze the toxicity and efficacy of Bv+AVD in patients with stage IV cHL, >18 years, treated outside clinical trials.

Methods. A retrospective multicentric study has so far involved 9 Italian centers. A control group of stage IV cHL patients treated with ABVD was included. The primary objective was to record peripheral neuropathy (PN) and hematologic toxicity. Survival events included progression, relapse, or death.

Results. By February 2024, 108 patients treated with Bv+AVD and 60 with ABVD were collected. Baseline characteristics were balanced (Table 1A). Any grade (G) PN (NCTCAE) was significantly higher in the Bv+AVD group compared to ABVD (48.2% *vs* 20%, p<0.0001), with comparable G3-4 PN (7.4% *vs* 1.6%, p=0.1) (Table 1B). PN resolution was more frequent in the ABVD group (87.5% *vs* 12.4%, p=0.02). Any G neutropenia was significantly higher in the ABVD group compared to Bv+AVD (66.6% *vs* 47.2%, p=0.03), as well as G3-4 infections (11.6% *vs* 4.6%, p=0.08). All Bv+AVD patients received primary prophylaxis with G-CSF *vs* 68.3% of ABVD group. Treatment schedule delays (32.1% *vs* 16.7%, p=0.03) and dose reductions (32.6% *vs* 9.6%, p=0.002) were more frequent in the Bv+AVD group. No difference was observed in the CR rate (Deauville score 1-3) at interim PET/CT, performed in 163/168 patients (76.2% Bv+AVD *vs* 71.7% ABVD, p=0.52) neither at final PET/CT (Bv+AVD 83% *vs* ABVD 83.3%, p=0.63). Treatment intensification was performed in 11.9% of ABVD patients and only in 4.8% of Bv+AVD for a DS=4 (2/5) or DS=5 (3/5) after 4 cycles. One death due to heart failure in elderly patients was observed in each group; another death due to disease progression in one patient of ABVD group. After a median follow-up of 16 months for the Bv+AVD and 40 months for the ABVD group, survival events were observed in 10.8% and 21.7% of patients, respectively (p=0.06).

Conclusions. The efficacy of BV+AVD was confirmed, with a reduced number of patients proceeding to early therapy intensification. There was a lower frequency of PN than that reported in the ECHELON-1 trial. Dose adjustment-delays were more frequent in Bv-AVD but did not prevent the achievement of CR. Further data on progression-free survival will be presented.

Table 1.

IA

Baseline characteristics		ABVD (N=60) N/Med	%/Range	Bv+AVD (N=108) N/Med	%/Range	p
Sex	Male	32	53.3%	53	49.1%	0.59
	Female	28	46.7%	55	50.9%	
Age	(Years)	34	17-83	37	18-79	0.4
Age category	< 65 years	55	91.7%	98	88.9%	0.56
	>=65 years	5	8.3%	10	11.1%	
COPD	No	59	98.3%	104	96.3%	0.45
	Yes	1	1.7%	4	3.7%	
Autoimmune diseases	No	58	98.3%	98	90.7%	0.15
	Yes	2	3.3%	10	9.3%	
Performance Status (ECOG)	0-1	57	95%	96	88.9%	0.41
	>=2	3	5%	12	11.1%	
Baseline SUVmax	Value	13.8	5.2-39	15.1	4.3-40	0.34
Bone Marrow uptake at PET/CT	No	32	54.2%	41	38.7%	0.05
	Yes	27	45.8%	65	61.3%	
Extranodal uptake at PET/CT	No	8	13.6%	6	5.6%	0.07
	Yes	52	86.4%	102	94.4%	
B Symptoms	No	27	45%	43	39.8%	0.51
	Yes	33	55%	65	60.2%	
Bulky Disease	No	41	68.3%	74	68.5%	0.98
	Yes	19	31.7%	34	31.5%	

IB

Treatment Features		ABVD N	%	Bv+AVD N	%	p
Any adverse event G>3	No	32	53.3%	72	66.7%	0.09
	Yes	28	46.7%	36	33.3%	
Treatment Delay	No	50	83.3%	72	67.9%	0.03
	Yes	10	16.7%	34	32.1%	
Dose Reduction	No	55	91.7%	64	67.4%	0.002
	Yes	5	8.3%	31	32.6%	
Neuropathy	G 1-2	11	18.3%	44	40.7%	0.03
	G 3-4	1	1.6%	8	7.4%	0.1
Neutropenia	G 1-2	14	23.3%	9	8.3%	0.03
	G 3-4	26	43.3%	42	38.8%	0.34
Infections	G 1-2	6	10%	14	13%	0.6
	G 3-4	7	11.6%	5	4.3%	0.08
CR interim-PET/CT (DS1-3)	No	17	28.3%	25	23.8%	0.37
	Yes	44	71.7%	80	76.2%	
Treatment intensification	No	52	88.1%	100	95.2%	0.09
	Yes	7	11.9%	5	4.8%	
CR EOT PET/CT	No	7	11.6%	9	8.57%	0.6
	Yes	50	83.3%	87	83%	

Table I. Table **IA**, Characteristics of cHL patients treated with BV+AVD versus ABVD. Table **IB**, Toxicity and response to treatment in patients treated with BV+AVD versus ABVD.

C029

THE SYSTEMIC IMMUNE INFLAMMATION INDEX (SII) AT DIAGNOSIS IDENTIFIES PATIENTS WITH POOR OUTCOME: RESULTS FROM A REAL-LIFE SINGLE-CENTER STUDY IN CLASSICAL HODGKIN LYMPHOMA

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Introduction. Classical Hodgkin Lymphoma (cHL) is characterized by an inflammatory background in which the reactive myeloid cells may exert an immune suppressive effect. An increasing number of studies have demonstrated the value of inflammatory response biomarkers based on peripheral blood cell counts, including the neutrophil-to-lymphocyte ratio (NLR), the systemic immune inflammation index (SII), and the systemic inflammation response index (SIRI).

Methods. In this retrospective, observational, single-center study, we evaluated 212 newly diagnosed HL patients, including 132 advanced-stage cases, to test new systemic inflammatory response biomarkers SII and SIRI. The NLR, SII, and SIRI were calculated using the following formula: NLR=neutrophil count/lymphocyte count, SII=platelet count × neutrophil count/lymphocyte count, SIRI=neutrophil count × monocyte count/lymphocyte count.

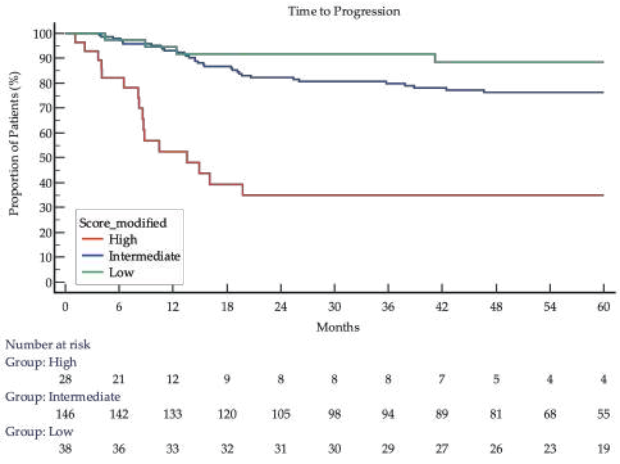

Figure 1.

Results. The median age was 31.8 [14.8-76.9], and half of the patients were males. The median NLR, SII, and SIRI at diagnosis were 4.79, 229, and 4439, respectively. After a median follow-up of 70.2 months [4.8-214.0], 188 patients (88.7%) were in continued complete remission (cCR), 6 (3.0%) progressed during therapy or the first six months, and 18 relapsed (8.4%) within two years from the end of treatment. A ROC curve analysis identified NLR ≥6, SII≥200, and SIRI≥3500 as capable of predicting CR achievement. In univariate analysis, predictors of inferior progression-free survival (PFS) at 5 years, available at diagnosis, were NLR ≥6, SII≥200, SIRI≥3500, IgM <50 mg/dL, male gender, presence of extranodal sites or large nodal mass (≥7 cm). In multivariate analysis, SII≥200, IgM <50 mg/dL, male, and presence of large nodal mass (≥7 cm) were independent baseline variables able to predict 5-yrs-PFS. For each of the independent parameters, a point was attributed to identify 3 classes of risk: low (score 0-1, N=38), intermediate (score 2, N=146), and high (score 3, N=28), disclosing that the 5-yrs-PFS were significantly different among the three risk groups, respectively: 88.4%, 74.6%, and 35.0% (p<0.0001 - Figure 1). Similarly, 5 yrs-OS significantly differed among the three risk groups, respectively, 98.2%, 97.7%, and 87.5% (p=0.01).

Conclusions. Combining inflammation markers and the amount of IgM with clinical variables available at diagnosis are low-cost, valuable prognostic factors earlier than PET -2, and helpful for identifying different HL classes at risk of treatment failure at baseline.

C030

GENE EXPRESSION PROFILING IDENTIFIES A PROTECTIVE ROLE OF B-CELL FOR PROGRESSION OF HODGKIN LYMPHOMA PATIENTS'

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In the treatment of Hodgkin Lymphoma the early identification of patients who experience relapse after completion of front-line therapy, currently represents an unsolved need. It is likely that disease progression reflects some innate features that escape the current prognostic criteria but that can be revealed by a deep analysis of the molecular assets of the lesions. Here we employed a deep gene expression analysis searching for molecular determinants that could anticipate the risk of relapse among patients who were homogenously treated.

Patients and Methods. We selected a retrospective cohort of patients with cHL, older than 18 years, who achieved a complete metabolic response (CMR) after 2 ABVD courses and with an available baseline FFPE diagnostic tissue. A gene expression analysis on a panel of 770 immune related genes was conducted. Data were correlated with clinical and radiomic information. Primary endpoint was Progression Free Survival (PFS) from the date of diagnosis.

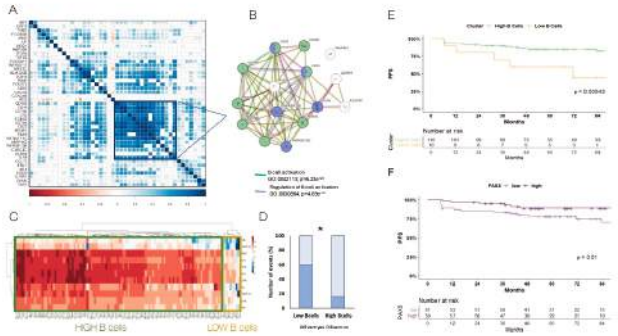

Figure 1.

Results. Out of 215 cHL patients (2004- 2019), 148 achieved a CMR after 2 ABVD courses and 120 hade available FFPE material. With a median follow up of 60 months (range, 6-162 months) we recorded 24 events for PFS. The resulting 4 year PFS rate was 84% (95% CI 77.7-91.2). Cox Proportional Hazard model analysis identified 54 genes whose expression was significantly associated with PFS (p<0.05). Of these, 43 were positively associated with improved PFS and 11 genes were significantly associated with reduced PFS. Gene Ontology analysis showed that protective genes were enriched in B-cells associated pathways (panel A, B). Unsupervised clustering

analysis using this B cell related genes identified two separate clusters of patients (Panel C) with different risk of PFS (Panel D, E). Finally, Kaplan Meyer curve analysis showed that, among overexpressed B-cell rated genes, the high expression of PAX5, the major cell fate determinant of B cells lineage, was associated with a marked reduction in the risk of PFS (Panel F).

Conclusion. Even if preliminary, these data indicate that gene expression analysis helps in the early identification of relapsing cHLs and that progression in this disease is restrained by an immune-protective microenvironment of which benign B-cells are crucial component.

Infections and quality of life

C031

REAL-WORLD EVIDENCE ON SHORT-TERM QUALITY OF LIFE CHANGES IN PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMAS TREATED WITH CAR-T-CELL THERAPY: RESULTS FROM THE GIMEMA -SIE CAR-T QOL STUDY

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Aims. Little real-world evidence (RWE) exists on health-related quality of life (HRQoL) and symptoms of patients with aggressive B-cell lymphomas treated with CAR T-cell therapy. The primary objective of this analysis was to assess short-term changes in HRQoL of these patients treated in real life.

Methods. This was a prospective observational study by the Italian GIMEMA Group including adult patients with diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma, and DLBCL transformed by indolent lymphoma and mantle cell lymphoma (MCL), scheduled to receive CAR T-cell therapy. Health-related quality of life (HRQoL) profile was assessed at baseline (just before CAR T-Cell infusion) and at 1,3,6,9,12,18 and 24 months. For the purpose of this analysis changes from baseline to 1-month were considered. The differences between the prevalence of clinically relevant problems and symptoms between baseline and 1-month was computed using the well-validated EORTC QLQ-C30 and the EORTC QLQ-NHL-HG29 questionnaires.

Results. Overall, a total of 171 patients were enrolled across 13 Italian centers between June 2022 and February 2024 and current analysis is based on 129 patients with completed HRQoL questionnaires at baseline and at 1 month after CAR -T cell infusion. Median age at study entry was 60.2 years (IQR, 50.4-66.7) and 87 (67.4%) were men. The median time since diagnosis was 1.6 years (IQR, 0.9-4.2). PMBCL was diagnosed in 12.6% of patients, MCL in 21% and DLBCL in 66.4%. The most frequently used CAR-T cell product was Axicabtagene ciloleucel (axi-cel) in 56.4% of patients. The top ten most prevalent differences of symptoms and worries by the EORTC QLQ-NHL-HG29, are reported in Table 1. The largest differences

was observed for sudden tiredness (Δ=21%), followed by muscle weakness and shortness of breath on exertion (both with Δ=18%), lack of energy, drowsiness and numbness in fingers or toes (Δ=15%, Δ=14% and Δ=13%). Overall, after 1 month from the CAR-T cell infusion, patients reported higher prevalence in all the selected scales compared to the baseline. The most frequently reported problems at both timepoints were Physical functioning (Baseline 42.6% and 1-month 65.9%), Role functioning (31% and 42.2%), Fatigue (27.3% and 42.6%) and Dyspnoea (39.5% and 46.1%)

Conclusion. To the best of our knowledge, this is the largest prospective RWE on early HRQoL changes of Italian patients with DLBCL treated with CAR T-Cell therapy. This data may help to identify most critical clinically relevant problems experienced by these patients in the short-term period, hence to provide more targeted supportive care interventions.

Table 1.

Table 1. Top 10 most prevalent differences of symptoms and worries by the EORTC QLQ-NHL-HG29, between baseline and 1-month timepoints.

Item of the EORTC QLQ-NHL-HG29	Baseline n (%). N = 129	1-month n (%). N = 129	Δ (%)
1. Have you had sudden tiredness?	65 (51%)	90 (72%)	21%
2. Have you had muscle weakness?	82 (64%)	105 (82%)	18%
3. Have you had shortness of breath on exertion?	55 (43%)	77 (61%)	18%
4. Have you had lack of energy?	91 (71%)	110 (86%)	15%
5. Have you felt drowsy?	72 (56%)	89 (70%)	14%
6. Have you had numbness in your fingers or toes?	54 (43%)	39 (30%)	13%
7. Have you had a dry mouth?	45 (35%)	58 (46%)	11%
8. Have you been dissatisfied with how your body functions?	78 (61%)	68 (53%)	8%
9. Have you felt a lack of confidence in your body?	61 (48%)	71 (55%)	7%
10. Have you felt you had a setbacks in your physical condition?	49 (38%)	40 (31%)	7%

The prevalence of patients who reported symptoms and worries on the QLQ-NHL- HG29 was based on the number of patients who answered, "a little," "quite a bit," or "very much" on a given item

C032

CARE-TOGETHER: THE FIRST ITALIAN PATIENT SUPPORT PROGRAM FOR CAR T PATIENTS

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Background. CAR T-cell therapy has changed the treatment of R/R hematological malignancies, offering outstanding clinical outcomes and reshaping the care landscape for patients. The introduction of this therapy presents substantial economic and organizational challenges for the Italian NHS and places a significant burden on patients and families. 66% of caregivers leave their jobs due to a lack of adequate support in patients' journey in Italy[1]. Patients identified for CAR T need to go through a complex treatment journey with multiple steps. This is the main reason behind our decision of creating a comprehensive support program, aimed at reducing both the emotional and practical burden throughout the care pathway.

Methods. We co-created and implemented the first Italian Patient Support Program (PSP) for patients who intended to receive CAR T-cell therapy aiming at facilitating the patient journey with personalized services. The PSP "CARe-Together" has been developed in collaboration with dedicated vendors, treating physicians, patients' representatives, and their caregivers to identify solutions that would have added value to the care pathway. An easy-to-use digital platform has been developed to assist patients in accessing a professional caregiving service and healthcare support. The former encompasses a range of services delivered by trained professional caregivers, including transportation, assistance with bureaucratic procedures, companionship, and support with daily activities. Healthcare support includes home blood collection, nutritional, psychological, physiotherapy services.

Results. The PSP started in July 2022 involving 4 Italian Qualified Treatment Centers and offered 10 slots in 2022 and 18 slots in 2023. Among a total of 140 patients intended to CAR T in these centers, 28 patients were enrolled as of December 31st, 2023. 372 services were provided: 283 professional caregiving services; 57 physiotherapy services; 27 nutritional services; 5 psychological services. Patients, caregivers and physicians positively evaluated the effectiveness of this PSP to improve their QoL during the CAR T Journey (Table 1).

Conclusions. These results highlight the crucial role that a caregiver plays in the journey of a patient intended to CAR T and the importance of social services, emphasizing the necessity for a more integrated care model that can support access to the healthcare system. This PSP represents an effective and innovative private-public partnership.

Table 1.

Table 1. Survey results (range score: 0-10; 0 represents the least positive perception, 10 represents most positive perception

Questions	HCP	Patient	Family Caregiver
How useful do you consider the CARe-Together support program?	8,0	9,8	9,7
Clarity of program objectives	8,0	NA	NA
How useful do you consider the steward's role and the support provided during the use of the CARe-Together program?	9,5	9,8	9,7
How do you evaluate the range of support services offered by the program?	8,0	9,4	9,8
How do you rate the quality of the support services provided?	9,0	9,7	NA
Has the support program been effective in improving patients/caregivers' QoL and in making the journey easier to manage?	8,0	9,6	9,7

Median value reported. HCP: Health Care Professionals. Number of participants who responded to the survey: HCP 4/4 (100%); Patients 21/28 (75%); Family Caregiver 9/28 (32%). NA: Not applicable, because questions not addressed to this target. The survey was in Italian.

C033

RISK ASSESSMENT AND MICROBIOLOGICAL PATTERNS OF LONG TERM INFECTIOUS EVENTS AFTER CAR T CELL TREATMENT

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As CAR T cell therapy evolves and consolidates its role in the treatment of hematologic malignancies, clinical impact of long lasting cytopenias and risk of late infections remains to be clarified. While short-term infections are a well-studied issue, data regarding late-onset infectious events is scarce. This retrospective study aims to describe epidemiology and potential risk factors for late-onset infections, defined as occurring from the third month since CAR T-cells infusion in patients who did not receive any further line of therapy. We enrolled a total of 129 patients receiving either CD19- or BCMA-targeting CAR-T therapy for NHL (n=117) and MM (n=12) between March 2019 and January 2024 in our Institution. At

the 90th day of follow-up, 98 patients were alive and suitable for analysis, median follow-up was 16 months. A median neutrophil count of 1790/mmc was observed at day 90 (range 390-15600), and G3 to G4 neutropenia was present in 23 patients (23%). Forty-nine (50% of patients) developed late infection for a total of 78 infectious events, 30 patients developed infection between day 90 and 180, 32 patients between day 90 and 360 and 13 of them were infected during both periods. Viral agents (58 %) were predominant among the causes, most prominently SARS-CoV2 airway infections (60%) whereas Cytomegalovirus reactivation caused only 13% of events. Bacterial infections accounted for 34% of infections, being the GI tract (23%), soft tissues (19%) and lower airways (19%) the most commonly affected systems. Fungal infections were the cause of 7% of the total events. Two MM patients in complete remission died from late-onset SARS-CoV-2 infection. (Table 1). Univariate analysis demonstrated a correlation between an increased incidence of late infections in MM *vs* NHL (91% *vs* 56% of patients) (p=0,007). No correlation was observed for age > 60 years, development of ICANS and CRS, exposure to steroids or tocilizumab, number of previous lines, previous autologous stem cell transplant, and G3-G4 neutropenia at day 90. In this study we observed late infections in 50% of patients with a predominance of viral respiratory infections, late infectious events were more frequent in MM patients, whereas neutropenia at 90 days doesn't appear to be a risk factor. With the limitations of a small sample size, no other major clinically detectable or laboratory-identifiable infectious risk factors emerged.

Table 1.

Late Infections		
	n	%
Total events	78	
Airway	34	44
Lung	8	10
Urinary Tract Infection	3	4
Gastrointestinal	8	10
Soft tissue	7	9
Sepsis	1	1
Central Venous Catheter	3	4
Febrile neutropenia	4	5
FUO	1	1
Viral reactivation	5	6
Other	4	5

Aetiology		
Viral	45	%
Influenza/rhinovirus	5	11
SARS-CoV2	27	60
CMV	6	13
JC	3	7
B19	3	7
VZV	1	2
Fungal	5	
Candidiasis	2	40
Aspergillosis	1	20
Fungal Suspected (radiological)	2	40
Bacterial	27	
Pneumonia	5	19
Soft tissue	5	19
Gastrointestinal	6	22
Urine tract Infection	3	11
Sepsis	1	4
Central Venous Catheter	3	11
Sinusitis	4	15
Unknown	1	4
Grade 5 late infections	2	4

C034

DIAGNOSTIC ACCURACY AND CLINICAL USEFULNESS OF LUNG ULTRASOUND IN ONCO-HEMATOLOGICAL PATIENTS WITH NEUTROPENIC FEVER: THE HEMATO-LUS STUDY

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Febrile neutropenia and pneumonia are common complications in onco-hematological pts undergoing intensive chemotherapy (IC) and stem cell transplantation (SCT). A rapid diagnosis and an effective clinical management are essential to avoid progression to acute respiratory failure. Chest X-ray (CXR) is the first diagnostic tool, but its accuracy is limited. High-resolution computed tomography (HRCT) is the reference test, however it is not always available. Lung ultrasound (LUS) is becoming a quick and reliable tool in the emergency setting for the bedside assessment of pneumonia, but data on neutropenic hematological pts are limited. We aimed to assess the diagnostic accuracy of LUS in onco-hematological pts with febrile neutropenia when performed by appropriately trained hematologists, compared to CXR and using HRTC as reference test. Clinical usefulness of LUS was compared to CXR. All consecutive onco-hematological pts with neutropenic fever hospitalized in our Institutions were enrolled between March 2023 and February 2024. At the onset of fever, all neutropenic (neu <1000/mm^3) pts underwent a bedside CXR and LUS. Both were performed blind to the result of the other test. In case of a positive CXR, persistent fever or respiratory failure, an HRTC was performed. We assessed the diagnostic accuracy of LUS and CXR compared to HRTC as sensitivity and specificity. Decision curve analysis (DCA) and net reclassification index (NRI) were used for evaluating clinical usefulness of LUS. 85 pts were enrolled. Median age was 60 ys, and the most frequent diagnosis was acute myeloid leukemia (42 pts, 49.4%). Most pts received IC (47, 55.3%), autologous (9, 10.6%) and allogenic (13, 15.3%) SCT. All enrolled pts were evaluated using CXR and LUS, and 39 of them (45.8%) also HRTC. When compared to HRTC, LUS showed a sensitivity of 100% (95%CI 87.7-100%) and a specificity of 70% (95%CI 34.8-93.3%). On the other hand, sensitivity and specificity of the bedside CXR were 70.4% (95%CI 49.8-86.2%) and 33.3% (95%CI 7.49-70.1%), respectively. LUS showed an area under the receiver operating characteristics curve (AUC ROC) of 83.3% (95%CI 67-99.7%, Panel A), while CXR of 51.9% (95%CI 33.3-70.4%, P .013). NRI of LUS was 29.6% for pneumonia, and 33.3% for no pneumonia cases using HRTC as reference test (Panel B shows the DCA). LUS performed by hematologists has a high diagnostic accuracy for assessing pneumonia among onco-hematological neutropenic pts and it appears superior to CXR.

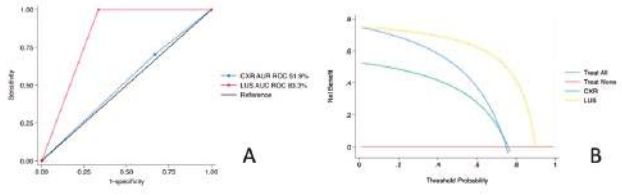

Figure 1.

C035

HIGHER INCIDENCE OF INVASIVE PULMONARY ASPERGILLOSIS IN ACUTE LYMPHOBLASTIC LEUKEMIA IN COMPARISON WITH ACUTE MYELOID LEUKEMIA: RESULTS OF A PROSPECTIVE MULTICENTRIC OBSERVATIONAL STUDY OF THE RETE EMATOLOGICA LOMBARDA (REL)

C. Cattaneo[1], M. Bernardi[2], N. Fracchiolla[3], F. Gigli[4], C. Basilico[5], L. Masina[1], E. Borlenghi[1], A. Bruno[2], G. Gela[3], G. Rossi[1], A. Tucci[1], D. Bertoli[6], F. Lussana[7,8], E. Todisco[9]

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The real impact of Invasive pulmonary aspergillosis (IPA) in acute lymphoid leukemia (ALL), beyond acute myeloid leukemia (AML), is still a matter of debate. To describe the incidence of IPA in AL patients (pts) and their clinical characteristics, as well as the predisposing factors, we carried out a prospective multicentric observational study within the Rete Ematologica Lombarda (REL). All consecutive AL patients diagnosed during a 3-year period and treated with curative intent were recorded. Data concerning age, gender, AL type, complete remission (CR) achievement, antifungal prophylaxis, neutropenia and mortality were collected. Between 2018 and 2020, 207 AL pts (AML: 165, ALL: 42) were evaluated in five Hospitals participating to the REL. Median age of the whole cohort was 58y, and M/F ratio 112/95. After induction treatment, CR was achieved in 153 of the 200 evaluable pts (76.5%), more frequently in ALL (38/42, 90.5%) than in AML pts (115/158, 72.8%) (p=0.0146). During induction, proven/probable (p/p) and possible (poss) IPA were diagnosed in 32/207 pts (15.4%), equally divided in p/p and poss (16 each, 7.7%). P/p IPA were more frequent in ALL than in AML (ALL: 7/42, 16.6% *vs* AML: 9/165, 5.4%; p= 0.0235); similarly, considering also poss IPA, incidence was higher, even if not significantly (9/42, 21.4% *vs* 23/165, 13.9%; p=0.2374). Antimould prophylaxis was protective against IPA in 202 evaluable pts (Yes: 22/171, 12.9%; No: 10/31, 32.3%, p=0.0134). Among ALL pts only 1/15 (6.7%) receiving antimould prophylaxis developed IPA, as compared to 8/27 (29.6%) of those not receiving antimould prophylaxis (p=0.1235). Both mean age and duration of neutropenia were significantly lower in ALL than in AML pts (46.02y *vs* 57.75y, p<0.0001 and 16.66d *vs* 27.96d, p<0.0001); however, an impact of duration of neutropenia on IPA incidence was observed only in ALL pts (IPA group: 24.38d; no IPA group: 14.79d, p=0.0359. Table 1 summarizes the clinical characteristics of AL pts in relation to IPA. After a median follow-up of 41 months, 116 (56%) pts are alive, without impact on mortality of IPA (IPA: 18/91, 19.8%, *vs* no IPA: 14/116, 12.1%, p=0.1746). Despite younger age, shorter duration of neutropenia and higher percentage of CR achievement, IPA, particularly p/p, was more frequently observed in ALL pts than AML during induction cht. However, probably thanks to the availability of new drugs and better management, IPA no longer seems to have an impact on long-term survival.

Table 1.

Table 1

	Whole cohort (n=207) (%)		AML (n=165) (%)		ALL (n=42) (%)	
	IPA (%)	No IPA (%)	IPA (%)	No IPA (%)	IPA (%)	No IPA (%)
Male gender	112 (54.1)		84 (50.1)		29 (69)	
	19 (59.4)	94 (53.7)	13 (56.5)	71 (53.4)	6 (66.7)	24 (63.2)
Median age (y, range)	58 (16-77)		59 (22-77)		48 (16-74)	
	58.5 (16-75)	58 (17-77)	60 (43-75)	59 (22-77)	48 (16-70)	48 (17-74)
Median duration of neutropenia (d, range)	23 (0-83)		26 (0-83)		14 (0-54)	
	26 (14-54)	23 (0-83)	29.5 (15-45)	25 (0-83)	21 (14-54)	13 (0-48)

Chronic lymphocytic leukemia and lymphoproliferative syndromes I

C036

MUTATIONAL STATUS OF KAPPA AND LAMBDA LIGHT CHAIN GENES INDEPENDENTLY PREDICTS TIME TO FIRST TREATMENT IN EARLY-STAGE CHRONIC LYMPHOCYTIC LEUKEMIA

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The mutational status of the immunoglobulin heavy chain variable region genes (IGHV) is a pivotal prognostic biomarker in chronic lymphocytic leukemia (CLL). Conversely, the repertoire and clinical impact of light chain genes has not been extensively explored in CLL. Tumor genomic DNA was extracted from peripheral blood mononuclear cells of 573 CLL patients, collected prospectively. Light chain gene rearrangements were amplified using leader or framework region 1 primers and sequenced by Sanger. The median follow-up was 11.6 years and patient characteristics were consistent with a real-world cohort of unselected CLL. A total of 530 productive rearrangements were identified. For kappa chains, the most frequent rearrangement involved IGKV4-1 in 83/404 (20.5%) patients, followed by IGKV3(D)-20 in 60/404 (14.8%). For lambda chains, the gene most frequently rearranged was IGLV3-21 in 32/168 (19.5%) followed by IGLV2-14 in 27/168 (16%). IGLV3-21^{R110} was recognized in 19/32 IGLV3-21 patients (representing 11.3% of the lambda rearrangements). The IGLV3-21 and IGLV3-21^{R110} rearrangements associated with IGHV3-21 genes, subset#2, borderline IGHV mutation percentage, and SF3B1 mutations (all p<0.001).

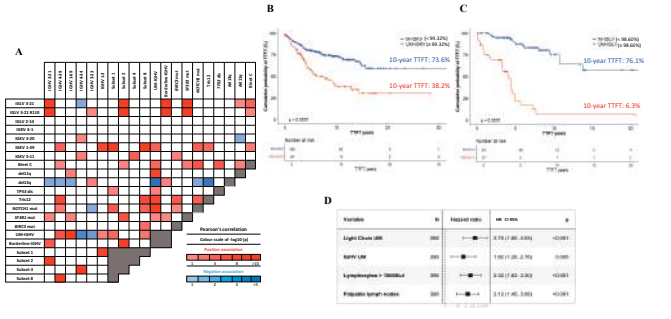

Figure 1.

Patients with IGKV1-39 gene rearrangements were likely to harbor IGHV4-39 (p<0.001) or IGHV1-2 (p=0.02) rearrangements, mutated NOTCH1, trisomy 12, and to belong to subset#1 and subset#8 (all p<0.001) (Figure 1A). Since there is no established cut-off of homology for light chain genes, the Maxstat algorithm was used to generate the optimal cut-off to predict time to first treatment (TTFT) in Binet A CLL patients (N=414). The optimal cut-off was 99.32% for kappa chain genes, and 98.60% for lambda. Using the new cut-offs, unmutated (UM) kappa patients exhibited a 10-year TTFT of 38.2% compared to 73.6% for mutated patients (p<0.001) (Figure 1B). Sim-

ilarly, UM-lambda patients presented a 10-year TTFT of 6.3% compared to 76.1% for mutated cases (p<0.001) (Figure 1C). More importantly, UM light chains (HR=2.70, 95% CI 1.80-4.05, p<0.001) maintained an independent association with a shorter TTFT when adjusted for the International Prognostic Score for Early-stage CLL (IPS-E) variables, namely UM-IGHV, palpable lymph nodes and lymphocyte count >15.000/ul (Figure 1D). The mutational status of the immunoglobulin light chain genes may represent a novel independent prognostic biomarker for early treatment requirements in early stage CLL. A validation cohort is currently under analysis.

C037

PREVALENCE AND CLINICAL IMPACT OF CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL (CHIP) IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Background. Clonal Hematopoiesis of Indeterminate Potential (CHIP) is associated with a variety of different diseases but its prognostic role in chronic lymphocytic leukemia (CLL) is unclear.

Methods. Tumor genomic DNA was extracted from granulocytes from CLL patients (N=367). Samples were analyzed by targeted next-generation sequencing (NGS), employing a custom panel of recurrently mutated genes in CHIP (N=28) and sequenced by MiSeq and NextSeq550 platforms (Illumina). Statistical analysis was performed using R studio and SPSS software.

Results. A total of 167 (45.5%) patients showed at least 1 CHIP mutation, which significantly correlated with older age (p=0.004). The most frequently mutated genes were *DNMT3A* in 89 (24.3%) patients, followed by *TET2* in 52 (14.2%) and *ASXL1* in 10 (2.7%) (Figure 1A). At the current median follow-up (13.9 years), CHIP$^+$ patients presented shorter overall survival (OS) compared to CHIP$^-$ patients (p=0.04) and this is mainly driven by *TET2* mutations, which emerge as an independent predictor of shorter OS (p=0.0076) when adjusted for age, *IGHV* and *TP53* status (Figure 1B, 1C). No difference in time to first treatment (TTFT) was observed between CHIP$^+$ and CHIP$^-$ patients. The potential clinical impact of CHIP in Richter transformation (RT) was also assessed. CHIP as a whole does not associate with an increased risk of RT, whereas *ASXL1* mutations independently associate with an in increased risk of RT (HR 6.80, 95% CI 1.54-30.14, p=0.01) even when adjusted for *TP53* disruption and *NOTCH1* mutations (Figure 1D, 1E). Subsequently, the clonal evolution of CHIP following therapy was assessed. Longitudinal analysis in 25 patients treated with chemoimmunotherapy (CIT) showed that CIT led to an increase in the number of CHIP mutations and in the variant allele frequency (VAF) of pre-existing mutations (p=0.004). At variance with CIT, CHIP dynamics during BCL2 inhibitors (BCL2i) (N=15) did not show significant differences in the VAF pre and post therapy (p=0.704). Notably, the presence of non *DNMT3A* CHIP mutations before starting BCL2i associated with higher risk grade ≥3 neutropenia (p=0.04) during BCL2i. In addition, the relationship between CHIP and cardiovascular side effects was assessed in BTK inhibitors (BTKi) treated patients (N=73). CHIP$^+$ *SF3B1* mutated patients showed an increased risk of atrial fibrillation compared to *SF3B1*$^-$ patients (p<0.0001).

Conclusions. This study suggests that CHIP may harbor potential clinical relevance in CLL and in RT.

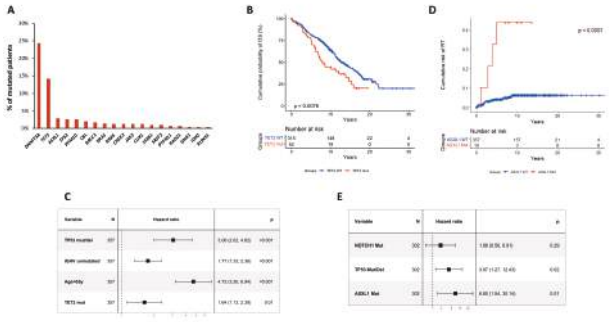

Figure 1.

C038

IGHV INTRACLONAL DIVERSIFICATION IDENTIFIES A CLL SUBSET WITH PARTICULARLY GOOD PROGNOSIS WITH FEATURE OF ANERGY AND EFFICIENT T-CELL INTERACTION

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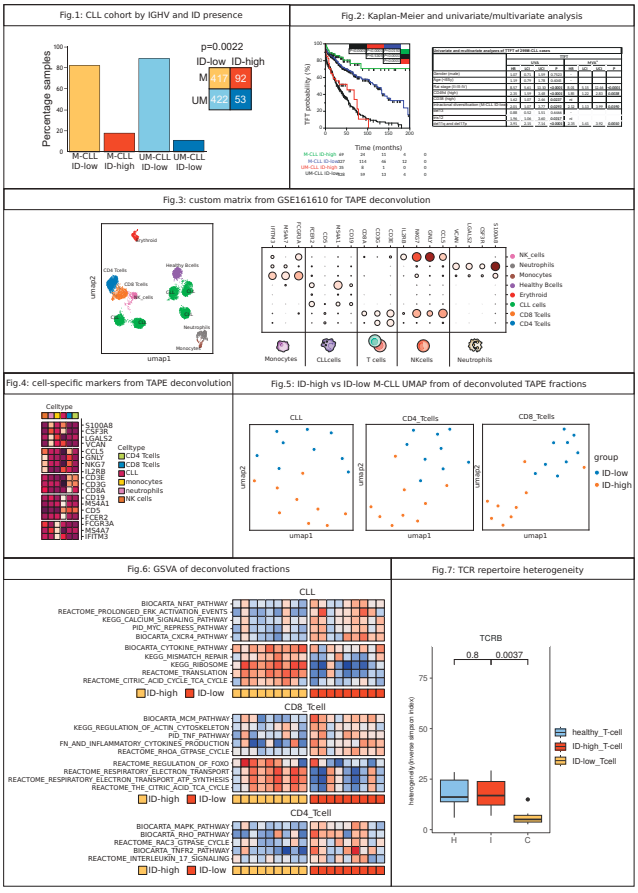
The mutational status of the IGHV gene is a prognostic/predictive marker in chronic lymphocytic leukemia (CLL). Despite the categorization in mutated (M) and unmutated (UM) IGHV, some CLL exhibit an ongoing somatic hypermutation, known as intraclonal diversification (ID). Here, we quantified ID from IGHV repertoire sequencing data (RepSeq), and evaluated its biological and clinical properties. Our original pipeline (patent n.102022000027138) for the ID evaluation identified among 983 CLL (508 M-CLL and 475 UM-CLL), 144 CLL with ID (14%, ID-high) and 839 without ID (ID-low, Figure 1). A significant overrepresentation of ID-high cases was found in M- over UM-CLL (P=0.002, Figure 1). Focusing on M-CLL, ID-high patients had significantly longer time-to-first treatment (TTFT) respect to ID-low patients (P=0.015; Figure 2). A multivariate analysis on M-CLL, confirmed ID as an independent variable along with Rai Stage, CD49d, and del11p/del17p (Figure 2). Bulk RNASeq performed on 18 whole blood M-CLL samples (9 ID-lo, 9 ID-high) were analyzed with Tissue-AdaPtive autoEncoder (TAPE) and cell type deconvolution was performed with a custom signature matrix extracted from published single cell RNA experiment (Figure 3). We observed high correlation between marker genes and RNASeq fraction (Figure 4). B- and T-cells showed distinct profiles between

ID-high and ID-low cell types (Figure 5). ID-high CLL cells displayed features of CLL anergy due to persistent ERK, NFATC1 activation and sustained calcium signaling (Figure 6). Conversely, ID-low CLL had an activated phenotype with the upregulation of translation and DNA reparation. In the context of CD8 T-cells, ID-high T-cells resembled cytotoxic CD8 in terms of upregulation of cytoskeleton remodeling, proliferation, cytokines production, down-regulation of FOXO transcription programs and TCA cycle/Oxidative respiration pathways. Lastly, on CD4 T-cell, the integrity of cytoskeletal pathways, the production of TNF and IL-17 suggested a polarization toward the Th17 phenotype in ID-high samples, known to associate with a favorable prognosis. In keeping, analysis of TCRB RepSeq data showed higher heterogeneity in the repertoire of T cell from M ID-high respect to M ID-low patients (Figure 7). In conclusion, we classified patients by ID presence demonstrating that ID is an independent prognostic factor in CLL. ID-high CLL display an anergic phenotype in combination with a more active T-cell compartment that would eventually control disease progression.



Figures 1-7.

C039

OUTCOMES IN HIGH-RISK SUBGROUPS AFTER FIXED-DURATION IBRUTINIB + VENETOCLAX FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)/SMALL LYMPHOCYTIC LYMPHOMA (SLL): UP TO 5.5 YEARS OF FOLLOW-UP IN THE PHASE 2 CAPTIVATE STUDY

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Background. The phase 2 CAPTIVATE study evaluated first-line ibrutinib (Ibr) + venetoclax (Ven) for CLL/SLL in 2 cohorts: minimal residual disease (MRD)–guided randomized discontinuation (MRD cohort) and Fixed Duration (FD cohort). Ibr±Ven retreatment was allowed in patients (pts) who had progressive disease (PD). Here, we report outcomes for pts with high-risk genomic features from the FD cohort and retreatment outcomes in pts from the FD cohort and MRD cohort placebo arm.

Methods. Pts aged ≤70 y with previously untreated CLL/SLL without restriction on genomic risk factors received 3 cycles of Ibr, then 12 cycles of Ibr+Ven (Ibr, 420 mg/d orally; Ven, 5-wk ramp up to 400 mg/d orally). On-study retreatment included single-agent Ibr (FD cohort or MRD cohort placebo arm); pts with PD >2 y after end of treatment (EOT) could be retreated with FD Ibr+Ven (FD cohort).

Table 1.

FD Cohort	With High-Risk Genomic Feature[a]		Without High-Risk Genomic Feature[a]	
	n	5-y PFS rate, % (95% CI)	n	5-y PFS rate, % (95% CI)
del(17p)/mutated *TP53*	27	41 (21–59)	129	73 (64–80)
Complex karyotype[b]	31	57 (37–72)	102	72 (61–80)
Unmutated IGHV[c]	40	68 (50–80)	44	85 (69–93)
del(11q)[c]	11	64 (30–85)	74	79 (67–87)

[a]Among pts with known baseline status.
[b]Defined as ≥3 chromosomal abnormalities.
[c]Excluding pts with del(17p)/mutated *TP53* or CK.

Results. In the FD cohort (n=159) with a median follow-up of 61.2 mo (range, 0.8–66.3), 5-y PFS and OS rates (95% CI) were 67% (59–74) and 96% (91–98), respectively. 5-y PFS rates were higher in pts with undetectable MRD at 3 mo after EOT in peripheral blood (83%) or bone marrow (84%) *vs* those without (48% and 50%, respectively). 5-y PFS rates (95% CI) in pts with genomic risk factors were: del(17p)/mutated *TP53* 41% (21–59), complex karyotype 57% (37–72), del(11q) 64% (30–85), and unmutated IGHV 68% (50–80) (Table). In total, 18 second malignancies occurred in 13 pts (10 events in 8 pts during FD Ibr+Ven, 6 events in 4 pts after EOT and before retreatment, and 2 events in 2 pts during retreatment). Of 202 pts who completed Ibr+Ven (FD cohort, n=159; MRD cohort placebo arm, n=43), 63 have had PD to date; PD occurred >2 y after EOT in 43 of 63 pts (68%), and 32 of 63 (51%) pts initiated retreatment with Ibr (n=25) or Ibr+Ven (n=7). With a median time on Ibr retreatment

of 21.9 mo (range, 0.03–50.4), ORR was 86% in 22 evaluable pts (best response: 1 CR; 1 nodular PR; 17 PR; 2 SD; 1 PD [Richter transformation]). With a median time on Ibr+Ven retreatment of 13.8 mo (range, 3.7–15.1), ORR was 71% in 7 evaluable pts (best response: 1 CR; 4 PR; 1 PR with lymphocytosis; 1 SD).

Conclusions. With up to 5.5 y of follow-up, FD Ibr+Ven continues to provide clinically meaningful PFS in pts with high-risk genomic features, as well as in the overall population. Ibr-based retreatment provides promising responses in pts needing subsequent therapy after the all-oral FD regimen of Ibr+Ven.

C040

COMBINATION OF ZANUBRUTINIB (ZANU) + VENETOCLAX (VEN) IN PATIENTS WITH TREATMENT-NAIVE (TN) CLL/SLL WITH DEL(17P) AND/OR TP53: PRELIMINARY RESULTS FROM SEQUOIA ARM D

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Background. Combination BCL2/BTKi treatment (tx) has been tolerable and led to durable responses in patients (pts) with CLL/SLL. Here, initial results are presented in pts with TN CLL/SLL with del(17p) and/or *TP53* mutation who received zanu+ven in SEQUOIA arm D.

Methods. SEQUOIA (NCT03336333) is an open-label, global, phase 3 study; arm D includes nonrandomized pts aged ≥65 y (or 18-64 y with comorbidities) who met iwCLL 2008 criteria for tx. After a 3-cycle zanu 160 mg BID lead-in, pts had 24 cycles of zanu+ven (ramp-up to 400 mg QD), then zanu monotherapy until PD, unacceptable toxicity, or early dose-stopping rules for zanu or ven were met (simultaneous CR/CR with incomplete hematopoietic recovery [CRi] and undetectable minimal residual disease [uMRD] $<1\times10^{-4}$ by flow cytometry in peripheral blood [PB] and bone marrow [BM] on 2 consecutive tests ≥12 wk apart). Responses were investigator assessed per modified iwCLL and Lugano 2014 criteria (SLL), with PB MRD assessment every 3 cycles for 2 y, then every 6 cycles. Safety per CTCAE and tumor lysis syndrome (TLS) risk per Cairo-Bishop criteria were also assessed. Pts with high TLS risk had any lymph node ≥10 cm or ≥5 cm with absolute lymphocyte count $\geq25\times10^9$/L.

Results. From Nov 2019-Jun 2022, 66 pts with centrally assessed del(17p) and/or *TP53* mutation were enrolled. By Oct 31, 2023 (median follow-up, 28.6 mo; range, 0.4-47.4), 55/63 pts (87%) who initiated zanu+ven remained on tx (16 zanu+ven; 39 zanu monotherapy after ven). Six pts discontinued the study (4 deaths; 1 withdrawal; 1 loss to follow-up); 3 discontinued tx during zanu lead-in. In 65 response-evaluable pts, ORR was 100% and CR+CRi rate was 45% (Table 1). uMRD occurred in 48% of pts in ≥1 PB sample. Median PFS was not reached; 36-mo estimated PFS was 92% (95% CI, 81%-97%). The most common all-grade nonhematologic TEAEs were COVID-19 (55%), diarrhea (41%), contusion (29%), and nausea (29%). Grade ≥3 nonhematologic TEAEs occurred in 44%; the most common were diarrhea (8%) and hypertension (8%). Neutropenia was the most common all-grade (21%) and grade ≥3 (17%) hematologic toxicity. At screening, 35% of pts had high TLS risk; this decreased to 3% after 3 zanu lead-in cycles. No TLS occurred.

Conclusions. Preliminary data show promising efficacy and good tolerability of zanu+ven in pts with high-risk TN CLL/SLL with del(17p) and/or *TP53* mutation. The safety profile of zanu+ven was consistent with prior studies, with no new safety signals identified.

Table 1.

Table. Efficacy Outcomes in Patients With del(17p) and/or *TP53* Mutation

	del(17p)+ or *TP53*+ (n=66)
Response evaluable, n (%)[a]	65 (98)
Best overall response, n (%)	
CR+CRi	29 (45)
Nodular PR	0
PR	35 (54)
PR with lymphocytosis	1 (2)
SD	0
ORR, n (%)	65 (100)
Best uMRD rate at any time in PB, n (%)	32 (48)

CRi, complete response with incomplete hematopoietic recovery; uMRD, undetectable minimal residual disease.
[a] Patients who received ≥1 dose of zanu with ≥1 post-baseline disease assessment.

Allogenic and autologous transplant II

C041

COMPARISON OF EFFICACY AND TOLERABILITY OF RUXOLITINIB PLUS EXTRACORPOREAL PHOTOPHERESIS COMBINATION VERSUS RUXOLITINIB ALONE VERSUS EXTRACORPOREAL PHOTOPHERESIS MONOTHERAPY FOR STEROID-REFRACTORY ACUTE GVHD: A GITMO RETROSPECTIVE STUDY

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Background. The aim of this retrospective multicenter GITMO study was to compare 3 different salvage treatments for steroid-refractory acute GvHD (SRaGvHD) in terms of overall and complete response rate (ORR, CRR) at day 28 after initiation of therapy, 1-year overall survival (1y-OS), non-relapse mortality (NRM) rate, incidence of chronic GvHD and infectious complications.

Methods. The study included 233 adult patients, allo-transplanted from 2015 to 2021, who were treated for SRaGvHD with: extracorporeal photopheresis (ECP) (group 1, n=124), ruxolitinib plus ECP (group 2, n=53) and ruxolitinib (group 3, n=56). Characteristics of patients and transplants were equally distributed, except for a higher median number of CD3+ infused cells in group 3; among SRaGvHD features, grade III-IV was significantly more frequent in group 2 and 3, multiorgan involvement in group 2, skin as single-organ involvement in group 1 (Table 1).

Results. No significant differences were found in ORR and CRR at day 28 (79% and 58% in group 1; 66% and 45% in group 2; 80% and 64% in group 3; p=.127 and p=.121 respectively). Among the 3 groups we couldn't find significant differences in ORR at day 28 either in patients with SRaGvHD grade III-IV (p=.631) or with multiorgan (p=.753) or liver-gut involvement (p=.465). Onset of moderate-severe chronic GvHD was observed in 65 patients (28%), without differences in the 3 groups (p=.229). Among the most commonly observed infectious events, incidence of bacteremia was more frequent in group 3 (10% group 1 *vs* 15% group 2 *vs* 27% group 3, p=.019); incidence of clinically significant CMV infections and pneumonia were 23% and 10% with no differences among the 3 groups (p=.385 and p=.747 respectively). At a median follow-up of 16.8 (1.7-91.5) months, NRM incidence was 34% and 1y-OS after transplant 67%, without significant differences in the 3 groups (p=.186 and p=.275 respectively).

Conclusions. This retrospective analysis confirms ruxolitinib as the new standard for SRaGvHD in real life and ECP as a valid option with a safe profile, that should be considered in patients with active infections or high risk of bacteremia due to cytopenia. Moreover, this study suggests that ruxolitinib in combination with ECP is safe and effective in overcoming the worst prognosis of difficult-to-treat patients with multiorgan and severe SRaGvHD, but the schedule and the real impact of this combination have still to be determined in prospective studies.

Table 1.

Characteristics	Overall n=233	Group 1 n=124	Group 2 n=53	Group 3 n=56	p-value
Median recipient age at transplant, years (range)	54 (18-75)	53 (18-73)	55 (20-75)	54 (19-71)	0.520
Median donor age at transplant, years (range)	35 (12-73)	34 (12-68)	38 (19-74)	35 (19-71)	0.168
Sex, n (%)					
• Male	150 (64)	81 (65)	36 (68)	33 (59)	0.587
• Female	83 (36)	43 (35)	17 (32)	23 (41)	
Recipient/donor sex match, n (%)					
• Male/male	101 (43)	54 (43)	25 (47)	22 (39)	0.892
• Male/female	49 (21)	27 (22)	11 (21)	11 (20)	
• Female/male	47 (20)	26 (21)	10 (19)	11 (20)	
• Female/female	36 (16)	17 (14)	7 (13)	12 (21)	
HCT-CI >2, n (%)	85 (36)	43 (35)	19 (36)	23 (41)	0.707
Recipient/donor CMV serology status, n (%)	n=232	n=123			
• Negative/negative	30 (13)	17 (14)	9 (17)	4 (7)	0.594
• Negative/positive	21 (9)	12 (10)	6 (11)	3 (5)	
• Positive/negative	63 (27)	34 (28)	12 (23)	17 (30)	
• Positive/positive	118 (51)	60 (49)	26 (49)	32 (57)	
Recipient/donor blood type, n (%)	n=228	n=123	n=49		
• Matched	106 (47)	54 (44)	25 (51)	27 (48)	0.860
• Minor mismatch	58 (25)	33 (27)	10 (20)	15 (27)	
• Major or bidirectional mismatch	64 (28)	36 (29)	14 (29)	14 (25)	
Diagnosis, n (%)					
• AML	95 (41)	47 (38)	24 (45)	24 (43)	0.791
• MDS	49 (21)	27 (22)	7 (13)	15 (27)	
• Lymphomas	33 (14)	19 (15)	8 (15)	6 (11)	
• ALL	33 (14)	17 (14)	9 (17)	7 (12)	
• other	23 (10)	14 (11)	5 (9)	4 (7)	
Active disease at transplant	n=221	n=119	n=48	n=54	0.051
• n (%)	62 (28)	36 (30)	7 (15)	19 (35)	
Conditioning regimen intensity, n (%)					
• MAC	144 (62)	79 (64)	33 (62)	32 (57)	0.701
• RIC	89 (38)	45 (36)	20 (38)	24 (43)	
Immunosuppressive prophylaxis, n (%)	n=225	n=120	n=50	n=55	
• ATLG regimen	110 (47)	56 (47)	19 (38)	35 (64)	0.054
• PTCy regimen	55 (24)	27 (22)	17 (34)	11 (20)	
• non ATLG-PTCy regimens	60 (26)	37 (31)	14 (28)	9 (16)	
Donor type and HLA match, n (%)					
• Matched sibling	48 (20)	25 (20)	12 (23)	11 (19)	0.330
• Haploidentical related	55 (24)	29 (23)	16 (30)	10 (18)	
• Matched unrelated	70 (30)	43 (35)	12 (23)	15 (27)	
• Mismatched unrelated	60 (26)	27 (22)	13 (24)	20 (36)	
Graft source, n (%)					
• PB	195 (84)	98 (79)	47 (89)	50 (89)	0.121
• BM	38 (16)	26 (21)	6 (11)	6 (11)	
Median CD34+ infused cells, x10^6/kg patient (range)	5.4 (0.7-15.2)	5.3 (0.7-15.2)	6.1 (1.6-12.2)	5.2 (1.3-13)	0.359
Median CD3+ infused cells, x10^7/kg patient (range)	17.4 (0.3-67.5)	15.1 (0.3-44.9)	19 (1.4-64)	21.4 (2.2-67.5)	**0.016**
Acute GVHD grading at onset, n (%)	n=228	n=121		n=54	
• I	39 (17)	23 (19)	8 (15)	8 (15)	0.322
• II	97 (43)	58 (48)	19 (36)	20 (37)	
• III	64 (28)	29 (24)	19 (36)	16 (30)	
• IV	28 (12)	11 (9)	7 (13)	10 (18)	
aGVHD post DLI, n (%)	13 (6)	4 (3)	4 (8)	5 (9)	0.200
Median time from transplant to SRaGVD, days (range)	56 (11-1707)	51 (17-1707)	60 (21-810)	63 (11-1208)	0.265
SRaGVHD grade, n (%)	n=230	n=121			**0.000**
• III-IV	108 (47)	35 (29)	39 (74)	34 (61)	
SRaGVHD multiorgan involvement, n (%)	102 (44)	45 (36)	34 (64)	23 (41)	**0.002**
SRaGVHD single-organ skin, n (%)	89 (38)	65 (52)	11 (21)	13 (23)	**0.000**
Median duration of ruxolitinib treatment, days (range)			144 (7-1142)	97 (10-980)	0.094
Median duration of ECP treatment, days (range)		82 (2-1295)	61 (2-883)		0.804
Median number of ECP procedures, n (range)		13 (2-99)	12 (2-51)		
Median interval of ruxolitinib-ECP start in group 2, days (range)			8 (0-14)		
Ruxolitinib-ECP first start in group 2, n (%)			n=47		
• ruxolitinib first			19 (40)		
• ECP first			22 (47)		
• simultaneous			6 (13)		
Ruxolitinib starting dose, n (%)			n=49	n=53	
• 20 mg/die			22 (45)	33 (62)	0.078
• 10-15 mg/die			27 (55)	20 (38)	

C042

PRE-EMPTIVE DONOR LYMPHOCYTE INFUSION IN THE TREATMENT OF ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROME RELAPSED AFTER ALLOGENEIC STEM CELL TRANSPLANTATION SIGNIFICANTLY IMPROVES OVERALL SURVIVAL: A FRENCH-ITALIAN EXPERIENCE ON 103 PATIENTS

E. Accorsi Buttini[1], C. Doran[2], M. Malagola[1], V. Radici[1], M. Farina[1], M. Galli[1], E. Morello[1], A. Leoni[3], F. Re[3], S. Bernardi[3], N. Polverelli[4], M. Mohty[2], D. Russo[1], E. Brissot[2]

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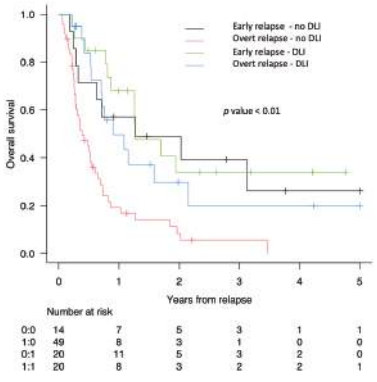
Background. Disease relapse after allogeneic stem cell transplantation (allo-SCT) is the main challenge for curing acute myeloid

leukemia (AML) and myelodysplastic syndrome (MDS). This study aimed to evaluate the overall survival (OS) of AML and MDS following allo-SCT relapse and identify the best therapeutic strategy to improve patients outcome.

Methods. We retrospectively analyzed 553 AML and MDS patients allotransplanted between 2015 and 2021, at Saint-Antoine University Hospital, Paris (n=420) and Spedali Civili di Brescia, Brescia (n=133). 134 (24%) patients relapsed. Among these, 103 (77%) received subsequent treatment and were included in the study. Forty/103 (39%) underwent a donor lymphocyte infusion (DLI)-based regimen, with 9 receiving DLI alone and the rest combining DLI with a hypomethylating agent (HMA), HMA+venetoclax, FLT3-inhibitors, intensive chemotherapy, a second allo-SCT or other therapies. The remaining 63/103 (61%) patients were treated with the same agents but not including DLI.

Results. With a median follow-up of 1.6 years, the 1-, 2-, and 5-year OS rates for patients treated following allo-SCT relapse were 40%, 20%, and 15%, respectively, compared to 6%, 3%, and 0% for untreated patients (p<0.01). The 1-, 2-, and 5-years OS for patients treated in a pre-emptive setting was 60%, 36%, and 30% respectively compared to 26%, 12%, and 6%, respectively (p<0.01) for patients treated in overt relapse. Regarding the type of treatment, patients who received DLI-based regimens demonstrated 1-, 2-, and 5-year OS rates of 55%, 32%, and 32%, respectively, compared to 27%, 16%, and 7% for patients treated with other therapies (p<0.01). Finally combining the timing of treatment (in early versus overt relapse) with the DLI administration (yes versus no) the optimal outcome occurred when relapse was promptly detected, and pre-emptive therapy was initiated, especially with DLI administration. The 1-year OS for patients treated pre-emptively was 67% for those receiving DLI and 54% for those treated without DLI, while for patients in overt relapse, the 1-year OS was 43% for those treated with the DLI-based regimen and 17% for those treated without DLI (p<0.01) (Figure 1). On multivariate analysis, DLI treatment and a pre-emptive setting were independent factors associated with better OS (p=0.03 and p< 0.01).

Conclusions. Relapse treatment with pre-emptive therapies results in improved outcomes, especially when combined with DLI administration.



The OS of the 103 patients treated after allo-SCT relapse based on treatment strategy.

Figure 1.

C043

CLINICAL SIGNIFICANCE OF CYTOKINE RELEASE SYNDROME FOLLOWING HLA-MISMATCHED HEMATOPOIETIC STEM CELL TRANSPLANTATION: A RETROSPECTIVE MONOCENTRIC STUDY ON 250 TRANSPLANTS

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Cytokine release syndrome (CRS) has been described after allogeneic hematopoietic stem cell transplantation (HSCT), mostly after haploidentical HSCT, peripheral blood HSCT, and in post-transplant Cyclophosphamide (ptCy) based platforms: we focused on the clinical significance of CRS following all HLA-mismatched transplants, regardless of stem cell source and GvHD prophylaxis regimen. The identification of CRS was conducted retrospectively on patients receiving haploidentical or single mismatch unrelated donor (MMUD) HSCT, experiencing a microbiologically negative fever after graft infusion. CRS was defined and graded basing on the revised American Society for Transplantation and Cellular Therapy criteria. Cox regression proportional hazard was used to assess the impact of CRS on clinical outcomes. 250 patients were included, 173 (69%) receiving haploidentical and 77 (31%) MMUD HSCT. The median age was 61 years (range 19-75), most common diagnosis was AML (117 patients, 47%).

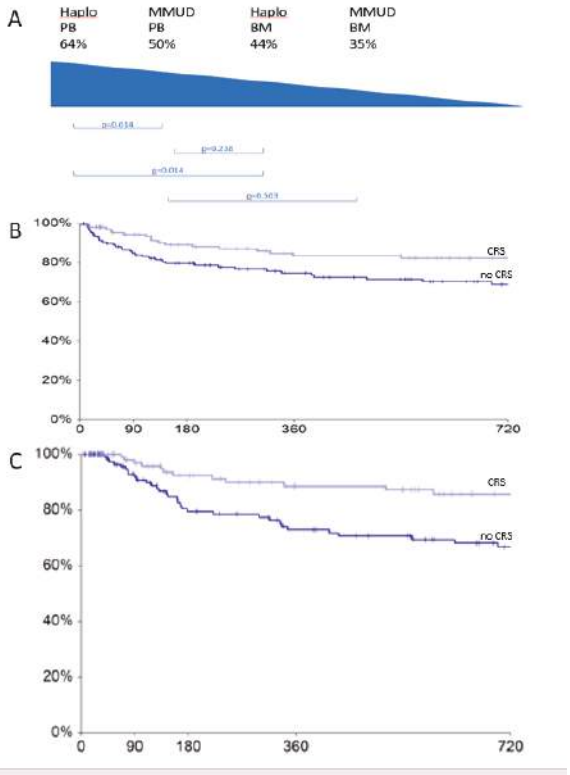

Figure 1
A. Incidence of the CRS according to graft source
B. Impact of CRS on NRM
C. Impact of CRS on RFS

Figure 1.

A myeloablative conditioning regimen was preferred in 107 (43%) patients; ptCy based GvHD prophylaxis was administered in

203 patients (81%). Stem cell source was bone marrow in 125 patients (50%) and peripheral blood in the other 50%; the total incidence of acute and chronic Graft versus Host Disease (GvHD) was 55% and 71% respectively. CRS was present in 117 patients (47%); more commonly of grade 1 (81% of all CRS). CRS occurred more frequently after haploidentical HSCT (p=0.037, HR 1.19), especially after peripheral blood graft (p=0.014 HR 1.79). When applying ptCy based GvHD prophylaxis, the totality of CRS fully resolved after the second administration. CRS occurrence correlates with lower 2-years non-relapse mortality (NRM) (18% versus 31% in CRS and non-CRS patients respectively, p 0.037). The cumulative incidence of 2-year NRM was lower in CRS patients (17%) versus non-CRS patients (29%, p 0.044). CRS also correlates with longer relapse free survival (RFS) (85% versus 66% in CRS and non-CRS patients respectively p <0.001). The 2-year cumulative incidence of relapse was higher in non-CRS patients (18%) versus CRS patients (10%), despite not reaching statistical significance (p 0.08). When looking at acute and chronic GvHD occurrence we found no difference between the two groups. Figure 1 resumes the results of our analysis. Mismatch-driven CRS correlates with longer RFS, with lower NRM after allogeneic HCST, and does not increase acute or chronic GvHD occurrence.

C044

INFECTIOUS COMPLICATIONS IN PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION (HSCT) FOR ACUTE MYELOID LEUKEMIA AFTER CPX-351 TREATMENT: A "REAL-LIFE" MULTICENTER RETROSPECTIVE EXPERIENCE BY THE SEIFEM GROUP

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In a previous study by SEIFEM group, we evaluated the risk of infection in 200 real-life AML patients (pts) treated with CPX-351, showing an incidence of infectious complications in line to the pivotal studies and a low rate of fungal infections and infection-related mortality. 88/200 (44%) pts underwent allogeneic stem cell transplantation (HSCT). The present study focused on this subgroup of transplanted pts in order to evaluate their outcome and infectious complications during HSCT. We analyzed 70/88 patients [(F/M 36/34; median age 63 y.o. (range 18-79)] with HSCT available data. The disease status at HSCT was: complete remission in 56 pts, partial remission in 5 pts and AML progression in 9 pts. 64/70 (91%) pts had experienced a febrile episode during previous CPX-351 treatment. Donors were unrelated in 26 pts, siblings in 10 pts and haploidentical in 35 pts. Stem cell source was peripheral blood in 60 pts, bone marrow in 9 pts and CBU in 1 patient. Most pts (56%) underwent conditioning with TBF-based regimens (Thiotepa, Busulfan and Fludarabine). GvHD prophylaxis schedules mostly included cyclophosphamide combined with mycophenolic acid and/or cyclosporine (53%) or thymoglobuline and methotrexate (30%). Engraftment was reached in all pts; the median time to neutrophil recovery (>0.5×109/L) was 18 days (range 15-57). Twenty-two pts (31%) developed acute skin GvHD (2 stage 1, 20 Stage 2-3) associated to only 3 gut (1 stage 1, 2 stage 2) and 1 pulmonary involvement. Febrile events occurred in 55/70 (88%) pts: 37 (67%) were classifiable as microbiologically documented infections, 2 (3%) as clinically documented infections and 16 (23%) as FUO. Most of the microbiologically documented infections were of bacterial origin (34/37), isolated (26) or associated to fungal (4) or viral infections (4). In particular, bacteremia occurred in 34 pts (49%). Fungal infections were diagnosed in 6 cases (8.5%) (5 probable Aspergillus spp. and 1 Pneumocystis jirovecii pneumonia). All pts received antibacterial therapy, while antifungal treatment was administered in 11 pts. Infection-mortality rate was 5.7% (4/70). Median overall survival as not reached with 57% of pts alive at 60 months (Figure 1). This study shows a low rate of HSCT related complications, such as GvHD and infections, in a population of pts with AML previously treated with CPX-351. We therefore confirmed the efficacy of CPX-351 in inducing prolonged survival in high-risk patients.

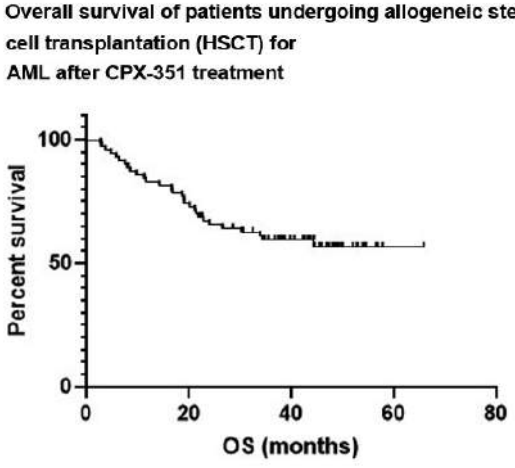

Figure 1.

C045

IMPACT OF DARATUMUMAB IN HEMATOPOIETIC STEM CELL MOBILIZATION AND TRANSPLANT OUTCOME IN NEWLY DIAGNOSIS MULTIPLE MYELOMA PATIENTS: REAL-WORLD EVALUATION IN TRIVENETO AREA

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Backgrounds. Autologous stem cell transplantation still represents the standard of care in transplant eligible (TE) newly diagnosis multiple myeloma (NDMM), therefore an adequate stem cell yield is essential for timely hematopoietic reconstitution after this treatment. In clinical trial, the addition of Daratumumab to VTd during induction has shown a negative impact in stem cell (HSC) harvesting, without affecting the feasibility and safety of transplantation, even though stem cell yield was lower.

Methods. In a retrospective observational trial, we aimed to evaluate the impact of adding daratumumab to VTd induction on HSCs mobilization and transplant outcome, comparing it with VTd induction alone in NDMM in Triveneto area. We evaluated 111 consecutive TE NDMM patients (pts) that were mobilized for HSC collection and which received induction with or without daratumumab. Descriptive analyses were used to summarize patient characteristics, stem cell mobilization yields, and engraftment outcomes.

Results. 61 MM pts in Dara-VTd group and 50 in VTd group were evaluated with no difference in term of MM characteristics. As mobilization agent, high dose cyclophosphamide plus G-CSF was used in 55 and 47 pts respectively, at different doses. Plerixafor was performed in 22 (37%) and 7 (14%) pts in Dara-VTd group and VTd group, respectively (p=0.008). No difference in term of n° of leukapheresis (LK) was observed (p=0.13) but a statistically significant difference in circulating CD34+/kg at first LK, 57 *vs* 85/mcl in Dara-VTd and VTd group, respectively (p=0.001) was found. Median harvested CD34+/kg in first LK and median total harvested CD34+/kg were lower in DaraVTD group than VTD group (p<0.01). Melphalan at different doses was used as conditioning regimen in all pts, with statistically significant difference between the 2 groups in term of CD34+/kg re-infused (p=0.023). Engraftment was observed in all pts with no delay in platelets recovery (14 *vs* 13 days after HSC reinfusion, respectively (p=0.15)) and neutrophilic recovery (11 days for both groups (p=0.90). 17 (28%) and 19 (40%) infectious complications were observed in the 2 groups (p=0.24). Days of hospitalization were 22 days and 21 days in the 2 groups, respectively.

Conclusions. We confirm in a real-world experience that Daratumumab impairs mobilization and stem cell collection, with lower HSCs collected and increased use of Plerixafor, without a severe impact on transplant outcome.

Chronic myeloid leukemia and cytogenetic

C046

TWO DECADES LATER: A 20-YEARS REAL-WORLD ANALYSIS OF 160 CP-CML PATIENTS TREATED WITH IMATINIB MESYLATE

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Since its FDA approval in 2001, Imatinib mesylate (IMA) has revolutionized Chronic Myeloid Leukemia (CML) treatment, and still has a pivotal role in its management. Our study aimed to assess the long-term outcomes and treatment-free remission (TFR) rates of IMA in 160 unselected CML patients (pts) between 1986 and 2023, with a median follow-up of 12.2 years (8.9-37.1). Median age at diagnosis was 59.3 years (24.3-96.6), with M:F ratio 1.2:1. All pts were in chronic phase; ELTS risk score was low, intermediate, and high in 95 (59.3%), 54 (33.7%) and 11 pts (6.8%), respectively. Comorbidities were present in 66.8% of pts. Previous therapies included interferon (IFN) single-agent (*n*=2), IFN+hydroxyurea (HU) (*n*=26) and IFN+cytarabine (*n*=2). Standard doses of IMA (400 mg QD) were administered in 144 (90%) of pts after median 0.9 months from diagnosis. All pts achieved the complete hematologic response (CHR) after median 0.5 months (0.07-12.7), and the 3-months complete cytogenetic response (CyR) was achieved in 92/112 (82.1%) evaluable pts.

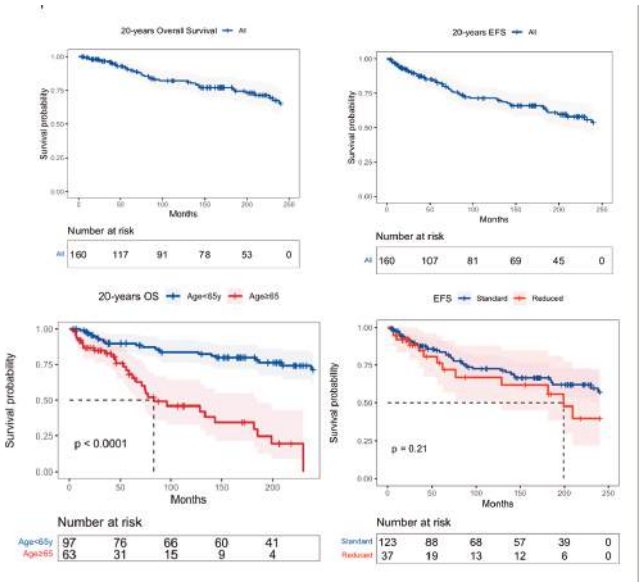

Figure 1.

The major molecular response (MMR) rates at 3, 6 and 12-months were respectively 6.3%, 38.0%, and 51.7%, with 74.4% of pts achieving an Early Molecular Response (*i.e.* 3 months-*BCR::ABL1*^{IS} ≤10%). The 20-year cumulative MMR and deep molecular response (DMR, MR4 and MR4.5) rates were 98.6% and 92.0%, respectively. In the whole cohort, the 20-year Overall Survival (OS) and Event-free survival (EFS) rates were respectively

65.1% (95% CI, 0.55-0.76) and 53.8% (95% CI, 0.44-0.65). While better OS and EFS rates was reported in pts aged <65 y (p<.0001) and without cardiovascular comorbidities at baseline (p<.0001), no differences were found according to gender in both OS (p=0.79) and EFS (p=0.21) . After median 7.3 months (0.69-188.4) from diagnosis, dose reduction was performed in 24 pts (15%), mainly due to toxicity (75%). No differences were found in 20-years EFS between patients who received standard dose *vs* reduced doses of IMA (p=0.21). Overall, 22 pts switched to a second-line TKIs, mainly due resistance (72.6%). TFR was successfully attempted in 21 pts after a median time from diagnosis of 166.3 months (88.8-246.2). Adverse events (AEs) were observed in 81.2% of pts, mainly of grade 1-2 (75.3%). Overall, 30 patients died, with one case of progression to a blast phase of disease. In conclusion, IMA demonstrates excellent outcomes with a favorable long-term safety profile.

C047

GENOMIC LANDSCAPE AND CLONAL HEMATOPOIESIS DYNAMICS IN PATIENTS WITH EPITHELIAL OVARIAN CANCER (EOC) DURING PARP INHIBITORS TREATMENT: PRELIMINARY RESULTS OF A PROSPECTIVE LONGITUDINAL STUDY

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Background. PARPi are used in EOC as maintenance therapy in platinum sensitive patients. We recently published an increased incidence (8.7%) of therapy related myeloid neoplasms (t-MNs) and persisten clonal cytopenias in EOC patients after PARPi treatment. Identification of "actionable" gene mutations that may raise risk for t-MNs during PARPi treatment is mandatory.

Aims. We present preliminary data of a prospective longitudinal biological study aimed at identifying genetic abnormalities, that may increase t-MNs risk during PARPi.

Methods. We performed genomic analyses using custom gene panels designed for assessment of germline and clonal hematopoiesis (CH) variants. For CH we used high-sensitivity technologies (VAF>0.05%). Germline analyses were done on buccal swab DNA at enrolment, while CH analyses on PB before and every six months post-PARPi therapy.

Results. We analyzed 32 EOC patients for both germline and CH variants, median age 60.5 years (38-76). Most patients received olaparib; 13 women (40,6%) received ≤6 cycles of platinum-based chemotherapy. We found 46 germline variants, 13 (28%) were pathogenic mutations (PM) in 38% patients; 11 involved BRCA1/2 genes, while 2 AK2 and SLC37A4 genes not commonly associated with EOC. CH analyses were performed on 32 patients pre-PARPi, 31 after 6, 7 after 12, 5 after 18 and 4 after 24 months of PARPi treatment. We identified 275 unique CH-mutations, 54.55% were defined as Potential Driver (PD-CH). The most frequently mutated genes were DNMT3A, TP53 and PPM1D (Figure 1a). All patients harbored CH-mutations before PARPi and at least 1 PD-CH mutation. The absolute number of CH or PD-CH mutations did not change over time while an increasing VAF of PD-CH variants was seen in 4 patients (Figure 1b). In particular, we identified 22 unique PD-CH mutations in PPM1D and 34 in TP53, in 62.5% (20/32) and in 71.9% (23/32) of patients, respectively. For both genes, after PARPi, we scored an increased VAF of at least one of these mutations in ~75% of patients (Figure 1c, 1d).

Conclusions. PPM1D gene encodes for a phosphatase that negatively regulates P53. C-terminal truncating mutations in PPM1D cause loss of its degradation, resulting in increased enzymatic functions. We hypothesize that concomitant PPM1D and TP53 clonal expansion, due to PARPi selective pressure, may result in increased PPM1D phosphatase activity towards mutated P53, resulting in a further detrimental effect of its activity translatinge in higher risk of t-MNs.

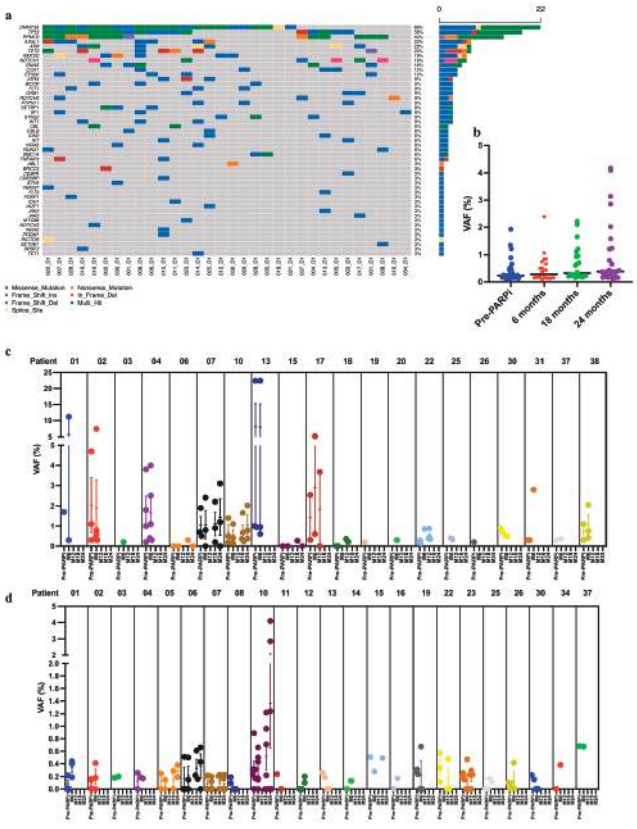

Figure 1 | a. Oncoplot for all patients at PrePARPi (D1) time point. **b.** Variant allele frequency (VAF) distribution of PD-CH mutations in four patients among time points: PrePARPi, 6, 18 and 24 months post PARPi therapy. **c.** For each patients harboring *PPM1D* mutations, we showed VAF at different time points: PrePARPi, 6, 18 and 24 months (M) post PARPi therapy. **d.** For each patients harboring *TP53* mutations, we showed VAF at different time points as for panel c.

Figure 1.

C048

RNA SEQUENCING BY NGS: A NEW PARADIGM FOR COMPREHENSIVE AND SIMULTANEOUS GENE FUSIONS IDENTIFICATION IN DIFFERENT HEMATOLOGIC MALIGNANCIES

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Introduction. The accurate molecular profiling is crucial for the proper risk-category allocation and management of Lymphoid and

Myeloid Acute/Chronic Leukemia (ALL/AML/CML) patients. Here we report a study in which mRNA-targeted Next-Generation Sequencing (NGS) has been retrospectively applied to better define conventional and rare fusion transcripts in different leukemias.

Methods. We analyzed 21 samples deriving from ALL, CML, CML in Blast Crisis, and AML patients at disease onset, relapse, or resistance. Patients were previously profiled by conventional cytogenetic, FISH, and molecular assays (Q-PCR, MLPA, and transcriptome analysis). RNAseq was performed using TruSeq Stranded mRNA kit (Illumina) and libraries were paired-end sequenced on NovaSeq platform (Illumina). Alignment to GRCh37 genome assembly was performed by DRAGEN tool and NGS data were visualized by Integrative Genomics Viewer and manually analyzed.

Results. Canonical chimeric transcripts deriving from t(9;22), t(4;11), t(1;19) and t(12;21) and rare fusions from t(8;13) and t(3;3) were confirmed in 14/21 patients. Alterations involving *P2RY8::CRLF2*, *ZMYM::FLT3*, and *IKZF1::ZPBP* were also confirmed in two Ph-like and one IKZF1+ patients, respectively. No fusions were detected in negative controls. In two patients previously unrecognized fusions involving *DUX4::UBQLN*1 and *TPM4::KLF2* genes were detected thus allowing in the first case the definition of Ph-like. In one patient carrying the *TRAD::TLX1* rearrangement (detected by FISH) no fusion transcript was detected as expected, while in a case harboring t(14;17), the gene fusion *IGH::AC091133.3* was not confirmed due to the involvement of a long noncoding RNA as *IGH* partner. In a t(14;20) ALL, the corresponding *IGH::CEBPB* fusion was not confirmed either by RNAseq as well as FISH. As expected, in Ph+ ALL the *BCR::ABL* chimeric transcript could not be detected when the leukemic burden was below 1%.

Conclusion. RNAseq improves the molecular characterization of patients with lymphoid and myeloid malignancies. It allows the identification of common and, most importantly, rare fusion genes. This approach is not designed for a specific disease, and it is applicable, in the same experimental session, to different hematologic conditions. It will lead to a remarkable change in the daily diagnostic work-up.

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EXPLORING INNOVATIVE METHODS TO DETECT MOLECULAR MINIMAL RESIDUAL DISEASE IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction. The most important prognostic factor in Acute Lymphoblastic Leukemia (ALL) is Minimal Residual Disease (MRD). The gold standard for MRD detection is Allele-Specific Oligonucleotides quantitative PCR (ASO-qPCR). This approach can reach high sensitivities but suffers from some limits: in a proportion of follow-up samples, it detects very low MRD levels classified as "Positive Not-Quantifiable" (PNQ) that could derive from few residual leukemia cells but also from non-specific amplification of normal lymphocytes. This uncertainty causes difficulties in clinical decision-making. We applied innovative molecular approaches, such as digital droplet PCR (ddPCR) and Next-Generation Sequencing (NGS) to overcome this limit.

Methods. We considered 67 MRD evaluations from 41 follow-up samples (52 performed with 2 ASO-primers) of 18 adult ALL patients. These samples proved PNQ, low-positive (MRD level ≤10E-4), or negative results by ASO-qPCR. Samples were re-analyzed by ddPCR (QX200 BioRad) by testing 1.5 μg of DNA per sample. Among them, 13 were also analyzed by amplicon-based NGS according to EuroClonality guidelines. Libraries were prepared using 600 ng of DNA per sample, sequenced on MiSeq platform (Illumina), and analyzed by Vidjil software.

Results. The 45 PNQ by ASO-qPCR were redefined by the ddPCR approach as follows: 14 positives and quantifiable, 29 negatives, and only 2 cases remained PNQ (as defined by the presence of 2 positive events). This result is consistent with a significant reduction in PNQ results ($p<0.00001$). The additional 22 low positive or negative ASO-qPCR evaluations were confirmed by ddPCR with an agreement of 86% (Cohen's $\kappa= 0.673$, 95% CI: 0.335-1.000). The NGS approach, applied on 13/41 samples, redefined the 9 PNQ as positive (6/9) or negative (3/9) ($p=0.00002$). Regarding the 2/13 positive samples by ASO-qPCR, they resulted as negative by NGS and the 2/13 negative resulted as positive. This latter finding could be due to the higher specificity of NGS. We observed a moderate agreement between results obtained by ddPCR and NGS (Cohen's $\kappa= 0.494$, 95% CI: 0.005-0.982).

Conclusions. ddPCR and NGS are promising tools to detect MRD in ALL. Both methods are associated with an increased specificity and, after standardization and validation within prospective clinical trials, they could define new standards for the resolution of ambiguous ASO-qPCR results.

C050

NILOTINIB AS FIRST-LINE TREATMENT IN NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE: A VERY LONG-TERM ANALYSIS OF THE OBSERVATIONAL CML0912 GIMEMA STUDY

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Introduction. Nilotinib (NIL) is second generation tyrosine-kinase inhibitor (TKI), approved in Europe for the first-line treatment Ph+ chronic myeloid leukemia (CML) since 2010. In the last update of the ENESTnd study, NIL showed higher response rates compared to imatinib, with lower rates of disease transformation and higher cumulative rates of treatment free remission (TFR) eligibility. The survival was comparable; however NIL exhibited higher cardiovascular (CV) and metabolic toxicity, which may limit its superior efficacy. Generic NIL will be available shortly: long-term efficacy and safety data from non-company sponsored studies are relevant to optimize treatment choice.

Aims and Methods. To investigate the long-term safety and efficacy of frontline NIL out of interventional studies, an analysis of the prospective observational CML0912 GIMEMA study has been performed. From 2013 trough 2016, a total of 124 patients (pts) (53% males and 47% females, median age 51years old) with new diagnosis of CML were enrolled from 27 Italian Centers. Molecular analysis was standardized and performed within the LabNet Network.

Results. Comorbidities at baseline were present in 37% of the pts. Sokal risk at baseline was 44%, 37% and 19% for low, intermediate and high risk. The median follow-up was 92 months (mos) (1-140), with an overall survival of 92% at 120mos. At 60mos, 72% of pts remained within the protocol, with a median dose of 600 mg. A progressive dose reduction was observed starting from 24mos, with an increasing rate of pts treated with 300 mg. Optimal response was reached by 81% at 3mos (≥ MR^1), 81% at 6mos (≥ MR^2), 71% at 12mos (≥MR^3). At 24mos, rate of ≥MMR, ≥MR^4 or ≥$MR^{4.5}$ was 64%, 39.5% and 25%, respectively. At 60mos the rate of ≥MMR, ≥MR^4 or ≥$MR^{4.5}$ was 57%, 47.5% and 32%. Study was discontinued by 35 pts (11 for failure, including 1 blastic phase, 4 for toxicity, 20 for other). The most frequent subsequent therapy was ponatinib. A total of 3 deaths from any cause occurred. TFR was attempted by 5 pts.Gastrointestinal toxicity, skin rash turn to be the most common adverse events. Metabolic modifications occurred in 10% of pts, major CV events occurred in 6.5%.

Conclusions. The study confirms the high rate of MMR and DMR induced by NIL. Most of pts managed to complete 5 years of therapy. The CV toxicity turned out to be lower than ENESTnd analysis, likely secondary to dose reductions. Data on TFR deserve a subsequent and more specific analysis.

Myeloproliferative neoplasms I

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REVISED "IRR6" MODEL IN INTERMEDIATE-1 RISK MYELOFIBROSIS PATIENTS TREATED WITH RUXOLITINIB

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The Response to Ruxolitinib (RUX) After 6 Months (RR6) model allows early identification of RUX-treated myelofibrosis (MF) patients (pts) with lower overall survival (OS). To validate the RR6 in a large cohort of MF pts and to develop a prognostic score specific for intermediate-1 DIPSS risk pts, we performed a sub-analysis of the "RUX-MF" retrospective study that currently includes 1055 pts treated with RUX according to standard practice. RR6 variables were evaluable in 776 pts. According to the RR6 model, 267, 371, and 138 pts were at low (score 0), intermediate (score 1-2) or high (score >2) risk, with 5-yr overall survival (OS) of 64.1%, 51.8% and 44.5%, respectively ($p<0.001$) (Figure 1A). In the 428 intermediate-1 pts, the RR6 model did not discriminate intermediate and low-risk pts, with comparable 5-yr OS of 74.4% and 72.0%, respectively (vs 57.4% in high-risk) (Figure 1B). Thus, new variables were tested based on clinical plausibility. Particularly: 1) spleen reduction ≥50% (SR50) from baseline was used instead of spleen reduction ≥30%; 2) underdosed RUX compared to PLT count at ≥1 timepoint replaced RUX

dose <20mg BID at all timepoints. Cox multivariate analysis confirmed the following risk factors for shorter OS: 1] underdosed RUX at ≥1 timepoint (HR, 3.9; p<0.001); 2] lack/loss of SR50 from baseline, including no SR50 at mos 3 and 6; no SR50 at mos 6 after SR50 at mos 3 (HR, 1.5; p=0.02); 3] RBC transfusions at all timepoints (HR, 1.9; p=0.01). In univariable analysis, RBC transfusion at 2 timepoints was also significant (HR, 2.1; p=0.05). Two points were assigned to underdosed RUX in ≥1 timepoint; 1.5 points to RBC transfusions at all timepoints and to lack/loss of SR50; 1 point to RBC transfusions at 2 timepoints. A revised model specific for intermediate-1 pts (iRR6) was built, identifying 3 groups: low (score 0, 20.3%), intermediate (score 1-2, 45.8%), and high risk (score >2, 33.9%), with 5-yr OS of 84.8%, 76.4% and 56.6%, respectively (p<0.0001) (Figure 1C). Here, we validated the RR6 in a large cohort of MF pts treated in a real-world setting. With specific adjustments, the 'iRR6' model was developed to achieve a more robust prognostication in intermediate-1 pts. Lack or loss of SR50, RUX underdosing and RBC transfusions are key factors for early detection of RUX-treated intermediate-1 pts who might benefit from early therapy switch.

Figure1: (**A**) Validation of RR6 model on total cohort; (**B**) RR6 model applied on Intermediate-1 risk cohort; (**C**) The "iRR6 (intermediate-1 RR6) model

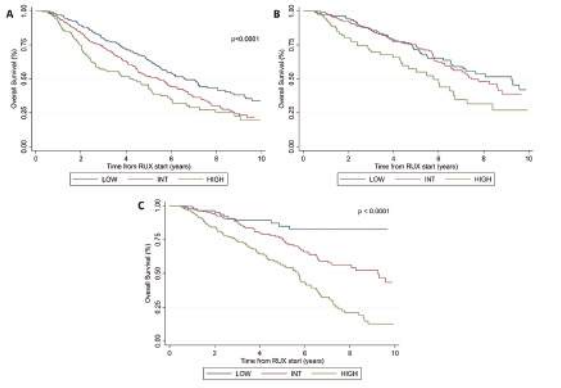

Figure 1.

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CALRETICULIN MUTATIONS INFLUENCE RESPONSE AND OUTCOME IN TRANSPLANT-AGE MYELOFIBROSIS PATIENTS TREATED WITH RUXOLITINIB

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Calreticulin (CALR) mutations are detected in around 20% of primary myelofibrosis (MF) patients (pts). Ruxolitinib (RUX) is a JAK2 inhibitor that has demonstrated clinical activity in MF pts regardless of the driver mutation. Data on large cohorts of CALR-mutated (CALR-mut) pts on RUX therapy are lacking. The "RUX-MF" retrospective study includes 1055 RUX-treated MF pts. At RUX start, 523 were transplant-age (<70 yrs) and CALR (n.82; type 1: 62.5%; type-2: 33.3%) or JAK2 (n. 441) mutated. These pts were included in this analysis.

Table 1.

Table 1: Baseline characteristics and outcome measures in transplant-age CALR vs JAK2-mutated patients

	CALR (n.82)	JAK2 (n. 441)	p
Median age, years (range)	60.6 (24.0-69.8)	62.8 (26.5-69.9)	0.17
Male Sex, n. (%)	51 (62.2%)	243 (55.1%)	0.24
RUX starting daily dose, n. (%), *on*			
10-20 mg	30 (36.6%)	283 (64.2%)	0.90
30-40 mg	52 (63.4%)	158 (35.8%)	
Lower than prescribing dose, n. (%)	27 (32.9%)	172 (39.2%)	0.28
Dose reduction @6mos, n. (%)	14/46 (30.4%)	77/273 (28.2%)	0.76
Grade of fibrosis < 2, n. (%)	12/77 (15.6%)	113/417 (27.1%)	**0.03**
DIPSS score, n. (%)			
INT-1	52 (63.4%)	301 (68.3%)	0.73
INT-2	25 (30.5%)	117 (26.6%)	
HIGH	5 (6.1%)	23 (5.2%)	
High Molecular Risk mutations, n. (%)	24/37 (64.9%)	63/135 (46.7%)	**0.05**
Platelet count, median (range), x 10^9/L	250.5 (53-982)	264.5 (14-1425)	0.64
Platelet count < 100 x 10^9/L	11 (13.4%)	37 (8.4%)	0.15
Leukocytes, median (range), x 10^9/L,	8.7 (2.9-71.1)	11 (2.1-80)	**0.01**
Leukocytes <4 x 10^9/L, n. (%)	8 (9.8%)	38 (8.6%)	0.76
Hemoglobin, median (range), g/dL	10.6 (5.6-14.4)	11.5 (6.0-18.3)	**0.001**
Hemoglobin < 10 g/dL, n. (%)	33 (40.2%)	129 (29.3%)	**0.05**
Blasts, mean (range), %	1.6 (0-9)	0.9 (0-10)	**<0.001**
Blasts ≥ 1%, n. (%)	45/81 (55.6%)	147/425 (34.6%)	**<0.001**
Spleen length below costal margin, median (range), cm	9 (0-30)	10 (0-35)	0.79
Spleen > 10 cm, n. (%)	36/81 (44.4%)	188/436 (43.1%)	0.83
Total Symptoms Score, median (range)	20 (0-87)	20 (0-100)	0.10
TSS ≥ 20, n. (%)	40/76 (52.6%)	258/416 (62.0%)	0.12
Spleen response @6mos, n. (%)	16/68 (23.5%)	91/376 (24.2%)	0.91
Symptoms response @6mos, n. (%)	31/59 (52.5%)	230/332 (69.3%)	**0.01**
Any grade Hematological Toxicity @6mos			
Overall anemia, n. (%)	40/73 (54.8%)	169/42.9%)	**0.05**
Treatment-emergent anemia, n. (%)	15/45 (33.3%)	67/277 (24.2%)	0.19
Overall thrombocytopenia, n. (%)	16/73 (21.9%)	77/393 (19.6%)	0.65
Treatment-emergent thrombocytopenia, n. (%)	12/67 (17.9%)	56/369 (15.2%)	0.57
Allogeneic transplant, n. (%)	27 (32.9%)	65 (14.7%)	**<0.001**
Leukemic transformation (LT), n. (%)	7 (8.5%)	67 (15.2%)	0.11
Incidence rate of leukemic transformation (%pts-years)	2.0	3.3	0.21
RUX discontinuation, n. (%)	56 (68.3%)	257 (58.3%)	**0.05**
Incident rate of RUX discontinuation (%pts-years)	24.0	16.1	**0.009**
Incidence rate of Events (death, RUX discontinuation, LT)	24.9	16.9	**0.01**
(%pts-yr)			
Event-free survival at 3 years, (%)	50.5%	55.9%	
Event-free survival at 5 years, (%)	20.2%	42.6%	
Death, n. (%)	32 (39.0%)	151 (34.2%)	0.19
Overall survival at 3 years, (%)	79.7%	81.5%	
Overall survival at 5 years, (%)	63.7%	69.1%	

At baseline (BL), median age of CALR-mut pts was 60.6 yrs. Large splenomegaly (>10cm BCM) and high symptoms burden (TSS≥20) were present in 44.4% and 52.6% of pts, respectively. At least one cytopenia (Hb<10 g/dl and/or PLT<100x10^9/L and/or

WBC<4x10^9/L) was present in 51.2%. Compared to JAK2-mut, CALR-mut pts had comparable spleen length, TSS, and DIPSS risk distribution, but significantly lower WBC/Hb levels, and higher incidence of G3-4 marrow fibrosis, peripheral blasts and high molecular risk mutations (Table 1). At 6 months, CALR-mut pts had significantly lower rates of IWG-MRT symptoms response (52.5% *vs* 69.3%, p=0.02) and higher rates of anemia compared to JAK2-mut pts (54.8% *vs* 42.9%, p=0.05). After a median RUX exposure of 2.4 yrs, 74 pts had a leukemic transformation (LT), 183 pts died and 313 discontinued RUX. The incidence rate ratio (IRR) of LT were comparable in CALR and JAK2-mut pts (2.0 *vs* 3.3%p-y, p=0.21), while rates of RUX discontinuation (24.0 *vs* 16.1%p-y, p=0.009) and allogenic transplantation (ASCT) (8.9 and 3.4%p-y, p<0.001) were higher in CALR-mut pts. Overall survival (OS) at 5 ys was 63.7% and 69.1% in CALR-mut and JAK2-mut pts, respectively. In multivariate analysis, predictors of worse OS in CALR-mut pts were BL cytopenia (HR: 2.3; p=0.04) and large splenomegaly (HR: 2.2; p=0.05). Event-free survival (EFS, including death, LT, and RUX discontinuation) was 20.2% and 42.6% in CALR and JAK2-mut pts (p=0.02). In transplant-age MF pts, CALR mutations were associated with significant BL clinical burden, higher rates of RUX discontinuation, and poorer EFS, with increased use of ASCT compared to JAK2-mut pts. In CALR-mut pts, BL cytopenia and large splenomegaly correlated with lower OS, suggesting more personalized therapy in these pts. These data will serve as a reference for clinical results with alternative drugs in CALR-mut pts.

C053

ANALYSIS OF CARDIOVASCULAR RISK IN 920 PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS USING NATURAL LANGUAGE PROCESSING

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Background. Thromboembolic events represent the most common cause of morbidity and mortality in myeloproliferative neoplasms (MPN). Natural language processing is a branch of machine learning involving computational interpretation and human language analysis. CogStack is an information extraction architecture incorporating structured and unstructured electronic health record (EHR) components.

Aims and Methods. We aimed to employ a machine-learning approach to determine the prevalence and impact of cardiovascular risk factors upon thrombotic events during follow-up. Data extracted from CogStack was processed by a medical concept annotation toolkit (MedCAT).

Results. We evaluated data from 360 polycythaemia vera (PV) and 560 essential thrombocythaemia (ET) patients seen at Guys' and St Thomas NHS Foundation Trust (GSTT) between 2005 and April 2023, including 24,155 individual EHR documents. In ET, hypertension (HTN) was the most prevalent comorbidity, identified in 21.3% (119) of patients, followed by hypercholesterolemia (9.6%), while, overall, 20% (112) experienced a thrombotic event. This included thrombosis not otherwise specified (NOS) in 8% (45), cerebrovascular accident (CVA) in 7.7% (43), and myocardial infarction (MI) in 3.6% (20). HTN was also the most identified condition in PV, seen in 23.1% (83) of patients. In PV, thrombosis NOS was observed in 19.4% (70), CVA in 14.2% (51), venous thromboembolism (VTE) in 23.3% (84) and MI in 3.1% (11). Overall, 35% (126) of cases had a thrombotic event. Comparing the two cohorts, a significantly greater frequency of events was observed in PV patients for CVA (p=0.002), portal vein thrombosis, and VTE (both p<0.001) when compared to those with ET (Table 1). ET patients with HTN were more likely to have CVA (p=0.032) and VTE than those without (p=0.021). Similarly, PV patients with HTN were more likely to develop CVA (p=0.004). On multivariate analysis, HTN was confirmed to increase the risk of any type of thrombotic event in both ET and PV cohorts (OR 2.5; 95% CI 1.5-4.2; p<0.001 in ET, and 1.5; 95% CI 1.1-2.8; p<0.016 in PV).

Conclusions. We describe a novel machine learning approach to assess cardiovascular comorbidities in patients with MPN, allowing big data analysis. We provide a rare 'real-world' report on the prevalence of comorbidities in this group, confirming increased CVA and VTE in patients with HTN and a significantly higher risk of thrombotic events in patients with a diagnosis of PV when compared with ET.

Table 1.

Type of thrombosis	ET (560 patients) n (%)	PV (360 patients) n (%)	*p*
Deep venous thrombosis	8 (1.4)	10 (2.8)	0.15
Pulmunary embolism	10 (1.8)	10 (2.8)	0.314
Myocardial infarction	20 (3.6)	11 (3.1)	0.673
Cerebrovascular accident	43 (7.7)	51 (14.2)	*0.002*
Portal vein thrombosis	7 (1.3)	18 (5)	*<0.001*
Cerebral venous thrombosis	6 (1.1)	1 (0.3)	0.177
Thrombosis, NOS	45 (8)	70 (19.4)	*<0.001*
Venous thromboembolism	65 (11.6)	84 (23.3)	*<0.001*
Overall thrombotic events	112 (20)	126 (35)	*<0.001*

C054

REAL-WORLD ASSESSMENT OF ROPEGINTERFERON ALFA-2B IN POLYCYTHEMIA VERA PATIENTS: INSIGHTS FROM A MULTICENTER STUDY IN CAMPANIA

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Ropeginterferon alfa-2b (Ropeg) emerges as a novel, long-lasting mono-pegylated IFN approved in Italy for treating polycythemia vera (PV) in adult patients without symptomatic splenomegaly and reimbursed for PV patient intolerant to hydroxyurea (HU), women of childbearing potential, and individuals with a history of skin cancer (SC). Ropeg proved effective and safe in phase 3 trials, but more data is needed to understand its real-world use. The study collected clinical data to assess the safety and efficacy of Ropeg in PV patients across five hematological centers in Campania. Ropeg was administered as per the data sheet, complete hematological response (CHR) was evaluated according to ELN criteria. Additionally, HCT, PLT, WBC and molecular responses were analyzed separately. A total of 47 PV patients were enrolled, with a median age at Ropeg start of 60 years (range 28-90), and 70% (33/47) were male. Thirty patients

switched from prior HU after a median time of 11.8 months (range 1-299), due to intolerance. Three patients also transitioned from ruxolitinib, and one from peg-IFN. Ropeg was used as first-line therapy for 3 women of childbearing age, 2 patients with prior SK, and 8 male patients who were intolerant to phlebotomies and declined HU. The median time from PV diagnosis and Ropeg initiation was 45 months (range 1-345). In the year prior to starting Ropeg, the median number of phlebotomies was 2 (range 1-5). The median time on Ropeg was 12 months (range 1-21), with the median starting dose being 125 mcg every two weeks (range 50-150). CHR rate as well as HCT, PLT and WBC response increased over treatment (Figure 1). At 12 months CHR rate was 64.7% for the 17 evaluable patients, all but one had JAK2V617F allele burden reduction. Ten patients (21.2%) required additional phlebotomy sessions. Three patients had grade 1 liver function test increases, which resolved after dose reduction, and one patient developed autoimmune thyroiditis without discontinuing treatment. After three months, four patients discontinued Ropeg for the following reasons: suspected Ropeg-related depression, gastrointestinal bleeding, worsening splenomegaly, autoimmune disease; one patient died from an unrelated cause. Our findings indicate that Ropeg is generally well-tolerated and shows improvements in hematologic parameters. Although some response rates may vary, the overall trend is positive, with several measures reaching complete or near-complete response over time.

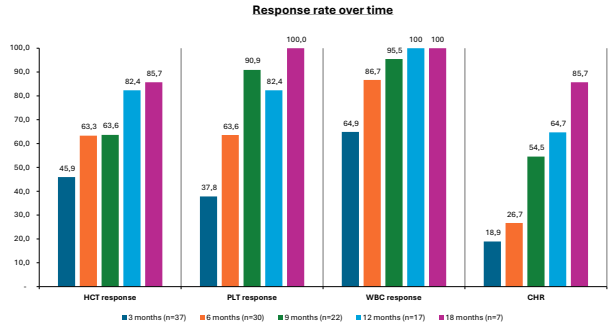

Figure 1.

C055

PELABRESIB PLUS RUXOLITINIB COMBINATION THERAPY IN JAK INHIBITOR-NAÏVE PATIENTS WITH MYELOFIBROSIS IN THE PHASE 3 MANIFEST-2 STUDY: PRELIMINARY TRANSLATIONAL EVIDENCE OF BONE MARROW RECOVERY

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Introduction. Pelabresib (PELA), an investigational, oral, small molecule, BET inhibitor, is being evaluated in the Phase 3 MANIFEST-2 study (NCT04603495) in combination with Janus kinase inhibitor (JAKi) ruxolitinib (RUX), *vs* placebo (PBO) + RUX, in JAKi-naïve pts with myelofibrosis (MF). Results show potential of PELA+RUX to improve the four hallmarks of MF, with significantly reduced splenomegaly, improved symptom score, improved anemia, and reduced bone marrow (BM) fibrosis at Week (W)24.

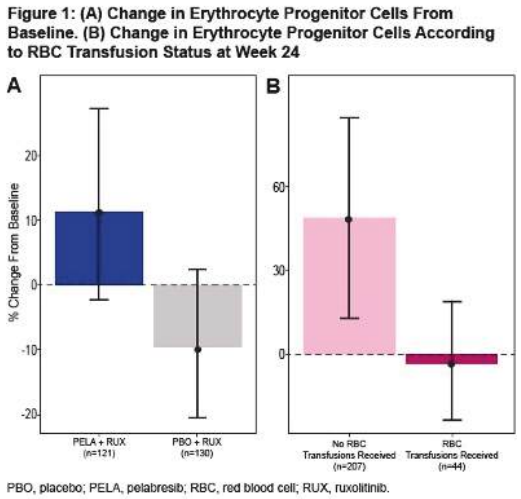

Figure 1.

Methods. Mutational analyses were conducted from peripheral blood samples by NGS. NF-κB–regulated proinflammatory cytokine (CK) levels were measured by bead-based multiplex assay from plasma. Reticulin fiber density (RFD), CD61+ megakaryocytes (MKs), and CD71+ erythrocyte progenitor cells (EPCs) were assessed by digital pathology.

Results. In total, 41.3% (19/46) *vs* 37.8% (14/37) of pts treated with PELA+RUX *vs* PBO+RUX had ≥20% *JAK2* variant allele fraction (VAF) reduction at W48. *JAK2* VAF reduction was associated with the primary endpoint SVR35 response (≥35% spleen volume reduction from baseline [BL]; p<0.001) at W24. A greater reduction in CK levels was observed with PELA+RUX *vs* PBO+RUX at W24 (-33.9% [CI -36.5, -31.1] *vs* -20.8% [CI -23.7, -17.9]; p<0.001), and decreased CK levels were associated with SVR35 (p<0.001) and TSS50 responses (≥50% reduction in total symptom score from BL; p=0.005). Greater reductions in RFD (-5.2 arbitrary units [CI -6.9, -3.5] *vs* -1.0 [CI -6.6, -1.7]; p<0.001) and in MK density (-54.5 cells/mm^2 [CI -70.8, -38.3] *vs* -27.4 cells/mm^2 [CI -42.9, -11.9]; p=0.012) were seen in PELA+RUX *vs* PBO+RUX at W24. An increase in EPC proportions from BL was observed with PELA+RUX *vs* a decrease with PBO+RUX (11.4% [CI -2.4, 27.2] *vs* -9.8% [CI -20.6, 2.5]; p=0.019) (Figure 1A). Pts who did not require RBC transfusions showed a greater increase in the proportion of EPCs at W24 (Figure 1B).

Conclusions Results from the MANIFEST-2 study indicate a potential for PELA to enhance clinical responses to RUX by further reducing *JAK2* VAF levels and decreasing NF-κB–regulated CKs. The latter was associated with SVR35 and TSS50 responses. PELA+RUX resulted in improvement of the BM microenvironment. EPC increase was associated with amelioration of anemia. This correlation suggests that PELA+RUX could lead to more profound and durable clinical responses in pts with MF.

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Haemostasis, thrombosis, thrombocytopenia and platelet diseases I

C056

ABSTRACT NOT PUBLISHABLE

C057

ITALIAN REGISTRY ON ACTIVE ADULT IMMUNE THROMBOCYTOPENIA (ITP) - GIMEMA ITP0918 STUDY: A GENERAL SNAPSHOT WITH A FOCUS ON TREATMENTS BEFORE AND AFTER THE INTRODUCTION OF TPO-RA

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Background. Registry studies are an important source of real-world clinical and patient-reported data. Italian registry on active adult ITP aims to produce a dynamic picture of disease natural history and therapeutic management of patients. This analysis focused on therapeutic choices analyzed by ITP phase.

Methods. From October 2018 to April 2024 26 hematological centers in Italy joined the Registry, sequentially recruiting adults with primary ITP (pITP) on active treatment at the time of enrollment: initiating a 1st line (group A) or modifying a previous treatment (group B) or on ongoing treatment (group C). Historical data are retrospectively collected at study entry and prospectively at annual visits, using REDCap. The study is sponsored by GIMEMA Foundation (Rome). Data collection and analysis are performed by Hematology Project Foundation (Vicenza).

Results. On April 15, 2024, 971 patients were recruited, of which 892 were evaluable for the analysis: 130 (14.6%) in group A and 762 (85.4%) in group B+C. Median time from diagnosis to enrollment was 3.9 yrs. Median age at diagnosis and at enrollment was 52 and 62 yrs respectively. Male were 384 (43%) and female were 508 (57%). Median platelet count was $95x10^9$/L at enrollment and $19x10^9$/L at diagnosis. At entry, 152 (91 A and 61 B+C) patients were newly diagnosed ITP, approximately 40% of whom required a 2nd line therapy; in these patients, most common 2nd line therapy was eltrombopag (57%), followed by romiplostim (18%) and rituximab (12%). 93 and 647 patients were in persistent or chronic phase of ITP at baseline, respectively. Median duration of ITP at study entry was 7 mo for persistent ITP patients and 81 mo for chronic ones. Median previous lines of therapy was 2. In patients treated before 2010, most prescribed 2nd line treatment was splenectomy (53%) followed by rituximab (25%) and azathioprine (9%). In those diagnosed after 2010, most prescribed 2nd line treatment was eltrombopag (62%) followed by romiplostim (14%) and rituximab (9%). Splenectomy was performed in 118 (12%) patients, 55 (47%) before 2010 and 63 (53%) after 2010 (23 in the last 5 yrs).

Conclusion. The Italian ITP registry represents the most important experience of real-life multicenter data in Italy on adult patients with active ITP. It captured the change in therapy management, highlighting an increasingly early use of TPO-RA. Splenectomy emerges as a valid therapeutic option still used in current clinical practice.

C058

HYPERCOAGULABILITY AND INFLAMMATORY BIOMARKERS PREDICT THE DISEASE PROGRESSION OF PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC): A PROSPECTIVE COHORT STUDY

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Background. NSCLC is a highly prevalent tumor with a poor outcome that calls for new prognostic tools. We have previously demonstrated that hypercoagulability and inflammatory biomarkers might be useful in evaluating tumor outcomes in breast cancer patients.

Aim. To determine if hypercoagulable and inflammatory biomarkers can predict 6-month disease progression (DP) in patients with advanced NSCLC.

Methods. We analyzed a cohort of NSCLC patients enrolled in the HYPERCAN study (ClinicalTrials.gov ID#NCT02622815). The patients were followed from enrollment, before beginning chemotherapy, up to DP. Blood samples were collected at enrollment and analyzed for complete blood cell count, fibrinogen, factor VIII (FVIII), D-dimer, and prothrombin fragment 1+2 (F1+2) levels.

Results. 719 patients (489M/230F, median age: 66 years) with a new diagnosis of advanced NSCLC (568 metastatic and 151 locally advanced) were analyzed. Within 6 months, we recorded a cumulative incidence of DP of 38% in a median time of 144 days (55-180). At enrollment, patients who developed DP had significantly higher levels of leukocytes, D-dimer, FVIII, and fibrinogen than patients who remained DP-free. By multivariable analysis, corrected for age and sex, leukocyte count, D-dimer, and fibrinogen levels were identified as independent risk factors for DP. Based on the coefficients of the 3 biomarkers, we generated a continuous risk score (AUC 0.603, p<0.001) able to stratify the patients in a high *vs* low risk of DP. By Kaplan Meier, the 6-month cumulative incidence of DP was 59% (IC 95% 53-64%) *vs* 30% (IC 95% 22-38%) in the high *vs* low-risk category HR 2.21 (IC95% 1.65-2.97; log-rank p<0.001).

Conclusions. This study demonstrates the utility of prechemotherapy hypercoagulation and inflammatory biomarkers in developing a prognostic score for NSCLC patients, which classifies patients into risk categories for DP. Upon external validation, clinicians may use the score to identify patients requiring more frequent surveillance and intensive therapy.

C059

ITALIAN REAL-WORLD EXPERIENCE WITH THE USE OF FOSTAMATINIB IN ADULT PATIENTS WITH CHRONIC IMMUNE THROMBOCYTOPENIA

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The results of FIT-1 and FIT-2 trials in adult patients (pts) with chronic immune thrombocytopenia (cITP) showed an initial response rate of 43% and a stable response rate of 18% to Fostamatinib (F), with approximately 25% of pts that received treatment for at least 6 months. The aim of this study was to evaluate in a real-world setting the impact of F in adult pts with refractory cITP treated in Italy. We performed a retrospective multicenter observational study that included consecutive cITP pts who received at least one dose of F outside clinical trials between October 1st, 2021 and April 1st, 2023. The primary endpoint of the study, as a possible surrogate of both efficacy and safety, was the proportion of pts who received F for at least 6 months. 91 pts were enrolled from 20 Italian centers, 59% female, median age 63 years (21-86). 4 pts had secondary ITP (APS 3, SLE 1).

Table 1.

Event	Any grade	Grade 1-2	Grade 3-4	F-related
Diarrhea	13	13	0	12
Hypertension	8	7	1	7
Transaminitis	8	6	2	7
Neutropenia	4	0	4	3
Asthenia	3	3	0	1
Pyrexia	3	3	0	0
Infections	3	2	1	0
• COVID19	1	1	0	0
• COVID19 Pneumonia	1	0	1	0
• Influenza	1	1	0	0
Nervous system	3	3	0	1
• Aphasia	1	2	0	0
• Carotid arteriosclerosis	1	2	0	0
• Headache	1	1	0	1
Neoplasm	2	0	2	0
• Colon cancer	1	0	1	0
• Lymphoma	1	0	1	0
Femur fracture	1	0	1	0
Peripheral oedema	1	1	0	0
Deep venous thrombosis	1	0	1	0
Hematoma	1	1	0	0
Urticaria	1	1	0	0
Other	7	5	2	0
Overall	**59**	**45 (76%)**	**14 (24%)**	**31 (52%)**

Median time from ITP diagnosis to F treatment was 7 years; 82% of pts previously received 3 or more lines of therapy. 57% received more than a TPO-RAs and 23% underwent splenectomy. At the time of this analysis 89/91 pts are evaluable for efficacy. 34 (38.2%) and 30 (33.7%) pts experience response (R) or complete response (CR) to F according to IWG criteria; R and CR were achieved within month 3 of therapy in 60 pts and from month 4 to 6 in 4. At months 6 the proportions of pts in R, CR, no response and loss of response was 16 (22%), 18 (25%), 38 (53%), respectively. At the time of data cut-off, the median duration of treatment was 3.7 months (range 0.5-19.4) and the projected Kaplan-Meyer 6 and 12-month proportion of pts still receiving F was 40% and 28%. During the period of treatment 69 pts (78%) required to increase F to 150 mg bid. Table 1 summarizes the safety profile. 59 adverse events were reported in 38 pts, mostly (76%) grade 1-2, 31 (52%) F-related. One single venous thrombotic event occurred in a pt who interrupted F 5 months before the event. Five pts discontinued F due to side effects: severe neu-

tropenia 1, transaminitis 1, diarrhea 2, hypertension 1. This Italian experience indicates F as an active and safe salvage treatment for heavily pretreated refractory cITP pts. F was used in most cases as fourth or further line of treatment, after failing TPO-RAs. Our results show that a significant proportion of pts (47%) benefit from F after 6 months suggesting that this treatment may be considered a manageable and effective therapeutic option in the real-world practice.

C060

MULTICENTRIC REAL-WORLD EXPERIENCE OF AVATROMBOPAG USE FOR THE TREATMENT OF PATIENTS AFFECTED BY CHRONIC ITP FROM FIVE ITALIAN HEMATOLOGY UNITS

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Introduction. Chronic immune thrombocytopenia (ITP) is a bleeding disorder characterized by a persistently low platelet count that lasts for 12 months or longer despite treatment. Initial treatment for ITP typically includes corticosteroids or intravenous immunoglobulins (IVIG) to increase platelet counts and reduce the risk of bleeding. If these first-line therapies are not effective or if the patient experiences side effects, second-line therapies may be considered. These can include Thrombopoietin receptor agonists (TPO-RA) such as Romiplostim, Eltrombopag or Avatrombopag, Rituximab, other immunosuppressive agents like azathioprine, mycophenolate mofetil, or cyclosporine. Splenectomy is typically considered a last resort when other treatments have failed or are not tolerated.

Aim of the study. To evaluate the efficacy and safety of Avatrombopag in patients (Pts) with chronic ITP with or without prior exposure to other TPO-RAs

Results. 57 ITP pts treated with Avatrombopag were collected from 5 Italian Hematology Units. Median age at start of treatment was 60.8 years (range 20.3-92.3) with a prevalence of females (32 pts, 56.1%). Patients received a median of 3 (range 0-10) previous therapies and 43 (75.4%) was previously exposed to at least one other TPO-RA. At start of treatment, median platelet counts (evaluated on 54 pts) were 11000/mmc (range 2000-50000). 3 more pts switched to Avatrombopag for intolerance to other TPO-RA, without a washout time and had a platelet basal count > 90000/mmc. The median time to platelet counts > 50000/mmc (evaluated on the 54 pts who started with low counts) was 27 days (range 3-456). At a median follow-up of 4.9 months (range 0.3-14.6), 40 pts (70.2%) are still on treatment with a median platelet counts of 96000 (range 13000-403000). Thrombotic and hemorrhagic events were observed in 4 (7%) and 5 (8.8%) pts, respectively but only in 3 cases cause treatment discontinuation. Only 4 deaths were observed (1 COVID infection, 1 acute renal failure, 1 subdural hematoma and 1 unrelated death).

Conclusions. To our knowledge, this is the first large Italian real-world experience reported for Avatrombopag treatment in ITP patients. Our data confirmed the high effectiveness of this kind of therapy even in heavily pretreated pts also with previous exposure to 1 or 2 TPO-RAs. The safety profile was acceptable with few adverse events (thrombotic and hemorrhagic included) causing discontinuation. Of course, more data and a longer follow-up are needed to evaluate the duration of response.

Myeloma and monoclonal gammopathies II

C061

IBERDOMIDE MAINTENANCE AFTER AUTOLOGOUS STEM-CELL TRANSPLANTATION IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: AN UPDATE FROM THE PHASE 2 EMN26 STUDY

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We previously showed that maintenance treatment with iberdomide improves post-transplant response in newly diagnosed multiple myeloma (MM) patients (pts), with a manageable safety profile. Here we report a longer follow-up including the first data from the 0.75 mg iberdomide cohort. The EMN26 study enrolled MM pts aged ≥18 years, who had achieved ≥PR after induction therapy with PIs plus IMiDs followed by 1 or 2 ASCT ± consolidation, into one of 3 different cohorts: iberdomide 0.75, 1.0, or 1.3 mg (on days 1–21 of each 28-day cycle; 40 pts in each cohort). The primary outcome was response improvement; secondary outcomes included conversion from MRD positivity to negativity (NGF, 10^{-5} sensitivity), safety, and PFS. At data cut-off (2-2-2024), 40 pts were enrolled in each of the 3 cohorts. Median follow-up was 8.4, 21.1, and 18.3 months for the 0.75, 1.0, and 1.3 mg cohorts, respectively (the 0.75 mg was added later). Baseline characteristics were well balanced among the 3 cohorts. Median age of these 120 pts was 59 years, and 54% were male. At diagnosis, 31% of pts presented with R-ISS 1, 57% with R-ISS 2, and 12% with R-ISS 3. High risk [del(17p), t(4;14), and/or t(14;16)] was present in 21%. All pts received PI/IMiD-containing induction (with also daratumumab in 53%). Quadruplet induction was more frequently used in the 0.75 mg cohort (88%) *vs* the other 2 cohorts (35% and 38%). Double ASCT was administered to 17% and post-

ASCT consolidation to 21%. After 6 cycles, substantial response improvements were observed in 66% (90% CI 50–79%) of pts in the 0.75 mg, 32% (90% CI 19–48%) in the 1.0 mg, and 41% (90% CI 26–57%) in the 1.3 mg cohorts (Figure 1). Response improvement during cycles 1–12 increased to 47% and 59% in the 1.0 and 1.3 mg cohorts, respectively (too early to evaluate for 0.75 mg cohort). Conversion from MRD positivity to negativity occurred in 30%, 32%, and 53% of pts in the 0.75 mg, 1.0 and 1.3 mg cohorts (overall 39%). 12-month PFS was 95%, 87%, and 90%, respectively. The most common grade (G)≥3 AEs during cycles 1–12 were neutropenia (42% in the 1.0 mg and 52% in the 1.3 mg cohorts) and infections (15% and 10%). In the 0.75 mg cohort, during cycles 1–6, G≥3 neutropenia occurred in 30%, and G≥3 infections in 2%. There were no G≥3 AEs of thrombocytopenia, anemia, diarrhea, or VTE. Only 1 pt (0.8%) developed G≥3 neuropathy.

Iberdomide maintenance showed a favorable safety profile and superior response improvement, as compared with lenalidomide.

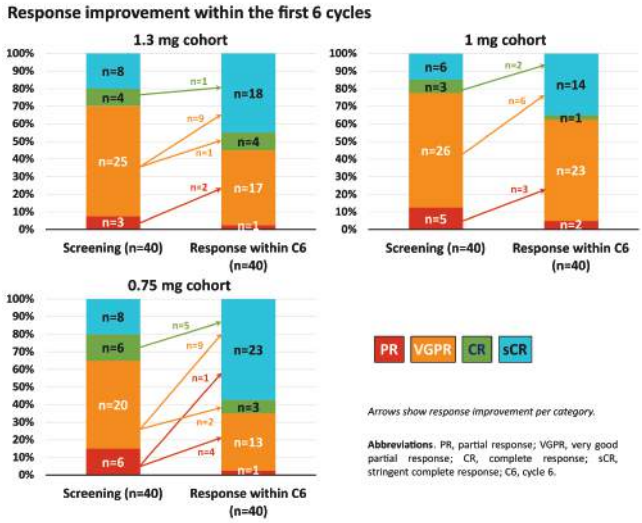

Figure 1.

C062

DARATUMUMAB (DARA)/BORTEZOMIB/LENALIDOMIDE/DEXAMETHASONE (D-VRD) WITH D-R MAINTENANCE (MAINT) IN TRANSPLANT-ELIGIBLE (TE) NEWLY DIAGNOSED MYELOMA (NDMM): ANALYSIS OF PERSEUS BASED ON CYTOGENETIC RISK

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In the primary analysis of the phase 3 PERSEUS study, DARA SC + VRd induction/consolidation (ind/consol) and D-R maint improved PFS and increased rates of deep and durable responses, including MRD neg and sustained MRD neg, *vs* VRd ind/consol and R maint in TE NDMM, regardless of cytogenetic risk status. We report an expanded analysis of PERSEUS based on the presence of HRCAs, including gain(1q21) and amp(1q21). TE pts with NDMM were randomized 1:1 to D-VRd or VRd. Pts received up to six 28-day cycles (4 pre-ASCT ind, 2 post-ASCT consol) of VRd (V 1.3 mg/m^2 SC on Days [D] 1, 4, 8, 11; R 25 mg PO on D 1-21; d 40 mg PO/IV on D 1-4, 9-12) and R maint (10 mg PO on D 1-28 until progressive disease [PD]). In the D-VRd arm, pts received DARA SC (DARA 1,800 mg + recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; Halozyme]) QW in Cycles 1-2, Q2W in Cycles 3-6, and Q4W during maint until PD. Cytogenetic risk was assessed by FISH and each level of risk was defined as per protocol or per revised protocol. MRD-neg rate was defined as the percentage of pts in the intent-to-treat population who achieved both ≥CR and MRD neg. 709 pts were randomized (D-VRd, n=355; VRd, n=354). At a median follow-up of 47.5 months, PFS favored D-VRd *vs* VRd across all cytogenetic risk subgroups (Figure 1). Overall MRD-neg rates (10^{-5}) were higher with D-VRd *vs* VRd across subgroups: standard risk (77.3% *vs* 48.1%; P<0.0001), high risk (68.4% *vs* 47.4%; P=0.0086), revised standard risk (75.3% *vs* 47.3%; P<0.0001), revised high risk (73.1% *vs* 49.3%; P<0.0001), gain(1q21) (69.5% *vs* 46.5%; P=0.0086), amp(1q21) (85.7% *vs* 55.6%; P=0.0104), 1 HRCA (75.3% *vs* 50.0%; P=0.0002), and ≥2 HRCAs (66.7% *vs* 47.4%; P=0.1044). Rates of sustained MRD negativity (10–5) for ≥12 months were higher with D-VRd *vs* VRd across subgroups: standard risk (69.3% *vs* 31.2%; P<0.0001), high risk (48.7% *vs* 25.6%;

P=0.0032), revised standard risk (66.1% *vs* 31.7%; P<0.0001), revised high risk (59.2% *vs* 27.7%; P<0.0001), gain(1q21) (62.7% *vs* 29.6%; P=0.0002), amp(1q21) (71.4% *vs* 27.8%; P=0.0006), 1 HRCA (61.9% *vs* 28.2%; P<0.0001), and ≥2 HRCAs (51.5% *vs* 26.3%; P=0.0303). The addition of DARA SC to VRd ind/consol and to R maint provided clinical benefit in terms of PFS and induced higher rates of deep and sustained responses *vs* VRd ind/consol and R maint across all cytogenetic risk subgroups. These results support D-VRd ind/consol and D-R maint as a new SOC for TE NDMM, regardless of cytogenetic risk status.

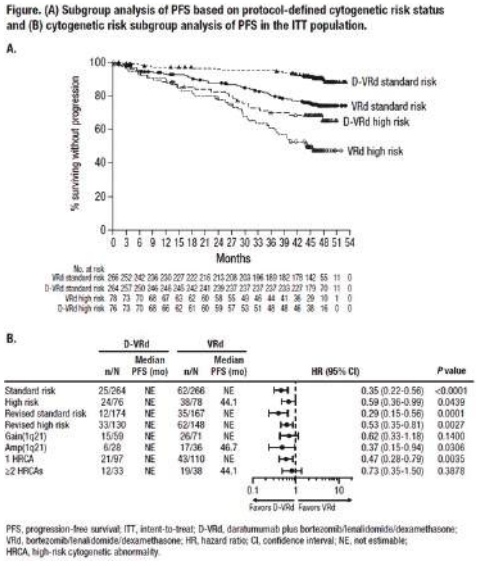

Figure 1.

C063

LONG-TERM FOLLOW-UP FROM THE PHASE 1/2 MAJESTEC-1 TRIAL OF TECLISTAMAB IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Teclistamab is the first approved BCMA×CD3 bispecific antibody for the treatment of pts with TCE RRMM, with weight-based dosing and the longest study follow-up of any bispecific antibody. Teclistamab has demonstrated rapid, deep, and durable responses in the pivotal MajesTEC-1 study. Here we report the updated MajesTEC-1 study results with an extended follow-up. Pts received teclistamab at the recommended phase 2 dose (once weekly (QW) preceded by step-up dosing) with the option to switch to Q2W dosing if a partial response or better after ≥4 cycles of therapy (phase 1) or ≥CR for ≥6 mo (phase 2) was achieved; pts not in ≥CR could switch due to AEs or switch to less frequent dosing if demonstrating a continued response. The primary endpoint was ORR assessed by independent review committee per IMWG 2016 criteria. AEs were graded per CTCAEv4.03. CRS was graded per ASTCT guidelines. All pts provided informed consent. At median follow-up (30.4 mo), 165 pts had received teclistamab at the RP2D. ORR was 63.0%, and responses continued to deepen, with 46.1% achieving ≥CR. 85.7% of MRD-evaluable pts were MRD negative. mDOR increased to 24.0 mo; mPFS and mOS improved to 11.4 and 22.2 mo, respectively. For pts with ≥CR, mDOR, mPFS, and mOS were not yet reached, and estimated 30-mo DOR, PFS, and OS rates were 60.8%, 61.0%, and 74.2%, respectively. Of the 38 pts who remain on treatment, 37 have switched to a less frequent dosing schedule, all of whom maintained responses. Hematologic AEs (any grade/grade 3/4) included neutropenia (72%/65%), anemia (55%/38%), thrombocytopenia (42%/23%), and lymphopenia (36%/35%). Infections occurred in 79% of pts (55% grade 3/4). Of grade 5 infections, 18/22 were due to COVID-19, reflecting study conduct during the COVID-19 pandemic. Onset of new grade ≥3 infections generally decreased over time, which aligned approximately with the median time of switch to Q2W dosing. AEs leading to dose reduction or discontinuation were infrequent. No new safety signals were reported. Teclistamab continues to demonstrate deep and durable responses, including in pts who switch to less frequent dosing. The safety profile of teclistamab remains consistent with that of BCMA-targeted bispecific therapies, with a notable decrease in new onset of severe infections with time.

C064

PROSPECTIVE FUNCTIONAL BONE DISEASE EVALUATION OF NEWLY DIAGNOSED MULTIPLE MYELOMA WITH COMBINED USE OF (18)F-FDG-PET/CT AND WHOLE-BODY DIFFUSION WEIGHTED MAGNETIC RESONANCE

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Background. FDG-PET/CT is the most widely used imaging technique to detect bone and extramedullary disease (EMD) in multiple myeloma (MM) and is recommended for response assessment by IMWG. In clinical practice, PET/CT is usually associated to magnetic resonance imaging (MRI); addition of diffusion-weighted imaging sequences in the recently introduced whole body-MRI

(WB-MRI) has further increased sensitivity and has been lately proposed for response assessment by MY-RADS guidelines.

Methods. We herein present a prospective single-center study aimed at comparing PET/CT and WB-MRI during diagnosis/staging of smoldering MM (SMM) and newly diagnosed MM (NDMM) and in defining treatment response in transplant-eligible (TE) and ineligible (TI) patients (pts). Pts undergo both imaging techniques at baseline (B) and prior to maintenance therapy (TE) or after 1 year of treatment (TI). Secondary aims are to define the prognostic role of the two techniques and to compare and validate imaging criteria (IMPeTuS and MY-RADS) in clinical practice.

Results. Between October 2022 and March 2024, 79 pts (25 SMM and 54 NDMM) underwent PET/CT and WB-MRI at B. Among NDMM pts with CT-assessed bone disease (61%), WB-MRI was positive in 100% and FDG-PET in 88%; in the remaining 39% pts, WB-MRI was negative in 43% (none with PET-assessed focal lesions, FLs) and positive in 57% (half with positive FDG-PET). WB-MRI detected FLs and paraskeletal disease (PSD) in more pts than FDG-PET (FLs:76% *vs* 54%,p=0.04; PSD:30% *vs* 20%,p=0.01); a slight concordance resulted in detecting diffuse disease (DD)(30% *vs* 46%,p=0.11,k=0.35). Presence of DD in WB-MRI and PET/CT was related to R-ISS III (p=0.048 and 0.04); DD in WB-MRI was also related to higher monoclonal protein concentration (p=0.048) and higher percentage of marrow plasma cells (p=0.02). Among SMM pts, FLs and DD detected by PET and WB-MRI were similar (FLs:12% *vs* 4%,p=0.99; DD:16%). To March 2024, 11 pts had imaging re-evaluation, with a concordance of 87.5% between techniques.

Conclusions. Our data support combined use of PET/CT and WB-MRI for MM staging at B; preliminary data also show a good concordance in response assessment. Further expansion of study population and larger number of pts who have reached the post-treatment timepoint are needed to properly define the role of WB-MRI *vs* PET/CT at diagnosis and response assessment. Updated data with extended follow-up and regarding response assessment will be presented at the meeting.

C065

INFLAMMATORY BIOMARKERS FOR THROMBOTIC RISK ASSESSMENT IN MULTIPLE MYELOMA PATIENTS ON IMID/ACD38-BASED REGIMENS: INSIGHTS FROM A PROSPECTIVE OBSERVATIONAL STUDY

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Thrombosis is a common complication in multiple myeloma (MM) patients exposed to immunomodulatory drugs (IMiDs). Nevertheless, IMiDs like thalidomide (thal), lenalidomide (len), and pomalidomide (pom) are essential in MM therapy and in combinations with anti-CD38 monoclonal antibodies have shown unprecedent efficacy. However, the emergence of thrombotic complications (TE) could significantly impact treatment outcomes by causing delays in therapy administration. Understanding the mechanisms underlying thrombosis in MM, the effects of IMiDs and anti-CD38 agents on coagulation pathways, and the implementation of appropriate thromboprophylaxis strategies are crucial for managing thrombotic risks in MM patients receiving these therapies. In this prospective study conducted as part of the MMVision monoinstitutional observational study, data was collected from 53 MM patients who started IMiDs+anti-CD38 treatment between May 2021 and December 2022, with a median follow-up of 18 months. Among these patients, 36 received len and 15 thal in combination with daratumumab, and 2 received pom with isatuximab. Of these, 38 patients were in frontline treatment, and all received thromboprophylaxis following current guidelines, with 73% using aspirin (ASA). We observed 5 TE cases (9.41%), with a median onset time of 48 days, effectively managed with short-term low molecular weight heparin (LMWH) treatment. Next, we analyzed 27 clinical and laboratory variables demonstrating that low levels of B2 microglobulin, ferritin, serum intact and free lambda light chains, as well as a low monocyte-to-lymphocyte ratio, were significantly associated with TE occurrence (Figure 1A). Notably, only 1 out of 5 patients with TE presented lytic bone disease, indicating a potentially less systemic inflammatory status and reduced benefit from the anti-inflammatory properties of ASA. Furthermore, in 2 of the 5 TE patients, peripheral blood and bone marrow plasma were examined, investigating 48 cytokines, and compared with other MM patients or pre-malignant conditions (MGUS and Smoldering MM). Interestingly, patients experiencing TE exhibited significantly lower levels of M-CSF, SCLF-beta, and MIP-1alpha, along with an increase in G-CSF (Figure 1B). These findings highlight the diverse immune and inflammatory mechanisms contributing to TE development in MM patients. Once extensively validated, these findings could help identify patients who may benefit more from anticoagulant therapy over antiplatelet therapy.

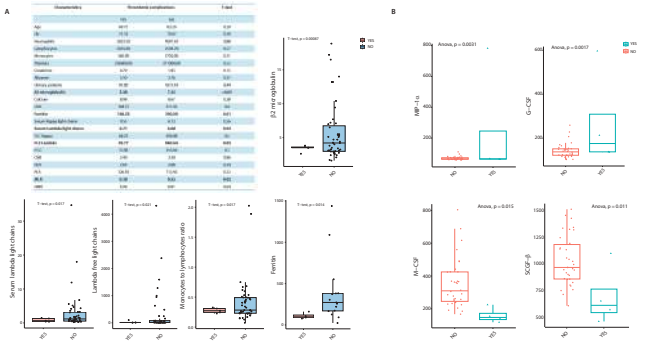

Figure 1.

Non-Hodgkin lymphoma II

C066

MYELOID CLONAL HEMATOPOIESIS AFFECTS OUTCOME IN YOUNGER MANTLE CELL LYMPHOMA PATIENTS: UPDATED RESULTS FROM THE FONDAZIONE ITALIANA LINFOMI MCL0208 CLINICAL TRIAL

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Background. Accumulating evidence has shown that myeloid clonal hematopoiesis (M-CH) of indeterminate potential may influence the clinical outcome of patients (pts) affected by lymphoma. Only sparse data are available in mantle cell lymphoma (MCL), so far, and a clear impact on clinical outcome has not been demonstrated, yet.

Aims. Here, we report a comprehensive analysis of baseline M-CH mutational landscape in pts enrolled in the Fondazione Italiana Linfomi (FIL) MCL0208 phase 3 trial (NCT 02354313), evaluating lenalidomide maintenance *vs* observation after chemoimmunotherapy and ASCT in untreated MCL pts ≤ 65 years.

Methods. NGS mutational analysis was performed by the TruSight Myeloid Panel in Ficoll-separated neutrophils from peripheral blood (PB) or bone marrow (BM) samples collected at baseline and within 12 months of ASCT. Oncogenic mutations were called down to 2% variant allele frequency (VAF). To avoid the bias of potential contamination by tumor cells in specimens analyzed for CH, mutations involving the most frequently mutated genes in MCL were considered of myeloid origin only when VAF was ≥4 times the MCL infiltration in the sample, as assessed by flow cytometry [Lewis *et al.,* 2020].

Results. Overall, 254/300 enrolled pts (85%) had a baseline sample available for CH analysis and 34 pts (13%) had at least one mutation involving M-CH candidate genes (CH+ pts, Figure 1A), being DNMT3A the most frequently mutated gene (17/254, 7%). After a median follow-up of 7 years, the presence of large CHIP clones (i.e. VAF ≥ 10%, n=8) predicted worse PFS (HR 2.93 [1.36-6.31], p=0.006) and OS (HR 3.02 [1.21-7.55], p=0.018) compared to CH- pts (Figure 1B,C). After applying propensity score adjustment for baseline factors (age, gender, MIPI, Ki67, bulky, BM involvement and blastoid subtype), pts affected by large CH clones still showed shorter PFS (HR 2.27 [1.03-5.01], p=0.042) and a trend towards worse OS (HR 1.87 [0.71-4.87], p=0.203) compared to CH- pts. Importantly, at competing risks analysis M-CH large clones specifically predicted for MCL progression (p<0.05). Finally, in pts with a paired sample collected after ASCT (191/300, 60%), the global prevalence of M-CHIP remained stable at 12% although CH clones showed variable trajectories throughout follow-up.

Conclusion. In conclusion, we provided the M-CH mutational landscape at baseline in younger MCL pts and we showed for the first time the unfavorable clinical impact of large CH clones on MCL progression.

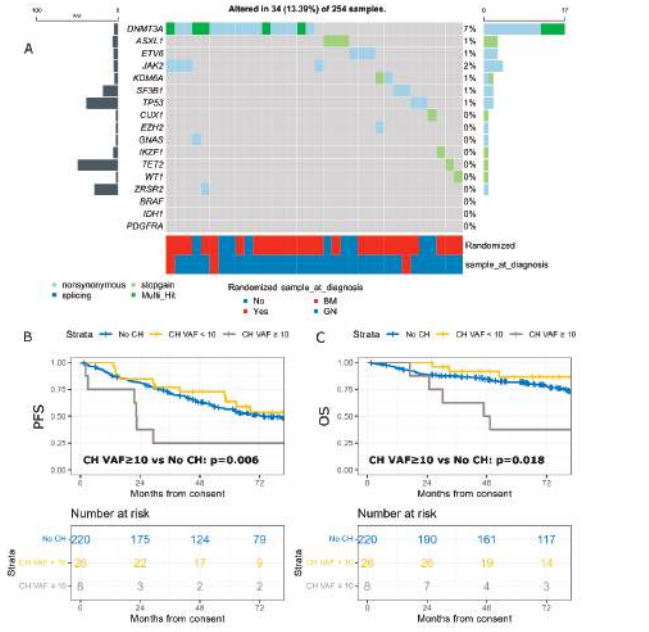

Figure 1.

C067

REAL-LIFE OUTCOMES OF RELAPSED/REFRACTORY PRIMARY MEDIASTINAL B-CELL LYMPHOMA (REPRIME STUDY): A MULTICENTRIC STUDY BY FONDAZIONE ITALIANA LINFOMI (FIL)

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Background. Although front-line chemoimmunotherapy and PET-guided radiotherapy consolidation allow a high cure rate in Primary Mediastinal B cell Lymphoma (PMBCL), about 10-20% of patients (pts) show early failure, with dismal prognosis. There is a lack of large prospective studies about relapsed/refractory (R/R) pts' outcomes.

Aims. To determine the features of R/R PMBCL and outcomes with salvage treatments in pre-CAR-T era by gathering multicentric, Italian real-life data.

Methods. This is a retrospective cohort study of an unselected population of adult PMBCL pts treated in 40 cancer centers affiliated with the FIL group and diagnosed from 1/1/07 to 31/12/19. Outcomes of the whole cohort were reported elsewhere (Iannitto ICML 2023); for RePrime study, only R/R pts were selected. Response was defined according to Lugano classification.

Results. Among 931 registered pts, 34 relapsed (REL) and 95 showed disease progression (PD); 6 pts were excluded due to unconfirmed PMBCL after re-biopsy, while 12 pts were lost to follow up. Thus, 111 R/R pts with available survival data were included in this sub-study (81 PD, 30 REL). All pts received rituximab; most received platinum-based chemo (DHAP, OXDHA, ICE or ESHAP, 73 pts, 65.8%) or anthracycline-based schemes (16 pts,14.4%); 2 pts received CNS-directed therapy, 1 nivolumab and 1 CAR-T cells. 39/111 (35.1%, 27 PD, 12 REL) received ASCT consolidation in II line. Beyond II line, 16 pts received ASCT, 16 anti PD-1 antibodies, 4 CAR-T cells, 3 allo-HSCT. After a median FU of 4.7 years (y), 3y-overall survival (OS) of R/R pts was 46.6% (95%CI:36.9;56.0), 60.7% for relapsed *vs* 41.6% for refractory pts (p=0.09). Observed OS was not impacted by baseline disease stage (p=0.488) or by type of II line treatment (anthracycline *vs* platinum-based, p=0.267); however, pts receiving ASCT in II line showed better OS (72.7 *vs* 32.6% at 3y, Figure 1). Survival benefit of ASCT pts was confirmed at landmark analysis at 6 months from REL/PD event (p=0.0024) and in the subgroup of pts with early PD (<6 months from initial therapy).

Conclusions. In this large real world PMBCL cohort in the rituximab era, the majority of R/R pts had dismal prognosis. Only 35% pts with chemosensitive disease received ASCT in II line, showing better OS; further analysis by a propensity score adjustment is underway to limit the risk of indication bias in ASCT pts. Broader access to anti PD1 and CAR-T is expected to improve pts survival.

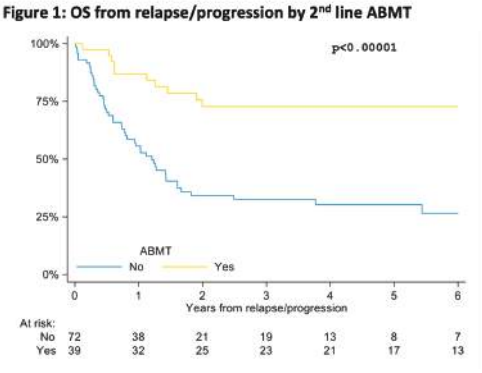

Figure 1.

C068

DESCRIPTION OF A CLINICAL SCORE TO IDENTIFY PMBCL PATIENTS AT HIGH RISK OF EARLY FAILURE AFTER RITUXIMAB-DOXORUBICIN BACK-BONE CHEMOIMMUNOTHERAPY. A FIL REAL-WORLD STUDY WITH EXTERNAL VALIDATION

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Primary mediastinal B-cell lymphoma (PMBCL) is an aggressive lymphoma typical of young adults that represents a significant clinical challenge in the relapsed/refractory setting. Approximately 10-20% of patients show refractoriness or early failure (EF) to front-line treatment. This retrospective study involved 931 adult PMBCL patients from 37 FIL centers across Italy and aimed to develop a clinical-based prognostic score to identify patients at risk of EF following anthracycline-rituximab-based chemoimmunotherapy. EF was defined as less than partial response, relapse or progression within 365 days since treatment start. Candidate predictors were clinical factors at diagnosis, including age, ECOG PS, LDH, Ann Arbor Stage, B symptoms, bulky mediastinum > 10 cm, number of Extra-Nodal sites (a 4-level scale: 0, 1, 2, or ≥ 3), and pericardial or pleural effusion. After the backward selection process, four factors were selected to construct the prognostic score (AUROC 0.6986, optimism-corrected 0.665).

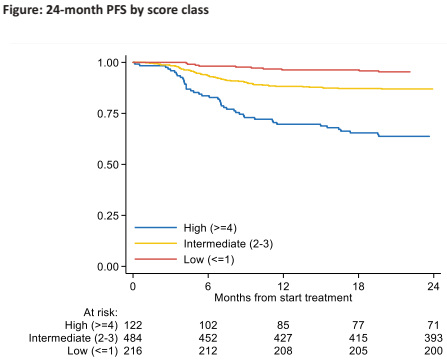

Figure 1.

We constructed a risk score by assigning each factor a weight proportional to the smallest coefficient, rounded to the nearest integer. These factors included Systemic B-symptoms (OR=1.76, p=0.007, weight=1), Bulky mediastinum > 10 cm (OR=2.12, p=0.017, weight=1), AA Stage II (OR=2.20, p=0.018, weight=1), AA Stage III-IV (OR=2.73, p=0.017, weight=2), and Number of Extra-Nodal sites ≥ 2 (OR=2.88, p<0.001, weight=2). The discrimination ability of the prognostic score was evaluated considering the time to progression or relapse (EF Survival) using the Kaplan-Meier method. The score classified patients into low (0-1, 232 pts), intermediate (2-3, 524 pts), and high-risk (≥4 135 pts) groups with distinct EF incidences of 3.7%, 11.8%, and 30.8%, respectively. At 24 months, progression-free survival rates were 95.4%, 87% and 63.7% respectively. Subsequently, we proceeded with the validation of the FIL prognostic score in an external cohort from an international retrospective series from the Mediterranean Arabic group, including 648 pts treated with R-CHOP (353) or R-DA-EPOCH (295). Also in this cohort, the score successfully stratified patients into three distinct risk groups, with a 2y PFS rate of 91.3%, 78.1% and 67.2% respectively, underlining its robustness and potential use in clinical decision-making. Moreover, it would be a useful tool to adjust the timing of reevaluation and to identify high-risk populations that could benefit from enrolment in clinical trials.

C069

CLINICAL OUTCOMES OF PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA TREATED WITH TISAGENLECLEUCEL: PHASE 2 ELARA 3-YEAR FOLLOW-UP

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Tisagenlecleucel is approved for adults with relapsed/refractory follicular lymphoma (r/r FL) after ≥2 lines of prior therapy. Here we report long-term efficacy, safety, pharmacokinetic and exploratory biomarkers analyses of the phase II ELARA study after a median follow-up longer than 3 years in r/r FL patients (grades 1-3A), previously treated with ≥2 lines of therapy (including an anti-CD20 monoclonal antibody and alkylating agent or after autologous stem-cell transplantation). These patients received a single tisagenlecleucel infusion (0.6-6×10^8 CAR+ viable T cells), and bridging therapy allowed. Baseline clinical characteristics and circulating blood naive T cells were correlated with clinical response; cellular kinetics were reported. A total of 97 patients were infused and had a median follow-up of 41 months (range 34.2-49.7). At baseline, 68% of patients were double refractory, 65% had bulky disease (>7 cm or 3 lesions >3 cm), and 63% had progression of disease within 2 years of frontline systemic therapy (POD24). Among 94 evaluable patients, the best overall response (BOR) of complete response (CR) rate was 68% (95% CI, 57.7%-77.3%), and the overall response rate (CR + partial response) was 86% (95% CI, 77.5%-92.4%). Median progression-free survival (PFS) was 37 months; 36-month PFS was 53% in the overall population and 69% in patients with a BOR of CR. The 36-month PFS was 50% and 59% in patients with and without POD24, respectively (Figure 1). CAR transgene persistence was observed for up to 1290 days; patients without POD24 had higher median *in-vivo* CAR expansion and longer persistence than POD24 patients. Median duration of response (DOR) was not reached. Among patients with a BOR of CR, 73% had an ongoing response at 36-month analysis. High baseline levels of circulating CD8+ naive T cells (>2.14% of total T cells) were associated with prolonged PFS and DOR. Median overall survival (OS) and time to next treatment were not reached. At 36 months, the OS rate was 82% (83% in the POD24 subgroup *vs* 81% in patients without POD24). No new safety signals were reported. Patients with r/r FL treated with tisagenlecleucel maintained a high rate of durable response with favourable safety profile after ≥3 years of tisagenlecleucel infusion, including patients in high-risk subgroups (e.g., POD24). Higher baseline levels of CD8+ naive T cells are associated with improved long-term clinical outcomes.

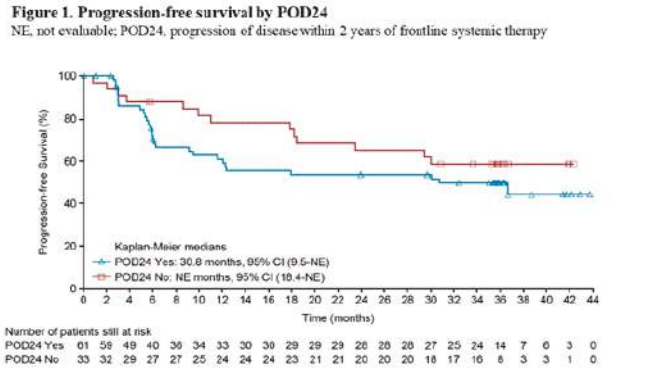

Figure 1.

C070

ABSTRACT NOT PUBLISHABLE

Acute leukemia II

C071

PROGNOSTIC RELEVANCE OF TP53 MUTATIONS WITH OR WITHOUT CONCOMITANT COMPLEX KARYOTYPE IN PATIENTS TREATED WITH CPX-351: EVIDENCE FROM A LARGE REAL-WORLD ITALIAN STUDY

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Background. The phase III trial by Lancet showed the superiority of CPX-351 over 3+7 for patients(pts) diagnosed with s-AML or t-AML. Long term results confirmed that this benefit was maintained regardless of further allogeneic stem cell transplantation (allo-SCT) consolidation. However, the information on the activity of CPX-351 in TP53 mutated (mut) s-AML and t-AML pts is still incomplete, as it was not evaluated in the trial and the subsequent studies reported conflicting results.

Aims. We analyzed the impact of TP53 mut in a large cohort of s-AML and t-AML pts who received CPX-351 since its approval, and the role of allo-SCT in this setting.

Methods. 513 elderly (median age 65.6 years, range 19-79) s-AML (n=108, 21,1%) or t-AML (n=405, 78,9%) pts who received CPX-351 (up to two induction and two consolidation cycles) in 38 italian Centers since January 2019 were retrospectively included. Eligible pts proceeded to allo-SCT as per internal standard of each Center.

Results. NPM1 mut was found in 31 pts (6%), FLT3-ITD mut in 24 (4.6%). ELN 2017 risk was favorable, intermediate or high in 27 (5.2%), 177 (34.5%) and 309 (60.3%) pts, respectively. Most pts had relevant comorbidities (84%), mainly cardiovascular (43%) and type II diabetes (39%). TP53 mut were evaluated in 335 pts (65%) and found in 49 (15%), 12 t-AML and 37 s-AML. In 33 pts (8 t-AML and 25 s-AML), it was found in the context of a complex karyotype(CK, 9%). After a median follow-up of 23.6 months (m) (CI 95% 23.11-26.01), median OS was 16.2 m (CI 95% 13.6-18.9). OS was significantly influenced by ELN 2017 risk ($p<0.05$), but not by TP53 mut, unless if a CK was also present (Figure 1). Furthermore, among pts with high risk cytogenetics, TP53 correlated with a worse outcome ($p<0.05$). In a landmark analysis including pts alive and in CR at day 90, allo-SCT was the strongest predictor of survival (median OS not reached *vs* 16.3 m for pts receiving or not allo- SCT, respectively, $p<0.05$), regardless of TP53 mut status. However, pts with TP53 mut + CK had a worse outcome even after allo-SCT (median OS 14.3 m *vs* not reached with or without TP53 mut + CK, respectively, $p<0.05$).

Conclusion. Overall, we confirm the efficacy of CPX-351 also in the difficult subset of TP53 mut pts. Pts with TP53 mut + CK have a worse outcome and allo-SCT may significantly improve survival in a small proportion of these. In a future perspective, the addiction of new targeted drugs may further improve results.

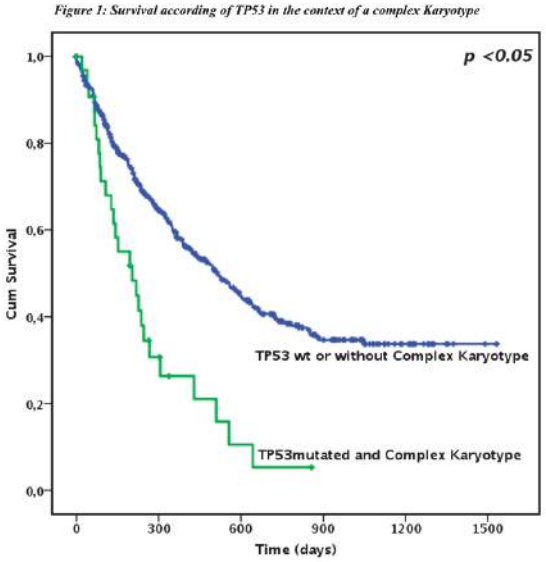

Figure 1.

C072

THE ROLE OF DIGITAL-DROPLET-PCR FOR BETTER RISK STRATIFICATION OF T-ALL

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Introduction. Minimal residual disease (MRD) represents the most important prognostic factor in acute lymphoblastic leukemia (ALL). However, approximately 25% of patients with ALL and MRD negativity assessed by standard real-time quantitative polymerase chain reaction (RQ-PCR), relapse. This project investigates whether digital droplet PCR (ddPCR) could refine prognosis better than RQ-PCR in a cohort of adult T-ALL enrolled in NILG 10/07 trial (NCT 00795756).

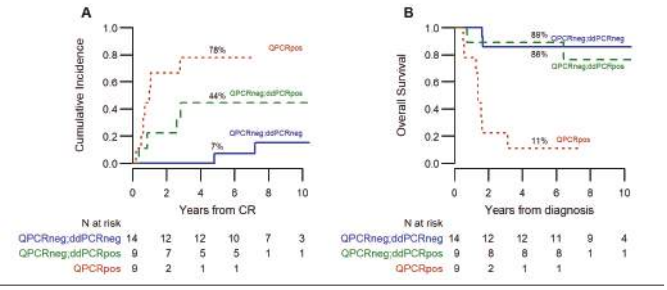

Figure 1.

Methods. We retrospectively analyzed by ddPCR samples of newly diagnosed adult T-ALL patients with MRD classified as positive non-quantifiable (PNQ) or negative MRD by RQ-PCR at clinically critical time point (TP-2) to clarify the potential contribution of ddPCR in improving ALL patients' stratification and outcome. Patients were assigned to alloHSCT based on the joint assessment of the conventional disease risk profile (WBC count >100x10^9/L, early/mature phenotype, and adverse genetics) and MRD status.

Results. Among 44 consecutive newly diagnosed T-ALL, 32 were included in this analysis since followed by MRD strategy. The median age was 37 years (range 17-65). The proportion of patients considered at standard risk or high risk was 28.1% and 71.9% respectively. A total of 21 patients underwent alloHSCT in first CR due to the presence of high-risk clinical features or MRD positivity by RQ-PCR. Twenty-three patients with molecular negativity or PNQ at TP2 by RQ-PCR were analyzed by ddPCR. Among them, 9 (39%) were re-classified as positive in ddPCR. Positive RQ-PCR and ddPCR patients were associated with a significantly worse 5-year cumulative incidence of relapse (78% and 44%, respectively) compared with 7% for negative MRD ddPCR (p=0.0042). Nonetheless, OS probability at 5 years was not significantly different in ddPCR MRD− and MRD+ patients (86%; versus 89%, p=0.89) (Figure 1 A-B).

Conclusions. The ddPCR identified a proportion of patients that were MRD negative with standard RQ-PCR, as positive. ddPCR negativity was associated with a significant benefit in terms of risk of hematologic relapse, suggesting the potential relevance of detecting MRD negativity in T-ALL with more sensitive and specific tools. However, we did not observe differences in terms of OS, probably due to the low number of patients and the high number of allogeneic transplantations performed, suggesting that these findings need to be confirmed with bigger casuistries.

C073

PERFORMANCE OF BLINATUMOMAB FOR MRD PERSISTENCE AND SUBSEQUENT ALLO-SCT RATE IN PH-NEGATIVE B-ALL PATIENTS TREATED WITH THE PEDIATRIC INSPIRED LAL1913 PROGRAM (SUBANALYSIS OF THE CAMPUS ALL-LAL1913 STUDY)

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Background. Persistence of minimal residual disease (MRD) in acute lymphoblastic leukemia (ALL) is known to have a negative prognostic impact and is one of the main indications for allogeneic hematopoietic stem cell transplantation (HSCT). Blinatumomab (BLINA) is approved to treat MRD-positive ALL, but few real-world data are available regarding its use to treat MRD as a sequential treatment after specific chemotherapy protocols.

Methods. The CAMPUS ALL-LAL1913 study included 421 Ph-neg ALL patients (pts) treated with the LAL1913 program. In this study, 221 (53%) had B-ALL. We analyzed the subgroup of cases who received BLINA to treat MRD in this real-life setting. The objectives of this study were: 1) to evaluate the performance of BLINA against MRD (in terms of MRD negativity and outcome) in a setting of pts homogeneously treated with the LAL1913 program; 2) to analyze the tolerability of BLINA when used sequentially to the LAL1913 program; 3) to evaluate the HSCT rate in this setting. The study is ongoing and data from pts treated with BLINA in 2023 and 2024 are currently being collected. The study was approved by ethical committee of FVG (approval number CEUR-2022-Os-03).

Results. This analysis includes the first 38/221 (17%) pts treated with the LAL1913 program who received BLINA for MRD positivity after their first-line therapy; median age was 43 years (range, 19-66), 53% of patients had HR or VHR disease. The MRD positivity was assessed by clonospecific IG/TR in 66% of cases and by flow cytometry in 34% of cases. The median number of BLINA cycles was 2 (range, 1-4). Overall, 34/38 (89%) of pts achieved a MRD negativity (30 after the first cycle and 4 after the second cycle) and 33/38 (87%) received subsequent HSCT (including 36% MUD and 24%

HAPLO). BLINA dose reduction was required in 8% of cases but definitive BLINA discontinuation was required in only 2 cases (5%). Grade 3 ICANS, CRS and infections were reported in 5%, 5% and 11% of pts, respectively. No deaths occurred with BLINA therapy. The median overall survival (OS) from the start of BLINA was not reached; the probability of OS at 3 years was 73%.

Conclusions. This interim analysis supports a strong benefit with good tolerability of BLINA as sequential therapy in MRD-positive cases following a pediatric-inspired chemotherapy regimen (LAL1913) with a complete response rate (MRD-negativity) of 89% and bridging to HSCT in 87% of cases.

C074

HYPOMETHYLATING AGENTS AND VENETOCLAX WITH OR WITHOUT DLI IN RELAPSED AML AND MDS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: A RETROSPECTIVE MULTICENTRIC STUDY

P. Chiusolo[1,2], F. Frioni[2], C. Secreto[3], F. Giglio[4], F. Lessi[5], F. D'Amore[5], I.M. Monella[4], M. Abbenante[6], G. Marconi[7], J. Nanni[8], G. Cristiano[8], R. Maggi[2], A. Mattozzi[2], A. Busca[3], S. Sica[1,2], C. Papayannidis[9]

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Acute myeloid leukaemia (AML) relapse accounts for 30-40% of allogeneic hematopoietic stem cell transplantation (HSCT) failure and has a dismal prognosis; in recent years hypomethylating agents (HMA) with Venetoclax (VEN) emerged as a safe and effective option for AML relapse after HSCT2. We retrospectively analysed 67 patients treated with the combination of HMA and VEN, with or without donor lymphocyte infusion (DLI), for relapse after HSCT for myeloid malignancies, taking advantage from an Italian multicentric cohort. The median age of the entire population was 56 years (range 21-72), with 28 (41%) female and 39 (59%) males. The most common indication to HSCT was AML in 60 patients (89%), while myelodysplastic syndrome in 5 patients (7%), myeloid sarcoma and chronic myelomonocytic leukaemia in 1 patient each. Positive minimal residual disease was detectable in 13 patients (19%) before allogeneic HSCT. 45 patients (67%) received HSCT from an HLA-identical donor, 21 patients (31%) from an haploidentical donor, and 2 patients from cord blood unit and single mismatch unrelated donor respectively; a myeloablative conditioning regimen was preferred in 30 (44%) patients. The incidence of acute and chronic Graft versus Host Disease (GvHD) was 43% and 44% respectively. The median time from HSCT of HMA+VEN treatment for relapse was 528 days (range 48-813); 15 patients (22%) received DLI in addition to HMA-VEN combination (at a median dose of $1.6x10^6$/Kg, range 1-6). Cycles of 28 days including Decitabine 20 mg/m^2/day for 5 consecutive days or Azacitidine 75 mg/m^2 for 7 consecutive days in addition to VEN at a variable dose (100 to 400 mg/day for 7 to 21 days) depending on tolerability or drug interactions were repeated until disease progression. Treatment was well tolerated with only 10 patients (15%) experiencing a grade 3 or 4 extra haematological toxicities; a grade 3 or 4 neutropenia or thrombocytopenia were present in 55 patients (82%). The overall response rate was 52% with 39% of complete response; the relapse rate was 23% for patients who achieved a complete response. The median overall survival (OS) from the time of transplantation was 941 days (range 138-4904, Figure 1), while the median OS from the start of HMA+VEN treatment was 183 days (range 18-1312). Our study demonstrates the safety of HMA in addition to VEN for relapsed AML after HSCT but confirms still unsatisfactory results in terms of response, relapse rate and survival.

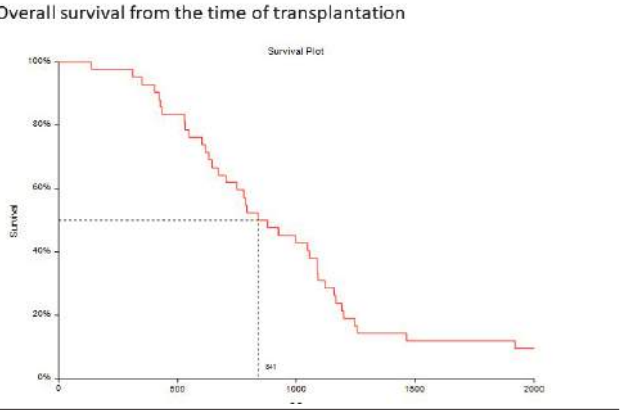

Figure 1.

C075

FLT3 MUTATIONAL STATUS IS ASSOCIATED WITH DIFFERENCES IN ACUTE MYELOID LEUKEMIA IMMUNE TRANSCRIPTOMIC PROFILE IMPACTING ON RESPONSE TO FLT3 INHIBITORS

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Background. FLT3 mutations (FLT3-mut) are one of the most frequent genetic alterations in acute myeloid leukemia (AML). FLT3 receptor exerts a central role in normal hematopoiesis. However, the impact of FLT3-mut on AML immune microenvironment has not been clarified to date.

Aims. this study aims at investigating whether FLT3-mut may be associated with a peculiar AML immune transcriptomic profile, thus influencing the response to FLT3 inhibitors (FLT3i).

Methods. We used RNA-Seq data from the Beat-AML Trial to build a FLT3-mut (FLT3-pos) and a FLT3-wt (FLT3-neg) cohort of samples. Published gene signatures were used as input. We then screened a cohort of FLT3-mut AML patients treated either with Midostaurin plus chemotherapy (M) or Gilteritinib (G) at Bologna

Hematology Institute by using the PanCancer IO 360 Panel (NanoString GEA). A public newly-diagnosed (ND) AML sc-RNA-seq dataset was used to map DEGs between Responders (R) and Non-Responders (NR) to FLT3i. MV411, MOLM13 and THP1 cell lines were used to validate *in vitro* some key immunological findings.

Results. Transcriptomic data of FLT3-pos (n= 173) and FLT3-neg (n=185) Beat-AML samples were compared: FLT3-pos cases had a lower ssGSEA score for CD8+ and CD4+ T-Cell function signatures (*e.g.* T-cell Activation/Effector function, Exhaustion and Interferon Response); FLT3-pos cases had a higher score in signatures associated with stemness, whereas FLT3-neg cases with a more differentiated state (Monocytic/Erythroid) (Figure 1A). We then enrolled 17 ND and 20 Relapsed/Refractory FLT3-mut AMLs receiving M and G therapy, respectively. Significant differences in immune transcriptomic profile were observed comparing R with NR: a higher expression of genes involved in T/NK function in G-R (Figure 1B); by projecting the top 30 DEGs genes between G-R and G-NR onto a sc-RNA-seq AML-BM map, we found that they were primarily expressed by CD8+ TEM, CD8+ TCM and NK cells (Figure 1C); instead, by projecting the top 30 DEGs between M-R and M-NR a wider contribution from different cell-types emerged (Figure 1E), with a higher expression of genes involved in innate immunity among M-R (Figure 1D). Preliminary in-vitro experiments supported in-vivo data: IFN type I-based immune response is modulated by G-therapy in FLT3-mut cell lines.

Conclusion. This study highlights how FLT3 mutational status is associated with T-Cell activation and AML maturation state. Differences in immune transcriptomic profile impact on FLT3i response.

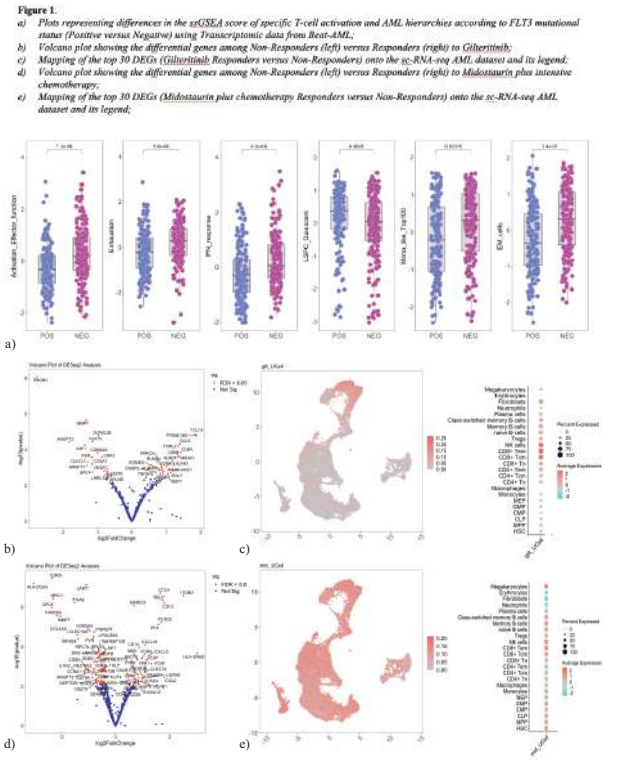

Figure 1.

C075 BIS

REVUMENIB MONOTHERAPY IN PATIENTS WITH RELAPSED/REFRACTORY KMT2AR ACUTE LEUKEMIA: TOPLINE EFFICACY AND SAFETY RESULTS FROM THE PIVOTAL AUGMENT-101 PHASE 2 STUDY

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Revumenib (rev), a menin-histone-lysine N-methyltransferase 2A (KMT2A) inhibitor, being investigated in R/R KMT2Ar and nucleophosmin 1-mutated (NPM1m) acute leukemias. Aim to report pivotal Ph2 data of rev for patients (pts) with R/R KMT2Ar acute leukemia (AUGMENT-101; NCT04065399).

Methods. Pts aged ≥30 days were enrolled in Cohort A (KMT2Ar ALL/MPAL) and B (KMT2Ar AML); Cohort C of NPM1m is not included in this analysis. Pts received rev (163 mg or 95 mg/m^2 if <40 kg) q12h with a strong CYP3A4 inhibitor orally in 28-day cycles. Treatment continued until unacceptable toxicity, lack of at least MLFS after 4 cycles, or consent withdrawal. Ph2 primary objectives were safety and tolerability and complete remission (CR)+CR with partial hematologic recovery (CRh) rate. Secondary endpoints were composite CR rate (CRc, CR+CRh+CR with incomplete platelet recovery+CR with incomplete count recovery) and ORR (CRc+MLFS+partial remission). A planned interim analysis (IA) was conducted.

Results. At the IA, 94 pts received ≥1 dose of rev and were included in the safety analysis. Median age was 37y (1.3-75y); 78 (83%) had AML. The most common co-mutations were RAS 13%, FLT3 7%, and p53 5%. Pts were heavily pretreated (median 2 [1-11] prior lines of therapy); 50% had prior HSCT. TRAEs were reported in 82% pts. Grade ≥3 TRAEs were observed in 54%, most common being differentiation syndrome (DS) 16%, febrile neutropenia 14%, and QTc prolongation 14% (Table 1). Overall, 6% of pts discontinued due to TRAEs; none due to DS or QTc prolongation.The IA efficacy population (n=57) included all treated pts with centrally confirmed KMT2Ar, ≥5% BM blasts at BL, and treated on or before the 38th adult AML efficacy evaluable pt. The IA was conducted when the 57 pts had sufficient FU. After median FU of 6.1 mo, 13 pts (23% [95% CI, 12.7-35.8]) achieved CR+CRh, surpassing the predefined IA efficacy boundary. Median duration of CR+CRh was 6.4 mo (95% CI, 3.4-not reached). ORR was 63% (95% CI, 49.3-75.6). Responses were observed in pts with co-mutations. Most pts with a CR or CRh response with MRD status reported achieved MRD negativity (7/10, 70%); 14 of 36 responders (39%) proceeded to HSCT, with half resuming rev post HSCT.

Conclusion. Revumenib demonstrated clinically meaningful results in heavily pretreated KMT2Ar pts, including high ORR and MRD negativity rates and subsequent HSCT. At IA, the study met its primary endpoint in the KMT2Ar cohorts and was stopped early for efficacy.

Chronic lymphocytic leukemia and lymphoproliferative syndromes II

C076

COMBINATION TREATMENT WITH SONROTOCLAX (SONRO; BGB-11417) + ZANUBRUTINIB (ZANU) IS WELL TOLERATED AND ACHIEVES DEEP RESPONSES IN PATIENTS WITH TREATMENT-NAIVE CLL/SLL: DATA FROM AN ONGOING PHASE 1/2 STUDY

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Background. Sonro (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and potent inhibitor of BCL2 than venetoclax in biochemical assays. Zanu, a next-generation BTK inhibitor, improved PFS with fewer cardiac AEs than ibrutinib in patients (pts) with CLL/SLL. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study of pts with B-cell malignancies. Presented here are data from pts with treatment-naive (TN) CLL/SLL treated with sonro + zanu.

Methods. Pts received zanu (320 mg QD or 160 mg BID) 8 to 12 wk before starting sonro with a ramp-up schedule to target doses of 160 or 320 mg QD. Pts were treated until progression or unacceptable toxicity. TLS was assessed per Howard 2011 criteria. Safety per CTCAE v5.0 (primary endpoint [EP]), ORR per iwCLL 2008 criteria (secondary EP), and minimal residual disease (uMRD4) in blood by ERIC flow every 24 wk (exploratory EP) were assessed.

Results. As of May 21, 2023, 94 pts with TN CLL/SLL were enrolled; 15 pts were still in zanu lead-in and 79 had started sonro (160 mg, n=32; 320 mg, n=47). Median follow-up was 8.5 mo (range, 0.6-18.2) for all pts, 12.1 mo (range, 0.6-18.2) for 160 mg, and 7.0 mo (range, 1.1-14.6) for 320 mg. No deaths occurred, and all pts remain on study. TEAEs in ≥20% of pts who received sonro + zanu were contusion (35%), neutropenia (35%), COVID-19 (23%), and diarrhea (23%; grade ≥3 in 1 pt). Neutropenia was the most common grade ≥3 TEAE (17%). No clinical or laboratory TLS occurred. No pts experienced atrial fibrillation. One TEAE (cryptococcal meningitis at 11 wk) led to treatment discontinuation. Sonro dose holds occurred in 17 pts (22%; median duration, 11 days [range, 3-37]); 3 pts (4%) had dose reduction. In 56 response-evaluable pts, ORR was 100% (CR: 160 mg, 36% [n=9]; 320 mg, 19% [n=6]). CR rate increased with time; the median time to CR was 10.1 mo (range, 5.4-17.1). No

progression events were reported in either cohort (Figure 1). Wk 24 blood uMRD4 rates were 50% (12/24) for 160 mg and 65% (13/20) for 320 mg. Wk 48 blood uMRD4 rates were 73% for 160 mg (11/15) and 100% (1/1) for 320 mg.

Conclusions. Sonro (160 and 320 mg) + zanu was well tolerated in pts with TN CLL/SLL. Only 1 pt discontinued treatment and 3 had dose reductions. No TLS was seen. Efficacy is encouraging, with 100% ORR in assessed pts, no PFS events, and high rates of blood uMRD4 occurring early. A phase 3 study assessing this combination is planned.

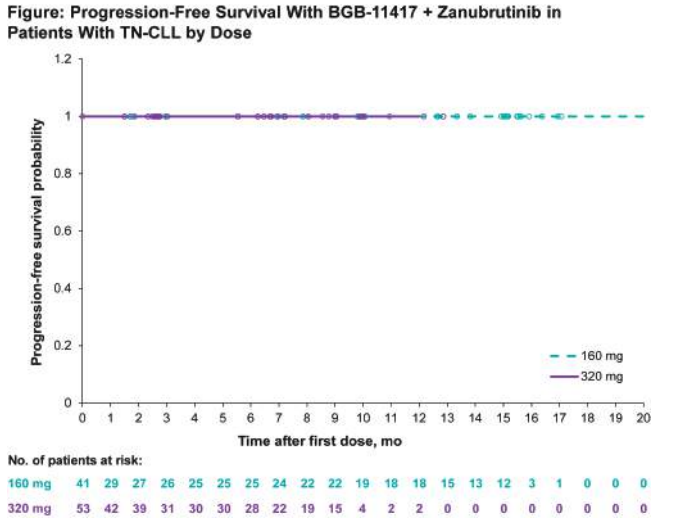

Figure 1.

C077

RESULTS FROM THE PHASE 1 STUDY OF THE NOVEL BCL2 INHIBITOR SONROTOCLAX (SONRO; BGB-11417) IN COMBINATION WITH ZANUBRUTINIB (ZANU) FOR RELAPSED/REFRACTORY (R/R) CLL/SLL SHOW DEEP AND DURABLE RESPONSES

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Background. Sonro (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and potent inhibitor of BCL2 than venetoclax in biochemical assays. Zanu, a next-generation BTK inhibitor (BTKi), has shown improved PFS and tolerability, including fewer cardiac AEs, *vs* ibrutinib in pts with R/R CLL/SLL. Updated safety and efficacy data for sonro + zanu in pts with R/R CLL/SLL in the ongoing BGB-11417-101 (NCT04277637) study are presented.

Methods. Pts received zanu (320 mg QD or 160 mg BID) 8 to 12 wk before starting sonro with ramp-up to target dose (40, 80, 160, 320, or 640 mg QD). Pts were treated until progression or unacceptable toxicity. The primary endpoint was safety (CTCAE v5.0); ORR (iwCLL 2008 criteria) and minimal residual disease in blood by ERIC flow every 24 wk (uMRD4) were secondary and exploratory endpoints, respectively.

Results. As of October 31, 2023, 45 pts with R/R CLL/SLL were enrolled (40 mg, n=4; 80 mg, n=9; 160 mg, n=6; 320 mg, n=20; 640 mg, n=6). Four pts were still in zanu lead-in and 41 had started sonro. Of tested pts, 28% (11/40) had del(17p) and 72% (13/18) had unmutated IGHV. The median number of prior tx was 1 (range, 1-3); 7 pts had BTKi as their last therapy. The median follow-up was 17 mo (range, 0.5-32.6). No DLTs occurred; MTD was not reached up to 640 mg. Dose expansion was completed with a recommended phase 2 dose of 320 mg. Any-grade TEAEs in ≥20% of pts were COVID-19 (27%), contusion (27%), neutropenia (27%), diarrhea (24%), nausea (24%), and fatigue (24%). Neutropenia was the most common grade ≥3 TEAE (20%). No cases of TLS or atrial fibrillation occurred. No TEAEs led to death, discontinuation, or dose reduction. Sonro dose holds occurred in 14 pts (median duration, 7 days). For 32 response-evaluable pts, ORR was 97% (31/32; 1 SD at 40 mg). CR rate was 50% (40 mg, 25%; 80 mg, 50%; 160 mg, 67%; 320 mg, 56%; 640 mg, 40%); median time to CR was 9.8 mo (range, 5.5-18.2). Of 4 response-evaluable pts with prior BTKi, 3 had PR (n=2) or CR (n=1). All pts treated with sonro + zanu (160, 320, or 640 mg) who reached wk 48 achieved uMRD4 (Figure 1). Tx is ongoing for all but 1 pt in the 40-mg cohort who discontinued due to progression.

Conclusions. Efficacy of sonro + zanu combination tx is encouraging, with a 97% ORR and deep responses, including uMRD, in pts with R/R CLL/SLL. This combination has demonstrated a tolerable safety profile across all dose levels tested.

Figure. Best MRD by Weeks 24 and 48

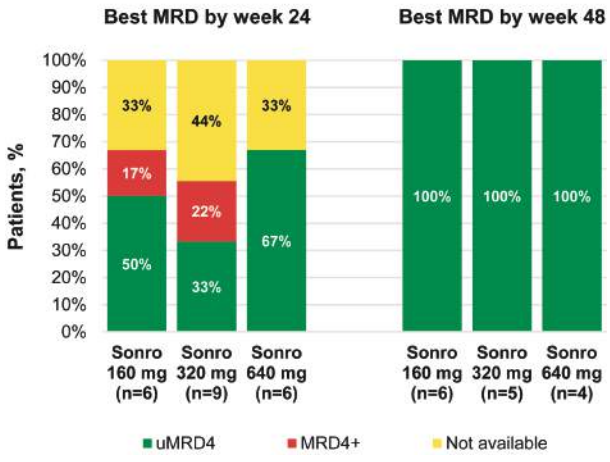

Figure 1.

C078

PIRTOBRUTINIB IN POST-CBTKI CLL/SLL: ~30 MONTHS FOLLOW-UP AND SUBGROUP ANALYSIS WITH/WITHOUT PRIOR BCL2I FROM THE PHASE 1/2 BRUIN STUDY

P. Ghia[1], J.A. Woyach[2], J.R. Brown[3], L.E. Roeker[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[11], B. Tessoulin[12], N.N. Shah[13], C. Ujjani[14], B. Fahkri[15], C. C. Coombs[16], I. Flinn[17], M.R. Patel[18], S.D. Nasta[19], J. B. Cohen[20], A.J. Alencar[21], C.Y. Cheah[22], S. Ma[23], J.M. Rhoades[24], D. Jagadeesh[25], P.L. Zinzani[26], A. Osterborg[27], K. Izutsu[28], D.E. Tsai[29], P. Abada[29], M. Balbas[29], J. Li[29], A.S. Ruppert[30], W. Jurczak[31], W. G. Wierda[32]

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The treatment of CLL/SLL has benefited from cBTKi, however, therapy can fail due to progression or intolerance. Sequential treatment with BCL2i venetoclax, either as monotherapy or combination therapy, has been the primary treatment option for CLL/SLL pts whose disease has progressed on cBTKi. We report the efficacy of pirtobrutinib treatment in CLL/SLL in the post-cBTKi setting, including subgroups with or without prior BCL2i, from the BRUIN study (NCT03740529) with more than 2 years follow-up. Pts with previously treated CLL/SLL were eligible for treatment with pirtobrutinib in the multicenter Phase 1/2 BRUIN study. Key endpoints included ORR (including PR-L) as assessed by an independent review committee per 2018 iwCLL response criteria, DoR, PFS, OS, and safety. A data cut of 05MAY2023 was utilized. This analysis included 282 pts with CLL/SLL who received prior cBTKi. Median age was 69 years (range, 36-88), 68% were male, and median number of prior therapies was 4 (range, 1-11). Of 282 pts, 154 (55%) were BCL2i-N and 128 (45%) were BCL2i-E. BCL2i-N pts were exposed to fewer prior therapies than BCL2i-E pts (median prior therapies 3 and 5, respectively). The ORR for all post-cBTKi pts was 72% (95% CI, 66.4-77.1). Post-cBTKi pts included a subgroup of 19 pts with one prior line of cBTKi-based therapy and second line therapy of pirtobrutinib, who had ORR including PR-L of 89.5% (CI 95%, 66.9-98.7. TMedian OS was not estimable for all cBTKi pre-treated pts, BCL2i-N, and BCL2i-E (median FU 29.3 mos). In the CLL/SLL cohort (N=282), the most frequent TEAEs, regardless of attribution, were fatigue (36.9%), diarrhea (28.4%) and cough (27.3%). The most frequent Grade ≥3 TEAE was neutropenia/neutrophil count decreased (28.4%). Grade ≥3 TEAEs of hypertension (4.3%) and atrial fibrillation/flutter (1.8%) were infrequent. The AE profile of BCL2i-N and BCL2i-E pts was overall similar. In total, 7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) pts had treatment-related AE leading to pirtobrutinib discontinuation. Pirtobrutinib continues to demonstrate promising and durable efficacy in pts with post-cBTKi heavily pretreated CLL/SLL. ORR was high regardless of prior BCL2i status. Longer PFS was observed in BCL2i-N pts than BCL2i-E pts, likely due to the more heavily pretreated status of the BCL2i-E population. Pirtobrutinib was well-tolerated with low-rates of discontinuation due to drug-related toxicity among both BTKi-N and BTKi-E pts.

Originally presented at ASH 2023.

Table 1.

	All post-cBTKi pts	BCL2i-N pts	BCL2i-E pts
ORR including PR-L, % (95% CI)	82 (76.5-85.9)	83.1 (76.2-88.7)	79.7 (71.7-86.3)
Median DoR, mos (95% CI)	18.4 (15.3-20.4)	24.9 (18.4-32.0)	14.8 (12.0-17.4)
Median PFS, mos (95% CI) [median FU – 27.5 mos]	19.4 (16.6-22.1)	23.0 (19.6-28.4)	15.9 (13.6-17.5)
24-month OS rates, % (95% CI)	73.2 (67.4-78.2)	83.1 (75.9-88.2)	60.6 (50.9-68.9)

C079

CAT RS 1001179 SINGLE NUCLEOTIDE POLYMORPHISM IDENTIFIES PATIENTS WITH POOR CLINICAL OUTCOME IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Chronic lymphocytic leukemia (CLL) is an incurable disease characterized by a highly variable clinical course. We have recently identified low *catalase* (*CAT*) expression as a major antioxidant element that identifies an indolent clinical behavior in CLL. 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. First, we studied 235 patients with CLL and 123 healthy donors (HDs), then we analyzed a cohort of 531 CLL patients for a validation independent study. The distribution of genotypes was consistent with the Hardy–Weinberg equilibrium among CLL patients and HDs, and no significant differences in genotype frequencies was found. In the first analyzed cohort 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. Furthermore, TT genotype refines risk stratification in patients with indolent disease, defined by low ZAP70 expression, favorable/neutral cytogenetics and Binet A stage. 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. In addition, 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 *TP53*. In bivariate analysis, the TT genotype combined with age at diagnosis, Binet stage B/C risk, ZAP70 positivity, unmutated *IGHV*, mutated *TP53*, or unfavorable cytogenetic predicted shorter TTFT. Importantly, the validation study with an independent patient cohort confirmed the prognostic ability of TT genotype. In accordance, patients bearing the TT genotype were characterized by a lower level of hemoglobin. Moreover, in early-stage disease the TT genotype identified patients with a faster disease progression and predicted shorter time to first treatment (TTFT) when combined with known prognostic factors. 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.

C080

CLINICAL AND BIOLOGICAL EFFECTS OF BENDAMUSTINE IN HIGH BURDEN T-LGLL PATIENTS

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T-cell Large Granular Lymphocyte Leukemia (T-LGLL) is a rare lymphoproliferative disorder characterized by CD3 T-LGLs expansion. LGLL therapy is based on Methotrexate, Cyclophosphamide and Cyclosporin A, immunosuppressive drugs with a broad-spectrum of side effects and unsatisfactory response rates. Bendamustine is an alkylating agent and a purine analogue hybrid widely used to treat many B-cell malignancies, with good safety profile. Even if it has been rarely used in T-cell neoplasms, including LGLL, promising results have been obtained. Thus, we evaluated this treatment on T-LGLL patients with high burden disease, defined by lymphocytosis >3x10^9 LGL/L or >30% bone marrow infiltration, with or without constitutional symptoms. According to these criteria, we assessed efficacy and safety of Bendamustine monotherapy in a retrospective single-center series of treatment-naive or relapsed/refractory T-LGLL patients. Clinical and biological data of 11 patients treated with Bendamustine at our center, between December 2010 and March 2024, were retrospectively collected. The drug was administered at a dosage variable from 60 to 90 mg/mq, according to patients' general conditions. Response status was evaluated according to Clinical Response Criteria proposed by *Brammer et al.* (Blood, 2023). Seven patients received up to 3 previous lines of therapy (3 of them as first line therapy). STAT3 mutations were detected in 5 patients. The main treatment triggers were severe neutropenia, moderate neutropenia associated with recurrent infections, and anemia <10 g/dL. The mean LGL count at the start of Bendamustine was 9.5 x10^9 g/L (range 0.8 - 22.4). The median number of courses was 6 and the median period of observation was 30 months (range 5-147). We observed clinical response in all 11 patients, with a median TTR of 4 months, and CR rate of 55%. No differences between STAT3 mutated and unmutated patients were seen. Three-year estimated PFS, OS and DoR were 90, 100 and 87.5%, respectively. Grade 3-4 neutropenia was registered in 28% of cases. Neither G3-4 anemia nor thrombocytopenia were reported. Only one patient developed a G3-4 extra-hematological toxicity. *in vitro* studies demonstrated a direct effect of Bendamustine on STAT3, inducing LGL apoptosis with a STAT3 inhibition related mechanism. This study shows the high efficacy and safety of Bendamustine as a single agent in the treatment of high burden T-LGLL patients, suggesting this drug as a new standard of care.

Myeloma and monoclonal gammopathies III

C081

MULTIPLE MYELOMA IN ITALY: AN EPIDEMIOLOGICAL MODEL BY LINE OF TREATMENT AND REFRACTORINESS STATUS

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Introduction. Multiple myeloma (MM) presents challenges in clinical management due to relapse and refractoriness to treatment. Understanding treatment patterns and refractoriness dynamics is crucial for optimizing patient care. We aimed to estimate MM prevalence by treatment line and refractoriness status in Italy.

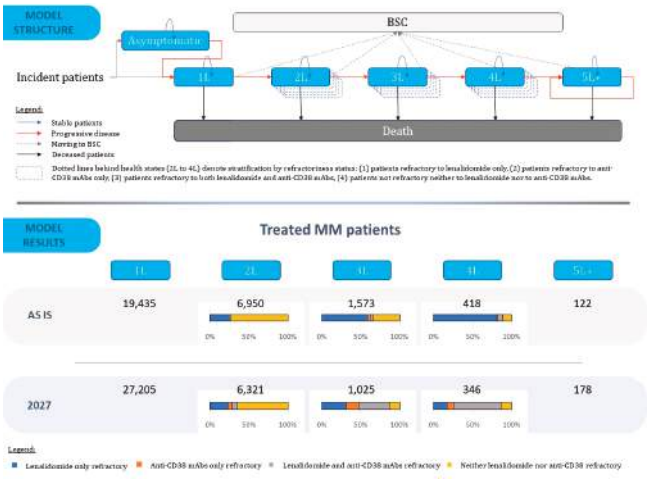

Figure 1.

Methods. We developed a comprehensive epidemiological model using a two-step approach. Firstly, we characterized the pool of prevalent MM patients in Italy as of 2020, by calibrating epidemiological and clinical inputs to align with literature data. Secondly, we incorporated incident patients from 2021 onwards, coinciding with the introduction of antiCD38-containing regimens in the first line of treatment in Italy. Clinical trials were used to obtain efficacy data specific for both treatment line and refractoriness status. The model employed a 1-year cycle Markov structure to simulate patient flow through treatment lines, considering the development of lenalidomide and anti-CD38 monoclonal antibody (mAb) refractoriness (see Figure 1).

Results. In 2020, Italy had an estimated 33,734 prevalent MM patients, consistent with AIOM-AIRTUM data. By 2027, treated MM patients were projected to increase to 35,074. Notably, the introduction of more effective treatments in early lines, such as daratumumab-based combinations, resulted in a significant increase in the absolute number of patients accumulating in the early lines of treatment (see Figure 1) with a slight decrease in the proportion of MM patients initiating each subsequent treatment line. In addition, the model gives an estimate of the changing scenario in the relapse set-

ting due to a progressive increase of patients refractory to lenalidomide and/or anti-CD38 mAbs across treatment lines. For instance, patients refractory to anti-CD38 mAbs in second to fourth lines were projected to increase from 1.7% in 2020 to 20.5% in 2027. At the same time, patients refractory to anti-CD38 mAbs were projected to constitute 2.5% of patient transitions in 2021, increasing to 40.4% in 2027.

Discussion. Our study reveals a rising prevalence of patients in initial therapy due to more effective treatments, yet a notable surge in refractory cases in subsequent lines underscores the urgency for innovative therapies and proactive management to tackle treatment resistance.

C082

OUTCOMES OF RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS CARRYING CHROMOSOME 1Q ABNORMALITIES RECEIVING ISATUXIMAB BASED REGIMENS: AN ITALIAN MULTICENTRIC RETROSPECTIVE STUDY

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Addition of Isatuximab (Isa) to Pomalidomide/dexamethasone (IsaPd) or Carfilzomib/dexamethasone (IsaKd) was reported to improve the outcome of patients (pts) with 1q abnormalities (1q+) treated within registrational studies. However, data in the real-world setting are lacking. To this aim, we retrospectively analyzed a cohort of 88 genetically profiled pts who were treated with IsaKd (n=49) or IsaPd (n= 39) in 8 Italian centers. 1q+ were stratified as follows: gain1q+ (3 copies), amp1q+ (≥ 4 copies), 1q+ with additional high risk chromosomal abnormalities [HRCA, t(4;14), t(14;16), del(17p)] and isolated 1q+. Due to the relatively low numbers, the analysis was not performed according to different Isa-based treatments and number of previous lines. Main pts features, 1q+ distributions and ORR are listed in Table 1. At a median follow-up of 14.5 months (mos), mPFS for the whole group was 26 mos and for IsaPd- and IsaKd-treated subgroups was 22 mos and NR (68% at 1 yr), respectively. 1q+ was associated with a shorter mPFS (18 mos) than 1q- (NR, 79% at 1yr; HR 2.22, p=0.026). In comparison with 1q-, mPFS was not significantly different for isolated 1q+ (18 mos; HR 1.92, p=0.129) and gain1q+ (21 mos; HR 1.63, p=0.24), while an adverse impact on mPFS was seen for amp1q+ (11 mos; HR 3.56, p=0.002) and 1q+ with additional HRCA (12 mos; HR 2.55, p=0.022) subgroups. Although cross-trial comparisons have major limitations, mPFS values for 1q+ subgroups treated with Isa-based triplets are consistent with previously published results from clinical trials (Martin T. *et al*; Haematologica 2022). Univariable analysis performed on the whole group showed that achievement of ≥VGPR predicted favorable PFS (HR 0.09, p<0.001) and OS (HR 0.19, p=0.004), while early relapse (ER, see Table 1 for definition) before Isa-based regimens was related with inferior PFS (HR 3.95, p<0.001) and OS (HR 3.33, p=0.011). Among different 1q+ abnormalities, only 1q+ with additional HRCA portended inferior PFS (HR 2.6, p=0.002). However, this negative relationship was not confirmed in a multivariable analysis which confirmed achievement of ≥VGPR (HR 0.09, p<0.001) and ER (HR 2.41, p=0.023) as the only independent predictors of PFS. These results from a real-world setting suggest that Isa-based triplets might mitigate the adverse prognostic role of 1q+ abnormalities, consistently with previous data from clinical trials. An updated analysis with extended follow up will be presented at the meeting.

Table 1.

	Overall Population, n= 88 (100%)	1q+ patients, n=45 (51%)		1q- patients, n=43 (49%)	
		IsaKd n=29	IsaPd n=16	IsaKd n=20	IsaPd n=23
Baseline features					
Age, years (median)	64	60	66	62	66
HRCA not associated with 1q+, n (%)	15 (17)	-	-	7 (17)	8 (21)
1q abnormalities					
1q+, n (%)	45 (51)	29 (59)	16 (41)	-	-
gain 1q+, n (%)	29 (33)	20 (41)	9 (23)	-	-
amp1q+, n (%)	16 (18)	9 (18)	7 (18)	-	-
1q+ with additional HRCA, n (%)	21 (24)	13 (27)	8 (21)	-	-
Isolated 1q+, n (%)	24 (27)	16 (32)	8 (21)	-	-
Previous lines					
Previous lines, median (min-max)	2 (1-4)	1 (1-2)	2 (1-4)	1 (1-3)	2 (1-4)
Early relapse before Isa (relapse < 18 mos after first line transplantation, < 12 mos after any previous line), n (%)	18 (20)	9 (31)	4 (25)	0 (0)	5 (22)
ORR / ≥ VGPR, n (%), Isa-triplets	72 (81) / 46 (52)	20 (74) / 14 (52)	12 (75) / 5 (31)	20 (100) /15 (75)	20 (87) /12 (52)

C083

IMPACT OF DARATUMUMAB - BORTEZOMIB - THALIDOMIDE - DEXAMETHASONE INDUCTION THERAPY ON HEMATOPOIETIC STEM CELL COLLECTION AND ENGRAFTMENT IN MULTIPLE MYELOMA PATIENTS ELIGIBLE FOR AUTOLOGOUS STEM CELLS TRANSPLANTATION: RESULTS OF THE PRIMULA STUDY

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Induction therapy utilizing daratumumab/bortezomib/thalidomide/dexamethasone (D-VTd) has become a standard of care for transplant-eligible patients with newly diagnosed multiple myeloma

(NDTEMM). Emerging evidence, however, suggests that daratumumab may influence stem cell mobilization and engraftment post-autologous stem cell transplantation (ASCT). The PRIMULA study (ImPact of induction theRapy with D-VTd on collection of hemopoietic stem cells and engraftment In patients with MULtiple myeloma eligible to Autologous transplantation) aims to evaluate the impact of daratumumab on peripheral blood hematopoietic stem cell (PBSC) mobilization, collection, and post-transplant engraftment in a real-world setting. A multicenter, observational, retrospective study was conducted across 14 Italian centers, enrolling 151 NDTEMM patients treated with D-VTD from February 2022 to July 2023. Stem cell mobilization was performed after 4-6 cycles of D-VTd induction, with data compared to a historical cohort of 43 patients treated with VTd. Overall, in the D-VTd group, the median number of CD34+ collected was significantly lower compared to the VTd group (6.73 CD34+ x 10^6/kg and 8.67 CD34+ x 10^6/kg, respectively, p<0.0001), necessitating higher use of plerixafor (57% in the D-VTd group versus 23% in the VTd group, p<0.0001) and more frequent mobilization attempts (15% of D-VTd patients with 2 attempts versus 2% of VTd patients, p=0.03). Accordingly, 56% of patients in the D-VTd group had at least 2 apheresis versus 26% in the VTd cohort (p=0.0005). The median number of CD34+ infused was higher in the VTd group versus D-VTd (4,5 x 10^6/kg versus 4 x 10^6/kg, p=0.0032). Moreover, the median time to neutrophil and platelet engraftment was longer in the D-VTd group compared to VTd (11 *vs* 10, p<0.0001 and 12 *vs* 11, p=0.0005, respectively). Despite these challenges, the outcomes of ASCT were not worsened by daratumumab in terms of feasibility and safety. The PRIMULA study highlights the impact of daratumumab on CD34+ mobilization, harvest, and ASCT outcomes in a multicenter, real-life cohort of patients. While daratumumab negatively affects CD34+ yield and engraftment kinetics, it does not compromise the transplant feasibility and safety. However, these findings may have implications for treatment planning, particularly for double ASCT strategies in NDTEMM patients.

C084

COULD CLINICAL-LABORATORY FEATURES RECOGNIZE FUNCTIONAL HIGH RISK MULTIPLE MYELOMA PATIENTS? A REAL-WORLD ANALYSIS

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Background. High-risk (HR) MM patients have dismal outcomes. Nevertheless, approximately 10-20% of not necessarily HR patients, termed functional HR (FHR), have PFS shorter than 12-18 months, despite optimal initial therapy. Only not routinely applied genomics or dynamic MRD assessment could well identify them.

Aim. The aim of this study was to describe and compare FHR MM patients features with those of patients with longer PFS and to build a simple score to assess FHR probability.

Methods. FHR was defined as PFS cut-off value ≤ 18 months for transplant eligible (TE) and ≤ 12 months for not-transplant eligible (NTE) patients. Factors associated with FHR status were searched by logistic regression univariate and multivariate analysis, assigning a hazard ratio-based score for each significant factor, fitting a weight Cox model to assess FHR cumulative incidence. Survival curve was performed by Kaplan-Meier methods and compared by log-rank test.

Results. Median age of 448 enrolled patients was 70 years (range 30-82), 180 patients received autologous stem cell transplantation and 268 standard therapy. Median follow-up was 82 months (95%CI: 36-156). FHR patients were 15 (8.5%) in ASCT and 75 (28%) in standard therapy group. FHR significantly differed from not-FHR group for ISS 2-3 (89% *vs* 57%; p<0.001) R-ISS 2-3 (91% *vs* 69%; p<0.001), platelets count<150.000/mcl (30% *vs* 15%; p<0.001), no maintenance/continuous therapy (94% *vs* 62%; p<0.001), response to therapy<VGPR (71% *vs* 22%; p<0.001). Logistic multivariate analysis selected ISS2-3 (OR: 5.5; 95%CI: 2.6-12), presence of 1q abnormalities (OR: 2.9; 95%CI: 1.2-6.9), platelets count<150.000/mcl (OR: 2.9; 95%CI: 1.4-5.8), response<VGPR (OR: 8.4; 95%CI: 4.7-15) and no maintenance/continuous therapy (OR: 9.1; 95%CI: 3.4-25) as factors significantly affecting FHR status. Scoring patients according to these criteria, FHR patients were 5 (5%) in the LR (score 0-2.5 points), 30 (34%) in the IR (score 3-4.5 points) and 55 (61%) in the HR group (score 5-6). FHR cumulative incidence was 7.5%, 18% and 42% at 12 months and 12%, 28% and 60% at 18 months in LR, IR and HR groups, respectively. Median OS was significantly shorter in FHR *vs* non-FHR patients (19 *vs* 104 months; p<0.001).

Conclusions. Our results suggest that simple clinical features available before (static assessment) and after (dynamic assessment) therapy could predict FHR status. Our prognostic score may be useful for planning therapeutic sequencing.

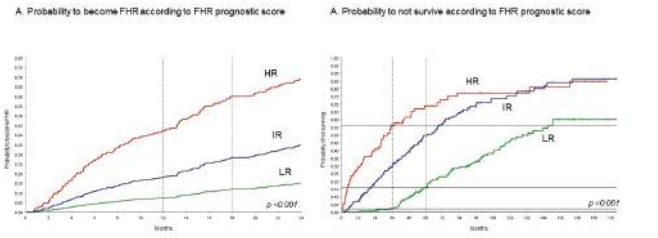

Figure 1.

C085

A FOUR-CLINICAL VARIABLES BASED SCORE TO IDENTIFY MGUS PATIENTS AT RISK OF PROGRESSION: A RETROSPECTIVE SINGLE-CENTER STUDY WITH 10 YEARS FOLLOW UP

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Background. Recently, an increasing number of studies have demonstrated the value of inflammatory response biomarkers, in predicting cancer outcome, based on peripheral blood cells counts, including the neutrophil-to-platelets ratio (NPR), the systemic immune inflammation index (SII) and the systemic inflammation response index (SIRI).

Methods. We investigated NPR, SII and SIRI in a retrospective series of 674 MGUS diagnosed in our Center between 2006 and 2016. The NPR, SII, and SIRI were calculated using the following formula: NPR=neutrophil count/ platelet count, SII=platelet count × neutrophil count/lymphocyte count, SIRI=neutrophil count × monocyte count/lymphocyte count.

Results. Median follow-up was 9.6 years (range: 0-10.6), while 118 patients died and 71 progressed and developed MM (N= 65), AL amyloidosis (N=3), lymphoma (N=1), or Waldenstrom-macroglobulinemia (N=2). According to IMWG criteria, 547 (90 %) patients were classified as low- and 59 (10%) as intermediate- risk MGUS. Median NPR, SII and SIRI were respectively 16.2 (range 1.6-59.6), 960 (range 74-7632) and 489 (range 26-2751). A Receiver Operating

Characteristic (ROC) curve analysis identified BMI ≥ 25, IgM ≤40 mg/dL, SIRI <700, NPR <10 and beta-2-microglobulin ≥ 2.5 mg/dL able in predicting progression to MM with at least 70% sensitivity and specificity. In univariate analysis predictors of inferior TTP at 10 years, available at diagnosis, were: BMI ≥ 25 (HR=4.1, 95%CI: 2.4-6.9, p<0.0001), suppressed uninvolved immunoglobulin, quantified as IgM ≤40 mg/dL (HR=3.3, 95%CI: 1.9-5.6, p< 0.0001), SIRI <700 (HR=1.6, 95%CI: 1.0-2.6), NPR <10 (HR= 2.5, 95%CI: 1.3-5.2, p=0.009) and beta-2-microglobulin ≥ 2.5 (HR= 2.2, 95%CI: 1.3-3.6, p=0.003). In multivariate analysis, BMI ≥ 25, IgM ≤40 mg/dL, NPR <10 and beta-2-microglobulin ≥ 2.5 g/dL were independent baseline variables able to predict 10-yrs-TTP. For each of the independent parameters identified in multivariate analysis a point was attributed to identify 3 classes of risk: low (score 0-1, N=234), intermediate (score 2, N=253) and high (score 3-4, N=119), disclosing that the 10-yrs-TTP were significantly different among the three risk groups, respectively: 90.2%, 81.3%, and 62.5% (p<0.0001).

Conclusions. Four low-cost parameters (BMI ≥ 25, IgM ≤40 mg/dL, NPR <10 and beta-2-microglobulin ≥ 2.5 g/dL) should be investigated in all non-IgM MGUS patients to improve clinician's ability to make therapeutic decisions for individual patients.

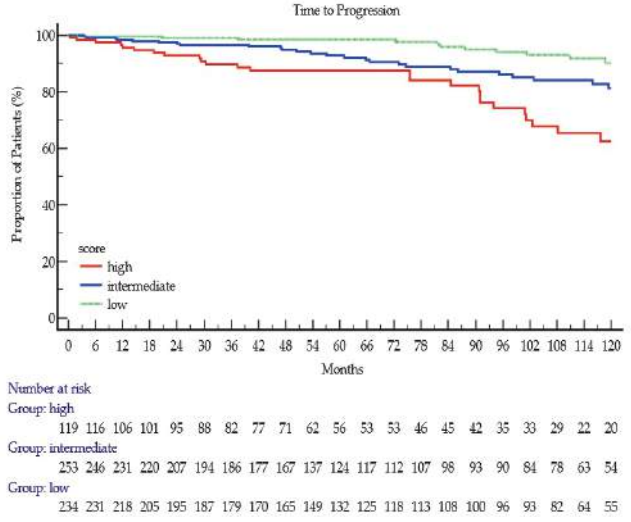

Figure 1.

Non-Hodgkin lymphoma III

C086

POTENTIAL ROLE OF PET QUANTITATIVE PARAMETERS IN EARLY IDENTIFICATION OF RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA PATIENTS NON-RESPONDER TO CAR T-CELL THERAPY

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CAR T-cell therapy has shown remarkable efficacy in treating relapsed/refractory large B-cell lymphomas (LBCLs). However, response to treatment varies among patients, with approximately half of them progressing or relapsing within one year after treatment. F-18 fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) is commonly used to assess treatment response, typically using Deauville score (DS), a visual scale. We investigated whether PET semiquantitative parameters (SUVmax, total lesion glycolysis [TLG], and metabolic tumor volume [MTV]) measured before CAR T-cell infusion (PET0) and one month after (PET1) could better identify non-responder patients. MTV, TLG, SUVMax, DS, and variations of these parameters between the two scans were calculated and associated with the duration of response (DoR), overall survival, and progression-free survival.

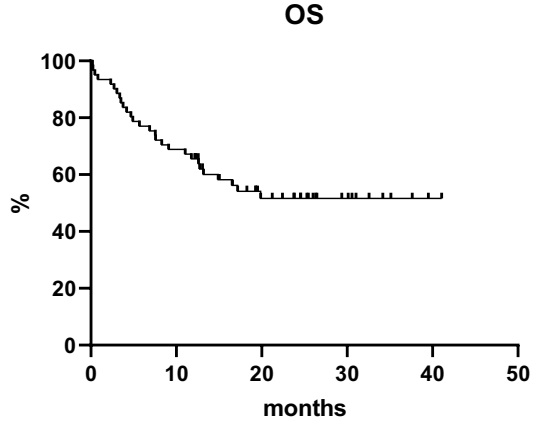

Figure 1.

We prospectively enrolled 61 patients with a median follow-up of 18 months (30% women, median age 59 years with 75.4% who received a bridging therapy to CAR T-cell treatment). Median PET0 parameters were 125.3 ml for MTV, 728.8 g for TLG, and 17.6 for SUVmax, respectively, whereas at PET1 were 1.8 ml, 5.0 g, and 4.4, respectively. Twenty-eight (45.0%) patients died during follow-up with an overall survival of 51.6% at 3.5 years (median not reached, Figure 1). Patients with SUVMaxPET0 > 14.7, TLGPET0 > 571.7 g, PET1MTV > 60.8 ml, TLGPET1 > 97.0 g, and DS PET1 ≥4 had a statistically significant increased risk of death (all p>0.05). Patients with MTVPET0 > 109.9 ml, SUVMaxPET0 > 11.8, TLGPET0 > 571.7 g, MTV PET1 > 48.3 ml, TLG PET1 > 204.6 g and PET1DS ≥4 had a statistically significant increased risk of disease progression

(all p<0.05). Patients with MTVPET0 > 225.7 ml and TLGPET0 > 728.8 g, were associated with a statistically significant reduced DoR. Also, MTVPET1 was associated with longer DoR. In conclusion, PET semiquantitative parameters measured before and one month after CAR T-cell infusion significantly correlate with overall survival, progression-free survival, and DoR. These findings suggest that PET-based metrics should be considered for early treatment decisions in LBCL patients.

C087

TP53 AND CDKN2A DISRUPTIONS ARE INDEPENDENT PROGNOSTIC DRIVERS IN MANTLE CELL LYMPHOMA: LONG TERM OUTCOME OF THE FONDAZIONE ITALIANA LINFOMI (FIL) MCL0208 TRIAL

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Background. The upfront identification of mantle cell lymphoma (MCL) patients (pts) rapidly progressing under chemoimmunotherapy (CIT) might be extremely useful in personalizing treatment strategies. Therefore, we exploited the updated results of the phase 3 Fondazione Italiana Linfomi MCL0208 trial (randomizing young MCL to lenalidomide maintenance *vs* observation after CIT and ASCT), to evaluate the prognostic relevance of mutations and copy number variations (CNVs) and to generate a simplified genetic prognostic model for clinical practice.

Methods. Tumor DNA was extracted from CD19+ BM cells. Gene mutations were evaluated with the TruSeq Custom Amplicon kit and CNVs with the Illumina HumanOmni2.5 array coupled to stringent bioinformatic pipelines.

Results. Out of 300 enrolled pts, 186 were analyzed for mutations and 165 for CNVs. After a median follow-up of 7 years, TP53 mutations (N=15, 8.1%), 17p deletion (N=24, 12.9%) and KMT2D mutations (N=23, 12.4%) significantly predicted poor PFS and OS. Besides TP53 deletion, 7 out of the 351 identified CNVs significantly predicted PFS by univariate analysis (Figure 1A). Pts with at least one of these 7 CNVs (CNV7) and devoid of TP53 disruption had both a shorter PFS (HR 4.17, p<0.0001) and OS (HR 6.20, p<0.0001) if compared to WT ones. Therefore, a "genetics only" prognostic model (MIPIgo) was devised according to PFS-based Cox regression analysis including KMT2D mutations (HR 2.03, p=0.029), TP53 disruptions (HR 2.28, p=0.008) and CNV7 (HR 2.42, p=0.001). The MIPIgo improved the C-statistics both for PFS (0.685) and OS (0.765) compared to MIPI (0.597/0.679) and MIPIc (0.584/0.696). Notably, the MIPIgo reclassified ~50% of MIPI cases. Moreover, after CNV7s were adjusted for validated prognostic markers (MIPI, Ki67, blastoid variant, TP53 disruption), only CDKN2A loss (HR 2.12, p=0.014) and TP53 disruption (HR 2.69, 95%, p<0.001) independently associated with shorter PFS. Pts with TP53 disruption only (N=18), with CDKN2A loss only (N=17) or both (N=11) had superimposable poor PFS, independent of MIPI and Ki67, while single hits showed only a slightly better OS compared to double hit MCL (Figure1B).

Conclusion. The MIPIgo model, including both CNVs and gene mutations captured more high-risk pts at baseline, independent of clinical prognosticators, thus improving outcome prediction. In particular, testing for both TP53 aberrations and CDKN2 loss should be added to the initial work-up of MCL pts since its independent prognostic value.

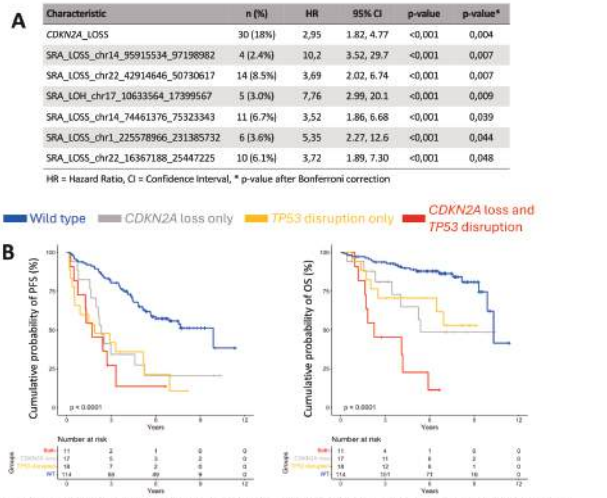

Figure 1. (A) Table showing the 7 CNV that predicted PFS by univariate analysis after Bonferroni correction; **(B)** Progression free survival and overall survival according to *CDKN2A* loss and *TP53* disruption.

Figure 1.

C088

INTEGRATION OF 18F-FDG–PET RADIOMICS WITH LIQUID BIOPSY IMPROVES OUTCOME PREDICTION IN NEWLY DIAGNOSED DLBCL PATIENTS

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Background. Baseline circulating tumor DNA(ctDNA) levels

and PET/CT parameters allow to identify DLBCL destined to early relapse,but their integration and the potential role of molecular clustering on ctDNA have not been extensively evaluated.

Aim. The aim of this study was to integrate the prognostic value of ctDNA levels, molecular clusters,and PET/CT variables to improve outcome prediction in DLBCL.

Methods. A real-world cohort of 120 newly diagnosed DLBCL, treated with R-CHOP and provided with ctDNA from plasma and with baseline ^{18}F-FDG-PET/CT scans, has been prospectively enrolled. Molecular clusters were identified using the LymphGen tool. Using the standardized uptake value(SUV) threshold of 4.0, the following were collected: *i)* maximum SUV(SUVmax), *ii)* total metabolic tumor volume(tMTV), *iii)* total total lesion glycolysis(tTLG), and *iv)* Dmax. The MaxStat test was used to identify the best cutoff values in predicting PFS for ctDNA levels and for each PET/CT variable.

Results. Using MaxStat, the best cutoff for predicting PFS was 2.68 Log_{10}hGE of ctDNA (p<0.001) and for SUVmax, tMTV, tTLG and Dmax were 17.66(p=0.037),639.2 cm^3 (p<0.001), 7138.34 (p<0.001) and 39 cm(p=0.003),respectively. Patients with ctDNA levels>2.68 Log10hGE(N=43), termed ctDNA-high, had 40-month PFS and OS of 42.9% and 55.4% compared to 77.4% and 86.5% for ctDNA-low patients (p<0.001 and p=0.001, respectively). Using the LymphGen tool, BN2 and ST2 clusters presented a very good outcome after R-CHOP. Therefore, patients with at least one PET/CT value(among tMTV, tTLG or Dmax) above the respective cutoff were grouped as PET+ patients (N=67). PET+ patients were characterized by worse outcome compared to PET-negative patients.By multivariate analysis, PET+(HR 3.98, p<0.001), ctDNA-high(HR 2.53, p=0.01) and BN2/ST2 cluster (HR 0.37, p=0.04) independently predicted PFS (Figure 1A). Therefore, based on the B coefficients,1.5 points were assigned to PET+, 1 point to ctDNA-high and -1 point to BN2/ST2 patients. Three different groups with unique PFS and OS were identified. Low-risk DLBCL(-1 to 0.5 points, N=51) presented 40-month PFS and OS of 92.0% and 96.0%, intermediate-risk DLBCL (1 to 1.5 points, N=46) presented 40-month PFS and OS of 58.0% and 75.5%,and high-risk DLBCL(2.5 points, N=23) presented 40-month PFS and OS of 20.9% and 30.4%,respectively(both p<0.001) (Figure 1B,C).

Conclusions. The integration of baseline PET/CT variables, ctDNA levels and molecular clusters improve the outcome prediction of DLBCL.

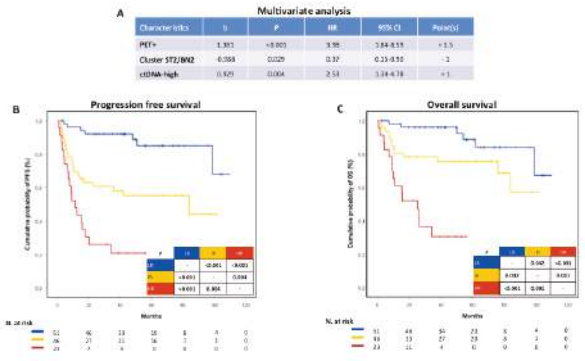

Figure 1.

C089

CAR T-CELL THERAPY IN HIGH-GRADE B-CELL LYMPHOMAS (HGBLS): PROGNOSTIC FACTORS AND OUTCOME

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HGBLs include Double-hit (DH) lymphomas with rearrangements of myc/bcl2 and the provisional entity with myc/bcl6 (Campo E, Blood 2022) and High-Grade not otherwise specified (HG-NOS) lymphomas. Despite intensive induction treatments, overall survival (OS) remains suboptimal. Approval of anti-CD19 chimeric antigen receptor (CAR) T-cell for second and third-line aggressive lymphomas resulted in long-term remission in up to 40% of pts. This study aimed to explore long-term outcomes and prognostic factors in these rare subtypes. The CART-SIE study is an ongoing multicenter prospective observational study. All pts eligible for CAR T-cell therapy were consecutively enrolled. We analyzed only pts treated with CAR T-cell in the third line or more. Pathological data and FISH analyses, when available, were collected. CAR-HEMATOTOX was calculated according to Rejeski et al, Blood 2021. Between February 2020 and January 2024, we included 71 HGBL pts (median age 63 years, range 22-76), 44 (62%) DH, 22 (31%) HG-NOS and 5 (7%) pts with myc/bcl6 [FISH analysis available in 59/71 pts (83%)]. The main patient's characteristics were as follows: 41(58%) male, 33(46%) elevated LDH, 31(44%) bulky disease, 40(56%) extranodal disease. Pts were infused with Axicel (n=34, 48%) or Tisacel (n=37, 52%). Most pts required bridging therapy (94%), resulting in 10 CR (14%). Grade ≥3 CRS and ICANS were 8,4% (n=6) and 7% (n=5), respectively. With a median follow-up of 13 months (range, 3-32 months), 36 pts (51%) were alive and 35 (49%) died of PD (n=32) and toxicity (n=3). A total of 43 pts (60%) experienced PD following CAR T-cell, of whom 33 (76%) received a salvage therapy (n=11

with bispecific antibodies), and 11 (25%) were still alive. The estimated 1-year PFS and OS were 33% (95%CI, 22%-44%) and 41% (95%CI, 29%-54%), respectively. We didn't observe a significant difference in outcome according to CAR T-cell product. The OS was influenced by CAR-HEMATOTOX (22% *vs* 63%, p=0.0015) but not PFS (24% *vs* 43%, p=0.08). Pts in CR at the time of CART infusion showed a trend for reduced risk of failure (68% *vs* 32%, p=0.07). The 1-year PFS (38% *vs* 23%, p-value=0.25) and OS (45% *vs* 36%, p=0.52) were not significantly different between DH and HG-NOS. CAR T-cell therapy is effective for HGBLs. The outcome was influenced by inflammatory status but not by subtype (DH versus HG-NOS). A higher PFS and OS will be expected using CAR T-cell therapy in the second line.

C90

ABSTRACT NOT PUBLISHABLE

Myeloproliferative neoplasms II

C091

AVAPRITINIB IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS (ADVSM): EFFICACY AND SAFETY ANALYSIS FROM THE PHASE 2 PATHFINDER STUDY WITH 3-YEAR FOLLOW UP

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AdvSM is a rare clonal hematologic neoplasm driven by the *KIT* D816V mutation in ~95% of cases. Avapritinib, a highly selective and potent *KIT* D816V inhibitor, showed deep and durable responses in adult patients (pts) with AdvSM in phase 1 and 2 studies. We report updated efficacy and safety from the phase 2 PATHFINDER study (3-year follow-up). Adults with centrally confirmed AdvSM were assessed for overall response rate (ORR, primary endpoint), time to response, duration of response (DOR), progression-free survival (PFS), overall survival (OS), changes in disease burden measures, and safety. At data cutoff, 107 pts with AdvSM (20% aggressive SM, 66% SM with an associated hematologic neoplasm, and 14% mast cell leukemia) had initiated avapritinib 200 mg (n=105) or 100

mg (n=2) once daily. Median age was 68 years, 58% were male, and 26% had Eastern Cooperative Oncology Group performance status 2 or 3; 64% had ≥1 prior systemic therapy (PST). Median ORR in the 83 response-evaluable (RE) pts was 73%, 87% in treatment-naïve pts, and 66% in PST pts. Similar responses were observed across subtypes. A high complete remission/complete remission with partial hematologic recovery rate (29%) was observed in RE pts and was twice as high in treatment-naïve (43%) *versus* PST pts (21%; Table 1). In the safety population (n=107), the median treatment duration was 33.2 months. Median DOR and PFS were not reached (NR) in RE pts. Median OS was NR regardless of subtype or PST. Clearance of bone marrow mast cell aggregates was seen in 71% of pts, 63% had reduction in *KIT* D816V variant allele fraction to <1%, 65% had a reduction in serum tryptase to <20 ng/mL, and 80% (43/54) had clinical resolution of palpable spleens. In pts with baseline monocytosis or eosinophilia, 96% (26/27) and 96% (22/23) had a ≥50% reduction in monocyte and eosinophil counts, respectively. Most frequent (≥25%) treatment-related adverse events (TRAEs) were (any grade; grade ≥3) periorbital edema (41%; 6%), thrombocytopenia (40%; 18%), peripheral edema (38%; 2%) and anemia (32%; 13%). Dose reductions, interruptions, and discontinuations due to TRAEs occurred in 76%, 63%, and 13% of pts. No intracranial bleeding events were seen since previous data cutoff. No treatment-related deaths occurred. With >3 years of follow-up, pts with AdvSM treated with avapritinib showed continued deep and durable responses with a favorable benefit-risk profile regardless of subtype or PST.

Table 1.

Table: Summary of efficacy patients with AdvSM

	All response-evaluable					
	AdvSM subtype					
	All (n=83)	ASM (n=13)	SM-AHN (n=55)	MCL (n=15)	Patients with ≥1 prior systemic therapy (n=53)	Treatment-naïve (n=30)
ORR[a] N (%)	**61 (73)**	10 (77)	41 (75)	10 (67)	**35 (66)**	26 (87)
95% CI	**63–83**	46–95	61–85	38–88	**52–79**	69–96
CR or CRh[b]	**24 (29)**	3 (23)	18 (33)	3 (20)	**11 (21)**	13 (43)
CR	**13 (16)**	1 (8)	9 (16)	3 (20)	**6 (11)**	7 (23)
CRh	**11 (13)**	2 (15)	9 (16)	0	**5 (9)**	6 (20)
PR[c]	**33 (40)**	7 (54)	19 (35)	7 (47)	**20 (38)**	13 (43)
CI	**4 (5)**	0	4 (7)	0	**4 (8)**	0
SD	**13 (16)**	3 (23)	7 (13)	3 (20)	**10 (19)**	3 (10)
PD[d]	**2 (2)**	0	1 (2)	1 (7)	**2 (4)**	0
NE	**7 (8)**	0	6 (11)	1 (7)	**6 (11)**	1 (3)
Median DOR (95% CI)	**NR (43–NR)**	NR (27–NR)	NR (37–NR)	NR (NR–NR)	**NR (43–NR)**	43 (37–NR)
Median PFS (95% CI)	**NR (45–NR)**	NR (NR–NR)	45 (31–NR)	NR (12–NR)	**NR (31–NR)**	48 (39–48)
Median OS (95% CI)	**NR (50–NR)**	NR (NR–NR)	NR (50–NR)	NR (14–NR)	**NR (50–NR)**	NR (NR–NR)

[a]Best confirmed response per modified International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis response criteria. CR + CRh + PR + CI. Data cutoff September 15, 2023. [b]CRh requires full resolution of all evaluable C-findings, elimination of BM mast cell aggregates, serum tryptase <20 ng/mL, resolution of palpable hepatosplenomegaly, and partial hematologic recovery (defined as absolute neutrophil count >0.5×10^9/L with normal differential, platelet count >50×10^9/L, and hemoglobin level >8.0 g/dL). [c]PR requires full resolution of ≥1 evaluable C-findings and ≥50% reduction in both bone marrow mast cells and serum tryptase. [d]Two patients had PD as best response.
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; OS, overall survival; PFS, progression-free survival; PR, partial response; PD, progressive disease; SD, stable disease; SM-AHN, systemic mastocytosis with associated hematologic neoplasm.

C092

SAFETY AND EFFICACY OF PELABRESIB IN COMBINATION WITH RUXOLITINIB FOR JAK INHIBITOR-NAÏVE PATIENTS WITH MYELOFIBROSIS: LATEST DATA FROM THE PHASE 3 MANIFEST-2 STUDY

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Introduction. Pelabresib (PELA) is an investigational, oral, small molecule BET inhibitor intended to decrease expression of myelofibrosis (MF) target genes. MANIFEST-2 (NCT04603495), a global, randomized, double-blind, Phase 3 study, investigated the efficacy and safety of PELA + ruxolitinib (RUX) *vs* placebo (PBO) + RUX in Janus kinase inhibitor (JAKi)-naïve patients (pts) with MF.

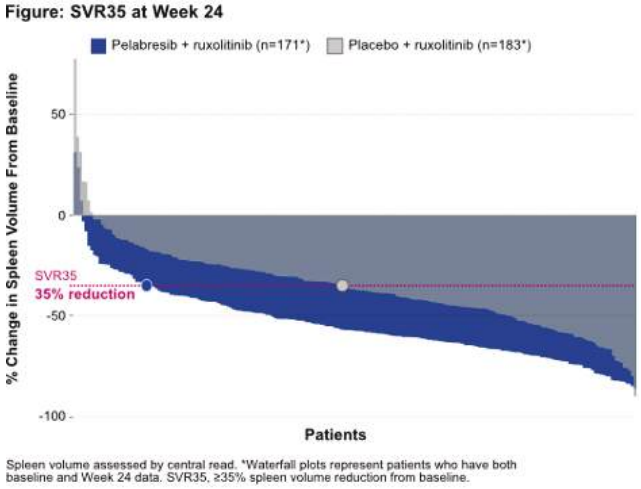

Figure 1.

Methods. Pts had DIPSS score ≥INT-1, platelet count ≥100 × 10^9/L, spleen volume ≥450 cm^3, ≥2 symptoms with an average score ≥3 or total symptom score (TSS) ≥10 (MFSAF v4.0), peripheral blast count <5%, and ECOG PS ≤2. PELA or PBO was administered (daily for 14 consecutive days of 21) with RUX (twice daily for 21 days [1 cycle]). Primary endpoint was ≥35% spleen volume reduction from baseline (BL) (SVR35) at Week (W)24. Secondary endpoints included absolute change in TSS and ≥50% reduction in TSS from BL (TSS50) at W24, and safety. Other endpoints included hemoglobin (Hb) response (≥1.5 g/dL mean increase from BL without

transfusions in the prior 12 weeks) and red blood cell (RBC) transfusion number.

Results. As of Aug 31, 2023, 430 pts were randomized. At W24, 65.9% (141/214) *vs* 35.2% (76/216) (p<0.001) of pts had an SVR35 response in the PELA+RUX *vs* PBO+RUX arms, respectively (Figure). Mean (SE) absolute change in TSS was -15.99 (1.028) *vs* -14.05 (0.986) (p=0.0545), and TSS50 response was 52.3% (112/214) *vs* 46.3% (100/216) (nominal p=0.216) at W24. Hb response was observed in 10.7% (23/214) *vs* 6.0% (13/216) of pts, with differences in mean Hb levels maintained at W48. In pts with anemia (Hb BL <10 g/dL), Hb response was observed in 16.4% (11/67) *vs* 14.1% (10/71). During the first 24 weeks, 27.6% (59/214) *vs* 37.5% (81/216) of pts required RBC transfusion. Of 426 pts evaluated for safety, the most common treatment-emergent adverse events in the PELA+RUX *vs* PBO+RUX arms were anemia (43.9% *vs* 54.7% [Grade ≥3, 23.1% *vs* 36.4%]), thrombocytopenia (52.8% *vs* 37.4% [13.2% *vs* 6.1%]), and diarrhea (23.1% *vs* 18.7% [0.5% *vs* 1.4%]).

Conclusions. PELA+RUX significantly reduced splenomegaly, with a trend toward reduced TSS at W24, and improved anemia at W24 and W48 compared with PBO+RUX in JAKi-naïve pts with MF, addressing key hallmarks of MF. Results support a potential paradigm shift to combination therapy for MF. The development of pelabresib was funded in part by the Leukemia and Lymphoma Society.

C093

LIFE AFTER RUXOLITINIB IN MYELOFIBROSIS PATIENTS: IMPACT OF DISEASE PHENOTYPE AND TREATMENT STRATEGIES

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Outcome after ruxolitinib (RUX) discontinuation is poor in patients (pts) with myelofibrosis (MF). To investigate the impact of disease phenotype at RUX stop and of subsequent therapeutic strategies on outcome, we performed a sub-analysis of the RUX-MF retrospective study, that includes 1055 MF pts treated with RUX according to standard practice. Overall survival (OS) was estimated from RUX stop or 2nd line therapy start. Cox models and delayed entry were used for estimated survival plots. After a median exposure of 1.4 yrs, 397 (37.6%) pts discontinued RUX in chronic phase. At RUX stop, 208 (52.4%) pts had a cytopenic phenotype (PLT≤100x10^9/L and/or Hb≤8g/dL) while 189 pts had either a fully proliferative phenotype (Hb>10 g/dl, PLT>100 x10^9/L and spleen palpable at ≥5cm below costal margin, BCM, n.55) or a mild anemia (Hb 8-10 g/dl) with or without palpable splenomegaly (n.134). OS at 3 yrs was 33.4% in cytopenic and 54.4% in non-cytopenic pts (median OS: 3.9 *vs* 1.5 yrs, p<0.001), with no differences between pts with fully proliferative or mildly anemic MF (p=0.73). After DIPSS adjustment, the difference in OS remained significant (p=0.002) (Figure 1A). At RUX stop, 175 pts (44.1%) had a large spleen (≥10cm BCM). OS at 3 yrs was 33.5% and 51.6% in pts with and without large spleen (median OS: 2.1 *vs* 3.3 yrs, p=0.01), confirmed after DIPSS adjustment (p=0.04) (Figure 1B). Within 1 year from RUX stop, 272 out of 298 living pts (91.3%) received a 2nd line therapy: conventional therapy (CT: including hydroxyurea, steroids, danazol, busulfan, RUX, splenectomy, supportive therapy; n.119), novel therapy (NT: experimental drugs and novel JAK2 inhibitors; n.71) and allogeneic transplant (ASCT: n.82). The 3 groups differed for DIPSS score, PLT count, spleen length. OS at 3 yrs was 22.8%, 49.1% and 62.5% in CT, NT and ASCT pts, respectively, and confirmed after adjustment for DIPSS/PLT/spleen (p<0.001) (Figure 1C). This was confirmed analyzing separately pts with/without large splenomegaly and pts with/without cytopenic phenotype (both p<0.001). In multivariable Cox analysis including cytopenic phenotype, CT (vs NT) and large spleen, cytopenic phenotype (HR: 1.46, p=0.02) and CT (HR: 2.10, p<0.001) remained significantly associated with OS (large spleen, HR: 1.24, p=0.17). Cytopenic phenotype and large spleen are main determinants of MF prognosis after RUX discontinuation. ASCT and NT represent superior approaches compared with CT and should be used whenever possible.

Figure 1: Cox survival plots

(A) Cytopenic vs non-Cytopenic (adjusted for DIPSS risk); **(B)** With vs without large splenomegaly (adjusted for DIPSS risk); **(C)** Conventional Therapy vs Novel Therapy vs ASCT after RUX discontinuation (adjusted for DIPSS risk, platelet count and spleen length).

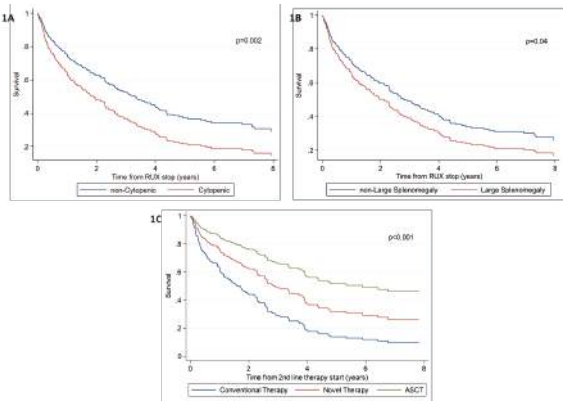

Figure 1.

C094

ENABLE: DECITABINE AND VENETOCLAX IN BLAST PHASE MYELOPROLIFERATIVE NEOPLASMS (MPN-BP). MUTATION LANDSCAPE OF PATIENTS ENROLLED IN THE MYNERVA-GIMEMA AML2420 TRIAL

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Management of pts with MPN-BP is challenging with median overall survival of 3-6 mo, unless for few pts bridged to transplantation. Clinical (age, performance status) and biological (prior exposure to chemotherapeutics, clonal complexity, resistance to conventional agents, enrichment of adverse mutations and complex karyotype) contribute to the intrinsic chemo refractoriness of MPN-BP. The combination of Venetoclax (VEN) and hypomethylating agents (HMA) has been recently established as standard for newly diagnosed, unfit patients with de novo AML ineligibile for intensive chemotherapy, but it has not been tested prospectively in MPN-BP and small retrospective series reported conflicting results. ENABLE is an open arm, phase 2 clinical trial aimed at verifying efficacy and safety of VEN plus Decitabine (DEC) in MPN-BP pts unfit for intensive therapy (Clinical trial.gov NCT04763928). Abbvie provided financial support for the trial. VEN and DEC are administered as per standard practice. Main study endpoint is event-free survival. Secondary objectives include assessment of mutation profile at baseline and correlation with response. We describe here the mutation profile in the first 51 pts (50% of total planned accrual, n=101). Between Dec 2021 and Apr 2024, 23 GIMEMA centers enrolled a total of 74 pts (73% of planned), of which 35.2% evolving after myelofibrosis (MF), 37% ET, 20% PV. Median age at BP onset was 72.6 (53.7, 82.3) y. 64% were male. NGS sequencing was performed with Oncomine™ assay on mononuclear cells at enrolment (50 PB, 1 BM). We found a total of 214 mutations and 139 variants, with a median of 4 variants per sample (range 1-9); most frequent was JAK2V617F (75%), ASXL1 (41%), TP53 (33%), SRSF2 (31%), RUNX1 (20%), TET2 (18%), IDH2 (16%; A140G) and CALR (12%); 2 pts (2.3%) had IDH1mut (A132C). Overall, 46 pts (90%) had driver-mutation in JAK2V617F (VAF 0.03-97%), CALR (4 Type 1, 2 atypical; VAF 48-59%) or MPL (2 W515x, 1 S505N, 2 S204x; VAF 3-97%), and 5 pts (10%) were triple-negative. Of interest, 1 pt was FLT3mut (double-hit mutation; p.V592A, VAF 14%; p.T824C, VAF 9%) and 1 pt was NPM1 mut (T288Cfs12, VAF32%). This is the largest available series on mutation profile of MPN-BP pts, and indicate that most BP are driver-mut positive and are enriched in targetable proteins including IDH1 and IDH2. Also, occasional pts had mutations associated with de-novo AML, including FLT3 and NPM1, suggesting that these mut should be searched as well in MPN-BP pts. Results will be updated at the meeting.

C095

ACCELERATED IMMUNE EFFECTOR CELL RECONSTITUTION IN MYELOFIBROSIS PATIENTS TREATED WITH MOMELOTINIB AFTER RUXOLITINIB

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Background. Momelotinib (MMB) has been shown to alleviate symptoms, anaemia, and splenomegaly in myelofibrosis (MF). Unlike the JAKi ruxolitinib (RUX), associated with significant immune suppression and increased risks of complications partly due to reduced cellular immunity, the effects of MMB on immune effector cell populations have not been previously described.

Aims. To evaluate MMB efficacy in a 'real-world' setting and compare its effects on immune effector cell frequencies after transitioning from RUX. Patients were monitored for 24 weeks after starting MMB. Peripheral blood mononuclear cells from 24 patients were analysed to assess changes in immune effector cell frequencies at baseline while on RUX, at 12 and 24 weeks (n=12). Ten healthy subjects were used as controls (HC).

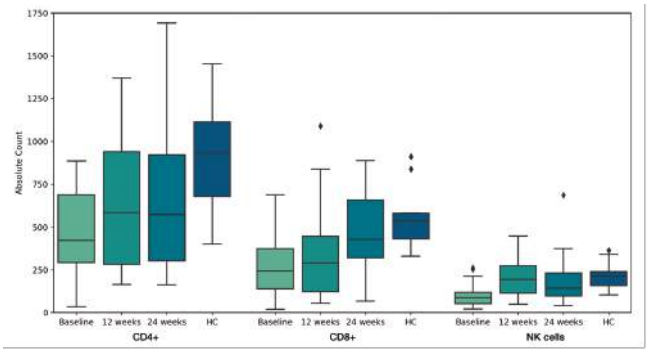

Figure 1.

Results. 24 MF patients (median age 69 years), starting MMB following prior RUX resistance/intolerance (median time on RUX=1.5 years), were included (primary MF n=9, secondary MF n=15; DIPSS intermediate-1 n=2, intermediate-2 n=12, high n=10) Patients showed reduced frequencies of CD3+, CD4+, and CD8+ T cells, and NK cells at baseline whilst on RUX compared to HC (p-values <0.004). However, a significant increase in total lymphocytes, CD3+, CD4+, and CD8+ T cells, and NK cells was noted 12 weeks post-MMB initiation *vs* baseline, returning towards levels observed in HC (p=0.02, 0.02, 0.02, 0.054, and 0.01 respectively). This increase was sustained at 24 weeks (p=0.0008, 0.02, 0.01, 0.002, and 0.015). At baseline, 33% (n=8) of patients were transfusion-depen-

dent, and 37.5% (n=9) required occasional transfusions. At 12 weeks, only 1 remained transfusion dependent and 14 (58%) achieved independence. A subset of 17 patients was followed for 24 weeks, where 5 further patients became transfusion independent (82%, n=14). Their mean Hb at baseline was 90.2g/L and 106.8g/L at 24 weeks (p=0.001). Both patients requiring regular platelet transfusion at baseline did not respond to MMB, remaining transfusion dependent at 24 weeks. 3 patients with advanced-stage CKD were included, achieving haematologic response. The most frequent non-haematological adverse events (50% of patients) were limited to grade 1 severity, predominantly peripheral neuropathy.

Conclusion. We observed a notable recovery in immune effector cell frequencies 12 weeks after starting MMB therapy, which persisted at the 24-week follow-up. MMB showed a favourable haematological response, significantly improving Hb levels.

Hemostasis, thrombosis, thrombocytopenia and platelet diseases II

C096

THROMBOPOIETIN-R AGONISTS EFFICACY AND SAFETY IN PREGNANT ITP PATIENTS AND THEIR NEWBORNS: A MULTI-CENTER RETROSPECTIVE ITP-NET ITALIAN STUDY ON BEHALF OF GIMEMA WORKING GROUP "ANEMIA & THROMBOCYTOPENIA"

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Background. Immune thrombocytopenia (ITP) can arise *de novo* during pregnancy (P) or be exacerbated by it. Steroids (S) and immunoglobulins (IVIG) are the main therapy (tx) for ITP during P although in some cases resistance, intolerance or adverse events related to these tx may occur. Data on the efficacy and safety of thrombopoietin receptor agonists (TPO-RA) during P are scarce. AIM: To evaluate data of efficacy and safety of TPO-RA in women with ITP and P in 7 Italian centers. METHOD: Retrospective data from hospital charts about ITP history, previous tx, dosage and duration of TPO-RA, , platelet count (plt) at delivery (D), adverse events, maternal and fetal outcome.

Results. We analyzed 16 P (1 twin P) in 13 women, and 17 newborns (Table 1). Median age at D was 33 yrs (22-46). 3 pts had a de novo ITP while in 13 P a chronic ITP was already known with a median disease duration of 12 yrs (1-41). Median n of previous lines of tx before P was 3 (0-6); these included 4 splenectomy and 7 tx with TPO-RA. All ps were steroid refractory; Romiplostim (median weekly dose 6 mcg/Kg) and Eltrombopag (median daily dose 25 mg) were administered in 10 and 6 pts respectively for a median of 33 days (5-280) before D. Median plt count at TPO-RA start was 29x 10e9/L. In 11 cases TPO-RA were combined: with S (7), S plus IVIG (1), IVIG (2) S and cyclosporin (1). In 6 P mucocutaneus bleeding were reported and resolved after the use of TPO-RA. All 16 P responded to TPO-RA, 11 with complete response and the median plt count at D was $112x10^9$/L (58-250). No thrombotic, hemorrhagic nor other complications were reported. Cesarean section (CS) was performed in 5 D (31%) and only in one case of vaginal D a peripartum bleeding occurred (WHO 2). There was only 1 case of premature D due to placenta previa with a planned CS without relevant bleeding. 10 newborns (59%) presented thrombocytopenia at birth (Figure 1) treated with IVIG in combination or alone with plt transfusion, with complete resolution. In 13 cases (81%) TPO-RA tx was continued after D. 6/12 known neonates received breastfeeding.

Conclusions. For pts with ITP during P, data on the efficacy/safety of other tx besides S and IVIG are scarce. In our case series TPO-RA tx appears safe, manageable and effective to increase plt count for D in pts with chronic, S-refractory disease. No thrombotic events nor specific complications for newborns were reported. These positive and encouraging data require confirmation in larger series

Table 1. Charactristics of the patient.

ITP phase during pregnancy – no. (%)	
De novo	3 (19)
Chronic	13 (81)
Median age at delivery (range) -yr	33 (22-46)
Median duration of ITP (range) - yr	12 (0-41)
Median no. of previous ITP therapies (range)	3 (0-6)
Previous splenectomy – no. (%)	4 (30)
TPO-RA pre-pregnancy – no. (%)	7 (53)
Romiplostin - no. pregnancy (%)	10 (62)
Eltrombopag - no. pregnancy (%)	6 (38)
Romiplostim median dose (range)	6 mcg/Kg (1-10)
Eltrombopag median dose (range)	25 mg/die (25-50)
Median duration of TPO-RA therapy (range) - days	33 (5-280)
Concomitant therapies with TPO-RA – no. (%)	Steroid 7 (44) IVIG 2 (12) Steroid+IVIG 1 (6) Steroid+CSA 1 (6) TPO alone 5 (32)
TPO-RA therapy ORR – no. (%)	16 (100)
CR	11 (69)
PR	5 (31)
Median platelet count at delivery (range) – x10e9/L	112 (58-250)
Cesarean section – no. (%)	5 (31)
Peripartum bleeding - no. (%)	1 (6)
Thrombosis during TPO-RA treatment – no. (%)	0 (0)
Bleeding during TPO-RA treatment – no. (%)	0 (0)
Other adverse events during TPO-RA treatment – no. (%)	0 (0)
Thrombocytopenic newborns no. (%)	10 (58)
Treatment of thrombocytopenic neonates (no. = 10)	
IVIG alone – no (%)	3 (30)
Platelet transfusion + IVIG – no (%)	7 (70)
Breastfeeded neonates (out of 12 known)	6/12

Fig. 1 Maternal and newborn platelet count in 13 women treated with TPO-RA during pregnancy

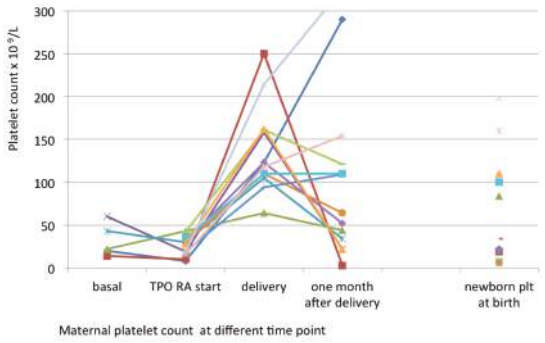

Figure 1.

C097

LAPAROSCOPIC SPLENECTOMY FOR PRIMARY IMMUNE THROMBOCYTOPENIA (ITP) AFTER 2000: A MONOCENTER STUDY

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Splenectomy (SPL) is the only procedure proved to achieve a long-term sustained response off therapy (SROT) in about 60% of patients (pts) with primary immune thrombocytopenia (ITP). Since 2000, with the introduction of rituximab (RTX) and thrombopoietin receptor agonists (TPO-RA), the use of SPL has significantly decreased. Safety and efficacy of laparoscopic SPL were evaluated in 57 ITP pts who were splenectomized between 2000 and 2023 at our Institute. Treatment response was defined according IWG criteria as platelet count (PLT)≥30.000/mm^3 and at least 2-fold increase the baseline count; complete response (CR) required a PLT>100x10^9/L. Grade 3-4 events after SPL (infections, thrombosis, hemorrhages) were recorded. At SPL, median age was 37.7 yrs (19.5-70.9); 24 (42.1%) pts were male; median PLT count was 74x10^9/L [1-481]. All pts were vaccinated against capsulated bacteria. Most pts underwent SPL in chronic phase (n. 39, 68.4%); 32 (56.1%) pts underwent SPL after ≥1 TPORA and/or RTX, 25 (43.9%) after 1st line therapy. Clinical-laboratory characteristics were comparable in the 2 groups. Overall, 52 (91.2%) pts achieved a response (CR: 84.2%) in absence of additional therapies. At 1,6 and 12 months from SPL, 89.5%, 84.2% and 78.6% of pts were in response, respectively. After a median time of 1.3 years (0.1-14.2) from first response, 15 (28.8%) lost the response. In the 37 pts with SROT, median observation time after SPL was 10.5 yrs [1.6-22.6].

Table 1.

Table 1: Patients' characteristics

Patients' cohort (n.57)			
Characteristics at Splenectomy			
Age, median (range), years	37.7 (19.5-70.9)		
Age < 60 years, n. (%)	48 (84.2%)		
Male Sex, n. (%)	24 (42.1%)		
Platelet count, median (range), x 10^9/L	74 (1-481)		
Platelet count < 50 x 10^9/L	20 (35.1%)		
Platelet count < 30 x 10^9/L	12 (21.1%)		
Chronic phase, n. (%)	39 (68.4%)		
Splenectomy in 2nd line, n. (%)	25 (43.9%)		
Lines of therapy, median (range)	3 (1-6)		
Events after Splenectomy			
Infections *(grade 3-4)*, IR, %patient-year	1.1 (n. 7)		
RTX pre-SPL pts	1.6		
No-RTX pre-SPL pts	0.9		
1 immunosuppressant post-SPL*	0.6		
≥2 immunosuppressant post-SPL*	0		
**on 20 evaluable*			
Hemorrhages *(grade 3-4)*, IR, %patient-year	0.6 (n. 4)		
Thrombosis *(grade 3-4)*, IR, %patient-year	0.2 (n. 2)		
Response, n. (%), *on 56 evaluable*			
12 months	44 (78.6%)		
SROT	36 (64.3%)		
Relapse, n. (%), *on 52 evaluable*	15 (28.9%)		
Death, n. (%)	6 (10.5%)		
Events respect line of therapy			
	SPL in 2nd line (n. 25)	**SPL in 3rd line or more (n. 32)**	**p-value**
Infections *(grade 3-4)*, IR, %patient-year	0.3 (n. 1)	2.2 (n. 6)	**0.03**
Hemorrhages *(grade 3-4)*, IR, %patient-year	0.9 (n. 3)	0.3 (n. 1)	0.41
Thrombosis *(grade 3-4)*, IR, %patient-year	0	0.6 (n. 2)	0.22
Response, n. (%), *on 56 evaluable*			
12 months	22 (88.0%)	22 (71.0%)	0.12
SROT	16 (64.0%)	20 (64.5%)	0.97
Relapse, n. (%), *on 52 evaluable*	8 (33.3%)	7 (25.0%)	0.51
Death, n. (%)	3 (12.0%)	3 (9.4%)	0.75

The remaining 20 pts received at least 1 additional therapy post-SPL: 60% achieved SROT, 35% pts a CR still needing treatment and

5% never got a response. In univariate analysis, only age <60 yrs was associated to SROT post-SPL [OR: 4.71; p=0.05]. Incidence rate (IR) of infections, thrombosis and hemorrhages were 1.1, 0.3 and 0.6%p-y, respectively. Four (57.1%) infective events occurred within 1month from SPL (2 pneumonitis, 2 pancreatitis); RTX pre-SPL and >1 immunosuppressant post-SPL had not a significant impact on infection IR (p=0.46 and p=0.66, respectively). Based on the number of pre-SPL treatments, infective events were more frequent in pts splenectomized in at least 3rd line, while responses and thrombotic and hemorrhagic events were similar (Table 1). In our cohort of ITP pts, although limited, SPL showed an acceptable efficacy and safety profile, even after ≥2 line of therapy. In relapsed/refractory pts, only a small group never obtained a response, representing the ideal candidates for clinical trials.

C098

SAFETY AND EFFICACY OF DIRECT ORAL ANTICOAGULANTS (DOACS) IN PATIENTS WITH PHILADELPHIA-NEGATIVE MYELOPROLIFERATIVE DISEASES: A COMPARISON WITH VITAMIN K ANTAGONISTS (VKA)

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Background. Chronic myeloproliferative neoplasms (MPN) are diseases characterized by a high risk of both thrombotic events (TE) and bleeding events (BE). However, only a few data are available regarding the safety and efficacy of vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs) in a real-world setting for MPN patients (pts).

Aims. The study aimed to compare the safety and efficacy of DOACs and VKA in MPN pts treated for venous thromboembolism (VTE) or for atrial fibrillation (AF).

Methods. We conducted an observational study which enrolled 156 MPN pts, followed at our Center, who received oral anticoagulant therapy (OAT) with VKA or DOACs for VTE or AF. TE were categorized by type and location. BE were classified according to ISTH classification. Common statistical tests were used for analyses.

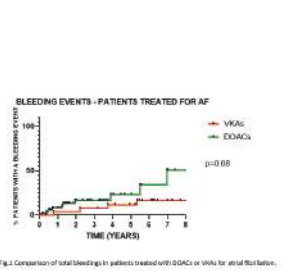

Fig.1 Comparison of total bleedings in patients treated with DOACs or VKAs for atrial fibrillation.

	DOACs	AVKs	TOTAL
N° PATIENTS	92	64	156
MALE	43	24	67
FEMALE	49	40	89
INDICATION FOR TREATMENT			
ATRIAL FIBRILLATION	55	27	82
VENOUS THROMBOEMBOLISM	37	37	74
HEMATOLOGICAL DISORDER			
MYELOFIBROSIS	33	31	64
POLICYTHEMIA VERA	25	13	38
ESSENTIAL THROMBOCYTEMIA	45	19	64
DRIVER MUTATION			
JAK2	75	55	130
CALR	11	8	19
MPL	1	2	3
TRIPLE NEGATIVE	3	3	6
PREVIOUS THROMBOSIS			
YES	57	44	101
NO	35	20	55
PREVIOUS BLEEDING			
YES	7	4	11
NO	89	60	149
THROMBOSIS DURING ANTICOAGULANT TREATMENT			
VENOUS	1	3	4
ARTERIAL	3	7	11
NO	87	55	142
BLEEDING DURING ANTICOAGULANT TREATMENT			
MINOR	1	0	1
NON MAJOR CLINICALLY RELEVANT	8	12	20
MAJOR	3	3	6
NO	79	50	129
CONCOMITANT ANTIPLATELET TREATMENT			
YES	33	12	45
NO	59	52	111

Table 1. Main characteristics of patients enrolled in the study

Figure 1.

Results. Pts features were resumed into Table 1. 64 pts received OAT with VKA (41%), and 92 with DOACs (59%). For 82 pts OAT was prescribed for AF (52.6%), and for 74 for VTE (47.4%). The median exposure time to OAT was 5.8 years in the VKA group (range 0.2-20 years) and 1.77 years in the DOACs group (range 0.2-10 years). After a median follow-up of 3.2 years, 14 TE were reported: 5 (35.7%) in the DOACs-treated group, and 9 (64.3%) in the VKA-treated group. Incidence rate of TE was 2.11 *vs* 2.14 thrombosis/pts/year in the VKA and DOACs group, respectively. No significant differences in terms of thrombosis free survival (TFS) between the two groups were reported (p=0.72). Overall, there were 27 BE: 13 in the DOACs (51.9%), 14 in the VKA group (48.1%). Among these, we report 8 major BE, 4 in both groups. The incidence rate of BE was 5.6 *vs* 3.3/pts/year in the DOACs and VKA group, respectively. No significant differences in terms of bleeding free survival (BFS) analyzing the whole population and the VTE group were reported (p=0.13 and p=0.75). We found a trend for lower BFS in pts treated with DOACs for AF (p=0.08-Figure 1). In a multivariate model the risk of BE was associated solely with DOACs administration (HR 3.7, p=0.01). We found no significant differences in the risk of TE and BE for the type of DOACs used.

Summary. To our knowledge, this is the largest study evaluating safety and efficacy of DOACs compared to VKA in MPN setting. Our findings suggest that DOACs are as effective as VKA, but they appear to exhibit a trend towards a higher overall risk of BE, especially in the group treated for AF. More data from prospective studies are needed.

C099

USE OF ULTRASOUND (US) FOR JOINT EVALUATION IN HEMOPHILIA: THE MONTREAL STUDY

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Background. For hemophilic patients, optimization of joint outcomes is still an important unmet need. Traditionally, most symptoms are ascribed to joint bleeding and addressed mainly by optimizing prophylaxis. Recently, a new emphasis is on early detection and treatment of arthropathy beyond improving treatment strategies. There is rising awareness that detection and management of asymptomatic findings are essential. For this purpose, the HEAD US (Hemophilia Early Arthropathy Detection) protocol was designed, in order to detect blood effusion and joint damage before clinical manifestations. The aim of this study is to investigate use of US monitoring in evaluating arthropathy in severe hemophilia A (HA) and B (HB) patients and to find any correlation between US score and HJHS (hemophilia joint health score), ABR (annualized bleeding rate) and NRS (Numeric pain Rating Scale) evaluated at baseline, after 6 months (T1) and 12 months (T2) of regular prophylaxis.

Methods. Adult severe hemophilia A/B patients were included.

At each visit articular function was evaluated with HJHS and US (HEAD US score). Joint pain (NRS), trough level, target joints and prophylaxis efficacy whit ABR were monitored.

Results. We evaluated 32 patients. Median age was 39 years old (IQR1-3 33-55,5), 7 patients had HB and had 25 had HA. Median trough level was 2.00 (IQR1-3 1.00-3.00) for HA and 10.00 (IQR1-3 10.0-11.00) for HB. Median target joints value was 2, without differences between HA and HB. Median HEAD US, NRS, HJHS and ABR at baseline, at T1 and T2 are shown in Table 1. As reported, no significant differences were found within the three timepoints and within type of hemophilia. A univariate correlation analysis was performed and no significant correlations within variables was found.

Conclusions. The exact frequency of performing US in HA and HB patients is not defined yet. Our analysis suggests that a every 6 months evaluation after baseline may be too early to detect significant intraarticular changes in patients treated with replacement therapy prophylaxis, regardless the trough level. No correlation between HEAD US score and the others parameters evaluated over time was found. These results are to be confirmed in longer follow up studies.

Table 1.

	ALL	HA	HB	p.overall
	N=32	*N=25*	*N=7*	
Trough	3.00 [2.00;5.25]	2.00 [1.00;3.00]	10.0 [10.0;11.0]	<0.001
n° target joint	2.00 [2.00;3.00]	2.00 [2.00;3.00]	2.00 [1.50;3.00]	0.700
HEAD US T0	8.00 [6.00;19.2]	8.00 [6.00;20.0]	13.0 [4.00;15.5]	0.537
HEAD US T1	9.50 [6.00;18.0]	9.00 [6.00;18.0]	13.0 [3.50;15.5]	0.615
HEAD US T2	10.0 [6.00;17.0]	11.0 [6.75;17.0]	7.00 [3.50;13.5]	0.236
NRS T0	2.00 [0.00;4.25]	2.00 [0.00;3.00]	3.00 [1.00;5.00]	0.437
NRS T1	2.00 [0.00;4.00]	2.00 [0.00;3.00]	4.00 [0.50;4.00]	0.385
NRS T2	2.00 [0.00;4.00]	2.00 [0.00;3.25]	3.00 [0.00;5.50]	0.576
HJHS T0	9.50 [5.75;14.5]	10.0 [6.00;16.0]	9.00 [3.00;13.0]	0.522
HJHS T1	11.0 [5.00;17.2]	10.0 [5.00;17.0]	15.0 [3.00;20.0]	0.982
HJHS T2	9.00 [6.00;19.5]	9.00 [7.50;18.8]	10.0 [3.00;22.0]	0.831
ABR T0	1.00 [0.00;2.00]	1.00 [0.00;2.00]	1.00 [0.00;4.00]	0.592
ABR T1	0.00 [0.00;1.00]	0.00 [0.00;1.00]	1.00 [0.00;2.50]	0.161
ABR T2	0.00 [0.00;1.00]	0.00 [0.00;1.25]	0.00 [0.00;1.00]	0.957
D.HEADUS	0.00 [-1.50;1.00]	0.00 [-1.00;1.25]	-1.00 [-4.00;0.00]	0.224
D.NRS	0.00 [-1.00;0.00]	0.00 [-1.00;0.00]	0.00 [0.00;0.00]	0.721
D.HJHS	0.00 [-1.00;2.00]	0.00 [-1.25;2.25]	0.00 [0.00;1.50]	0.416
D.ABR	0.00 [0.00;0.50]	0.00 [0.00;1.00]	0.00 [0.00;0.00]	0.319

volvement in 2 cases. Romiplostim and Eltrombopag were used respectively in 6 (46%) and 7 patients (54%). Median treatment duration was 6 months (IQR 12). Twelve/13 (92%) achieved a platelet count >100×10^9/L within a median of 14 days (IQR 10) and maintained persistent response. This allowed them to correctly attend oncologic treatments. Moreover, 3 (23%) were even able to discontinue TPO-RAs administration. MMPC reached during TPO-RAs was 244×10^9/L (IQR 161×10^9/L); median follow-up was 7 months (IQR 10). At last visit, median platelet count was 133×10^9/L (IQR 114×10^9/L). No thrombotic complications occurred. Three patients deceased due to infection or cancer progression. TPO-RAs seemed to be efficacious, well tolerated and safe in CIT management, enabling patients to undergo anticancer therapy without RDI reduction, which is a crucial outcome for both the oncologic course and psychological well-being. However, further studies on larger cohorts are needed to validate these findings.

Characteristics	Total N=13
Male sex – no. (%)	7 (54)
Female sex – no. (%)	6 (46)
Previous ITP diagnosis – no. (%)	4 (31)
Bone marrow (BM) assessment – no. (%)	
Biopsy	7 (54)
Aspirate	6 (46)
BM metastatic involvement – no. (%)	2 (15)
Metastatic cancer – no. (%)	7 (54)
Age (yrs) at TPO-RA start – Median (IQR)	55 (53-69)
TPO-RA treatment (mths) – Median (IQR)	6 (4-16)
Follow-up (mths) – Median (IQR)	7 (4-14)

Figure 1a

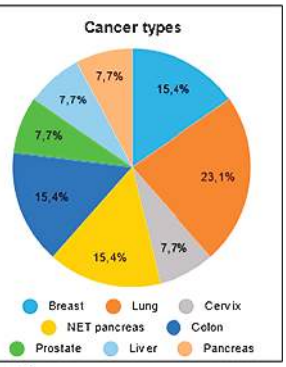

Figure 1b

Figure 1.

C100

THROMBOPOIETIN RECEPTOR AGONISTS (TPO-RAS): A PROMISING THERAPY FOR CHEMOTHERAPY INDUCED THROMBOCYTOPENIA (CIT)

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Chemotherapy-induced thrombocytopenia (CIT) can be an adverse event of oncologic treatments and affects about 1/3 of patients with solid tumor. CIT can lead to morbidity and mortality from hemorrhagic events and can complicate the whole management of oncologic patients. A platelet count below 100×10^9/L is often managed with reduction of therapy relative dose intensity (RDI), influencing oncologic outcomes and patients psychological well-being. The use of thrombopoietin receptor agonists (TPO-RAs) in managing CIT aims to increase platelet production by stimulating bone marrow megakaryocytopoiesis, but their use is debated. We aimed to evaluate TPO-RAs efficacy in treating CIT and assess their safety profile. Thirteen oncologic patients with CIT were treated off-label with TPO-RAs at Policlinico Umberto I-Sapienza University of Rome. Data were collected retrospectively. The characteristics of patient population are listed in Figure 1a/b: all had platelet count <100×10^9/L and this hindered the administration of proper cancer therapy. First-line corticosteroid treatment was ineffective in achieving persistent platelet response, with a median maximum platelet count (MMPC) of 58×10^9/L, (IQR 38×10^9/L). Bone marrow assessments were performed before TPO-RAs administration, revealing metastatic in-

DISCUSSED POSTERS

Lymphomas I

DP001

INTRAPATIENT COMPARATIVE ANALYSIS OF ZANUBRUTINIB PLUS OBINUTUZUMAB EFFICACY IN RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL) USING THE GROWTH MODULATION INDEX (GMI)

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Background. In ROSEWOOD (NCT03332017), a global, randomized, open-label, phase 2 study, median PFS in patients (pts) with R/R FL was significantly longer with zanubrutinib + obinutuzumab (ZO) *vs* obinutuzumab (O) alone and compared favorably with the PFS with their last prior treatment. To overcome limitations of cross-study comparisons, the GMI uses each pt as their own control to evaluate tx efficacy by comparing PFS with each successive tx (GMI >1, present tx extends PFS *vs* prior tx; GMI ≥1.33, significant clinical activity). ZO efficacy was analyzed in the tx sequence received by ROSEWOOD pts using an intra-pt comparison analysis with the GMI clinical endpoint.

Figure. KM Analysis of GMI in the ZO Arm

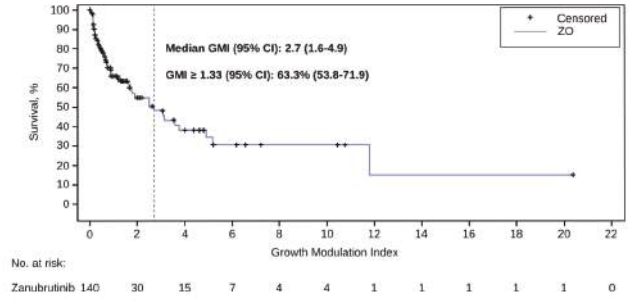

Figure 1.

Methods. PFS was assessed by independent central review; ROSEWOOD censoring rules were used. GMI was defined as (PFS_n from ZO or O)/(PFS_{n-1} from last prior line) with the distribution estimated by the Kaplan-Meier (KM) method. The 95% CIs were estimated using the Brookmeyer and Crowley method (median GMI) and Greenwood's formula with logit transformation (proportion within each interval).

Results. In ROSEWOOD, pts were randomized to ZO (n=145) or O (n=72); 5 pts in the ZO arm and 3 in the O arm were excluded from the analysis (PFS_{n-1} data unavailable). KM curve analysis confirmed prior observations that median PFS with ZO, but not O, was longer than with the last tx (ZO, 28.0 *vs* 12.1; O, 10.4 *vs* 11.5 months), the most frequent of which were rituximab-containing regimens (ZO, 69%; O, 60%) and immunochemotherapy (ZO, 54%; O, 51%). In the overall population, median GMI for ZO and O, respectively, was 2.7 (95%CI, 1.6-4.9; Figure) and 0.9 (95%CI, 0.5-1.7). With ZO, 63.3% (95%CI, 53.8-71.9) of pts had a GMI ≥1.33 and 34.1% (95%CI, 25.9-43.3) had a GMI <1. In a subgroup analysis, pts in the ZO arm with 2 prior lines (n=63) had a median GMI of 2.5 (95%CI, 0.9-NE); 65.6% (95%CI, 50.8-77.8) of pts had a GMI ≥1.33. Pts in the ZO arm with >2 prior lines (n=77) had a median GMI of 3.1 (95%CI, 1.3-4.9); 61.8% (95%CI, 49.2-73.0) of pts had a GMI ≥1.33.

Conclusions. Post hoc GMI analysis of ROSEWOOD efficacy data showed that the majority (>60%) of pts with R/R FL who received ZO had a significant (GMI ≥1.33) improvement in PFS *vs* their last prior tx, regardless of the number of prior tx. The median GMI of 2.7 in the overall population was more than double the 1.33 threshold for meaningful clinical activity compared with the last prior tx. These data further support the benefit of ZO as a novel tx for R/R FL.

DP002

ABSTRACT NOT PUBLISHABLE

DP003

PIRTOBRUTINIB IN RELAPSED/REFRACTORY (R/R) MANTLE CELL LYMPHOMA (MCL) PATIENTS WITH PRIOR CBTKI: UPDATED SAFETY AND EFFICACY INCLUDING HIGH-RISK SUBGROUP ANALYSES FROM THE PHASE 1/2 BRUIN STUDY

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Despite the efficacy of cBTKi in R/R MCL, disease relapse arises through evolution of resistance mechanisms or development of

cBTKi intolerance. Pirtobrutinib is approved in the USA to treat R/R MCL after at least two lines of systemic therapy including a prior cBTKi. We report updated results of pirtobrutinib therapy in all pts, including those with biologically high-risk R/R MCL with a median survival follow-up of 24.2 months (range, 18.2-29.8). Pts with R/R MCL received pirtobrutinib in the multicenter Phase 1/2 BRUIN trial (NCT03740529). Efficacy was assessed in all cBTKi pretreated pts, as well as in cBTKi naïve pts. Key endpoints included ORR as assessed by IRC per Lugano 2014 criteria, DOR, PFS, OS, and safety. Pts were included across the dose escalation range and expansion (25-300 mg/day) with 93% (n=141) receiving at least one dose of 200 mg/day, the FDA-approved dose. A data cut of 05May2023 was utilized. Among all 152 pts with R/R MCL who received a prior cBTKi, the median age was 70 years (range, 46-88). Median prior lines of therapy were 3 (range, 1-9). ORR for cBTKi pretreated pts was 49.3% (95% CI, 41.1-57.6), including 15.8% CRs (n=24) and 33.6% PRs (n=51), whilst cBTKi naive pts (n=14) had an ORR of 85.7% (95% CI, 57.2-98.2). Among 75 responding cBTKi pretreated pts, median DOR was 21.6 mths (95% CI, 9.2-27.2). The 18- and 24-mo DOR rates were 51.9% (95% CI, 37-64.8) and 38.9% (95% CI, 22.7-54.8), respectively. The 18- and 24-mo DOR rates among 12 responding cBTKi naïve pts were both 90.0% (95% CI, 47.3-98.5). Median PFS and OS for cBTKi pretreated pts was 5.6 mos (95% CI, 5.3-9.2), and 23.5 mos (95% CI, 17.1-NE), respectively. In the MCL cohort (n=166), the most frequent TEAEs were fatigue (31.9%), diarrhea (22.3%), and dyspnea (17.5%). The most common Grade ≥3 TEAE was neutropenia/neutrophil count decreased (13.3%) and the rate of Grade ≥3 infections was (19.9%). Grade ≥3 hemorrhage/hematoma (2.4%) and all-grade atrial fibrillation/flutter (3.6%) were infrequent. Overall, 8 pts (5%) had TRAEs leading to dose reductions and 5 (3%) had TRAEs leading to pirtobrutinib discontinuation. Pirtobrutinib continues to demonstrate durable efficacy and a favorable safety profile in heavily pre-treated R/R MCL cBTKi pretreated pts. Originally presented at ASH 2023

Table 1.

		cBTKi pre-treated MCL (n [%])	Number with Response (n)	ORR, % (95% CI)	DOR, median (95% CI)
Overall		152 (100)	75	49.3 (41.1-57.6)	21.6 (9.2-27.2)
MCL histology	Classic/Leukemic	120 (78.9)	61	50.8 (41.5-60.1)	17.7 (7.7-NE)
	Blastoid	15 (9.9)	6	40.0 (16.3-67.7)	NE (1.4-NE)
	Pleomorphic	17 (11.2)	8	47.1 (23.0-72.2)	21.6 (3.7-NE)
TP53 mutation[c]	Yes	30 (50)	13	43.3 (25.5-62.6)	17.6 (1.7-NE)
	No	30 (50)	15	50.0 (31.3-68.7)	14.8 (1.9-NE)
Ki-67 Index[a]	<30%	18 (28.6)	12	66.7 (41.0-86.7)	17.7 (1.9-NE)
	≥30%	45 (71.4)	20	44.4 (29.6-60.0)	21.6 (5.6-27.2)
sMIPI	Low	30 (19.7)	20	66.7 (47.2-82.7)	27.2 (6.5-NE)
	Intermediate	79 (52.0)	42	53.2 (41.6-64.5)	17.7 (7.4-NE)
	High	43 (28.3)	13	30.2 (17.2-46.1)	14.8 (5.2-21.6)
Discontinuation from any prior BTKi[a, b]	Disease Progression	128 (85.9)	55	43.0 (34.3-52.0)	14.8 (7.3-27.2)
	Toxicity/Other	21 (14.1)	19	90.5 (69.6-98.8)	25.3 (9.2-NE)

Table. ORR and DOR in cBTKi pre-treated pts and high-risk subgroups
[a]Patients with missing data were not included in the analysis.
[b]Disease Progression" is selected if "PD" for any prior BTK; otherwise "Toxicity" is selected if toxicity from any prior BTK; otherwise "Other".
Abbreviations: cBTKi = covalent BTK inhibitor; CR = complete response; DoR = duration of response; IRC = independent review committee; mo = month; ORR = overall response rate; PFS = progression-free survival; PR = partial response; pts = patients; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event

DP004

ABSTRACT NOT PUBLISHABLE

DP005

FIXED-DURATION GLOFITAMAB MONOTHERAPY IN RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA: PHASE II EXTENDED FOLLOW-UP AND SUBGROUP ANALYSES

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Introduction. The CD20xCD3 bispecific antibody glofitamab engages and redirects T cells to eliminate B cells. In a phase II study (NCT03075696), fixed-duration glofitamab monotherapy induced high complete response (CR) rates and had a manageable safety profile in patients (pts) with relapsed and/or refractory (R/R) large B-cell lymphoma (LBCL). We present extended follow-up data and subgroup analyses in pts with prior CAR T-cell therapy and by baseline total metabolic tumor volume (TMTV).

Methods. Pts with LBCL and ≥2 prior therapies received obinutuzumab pretreatment (1000mg) on Day (D)1 of Cycle (C)1. Intravenous glofitamab was given in step-up doses during C1 (D8:2.5mg; D15:10mg), then 30mg on D1 of C2–12 (21d cycles). CR rate (primary endpoint; Lugano criteria), cytokine release syndrome (CRS; ASTCT criteria) and associations between TMTV (derived from PET images) and progression-free survival (PFS) and CRS were assessed.

Results. As of 4/9/2023, 154 pts received ≥1 dose of study drug, with 3 median prior therapies; 33.1% had prior CAR T-cell therapy; 85.1% were refractory to their latest regimen. Median time on study was 32.1 months (0–43). Overall response/CR rates were 52%/40%; 55% CRs were ongoing at data cut-off. Median duration of CR (DoCR) was 26.9 m (95%CI: 19.8–not evaluable [NE]); ~ 55% of pts with CR at any time remained in remission at 24 m. PFS/OS rates at 18 m in pts with CR at end of treatment (EOT) were 66.6%/80.7%. In pts with prior CAR T-cell therapy (n=52), CR rates were consistent with the overall population; median DoCR was 22.0 m (95%CI: 6.7–NE). Safety was consistent with previous reports. Median TMTV was 128.7mL (n=144;0–3820). Higher TMTV was associated with increased risk of Grade [G]≥2 CRS. The proportion of patients with G≥2 CRS events in the 1st/2nd/3rd/4th TMTV quartiles was 2.8%/11.1%/16.7%/38.9% (Chi-square=16.3; degrees of freedom=1; p<0.0001). Pts with TMTV≥median (n=72) had a 24-m PFS rate of 11.8% (95%CI: 6.0–23.5) *vs* 41.6% (95%CI: 31.1–55.6) amongst pts with TMTV<median (n=72; HR: 2.4, 95%CI: 1.6–3.6).

Conclusions. Fixed-duration glofitamab showed durable responses in pts with R/R LBCL, with most pts with CR at EOT still in remission and no new safety signals. CR rates in pts with prior CAR T-cell therapy were durable and consistent with the overall population. Higher TMTV was associated with increased risk of G≥2 CRS, suggesting that TMTV may be prognostic for PFS.

DP006

PLASMA CIRCULATING TUMOR DNA (CTDNA) AS AN ALTERNATIVE TO TISSUE DNA FOR GENOTYPING OF DLBCL: RESULTS FROM THE POLARIX STUDY

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In POLARIX (NCT03274492), Pola-R-CHP demonstrated prolonged progression-free survival (PFS) *vs* R-CHOP in patients (pts) with previously untreated diffuse large B-cell lymphoma (DLBCL; Tilly *et al.* 2022). We previously validated the prognostic value of ctDNA (Herrera et al. 2022); here, we analyse the mutation landscape and molecular subtyping of DLBCL by plasma ctDNA *vs* tissue DNA. Baseline (BL) plasma ctDNA single nucleotide variants (SNVs) were identified using the AVENIO ctDNA NHL assay (Research Use Only) with an allelic frequency (AF) of 0.5% (Stokowski et al. 2022). At BL, tissue SNVs were determined by whole exome sequencing (WES; AF cutoff 5%) and plasma-depleted whole blood was used as a source of germline DNA to filter non-tumour-specific variants for both ctDNA and WES assays. Comparison of mutation landscapes in tissue DNA and plasma ctDNA focused on genomic regions covered by both assays and variants within the coding regions. Genetic subtypes were defined by the LymphGen classifier using tissue and ctDNA SN*vs.* At BL, 443 pts had WES and ctDNA data. When comparing mutation landscapes between tissue and ctDNA, a median 82% (lower quartile 0.5, upper quartile 1.0) of tissue SNVs/pt were also found in their matched ctDNA samples. Overall, tissue and ctDNA SNVs were found in 163 and 202 genes, respectively. Among these genes, 154 had SNVs in both samples, representing 96% and 78% of mutated genes identified in tissue and ctDNA, respectively. Eleven genes showed statistically significant differences in distribution between tissue and ctDNA (Fisher's exact test, false discovery rate <0.01; Benjamini and Hochberg. 1995); all but one showed higher mutation frequencies in ctDNA than tissue. Based on tissue SNV data, LymphGen was able to determine the molecular subtypes of 442 pts. Of these, 333 (75.3%) pts had the same subtype designation by tissue (reference) and ctDNA SNVs; 109 (24.7%) had different designations. In a pooled analysis, 2-year PFS estimates of individual subtypes by tissue *vs* ctDNA SNVs were consistent. The mutation landscape of ctDNA in DLBCL characterised by the AVENIO ctDNA NHL assay resembles that of tumour tissue determined by WES. Pts with molecular subtypes defined by WES or ctDNA had similar PFS outcomes, supporting the use of plasma ctDNA as an alternative to tumour tissue for DLBCL genotyping.

DP007

THE CD4/CD8 RATIO IN LEUKAPHERESIS, INFUSION PRODUCTS AND POST-INFUSION PERIPHERAL BLOOD SAMPLES INFLUENCES RESPONSE TO CART-CELL THERAPY IN PATIENTS AFFECTED BY RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMAS

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Background. The advent of chimeric antigen receptor T cells (CARTs) has revolutionized the treatment of relapsed/ refractory (R/R) B-cell lymphomas. Although several patient and tumor related factors have been identified as predictors of efficacy, the majority are studied after CART production. Aim of this study was to characterize the phenotypic composition of T cells before and after CART manufacturing to identify determinants of response to therapy in large B-cell lymphoma patients (pts) and possibly avoid unnecessary costs for CART production in patients not likely to respond.

Methods. Leukapheresis (LK) and infusion product (IP) leftovers of 90 pts were analysed using multi-parametric flow cytometry (MFC) to characterize T cell subsets. Circulating CARTs were monitored *in vivo* using MFC using the CD19 CAR FMC63 antibody (Miltenyi) and analysed with a panel including CD3, CD4, CD8, CD45RO, CD45RA, CCR7, PD1, TIM3 and LAG3. Disease response was assessed at day 90.

Results. We demonstrated that a low CD4/CD8 ratio in leukapheresis products is associated with response [(0.61 in responders (RE) *vs* 0.96 in non-responders (NR), $p<0.05$]. Additionally, RE display a lower CAR+ CD4/CD8 ratio in IPs (1.5 in RE *vs* 2.2 in NR, $p<0.05$). When pts were stratified based on the median CAR+ CD4/CD8 ratios in IPs (1.83), lower ratios were also associated with longer progression-free survival ($p<0.05$). The CD4+/CD8+ ratio in LK products moderately correlates with the CAR+ CD4/CD8 ratio in IPs ($r=0.37$, $p<0.01$), that in turn correlates with the CAR+ CD4/CD8 ratio at peak expansion ($r=0.35$, $p<0.01$). This suggests that the T-cell subset composition of the starting material recapitulates the one of IPs and of expanding CART *in vivo*, that are relevant for response (87.3 CARTs/uL at peak expansion in RE *vs* 28.3 in NR, $p<0.05$). At peak expansion, strong expanders (SE) (defined as patients with levels of CARTs/uL higher than the median) display a lower CAR+ CD4/CD8 ratio compared to poor expanders (PE) (0.35 in SE *vs* 0.56 in PE, $p<0.05$). Additionally, SE also have more CAR+CD8+T central memory (34.9% in SE *vs* 17.4% in PE, $p<0.05$) and less exhausted CAR+CD8+PD1+TIM3+LAG3+ cells (0.35% in SE *vs* 1.1% in PE, $p<0.05$) at peak.

Conclusions. These results suggest that a low CD4/CD8 ratio both before and after infusion is associated with response to CART-cell therapy and *in vivo* expansion. Moreover, expanding CARTs are predominantly CD8+ displaying a less differentiated and exhausted phenotype.

DP008

ABSTRACT NOT PUBLISHABLE

DP009

ABSTRACT NOT PUBLISHABLE

DP010

CLINICAL RESULTS OF A RETROSPECTIVE ITALIAN STUDY ON MEDIASTINAL GRAY ZONE LYMPHOMA

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Mediastinal gray zone lymphoma (GZL) is a rare entity, with a high rate of pathological reclassification. The bio-GZL2020 study collected histological samples and clinical data of patients (pts) diagnosed with GZL between 2006 and 2020. The study enrolled 68 pts; after the exclusion of pts lacking mediastinal involvement (according to 2022 WHO/ICC classifications) and the central pathology review 17 pts (25.0%) were confirmed as GZL. Median age at diagnosis was 41 (range 16-62), 12 pts were female (70.6%), stage was I-II in 11 pts (64.7%); 10 pts had a mediastinal bulky (58.8%), half of them with a mediastinal syndrome. Other baseline characteristics are reported in Table 1. First line chemotherapy was DA-EPOCH in 10 pts, CHOP-like regimens in 5 pts, ABVD and MACOP-B in one case. All pts but the ABVD one received rituximab. DA-EPOCH was escalated in 62.5% of pts, in 50% level 3 or higher was attained. Two advanced stage pts received central nervous system prophylaxis. Only 3 pts performed an interim PET-scan; Deauville score was available in 2 cases (Deauville score 3 and 5). Restaging after first line CHT showed 10 pts in complete remission (CR; 58.8%), three pts in partial remission (PR; 17.6%), two pts each in stable disease (SD; 11.8%) or progressive disease (PD; 11.8%). Nine pts (52.9%) received radiotherapy (RT) consolidation, one of them underwent also an autologous transplant. Restaging after consolidation showed 13 CR (76.5%), one PR (5.9%), one SD (5.9%) and two PD (11.8%). Five pts underwent subsequent treatments (four refractory, one relapsed after 14 months); during salvage phase three pts were treated with brentuximab vedotin, one patient only received a checkpoint inhibitor. Median follow up was 60 months. Two pts died, with an overall survival of 94.1% at 5y and 70.6% at 10y. Progression-free survival (PFS) was 69.5% at 5y. A non-significant difference in PFS was observed for treatment choice (intensified 79.5% *vs* standard 50.0% at 5y) and administration of a consolidation (76.2% at 5y) *vs* no consolidation (62.5% at 5y). The low percentage of cases confirmed as GZL proved the difficulties in the diagnosis of GZL and the need of tools to help pathologists in this tricky diagnosis. Despite the relatively small number of confirmed GZL we observed an advantage in terms of PFS for patients treated with intensified regimens, with R-DA-EPOCH as the primary choice of treatment. The role of consolidative RT ought to be evaluated in larger cohorts.

Table 1.

Table 1

Median age (range)	41 years (16-62)
Sex	
Male	5 (29.4 %)
Female	12 (70.6 %)
Stage	
I-II	11 (64.7 %)
III-IV	6 (35.3 %)
Mediastinal bulky disease	10 (58.8 %)
Mediastinal syndrome (only mediastinal bulky pts)	5 (50.0 %)
Extranodal sites	5 (29.4 %)
B-symptoms	
Absence	9 (52.9 %)
Presence	8 (47.1 %)
Elevated LDH (data available in 16 pts)	10 (37.5 %)
Elevate ERS (data available in 11 pts)	5 (45.5 %)
Elevated beta2-microglobulin (data available in 11 pts)	4 (36.4 %)
Median WBC (range) (data available in all pts)	7900/microl (4690/microl - 19610/microl)
Lymphocytopenia (data available in 16 pts)	3 (18.8 %)
Hemoglobin (data available in all pts)	12.1 g/dl (8.8 g/dl – 14.4 g/dl)
IPI (data available in 16 pts)	
Low	12 (75.0 %)
Low-intermediate	2 (12.5 %)
High-intermediate	2 (12.5 %)
High	0 (0.0 %)

DP011

CLINICAL EXPERIENCE OF TABELECLEUCEL IN EPSTEIN–BARR VIRUS-POSITIVE POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE (EBV+ PTLD) INVOLVING THE CENTRAL NERVOUS SYSTEM

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Background. Tabelecleucel is an investigational, off-the-shelf, allogeneic EBV-specific T-cell immunotherapy being studied in patients (pts) with EBV+ diseases, including EBV+ PTLD with central nervous system (CNS) involvement. Pts with relapsed/refractory (R/R) EBV+ CNS PTLD have very limited treatment options and

poor prognosis. We previously reported results from pts with R/R EBV+ CNS PTLD treated within 2 single-center studies. We report here a combined analysis from 4 open-label studies.

Methods. Safety and efficacy were evaluated using data from 4 open-label studies: 2 single-center, phase 2 (P2) trials (NCT00002663, n=10; NCT01498484, n=2), a multicenter, expanded-access protocol (EAP-201 [2016-2020]; NCT02822495, n=2) and the multicenter, P2 EBVision (study 205) trial (NCT04554914, n=4). Pts with R/R or treatment naive EBV+ CNS PTLD received cycles of 3 weekly infusions of tabelecleucel at ~2x10^6 cells/kg. Response was assessed by study investigator. Key endpoints were objective response rate (ORR), overall survival (OS), and safety parameters.

Results. Eighteen pts were included in this pooled analysis. Pts received a median (range) of 1 (0 to 5) lines of prior therapy. In all pts, ORR was 77.8% (95% CI: 52.4, 93.6), 1 yr and 2 yr OS rates were 70.6% and 54.9%, respectively (Table 1). There were no treatment-related fatal or life-threatening treatment-emergent adverse events (TEAEs) reported or serious treatment-related TEAEs of neurotoxicity, organ rejection, GVHD, or tumor flare reaction of any grade.

Conclusions. In this combined analysis that includes the 1st reported EBVision data, tabelecleucel induced a high response rate of ~78% and demonstrated promising survival among pts with EBV+ CNS PTLD, consistent with previous single-center experience. Tabelecleucel was also well tolerated. The P2 trial, EBVision is ongoing to further investigate the clinical benefit of tabelecleucel in pts with EBV+ diseases.

Table 1. Key efficacy outcomes in EBV+ CNS PTLD pts treated with tabelecleucel.

	All (N=18)
ORR, n (%)	14 (77.8)
Best overall response, n (%)	
Complete response	7 (38.9)
Partial response	7 (38.9)
Stable disease	1 (5.6)
Progressive disease	3 (16.7)
Median time to response, mo (range)	1.8 (0.7–6.4)
Median duration of response, mo (95% CI)	NE (0.5–NE)
1 yr OS rate, % (95% CI)	70.6 (43.0–86.6)
2 yr OS rate, % (95% CI)	54.9 (27.1–75.9)
Responders, n	14
1 yr OS, %	85.7
2 yr OS, %	66.7
Nonresponders, n	4
1 yr OS, %	0.0
2 yr OS, %	0.0
Median follow up, mo (range)	14.8 (1.4–55.4)

CI = confidence interval; NE = not estimable; ORR = objective response rate; OS = overall survival

DP012

ULTRASOUND-GUIDED FINE NEEDLE BIOPSY OF NODULAR LESIONS OF THE SPLEEN IN HEMATOLOGY CLINICAL PRACTICE

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Solid splenic lesions may be the expression of a lymphoproliferative disease spreading to the spleen or appear as the only manifestation of possible neoplastic diseases, mainly hematologic malignancies. Biopsy is of uttermost importance in clarifying the nature of nodular lesions of the spleen. Forty-four patients with splenic nodular lesions underwent contrast-enhanced ultrasonography (CEUS) and contextual biopsy using an 18-gauge needle. All procedures were performed on an outpatient basis provided coagulation tests and platelet count were adequate and all anticoagulants/antiplatelet agents discontinued. Patients with inconclusive findings or with a diagnosis of unaffected splenic tissue were followed-up to discriminate between true and false negative results. Sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were the main goals of the study, along with safety. All the procedures ended up with sampling of splenic tissue without any severe complication requiring hospitalization or supportive countermeasures. None was interrupted because of an adverse event. Out of 44 samples, a final diagnosis was accomplished in 39 cases. Among the 5 patients with insufficient sampling, 3 never received a diagnosis of a neoplasm during follow-up; 1 had myelofibrosis and 1 had angiosarcoma. A diagnosis of lymphoma was made in 22 cases (non-Hodgkin lymphoma in 19 cases and Hodgkin lymphoma in 3 cases). Other diagnoses included: splenic metastases of carcinoma (3 cases), splenic sarcoma (3 cases), non-neoplastic lesions (3 cases). In 8 cases, the final diagnosis was unaffected splenic tissue: among these patients, 1 later received a diagnosis of Hodgkin lymphoma by marrow biopsy, while the others never received a diagnosis of a neoplasm and were true negative. All the 22 patients with a final diagnosis of lymphoma displayed a hypoechoic lesion at B-mode, with CEUS iso-, hyper- and hypoenhancement in 55%, 32% and 9% of cases (CEUS not done in 1 patient), and washout in 86%. Most patients had no or mild splenomegaly with a positron emission tomography positive lesion in 77% of cases. Table 1 summarizes the main findings of the study. Ultrasound-guided fine needle biopsy of splenic nodular lesions can be safely performed on an outpatient basis with no clinically severe adverse events and no need of overnight hospitalization. It allows a timely and accurate diagnosis of lymphoid or neoplastic disease obviating diagnostic splenectomy.

Table 1.

Results	*N*	*Endpoint*	*%*
True positive for malignancy	28	Sensitivity (*)	96.6
True negative for malignancy	10	Specificity (*)	100
False negative for malignancy	1	Positive predictive value (*)	100
Insufficient material	5	Negative predictive value (*)	90.9
False positive for malignancy	0	Overall accuracy (*)	86.4
Total	44	Diagnostic yield (**)	88.6

(*) It pertains to the diagnosis of a splenic neoplastic disease
(**) This refers to any type of diagnosis

DP013

MONITORING CAR T CELL EXPANSION IN THE ITALIAN CART-SIE OBSERVATIONAL PROSPECTIVE STUDY: AN EFFECTIVE TOOL TO PREDICT TOXICITIES AND DISEASE RESPONSE

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Introduction. Clinical response to CD19-directed chimeric antigen receptor (CAR) T-cell therapy in relapsed/refractory (R/R) large B-cell lymphoma (LBCL) has been associated with *in vivo* expansion and long-term persistence of Tisa-cel and Axi-cel CAR T products in clinical trials. To date, the relevance of CAR T expansion in real life settings has been assessed only in monocentric or pivotal studies, employing small cohorts of patients (pts).

Methods. the CAR T-SIE is an ongoing multicenter prospective observational study enrolling all lymphoma pts treated with Axi-cel or Tisa-cel as standard of care in Italy. Within this study, 231 R/R LBCL pts were selected based on the availability of biological samples and paired clinical data. Pts received either Tisa-cel or Axi-cel in 13 centers from Dec 2019 to Dec 2023. Absolute quantification of circulating CAR T cells was performed by flow cytometry with CD19 CAR FMC63 antibody (Miltenyi).

Results. Circulating CAR T were monitored on days 7, 10, 14, 21 and 30 after infusion and then monthly until their disappearance. Median CAR T levels at day 10 (C10) was 19.97 c/µl, median CAR T levels at peak expansion (Cmax) was 34.98 c/µl, median cumulative CAR T levels within the first month (AUC_{0-30}) was 74.86. Kinetic parameters were strongly correlated (Spearman's: C10-Cmax r=0.8162, C10-AUC_{0-30} r=0.8422, Cmax-AUC_{0-30} r=0.9787, P<0.0001). No differences were reported when pts were stratified according to the infusion products received (median AUC_{0-30}: 72.9 in Tisa-cel *vs* 80.7 in Axi-cel, p=ns). CAR T expansion was positively associated with the expected toxicities (CRS P>0.0001, ICANS P=0.0452) and with response at day 90 [median AUC_{0-30}: 92.5 versus 54.2 for responders and non-responders (P=0.0022), and OR 2.22 (CI1.28–3.87) P=0.0048 in univariable logistic models] and retained its association also in multivariable analysis [OR 2.75 (CI 1.47-5.13) p=0.0015]. When pts were dichotomized into expanders and poor-expanders based on the median AUC_{0-30}, expanders had significantly longer progression-free survival (PFS) (median PFS: 317 *vs* 158 days for expanders and poor-expanders, P=0.0336). Both univariable and multivable Cox models confirmed the positive association of expansion with PFS [HR 0.67 (CI 0.47–0.95) P=0.0233; HR 0.65 (CI 0.45-0.95) P=0.0245].

Conclusions. these data demonstrate for the first time the clinical relevance of CAR T cell monitoring in the context of a multicenter prospective real life study.

DP014

RELAPSE PATTERNS AND OUTCOMES OF PATIENTS WITH FOLLICULAR LYMPHOMA ACHIEVING COMPLETE METABOLIC RESPONSE AFTER INDUCTION THERAPY. A FIL FOLL12 SUB-STUDY

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Background. So far, several factors such as disease heterogeneity and the lack of ubiquitous molecular markers, have hindered the identification of reliable prognostic factors in patients with follicular lymphoma (FL). Analogously, data concerning management of disease recurrence and patient's prognosis outside interventional clinical trials are scant. This study aims at analyzing relapse patterns in pa-

tients who achieve a complete metabolic response (CMR) after first line induction immunochemotherapy (ICT), thus evaluating potential correlations with clinical behavior.

Methods. This study included FL patients treated within the FOLL12 who achieved a CMR at the EOI. CMR was defined as a centrally reviewed Deauville score 1 to 3. Primary endpoint of current sub-study was 3-year progression free survival (PFS2) and survival (SAR) both calculated from the time of relapse.

Results. Of 786 patients enrolled, 641 achieved a CMR at the EOI and, after a median follow-up of 69 months, 176 (27%) patients relapsed. Median age at relapse was 62 years (53-70). Relapse occurred within 24 months from initial diagnosis in 67 patients (38%). We identified 15 transformed FL cases among the 87 re-biopsed patients (49%), 7 of which before 24 months from diagnosis. Median duration of first remission was 28 months (range: 10-27 months). Second line therapy was started in 141 patients with a median time from relapse to therapy of 2 months (range 0.5 to 5). R-CHOP, RB and R-DHAP were the most frequent treatment options, and consolidation with ASCT was prescribed in 39 cases (29%). After a median follow-up of 36 months from first relapse, 71 second relapses and 19 deaths occurred, with a 3-year PFS2 and a 3-year SAR for all 176 patients of 60% (50-67) and 94% (89-97) respectively. No statistically significant difference was found in 3-yr PFS2 and SAR comparing first line therapy (R-CHOP *vs* R-benda), time to relapse within or after 24 months from diagnosis, use of rituximab maintenance or not, salvage strategy adopted. Patients with tFL showed a worst PFS2 compared to FL patients biopsied or not (p=0.012) and a better PFS2 when treated with ASCT (p=0.036)

Conclusions. The outcome of FL who relapse after having achieved a CMR at the end of first line ICT is overall good and is not influenced by initial treatment, salvage therapy and time to relapse (POD24). Only patients with histologic transformation at relapse showed relatively poorer outcomes and benefited from consolidation ASCT.

DP015

ABSTRACT NOT PUBLISHABLE

DP016

ALL-IN-ONE TRANSCRIPTOMIC APPROACH TO DISSECT DIFFUSE LARGE B CELL LYMPHOMA HETEROGENEITY

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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%. Different genomic approaches have been used to dissect its complexity in clinical settings, but low input material and FFPE derived artifact remain obstacles for a comprehensive evaluation. Here we aim to validate the capacity of RNA approaches to dissect DLBCL heterogeneity, from transcriptional programs to mutational status, on 186 FFPE samples treated with R-CHOP. RNASeq data was used for deconvolution of cell states through EcoTyper, and for mutational analysis. Single nucleotide variants on exonic positions were filtered considering mutations reported on cBioPortal for hematologic malignancies (VAF>10%). EcoTyper detected 5 malignant B cell states (S1-S5) corresponding to 5 different transcriptional programs, reflecting the B cells differentiation/maturation. State-associated event free survival (EFS) curves showed significant distinct outcomes (S1 *vs* S5 p=0.0029; Figure A).

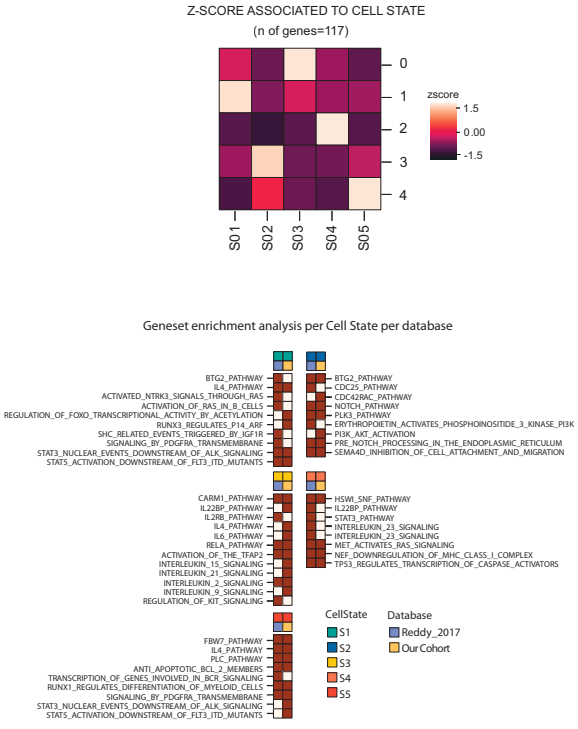

Figure 1.

Our variant calling pipeline identified 117 mutated genes, with a mean mutation rate of 4 (range 0-28). As reported in Figure B the most frequently mutated genes were PIM1, BTG2, MYD88, CD79B. Using the 117 mutated genes we identified 5 distinct mutational clusters associated with B cell states (Figure C), as confirmed by z-score (Figure D). Notably, Cluster S1 displayed enrichment for genes regulating germinal center development (BCL6, DUSP2, STAT3), TME interactions (BTG2), and epigenetic regulation (EZH2, KMT2D). In contrast, Cluster S5 harbored mutations in genes involved in proliferation pathway dysregulation (PI3K/AKT, NF-κB, BCR signaling; PIM1, MYD88, CD79B, CARD11) and apoptosis deregulation (MPEG1, BCL2). Gene Set Enrichment (GSE) based on mutational profile revealed superimposable results with an external cohort (Reddy et al 2017, n=558; Figure E). Particularly, S1 Cluster was enrichment of gene sets related to cell cycle regulation, inflammatory response modulation, and TME interactions, while S5 Cluster for gene sets related to chronic BCR and NF-κB activation. Importantly, differentially expressed genes for deconvolved B cells mirrored these enrichments, suggesting a phenotype of concordant alterations at

both the mutational and transcriptional levels. Here we confirm how our transcriptome based mutational calling approach is able to uniquely recapitulate the transcriptional programs of DLBCL, potentially leading to a better risk stratification.

DP017

ABSTRACT NOT PUBLISHABLE

DP018

CAMPUS ALL RETROSPECTIVE MULTICENTER STUDY ON THE OUTCOME OF ADULT LYMPHOBLASTIC LYMPHOMA PATIENTS TREATED IN REAL-LIFE WITH AN INTENSIVE PROGRAM INSPIRED BY THE GIMEMA LAL1913 CLINICAL TRIAL

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Background. GIMEMA LAL 1913 published trial (Bassan R, Blood Advances 2023; 16(7): 4448-61) was a phase 2, pediatric-inspired, PEG-asparaginase based and MRD-oriented protocol for adult patients with both acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LL). Indeed, LL-patients are currently treated with various antineoplastic approaches, infrequently incorporating earlier and more intensive central nervous system (CNS) prophylaxis and higher cumulative doses of the non-myelosuppressive components such as steroids and asparaginase. Accordingly, post-treatment outcomes may vary in terms of response and survival rates. Therefore, we retrospectively collected data from 50 LL-patients homogeneously treated according to LAL 1913 trial, with the aim to confirm the trial results in a real-world scenario.

Patients and methods. Data from 50 patients, belonging to 23 GIMEMA centers, affected by LL were retrospectively collected. The study population median age was of 37 years (range, 19-58) and the ECOG distribution was 0,1,2 and 3 in 20 (40%), 20 (40%), 5 (10%) and 5 (10%) patients, respectively. Lineage was prevalently T (n=45, 90%). The extranodal involvement was reported for 1 or ≥2 sites in 7 (14%) and 7 patients (14%), respectively. Stage was I, II, III and IV in 24 (48%), 10 (20%), 10 (20%), 6 (12%) patients, respectively. An adverse phenotype (ie, CD1a negativity) was reported in 5 out of the 45 T-LL (11%).

Results. The post-high-dose consolidation (C) cycle 3 (C3) evaluation of response documented complete, partial and no response in 39 (78%), 2 (4%) and 9 (18%) patients, respectively. The 5-year whole population OS, DFS and EFS was of 64, 70 and 65%, respectively (Figure 1). A benefit by age (≤40) was documented for 5-year DFS (80%) if compared with age>40 (56%). The 6 (out of the 12) allotransplated patients in first line (after C3-complete response) showed better 5-year OS if compared to allotransplanted ones after other than first line allotransplant-positioning (73% *vs* 23%, p=0.01). Peg-asparaginase dose reduction (performed in 12 and 29% at C1 and C2, respectively) did not impact any survival rates. In multivariate analyses, the ECOG≥2 impacted both OS (HR=3.47; IC95% 1.084-11-112, p=0.036) and DFS (HR=10.50, IC95%: 2.809-39.255, p<0.001).

Conclusions. Our study promising results in terms of OS and DFS (Figure 1), with a successful usage of peg-asparaginase even in case of its dose-reduction, suggest the LAL1913-protocol as the reference one for LL-patients.

Figure 1

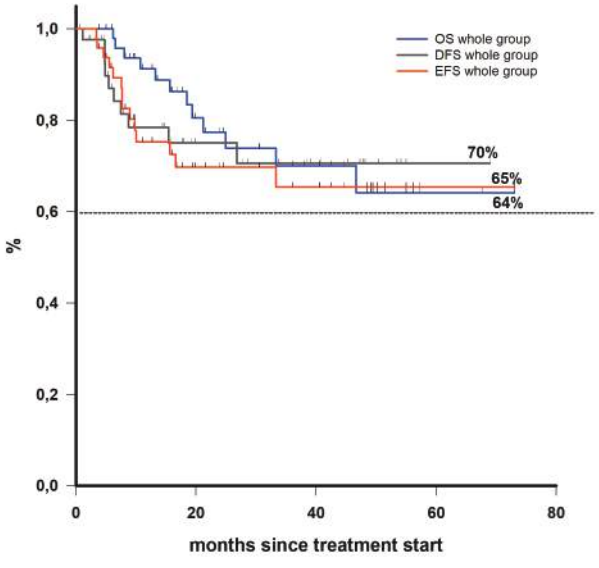

Figure 1.

Acute leukemia I

DP019

DURABLE OUTCOMES WITH MANAGEABLE SAFETY LEADING TO PROLONGED SURVIVAL WITH TAGRAXOFUSP FOR TREATMENT-NAIVE PATIENTS WITH BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM (BPDCN): UPDATED RESULTS FROM A EUROPEAN NAMED PATIENT PROGRAM (NPP)

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Introduction. BPDCN is an aggressive orphan hematologic malignancy characterized by clonal expansion of plasmacytoid dendritic tumor cells that express specific markers, including CD123. Tagraxofusp (TAG) is a CD123-directed therapy approved in the US and EU to treat BPDCN. In August 2019, a global Named Patient Program (NPP) was initiated in Europe to increase patient (pt) access to TAG. We present updated results, including over two years of follow-up, in treatment-naïve pts with BPDCN from the NPP to assess TAG safety and efficacy in the real-world setting.

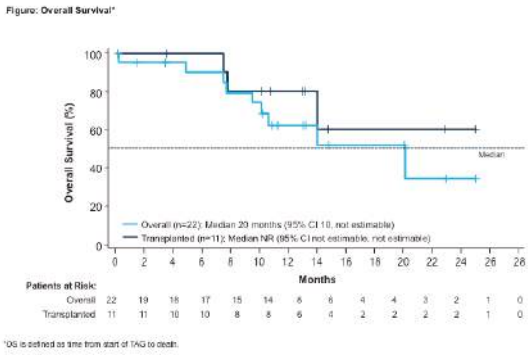

Figure 1.

Methods. This European multicenter, non-interventional, retrospective study included adult BPDCN pts who had access to TAG via the NPP. Intravenous TAG as first-line therapy was given at 12 mcg/kg once daily on days 1–5 (up to day 10 allowed) of a 21-day cycle. Training on clinical management guidelines was mandatory before treatment initiation. The main endpoints were complete response (CR) rates and incidence and grade (G) of capillary leak syndrome (CLS). Secondary outcomes included the number of pts bridged to HSCT, OS, and safety.

Results. 22 treatment-naïve adult pts were enrolled in the European NPP from 08/2019 to 12/2021. At a median follow-up of 10 mos, 18 pts had at least 1 tumor assessment. The overall response rate (ORR) was 89% (95% CI, 65–99), including a CR rate of 67% (95% CI, 41–87) and a partial response (PR) rate of 22%. Allogeneic HSCT was undertaken in 11 (50%) pts; of these 7 pts were in CR prior to HSCT, and 4 pts were in PR. Of the 2 pts with CNS involvement at baseline, both had CNS clearance by intrathecal chemotherapy (IC), achieved a CR with TAG, and were transplanted. Median OS for all pts was 20 mos (Figure 1). The majority of G3/4 treatment-emergent adverse events (AEs) or serious AEs occurred during cycle 1, including thrombocytopenia (32%) and neutropenia (18%). 10 pts experienced mild to moderate CLS events, (69% G≤2; 31% G3; no G4/5 events), which were managed with albumin supplementation (92%) and temporary changes in TAG scheduling (69%); all events resolved. As of the data cut-off, 2 pts (9%) remain on treatment.

Conclusion. First-line TAG achieved durable outcomes with prolonged survival and a manageable safety profile. These real-world results from a European NPP are consistent with the long-term safety and efficacy results demonstrated in the pivotal TAG monotherapy study (Pemmaraju JCO 2022) and further support TAG treatment for pts with BPDCN.

DP020

A SYNTHETIC DATA-DRIVEN APPROACH TO INVESTIGATE MUTANT NPM1-RELATED GENETIC NETWORK IN ACUTE MYELOID LEUKEMIA (AML)

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Synthetic data are artificial data generated by machine learning algorithms trained to learn the essential characteristics of a real source dataset, allowing to increase information by data augmentation and integration. *NPM1* mutations in absence of *FLT3*-ITD define a favorable prognostic group in AML according to ELN, although other factors could further stratify clinical outcome. Here we designed a synthetic data-driven approach to investigate mutant *NPM1*-related genetic networks and generated several augmented synthetic datasets through different machine learning algorithms. For this purpose we used the 'synthpop' R package and original data from 429 newly diagnosed AML patients of the "Beat AML Program" dataset, all with both clinical and RNAseq information. Our approach showed that synthetic data were able to recapitulate both ELN risk ($p<0.0001$ - Figure 1a) and *NPM1* mutational status ($p<0.0001$). However a subgroup of *NPM1*mut *FLT3*wt with synthetic "ELN Intermediate/Adverse" risk was identified; this group was confirmed to have indeed a worst prognosis.

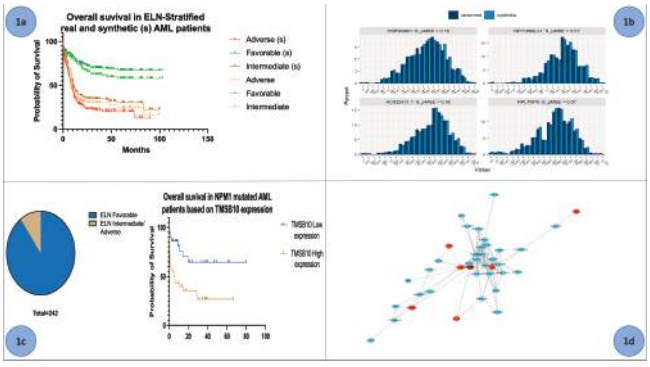

Figure 1.

Therefore we performed several analyses to investigate whether synthetic data could aid in identifying factors able to discriminate *NPM1*-mutated AML with poorer prognosis. Specifically global ex-

pression profiling data has been normalized using the z-score and only genes with median value > 0 were considered. A panel of 192 Differentially Expressed Genes (DEGs) in *NPM1*-mutated AML was identified. Cox regression spotted 40 DEGs with prognostic impact, and a Weighted Correlation Network Analysis identified 4 different highly co-expressed genes modules and several hub genes. Hub genes were selected and integrated in the synthetic data generation (Figure 1b). A 300 times augmented dataset was generated with classification and regression trees method. Again a sub-group of *NPM1*mut *FLT3*wt with synthetic "ELN intermediate or adverse" risk emerged and a poorer prognosis was confirmed (Figure 1c). Thymosin beta-10 (*TMSB10*) was identified as DEG discriminating the two synthetic prognostic groups. *TMSB10* was tested on the original AML real dataset, confirming its expression is able to identify a poor prognosis group in *NPM1*-mutated AML (Figure 1c). *TMSB10* plays a role in cytoskeleton organization and has never been studied in AML. We built a network of *TMSB10*-highly correlated genes and unveiled by gene ontology analysis an enrichment in focal adhesion (Figure 1d). Bioinformatic and biological validation are ongoing.

DP021

ROLE OF MRD AS A BIOMARKER TO OPTIMIZE OUTCOME IN ELN2017 INTERMEDIATE RISK ACUTE MYELOID LEUKEMIA: COMPARISON BETWEEN GIMEMA AML1310 MRD-DRIVEN PROTOCOL AND REAL-LIFE DECISION-MAKING PROCESS

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Optimal treatment of ELN2017 intermediate-risk AML patients (ELN2017-IR) is still debated. Measurable residual disease (MRD) may represent a reliable tool to discriminate patients (pts) suitable for hematopoietic stem cell transplantat (ASCT) from those benefitting from chemotherapy or autologous transplant (AuSCT). To explore this hypothesis, we compared the outcome of ELN2017-IR pts from the prospective GIMEMA AML1310 trial to a similar real-world group (RWG) from Tor Vergata Hospital (Rome) and Spedali Civili (Brescia). Overall, we analyzed 298 pts (178 from AML1310 and 120 from RWG) receiving "7+3"-like regimens. MRD was assessed by multiparametric flow cytometry (MFC) after 2 courses of chemotherapy adopting the 0.035% threshold to discriminate between MRD negativity (MRDneg) *vs.* positivity (MRDpos). Pts from AML1310 received ASCT if MRD+, AuSCT/high-dose cytarabine if MRD-. In RWG the strategy was similar, but the transplant selection was not systematically driven by MRD status. Median age was 51 years (range 18-80): 49 [range 18-61] *vs* 57 years [range 19-80] for AML1310 and RWG. After induction chemotherapy 207/293 (69%) pts entered complete remission: 113/178 (63.5%) in AML1310 and 94/120 (78.3%) in RWG, respectively (p=0.019). After consolidation 178/207 (85.9%) pts were evaluable for MRD. In AML1310, 32 pts were not evaluable due to lack of aberrant immunophenotype and were addressed to AuSCT. Overall, 73/178 (41.0%) tested MRDneg (41/86[47.7%] in AML1310 and 32/92 [34.8%] in RWG), 105/178 (59.0%) MRDpos (45/86 [52.3%] in AML1310 and 60/92 [65.2%] in RWG, p=0.094). In AML1310, more pts received ASCT (64/113 [56.6%] *vs* 36/94 [38.3%] in AML1310 and RWG, respectively) and AuSCT (16/113 [14.1%] and 1/94 [1%] in AML1310 and RWG, respectively). Six-years DFS was 36.4% *vs.* 27.6% in AML1310 and RWG pts, respectively (p=0.0346) [Figure 1A]. Such a DFS advantage of AML1310 was counterbalanced by higher 6-years non-relapse mortality (NRM) (20% *vs* 3.6% for AML1310 and RWG, respectively; p=0.0016) [Figure 1B]. Six-years OS was 36.2% *vs*. 31.9% for AML1310 and RWG pts, respectively (p=0.82) [Figure 1C]. In AML1310 trial, the systematic MRD-driven transplant allocation and the higher ASCT rate led to a better DFS as compared to RWG. However, the higher NRM observed in AML1310 translated into similar OS of the 2 cohorts. We confirmed that MFC MRD is informative in pts with ELN2017-IR AML, although mitigation of ASCT toxicity is needed to improve the outcome of these pts.

Figure 1. ELN2017 intermediate risk patients belonging to the protocol group showed a significantly better outcome as compared to the control group in terms of DFS (1A) but not of NRM (1B). Overall, the two groups did not significantly differ in terms of OS (1C).

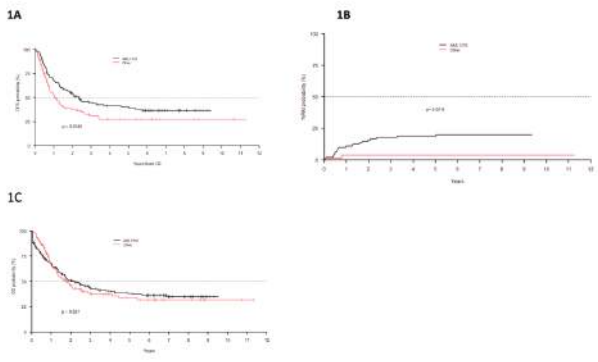

Figure 1.

DP022

EVOLUTION OF TRANSCRIPTOMIC PROFILES IN UNFAVORABLE INV(16) ACUTE MYELOID LEUKEMIA

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Acute Myeloid Leukemia (AML) with inv(16) is typically associated with a favourable prognosis, according to the European LeukemiaNet2022 recommendations. Despite the sensitivity to chemotherapy, up to 40% of patients will eventually experience relapse. The aim of our study was to dissect the genomic and transcriptomic profile of inv(16) AMLs to identify potential markers, able to predict disease progression and facilitate the design of novel therapeutic strategies. We explored the mutational landscape, taking advantage of NGS data of 222 diagnostic samples, derived from publicly available sources, including a group of patients who subse-

quently relapsed or were refractory to treatment (n=44). While several mutations cooperated with inv(16) during leukemogenesis, the mutational landscape at diagnosis did not differ in patients experiencing primary induction failure or relapse, when compared to the rest of the cohort (Figure 1A,B). To identify molecular mechanisms underlying disease-relapse, we analysed the transcriptome of unpaired samples collected at relapse (n=6) and at diagnosis (n=7). Of these, 3 pts were in prolonged remission (median of 26 months of follow-up) and 4 subsequently relapsed at a median of 22 months from initial diagnosis. For RNA-Seq analysis, statistical significance threshold was set with an adjusted-p-value<0.05 and |log2(Fold Change)|≥1 to identify differentially expressed genes. Gene Set Enrichment Analysis (GSEA) allowed the identification of oxidative phosphorylation (OXPHOS) as one of the most significantly downregulated pathways at relapse. The downregulation of OXPHOS correlated with venetoclax sensitivity, making this drug potentially useful in this context. The OXPHOS can be targeted by the venetoclax/azacitidine combination, which we tested using the inv(16)-ME-1 cell-line. However, we did not observe any additional advantage in terms of proliferation suppression over azacitidine alone. We searched for synthetic-lethality and enhanced the effect of venetoclax by adding metformin, a mitochondrial transfer inhibitor. *in vitro* treatment with this combination highlighted a significant synergistic interaction, at least similar to that of ven/aza (Figure 1C,D). Remarkably, the study of transcriptomic profile of inv(16) AML at relapse unveiled OXPHOS as a potential target. The cytotoxicity of metabolic-oriented and synthetic-lethal treatment approaches may provide a rationale for future clinical use of venetoclax/metformin combination.

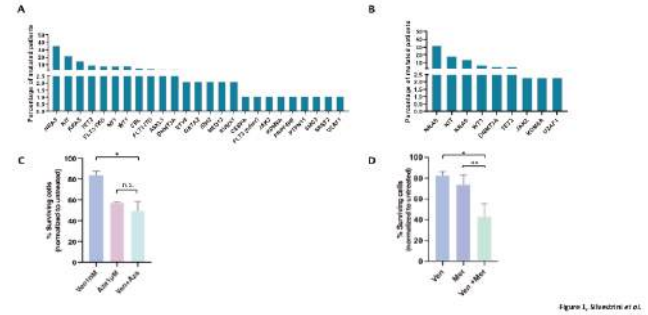

Figure 1.

DP023

PROGNOSTIC STRATIFICATION IN VEN-BASED ACUTE MYELOID LEUKEMIA TREATMENTS: VALIDATION OF THE MPRS MODEL ON A REAL-WORLD POPULATION

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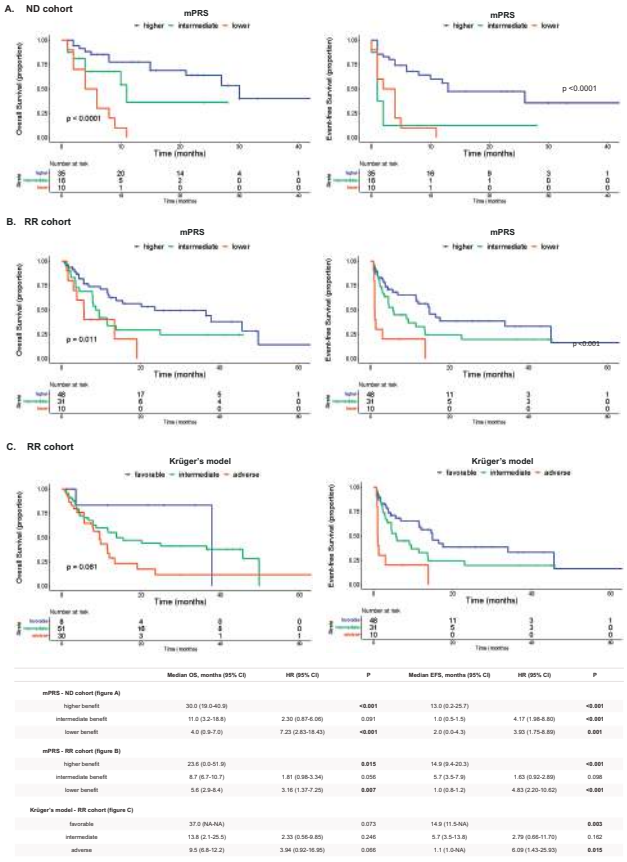
Background. Genotype-based prognostic stratification models commonly used in acute myeloid leukemia (AML), such as the European LeukemiaNet (ELN) 2022 classification, are largely derived from the conventional chemotherapy setting and their performance with respect to outcome prediction for patient (pts) treated with venetoclax (VEN)-based combinations is unsatisfactory. According to the recently proposed molecular prognostic risk signature (mPRS), newly diagnosed (ND) AML pts treated with VEN-based combinations are allocated to a lower- (*TP53*^{mut}), an intermediate- (*FLT3*-ITD or *N/KRAS*$_{mut}$) and a higher benefit group. Such model has been shown to outperform ELN 2022 stratification system in the setting of treatment-naïve pts. A different stratification model based on molecular genetics has been proposed by Krüger for relapsed/refractory (R/R) AML pts treated with VEN-based combinations, although its performance with respect to ELN 2022 and mPRS has not been assessed.



	Median OS, months (95% CI)	HR (95% CI)	P	Median EFS, months (95% CI)	HR (95% CI)	P
mPRS - ND cohort (figure A)						
higher benefit	30.0 (19.0-40.9)		**<0.001**	13.0 (0.2-25.7)		**<0.001**
intermediate benefit	11.0 (3.2-18.8)	2.30 (0.67-6.06)	0.091	1.0 (0.5-1.5)	4.17 (1.98-8.80)	**<0.001**
lower benefit	4.0 (0.9-7.0)	7.23 (2.83-18.43)	**<0.001**	2.0 (0.0-4.3)	3.93 (1.75-8.89)	**0.001**
mPRS - RR cohort (figure B)						
higher benefit	23.6 (0.0-51.9)		**0.015**	14.9 (9.4-20.3)		**<0.001**
intermediate benefit	8.7 (6.7-10.7)	1.81 (0.98-3.34)	0.056	5.7 (3.5-7.9)	1.83 (0.92-2.89)	0.098
lower benefit	5.6 (2.9-8.4)	3.16 (1.37-7.25)	**0.007**	1.0 (0.8-1.2)	4.83 (2.20-10.62)	**<0.001**
Krüger's model - RR cohort (figure C)						
favorable	37.0 (NA-NA)		0.073	14.9 (11.5-NA)		**0.003**
intermediate	13.6 (2.1-25.5)	2.33 (0.56-9.65)	0.246	5.7 (3.5-13.8)	2.79 (0.66-11.70)	0.162
adverse	9.5 (6.8-12.2)	3.94 (0.92-16.95)	0.066	1.1 (1.0-NA)	6.09 (1.43-25.93)	**0.015**

FIGURE 1. Clinical outcome according to the mPRS model in the ND cohort and to the mPRS and the Krüger's model in the RR cohort - OS and EFS according to the mPRS in the ND cohort. (A) OS and EFS according to the mPRS in the RR cohort. (B) OS and EFS according to the Krüger's model in the RR cohort. (C)

Figure 1.

Methods. We evaluated the performance of the mPRS on a real-world cohort of 150 pts with available NGS data receiving VEN-based combinations at our Center between January 2015 and December 2023 for ND (n=61) or R/R (n=89) AML. A 45 genes Oncomine Myeloid Assay (Ion Torrent Genexus) was used for NGS genotyping.

Results. In the entire cohort 56%, 31% and 13% pts were allocated to the higher-, intermediate- and lower-benefit mPRS group. Their overall response rates (ORR) were 75%, 36% and 35% (p<.001). Median OS was 30, 9, and 6 months in the three mPRS categories (p<.001; C-index=.64) and 46, 14, and 11 months for pts in the favorable, intermediate, and adverse ELN 2022 category (p=.016; C-index=0.56). Median EFS was 15, 3, and 1 months in the mPRS groups (p<.001; C-index=.66) and 46, 6, and 6 months for the ELN 2022 categories (p=.013; C-index=0.55). The Z-score for mPRS *vs* ELN 2022 was 2.28 (p=.020) and 3.21 (p=.001) for OS and EFS, respectively. When restricting to ND cohort mPRS outperformed ELN 2022; conversely, in the R/R cohort, the mPRS didn't prove statistically superior to ELN 2022, while retaining its predic-

tive power. Finally, we tested the Krüger model on our RR cohort where it exhibited a slightly better performance than the ELN 2022, but not the mPRS model (Figure 1).

Conclusions. Our data is confirmatory of the goodness of fit of mPRS in the ND setting and suggest potential role also for R/R pts; further efforts are warranted to validate this model on larger multicentric cohorts.

DP024

RECOMMENDED PHASE 3 DOSAGE OF VENETOCLAX IN THE VIALE-T STUDY OF VENETOCLAX PLUS AZACITIDINE AS MAINTENANCE AFTER ALLOGENEIC STEM CELL TRANSPLANTATION IN PATIENTS WITH AML

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Background. While alloHSCT remains the most effective curative treatment for patients with intermediate and poor-risk Acute Myeloid Leukemia (AML), prevention of relapse and GvHD remains an unmet need. VIALE-T is a Phase 3, randomized, open-label trial that evaluates safety and efficacy of Venetoclax (Ven)+Azacytidine (Aza) compared to best supportive care as maintenance therapy in patients with AML after alloHSCT. Here, we report the results of dose confirmation and safety expansion from Part 1 of the study.

Methods. Adult patients with AML in remission who received alloHSCT were enrolled in 3 cohorts. The Bayesian Optimal Interval design guided dose escalation and de-escalation based upon the cumulative number of dose-limiting toxicities (DLTs) observed at the current dose level. The first cohort of 6 patients (pts) received a starting dose (dose level 1, DL1) of 200mg Ven daily for 28days of each 28-day cycle + 20mg/m of Aza for 5days. A second cohort of 5 pts received DL-1 of 200mg Ven daily for 14days of each 28-day cycle + 20mg/m of Aza for 5days. A third cohort of 10 pts was re-tested at DL1 prior to safety expansion, which included 14 additional patients at DL1. Ven+Aza was administered for 6 cycles, followed by Ven mono for an additional 18 cycles.

Results. 4/5 (80%) and 13/16 (81.3%) pts enrolled in the DL-1 and DL1 groups respectively in dose escalation/de-escalation, were DLT evaluable. No DLT observed at DL-1. At DL1, the DLT rate was 3/13 pts (23.1%); 2/13 pts (15.4%) experienced neutropenia (G. ≥3 lasting ≥14days), and 1/13 patient (7.7%) experienced G. 2 diarrhea resulting in >20% Ven dose omission. DL1 was selected as the recommended phase 3 dose (RPTD) for safety expansion. For Part 1 of the study, 3/5 (60%) and 22/30 (73.3%) pts who received DL-1 and DL1 respectively, experienced a G. 3 or 4 treatment-emergent adverse event: the most common was neutropenia, followed by thrombocytopenia. Both neutrophil and platelet counts were stable or improved for pts who continued on the study drugs. 8/30 (26.7%) pts in the DL1 group and 2/5 (40%) pts in the DL-1 group experienced a serious adverse event, the most common being sepsis and diarrhea. There were 2 deaths from adverse events in the DL1 group, unrelated to the study drugs (1 due to GvHD and 1 due to sepsis during the second alloHSCT).

Conclusions. Based on the safety data in Part 1 of the study, DL1 (200mg Ven x 28days and Aza 20mg/m x 5days) was selected as the RPTD for Part 2 randomization.

Figure 1: VIALE-T Part 1 Study Design

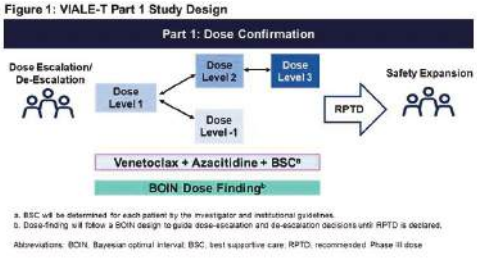

Table 1: Baseline demographics and Grade 3 or higher toxicities observed in ≥ 10% patients treated with DL 1 and DL -1 of venetoclax in combination with azacitidine during the safety expansion phase

	Dose Level 1 Ven 200 mg QD 28 Days + Aza 20 mg/m2 QD 5 Days (N = 30)	Dose Level -1 Ven 200 mg QD 14 Days + Aza 20 mg/m2 QD 5 Days (N = 5)
Baseline Demographics		
Age, years		
Median (min, max)	58 (20, 77)	50 (45, 60)
Gender, n (%)		
Male	19 (63.33)	2 (40)
Female	11 (36.66)	3 (60)
Geography, n (%)		
North and South America, Australia, Europe	25 (83.33)	4 (80)
Japan	2 (6.66)	0
Other Asian countries	3 (10)	1 (20)
Toxicities		
Any adverse event, n (%)	22 (73.33)	3 (60)
Neutropenia	15 (50)	3 (60)
Thrombocytopenia	10 (33.33)	2 (40)
Anemia	5 (16.67)	1 (20)
Leukopenia	4 (13.33)	0
Sepsis	2 (6.67)	1 (20)
ALT increased	2 (6.67)	1 (20)

Figure 1.

DP025

INCIDENCE AND DISTRIBUTION OF CSF3R MUTATIONS IN A COHORT OF 367 MYELOID NEOPLASMS AND CHARACTERISTICS OF MUTATED CASES

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The colony-stimulating factor 3 receptor (CSF3R) plays an es-

sential role in differentiation, growth, and survival of granulocytes. Driver mutations in CSF3R gene represent a specific diagnostic marker of chronic neutrophilic leukemia (CNL). Less commonly, these mutations are observed in other myeloid neoplasms but their pathogenetic and prognostic role are still unclear. In the current study, we analyze a large cohort of myeloid neoplasms, throughout a molecular, morphologic and immunophenotypic analysis, to evaluate the incidence of CSF3R mutations, co-mutational profile and to characterize patients harboring mutated CSF3R. Mutational analysis was performed using targeted NGS myeloid panel in a consecutive cohort of 367 myeloid neoplasms. In addition, Real-Time PCR was applied to analyze CD177, LYN and GLI2 expression levels in CSF3R mutated AML patients. Overall, mutations in CSF3R were identified in 19/367 (5%) of analyzed cases. A CSF3R gene mutation was present in 12/181 AML cases (7%), in 2/27 (7%) of CMML cases, in 1/94 (1%) of MDS cases and in 4/65 (6%) of other myeloid neoplasms. A total of 21 mutations of CSF3R gene were detected, with 14 missense mutations, 3 nonsense, 2 splice-donor, 1 frameshift and 1 inframe mutation (Table 1). Two patients showed 2 concomitant CSF3R mutations. Eleven CSF3R mutations were classified as pathogenic or likely pathogenic, the remaining 10 were defined as of uncertain significance (VUS). In AML, CSF3R mutations were more frequent in patients harboring core-binding factor alterations (25%) and CEBPA mutations (12%), followed by TP53 mutated AML (7%) and NPM1 mutated AML (6%). Clinically, the 5 AML patients with pathogenetic mutations in CSF3R were very heterogeneous (age, sex, AML morphology, ELN classification and immunophenotype). One patient acquired the pathogenic variant T618I of CSF3R gene at relapse (VAF 39%) with a concomitant increase of gene expression of CD177, a key factor regulating neutrophil activation, GLI2, effector of hedgehog signaling, and the Src-family tyrosine kinase LYN. Interestingly, gene expression analysis showed elevated levels of CD177 expression in AML patients with CSF3R mutations. Overall, we described the distribution and frequencies of CSF3R mutations in a large cohort of patients with myeloid neoplasia, observing correlations with other genetic lesions and gene expression of factors related to neutrophil activation and hedgehog pathway.

Table 1.

Table 1. List of CSF3R mutations detected in a consecutive cohort of 367 patients with myeloid neoplasia

Patient	Diagnosis	Variant (nucleotide)	Variant (protein)	Mutation type	Exon	VAF (%)	[illegible]	MutationTaster	DANN score	Pathogenicity
1	AML	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
2	AML	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
3	AML	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
6	AML	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	VUS
7	AML	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	VUS
8	AML	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	VUS
9	AML	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	VUS
10	AML	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	VUS
11	AML	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	VUS
12	AML	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	VUS
13	CMML	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Pathogenic
14	CMML	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
15	CNL	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
16	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
17	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	VUS
18	MF	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	VUS
19	MDS	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	VUS

[illegible]

DP026

QUANTUM-FIRST: SAFETY BY TREATMENT PHASE AND BY AGE IN NEWLY DIAGNOSED (ND) PATIENTS (PTS) WITH FMS-LIKE TYROSINE KINASE 3–INTERNAL TANDEM DUPLICATION (*FLT3*-ITD) POSITIVE ACUTE MYELOID LEUKEMIA (AML)

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Background. In the phase 3 QuANTUM-First (Q-F) trial, quizartinib (Quiz) significantly improved OS *vs* placebo (Pbo) when added to intensive chemotherapy and as maintenance monotherapy in pts with *FLT3*-ITD+ ND-AML. We describe Quiz safety by treatment (Tx) phase (Induction [IND], Consolidation [CONS], Continuation [CONT]) and age (<60, 60-64, ≥65 years [y]) in Q-F.

Methods. Pts aged 18-75 y were randomized 1:1 to Quiz 40 mg/d or Pbo with standard IND chemotherapy; pts in remission then received CONS chemotherapy + Quiz (40 mg/d)/Pbo, followed by monotherapy CONT with Quiz (30-60 mg/d)/Pbo for up to 36 cycles. Safety was evaluated in pts who received study drug.

Results. TEAE rates were similar between arms in IND & CONS; grade ≥3 TEAEs were more common with Quiz in CONT (Table). Common TEAEs were GI events, infections, hypokalemia, pyrexia, febrile neutropenia, rash in IND & CONS; and upper respiratory tract infections, GI events, cytopenias, increased ALT in CONT. In IND & CONS, most pts in both arms had myelosuppression (median <4 wk to count recovery); in CONT, more pts had myelosuppression with Quiz. QT prolongation was more common with Quiz in all phases. QTcF >500 ms was low and only seen in IND & CONS. Ventricular arrythmias with Quiz in 2 pts (0.8%): cardiac arrest/ventricular fibrillation with severe hypokalemia. Infections were the most common serious TEAEs (SAEs). TEAEs leading to death were numerically higher with Quiz in IND & CONS, mainly due to infections in older pts, but lower with Quiz in CONT. TEAEs leading to discontinuation (disc) were higher with Quiz *vs* PBO. TEAEs leading to disc of Quiz were mostly infections in IND & CONS and cytopenias in CONT. SAEs, TEAEs leading to death, and TEAEs leading to disc were more common in older (≥65 y [n=134]) *vs* younger pts (<60 or 60-64 y [n=399]). Infections in the elderly were most commonly severe, serious, or fatal and a main cause of early death. With Quiz, cytopenias were more common in younger *vs* older pts; QT prolonged was highest in the 60-64 y group. GI AEs were more common in older pts with Quiz. QTcF >500 ms occurred mainly with Quiz in pts 60-64 y.

Conclusions. In Q-F, Quiz-associated infections and cytopenias were observed across phases; QTcF >500 ms was rare. In both arms, pts ≥65 y had more SAEs and TEAEs leading to death or disc, *vs* younger pts. Quiz safety profile in different Tx phases and age subgroups supports an overall positive benefit/risk.

Table 1.

Figure. Summary of Overall Safety of QuANTUM-First by Treatment Phase and Patient Age

	IND		CONS		CONT		Quiz			Pbo		
	Quiz (n = 265)	Pbo (n = 268)	Quiz (n = 173)	Pbo (n = 175)	Quiz (n = 116)	Pbo (n = 92)	< 60 y (n = 159)	60-64 y (n = 37)	≥65 y (n = 69)	<60 y (n = 160)	60-64 y (n = 43)	≥65 y (n = 65)
Any TEAE	260 (98.1)	261 (97.4)	160 (92.5)	160 (91.4)	109 (94.0)	84 (91.3)	159 (100.0)	37 (100.0)	68 (98.6)	159 (99.4)	42 (97.7)	64 (98.5)
Drug-related	102 (38.5)	77 (28.7)	50 (28.9)	48 (27.4)	85 (73.3)	34 (37.0)	95 (59.7)	26 (70.3)	39 (56.5)	54 (33.8)	16 (37.2)	27 (41.5)
Grade ≥3 TEAE	187 (70.6)	200 (74.6)	120 (69.4)	121 (69.1)	91 (78.4)	53 (57.6)	145 (91.2)	35 (94.6)	64 (92.8)	142 (88.8)	39 (90.7)	59 (90.8)
Drug-related	56 (21.1)	43 (16.0)	34 (19.7)	26 (14.9)	62 (53.4)	16 (17.4)	69 (43.4)	20 (54.1)	29 (42.0)	33 (20.6)	12 (27.9)	20 (30.8)
Serious TEAE	75 (28.3)	66 (24.6)	59 (34.1)	54 (30.9)	39 (33.6)	34 (37.0)	84 (52.8)	19 (51.4)	40 (58.0)	64 (40.0)	17 (39.5)	42 (64.6)
Drug-related	21 (7.9)	14 (5.2)	16 (9.2)	11 (6.3)	8 (6.9)	5 (5.4)	24 (15.1)	7 (18.9)	10 (14.5)	17 (10.6)	5 (11.6)	7 (10.8)
Grade 5 (fatal) TEAE	19 (7.2)	13 (4.9)	8 (4.6)	5 (2.9)	3 (2.6)	7 (7.6)	14 (8.8)	4 (10.8)	12 (17.4)	12 (7.5)	3 (7.0)	11 (16.9)
Drug-related	2 (0.8)	1 (0.4)	2 (1.2)	2 (1.1)	0	0	2 (1.3)	0	2 (2.9)	3 (1.9)	1 (2.3)	0
TEAE leading to discontinuation	26 (9.8)	11 (4.1)	10 (5.8)	5 (2.9)	18 (15.5)	7 (7.6)	26 (16.4)	8 (21.6)	20 (29.0)	11 (6.9)	4 (9.3)	8 (12.3)
Drug-related	7 (2.6)	2 (0.7)	4 (2.3)	2 (1.1)	12 (10.3)	3 (3.3)	12 (7.5)	4 (10.8)	7 (10.1)	4 (2.5)	2 (4.7)	1 (1.5)
TEAE leading to dose interruption	24 (9.1)	30 (11.2)	14 (8.1)	13 (7.4)	65 (56.0)	22 (23.9)	55 (34.6)	9 (24.3)	26 (37.7)	26 (16.3)	8 (18.6)	20 (30.8)
Drug-related	8 (3.0)	14 (5.2)	6 (3.5)	5 (2.9)	46 (39.7)	11 (12.0)	32 (20.1)	7 (18.9)	18 (26.1)	11 (6.9)	4 (9.3)	10 (15.4)
TEAE leading to dose reduction	7 (2.6)	3 (1.1)	4 (2.3)	0	42 (36.2)	14 (15.2)	34 (21.4)	7 (18.9)	9 (13.0)	10 (6.3)	0	7 (10.8)
Drug-related	3 (1.1)	1 (0.4)	2 (1.2)	0	32 (27.6)	8 (8.7)	23 (14.5)	6 (16.2)	6 (8.7)	5 (3.1)	0	4 (6.2)
QTcF prolongation												
>450 ms	61 (23.0)	32 (11.9)	39 (22.5)	13 (7.4)	31 (26.7)	14 (15.2)	55 (34.6)	17 (45.9)	19 (27.5)	21 (13.1)	8 (18.6)	19 (29.2)
>480 ms	10 (3.8)	4 (1.5)	7 (4.0)	3 (1.7)	8 (6.9)	0	11 (6.9)	6 (16.2)	3 (4.3)	1 (0.6)	2 (4.7)	3 (4.6)
>500 ms	2 (0.8)	2 (0.7)	4 (2.3)	0	0	0	1 (0.6)	4 (10.8)	1 (1.4)	0	0	2 (3.1)
Early deaths												
30 days*							6 (3.8)	2 (5.4)	7 (10.1)	3 (1.9)	2 (4.7)	4 (6.2)
60 days*							7 (4.4)	2 (5.4)	11 (15.9)	6 (3.8)	2 (4.7)	5 (7.7)

*Within 30/60 days of treatment.
TEAEs were coded by MedDRA v24.0 and graded for severity by NCI-CTCAE v4.03.
CONS, consolidation; CONT, continuation; IND, induction; MedDRA, Medical Dictionary for Regulatory Activities; ms, milliseconds; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; Pbo, placebo; QTcF, QT interval corrected using Fridericia's formula; Quiz, quizartinib; TEAE, treatment-emergent adverse event; y, years.

DP027

COMBINED EVALUATION OF MRD WITH MOLECULAR (WT1) AND CYTOFLUORIMETRIC ANALYSIS POST-INDUCTION AND PRE-TRANSPLANT IMPROVES PROGNOSTIC STRATIFICATION IN ACUTE MYELOID LEUKEMIA

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Introduction. Nowadays there is no validated combination of different Measurable Residual Disease (MRD) detection techniques useful to improve prognostic stratification in Acute Myeloid Leukemia (AML). In this study, we analyzed the prognostic value of MRD using a combinative approach with quantitative WT1 and cytofluorimetric leukemia-associated immunophenotype (LAIP) at two time points: post-induction and pre-HSCT.

Materials and Methods. We included 74 adult patients (pts) with AML overexpressing WT1 at diagnosis and with a monitorable LAIP. MRD assessment followed ELN recommendations (cut-offs for WT1 of 250/10.000 ABL and 0,1% for LAIP). All pts were intensively treated and had available post-induction and pre-HSCT (for patients undergoing HSCT) MRD assessments with the two markers. The primary endpoint of the study was overall survival (OS).

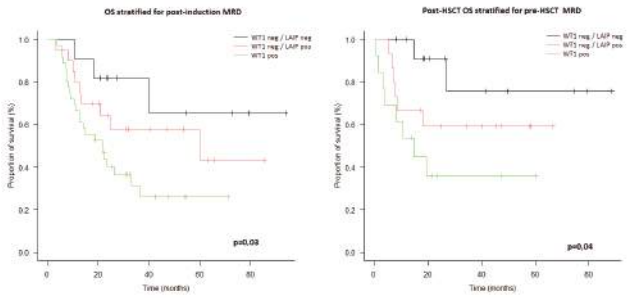

Figure 1.

Results. Median age of pts was 61 (range 19-78). Forty-four (59%) had MRC-AML, 42 (57%) were intermediate-risk and 32 (43%) were high-risk according to ELN 2022. Forty pts (54%) attained complete remission (CR) after induction. Forty-nine (66%) underwent HSCT, of which 35 (71%) in CR. After induction we observed that WT1-MRD positivity per se predicted a worse OS (2-year OS 39% *vs* 70%, p=0.007), while LAIP-MRD did not stratify the prognosis (p=0.2). However, in WT1-MRD negative cases, a LAIP-MRD positivity predicted a worse OS compared to the WT1-MRD and LAIP-MRD negative pts (2-year OS 64% *vs* 81%, p=0.03). LAIP-MRD did not stratify the prognosis in WT1-MRD positive pts. Other factors predicting a worse OS are age ≥ 65 years (p=0.01), AML-MRC diagnosis (p=0.005), high-risk disease (p=0.003). HSCT predicted a better OS only in WT1-MRD positive pts (p=0.016). In HSCT pts we observed that WT1-MRD and LAIP-MRD negative cases had a very good post-HSCT OS (2-year OS 91%) compared to WT1-MRD negative but LAIP-MRD positive pts (2-year OS 59%) and WT1-MRD positive pts (regardless of LAIP-MRD, 2-year OS 36%, p=0.04). Moreover, worse post-HSCT OS was related to the presence of MRC-AML (p=0.0157) and high-risk disease (p=0.01).

Conclusions. Our study included AML pts mainly with an adverse prognosis, in which the combination of two MRD detection techniques allowed us to identify pts with an excellent prognosis. Particularly, WT1-MRD is able to perform an initial stratification that is refined with the LAIP-MRD information. This is even more important in HSCT patients, where it could drive early post-HSCT interventions.

DP028

CPX-351 INDUCES A SIGNIFICANT BETTER RESPONSE IN AML WITH MDS-RELATED GENE MUTATIONS COMPARED TO AML MDS-RELATED CYTOGENETIC ABNORMALITIES AND TP53-MUTATED AML: A SINGLE CENTER EXPERIENCE

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CPX-351 is a liposomal formulation of daunorubicin and cytosine arabinoside approved for the treatment of therapy-related AML (t-AML) or AML with Myelodysplastic-related changes (AML-MRC). Despite the pivotal study showed significant improvements in OS compared to '7+3' conventional chemotherapy, a recent study (UK NCRI AML19 trial) suggests that in patients <60 years of age CPX-351 does not improve results as compared to FLAG-IDA chemotherapy. Specifically, in this study, overall response rates (CR/CRi) were 64% and 76% with CPX-351 and FLAG-IDA, respectively, whilst there were no differences in terms of OS (13.3 *vs* 11.4 months). However, in an exploratory subgroup analysis, a significant improvement in OS was observed with CPX-351 in AML with MDS-related gene mutations (median, 38.4 *vs* 16.3 months). This is a new high-risk entity introduced in ICC/ELN 2022 characterized by the presence of at least one mutation among *SRSF2*, *ASXL1*, *BCOR*, *EZH2*, *STAG2*, *SF3B1*, *U2AF1*, *ZRSR2* and *RUNX1*. Actually, CPX-351 is not specifically indicated in this AML. We therefore studied patients treated at our Center with CPX-351 between September 2019 and March 2024, aiming to evaluate the CR/CRi after induction cycle (1 or 2 cycles) and the rates of allo-HSCT focusing on the new 'AML with MDS-related gene mutations'.

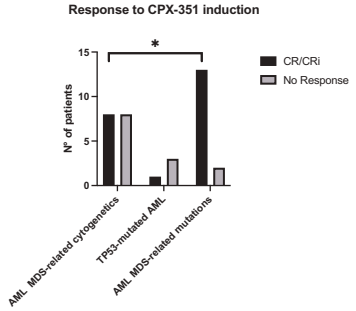

Figure 1.

A total of 35 patients (median age 63 yrs, range 46-74) were treated, of which 15 (43%) had AML with MDS-related gene mutations, 16 (45%) AML with MDS-related cytogenetic abnormalities, and 4 (11%) TP53-mutated AML. Strikingly, all 15 AML with MDS-related gene mutations had dysplastic features on BM smears, suggesting that this morphological criteria still represents a clinical indication to CPX-351. In AML with MDS-related gene mutations we observed higher CR/CRi rates as compared to AML with MDS-

related cytogenetic abnormalities and TP53-mutated AML: 87% *vs* 50% and 25% respectively (p 0.02)(Figure 1). Seven out of 15 patients with AML with MDS-related gene mutations underwent to allo-HSCT, while 3 are presently candidate. Our results show that CPX-351 is highly effective in AML with MDS-related gene mutations ICC 2022 entity allowing high rates of response and allo-HSCT.

DP029

MECOM-REARRANGED AML SHOWS LOW RESPONSE RATES TO HYPOMETHYLATING AGENTS PLUS VENETOCLAX

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Acute myeloid leukemia (AML) with MECOM rearrangement (MECOMr) is recognized as distinct entity in the WHO classification of hematolymphoid tumors. Although MECOMr are detected in 1-3% of AMLs, they confer very poor prognosis with an estimated 2-year overall survival (OS) of 10% in patients treated with chemotherapy. Venetoclax with hypomethylating agents (HMA/VEN) may represent a new therapeutic opportunity for patients with poor response to chemotherapy or those unfit for intensive treatment, including those with MECOMr. However, no data on HMA/VEN is available in patients with MECOMr AML. We retrospectively collected data of 26 MECOMr AML patients from 8 Italian centers treated in first line (FL) or subsequent lines (R/R) with HMA/VEN between 2018 and 2023. The primary endpoint was the composite complete response rate (cCR=CR+CRi). Other data collected included event-free survival (EFS), OS, cytogenetics, DNA sequencing (NGS), number of cycles and major adverse events. Survival was landmarked at HMA/VEN start. Patient characteristics are summarized in Table 1. Ten patients received FL HMA/VEN, while 16 were R/R. Fifteen out of 16 R/R patients had received intensive treatment, including 5 patients who had undergone transplant (HSCT). cCR in the whole cohort was 23%, with a CR rate of 15%. cCR was achieved by 2 out of 10 (20%) FL and 4/16 (25%) R/R patients. Two FL and 3 R/R patients underwent HSCT. With a median follow-up of 15 months, median EFS was 5 months in the whole cohort, with a trend towards longer EFS in FL patients compared to R/R (10.6 *vs* 2.2, p=0.1). Fifteen patients had GATA2::MECOM fusions, 6 patients had other MECOMr and in 5 patients MECOM partner was not established. Outcomes were not different in patients with GATA2::MECOM compared to other MECOMr. NGS was available in 14 patients. The most frequently mutated gene was SF3B1 (9 patients, 56%). SF3B1 mutations had high variant allele frequencies (median 44%) and were enriched in R/R patients (p=0.02), suggesting SF3B1mut may be linked to resistance to intensive treatment. Also, SF3B1mut patients displayed lower overall response to HMA/VEN compared to SF3B1wt (p=0.02). Mutations of the RAS pathway (RASmut) were detected in 6 patients (38%). Consistent with lower efficacy of VEN in AML with RASmut, no patient achieved cCR. Interestingly, all 4 patients with no RAS nor SF3B1 mutation showed response to HMA/VEN. The poor prognosis of MECOMr AML does not seem to be impacted by HMA/VEN.

Table 1.

Characteristic	Whole cohort	First line	Relapsed/Refractory
Number of patients (N)	26	10	16
Age (median, range)	62, 30-78	71, 56-78	59, 30-71
Prior lines of therapy (median, range)	1, 0-5	NA	1, 1-5
HSCT prior to HMA/VEN (N, %)	5, 19%	NA	5, 31%
HSCT after HMA/VEN (N, %)	5, 19%	2, 20%	3, 19%
-7/del7q (N, %)	10, 38%	3, 30%	7, 43%
FLT3-ITD (N, %)	2, 8%	0, 0%	2, 12%
Azole prophylaxis (N, %)	17, 65%	6, 60%	11, 69%

DP030

VENETOCLAX PLUS AZACITIDINE DELAYS DETERIORATION OF HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA: VIALE-A LONG-TERM FOLLOW UP

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Background. AML pts have reduced health-related QoL Even less aggressive treatments may be associated with negative impacts on HRQoL (high transfusion needs-hospitalization). HRQoL measurements are important when evaluating the LT benefits of AML treatments.

Aims. To characterize HRQoL, particularly delay in deterioration, of AML pts receiving VEN+AZA or PBO+AZA in the LTFU of VIALE-A trial.

Methods. TN adults IC ineligible were randomized 2:1 to receive VEN+AZA or PBO+AZA. PROs included: EORTC QLQ-C30 global health status (GHS/QoL), PF/EF subscales; PROMIS Cancer Fatigue Short Form 7a;EQ-5D-5L VAS. PRO were collected on D1 of each cycle. Time to deterioration (TTD) was calculated as number of days from BL to first documented worsening of ≥1 pre-established PRO-specific meaningful clinical threshold (MCT). Pre-established MCTs for deterioration were a reduction of ≥10 for GHS/QoL, PFEF, of 7 for EQ-5D-VAS or an increase of 5 for fatigue. Association between patient characteristics and PROs was assessed, and the within-group level of change in each score was expressed as a standardized effect size (SES) and magnitude of responsiveness (SES=0-0.19 none; 0.20-0.49 small; 0.50-0.79 moderate; ≥0.8 large).

Results. VIALE-A included 431 pts, age 76 years, mLTFU of 43.2 mo. LTFU analysis identified extended TTD for all PROs for pts treated with VEN+AZA and significantly longer for VEN+AZA *vs* PBO+AZA for EF, PF, and EQ-5D-VAS (Table 1). Pts treated with VEN+AZA had longer TTD across most PROs in key subgroups (age <75 years, ECOG >2, CR or CR+CRi, MRDneg and post-baseline

TI. Several clinical factors were associated with PRO improvement. For PF subscale, pts in CR, CR/CRi, TI, and/or had an ECOG >2, had overall moderate SES(0.5–0.79), tending to increase from C3 to C33. Similar trends for EF, GHS, and fatigue in pts in those same subgroups, while pts not in CR,CR/CRi, TI, or with ECOG <2 tended to have no or small magnitude in SES (0-0.49)indicating small to no PRO improvements. Among those in CR/CRi, those with also MRD neg tended to moderate to large SES across PROs, while small to no improvement was observed in those without MRD neg. Pts in CR/CRi at C2 achieved HRQoL improvement earlier.

Conclusion. The longer preservation of PROs as PF, EF, fatigue and a longer TTD observed with VEN+AZA *vs* PBO+AZA suggests VEN positively impacts HRQoL of pts. Based on SES analysis, achieving remission and MRDneg, ECOG>2, or TI might be associated with improved PF, EF and fatigue.

Table 1.

Table/Figure:

Table 1. Median Time to Deterioration in Months in Overall Health/QoL, Physical and Emotional Function, and Fatigue

PRO Measure, median (95% CI)	VEN+AZA (n=286)	PBO+AZA (n=145)
EORTC QLQ-C30 GHS/QoL	19.1 (10.19, 27.55)	9.3 (4.67, NE)
EORTC QLC-C30 PF	10.2 (7.30, 16.01)*	6.2 (4.67, 9.47)
EORTC QLC-C30 EF	27.3 (18.71, 33.90)*	15.7 (7.86, 24.89)
PROMIS Fatigue	9.5 (7.30, 19.04)	8.6 (4.18, 15.19)
EQ-5D-5L VAS	10.7 (7.53, 19.04)**	3.9 (2.37, 7.40)
PRO Measure by subgroups, median		
Age <75 years		
EORTC QLQ-C30 GHS/QoL	21.3*	4.7
EORTC QLC-C30 PF	16.0	9.5
EORTC QLC-C30 EF	NE*	18.2
PROMIS Fatigue	19.2*	6.2
EQ-5D-5L VAS	13.4*	3.8
ECOG >2		
EORTC QLQ-C30 GHS/QoL	21.3	7.9
EORTC QLC-C30 PF	12.3*	6.1
EORTC QLC-C30 EF	NE*	11.5
PROMIS Fatigue	12.0	8.6
EQ-5D-5L VAS	12.5*	3.7
CR+CRi		
EORTC QLQ-C30 GHS/QoL	21.3	16.6
EORTC QLC-C30 PF	12.0	18.4
EORTC QLC-C30 EF	27.3	15.7
PROMIS Fatigue	9.9	15.2
EQ-5D-5L VAS	13.1	7.4
Transfusion Independence -RBC		
EORTC QLQ-C30 GHS/QoL	21.6	16.6
EORTC QLC-C30 PF	15.7	14.1
EORTC QLC-C30 EF	31.4	19.4
PROMIS Fatigue	12.0	11.2
EQ-5D-5L VAS	13.1*	6.8
Transfusion Independence -platelet		
EORTC QLQ-C30 GHS/QoL	21.3	11.0
EORTC QLC-C30 PF	15.7	14.1
EORTC QLC-C30 EF	30.6*	19.7
PROMIS Fatigue	10.7	9.2
EQ-5D-5L VAS	12.5*	6.2
MRD Negative		
EORTC QLQ-C30 GHS/QoL	NE	NE
EORTC QLC-C30 PF	14.7	12.8
EORTC QLC-C30 EF	41.5*	9.7
PROMIS Fatigue	12.9	3.7
EQ-5D-5L VAS	13.4*	6.2

*P<0.01. **P<0.001.

AZA, azacitidine; CI, confidence interval; CR+CRi, complete response with incomplete blood cell recovery; EF, emotional functioning; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; EQ-5D-5L, EuroQol 5-Dimension 5-Level; GHS, global health status; MRD, measurable residual disease; NE, not estimable; PBO, placebo; PF, physical functioning; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, quality of life; VAS, visual analog scale; VEN, venetoclax.

DP031

ABSTRACT NOT PUBLISHABLE

DP032

THE IMPACT OF BASELINE GENETIC PROFILE AND TREATMENT ON PROGNOSIS AND HEMATOLOGICAL TOXICITY IN CEBPA-MUTATED ACUTE MYELOID LEUKEMIA

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Background. CEBPA-mut acute myeloid leukemia (AML) is a separate entity in WHO/ICC classifications, with favorable outcome correlated with bZIP mutations and enrichment in mutations (ie, GATA2, CSF3R, WT1) rarely observed in CEBPA-wt, without conclusive findings for their prognostic value. Although correlating with favorable prognosis, high incidence of treatment-related mortality in CR (around 10%) has been reported in two large studies (Schlenk Blood 2013; Pastore J Hematol Oncol 2014).

Aims. To correlate baseline and treatment characteristics with outcome and hematological toxicity in an intensively treated cohort of CEBPA-mut AML pts.

Methods. Study pts had CEBPA-bZIP AML and were characterized by NGS with Ion Torrent covering 40-genes panel. The first two chemotherapy cycles were categorized according to the delivery of an anthracycline (ANTHRAC) and high dose cytarabine (HDAC).

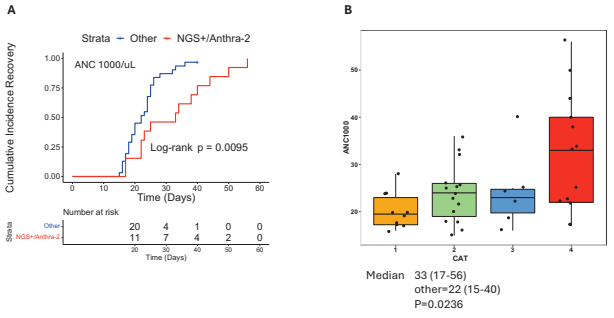

Figure 1.

Results. From 2004 to 2023, 49 CEBPA-mut AML pts met inclusion criteria at study sites. CR rate was achieved in 45 of 49 pts (91.8%). Based on NGS, at least one additional mutation was identified in 18 (36.7%) pts (NGS+), the majority involving GATA2 (n=14, 28.6%). Forty-four pts received at least two cycles, of which no (n=2, 4.6%), one (n=14, 31.8%), or two (n=28, 63.6%) ANTHRAC-containing. A longer DFS was observed in NGSwt pts (HR=4.56; P=0.042), whereas OS did not differ (P=0.43). Then we focused on hematopoietic recovery after consolidation. NGS+ pts showed slower neutrophil (ANC) recovery (median, 25 days to >500/uL after consolidation) compared to NGS- group (19 days, P=0.018). Such effect was enhanced by treatment with ANTHRAC: NGS+ pts receiving two such cycles required significantly longer

time to recover from first consolidation, both for ANC (30 days, Figure 1) and platelet count (34 days) *vs* 22 (P=0.012) and 27 (P=.010) days, respectively, of other categories. A proportion of 46.1% (6/13) NGS+/ANTHRAC-2 pts could not complete the planned treatment program due to persistent cytopenias compared to 18.7% (6/32, P=0.075) in other categories. No significant prolongation of recovery was observed for HDAC.

Conclusions. CEBPA-mut AML is featured by delayed hematopoietic recovery in pts bearing additional mutations (especially GATA2) when treated with anthracyclines in first two cycles. Our findings suggest the cumulative dosage of anthracyclines should be limited in CEBPA-mutated/NGS+ pts to spare hematological toxicity on turn impairing the therapeutic plan.

DP033

SEX-ASSOCIATED DIFFERENCES AND PROGNOSTIC IMPLICATIONS OF GENETIC ALTERATIONS IN ADULTS WITH ACUTE MYELOID LEUKEMIA ENROLLED IN THE GIMEMA AML1310 TRIAL

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Aims. In AML genetic alterations provide prognostic information with clinical relevance through choice of treatment, but little attention at sex-associated differences has been directed. The AML1310 GIMEMA trial for adults with *de novo* AML consisted of the prognostic integration of pretreatment cytogenetics and mutations with postconsolidation MRD . The objective of this study is to carry out a comprehensive analysis of sex differences in this trial and to investigate the impact of sex on outcome.

Materials and Methods. Mutational profiling, cytogenetic and outcome analysis by sex in 500 adults with AML (male 52% female 48%) treated in the AML1310 trial. Patients received postconsolidation AuSCT or AlloSCT depending on their risk profile. Four categories of risk were identified according the NCCN 2009: favorable or poor-risk , submitted to AuSCT or AlloSCT, respectively; intermediate (IR)-MRD neg or pos , who received AuSCT or AlloSCT, respectively.

Results. Analysis by sex of demographic and baseline characteristics showed comparable results, except for lower Hb values in females (p 0.023). Compared with men, females had the same incidence of FLT3-ITD, NPM1, CBFb/MYH11 and RUNX1T1 mutations, concomitant mutations of NPM1 and FLT3-ITD or CBFb/MYH11 with NPM1mut or FLT3ITD. No differences in Cytogenetic or Risk Categories, MRD (in IR) stratification and final treatment were also observed. Analysis of efficacy by sex showed no differences in CR rate, death or cause of off-study. Interestingly, prognostic effect had a dependence on sex and NMP1mut. Compared with men, better 6 years OS was observed in females with NPM1mut (52.4% *vs* 33.8% p.0.032) or MRD positivity (66.5% *vs* 45% p 0.015) respectively. Females NPM1mut had a better DFS at 6 years (47% *vs* 35%, p 0.085). Better DFS was observed in males 18-40 years older (67.3% *vs* 41,4% P 0.030) and in females aged 40-50 years (56.4% *vs* 36.0% p 0.0148). Cumulative Incidence of Relapse (CIR) was 42% at 6 years with higher CIR in males *vs* females (54% *vs* 35% p 0.028). Six years OS by final treatment received was statistically different (AlloSCT 50.6 *vs* AutoSCT 67.4 p=0.007). OS by type of graft (AutoSCT) resulted in better outcome for female (76% *vs* 60% p0.032), no significant differences for AlloSCT in OS or DFS by sex were observed.

Conclusions. Our results show that sex differences in AML-associated mutations are likely to have clinical relevance for risk grouping, prognostication and choice of therapy.

DP034

LONG-TERM OUTCOMES OF STEM CELL TRANSPLANT IN OLDER PATIENTS WITH ACUTE MYELOID LEUKEMIA TREATED WITH VENETOCLAX PLUS HMA THERAPIES

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Background. Allogeneic SCT remains the most effective curative treatment for pts with intermediate/ poor-risk AML; however, pts who are IC ineligible due to age or comorbidities have typically not been viable candidates. Venetoclax (Ven+ hypomethylating agents (HMAs) leads to rapid and durable remissions in pts with ND AML who are IC ineligible.

Aims. To evaluate the LT clinical outcomes of SCT after Ven+HMA treatment in the aforementioned population.

Methods. Pts with ND AML IC ineligible who received Ven+HMA and proceeded to SCT on the P1b trialof Ven+ decitabine (Dec) or azacitidine (Aza) and the P3 VIALE-A trial of placebo + Aza *vs* Ven+Aza were included. Pts in the P1b trial received Ven daily (400,800,or1200 mg) with 20 mg/m^2 IV Dec on days 1-5 or 75 mg/m^2 SC or IV Aza on days 1-7/28-day cycles. Pts in VIALE-A received Ven daily (400 mg) with 75 mg/m^2 SC or IV Aza on days 1-7/28-day cycles. Pts were evaluated for efficacy outcomes before and after SCT that included best response (CR or CRi or CRh, MLFS), time to best response, MRD negativity before SCT, 2-year post-SCT remission and 2-year post-SCT OS.

Results. 33 pts were included (31 from theP1b trial and 2 from VIALE-A). Pts had a median age of 69 yrs, 70% had *de novo* AML, and 60% had adverse risk disease based on ELN 2022 (Table). Mutations were observed at baseline: FLT3 in 5/20 pts (25%), NPM1 in 5/18 pts (28%), IDH1/2 in 7/20 pts (35%), TP53 in 2/18 pts (11%). The median time on Ven before SCT was 4.18 mo (range, 0.9-31.8), and the median time from last dose to SCT was 1.22 mo (range, 0.4-10.3). Before SCT, 27 pts (82%) achieved a best response of CR/CRi, 3 achieved MLFS, and 3 had resistant disease. Median time to CR/CRi was 1.9 mo (range, 0.8-7.1), and 9pts (27%) had an MRD

response of <10-3. Median OS after SCT was 29.9 mo (95% CI, 15.8-NR), with a 69% 12-mo post-SCT OS rate. In pts who had MRD responses before SCT, the 12-mo post-SCT OS rate was 76%. In 18 pts with adverse ELN risk, mOS was 15.8 mo (95% CI, 4.5-29.9), and the 12-mo post-SCT survival rate was 56%. Of the 2 TP53 mutated pts, 1 died within 12 mo of SCT, and 1 was alive 24 mo following SCT.

Conclusions. Ven + Aza/Dec can lead to rapid and deep responses in pts with ND AML who were IC ineligible. Most pts were alive ≥12 mo after SCT, including approximately half of those with adverse ELN risk disease. These results suggest that Ven+HMA can enable receiving curative SCT and long term disease free state in IC ineligible pts.

Table 1.

Table: Demographics and disease characteristics for patients who received Ven+HMA therapies and proceeded to SCT

Characteristic	N=33
Treatment regimen, n (%)	
Ven+Aza	21 (64)
Ven+Dec	12 (36)
Median age (range), y	69 (63-76)
Bone marrow blasts ≥50%,[a] n (%)	12 (36)
AML type, n (%)	
De novo	23 (70)
Secondary	10 (30)
ECOG performance score	
0	12 (36)
1	10 (30)
2	11 (33)
ELN 2022 category,[b] n/N (%)	
Intermediate	7/30 (23)
Adverse	18/30 (60)
Baseline mutations, n/N (%)	
TP53	2/18 (11)
FLT3 (ITD or TKD)	5/20 (25)
NPM1	5/18 (28)
IDH1/2	7/20 (35)
Best response before transplant, n (%)	
CR	15 (45)
CRi	12 (36)
CRh	9 (27)
MLFS	3 (9)
MRD status, n (%)	
MRD response (<10^{-3})	9 (27)
MRD positive (≥10^{-3})	16 (48)
MRD not evaluable	8 (24)

[a]At the time of study enrollment. [b]ELN classification based on 2022 ELN guidelines.
CR, complete response; CRi/CRh, CR with incomplete blood count or partial hematologic recovery; ECOG, Eastern Cooperative Oncology Group; HMA, hypomethylating agent; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; SCT, stem cell transplant; Ven, venetoclax.

Myeloma and monoclonal gammopathies

DP035

A MULTICENTER OBSERVATIONAL RETROSPECTIVE STUDY OF SECOND-LINE TREATMENT WITH DARATUMUMAB-BORTEZOMIB - DEXAMETHASONE (DARAVD) IN MULTIPLE MYELOMA (MM) PATIENTS REFRACTORY TO LENALIDOMIDE

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Up-front use of lenalidomide (len) as maintenance therapy after ASCT or as continuous treatment in combination with other agents has become the gold standard for newly diagnosed MM patients (pts). The management of len-refractory (ref) pts at first relapse is challenging and requires careful evaluation of available treatment options. Daratumumab(Dara)-bortezomib(B)-dexamethasone (DaraVd) has been approved for RRMM after at least one prior line of therapy but few data were provided in pts ref to upfront len. We run a retrospective study to assess the outcomes of len-ref pts treated with DaraVd at first relapse in 9 Italian centers. The baseline characteristics of 79 analyzed pts were representative of a general MM population, but median age (57 years) was lower. Pts with high-risk (HR) cytogenetics (t(4;14) and/or t(14;16) and/or del17) were 16 (27%) at diagnosis, and 7 (29%) at relapse (data available in 24 pts only). Toxicity-related B dose-reduction occurred in 39 pts (49.4%); 27 (44%) pts delayed a median of 1 dose of Dara (range 1-5), mostly for infections. At least one grade ≥2 adverse event (AE) occurred in 67 (85%) pts. 73 pts started with IV Dara, 6 with SC, with 14% of infusion related reactions (IRR) (grade 1-2). Most common AEs were hematological (72%), infections (30%, 8% grade 3, 1% grade 5), pneumonia (14%) and asthenia (38%). Peripheral neuropathy rate was 58% (46 pts), 8% of grade 3. Three pts discontinued for toxicity. Overall response rate (ORR) was 86% (61% ≥VGPR). With a median follow-up of 25 months (mos), median PFS and OS were 15 and 47 mos, respectively. The dose and duration of previous len exposure did not influence PFS, which was favorably affected by the absence of amp1q (p=0.04), BM plasma cells <60% (p=0.003), absence of extramedullary disease (p=0.009) and a best response ≥VGPR (p<0.001) or ≥CR (p=0.012). In a multivariate model, a response ≥VGPR was confirmed to be independently associated to PFS (HR=0.08, p<0.001, 95% CI 0.018-0.359), with a median of 26 *vs* 7 mos. In len-ref pts, second line DaraVd was manageable and safe. PFS was shorter than in the general population (27 mos), except for pts with ≥VGPR, but two-fold longer than previously reported in the

CASTOR study (7.8 mos), regardless the number of prior lines of therapy. Overall, DaraVd remains an alternative option for len-ref pts at first relapse, especially for those ineligibles to receive pomalidomide-or carflizomib-based regimens.

DP036

ABSTRACT NOT PUBLISHABLE

DP037

CLONAL PLASMA-CELLS IN STEM CELL APHERESIS AS A PREDICTOR OF PROGRESSION IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS ELEGIBLE FOR AUTOLOGOUS STEM CELL TRANSPLANTATION

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Background. Bone marrow minimal residual disease (MRD) in patients with multiple myeloma (MM) has a well-established prognostic role in terms of PFS and OS. One of the main methods used to analyse MRD is multiparametric flow cytometry (MFC). Nowadays, there are also emerging data about the prognostic role of circulating plasma cells in peripheral blood samples. Conversely, far limited information is available on the use of MFC for the research of clonal plasma cells on stem cell apheresis as well as its clinical significance.

Methods. We conducted a prospective analysis of 100 patients with newly diagnosed MM, eligible for autologous stem cell transplant (ASCT), diagnosed and treated at AOU Careggi Hospital between July 2017 and November 2021. We analysed apheresis samples of stem cells using MFC with a sensitivity of 10^{-5}, in order to identify contamination of graft with clonal plasma cells (CPs). In addition, bone marrow samples after induction phase (prior to stem cell apheresis) and three months after ASCT were collected and evaluated with the same technique.

Results. The median age of the patients was 59 years, all received treatment with bortezomib-based triplet induction regimens (VTD 96%, PAD 4%). Stem cell mobilization was carried out using cyclophosphamide and G-CSF in 89 patients, while in 11 patients stem cells were collected only after G-CSF stimulation. Flow cytometric analysis of the stem cell apheresis revealed the presence of CPs in 21 cases (aMRD+). Concurrently, bone marrow MRD after induction was positive in 62% (bmMRD+) and negative in 38% of patients (bmMRD-). All 21 patients with positive aMRD also exhibited concurrent bmMRD positivity (p<0.001). Among our cohort, 7 patients did not undergo ASCT eventually, while 13 received a second-line treatment due to progression before ASCT. Among the remaining cohort of 80 patients, the median follow-up was 52 months (range 18-81 months), and the median PFS was 38 months in the aMRD+ group compared to not reached in aMRD- patients (p=0.025). Additionally, we observed a significant correlation between graft contamination (aMRD+) and lower bmMRD negativity after ASCT (p=0,03). Patients with aMRD+, were also associated to a reduced OS: median OS 60 months *vs* not reached (p=0,003).

Conclusions. Our data indicate a potential negative impact of clonal plasma cells in apheresis product, in terms of reduced post-transplant bone marrow MRD negativity, as well as lower PFS and OS.

DP038

MAINTENANCE THERAPY WITH LENALIDOMIDE FOR PATIENTS WITH MULTIPLE MYELOMA AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION: THE REAL-LIFE EXPERIENCE OF THE "RETE EMATOLOGICA PUGLIESE" (REP)

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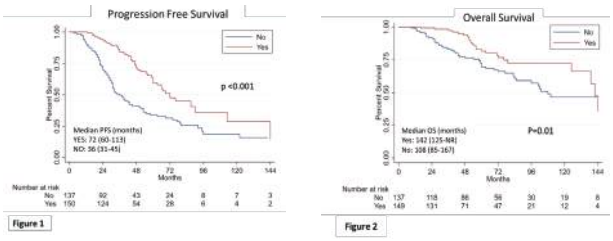
Lenalidomide maintenance (LM) therapy is still considered the current standard of treatment after ASCT in patients with multiple myeloma (MM). However, real-life evidence of the advantage of LM after ASCT, in terms of progression-free survival (PFS) and overall survival (OS) is quite limited. Thus, we investigated the role of LM evaluating 257 MM patients not included in clinical trials who underwent ASCT between 2001 and 2020 and treated within the "Rete Ematologica Pugliese" (REP). One-hundred-seven patients received LM (LM cohort) after ASCT (10 mg/d for 21-28 days, every 4 weeks), for a median time of 19.5 months (range 1-118 months), while 150 patients did not (non-LM cohort). Age, gender, M-component isotype, comorbidities, ISS stage (R-ISS when available), renal function, serum calcium, hemoglobin levels, cytogenetics, induction treatments (all including bortezomib based regimens, such as VTD, VCD or PAD), conditioning regimens and number of ASCT (1 *vs* 2), were comparable between the two groups. According to the IMWG criteria, the overall response rate (ORR) after ASCT was 98% in both groups and no difference emerged, in terms of quality of response, between LM group (CR+sCR 47%; ≥VGPR 90%; PR 8%) and non-LM group (CR + sCR 45%; ≥VGPR 89%; PR 9%) (p: NS). With a median follow-up of 47 months (range:13-144) in LM group and 67 months (range: 9-167) in non-LM group, median PFS was significantly longer in the LM cohort (72 *vs* 36 months; P<0.001) (Figure 1). Similarly, median OS was significantly better in patients receiving LM (142 *vs* 108 months; p=0.01) (Figure 2). ISS stage, induction treatments and number of ASCT did not influence neither PFS, nor OS. Main adverse events observed in LM-group were leucopenia, skin rashes and diarrhea; they were generally well managed by dose adjustment of lenalidomide and caused the interruption of maintenance in a minority of patients. Three secondary primary malignancies (SPM) occurred in the LM-group (one acute myeloid leukemia, one colon carcinoma and one bladder carcinoma). In summary, in our retrospective study LM was well tolerated, doubled PFS and significantly improved OS, validating its positive impact in a real-world setting of MM patients who underwent ASCT in the era of novel agents. However, based on recent evidences, new strategies (i.e. daratumumab +/- lenalidomide, carfilzomib plus lenalidomide, or CELLMoDs) will probably change soon the current scenario of maintenance therapy in MM.



Figures 1 and 2.

DP039

IMPACT OF DARATUMUMAB ON HEMATOPOIETIC STEM CELL MOBILIZATION WITH G-CSF AND ON-DEMAND PLERIXAFOR IN NEWLY-DIAGNOSED MULTIPLE MYELOMA PATIENTS

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Introduction. Autologous stem cell transplantation (ASCT) is a SOC in transplant eligible, newly diagnosed Multiple Myeloma (NDMM) patients (pts). Pts treated with upfront daratumumab who underwent chemotherapy-based hematopoietic stem-cell (HSC) mobilization had lower HSC yield and higher rates of plerixafor (PLX) use, compared to daratumumab-naïve pts. We report the results of a multicentre, observational study to evaluate HSC collection and engraftment with G-CSF+on-demand PLX in pts treated with VTd or VTd+daratumumab (DVTd).

Methods. NDMM pts undergoing a 1st HSC mobilization attempt with G-CSF (10 mcg/kg/day) were enrolled. PLX was administered in pts with <20 CD34+ cells/μL after ≥4 days of G-CSF or in case of $<1\times10^6$ CD34+cells/kg collected on the 1st apheresis day. The primary endpoint of the study was the rate of poor mobilizing pts defined as $\leq2x10^6$ CD34+ cells/Kg collected or need for PLX to reach adequate yield.

Table 1.

Variables		Overall (n=217)	DVTd (n=83)	VTd (n=134)	p-value
CD34+/L Day 4 of count	Median (IQR)	21 (11-33)	18 (7-26.5)	24 (14-42)	<0.001
	<20	90 (41.5)	46 (55.4)	44 (32.8)	0.08
	≥20	107 (49.3)	34 (41)	73 (54.5)	
	Missing	20	3	17	
CD34+/L increase after first PLX administration	Median (IQR)	50.5 (33.8-66.3)	45 (29.5-62)	55 (38-70)	0.48
WBC Day 4 of count	Median (IQR)	36000 (28400-46300)	39300 (27100-46000)	34900 (29200-46300)	0.72
	Missing	21	3	18	
Plerixafor administration	No, n (%)	135 (62)	36 (43)	99 (74)	**0.006**
	Yes, n (%)	82 (38)	47 (57)	35 (26)	
Reason for Plerixafor administration	<1x10⁶ CD34+/Kg after first apheresis	6 (2.8)	3 (3.6)	3 (2.2)	1
	<20 CD34+/l	74 (34.1)	43 (51.8)	31 (23.1)	
	Missing	2	1	1	
CD34+ x10⁶ cells/Kg	Median	7.52 (6.10-9.37)	7.04 (5.76-8.85)	7.84 (6.30-10.1)	0.08
	Suboptimal	12 (5.5)	4 (5)	8 (6)	0.7
	Optimal	196 (90.3)	73 (88)	123 (92)	0.4
Successful mobilization	No, n (%)	10 (5.1)	6 (7)	4 (3)	0.58
	Yes, n (%)	206 (94.9)	77 (92.8)	129 (96.3)	
Poor mobilization patients	No, n (%)	124 (57)	30 (36)	94 (70)	**0.002**
	Yes, n (%)	93 (43)	53 (64)	40 (30)	
Apheresis days, median	1	101 (46.5)	32 (38.6)	69 (51.5)	0.58
	2	100 (46.1)	42 (50.6)	58 (43.3)	
	3	5 (2.3)	3 (3.6)	2 (1.5)	

Results. 217 NDMM pts, (DVTd n=83, VTd n=134) were enrolled, with a median of 4 induction cycles in both groups. The rate of poor mobilizing patients was 64% (53/83) for DVTd and 30% (40/134) for VTd (p=0.002), due to a higher PLX use in the DVTd group (57% *vs* 26%; p=0.006). No significant differences in the rate of pts who failed to collect $\geq2x10^6$ CD34+cells/kg (7% *vs* 3%; p=0.6). The median number of CD34+/Kg collected was similar: DVTd (7.04); VTd (7.84; p=0.1). No difference in the rate of pts who collected 2-4 (5% *vs* 6%; p=0.7) and ≥4 CD34+ cells/Kg (88% *vs* 92%; p=0.4) was observed (DVTd *vs* VTd). The median number of CD34+/L on the first day of count was 18 for DVTd *vs* 24 for VTd (p=<0.002). The median increase of CD34+/L after the 1st PLX dose was 45 CD34+/μL (DVTd) and 55 CD34+/μL (VTd) (p=0.4). No differences were observed in the median number of apheresis (DVTd=2 *vs* VTd=1; p=0.6). Among pts who received post-transplant G-CSF starting at day +3 to 5 (DVTd, 51; VTd, 57), the median number of CD34+/kg re-infused was 3.60 and 3.28, respectively (p=0.4). The median time to recovery was 12 *vs* 13 days (p=0.02) for neutrophils and 13 *vs* 15 days for platelets (p=0.1).

Conclusion. GCSF+on-demand PLX is an effective HSC mobilization strategy due to low rates of mobilization failures irrespective of the use of daratumumab, which did not impact HSC collection or engraftment. Our results, along with the lack of chemotherapy-associated toxicity, support the use of G-CSF and on-demand PLX for HSC mobilization in pts receiving daratumumab upfront.

DP040

IMMUNOSUPPRESSIVE TREATMENTS DO NOT INFLUENCE PROGRESSION OF MGUS IN PATIENTS WITH CONCOMITANT AUTOIMMUNE DISORDERS: PRELIMINARY DATA FROM A RETROSPECTIVE, SINGLE-CENTER STUDY

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Monoclonal gammopathy of undetermined significance (MGUS) is a "premalignant" condition occurring in approximately 3-5% of persons 50-70 year-old, respectively. MGUS does not require any treatment and is defined by the presence of a serum monoclonal protein (M-protein) at a concentration of less than 3/dL, bone marrow clonal plasma cells less than 10% and absence of CRAB/SLIM "myeloma-defining" criteria. Interestingly, MGUS is often reported coexistent to autoimmune disorders (rheumatologic, inflammatory bowel disease, neurologic, skin and others), where "biologic", specific immunosuppressive therapies are frequently required. In this setting, however, limited data are available concerning a possible impact of these drugs on MGUS progression while, in our clinical practice, hematologists are instead frequently asked to answer to this question. Therefore, we retrospectively evaluated the trend of M-protein in 23 MGUS patients followed at our institution and, at the same time, under treatment for autoimmune disorders. Only patients with measurable M-protein and non-IgM isotype were included in the analysis; their clinical characteristics are summarized in Table 1. The median age was 65 years (range: 29-83), with a female predominance (69.6%). Regarding MGUS risk-stratification according to Mayo Clinic model, all patients scored as low or low/intermediate risk, while IgG kappa was the most frequent isotype (52.2%). Regarding concomitant autoimmune diseases, 19 patients (82.6%) were affected by rheumatologic disorders, 2 (8.7%) by inflammatory bowel diseases, 2 (8.7%) by neurologic diseases. Specific treatments for these disorders included immunosuppressive drugs and biological agents, sometimes associated. With a median time of observation of approximately 49 months (range: 4-174), no significant difference (p=0.51, Mann–Whitney test) was reported in M-protein concentration and

no patient developed multiple myeloma. Likewise, no decrease in M-component was observed, independently upon the efficacy of the treatment, thus suggesting no relationship between MGUS and underlying autoimmune disorders. These data are apparently reassuring, as they would not support a link between MGUS progression and treatments necessary for contemporary autoimmune diseases. Studies on a larger number of patients with extended follow-up are ongoing to achieve greater generalizability of our preliminary findings: updated results will be presented at the meeting.

Table 1.

Table 1. Clinical and laboratory characteristics of patients with MGUS and autoimmune diseases

Median age, years (range)	65 (29-83)
Gender, n. (%)	
Female	16 (69.6)
Male	7 (30.4)
M-protein isotype, n. (%)	
IgG kappa	12 (52.2)
IgG lambda	5 (21.7)
IgG kappa + IgG lambda	3 (13)
IgA lambda	2 (8.7)
IgA lambda + IgGk	1 (4.4)
MGUS risk*, n. (%)	
0 Low	20 (87)
1 Low-intermediate	3 (13)
Autoimmune disease	
Rheumatologic, n. (%)	**19 (82.6)**
Rheumatoid Arthritis	5
Psoriasic Arthritis	11
Lupus Erithematosus Sistemic	2
Pleuropericarditis	1
Inflammatory bowel disease, n. (%)	**2 (8.7)**
M. di Chron	1
Inflammatory bowel disease	1
Neurologic, n. (%)	**2 (8.7)**
Multiple Sclerosis	2
Current autoimmune disease regimen, n. patients	
Contains immunosuppressive drugs	
Methotrexate	12
Hydroxychloroquine	3
Leflunomide	3
Salazopyrine	5
Colchicine	1
Ciclosporin	3
Contains biological drugs	
anti-CD20 (rituximab, ocrelizumab)	3
anti-TNF (adalimumab, etanercept, certolizumab, infliximab, belimumab)	7
anti-IL (tocilizumab, anakinra, ustekinumab)	4
Median duration of follow-up, months (range)	49 (4-174)
Variations in the M-protein level, between the beginning and the end of the follow-up p-Value (Mann–Whitney test)	0.51 (N.S.)

DP041

BELANTAMAB MAFODOTIN IN RELAPSED-REFRACTORY MULTIPLE MYELOMA PATIENTS: EFFICACY DATA AND OCULAR TOXICITY IN A REAL-LIFE SINGLE CENTER EXPERIENCE

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Introduction. Belantamab mafodotin is an antibody-drug-conjugate (ACD) targeting B-cell maturation antigen (BCMA) that had been temporarily approved for the treatment of relapsed-refractory multiple myeloma in patients who had previously received at least four lines of therapy. Here we present efficacy data and adverse events, focusing on ocular toxicities, in a single center experience.

Methods. 45 patients were treated with Belantamab mafodotin from May 2020 to March 2024, at the starting dose of 2,5 mg/kg Q3W. Response rates, progression free survival (PFS), overall survival (OS) and safety were analyzed.

Results. Patients' characteristics are listed in Table 1. 22 of them (49%) had high risk cytogenetics, 20 (44%) had an ISS stage of 3 and the median number of prior therapies was 4 (3-8). After a median follow up of 16,7 months (mo), response rates were: MR 31% (14/45), PR 11% (5/45), VGPR 13% (6/45) and CR 16% (7/45), with an ORR of 38% (17/45). Median PFS was 3,7 mo (1-year PFS: 27%); median OS was 14,4 mo (1-year OS: 59%). In patients with ≥ PR, median PFS was 28 mo (1-year PFS: 61%) and median OS was NR (1-year OS: 87%). Overall ocular toxicities (any grade) were observed in 31/45 (72%) patients, of whom grade ≥3 in 10/45 (22%), and were managed by reducing dose in 28/45 patients (62%). With the intent to maintain these patients on Belantamab therapy, subsequent infusions have been planned every 6 to 8 weeks in 17/45 patients (38%) with better tolerability and management of the toxicity. Median PFS of this subgroup was NR (18mo-PFS 65%).

Conclusion. We confirm efficacy and safety of Belantamab mafodotin in our real-life experience. A delayed schedule (6-8 weeks) allowed a good balance between disease control and reduced severe ocular toxicities, preventing the discontinuation of treatment.

Table 1.

PATIENTS' CHARACTERISTICS (N=45)	
ISS stage 3, n (%)	20 (44%)
High Risk cytogenetics, n (%)	22 (49%)
Extramedullary disease, n (%)	11 (24%)
Nr of prior therapies, median (range)	4 (4-8)
Prior ASCT, n (%)	39 (87%)

DP042

MAPPING IMMUNE SYSTEM DYSFUNCTION AND GUT MICROBIOTA COMPOSITION THROUGHOUT THE EVOLUTION OF MULTIPLE MYELOMA FROM PREMALIGNANT CONDITIONS

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Multiple myeloma (MM) is a relentless hematologic cancer characterized by abnormal plasma cell growth in the bone marrow (BM), typically following monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM). Despite the rare transition from MGUS to active MM (5-10% of cases), predicting this shift remains challenging. Mounting evidence highlights the pivotal role of the immune microenvironment in MM progression, underscoring the need to understand immune alterations for targeted therapies. This study explored immune landscape changes and fecal microbiota fluctuations during the MGUS-to-MM transition. Immune composition, including myeloid/lymphoid T/B/NK subpopulations and immune checkpoint distribution, was comprehensively assessed in BM and peripheral blood. Samples from 13 MGUS, 12 SMM, and 63 newly diagnosed MM patients were analyzed using six 10-color and two 8-color flow cytometry panels. Additionally,

cytokine/chemokine abundance in BM and peripheral blood was evaluated using a 48-plex Luminex plate on 72 samples from the same patients, alongside samples from 4 healthy donors. Fecal microbiome profiling was performed on samples from 3 MGUS, 6 SMM, and 9 MM patients to explore potential relationships between bacterial composition and MM evolution. Unsupervised analysis of T cells using FlowCT revealed significant immune cell population shifts. Circulating TEMRA CD8 T cells, particularly CD57+ cells, substantially increased in SMM and MM. Conversely, naïve TIGIT+ and TIGIT+ TIM3+ CD8 T cells significantly decreased. Among CD4 T subsets, bone marrow effector memory phenotype declined, while IL17-producing bone marrow CD4 T cells increased throughout disease progression. Non-classical monocytes HLA-DR+ CD11c+ and mature granulocytes in BM decreased as MM advanced. Further analysis of cytokines and chemokines levels within BM plasma showed reduced levels in MM patients (e.g., GM-CSF, IL10, IFN-γ), suggesting potential impairment in myeloid function and T cell effector activity. Fecal microbiota analysis identified specific bacterial genera significantly more abundant in MM patients, with distinct phyla patterns across disease stages: Firmicutes D and Lactobacillales increased in MM, Actinobacteriota prevailed in SMM, and Proteobacteria and Bacteroidota in MGUS. These findings provide valuable insights into immune alterations and microbiota dynamics during the MGUS-to-MM transition, informing potential therapeutic strategies.

DP043

PROGNOSTIC ROLE OF TRABECULAR ATTENUATION OF L1 AT LOW DOSE CT IN PATIENTS WITH NEWLY DIAGNOSIS OF PLASMACELLULAR DISCRASIA.

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The aim of this study was to evaluate the impact of trabecular attenuation of the L1 vertebral body in low-dose CT in adult patients with multiple myeloma (MM), smoldering multiple myeloma (SMM) and monoclonal gammopathy of undetermined significance (MGUS). We evaluated 79 patients of which 22, 21 and 36 with MGUS, SMM, MM respectively. CT scans were conducted using a 128-slice CT scanner (Somatom go.Top, Siemens). Low dose whole-body CT scans were performed at a single time point for each patient. Trabecular bone density (Hounsfield Unit, HU) values were obtained by defining regions of interest on non-contrast images at the level of L1 vertebra. The median HU value in patients with MGUS, SMM, and MM was 148 HU (range 81-190), 130 HU (range 93-193), and 92 HU (range 26-190) respectively, with a statistically significant difference between the groups (P=0.0015). According to the most important prognostic factor such as level of Hb, M-protein, K/L free light chains, β2-microglobulin and % of bone marrow infiltration by plasma-cells, we found a statistical difference between the 3 groups. Age, BMI and female sex were similar between cohort. Patients with MM were divided into 2 groups according to the HU value: 18 had an HU value ≤ 92 and 18 > 92. As results patients with a HU value ≤ 92 presented with a more aggressive disease: 8/18 (45%) has ISS 3 at diagnosis *vs* 4/18 (22%) of the other group; 13/18 (72%) of patients with HU value ≤ 92 had a bone marrow infiltration of plasma-cells >60% *vs* 9/18 (50%) of the other cohort. Moreover, the group with HU value ≤ 92 presented more cases with high K/L ratio (10/18, 55% *vs* 4/18, 22%) (considering median value of the MM group 19,5) (P=0.0402), at CT total body in 12/18 (67%) *vs* 6/18 (33%) cases more than 3 osteolytic lesions (P=0.045). Median OS was not reached for the 2 groups at a median follow up of 25 months. Finally, patients with HU value ≤ 92 had a lower event free survival (EFS) with a median time of 28 months with statistically significant difference compared to the group with HU value> 92 (P<0.049). This is the first evidence of the importance of evaluating L1 attenuation values in low-dose CT in patients with MGUS, SMM and MM. The L1 attenuation values obtained provide a non-invasive and available parameter that can contribute to differentiation between the 3 categories. The lower attenuation values observed in patients with MM may reflect the higher tumor-burden in this advanced malignancy.

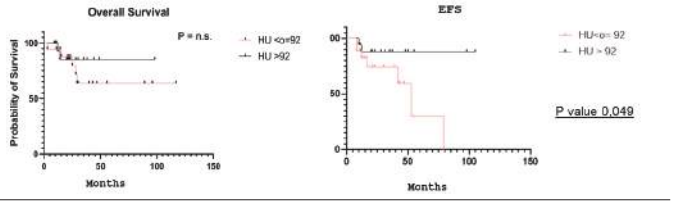

Figure 1.

DP044

WAS TANDEM COMPARED TO SINGLE TRANSPLANT ABLE TO IMPROVE OUTCOMES OF HIGH-RISK MULTIPLE MYELOMA PATIENTS? A REAL-LIFE SINGLE-CENTRE ANALYSIS

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Background. Autologous stem cell transplant (ASCT) remains the recommended treatment in eligible Multiple Myeloma (MM) patients. Some studies suggested tandem ASCT to be beneficial in high-risk (HR) MM, leading it to be the standard of care in many European countries, despite data being based on post-hoc analyses including a very small number of patients.

Methods. We retrospectively analyzed data from newly diagnosed MM patients who underwent ASCT in a single tertiary care centre in order to evaluate outcomes of single (S) *vs* tandem (T) ASCT in HR patients according to cytogenetics [t(4;14, t(14;16), del17p, chromosome 1 abnormalities] and R2-ISS. PFS and OS were analysed by Kaplan-Meier methods and compared by log-rank test. Factors affecting PFS were searched by Cox regression analysis.

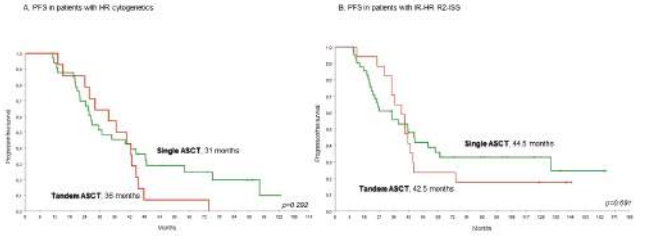

Figure 1.

Results. A total of 157 patients were included in the study, 105 who received S (67%) and 52 (33%) T ASCT. The two groups were similar regarding median age (60 years in both populations), ISS

stage 3 (23% in the S subgroup *vs* 17% in the T), HR cytogenetics (31.5% *vs* 27%), R-ISS stage IR-HR (67% *vs* 65.4%), R2-ISS 3-4 (39% *vs* 33%), renal failure (13.3% *vs* 17.3%), as well as the proportion of patients receiving 3 drugs induction treatment (66.3% *vs* 67.5%), undergoing consolidation (33.3% *vs* 23%) and post ASCT maintenance (49.5% *vs* 42.3%). Post-transplantation, CR or better was achieved by 53.3% and 50% of S and T ASCT (p=0.411), respectively. After a median follow-up of 84 months (range 36-160), PFS of patients receiving S or T ASCT were not significantly different either according to cytogenetic HR (31.3 *vs* 36.5 months; p=0.292), or to R2-ISS 3-4 (44.7 *vs* 42.7 months; p=0.691). The same happened for OS as per cytogenetic HR (78.4 *vs* 65.5 months, p=0.855) and R2-ISS 3-4 (82.3 *vs* 85.1 months; p=0.983). Univariate Cox regression analysis selected HR cytogenetics, R2-ISS 3-4, no consolidation, no maintenance and response<CR but not single ASCT as factors negatively affecting PFS. HR cytogenetics (HR=2.9; CI 95%: 1.5-5.8; p<0.001), no maintenance (HR=1.8; CI 95%: 1.2-2.8; p=0.008) and suboptimal response (HR=2.1; CI 95%: 1.4-3.2; p=0.001) remained significant in multivariate analysis.

Conclusions. In the pre-daratumumab era, S ASCT seems to have the same effectiveness as T ASCT in HR MM patients defined by cytogenetics or R2-ISS. Novel trials are moving up novel immunotherapies to manage HR MM and this may be will leave T ASCT in the past.

DP045

EARLY OUTCOMES OF TANDEM AUTOLOGOUS STEM-CELL TRANSPLANTATION AFTER DARATUMUMAB VTD INDUCTION IN NEWLY DIAGNOSED MULTIPLE MYELOMA.

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The introduction of anti-CD38 monoclonal antibodies in frontline treatment of newly diagnosed multiple myeloma (NDMM) significantly improved response and survival, but high-risk patients still have dismal outcomes. Whereas CASSIOPEIA trial included single autologous stem-cell transplantation (ASCT), previous studies clearly showed a survival benefit with tandem ASCT in HR-NDMM and ongoing trials still include tandem ASCT. We report a retrospective multicenter analysis of HR-NDMM who underwent tandem ASCT following Daratumumab/Bortezomib/Thalidomide/Dexamethasone (Dara-VTd) induction. Criteria for HR-NDMM were the presence of FISH abnormalities as del17p13, t(4;14), t(14;16), gain/ampl1q21, advanced disease stage (R-ISS stage 3, R2-ISS stage 3-4), extramedullary disease (EMD) or less than complete response (CR) after I ASCT. From 1st December 2021 to 30th September 2023, 40 HR-NDMM consecutively received Dara-VTd induction followed by tandem ASCT. Median age at diagnosis was 52 years (range: 32-70). After a median of 4 Dara-VTd (range: 4-6) overall response rate (ORR) was 100%, with 31% CR/sCR (Figure 1). After cyclophosphamide and G-CSF, patients collected a median amount of 10,3 x10^6 CD34+cells/kg (range: 6,5-34); 33% required Plerixafor. After a median of 207 days from start of induction (range: 168-310), 40 patients underwent ASCT (Table 1). After I ASCT, response rates deepened, with 55% CR/sCR. After a median of 129 days from I ASCT (range: 82-242), 40 patients underwent tandem ASCT because of high-risk FISH abnormalities (n=17; 42%), advanced disease stage (n=3, 8%), EMD (n=2, 5%), less than CR after I ASCT (n=12, 30%) or other (n=6, 15%). Neutrophils and platelets engraftments were obtained after a median of 11 days (range: 7-14) and 14 days (range: 7-22), respectively (Table 1). Response rates further improved after tandem ASCT, with 68% CR/sCR. Twenty patients (50%) received 2 cycles of Dara-VTd consolidation without relevant toxicities, whereas 30 patients (75%) already started maintenance. At last disease assessment, 1 patient had disease progression and ORR was 98% (CR/sCR 76%). After a median follow up of 573 days (range: 350-745), all patients were alive. Tandem ASCT proved feasible and effective in HR-NDMM who received Dara-VTd induction, with limited toxicities. Although longer follow-up is required to further elucidate its benefit, tandem ASCT increased the depth of response in HR-MM.

Table 1.

Table 1. Characteristics of autologous stem-cell transplantations (ASCT)

	I ASCT	II ASCT
Days from start of induction to ASCT: median (range)	207 (168-310)	342 (279-453)
Conditioning regimen: n (%)		
– Melphalan 200 mg/m^2	37 (92%)	37 (92%)
– Melphalan 140 mg/m^2	3 (8%)	3 (8%)
Number of infused CD34+cells x10^6/kg: median (range)	4,6 (2,6-8)	4,6 (2,1-8,5)
Days to neutrophils engraftments: median (range)	12 (9-14)	11 (7-14)
Days to platelets engraftments: median (range)	15 (7-21)	14 (7-22)
Bacterial adverse events: n (%)		
– Febrile neutropenia (grade 3)	12 (30%)	7 (18%)
– Sepsis (grade 3)	2 (5%)	4 (10%)
– Pneumonia (grade 3)	0 (0%)	4 (10%)
– Soft tissue infection (grade 2)	1 (2%)	0 (0%)
– Urinary tract infection (grade 2)	1 (2%)	1 (2%)
Viral adverse events: n (%)		
– CMV viremia (grade 2)	4 (10%)	3 (7%)
– CMV viremia (grade 3)	0 (0%)	1 (2%)
– HHV6 viremia (grade 2)	0 (0%)	2 (5%)
– Respiratory syncytial virus infection (grade 2)	0 (0%)	1 (2%)
Fungal adverse events: n (%)		
– Probable IFI (grade 3)	0 (0%)	1 (2%)
– Candidemia (grade 3)	0 (0%)	1 (2%)
Other adverse events: n (%)		
– Atrial fibrillation (grade 3)	2 (5%)	2 (5%)
– Pulmonary edema (grade 3)	0 (0%)	1 (2%)
– Deep vein thrombosis (grade 2)	0 (0%)	1 (2%)
Late hematological adverse events: n (%)		
– Neutropenia (grade 3)	0 (0%)	1 (2%)
– Platelet count decreased (grade 3)	0 (0%)	1 (2%)

DP046

EFFICACY OF ISATUXIMAB PLUS CARFILZOMIB-DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS: AN ITALIAN REAL-LIFE MULTI-CENTER RETROSPECTIVE EXPERIENCE

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Introduction. Isatuximab, a novel anti-CD38 monoclonal antibody, has demonstrated efficacy in combination with carfilzomib and dexamethasone (isa-KD) in patients with relapsed/refractory multiple myeloma (RRMM) in the phase III IKEMA trial (NCT03275285). Despite its promising results in clinical trials, its real-world effectiveness remains largely unexplored. In this multi-center retrospective study, we present the outcomes of isa-KD treatment in RRMM patients in a real-world setting

Methods. Seventy-seven RRMM patients from fourteen Hematology Units in Italy, who initiated isa-KD outside clinical trials (previous treatment lines 1-3), were enrolled from March 2022 to March 2024. High genetic risk MM and lenalidomide refractoriness were evaluated based on IMWG criteria.

Table 1.

Characteristics	Isa-KD N = 77
Median age, years (range)	64 (45-84)
Male, n (%)	40 (52)
ECOG scale, n (%)	
0-1	66 (86)
≥ 2	11 (14)
M-protein type, n (%)	
IgG	48 (62)
IgA	15 (20)
Only light chain	13 (17)
Not secernent	1 (1)
Light chain type, n (%)	
Kappa	43 (56)
Lambda	33 (44)
High genetic risk MM, n (%)	30 (39)
Extramedullary disease, n (%)	15 (20)
Glomerular filtration rate < 40 ml/min, n (%)	8 (10)
Revised international staging system, n (%)	
I	18 (23)
II	30 (39)
III	10 (13)
Not available	19 (25)
Previous therapy lines, n (%)	
1	53 (69)
2-3	24 (31)
Previous autologous stem cell transplantation, n (%)	62 (81)
Previous bortezomib treatment, n (%)	70 (91)
Previous anti-CD38 treatment, n (%)	10 (13)
Previous thalidomide treatment, n (%)	60 (78)
Previous lenalidomide maintenance, n (%)	45 (58)
Median duration of lenalidomide maintenance, months (range)	24 (4-62)
Lenalidomide exposed, n (%)	16 (21)
Lenalidomide refractory, n (%)	53 (69)
Overall response rate after one cycle, n (%)	53 (69)
Complete response, n (%)	2 (3)
Very good partial response, n (%)	13 (17)
Partial response, n (%)	38 (51)
Overall response rate as best response, n (%)	63 (82)
Complete response	12 (16)
Very good partial response	35 (46)
Partial response	16 (22)
Time to best response, months, median (range)	3 (1-20)
Total isa-KD administrations, median (range)	6 (1-24)
Number of MM progressions, n (%)	25 (33)
Progression free survival, median, months (95%CI)	19 (-)
One-year PFS, %	67
Number of deaths, n (%)	17 (22)
Overall survival, median, months (95%CI)	Not reached
One-year OS, %	76
-Hypertension, n (%)	15 (20)
Grade I-II	13 (17)
Grade III-IV	2 (3)
- Cardiac tachyarrhythmias, n (%)	5 (7)
- Hematological toxicity, n (%)	39 (51)
Grade I-II	21 (28)
Grade III-IV	18 (23)
-Pneumonia, n (%)	8 (10)

Results. The baseline characteristics are summarized in Table 1. The cohort exhibited a high representation of high genetic risk (39%), extramedullary disease (EMD; 20%), and severe renal dysfunction (GFR <40 ml/min; 10%). The median follow-up time was 12 months (95%CI: 10.3-13.6). Most patients (81%) had undergone autologous stem cell transplantation (ASCT), with rates of lenalidomide maintenance, lenalidomide exposure, and refractoriness of 58%, 21%, and 69%, respectively. The overall median progression-free survival (PFS) was 19 months (95%CI: not estimable). PFS was shorter in heavily treated patients (10 months [95%CI: 6.5-13.4] *vs.* not reached [NR]; ≥2 *vs.* 1 lines; HR: 2.4; 95%CI: 1.1-5.4; P=0.02), high genetic risk (19 months; 95%CI: 7.1-30.8 *vs.* NR; HR: 2.4; 95%CI: 1-5.8; P=0.04), and EMD (14 months [95%CI: 9.7-18.2] *vs.* NR; HR: 2.2; 95%CI: 0.8-5.3; P=0.08). Previous exposure to anti-CD38 agents was associated with poorer outcomes (7 months *vs.* NR; HR: 5.6; 95%CI: 2.1-14.5; P<0.005). The overall response rate (ORR) as the best response was 82%, with a ≥ very good partial response rate of 62%. Isa-KD treatment was well-tolerated, with cardiac toxicity (hypertension, 20%; tachyarrhythmias, 7% of cases) and pneumonia (10%) being the most common serious adverse events

Conclusion. Our real-world experience indicates that Isa-KD is a viable treatment option even in a challenging patient population, including those with high genetic risk, EMD, lenalidomide refractoriness, and prior exposure to anti-CD38 agents. These high-risk patients remain a clinical challenge with poor outcomes, suggesting that early incorporation of T-cell reconditioning therapies may offer potential for improved prognosis

DP047

FLOW CYTOMETRY-BASED MINIMAL RESIDUAL DISEASE ASSESSMENT AND IMMUNE CORRELATES IN MULTIPLE MYELOMA: A REAL-WORLD EXPERIENCE

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Recent studies emphasized the significance of minimal residual disease (MRD) assessment using next-generation flow cytometry (NGF) or sequencing (NGS) as a reliable predictor of progression-free survival and overall survival in newly diagnosed or relapsed/refractory multiple myeloma (MM) patients. The adoption of MRD evaluation in various clinical trials is increasingly guiding treatment decisions, making its assessment pivotal in the near future. While the International Myeloma Working Group guidelines advocate for a standardized approach like the Euroflow protocol for NGF-based MRD evaluation, its practical implementation presents challenges in real-world clinical settings. This study presents a two-year mono-institutional experience with a real-world NGF MRD evaluation method based on 2 commercial standardized tubes (PCD/PCST) and analyzed using Infinicyt software. Additionally, as a secondary objective, correlations between bone marrow (BM) immune populations and clinical outcomes were explored. BM samples were collected from MM patients achieving at least a very good partial response (VGPR) at specific time points, and evaluated for CD45, CD19, CD38, CD138 (used as backbone markers), CD28, CD27, CD81, CD117, CD56, β2-microglobulin, κ, and λ chains expression. Between March 2022 and December 2023, 67 MM patients underwent a total of 88 MRD assessments (Figure 1 A). Notably, 45% of the MRD samples analyzed were undetectable (MRD-), with 1 pa-

tient deemed unevaluable due to low sample quality. Among the patients, 15 underwent multiple MRD assessments during follow-up. In the MRD-persistent (MRD+) group, after a median follow-up of 12 months, 15 patients experienced relapse, 2 succumbed to disease progression, and 1 patient died due to an infectious disease. Conversely, no relapses have been reported among the MRD- patients to date. A 12-month MRD surveillance program is currently ongoing to monitor sustained MRD negativity. Furthermore, a bioinformatic semi-supervised analysis (FlowCT) was conducted on 20 patients treated with Dara-VTD regimen, revealing a notably higher percentage of granulocytes and erythroblasts, a lower percentage of T-lymphocytes and NK CD56dim lymphocytes, and an increased neutrophil-to-lymphocyte (N/L) ratio at baseline in MRD- patients (Figure 1 B). These findings support the importance and feasibility of MRD assessment via flow cytometry in routine clinical practice and its critical role in the (immune-)monitoring of MM patients.

A

Sex:	
- Male	35/67 (61)
- Female	32/67 (39)
Timepoint:	
- Induction	26/88 (30)
- Post-ASCT	34/88 (39)
- NTE or > 12 months ASCT	21/88 (24)
- Other	7/88 (7)
MRD status:	
- Positive	49/88 (56)
- Negative	38/88 (43)
- NV	1/88 (01)
MRD+ disease status	
- Relapsed	15/39 (38)
- No relapse	24/39 (62)
MRD- disease status	
- Relapsed	0/27 (0)
- No relapse	27/27 (100)

B

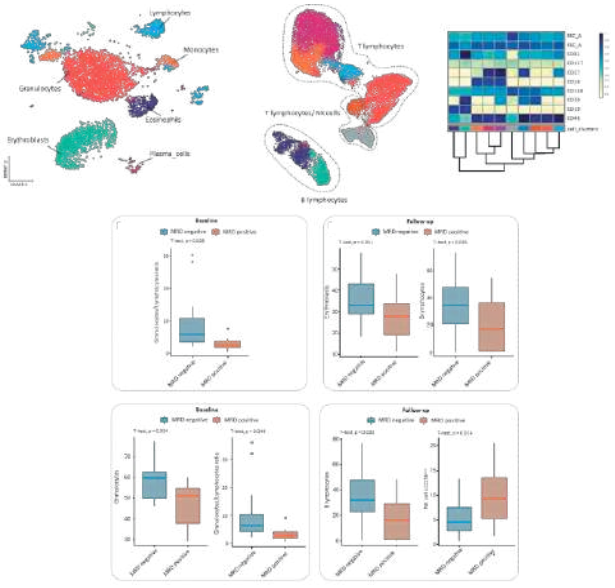

Figure 1.

DP048

DETECTION OF ALTERNATIVE SPLICING EVENTS AND SMALL DOWNSTREAM ORFS BY RIBOSOME PROFILING IN MULTIPLE MYELOMA CELL LINES CULTURED IN ARGININE DEPRIVATION

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In multiple myeloma (MM) a supportive tumor microenvironment (TME) plays an active role in selecting an array of multiple clones, each potentially associated with different clinical behaviour. Our previous work disclosed how the reduction of arginine (arg) concentration in the TME triggers metabolic reprogramming in PCs, enhancing their survival *in vitro* (Romano, 2020) and in vivo (Trudu, 2022). By combining mRNA-sequencing (RNA-seq) and ribosome profiling (Ribo-seq) with *in vitro* assays and FACS analysis, we investigated the adaptive response to acute and chronic arg deprivation, in two human myeloma cell lines (U266 and NCI-H929) cultured up to 10 days in arginine deprivation, correspondent to the arg concentration in MM-TME. According to the expression changes at the transcriptional level and the translational efficiency changes we identified a set of genes significantly different after arg deprivation in both cell lines, including CACYBP, CDKN2C (mapped on chr 1p32.3) and CRIP2 (mapped on chr 14q32.3). To validate the clinical relevance of *in vitro* observations, DEGs identified in both cell lines were further investigated in 767 RNA-Seq obtained from NDMM patients enrolled in the CoMMpass study, comparing patients with different expressions of each gene (subdivided on median value or quartiles) by log-rank test. After setting p-adjusted <0.01, we found that 39/888 DEGs were associated with reduced progression-free survival and overall survival, including CACYBP, CDKN2C (mapped on chr 1p32.3) and CRIP2 (mapped on chr 14q32.3), previously identified as a target of increased translational efficiency in arg deprivation. We identified peptides translated from short-coding or noncoding regions of the genome, including BCL2, DDIT3, ATF3, ATF4 and ATF5 providing a basis for subsequent further functional studies. Applying AS-Quant we identified novel alternative splicing events common in both cell lines occurring in the skipped exons (leading to a significant increase in the expression of ASNS, ATF5, Caspase 4-6-8) and in mutually exclusive exons. Taken together, our findings suggest that arg deprivation in TME conveys a complex transcriptional and translational response, leading to peptides translated from short-coding or noncoding regions of the genome, providing a basis for screening new neo-antigens to apply for immunotherapy development.

This research was supported by the "PIANO NAZIONALE DI RIPRESA E RESILIENZA - PNRR" mission 4 - Component C2, PRIN.

DP049

EFFICACY OF T-CELL ENGAGING BISPECIFIC ANTIBODIES IN REFRACTORY/RELAPSE MULTIPLE MYELOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Multiple Myeloma (MM) patients may benefit from several effective therapies, yet it remains an incurable disease1. MM patients' progress through standard therapy showed poor outcomes in real-life studies (Overall Response Rate (ORR): LoocoMMotion 29,8%). New treatment options are arising for this type of patient: antibody drug conjugate (ADC), bispecific antibodies (BsAbs) and Chimeric Antigen Receptor T cells (CAR-T). Among them, the BsAbs treatment is better tolerated and easily available than CAR-T cells. To understand the real efficacy in inducing a response (measured as ORR), we performed a systematic review and meta-analysis on clinical trials available in relapse/refractory MM (RRMM) treated with BsAbs. We edited the present study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Protocol registered on PROSPERO number CRD42023474035. Both authors retrieved available literature independently on Medline, Scopus and Embase, in addition to the principal hematological/oncological congress sites (ASH, ASCO, EHA) and clinicaltrials.gov registries, were screened to find unpublished results. The research was performed on 27/08/2023. Publication bias was evaluated with ROBINS-I. Overall, the records included in the systematic review were mostly phase 1 clinical trials, where 11 different BsAbs were used to treat 1650 patients (16-288), heavily pre-treated, often triple refractory/ exposed. In case patients were often split in dose/route of drug administration subgroups, for the meta-analysis, data from the subgroup with higher ORR were considered. Overall, 790 patients (143-9) were included in meta- analysis. Overall, 790 patients (143-9) were included in meta-analysis. The ORR was 0,68 (IC 0,62-0,73). To explore the depth of response we analyzed the Very Good Partial Response Rate, 0,57 (IC 0,34-0,44); the Complete Remission Rate, 0,39 (IC 0,32-0,47); stringent Complete Remission rate, 0,2 (IC 0,1-0,3). CRS (all grade) was 0,7 (IC 0,61-0,79). The DerSimonan-Lair estimator random-effects was used.

In conclusion, BsAbs appears to be a promising treatment which allows to get a deeper response than traditional therapy in RRMM patients. CRS is a common therapeutic related adverse effect in BsAbs therapy, but it usually occurs at lower grade.

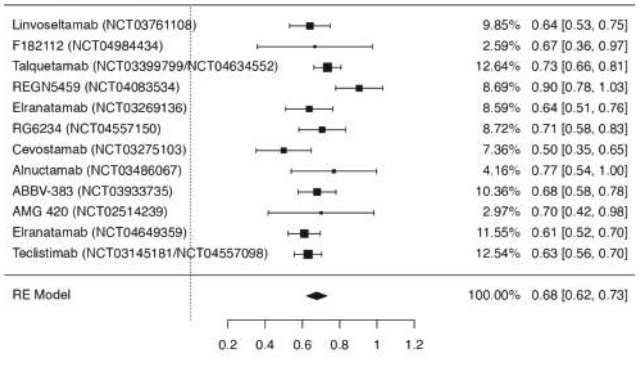

Figure 1.

DP050

HOME CARE FOR PATIENTS WITH PLASMA CELL DISORDERS: THE 10-YEAR EXPERIENCE OF AIL BOLOGNA

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Advanced age at diagnosis, comorbidities and invalidating symptoms can debilitate Multiple Myeloma (MM) and AL Amyloidosis (ALA) patients (pts), potentially precluding access to optimal therapy. The Associazione Italiana contro le Leucemie, Linfomi e Mieloma (AIL) has provided home care to haematological pts since 1993. Between 2014 and 2024, 84 MM and ALA pts received home infusion therapy through AIL in Bologna. Half were newly diagnosed, and half had undergone 1 to 7 prior lines of therapy. The median age was 79 years and 57% of pts had a performance status of ≥2. Notably, 19 pts were under 70 years and severely debilitated due to bone disease or amyloid cardiomyopathy.

Table 1. Baseline patients' characteristics and schedule of home care and therapy.

	N=84
Males, n (%)	40 (48)
Females, n (%)	44 (52)
Age, median [IQR] (range)	79 [71;82] (43;91)
Age > 70 years, n (%)	65 (77)
ECOG PS, median [IQR] (range)	2 [1;3] (0;4)
ECOG PS ≥2, n (%)	48 (57)
ECOG PS ≥3, n (%)	27 (32)
Charlson's Comorbidity index, median [IQR] (range)	4 [3;5] (0;8)
Katz ADL score, median [IQR] (range)	6 [4;6] (0;8)
IADL score, median [IQR] (range)	5 [3;6] (3;8)
Home visits per patient (n), median [IQR] (range)	12 [6;22] (1;59)
Home infusion therapy administrations per patient (n), median [IQR] (range)	11 [6;22] (1;59)
Hospital haematologic visits during home therapy with AIL, median [IQR] (range)	0 [0;1] (0;10)
Total duration of home infusion therapy with AIL (days), median [IQR] (range)	109 [36;210] (1;750)
Total duration of AIL home care (days), median [IQR] (range)	221 [98;518] (7;2337)
AIL home care still active, n (%)	18 (21)

ADL: activities of daily living; AIL: Associazione Italiana contro le Leucemie, Linfomi e Mieloma; ECOG PS: Eastern Cooperative Oncology Group performance status; IADL: instrumental activities of daily living; IQR: interquartile range; n: number.

The distance from the hospital ranged from 0.5 to 39 km. The most frequently administered drugs were bortezomib (V, 82%), daratumumab (15%) and bendamustine (9%), and the most frequent combinations were V-dexamethasone (VD, 33%) and VD-melphalan (27%). In 56% of pts home care was activated after therapy had begun in the hospital setting. During the median 109-day therapy duration (range: 1-750), pts received a median of 11 drug administrations and 12 home visits (range: 1-59). Two-thirds of pts never attended the outpatient clinic during home therapy. Infections occurred in 28% of pts, 37% accessed the emergency department, and 31% were admitted to the hospital at least once, with a median hospitalisation of 12 days. A partial response was achieved in 58% of pts. Median progression free survival was 12 months (22 months in newly diagnosed pts) and overall survival 24 months. Discontinuation reasons included end of therapy (35%) and performance status improvement (17%), which allowed return to outpatient care, progressive disease (13%), or death (19%). Eight pts underwent a second line of home infusion therapy,

19 pts received subsequent oral therapies and 16 pts underwent outpatient infusion therapies. Twenty-five pts maintained AIL home care during subsequent treatments; the median total duration of assistance was 221 days (range 7-2337) [Table 1]. AIL provided zoledronic acid administration (19 pts), transfusions (19 pts), blood draws and medications. AIL granted anti-MM therapy and care for many elderly and/or unfit pts, reducing accesses to the haematology clinic and alleviating the care burden for pts, families, and hospital staff. The success of therapy allowed return to outpatient care for younger pts. Collaboration with general practitioners and pts' caregivers played a crucial role.

DP051

CLINICIANS' PERSPECTIVES AND METHODOLOGICAL APPLICATION OF FISH TO DEFINE CYTOGENETIC RISK IN MULTIPLE MYELOMA: AN ITALIAN, REAL-WORLD, SURVEY-BASED REPORT FROM THE EUROPEAN MYELOMA NETWORK (EMN) ITALY

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Fluorescence *in situ* hybridization (FISH) is the standard technique currently used to detect cytogenetic abnormalities (CA) in multiple myeloma (MM). Its main aim is to better define patient prognosis. Although tailored treatment according to CA is not yet a standard procedure, initial evidence about the efficacy of specific treatments in some cytogenetic subgroups is emerging. Practical guidelines for FISH testing in clinical studies have been developed, but their application in the Italian real-world setting, the degree of standardization of laboratory techniques and the availability of the procedure are largely unknown. We developed a survey that was distributed from April to July 2023 among 70 Italian MM-treating centers associated with the European Myeloma Network (EMN) Italy, geographically well distributed across Italy. We aimed to record laboratory and clinicians' perspectives about the application of FISH in the Italian real-world setting, focusing on its availability, methodology and use in current clinical practice. Our survey results showed that FISH was widely available across the country, with 71% of the participating centers capable of performing it locally, while the remaining centers (predominantly centers with <30 newly diagnosed MM cases/year) sent the samples to external laboratories. We observed a lack of uniformity in terms of laboratory techniques, such as CD-138$^+$ cell purification or the cut-off used to identify CA. Among the CA, 100% of laboratories at the participating centers routinely analyzed del(17p) and t(4;14), 98% analyzed t(14;16), 96% 1q+ (with 70% of laboratories distinguishing between gain *vs* amp(1q) according to copy number), 90% t(11;14), 88% del(1p32), 68% del(13q) and 52% hyperdiploidy. Prognostically, FISH emerged as a crucial technique, since 94% of centers used the Revised International Staging System (R-ISS) score at diagnosis, and 69% already implemented the newly described R2-ISS. Most of the centers performed FISH at diagnosis in all patients, while some centers did not routinely perform FISH in some categories of patients (e.g., patients aged >80 years). At relapse, 53% of centers routinely repeated FISH, only 9% never repeated FISH, while other centers repeated FISH in selected categories of patients. These data allowed us to obtain an updated overview of the use of FISH in Italy, serving as a benchmark to identify improvement strategies in the near future. [Study funded by Sanofi].

DP052

TRICUSPID REGURGITATION IN CARDIAC AMYLOIDOSIS (CA) DEFINES DIFFERENT OUTCOMES IN LIGHT CHAINS AMYLOIDOSIS (AL) AND TRANSTHYRETIN WILD TYPE AMYLOIDOSIS (ATTRW): A SINGLE CENTRE EXPERIENCE

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Light chain (AL) and Transthyretin (ATTRw) are the most frequent types of amyloidosis. The restrictive hemodynamic pattern is responsible of functional Tricuspid Regurgitation (TR). The data currently available are not sufficient to examine the role played by therapies, both hematological and cardiological, in improving TR. This study aims to investigate tricuspid valve damage in CA, both ATTRw and AL, in order to assess different overall survivors (OS) in the two groups. The study population consisted of 35 patients diagnosed at the University Hospital Campus Bio-Medico of Rome between 2017 and 2024, including 19/35 diagnosed with AL and 16/35 with ATTRw. At baseline, all patients underwent echocardiographic study

with diagnosis of TR. TR severity was assessed according to Echocardiography criteria: 7/16 patients with ATTR had a TR grade 3, while only 1/19 of AL group (P=.01). TR was present at diagnosis in all patients.According to the Mayo 2004 Staging, the majority of AL patients (12/19) were stage II. In the AL group, 16/19 patients received chemo-immunotherapy as front-line approach. In this subgroup we observed no changes in terms of TR echocardiographic characteristics during hematological treatment, neither in patients obtaining hematological response. On the other hand, TR seems to enhance using diuretics, but the use of diuretic drug was hemodynamically not well tolerated due to the restrictive physiology of CA. Among them, 3/35 suffering from severe TR (all ATTRw) underwent successful transcatheter edge-to-edge repair. In our cohort, deaths were 14/35, 8/19 in the AL population and 6/16 in the ATTRw. However, among patients with AL, moderate-to-severe TR was not associated with mortality (0/19 deaths) compared to the ATTRw group (3/16 of deaths had a severe TR) (P=0.08). Patients with ATTRw presented a median OS of 16 months while median OS in AL patients was not reached. It is reasonable to think that a severe TR is associated with an increased mortality in patients with ATTRw but had a poor impact on survival in patients with AL. In conclusion, amyloidosis-associated TR poses a multifaceted clinical challenge due to the possibility of reduce mortality and improve the quality of life of these patients with a prompt diagnosis and treatment at onset. In selected patients transcatheter tricuspid valve intervention should be considered as a new tool in the armamentarium for advanced TR therapy.

Chronic lymphocytic leukemia and lymphoproliferative syndromes

DP053

ABSTRACT NOT PUBLISHABLE

DP054

PRELIMINARY EFFICACY AND SAFETY OF THE BRUTON TYROSINE KINASE (BTK) DEGRADER BGB-16673 IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) CLL/SLL: RESULTS FROM THE PHASE 1 BGB-16673-101 STUDY

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Background. BGB-16673 is a heterobifunctional small molecule that induces BTK degradation via ubiquitination. In preclinical models, BGB-16673 degraded wild-type BTK and BTK-mutant proteins resistant to covalent (cBTKis) and noncovalent BTK inhibitors (ncBTKis), leading to tumor regression. Updated results in pts with CLL/SLL from phase 1 of the first-in-human BGB-16673-101 (NCT05006716) study are presented.

Methods. Eligible pts had CLL/SLL and ≥2 prior therapies, including a cBTKi (US, EU, and Australia). BGB-16673 was dosed QD orally in 28-day cycles. A 6-level dose escalation (50-600 mg QD) was planned. Primary objectives were to assess safety per CTCAE v5.0 and iwCLL hematologic toxicity criteria and establish the maximum tolerated dose (MTD) and recommended phase 2 dose. DLTs were assessed in cycle 1. Response was assessed per iwCLL 2018 criteria (Cheson 2014 for SLL), beginning after 12 wk of treatment.

Results. As of Nov 9, 2023, 42 pts with CLL were enrolled (median age, 70 y; range, 50-91) and 39 were treated (50 mg, n=1; 100 mg, n=5; 200 mg, n=15; 350 mg, n=14; 500 mg, n=4). Pts had a median of 4 (range, 2-8) prior therapies, including cBTKis (n=37; 95%), BCL2 inhibitors (n=34; 87%), and ncBTKis (n=10; 26%). Of tested patients, 54% (20/37) had del(17p) and/or *TP53* mutation, 87% (27/31) had unmutated IGHV, and 43% (12/28) had ≥3 karyotypic abnormalities. Median follow-up was 3.3 mo (range, 0.1-16.7). One DLT occurred (200 mg; grade [gr] 3 maculopapular rash; assigned dose was reinitiated with persistent gr 1 rash). MTD was not reached. The most common TEAEs were contusion (31%; no gr ≥3), fatigue (31%; no gr ≥3), diarrhea (26%; no gr ≥3), and neutropenia (23%; gr ≥3, 18%). One pt (500 mg) had gr 3 hypertension. No atrial fibrillation was observed. TEAEs led to 2 deaths (septic shock and pneumonia, both unrelated to treatment), 2 treatment discontinuations (subdural hemorrhage and thyroid cancer), and 1 dose reduction (gr 2 arthralgia). Thirty-five pts (90%) remain on therapy (discontinuations: 1 progressive disease, 3 AEs). In 24 response-evaluable pts, ORR was 67%, with all but 1 response ongoing. Responses occurred in pts with prior cBTKi (n=16) and ncBTKi (n=2) and in pts

with and without BTK mutation (Figure 1).

Conclusions. Emerging data from this ongoing study of the novel BTK degrader BGB-16673 show a tolerable safety profile and antitumor activity in heavily pretreated pts with CLL/SLL, including those with BTK inhibitor–resistant mutations.

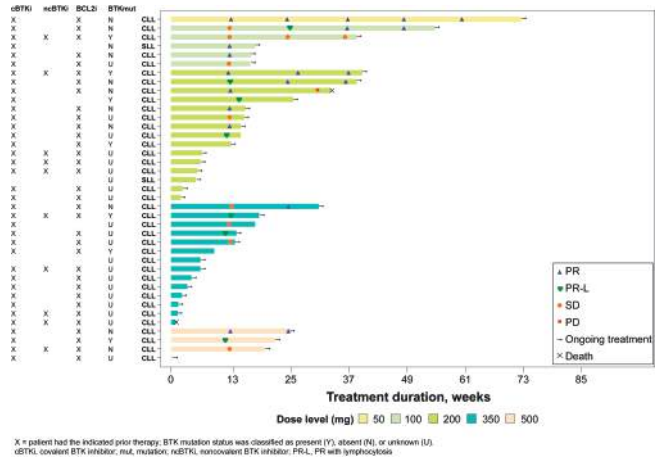

Figure 1.

DP055

LATEST RESULTS FROM AN ONGOING FIRST-IN-HUMAN PHASE 1A/B STUDY OF NX-5948, A SELECTIVE BRUTON'S TYROSINE KINASE (BTK) DEGRADER, IN PATIENTS WITH RELAPSED/REFRACTORY CLL AND OTHER B-CELL MALIGNANCIES

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Background. Emerging BTK inhibitor (BTKi)-resistance mutations and the scaffolding function of BTK present a need for approaches beyond BTKi for treating B-cell malignancies. NX-5948 is a novel, orally administered, small molecule that induces specific degradation of wild-type and mutant forms of BTK in B-cells by the cereblon E3 ligase complex. NX-5948 can also cross the blood-brain barrier.

Methods. NX-5948-301 is a Phase 1, first-in-human dose-escalation trial evaluating safety, tolerability, and clinical activity of NX-5948 in patients (pts) with R/R CLL and NHL. Key eligibility criteria: ≥2 prior therapy lines; measurable or other evaluable disease per indication-specific response criteria; ECOG PS 0–1. Primary objective: evaluate safety and tolerability of NX-5948 and establish maximum tolerated dose and recommended Phase 2 dose. Key secondary objectives: characterize PK/PD profile and assess preliminary efficacy of NX-5948.

Results. As of 16 Jan 2024, 46 pts (16 CLL, 30 NHL of which 6 had CNS involvement) were enrolled at 6 daily oral dose levels: 50 mg (n=7), 100 mg (n=8), 200 mg (n=9), 300 mg (n=12), 450 mg (n=6), 600 mg (n=4). Median age: 64 (range 42–88) years; 67.4% of pts were male; median prior lines of therapy: 4 (range 2–14). Median duration of follow-up: 3.4 (range 0.2–20.1) months. NX-5948 was well tolerated across all doses with no treatment-related SAEs and no discontinuations due to TEAEs. The most common TEAEs were purpura/contusion (39.1%, no Grade ≥3), thrombocytopenia (37.0%, 10.9% Grade ≥3), neutropenia (26.1%, 19.6% Grade ≥3). No atrial fibrillation/flutter was reported. A single DLT was observed with 450 mg (DLBCL; dose hold due to rash; did not recur with rechallenge). NX-5948 PK supported once-daily dosing. Rapid, robust, and sustained BTK degradation was observed in all pts regardless of absolute BTK starting level, tumor type or dose. 7 PRs out of 10 disease evaluable pts with CLL were observed (ORR 70%, see fig). In NHL, out of 24 disease-evaluable pts treated with 50–600 mg NX-5948, 8 pts responded.

Summary and Conclusion. Findings demonstrate a tolerable safety profile of NX-5948 across B-cell malignancies. Clinical responses were observed in a heavily pre-treated population of pts with CLL and NHL, some with BTKi resistance mutations, high-risk molecular features, and CNS involvement. These data suggest a role for NX-5948 in CLL and warrant its continued investigation in NHL, including subtypes where BTKi may not be sufficient.

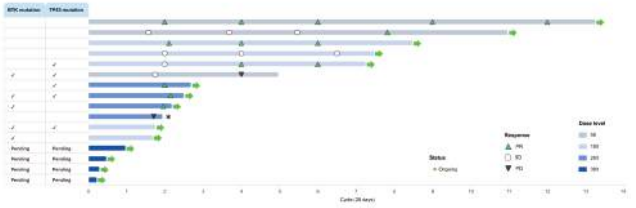

Figure 1. NX-5948 responses in pts with CLL.

DP056

SIMULTANEOUS BCL-2 AND MCL-1 ANTI-APOPTOTIC DEPENDENCIES IN LYMPHOPLASMACYTIC LYMPHOMA

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Introduction. Lymphoplasmacytic lymphoma (LPL) is a low-grade B-cell malignancy characterized by the clonal expansion of mature B-cells and related IgM-expressing plasma cells. Despite the efficacy of current treatments, most patients relapse and need novel therapeutic strategies. The mitochondrial pathway of apoptosis has emerged as a successful therapeutic target in cancer.

Aim of study. We investigated the apoptotic priming and the anti-apoptotic dependencies of LPL cells to design new therapeutic approaches for LPL patients.

Materials and Methods. LPL cells were collected from periph-

eral blood or bone marrow of 19 patients, and were subjected to BH3 profiling, a flow cytometry-based assay which measures the percentage of cytochrome c (Cyt-c) release from mitochondria after incubation with pro-apoptotic peptides. Promiscuous peptides interrogate the apoptotic priming, whereas specific peptides (i.e. BAD, HRK, MS-1, FS-1) or small molecules (i.e. Venetoclax and BGB-11417, which antagonize Bcl-2), inform about the anti-apoptotic dependencies. Lymphoid (Ly, $CD19^{+}CD138^{-}$) and plasma cell (Pc, $CD138^{+}$) components of LPL were discriminated during the analysis. Nine patients with chronic lymphocytic leukemia (CLL), a paradigmatic example of Bcl-2-dependent malignancy, were enrolled as comparison group.

Results. LPL cells were primed for apoptosis, with high priming in the Ly component as compared to the Pc one. Bcl-2 dependence was observed in both cell subsets, with no significant differences between them. Noteworthy, Mcl-1 dependence was observed particularly in Pc subset, suggesting a specific anti-apoptotic dependence for this component. Although Bfl-1 and Bcl-xL were less relevant in the anti-apoptotic defense of LPL cells, data suggest a partial role for these anti-apoptotic members in protecting the Pc subset from committing apoptosis (Figure 1 A-B). The comparison between CLL and LPL highlighted a slight but significant lower apoptotic priming in LPL cells than CLL. While Bcl-2 dependence did not show any appreciable difference between the two diseases, LPL cells had higher no Bcl-2 (Mcl-1, Bcl-xl, Bfl-1) anti-apoptotic dependencies compared to CLL (Figure 1 C).

Conclusions. LPL cells are relatively primed for apoptosis and depend mainly on Bcl-2 and Mcl-1 for survival, with a specific Mcl-1 dependence in Pc component. Our preliminary data suggest that dual antagonism of these anti-apoptotic proteins could be explored as a new therapeutic strategy for LPL patients.

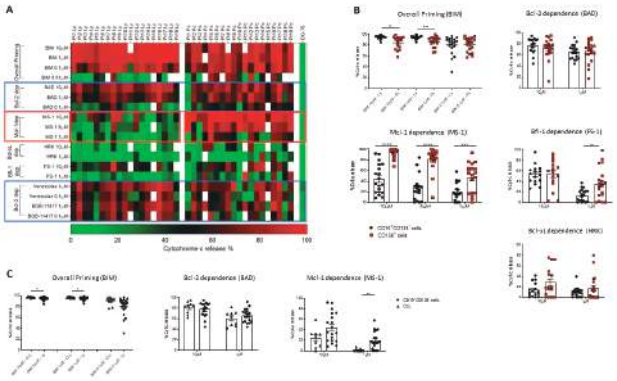

Figure 1.

DP057

CD49D EXPRESSION IS VARIABLE IN TONSILLAR B-CELL SUBPOPULATIONS: INSIGHTS INTO THE MECHANISMS OF CD49D REGULATION IN CHRONIC LYMPHOCYTIC LEUKEMIA

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CD49d, the alpha-chain of the VLA-4 integrin heterodimer is variably expressed in chronic lymphocytic leukemia (CLL) due to genetic/epigenetic mechanisms (Zucchetto *et al*, Blood, 2013; Benedetti et al Leukemia, 2017) only partially elucidated so far. As a model to study the regulatory mechanisms of CD49d, here we analyzed the modulation of CD49d expression in normal B cells from the tonsil, a secondary lymphoid organ rich of B cells at different stages of differentiation. Tonsils (n=6) were collected from patients undergoing routine tonsillectomy, and processed to single-cell suspension. Samples were stained with 12 antibodies (CD3, CD19, CD38, CD27, CD45RB, CD39, CD49d, CD95, CD73, IgD, IgG, IgM) combined in a single tube in order to distinguish nine subpopulations of B cells (Glass et al, Immunity, 2020). The most represented populations were germinal center (GC) cells (mean±SD =24.2%±7.7), followed by Naïve CD73+ (mean±SD =20.7%±10.2), Memory CD27-CD45RB+ (mean±SD =10.2%±4.4), Naïve CD73- (mean±SD =8.3%±6.8), Memory CD27+CD45RB+CD73- (mean±SD =6.8%±1.5), Memory CD27+CD45RB+CD73+ (mean±SD=6.6%±5.6), Memory CD27+CD45RB- (mean±SD =5.3%±4.5), Memory CD95+ (mean±SD =5.2%±1.2), and plasmablasts (mean±SD =1.8%±1.2). Analysis of the mean fluorescence intensity (MFI) of CD49d expression within these subpopulations (Figure 1), revealed unexpectedly highly variable levels of CD49d expression, the highest expression levels in the memory compartment (meanMFI±SD =1010±207 and meanMFI±SD =938±260 in Memory CD27+CD45RB+CD73+ and Memory CD95+ populations respectively), the lowest expression levels in GC cells (meanMFI±SD =269±39), and intermediate levels in Naïve cells (meanMFI±SD =517±123 and 371±141 in Naïve CD73- and Naïve CD73+ respectively). Preliminary analysis of the methylation status/ATAC-seq at the ITGA4/CD49d promoter, carried out by NGS on CD19+ cells, showed patterns of chromatin landscape consistent with CD49d expression data indicating the presence of subpopulations with different epigenetic regulators. Further analyses are currently ongoing. The variable and epigenetically modulated expression of CD49d in B cell development, not yet investigated in detail, suggests a key role of this integrin in the selection of specific B cell subsets during antigen-driven B cell differentiation. These data may have implications in identifying the putative cell-of-origin of CLL cells expressing variable CD49d levels, an as yet unsolved conundrum of CLL pathogenesis.

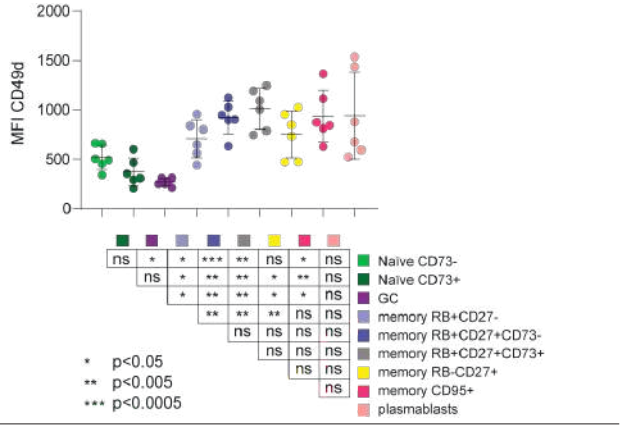

Figure 1.

DP058

REAL-WORLD VENETOCLAX-OBINUTUZUMAB IN TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) PATIENTS: A RETROSPECTIVE MULTICENTRIC ITALIAN STUDY ON FEASIBILITY AND TOLERABILITY[/^]

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Venetoclax-obinutuzumab (VO) is approved for TN CLL showing efficacy in pts with coexisting conditions and younger pts (CLL14 and CLL13 trial). This retrospective, multicenter Italian study evaluates VO feasibility in clinical practice and the reasons for choosing fixed-duration therapy. It analyzes the impact of clinical, biological, demographic characteristics, and toxicity mitigation strategies on VO feasibility (treatment discontinuation or schedule changes due to toxicity). The debulking (Deb) phase (D1-D56) was evaluated separately to understand its impact on treatment management.

In the first year of approval, from May 2022 to June 2023, 790 TN pts were treated in 49 centers: 558 with BTKi and 232 with VO (the latter represents the population analyzed, Table 1). Reasons for choosing VO included biology (46%), fixed duration (33%), comorbidities (15%), and pts preference (6%). VO schedule was *a priori* modified in 22 pts: V lead-in, 12; O omitted, 10. Steroids pre-treatment was administered in 110 (47%) pts to minimize IRR. At a median follow up of 8.4 m, 74(32%) pts concluded full treatment program, in 136 treatment is ongoing, median of 9 cycles. 22 pts (9.5%) definitively discontinued treatment for AEs, predominantly infections. Among them, 8 pts (36%) died due to infections (6 pts) and worsening of pre-existing comorbidities (2 pts). Most of definitive treatment discontinuations occurred during the Deb-phase (12/22 pts, 54%).

Overall, treatment modifications were recorded in 102(44%) pts, 65(64 %) during the Deb-phase. TLS occurred in 13 pts (4 clinical), O-related in 11 cases with splenomegaly and adenopathies>10 cm as predictors. Steroids pre-treatment raised severe infection risk (HR 2.3, p=.02) without reducing IRR; endocrine comorbidity also increased infections (HR 3, p=.007). No IRRs (p=.004) or TLS occurred in the 12 pts with V lead-in. In multivariate analysis, age and prolonged use of steroids independently affected treatment feasibility. Definitive discontinuation was independently related to need of caregiver, endocrine comorbidities and steroids pre-treatment.

The study confirms VO safety in real-world, suggesting that a V lead-in may reduce IRR without rising TLS risk. Steroid pre-treatment didn't improve IRR and increased infection risks, emphasizing the need for patient-specific treatment considerations in CLL. Treatment completion for all pts is planned by Aug 2024, data on the whole population will be available for the Meeting.

Table 1. Patients' characteristics.

Baseline Charachteristcs	All patients (N=232) N (%)
Males	149 (64.2%)
Age (yrs), m (range)	66 (34 – 89)
Need of caregiver	25 (10.8%)
ECOG>1	15 (6.5%)
CIRS, m (range)	4 (0 -14)
CIR3+	47 (20.3)
CLL-CI Risk cat	
Low	153 (65.9%)
Intermediate	56 (24.1%)
High	23 (9.9%)
Cardiac Comorbidities	57 (24.6%)
Hypertension	88 (37.9%)
Concomitant Medications	156 (67.3%)
Polypharmacy	77 (33.2%)
Venetoclax - Interaction	11 (4.7%)
Anticoagulant	24 (10.3%)
Antiplatelet agents	33 (14.2%)
PPI	52 (22.4%)
eGFR, m (range)	75 (23 - 142)
IgHV	
Unmutated	110 (47.4%)
del(17p)/TP53	9 (3.9%)
Complex karyotype	7 (3%)
Rai stage	
III – IV	127 (54.7%)
Hb g/dl, median (range)	11.7 (7 – 16.9)
ANC 10^9/l, median (range)	4.19 (0.14 – 20.85)
ALC 10^9/l, median (range)	48 (0.17 – 753.56)
Plts 10^9/l, median (range)	147.5 (2 – 572)
LN>10cm	18 (7.8%)
Splenic bulky	53 (22.8%)
TLS risk	
Low	40 (17.2%)
Medium	138 (59.5%)
High	54 (23.3%)
IgG<500	54 (23.3%)

ECOG: Eastern Cooperative Oncology Group Performance Status; CIRS: Cumulative Illness Rating Scale; CLL-CI: Chronic Lymphocytic Leukemia Comorbidity Index; PPI: Proton Pump Inhibitor; Hb: Hemoglobin ANC: Absolute Neutrophil Count ALC: Absolute Lymphocyte Count; Plt: Platelets LN: Lymph Nodes; TLS: Tumor Lysis Syndrome.

DP059

ACALABRUTINIB IN HIGH-RISK CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS. AN ITALIAN MULTICENTER EXPERIENCE OF REAL LIFE

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Background. Before target therapies, patients (pts) with chronic lymphocytic leukemia (CLL) with high-risk genetic features, as del(17p), TP53 mutation (TP53m), unmutated immunoglobulin heavy chain variable region genes (uIGHV), had very poor prognosis. Bruton tyrosine kinase inhibitors allowed to obtain high response rates in CLL, but there are few data regarding the use of Acalabrutinib in high-risk (HR) pts in Real life.

Aims. This study aims to evaluate efficacy and safety profile of Acalabrutinib in HR treatment-naive (TN) and relapsed/refractory (R/R) CLL pts.

Methods. A retrospective analysis was conducted on TN and R/R HR CLL pts (del(17p), TP53m, uIGHV), who started Acalabrutinib between June 2021 and June 2023, from 14 Italian centers. For each pt we collected data about demographic, biological and clinical features at baseline. Response evaluation was done at 6 and 12 months since the start of treatment. PFS, OS, and safety data were also evaluated.

Results. 123 pts were included, whose 75.6% TN and 24.4% R/R. Among all, 88.6% had uIGHV, 21.1% had TP53m, and 24.4% had del(17p). Demographic, clinical and biological features at the start of Acalabrutinib are in Table 1. Median follow up was 16.9 months for TN and 13.6 for R/R pts. In the TN group, ORR at 12 months was 87%, 100% and 94% in del(17p), TP53m, uIGHV pts respectively. In the R/R group, ORR at 12 months was 86%, 78% and 86% in del(17p), TP53m, uIGHV pts. At longest avalaible follow up, for del(17p), TP53m, uIGHV pts of TN cohort, PFS were 68%, 70%, 84% and OS were 90%, 86% and 89%. For del(17p), TP53m, uIGHV pts of R/R cohort PFS were 66%, 75% and 67% and OS were 66%, 75% and 53% (Figure 1 A-F). Definitive discontinuation was 15% and 10% in TN and R/R pts, and was dued more to adverse events in TN pts (28%) and equally to adverse events and progressive disease in R/R pts (33%) (Table 1). The most common toxicity was headache reported in 14.6% but it was quite always of mild severity (G1-2 in 100% of cases according CTCAE).

Conclusions. Acalabrutinib is whidely used in HR TN and R/R CLL pts. With a median follow up little more than a year, our study demostrated good effectiveness, long term benefits and low rate of treatment discontinuation by the use of acalabrutinib as continuous drug in HR CLL population, both for TN and R/R pts. No clear differences in efficacy have been observed between the 3 classes of pts, but larger sample size and longer follow up are needed to strenghter our results.

Table 1. Clinical and biological features of high-risk patients treated with Acalabrutinib and Results.

14 Italian centers (June 2021 and June 2023)		TN CLL n =93	R/R CLL n =30	Total n=123	P value
Age, years (median, IQR)		70 (65-76)	76 (65-82)	71 (65-78)	0.09
Gender, n (%)	M	61 (65.6)	20 (66.7)	81 (65.9)	0.67
	F	32 (64.4)	10 (33.3)	42 (34.1)	
Del(17p), n (%)		22 (23.7)	8 (26.7)	30 (24.4)	0.73
TP53m, n (%)		16 (17.2)	9 (30)	25 (21.1)	0.13
uIGHV, n (%)		83 (89.2)	26 (86.7)	109 (88.6)	0.67
Rai stage, n (%)	Low (I-II)	42 (45.2)	11 (36.6)	53 (43.1)	0.41
	High (III-IV)	51 (54.8)	19 (63.3)	70 (56.9)	
Binet stage, n (%)	A	5 (5.4)	0	5 (4.1)	0.39
	B	43 (46.2)	16 (53.3)	59 (48)	
	C	45 (48.4)	14 (46.7)	59 (48)	
ORR 12 months, %	Del(17p), n (%)	14 (87.5)	6 (85.7)	20 (87)	
	TP53m, n (%)	11 (100)	7 (77.8)	18 (90)	
	uIGVH, n (%)	65 (94.2)	18 (85.7)	83 (92.2)	
Results					
Pts remaining on treatment, n (%)		79 (84.9)	27 (90)	106 (86.2)	
Definitive treatment discontinuation, n (%)		14 (15.1)	3 (10)	17 (13.8)	
Reason for treatment discontinuation					
Progressive disease, n (%)		2 (14.3)	1 (33.3)	3 (17.6)	
Richter tranformation, n (%)		3 (21.4)	0	3 (17.6)	
Adverse event, n (%)		4 (28.6)	1 (33.3)	5 (29.4)	
Death, n (%)		3 (21.4)	1 (33.3)	4 (23.5)	
Other, n (%)		2 (14.3)	0	2 (11.8)	

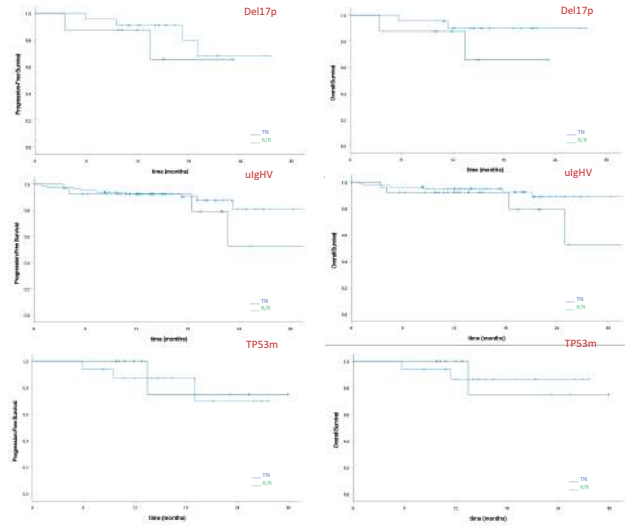

Figure A) Progression free survival in del17p TN and R/R pts; Figure B) Overall survival in del17p TN and R/R patients;
Figure C) Progression free survival in uIGHV TN and R/R patients; Figure D) Overall survival in uIGHV TN and R/R patients;
Figure E) Progression free survival in TP53m TN and R/R patients; Figure F) Overall survival in TP53m TN and R/R patients.

Figure 1.

DP060

PATIENT-REPORTED OUTCOMES (PROS) AMONG PATIENTS (PTS) WITH PREVIOUSLY TREATED CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL) RECEIVING PIRTOBRUTINIB: ANALYSIS FROM THE BRUIN PHASE 1/2 STUDY

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PROs such as health-related quality of life (HRQoL) and symptom burden can provide helpful info to support benefit-risk assessment of a new treatment. BRUIN (NCT03740529) is an ongoing, open-label, multi-center phase 1/2 study investigating the safety and efficacy of pirtobrutinib for the treatment of B-cell malignancies. We report PROs among pts enrolled in the BRUIN study with R/R CLL/SLL treated with prior covalent Bruton tyrosine-kinase inhibitor (cBTKi)-containing regimens. Pretreated pts with R/R CLL/SLL in the BRUIN study completed PRO assessments at each clinic visit. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 was used to measure physical function (PF) and HRQoL. Pt-reported CLL/SLL symptoms and fatigue were assessed using 13 and 6 EORTC Item Library items, respectively. Higher scores represent better PF and HRQoL, and worse CLL/SLL symptoms and fatigue, respectively. Pre-specified clinically meaningful within pt change thresholds of at least 10-point changes in each PRO score were used to categorize pts based on their individual change from Cycle 1 Day 1 (baseline). PRO data were presented from Cycle 1 to 24 (28-day cycle) as the study median PFS by investigator assessment was 19.6 months. Data cutoff date was 22 July 2022. The analysis included 263 pts with CLL/SLL; median (Quartile 1, 3) age was 69 (62, 74) years and majority were male (68%). All pts received prior cBTKi; 21% received 2 or more prior cBTKi lines and 20% discontinued their most recent cBTKi treatment due to toxicity. Mean overall completion rate of PRO instruments was 83% at baseline. 76% of pts completed at least one subsequent PRO assessment. Baseline mean (±SD) score was 80.8 (±19.5) for PF, 61.6 (±23.2) for QoL, 24.8 (±18.4) for CLL/SLL symptoms, and 33.5 (±24.7) for fatigue. The majority of pts reported stable or clinically improved outcomes from baseline at each post-baseline visit (through Cycle 24) for PF (proportion of stable/improved ranged from 72.5%-95.5%), QoL (80.4%-95.0%), CLL/SLL symptoms (77.8%-96.3%), and fatigue (77.3%-89.9%). Overall, consistent with the favorable safety profile of pirtobrutinib, HRQoL and symptoms were stable/improved for over 70% of pts with pretreated R/R CLL/SLL throughout the first 24 cycles of pirtobrutinib treatment. These data should be interpreted with caution due to single arm trial design and small numbers of assessments in later cycles.

Originally presented at ASH 2023.

DP061

REAL-WORLD USE AND OUTCOMES OF THERAPIES, INCLUDING VENETOCLAX-BASED TREATMENTS, AFTER DISCONTINUATION OF A COVALENT BTK INHIBITOR IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

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Current ttmt guidelines for CLL/SLL support the use of cBTKi-based regimens in the 1L setting. Optimal ttmt sequencing following the discontinuation of cBTKi therapy remains unknown. Ven-based regimens, such as ven plus rituximab (VenR), are commonly used in the ttmt of R/R CLL/SLL; however, published clinical trial evidence is limited in the post-cBTKi setting.

Table 1.

Table. Patient characteristics and clinical outcomes

Characteristic[a]	Overall post-cBTKi *N=1243*	Non ven-containing post-cBTKi *N=955*	All ven-containing post-cBTKi *N=288*	VenMono OR VenR as post-cBTKi[b] *N=183*
Age, median (range)	72 (37, 86)	72 (37, 85)	71 (40, 86)	73 (40, 86)
Male sex, n (%)	793 (64)	600 (63)	193 (67)	123 (67)
Received post-cBTKi treatment in community setting, n (%)	1026 (83)	782 (82)	244 (85)	164 (90)
ECOG PS 0-1[c], n/N (%)	844/988 (85)	634/753 (84)	210/235 (89)	129/144 (90)
Deletion of 17p present[c], n/N (%)	234/1080 (22)	157/813 (19)	77/267 (29)	47/165 (28)
IgHV unmutated[c], n/N (%)	388/624 (62)	291/474 (61)	97/150 (65)	55/85 (65)
Rai stage at initial diagnosis[c], n/N (%)				
0	271/791 (34)	209/606 (34)	62/185 (34)	36/111 (32)
I	183/791 (23)	137/606 (23)	46/185 (25)	29/111 (26)
II	105/791 (13)	80/606 (13)	25/185 (14)	13/111 (12)
III	86/791 (11)	64/606 (11)	22/185 (12)	14/111 (13)
IV	146/791 (18)	116/606 (19)	30/185 (16)	19/111 (17)
Line of therapy in which post-cBTKi treatment received, n (%)				
2	754 (61)	590 (62)	164 (57)	105 (57)
3	351 (28)	256 (27)	95 (33)	62 (34)
4	87 (7)	65 (7)	22 (8)	11 (6)
5 or greater	51 (4)	44 (5)	7 (2)	5 (3)
Endpoint	**Overall post-cBTKi** *N=1243*	**Non ven-containing post-cBTKi** *N=955*	**All ven-containing post-cBTKi** *N=288*	**VenMono OR venR as post-cBTKi[d]** *N=183*
TTD-D, median months (95% CI)	6.5 (5.8, 7.5)	5.2 (4.7, 6.0)	12.9 (10.6, 16.5)	10.6 (7.5, 16.0)
TTNT-D, median months (95% CI)	18.8 (16.1, 21.7)	15.7 (13.4, 18.8)	30.1 (23.8, 39.4)	29.5 (18.6, 39.4)
OS rate at 4 years[e], rate (95% CI)	0.71 (0.67, 0.75)	0.69 (0.64, 0.74)	0.76 (0.69, 0.82)	0.76 (0.67, 0.82)

[a] characteristics at initiation of post-cBTKi treatment unless otherwise stated; [b] excludes n=105 patients who received venetoclax in combination regimens other than those included in this sub-group; [c] number of patients with non-missing data used as denominator when calculating the proportion; [d] excludes n=105 patients who received venetoclax in combination regimens other than those included in this sub-group; [e] median OS was not reached for any of the cohorts investigated.

Abbreviations: 1L = first line; 2+L = second or later; 2L = second line; 3L = third line; cBTKi = covalent BTK inhibitor; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; KM = Kaplan Meier; OS = EHR = electronic health record; months = mos; N = denominator; OS = overall survival; pts = patients; R/R = relapsed/refractory; RW; real-world; TTD-D = time to treatment discontinuation or death; ttmt = treatment; TTNT-D = time to next treatment or death; Ven – venetoclax; VenMono = venetoclax monotherapy.

This RW study evaluated pt characteristics, ttmt patterns, and clinical outcomes associated with immediate subsequent ttmt, including the use of ven-based ttmt, after initial cBTKi discontinuation among US pts with CLL/SLL. This descriptive, retrospective observational study used the nationwide Flatiron Health EHR-derived deidentified database. Pts with CLL/SLL aged 18+ years were included who received at least one cBTKi (ibrutinib, zanubrutinib or acalabrutinib) and at least one additional line of ttmt immediately after their initial cBTKi ttmt discontinuation from Dec 01, 2011, to Mar 31, 2022.

Initial cBTKi ttmt could be 1L or 2+L of therapy. Pt characteristics and outcomes (TTD-D, TTNT-D, and OS) were reported. KM method was used for time-to-event outcomes, which were measured from the start of the post-cBTKi ttmt. In this study, n=1,243 pts were analyzed. Most pts received their immediate post-cBTKi ttmt in 2L (61%) or 3L (28%). Twenty-three percent (n=288) of pts received ven-based regimens as the immediate post-cBTKi therapy, 10% (n=120) received VenMono, 5% (n=63) VenR, and 8% (n=105) ven plus other (e.g., chemoimmunotherapy, obinutuzumab). In the entire post-cBTKi cohort, the median TTD-D and TTNT-D were 6.5 (95% CI, 5.8-7.5) and 18.8 (95% CI, 16.1-21.7) mos, respectively. The median TTD-D and TTNT-D in the cohort that included all ven-containing ttmts were 12.9 (95% CI, 10.6-16.5) and 30.1 (95% CI, 23.8-39.4) mos, respectively. For pts who received VenMono or VenR, the median TTD-D was 10.6 (95% CI, 7.5-16.0) mos and median TTNT-D was 29.5 (95% CI, 18.6-39.4) mos. Median OS was not reached for any of the cohorts investigated. These data suggest that outcomes observed in clinical trials of ven-based regimens, where pt populations may differ, may not be routinely extrapolated to pts who received a prior cBTKi. Outcomes for pts treated in the post-cBTKi setting appear to be suboptimal overall. These data suggest the need for additional ttmt options and sequencing data to determine the best ttmt strategy following the discontinuation of initial cBTKi therapy.

Originally presented at ASH 2023.

DP062

PIRTOBRUTINIB IN RELAPSED/REFRACTORY CLL/SLL: RESULTS FROM BTKI NAÏVE COHORT IN THE PHASE 1/2 BRUIN STUDY

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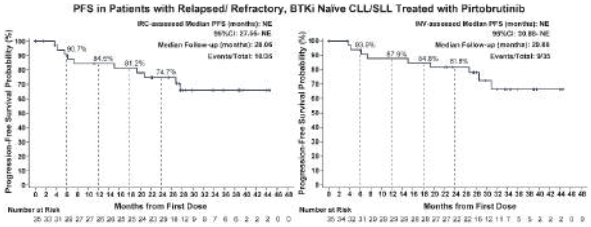
Early lines of therapy for pts with CLL/SLL often use targeted single-agent options such as BTKi. Despite their efficacy, cBTKi have low oral bioavailability and a short half-life that may lead to suboptimal BTK target coverage. Pirtobrutinib has demonstrated promising efficacy and safety in pts with R/R CLL/SLL and was granted accelerated approval after at least two lines of therapy, including a BTKi and a BCL2i. However, outcomes in BTKi naïve CLL/SLL pts treated with pirtobrutinib have not been reported to date. We report safety and efficacy of pirtobrutinib in BTKi naïve pts with R/R CLL/SLL from the phase 1/2 BRUIN study (NCT03740529). Pts with R/R BTKi naïve CLL/SLL received pirtobrutinib. Key endpoints included ORR; including PR-L as assessed by an IRC and INV per 2018 iwCLL response criteria, PFS, and safety. Data cutoff was 05May2023. This analysis included 35 pts with R/R BTKi naïve CLL/SLL treated with pirtobrutinib. Med age was 67 years (range 38-81), 18 pts (51.4%) were male, and 33 (94.3%) had ECOG PS 0-1. Med number of prior therapies was 2 (range 1-8). Of pts with available data, 20/25 pts (80.0%) had unmutated IGHV and 10/27 (37.0%) had TP53 mutation and/or del(17p). Med ToT was 28.8 mo, and med ToS was 31.5 mo.IRC-assessed ORR was 88.6% (95%CI, 73.3-96.8), with 1 (2.9%) CR and 30 (85.7%) PR. ORR including PR-L was 91.4% (95%CI, 76.9-98.2) with 1 pt (2.9%) achieving PR-L. INV-assessed ORR was 85.7% (95%CI, 69.7-95.2), and including PR-L (n=3, 8.6%), was 94.3% (95%CI, 80.8-99.3). IRC-assessed mPFS was NE (95%CI, 27.6-NE), and 24-mo PFS rate was 74.7% (95%CI, 55.7-86.5) (med fu 28.1 mo). INV-assessed mPFS was also NE (95%CI, 30.9-NE), and 24-mo PFS rate was 81.8% (95%CI, 63.9-91.4). The most frequent TEAE, regardless of attribution, were COVID-19 (n=16, 45.7%), neutropenia* (n=15, 42.9%) and diarrhea (n=11, 31.4%). The most frequent grade ≥3 TEAE were infection (n=16, 45.7%; n=9, 25.7% excluding COVID-19) and neutropenia* (n=12, 34.3%). Grade ≥3 TEAE of hypertension (8.6%, n=3), hemorrhage/hematoma (n=1, 2.9%) and atrial fibrillation/flutter (2.9%, n=1) were observed. TEAE led to pirtobrutinib dose reduction in 5 pts (14.3%) and discontinuation in 2 (5.7%). Two pts (5.7%) experienced fatal TEAE, both due to COVID-19 infection considered by INV unrelated to pirtobrutinib. Pirtobrutinib demonstrated promising efficacy in pts with R/R BTKi naïve CLL/SLL and was well tolerated with a low rate of discontinuation.

Originally presented at EHA 2023



Abbreviations/notes: BTKi = Bruton tyrosine kinase inhibitors; cBTKi = covalent BTKi; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; CR = complete response; fu = follow-up; INV = investigator; IRC = independent review committee; med = median; mo = months; mPFS = median progression-free survival; NE = non-estimable; neutropenia = neutropenia and neutrophil count decreased; ORR = overall response rate; PR = partial response; PR-L = partial response with lymphocytosis; PFS = progression-free survival; pts = patients; R/R = relapsed or refractory; TEAE = treatment-emergent adverse events; ToS = time on study; ToT = time on treatment.

Figure 1.

DP063

OUTCOMES ≥1 YEAR AFTER TRANSITIONING FROM TREATMENT WITH IBRUTINIB (IBRU) IN THE ASPEN STUDY TO ZANUBRUTINIB (ZANU)

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Background. ASPEN (NCT03053440) compared BTK inhibitors (BTKi) zanu and ibru in patients (pts) with *MYD88*-mutated Waldenström macroglobulinemia (WM). LTE1 (NCT04170283) is a zanu long-term extension study. We report clinical outcomes ≥1 yr after transition from ibru in ASPEN to zanu in LTE1.

Methods. In LTE1, ibru-treated pts from ASPEN began zanu 320 mg/day. Disease response was assessed every 6 months by modified Owen criteria or as "no evidence of progressive disease" at investigator discretion. Safety and efficacy outcomes were analyzed ad hoc.

Results. Between Jun 26, 2020 and Jun 23, 2022, 47 ibru-treated pts from ASPEN enrolled in LTE1; most (79%) had relapsed/refractory WM prior to ASPEN. At LTE1 enrollment, median age was 73 yrs; median time from ASPEN discontinuation to zanu initiation was 0.07 months. As of Jun 23, 2023, 40 pts (85%) remained on study treatment. Median treatment duration was 50.4 months for ibru prior to transition and 15.3 months for zanu. During LTE1, grade ≥3/serious treatment-emergent AEs (TEAEs) occurred in 23%/13% of pts. Infections (6.4%; all COVID-19) were the only grade ≥3 TEAEs in >2 pts; no serious TEAEs affected >2 pts. Most ibru TEAEs of interest for BTKis did not recur/worsen after zanu transition (except infections [n=3, all COVID-19], anemia [n=1], neutropenia [n=1]). Six of 7 pts with cardiovascular AEs (8 events) in LTE1 had ≥1 ibru-emergent cardiovascular AE during ASPEN. No worsening or new hypertension occurred after zanu transition. There was no recurrence or worsening of atrial fibrillation (AF)/flutter; 1 new case of AF occurred (LTE1 day 12) in a pt with extensive cardiovascular history and concurrent pericarditis (LTE1 day 10). No cardiovascular TEAE led to death in LTE1. Two deaths occurred (both due to COVID-19). Overall response at end of ASPEN was maintained or improved at BOR in LTE1 in 96% (n=44/46) of efficacy-evaluable pts. Median [IgM] change was –36 mg/dL; [IgM] was stable/decreased in 29 pts (73%) from the last ASPEN response assessment to BOR in LTE1.

Conclusions. Following transition to zanu, at a median ibru treatment duration of 50.4 months, most ibru-emergent TEAEs of interest for BTKis did not recur/worsen at a 15-months median zanu treatment duration. Response was maintained or improved in 96% (n=44/46) of efficacy-evaluable pts. Although limited, these data suggest that transitioning ibru-tolerant pts with WM to zanu does not compromise safety or efficacy; long-term follow-up is ongoing.

DP064

PROGNOSTIC IMPACT OF HIGH-RISK GENETIC FEATURES IN CLL PATIENTS TREATED WITH IBRUTINIB: A COMPARISON BETWEEN FRONTLINE AND SUBSEQUENT LINES

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Complex karyotype (CK) is recognized as a high-risk marker in chronic lymphocytic leukemia (CLL) together with del(17p), del(11q), unmutated (um) immunoglobulin heavy chain variable region (IGHV) status. Ibrutinib, a BTK inhibitor, demonstrated exceptional efficacy in CLL treatment, irrespective of therapeutic line or genetic profile and it is now considered a first choice, alongside other BTK inhibitors, for high-risk CLL. Our aim was to evaluate the prognostic impact of high-risk genetic features in patients with CLL treated either in the frontline or subsequent lines with ibrutinib. We conducted a retrospective study on 150 patients who underwent treatment with Ibrutinib either as initial therapy (N=81) or in the relapsed/refractory (R/R) setting (N=69) between 2015 and 2023 at the University Hospital of Padua. The patients' cytogenetic and FISH profiles, IGHV mutational status, as well as TP53 and NOTCH1 mutations (m), were assessed. CK and High CK were defined by the presence of 3 and 5 chromosomal abnormalities, respectively. Median age at enrollment was 72 years (range 43-93), with no differences observed between the first-line and R/R cohorts. Patients in the R/R group received a median of 3 (range 2-6) prior lines of therapy. Regarding genetic characteristics, 25% exhibited a CK, 9% had a High CK, 19% showed del(17p), 19% displayed del(11q), and 25% harbored TP53 m, with no statistical differences between patients treated in the first line *vs* R/R setting. The incidence of IGHV um status was found to be higher in the R/R setting in our population (54%vs74%, p=.03). Considering the whole population, the median progression free survival (PFS) was 49 months while median overall survival (OS) was NR. In multivariate analysis CK (p=.005) and treatment line (p=.002) were significant predictors of PFS. Instead, only High CK demonstrated a significant association with OS in multivariate analyses (p=.01). IGHV um, TP53 m, del(17p) and del(11q) did not impact in PFS and OS. Assessing the impact of high-risk lesions in patients treated in the frontline and subsequent lines, a significant negative impact on PFS emerges for CK (p=.03) and del(17p) (p=.02) in the frontline setting, while no impact was observed in R/R patients. Our findings highlight the negative impact of CK on PFS in patients receiving ibrutinib as first line, while only patients with high CK had a shorter OS likely due to a poor response to subsequent venetoclax regimens (Serafin, BJH 2024).

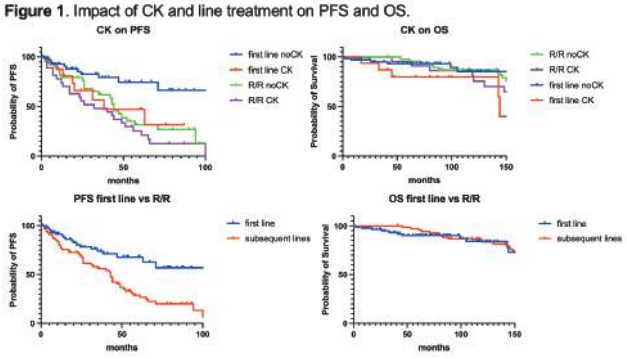

Figure 1.

DP065

SILTUXIMAB AS FIRST-LINE TREATMENT IN IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE: REAL WORLD DATA FROM THE HEMATOLOGY UNITS OF THE LAZIO REGION

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Background. Idiopathic Multicentric Castleman Disease (iMCD) is a rare condition characterized by polyclonal lymphoproliferation associated with systemic symptoms and generalized lymphadenopathies leading to multi-organ dysfunction. The IL-6 hyperinflammatory state represents the main pathogenetic feature of iMCD. Currently, the first-line treatment for iMCD is based on the use of Siltuximab with or without steroid therapy. Siltuximab (SYLVANT) is a chimeric murine monoclonal antibody that forms stable, high-affinity complexes with biologically active soluble forms of human IL-6. About 50% of patients do not achieve response during first-line Siltuximab therapy. The aim of this study is to retrospectively analyze the outcomes and toxicities of patients affected by iMCD treated in the first-line with Siltuximab, outside clinical trials, in the Lazio region.

Methods. We collected real world data (RWD) on iMCD treated with at least one dose of Siltuximab in accordance with clinical practice (11 mg/kg every 3 weeks, until disease progression), from 2018 to March 2024 at the Hematology Units of Lazio region (University Hospital Sant'Andrea, University Hospital Umberto I, Catholic University S. Cuore, Tor Vergata University, Campus Biomedico University, Hematology Unit ASL-RM1 and Belcolle Hospital Viterbo). Responses were defined according the CDCN criteria based on evaluation of biochemical, lymph node, and symptom response. Safety was evaluated according to NCI CTCAE version 5.0.

Results. Fifteen patients were enrolled in this study. Their median age was 54 years (range 17-81). Median duration of treatment was 672 days (range, 1-1306 days). The complete remission rate (CRR) was 33%, however the overall response rate (ORR) was achieved 86.7%. Fourteen out of fifteen (93%) patients are alive. No patient shown infusion related reactions. Grade ≥2 adverse events occurred in 3 patients (20%): hypertension Grade 3; elevated transaminases Grade 2; pneumonia Grade 3 and 5. Conclusion: Our preliminary real-world data on Siltuximab as first line treatment for iMCD confirm its efficacy in disease control in almost all patients, showing safety and manageability. We further prompt to extend this study nationwide to better define the real incidence of this rare disease and the effectiveness of Siltuximab.

DP066

RISK OF HYPERTENSION IN PATIENTS WITH CLL/SLL WHO PARTICIPATED IN THE ALPINE STUDY: A POST HOC ANALYSIS

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Background. Bruton tyrosine kinase (BTK) inhibitors are an important therapeutic option for patients with CLL/SLL. The first-generation BTK inhibitor, ibrutinib, is associated with an increased risk of hypertension. Zanubrutinib is a next-generation BTK inhibitor designed to maximize BTK occupancy and minimize toxicity with fewer off-target effects. This analysis evaluated the risk of developing hypertension based on initiation of antihypertensives (anti-HTN) in a post hoc analysis of ALPINE (NCT03734016).

Methods. Anti-HTN use in the zanubrutinib (n=324) and ibrutinib (n=324) treatment arms was assessed. The definition of anti-HTN was based on Standardized Drug Grouping; concomitant anti-HTN were adjudicated by an independent hypertension specialist blinded to BTK inhibitor assignment. Time to initiating new anti-HTN and time to adding a new class of anti-HTN were assessed using the Kaplan-Meier method. Comparisons of time-to-onset endpoints were analyzed based on the log-rank test.

Results. At baseline, patient characteristics were generally balanced between the zanubrutinib and ibrutinib arms (median age, 66.7 *vs* 67.1 years; male, 65.1% *vs* 71.4%; history of hypertension, 50.9% *vs* 50.0%; type 2 diabetes mellitus, 10.1% *vs* 8.9%). Among patients not on anti-HTN at baseline, 20.7% (n=35/169) of zanubrutinib- and 28.7% (n=51/178) of ibrutinib-treated patients initiated anti-HTN during the study. Among all participants, fewer patients in the zanubrutinib arm initiated new anti-HTN (28.4% [n=92/324] *vs* 32.4% [n=105/324]) and the anti-HTN were initiated later (hazard ratio [HR], 0.77; P-value=.071). Additionally, statistically fewer patients in the zanubrutinib arm compared with the ibrutinib arm started anti-HTN in a new class (24.1% [n=78/324] *vs* 29.3% [n=95/324]) and the anti-HTN were started later (HR, 0.72; P-value=.034). The event rates for initiation of new anti-HTN or a new class of anti-HTN were consistently lower in the zanubrutinib *vs* ibrutinib arm at each timepoint (Table 1).

Conclusions. In ALPINE, initiation of new anti-HTN or a new class of anti-HTN occurred less frequently in the zanubrutinib arm *vs* the ibrutinib arm in patients with CLL/SLL. Adoption of anti-HTN occurred sooner with ibrutinib than zanubrutinib. These findings should be considered when initiating BTK inhibitor therapy in patients with CLL/SLL who have an elevated cardiovascular risk.

Table 1.

	Initiation of new anti-HTN				Initiation of new class of anti-HTN			
	Zanubrutinib		Ibrutinib		Zanubrutinib		Ibrutinib	
	No. at risk	Cumulative event rate, %	No. at risk	Cumulative event rate, %	No. at risk	Cumulative event rate, %	No. at risk	Cumulative event rate, %
3 mo	289	8.4	271	11.0	295	6.5	277	9.1
6 mo	268	12.9	238	19.0	276	10.4	246	16.4
12 mo	238	19.5	208	24.6	252	14.7	216	22.0
18 mo	214	23.7	169	30.7	225	19.5	179	27.0
24 mo	149	28.0	115	33.8	157	23.5	127	29.2
30 mo	106	29.2	76	36.5	109	25.4	84	33.0

DP067

EXPLORING THE IMMUNE SYSTEM IMPACT OF BTKI TREATMENT IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

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Background. Chronic lymphocytic leukemia (CLL) disrupts immune function, increasing infection risk. Bruton's tyrosine kinase inhibitors (BTKi), like ibrutinib (IBR) and acalabrutinib (ACALA), are effective CLL treatments but can lead to infections initially. Over time, BTKis may improve immune function and lower infection risk. This study explores the impact of IBR and ACALA on immunity in CLL patients (pts).

Material and Methods. We analyzed data from 31 pts treated with IBR(26) or ACALA(5), using flow cytometry to track immune

cell changes at baseline, 3, 6, 9, and 12 months of therapy. Pts varied in treatment history (19 first-line pts, 12 relapsed/refractory pts), with 11 in the IBR group having had prior chemoimmunotherapy and 1 in the ACALA. All cell counts are expressed as medians x10^9/L (Table 1).

Results. No differences in immune cell populations were observed between IBR and ACALA pts. Pts receiving BTKi as first-line treatment showed higher baseline values of CD3+HLA-DR+ cells (0.58 *vs* 0.28; p=0.043) and CD4+ (1.46 *vs* 0.62; p=0.016) compared to relapsed/refractory pts. This difference was reflected in significantly higher numbers of CD4+(1.29 *vs* 0.62; p=0.037), CD8+(1.11 *vs* 0.55; p=0.032), CD3+(2.78 *vs* 1.24; p=0.022), and NK (0.21 *vs* 0.01; p=0.007) cells after 3 months for first-line pts. Only CD4+ cell counts remained significantly higher at 6 months (1.15 *vs* 0.49; p=0.026). By 12 months, no differences were observed between first line and relapsed/refractory pts. Pts who developed infections during the first year of BTKi treatment displayed higher CD19+ counts at 6 months (37 *vs* 19; p=0.013), but this difference resolved by 12 months. 17 pts (55%) experienced infections (9 COVID-19, 7 pneumonias, 3 urinary tract infections), with 2 experiencing more than one.

Conclusions. In this study, we assessed the effect of treatment with BTKi on cellular and humoral immunity in CLL pts. Our results indicate no differences in lymphocytic subclasses between pts treated with IBR and those treated with ACALA. Pts receiving BTKi in first line showed a more rapid expansion of T helper cells compared to relapsed/refractory pts, suggesting a potential benefit of early treatment. Furthermore, we found that who developed infections showed an increased number of CD19+ at 6 months compared to those without infections. However, at 1 year of treatment, this difference disappeared, suggesting a resolution of the observed immune cell changes associated with infection.

Table 1.

Table 1: Median cells values at different time-points

MEDIAN VALUES (x10^9/L)	TIMEPOINTS			
	Baseline	3 months	6 months	12 months
WBC (n.v: 4-10)	32,3 (4,34-346)	30,9 (0029-211)	10,9 (5,2-130)	9,11 (5,3-33,3)
Lympho (n.v: 0,5-5)	25,9 (1,12-345)	25 (1,72-200)	6,52 (0,83-124)	3,5 (0,09-9,22)
CD3+HLA-DR+ (n.v: 0-0.59)	0,4 (0-2,81)	0,39 (0-2,15)	0,28 (0,07-1,75)	0,15 (0,01-1,85)
CD4/CD8 ratio (n.v: 1-3,5)	1,2 (0,3-6)	1,1 (0,6-6,2)	1,3 (0,4-3,3)	1,4 (0,2-3,1)
CD3+CD8+ (n.v: 0,11-0,8)	0,93 (0,92-5,63)	0,9 (0,02-2,47)	0,8 (0,09-2,24)	0,48 (0,04-3,84)
CD19+ (n.v: 0,1-0,5)	21,5 (0,09-341)	25,6 (0-196)	5 (0,16-122)	0,92 (0,04-7,02)
CD3+CD4+ (n.v: 0,6-2)	1,15 (0,29-4,98)	1,2 (0,04-6,5)	0,9 (0,3-3,19)	0,82 (0,29-1,34)
CD3+ (n.v: 0,57-2,8)	2,18 (0,39-9,06)	2,5 (0,72-10,2)	1,8 (0,41-5)	1,7 (0,07-4,86)
LAK cells	0,24 (0-1,48)	0,15 (0-0,5)	0,1 (0,02-0,92)	0,09 (0-0,48)
NK cells (n.v: 0,2-0,4)	0,5 (0-1,27)	0,34 (0,02-1,25)	0,06 (0-1,19)	0,150 (0-0,78)

DP068

CLINICAL OUTCOMES AFTER VENETOCLAX FOLLOWING A BCRI IN CLL PATIENTS IN ITALY

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After the introduction of covalent B-cell receptor inhibitors (cBCRi: ibrutinib, idelalisib) and B-cell lymphoma-2 inhibitor (BCL2i: venetoclax) in chronic lymphocytic leukemia (CLL), the outcome of patients (pts) has improved. Nonetheless, pts who relapse after two inhibitors still represent an unmet clinical need. This multicenter real-life study aims at analyzing the outcome of CLL pts relapsing after being exposed to both BCRi and BCL2i between May 2017 and Sept 2023 in Italy. Of 153 double-exposed pts, 104 (68%) discontinued venetoclax and 53 of them (51%) received a subsequent treatment. Reasons for discontinuation were progressive disease (PD) in 51 pts (49.0%), hematological toxicity in 5 pts (4.8%), extrahematological toxicity in 11 pts (10.6%), resistance in 2 pts (1.9%) and other reasons (end of treatment, allogeneic hematopoietic stem cell transplantation (HSCT), MRD negativity) in 35 pts (33.7%); 9 pts interrupted for death after rapid PD without receiving any further treatment. Of the 53 retreated pts, 29 pts (54.7%) received inhibitors (13 pts cBTKi, 11 pts idelalisib, 2 pts BCL2i, 3 pts non covalent BTKi), 19 pts (35.8%) received chemoimmunotherapy (CT: 16 pts intensive, 3 palliative), 5 pts (9.4%) received HSCT (Figure 1). Overall response rate was 50%; median event free survival (EFS) in the groups of inhibitors, CT and HSCT was 11 months (95% CI: 6.3-15.6), 2.0 months (95% CI: 1.3-2.7) and 10 months (95% CI: not ev), respectively (p<0.0001, Figure); median overall survival (OS) was 12 months (95% CI: 10.1-13.9), 5.0 (95% CI: 1.2-8.8) and 10 months (95% CI: not ev), respectively (p=0.020, Figure 1). Pts who progressed during venetoclax treatment had subsequent shorter EFS than pts who discontinued treatment for other reasons, even if not significant (median EFS 4.0 (1.8-6.2) *vs* 10.0 (not ev); p=0.11). EFS did not worsen significantly if pts were del17p, nor p53, if pts received venetoclax without rituximab or if they were treated with single *vs* double BCRi. Despite its limitations, this real-life study provides additional insights in a subgroup of patients still difficult to treat. The differences in outcome between inhibitors, which are the most frequent choice with a better efficacy, and CT could primarily be attributable to evolution into more aggressive forms. This setting of double-exposed pts represents a CLL challenge and trials with BTK degraders, bispecific antibodies and CAR-T could try to solve an unmet clinical need.

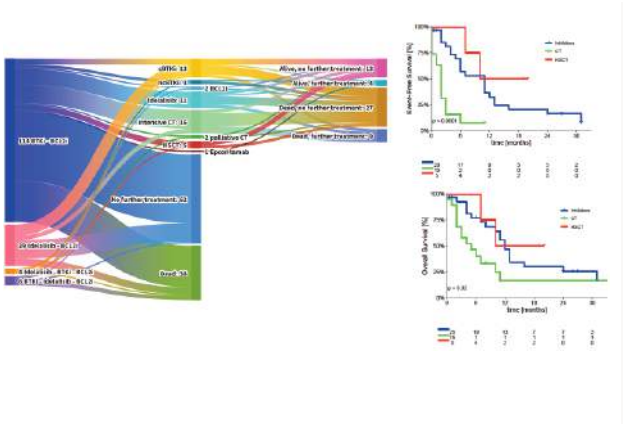

Figure 1. Sankey plot of therapies after being double-exposed and Kaplan-Meier of event-free survival and overall survival according to the treatment received.

DP069

VENETOCLAX-RITUXIMAB IN R/R CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS: REAL LIFE MULTICENTRIC EXPERIENCE

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Introduction. Target fixed duration therapy (TFD) is transforming the therapeutic landscape of Chronic ymphocytic Leukemia (CLL). Venetoclax-Rituximab (VR) regimen, reimbursed in Italy since 2019, heralded the introduction of the first TFD, signalling the beginning of this paradigm shift and transforming the treatment approach for patients (pts) with R/R CLL.

Aim. This retrospective study evaluates the efficacy and safety of VR in a cohort of R/R CLL pts.

Methods. Data of 72 consecutive pts treated with VR between February 2015 to April 2014 in 6 Tuscan centers were collected.

Results. The median age at VR start was 79 yr(range 47-84), with a median of 1 previous therapy (range 1-3) and 35% pts previously exposed to BTK inhibitors(BTKi). TP53 abnormalities (TP53ab) and an unmutated IGHV status was documented in 25% and 54% of pts, respectively. After a median follow up of 23 months, overall survival (OS) and progression-free survival (PFS) at 30 months were 89% and 81%, respectively. The overall response rate (ORR) was 79.2%, with 54.2% of pts achieving complete remission (CR). Minimal residual disease (MRD) was evaluated in 25 pts (35%) at the end of treatment and was found undetectable in 19 (76%). Median PFS was shorter in pts with TP53abs (31 months *vs* 41 months, p=0.026); No significant differences in terms of PFS were observed by IGHV status or previous exposition to BTKi. Undetectable MRD did not had a prognostic impact on PFS or OS. The most common (G3-G4) haematological AE was neutropenia (12.5%). COVID pneumonia occurred in 12.5%, bacterial or fungal pneumonia in 10%. No tumor lysis syndromes occurred. One patient received allogenic stem cell transplant in CR. 5 pts received a new therapy: 2 ibrutinib, 1 idelalisib rituximab, 1 retreated with venetoclax, and 1 received Da-EPOCH for Richter transformation. During treatment, 7 pts died: 2 due to COVID complications, 2 for hemophagocytic lymphohistiocytosis (1 during rump up, 1 after 1 year of treatment), 2 for mpneumonia and 1 for CLL progression.

Conclusions. Despite the retrospective design and the limited pts enrollment, our results are consistent with those of the Murano trial and confirm the efficacy of VR treatment in real-life setting. The study was conducted during the COVID-19 pandemic, which may have also worsened the results. Further studies with longer follow up are needed to confirm this preliminary data.

DP070

EVALUATION OF MRD AND IMMUNOLOGICAL ASPECTS IN PATIENTS AFFECTED BY RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA TREATED WITH RITUXIMAB-VENETOCLAX: THE "DEDALUS" EXPERIENCE

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Background. The combination of Venetoclax (Ven) with the anti-CD20 monoclonal antibody Rituximab (R) has revolutionized the treatment landscape for relapsed/refractory chronic lymphocytic leukemia, with 7-year OS of 69.6%. Ven decreases naïve CD4/CD8 T cells and B cells, increases effector memory CD4+ and CD8+, and reduces Tfh, T-regs and PD-1+ CD8+ cells.

Methods. As part of the "Dedalus" protocol, 22 patients with relapsed/refractory CLL treated according to the R-Ven regimen at the Hematology of Pisa were analysed over a total duration of 2 years. The aim of the study was to assess the rate of negative MRD by MFC and by NGS, and to observe the effect of Ven on the different T-cell subsets. These analyses were performed after 1, 6, 12, and 18 months and in case of treatment interruption.

Results. 20 patients achieved CR; 15 of them achieved MRD negativity at the first time point; 5 were still MRD-positive but 4 of them reached MRD-negativity later. Overall, one patient remained MRD-positive and subsequently experienced a relapse. Another patient, MRD-negative during the first year, developed a Richter's transformation. In all cases, the MRD results were superimposable by MFC and NGS. In the 2 cases in PR, MCF was negative while NGS detected the same IgH clone as at diagnosis either after 6 (3 clonal cell equivalents/10^6 cells) or 12 cycles (6 clonal cell equivalents/10^6 cells). The limit of detection was 10 -4 in all assays for MCF; the NGS reached 10 -5 in 15% of tests. The immunological analysis documented a significant depletion of B lymphocytes occurring since the early stages of treatment and persisting up to 9 months. T lymphocytes decrease early but remain stable over the long term; the most affected is the CD4+ subpopulation, with a reversal of the CD4/CD8 ratio in 25% of cases. The NKs show a slight downward trend. T naive, TCM and TEMRA in both the CD4+ and CD8+ subpopulations remained stable, with a reduction in the absolute values in accordance with the reduction in the values of the total T lymphocytes. No correlation between T status and MRD was observed.

Conclusions. our study confirms the efficacy of R-Ven; the data regarding MRD are consistent with those from literature; the eventual immunomodulating effect exerted by Ven has to be further evaluated in larger series.

DP071

CELESTIAL-TNCLL: AN ONGOING, OPEN-LABEL, MULTIREGIONAL, PHASE 3 STUDY OF SONROTOCLAX (BGB-11417) + ZANUBRUTINIB *VS* VENETOCLAX + OBINUTUZUMAB IN TREATMENT-NAIVE CLL

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Background. The combination of venetoclax (ven), the first-generation BCL2 inhibitor, and ibrutinib, a BTK inhibitor, has efficacy in CLL. However, the toxicity profile of this regimen suggests a need for a more tolerable combination of BTK and BCL2 inhibitors. Sonrotoclax, a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than ven in biochemical assays. Zanubrutinib, a next-generation BTK inhibitor, significantly improved progression-free survival (PFS) and had a more tolerable safety profile, including fewer cardiac adverse events, *vs* ibrutinib in a randomized head-to-head study in patients with CLL/SLL. In a phase 1 study in patients with treatment-naive (TN) CLL treated with sonrotoclax + zanubrutinib, the ORR and 1-year PFS rate were 100%, and deep responses based on undetectable measurable residual disease at $<10^{-4}$ sensitivity (uMRD4) were observed. The most common grade ≥3 TEAE was neutropenia, and no tumor lysis syndrome or cardiac toxicity was observed. The design of a phase 3 trial to compare the efficacy of sonrotoclax + zanubrutinib *vs* ven + obinutuzumab (obi) in patients with TN CLL is presented.

Methods. CELESTIAL-TNCLL (BGB-11417-301; NCT06073821) is a randomized, open-label, phase 3 study. Eligible patients have previously untreated CLL that requires treatment per 2018 iwCLL criteria, measurable disease by CT/MRI, an ECOG performance status of 0 to 2, and adequate hematologic and organ function. Approximately 640 patients will be randomized 1:1 to receive either 3 cycles of oral zanubrutinib monotherapy (320 mg daily) followed by zanubrutinib + sonrotoclax or standard ven + obi for 12 cycles. Randomization will be stratified by age (<65 *vs* ≥65 years) and IGHV and del(17p)/*TP53* mutation status. The primary endpoint is PFS assessed by independent review committee (IRC) per 2018 iwCLL guidelines, with modifications for treatment-related lymphocytosis in patients with CLL. Key secondary endpoints include complete response rate (CRR), defined as CR or CR with incomplete hematopoietic recovery, assessed by IRC; rates of uMRD4 in bone marrow and peripheral blood at the first post-treatment follow-up visit by next-generation sequencing (clonoSEQ®); and overall survival. Other secondary endpoints include investigator (INV)-assessed PFS, CRR-INV, uMRD4 rate by flow cytometry, ORR-IRC and -INV, DOR-IRC and -INV, patient-reported outcomes, and safety and tolerability. Recruitment is ongoing.

DP072

VENETOCLAX-BASED TREATMENTS IN OCTOGENARIAN CLL PATIENTS: FEASIBILITY AND COMPARISON WITH BTK *INHIBITORS* IN AN ITALIAN MULTICENTRE RETROSPECTIVE STUDY

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Introduction. Although a significant fraction of Chronic Lymphocytic Leukemia (CLL) is represented by patients aged over 80 years, with most of them being treated with BTK inhibitors (BTKi) and/or Venetoclax (V), data in this specific subset of patients is lacking.

Aim. To retrospectively evaluate efficacy and safety of V based therapies in octogenarian patients with CLL and to compare them with patients treated with BTKi.

Methods. Patients affected by CLL with age >80 years (yr) and treated with V or BTKi based therapies between 2014 and 2023 were retrospectively enrolled in 21 Italian centers.

Results. A total of 116 patients underwent V-based therapies (46% V monotherapy, 39% V-rituximab and 15% V-obinutuzumab), 17% as frontline therapy. Median age at V start was 81yr (range 80-94), 54% patients had a CIRS≥6. The median number of previous therapies was 2 (range 0-6) and 40% patients had been previously exposed to BTKi (peBTKi). TP53 abnormalities (TP53abn) and an unmutated IGHV gene (U-IGHV) were documented in 28% and 54% individuals, respectively. After a median follow up of 21 months, 2-yr overall survival (OS) and progression-free survival (PFS) were 79% and 71%, respectively. The overall response rate (ORR) was 92%, with 33% of patients achieving a complete remission (CR). Outcomes were worse in peBTKi ($p<0.01$). A total of 324 adverse events (AE) were recorded (29% G≥3). The most common AE was hematological toxicity (n=178) with neutropenia (G1-2 29%; G3-4 25%) having the highest incidence. Seventy-one infectious events were described, with 37% being G≥3. Four tumor lysis syndromes occurred (3 laboratoristic, 1 clinical). V discontinuations due to progression or death were recorded in 20% patients, whereas 7% individuals had permanent therapy suspension due to toxicity. A comparison with a similar CLL population treated with BTKi was made (119 patients; age range 80-87yr, U-IGHV 53%, TP53abn 32%), finding lower CR rates (BTKi ORR 90%; CR 15%) without any difference in survival times (BTKi 2-yr OS 87%; 2-yr PFS 74%).

Patients undergoing BTKi therapy had a lower rate of infections (29% *vs* 37%, p<0.01), but the proportion of G≥3 infections was similar (20% *vs* 22%). More patients discontinued BTKi due to side effects (26% *vs* 7%; p<0.001).

Conclusions. With the limitation of its retrospective nature, our study provides further insights into the feasibility of V compared to BTKi therapy in CLL patients aged >80 yr, reporting on the largest cohort to date.

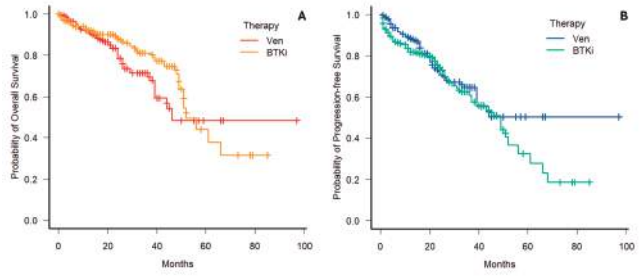

Figure 1. Comparison of Overall Survival (A) and Progression-free Survival (B) in octagenarian CLL patients treated with Venetoclax or BTKis

Figure 1.

Hemostasis, thrombosis, thrombocytopenia and platelet diseases

DP073

ANTI-PHOSPHATIDYLSERINE/PROTHROMBIN AND ANTIPHOSPHOLIPID ANTIBODIES IN IMMUNE THROMBOCYTOPENIA: A DISTINCT CLINICAL FORM OF PRIMARY ITP OR A MISDIAGNOSIS OF SECONDARY ITP?

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Antiphospholipid syndrome (APS) and immune thrombocytopenia (ITP) are two distinct autoimmune diseases, however potentially related. ITP can be secondary to immunological disorders, including APS; thrombocytopenia is one of the clinical diagnostic criteria for APS. The diagnosis of APS consists of testing for lupus anticoagulant (LA), anti-cardiolipin (aCL), and anti-beta2-glycoprotein I (aB2GP1) antibodies. Anti-phosphatidylserine/prothrombin (aPS/PT) antibodies are aPL extra-criteria. This report examines the frequency of conventional and extra-critical antiphospholipid antibodies in a cohort of 85 ITP patients. aCL, aB2GPI and aPS/PT antibodies were detected by ELISA. LA was tested with Silica Clotting Time and dRVVT Screen and Confirm. The ITP cohort consisted of 85 patients, 67 (78.8%) were classified as having primary ITP. Out of them, 57 were tested for the presence of conventional antiphospholipid antibodies (LA, aCL, and aB2GPI) and 12 (21.1%) were found to be aPL positive. Interestingly, in the sub-cohort of patients with unclassified ITP, 5 patients (13.5%) were positive for aPS/PT antibodies. 2 had positivity for both conventional aPL and aPS/PT antibodies, while 3 had positivity for aPS/PT antibodies only. A re-evaluation of the clinical histories of 2 patients, who tested positive for aPL, revealed that they met the criteria for the diagnosis of APS. We compared patients with primary ITP and aPL positivity (considering both traditional and extra-critical aPL) with those aPL negative. A difference was observed in the degree of thrombocytopenia. We considered mild thrombocytopenia if the platelet count was 100,000-50,000/uL, moderate 50,000-20,000/uL and severe<20,000/uL. APL-negative patients developed severe thrombocytopenia in 69% of cases, whereas only 38.4% of aPL-positive patients developed severe thrombocytopenia. Therefore, aPL negative patients more frequently develop more severe thrombocytopenia than aPL positive patients (p=0.0018). aPL negative ITP patients required treatment more frequently than aPL positive patients (88% *vs.* 70%, p=0.17) and required second-line therapy (59.65% *vs.* 46.15%, p=0.37). aPL-positive patients treated with TPO-mimetics as second-line therapy did not reported thrombotic events. The determination of traditional aPL and aPS/PT antibodies is of significant importance in the diagnostic workup of ITP patients, as it allows for the identification of a potential subgroup of patients with a distinct form of ITP.

DP074

HIGH EFFICACY OF FOSTAMATINIB IN IMMUNE THROMBOCYTOPENIA PATIENTS WITH ANTI-PHOSPHOLIPID ANTIBODIES: A REAL-LIFE MONOCENTRIC EXPERIENCE

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Immune thrombocytopenia (ITP) is an immune-mediated disease that, in some cases, can occur as part of an antiphospholipid (aPL) syndrome, an auto-immune disease characterized by positivity of lupus anticoagulant (LAC), anticardiolipin antibodies (aCL) IgG/IgM, and anti-β2 glycoprotein I antibodies (aβ2GPI). In recent years the management of ITP has involved using steroid-based therapies as first-line treatment, followed by thrombopoietin receptor agonists (TPO-RAs) and fostamatinib for chronic ITP (cITP). We present our experience with Fostamatinib in 13 cITP patients, four males and nine females with a median age of 60.3 years (range: 33-82), diagnosed with ITP for a median of 14 years (range: 2-45) and had undergone a median of 3 lines of treatment (range: 2-9), including splenectomy for three patients. Six of thirteen patients were positive for aPL, four of these were triple-positive, three of which had experienced a previous thromboembolic event, one occurring during TPO-RA treatment. One patient was taking anticoagulant (warfarin), one low molecular weight heparin (LMWH) and one acetylsalicylic acid (ASA). At the start of fostamatinib, the median platelet count was 25,153/μL (range:5000-49000/μL). Out of the total 13 patients, 8 (61.5%) achieved a complete response (CR), maintaining an average dose of fostamatinib of 100 mg bid. Notably, all six patients with aPL had a CR, with higher platelet counts compared to aPL-negative patients, 5 of whom showed refractory responses (38.4%), leading to treatment discontinuation after three months. All six responsive patients continuing the treatment, and in two cases the treatment was temporarily discontinued due to transaminitis and increased tensive values, but these issues did not reoccur when the treatment was restarted. There have been no recorded thromboembolic or hemorrhagic event during fostamatinib, and all patients have maintained stable platelet counts, always > 100,000/μL, expect for one patient with sustained platelet counts above 80,000/μL. Our report demonstrates that it is highly effective in patients with aPL, who, from our experience, should promptly start this treatment when their platelet count does not allow them to continue anticoagulant therapy or when they are at risk of bleeding. Furthermore, the inhibitory effect on platelet aggregation demonstrated in *in vitro* experiments, supports its use in this category of patients, which is likely to have a positive impact on their thrombotic risk.

DP075

TREATMENT WITH AVATROMBOPAG IN ITP PATIENTS AFTER TREATMENT FAILURE WITH ELTROMBOPAG AND/OR ROMIPLOSTIM: A MULTICENTER EXPERIENCE FROM "RETE EMATOLOGICA PUGLIESE" (REP)

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Background. The thrombopoietin receptor agonists (TPO-RAs) represent the second line in the management of immune thrombocytopenic purpura (ITP). Avatrombopag (AVA) is the most recently approved TPO-RA for the treatment of chronic ITP. Data describing effectiveness of AVA following treatment failure with another TPO-RA are limited. **Aim.** We report the efficacy and safety of AVA in a real-life setting of ITP patients followed in 5 Centers of "Rete Ematologica Pugliese" (REP) who are unresponsive or have lost response to eltrombopag (ELT) and/or romiplostim (ROMI).

Patients and Methods. We evaluated 27 patients (15 female; 12 men) with median age of 59 years (range 21-82) with persistent/chronic ITP. At avatrombopag initiation, patients had an ITP diagnosis for a median of 78 months (range 6-696) and had received a median of 3 (range 2-9) prior ITP therapies, including splenectomy (4/27 patients, 15%) and fostamatinib (7/27 patients, 26%). In particular, 25/27 patients were previously treated with ELT, 16/27 with romiplostim and 14/27 with both.

Results. The median platelet count before AVA was 9 × 10^9/L (range 1-41). The median duration of AVA treatment was 8 months (range 2-25) and the median weekly dose of AVA was 280 mg (40-280). Among the total group, 5/27 patients (19%) achieved a platelet response (≥50 × 10^9/L) and 9/27 patients (33%) achieved a complete response (≥100 × 10^9/L). Patients before treated with both ELT and ROMI, platelet response was observed in 3/14 patients (21%) and complete platelet response was observed in 3/14 patients (21%). Patients before treated with fostamatinib, platelet response was observed in 1/7 patients (14%) and complete platelet response was observed in 2/7 patients (29%). Among splenectomized patients, 1/4 (25%) achieved complete platelet response. During treatment with AVA, 11/27 patients (41%) were receiving concomitant ITP medication (corticosteroids, intravenous immunoglobulin, rituximab, methotrexate), one patient experienced liver toxicity and 2 patients were diagnosed with non hematological malignancies (breast cancer and liver cancer).

Conclusions. On the basis of our observation, AVA is effective and safe in a heavily pretreated ITP population with inadequate response to a prior TPO-RAs.

DP076

IMMUNE THROMBOCYTOPENIA: EFFICACY AND SAFETY ON THE COMBINED USE OF FOSTAMATINIB AND TPO RECEPTOR AGONIST

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Background and aims. The treatment for immune thrombocytopenia (ITP) has expanded in recent years. For second line of treatment, clinicians have at their disposal thrombopoietin receptor agonist (TPOra) and fostamatinib (FOS). The last one was approved by EMA in Jan 2020 for the treatment of adults with chronic ITP with insufficient response to previous treatments. However, data supporting safety and efficacy of this clinical practice are actually lacking.

Methods. Data of patients (pts) treated with FOS associated with TPOra between Jan 2022 and Apr 2024 was retrospectively collected and analyzed. Response (R) and complete response (CR) was defined as in the FIT study.

Results. 15 pts have received FOS in our Center, in 8 pts FOS was used with TPOra (ELT in 5 pts, ROM in 2 pts and AVA in 1 pts) in order to stop the last one after tapering period. 50% were women and mean age was 61 years (range 86-20). 3 pts are suffering from hypertension, 1 had ischemic stroke in 2020, 2 have a thromboembolism history and 1 had peripheral artery disease. 2/8 pts were on antiplatelet therapy (tp) and 1/8 on direct oral anticoagulant. 5 pts started FOS for loss of response to TPOra, 1 pts for elevated thrombotic risk and 2 pts for both conditions. At the start of FOS, median previous tp for ITP was 2.5, 1 pts was splenectomized; all pts had been exposed to at least one TPOra, 25% to rituximab and 12% to vincristine. Median exposure to TPOra before starting FOS was 28 months (range 4-106). Mean platelet count was 18.000 (pts with loss of response) and median ITP duration was 11 years (range 1-30). After starting FOS 3 pts needed 1 rescue tp, median time to R was 6 days for 7 pts (1 pts have not reached R) and median time to CR was 8 days for 6 pts (2 pts have not reached CR). Four pts start TPOra decalage; 1 of them discontinued TPOra in CR, 3 pts not discontinued TPOra because loss of response. One pts stopped FOS for uncontrolled hypertension. The median follow-up time undergoing FOS plus TPOra was 71,5 days (range 587-27). 2 pts experienced diarrhea, nor transaminitis neither thrombotic events were observed.

Conclusions. In our experience combination of TPOra plus FOS has showed to be effective and safe both in relapse and increased thrombotic risk setting. A shorter time to response was observed than in the FIT study, which could be explained by the synergy of TPOra and FOS. Certainly, there is a need for these results to be validated by larger case series and studies.

DP077

ROLE OF PREEMPTIVE RITUXIMAB IN THROMBOCYTOPENIC THROMBOTIC PURPURA PATIENTS TREATED IN REAL LIFE

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Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is an acute disease with a high risk of mortality. The cornerstone of life-saving therapy in iTTP has been therapeutic plasma exchange (TPE) combined with immunomodulatory strategies. Caplacizumab has resulted in a significantly faster iTTP recovery with a generally safe profile. However, high rates of relapses may occur and the introduction of Rituximab has represented the second breakthrough in iTTP management. Rituximab has been proposed as part of a first-line strategy for patients with unfavorable outcomes, but most patients received it during a relapse of the disease. This study analyzed the effectiveness of Rituximab as a first-line or preemptive treatment to prevent iTTP relapse in a real-life cohort of patients. From August 2014 to January 2024, we analyzed data from 41 iTTP patients treated with Rituximab at the Hematology Unit, Ospedale Businco Cagliari (table 1). Among them, 17 (41,5%) underwent Rituximab as first-line or preemptive use (if Adamts13 <10% after first-line treatment) and 24 (58,5%) at the relapse. The median follow-up was 71 months (range 2-146) for the first group and 124 months (range 3-379) for the second group. Overall, 17 (41,5%) patients received rituximab as the first line of therapy or preemptive, 24 (58,5%) in the relapse course. The mean age at diagnosis was 39 years (18-58) in the first group and 37 years (17-56) in the second group. The median TPE sessions ranged from 11.31 to 7.91 between the two groups, with hospitalization lasting from 15.5 to 13.4 days. Concomitant treatment with Caplacizumab was administered to 5 and 17 patients, respectively. There were 3 cases (17.6%) of hematological relapse in the preemptive group, compared to 18 cases (75%) in the relapse group, p <0,001. The 120-month relapse-free survival was 100% *vs* 25.4% ± 19.9, p=0.01. There were 6 adverse events in the relapse group (metrorrhagia, epistaxis, arthromyalgia, and chest pain), while only 1 event (mild left ventricular dysfunction with impaired repolarization) occurred in the preemptive group. The mean follow-up of retreated patients was 55 months in the first group versus 37 months in the second group, p=ns.In conclusion, our results showed that the early use of Rituximab has a safe profile and is effective in reducing episodes of hematologic recurrence of iTTP.

Table 1.

	First-line or preemptive treatment (n=17)	Relapse (n=24)	p value
Sex female, n° (%)	13 (76,5)	17 (70,8)	ns
Age at treatment, median years (range)	39 (18 – 58)	37 (17 – 56)	ns
Hemoglobin g/dL, median (range)	11,4 (7,5 – 15,4)	7,78 (5,9 – 10)	<0,01
Platelet $\times 10^3$/uL, median (range)	116,8 (6 – 325)	13,6 (7 – 24)	<0,01
Creatinine mg/dL, median (range)	0,83 (0,6 – 1,83)	1,05 (0,4 – 2,7)	ns
LDH mU/mL, median (range)	1570,29 (271 – 4890)	1501,75 (531 – 4468)	ns
TPE, median n° (range)	11,31 (0 – 22)	7,91 (2 – 26)	ns
Caplacizumab n° (%)	5 (29,4)	17 (70,8)	<0,01
Days of hospitalization, median n° (range)	15,5 (4 – 27)	13,41 (4 – 46)	ns
Previously iTTP acute events to Rituximab, n° (%)	3 (17,6)	18 (75)	<0,01
Adverse event, n° (%)	1 (5,9)	6 (25)	ns
Time to relapse, median months (range)	55,12 (1 – 120)	37,13 (1 – 145)	ns
Follow-up, median months (range)	71,13 (2 – 146)	124,04 (3 - 379)	ns

Table 1. Characteristics of patients treated with Rituximab.
TPE=therapeutic plasma exchange; iTTP=Immune-mediated thrombotic thrombocytopenic purpura

DP078

FOSTAMTINIB IN POLYMORBID CARDIOVASCULAR PATIENTS: WHEN AND WHOM? A MONOCENTRIC REAL LIFE EXPERIENCE

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Introduction. Fostamatinib(FST) is a SYK inhibitor used as a second-line therapy for chronic ITP.Its mechanism of action, which is based on blocking autoab-mediated plt phagocytosis rather than supporting thrombopoietin-driven plt production, makes it a candidate not only in cases of non-response to TPO receptor agonists (TPOra) but also in pts with multiple comorbidities, where secondary thrombocytosis should be avoided.This calls for research from the early stages of treatment to develop tailored therapies aimed at reducing polypharmacy and the risk of multi-refractoriness.We report our real-life experience in FST managing

Patients and Methods. We analyzed 22 ITP patients (5M &17 F) with a median age at diagnosis of 45 yo(12-87).14 patients had CV comorbidities, with 5 having more than 2 risk factors, and 3 had already experienced thrombotic events. Pts had been exposed to a median of 3 lines of therapy (1-10) before starting FST; TPOra were administered in 82% of patients. Only 4 patients did not receive TPOra therapy before (2 in the 3L after rituximab, 2 in the 2L). The median age at the start of FST therapy was 63.5 yo(24-87).The main reason for starting therapy was loss of response or non-response to previous lines(14 pts).In 4 patients, we chose FST due to its suitability for their thrombotic history (2 heart attacks, 1 arteriopathy, 1 venous thrombosis).Pts achieved responses:7 CR, 4 R and 8 NR. 7 pts had been exposed to 4L+, with a median maintenance of response of 73 d(32-525); in the others it was 88 d(9-98). Median time to response was 15 d(9-98).Pts not exposed to TPOra achieved R/RC. No

CV events occurred during treatment. Out of the total, 13 pts were still on treatment.

Discussion. There was no significant difference in the maintenance of response between pts with multiple exposures and those who received it earlier in their treatment history.However, those TPOra naive who received FST as the 2L or 3L achieved a deeper and slightly faster response (13d); one achieved such an good response that discontinuation was possible.Pts who had major cv events maintained a safer profile without any new episodes.CV risk factors/episodes did not interfere with the action of FST in restoring plt count.

Conclusion. Our small-scale data provides insights into the place FST could occupy in the decision-making algorithm. Its primarily destruction-modulating action could leave an open position for earlier lines of therapy, favoring pts with multiple comorbidities.

Table 1.

Tab.1

CV risk factors	Pts n.	Pts %
AI	11	50
Diabetes	4	18
Heart/Vascular disease	4	18
Dislipidemia	7	32
Obesity	3	14

DP079

CHARACTERIZATION OF PATIENTS WITH IMMUNE THROMBOCYTOPENIA (ITP) AND MULTIPLE REFRACTORINESS IN THE AGE OF NEW TARGETED DRUGS: A SINGLE CENTER EXPERIENCE

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Background. Different targeted drugs in ITP contribute to increase overall response (OR) rate, but some patients (pts) are able to keep a R only taking a chronic long term or combination treatment (tx), showing refractoriness (REF) to many single agents. Recently a new definition of REF in ITP was given: "persistence of low plt counts despite appropriate use of all conventional tx deemed safe for the specific patient, regardless of hemorrhagic manifestations" (Vianelli *et al.,* 2022). Aim: To describe a real world case series of ITP pts looking specifically at REF. Method: Retrospective data of ITP pts from hospital charts, describing single and combination tx, R and adverse events (AE).

Results. 109 adult pts (F= 67), median age 47 yrs (2-89) at diagnosis (dx). 16 (14,6%) had first dx at age<18. 50.4% had at least 1 comorbidity at dx, [dystyroidism (8), cardiovascular risk factors (20), previous vascular events (3), other autoimmune conditions (12), previous cancer (3) or HCV/HIV infectious (2), chronic neurological (4) or lung diseases (3)]. Splenectomy (S) was performed in 13 pts (11.9%) at a median age of 30 yrs (10-64), after a median time of 3 yrs (1-28) from dx. Of these, 7 had complete R (CR), 3 R and 3 No R. 2/7 pts with CR had a relapse (1 case during pregnancy) after 4 and 30 yrs respectively. All 3 splenectomized pts with a R eventually relapsed after a mean of 3 months in all but 1 who relapsed after 7 yrs. Overall 36.6% has received only first line of tx, and 19.2% more than 2 lines (3-12). About targeted drugs, 35.7% received a TPO-RA but not fostamatinib (FS), 2.7% received FS but not a TPO-RA and 7.3% had received at least one TPO-RA and subsequently FS. 11% showed REF following Vianelli' s definition and they are receiving an ongoing combo tx (Table 1). 4 had S and the others showed an older age at dx (median 67 yrs, 30-82) than the entire population even if not statistically significant (p= 0.065). 49.5% of pts actually receive ongoing tx with an OR of 92.5% (CR 68,5%, R 24,1%). AEs were mainly bleeding (WHO >2 in 6 pts), need of hospitalization (7 pts), transfusion of plt or red blood cells (6) due to bleeding or persistent very low plt count (< 10 x10^9/L).

Conclusions. Despite the high rate of OR, a number of ITP pts showed strong REF, need chronic ongoing tx or a combo chronic tx. Better knowledge of biological and clinic characteristics of the pts, and tailored treatment are strongly required to limit chronicity and hopefully REF.

Table 1.

Table 1. Patients'overview

Total N	109
M/F	42/67
median age at diagnosis	47 (2-89)
first diagnosis at age < 18 yrs	16 (14,6%)
comorbidities at diagnosis	55 (50,4%)
median n lines of tx	1 (1-12)
splenectomized	13 (11,9%)
median age at splenectomy	30 (10-64)
median time from Dx to splenectomy (yr)	3 (1-28)
response to splenectomy (CR/R/NR)	7/3/3
therapy ongoing	54(49,5%)
steroid ongoing	4 (3,6%)
received only first line	40 (36,6%)
received at least one course of Rituximab	7 (6,4%)
received more than 2 lines	21 (19,2%)
received TPO-RA but no fostamatinib	39 (35,7%)
received fostamatinib but no TPO-RA	3 (2.7%)
received TPO-RA and fostamatinib	8 (7,3%)
Combination therapy ongoing	12 (11%)
avatrombopag+ MMF	3
fostamatinib + eltrombopag	1
fostamatinib + azathioprine	1
fostamatinib + MMF	1
fostamatinib + romiplostim	2
romiplostim + CyA	1
romiplostim + MMF	1
eltrombopag+ azathioprine	1
eltrombopag + MMF	1
Overall response in pts with ongoing tx: plt> 30x 10e9L	50/54 (92,5%)
CR in pts ongoing tx	37/54 (68,5%)
R in pts ongoing tx	13/54 (24,1%)
Adverse event during treatment in the last 12 months	
bleeding WHO ≥ 2	6 (5,5%)
venous or arterial thromboembolic event	1 (0.9%)
n pts who need of hospital admission	7 (6.4%)
n pts who need of transfusion (platelet and or red blood cells)	6 (5,5%)
n serious infection (need hospitalization)	2 (1,8%)

CR: complete response (plt > 100 x 10e9/L
R: response (plt > 30 x 10e9/L)
NR: no response (plt < 30 x 10e9/L
MMF: mycophenolate mofetil
CyA: cyclosporin A
TPO-RA: thrombopoietin receptor agonist
tx: treatment

DP080

ACQUIRED HEMOPHILIA A (AHA): A SINGLE CENTRE EXPERIENCE ON 38 CONSECUTIVE PATIENTS

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Background. Acquired hemophilia A (AHA) is a rare bleeding disorder occurring in subjects without family or previous personal history of bleeding; it is associated with the onset of autoantibodies neutralizing self-FVIII (inhibitors). Despite clinical picture may range from asymptomatic patients to life-threatening hemorrhages, common presentations are extensive soft-tissue bleeding. Although in most cases AHA is idiopathic, an underlying triggering condition (malignancy, puerperium or autoimmune disease) has to be ruled out. Management includes hemostatic agents, treatment of underlying pathology and immunosuppressants.

Methods. This single centre retrospective study included n 38 consecutive patients with AHA managed at our Centre over a period of 24 years. Diagnosis of AHA was based on a recent onset of bleeding and/or a prolonged PTT and reduced FVIII levels. Inhibitor testing was performed at our internal Hemostasis Laboratory with mixing test, after incubation for 2 h; FVIII levels and inhibitor titre were determined using the one stage assay and Nijmegen-Bethesda method, respectively. An associated condition was detected in 45%, all the other cases were idiopathic. Patients were treated according to current recommendations.

Results. An acute bleeding was reported at diagnosis in 95%; mucocutaneous or muscle bleeding represented the onset of disease in half cases. A minority of bleeding patients had a life-threatening hemorrhage (CNS in 5%, gastrointestinal in 10%, haemoperitoneum in only 1 patient). With regard to inhibitor eradication, a complete remission was obtained in 79% (n =30) after first line treatment (oral prednisone 1 mg/kg/die +/- cyclophosphamyde 2 mg/kg/die) and 1 patient obtained PR. In this subgroup, relapse rate was 16% (n=5). At relapse n 4 patients obtained CR to second line treatment (rituximab 375 mg/mq on days 1,8,15,22 in most cases). 1 patients did not respond to salvage treatment but died for acute renal failure. Among the refractory cases to first line therapy (n=7), 3 patients died (only 1 died due to AHA), 3 patients achieved CR after two or more lines of treatment. 1 patient with coexistent indolent lymphoma achieved only short lived responses, though he did not show any hemorrhage. At the end of our analysis 19 patients result lost at follow up or died. 73% of them (n=14) were on CR at last follow up visit. Overall survival after a median follow- up of 45 months in our retrospective cohort is represented in Figure 1.

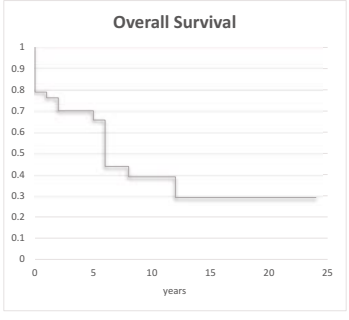

Figure 1.

DP081

THROMBOEMBOLISM PROPHYLAXIS WITH LONG-TERM REDUCED-DOSE DOAC IN CANCER PATIENTS: SINGLE-CENTER EXPERIENCE

C. Sella[1,2,3], F. Valeri[1,2], C. Dainese[1,2], G. Murante[1,2,3], S. Bergonzi[1,2,3], A. Porreca[4], B. Bruno[2,3], A. Borchiellini[1,2]

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Background. Risk of venous thromboembolism (VTE) is 4 to 6-fold increase in cancer patients (pts). For these pts guidelines suggest long-term anticoagulation for secondary prophylaxis using low molecular weight heparin (LMWH), dicumarolics or direct oral anticoagulants (DOAC). Retrospective studies and randomized trials showing that DOAC appears to be as effective and safe as LMWH, also in long term utilization, in the treatment of VTE in cancer pts are published. In contrast, fewer data are available for secondary prophylaxis in cancer pts using reduced-dose DOAC.

Methods. Data on an oncological subgroup of pts with VTE history treated in secondary prophylaxis with reduced-dose DOAC (rd-DOAC) between April 2017 and March 2024 was retrospectively collected and analyzed.

Table 1.

	Apixaban (A) *N=40*	Rivaroxaban (R) *N=70*	p.overall
Age at last VTE (years)	71.6	67.5	0.067
Male	26 (65.0%)	32 (45.7%)	
BMI > 30	1 (2.50%)	6 (8.57%)	0.419
Mean number of previously TEV	0.75	0.63	0.498
Follow-up in rdDOAC (months)	26.6	17.6	
Thrombophilia	9 (22.5%)	7 (10.0%)	
Median time in full dose anticoagulation before rdDOAC (months)	18.0	21.0	0.544
Bleeding during rdDOAC	3 (8.11%)	8 (11.4%)	**0.744**
Median time in rdDOAC at bleeding event (months)	16.3	18.0	0.885
VTE events in rdDOAC	4 (10.5%)	5 (7.14%)	**0.717**
Median time in rdDOAC at TEV event (months)	13	12	0.019
Status at last Follow-up visit:			
Alive	29 (72.5%)	52 (74.3%)	
Death	11 (27.5%)	17 (24.3%)	
Lost at follow-up	0 (0.00%)	1 (1.43%)	

Results. A total of 110 oncological pts were treated with rd-DOAC in secondary prophylaxis; 70 received rivaroxaban 10mg/d (R group; Rg) and 40 received apixaban 2.5mg BID (A group; Ag). Median observation period in rdDOAC was 26.6 months (m) in Ag and 17.6m in Rg. Characteristics of population are summarized in Table 1. Central venous catheter-related thrombosis was first VTE event in 13/110 pts. During rdDOAC 9 pts had a VTE event; 4 pts (10.5%) in the Ag and 5 pts (7.14%) in the Rg. 7/9 had an additional thrombotic risk factor. Recurrence was observed in pts with colorectal carcinoma (2), hematological malignancies (2), breast cancer (2), astrocytoma (1), prostate adenocarcinoma (1) and carcinoma of the oropharynx (1). The median duration of prophylaxis at time of event was 13m (IQR 10,5-18,5) in the Ag and 12m (IQR 11-28) in the Rg. At 12 months, 6.7% of pts in Ag and 6.5% in Rg experienced a VTE

event. During rdDOAC 11 pts had a hemorrhagic event; 3 pts (8.11%) in the Ag and 8 pts (11.4%) in the Rg. 6/11 pts had an additional hemorrhagic risk factor. Neither major bleeding was recorded nor discontinuation of therapy was needed.

Conclusions. In our experience the use of DOAC at reduced dosage in order to prevent recurrence of VTE in cancer pts has been shown to be safe and effective without significant difference between the two drugs. Our cohort shows a comparable recurrence rate of VTE than in studies of full-dose DOACs in cancer patients (equal VTE recurrence rate between Ag and Rg) with lower risk of bleeding and longer follow-up available.

DP082

LONG TERM USE OF CAPLACIZUMAB IN IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA

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Background. Immune-mediated Thrombotic Thrombocytopenic Purpura (iTTP) is a hematological emergency due to a ADAMTS13 deficiency and anti-ADAMTS13 antibodies. The gold standard of treatment is plasma exchange, immunosuppression and Caplacizumab (CPL). Phase 2 and 3 studies have shown that CPL significantly reduces time to platelet count normalization and rate of refractoriness, recurrences and death during treatment. CPL is generally administered until ADAMTS13 activity is restored, however the data sheet reports treatment times up to 65 days. No reports on safety and efficacy are available for longer treatment.

Methods. Data on 12 patients (pts) affected by iTTP, followed at the Hematology Department of Molinette Hospital in Turin and Santa Croce e Carle Hospital in Cuneo between 2021 and 2024, was retrospectively collected and analyzed. Pts were divided in Short-Term group (STg) if they had received CPL<65 days (5 pts) and in Long-Term group (LTg) if they had received CPL > 65 days (7 pts).

Results. 9/12 pts were treated with CPL for a first episode of iPTT, 3/12 were treated for a iPTT relapse (they hadn't received CPL before). Characteristics of pts are summarized in Table 1. In two LTg pts, CPL had been discontinued early but due to failure to maintain clinical remission was reintroduced after few days, therefore total days were counted. To date, two pts in the LTg have not reached drug interruption. In the STg, bleeding events (BE) were hematoma at coaxial catheter implantation and melena with anemia (major bleeding). In the LTg, in the first 2 months of CPL, BE were nosebleed, ecchymosis at the injection site and small spontaneous ecchymosis, while after 2 months of CPL were nosebleed, ecchymosis at the injection site and an episode of metrorrhagia. No further effects on clinical efficacy possibly linked to the presence of neutralizing antibody (ADA) were noted in LTg.

Conclusions. In our cohort, CPL shows to be effective and safe even when used for > 65 days. With the limitation of low sample size, at diagnosis LTg has platelets count and hemoglobin levels lower than STg although not significantly, further ADAMTS13 inhibitor title is significantly higher in LTg than in STg as well as the Rituximab use. CPL has changed the treatment paradigm; criteria are therefore needed to improve the natural history of the disease, to personalize therapy and to obtain the best cost-effective solution.

Table 1.

***Table 1*. Patient's Characteristics**

	Short Term group	Long Term group	P. overall
Age at diagnosis (years)	67.0 [62.0;70.0]	43.0 [37.5;56.5]	**0.028**
Gender	Male 0 (0.00%) Female 5 (100%)	Male 2 (28.6%) Female 5 (71.4%)	0.470
Days in Caplacizumab	32.0 [30.0;32.0]	109 [85.5;146]	**0.004**
ADAMTS13 inhibitor at diagnosis (BU/ml)	23.0 [17.0;51.0]	100 [80.0;122]	**0.015**
ADAMTS13 activity at diagnosis (IU/ml)	0.01 [0.01;0.01]	0.01 [0.01;0.02]	0.428
Plt at diagnosis (/µl)	18000 [9000;51000]	10000 [8500;13000]	0.414
Hb at diagnosis (g/dl)	8.90 [7.60;9.50]	7.70 [6.95;8.15]	0.255
LDH at diagnosis (IU/l)	1019 [590;2013]	1468 [1394;2558]	0.372
PEX number	4.00 [4.00;4.00]	5.00 [4.50;5.50]	0.059
Administration of RTX	Yes 2 (40.0%) No 3 (60.0%)	Yes 7 (100%) No 0 (0.00%)	0.045
Additional therapy[1]	Yes 0 (0.00%) No 5 (100%)	Yes 2 (28.6%) No 5 (71.4%)	0.470
All bleeding	Yes 2 (40.0%) No 3 (60.0%)	Yes 5 (71.4%) No 2 (28.6%)	0.558
Major bleeding	Yes 1 (20.0%) No 4 (80.0%)	Yes 0 (0.00%) No 7 (100.0%)	

[illegible]

DP083

SYK INHIBITION WITH FOSTAMATINIB IN REFRACTORY THROMBOTIC THROMBOCYTOPENIC PURPURA (R-TTP): FIRST CASE DESCRIPTION AND REVIEW OF THE LITERATURE ON IMMUNOSUPPRESSION IN R-TTP

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Background. Patients with Immune Thrombotic Thrombocytopenic Purpura (iTTP) have an expected relapse rate of 40% at 4 yrs. Recent guidelines suggested to consider pre emptive therapy in patients with ADAMTS13 (A13) activity<20% to prevent clinical relapse. Data on immunosuppression (IST) with rituximab (RTX), bortezomib (B), daratumumab (D) or Cyclosporin (Cya) given to treat relapsed/refractory (R/R) iTTP have been published so far. Fostamatinib (F) is a recently approved SYK inhibitor for chronic immune thrombocytopenia studied also in arthritis rheumatoid and GvHD due to its effect abrogating the B-cell receptor signaling pathway, but it has never been used in iTTP.

Aim. To describe a multirefractory TTP (rTTP) patient treated with F as pre emptive therapy and to review the published data on IST for R/R TTP.

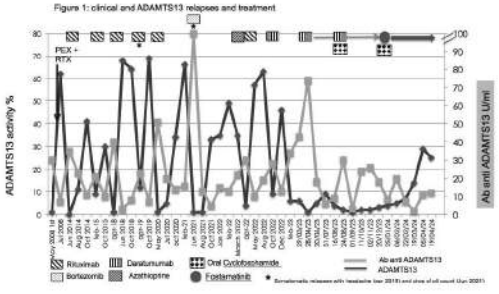
Method. The patient gave a written informed consent to use F as off label therapy and to describe the efficacy and safety data. Moreover, a search of literature was performed on rTTP treatment.

Results. A 44 yrs female was previously treated with PEX and

steroid at first episode of TTP at the age of 28. Afterwards she had 9 episodes of A13 relapses (Figure 1), 2 with clinical symptoms. She received 6 courses of RTX, azathioprine, one cycle of B and 3 course of D. A NGS panel confirmed she has not a genetic deficiency of A13. Off label use of F for persistent A13 deficiency was approved by our hospital Ethical Committee, starting with 100 mg bid and increased at 150 bid after 4 weeks. After 13 weeks of treatment, A13 levels increased and anti-A13 Ab decreased concomitantly (Fig 1). A mild diarrhea (CTCAE G2) was managed with supportive care (probiotics and loperamide). This is the first description of immune modulation with SYK inhibition in rTTP. Hundreds cases of iTTP patients treated with RTX have been published so far, demonstrating a lower rate of relapse than not treated patients. 12 publications described treatment of rTTP with therapy other than RTX, all were case reports or case series (Table 1): 6 with CyA, 1 with azathioprine, 3 with bortezomib, 2 with daratumumab, stating an OR variable between 33 to 100%. All these studies had high bias for selection and reporting.

Conclusion. SYK inhibition with F seems to play a role in immune modulation in this multirefractory TTP patient. Published data about rTTP showed a variable efficacy of different immunosuppressant therapy. Well designed clinical studies addressing this topic are urgent needed.

Figure 1 and Table 1.



Tab 1. Publications on immunosuppressive therapy other than rituximab in iTTP

Publication	n cases	Drug for R/R iTTP	Response
Jhaveri, 2009 [1]	2	CyA	both remission
Yilmaz M, 2013 [2]	1	CyA	refractory-no respons
Acedillo RR [3]	1	CyA	remission
Uchino K, 2021 [4]	1	CyA	remission
Nosari A, [5]	7	CyA	OR 57%
Cataland SR [6]	19	CyA	OR 53%
Bichard C [7]	21	Azathioprine	CR 33%, PR48%
Yin J [8]	4 + review of 9 previous published	Bortezomib	OR 100% (4/4)
Giannotta J [9]	17	Bortezomib	OR 59%
Chen M [10]	17	bortezomib	CR 86%, PR 7%
Aggarwal A [11]	2	Daratumumab	1 response
Van den Berg [12]	2	Daratumumab	CR 50%, PR 50

CyA: cyclosporin A; OR: overall response; CR: complete response; PR: partial response

[1] Jhaveri KD, Scheuer A, Cohen J, Gordon B. Transfus Apher Sci. 2009;41(1):19
[2] Yilmaz M, Eskazan AE, Unsal A, Taninmis H, Kara E, Cetinor M, et al.Transfusion. 2013;53(7):1586–93
[3] Acedillo RR, Govind M, Kashgary A, Clark WF. BMJ Case Rep. 2016
[4] Uchino K, Sakai K, Shinohara S, Matsuhisa A, Ilda Y, Nakano Y et al. Intern J of Hem (2022) 116:295–301
[5] NosariA, Rezzelli R, Calani MT, Mostarda G, Morra E. Am J Hematol, Feb 2009
[6] Cataland SR, Jin M, Lin S, et al Am J Hematol 2008;83:911–915
[7] Bichard C, Mancini I, Agosti P, Capecchi M, De Leo P, Arcudi S et al. Blood Adv 2022; 6(18): 5463–5466
[8] Yin J, Tian H, Kong D, Li Y, Gu C, Wang Z et al. Br J Haematol. 2022;199:619–622
[9] Giannotta J, Artoni A, Mancini I, Agosti P, Carpenedo M et al.et al. To be presented at ISTH 2024, Bangkok
[10]Chen M, Shortt J. Transfusion Medicine Reviews 36 (2022) 204–214
[11] Aggarwal A, White D, Pevord S, Thomas W, Desborough MJR. Br J Haematol. 2023;202:429–433.
[12] van den Berg J, Kremer Hovinga JA, Pfleger et al.Blood Adv. 2022;6(3): 993–7

Chronic myeloid leukemia and cytogenetic

DP084

EFFICACY AND SAFETY OF PONATINIB TREATMENT IN PATIENTS AGED >60 YEARS RESISTANT/INTOLERANT TO PREVIOUS TYROSINE-KINASE INHIBITORS

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Few data are available on the use of ponatinib in older patients This retrospective study sheds light on the efficacy and tolerability of ponatinib in CML older patients and those with cardiovascular complications, a population for which data are limited. The findings indicate that despite baseline comorbidities and cardiovascular risks, ponatinib demonstrated promising results in terms of molecular response and tolerability. Data of 17 CML elderly pts were collected from 8 Italian hematological centers. The median age at the onset of ponatinib was 70 years (range 61-77), Most had co-morbidities at baseline (16/17), 15/17 with pre-existing cardiovascular risk (essential hypertension, diabetes, dyslipidemia, carotid stenosis, atrial fibrillation); 4 patients had previous diagnosed ischemic heart disease. Charlson Comorbidity Index (CCI) calculated at baseline was predominantly between 3 and 5. Patients had previous exposure to multiple TKIs, with a median of 2 prior lines of therapy, suggesting a population with advanced disease and prior treatment failures. 10 pts were resistant, 7 were intolerant; 3 pts showed mutations, only one was T315I. It's noteworthy that 53% of patients started ponatinib at a low dose of 15 mg per day, which could be a strategy to manage potential adverse events, especially in older or high-risk patients. We observed a cumulative incidence of molecular response of 53% at a median time of 8 months of ponatinib treatment, with 4 out of 17 patients achieving a deep response. This indicates that ponatinib has the potential to induce significant molecular responses in this challenging patient population. Adverse events were mild (PE, dermatitis, cytopenia), with only one CV event recorded. Long term follow-up data are valuable for assessing both efficacy and safety outcomes. At a median follow-up of 42 months, nearly half of the patients (9/17) continued ponatinib treatment, with some at a reduced dose, suggesting that ponatinib was generally well-tolerated over an extended period. 4 pts died (2 BP, 1 acute renal failure, 1 CV side effect). Importantly, only one cardiovascular event was recorded during the follow-up period, indicating that ponatinib therapy did not significantly exacerbate cardiovascular complications in this cohort. Overall, despite the small sample size and retrospective nature of the study, these findings provide valuable insights into the use of ponatinib in older patients with cardiovascular complications, highlighting its efficacy and tolerability in this challenging population.

DP085

ROLE OF GUT MICROBIOTA IN DEFINING THE CLINICAL OUTCOMES OF PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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Backgroud. Philadelphia-positive Chronic Myeloid Leukemia (CML) treatment is based on tyrosine-kinase inhibitors (TKIs). In recent years, the human gut microbiome (GM) has acquired increasing importance in human health and disease. The GM can be altered by several factors, such as dietary changes, disease status and medications. However, there is no literature on the effects of GM on CML outcomes. By bridging this gap, this project aims to identify a microbial signature associated with a higher probability of achieving and maintaining deep molecular response (DMR).

Methods. We enrolled patients with a diagnosis of Ph+CML, treated with any TKIs in any line; patients in treatment-free remission (TFR) were also included. In addition to routine examinations, we tested plasma inflammatory indices, markers of autoimmunity, assayed trimethylamine n-oxidase (TMAO), diaminoxidase (DAO), serum zonulin and fecal calprotectin. Phylum GM composition was assessed through 16S rRNA gene amplicon data. Moreover, we measured by flow cytometry the distribution of cellular lines involved in adaptive and innate immunity to evaluate patients immunological state. We employed the HDBSCAN algorithm to cluster patients based on their GM composition. Subsequently, we applied a Bayesian logistic regression model to evaluate the relationship between clusters and DMR.

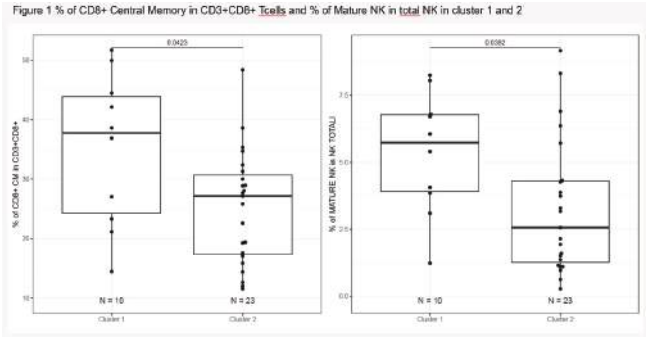

Figure 1.

Results. Our analyses of the GM composition identified two groups of patients (Cluster 1, N=10;Cluster 2, N=23), with 13 patients not assigned to any cluster. Patients in Cluster 1, who were more likely to have a DMR, had more Firmicutes (p=0,055), Tenericutes (p=0.005) and Verrucomicrobia (p=0.028). They also had fewer concomitant therapies (p=0.013) compared with Cluster 2, which was characterized by a higher prevalence of Bacterioidetes (p=0.013) and by a more frequent acquisition of side effects during treatment. By testing all the selected cell lines and comparing their distributions, we found that % of CD8+ Central Memory Tcells and of Mature NK were statistically significantly higher (p<0.05) in Cluster 1. (Figure 1)

Conclusions. Given the substantial impact of the immune system in tumor surveillance and the established effect of the GM on immune activity, it's logical to suggest that microbiota contributes to attaining and maintaining DMR. This is the first study exploring the role of the GM on CML outcomes.

DP086

DIFFERENT BCR:ABL1 TRANSCRIPT LEVELS @ 3 AND 6 MONTHS MIGHT BE USEFUL IN IDENTIFYING WARNING/ RESISTANT CML PATIENTS WHEN USING 2G-TKIS AS FRONTLINE TREATMENT

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Current ELN recommendations suggest the achievement of a BCR::ABL1IS transcript level ≤10% at 3 months as mandatory for optimal response to initial TKIs-therapy. Nevertheless, this cut-off level was made equal for both 1G- and 2G-TKIs. Therefore, no molecular data at 3 and 6 months, with the exception of Marin D. et al. findings (Blood 2012), may help to identify those CML patients (pts) treated frontline with 2G-TKIs who both might have a low probability of achieving an optimal response and be candidates for a 3G-TKIs treatment. With this aim we investigated at diagnosis 104 CP-CML pts, evaluated in two hematological centers, who received 2G-TKIs as frontline therapy at standard dose. Clinical and molecular features are depicted in Table 1.

Table 1.

Patients (N)		104
Sex (M/F)		58/46
Age (median, years)		50.3
Sokal risk	Low Intermediate High missing	40 41 18 5
ELTS score	Low Intermediate High missing	62 28 8 6
Hb (median, g/dl)		11.5
WBC x 10^9/l(median)		150,0
PLT x 10^9/L (median)		492,3
Ph-positive (%)		100
Complex Kariotype and ACA (N)		13/104
Transcript Type	e13a2 (b2a2) e14a2 (b3a2) e1a2 (p190)	49 54 1
Frontline 2G-TKI	DAS NIL BOS	32 70 2

All 104 pts received 2G-TKI as firstline therapy and all had a valid sample for quantitative RT-PCR for BCR::ABL1IS analysis. CML pts were monitored for molecular response (MR) in the same laboratory according to ELN 2020. Our findings showed a median BCR::ABL1IS transcript level of 109,8% at diagnosis. CML pts were then stratified according to their MR to treatment. At 3 months

86/104 pts achieved an optimal response (OP: BCR::ABL1IS ≤10%) with a median BCR::ABL1IS level of 1,65%, whereas 18/104 displayed a warning/failure (W/F: BCR::ABL1IS ≥10%) feature with a BCR::ABL1IS level of 25,38%. At 6 months 81/104 showed an OP (BCR::ABL1IS ≤1%) with a median BCR::ABL1IS level of 0,2%, 12/104 had a W (BCR::ABL1IS >1-10%) with a median BCR::ABL1IS level of 3,2%, 5/104 had a F (BCR::ABL1IS >10%) with a median BCR::ABL1IS level of 23,1%, 6/104 not reached the follow-up. Data correlations and receiver operating characteristic curves will be also presented. In conclusion, these results are consistent with those of Marin D. et al, are significantly different from those reported for 1G-TKI and highlight the need to revise the front-line MR kinetics of 2G-TKIs in the light of the possible sequential use of 3G-TKIs.

DP087

DURABLE EFFICACY AND SAFETY OF PONATINB TREATMENT IN A REAL WORD POPULATION OF RESISTANT OR INTOLERANT CHRONIC MYELOID LEUKEMIA PATIENTS.

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The third generation TKI ponatinib was approved for chronic myeloid leukemia (CML) in chronic, accelerated or blast phase, resistant or intolerant to II gen TKIs and for whom subsequent treatment with imatinib it is not clinically appropriate; or in which the T315I mutation has been identified. The aim of our study was to assess the durable efficacy and safety profile of ponatinib in a retrospective analysis of a real-word cohort of 67 patients with resistant/refractory or intolerant CML from 12 Italian Hematological Institution. 67 patients were analyzed (median age 52 years [range 23-77], 47 male, 63 CP, 4 AP). Majority of patients, showed low/ intermediate ELTS score, The Score2, calculated in patients >40y or <=70y without preexisting CV risk, was high in 20 pts. The switch to ponatinib was due in 50 pts to resistance, in 17 to intoleranc;.27 pts received ponatinib in second line,19 in third line and 14 ≥4 line. Last TKI before starting ponatinib was: dasatinib 34 (%), nilotinib 17 (%), bosutinib 1 (7.5%), imatinib 4 (6.7%). Of 67 evaluated patients, 5 (7 %) had the T315I mutation whereas 11 (16 %) had other ABL1 mutations. Ponatinib starting doses were 45mg (37%), 30mg (28%) or 15mg (23%). At baseline, 22 (33%) patients had less than CCyR and 45 (67%) were in CCyR or better. At median follow-up of 52 mo, 10/67 (15%) evaluable patients were in CHR or less only; 13/67 (19%) achieved and maintained at least a CCyR or improved response vs baseline. Additionally,17/67 (25%) achieved a major molecular response (MR3) and 25/67 (37%) a DMR (≥MR4). Overall, the molecular response was obtained in 80% of patients in second line (16 MMRr, 11 DMR); in 70% of pts in third line (13 MMR, 8 DMR) and in 44% of pts beyond third line (4 MMR). In the whole cohort, 34/67 (50%) experienced at least one treatment-related AE, most commonly dermatological AE (7%), hypertension (7%), headhech (4%) and cytopenia (6%). Only 3 treatment-related arterial occlusive events were reported (2 with high ESC2 score), only one cardiac failure and one stroke. Dose modifications occurred in 26 patients: 12 (46%) due to AEs, of which 5 were CV AEs not severe; 9 (34%) reduced the dose after at least an MCyR; 2 (7%) increased the dose due to lack of efficacy. At median follow up of 43,7 mo of treatment, 39 patients are still on Ponatinib. Among 11 patients who permanently discontinued ponatinib main reasons were AEs 4/11 (36%), resistance 3/11 (27%) progression or death 3/11 (27%), and other reasons 1/11 (9%), e.g., loss to follow up.

Conclusions. Overall, ponatinib maintains favorable long-term efficacy and safety profile in real-world clinical practice for CML patients. Early use of ponatinib and dose optimization are highlighted as important factors for achieving positive outcomes. Our data suggest that with appropriate monitoring and screening for risk factors, ponatinib can be a valuable treatment option for patients with resistant or intolerant CML.|

DP088

SECONDARY CHRONIC MYELOID LEUKEMIA: ITALIAN GIMEMA REGISTRY AND CAMPUS CML DATA

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Haematological diseases developing after chemotherapy or radiotherapy for previous neoplasia are a well-known entities described in ELN classification as "therapy related myeloid neoplasms". The definition includes acute myeloid leukemia and myelodysplastic syndrome usually characterized by adverse cytogenetics and worst prognosis than *de novo* disease. Recently some authors also described an increased incidence of Chronic myeloid leukemia in patients treated for breast cancer and after radiotherapy in patients affected by prostatic neoplasia. We report the incidence of "secondary CML "in the italian CML and CAMPUS CML registry and the outcome of these patients treated with TKIs. We retrospectively analyzed 2181 patients who received CML diagnosis from January 2011 and December 2022. The incidence of secondary CML was 13 % (287 out of 2181). Patient's characteristics are shown in Table 1. Median follow up was 70 months (range 1-137). Patients with primary and secondary CML were comparable in terms of gender, Sokal risk, but not in median age at diagnosis that was significantly higher (68.9 years *vs.* 57.7 years, p<0.001) in patients with secondary CML. We also analyzed the optimal response rates at 3, 6, and 12 month as reccomanded in the European Leukemia Net (ELN) criteria and overall survival rate (OS). We did not reveal statistical differences in the optimal response rates at the different time points between the two cohorts as well as the molecolar response rate at 36 months. Indeed the median OS was shorter in secondary CML group (10 years *vs* not reached, p<0.01), but only one patient died for CML progression in the secondary CML group as compared to 13 patients in "*de novo*" subgroup. From a preliminary analysis, on a large group of patients analyzed, patients with secondary CML are generally older, received imatinib as first line treatment and exhibit shorter overall survival. The response to the treatment is not different compared to patients affected by primary CML. Further research is needed to optimize treatment strategies for this subgroup.

Table 1.

Table 1 Characteristics of the patients

	De novo CML (1894 pts)	Secondary CML (287 pts)	P value
Gender (M/F)	1083/811 (57/43%)	176/111(61/39%)	0.18
Median age	58 (14 - 95)	69 (25 - 95)	< 0.001
High Sokal risk	266 (14%)	46 (16%)	0.37
1G TKI	1009 (53%)	200 (70%)	0.002
2G TKI	885 (47%)	87 (30%)	0.002

DP089

CHRONIC MYELOPROLIFERATIVE NEOPLASM CHARACTERIZED BY AN ATYPICAL REARRANGEMENT OF CHROMOSOMES 5 AND 14 WITH FORMATION OF THE FUSION GENE PDGFRB-CCDC88C

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Chronic myeloproliferative neoplasm (CMN) represent an eterogeneous group of diseases originating from neoplastic transformation of hematopoietic stem cell, and characterized by clonal proliferation of one or more hematopoietic progenitors with accumulation of increased numbers of mature blood cells in the bone marrow, peripheral blood and eventually extramedullary sites. Among them, a specific subset is the myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase (TK) gene fusions defined by rearrangement of the PDGFR A or B gene whit high sensitivity to TK inhibitors treatment. Here we report a rare case of a 21 y/o patient who presented as a myeloproliferative/myelodysplastic neoplasm and underwent a full genomic characterization at CEINGE Oncohematology laboratory. Patient was admitted with hyperleukocytosis, anemia, thrombocytopenia and increased levels of LDH; peripheral blood smear revealed the presence of a high concentration of hypogranular neutrophils, eosinophils, basophils and myeloid precursors. Abdominal ultrasound revealed enlarged spleen (1000ml). Absence of the BCR-ABL1 rearrangement on peripheral blood and bone marrow, led to molecular investigations for other CMNs, tests for mutations in JAK2, CALR and MPL genes resulted negative, excluding common CMN. Cytogenetics investigations on bone marrow, showed presence of a rearrangement between chromosome 5 (Chr5) and chromosome 14 (Chr14). To understand the nature of this rearrangement, FISH analysis was performed using WCP probes for Chr5 and 14, followed by LSI probes for the chromosomal regions 5q31, 5q33 and 14q32. The results revealed an inverted insertion of a segment from the long arm of a Chr5 into the long arm of a Chr14. This finding indicated the involvement of the 5q32 region, where the PDGFRB gene is located. Following a combined WGS and RNAseq, a fusion between the PDGFRB and CCDC88C genes was identified, responsible for the constitutive activation of PDGFRB. To confirm the predicted sequence, a pair of specific primers was designed to amplify and sequence the cDNA of the fusion gene. Thanks to the rapid identification of the rearrangement of the PDGFRB gene, the patient benefited from target therapy with TKI, and just one month after imatinib starting, a full blood count normalization with reduction of spleen volume was obtained. To date, the patient remain on imatinib therapy (200mg/day) and is in molecular remission continuing to be monitored by RT-qPCR.

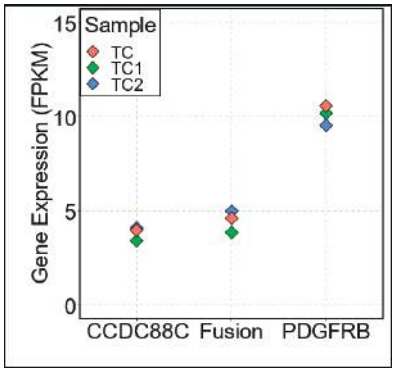

Figure 1.

DP090

IDENTIFICATION OF CIRCULATING CELL-FREE DNA CHROMOSOMAL ABNORMALITIES IN AGGRESSIVE HEMATOLOGICAL MALIGNANCIES BY NON-INVASIVE PRENATAL TEST

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Introduction. Liquid biopsy is a minimally invasive diagnostic tool for identification of tumor-related mutations in circulating cell-free DNA (cfDNA), while non-invasive prenatal test (NIPT) is routinely used for catching fetal-related chromosomal abnormalities in prenatal screening. The aim of this study was to investigate feasibility, sensitivity, and specificity of NIPT for identification of chromosomal abnormalities in cfDNA in hematological malignancies.

Methods. A total of 78 patients with hematological malignancies (plasma cell dyscrasias, N=20; chronic lymphocytic leukemia [CLL], N=22; Hodgkin lymphoma, N=10; and B-cell lymphomas, N=26), from 2016 to September 2023 at the Hematology and Transplant Center, University Hospital "San Giovanni di Dio e Ruggi D'Aragona", Salerno, Italy, were included in this study. Whole peripheral blood samples at diagnosis or at disease relapse was collected in appropriate tubes for preventing clotting and maintaining high DNA stability (STRECK Cell-Free DNA BCT, Streck Corporate, NE 68128, USA). NIPT was performed using the Illumina Next-Generation Sequencing (NGS) technology.

Results. By NIPT-based liquid biopsy, at least one chromosomal abnormality in cfDNA was detected in half of patients, more frequently on chromosome 6 (23.1%), 9 (20.5%), 3 and 18 (16.7%), with losses of chromosome 6 and gains of chromosome 7 negatively impacting on overall survival (OS), with a 5-year OS of 26.9% and a median OS of 14.6 months, respectively (P=0.0009 and P=0.0004). Among hematological malignancies investigated, B-cell lymphomas displayed the highest NIPT positivity, especially aggressive lymphomas. Moreover, plasma cell dyscrasia with extramedullary disease had a higher NIPT positivity compared to conventional cytogenetics analysis.

Discussion. In conclusions, NIPT-based liquid biopsy could be employed as a complementary minimally invasive tool for chromosomal abnormality detection in hematological malignancies, especially in plasma cell dyscrasia and B cell lymphomas. However, prospective studies on larger cohorts are needed to validate clinical utility of NIPT-based liquid biopsy in routinely clinical practice.

DP091

THE ASSOCIATION OF TYROSINE KINASE INHIBITORS AND DIRECT-ACTING ORAL ANTICOAGULANTS IN CHRONIC MYELOID LEUKEMIA PATIENTS IS FEASIBLE AND DOES NOT INCREASE THE RISK OF ADVERSE EVENTS

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In vitro studies suggested the possibility of significant drug-drug interactions mediated by P-glycoprotein between Tyrosine Kinase Inhibitors (TKIs) and direct-acting oral anticoagulants (DOACs). However, there is a complete lack of information about this therapeutic association *in vivo*. Four Italian centers were involved.

Table 1. Patients's baseline characteristics and outcome according to treatment.

Clinical characteristics	N pts
Males, n° (%)	29 (80.6)
Median Age, years (range)	71 (47-93)
Median follow-up from diagnosis, months (range)	107 (2-304)
Median time of simoultaneaous TKIs-ACT, months (range)	21 (1-110)
ELTS score, n **Low,** n (%) **Intermediate,** n (%) **High,** n (%)	32 13 (40.6) 9 (28.1) 10 (31.3)
SOKAL score, n **Low, n (%)** **Intermediate, n (%)** **High, n (%)**	32 9 (28.1) 18 (56.3) 5 (15.6)
Transcript type, n **p210,** n (%) **p190,** n (%) **p230,** n (%)	34 31 (91.2) 1 (2.9) 2 (5.9)
TKIs-therapy line at the start of DOACs, n **1st,** n (%) **2nd,** n (%) **3rd,** n (%)	36 25 (69.4) 8 (22.2) 3 (8.4)
TKIs, n **Imatinib,** n (%) **Nilotinib,** n (%) **Dasatinib,** n (%) **Bosutinib,** n (%)	36 26 (72.2) 3 (8.3) 3 (8.3) 4 (11.2)
Type of DOACs, n **Edoxaban,** n (%) **Apixaban,** n (%) **Rivaroxaban,** n (%) **Dabigatran,** n (%)	36 10 (27.8) 11 (30.6) 10 (27.8) 5 (13.8)
CONCOMITANT TKIs and DOACs	
Reason for starting DOACs, n **Atrial fibrillation,** n (%) **Venous Thromboembolism,** n (%) **&** **Other,** n (%) *	36 28 (77.8) 6 (16.7) 2 (5.5)
TKIs dose modification for DOACs therapy, n (%) **TKIs STOP for DOACs therapy,** n (%)	0 / 36 (0) 0 / 36 (0)
DOACs STOP, n (%) **DOACs STOP reason** **Hemorrhage,** n (%) **CML progression,** n (%) **Reduced DOAC dose, n (%) #**	4/36 (11.8) 3 (75) 1 (25) 8 / 36 (22.2)
TKI changing/stop reason, n (%) **Toxicity/Intollerance,** n (%) **CML resistance,** n (%) **TFR,** n° (%)	9 (25) 4 (44.4) 1 (11.2) 4 (44.4)
Hemorrage AEs, n (%) **§** **G1,** n (%) **G2,** n (%) **G3,** n (%)	4 (11.1) 1 (25) 1 (25) 2 (50)

TKIs tyrosine kinase inhibitors, ACT anticoagulant therapy, DOACs direct oral anticoagulants, CML Chronic Myeloid Leukemia, TFR treatment free remission, AEs Adverse Events
& **Venous Thromboembolism**: 4 pts for Deep vein thrombosis, 2 pts for pulmonary embolism
***** **Other**: 1 patient for recurrent Transient Ischemic Attacks, 1 patient for mitral valve valvuloplasty
# **Reduced DOAC dose**: 7/8 patients on apixaban (median dose 5 mg/day), 1/8 on rivaroxaban (10 mg/day)
§ Grading AEs in according to CTCAE v5.0

We retrospectively examined 36 CML patients (pts) treated with TKIs and DOACs between 2003 and 2023, aiming to assess the safety and feasibility of concurrent therapy. Twentynine male pts (80.6%), median age at diagnosis 71 years (range 47-93). Median follow-up time for this cohort was 107 months (range 2-304) and median time on concurrent DOACs and TKIs was 21 months (range 1-110). At the initiation of DOAC, 29 out of 36 pts (79.6%) were already on TKI treatment. Among these patients, 69.4% were on first-line, 22.2% on second-line, and 8.3% on third-line TKI therapy. The TKIs used were imatinib (20/29, 68.9%), bosutinib (4/29, 13.8%), nilotinib (3/29, 10.4%), and dasatinib (2/29, 6.9%). The remaining 7 pts started frontline TKI while already on DOAC treatment: in these case TKI was imatinib (6/7, 85,7%) and dasatinib (1/7, 14,3%). The main reasons for starting DOACs were atrial fibrillation (28/36,77.8%) and venous thromboembolism (VTE, 6/36,16.7%). The most commonly used DOACs was apixaban (11/36, 30.6%). During combined therapy, TKIs were interrupted or modified in 9/36 pts (25%) due to toxicity or intolerance (4 cases), treatment-free remission (4 cases), and CML resistance (1 case). Hemorrhagic adverse events (HAEs) occurred in 4 pts (11.1%), two of which were grade 3. DOACs were discontinued in 3 pts (9%), all due to hemorrhage. At the time of analysis, 27/36 pts (75%) were alive, with no deaths attributable to major HAEs. Of the total, 30/36 pts (83.3%) were on TKI treatment and 33/36 pts (91.7%) were still on anticoagulant therapy. No cases of VTE or stroke were registered during combined treatment. The sole case of resistance observed involved a pt on first-line imatinib, already on apixaban, who experienced failure within three months, necessitating a switch to bosutinib, resulting in treatment response. In conclusion, our data suggest that all available DOACs may be associated with ongoing TKI therapy. Compared to data with DOACs in the general population, there does not appear to be an excess of HAE, and pts mainly maintained a stable TKI dose. A larger cohort of pts will be needed to confirm this observation.

DP092

BASELINE FEATURES, TREATMENT CHOICE AND EARLY FRONTLINE TKI PERMANENT DISCONTINUATION IN PATIENTS WITH NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA AGED 50-60 YEARS: A "CAMPUS CML" STUDY

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Introduction. Median age at diagnosis in patients (pts) with Chronic Myeloid Leukemia (CML) is 58 - 60 years: while Second Generation Tyrosine-Kinase Inhibitors (2G-TKIs) are preferred in younger pts and imatinib (IMA) in elderly pts, there is no definite consensus on the best choice in middle-aged cases Aim: To analyze initial features, choice of frontline TKI and early adverse events leading to permanent TKI discontinuation in the first 12 months from TKI start in newly diagnosed subjects aged 50 - 60 in a large real-life cohort of CML pts.

Table 1. Clinical features and causes of early frontline TKI discontinuation according to frontline TKI treatment.

	All pts (424)	Pts treated with IMA (191)	Pts treated with 2G-TKI (233)	p
Gender, M/F (%)	236/188 (55.7 – 44.3)	105/86 (55.0– 45.0)	131/102 (56.0 – 44.0)	0.827
Median age (years) (IQR)	55.0 (52.6 – 57.6)	55.8 (53.3 – 58.1)	54.5 (52.0 – 57.1)	**0.005**
Hb, g/dl (IQR)	12.6 (11.0 – 14.0)	12.6 (11.4 – 13.9)	12.4 (10.7 – 14.0)	0.842
WBC, x 10^9/l (IQR)	62.0 (31.4 – 149.7)	48.8 (26.1 – 116.7)	69.0 (36.9 – 172.4)	**0.002**
PLTS, x 10^9/l (IQR)	344 (246 – 544)	330 (242 – 545)	362 (257 – 544)	0.149
Spleen, n° evaluable (%):	406	183	223	
Not palpable	203 (50.0)	101 (55.2)	102 (45.9)	
< 5 cm below costal margin	123 (30.3)	56 (30.6)	67 (29.7)	0.061
≥ 5 cm below costal margin	80 (19.7)	26 (14.2)	54 (24.4)	
Sokal score, n° evaluable (%):	404	180	224	
Low	204 (50.5)	104 (57.8)	100 (44.4)	
Intermediate	158 (39.1)	65 (36.1)	93 (41.7)	**0.006**
High	42 (10.4)	11 (6.1)	31 (13.9)	
Arterial hypertension, n° (%)	148 (34.9)	77 (40.3)	71 (30.6)	**0.037**
Diabetes, n° (%)	42 (9.9)	24 (12.6)	18 (7.8)	0.100
Previous neoplasm, n° (%)	43 (10.1)	31 (16.2)	12 (5.2)	**<0.001**
COPD, n° (%)	23 (5.4)	12 (6.3)	11 (4.7)	0.487
Acute myocardial infarction, n° (%)	21 (5.0)	15 (7.9)	6 (2.6)	**0.013**
Concomitant drugs, n° evaluable (%):	423	190	233	
0	174 (41.1)	56 (29.5)	118 (50.4)	
1 – 2	144 (34.1)	65 (34.2)	79 (34.1)	**<0.001**
3 - 5	78 (18.4)	50 (26.3)	28 (12.1)	
> 5	27 (6.4)	19 (10.0)	8 (3.4)	
Pts with permanent TKI discontinuation, n° evaluable(%):	398	185	213	
All causes	73 (18.6)	51 (27.6)	22 (10.3)	**<0.001**
Haemathologic toxicity	11 (2.8)	8 (4.3)	3 (1.4)	0.077
Extra-haematologic toxicity	19 (4.8)	10 (5.4)	9 (4.2)	0.582
Primary resistance	38 (9.5)	31(16.8)	7 (3.3)	**<0.001**
Secondary resistance	1 (0.3)	/	1 (0.5)	0.351
Evolution in blastic phase	2 (0.6)	/	2 (0.9)	0.186
Unrelated death	2 (0.6)	2 (1.1)	/	0.128

Methods. Among 1967 CML pts newly diagnosed from 1/2012 to 12/2019 in 38 Italian Centers participating at the "Campus CML" project, 424 (21.5%) aged 50 - 60 years: their features at diagnosis and during the first year of TKI treatment were collected and analyzed in the present report.

Results. According to responsible physician choice, 191 pts (45.0%) received frontline IMA and 233 (55.0%) a 2G-TKI (dasa-

tinib in 78, nilotinib in 135). Features at diagnosis in the whole cohort and according to frontline TKI are reported in the Table 1: pts treated with 2G-TKI had higher WBC count and int/high-risk Sokal score, while pts treated with IMA had higher rates of comorbidities/concomitant drugs. Twenty-six pts had only baseline data and were not evaluable for early adverse events: the numbers/rates of evaluable pts who needed permanent frontline TKI discontinuation and the causes of discontinuation in the first 12 months according to treatment are reported in the Table 1. On the whole, 51/185 pts treated with IMA (27.6%) discontinued frontline TKI treatment versus 22/213 (10.3%) treated with 2G-TKI (p<0.001). Cumulative incidence of discontinuation at 12 months was 25.8% (95%CI 19.5-32.1) in pts treated with IMA versus 9.5% (95%CI 5.6-13.4) in pts treated with 2G-TKI (p<0.001). The difference remained significant also considering different Sokal risk groups [17.8% versus 4.5% in low risk (p=0.004), 34.4% versus 13.1% in intermediate risk (p=0.002) and 55.6% versus 13.8% in high risk (p=0.003)].

Conclusions. Frontline treatment of pts in this age group is still heterogenous in the current clinical practice: concomitant diseases, which are very rare in younger pts, start to be more common in this age group and represent an important criterion of TKI choice. Present data seem to encourage the use of frontline 2G-TKI in this subset, but data on molecular response and late toxicities are warranted to complete present analysis.

Lymphomas II

DP093

ABSTRACT NOT PUBLISHABLE

DP094

ROLE OF CIRCULATING TUMOUR DNA IN PREDICTING SURVIVAL OF PERIPHERAL T-CELL LYMPHOMAS AT DIAGNOSIS

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Background. Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of non-Hodgkin lymphomas associated with a poor prognosis. We observed that higher concentration of cell free DNA (cfDNA) at diagnosis correlated with worse survival. However, little is known about the role of circulating tumour DNA (ctDNA) in predicting clinical outcome. Therefore, we aimed at understanding the association of ctDNA with clinical parameters and survival, and assessing pre-treatment PTCL mutational profile in plasma.

Methods. We performed analysis on a cohort of 51 newly diagnosed patients with different PTCL histologies (nodal T-follicular helper lymphoma (nTFHL;n=18); Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS; n=21); Anaplastic Lymphoma Ki-

nase-negative Anaplastic large-cell lymphoma (ALK^{neg} ALCL;n=12). After cfDNA extraction and library preparation, a targeted sequencing panel of 60 genes was used to identify somatic mutations. Sequencing was performed on NextSeq 550 (Illumina). Variants were called and annotated with a bioinformatic pipeline.

Results. Pre-treatment ctDNA levels had a high correlation with cfDNA concentration (r=0.92, p<0.0001). Higher pre-treatment ctDNA levels were associated with high IPI (>2, p=0.0015) and PIT scores (≥2, p=0.0054), increased LDH (greater than upper normal limit, p<0.0001), and worse performance status (ECOG status >0, p= 0.014). By receiver operating characteristic (ROC) curve we identified a cut-off value of ctDNA (3.14 log hGE/mL) associated with survival (PFS p=0.014; OS p=0.003). Additionally, somatic mutations in plasma were detected in 48/51 patients. Frequently mutated genes included TET2 (29%), IDH2 (20%), RHOA (16%) and TP53 (14%). TET2 mutations were found to be significantly associated with nTFHL histology (11/18, p=0.0011) as compared to other histologies. Interestingly, we found that irrespective of histology, the co-occurence of TET2 and IDH2 mutations conferred a better progression free survival probability (p=0.03) as compared to patients with only TET2 mutations.

Conclusions. We demonstrated that higher ctDNA levels at baseline associate with adverse clinical characteristics and poor prognosis. Therefore, ctDNA can be used as a complementary tool in the assessment of PTCL prognosis. Additionally, the presence of TET2/IDH2 co-mutations in pre-treatment plasma was associated to a better survival, highlighting the importance of understanding the diverse mutational profile of PTCLs

DP095

UPDATED RESULTS FROM THE PHASE 2 WAVELINE-004 STUDY OF ZILOVERTAMAB VEDOTIN (ZV) IN RELAPSED OR REFRACTORY (R/R) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Treatment options are limited for patients (pts) with DLBCL whose disease progressed after or are ineligible for autologous stem cell transplantation (ASCT) or chimeric antigen receptor T-cell (CAR-T) therapy. ZV is a ROR1-targeting antibody-drug conjugate that was shown to have antitumor activity and manageable safety in pts with R/R DLBCL whose disease progressed after or who were ineligible for ASCT and/or CAR-T therapy in the phase 2 waveLINE-004 study (NCT05144841). Here, we present additional follow-up from waveLINE-004. Eligible pts were ≥18 y old and had R/R DLBCL that progressed after ≥2 lines of therapy including an alkylating agent, anthracycline, and an anti-CD20 antibody and had progressed after or were ineligible for ASCT and CAR-T therapy. All pts received ZV 2.5 mg/kg IV Q3W until disease progression, unacceptable toxicity, or withdrawal. The primary end point was ORR per Lugano 2014 criteria by investigator review. Secondary end points were DOR per Lugano 2014 criteria and safety/tolerability. DCR (CR + PR + SD) and PFS per Lugano 2014 criteria and OS were exploratory. Ninety-eight pts were enrolled and received ≥1 dose of ZV. At data cutoff (Apr 26, 2023), 61 pts (62%) had discontinued ZV and 37 pts (38%) were ongoing. Median age was 66 y, 64% of pts were male, and 71% had received ≥3 prior lines of therapy; 15% of pts had undergone prior ASCT, 18% prior CAR-T therapy, and 5% both. Median follow up was 4.5 mo (range, 0.2-13.2) for pts who received ≥1 dose of ZV and 5.6 mo (range, 0.9-13.2) for the 79 pts with ≥1 postbaseline scan. ORR was 29% (95% CI, 19.4-40.4; 10 CR, 13 PR) and DCR was 42% (95% CI, 30.8-53.4; 10 SD). Median DOR was 3.0 mo (range, 0.0+ to 8.8+). Median PFS was 2.5 mo (95% CI, 1.9-3.0); 6-mo PFS was 15%. Median OS was 10.6 mo (95% CI, 5.1-NR); 6-mo OS was 62%. TRAEs occurred in 80% of pts, most commonly (≥25%) neutrophil count decreased (48%) and anemia (26%). Grade 3-5 TRAEs occurred in 52% of pts. Two pts (2%) died because of TRAEs (septic shock, acute kidney injury). Four pts (4%) discontinued ZV because of TRAEs. Peripheral neuropathy occurred in 18% of pts (grade 3 or 4, 2%) and led to dose modification in 10%. One pt (1%) experienced a grade 2 treatment-related infusion reaction. With additional follow-up, ZV continued to demonstrate clinically meaningful antitumor activity and manageable safety in pts with R/R DLBCL whose disease progressed after or were ineligible for ASCT and/or CAR-T therapy.

DP096

ABSTRACT NOT PUBLISHABLE

DP097

MONOMORPHIC LYMPHOPROLIFERATIVE DISORDERS FOLLOWING HEART TRANSPLANTATION: A SINGLE CENTER EXPERIENCE ON 1055 TRANSPLANTS

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Background. Post-transplant lymphoproliferative disorder (PTLD) refers to a wide array of immunosuppression-related complications following solid organ transplantation among which monomorphic-PTLD (M-PTLD) is rare but potentially fatal.

Aim. To evaluate the incidence and clinical outcome of M-PTLD in heart transplant patients, a population at high risk for this complication

Method. In the last 39 years, 1055 pediatric and adult patients underwent heart transplantation at ASST-Papa Giovanni XXIII, Bergamo. All adult patients who developed M-PTLD were enrolled in the study.

Results. Forty patients developed M-PTLD (3.8%): 20 diffuse large B cell Lymphoma, 5 Plasmablastic Lymphoma, 1 High Grade B Cell Lymphoma, 5 Burkitt Lymphoma, 1 Marginal zone lymphoma, 1 MALT lymphoma, 6 Hodgkin lymphoma and 1 Peripheral T Cell lymphoma. Median time from transplant to M-PTLD was 12 years (range 8 months-34 years). At PTLD diagnosis median age was 52 years (range 18-80) and adverse clinical characteristics were: stage III-IV (n=28), B symptoms (n=14), bulky disease (n=10), IPI intermediate-high/ high (n= 30). EBV-DNA integration in lymphoma

cells was documented in 17 of the 27 evaluable cases. Twenty-three aggressive B cell M-PTLD were treated with R-CHOP and R G-MALL chemotherapy programs, 4 with P-VABEC, 1 with CODOX-M-IVAC, 3 with Rituximab monotherapy. Rituximab monotherapy was used also in Marginal zone lymphoma, anti H. Pylori antibiotics in MALT. All but one Hodgkin patients received ABVD. Peripheral T Cell Lymphoma received CHOP. Complete remission (CR) rate was 75%. After a median follow up of 3 years (range 0-16), median EFS and OS were 6.6 and 7 years, respectively (Figure 1). Twenty-one patients died during follow up. Nine patients experienced an early death: 5 during induction, 4 within 6 months from the end of chemotherapy (3 while in CR; 1 early relapse). Four patients were refractory to first line therapy and died due to progressive disease. The other 8 patients died in CR mainly due to infections. By univariate analysis, the presence of B symptoms was associated with worse EFS (p=0.01) and OS (p=0.01), while late occurring M-PTLD showed a better EFS (p=0.05) and OS (p=0.02).

Conclusions. Early mortality represents an unmet clinical need in M-PTLD: in our experience up to 43% of M-PTLD patients died during induction chemotherapy or within the first 6 months after. Remarkably, patients who achieve CR enjoy sustained and prolonged responses.

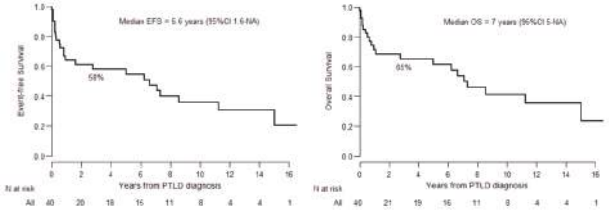

Figure 1.

DP098

CLINICAL PRESENTATION, DIAGNOSIS, AND TREATMENT O F VITREORETINAL LYMPHOMA: ANALYSIS OF A LARGE COHORT FROM TWO ITALIAN REFERRAL CENTRES

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Large B-cell lymphomas may involve vitreous and/or retina exclusively (Primary Vitreoretinal Lymphoma; PVRL) or in association with CNS disease, as well as may represent a secondary localization from systemic lymphoma. Data describing main characteristics at presentation and optimal management are limited. Herein, we present data collected on lymphoma pts with initial ocular symptoms diagnosed at two Italian referral centres. Pts referred primarily to ophthalmologists due to ocular symptoms were considered. VRL diagnosis was obtained by cytological assessment and/or presence of molecular results ($MYD88^{L256P}$ mutation, high L-10, clonal IgH by PCR) in the ocular fluids, along with a suggestive ophthalmological assessment. Detection of concurrent extra-ocular disease at staging was not an exclusion criterion. Sixty-two pts (median age 66y; 35-88, 23 males) assessed between 2011 and 2024 were included. Median time from symptom onset to diagnosis was 10 months (0.3-43). Vitrectomy was performed in 60 (97%) pts. VRL suspicion was confirmed by conventional cytology in 19 (31%) pts, by molecular markers in 12, and by both in 31. Thirteen (21%) pts had a concurrent systemic or CNS involvement (SVRL); 56 pts (90%) received an active treatment (13 local, 8 systemic, 35 combined). Intravitreal MTX or rituximab were used for local treatment (median 25 injections, 1-25). Pts received at least 2 cycles of systemic therapy. 43 pts received HD-MTX- based chemo, associated with HD-ARAC in 32. Systemic therapy was consolidated with ASCT in 7 and with local RT in 2. Best response was CR in 33 pts (64%) and PR in 4 (10%) with an ORR of 74%. At a median follow-up from diagnosis of 28 months (0.1-82), 18/49 evaluable pts (37%) remain free of relapse; systemic therapy was superior to local (mPFS 9 mo *vs* 21 mo; p=0.007) one. Median PFS was 17 mo (95% CI 11-30). CNS progression occurred in 29/49 treated pts, 11/13 (85%) after local *vs* 16/43 (37%) after systemic therapy. Two pts rapidly progressed before any treatment. Local progression occurred in 15 pts, concurrent to CNS in 6. Median OS was 29 mo (95% CI 21-38), 28 pts died (lymphoma=12; UNK=12; others=4). Survival did not differ between PVRL and SVRL. Molecular approaches resulted very helpful in the diagnostic workup of pts with VRL involvement. Staging procedures are mandatory to properly stratify pts at disease onset. Treatment of PVRL remain challenging and systemic therapy is associated with a better PFS and reduced CNS events.

DP099

NAVAL-1: PHASE 2 TRIAL EVALUATING NANATINOSTAT IN COMBINATION WITH VALGANCICLOVIR IN PATIENTS WITH EPSTEIN-BARR VIRUS-POSITIVE RELAPSING/REFRACTORY LYMPHOMAS (EBV+). ONGOING TRIAL

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Purpose. Epstein-Barr virus-positive lymphomas are a heterogeneous group of malignancies with the outcomes typically inferior compared to the EBV– counterpart. Nanatinostat is a potent Class-I histone deacetylase inhibitor (HDACi) with a novel MoA. Nstat induces expression of the lytic BGLF4 PK, which activates the nucleoside analog ganciclovir via phosphorylation. Incorporation of phosho-ganciclovir into cellular DNA results in termination of DNA replication and apoptosis. In a Phase 1b/2 study (NCT05011058) of patients with R/R EBV+ lymphoma, the combination of Nstat and valganciclovir (Nana-val) was generally well-tolerated and showed promising preliminary activity (Haverkos 2023). Among the 8 patients with R/R EBV+ PTCL-NOS or AITL evaluable for response, the ORR was 50% with a median DOR of 17.3 months and a CRR of 37.5%.

Materials and Methods. NAVAL-1 (NCR05011058) is a Phase 2, international, open-label, multicenter, single-arm, two-stage, bas-

ket trial currently enrolling patients with R/R EBV+ DLBCL, PTCL (including PTCL NOS and AITL), PTLD and other lymphoma subtypes. The PTCL cohort completed Stage 1 and was therefore selected for this analysis. Eligible PTCL patients had received ≥1 prior systemic therapies. First twenty Stage 1 patients were randomized 1:1 to receive Nstat alone or together with VGCV and followed for efficacy and safety. Monotherapy patients were eligible for crossover to combination therapy for stable disease. Efficacy endpoints included ORR, CRR, and DOR.

Results. As of 07FEB2024, of the 10 patients in the Nana-val arm, the ORR was 50% and the CRR was 20% in the intent-to-treat population (71% and 29% in the efficacy-evaluable population), whereas in the Nstat monotherapy arm, the ORR and CRR were 10% and 0%, respectively. Treatment-related adverse events (TRAEs) have been primarily Grade 1-2 in severity, and most Grade 3-4 TRAEs have been haematologic in nature and generally manageable or reversible with only 1 Grade 5 TRAE. Treatment-related serious adverse events have included pancytopenia, angina pectoris, pyrexia, influenza, pneumonia, sepsis, upper respiratory tract infection, muscular weakness, confusional state, and pharyngeal haemorrhage (each n=1).

Conclusions. Nana-val therapy is emerging as a promising treatment for patients R/R EBV+ PTCL. The R/R EBV+ PTCL cohort met the efficacy threshold for expansion into Stage 2 of the study (Figure 1). Additional data from Stage 2 of combination therapy will be presented.

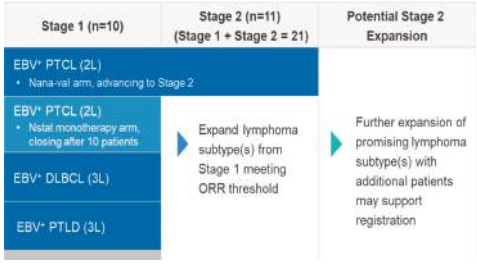

Figure 1.

DP100

RITUXIMAB AND LENALIDOMIDE (R2-MANT) VS RITUXIMAB ALONE (R-MANT) AS MAINTENANCE TREATMENT AFTER CHEMOIMMUNOTHERAPY FOR ELDERLY PATIENTS WITH R/R FOLLICULAR LYMPHOMA (FL): FINAL ANALYSIS OF RENOIR PHASE III STUDY OF THE FONDAZIONE ITALIANA LINFOMI (FIL)

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Background. R2 in induction showed a good clinical activity with low toxicity in both untreated and R/R FL patients. R2 as maintenance treatment is less studied.

Methods. RENOIR (NCT02390869) is a FIL multicenter randomized phase III open-label study for elderly patients or those not eligible for more intensive therapy with advanced stage R/R FL who received 1 or 2 prior therapies. Induction treatment was 4-6 cycles of standard Rituximab-Bendamustine or CHOP or CVP. Responders were randomized 1:1 to standard arm (R-MANT) with Rituximab maintenance (375 mg/m^2 IV every 12 weeks for 8 doses) or to experimental arm (R2-MANT) with R2 maintenance (Rituximab maintenance and Lenalidomide 10 mg/day, days 1-21 per 28-day cycle for 24 cycles. The primary endpoint was 2-yr progression-free survival (PFS) comparing R2-MANT *vs* R-MANT. A 2yr PFS improvement from 60% to 78% favoring R2 arm was considered relevant.

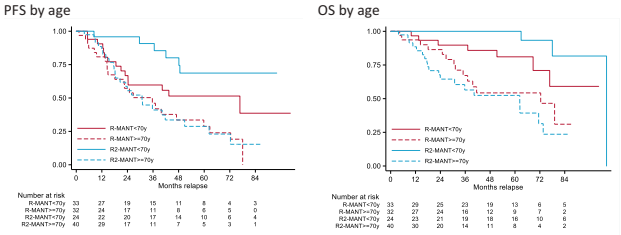

Figure 1.

Results. From May 2014 to October 2022, 152 subjects were enrolled. Median age was 71 years (IQR, 67-77), 55% male, 41% and 39% were at FLIPI intermediate-high or high risk, 78% relapsed and 22% were refractory to last treatment. At the end of induction ORR was 85% (n=129) with CR 58% (n=88). One hundred and twenty-nine patients were randomized (R-MANT 65 and R2-MANT 64). With a median follow up of 60 months, 2-yr PFS rate was higher in R2 arm, though not statistically significant: R2-MANT *vs* R-MANT 2-yr PFS 71% *vs* 62% (HR 0.75, 95%CI 0.46-1.21,p=.243). Two-yr OS rates for R2-MANT *vs* R-MANT were: 78% *vs* 88% (HR 1.06, 95%CI 0.58-1.94, p=.855). Subgroup analyses suggest a benefit for R2 only in patients <70yr (HR=0.37, p-interaction=0.087 and HR=0.27, p-interaction=0.047, for PFS and OS, respectively). The most common grade 3/4 AEs in R-MANT *vs* R2-MANT were: neutropenia (15% *vs* 41%, p=.002), gastrointestinal disorders (2% *vs* 9%, p=.116), infections (3% *vs* 11%, p=.166). Treatment interruption

for toxicity increased with age: 39% <70yrs and 51% >=70 yrs. Deaths were 49: 10 patients not randomized; R-MANT 20 and R2-MANT 19.

Conclusions. RENOIR study showed no evidence that the addition of Lenalidomide to Rituximab as maintenance treatment in elderly R/R FL improves PFS and OS overall, and increased the incidence of adverse events. However, the trial suggests that R2 may be effective in patients <70yrs, with a potentially relevant improvement of PFS, OS and a reduced toxicity.

DP101

BURKITT INTERNATIONAL PROGNOSTIC INDEX FOR DEFINING RISK GROUPS IN ADULT BURKITT LYMPHOMA AND LEUKEMIA TREATED WITH THE R-GMALL PROTOCOL

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Background. Burkitt Lymphoma and Leukemia (BL) are highly aggressive lymphoid malignancies. High cure rates are reported with dose-intense chemotherapy derived from pediatric leukemia regimens. The prognostic Index for Burkitt Lymphoma (BL-IPI), based on age ≥ 40 years, performance status ≥ 2, serum lactate dehydrogenase > x3 upper limit of normal, and CNS involvement extensively stratifies the probability of achieving a complete response in patients receiving intensive chemotherapy, such as R-daEPOCH or R-CODox-M/R-IVAc. This retrospective observational analysis aims to evaluate the prognostic utility of the BL-IPI score in adult patients affected by BL treated with the GMALL BALL/NHL 202 protocol (GMALL).

Figure 1 A-B: OS and PFS according to BL-IPI risk group

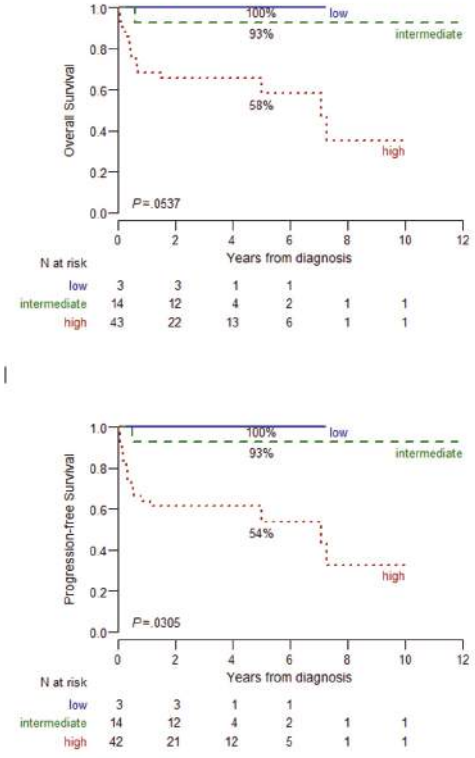

Figure 1.

Methods. Between December 2002 and December 2022, 60 patients with BL were included in this analysis. The diagnosis of Burkitt lymphoma was based on histological examination and cytogenetic translocation according to the World Health Organization (WHO) 2022 criteria. According to the protocol, patients younger than 56 years received the full dose of GMALL (6 blocks of intensified chemotherapy), while patients aged over 55 years received a de-intensified drug dosage. Patients with stage III–IV disease or mediastinal and extra-nodal involvement received a total of six courses, whereas patients with stage I–II diseases were scheduled for four cycles.

Results. This cohort of 60 patients was characterized by a median age of 48 years (range 16- 79). According to the BL-IPI 3 patients (5%) were stratified as low risk (no risk factor), 14 (23%) as intermediate-risk (1 risk factor), and 43 (72%) as high risk (≥2 risk factors). There were significant differences in progression-free survival (PFS) and overall survival (OS) between patients with high, intermediate, and low risk. The 5-year OS was 100% ,93%, and 58% in low, intermediate, and high risk, respectively (P=0.0537), while the 5-year PFS was 100%, 93%, and 54% (P=0.0305) in patients with low, intermediate and high-risk B-IPI, respectively (Figure 1 A-B).

Conclusions. In patients treated with the R-GMALL program, the BL-IPI is a strong predictor of clinical response and survival. Furthermore, our analysis confirmed the overall effectiveness of this treatment in BL patients.

DP102

EPCORITAMAB WITH RITUXIMAB + LENALIDOMIDE (R2) IN PREVIOUSLY UNTREATED (1L) FOLLICULAR LYMPHOMA (FL) AND SINGLE-AGENT EPCORITAMAB MAINTENANCE THERAPY IN FL: EPCORE NHL-2 ARMS 6 AND 7

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There is an unmet need for treatment (tx) options that induce complete responses (CRs) in patients (pts) with 1L FL and improve long-term outcomes for pts whose disease responds to tx. We present results from arms 6 and 7 of EPCORE® NHL-2 (phase 1/2; NCT04663347), with longer follow-up for epcoritamab + R^2 in 1L FL (arm 6) and initial results for epcoritamab maintenance tx in pts with FL in CR or partial response (PR) after 1–2 lines of standard-of-care tx (arm 7). Adults with $CD20^+$ FL grade (G) 1–3A received subcutaneous epcoritamab 48 mg (arm 6: QW cycle [C] 1–2, Q4W C3–26 [28 d/C]; arm 7: QW C1 [28 d/C], Q8W C2–13 [56 d/C]). In arm 6, pts also received R^2 for ≤12 Cs. Pts received step-up doses of epcoritamab and corticosteroid prophylaxis in C1 to mitigate CRS. Primary endpoints were overall response rate (ORR) per Lugano in arm 6 and safety/tolerability in arm 7. As of Nov 22, 2023, 41 pts received epcoritamab + R^2 in arm 6 and 20 pts received epcoritamab maintenance tx in arm 7. In arm 6, median age was 57 y and 34% of pts had FLIPI 3–5. Median follow-up (mFU) was 21.1 mo. ORR was 95% and CR rate was 85%. At 18 mo, an estimated 86% of responders remained in response, 93% of pts with CR remained in CR, 89%

of pts were progression free, and 90% of pts remained alive. In arm 7 (mFU, 19.7 mo), median age was 54.5 y, 25% of pts had FLIPI 3–5, and 60% had CR and 40% had PR prior to epcoritamab maintenance. Prior tx included anti-CD20 tx (100%), alkylating agents (80%), and anthracyclines (50%); 80% of pts had 1 prior tx line. All 8 pts enrolling with PR converted to CR. At 21 mo, an estimated 83% of pts remained in response and 90% were alive. The most common tx-emergent AEs (TEAEs) were COVID-19 (63%), CRS (56%), and neutropenia (56%) in arm 6 and COVID-19 (70%) and CRS (55%) in arm 7. CRS events were all low grade (arm 6: 41% G1, 15% G2; arm 7: 40% G1, 15% G2), most occurred after the first full dose, all resolved, and none led to tx discontinuation. No ICANS or clinical tumor lysis syndrome occurred in either arm. Two pts in arm 6 and 1 pt in arm 7 had fatal TEAEs. Longer follow-up of pts with 1L FL treated with epcoritamab + R^2 showed deep, durable responses and manageable safety consistent with prior reports. In these initial results for arm 7, epcoritamab maintenance tx induced conversions from PR to CR with manageable safety and no new safety signals. These data support further investigation of epcoritamab-based, chemotherapy-free tx regimens in FL.

DP103

UPDATED RESULTS FROM THE EPCORE NHL-2 TRIAL: EPCORITAMAB + GEMOX INDUCES DEEP AND DURABLE RESPONSES IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (R/R DLBCL)

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Outcomes are suboptimal for patients (pts) with R/R DLBCL treated with gemcitabine + oxaliplatin (GemOx) and rituximab: complete response (CR) rate, 33%; median progression-free survival (PFS), 5 mo; median overall survival (OS), 10 mo (Cazelles et al, *Leuk Lymphoma* 2021). We report efficacy and safety of epcoritamab + GemOx for the treatment (tx) of autologous stem cell transplant (ASCT)-ineligible pts with difficult-to-treat R/R DLBCL in a larger cohort from the EPCORE® NHL-2 trial (phase 1/2; NCT04663347). Pts with R/R CD20$^+$ DLBCL who were ineligible for ASCT or for whom ASCT had failed received subcutaneous epcoritamab (2 step-up doses followed by 48-mg full doses) in 28-d cycles (C; QW, C1–3; Q2W, C4–9; Q4W, C≥10) until unacceptable toxicity or disease progression. GemOx was given Q2W for the first 4 cycles. As of Sept 1, 2023, 97 pts with ≥6 mo of follow-up were treated (median follow-up, 9.7 mo). Median age was 72 y, with 34% of pts ≥75 y. Pts had a median of 2 prior lines of tx (pLOT; range, 1–6); 61% of pts had ≥2 pLOT. Overall, 55% of pts had primary refractory disease, 38% had bulky disease (>6 cm), 30% had prior CAR T, and 9% had prior ASCT. Tx was ongoing in 46% of pts. The overall response rate was 78%; CR rate was 55% (median time to CR, 1.7 mo). At 9 mo, an estimated 78% of pts with CR remained in CR. In subgroups, CR rates were: 42%, primary refractory disease; 70%, non–primary refractory disease; 41%, prior CAR T; 60%, CAR T naive. The Table 1 shows additional efficacy outcomes. The most common tx-emergent AEs (TEAEs) of any grade (G) were hematologic AEs (68% thrombocytopenia; 59% neutropenia [6% febrile neutropenia]; 51% anemia) and CRS (51%). CRS events were primarily low grade (27% G1, 23% G2, 1% G3); all resolved without leading to tx discontinuation. G1 (n=2) and G3 (n=1) ICANS were reported; all ICANS resolved, but 1 pt discontinued tx. COVID-19 was reported in 24 pts (25%; G≥3 in 10 pts). Fatal TEAEs occurred in 13 pts; in 3 cases, the contribution of epcoritamab + GemOx could not be ruled out: COVID-19, multiple organ dysfunction syndrome, and small intestinal perforation. Epcoritamab + GemOx continues to yield deep, durable responses that translate to high PFS and OS rates for complete responders in high-risk, challenging-to-treat R/R DLBCL. High CR rates were seen across subgroups, with higher rates observed in non–primary refractory, CAR T–naive, and second-line pts. Results support the combinability of epcoritamab in R/R DLBCL.

Table 1. Efficacy outcomes overall and by prior line of treatment

		Overall N=97	1 pLOT n=38	≥2 pLOT n=59
CR rate, n (%)		53 (55)	24 (63)	29 (49)
PFS[a] among complete responders, %	9 mo	93 (79–98)	100 (100–100)	88 (67–96)
	12 mo	88 (69–96)	100 (100–100)	79 (50–92)
OS[a] among complete responders, %	9 mo	96 (86–99)	100 (100–100)	93 (75–98)
	12 mo	90 (66–97)	100 (100–100)	84 (52–95)

[a]COVID-19–adjusted analyses. Kaplan–Meier estimates for PFS and OS are shown with 95% confidence intervals.

DP104

UPFRONT AUTOLOGOUS STEM CELL TRANSPLANTATION CAN CURE A HIGH PERCENTAGE OF HIGH-INTERMEDIATE/HIGH RISK AGGRESSIVE LYMPHOMA: A MONOCENTRIC RETROSPECTIVE ANALYSIS

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Upfront autologous stem cell transplant (ASCT) in aggressive lymphoma demonstrated a benefit in progression free survival (PFS), but overall survival (OS) improvement was never reported. However, about 40% of patients (pts) are not cured with standard R-CHOP therapy. Aim of this study was to evaluate the efficacy and safety of upfront ASCT in pts with aggressive lymphoma and unfavorable features treated in our center from 2012 to 2021. We analyzed all consecutive transplant eligible pts with DLBCL or advanced-stage PMBCL and HI/H IPI score. Induction treatment was R-CHOPx4 and R-MADx2 in 60 yrs old pts or younger (T1), R-CHOPx6 and R-AraC (T2) in 61-65 yrs pts and R-DA-EPOCH (T3) in pts with MYC rearrangement (rr) by FISH (translocation, increased copy number >4, amplification) or double expressor (DE). Stem cells were mobilized with R-MAD, R-AraC or R-DA-EPOCH respectively, all pts received BEAM or FEAM conditioning. We recorded 124 pts. Median age was 57 yrs (range 20-65), M/F 77/47, HI/H-IPI 78/46, DLBCL/PMBCL 110/14. 23 pts had MYC rr with (65.2%) or without (34.8%) BCL-2 rr, 61 received T1, 23 T2 and 40 T3. With a median

follow-up of 59 months (mo) (range 1-139), 5 yrs PFS and OS were 73.3% and 82.9%, respectively. Age did not impact on OS [<60 yrs (81pts) 83.8% *vs* 60-65 yrs (43 pts) 80.9%, p=0.923] nor different histology (DLBCL 82.6% *vs* PMBCL 85.7%, p=0.708) nor MYC rr (MYC+ 73.9% *vs* MYC- 84.9%, p=0.2437), while HI-IPI pts had better OS (89.6%) than H-IPI (71.5%), p=0.006. Transplant was not performed in 28 pts due to progressive disease (PD) (13), toxicity during induction (12), no mobilization (2) or refusal (1). Among transplanted pts, 5 yrs PFS and OS were 83.5% and 90.5% respectively: 4 pts died from pneumonia (3 COVID-19) after 4-114 mo from ASCT; 13 pts had PD and 6 are still alive after salvage therapy (CAR-T in 2 pts, platinum-based therapy and lenalidomide in 4). No 100 days TRM was recorded. Since October 2018, pre-transplant PET was performed (39 pts) and evaluated according to Deauville score (DS). Pts with DS1-3 (24) and DS4 (12) had similar 3 yrs OS (85.9% *vs.* 83.3% p=0.631), while pts with DS5 (3) did worse (33.3%, p=0.012) (Figure 1). In conclusion, upfront ASCT is still an effective and safe strategy which can cure more than 80% of high-risk aggressive lymphoma pts with a single line of therapy. Pre-transplant PET is a predictive tool, but more specific biomarkers, such as ct-DNA, could help better tailor therapy in the near future.

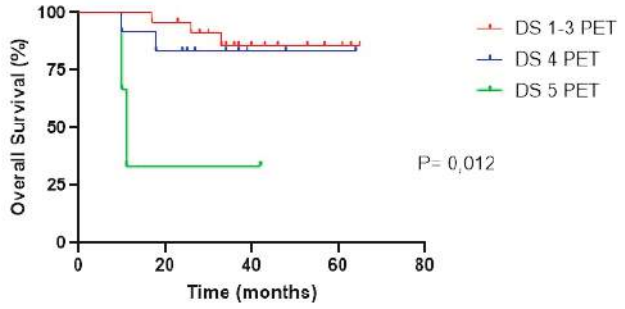

Figure 1.

DP105

IBRUTINIB OR CHEMO-IMMUNOTHERAPY AS SECOND LINE TREATMENT IN WALDENSTROM MACROGLOBULINAEMIA? A REAL-LIFE MULTICENTRE STUDY

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In the setting of relapsed patients (pts) affected by Waldenström Macroglobulinaemia (WM) chemo-immunotherapy (CT) has been substantially substituted by BTKis. Previous trials have investigated efficacy and safety of BTKis in second line without a direct comparison to CT. The aim of our retrospective study was to assess responses and outcomes with the treatment of BTKi or CT in second line. We enrolled 169 WM pts relapsed in the period 2008-2022 from 15 FIL centres: 85 pts were treated with ibrutinib and 84 pts with CT; 34 pts with BR (bendamustine-rituximab), 21 DRC (dexamethasone-rituximab-cyclophosphamide), 15 bortezomib-based regimens and 14 palliative regimens (i.e. alkylants). The two cohorts of ibrutinib and CT showed similar basal clinical characteristics, prognostic factors and comorbidities. Overall response rate (ORR) was achieved in 84.7% of pts after ibrutinib and in 69% after CT (p=0.026), ibrutinib pts showed a better progression free survival (PFS) than CT pts (4-y PFS of 67% *vs* 48%, p=0.0045), but we did not find statistical differences in terms of time to next treatment (TTNT) and overall survival (OS); in particular 4-y TTNT was 67% for ibrutinib and 55% for CT, 4-y OS was 78% for both. Considering the 4 different groups within the CT cohort, they showed the same characteristics except for the median age at treatment (bortezomib-based: 69 yy, BR: 70 yy, DRC: 75 yy, palliative: 83 yy; p=0.007). Nonsignificant difference among the 4 groups was seen in terms of ORR and PFS nor of TTNT and OS, even if we registered a better PFS for BR with a median PFS of 58.2 months, followed by bortezomib-based (PFS 53.6 mo), DRC (PFS 44.6 mo) and palliative (PFS 33.6 mo). When comparing ibrutinib to each of the 4 CT groups, ORR of ibrutinib was superior to each group (p=0.023), PFS of ibrutinib was superior to PFS of DRC, bortezomib-based and palliative regimens (p=0.028, p=0.023 and p=0.04, respectively) but not significantly to PFS of BR (p=0.055). Figure 1 showed the significant trend (p=0.057) in terms of better PFS of ibrutinib in comparison to the other 4 curves. For TTNT and OS no difference was reported based on ibrutinib and type of CT. Multivariate analysis found choice of the treatment (ibrutinib *vs* CT), age inferior to 75 years and female gender as significant variables that favourably impact on PFS. This large retrospective real-life study showed advantages of ibrutinib *vs* CT in terms of ORR and PFS, except for BR, but not for TTNT and OS.

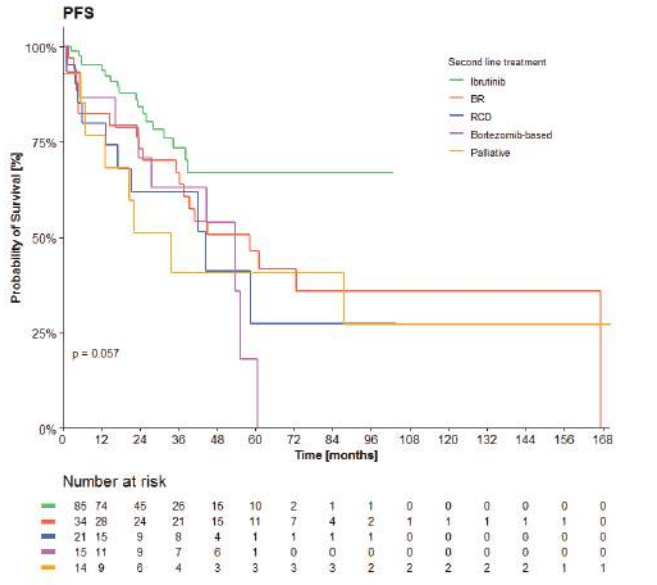

Figure 1. PFS of ibrutinib in comparison to the 4 curves of the different CT.

DP106

ABSTRACT NOT PUBLISHABLE

DP107

EFFICACY AND TOLERABILITY OF THE DOSE-DENSE SHORT-TERM "CARMEN" REGIMEN IN PATIENTS WITH HIGH-GRADE B-CELL LYMPHOMAS

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Introduction. Patients (pts) with high-grade B-cell lymphoma (HGBCL) exhibit poor outcome if treated with R-CHOP. Intensified regimens showed better survival rates [Petrich et al. Blood 2014] but need long delivery time and are associated with relevant toxicity and high treatment-related mortality. A dose-dense, short-term regimen called "CARMEN" is safe and effective in pts with aggressive B-cell lymphomas carrying MYC rearrangement, but only few cases of HGBCL were reported [Ferreri et al. Blood Adv 2022]. Herein, we report efficacy and safety results of a multicenter series of HGBCL pts treated with CARMEN.

Table 1.

	Tot n=38 (100%)
Median age (range)	57 (26-77)
Gender - males	26 (64%)
ECOG-PS >1	17 (45%)
Stage (Ann Arbor) III-IV	35 (92%)
CNS involvement	3 (8%)
Bone marrow infiltration	8 (21%)
Bulky disease	23 (61%)
High LDH serum level	34 (90%)
IPI >2	23 (61%)
HIV seropositivity	15 (40%)
HBV or HCV seropositivity	10 (26%)
Transformed from indolent lymphoma	5 (13%)
MYC not rearranged	8 (21%)
Single hit (*MYC-R*)	15 (40%)
Double Hit (*MYC-R + BCL2-R and/or BCL6-R*)	13 (34%)
MYC-R + BCL2-R	7 (18%)
MYC-R + BCL6-R	6 (16%)
Triple hit (*MYC-R + BCL2-R + BCL6-R*)	2 (5%)

Methods. HIV-pos or -neg adults with HGBCL (ICC and WHO criteria), treated with CARMEN at 6 Italian centers, from Jan 2010 to Jul 2023, were included. CARMEN drugs and doses were previously reported [Ferreri et al. Blood Adv 2022]. Response and survival estimations were performed according to the Lugano criteria.

Results. 38 pts were considered (Table 1): 32 (84%) completed induction, 25 (65%) received consolidation, and 10 (26%) required ASCT. As expected, toxicity was mostly hematological; G4 neutropenia, thrombocytopenia, and anemia occurred in 32 (84%), 19 (50%), and 2 (5%) pts, respectively. G4 non-hematological toxicities were episodic and manageable: mucositis (3), infections (7), hepatotoxicity (2), acute kidney failure (1), and tumor lysis syndrome (1). Five (13%) pts died of toxicity: COVID-19 in 2, pneumonia, post-surgical complication, poor graft function. Two pts experienced MDS after 10 and 40 months. Twenty-four pts achieved a CR (CRR= 63%; 95%CI 48-78%). At a median follow-up of 50 (10-141) months, 19 (50%) pts experienced an event: lymphoma relapse or progression in 11, death of toxicity in 5, and death due to other causes in 3. The 4-year PFS and OS were 50% (95%CI 38-62%) and 59% (95%CI 44-74%), respectively. HIV seropositivity was not associated with poorer outcome. The 4-year OS was 43% (95%CI 17-79%) for MYC-R+BCL2-R lymphomas and 80% (95%CI 48-100%) for MYC-R+BCL6-R lymphomas.

Conclusions. In this retrospective HGBCL series, CARMEN regimen showed encouraging safety and efficacy profiles, with improved survivals compared to published series treated with R-CHOP. The comparison of the present results with those recorded on HGBCL pts formerly treated with other regimens at the same institutions will be presented. This cost-effective treatment deserves to be compared to more demanding combinations in a prospective trial.

DP108

GERIATRIC FITNESS AND REAL-LIFE OUTCOMES IN ELDERLY PATIENTS WITH HODGKIN'S LYMPHOMA

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Hodgkin's lymphoma (HL) in patients aged ≥60 years still represents an unmet clinical need. Distinctive biological features, comorbidities, impaired functional/nutritional status reduce the eligibility and tolerance to standard therapy. The Age, Comorbidities and Albumin (ACA) index has not been tested in HL; it comprises age (≥75 years), hypoalbuminemia (<3.7 g/dL), and comorbidity burden (CCI ≥3). We aimed to retrospectively evaluate treatment strategies and outcomes in elderly HL patients and analyze the ACA index's impact on survival prediction. We used a modified ACA index (mACA), employing a CIRS-G score>6 to identify patients with a high degree of comorbidity. Based on this index, patients were stratified into *excellent* (0 points), *good* (1 point), *moderate* (2 points), and *poor* (3 points) risk groups. We included a total of 154 consecutive HL patients aged ≥60, treated at our institution from 2000 to 2022. Median age was 69 years (range 60-89) and median follow-up (FU) was 65.5 months (range 1.3-224). Overall, 86 patients (55.8%) were male, 53 (34.4%) were ≥70 years and 19 (12.3%) ≥80 years. Median CIRS-G score was 4 (range 0-14); 30 patients (19.5%) had a score >6. CIRS-G >6 was progressively more frequent according to age (60-69, 70-79, ≥80 years; p<0.0001). Median serum albumin was 3.9 g/dL (range 1.6-4.8), and 53 (38%) patients had hypoalbuminemia (<3.7 g/dL). All patients underwent first-line treatment and 133 (86.4%) received the standard ABVD or AVD-based regimens. The overall survival (OS) was 66.2%; ABVD/AVD-based regimens correlated with better OS (70.7% vs 38.1%, p=0.05). Baseline characteristics associated with shorter OS were older age (≥75 years, p=0.001), CIRS-G >6 (p=0.021) and ECOG ≥2 (p=0.005), B-symptoms (p=0.03), stage III-IV (p=0.001) and GHSG risk groups (p<0.0001).

The mACA score was calculated in 141 patients (91.6%): 62 (44%) had an *excellent* score, 46 (32.6%) *good*, and 33 (23.4%) *moderate-poor*, which was significantly associated to early treatment discontinuation (p=0.006), infections (p=0.022) and inferior OS (p=0.003). The 3y-OS was 90.3%, 85% and 70% for patients with *excellent*, *good* and *moderate-poor* score, respectively (Figure 1). The impact of the mACA index on OS was still maintained if we consider only the patients treated with AVD-based regimens (p=0.041). In conclusion, the mACA index could be a useful tool to predict outcomes in elderly HL patients when a comprehensive geriatric assessment is not feasible.

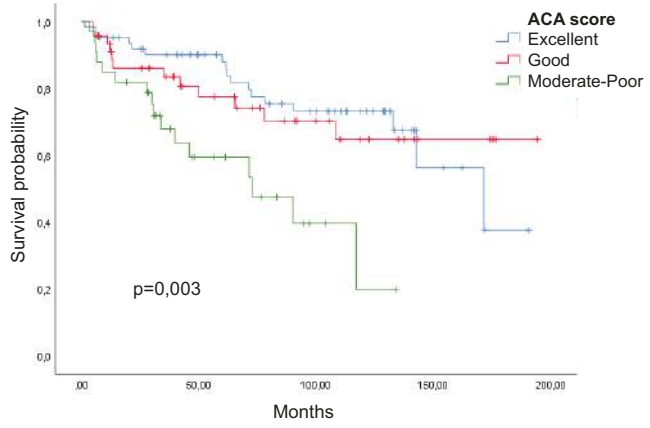

Figure 1. OS in the entire cohort according to the modified ACA score at diagnosis.

DP109

MANUFACTURING COMMERCIAL AXICABTAGENE CILOLEUCEL (AXI-CEL) IN ITALY FOR PATIENTS WITH RELAPSED/REFRACTORY NHL: A 2-YEAR RETROSPECTIVE ANALYSIS

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Background. Axi-cel is reimbursed in Italy for relapsed/refractory (R/R) large B-cell lymphoma after ≥2 previous treatments, for diffuse large B-cell lymphoma and high-grade B-cell lymphoma refractory to first-line chemoimmunotherapy (CIT) or relapsing ≤12 months after first-line CIT and for R/R follicular lymphoma after ≥3 previous treatments. The experience of manufacturing and supplying commercial axi-cel lots in EU countries has been reported (van de Wiel L. EBMT2023. P198). The aim of this abstract is to describe the experience of manufacturing and supplying commercial axi-cel lots to patients (pts) treated in Italy.

Methods. Fresh leukapheresis (LK) material was collected from pts intended to receive commercial axi-cel at authorized treatment centres in Italy and shipped to the cell therapy manufacturing facility in the Netherlands for manufacturing. If additional LK was needed, the first LK was considered for each patient and was then referred to as that patient's lot. The lot of the finished product remained at the manufacturing facility until it was released by the Qualified Person or the Physician and then sent to the hospital for administration. Manufacturing success rate (MSR) is defined as percentage of lots Qualified Person-released or Physician's released out of the total lots dispositioned in the time period of data extraction. Delivery success rate (DSR) is defined as the percentage of patient lots shipped (dispositioned as Qualified Person–released or physician's release) out of the total number of pts leukapheresed in the time period (excluding those patient lots in process and patients withdrawn). Turnaround time (TAT) is defined as the time from date of LK to date of quality release of final product.

Results. From 1 January 2022 to 31 December 2023, 415 pts were registered on Kite Konnect and underwent LK (Table 1). The median TAT was 20 days (range, 17-30). In total, 409 out of 410 lots were delivered to the treatment centres, resulting in a DSR of 99.8%. In addition, 397 lots were released by the Qualified Person or Physician out of 405 lots dispositioned, with a MSR of 98%.

Conclusions. The Italian experience of commercial Axi-cel for R/R NHL demonstrates a high DSR and MSR with a short TAT. Real-world experiences show that pts outcome depend on fast and reliable manufacturing capability (Locke FL. ASH 2022. abs3345). Kite manufacturing confirms to be rapid, reliable and predictable, ensuring timely axi-cel administration.

Table 1.

Date range	1 January 2022 - 31 December 2023
Unique patients registered on Kite Konnect and leukapheresed[a], n	415
Unique Patients lots evaluable for analysis, n	410
Median turnaround time[b], days (range)	20 (17-30)
Delivery success rate, % (n/N lots)	99.8% (409/410)
Manufacturing success rate, % (n/N lots)	98% (397/405)

a Only patients from Italy are included in this analysis. b Median TAT calculation is based on first time fresh apheresis material, manufactured at Hoofddorp, Netherlands. Patients who required a second leukapheresis or re-manufacturing from excess of PBMCs were excluded from this calculation.

DP110

PRELIMINARY EFFICACY AND SAFETY OF THE BRUTON TYROSINE KINASE (BTK) DEGRADER BGB-16673 IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) INDOLENT NON-HODGKIN LYMPHOMA (NHL): RESULTS FROM THE PHASE 1 BGB-16673-101 STUDY

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Background. BGB-16673 is a heterobifunctional small molecule that induces BTK degradation via ubiquitination. In preclinical models, BGB-16673 degraded wild-type BTK and BTK mutants resistant to covalent (cBTKis) and noncovalent BTK inhibitors (ncBTKis), leading to tumor regression. BGB-16673-101 (NCT05006716) is a first-in-human phase 1 study of BGB-16673 in pts with B-cell ma-

lignancies. Updated data from pts with follicular lymphoma (FL), marginal zone lymphoma (MZL), and Waldenstrom macroglobulinemia (WM) will be presented.

Methods. Eligible pts had R/R NHL and ≥2 prior therapies, including prior anti-CD20 (FL, WM, and MZL in US and EU) and cBTKi (WM in US and EU; MZL in US). BGB-16673 was dosed QD orally in 28-day cycles. Dose escalation with 6 dose levels (50-600 mg QD) was planned. Primary objectives were to assess safety per CTCAE v5.0 and establish the maximum tolerated dose (MTD) and recommended phase 2 dose. DLTs were assessed in cycle 1. Response assessment per 2014 Lugano classification or IWWM-6 criteria began after 4 (WM) or 12 wk (FL and MZL) of treatment (tx).

Results. As of Nov 9, 2023, 24 pts (FL, n=7; MZL, n=4; WM, n=13) were enrolled and 23 were treated (100 mg, n=5; 200 mg, n=11; 350 mg, n=7); 1 pt with WM had not started tx. Pts had a median of 4 (FL and WM) and 2 (MZL) prior therapies, including cBTKis (14/23), BCL2 inhibitors (5/23), and ncBTKis (3/23). Median follow-up was 6.6, 5.9, and 1.9 mo in FL, MZL, and WM, respectively. TEAEs in >10% of pts were contusion (22%), fatigue (22%), amylase increased (17%), headache (13%), lipase increased (13%), neutropenia (13%), and upper respiratory tract infection (13%). Neutropenia was the only grade ≥3 event in >1 pt (n=2). No hypertension or atrial fibrillation occurred. TEAEs led to tx discontinuation in 1 pt with WM (350 mg; bronchopulmonary aspergillosis; present prior to tx) and death in 1 pt with WM (200 mg; septic shock; not tx related). No TEAEs led to dose reduction. No DLTs occurred. Of 23 pts, 17 remain on tx (discontinuations: progressive disease, n=4; AE, n=1; pt withdrawal, n=1). In 14 response-evaluable pts, ORR was 50% (2/4) in FL, 100% (2/2) in MZL, and 75% (6/8) in WM, including pts with prior cBTKi (n=7; 6 WM, 1 MZL) and ncBTKi (n=2) (Figure 1).

Conclusions. Preliminary data from this ongoing study of BTK degrader BGB-16673 demonstrate a tolerable safety profile and antitumor activity in heavily pretreated pts with NHL, including those with BTK inhibitor–resistant disease.

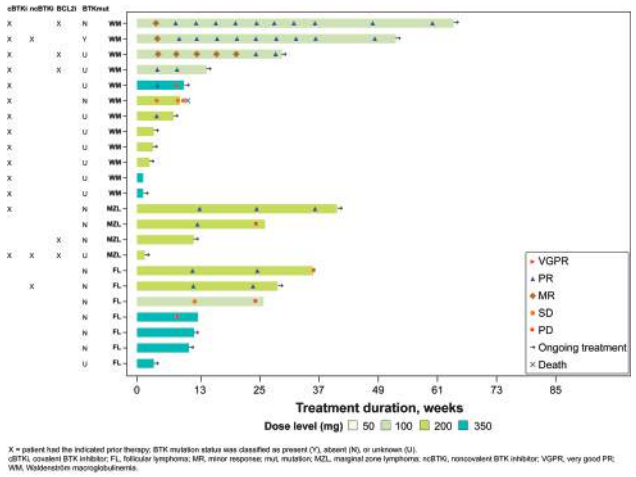

Figure 1.

DP111

ABSTRACT NOT PUBLISHABLE

Acute leukemia II

DP112

RUNX1A ISOFORM IS OVEREXPRESSED IN ACUTE MYELOID LEUKEMIA AND IS ASSOCIATED WITH FLT3 INTERNAL TANDEM DUPLICATIONS

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Background. RUNX1 is a transcription factor that plays the role of "master regulator of hematopoiesis" through the antagonistic action of its three major protein isoforms, RUNX1a, b, and c. RUNX1a represents a minor fraction of the isoform pool. It enhances self-renewal activity and suppresses myeloid differentiation, and its overexpression can be leukemogenic. We evaluated the expression of RUNX1 isoforms in our acute myeloid leukemia (AML) series to elucidate the role of RUNX1a in AML pathogenesis.

Methods. In this context, we quantified the RUNX1a/b/c expression in 181 bone marrow (BM) samples: 138 newly diagnosed AMLs, 21 disease relapses (DR), 11 cases in complete remission (CR), 10 healthy controls (HC) donors, a commercial pool of 56 HC samples. Three droplet digital PCR gene expression assays were performed. The target quantification [the ratio between each RUNX1 isoform and GUSB number of copies (R/G)] was associated with the main clinical and biological data.

Results. Comparing AML cases at diagnosis with HC, we observed the overexpression of RUNX1a (0.027 *vs* 0.003 R/G; p<0.0001) and RUNX1b (0.827 *vs* 0.433; p=0.006), whereas no difference was observed for RUNX1c. Thrombocytopenic cases (n=93) showed higher levels of these two isoforms compared to AMLs with normal PLTs levels (n=23) (0.030 *vs* 0.014 R/G; p=0.002 and 0.876 *vs* 0.517 R/G; p=0.007 respectively). The RUNX1a levels were higher in more immature AML phenotypes (M0-M3) than in more differentiated cases (M4 and M5). According to the mutational profile, FLT3-ITD positive cases presented the highest RUNX1a levels (0.071 R/G), and the presence of FLT3-ITD was the only molecular variable able to influence the RUNX1a expression (p=0.0005). FLT3-ITD AMLs (n=23) showed higher RUNX1a levels than FLT3-wt cases (n=82) (0.071 *vs* 0.020 R/G, p<0.0001), on the contrary FLT3-TKD patients (n=10) showed lower RUNX1a levels than FLT3-wt ones (0.006 *vs* 0.020 R/G, p=0.025). RUNX1a overexpression was higher in long ITD cases (>50bp; n=11) when compared with short ITD ones (n=8) (0.131 *vs* 0.037 R/G, p=0.02). At the DR, the RUNX1a overexpression reappears without a clear kinetics except from cases FLT3-ITD negative at diagnosis (n=4), but FLT3-ITD mutated at the DR who exhibited an increased RUNX1a expression (p=0.033).

Conclusions. Overall, we report the RUNX1a overexpression in AML patients, particularly in FLT3-ITD cases. Further studies could explore its possible role as a new AML therapeutic target.

DP113

THE PROGNOSIS OF NPM1 ACUTE MYELOID LEUKEMIA REMAINS VERY FAVOURABLE EVEN IN THE SETTING OF FIRST RELAPSE. A SINGLE CENTER EXPERIENCE ON 118 PATIENTS

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NPM1 mutation confers a favourable prognosis in Acute Myeloid Leukemia (AML), and allo-transplant (SCT) in first complete remission (CR) remains controversial. Monitoring measurable residual disease (MRD) can predict relapse and guide pre-emptive therapy. We evaluated 138 NPM1-AML patients (pts), representing 32% of the entire *de novo* AML population (429 pts), treated from 2010 to 2023 at our institution according to NILG AML-01/00 protocol. We analysed the impact of MRD monitoring and outcome after first relapse (molecular or hematological). NPM1 was monitored by qRT-PCR on BM and PB at diagnosis (TP0), after induction (TP1), 1st consolidation (TP2) and 1st cycle of high dose Arac (TP3), and at the end of therapy (TP4). We focused on a cohort of 118 pts (85,5%) obtaining CR, detailed in Table 1.

Table 1. Features of study population

Characteristics	Total (118 pts)	Relapsed (42 pts)	Non-relapsed (76 pts)	P value
Age, median (range), y	58 (18-74)	61 (27-74)	58 (18-73)	ns
Male/female sex	58/60	16/26	42/34	
Karyotype				
Normal, n. (%)	106 (90)	37 (88)	69 (91)	ns
Other-abnormal n. (%)	12 (10)	5 (12)	7 (9)	
Intermediate n. (%)	9 (75)	3 (60)	6 (86)	
Adverse n. (%)	3 (25)	2 (40)	1 (14)	
PCR-RT				
NPM1 baseline (TP0)				
median (x10^4/ABL)	54.329	20.291	21.889	ns
range (x10^4/ABL)	77-220.790	81-179.460	77-220.790	
FLT3-ITD mutation, n. (%)	36 (30,5)	13 (31)	23 (30)	ns
NGS	42	19	23	
Number of mutations	4 (1-8)	4 (1-8)	3 (2-8)	ns
NPM1-A	32	15	17	ns
NPM1 non-A	10	4	6	ns
FLT3	23	10	13	ns
FLT3-ITD	11	6	5	ns
DNMT3A	26	10	16	ns
IDH1/2	12	4	7	ns
KRAS/NRAS	13	5	6	ns
SRSF2	3	2	1	ns
Therapy at diagnosis				
CT+Midostaurin	9	4	5	-
CT	109	39	70	-
Allo-SCT in 1^ CR	3	-	3	-
MRD evaluation				
MRD negativity				
TP1 in BM	6/117 (5%)	0/41	6/76 (8%)	0.089
TP2 in BM	34/111 (30%)	8/40 (20%)	26/71 (37%)	0.087
TP2 in PB	50/86 (58%)	14/33 (42%)	36/53 (68%)	**0.025**
TP3 in BM	64/105 (61%)	18/33 (55%)	46/72 (64%)	0.39
TP3 in PB	74/89 (83%)	19/30 (63%)	55/59 (93%)	**0.0007**
TP4 in BM	62/98 (63%)	13/30 (43%)	49/68 (72%)	**0.0116**
TP4 in PB	68/82 (83%)	18/27 (66%)	50/55 (91%)	**0.0109**
Therapy after relapse	40 (95%)	40 (95%)	-	-
Best supportive care	2 (5%)	2 (5%)	-	-
Non-intensive	23 (55%)	23 (55%)	-	-
D-actinomycin	13	13	-	-
FLT3-inhibitor	3	3	-	-
ven-HMA	3	3	-	-
other	3	3	-	-
Chemotherapy (MEC, FLAI..)	17 (41%	17 (41%	-	-
Allo-SCT	26 (63%)	26 (63%)	-	-
In 2^ hematological CR	23 (88%)	23 (88%)	-	-
In 2^ molecular CR	4 (15%)	4 (15%)	-	-

NGS comutations, evaluated in 42 pts, were more frequently DNMT3A (61%), FLT3 (52%), TET2 (35%), PTPN11 (22%), NRAS/KRAS (35%), IDH1/2 (28%). Overall survival (OS) of our population at 3y- and 5y was 82% and 76%, respectively, and relapse free survival (RFS) at 3y and 5y was 65% and 61%, respectively. Relapse occurred after a median of 11.4 months (m) (3-62) in 42 pts (35%), in 18 of them (43%) only at molecular level (mol-R); 71% of those with mol-R and 54% of those with hematological relapse underwent allo-SCT. Neither age, NPM1 burden at TP0, FLT3-ITD mutation, abnormal karyotype nor NGS comutations had impact on relapse risk. Better RFS was significantly associated with MRD negativity in PB at TP2 (p 0.013), TP3 (p<0.0001), and TP4 (p 0.0011) and in BM at TP4 (p 0.0008). MRD negativity in PB was strongly associated with better OS at TP3 (p 0.001) and TP4 (p 0.0005). After relapse, 2 pts received supportive care, 17 chemotherapy (2 in mol-R) and 23 non-intensive therapy (16 in mol-R), obtaining in 29 pts (73%) hematological CR and in 7 (24%) also mol-CR. Twenty-six pts (68%) proceeded to allo-SCT, 23 (88%) pts in hematological CR and 4 also in mol-CR. Transplant related mortality was 11%. OS after relapse was 65% at 3y and 48% at 5y (median 56 m). It was significantly better in mol-R pts (median not-reached *vs* 23 m, p:0.0014) and in allografted pts (median not-reached *vs* 16,5 m, p:0.0012). In our experience, survival of NPM1-AML was good, even after relapse. Allo-SCT was a feasible and safe strategy in 2nd line. Molecular MRD monitoring in BM and PB was useful allowing to anticipate treatment decisions and to guide pre-emptive therapy and early intensification.

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THE USE OF FLUOROQUINOLONE PROPHYLAXIS DOES NOT AFFECT SURVIVAL OR THE INCIDENCE OF FEBRILE NEUTROPENIA IN A MULTICENTER CASE SERIES OF PATIENTS TREATED WITH AZACITIDINE (AZA) VENETOCLAX (VEN)

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Azacitidine (Aza) Venetoclax (Ven) represents the gold standard of treatment for AML patients older than 74 years or unfit for intensive chemotherapy. The VIALE-A randomized trial reported a 42% incidence of febrile neutropenia (FN) in AZA- VEN *vs.* 19% in the AZA arm. No clinical trial has evaluated the use of prophylaxis in HMA VEN patients. In our multicenter study, we retrospectively analyzed data from patients with AML treated with HMA + VEN. FN incidence and correlation with the use of FQ prophylaxis was primary objective of the study, secondary objectives were OS, FN-related mortality, predictive factors of FN, and FN-related mortality. We analyzed 87 AML patients, median age 72 years (range 40-88), 40 from Ancona, 24 from Perugia and 23 from Pescara, 68% (N=59) > 69 yrs, 20% with ECOG ≥ 2, 17% with R/R AML and 76% with intermediate or unfavorable ELN 2017 risk (40% and 36%, respectively). Aza was used in 75% (N=65) while decitabine was used in the remaining 25% patients (N=22). Characteristics of patients were evenly distributed in the 35 prophylactic and 52 nonprophylactic patients, with the only exception of the presence of DVA, which was more prevalent among the nonprophylactic patients (p=0.03). In our series, 39 out of 87 patients (44%) experienced an FN episode: 33 (85%) in first-line, 6 (15%) in second-line, 21 (54%) were undergoing prophylaxis. FN etiology was found in 51% of episodes (20/39) mainly by blood cultures (33%), 45% from GRAM+ and 55% from GRAM-; 11 isolates (55%), were multidrug-resistant (MDR) or FQ-resistant strains (60% GRAM- and 40% GRAM+), and 9 of these

patients (81%) were on prophylaxis with a trend between MDR and FQ prophylaxis (p=0.07). The cumulative incidence of FN was 54.6%, highest in the first 30 days of therapy, where 56% of episodes occurred, with a 26.4% probability of FN. Prophylaxis with FQ (HR 2.79;95%CI: 1.35-5.76, p=0.005) and the presence of DVA (HR 2.33;95%CI: 1.13-4.80; p=0.02) predicted FN. In the first 30 days, the presence of VPA is the only predictor of FN in both univariate and multivariate (HR: 2.65; CI95%: 1.13- 6.21, p=0.02). In contrast, prophylaxis with FQ predicts FN after 30 days (HR 4.2; p=0.007) (Figure 1). The FN event was predictive of OS at multivariate analysis (p=0.04, HR 1.78). No factors were found to be predictive of FN mortality. These findings certainly needs confirmation in prospective studies with larger numbers of patients.

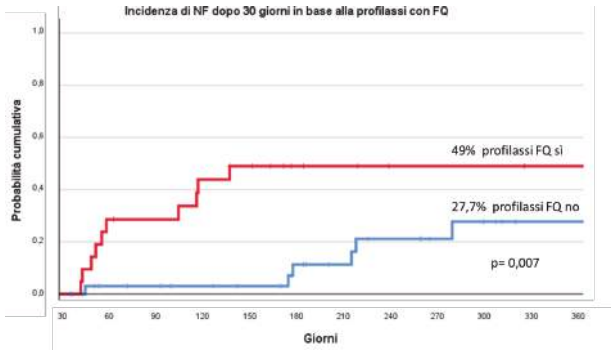

Figure 1.

DP115

HOW PEG-ASPARAGINASE DOSE REDUCTION AFFECTS SURVIVAL IN ADULT ALL PATIENTS: A SINGLE-CENTER RETROSPECTIVE STUDY

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Background and aims. The use of Pegylated Asparaginase (PegAsp) has emerged as the standard of care in pediatric-like protocols for adult patients with acute lymphoblastic leukemia (ALL), yielding favorable outcomes in terms of response and survival, albeit accompanied by notable toxicity. The objective of this study is to assess whether dose reduction of PegAsp affects response rates and overall survival.

Methods. We conducted a retrospective observational study at the University Hospital of Ancona, involving 25 patients diagnosed with acute lymphoblastic leukemia between 2015 and 2023 who received treatment with PegAsp. Data were collected regarding the dosage administered during induction and consolidation phases, documented toxicities, second-line therapy, and allogeneic hematopoietic stem cell transplant.

Results. Overall, ALL T-cell subtype accounted for 56% of cases, while ALL B-cell Ph-negative subtype accounted for 44%, with a median age of 41 years. The majority of patients received treatment according to the GIMEMA LAL 1913 protocol. Among the recorded toxicities, particularly during the induction phase, the most frequent were hepatotoxicity with elevated transaminases (84%), hypertriglyceridemia (40%), and coagulation abnormalities associated with thrombotic events (36%).Second-line therapy was required by 36% of patients, and 10 patients underwent allogeneic transplantation. In 40% and 54% of patients, low-dose PegAsp was administered during induction and consolidation treatment, respectively. Logistic regression analyses aimed at identifying predictors of early relapse or non-response to treatment revealed that low-dose PegAsp during induction (p=0.0036) emerged as a significant variable.The 1-year overall survival (OS) and 5-year OS rates were 82.8% and 57.3%, respectively. In the univariate analysis, reducing the dose of PegAsp during induction (p-value 0.0270) showed a statistically significant effect on overall survival (OS), as the occurrence of a thrombotic event (p-value 0.0146) and failure to attain post-induction complete remission (CR)(p-value 0.0313).

Conclusion. Dose reduction, compared to the dosages typically utilized in pediatric-like protocols designed for the treatment of ALL in adults, has a negative impact on overall survival and the attainment of treatment response. Our findings indicate that maintaining full dose intensity, particularly during induction therapy, is crucial for enhancing OS and response to therapy.

DP116

RESPONSE RATES AND IMPACT OF TRANSPLANTATION IN A MULTICENTER COHORT OF 63 PATIENTS WITH RELAPSED ACUTE PROMYELOCYTIC LEUKEMIA

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While significant progress has made Acute Promyelocytic Leukemia (APL) the most curable form of acute leukemia, a subset of patients (pts) still experience relapse, prompting questions about optimal care strategies. To gain more insights into this, we gathered data from two highly-specialized Italian Hematology centers to evaluate (I) response rates to salvage therapies, (II) impact of stem cell transplantation (HSCT), and (III) overall survival in this setting. We retrospectively collected data from 63 relapsed APL pts diagnosed between 1981-2021 (Table 1). Median age at relapse was 46.8 years (IQR: 34.0-59.9), with a 1.34 M:F ratio. At diagnosis, 12 pts were classified as low risk, 31 as intermediate, and 20 as high risk according to Sanz's criteria (Sanz *et al*., Blood. 2000). Eleven pts (17.4%) also experienced extramedullary relapse (central nervous system, *n*=9; paravertebral mass, *n*=1; skin, *n*=1), after a median of 24.4 months (IQR: 19.1-26.0) from diagnosis. Overall, 5 pts died due to disease progression before treatment start. Of the remaining 58 pts, 57 received salvage therapy with chemo-based regimens (*n*=26), ATO-based regimens (*n*=24), and ATRA±gemtuzumab ozogamicin (*n*=7), while one patient received localized radiotherapy for a paravertebral mass. Among treated pts, 27.7% achieved a morphological second complete remission (CR2) but tested positive for minimal residual disease (MRD), while 72.2% attained MRD negativity; three pts were refractory to treatment. No differences were found in CR2 rates between treatment cohorts (Table 1). Overall, 24 pts underwent consolidation with HSCT, 16 with autologous and 8 with allogenic HSCT. In CR2, pts undergoing auto-HSCT showed a lower second relapse rate compared to those without auto-HSCT consolidation (31.2% *vs.* 60.9%, *p*=0.043). Considering only pts who received chemo-based regimens, a lower rate of second relapses was also no-

ticed for transplant recipients compared to non-HSCT recipients (21.4% *vs.* 73.0%, *p*=0.005). This was not observed in pts receiving ATO-based regimens (*p*=.30). However, no significant impact on OS rates was found between pts undergoing HSCT (36.1% *vs.* 28.1% non-transplanted cases, *p*=0.52). Finally, median OS and relapse-free survival were 83 months (95% CI, 61.39-104.61) and 27.9 months (95% CI, 6.8-49.0). This study suggests that ATO could be considered as a second-line option instead of HSCT. However, further studies are needed to refine salvage therapy for relapsed APL pts.

Table 1.

Table 1. Patients' characteristic

	Total cohort	Chemo-based	ATO±ATRA	ATRA±GO	p†
Total cohort	63	26 (45.6)	24 (42.1)	7 (12.2)	
Median age at relapse, years (IQR)	46.8 (34.0-59.9)	38.0 (33.1-52.6)	50.4 (34.0-61.0)	54.2 (43.5-70.4)	.76
Gender, n (%)					
Male	34 (53.9)	11 (42.3)	15 (62.5)	5 (71.4)	.003*
Female	29 (46.1)	15 (57.6)	9 (37.5)	2 (28.5)	
Sanz risk score at diagnosis, n (%)					
Low	12 (19.0)	7 (26.9)	4 (16.6)	0	.42
Intermediate	31 (49.2)	10 (38.4)	11 (45.8)	6 (85.7)	
High	20 (31.8)	9 (34.6)	9 (37.5)	1 (14.2)	
Median time to relapse from diagnosis, months (IQR)	20.5 (12.4-35.4)	17.3 (13.1-23.6)	24.6 (15.3-43.6)	22.3 (13.2-29.6)	.74
First line-regimen, n (%)					
AIDA0493	24 (38.0)	17 (65.3)	1 (4.1)	1 (14.2)	<.001*
AIDA2000	29 (46.0)	4 (15.3)	21 (87.5)	2 (28.5)	
APL0406	3 (4.7)	2 (7.7)	1 (4.1)	0	
AIDA+GO	1 (1.5)	1 (3.8)	0	0	
IDA+AraC	3 (4.7)	1 (3.8)	0	2 (28.5)	
Daunorubicin	3 (4.7)	1 (3.8)	0	2 (28.5)	
Response to salvage therapy, n (%)					
Morphological CR2	15 (27.7)	7 (26.9)	5 (20.8)	3 (42.8)	.25
Molecular CR2	39 (72.2)	19 (73.0)	16 (58.33)	4 (57.1)	
No response	3 (5.5)	0	3 (20.8)	0	
Consolidation at CR2, n (%)					
AutoSCT, n (%)	16 (28.0)	11 (42.3)	1 (4.1)	4 (47.1)	<.001*
AlloSCT, n (%)	8 (14.0)	3 (11.5)	5 (20.8)	0	
Second relapse, n (%)	30 (52.6)	14 (53.8)	12 (50)	4 (57.1)	.93
Median time from diagnosis to 2nd relapse, months (IQR)	11.6 (5.3-22.4)	9.09 (6.9-21.3)	13.5 (3.6-29.0)	11.6 (7.23-15.9)	.97

Ara-C, cytarabine; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; AutoSCT, autologous Stem Cell Transplant; AlloSCT, allogenic stem cell transplant; CR2, second Complete Remission; GO, gemtuzumab ozogamicin; IDA, idarubicin; SD, standard deviation.

†The *p*-value refers to the distribution of patients across different subgroups of treatment.

DP117

STARRY SKY PATTERN PREDICTS RAS PATHWAY ACTIVATION IN NPM1-MUTATED AML

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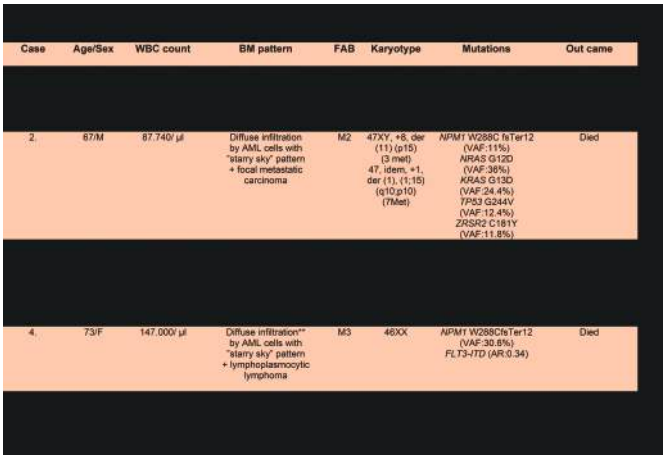
Introduction. NPM1-mutated AML shows peculiar molecular and clinico-pathological features and represents a distinct leukemia entity in the ICC and WHO classifications (Falini B Blood, 136(15):1707-1721, 2020). NPM1-mutated AML exhibits a wide morphological spectrum including multilineage involvement and cup-like nuclei, but whether morphological features are predictive of mutational profile has been never investigated.

Materials and Methods. we reviewed the bone marrow (BM) biopsies from 450 NPM1-mutated AML. M4 and M5 were the most common FAB categories and multilineage involvement was seen in about 25% of cases. Notably, we observed 5 cases with a "starry sky pattern" resembling that seen in Burkitt-lymphoma/L3-acute lymphoblastic leukemia. All cases were extensively investigated by immunohistochemistry (IHC) and targeted sequencing for commonly myeloid mutated genes.

Results. BM biopsies from all cases showed diffuse infiltration by blasts with myeloid (M1-M2), myelomonocytic (M4) or monoblastic (M5) appearance. Tingible body macrophages were dramatically increased and imparted to the histological picture a starry sky pattern, consistent with the high proliferative index of leukemic cells. At IHC, the anti-N terminus NPM1 monoclonal antibody labelled both the nucleus and cytoplasm of tumor cells, whilst the tingible body macrophages showed a nucleus-restricted NPM1 expression. The antibody specific for NPM1 mutant A labelled exclusively the cytoplasm of the leukemic cells but not the tangible body macrophages. Targeted sequencing revealed mutations activating the RAS pathway in all cases (Table 1). In particular, one patient harbored a missense mutation in the RING domain of CBL (R420Q; VAF 40.7%, hence possibly hemizygous or homozygous). This mutation disrupts the CBL ubiquitin ligase activity interfering with wild-type CBL and leading to activation of FLT3 signaling (Sargin B et al, Blood 110(3):1004-1012, 2007). Two cases were triple mutated for NPM1/FLT3-ITD/DNMT3A that associates with worse prognosis. All patients presented with high blood cell count (usually >100.000/µl) and increased LDH (Table 1).

Conclusions. NPM1-mutated AML with starry sky pattern is a distinctive morphological variant that predicts co-mutations leading to RAS pathway activation. Whether tingible body macrophages are reactive or belong to the leukemic clone remains unclear. Allogeneic transplant was curative in the two patients with NPM1/FLT3-ITD/DNMT3A mutated AML.

Table 1.



Case	Age/Sex	WBC count	BM pattern	FAB	Karyotype	Mutations	Out came
2.	67/M	87.740/ µl	Diffuse infiltration by AML cells with "starry sky" pattern + focal metastatic carcinoma	M2	47XY, +8, der (11) (p15) (3 met) 47, idem, +1, der (1), (1;15) (q10;p10) (7Met)	*NPM1* W288C fsTer12 (VAF:11%) *NRAS* G12D (VAF:36%) *KRAS* G13D (VAF:24.4%) *TP53* G244V (VAF:12.4%) *ZRSR2* C181Y (VAF:11.8%)	Died
4.	73/F	147.000/ µl	Diffuse infiltration** by AML cells with "starry sky" pattern + lymphoplasmocytic lymphoma	M3	46XX	*NPM1* W288CfsTer12 (VAF:30.8%) *FLT3-ITD* (AR:0.34)	Died

DP118

TOXICITIES AND EARLY MORTALITY IN TREATED ACUTE LEUKEMIAS: A SINGLE CENTRE EXPERIENCE COHORT

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Toxicities and early mortality are still an issue in Acute Leukemia due to the increasing age of the treated patients and the ongoing evolution of the therapeutic approaches. We analyzed 106 patients with newly diagnosed Acute Leukemia between 2022-2023 (see Table 1) to evaluate treatment toxicities, as well as factors associated with therapy discontinuation and early outcome. A p-value<0.05 was considered significant in statistical analysis. Overall mortality rate was 2%, 5% and 22% at day +7, +30 and +100: 10 patients (43.5%) had disease persistence, 12 (52.2%) likely died from therapy-related toxicities, while 1 (4.3%) - with Acute Promielocytic Leukemia - died after refusing transfusion support. In multivariate analysis, treatment related mortality (TRM) (cumulative incidence-CI: 5% at day +30 and 15% at day +100) was associated with CCI >2 (HR 74.2), bleeding (HR 61.6) and intensive care unit (ICU) admission (HR 8.8). Disease persistence resulted significant in univariate analysis only. Stratifying for AML patients, age >63 (HR 7.2), CCI >2 (HR 3.2), non-intensive treatment (NIT) (HR 2.7) and ICU admission (HR 6.8) were associated to TRM. The rate of ICU admission was 15%. The risk was significantly associated to bacterial infections (OR 7.0, C.I. 1.4-30) in multivariate analysis. CI of therapy discontinuation (therapy suspension or de-escalation to a less intensive therapy) was 10% and 27% at day +30 and +100. Variables correlated to therapy discontinuation were: age >63 years (39% *vs* 16%), unfitness (39% *vs* 19%), AML *vs* ALL (34% *vs* 7%), NIT (42% *vs* 18%), bacterial infection (36% *vs* 16%) and organ toxicity (42% *vs* 20%). In multivariate analysis, NIT (HR 2.7), organ toxicity (HR 4.2) and AML (HR 5.7) were significant. TRM also prevailed in AML in comparison to ALL patients (CI: 24% *vs* 4%), probably due to higher median age and associated comorbidities (Table 2).

Table 1.

Table I. Demographics of 106 Acute leukemia patients

Diagnosis, n (%)	**AML** 79 (69)	**ALL** 27 (25)	Total 106 (100)
AML non-APL	67 (85)		
APL	6 (8)		
BPDCN	3 (4)		
ALAL	2 (2)		
MPAL	1 (1)		
B-ALL Ph-		14 (52)	
B-ALL Ph+		8 (30)	
T-ALL/LBL		5 (18)	
Median Age, yrs (range)	68 (26-85)	50 (21-84)	63 (21-85)
Age (yrs), n (%)			
<50	12 (15)	13 (48)	25 (24)
50-59	13 (16)	6 (22)	19 (18)
60-69	17 (22)	3 (11)	20 (19)
70-79	29 (37)	4 (15)	33 (31)
>80	8 (10)	1 (4)	9 (9)
Sex, n (%), M / F	34(43) / 45(57)	14(52) / 13(48)	48(45) / 58(55)
Charlson Comorbidity Index (**CCI**) n (%)			
0-1	19 (24)	18 (67)	37 (35)
2-4	44 (56)	8 (30)	52 (49)
≥ 5	16 (20)	1 (3)	17 (16)
Fit / **Unfit**, n (%)	39(49) / 40(51)	23(85) / 4(15)	62(59) / 44(41)
Comorbilities, n (%)			
None	17 (22)	13 (48)	30 (28)
Cardiovascular	9 (11)	0 (0)	9 (9)
Metabolic	22 (28)	5 (19)	27 (26)
Pneumological	4 (5)	0 (0)	4 (4)
Autoimmunity	6 (8)	2 (7)	8 (8)
Non-Hema Malignancy	16 (20)	2 (7)	18 (17)
Hema Malignancy	11 (14)	0 (0)	11 (10)
Prior CT/RT	15 (19)	1 (4)	16 (15)
Neurological	6 (8)	2 (7)	8 (8)
Psichiatric/Dementia	4 (5)	1 (4)	5 (5)
Leukocytes at diagnosis, n (%)			
<10 x10^3/mmc	47 (60)	12 (44)	59 (56)
10-100 x10^3/mmc	24 (30)	10 (37)	34 (32)
>100 x10^3/mmc	8 (10)	5 (19)	13 (12)
Clinical presentation at diagnosis, n (%)			
CNS involvement	1 (1)	1 (4)	2 (2)
Extra bone marrow involvement	7 (9)	5 (19)	12 (11)
Coagulopathy	7 (9)	0 (0)	7 (7)
Bleeding	8 (10)	3 (11)	11 (10)
Infections	13 (17)	2 (7)	15 (14)
Diagnostic qualifiers (CCI 2022), n (%)			
De novo	49 (62)	26 (96)	75 (70)
Therapy-related	16 (20)	1 (4)	17 (16)
Prior history of MDS	7 (9)	0 (0)	7 (7)
Prior history of MPN	7 (9)	0 (0)	7 (7)
Treatment, n (%)			
Intensive Treatment	37 (47)	24 (89)	61 (58)
Non-intensive Treatment	42 (53)	3 (11)	45 (42)

Table II. Toxicities, treatment discontinuation and early mortality in 106 Acute leukemias patients, according to intensity of treatment

	Intensive CT, n=61	**Non-intensive CT**, n=45	**Total** 106
AML, n(%)	37 (47)	42 (53)	79 (75)
ALL, n(%)	24 (89)	3 (11)	27 (25)
Charlson Comorbidity Index (**CCI**), n(%)			
0-1	37 (61)	0 (0)	37 (35)
2-4	24 (39)	28 (62)	52 (49)
≥ 5	0 (0)	17 (38)	17 (16)
AML therapy, n(%)			
	ATRA+ATO 5 (6,3)		
	ATRA+CT 1 (1,3)		
	3+7 2 (2,5)		
	3+7+GO 5 (6,3)		
	3+7+Midostaurin 7 (8,9)		
	ICE 3 (3,8)	HMA-Ven 16 (20,3)	
	FLAI 1 (1,3)	AZA 14 (17,7)	
	CPX-351 10 (12,7)	DEC 9 (11,4)	
	Other 3 (3,8)	Other non-intensive 3 (3,8)	
ALL therapy, n(%)			
	CT+TKI 4 (14,8)		
	Blina+TKI 4 (14,8)	TKI+steroid 0 (0)	
	LAL1913 11 (20,7)	Rivera modified 1 (37)	
	Other pediatric-like based 5 (6,3)	Other non-intensive 2 (25)	
Toxicities within day +100, n(%)			
Bacterial Infections	47 (77)	25 (55,6)	72 (67,9)
Fungal Infections	2 (3,3)	5 (11,1)	7 (6,6)
Mucositis ≥ G3	20 (32,8)	2 (4,4)	22 (20,8)
Bleeding	9 (14,8)	1 (2,2)	10 (9,4)
Organ toxicities	29 (47,5)	12 (26,7)	41 (38,7)
ICU admission	15 (24,6)	3 (6,7)	18 (17)
Early treatment discontinuation rate, n(%)			
All cases			
within day +30	8 (13,1)	9 (20)	17 (16)
within day +100	17 (27,9)	22 (48,9)	40 (37,7)
AML			
within day +30	7 (18,9)	9 (21.4)	16 (20.2)
within day +100	14 (37.8)	22 (52.4)	36 (45.6)
Early mortality, n(%)			
All cases			
within day +7	2 (3,3)	0 (0)	2 (1,9)
within day +30	2 (3,3)	5 (11,1)	5 (4,7)
within day +100	6 (9,8)	17 (37,8)	23 (21,7)
AML			
within day +7	2 (5,4)	0 (0)	2 (2,5)
within day +30	2 (5,4)	9 (21,4)	11 (13,9)
within day +100	5 (13,5)	17 (40,5)	22 (27,9)
Cause of early death, n(%)			
Refractory disease	1 (1,6)	9 (20)	10 (9,4)
Toxicities	4 (6,6)	8 (17,8)	12 (11,3)
Other	1 (1,6)	0 (0)	1 (0,9)

Even taking into account the limits due to the size of the cohort, we observed that:

1. the favourable fitness of ALL patients could explain the better early outcome. However, a role for different therapeutic regimens cannot be excluded;
2. severe bacterial infections with ICU admission affect early outcome as independent factor;
3. NIT did not avoid early toxicity and mortality in a undefined setting of unfit patients.

Balance between disease control and related toxicities is still lacking in unfit patients. Further studies may lead to improve their therapeutic approaches and outcomes.

DP119

ARSENIC TRIOXIDE-INDUCED PERIPHERAL NEUROPATHY: PROSPECTIVE CLINICAL AND NEUROPHYSIOLOGICAL EVALUATION IN A COHORT OF PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA

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Introduction. Arsenic Trioxide (ATO) has become a mainstay in the therapy for Acute Promyelocytic Leukaemia (APL), leading to high response rates when used in combination with All-Trans Retinoic Acid (ATRA). While neurotoxicity is a well-known effect associated with arsenic poisoning, data regarding patients being treated with the ATO/ATRA regimen is scarce.

Aim. To prospectivelly evaluate the incidence and characteristics of ATO-associated neurotoxicity in APL patients.

Methods. A prospective study was conducted, enrolling patients treated with the ATO/ATRA regimen in one Italian and one Spanish centre between 2015 and 2020. The Total Neuropathy Score clinical version (TNSc) was employed to score peripheral neuropathy (PN). Values >2 were considered significant for PN.

Results. A total of 19 patients were enrolled (58% male, median age at diagnosis of 53 years). No notable findings were reported at the basleine neurological evaluation. At the end of induction, 9 (47%) patients presented with a TNSc >2 (median TNSc 3), with distal sensory symptoms being the most commonly reported. After completion of consolidation therapy, 6 (33%) of the evaluable patients still had a TNSc >2, although a decrease in TNSc between the two timepoints was documented in all but 2 patients. Clinical data after 1 year of follow-up was available in 13 individuals, of whom only 2 (23%) displayed a TNSc >2. Neurophysiological examination (NP) was performed at symptom onset in 16 patients, reporting findings consistent with an axonal neuropathy in 7 subjects (all of whom with TNSc >2), with unremarkable findings in the remainder of individuals (of whom 2 had TNSc >2). One year after treatment completion, NP was available in 7 individuals, with 2 having persisting signs of axonal neuropathy, whereas a resolution of the neurophysiological picture was documented in 2 patients who previously had findings consistent with axonal PN at symptom onset. No significant diffrences in ATO cumulative dose were documented between those who did or did not develop PN (p=0.44).

Conclusions. Although almost half of the enrolled subjects in our study manifested clinical and/or neurophysiological evidence of sensory axonal PN during ATO treatment, such toxicity seems to be reversible, with clinical and neurophysiological improvement being documented at follow-up evaluations, and only a minority of patients still being symptomatic after treatment interruption.

DP120

APL-LIKE SUBSET CORRELATES WITH EARLY-ONSET VASCULAR COMPLICATIONS AND MORTALITY WITHIN NPM1-MUTATED ACUTE MYELOID LEUKEMIA: ANALYSIS FROM A LARGE MULTI-CENTER DATASET

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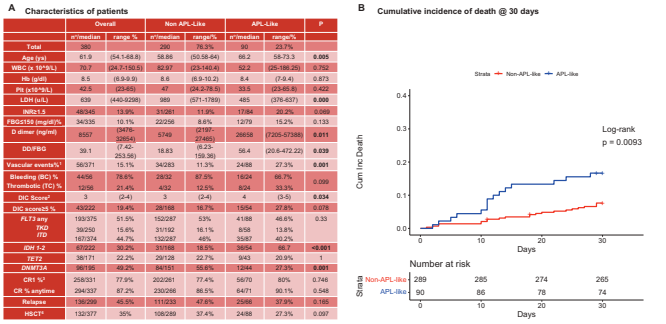
Background. Despite progress in the management of acute myeloid leukemia (AML), the initial phase remains critical due to potential complications that may compromise treatment; among these, the actual incidence of severe vascular complications is underestimated. Current assessment of haemorrhagic risk is focused on the diagnosis of acute promyelocytic leukemia (APL); once excluded, it is based on clinical, hemochrome and coagulation parameters, but not on biological markers. A subtype of NPM1mut AML has been described that displays a phenotypic profile similar to APL.

Aims. To confirm in a large multicenter dataset previous finding on APL-like subset as a potential predictor of susceptibility to early vascular events.



	Overall		Non APL-Like		APL-Like		P
	n°/median	range %	n°/median	range%	n°/median	range%	
Total	380		290	76.3%	90	23.7%	
Age (yo)	61.9	(54.1-68.8)	58.86	(50.58-64)	66.2	58-73.3	**0.005**
WBC (x 10^9/L)	70.7	(24.7-150.5)	62.97	(23-140.4)	52.2	(25-186.25)	0.752
Hb (g/dl)	8.5	(6.9-9.9)	8.6	(6.9-10.2)	8.4	(7-9.4)	0.873
Plt (x10^9/L)	42.5	(23-69)	47	(24.2-78.5)	33.5	(23-65.5)	0.422
LDH (u/L)	639	(440-9298)	989	(571-1789)	485	(376-637)	**0.000**
INR≥1.5	48/345	13.9%	31/261	11.9%	17/84	20.2%	0.069
FBG≤150 (mg/dl)%	34/335	10.1%	22/256	8.6%	12/79	15.2%	0.133
D dimer (ng/ml)	8557	(3675-32654)	5749	(2197-27465)	26658	(7205-57388)	**0.011**
DD/FBG	39.1	(7.42-253.56)	18.83	(6.23-159.36)	56.4	(20.6-472.22)	**0.039**
Vascular events%[1]	56/371	15.1%	34/283	11.3%	24/88	27.3%	**0.001**
Bleeding (BC) % Thrombotic (TC) %	44/56 12/56	78.6% 21.4%	28/32 4/32	87.5% 12.5%	16/24 8/24	66.7% 33.3%	0.099
DIC Score[2]	3	(2-4)	3	(2-4)	4	(3-5)	**0.034**
DIC score≥5 %	43/222	19.4%	29/168	16.7%	15/54	27.8%	0.078
FLT3-any TKD ITD	193/375 39/250 167/374	51.5% 15.6% 44.7%	152/287 31/192 132/287	53% 16.1% 46%	41/88 8/58 35/87	46.6% 13.8% 40.2%	0.33
IDH 1-2	67/222	30.2%	31/168	18.5%	36/54	66.7	**<0.001**
TET2	38/171	22.2%	29/128	22.7%	9/43	20.9%	1
DNMT3A	96/195	49.2%	84/151	55.6%	12/44	27.3%	**0.001**
CR1 %[3]	258/331	77.9%	202/261	77.4%	56/70	80%	0.746
CR % anytime	294/337	87.2%	230/266	86.5%	64/71	90.1%	0.548
Relapse	136/299	45.5%	111/233	47.6%	25/66	37.9%	0.193
HSCT[4]	132/377	35%	106/289	37.4%	24/88	27.3%	0.097

[1]Vascular events: defined according to the revised World Health Organization (WHO) bleeding scale and to the CTCAE grading of thromboembolic events.
[2]DIC: ISTH Criteria for Disseminated Intravascular Coagulation.
[3]CR: complete remission.
[4]HSCT: hematopoietic stem cell transplantation.

Figure 1.

Methods. The study cohort included conventionally-defined NPM1mut AML pts. Early (within 30 days from diagnosis) vascular events were defined according to revised WHO bleeding scale and CTCAE grading of thrombosis. APL-like profile was defined by CD34/HLA-DR negativity, heterogenous CD117 and dim CD13 expression.

Results. From 2007 to 2023, 379 NPM1mut AML pts were recruited from Florence (n=150), Bergamo (n=131), Rome (n=57), Bologna (n=41) sites, of whom 90 (23.7%) APL-like (Figure 1A). APL-like pts were older (66 *vs* 59 y, P=.005) without further differences at baseline. Vascular complications (bleeding and thrombotic), were significantly more frequent in APL-like (n=24, 27.3%) than non (n=34, 15.1%, P=.001). In APL-like group median DIC score (4), D-dimer (DD, 26,658 ng/ml) and DD/FBG ratio (56.4) were significantly higher than in non-APL-like (3, P=.34; 5,749 ng/ml, P=.001, and 18.83, P=.003, respectively). Molecular data showed enrichment in IDH1-2 mutations in APL-like *vs* non (66.7% *vs* 18.5%, P=.000). A trend for more pts receiving less intensive treatment (ie, hypomethylating agents +/- venetoclax) was observed for APL-like (n=14, 17.1% *vs* n=30, 10.9%, P=.081) likely due to the older age. Complete remission rate was similar in APL- (90.1%) and non-APL-like (86.5%, P=.578) groups. Of note, cumulative incidence of death at 30 days was significantly higher in APL-like subset (P =.0093, Figure 1B). A trend for inferior overall survival was also observed in APL-like *vs* non-APL-like pts (15.9 *vs* 24.6 mop, P=.051).

Conclusions. Data from a large dataset confirmed APL-like subset may serve as a biomarker for early vascular events and mortality, potentially prompting specific supportive and monitoring measures, similarly to the current approach in APL.

DP121

VENETOCLAX AND AZACITIDINE FOR RELAPSE PREVENTION IN NPM1-MUTATED ACUTE MYELOID LEUKEMIA IN MOLECULAR FAILURE: PRELIMINARY RESULTS FROM THE GIMEMA AML2521 PHASE 2 TRIAL

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Background. Molecular failure (MF) in *NPM1*-mutated (*NPM1*m) AML inevitably progresses to overt disease if untreated and identifies higher risk patients who require allogeneic stem cell transplantation (alloSCT) consolidation. No therapy is available in the measurable residual disease (MRD) setting, although increasing evidence supports the efficacy of venetoclax (VEN) and azacitidine (AZA) in NPM1m AML.

Aim. To evaluate the efficacy of VEN-AZA in preventing morphological relapse before alloSCT in adult *NPM1*m AML patients who experience MF during intensive chemotherapy (IC) or subsequent follow-up monitoring.

Methods. This is a phase 2, non-randomized, interventional,

open-label, multicenter trial enrolling fit-for-transplantation adult *NPM1*m AML patients in molecular relapse or progression after having received at least 2 cycles of IC. Inclusion criteria comprise: 1) morphological complete remission (CR); 2) centralized MRD positivity defined as ratio *NPM1*mut/*ABL* × 100 transcript ≥ 0.01% evaluated with qRT-PCR. Patients receive VEN 400 mg (50 mg if concomitant posaconazole) days 1-28 in association with azacitidine 75 mg/m^2 days 1-7. AlloSCT is recommended at any time at MRD-negativity (MRDneg), defined as *NPM1*mut/*ABL* × 100 <0.01%, from cycle (C)1 onwards.

Results. Fifteen *NPM1*m AML patients have been enrolled. Median patient age is 55 y (IQR 48-62), 7 of 15 (47%) are male. AML characteristics at diagnosis show concomitant *FLT3*-ITD mutation in 5 (33%) of patients and *FLT3*-TKD in 3 (20%); 1 patient presented ELN2022 adverse risk for *TP53* mutation. At enrolment, all patients were in CR, median *NPM1*m values were 0.188% (IQR 0.087-1.615), no patients had detectable *FLT3* mutations at screening. Patients received a median of 3 cycles (range 1-6) of VEN-AZA. Concerning primary endpoint, no patients experienced morphological relapse on study treatment. Overall, 9 (60%) patients achieved MRDneg during treatment and 3 (20%) a molecular response (*NPM1*m decrease ≥1 log), for an overall molecular response (OMR) of 80%. Median time to MRDneg is 1.64 months (1.31, 3.02). So far 13 (87%) of patients have been bridged to alloSCT in CR or better. Median time to transplant is 3.45 mo (IQR 3.09, 4.24). With a median follow-up of 8.9 mo (IQR 4.6-17.0), all patients are alive.

Conclusions. This preliminary data shows promising results for AZA-VEN in preventing disease relapse and bridging *NPM1*m AML patients in MF to alloSCT. Updated data will be presented at meeting.

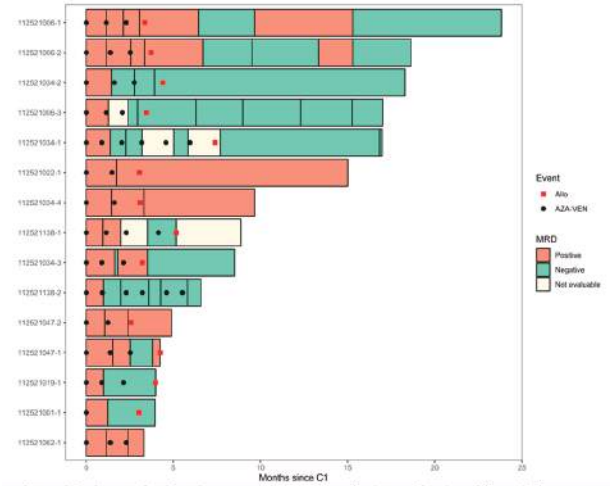

Figure 1. Swimmer plot of patients treated with venetoclax in combination with azacitidine within the GIMEMA AML2521 protocol from treatment start to last follow-up.

Abbvie provided financial support for the trial.

Figure 1.

DP122

IS THERE A BETTER THERAPEUTIC TIME WINDOW FROM DIAGNOSIS TO TREATMENT IN VERY ELDERLY ACUTE MYELOID LEUKEMIA PATIENTS RECEIVING HYPOMETHYLATING AGENTS?

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In fit patients with newly diagnosed acute myeloid leukemia (ND-AML), immediate treatment is recommended due to the poor prognosis of untreated acute leukemia; however, this paradigm has been challenged by a German study. Authors stratified patients into 4 groups for time from diagnosis to treatment start (TDT), showing no difference in waiting before starting intensive chemotherapy. In this study, data were collected from 220 patients treated with azacitidine (AZA) (164) and decitabine (DEC) (56) (median age 78 years). Patients were divided into 4 cohorts: those that started therapy in <15 days (n= 85 patients), 15-30 days (n=64 patients), 31-45 days (n= 33 patients), 46 days and beyond (n= 38 patients) from their initial diagnosis of AML. We analyzed survival using the Kaplan-Meier curves, with significance determined by the log-rank test. The event for calculating the overall survival (OS) was the date of death and for event-free survival (EFS) was time to progressive disease, relapse, or death. Patients were otherwise censored at the date of last follow-up.

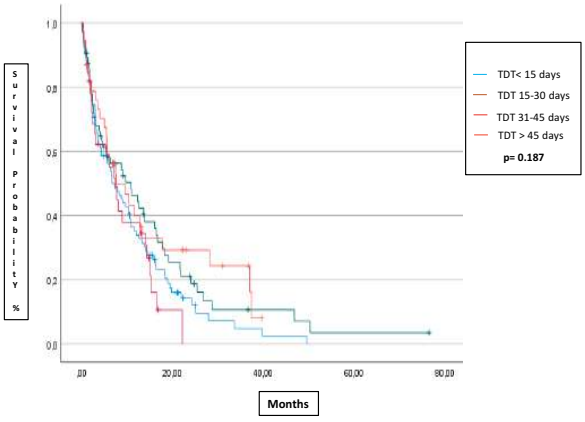

Figure 1.

The median TDT of patient treated with AZA or DEC was 21 (range: 0-43 days) or 15 (range: 0-31 days) days, respectively; overall was 19 days (range: 0-55 days). The median OS (Figure 1) was of 7.5 months (95%CI 4.5-10.5 mts), 11 months (95%CI 4.5-17.4), 7.4 months (95%CI 4.7-10.1) and 7.6 months (95%CI 2.3-13) for the subgroups of TDT <15, 15-30, 31-45 and >46 days, respectively (p=0.224). The median EFS was of 5.8 months (95%CI 2.4-9.1), 9.8 months (95%CI 7.9-11.7), 5.0 months (95%CI 0.9-9.1) and 5.7 months (95%CI 0.5-12.2), for the subgroups of TDT <15, 15-30, 31-45 and >45 days, respectively (p=0.187). No statistically significative difference was noted when considering patients receiving AZA or DEC in terms of OS (p=0.08) and EFS (p=0.083) considering the

four different groups. TDT did not show prognostic significance in our cohort treated with HMAs, although a trend for better outcome can be seen in the subgroup that started treatment 15-30 days from initial diagnosis. These results confirm the lack of difference found in the German study but, at the same time, do not contrast with the results from Bouligny et. al, who considered the impact of TDT on patients treated with VEN + HMAs. In this study OS was 5.8 months for patients included in the 0-7 day cohort, significantly worse than 8.9 months for the 8-14 day cohort and the 12.7 months for 15 days and beyond (p=0.023).

DP123

THE ROLE OF CLONAL HEMATOPOIESIS IN THE DEVELOPMENT OF THERAPY-RELATED MYELOID NEOPLASMS

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Therapy-related myeloid neoplasms (t-MN) are characterized by aggressive features and a dismal prognosis, due to frequent adverse genetic features. Recent evidence suggests a higher incidence of t-MN in individuals harboring clonal hematopoiesis of indeterminate potential (CHIP). To gain insight into CHIP-driven malignant progression, we gathered data from ten published reports with available detailed patient characteristics, at the time of primary malignancy and t-MN development. Detailed clinical and molecular information on primary malignancy and t-MN were available for 109 patients. At the time of the primary malignancy, 76 mutations, CHIP-defining (t0), were identified in the PB of 47 patients (43%), while 210 gene mutations were present in 92 patients at t-MN development (84%, p<0.0001, Figure 1).

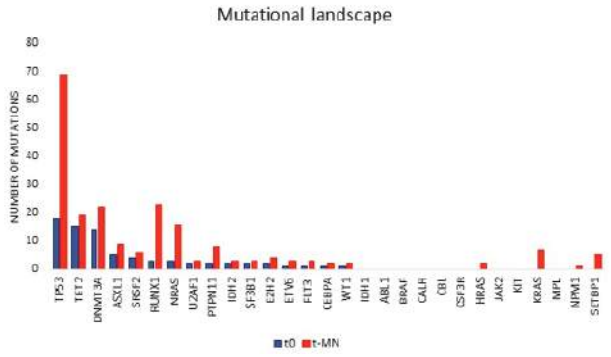

Figure 1. Mutational landscape in the patient population. Blue columns show mutations at the time of diagnosis of first malignancy (t0) and red columns at t-MN development. t-MN: Therapy-related myeloid neoplasms.

The most common mutations at t0 were TP53 (16%), TET2 (12%), DNMT3A (12%) and ASXL1 (4%). TET2 and TP53 mutations showed a significant increase of variant allele frequency (VAF) from CHIP to t-MN (p=0.019 and p=0.005, respectively). Of note, in patients with TP53 mutations at t0, the rare INDEL variants (n=2) showed increasing VAF over time, whereas missense mutations expanded only in half of the cases (6 out of 12; p=ns). ASXL1-associated CHIP significantly correlated with the emergence of TET2 (p=0.024) and CEBPA (p=0.046) mutations at t-MN, as well as U2AF1-driven CHIP with EZH2 (p=0.037), and IDH2 and SRSF2-driven CHIP with FLT3 (p=0.037 and p=0.001, respectively). DNMT3A-driven CHIP was more "benign" and correlated with lower incidence of TP53 mutation at t-MN (p=0.031). In contrast, TP53-driven CHIP correlated with complex karyotype (p>0.001) and a lower tendency to acquire new mutations at t-MN (p>0.001). Patients with multiple myeloma as their first malignancy presented a significantly higher rate of TP53 mutations at t-MN (p=0.039). Our findings suggest that TET2 and TP53-driven CHIP may play a pivotal leukemogenic role. Furthermore, we highlighted a preferential leukemogenesis process by TP53-driven CHIP, based on clone expansion rather than mutations acquisition. Consistent with previous reports, our results suggest that, when compared to other CHIP-drivers, DNMT3A-driven CHIP may have a minor role in t-MN development and eventually cause a milder disease phenotypes.

DP124

LEUKOCYTOSIS DURING INDUCTION THERAPY WITH ALL-TRANS-RETINOIC ACID AND ARSENIC TRIOXIDE IN ACUTE PROMYELOCYTIC LEUKEMIA: PREDICTIVE FACTORS AND IMPACT ON TREATMENT COMPLICATIONS

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All-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) represent the standard of care for low-intermediate risk acute promyelocytic leukemia (APL). Leukocytosis during induction with ATRA-ATO represents a common complication with up to 60% incidence. We studied the clinical characteristics and predictive factors for the development of leukocytosis during induction in low-intermediate APL patients treated with ATRA-ATO front-line. A total of 65 consecutive APL patients diagnosed between 2009 and 2023 at 3 University Hospitals, University Hospital Santa Maria Goretti (Latina), Sapienza University and University Tor Vergata (Rome) were included in this study. 39/65 (60%) patients developed leukocytosis with peak in leukocyte count being most frequent in the second week from diagnosis (26/39, 66%). All cases were successfully managed with hydroxyurea. Clinical and biological characteristics of patients developing and not developing leukocytosis are reported in Table 1. Predictive factors for leukocytosis in univariate analysis were lower platelet counts (OR 0.98, 0.97-1.00, p=0.018) , lower fibrinogen levels (OR 0.36,0.17-0.66, p=0.003), higher bone marrow blast infiltration (OR 1.03, 1.01-1.07-1.00, p=0.021) and CD117 expression by flow (OR 1.04, 1.01-1.08, p=0.012). Multivariate analysis confirmed lower levels of fibrinogen at diagnosis as the strongest predictive factor for the development of leukocytosis (OR 0.36,0.15-0.72, p=0.009). Differentiation syndrome occurred only in patients developing leukocytosis showing a stringent correlation with rising leukocytes counts (16 *vs* 0, p=<0.001). In addition, also other treatment-related complications including QTc prolongation, cardiac events, liver and hematologic toxicities were significantly more frequent in patients with leukocytosis (22 *vs* 2, p=<0.001). In conclusion, APL patients undergoing ATRA-ATO therapy with lower fibrinogen levels and platelet count at diagnosis and with a massive BM infiltrate should be carefully monitored for the development of leukocytosis during induction therapy. Differentiation syndrome and other treatment-related complications seem to occur almost exclusively in patients developing leukocytosis; those patients should nec-

essarily receive DS prophylaxis to prevent this life-threatening complication and more intensive monitoring and supportive therapy to prevent treatment toxicities.

Table 1.

Table 1. Clinical and biological characteristics of patients developing and not developing leukocytosis during induction therapy with ATRA-ATO.

		Leukocytosis		
Characteristic	**Overall**, N = 65	**No**, N = 26	**Yes**, N = 39	**p-value**
Age*	53 (41-68)	56 (41-69)	53 (41-67)	0.9
Sex, n (%)				0.8
F	41 (63%)	17 (65%)	24 (62%)	
M	24 (37%)	9 (35%)	15 (38%)	
Risk, n (%)				0.085
Low	34 (52%)	17 (65%)	17 (44%)	
Intermediate	31 (48%)	9 (35%)	22 (56%)	
BCR , n (%)				0.9
BCR 1-2	40 (63%)	16 (62%)	24 (63%)	
BCR 3	24 (38%)	10 (38%)	14 (37%)	
N/a	1	0	1	
BMI#>25, n (%)				0.6
No	43 (68%)	18 (72%)	25 (66%)	
Yes	20 (32%	7 (28%)	13 (34%)	
n/a	2	1	1	
WBC+ (109/L)*	1.2 (0.8-1.97)	1.0 (0.7- 1.5)	1.47 (0.92-2.05)	0.3
Hb§ (g/d)*	10.2 (7.4-11.7)	9.7 (7- 11.8)	10.2 (8.2-11.6)	0.5
PLTS^ (109/L)*	46 (25-73)	67 (39.7-87.5)	30 (23.5-68.5)	**0.021**
BM" Blasts(%)*	84 (70, 90)	72 (50, 88)	88 (74, 90)	**0.033**
CD117(%)*	71 (55, 81)	61 (47, 73)	78 (66, 86)	**0.005**
INR@*	1.1 (1.0-1.28)	1.11 (1.04-1.24)	1.20 (1.10-1.30)	0.2
APTT£ ratio *	1 (1-22)	1 (1-22)	1 (1-12)	0.3
Fibrinogen(mg/dL)*	173 (127-243)	233 (161-343)	142 (118-208)	**0.002**
D-dimer (mg/dL)*	8.240 (4.418-19.367)	4,582 (4.308-10.630)	11.486 (5.575, 26.199)	**0.015**
Creatinine (mg/dL) *	0.76 (0.70-0.99)	0.74 (0.70-0.98)	0.78 (0.62-0.99)	0.5
Albumin (mg/dL)*	4.2 (3.8-4.6)	4.2 (4.0-4.6)	4.1 (3.8-4.6)	0.5
LDH‡ (U/L) *	224 (181-298)	195 (174-280)	234 (192-305)	0.11

* Median (range); °BCR: breakpoint cluster regione;#BMI, body mass index; + WBC, white blood cell count; §Hb, haemoglobin;^PLTS, platelets;" BM, bone marrow; @ International normalized ratio; £ activated partial thromboplastin time; ‡lactate dehydrogenase

DP125

PROTOCOL GIMEMA AML2220: ROLE OF ADRENOMEDULLIN IN LEUKEMIC ENDOSTEAL/VASCULAR NICHES

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Introduction. Endothelial cells (ECs) and their released factors exert a crucial role in bone marrow (BM) vascular niches for the survival and maintenance of normal hematopoietic stem/progenitor cells. However, in the last two decades, the deregulation of angiogenetic mechanisms has been reported in solid tumors and hematological malignancies. The first evidence that endothelial cells could be involved in leukemia progression was reported in the late 1990s when Fiedler et al. demonstrated that acute myeloid leukemia (AML) cells secrete angiogenic cytokines (e.g., VEGF), thus giving rise to the concept of paracrine interaction between leukemic and endothelial cells. To date, it is known that AML cells express cytokine-related receptors (e.g., VEGFR), and adhesion molecules to mediate physical interaction with ECs (e.g., VLA-4/VCAM-1; CD44/E-selectin) of type H [high CD31/endomucin (Emcn)], or type L (low CD31/Emcn), corresponding to transitional and sinusoidal vessels, respectively. Recently, targeting molecules involved in the interaction of leukemic and endothelial cells is certainly one of the most advanced approaches to influence on leukemic stem cell homeostasis. Among vascular regulatory peptides, adrenomedullin (ADM), a 52 amino acid protein belonging to the calcitonin gene-related peptide family, has been shown to potentially contribute through calcitonin receptor-like receptor (CRLR) and Receptor-Activity-Modifying Proteins (RAMP2/3) to the pathogenesis of several tumors.

Methods. We performed preclinical screening of BM and peripheral blood (PB) from eligible and newly diagnosed AML patients (n=49) to study by flow cytometry (FCM) the expression of ADM, RAMP2/3, CRLR, and adhesion molecules (CD31, CD38, CD44). Data were correlated to BM/PB blasts, mutation status, and risk assessment of patients.

Results. An altered ($P<0.05$) relative expression of RAMP2 and RAMP3 was observed in all samples. In BM, the significant reduction of the RAMP2/RAMP3 ratio due to an overexpression of RAMP3 correlated to i) an increased number of blasts (>90%) in both BM and PB; ii) the upregulation of adhesion molecules (CD31, CD44) and ADM+ cells. In contrast, an increased RAMP2/RAMP3 ratio correlated with a higher number of blasts in PB (>80%) compared to BM (≤60%) along with a depletion of ADM+ and a reduced expression level of CD31 and CD44.

Conclusions. These preliminary data offer a rationale for deeply exploring the biological effects of abnormal ADM signaling in the bone marrow and peripheral blood of AML patients.

DP126

IMMUNOHISTOCHEMICAL PATTERNS, MOLECULAR FEATURES AND OUTCOME OF EXTRAMEDULLARY DISEASE IN NPM1-MUTATED AML

B. Falini[1], A. Venanzi[1], V. andresen[2], B. T. Gjertsen[2], V.M. Perriello[1], A. Marra[3], E. Sabattini[4], S. Bertoli, A. Pigneux[6], P. Y. Dumas[6], E. Tiacci[1], C. Recher[5]

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Introduction. Despite a great bulk of information is now available on NPM1-mutated AML, (Falini B, NEJM 352(3):254-266, 2005; Falini B Blood, 136(15):1707-1721, 2020), little is known about the characteristics of extramedullary disease occurring in patients affected by this leukemia entity.

Materials and Methods. Myeloid sarcomas (MS) (n=56) observed during 2002-2020 were retrieved from the archive of Hematopathology, Institute of Hematology, Perugia University. Ten NPMc+ (cytoplasmic-positive) MS from the Hematopathology Unit, S. Orsola Hospital, were also available for study. All cases were investigated by immunohistochemistry (IHC) for cytoplasmic expression of nucleophosmin that is predictive of NPM1 mutation (Falini B et al, Blood, 108(6):1999-2005, 2006). Seven cases of NPMc+ MS for which adequate material was available were subjected to targeted sequencing and the results compared to those obtained in bone marrow. Impact of extramedullary disease on survival was investigated

in 734 NPM1-mutated AML patients from the Toulouse-Bordeaux AML database (DATAML), observed in the period 2000-2020 and treated with intensive chemotherapy.

Results. Twenty-three out of the 56 MS (41.07%) expressed cytoplasmic NPM1 mutant at IHC. The most frequently involved extramedullary site was skin but other sites, including lymph nodes, testicle, kidney, and pharynx were affected. The anti-N terminus NPM1 monoclonal antibody labelled both the nucleus and cytoplasm of the tumor cells whilst the antibody specific for NPM1 mutant A labelled exclusively the cytoplasm of leukemic cells and was tumor specific. Targeted sequencing of seven extramedullary sites and paired bone marrow samples showed, with minimal variations, an overlapping mutational profile between extramedullary and medullary disease. No impact of extramedullary disease on survival was observed (no EMD: median OS 77 months *vs* EMD: 49 months, P=0.08). 3y and 5y OS was 61% and 53% in the no EMD group *vs* 53% and 49% in the EMD group.

Conclusions. the NPM1c+ (mutated) genotype was frequent (41,07%) among MS in our series. IHC is an ideal technique for diagnosing these cases, for which only a small amount of material is often available (especially skin biopsies). Molecular studies point to a stability of the mutational profile among medullary and extramedullary sites. This genetic stability may account for the lack of negative impact on survival of the extramedullary involvement in NPM1-mutated AML.

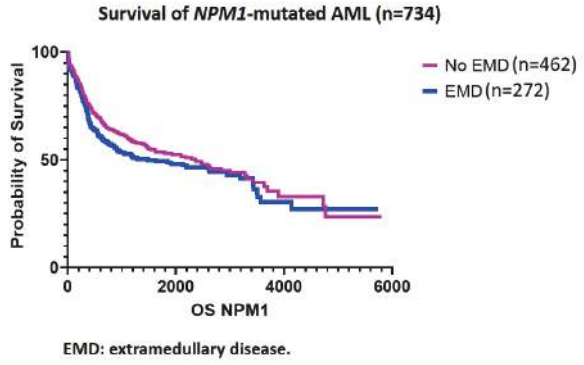

Figure 1.

Allogenic and autologous transplant

DP127

GVHD PROPHYLAXIS IN MISMATCHED UNRELATED DONOR TRANSPLANTATION: ADVANTAGE OF POSTTRANSPLANT CYCLOPHOSPAMIDE OVER ATG IN A REAL-LIFE SINGLE CENTER EXPERIENCE

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Background. Optimal graft-versus-host disease (GVHD) prophylaxis in mismatch unrelated donor transplantation (MMUD) is unclear. Recent EBMT guidelines 2024 leave the centers free to choose between ATG and posttransplant cyclophosphamide (PTCy) due to lack of large comparative studies in this setting.

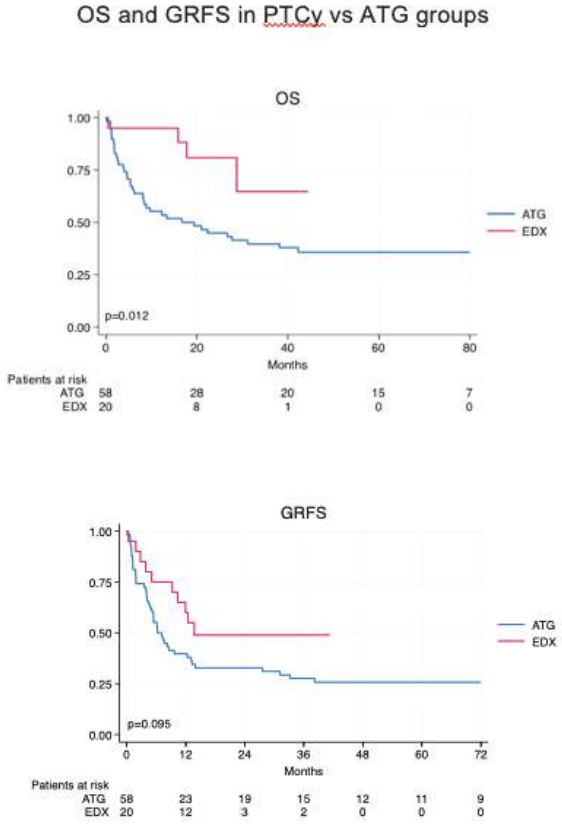

Figure 1.

Methods. In this retrospective study we compared OS, PFS, GRFS, incidence of relapse and GVHD in 78 consecutive adult patients who underwent one-antigen or allele (HLA A,B,C or DR) MMUD at our Center with prophylaxis based on PTCy+MMF+cyclosporine (PTCy group, n=20) or with calcineurin inhibitor+MTX+ATG (ATG group, n=58). ATG was administered from 2015 and 2019 and it was substituted by PTCy since 2020 with the aim of reducing GVHD and NRM.

Results. Median age at transplant was 58 years. Acute leukemia was the most common underling disease in both groups (70% *vs* 71%). In PTCy group more patients (pts) were in complete remission at transplant (75%vs49%, p0,020) and received letermovir prophylaxis (90%vs25%, p<0,001). Other transplant characteristics were well balanced between two groups. With a median follow up of 18 months (IQR 4-62) in ATG group *vs* 19 months (IQR16-26) in PTCy group, incidence of acute GVHD (aGVHD), relapse, infections, VOD, microangiopathy, renal and cardiac toxicity were similar between two grups. There was a tendency of reduction of grade III-IV aGVHD cumulative incidence (CI) and a significant decrease of steroid refractory aGVHD CI in PTCy cohort (0%vs12%, p0,071 and 5%vs31%, p0,019, respectively) as well as liver toxicity and FUO (0%vs19%, p0,036; 20%vs48%, p0,027). The 1yrOS in the ATG group was 55% (95%CI:41%-67%) *vs* 95% (95%CI:69%-99%) in the PTCy group (p0,011). Figure 1 The 1yrPFS was 52% (95%CI:38%-63%) *vs* 75% (95%CI:50%-89%) (p0,016). 1yrGRFS was lower in PTCy group than in ATG group, albeit not significant (40%vs60%, p0,095). One year NRM was 36,2% (95% CI 2,41-48,39) in ATG group *vs* 0% in PTCy group. In multivariate analysis GVHD prophylaxis was the only factor that impacted on 1yrPFS and 1yrOS while NRM was affected also by conditioning intensity.

Conclusions. In PTCy in MMUD setting resulted in a significant reduction of steroid refractory GVHD and NRM rate, a significantly higher 1yrPFS and OS and in trend of better 1yrGRFS, therefore it was confirmed as the optimal GVHD strategy in our real life setting Studies with larger number of cases and prospective trials are needed to implement recommendations in MMUD setting.

DP128

COMPARATIVE ANALYSIS OF GVHD PROPHYLAXIS STRATEGIES IN UNRELATED DONOR STEM CELL TRANSPLANTATION: FOCUS ON IMMUNOLOGICAL RECOVERY AND GVHD INCIDENCE

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Background. Stem cell transplantation (SCT) from unrelated donors (UD) is a pivotal treatment for hematologic malignancies; however, graft-versus-host disease (GVHD) still represents a challenge. Anti-thymocyte globulin (ATG) and post-SCT cyclophosphamide (PtCy) are strategies used to mitigate GVHD, with a recent trend favoring PtCy. However, comparative data on their efficacy in UD SCT are limited. This single center study compares the outcomes of UD SCT patients receiving either ATG or PtCy-based GVHD prophylaxis, focusing on immunological recovery and GVHD incidence.

Methods. Between 2021 and 2023, 74 patients underwent peripheral blood SCT from UD at our unit. All patients received either ATG or PtCy, the latter was employed instead of ATG mainly from 2022 as a change in our institutional practice. Immunological recovery was assessed by lymphocyte subsets levels (CD3+, CD3+CD4+, CD3+CD8+, and CD19+ cells) at 3, 6 and 12 months post-SCT. Cumulative incidence (CI) of grade 2-4 acute GVHD (aGVHD) and moderate-severe chronic GVHD (cGVHD) was evaluated. Since the median follow-up time was shorter in PtCy-treated cohort (7.5 *vs* 22 months), a landmark analysis was performed at 8 months.

Results. Thirty-eight patients received ATG, and 36 PtCy. Median age was 59.4 years with no significant differences in terms of gender, age, and donor type (matched or mismatched UD). The primary disease was acute myeloid leukemia, accounting for 21 patients in each group. A myeloablative conditioning regimen was adopted in 26 patients in the ATG group and 20 in the PtCy group. Immunological recovery was similar at each time-point. PtCy showed delayed platelet engraftment (median 22 *vs*. 14 days, p=0.002), but comparable neutrophil recovery. The CI of aGVHD was similar (ATG: 34.2%, PtCy: 29%, p=0.54). Interestingly, cGVHD CI was lower with PtCy (7% *vs*. 36.8% for ATG, p=0.01) (Figure 1A). The 8-month landmark analysis confirmed these results (PtCy: 7%, ATG: 26.3%, p=0.04) (Figure 1B). Significantly, only in ATG group, delayed CD19+ recovery at 3 months appeared to predict cGVHD onset (AUROC: 0.79, p=0.011) (Figure 1C-D). Non-relapse mortality and relapse incidence were superimposable.

Conclusion: PtCy yielded a delayed platelet engraftment but lower cGVHD incidence, with comparable immunological recovery. These preliminary results suggest PtCy's advantage in reducing cGVHD without compromising other outcomes. Further research is warranted for optimizing GVHD prophylaxis in UD SCT.

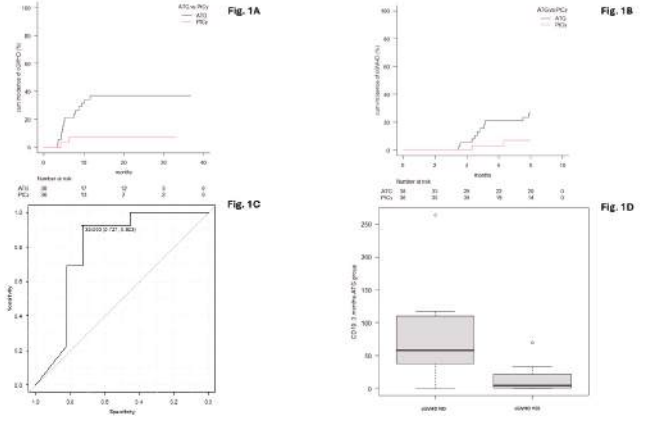

Figure 1.

DP129

HOW GRAFT IMMUNE COMPOSITION AFFECTS IMMUNE RECOVERY AND TRANSPLANT OUTCOME: A SINGLE CENTER EXPERIENCE

S. Leone[1], S. Marotta[1], M. Celentano[1], M. Pedata[1], C. Luise[1], A. Carobene[1], I. Migliaccio[1], A. Fiumarella[2], A. Leone[2], M. Toriello[3], D. Graziano[4], M. Alberti[4], SM Muggianu[5], M Caputo[5], A. Viola[5], R. Penta[3], C. Falco[4], A. Picardi[1]

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The success of a Hematopoietic Stem Cell Transplantation (HSCT) relies on the generation of an efficient immune cell recovery (IR), able to both control disease and to limit infectious complications. Several pre and post-transplant factors influence IR, but the heterogeneity of the cohorts and of monitoring strategies limits their application in clinical practice. As well, graft immune composition (GC) is associated to HSCT outcomes. However, the relationship between GC and IR is still unconsidered. We evaluated retrospectively GC and IR of 110 allogeneic HSCT performed at AORN Cardarelli of Naples, from June 2019 to August 2023. GC data were available for 79 patients; CD34+, CD3+, CD4+, CD8+, CD56+, CD20+ cell

subsets were identified in the graft. For IR evaluation, CD20, CD4 and CD56 lymphocytes were detected at 6 months and 1-year post HSCT, respectively, in 57 and 39 patients.

First, we analyzed the relationship between the graft immune subsets and the absolute count of CD20, CD4 and CD56 lymphocytes at 6 months and 1 year: only CD20 at 1 year has a direct correlation with CD34 cell dose (R=0.46, p=0.003). To distinguish subjects with a higher IR, we categorized patients in two groups, using as thresholds the 50th percentile of the absolute numbers of each cell type at 1 year or the 75th percentile at 6 months. Univariate and multivariate regression analysis on CD20, CD4 and CD56 IR are shown in Figure 1. The amount of graft cell subsets infused does not influence the IR of all the three lymphocytes populations. MAC regimen, GVHD prophylaxis with ATG and the occurrence of aGVHD get worse CD4 IR; CD20 and CD56 IR are negatively influenced, respectively, by aGVHD and MAC conditioning. With a median follow-up of 17.9 months, OS is favored by a higher CD4 IR (HR=0.18, p=0.03), while CD20 IR protects from 1-year NRM (HR=0 P=<0.001). Regarding GC impact on clinical outcome, CD8 dose significantly affects 1-year NRM (HR=0.83, p=0.04), while CD56 dose protects from relapse (HR=0.16, p=0.03).

In our cohort, CD20 IR is related to CD34+ cell dose. As several pre and post-transplant factors influence CD20, CD4 and CD56 IR, it is possible that the relationship between GC and IR is conditioned by these ones and, thus, needs further investigation. We confirmed the IR effect on prognosis in terms of OS and NRM, as well as revealed the impact of higher CD8 and CD56 graft cell dose, respectively, on 1-year NRM and relapse.

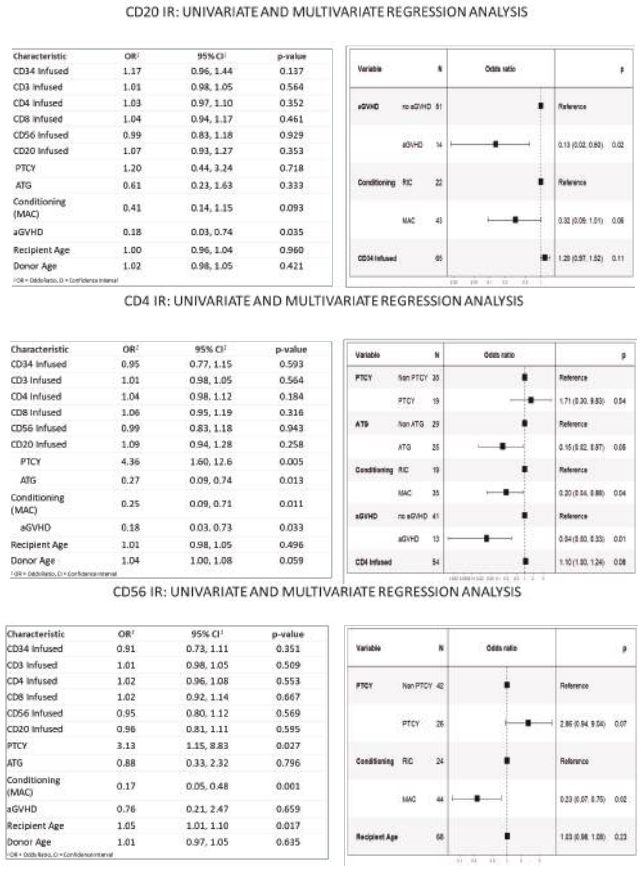

Figure 1.

DP130

HEALTH ASSESSMENT AND ELIGIBILITY OF ADULT-RELATED HEMATOPOIETIC STEM CELL DONORS: RESULTS OF AN ITALIAN MONOCENTRIC EXPERIENCE

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The safety and welfare of the hematopoietic progenitor cells (HPC) donors are major concerns for the transplantation community. Herein we report our real-world experience of adult HPC donor assessment during a 5-year study period (2018-2023): we have retrospectively revised the anamnestic data of 455 potential related stem cell donors, consecutively evaluated at our center. Donor medical history was assessed by a questionnaire and an interview with a trained physician experienced in donation procedures, to evaluate donor fitness, medical history, and willingness to donate before HLA-typing.

Table 1. Characteristics of 233 allogeneic stem cell transplantations, and results of univariate analysis comparing transplants from healthy donors with those from HPC-related donors with pre-existing medical conditions.

	Transplants from healthy donors N=206	Transplants from donors with CVD N=16	P value*	Transplants from donors with allergy N=11	P value**
Age, years	56 (45-63)	56 (46.7-58.7)	0.459	52 (40-62)	0.830
> 60 years	73 (35.4)	4 (25.0)	0.586	5 (45.4)	0.529
Males / Females	130/76 (63.1/36.9)	8 (50.0) / 8 (50.0)	0.600	7 (63.6) / 4 (36.4)	0.109
Weight, kg	75 (65-85)	76 (61-85)	0.717	65 (60-75)	0.166
Diagnosis					
Acute Myeloid Leukemia/MDS	104 (50.5)	6 (37.5)		8 (72.7)	
Myeloproliferative neoplasms++	39 (18.9)	6 (37.5)		0 (0.0)	
Lymproliferative disorder+	32 (15.5)	1 (6.3)	0.300	1 (9.1)	0.321
Acute Lymphoid Leukemia	25 (12.1)	3 (18.7)		1 (9.1)	
Severe Aplastic Anemia	6 (2.9)	0 (0.0)		1 (9.1)	
HCT-CI score > 2	116 (56.9)	9 (56.3)	0.794	8 (72.7)	0.362
DRI high/very high	71 (36.0)	11 (68.7)	**0.005**	5 (45.5)	0.503
Complete remission	98 (47.6)	8 (50.0)	1.000	5 (45.5)	1.000
ABO mismatch major/bidirectional	51 (24.7)	3 (18.7)	0.766	0 (0.0)	0.071
MA conditioning regimen	46 (22.3)	6 (37.5)	0.216	3 (27.3)	0.714
NMA conditioning regimen	160 (77.7)	10 (62.5)		8 (72.7)	
Female donor to male	42 (20.4)	2 (12.5)	0.744	3 (27.3)	0.701
PBSC graft	137 (66.5)	14 (87.5)	0.099	7 (63.6)	1.000
BM graft	69 (33.5)	2 (12.5)		4 (36.4)	
HLA match 7/8	1 (0.5)	0		0	
HLA-identical sibling	75 (36.4)	10 (62.5)	0.116	4 (36.4)	0.973
Haploidentical sibling	130 (63.1)	6 (37.5)		7 (63.6)	
TNC x 10^8/kg§	6.4 (4.5-8.6)	8 (6.0-9.4)	0.069	6.8 (4.8-7.7)	0.964
CD34+ cells x 10^6/kg§	5.7 (3.8-7.5)	6.4 (2.8-7.8)	0.841	6.8 (3.9-8.3)	0.539
CD3+ cells x 10^6/kg§	180.7 (43.6-266.1)	160.2 (80.0-252.5)	0.798	202.5 (39.3-247.6)	0.981
Neutrophil engraftment (days)	21 (17-25)	17 (17-22)	0.327	17 (16.75-21.75)	0.154
Platelet engraftment (days)	21 (15-29)	20 (16-33)	0.897	19 (14-24)	0.238
Erythrocyte engraftment (days)	30 (22-36)	23 (18-33.5)	0.265	25.5 (18.75-29.25)	0.197
Day +30 neutrophil engraftment	172 (83.9)	10 (62.5)	**0.042**	10 (90.9)	1.000
Day +30 platelet engraftment	138 (67.3)	8 (50.0)	0.176	9 (81.8)	0.508
Day +30 erythrocyte engraftment	90 (43.9)	6 (37.5)	0.794	7 (73.6)	0.227
aGVHD	42 (20.6)	2 (12.5)	0.744	1 (9.1)	0.697
cGVHD	37 (18.4)	1 (6.3)	0.694	1 (9.1)	0.693
Relapse	40 (19.4)	6 (37.5)	0.107	2 (18.2)	1.000
Death	69 (33.5)	9 (56.3)	0.099	3 (27.3)	1.000

MDS, Myelodysplastic Syndromes; +Lymphoproliferative disorders include Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, and plasmacellular discrasias; ++ Myeloproliferative neoplasms include idiopathic or post-myeloproliferative neoplasm myelofibrosis and myeloid chronic leukemia.

P* and P** indicate difference in comparison with other donations; § recipient's body weight. Continuous variables are given as median (interquartile range). Categorical variables are given as number (%). Significant P values are highlighted in bold.

CVD, Cardiovascular Diseases; HLA, Human Leukocyte Antigen; PBSC, Peripheral Blood Stem Cell transplant; BM, Bone Marrow; HCT-CI, Hematopoietic Cell Transplantation-Comorbidity Index; DRI, Disease Risk Index; MA, myeloablative regimen; NMA, non-myeloablative regimen; TNC: Total Nucleated Cells; MNC, Mononucleated Cells; aGVHD, acute Graft Versus Host Disease; cGVHD, Chronic Graft Versus Host Disease. Continuous variables are given as median (interquartile range). Categorical variables are given as a number (%). Significant values are in bold type.

Pre-existing health disorders were fully investigated to explore the presence of malignancies, autoimmune diseases, inherited or genetic affections, and cardiovascular, endocrine, and metabolic disorders. Behavioral risk factors for communicable infectious diseases were also routinely investigated. Overall, 351 donors (77%) were finally assessed as eligible for HPC donation and 233 underwent stem cell collection, 158 (68%) through apheresis from mobilized peripheral blood, and 75 (32%) through bone marrow (BM) harvest. Among them, 27 donors

were selected despite the presence of pre-existing health conditions, that would be potential exclusion criteria for unrelated donors: 16 suffered from well-controlled cardiovascular diseases (CVD), and 11 from a known drug allergy. Most of the selected donors with pre-existing disorders were candidates for apheresis HPC collection (21, 78%), while only 6 (22%) underwent BM harvest. We then analyzed the data relative to the corresponding 233 allogeneic HSCT to explore if the presence of pre-existing diseases in the donors could show any association with transplant characteristics or influence transplant outcomes (Table 1). Transplants from CVD and allergy donors showed no significant disparities in comparison with those from healthy donors, except for a significant difference emerging about the disease severity, with a higher proportion of patients with high/very high disease risk index (DRI) among those receiving grafts from CVD donors (68.7% in transplants from CVD donors in comparison with 36.0% in transplants from healthy donors, p=0.005). Multivariate analysis confirmed that high/very high DRI patients had an increased probability of receiving donations from CVD donors (OR 4.89, 95% CI 1.15-20.86, p=0.031). In this group of donors with well-controlled pre-existing conditions, no adverse events were recorded during stem cell collection nor at subsequent follow-up. Comprehensively, our results suggest that in patients at high risk for relapse requiring a prompt allogeneic transplant, a familiar donor may be accepted for safe HPC donation based on less strict criteria than unrelated donors. Further multicenter studies on larger donor populations are worthy to compare donor selection policies and reach definitive conclusions.

DP131

EBV INFECTION AND POST TRANSPLANT LYMPHOPROLIPHERATIVE DISEASE IN ALLOGENEIC HSCT IN THE LETERMOVIR ERA: RESULTS OF A SINGLE CENTER RETROSPECTIVE STUDY

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Epstein-Barr Virus (EBV) reactivation and EBV-related post transplant lymphoproliferative diseases (PTLD) are rare and severe complications of allogeneic hematopoietic stem cell transplant (aHSCT). The incidence of EBV DNA-emia and EBV-PTLD is variable; letermovir for anti-CMV prophylaxis may also interfere with the antiviral immune response. We conducted a retrospective single center analysis of 227 adult patients who consecutively underwent aHSCT between 2015-2023. The aim of the study was to assess potential risk factors for clinically significant EBV reactivation and subsequent evolution to PTLD. EBV-DNAemia plasmatic loads were monitored weekly in the first 100 days from aHSCT in all patients. Clinically significant EBV infection was considered as EBV-DNAemia requiring preemptive treatment with rituximab (EVB-DNA >1000 copies/ml). Twenty-nine of 227 patients presented clinically significant EBV DNAemia (12.8%). Median time between transplant and first clinically significant EBV-DNAemia was 62 days (27-244 days). Proven or probable PTLD was reported in 16 patients (7%). Histological assessment showed 4 cases of monomorphic PTLD (25%) and 4 cases (25%) of polymorphic PTLDs; in the other 8 cases histological diagnosis was not feasible and probable PTLD diagnosis was clinically established. At univariate analysis no pre-transplant or post-transplant factor, including letermovir prophylaxis and EBV recipient/donor serology, was significantly associated with EBV DNAemia or PTLD. In order to define any predictive factor for PTLD evolution in the cohort of EBV reactivated patients, LDH values and lymphocyte count at the time of the first significant EBV-DNAemia detection were collected: grade >3 lymphopenia (lymphocytes count <500/mmc) was statistically associated to progression to PTLD (p=0.036). Overall survival at one year from transplant was 76%. In the cohort of EBV positive patients 12 out of 29 died at one year from transplant (OS 58.6%), 7 for PTLD related causes, with median time to death of 2 months (15 days-4 months). PTLD has a strong negative impact on global OS. In our population no pre- or post-transplant factor was predictive of clinically significant EBV DNAemia; a lower count of lymphocytes at the first EBV reactivation was associated with progression to PTLD. This study remarks on the importance of identifying high-risk patients for PTLD development, who could benefit from early preemptive therapies and early investigation for PTLD.

DP132

FEASIBILITY AND OUTCOME OF ALLOGENEIC HEMATOPOIETIC STEM-CELL TRANSPLANTATION IN OLDER AML PATIENTS: A SINGLE-CENTER EXPERIENCE

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Allogeneic hematopoietic stem-cell transplantation (alloHSCT) is a potentially curative option for acute myeloid leukemia (AML); however, its use remains a matter of debate in older patients, due to treatment-related toxicity. From 2010 until January 2024, one hundred and four (104) AML patients aged ≥ 60 years underwent alloHSCT at our hospital.

Figure 1.

The median age at transplant was 64.5 years (range 61-71), and 52 pts (50%) were aged ≥ 65 years. According to the European LeukemiaNet (ELN) 2022 Genetic Risk Classification, the risk profile was favorable in 16 patients (15.4%), intermediate in 39 (37.5%) and high in 49 (47.1%). AlloHSCT was performed in 1st Complete Response (CR) in 71 patients (68.3%), in 2nd CR in 9 (8.7%) and in active disease in 24 (23.1%). The Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) was 0 in 27 patients (26%), 1 or 2 in 40 (38.5%), and ≥ 3 in 37 (35.6%). Most patients

(82.7%) received Peripheral Blood Stem Cells as stem cells source, while 13 patients (12.5%) received a single cord blood unit. The Conditioning regimen was Myeloablative (MAC) in 21 patients (20.2%) and at Reduced Intensity (RIC) in 83 (79.8%). With a median follow-up of 16.8 months (range 1-156), 5-years Overall Survival (OS), Leukemia-Free Survival (LFS) and Non-Relapse Mortality (NRM) for the whole population were 51% (CI 95%: 41%-64%), 45% (CI 95%: 35%-57%) and 16% (CI 95%: 9%-24%), respectively. Age ≥ 65 years did not significantly affect OS (p=.51) or NRM (p=.87). ELN 2022 Intermediate risk and Adverse risk were associated with a worse LFS (p=.03 and p=.05 respectively). HCT-CI 1-2 or ≥ 3 were not associated with a significant difference in OS (p=.58 and p=.35 respectively) or NRM (p=.41 and p=.17 respectively). Cord blood source did not significantly affect neither OS (p=.16) nor NRM (p=.2) compared to other stem cells sources. In this analysis, the intensity of conditioning regimens did not significantly affect neither OS (p=.53) nor NRM (p=.1). In conclusion, these results support our intent to offer, whenever indicated, an alloHSCT to AML patients up to the age of 70 years.

DP133

ROLE OF IMMUNE MONITORING BY QUANTIFERON CMV IN PREDICTING LATE CMV REACTIVATIONS

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Background. Letermovir prophylaxis has reduced incidence and morbility of CMV after HSCT; however, late CMV reactivations after letermovir suspension on day 100 are frequent.

Methods. We retrospectively analyzed 113 consecutive adult patients (pts) who underwent HSCT between January 2022 and December 2023, in order to evaluate if immune monitoring by QuantiFERON-CMV (QF-CMV) can predict CMV late-onset reactivations. CMV-DNA was evaluated weekly post-HSCT. DNAemia ≤ 100 UI/mL was defined as "blip" while >100 UI/mL was considered clinical significant (CS). Treatment was initiated for CMV-DNA >1000 UI/mL or due to an increasing viral load in two consecutive determinations. QF-CMV was monitored at months 2, 4 and 6.

Results. Median age was 58 years (22-76), and the main underlying hematological disease was acute myeloid leukemia. Ninety-six pts received Letermovir prophylaxis up to day 100 after HSCT based on positive CMV serostatus. The mean time from transplant to reactivation was 157 days (10-642 days). Eight reactivations (7%) occurred before day 100, 4 were blips (mean viral load 70.4 IU/mL) and 4 were CS (mean viral load 3014 IU/mL). Of the 39 reactivations occurring after day 100 post-HSCT, 22 (59%) were CS with a mean viral load of 7449 IU/mL (84-95100 IU/mL), and were treated mainly with valganciclovir (median dose 450 mg twice daily due to cytopenia). The mean duration of therapy was 55 days. Thirty of 39 patients (77%) had concomitant graft-versus-host disease (GVHD), mostly in second-line therapy (67%). In 3/23 (13%) pts there was an organ CMV localization (2 enteric, 1 pulmonary). There was a trend in QF-CMV negativity before the reactivation in CS CMV pts compared to negative or non-CS CMV pts (83% *vs* 54%, p=0.065).

Conclusions. These real-life analysis confirmed that most CMV reactivations occurred between day 100 and 200 post-HSCT especially in patients with steroid refractory GVHD: 59% of these late reactivations were CS requiring treatment and 8% were CMV diseases. QF-CMV monitoring could be helpful to predict late reactivations, but we need to enroll more patients and extend follow-up to confirm this trend. Disclosure: no one

Myeloproliferative neoplasms

DP134

RUXOLITINIB STARTING DOSE REDUCTION AFFECT OVERALL SURVIVAL IN MYELOFIBROSIS: AIFA MONITORING REGISTRIES ANALYSIS

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Background. Ruxolitinib is a JAK1/JAK2 inhibitor approved for the treatment of primary myelofibrosis (PMF) or secondary MF (PPV-MF and PET-MF). From sponsored and real-world evidence, the efficacy has been demonstrated on splenomegaly or MF-related symptoms. The recommended starting dose depends on baseline platelet count, regardless of initial hemoglobin level. In the COMFORT prospective studies, an overall survival (OS) advantage was reported in patients treated with ruxolitinib compared to best available therapy. OS advantage over standard therapy was confirmed in other analyses (Medicare, ERNEST registry).

Aims. To analyze the outcome of MF patients treated with 1st line ruxolitinib according to starting dose.

Methods. We analyzed a large Italian series of 3647 MF patients identified by Italian Medicines Agency (AIFA) monitoring registries. AIFA web platform is an administrative database whose main scope is monitoring the appropriateness of drug prescription in Italy; all patients receiving ruxolitinib outside clinical trials are registered in this platform. This analysis includes MF patients who, as of April 30, 2023, received front-line ruxolitinib for at least 3 years. The focus of the analysis is to compare OS of patients who started ruxolitinib at the full dose, according to the platelet count, and of those who start with a lower-than expected dose for any reason. To adjust for confounding factors, the Inverse Probability of Treatment Weighting (IPTW) was used. The IPTW is a validated propensity score that calculates a system of weights, based on the probability of patients being assigned to the subpopulation to which they belong. The calculated weights are of the ATE type (Average Treatment Effect on the combined population).

Results. Of the whole cohort of 3647 MF patients, 2448 (67%) started at reduced dose. Comparing with patients who started at full dose, patients who started at reduced dose were older (median age 70 *vs* 67 years), with large splenomegaly (longitudinal diameter 20 *vs* 19 cm, volume 64 *vs* 62), with higher IPSS risk (30.8% *vs* 26%), worse ECOG score (more than 1 in 14.3% *vs* 9.6%). Kaplan Meier analysis showed a median OS of 78.8 months (68.8-na) for patients who started at full dose and 52.8 months for patients who started with reduced dose, with an HR of 1.467 (1.318-1.632) and a log-rank<0.001. OS was calculated according to IPSS at baseline: only 285 patients (7.8%) were classified as interm-1 risk and for them, the low mortality recorded in a period of 5 years, the shorter follow-up and the small size of the population examined do not allow us to observe a significant difference. Of 2294 patients (62.9%) identified as interm-2 risk, 789 patients started at full dose and 1505 at reduced dose: Kaplan Meier adjusted analysis revealed a statistical difference [HR 1.501 (1.305-1.727)]. Of 1068 patients identified as high risk, 313 started at full dose and 755 with reduced dose. OS evaluated by Kaplan Meier analysis detected an advantage for patients who started

with the correct full dose with an HR of 1.452 (1.224-1724).

Summary. In this real-world analysis, most MF patients started with a lower-than-expected dose of ruxolitinib. In intermediate-2/high risk patients, the use of inappropriate starting doses was independently associated with worse outcome. Larger cohorts should be analyzed to test the same effect in intermediate-1 risk patients.

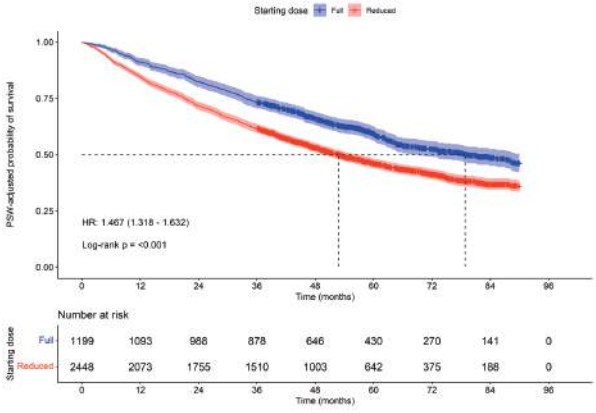

Figure 1.

DP135

ABSTRACT NOT PUBLISHABLE

DP136

MDS/MPN-NOS' FEATURES AND MUTATIONAL LANDSCAPE, A REPORT FROM GRUPPO LAZIALE FOR THE STUDY OF PH-NEGATIVE MPN

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According to WHO 5th and ICC classifications, Myelodysplastic/Myeloproliferative syndromes (MDS/MPN) include chronic myelomonocytic leukemia (CMML), MDS/MPN with neutrophilia or atypical chronic myeloid leukemia (aCML), MDS/MPN neoplasm with SF3B1 mutation and thrombocytosis and MDS/MPN not otherwise specified (NOS), not meeting the criteria for a defined category. Due to its undefined nature, clinical and biologic features of this latter entity are poorly investigated. To shed light on this topic, we analyzed clinical data and genetic characteristics of MDS/MPN diagnosed within Gruppo Laziale for the study of Ph-negative MPN. The study included 30 patients (16 CMML, 10 MDS/MPN NOS, 3 aCML and 1 MDS/MPN with SF3B1 mutation and thrombocytosis) with a median age of 70 years and a male/female ratio of 1.3. Mutational screening included at least 30 genes among the most common myeloid malignancy drivers and was performed in 18 patients (62 variants identified with a median of 3 mutations per patient; the most common observed were ASXL1 50%, TET2 33%, NRAS 28%, JAK2 17%, SRSF2 17%); karyotype analysis was available in 23 patients, revealing anomalies in 22% of cases. MDS/MPN NOS subgroup presented a median age of 69 years and a predominance of female gender (M/F: 0.4). Mutational screening was available in 6 patients and 14 variants were detected (median of 3 mutations). Karyotype analysis showed a normal karyotype in 78% of patients (1 patient carrying trisomy 17; 1 patient trisomy 8 and trisomy 13; 1 patient not available). When compared to CMML patients [divided in myeloproliferative (MP) and myelodysplastic (MD) according to WBC (>13.000/mm^3 *vs* <13.000/mm^3); Table 1], although not significant, we observed differences in the rate of ASXL1 mutations [33% *vs* 0% in MD-CMML (p=0.5) *vs* 100% in MP-CMML (p=0.06)] and RAS genes mutations [one among NRAS, KRAS, NF1, c-CBL, PTPN11: 17% *vs* 33% in MD-CMML (p=1) *vs* 80% in MP-CMML (p=0.08)]. Survival analysis showed a poorer prognosis of MP-CMML patients both in terms of overall survival [median of 22.9 months *vs* not reached at a median of 8.4 and 24.9 months of follow-up in MDS/MPN-NOS (p=0.9) and MD-CMML (p=0.085), respectively] and event-free survival [median of 14.1 months *vs* not reached in MDS/MPN-NOS (p=0.6) and MD-CMML (p=0.019)]. Our preliminary report suggests that the mutational landscape shapes phenotype and features among MDS/MPN entities. The expansion of our cohort will allow further analyses.

Table 1. Demographic data, genetic features and outcome of study population. 5-HU: 5-hydroxyurea; CMML: chronic myelomonocytic leukemia; EPO: erythropoietin; HMA: hypomethylating agents; MDS/MPN: Myelodysplastic/Myeloproliferative syndromes; NOS: Not otherwise specified.

		MD-CMML (6)	MP-CMML (9)	MDS/MPN NOS (10)
Age (yo)	Median (Range)	75 (66-86)	70 (61-89)	69 (49-73)
Gender (M)	n (%)	4 (67)	6 (67)	3 (30)
Hb (g/dl)	Median (Range)	12 (8.2-14.3)	11 (9.2-15.4)	10 (8.2-14.4)
WBC (/mm3)	Median (Range)	4.9 (4.1-10.8)	31.6 (14.7-74.2)	8.8 (2.8-26.5)
Plts (/mm3)	Median (Range)	137.5 (64-234)	112 (18-270)	503 (96-990)
Karyotype	Available	3	6	9
	Normal, n (%)	3 (100)	5 (83.3)	7 (78)
Genetic analysis	Available	3	5	6
	Mutations, median (Range)	3 (0-4)	5 (3-7)	3 (0-6)
	Splicing genes, n (%)	1 (33)	2 (40)	1 (17)
	RAS genes, n (%)	1 (33)	4 (80)	1 (17)
Treatment	HMA, n (%)	0	1 (11.1)	1 (10)
	5-HU, n (%)	1 (20)	7 (77.8)	6 (60)
	EPO, n (%)	3 (50)	2 (22.2)	0
Survival	Follow-up, median (months)	24.9	13.5	8.4
	Overall, median (months)	NR	22.9	NR
	Event-free, median (months)	NR	14.1	NR

DP137

INFLUENCE OF THE PANDEMIC PERIOD ON TIME TO DISCONTINUATION AND MORTALITY IN MYELOFIBROSIS PATIENTS TREATED WITH RUXOLITINIB: AN AIFA MONITORING REGISTRIES ANALYSIS

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An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in December 2019 and then become pandemic in March 2020, with Italy being one of the first and most affected countries. It has been reported that COVID-19 infection led to a particularly dismal outcome in Myeloproliferative neoplasms patients receiving immunosuppressive agents or reporting multiple comorbidities. To analyze the outcome of patients affected by myelofibrosis (MF) treated with ruxolitinib before and after COVID-19 pandemic. From the AIFA monitoring registries two populations

of MF were defined: the pre- COVID-19 one is made up of patients who as of 31 December 2019 had at least two years of maximum potential follow-up; the second, the post- COVID-19 one, is made up of patients who at the cut-off date (30/04/2023) had at least two years of potential follow-up, having started treatment from March 2020. Intermediate-1 IPPS risk patients were excluded from the analysis because they are present only in the post- COVID-19 population. The two populations have been balanced through the Inversity Probability of Treatment Weighting (IPTW), a validated propensity score method that calculates a set of weights, based on the probability of patients being assigned to the cohort to which they belong. Out of 2478 MF patients, 1905 (88%) started in the pre-COVID era and 573 (12%) in the post- COVID-19era. No unbalance was revealed in terms of gender, whereas the median age was 67.4 years in the pre- and 71.4 in the post- COVID-19era. No unbalance was reported in most patients for the spleen dimensions at baseline before treatment start, but an unbalance was detected in the mean spleen lower costal margin diameter, being 11.4 cm in the pre-era and 9.0 cm in the post-era. Overall, intermediate-2 IPSS risk were 66.6% in the pre- and 71.5% in the post-era, whereas the high-risk category was 33.3% and 28.4%, respectively. After balancing of the differences, an analysis of overall survival (OS) was conducted: patients who started treatment post- COVID-19 have a risk of death in the considered follow-up of approximately 22% greater than those who began treatment before the pandemic (HR 0.78, p=0.02). Median OS was not reached in both groups. Then, time to discontinuation was analyzed, including, as events, all patients with more than 90 days of discontinuation of treatment. Patients who started treatment post-COVID-19 have a risk of discontinuation, in the considered follow-up approximately 17% greater than those who started treatment before the pandemic (HR 0.83%, P=0.03). In a large cohort of MF patients treated with ruxolitinib, COVID-19 seems to be associated to an increase in the risk of mortality and treatment discontinuation.

DP138

LONG-TERM FOLLOW-UP OF PATIENTS WITH MYELOPROLIFERATIVE NEOPLASM-ASSOCIATED SPLANCHNIC VEIN THROMBOSIS: A COMPARATIVE ANALYSIS BETWEEN TWO DIFFERENT COHORTS

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Background. MPN-SVT is a unique condition requiring interdisciplinary collaboration for diagnosis and management. While emerging data suggest the potential benefit of DOACs as the first choice of treatment in MPN-SVT, real-world practice data in this context are currently lacking.

Aim and Methods. Describe clinical and biological features of MPN-SVT, management, and long-term outcomes in two cohorts. Subsequent analysis, including a larger cohort, aims to assess recurrence risk, MPN evolution, and effectiveness of current anticoagulation strategies. Retrospective analysis compared 85 MPN-SVT patients at Guy's Hospital with 55 from an Italian cohort.

Results. The two cohorts of 85 and 55 patients with MPN-SVT were analysed over median follow-up times of 7.7 years and 8.1 years, respectively (p=0.73). Patients from the UK cohort were younger at MPN diagnosis than those from the Italian group (median age 44 years *vs.* 52, p=0.038). In the UK cohort, MPN and SVT diagnoses coincided in 56 patients (65.9%), while in the Italian cohort, the two diagnoses coincided in 29 patients (52.7%). The portal vein was the most common site of thrombosis in both cohorts. PV was the most frequent MPN-SVT subtype in the UK cohort, unlike the Italian cohort, where ET was prevalent (63.5% *vs.* 23.6%, p<0.001). Driver mutation frequencies were not significantly different between the cohorts. After SVT, most patients from both cohorts were prescribed VKAs (70% *vs* 75%, p=0.73), with 20% of the UK cohort and one patient from the Italian cohort initially prescribed DOACs. At the last follow-up, 47% of UK patients were on DOACs, and 11% of Italian patients had shifted from VKAs. No differences were found in thrombotic recurrence incidence between the cohorts (p=0.32), while major hemorrhage incidence was significantly higher in the UK cohort (24% *vs.* 7.3%, p=0.009). OS at last follow-up was 89.4% *vs.* 76% in the UK and Italian cohorts, respectively, with no significant difference in median OS between the cohorts (29.8 years *vs* 27.9 years, p=0.30).

Conclusion. We confirmed a similar phenotype in both MPN-SVT cohorts and observed increased use of DOACs. The complexity of managing this rare entity was evident in the variation of antithrombotic strategies observed from initial diagnosis to recent follow-up. This highlights the importance of enhancing data availability to identify reliable predictors of vascular events and optimise patient outcomes.

Table 1.

Table 1. Clinical and laboratory findings of two cohorts of MPN-SVT patients.

	GSTT cohort (85)	AOU Marche cohort (55)	*p*
Age at MPN diagnosis (years), median (range)	44 (13-70)	52 (11-79)	**0.038**
Age at SVT diagnosis (years), median (range)	45 (13-75)	57 (17-81)	**0.015**
Gender (M/F), n	35/50	24/31	0.77
MPN subtype, n (%)			
Polycythaemia Vera	54 (63.5)	13 (23.6)	**<0.001**
Essential Thrombocythaemia	11 (12.9)	18 (32.7)	0.05
Primary and Secondary Myelofibrosis	10 (11.8)	17 (31)	0.05
MPN-U	10 (11.8)	7 (12.7)	0.86
Sites of SVT (single/multiple)	29/56	28/27	0.07
Hb at MPN diagnosis (g/dL), median (range)	13.5 (8-20.9)	14 (7.2-21.2)	0.76
Hct at MPN diagnosis, median (range)	44.2 (25-65.4)	44.8 (22.3-65.7)	0.92
WBC at MPN diagnosis (x10^9/L), median (range)	8 (4-41.9)	7.45 (3-16.8)	0.74
PLT at MPN diagnosis (x10^9/L), median (range)	389 (130-1800)	335 (44-1384)	0.14
NLR at MPN diagnosis, median (range)	3.6 (0.8-14.9)	2.95 (0.43-25.4)	0.48
Hb at SVT diagnosis (g/dL), median (range)	13.5 (8-20.9)	14 (7.2-21.2)	0.46
Hct at SVT diagnosis, median (range)	41 (25-57)	39.7 (22.3-65.7)	0.67
WBC at SVT diagnosis (x10^9/L), median (range)	7.2 (4-42)	8.6 (1.15-31)	0.47
PLT at SVT diagnosis (x10^9/L), median (range)	382 (130-1395)	347 (44-1362)	0.35
Constitutional symptoms at MPN diagnosis, n (%)	46 (54.1)	12 (21.8)	**<0.001**
Splenomegaly at MPN diagnosis, n (%)	63 (74.1)	44 (80)	0.42
*JAK2*V617F, n (%)	79 (92.9)	47 (85.5)	0.14
*JAK2*V617F VAF (%), median (range) N evaluable (GSTT/Italian=35/28)	24 (4-91)	20.1 (0.8-89)	0.88

DP139

IMPROVEMENT OF THE CLINICAL OUTCOME AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN MYELOFIBROSIS OVER THE LAST 15 YEARS: A SINGLE-CENTER EXPERIENCE

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Introduction. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative approach for Myelofibrosis (MF), but the decision to advise transplant remains challenging. Despite this, the number of transplants for MF in the last decade has been steadily increasing worldwide.

Methods. We retrospectively analyzed the clinical outcome of 74 consecutive MF patients transplanted at the Bergamo Bone Marrow Transplant Unit between 2007 and 2023. The median age was 58 years (36-67). All patients were molecularly characterized by myeloid NGS sequencing. A driver mutation was detected in 68 patients (38 *JAK2V617F*/22 *CALR*/8 *MPL*) and at least one high molecular risk (HMR) mutation was present in 54% of patients. Twenty-four patients (32%) underwent HSCT after being progressed to blastic phase MF. MIPPS70+ at transplant was high/very high in 50%/24% of patients.

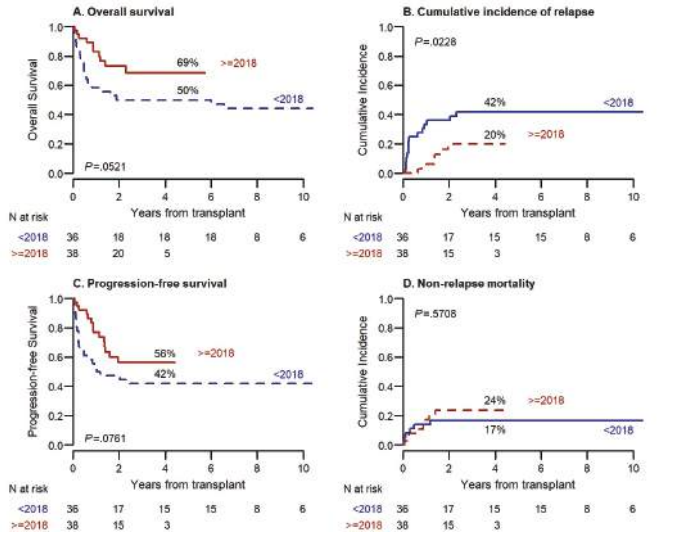

Figure 1.

Results. With a median follow-up of 2.1 years (0.02-15.5), the 5-year Overall Survival (OS), Progression Free Survival (PFS), Cumulative Incidence of Relapse (CIR) and Non-relapse Mortality (NRM) were 60%, 49%, 31% and 20% respectively. By univariate analysis, MIPSS70+ very high, *TP53, EZH2* or *DNMT3A* mutation, or the presence of at least 2 HMR mutations were associated with worse survival. We then analyzed the clinical outcome of patients transplanted after 2018 (n=38) or before 2018 (n=36). The two cohorts of patients differed for median age (61 versus 56 years), spleen size at transplant>20 cm (21% versus 47%), MIPPS70+ risk score (high+very high 65% *versus* 86.2%) and conditioning (Thiotepa-Busulfan-Fludarabine 100% versus 11%) respectively for transplant after and before 2018. We observed a significant improvement in 3-year OS for patients transplanted after compared to patients transplanted before 2018 (69% versus 50% respectively, p=0.05, Figure 1A), with a lower 3-year CIR (20% after and 42% before 2018, p=0.02, Figure 1B) and a trend for a higher PFS (56% after and 42% before 2018, Figure 1C). On the contrary, the 3-year NRM was not significantly different (17% after and 24% before 2018, Figure 1D).

Conclusion. HSCT can lead to a significant cure rate for MF patients. Patients with a progression to a blast phase of the disease should not be excluded a priori from a transplant program. We observed a significant improvement in OS and CIR for patients transplanted after 2018, which could be related to better patient selection, timing of the transplant, and an improved conditioning platform.

DP140

THE *KIT*D816V ALLELIC BURDEN CORRELATES WITH SYMPTOM BURDEN AS EVALUATED WITH THE INDOLENT SYSTEMIC MASTOCYTOSIS SYMPTOM ASSESSMENT FORM IN A REAL-LIFE PATIENT COHORT OF INDOLENT SYSTEMIC MASTOCYTOSIS

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Background. Indolent systemic mastocytosis (ISM) is characterized by a broad clinical spectrum driven by activating mutations of the *KIT* tyrosine kinase gene. Treatment goals for ISM include anaphylaxis prevention, mediator-related symptom control and osteoporosis treatment. Recently KIT-targeting agents have been introduced in clinical practice for patients with a moderate-high Total Symptom Score (TSS≥28) assessed with the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF). Until now, no clinical correlation with *KIT*D816V allele burden (AB) and symptoms has been identified.

Aims. To investigate the relationship between the *KIT*D816V AB and the symptom burden, evaluated with the ISM-SAF.

Methods. Inclusion criteria comprised 1) diagnosis of ISM according to WHO2022; 2) availability of *KIT*D816V AB in bone marrow (BM) determined with digital droplet (dd)PCR, 3) Mediator-related symptom burden evaluated with the ISM-SAF. Bone mineral density (BMD) was evaluated with dual-energy x-ray absorptiometry (DEXA). Correlation analysis was employed to assess association between continuous variables.

Results. Overall, 56 patients, have been enrolled. Median age is 52.3 (IQR 45.5-59.2), 26 (46.4%) are male. Thirty-five (62.5%) patients have skin mastocytosis; osteoporosis and osteopenia affect 42.6% (23/54) and 31.5% (17/54) respectively, 14 (25.9%) show normal BMD, 11 patients (19.6%) experienced bone fractures. Median mast cell BM infiltration is 10% (IQR 5-15), median tryptase level 25.1 ng/mL (IQR 16.4-40.8) and median *KIT*D816V AB 0.2% (IQR 0.06-0.79, range 0.01-27.2). Median TSS is 16 (IQR 9-30); 19 (33.9%) patients present a TSS≥28. The correlation between ISM-SAF and *KIT*D816V AB is significant with p .05. Symptom subanalysis showed strong correlation between bone pain (p .017), but not with gastro-intestinal SS, skin SS, nor neuropsychiatric symp-

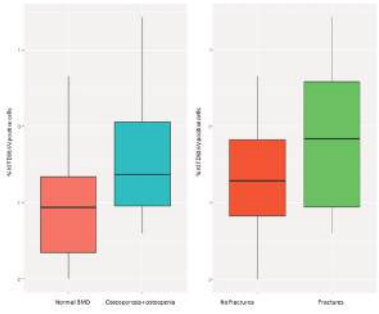
toms. TSS≥28 cut-off, was applied: group 1 (TSS<28, n=37) has a median *KIT*D816V AB of 0.17 (IQR 0.06-0.31) and group 2 (TSS ≥28, n=19) of 0.93 (IQR 0.16-3.49), p .003. Relationship between *KIT*D816V AB and bone disease was assessed. Significant difference was detected when comparing osteopenia and osteoporosis group to normal BMD group (p .02); no difference in fracture incidence was observed.

Conclusions. Patient symptom burden evaluated with ISM-SAF correlates significantly with *KIT*D816V AB, driven mainly by bone pain, possibly reflecting a superior bone involvement as confirmed by inferior BMD.

A

Patient characteristics	N= 56
Age at diagnosis years, median (IQR)	52.26 (45.48 - 59.23)
Time from symptoms to diagnosis years, median (IQR)	7.6 (1.2 – 12.0)
Follow-up from diagnosis months, median (IQR)	26.0 (13.0 – 49.3)
Sex male, n° (%)	26 (46.4)
Skin mastocytosis, n° (%)	35 (62.5)
Anaphylaxis, n° (%)	22 (40%)
Mast cell infiltration, % (IQR)	10 (5 - 15)
KITD816V allelic burden BM, % (IQR)	0.2 (0.06 - 0.79)
KITD816V allelic burden PM, % (IQR)	0.15 (0.03 - 0.53)
KITD816V allelic burden BM ≥ 1%, n° (%)	13 (23.2%)
Tryptase value baseline, ng/mL (IQR)	25.1 (16.4 - 40.82)
Bone mineral density (DEXA)*	
Osteoporosis	23 (42.5)
Osteopenia	17 (31.5)
Normal	14 (26.0)
Bone fractures, n° (%)	11 (19.6)
ISM SAF TSS, median (IQR)	16.5 (8.75 - 30.25)
ISM SAF GSS, median (IQR)	0.5 (0 - 7)
ISM SAF SSS, median (IQR)	6.5 (2 - 10.25)

B



C

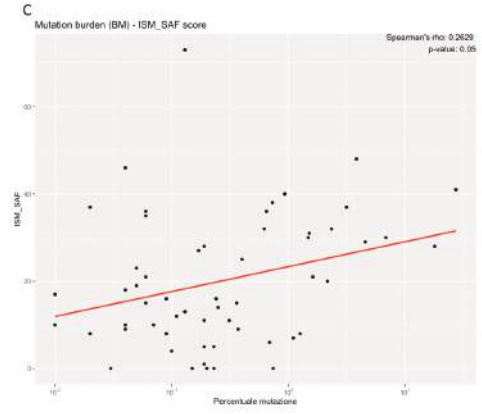


*Figure 1A. patient characteristics. IQR: interquartile range, BM: bone marrow, PB; peripheral blood, DEXA: dual-energy x-ray absorptiometry; ISM SAF: Indolent Systemic Mastocytosis Symptom Assessment Form, TSS: Total Symptom Scale, GSS: Gastrointestinal symptom scale, SSS: Skin Symptom Scale. *DEXA available for 54 of 56 patients*

Figure 1B: Box plot of mutation burden in relation to osteoporosis/osteopenia and fractures

Figure 1C: Mutation burden in BM in relation to ISM SAF p 0.05

Figure 1.

DP141

DIFFERENCES IN MUTATION PROFILE IN PATIENTS AFFECTED BY MYELOFIBROSIS ACCORDING TO PRIMARY OR SECONDARY NATURE AND EARLY *VS* OVERT STAGES

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Myelofibrosis (MF) is a chronic myeloproliferative neoplasm (MPN) characterized by progressive bone marrow fibrosis, extramedullary hematopoiesis, and possible transformation into acute leukemia. The disease can appear *de novo* (primary MF, PMF) or because of disease progression from another MPN (secondary MF, SMF), such as polycythemia vera (PV) or essential thrombocythemia (ET). Among classical BCR::ABL1-negative myeloproliferative neoplasms, primary myelofibrosis (PMF) is the most aggressive subtype, posing a great challenge to clinicians, in particular in cytopenic forms. In the past decade, the molecular pathogenesis of the disease has been deeply dissected. In particular, genomic studies have provided evidence of deregulated oncogenes in MF and other MPNs. With the integration of targeted next-generation sequencing (NGS) panels into clinical practice, the clinical significance of concomitant mutations in MPNs has become clearer. The increasing use of molecular genetics for early risk stratification of patients offers the possibility of earlier intervention to prevent disease progression in MPNs. The aim of our work is to evaluate the genomic landscape in a large series of patients with myelofibrosis, considering whether they are early- *vs* overt-stage MF, PMF or SMF. The study included 256 patients, 98 SMF *vs* 104 PMF and 202 overt PMF *vs* 54 early-MF. The molecular landscape was studied by high-throughput sequencing of 77 frequently mutated genes in MPNs involved in: (1) DNA methylation pathways, (2) chromatin modification, (3) RNA splicing, (4) signaling pathways, (5) transcription factors, and (6) DNA damage response/stress signaling. Median age at diagnosis was 53, 54, 53.5 and 47 years, respectively. Our results showed no differences in the rate of driver mutations among different groups analyzed: JAK2 V617F mutation was detected in 55% of overt MF, 52% of early, 60% of SMF, and 51% in PMF. CALR mutation was detected in 23%, 20%, 23%, and 23% of patients, respectively whereas MPL was observed in 8%, 6%, 7%, and 9%, respectively. As to the non-driver mutations, we confirmed that both PMF and SMF have distinct molecular landscapes. ASXL1 mutation was detected in 17% of SMF and 32% of PMF with at least 1 HMR mutation found in 19% of SMF and 24% of PMF, 2 HMR in 2% and 12% and 3 HMR 1% and 4%, respectively. We also found that the proportion of RAS pathway mutations in genes such as KRAS, NRAS in PMF (7%) was higher than in SMF (2%). Increased rates of somatic mutations were detected in overt compared to early MF, with less evidence of splicing mutations (SF3B1, SRSF2, U2AF1, ZRSR2, LUC7L2) and more in signaling pathway. In conclusion, different genomic profiles could be detected that may help to identify different prognostic categories and different therapeutic strategies in the future.

DP142

POLYCYTHEMIA VERA IN PATIENTS AGED > 80 YEARS: REAL-LIFE EXPERIENCE OF THE NPM PH NEGATIVE LATIAL GROUP

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Background. Increasing life expectancy has lead to a progressive increment in the proportion of patients (pts) with myeloproliferative neoplasms (MPN) aged ≥ 80 years at diagnosis. However, so far, few studies have evaluated very elderly pts with polycythemia vera (PV)

Aim. To describe the clinical features and the course of disease in a real-life cohort of PV pts aged ≥80 years.

Methods. From 1/2000 to 12/2023, 100 consecutive pts aged ≥ 80 years were diagnosed in 7 hematologic Centres and enrolled in the retrospective and prospective databases of the Latial group for Ph-negative MPN. Diagnosis was revised according to WHO 2022 criteria.

Table 1. Clinical features at diagnosis.

N° of patients	100
M/F, n° (%)	42/58 (42.0/58.0)
Median age, years (IQR)	83.1 (81.3 – 85.9)
Median Hb, g/dl (IQR)	17.5 (16.0 – 18.5)
Median Ht, % (IQR)	53.7 (50.5 – 57.9)
Median WBC, x 10^9/l (IQR)	10.2 (8.7 – 13.5)
Median PLTS, x 10^9/l (IQR)	520 (370 – 690)
Spleen enlargement, n° (%):	
Evaluable	92
No spleen enlargement	72 (78.3)
< 5 cm below costal margin	19 (20.6)
≥ 5 cm below costal margin	1 (1.1)

Results. Main features at diagnosis are shown in the Table 1. Marrow biopsy was performed in 13/89 evaluable cases (14.5%), median JAK2 V617F allele burden was 40% (IQR 17.8-66.2). Symptoms at diagnosis were present in 18/86 evaluable pts (20.9%), with pruritus accounting for 50% of cases (9/18). Arterial hypertension, diabetes, dyslipidemia and smoke attitude were present in 69.7%, 13.1%, 32.0% and 23.1% of pts, respectively. Previous thrombotic events were reported in 28/90 evaluable pts (38.1%). Hydroxyurea (HU) was started in 96/100 pts, after a median time of 1 month (IQR 0.1-3.8) from diagnosis. HU was discontinued in 20/96 pts (20.8%), mostly due to intolerance (12/20). Only 3/20 pts (15%) received Ruxolitinib as 2nd line, while no other drug was used in 11/20 pts (55%). Thrombotic events during follow up were reported in 10/86 evaluable pts (11.6%), while evolution in fibrotic and blastic phase was observed in 2 cases. At the last follow up, 18 pts died, 40 were lost to FU and 42 were still alive: 60-month and 120-month cumulative overall survival were 82.2% (95%CI 92.6-71.8) and 52.3% (95%CI 73.9-30.7), respectively Conclusion: Our data in a relatively large real-life cohort of very elderly PV pts highlight some points of the current clinical practice: as expected, few pts underwent marrow biopsy at diagnosis and quite all pts received HU as frontline cytoreductive therapy at a short interval after diagnosis. However, responsible physicians were still reluctant after HU discontinuation in prescribing 2nd line treatment with ruxolitinib in this setting. The high number of cases lost to follow-up, probably due to difficulties in reaching hematologic Center by these aged pts, made difficult a correct evaluation of OS, which however was similar to that of general population in the same age group.

DP143

INCIDENCE OF THROMBOTIC EVENTS PRE AND POST DIAGNOSIS IN JAK2 POSITIVE PATIENTS IN LATIUM FROM 2011 TO 2018

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Background. Polycythemia Vera (PV) and Essenthial Thrombocythemia (ET) are a Ph negative Chronic Myeloproliferative Neoplasms (Ph-MPNs) which features are dominated, respectively, by erythrocytosis and thrombocytosis and a consequent high risk of thrombotic events and transformation to myelofibrosis or acute myeloid leukaemia. In the present report, we evaluated the incidence of thrombotic events in ET and PV patients before and after the diagnosis received in the hematologic center in the Latium region (approximately six milions of residents) across a 9-year retrospective observation.

Method. The present analysis was conducted in 15 centers (academic/ community-based hospitals), collecting data at onset in all newly diagnosed ET and PV patients aged >18 years from January 2011 to December 2018. The diagnosis of ET and PV was made according to 2008 WHO and revised 2016 WHO criteria.

Results. In the 9-year period of observation, 1389 adults received a new diagnosis of ET (62%) and PV (38%). JAK-2 mutation was tested in 1314 patients (94.6%): Of them, 1057 patients resulted JAK-2 positive: 527 (48.9%) were males, and 530 (51.1%) females. Median age at diagnosis was 64 years (+/- 14.72). The mean follow-up was 44.0+/-28.3 months. 268/1314 patients (20.4%) developed a thrombotic episode prior to diagnosis: the incidence was 21.4% in JAK-2 positive patients versus 16.3% in JAK2 negative patients. Splanchnic thrombosis was 4% in JAK-2 positive versus 0% in JAK2 negative patients. Fifty-seven patients (4.3%) developed post-diagnosis thrombosis with an incidence of about 4% in both groups. In 13 patients (22.8%) a recurrence of thrombotic events was detected, although all the patients assumed oral anticoagulant therapy: of them,

11 were JAK-2 positive patients. Patient features are summarized in the Table 1.

Conclusion. The results, even if limited by its retrospective nature, showed that 20.4% of patients had a thrombotic event before the PV/ET diagnosis, while only 4% had thrombosis post-diagnosis although all patients assumed antiplatelet therapy. The recurrence of thrombosis in JAK2 positive patients suggested that more aggressive anticoagulant/antiaggregant prophylactic therapy should be taken into account in this setting of patients.

Table 1.

Characteristic	N	Overall N = 1389	Jak2- N = 259 (19%)	Jak2+ N = 1130 (81%)	Missing
Gender	1314				
M/F		645/ 669	118/139	527/ 530	
Age to diagnosis, yrs (mean±SD)		64.3±4.8	64.0±15.1	64.3±14.72)	
Thrombosis pre diagnosis	1314				
No/**Yes**		1046/**268** (yes 20.4%)	215/**42** (yes 20.4%)	813/**226** (21.4%)	18
Thrombosis Pre diagnosis	80 avaible				
Superficial		3/80	1/15 (6.7%)	2/65 (3.1%)	
Deep		17/80	3/15 (20.0%)	14/65 (22.0%)	
Splachnic		4/80	0/15 (0%)	4/65 (6.2%)	
Arterial		56/80	11/15 (73.0%)	45/65 (69.0%)	
Thrombosis post diagnosis	1314				
No /**Yes**		1257/**57**	245/**12** (yes 4%)	1012/**45** (yes 4%)	
Thrombosis type	9				
Deep		5 / 9 (56%)	1 / 1 (100%)	4 / 8 (50%)	
Thrombosis relapse Patients in TAO	13		2 (4.8%)	11 (4.9%)	
Thrombosis type					
Deep			1 (50.0%)	4 (36.4%)	
Arterial			0 (0.0%)	4 (36.4%)	
Unknown			1 (50.0%)	3 (27.2%)	

DP144

TRIPLE A MODEL GLOBALLY RECAPITULATES ADVERSE OUTCOMES IN ESSENTIAL THROMBOCYTHEMIA

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Background. Essential thrombocythemia (ET) course may be adversely affected by vascular events (thrombosis and hemorrhages) occurrence, progression to myelofibrosis (MF) or acute myeloid leukemia (AML). IPSET-t and r-IPSET-t scores estimate thrombosis probability in ET patients (pts), and guide treatment. Recently, "triple A" (AAA) model - based on Age, Absolute neutrophil count (ANC) and Absolute lymphocyte count (ALC) at first referral (FR)-emerged as a novel survival model for ET. Age (4 pts > 70, 2 pts 50-70), ANC (1 pt >8x10^9/L), ALC (1 pts <1.7x10^9/L) define the AAA risk as low (L, 0-1 pt), intermediate-1 (Int-1, 2-3 pts), intermediate-2 (Int-2, 4 pts), and high (H, 5-6 pts). Aim of the study was to apply AAA model in our ET cohort to test its role in predicting main adverse outcomes.

Methods. We analyzed 362 ET pts diagnosed from 1984 to 2024 at the Division of Hematology of Udine. Overall survival (OS) and event-free survival (EFS; including thrombosis, major bleeding, MF or AML progression) were estimated from diagnosis to first event/last contact using Kaplan-Meier method. Cox regression was used to evaluate outcome predictors in univariable analysis, in terms of hazard ratio (HR).

Results. Of 362 evaluable pts (55% females), median age at FR was 58 yrs and median follow up was 10 yrs. Molecular status was JAK+ in 227 (63%), CALR+ in 77 (21%), MPL+ in 14 (4%), TN in 33 (9%), and unknown in 10 (3%). Overall, 43 (12%) thrombosis, 19 (5%) major bleedings, 38 (11%) MF/AML progressions, and 49 (14%) deaths occurred during follow up. AAA risk was computable in 309 (85%) pts: 35 (11%) H, 50 (16%) int-2, 138 (45%) int-1, 86 (28%) L risk. AAA risk associated with different vascular events rates (p<0.001; Figure 1A) with H, Int-2 and Int-1 pts having HR of 10.9 (p<0.001), 2.9 (p=0.074) and 2.0 (p=0.104) compared to L risk pts, respectively. Hence, EFS was statistically different among AAA risk classes (p<0.001, Figure 1B) with 10 yrs EFS of 90% (IC95: 84-98), 83% (IC95: 75-91), 76% (IC95: 59-99), 43% (IC95: 25-74) in L, Int-1, Int-2 and H risk pts, respectively.

Conclusions. The AAA model is a new easy tool that may flank the classical IPSET-t and rIPSET-t systems for ET risk evaluation. In our study, AAA model proved able to predict not only OS, but also to globally foresee ET-associated adverse outcomes. In summary, we propose AAA model to identify high risk ET pts at FR.

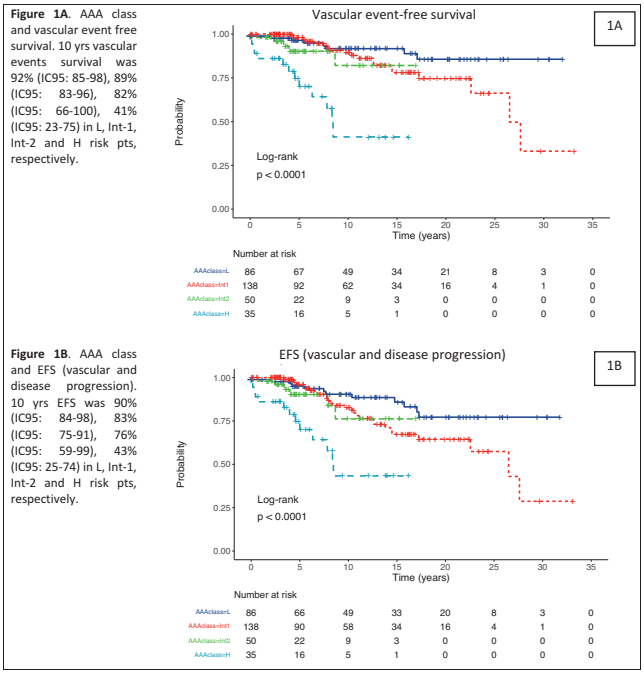

Figure 1A. AAA class and vascular event free survival. 10 yrs vascular events survival was 92% (IC95: 85-98), 89% (IC95: 83-96), 82% (IC95: 66-100), 41% (IC95: 23-75) in L, Int-1, Int-2 and H risk pts, respectively.

Figure 1B. AAA class and EFS (vascular and disease progression). 10 yrs EFS was 90% (IC95: 84-98), 83% (IC95: 75-91), 76% (IC95: 59-99), 43% (IC95: 25-74) in L, Int-1, Int-2 and H risk pts, respectively.

Figure 1.

DP145

RETINAL VESSEL ANALYSIS AND MICROVASCULAR ABNORMALITIES IN PATIENTS WITH PH-NEGATIVE CHRONIC MYELOPROLIFERATIVE NEOPLASMS

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Ph-negative chronic myeloproliferative neoplasms (MPNs) represent a group of clonal hematopoietic disorders characterized by an increased risk of thrombotic complications. In MPNs thrombosis can occur either from the very early stages of the disease or may also complicate the course of the follow-up. Therefore, there is a current need in identifying useful prognostic biomarkers of thrombotic risk.

Previous studies have highlighted that the vessels of the retina may offer the opportunity to visualize in vivo the damage to the microcirculation and have demonstrated a direct correlation between the calibers of the retinal vessels and the cardiovascular risk (Bakhoum CY,2023; Azanan MS,2020). Therefore, we hypothesized that through investigating in patients with MPNs the retinal vessels it could be possible to visualize in vivo the damage to the microcirculation and might be also possible a stratification of the thrombotic risk. In this view, we studied 40 patients affected by different MPNs to verify the investigating hypothesis (18 ET, 15 PV, 7 PM). Clinical and molecular features will be further depicted and a group comparable in age and sex was used. Patients underwent ophthalmological examination, using non-invasive imaging techniques (structural OCT images and OCTA scans), in order to analyze the retinal vascularization. The arteriole/venule ratio (AVR) was calculated as an index of arteriolar narrowing, where a smaller AVR indicates greater narrowing. The relative risk of stroke increased as the arteriole/venular ratio decreased. Retinal changes such as vascular density (VD) and vascular tortuosity (VT), the intraocular pressure (IOP), the foveal avascular zone (FAZ) were correlated with blood parameters and MPNs' driver mutations. Our results demonstrated how retinal imaging showed major and significant changes in the microcirculation, with a significant reduced VD of the deep capillary plexus (DCP, p<0.0001) but not SCP (p=0.07) as compared to normal controls and a significant increase in VT of both DCP and SCP (p<0.0001, respectively). The FAZ revealed a reduction in size (p<0.0001) and a statistically significant correlation was found between red cells and IOP of both eyes (p<0.01). These findings obtained on vessel retinal changes, although preliminary and restricted to a small cohort of patients, if further confirmed on a larger cohort, might allow to consider the study of retinal circulation as a useful biomarker of thrombotic risk in MPNs.

Table 1.

Diagnosis	n. Pat.	Age	Driver Mutations	Treatm.	Precard	Framingham Score	Fibrinogen mg/dL	FdPs mcg/dL	D-Dimer ng/L	Hb g/dL	Hct %	WBC Mmc	PLT Mmc	Comorb.
ET	18	64 ± 11.53	JAK2 12 MPL 4 CALR 1 Triple neg. 1	HY + ASA 12 ASA 5 PegIFN + ASA 1	(range 1–9)	4 ± 10.27 (range 0.7–20.1%)	297.5 ± 54.06 (range 200–436)	3 ±1.70 (range 1–6)	201 ±155.96 (range 70–700)	13.5 ± 1.68 (range 10.8–17.5)	39.8 ± 4.38 (range 31.6–47.9)	7745 ± 5188 (range 4240–17,400)	324.000 ± 1,380,000 (range 503,500 ± 252,959)	Hypert. 7 Atrial Fibr. 1 Diabetes 1 Thromb. 5
PV	15	73 ± 7.6	JAK2 14 Triple neg. 1	HY + ASA 12 Ruxo 1 ASA 2	(range 2–14)	16.35 ± 5.54) (range 4.7 ± 20.4)	238 ± 70.4 (range 147–400)	2.3 ± 1.17 (range 0–4)	217 ± 269 (range 115–1216)	14.4 ± 1.83 (range 11.5–17.3)	43.3 ±5.04 (range 32.4–49.4)	9000 ± 4678 (range 4840–23,600)	489,000 ± 269,227 (range 88,000 ± 740,000)	Hypert. 12 Atrial Fibr. 2 Diabetes 1 Thromb. 6
PM	7	67 ± 7.1	JAK2 4 CALR 1 Triple neg. 2	HY + ASA 3 Ruxo 2	(range 2–14)	14.3± 5.8 (range 5.9–19)	265 ± 64.3 (range 205–410)	3.4 0.8 (range 1–4)	379 ± 186.3 (range 170–690)	11.8 ± 1.53 (range 11.1–13.5)	34.6 ± 3.75 (range 31.3–42.7)	6340 ± 2663 (range 4340 ± 13,300)	406,000 ± 317,601 (range 281,000–1,166,000)	Hypert. 5 Thromb. 1

DP146

RETROSPECTIVE ANALYSIS OF THE RELATIONSHIP BETWEEN TRANSFUSION INDEPENDENCE AND BONE MARROW FIBROSIS REDUCTION IN PATIENTS WITH MYELOFIBROSIS TREATED WITH PACRITINIB VERSUS RUXOLITINIB

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Background. Pacritinib is a JAK1-sparing JAK2/IRAK1 /ACVR1 inhibitor for treatment of myelofibrosis (MF). Pacritinib improves spleen volume, symptoms and is associated with anemia benefit in MF patients. In vivo studies have shown that dual JAK2/IRAK1 inhibition is associated with improvement in cytopenias and bone marrow reticulin fibrosis (BMF) in an inflammation-driven murine MF model (Cuenca-Zamora, et al. EHA 2023; P987/P990). We retrospectively analyzed the relationship between achieving transfusion independence (TI) and reduction in BMF in MF patients treated with pacritinib 200mg twice daily (BID) *vs* ruxolitinib on the phase 3 PERSIST-2 study.

Methods. PERSIST-2 (NCT02055781) enrolled patients with platelet counts ≤100 x 10^9/L. This analysis focused on pacritinib and on patients who received ruxolitinib as best available therapy who enrolled ≥12 weeks prior to study termination and required red blood cell (RBC) transfusions at baseline. The proportion of patients who achieved TI-response (TI-R, any 12-week interval with no RBC transfusions) was ascertained for pacritinib *vs* RUX. The proportion of patients with BMF reduction (≥1 grade decrease in BMF from baseline at week 24) was reported among patients on pacritinib achieving TI-R *vs* non-responders (NR).

Results. The analysis included 41 patients on pacritinib and 18 on ruxolitinib. Baseline characteristics were similar between the groups. A significantly greater proportion of patients treated with pacritinib *vs* ruxolitinib achieved TI through week 24: 37% *vs* 6%, P=0.023. Similarly, a greater percentage achieved a 50% reduction in RBC transfusions over any 12 weeks (49% *vs* 6%, P=0.001). Paired bone marrow assessments at baseline and week 24 were available for 18/41 of patients on pacritinib, of whom 44% (8/18) achieved TI-R on study. The proportion of patients who experienced BMF reduction (≥1 grade at any point) was significantly greater among TI-R (62.5%, n=5/8) compared to TI-NR (10%, n=1/10) on pacritinib (P=0.043, Figure 1).

Conclusions. In this analysis TI-R on pacritinib was associated with BMF improvement. Although the sample size is small, this contrasts with previous data suggesting there is no correlation between BMF reduction and TI-R in other JAK1/2 inhibitors. Further studies are warranted to confirm the results of this analysis.

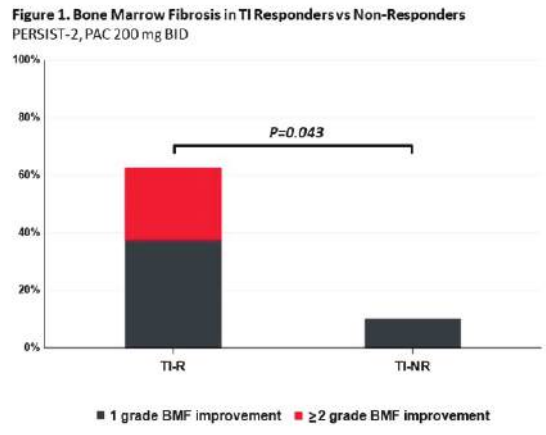

Figure 1.

DP147

ASSOCIATION OF HYPOMETILATING AGENTS (HMA) + VENETOCLAX (VEN) IN THE TREATMENT OF SECONDARY AML EVOLVED FROM CHRONIC MYELOMONOCYTIC LEUKEMIA

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Background. Prognosis of patients with secondary acute myelogenous leukemia (sAML) evolved from Chronic Myelomonocytic Leukemia (CMML) is still very poor, with an overall survival (OS) generally not exceeding 3 months. While the association of hypomethylating 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) affected by sAML from CMML.

Methods. Data of 15 pts with sAML from CMML treated frontline with HMA+VEN in 11 hematologic Centres in Italy outside clinical trials from 12/2020 to 12/2023 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 and type of treatment.

N° of patients	15
M/F, n° (%)	13/2 (86.7/13.3)
Median age, years (IQR)	73.5 (71.7 – 75.4)
Median Hb, g/dl (IQR)	9.3 (8.7 – 10.6)
Median WBC, x 10^9/l (IQR)	12.8 (3.7 – 25.3)
Median PLTS, x 10^9/l (IQR)	80 (32 – 177)
Median marrow blasts, % (IQR)	30 (22 – 45)
Treatment, n° (%): Aza + VEN	9 (60)
Dac + VEN	6 (40)
VEN starting dose (1st cycle), n° (%):	
50 mg	2 (13.3)
100 mg	10 (66.7)
200 mg	1 (6.7)
400 mg	2 (13.3)
Response to treatment, n° (%):	
CR/iCR	4 (26.7)
PR	5 (33.2)
HI	1 (6.7)
SD	1 (6.7)
PD	3 (20)
ED	1 (6.7)

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. At initial diagnosis, 6 pts had a proliferative-CMML and 9 a dysplastic-CMML. Median interval from initial CMML diagnosis to sAML evolution was 24.1 months [interquartile range (IQR) 11.8–39.9]. Baseline characteristics at evolution in sAML are reported in the Table 1: 4/9 pts (44%) with an evaluable NGS had ASXL1 mutations. Pts were treated for a median of 2 courses (range 1 - 18): HMA were administered at standard dosage, VEN daily doses in the 1st cycle are reported in the Table 1. Twelve 12 pts (80%) had at least one hematologic toxicity of grade 3-4: in particular, severe neutropenia (PMN<0.5 x 10^9/l) was reported in 10 pts (67%). Eight pts (53.3%) had at least one infective episode during the treatment: pulmonary infections were reported in 4 pts (26.7%). Different responses to treatment are shown in the Table 1: the ORR was 66.7%, with a median response duration of 8.9 months (95%CI 1.7-37). At the last follow-up, 10 pts (66.7%) died and 5 (33.3%) were alive. Median OS from AML evolution of the whole cohort was 8.0 months (95%CI 0.1-15.6): pts with any response to HMA+VEN had a longer OS compared to pts with progressive/stable disease [11.5 (95%CI 3.5–19.6) versus 3.7 (95%CI 2.5–4.8) months, respectively (p=0.038)].

Conclusions. Present data on our small real-life cohort of pts with sAML from CMML suggest that HMA + VEN combination could offer a chance also in this rare and dismal condition, with an ORR exceeding 50%: however, toxicities were severe and OS still short. Further studies to analyse factors predicting better response as well as new approaches are thus warranted

Anemias and myelodysplastic syndromes

DP148

CLINICAL PREDICTORS OF RESPONSE TO LUSPATERCEPT IN REAL WORLD COHORT OF MDS-RS PATIENTS

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Introduction. Luspatercept (luspa) is a first-in-class erythroid-maturation agent approved for red blood cells transfusion dependent (RBC-TD) lower risk myelodysplastic syndrome (LR-MDS) with ring sideroblasts (RS) based on MEDALIST clinical trial. Real world data (RWD) were recently published and lower transfusion burden (TB) seems to correlate with higher response to this agent.

Aims and Methods. We aimed to explore morphological predictors of response evaluating a large cohort of 331 patients (pts) treated with luspa, collected from Fondazione Italiana Sindromi Mielodisplastiche (FISiM) and from Moffitt Cancer Center (MCC) . Baseline morphologic bone marrow (BM) data were defined as the closest one prior to first dose of drug. Baseline RBC TB was defined as: non-transfusion dependent (NTD) (0 units in 8 weeks prior luspa), low TB (LTB) (1-5/8 weeks) and high TB (HTB) (≥ 6/8 weeks). Hematological improvement (HI) was defined as (i) objective Hgb increase of > 1.5 g/dl in NTD, and (ii) RBC-TI with Hgb increase of 1.5 g/dl, or RBC-TI without Hgb 1.5 g/dl increase, or >50% reduction in RBC TB among RBC-TD. The median percentage of myeloblasts and RS were 1% and 30%. Among 179 cases with available BM biopsy, 74.3% were hypercellular, 3.4% were hypo, and 22.3% were normo (age-adjusted cellularity).

Results. A total of 166 patients (50.2%) obtained a response: Hgb increase of > 1.5 g/dl in NTD, or similar increase with RBC-TI in RBC-TD pts, accounting for 23.9% of pts. Additionally, 16.6% of pts achieved RBC-TI without Hgb increase > 1.5 g/dl, while 9.7% exhibited reduced TB. Response rate (ORR) was higher in NTD and LTB pts ($p<0.001$): 81% (17/21) of NTD pts achieved a HI, while in LTB pts, 32.5% achieved RBC-TI with increase in Hgb > 1.5 g/dl, 17.5% achieved RBC-TI, and 7.1% achieved TB reduction. For HTB pts, the ORR was 41.8% (77/184): 11.4% increase in Hgb > 1.5 g/dl plus RBC-TI, 17.9% RBC-TI, and 12.5% reduction in TB. Median percentage of RS was similar in responders and non-responders ($p=.181$) and was not predictive of response. Pts with hypercellular BM had higher response to luspa compared with the hypo- and normocellular groups ($p=.005$, OR1.5, CI 0.27-8.48).

Discussion. Our study is the largest RWD in luspa treated MDS-RS patients. We demonstrate ORR consistent with data previously published. Low baseline RBC-TB and BM hypercellularity correlates with higher response rates.

DP149

EXPLORING THE IMPACT OF VENETOCLAX AND AZACYTIDINE ON APOPTOSIS AND PHOSPHOLIPASES C IN MYELODYSPLASTIC NEOPLASMS (MDS)

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The combined administration of Azacytidine (AZA) and Venetoclax (VEN) is effective in MDS (Bazinet A et al, Curr Treat Options Oncol, 2022). Phospholipases C (PLCs) and their associated pathways, which target BCL-2, influence MDS therapy response (Mongiorgi S et al, Clinical Epigenetics, 2023). Therefore, this study aimed to study AZA/AZA+VEN impact on higher-risk MDS patients and hematopoietic cell lines, focusing on PLC-related pathways and apoptotic markers. Higher-risk MDS (IPSS-R intermediate, high or very high) (Greenberg et al, Blood, 2012) were collected at baseline and during therapy at the Institute of Hematology "L e A Seràgnoli", Bologna, Italy. 6/10 patients were treated with AZA alone (75 mg/m^2/day for 7 days), while 4/10 received AZA combined with VEN (400 mg/day on days 1-14). AZA Responders (R, achieving Complete Remission (CR) or any Hematologic Improvement (HI), 4/6), showed reduced BCL-2 levels and increased BAX (BCL-2-associated X) expression within the first 6 cycles, while Non-Responders (NR, showing SD, 2/6) exhibited increased BCL-2 and decreased BAX levels. All 4 patients treated with AZA+VEN exhibited a rapid hematological response (CR or HI) and an early upregulation of BCL-2 and BAX, followed by decreased expression of these apoptotic genes in later cycles. Notably, one CR patient treated with AZA+VEN, later progressing to AML, showed increased BCL-2 expression shortly before AML evolution, with no significant changes in BAX levels. THP-1 cells underwent treatment with AZA, VEN, or AZA+VEN for 72h. Flow cytometry analysis revealed a rapid and strong increase in apoptotic cell death post AZA+VEN treatment, confirmed by annexin V staining, and alterations in pro-apoptotic (BCL-2 decrease) and anti-apoptotic markers (BAX, BIM, BAK-1 and PUMA increase). Moreover, AZA+VEN increased G0-G1 cell cycle phase at 24h, while at 72h, both AZA and AZA+VEN induced a significant decrease of G0/G1 and an increase in S phase. Even PLCβ1 and cyclinD3 exhibited an increase after AZA, while AZA+VEN positively influenced myeloid differentiation markers expression, particularly enhancing CD11 and CD14 expression.nAll in all, our results, that must be validated in a larger number of MDS patients and other leukemic cell lines, confirm that PLCβ1 and cyclinD3 are involved in cell cycle of leukemic cells and that apoptotic molecules, possibly regulated by inositides and inositide-related pathways, may be associated with AZA+VEN response/resistance.

DP150

CANCER CELLS ADHERENCE TO MESENCHYMAL STROMAL CELLS: A NEW MECHANISM OF HEMATOPOIETIC DIFFERENTIATION FOR ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC NEOPLASMS?

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The bone marrow microenvironment plays a pivotal role in myelodysplastic neoplasms (MDS), and mesenchymal stromal cells (MSCs) are believed to regulate hematopoietic cell behavior, potentially affecting MDS leukemic progression.

To further analyze the influence of MSCs on MDS/AML, we set up direct contact co-cultures using MSCs obtained from different sources (HS-5 cell line and dental pulp-derived MSCs) and hematopoietic cells (both cell lines and primary samples). Cellular behavior was assessed via microscopic examination, while cytofluorimetric analyses evaluated CD11b expression. Analyses were carried out in suspension cells and in cells adherent to MSCs, using CD73 and CD44 markers to distinguish adherent cell populations. Co-cultures exploiting MDS cells and MDS-MSCs from at least 10 higher risk MDS samples (firstly divided into CD11b+/-) are under analysis, as well as co-cultures between mononuclear cells (MNCs) isolated from healthy buffy coats and diseased MSCs. Our findings show that MSCs stimulate hematopoietic cell adhesion and induce cells to divide in two sub-populations: suspended and adherent to MSCs. This behavior was most pronounced in KG-1 cells, while THP-1 cells showed intermediate adhesion and MV-4-11 cells exhibited minimal attachment. Interestingly, cytofluorimetric analyses revealed a progressive increase in CD11b expression on THP-1 cells over time (14h, 24h, 48h after co-culture), suggesting that MSCs may affect myeloid differentiation. This hypothesis is further supported by the highest level of adherence to MSCs of undifferentiated (100% CD34+ at baseline) KG-1 cells and the lowest one of MV-4-11 cells (60% CD11b+ at baseline), but also by the observation that THP-1 cells already induced to macrophage differentiation by phorbol myristate acetate (PMA) were less adherent to MSCs. Even our ongoing analyses on CD11b+/- MDS samples, before and after Azacitidine treatment, are showing that the MDS-MSCs interactions are important in MDS/AML. Additionally, our transwell experiments are providing insights into the significance of direct cell contact in this molecular mechanism. All in all, our findings may further elucidate the effect of MSCs on MDS during myeloid differentiation or leukemic progression, possibly leading to novel therapeutic strategies targeting the bone marrow microenvironment in MDS.

DP151

CLINICAL HETEROGENEITY AND OUTCOME OF ACQUIRED PURE RED CELL APLASIA (PRCA): A MULTICENTER INTERNATIONAL STUDY

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PRCA is characterized by severe reticulocytopenic isolated anemia and significant depletion of bone marrow erythroid precursors (BM). Acquired PRCA can be idiopathic or secondary to different conditions. Due to its rarity and the absence of clinical-trials, guidelines on the management of PRCA are lacking. We conducted an international multicenter study including 43 patients with acquired PRCA from 13 European Centers. Clinical and laboratory features at diagnosis, therapy lines and responses (complete: Hb > 12g/dL, partial: transfusion independence) were retrospectively collected. As shown in Table 1, 60 % of patients had a secondary PRCA due to autoimmune diseases (23%), thymoma (21%) or lymphoproliferative disorders (14%), and 1 associated PVB19 infection.

Table 1.

Table 1. Clinical features, treatment and outcome

Values are expressed as median (range) if not otherwise specified.

	N= 43
Follow-up, months	37 (1-209)
Age, years	62 (29-93)
Sex, N (%)	Male 18 (42) Female 25 (58)
Associated condition, N (%)	27 (63)
Specifics of associated condition, N (%)	Autoimmune disease: 10 (23) Thymoma: 9 (21) CLL: 3 (7) T-LGL leukemia: 2 (5) Follicular lymphoma: 1 (2) MDS: 1 (2) Parvovirus B19: 1 (2)
BM lymphocyte infiltration, N (%)	22 (51)
% BM lymphocyte infiltration	19 (6-91)
Hb, g/dL	5,7 (3,5-9,6)
Reticulocyte count, x10^9/L	6 (0,6 – 300)
EPO, U/L	876 (29-3000)
Number of therapies	3 (0-6)
Steroid therapy, N (%)	35 (81)
Response, N (%)	CR 13 (37) PR 8 (22) NR 14 (41)
CsA therapy, N (%)	31 (72)
Response, N (%)	CR 17 (54) PR 6 (19) NR 8 (25)
Thymectomy, N (%)	8 (19)
Response, N (%)	PR 2 (25) NR 6 (75)
Other therapies, N (%)	Erythropoietin 6 (14) Cyclophosphamide 10 (23) Rituximab 10 (23) mTOR inhibitor 5 (12) Thymus irradiation 2 (5)
Alive, N (%)	34 (79)

BM evaluation showed erythroid aplasia and, in 51% of patients,

a lymphoid infiltrate (median of infiltration 19%, 6-91) with a predominant T-cell phenotype in 54% of cases. At diagnosis all patients had a severe reticulocytopenic anemia (median Hb 5.7, 3.5-9.6), serum erythropoietin was increased in most subjects, and 4 had positive direct antiglobulin test, without signs of hemolysis. Median number of therapies was 3 (0-6); 81% of patients underwent steroid therapy, with 59% overall response. Cyclosporine (CsA), used in 72% of patients, induced a response in 75%, complete in 59%; 13% of patients experienced dose reduction or withdrawal due to toxicity. Eight out of 9 patients with concomitant thymoma underwent thymectomy and 2 received thymus irradiation, without response. Further lines included mTOR inhibitors (6 patients, 4 responding), rituximab, cyclophosphamide, rEPO, anti-thymocyte globulin and anti-IL6. One patient died after an ineffective allogeneic transplant. NGS analysis, available in 11 patients (23%), showed a single somatic mutation in 4, and multiple mutations in 1. No clear predictors of response to immunosuppressive therapy emerged except for a higher T-cell infiltrate in the BM of subjects responding to cyclosporine. At last follow up 21% of patients had died, mostly due to infection (67%). Mortality was associated with a diagnosis of secondary PRCA (94 *vs* 69%, p=0.05). Our data suggest that PRCA usually presents in patients with severe transfusion-dependent anemia and an associated condition in 2/3 of cases. Immunosuppression, mainly with cyclosporine, is effective in >70% of patients; however, toxicity and underlying disease are associated with a non-negligible mortality rate.

DP152

SERUM BIOMARKERS AS PREDICTORS OF RESPONSE TO SUTIMLIMAB IN COLD AGGLUTININ DISEASE (CAD): A POST-HOC ANALYSIS OF PHASE 3 CARDINAL AND CADENZA STUDY DATA

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Background and Aim. Sutimlimab (SUT) is a C1s inhibitor approved for cold agglutinin disease (CAD). This study assessed if baseline serum markers are associated with response, as defined by the primary endpoints of the Phase 3 CARDINAL and CADENZA studies.

Methods. All patients who received SUT during Part A (26 weeks) of the CARDINAL (n=22) and CADENZA (n=19) trials were included in this combined analysis. Serum markers collected at baseline were evaluated for predicting responder status. For a patient to be a responder in the CARDINAL trial, a hemoglobin (Hb) increase ≥2.0 g/dL from baseline at the treatment assessment timepoint (TAT; defined as the mean value from Weeks 23, 25, and 26) or Hb level ≥12.0 g/dL at TAT was required. For the CADENZA trial, a Hb increase ≥1.5 g/dL from baseline at TAT was required. Other mandatory conditions for responder status were: no blood transfusion from Week 5 through Week 26, and no treatment for CAD except as per protocol. Descriptive statistics, frequency, or percentage were used to analyze outcomes.

Results. Of the 41 patients, 29(70.7%) were classified as responders (n=13 CARDINAL; n=16 CADENZA). The mean age (standard deviation [SD]) of responders (67.0 [9.9] years) was significantly lower than non-responders (74.3 [7.3] years; p-value=0.0262). No significant differences were noted for ethnicity, race, sex, geographic location, or body mass index. The median (range) reticulocyte count in responders (164.9 [28–301] 10^9/L) was significantly higher at baseline than in non-responders (102.0 [4–185] 10^9/L; p-value=0.0055). Significant differences in the median (range) reticulocyte index (semi-quantitative index of the adequacy of bone marrow response to anemia) between responders (4.7 [1–9]) and non-responders (2.6 [1–5]; p-value=0.0091) were also observed. Lower levels of median (range) IgM antibodies were noted in responders (2.37 [0.5–22.4 g/L]) compared with non-responders (6.22 [1.2–12.4] g/L; p-value=0.0080); upper limit of normal for IgM was 3.0 g/L. No significant differences in bilirubin, C4, CAD titer, erythropoietin, ferritin, Functional Assessment of Chronic Illness Therapy-Fatigue, haptoglobin, hemoglobin, lactate dehydrogenase, or total iron-binding capacity were noted at baseline between responders and non-responders.

Conclusion. Predictive serum biomarkers for SUT response in patients with CAD may exist (such as reticulocyte count, reticulocyte index and IgM levels) and should be explored further.

DP153

IMPROVEMENTS IN HEALTH-RELATED QUALITY OF LIFE AFTER EXAGAMGLOGENE AUTOTEMCEL IN PATIENTS WITH TRANSFUSION-DEPENDENT BETA-THALASSEMIA AND SEVERE SICKLE CELL DISEASE

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Background. Exagamglogene autotemcel (exa-cel) is a CRISPR/Cas9 gene-edited cell therapy shown to eliminate red blood cell (RBC) transfusions in patients (pts) with transfusion-dependent β-thalassemia (TDT) and VOCs in pts with severe sickle cell disease (SCD).

Methods. CLIMB THAL-111 and CLIMB SCD-121 are 24-mo, phase 3 trials of exa-cel in pts age 12-35 years (y) with TDT and SCD, respectively. Changes in patient reported outcomes measures EQ-5D-5L (including descriptive system and visual analog scale[VAS]), Functional Assessment of Cancer Therapy Bone Marrow Transplant (FACT-BMT including FACT-General[FACT-G] and bone marrow transplant subscale[BMTS]), Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me; SCD), and 11-point pain Numerical Rating Scale (NRS; SCD) for adults and EQ-5D-Y and Pediatric QoL Inventory (PedsQL) for adolescents were assessed as secondary endpoints.

Results. As of 16 April 2023, 29 adults (≥18-≤35y) and 13 adolescents (≥12-< 18y) with TDT followed for ≥16 mo were evaluated. At baseline, mean EQ-5D-5L health utility US index score (0.87[SD,0.17]; n=29) was near general population norm and in line with adults with TDT. By month 24, improvements were seen in EQ-5D-5L health utility US index and EQ VAS (mean[SD] change 0.06[0.28] and 10.7[18.6]; MCID 0.078 and 7-10, respectively;n=19), FACT-G Total (8.3[16.9]; MCID 3 to 7;n=19) and BMTS (5.6[5.6]; MCID 2 to 3;n=19). For adolescents, EQ VAS improved through month 12 (7.9[18.7];n=13); PedsQL score improved through month 18 (11.5[12.4];MCID 4.36; n=10). As of 14 June 2023, 24 adults with SCD followed for ≥16 months were evaluated. At baseline, mean EQ-5D-5L health utility US index (0.78[SD,0.23]; n=23) and EQ VAS (68.8[22.7]; n=24) scores were lower than US general population norm and similar to adults with SCD and recurrent VOCs. By month 24, improvements were seen in EQ-5D-5L health utility US index (mean[SD] change 0.13[0.19]; MCID 0.078; n=17), EQ VAS (26.9[22.6];MCID 7 to 10;n=17), FACT-G Total Score (21.0[18.1];MCID 3 to 7; n=17), BMTS (3.9[5.3]; MCID 2 to 3;n=17) and most ASCQ-Me subscales, including emotional (10.3[10.9]), social (16.4[11.0]), and stiffness impacts (6.6[10.5]; MCID 5 for all). For ASCQ-Me pain-related subscales, largest improvement was in pain episode frequency (-21.0[7.7];MCID -5;n=17); pain NRS also improved (-1.7[2.5];MCID -1;n=17).

Conclusion. Participants infused with exa-cel reported sustained and clinically meaningful improvements in HRQoL.

DP154

THE ROLE OF IPSS-M IN PATIENTS AFFECTED BY MDS UNDERGOING ALLOGENEIC TRANSPLANTATION: A SINGLE CENTRE EXPERIENCE

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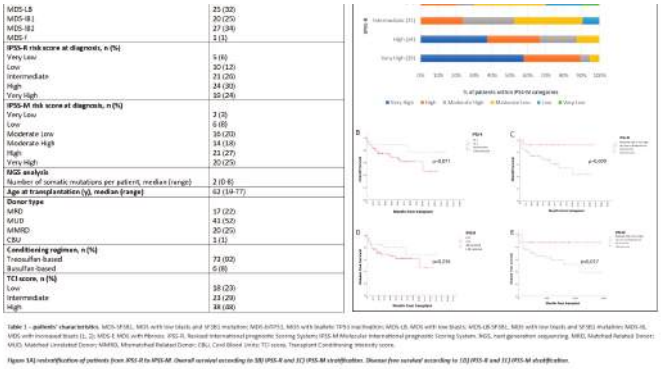
Introduction. allogeneic hematopoietic stem cell transplantation (alloSCT) is the only curative strategy for MDS, offered to higher-risk patients according to IPSS-R (Revised IPSS). Recently, a molecular-based prognostic risk classification model, the IPSS-M (Molecular IPSS), has been developed. Its application in clinical practice, particularly in the context of alloSCT, remains a subject of debate. The aim of our study is to evaluate the significance of IPSS-M in a cohort of MDS patients transplanted at our centre.

Methods. we retrospectively analyzed a cohort of 79 MDS patients who underwent alloSCT at our centre between 2010 and 2022. NGS testing for somatic myeloid mutations was retrospectively performed on DNA from cryopreserved marrow cells obtained at diagnosis. MDS risk score was calculated according to IPSS-R and IPSS-M.

Results. Median age at diagnosis and transplantation was 61 and 62 years respectively (Table 1). At diagnosis, 26 patients (33%) were lower risk (≤3.5) according to IPSS-R and underwent alloSCT at disease progression, while the other 53 patients (67%) received alloSCT soon after diagnosis for higher risk disease. After reclassification according to IPSS-M, 25 patients (32%) were upstaged and 19 (24%) were downstaged (Figure 1A). At a median follow-up of 59 months from transplant, 52 (66%) of patients were alive in CR, 22 (28%) were dead, while 5 (6%) were lost to follow-up. The 5-years OS probability was 88% for IPSS-R ≤3.5 and 70% for IPSS-R >3.5, without reaching statistical significative difference (Figure 1B). When stratifying according to IPSS-M, analysis showed a 5-years OS probability of 92% for the lower and 68% for the higher IPSS-M risk cohorts - p=0.009 (Figure 1C). Also regarding DFS, there was no statistically significant difference between IPSS-R ≤3.5 and >3.5 risk groups (62 *vs* 80%, Figure 1D), while patients belonging to IPSS-M lower-risk groups showed a significantly better 5-years DFS (87% versus 59%, p=0.017, Figure 1E) compared to those assigned to the higher-risk.

Discussion. This retrospective study demonstrates that integrating genetic profiles into a personalized scoring system results in a better discrimination across clinical endpoints (OS and DFS) compared to standard prognostic tools. While allogeneic HSCT remains the only curative strategy for patient diagnosed with MDS, the implementation of more personalized tools like IPSS-M could optimize the best time-up-to transplant procedure.



MDS-LB	25 (32)
MDS-IB1	20 (25)
MDS-IB2	27 (34)
MDS-F	1 (1)
IPSS-R risk score at diagnosis, n (%)	
Very Low	5 (6)
Low	10 (12)
Intermediate	21 (26)
High	24 (30)
Very High	19 (24)
IPSS-M risk score at diagnosis, n (%)	
Very Low	2 (3)
Low	5 (6)
Moderate Low	16 (20)
Moderate High	14 (18)
High	21 (27)
Very High	20 (25)
NGS analysis	
Number of somatic mutations per patient, median (range)	2 (0-6)
Age at transplantation (y), median (range)	62 (19-77)
Donor type	
MRD	17 (22)
MUD	41 (52)
MMRD	20 (25)
CBU	1 (1)
Conditioning regimen, n (%)	
Treosulfan-based	71 (92)
Busulfan-based	6 (8)
TCI score, n (%)	
Low	18 (23)
Intermediate	23 (29)
High	38 (48)

Table 1 - patients' characteristics. MDS-SF/BL: MDS with low blasts and SF3B1 mutation; MDS-IB1/IB2: MDS with biallelic TP53 inactivation; MDS-LB: MDS with low blasts; MDS-LB SF3B1: MDS with low blasts and SF3B1 mutation; MDS-IE: MDS with increased blasts (1, 2); MDS-F: MDS with fibrosis. IPSS-R: Revised International Prognostic Scoring System; IPSS-M Molecular International prognostic Scoring System. NGS: next generation sequencing. MRD: Matched Related Donor; MUD: Matched Unrelated Donor; MMRD: Mismatched Related Donor; CBU: Cord Blood Units; TCI score: Transplant Conditioning Intensity score.

Figure 1A) reclassification of patients from IPSS-R to IPSS-M. Overall survival according to 5B) IPSS-R and 5C) IPSS-M stratification. Disease-free survival according to 5D) IPSS-R and 5E) IPSS-M stratification.

Figure 1.

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COMBINED SAFETY DATA AND THROMBOEMBOLIC EVENTS FOR SUTIMLIMAB IN COLD AGGLUTININ DISEASE: A POST-HOC ANALYSIS OF THE PHASE 3 CARDINAL AND CADENZA STUDIES

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Background. Sutimlimab (SUT) is a C1s inhibitor approved for cold agglutinin disease (CAD), also associated with increased risk of thromboembolic (TE) events and mortality. These post-hoc analyses reported combined safety data (Part A & B) and assessed TE events (PRE- and ON-SUT treatment) from the CARDINAL and CADENZA studies.

Methods. Data from enrolled patients (pts) receiving at least 1 dose of SUT in CARDINAL (N=24) and CADENZA (N=42), including a post-treatment follow-up 9 weeks after the last dose, were assessed. Endpoints were the incidence of treatment-emergent adverse events (TEAEs), TE serious AEs (TESAEs), and AEs of special interest (AESIs; selected based on list of important identified and

potential risks for SUT). ON-SUT TE events included all events from treatment initiation until 17 days post last dose of SUT. PRE-SUT and ON-SUT follow-up times were matched for each patient.

Results. The safety analysis included 66 pts; 64 (97.0%) experienced ≥1 TEAE. Four (6.1%) pts each experienced one TESAE assessed by the investigator as possibly SUT-related (vitreous haemorrhage, viral infection, hypertension, and severe cerebral venous thrombosis). Seven pts discontinued SUT due to ≥1 TEAE. Four pts died, but none of the events were SUT-related. Eighteen TEAEs of serious infection were reported in 10 pts, and 36 TEAEs of hypertension, 39 TEAEs of acrocyanosis and/or Raynaud's phenomenon, and 4 TEAEs of TE events were reported in 20 (30.3%), 17 (25.8%), and 4 (6.1%) pts respectively. No TEAEs of serious hypersensitivity reaction and/or anaphylaxis, meningococcal infection or development of systemic lupus erythematosus were reported. For the TE analysis, 8/66 PRE-SUT and 5/66 pts in ON-SUT group had ≥1 TE event (p=0.3657). The TE incidence rate was 7.5 per 100 pt-years PRE-SUT versus 4.4 ON-SUT (p=0.3056). TE events in the ON-SUT period included cerebral venous sinus thrombosis (CVST), device-related thrombosis, transient ischemic attack (TIA), deep vein thrombosis, and peripheral artery thrombosis (in left hand digit, consistent with vascular event related to agglutination) (n=1, each). Only the CVST led to temporary interruption of SUT. Participants experiencing a TE event in the ON-SUT period, 4/5 had a history of TE risk factors and of those, 1 had a confirmed previous TIA.

Conclusion. SUT was generally well tolerated, and analysis of matched adjudicated TE events suggested a trend toward a reduced risk of TE ON-SUT versus PRE-SUT period.

DP156

THROMBOCYTOPENIA IN PATIENTS WITH MYELODYSPLASTIC SYNDROMES: A SINGLE CENTER ANALYSIS

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Myelodysplastic syndromes (MDS) with thrombocytopenia represent an unmet need lacking specific guidelines. We evaluated a single-center series of 260 MDS cases followed from 2001 to 2023 and compared clinical and laboratory features, bone marrow data, therapies and outcomes in patients with PLT< 50×10^9/L versus those without. As show in Table 1, 35 out of 260 patients (13.5%) displayed moderate to severe thrombocytopenia [median PLT at diagnosis $38x10^9$/L ($9\text{-}50x10^9$/L) and 25% showed signs of bleeding either at diagnosis or during the follow-up, mostly grade 1-2. Thrombocytopenic MDS more commonly belonged to intermediate IPSS-R group (40% *vs* 12%, p=0.0001), and displayed higher median Hb [10.7 (7-16.4) *vs* 9.9 (5.5-15.5), p=0.01] and LDH levels [227 (151-472) *vs* 193 (85-703), p=0.006] at diagnosis. Bone marrow features were comparable between the two groups except for hypocellularity (26% *vs* 8.4%, p=0.005), and the higher frequency of abnormal karyotype (46% *vs* 27%, p=0.04); the most common alterations were trisomy 8 (14% *vs* 2%, p=0.002) and complex karyotype (14% *vs* 1%, p<0.0001). Sixteen thrombocytopenic patients (46%) underwent NGS for genes commonly mutated in myeloid neoplasms, detecting at least a mutation in 10 (63%). Type and distribution of molecular alterations were similar to non-thrombocytopenic MDS. In a subgroup analysis in thrombocytopenic MDS we evaluated immunoglobulin and complement deposits by immunohistochemistry: serous IgM and IgG were present in 80% and 70% respectively (score>3) and deposits were detected on megakaryocytes in 70%; C3 and C4 serous deposits were present in 60% and 40% respectively (score>2) and on megakaryocytes in 40%. Concerning treatment, thrombocytopenic patients more frequently received steroids (66% *vs* 15%), eltrombopag (20% *vs* 0%), danazol (11% *vs* 2%), and cyclosporine (9% *vs* 1%) as compared to the others and had a better response to eltrombopag (4/7), cyclosporine (3/3) and steroids (11/22). Conversely, thrombocytopenic patients had a lower response rate to erythropoietin (33% *vs* 70%, p=0.02). Finally, AML transformation rates were superior in thrombocytopenic MDS (11.4% *vs* 1.8%, p=0.01), whilst mortality was similar. Clinically significant thrombocytopenia occurred in 13.5% of MDS patients being associated with marrow hypocellularity, intermediated IPSS-R risk, aberrant cytogenetics and increased risk of AML transformation. Treatment strategies appear highly heterogeneous and require further investigation.

Table 1.

	ALL (N=260)	PLT < 50x10^9/L (N=35)	PLT > 50x10^9/L (N=225)	*p value
Median Age, years (range)	76 (41-101)	77 (52-92)	76 (41-101)	NS
M/F	150/110	22/13	128/97	NS
IPSS-R VL/L/I/H/VR	90/119/42/6/3	5/11/14*/4/1	85/108/28*/2/2	0.0001
Hb, gr/dl, median (range)	10 (5.5-16.4)	10.7 (7.0-16.4)*	9.9 (5.5-15.5)*	0.01
PLT, 10^9/L, median (range)	145 (9-1.024)	38 (9-50)	167 (54-1.024)	NS
N, 10^9/L, median (range)	2.15 (0.21-12.12)	2.08 (0.63-12.12)	2.16 (0.21-11.65)	NS
LDH, UI/L, median (range)	197 (85-703)	227 (151-472)*	193 (85-703)*	0.006
Reticulocytes, 10^9/L, median (range)	51 (6-1020)	56 (24-220)	50 (6-1020)	NS
Indirect Bilirubin, mg/dl, median (range)	0.6 (0.1-3.3)	0.6 (0.2-1.0)	0.6 (0.1-3.3)	NS
Erythropoietin, mg/dl, median (range)	49 (6.1 – 4368)	61.2 (6.1 – 566)	48.9 (7,9 - 4368)	NS
Creatinine, mg/dl, median (range)	0.97 (0.23-4.30)	1.0 (0.5-4.3)*	0,96 (0.23-2.46)*	0.01
Marrow cellularity, % (range)	40 (10-95)	40 (10-90)	40 (10–95)	NS
Hypocellularity, N (%)	27 (10)	9 (26)*	19 (8.4)*	0.005
Cytogenetic . Normal (%) . Del5q (%) . Del20 (%) . DelY (%) . Tris8 (%) . Complex karyotype (%) . Others (%)	 183 (70) 17 (7) 7 (3) 14 (5) 10 (4) 7 (3) 22 (8)	 19 (54)* 1 (3)* 1 (3)* 3 (9)* 5 (14)* 5 (14)* 1 (3)*	 164 (73)* 16 (7)* 6 (3)* 11 (5)* 5 (2)* 2 (1)* 21 (9)*	 0.04 0.55 0.61 0.61 0.002 < 0.0001 0.34
NGS mut./unmut. . 1 mutation (%) . 2 mutations (%) . > or = 3 mutation (%)	85/39 39 (32) 26 (21) 20 (16)	10/6 6 (38) 2 (12) 2 (12)	75/33 33 (31) 24 (22) 18 (17)	NS
AML transformation, N (%)	8 (3)	4 (11.4)*	4 (1.8)*	0.01
Mortality, N (%)	47 (18)	8 (23)*	39 (17)*	NS

DP157

PREVALENCE AND OUTCOME OF PURE RED CELL APLASIA IN PATIENTS WITH MYELODYSPLASTIC NEOPLASMS

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About 70% of myelodysplastic neoplasm (MDS) patients presents with anemia and many of them become transfusion-dependent. Acquired pure red cell aplasia (PRCA), a rare condition consisting in severe anemia and profound reticulocytopenia, is a possible differential diagnosis. Here, we assessed the prevalence of misdiagnosed PRCA within a monocentric cohort of low-risk MDS patients, diagnosed between 2001 and 2023. We systematically evaluated the presence of erythroid hypoplasia on bone marrow (aspirate and/or trephine) at diagnosis, along with clinical, hematological, molecular

data, as well as treatments and outcomes, to unravel associations with PRCA diagnosis. Among 273 patients, 14 showed erythroid hypoplasia on bone marrow evaluation (1 and 8 on aspirate or trephine only, respectively; 2 both). Table 1 shows clinical and hematological characteristics according to erythroid hypoplasia. Patients with PRCA had lower median Hb levels (8.5 *vs* 10 g/dl, p 0.06), higher endogenous erythropoietin values (474 *vs* 52 U/L, p<0.05) and a greater red blood cell (RBC) transfusion burden. Bone marrow cellularity was significantly lower in patients with erythroid hypoplasia (25 *vs* 50%, p<0.05), and most subjects had a T-cell lymphoid infiltrate (median 9%, range 5-30). Next generation sequencing analysis (NGS) showed a lower prevalence of genomic alterations in PRCA *vs* MDS patients (40 *vs* 70%, p<0.05), whilst no differences in cytogenetics profile were noted. Treatment with erythropoiesis stimulating agents had similar outcomes in both subgroups (about 70% response rate). Specific PRCA therapies included: corticosteroids (2), thrombopoietin receptor agonists (1) and cyclosporin (CyA) (4). Regarding CyA, 100% of patients responded with a complete hematologic remission and transfusion independence, one patient self-discontinued therapy for intolerance. Notably, CyA responders had a higher T-cell lymphoid infiltrate (median 22.5%, range 8-30). In conclusion, our data show that erythroid hypoplasia may be disregarded in more than 5% of low risk MDS patients, with possible discordances between bone marrow aspirate and biopsy. PRCA correlates with severe anemia and increased transfusion requirements, and negative NGS. Cyclosporine treatment, effective in 100% of our cases, should be considered.

Table 1. Patient characteristics.

	All patients (n= 273)	Erythroid hypoplasia (n= 14)	Erythroid normo/hyperplasia (n= 229)	p value
Median age, years (range)	76.4 (41-101)	77 (59-84)	75.8 (41-101)	ns
Median follow-up, months (range)	39 (0-260)	12,7 (0-72.9)	37,7 (0-260)	ns
Death, N (%)	49 (18%)	2 (14.3%)	32 (14%)	ns
Sex, N (%)				ns
Male	153 (56%)	8 (57.1%)	127 (55.5%)	
Female	120 (44%)	6 (42.9%)	102 (44.5%)	
Laboratory values, median (range)				
Hemoglobin (g/dl)	9.9 (5.5-16.4)	8,5 (7-14.5)	10 (5.5-16.4)	0.06
Reticulocytes (x10^9/L)	0.051 (0.005-0.87)	0.0.25 (0.005-0.29)	0.052 (0.006-0.87)	ns
ANC (x10^9/L)	2.100 (210-12,120)	1.970 (440-3,890)	2.080 (210-11,650)	ns
Platelet count (x10^9/L)	136 (7-1024)	89 (23-309)	141 (11-1024)	ns
Endogenous erythropoietin (U/L)	49 (6-4368)	474 (9,41-4368)	52 (6-793)	< 0.05
RBC-TD, N (%)	89 (32.6%)	9 (64.3%)	68 (29.7%)	< 0.05
Rhepo				ns
Yes, N (%)	104 (38.1%)	8 (57.1%)	82 (35.8%)	
No, N (%)	169 (61.9%)	6 (42.9%)	147 (64.2%)	
Rhepo response				ns
Yes, N (%)	94 (67.6%)	7 (70%)	75 (68.2%)	
No, N (%)	45 (32.4%)	3 (30%)	35 (31.8%)	
Bone marrow cellularity				
Median, % (range)	40 (10-95)	25 (10-80)	50 (10-95)	< 0.05
Normocellular, N (%)	92 (36.1%)	3 (23%)	81 (35.7%)	
Hypercellular, N (%)	131 (51.4%)	5 (38.5%)	121 (53.3%)	
Hypocellular, N (%)	32 (12.5%)	5 (38.5%)	25 (11%)	
Erythroid hypoplasia				< 0.05
Yes, N (%)	14 (5.7%)	14 (100%)	0	
No, N (%)	232 (94.3%)	0	229 (100%)	

Infections and quality of life

DP158

THE ROLE OF DISTRESS IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA: SINGLE CENTER EXPERIENCE

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Background. The PsychoNeuroEndocrineImmunology (PNEI), a new medical science which integrates the microscopic dimension (immune, endocrine, nervous networks) with the macroscopic vision (individual-social context interaction) of the person, demonstrated that interactions exist between immune system and stress system (Ader,1981), posing new paradigms in the pathogenesis and treatment of neoplasms.

Study design. In April 2022, we have undertaken a single-center study on the psychological discomfort in patients with chronic myeloid leukemia (CML). The primary endpoint of study was to evaluate degree of distress (DT scores) at the onset of the disease and over time; secondary endpoints were the correlations of distress (DT score) with: coping strategies (Brief-cope score), TKI adherence (Morisky score). Timepoints were set at T0 (within 12 months from diagnosis) and months 6, 12, 24, 36, 48.

Results. At m + 24, the patients enrolled were 43, of which 33 completed at least 3 administrations. From frequency analysis of responses to DT test, our sample at onset shows degrees of psychological distress >4 in 65% of cases; the mean DT scores were 8.3 (SD 1,8). An effective decrease is observed al m +24 *vs* T0, with final mean DT score 6 (SD 3.2). DT administered at the beginning of treatment shows a positive correlation with a dysfunctional coping strategy (Pearson's r=0.47222 p<0.05). Distress and adherence to treatment show a statistically significant inverse correlation (Pearson's r= - 0.43826 p<0.05).

Conclusions. The DT test can be used as an early screening tool to identify clinical levels of psychological discomfort in patients with CML; its early monitoring could represent a simple and effective way of evaluating the patient's psychological state in routine outpatient visits, as a check on the clinical course and therapeutic efficacy. Furthermore, in CML, the DT administration can be considered an innovative strategy for detecting and correcting poor therapeutic adherence, in turn responsible for increased treatment failure, with serious welfare and economic consequences (Osterberg, 2005).

Keywords: PNEI, CML, distress, coping, adherence

DP159

CYTOMEGALOVIRUS REACTIVATION IN DARATUMUMAB-TREATED MULTIPLE MYELOMA PATIENTS: UPDATES OF A SINGLE-CENTER RETROSPECTIVE EXPERIENCE

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Introduction. Viral reactivations are frequent causes of morbid-

ity 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, by targeting neoplastic plasma cells, and CD38-expressing lymphocytes, eventually leading to immunosuppression. Studies on cytomegalovirus (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.

Table 1. Patient characteristics.

Table 1. Patients' characteristics

Characteristics	Daratumumab cohort N = 51	Control cohort N= 50	P value
Median age, years (range)	66 (44-86)	67 (45-83)	0.47
Gender, n (%)			
Male	30 (59)	29 (58)	0.9
Female	21 (41)	21 (42)	
M-protein type, n (%)			
IgG	39 (76)	37 (74)	
IgA	8 (16)	2 (4)	0.19
Micromolecular	3 (6)	11 (22)	
Not secernent	1 (2)	-	
Light chain type, n (%)			
Kappa	30 (59)	36 (72)	0.17
Lambda	21 (41)	14 (28)	
Extramedullary disease, n (%)	6 (12)	4 (8)	0.4
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	23 (45)		
Dara-VMP	6 (12)		
Dara-RD	11 (21)		
Dara-VD	2 (12)		
Dara-PD	1(2)		-
Daratumumab single agent	4 (8)		
VRD		41 (82)	
KRD		7 (14)	
VMP		1 (2)	
KD		1 (2)	
Therapy setting, n (%)			
First line	37 (72)	42 (84)	
Second line	14 (28)	8 (16)	0.13
Prior ASCT	3 (6)	5 (10)	0.23
Lymphocyte count, median, x 10^3/µL (range)	0.47 (0.1-1.8)	0.48 (0.2-1.19)	0.25
Antiviral prophylaxis with acyclovir, n(%)	32 (62)	43 (86)	**0.017**
Overall IgG, median, mg/dl (range)	346 (37-2470)	490 (79-1150	0.39
Overall IgG < 400 mg/dl, n (%)	31(61)	24 (48)	0.15
Positive anti-CMV IgG at diagnosis, n (%)			
Yes	16 (31)	5 (10)	**0.03**
No	3 (6)	2 (4)	
Not available	32 (63)	43 (86)	
CMV reactivation, n (%)	17 (33)	2 (4)	**<0.001**
CMV DNA at peak, median UI/mL (range)	192 (34.5-141,000)	137 (137-137)	0.64
CMV DNA at peak > 1000 UI/mL	6 (12)	0	**0.03**
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	16 (31)	2 (4)	**<0.001**
- Treatment with anti-CMV agents	7 (14)	0	**0.02**

[§] Daratumumab-bortezomib-thalidomide-dexamethasone, dara-VTD; daratumumab-bortezomib-melphalan-prednisone, dara-VMP; daratumumab-lenalidomide-dexamethasone, dara-RD; daratumumab-bortezomib-dexamethasone, dara-VD; daratumumab-pomalidomide-dexamethasone, dara-PD; bortezomib-lenalidomide-dexamethasone, VRD; carfilzomib-lenalidomide-dexamethasone, KRD; bortezomib-melphalan-prednisone, VMP; carfilzomib-dexamethasone, KD

Materials and Methods. A total of 101 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 higher in the daratumumab cohort compared to control group (33% *vs* 4%; P< 0.001), especially during the first cycle (median time to reactivation, 29 days). Moreover, at reactivation, CMV-DNA levels were higher in the study group compared to controls (>1000 UI/mL in 12% of cases; P<0.05). However, only one subject developed a CMV disease with severe pneumonia, while 12% of reactivated cases were successfully treated with preemptive therapy using valganciclovir. No subjects in the control cohort required anti-CMV agents (P=0.02).

Discussion. In 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. Therefore, we proposed a strict monitoring of CMV-DNA levels to promptly initiate preemptive therapy and to prevent CMV disease development. To our knowledge, this is the first study reporting CMV reactivation risk in daratumumab-treated patients; however, further validation on larger and prospective clinical trials are required.

DP160

INCIDENCE OF INFECTIONS IN PATIENTS TREATED WITH RITUXIMAB FOR AUTOIMMUNE DISORDERS OF HEMATOLOGICAL INTEREST

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Rituximab, a monoclonal anti-CD20, is widely employed for the treatment of indolent non-Hodgkin lymphomas [iNHL: low tumor burden Follicular lymphoma, Splenic marginal zone lymphoma (SMZL)] and autoimmune disorders of hematological interest (AID), namely Autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), and acquired hemophilia A (AHA).

Table 1. Demographic and clinical features of study cohort. Name of variable (representative value); number (%), unless stated otherwise.

SEX	
MALE (1)	72 (53)
FEMALE (0)	65 (47)
AGE AT DIAGNOSIS	MEDIAN (Q1;Q3)
	63 (52;74)
AGE AT RITUXIMAB	MEDIAN (Q1;Q3)
	64 (52;75)
DIAGNOSIS	
NHL	90 (66)
AIHA (AID)	32 (23)
AHA (AID	8 (6)
ITP (AID)	7 (5)
PROPHYLAXIS	
PJP (1)	130 (95)
NO PJP (0)	7 (5)
DURATION OF PROPHYLAXIS (MONTHS)	MEDIAN (Q1;Q3)
	9 (6;12)
GAMMAGLOBULINEMIA AT THE END OF RITUXIMAB	
ELEVATED (H)	10 (8)
NORMAL (N)	17 (12)
REDUCED (L)	110 (80)
INFECTIOUS COMPLICATIONS	
YES (1)	33 (24)
NO (0)	104 (76)
SITE OF INFECTION	
AIRWAYS	18 (54)
GASTROINTESTINAL	3 (10)
GENITOURINARY	5 (15)
OTHER	7 (21)
GRADE OF INFECTION (CTCAE)	
I	8 (27)
II	16 (48)
III	5 (15)
IV	3 (10)
STATUS AT END OF OBSERVATION	
ALIVE (1)	115 (84)
DECEASED (0)	22 (26)
CAUSE OF DEATH	
RELATED TO INFECTION (1)	4 (23)
UNRELATED TO INFECTION (0)	17 (77)

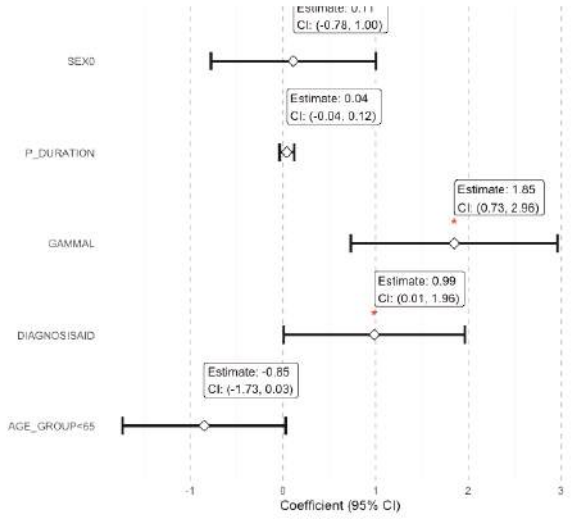

Figure 1. Effect of predictor variables on risk of infectious complications. Forest plot. Age lower than 65 years appears to be protective but p-value is not significant. Hypogammaglobulinemia and a diagnosis of autoimmune disease instead of lymphoma appear to increase risk of infection, however, their CI includes 1.

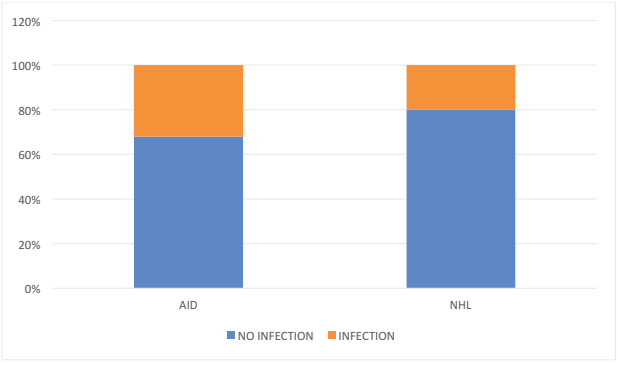

Figure 2. Rate of infections categorized by diagnosis (AID = autoimmune disease; NHL = non-Hodgkin lymphoma). P-value not significant (0.123).

Methods. We performed a retrospective, multicentric study to compare two cohorts of patients with iNHL or AID treated with rituximab between 2014-2024, to evaluate the incidence and characteristics of infections, and antimicrobial prophylaxis. We collected chart data from 4 hematologic centres. This study was approved by the IRB of the coordinating center and conducted according to the Helsinki declaration.

Results. We retrieved 137 patients (72 males, 65 females), the median age was 63 years; 90 patients had NHL (66%), 33 AIHA (23%), 8 AHA (6%), 7 ITP (5%), subjects with iNHL received rituximab as single agent front line treatment, patients affected by AID were previously or concomitantly treated with steroids. Most patients (95%) received anti-Pneumocystis jiroveci prophylaxis (PYP), for a median of 9 months. After rituximab, 80% of patients had hypo-gammaglobulinemia. Thirty-three patients (24%) experienced infectious complications: airways (n=18), gastrointestinal (n=3), genitourinary (n=5), others (n=7). At the end of observation, 22 patients [14 (64%) with NHL and 8 (36%)] died, of these, 4 patients died of complications related to infection. Among patients treated with rituximab for AID 32% experienced infections, while among those with NHL only 20% had infections. Concomitant exposure to corticosteroids and an older age are the main risk factors for infection. Age lower than 65 years appears to be a protective factor against infections, but p-value is not significant. Hypogammaglobulinemia and a diagnosis of AID instead of NHL increases the risk of infection, however, CI includes 1.

Discussion. This is a large multi-centric retrospective study, showing the Italian real-life prevalence of infections, prophylaxis, and mortality rate in patients treated with rituximab for AID and NHL. Patients with AID have an increased risk of infections that, albeit statistically not significant, appears higher than in patients with NHL. The incidence of infections in AID is quite high; therefore, the administration of only anti PYP prophylaxis, may not be sufficient. In conclusion, we need to expand the cohort of patients with AID to increase statistical power of our analysis, and further research is warranted in the field to explain the occurrence of infections in patients with AID.

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SYMPTOM BURDEN PROFILE OF ITALIAN PATIENTS WITH PHILADELPHIA-NEGATIVE MYELOPROLIFERATIVE NEOPLASM: RESULTS FROM THE GIMEMA PROPHECY STUDY

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Background. In Philadelphia-negative chronic myeloproliferative neoplasms (MPNs, Polycythemia vera [PV], Essential Thrombocythemia [ET], and Myelofibrosis [MF]), a considerable symptom burden affects patients' health-related quality of life (HRQoL). Despite advancements in MPN management, effectively managing

symptoms remains challenging.

Objective. The primary objective of this analysis was to describe and compare baseline symptom burden of MPN patients included in the GIMEMA-PROPHECY prospective observational study.

Methods. Patients newly diagnosed with MPN according to the 2016 WHO classification and an initial diagnosis within one year before study inclusion (baseline assessment for the purpose of this study) were considered eligible. Patients were asked to complete a series of patient-reported outcome (PRO) measures, including the well-validated EORTC QLQ-C30 and the MPN-SAF TSS questionnaires at baseline and at 3, 6, 12, 18, and 24 months.

Results. Analysis was based on a cohort of 552 assessable MPN patients recruited from 26 Italian centers between June 2020 and November 2023. The median age was 67 years (IQR 54.9-74.6), with males comprising 52.1% of the cohort. Among them, 202 were diagnosed with PV, 219 with ET, and 131 with MF. Notably, 81.9% were concurrently taking medications (excluding MPN treatment). Symptom prevalence was assessed by items of the MPN-SAF TSS, as shown in Table 1. Fatigue was predominant (77.6%), followed by gastrointestinal symptoms (early satiety, 41.9%; abdominal discomfort, 39.1%). Inactivity (40.7%) and concentration problems (42.9%) were also prevalent, underscoring cognitive and physical challenges. Night sweats (36.4%) and itching (38.4%) were common. While less frequent, weight loss (2.7%) and fever (21.2%) were notable. MF patients reported the highest scores for fatigue, pain, dyspnoea and diarrhoea compared to PV and ET patients. PV patients reported higher scores for nausea/vomiting, insomnia, appetite loss and constipation scales compared to MF and ET patients, while ET patients reported higher financial difficulties with respect to the other two groups.

Conclusion. This is one the largest analysis reporting on patient-reported symptoms across Italian MPNs patients in the real-life. A better understanding of the symptom patterns experienced by these patients may be critical for optimizing HRQoL and treatment outcomes.

Table 1.

Table 1. Symptom's Severity and prevalence (score > 0) of MPN-SAF TSS questionnaire, overall and by MPN diagnosis (N=552)

Scales	Overall, N = 552		Polycythemia Vera (PV), N = 202		Essential Thrombocythemia (ET), N = 219		Myelofibrosis (MF), N = 131	
	Mean (SD)	Prevalence	Mean (SD)	Prevalence	Mean (SD)	Prevalence	Mean (SD)	Prevalence
Worst fatigue	2.8 (2.5)	77.6%	3.0 (2.6)	81.5%	2.7 (2.5)	75.3%	2.6 (2.4)	75.4%
Early satiety	1.4 (2.2)	41.9%	1.4 (2.3)	42.1%	1.4 (2.2)	38.4%	1.5 (2.2)	47.3%
Abdominal discomfort	1.4 (2.2)	39.1%	1.4 (2.2)	39.1%	1.5 (2.4)	40.2%	1.2 (2.0)	37.4%
Inactivity	1.4 (2.2)	40.7%	1.3 (2.1)	42.3%	1.3 (2.2)	38.4%	1.6 (2.4)	42.0%
Concentration problems	1.4 (2.2)	42.9%	1.3 (2.1)	46.0%	1.4 (2.3)	39.6%	1.4 (2.2)	43.5%
Night sweats	1.4 (2.5)	36.4%	1.5 (2.5)	38.6%	1.4 (2.4)	37.0%	1.3 (2.5)	32.1%
Itching	1.4 (2.4)	38.4%	1.6 (2.6)	42.1%	1.2 (2.3)	34.4%	1.5 (2.4)	39.2%
Bone pain	1.4 (2.5)	35.2%	1.4 (2.4)	36.6%	1.4 (2.5)	34.7%	1.4 (2.5)	33.8%
Weight loss	0.1 (0.8)	2.7%	0.1 (1.1)	2.0%	0.1 (0.7)	3.7%	0.0 (0.2)	2.3%
Fever (>37.7)	0.8 (1.9)	21.2%	0.8 (2.0)	20.3%	0.7 (1.7)	21.1%	0.8 (2.0)	22.9%
MPN SAF-TSS	13.4 (13.9)	-	13.8 (14.0)	-	13.1 (14.1)	-	13.3 (13.7)	-

MPN indicates Myeloproliferative Neoplasm; SD, standard deviation.

P-values has not been reported since no statistically significant differences has been found for mean or prevalence between the 3 MPN disease group.

DP162

UNMET NEEDS OF PALLIATIVE CARE AND END OF LIFE PLANNING IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS: REPORT FROM A SINGLE CENTER EXPERIENCE

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Despite undergoing a potential life-saving procedure, allogeneic hematopoietic stem cell transplant (alloHSCT) patients may experience severe symptom burden and treatment failure. Several studies have recently emphasized the role of palliative care (PC) in alloHSCT. We evaluated PC use and end-of-life planning in 62 patients who underwent alloHSCT in our Institution, and died in the last 5 years. Data were retrieved from hospital and at home patient records. The median age of patients was 57 (23-75) years: 50% were affected by acute leukemia, 24% by myelodysplasia, 11% by lymphoma, 10% by chronic myeloid neoplasia, and 5% by multiple myeloma. The median time from alloHSCT to death was 8.3 (0.1-127) months. Death occurred in hospital in 54 (87.1%) patients, with 27 (50%) being admitted from the Emergency Department (ED), with a median time to death of 12 (0-102) days. Twenty-six (48%) of hospitalized patients died in Intensive Care Unit (ICU), 16 (30%) in Hematology, and 12 (22%) in Internal Medicine Ward. Seven (11.3%) patients died at home, 1 (1.6%) in hospice.

Table 1.

Table 1. Patient outcomes according to hematologic disease status.

PARAMETERS	RELAPSED DISEASE n=31	NO DISEASE n=31
Place of death, n (%)		
• ICU	9 (29)	17(55)
• Hematology	10 (32)	6 (19)
• Internal Medicine	8 (26)	4 (13)
• Home	3 (10)	4 (13)
• Hospice	1 (3)	0
Time from alloHSCT to death, months (range)	9.5 (0.7-77)	6.9 (0.1-127)
Hospital admission from ED, n (%)	13 (48)*	14 (52)*
Time from ED to death, days (range)	10 (2-102)	21 (0-76)
Home Care activation, n (%)	5 (16)	8 (26)
Time from activation to death, days (range)	47 (14-326)	115 (22-455)
Palliative Care, n (%)	1 (3)	2 (6)
Time from activation to death, days (range)	3	239 (23-455)
Blood transfusion support, n (%)	29 (93.5)	14 (45)
Advanced directives, n (%)	3 (10)	0

ICU: Intensive Care Unit; ED: Emergency Department; alloHSCT: Allogeneic Hematopoietic Stem Cell Transplant.

*It refers to hospitalized patients only.

Overall, home care was active in 13 (21%) out of 62 cases, with 3 (4.8%) receiving PC. Advance directives were expressed in 3 (4.8%) cases only. Thirty-one (50%) patients died of relapsed disease, while 31 (50%) in disease remission, 5 (16%) due to secondary neoplasia, 26 (84%) due to transplant-related complications. Re-

lapsed patients died in hospital in 27 (87%) cases [9 (33%) in UTI], with 13 (48%) being admitted from the ED, with a median time to death of 10 (2-102) days. Nineteen (61.9%) patients were under disease-specific therapy, 1 (3.2%) in PC. Patients in disease remission died in hospital in 27 (87%) cases [17 (62.9%) in ICU], with admission from ED in 14 (52%), and a median time to death of 21 (range 0-76) days. Only 2 (6%) patients were under PC. Details on patient outcomes according to hematological disease status are resumed in Table 1. Our data confirm previous studies reporting the underutilization of PC in alloHSCT settings. Moreover, the high percentage of ED admissions, the intensity of end-of-life care, and the limited use of advance directives, reveal poor end-of-life plannings. These findings highlight the urgency of implementing PC facilities in our center to accurately assess patient needs and improving end-of-life care. Finally, special attention should be paid to the role of PC in alloHSCT to ensure patient optimal and respectful treatments and reduce caregiver burden.

DP163

ASSESSMENT OF INFECTIOUS RISK IN LYMPHOMA AND MYELOMA PATIENTS TREATED WITH BISPECIFIC ANTIBODIES OUTSIDE CLINICAL TRIALS

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Treatment with bispecific antibodies (bi-Ab) represents an increasingly available option among patients affected by Non-Hodgkin Lymphomas (NHL) and multiple myeloma (MM). However, concerns regarding infectious toxicity are arising and data on infectious events outside clinical trials are missing. With the aim to assess incidence, risk factors and microbiological characteristics of infectious events after therapy with bispecific antibodies, we retrospectively analyzed clinical and laboratory records in patients affected by NHL and MM treated at our Institution with bi-Abs within compassionate use programs from February 2021 to February 2024. Patients' characteristics are listed in Table 1.

Table 1.

Characteristics	N	%
Median age (range) - yr	56	(27 – 77)
< 65	22	76
Male	18	60
NHL	22	73
MM	7	27
Ann Arbor I/II at BiAb	2	9
Ann Arbor III/IV at BiAb	20	91
Relapsed/refractory status - no. (%)		
Relapsed	10	34
Refractory	19	66
Median no of previous therapy lines (range)	4	(3 – 6)
Previous therapy with purine analogues	15	52
Autologous stem-cell transplantation	14	48
Allogeneic stem-cell transplantation	1	3
Previous CART therapy	12	41
IVIG supplementation	14	48
CRS G1/2	17	57
CRS 3/4	0	0
ICANS G1/2	1	3
ICANS G3/4	0	0
Grade ≥ 3 neutropenia at infection	3	14
Hypogammaglobulinemia at infection	10	45

Results	N	%
Total Infectious Events	22	
Median time to infection onset (days)	46	(3-166)
Pts with at least 1 infection	14	46
Pts with at least 2 infections	6	20
Pts with Grade ≥ 3 infection	5	17
Pts with Grade 5 infections	1	3
Bacterial infections	4	18
Viral Infections	10	45
Fungal infections	1	4
Unknown Agent	7	32

Twenty-nine patients affected by NHL (n=22) and MM (n=7) treated with bi-Ab targeting CD3xCD20 (n=22), CD3xBCMA (n=2), CD3xGPRC5D (n=5) as single agent were included; one patient received more than one Bi-Ab. All patients received antiviral and anti-PJP prophylaxis and 14 also received monthly immunoglobulin replacement therapy (IGRT). At a median follow-up of 8 months, 14 patients (48%) developed a total of 22 infections. Median time to occurrence of any infection was 46 days (3-166). Only 32 % were G>2 and in one case G5 (COVID-19 pneumonia). Regarding etiology, 46% infectious events were due to viral agents (six SARS-CoV-2, one Parvovirus B19, one Influenza A, one RSV, one CMV reactivation); 18% events were caused by bacterial agents (three Pseudomonas spp infections and one Klebsiella) and 4% by candida spp. In 32% of cases etiology remained unknown. Only two patients (7%) had to permanently discontinue treatment due to infection, namely G3 Parvovirus infection and G3 CMV reactivation. Using univariate analysis, we observed no significant correlation between incidence of infections and histology (lymphoma *vs* myeloma), age >= 65 years, relapsed or refractory disease at bi-Ab start, exposure to > 4 therapy lines, previous exposure to bendamustine, previous CART, immunoglobulin replacement therapy, occurrence of CRS, baseline ferritin levels, G4 neutropenia or hypogammaglobulinemia at the time of infection. The observed infectious events rate of 48% in this cohort of patients is superimposable to data reported in clinical trials. Though a greater sample is probably needed to speculate on risk factors, the elevated incidence of viral events prompts vigilance on this occurrence.

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ANAEROBIC BLOODSTREAM INFECTIONS IN HEMATOLOGIC PATIENTS: A RARE BUT DANGEROUS EVENT. 9-YEAR SINGLE CENTER EXPERIENCE

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Anaerobic bloodstream infections (AnBSI) represent less than 5% of all BSI in cancer patients (pts), but a very high mortality rate up to 40-50% is reported. However, large epidemiological studies are scanty, and often report heterogeneous case series including also solid cancer patients undergoing abdominal surgery. To describe the epidemiology, clinical characteristics, and outcome of AnBSI in hematologic pts, we extracted data from a prospective database collecting all the febrile/infectious episodes of pts admitted at our Institution during a 9-year period. Data concerning age, gender, hematologic diagnosis and disease status, presence of neutropenia and mortality were also analyzed. Between 2015 and 2023, 699 BSI were recorded; in 14 (2%) cases an anaerobic bacterium was isolated. AnBSI characteristics are reported in Table 1; when compared to other BSI, no correlations with age and gender, as well as with hematologic diagnosis and disease status, were observed. AnBSI were more frequently polymicrobial as compared to other BSI (4/14, 28.6% *vs* 36/685, 5.3%, respectively) (p=0.0061). In all but one case of polymicrobial AnBSI, enteric bacteria were associated (2 E. coli, 1 E. faecium). Indeed, mucositis and abdominal symptoms were frequently observed (8 cases, 57.1%) in AnBSI pts. Thirty-day mortality was 28.6% (4/14) in AnBSI (L. bucchalis, L. mesenteroides, Bacteroides and Clostridium spp, 1 case each), significantly higher than in other BSI (17/685, 2.5%) (p=0.0005). In one fatal case, a polymicrobial BSI (E. faecium+Bacteroides spp) was documented. Of note, among AnBSI pts, one death was observed in one patient with controlled hematologic disease (myeloma undergoing autologous stem cell transplant), as compared to none among other BSI pts. Empiric antibiotic treatment was appropriate in 7 (70%) of 10 surviving pts and in 2 (50%) of 4 deceased pts. We confirm that AnBSI are rare events in hematologic pts; as compared to other BSI, they are associated to a significantly higher mortality, that may also occur in pts with a controlled phase of hematologic disease. AnBSI are often polymicrobial and, therefore, they reflect a complex clinical picture.

Finally, an appropriate empiric antibiotic treatment in pts with mucositis/abdominal symptoms should be promptly considered, in order to minimize unfavorable outcomes.

Table 1.

AnBSI	Tot. N= 14
M/F ratio	9/5
Median Age, y (range)	52.5 (28-74)
Type	
• *Clostridium* spp	5
• *F. nucleatum*	3
• *Bacteroides* spp	2
• *L. bucchalis*	2
• *L. mesenteroides*	1
• *Actinomyces* spp	1
Polymicrobial (%)	4 (28.6%)
Hematologic disease	
• Acute leukemia	6
• Lymphoma	4
• Myeloma	4
Hematologic disease status	
• Uncontrolled	8
• Controlled	6
Neutropenia (%)	9 (75%)
Mucositis/abdominal symptoms	8 (57.1%)
30-day mortality	4 (28.6%)

DP165

NURSING MANAGEMENT OF SUBCUTANEUS DARATUMUMAB AT HOME: 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 and/or long distance from the hospital. The availability in the Viterbo province of a Domiciliary Hematologic Care Unit (DHCU) allowed to overcome these difficulties

Methods. Herein, the nursing experience in 22 patients with MM treated as outpatients with subcutaneous (sc) daratumumab (dara) is reported, as part of the Myel-Home project. 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. The main clinical features of pts at baseline of dara are shown in the Table. Distance from DHCU to pts home was<20 Km in 2 cases (9.1%), ≥ 20<40 Km in 13 (59.1%) and ≥ 40 Km in 7 (31.8%). Among 11 pts treated in 1st line, 5 were transplant eligible and 6 transplant ineligible. On the whole, 199 administrations of sc-dara were performed by DHCU nurses as outpatient: during and/or immediately after home administration, only one pt had adverse events (grade 2 allergic reaction according WHO), leading to dara permanent discontinuation after the 2nd dose at home. Main adverse events during the course of domiciliary treatment were infections (pneumonia in 5 pts, sepsis in 2, cystitis in 1) and deep vein thrombosis in 1 pts. One pt was not yet evaluable for response and one pt discontinued early: among the evaluable 20 pts, 3 achieved a stringent complete remission, 7 a very good partial remission and 2 a partial remission, with an overall response rate of 60%, 6 pts had a stable disease and 2 pts a disease progression. At the last follow-up, 13 pts are alive and 9 pts died (5 from disease progression, 3 from infective complications and 1 from heart disease).

Conclusions. Nursing treatment at home with sc-dara in frail pts with MM is feasible and safe, making possible a curative approach frontline as well as in advanced phases of disease also in subjects otherwise excluded by best available therapies or forced to long periods of hospitalization. At present, within the Myel-Home project, other monoclonal antibodies (belantamab-mafodotin and talquetamab) are already available for home administration

Table 1. Clinical features at baseline of DARA treatment.

N° of patients	22
M/F, n° (%)	10/12 (45.5/54.5)
Median age, years (IQR)	71.8 (64.3 – 78.8)
Patients aged ≥ 80, n° (%)	5 (22.7)
Type of MM, n° (%)	
IgG-k	8 (36.4)
IgG-λ	2 (9.1)
IgA-k	2 (9.1)
IgG-λ	2 (9.1)
Light chain k	3 (13.6)
Light chain λ	5 (22.7)
Phase of disease, n° (%):	
1st line treatment	11 (50.0)
2nd line treatment	10 (45.5)
> 2nd line treatment	1 (4.5)
Treatment schedule, n° (%):	
Dara-VTD	6 (27.3)
Dara-RD	10 (45.5)
Dara-VMP	3 (13.6)
Dara-VD	2 (9.1)
Dara-d	1 (4.5)
Reason for home management, n° (%):	
Disease complications	15 (68.2)
Age > 80 years	2 (9.1)
Distance from DH	3 (13.6)
Social condition	2 (9.1)

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PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY AND HEMATOLOGIC MALIGNANCIES: A SEIFEM RETROSPECTIVE SURVEY

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Background. Progressive multifocal leukoencephalopathy

(PML) is a rare opportunistic infection caused by John Cunningham polyomavirus (JCV). In immunocompromised patients a viral reactivation leads to demyelinating disease, causing a high morbidity and mortality rate, especially in hematological malignancy (HM) patients with over 80% of patients dying within two months from diagnosis. In recent decades, the introduction of immunological therapies led to an increase in PML.

Aim. To evaluate clinical, radiological and treatment characteristics of PML in a cohort of HM patients.

Methods. we conducted a survey among SEIFEM (Sorveglianza Epidemiologica delle InFezioni nelle EMopatie) affiliated Italian hematology centers. Inclusion criteria were cerebrospinal fluid (CSF)

positive for JCV by polymerase chain reaction (PCR) or brain biopsy–proven PML in patients with HM.

Results. Ten centers joined the survey with a total of 22 patients, 14 of whom were men (63.6%); the median age was 65 years (range, 47-80 years). The main diagnoses were 5 (22.7%) chronic lymphocytic leukemia, 5 (22.7%) multiple myeloma and 3 (13.6%) acute leukemias. All the patients received cancer directed therapy, 21 (95.4%) received conventional chemotherapy, and 9 (40.9%) underwent transplantation. Seventeen patients (77.3%) received immunomodulating therapy (mostly rituximab). The median time from HM diagnosis to PML diagnosis was 33.1 months. PML was diagnosed a median of 36 days from symptom onset. PML was diagnosed by CSF in 19 patients and by brain biopsy in 3 patients. Median survival from PML diagnosis was 2.25 months (range 0.07-88.6 months). As illustrated in the figure, in univariate analysis, there is a statistically significant difference in median overall survival (OS) for patients with myeloma compared with others (57.3 *vs* 1.7 months, p=0.01), patients undergoing autologous stem cell transplantation (55.8 *vs* 1.8 months, p=0.036) and non-neutropenic patients (3.4 *vs* 0.25 months, p=0.01). We also observed a better OS in patients who received PML directed therapies(5.9 *vs* 1.1 months, p=0.046).

Conclusions. PML is a rare but life-threatening complication in HM patients. In our study, we observed a longer survival for myeloma patients, ASCT patients, non-neutropenic patients, and patients who received PML directed therapy.

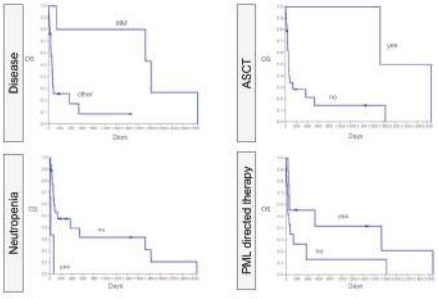

Figure 1. Kaplan Meier curves according to disease, ASCT, neutropenia or PML directed therapies. MM, multiple myeloma; ASCT, autologous stem cell transplantation, PML, Progressive multifocal leukoencephalopathy.

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CEREBRAL TOXOPLASMOSIS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background. Opportunistic infections represent a serious complication that can occur in the HSCT setting. Toxoplasmosis' infection can reactivate after transplant, usually in the first 6 months, and the clinical presentation can involve different organs, often developing in the CNS, both in a localized (isolated cerebral infection) or disseminated pattern.

Methods. In our center all patients tested toxo IgG and IgM serology before allogeneic stem cell transplantation and received prophylaxis with Trimetoprim-sulfametoxazole after engrafment. In patients with a positive serology Toxo PCR has been performed every 7-10 days until engrafment.

Results. In our center, 686 patients underwent HSCT from 2021 and 2023 and 4 cases of toxoplasmosis (<1%) were observed. Of these, 3 had a CNS localization. Infection occurred respectively at 9, 2 and 3 months from transplant. While two of these began with typical neurological symptoms, the third had an ocular presentation, with scotomas, visual blurring and a peculiar picture at the fundus exam. In all of them brain involvement was detected by CT and MRI. Trimetoprim-sulfametoxazole prophylaxis was not administered in one of the 3 patients due to drug intolerance. Infection developed after the start of IS therapy for a concomitant GVHD suggesting the role of severe immunosuppression, even with a proper antibiotic prophylaxis. Diagnosis was performed on the basis of PCR positivity on blood, vitreal or CSF samples, while serology remained negative in all the patients. All 3 patients had humoral severe hypogammaglobulinemia, and CD4+ lymphocytes counts lower than 200/mm^3. Two cases were treated with Pyrimethamine and Sulfadiazine and one with trimethoprim-sulfamethoxazole. The outcome was different for each case: in the first the infection progressed until the patient's death, the second showed a complete recovery, while the third (with ocular localization) obtained only a partial reduction of ocular symptoms and brain lesions

Conclusions. management of toxoplasmosis' infection in the post-HSCT setting remains a challenge.

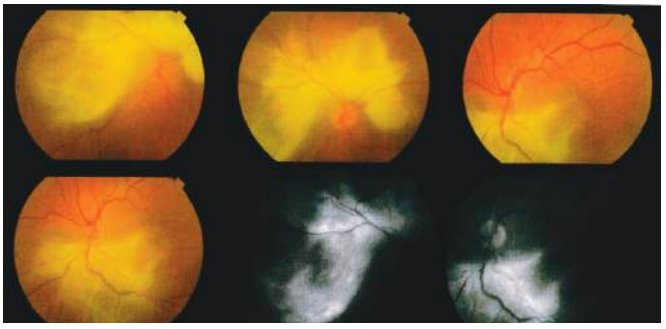

Figure 1.

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PREVALENCE OF LATENT TUBERCULOSIS INFECTION BY QUANTIFERON-TB TEST IN 180 PATIENTS WITH MULTIPLE MYELOMA RECEIVING NOVEL DRUGS AND ROLE OF REACTIVATION PROPHYLAXIS: A RETROSPECTIVE, SINGLE-CENTER, CROSS-SECTIONAL STUDY

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Once infected, patients with hematologic malignancies have a risk of progressing to overt tuberculosis (TB) that is 2 to 40 times higher compared to the general population. Consequently, it could be important to diagnose latent TB infection in these patients and to consider a prophylaxis that could avoid a possible reactivation. In this setting, limited data are available about patients with multiple myeloma (MM) treated with novel drugs (proteasome inhibitors, IMiDs and monoclonal antibodies). Therefore, we retrospectively evaluated the prevalence of latent TB infection by the LIAISON® QuantiFERON®-TB Gold Plus (QFT-Plus) assay in 180 patients with active MM observed at our Institution since January, 2020, to June, 2023. The test was performed at diagnosis or at disease progression, before starting treatment. QFT-Plus test was found positive in 26 subjects (14.4%), whose clinical characteristics are summarized in Table 1.

Table 1. Clinical features at baseline of DARA treatment.

Table 1. Baseline characteristics of patients with multiple myeloma and quantiferon positive

Median age, years (range)	75 (42-83)
Gender, n. (%)	
Male	14 (53.9)
Female	12 (46.1)
Country of origin, n. (%)	
Italy	23 (88.5)
Eastern Europe	2 (7.7)
Africa	1 (3.8)
MM isotype, n. (%)	
IgG	15 (57.7)
IgA	10 (38.5)
Light chain	1 (3.8)
History of previous active tuberculosis, n. (%)	
Yes	2 (7.7)
No	24 (92.3)
Pharmacological prophylaxis, n. (%)	
Yes	21 (80.8)
No	5 (19.2)
Drugs used for tuberculosis prophylaxis, n. (%)	
Isoniazid with pyridoxine supplementation (6 months)	14 (66.7)
Rifampicin (4 months)	7 (33.3)
Concomitant hepatitis-B virus prophylaxis, n. (%)	
Yes (lamivudine)	11 (42.3)
No	15 (57.7)
MM treatment regimen used, n. (%)	
Contains proteasome inhibitor	
Bortezomib	16 (61.5)
Carfilzomib	4 (15.4)
Contains IMiDs	
Thalidomide	8 (30.8)
Lenalidomide	20 (76.9)
Pomalidomide	4 (15.4)
Contains monoclonal antibodies	
Daratumumab	20 (76.9)
Isatuximab	1 (3.8)
Elotuzumab	4 (15.4)
Autologous hematopoietic stem cell transplant, n. (%)	
Yes	4 (15.4)

Twenty-one (80.8%) patients with latent TB received prophylactic treatment (isoniazid or rifampicin) according to indications provided by the infectious disease specialist, while 5 did not (two patients had been treated for active TB several years before; three patients were excluded from prophylaxis due to poor kidney function and other important comorbidities). Fourteen patients (66.7%) received isoniazid at dose of 300 mg/day in combination with pyridoxine supplementation for six months, while 7 patients (33.3%) received rifampicin at dose of 600 mg/day for 4 months. In one patient, isoniazid was stopped because of liver toxicity. Eleven patients also required prophylaxis with lamivudine at the dose of 100 mg/day, to avoid HBV reactivation. With a median time of observation of 692 days, none of the QFT-Plus-test positive patients developed TB reactivation during or after MM treatment. Moreover, TB prophylaxis was not associated with any significant toxicity in all but one cases. In conclusion, TB screening using QFT-Plus-test revealed a not negligible proportion of MM patients with latent TB infection before treatment. Specific prophylaxis in these subjects was generally safe (including those also receiving lamivudine) and could have avoided possible reactivations of latent TB. This could be particularly important for MM patients planned to receive T-cell redirecting therapies (i.e. bispecific antibodies and CAR-T), characterized by high incidence of infectious complications.

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INFLUENZA VIRUS INFECTION IN PATIENTS WITH HAEMATOLOGICAL DISORDERS: MONOCENTRIC EXPERIENCE

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Background. influenza virus infection is a common cause of self□limiting upper respiratory tract infection, but in hematological patients, that often suffer of more severe life-threatening infections, it progress to the lower respiratory tract. However, not much data is available on the actual incidence, morbidity and mortality of influenza A and influenza B in this patient cohort.

Table 1.

	Sex	Age	Influenza A	Influenza B	Sars Cov 2	Pneumonia	Pct (ng/ml)	Time Negative swabs (days)	Oseltamivir	Antibiotic therapy
Acute promyelocytic leukemia meningeal relapse	m	47	+	-	-	no		5	no	no
Diffuse large B-cell lymphoma	m	77	+	-	-	yes	0.36	none	yes	Piperacillin/Tazobactam
Diffuse large B-cell lymphoma	f	64	+	-	-	yes	0.82	10	no	Piperacillin/Tazobactam Meropenem
Myelodysplastic syndrome	m	49	+	-	-	yes	4.39	14	no	Piperacillin/Tazobactam Meropenem/Teiclopanin
Marginal zone lymphoma	m	70	+	-	+	yes	0.11	3	no	Meropenem/Clarithromycin, Remdesivir
Autoimmune thrombocytopenia	f	55	+	-	+	no		15	no	
Cold Autoimmune Hemolytic Anemia	m	67	-	+	-	yes	15	9	yes	Meropenem/Teicoplanin

Method. In our virology laboratory were analysed from 10/11/2022 to 5/04/2024, 1704 haematological patients' nasopharyngeal swabs using polymerase chain reaction (PCR) molecular test (Abbot Resp- 4 -Plex) to detect respiratory syncytial virus (RSV), influenza virus A/B and Sars Cov2, to monitor sars cov2 infection , in febrile and asymptomatic patiens.

Results. No positive swabs for RSV were identified; on the con-

trary, we identified 180 positives for Sars Cov2, 33 positives for influenza: 31 for influenza A and 2 swabs for influenza B. The 33 swabs belonged to 6 patients with influenza A and 1 patient with influenza B, two of these patients were positive for both influenza A and Sars Cov2. Median age was 64 years (47-77), 2 females and 5 males. Patients with oncohematologic pathology were 5, 2 with non-oncological haematological pathology (see the Table 1). 5 patients had pneumonia, 4 with procalcitonine suggestive of bacterial infection. Only two patients were treated with oseltamivir, and one of this did not have a negative swab (positive after 65 days). No patients died, and upon resolution of the radiological picture of pneumonia, regardless of the result of the swabs, patients were udergoing to chemo or immunotherapy, where provided.

Conclusion. We conclude that influenza A/B in immunocompromised patients, in our experience, is mild and self-limiting, however, further studies need to be carried out with larger samples.

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LOW RATE OF INFECTIOUS COMPLICATIONS OMITTING FLUOROQUINOLONE PROPHYLAXIS AFTER HIGH-DOSE CHEMOTHERAPY IN NON-HODGKIN LYMPHOMAS, A SINGLE CENTER EXPERIENCE

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Infectious complications after high-dose (HD) chemotherapy (cht) in Non-Hodgkin Lymphomas (NHL) are been little investigated due to rarity of patients (pts) in this setting. The emerging category of High-Grade Lymphomas (according to the 2022 revision of the World Health Organization classification) will require more frequently HD cht than in the past. To reduce infection rate during neutropenia, several guidelines still recommend Fluoroquinolone (FQ) antibiotic prophylaxis, although the development of Multi-Drug Resistant (MDR) bacteria is growing in multiple geographies. On this evidence we started to omit FQ prophylaxis during prolonged neutropenia attempting to develop an efficient protocol for the early treatment of febrile neutropenia (FN). We describe a retrospective real-life experience of severe neutropenia (≥7 days) during 43 HD cht treatment in 27 NHL pts, treated from January 2015 till December 2022, omitting FQ prophylaxis. The median age at diagnosis was 56 years. 21/27 pts were male and 6/27 female. 12/27 pts had Diffuse Large B Cell Lymphoma, including 2 with CNS involvement, 6/27 had Burkitt Lymphoma, 5/27 had Primary Central Nervous System Lymphoma and 4 had T-cell NHL. In 11/27 pts bone marrow was involved. The spectrum of HD cht embraced several protocols according disease guidelines, including 18/43 CODOX-M/IVAC (with or without Rituximab), 13/43 MATRix and 12/43 other HD regimens. Our cohort median hospitalization lasted 20 days whose 10 days were the median period of neutropenia (absolute neutrophil count (ANC)<500/mmc). Specifically, induction cht implicates longer hospitalization and longer neutropenia than consolidation courses ($p<0.002$). FN was recorded in 33/43 HD cht cycles: 10 fever of unknown origin, 17 sepsis, 5 bacterial organ infections, 1 fungal infection. Additionally, among the sepsis, 6 were gram positive bacteremia, 11 were gram negative, and 5 were complicated by septic shock. Nevertheless, no death from infection was reported. In 6/43 courses MDR bacteria colonization was documented: 5 extended spectrum beta-lactamases cases and one carbapenem-resistant enterobacterales. Pts characteristics are summarized in Table 1. Despite the availability of limited data, these results encourage to safely omit FQ prophylaxis in NHL pts treated with HD cht, without increasing infection related mortality and containing MDR infections risk, although it is mandatory to promptly deal with FN.

Table 1.

	NHL[1]
Pts[2]	27
Median Age (range)	56.4 (20-84)
Sex	
Male (%)	21/27 (77.8)
Female (%)	6/27 (22.2)
DLBCL[3] (%)	12/27 (44.5)
with CNS[4] involvement	2/12 (16.7)
PCNSL[5] (%)	6/27 (22.2)
Burkitt Lymphoma (%)	5/27 (18.5)
T-cell NHL (%)	4/27 (14.8)
Bone marrow involvement (%)	11/27 (40.7)
Cht[6] treatment	43
Induction (%)	27/43 (62.8)
Consolidation (%)	16/43 (37.2)
CODOX-M/IVAC (%)	18/43 (41.9)
MATRix (%)	13/43 (30.2)
Others (%)	12/43 (27.9)
Hospitalization (days) (range)	20 (17-23)
Neutropenia (days) (range)	
ANC[7] < 500/mmc	10 (8-12)
ANC < 100/mmc	6 (5.5-9)
Fever (%)	33/43 (76.7)
FUO[8] (%)	10/33 (30.3)
Sepsis (%)	17/33 (51.5)
Gram-positive (%)	6/17 (35.3)
Gram-negative (%)	11/17 (64.7)
Both (%)	0/17 (0.0)
Organ infections (%)	5/33 (15.2)
Septic Shock (%)	5/33 (15.2)
Rectal Swab (%)	6/43 (14.0)
ESBL[9] (%)	5/6 (83.3)
CRE[10] (%)	1/6 (16.7)
30-day mortality (%)	3/43 (7.0)
Infectious related (%)	0/3 (0.0)

1. Non-Hodgkin Lymphoma
2. Patients
3. Diffuse Large B-Cell Lymphoma
4. Central Nervous System
5. Primary Central Nervous System Lymphoma
6. Chemotherapy
7. Absolute Neutrophil Count
8. Fever of Unknown Origin
9. Extended Spectrum Beta-Lactamases
10. Carbapenem-Rresistant Enterobacterales

POSTERS

Lymphomas

P001

EXPLORING TREATMENT APPROACHES AND OUTCOMES OF OCULAR ADNEXAL LYMPHOMA: A RETROSPECTIVE MULTICENTER STUDY

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Non-Hodgkin lymphomas (NHL) of the orbit and ocular adnexa (OALs) are rare, comprising 8% of all extranodal NHL cases, with 57% being MALT lymphomas (OAL-MALT). Despite evolving therapeutic approaches, consensus on optimal treatment remains elusive. Local radiotherapy is evolving as the favored strategy over systemic therapy. The aim of our study was to evaluate different treatment strategies and compare their effectiveness. We conducted a retrospective, multicenter study on 62 patients with OAL-MALT diagnosed between 2011 and 2023 in 7 Italian centers. Patients with extraocular involvement were excluded. The median age was 67 years (range 21-96).

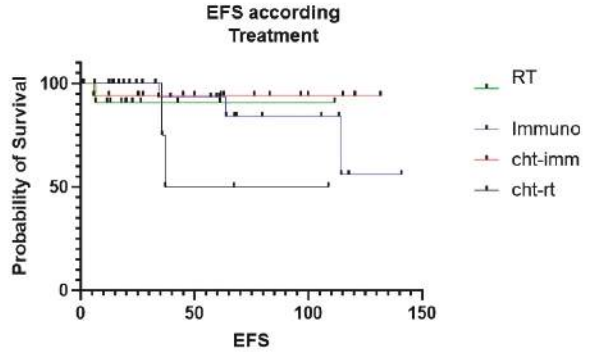

Figure 1.

According to the TNM staging system, 48 patients (77%) were classified as T2N0M0, 11 patients (17%) as T1N0M0, 2 patients (3%) as T4N0M0, 1 patient (1.5%) as T3N0M0, and 1 patient (1.5%) as T3N1M0. Treatment modalities included chemo-immunotherapy or chemotherapy alone (22 pts, 35.4%), immunotherapy alone (18 pts, 29%), radiotherapy (15 pts, 24.2%), and combined treatment (7 pts, 11.4%). Various regimens were employed as chemotherapy backbone: R-Bendamustine in 4 pts, R-CHOP-like therapy in 3 pts, and Chlorambucil in 7 pts. According to the international response criteria for malignant lymphoma, at the end of treatment, 45 patients (72.5%) were in complete response (CR), 13 patients (21%) were in partial response (PR), and 4 patients (6.5%) were in stable disease (SD). Notably, the porptotion of CR was similar in patients treated with RT (73%), with immunotherapy alone (72%), and with immunochemotherapy (75%), while CR was only 43% in patients treated with combined treatment. Relapse with ocular involvement occurred in 9.6% of patients. Median Overall Survival (OVS) and Event-Free Survival (EFS) were not reached at a median follow-up of 46 months. Notably, patients treated with Chemotherapy and RT exhibited inferior median EFS compared to other groups. (Figure 1). Our study underscores the diverse treatment landscape in OAL-MALT, emphasizing the need for standardization and caution against aggressive approaches.

P002

DIAGNOSTIC AND PROGNOSTIC ROLE OF 18F-FDG PET AND ITS PARAMETERS IN PREDICTING HIGH-GRADE TRANSFORMATION AND SURVIVAL IN INDOLENT NON-FOLLICULAR NON-HODGKIN LYMPHOMAS

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The role of 18-Flurodeoxyglucose Positron Emission Tomography (18F-FDG PET) in FDG-avid lymphoma is well established, while in indolent non-Follicular Non-Hodgkin Lymphomas (non-FL iNHLs) is not yet clear. This study aims to investigate the potential role of 18F-FDG PET semiquantitative variables in predicting high-grade transformation (HGT) and their prognostic role in pre-treatment transformed non-FL iNHLs. Between 2008 and 2023 we retrospectively analyzed 51 patients (pts) with transformed non-FL iNHL in our Center: among them, 49 had a 18F-FDG PET/CT performed at HGT and 24 at iNHL diagnosis. Their demographic and clinical characteristics at diagnosis and at HGT were reported on Table 1. Median time to transformation (TTT) was 28 months (range 0-215). At HGT 44 pts (88%) underwent curative treatment, with ORR 84% (77% CR, 7% PR). Recurrent/refractory disease was observed in 49%. After a median follow-up of 17 months (range 2-173), 61% of pts was alive in CR.

Table 1.

Patient Characteristics	At diagnosis (51 pts)	At HGT (51 pts)
Median age, yrs (range)	64 (42-86)	69 (46-92)
M/F	23/28	
Histology (%)	EMZL 18 (35) NMZL 13 (25) SMZL 9 (18) LPL 9 (18) Nos 2 (4)	DLBCL 49 (96) Burkitt 1 (2) Primary cutaneous DLBCL, leg-type 1 (2)
Stage (%)	I-II 11 (22) III-IV 29 (56) Unknown 11 (22)	I-II 15 (29) III-IV 36 (71) Unknown 0
IPI (%)		L/HL 21 (43) IH/H 27 (53) Unknown 2 (4)

A control-population of 141 not transformed non-FL iNHLs with baseline PET/CT was also analyzed: 114 Extranodal Marginal Zone Lymphomas (EMZL - 81%), 17 Nodal MZL (NMZL - 12%), 6 Splenic MZL (SMZL - 4%), 1 Lymphoplasmacytic Lymphomas (LPL), 3 iNHL not otherwise specified (NOS). Median age at diagnosis was 65y. M/F ratio was 75/66. After a median follow-up of 102 months 77% of pts were alive. From each PET/CT study, several metabolic parameters were extracted: Standard Uptake Volume max

(SUVmax), ratio to liver (r_liv), ratio to blood-pool (r_bp), Metabolic Tumor Volume (MTV), Total Lesion Glycolysis (TLG). All these parameters at HGT were significantly associated with PFS and OS. SUVmax was the best performing, and its threshold derived was 16.5 (sensitivity 72%, specificity 64%, AUC 0.671). Mean PFS and OS were 135.3 months ±14.7SEM *vs* 48.8 months ±10.7SEM (p=0.0051) and 130.6 months ±16.3SEM *vs* 55.5 months ±10.2SEM (p=0.0089) in pts with SUVmax <16.5 and >16.5, respectively. At iNHL diagnosis, SUVmax >8.2 was able to identify pts at increased risk of transformation (p=0.002, sensitivity 73.7%, specificity 68.1%, AUC 0.713), with also a significantly shorter mean TTT (28 *vs* 43 months, p=0.001). In conclusion, we demonstrated that semiquantitative PET/CT variables at HGT have a prognostic role in non-FL iNHLs, while SUVmax at diagnosis can identify a group of patients at higher risk of early transformation.

P003

LIPOSOMAL DOXORUBICIN, VINBLASTINE AND DACARBAZINE PLUS CONSOLIDATION RADIOTHERAPY OF RESIDUAL NODAL MASSES FOR FRONTLINE TREATMENT IN OLDER ADULTS WITH ADVANCED STAGE CLASSIC HODGKIN LYMPHOMA (C-HL): IMPROVED OUTCOME IN A SINGLE-CENTER REAL-LIFE STUDY

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Patients aged ≥60 years (20% of all cases of c-HL) often present with negative prognostic factors (advanced stage and B symptoms); comorbidities are frequent thus outcomes are dismal and the optimal therapy remains poorly defined. A retrospective, single-center study of patients ≥60 y with previously untreated c-HL referring to the Hematology Unit of Federico II University from 1 January 2013 to 1 January 2023 was carried out. All patients received a frontline regimen with 25 mg/m^2 of liposomal doxorubicin (NPLD), standard Vinblastine and Dacarbazine without bleomycin (MVD), for a total of 6 cycles, followed by radiation of residual nodal masses (RNMs)≥2.5 cm. The primary endpoint was OS and PFS at 5-years median follow-up. Secondary endpoints were the rates of response at EoT FDG-PET, toxicity (in terms of global systolic longitudinal myocardial strain [GLS] and left ventricular ejection fraction [LVEF]) and feasibility. Patients received primary anti-infectious prophylaxis with lipegfilgrastim s.c. on days 4, 18 of every cycle; trimethropin-sulfamethoxazole at 960 mg orally every 12h for 2 days a week and acyclovir at 800 mg orally daily from the start of chemotherapy until 1 month; allopurinol at 300 mg orally in every course; FDG-PET with Deauville score (DS) at staging, EoT and every 3-6 months and 2D echocardiography and speckle tracking echocardiography at baseline, interim, EoT and within six months from EoT. 50 older adults (median age, 69 y; range, 60-89) with advanced stage c-HL were enrolled. The mean dose intensity of MVD was 92% (33%-100%) and the feasibility endpoint (≤10% of patients receiving <85% of the planned dose) was reached. At EoT-FDG-PET, 90% (45/50; one failed due to early death for Covid infection) reached complete remission. 17 patients (34%) received consolidation radiotherapy of RNMs with DS ≥3. At 5-year median follow-up, the OS and PFS of the entire population were 87.5% and 81.6%, respectively. In the chemotherapy alone cohort, the 5-year OS was 84.1% and the 5-year PFS was 81.5% while in the combined modality treatment cohort, the 5-year OS was 94.1% and the 5-year PFS 81.9% (Figure 1). Cox regression analyses confirmed that patients 60-69 y and 70-79 y (5-year OS: 92.4% and 93.7%, respectively) appeared to benefit more from MVD ± irradiation as compared to patients ≥80 y (5 year OS: 50%; P=0.0049). 11 experienced grade ≥3 adverse events, and 4 of them required hospitalization. At cardiological assessment only minor changes in GLS and LVEF (10% of patients) were recorded after treatment. Our data suggest that in older adults with high-risk c-HL, NPLD-driven strategy (without bleomycin) plus consolidation radiotherapy (if needed) may be a promising up-front option, to test in phase II clinical trials for improving survival incidence.

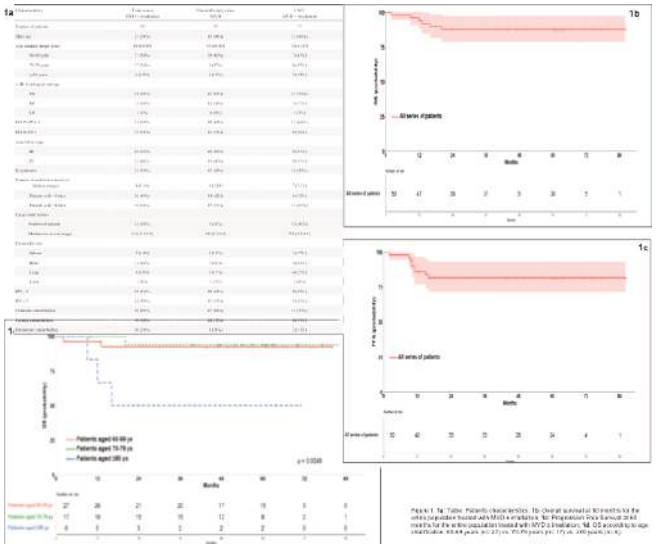

Figure 1.

P004

ANALYSIS OF BACKGROUND PARENCHYMAL ENHANCEMENT IN BREAST MRI OF LONG-TERM CHEST RADIOTREATED HODGKIN'S LYMPHOMA SURVIVORS

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Hodgkin lymphoma (HL) is a highly curable disease, although the excellent life expectancy is offset by the late effects of successful radiotherapy (RT) and chemotherapy, particularly the development of second malignancies, such as breast cancer (BC). Increased background parenchymal enhancement (BPE) is an imaging biomarker

of higher risk of BC, regardless of the amount of fibroglandular tissue, in high-risk women. The aim of this prospective study was to evaluate the distribution of BPE patterns and the possible onset of BC in long-term HL survivors treated with chemotherapy and RT and to compare them with age-matched women with BRCA mutation carriers and without a history of cancer.

Methods. 62 women, aged between 22 and 49 years (median 35 years), long-term survivors of HL for at least 15 years (range 15-18 years) and 62 consecutive women of the same age with BRCA mutation carriers, underwent screening with dynamic contrast magnetic resonance imaging (DCE-MRI).

Results. The analysis of BPE was comparable in the two groups: 31 cases (50%) of moderate and marked BPE in the long-surviving HL group and 30 (48%) in the BRCA carrier control group. In the long-surviving HL group, 3 (5%) malignant lesions were found, two of these (ductal carcinoma in situ-DCIS, n=1; non-special type-NST, n=1) had moderate BPE lesions in the contralateral breast and one (NST) marked BPE.

Conclusions. In HL survivors, the incidence of BC is higher than in the general population, furthermore we found a BPE comparable to healthy women at high risk for BC with BRCA mutation carriers. Future research should be directed at examining the underlying cancer biology and genetic susceptibility of treatment-induced tumors.

P005

INDIPENDENT EXTERNAL VALIDATION OF THE ADVANCED-STAGE HODGKIN LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (A-HIPI) IN AN ITALIAN MULTI-CENTRE PATIENT COHORT

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Background. The evolution of the therapeutic landscape for classical Hodgkin Lymphoma (HL) is accompanied by the need for better prognosis prediction, in an effort to develop risk-tailored approaches. The Advanced-Stage Hodgkin Lymphoma International Prognostic Index (A-HIPI) was recently modelled in a cohort of patients treated with PET/CT guided ABVD, using baseline risk factors to predict individual patient prognosis.

Aim. To perform independent external validation of the A-HIPI risk model.

Methods. Patients diagnosed with advanced-stage HL from 4 different Italian institutions between 2004 and 2023 were enrolled. All individuals were treated with PET/CT-guided ABVD. The A-HIPI survival estimates were calculated as previously described [Rodday *et. al,* JCO 2022]. Discrimination was assessed by the means of Harrel's c-index of concordance and by visual inspection of the survival curves for each quartile of the A-HIPI predicted risk.

Results. A total of 355 patients were enrolled, of which 49% were female, 81% presented with B symptoms and 38% had bulky disease, with median age at diagnosis being 37 (range 18-65); 37% of subjects had stage IIB HL, whereas 26% and 37% had stage III and IV HL, respectively. After a median follow-up of 63 months, 5-year overall-survival (OS) and progression-free survival (PFS) were 92.8% and 70.6%, respectively. Ninety-five (27%) patients had relapsed/refractory disease and 29 (8%) died. After the application of the A-HIPI model to the patient cohort, c-index was 0.64 (SE 0.06) for OS and 0.62 (SE 0.03) for PFS. The patient population was then divided into quartiles according to the predicted risk for both OS and PFS. In both cases, good separation between the highest and lowest predicted risk groups was observed (OS: Q1 89%, Q4 92%; PFS: Q1 55%, Q4 80%), with the middle quartiles showing some significant overlap between themselves (OS: Q2 92%, Q3 97%; PFS: Q2 72%, Q3 75%).

Conclusions. In this study, we show how the A-HIPI is of use in predicting the individual prognosis of subjects affected by advanced-stage HL, as the obtainment of c-index values comparable to the ones reported in the development cohort makes this validation effort successful. Moreover, the division of patients into quartiles displays good discrimination especially between the lowest and highest predicted risks. However, such division, made for validation purposes only, needs to be further refined if the A-HIPI is to be used to create specific risk groups.

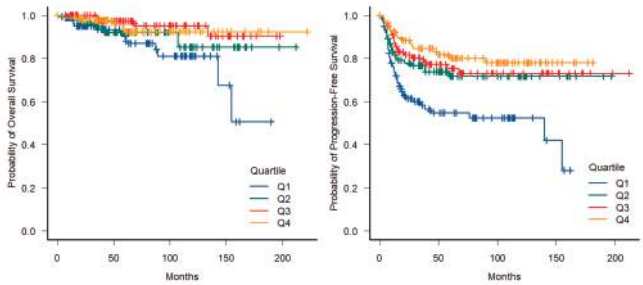

Figure. 5-year Overall Survival (A) and Progression-Free Survival (B) of the enrolled patients after the subdivision in the respective A-HIPI predicted risk quartiles.

Figure 1.

P006

NK-CITOTOXICITY MEDIATES EXCELLENT RESPONSES IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA FOLLOWING POST TRANSPLANT NIVOLUMAB ADMINISTRATION AND UNSELECTED AUTOLOGOUS LYMPHOCYTES INFUSIONS

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In relapsed/refractory Hodgkin Lymphoma (RHL), the achievement of complete remission (CR) is fundamental in order to proceed with curative allogeneic stem cell transplantation (HSCT) consolidation. Immune checkpoint inhibitors (CI) have demonstrated clinical activity in patients relapsing after autologous stem cell transplantation (ASCT), although with only 20% CR. To improve those results, we designed a treatment based on early CI therapy after ASCT, supported by the reinfusion of unselected autologous lymphocytes (ALI). The rationale is to exploit the disease debulking of-

fered by ASCT conditioning and proceed with early post ASCT administration of CI on a minimal disease burden. ALI are aimed to reduce the post ASCT immune depression eliciting CI efficacy. 21 pts with RHL (median age 32 years) underwent lymphocyte apheresis. All patients received 2nd line chemo followed by 3rd line Brentuximab-Vedotin (BV) in non-responding pts. 14 patients failed to respond to salvage therapy and thus received early post-transplant CI supported with 4 ALI. 8 patients responded to 2nd line (n=6) or 3rd line BV (n=2) and received ASCT in CR followed by ALI without CI, as a control group (Figure 1A). Median follow-up was 38 months (95% CI 29.4-52.3). All patients receiving ALI + CI achieved CR and 8 received HSCT consolidation. All patients in the treatment arm are alive. Median DFS was not reached in treatment arm (Figure 1B). 4 of the patients in the control arm relapsed (50%). Three of them responded to 3rd line therapy and proceeded to HSCT. 2 patients died because of RHL in control arm. Median DFS in the control arm was 22 months (Figure 1B). NK cells showed higher expansion and a faster maturation in the treatment arm, compared to the control arm ($p<0.05$). Preliminary results confirmed that HL cells lines do not express HLA class I and II but do express several ligands of activating NK cells receptors such as aNKG2D, aNKp30, aNKp46, aDNAM-1. Those receptors were able to trigger *in vitro* NK cells degranulation, that was further increased by PD-L1 and PD-L2 blockade on HL cell lines ($p<0.05$). Our data, with a long follow-up, show very high anti-tumour activity of ALI + CI for RHL, allowing most patients to proceed to HSCT. RHL patients in the treatment arm had an excellent outcome if compared to the control arm, which included patient in CR at ASCT. This approach may accelerate NK cell development/maturation and favour the expansion of the "adaptive" NK cell compartment.

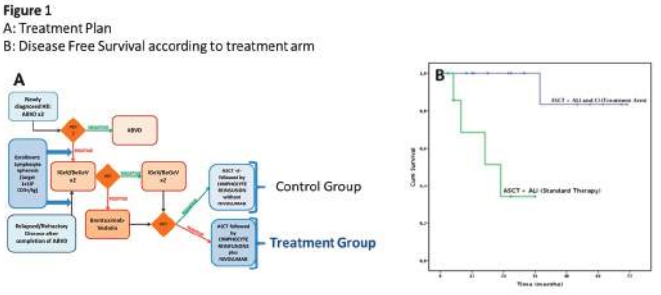

Figure 1.

P007

ABSTRACT NOT PUBLISHABLE

P008

ULTRASOUND-GUIDED NEEDLE BIOPSY OF ABDOMINAL LYMPH NODES IS A RELIABLE AND SAFE METHOD FOR THE DIAGNOSIS OF LYMPH NODE MALIGNANCIES: A RETROSPECTIVE, MONOCENTRIC STUDY

C. Mazzoni[1,2], C. Serra[3], L. Argnani[1], D. Agostinelli[3], S.M. Bakken[3], D. Di Benedetto[3], M. Machado[3], L. Masi[3], N. Venturoli[3], B. Casadei[2], G. Gugliotta[2], C. Pellegrini[2], V. Stefoni[1,2], A. Broccoli[1,2], P.L. Zinzani[1,2]

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Background. The differential diagnosis of suspected neoplastic diseases of deep lymph nodes can be challenging. Although considered the gold standard for histologic diagnosis in both lymphomatous and solid tumors, excisional biopsy becomes more complex and it is associated with higher procedural risks when dealing with abdominal disease. In this setting, needle biopsy could be a valuable option for diagnostic purposes.

Methods. This retrospective, monocentric study aimed to analyze the feasibility and safety of ultrasound-guided needle biopsy for diagnosing neoplastic disease in deep abdominal nodes. We also evaluated the detection rate and diagnostic accuracy of this approach.

Results. Seventy-seven needle biopsies of abdominal lymph nodes were evaluated: 15/77 (19.5%) were non-diagnostic. Of these, 7 (46.7%) required a second biopsy, 5 of which were performed using a different sampling technique, while only 2 patients underwent a second needle biopsy. Of the 62 diagnostic biopsies, 40 (64.5%) were lymphomas, 17 (27.4%) were solid cancers, and 5 (8.1%) were non-neoplastic conditions. Of the 57 biopsies positive for neoplastic disease, 32/40 (80%) and 6/17 (35.3%) were newly diagnosed lymphoma and solid cancer, respectively, while the remainder were histologically confirmed. Three out of 40 lymphoma-positive biopsies were inconclusive for definite histologic type and were repeated with a different diagnostic approach, leading to a diagnosis of Hodgkin disease in 2 cases, while the other one was negative for lymphoma. The median diameter available for 70 lymph nodes was 47.4 mm (range 9-200) and was smaller for non-diagnostic biopsies compared to diagnostic biopsies (28 mm *vs* 36.5 mm). Needle sizes used were 14 gauge (G), 16G, and 18G in 2 (2.6%), 23 (29.9%), and 53 (67.5%) biopsies, respectively. An 18-gauge needle was used in 60% of non-diagnostic and 62.5% of diagnostic biopsies. No procedure-related adverse events were observed. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 100%, 83.3%, 98.2% and 100%, respectively. The diagnostic yield was 80.5% and the diagnostic accuracy was 98.4%.

Conclusions. Ultrasound-guided needle biopsy may represent a valid diagnostic tool for the suspected neoplastic disease of deep abdominal lymph nodes, with a favorable safety profile, a good diagnostic detection rate, and a high sensitivity.

P009

MOSUNETUZUMAB DEMONSTRATES CLINICALLY MEANINGFUL OUTCOMES IN HIGH-RISK PATIENTS WITH HEAVILY PRE-TREATED RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL) AFTER ≥3 YEARS OF FOLLOW-UP: SUBGROUP ANALYSIS OF A PIVOTAL PHASE II STUDY

I. Del Giudice[1], S. Assouline[2], N.L. Bartlett[3], M. Matasar[4], S.J. Schuster[5], L.H. Sehn[6], J. Kuruvilla[7], P. Giri[8], M. Shadman[9], C.Y. Cheah[10], S. Dietrich[11], K. Fay[12], M. Ku[13], L. Nastoupil[14], M.C. Wei[15], S. Yin[15], I. To[15], S. Tracy[15], A. Kwan[15], E. Penuel[15], L.E. Budde[16]

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Introduction. In a pivotal phase II study (NCT02500407) mosunetuzumab, a CD20xCD3 T cell-engaging bispecific antibody, demonstrated high rates of complete responses (CR) and manageable safety in patients (pts) with R/R FL and ≥2 prior lines of therapy. Here, we present a subgroup analysis of this study in high-risk pts with heavily pre-treated R/R FL after ≥3 years of follow-up.

Methods. Eligible pts had R/R FL Grade (G)1–3a and ≥2 prior therapies. Efficacy and safety were assessed in pts with a history of progression of disease within 24 months (POD24) from start of first-line therapy, pts receiving mosunetuzumab in third (3L) *vs* fourth or later line (4L+), and pts aged ≥65 years.

Results. As of 05/02/2023, 90 pts had received mosunetuzumab; 52% had POD24, 61% had 4L+ therapy, and 33% were aged ≥65 years. CR rates in pts with POD24 (60%), pts ≥65 years (67%), and 4L+ pts (55%; Table 1) were consistent with the overall population (60%). A numerically lower 30-month duration of CR rate was observed in 4L+ (66%) *vs* 3L (77%) pts. The 3-year progression-free survival (PFS) rate was 44% in pts with POD24, 47% in pts ≥65 years and 43% in the overall population. 3-year PFS rate was lower in 4L+ (36%) *vs* 3L (54%) pts. Safety across subgroups was consistent with the overall safety cohort (OSC). Incidence of cytokine release syndrome events was 51% in pts with POD24, 47% in 4L+ pts, 30% in pts ≥65 years, and 44% in the OSC. In the OSC, any-grade infections occurred in 51% of pts; after Cycle (C)8, 8 events were reported in 8 pts. G≥3 infections were observed in 17% of pts. Most common G≥3 infections were pneumonia (3%), upper respiratory tract infection (2%), septic shock (2%), and COVID-19 (2%). Most serious infections (14/19 [74%]) occurred in the first 4 C; after C8, 3 events were reported in 3 pts. Serious infections concurrent with neutropenia were rare (1%). Hypogammaglobulinemia was reported in 2% of pts.

Conclusions. Fixed-duration mosunetuzumab monotherapy showed durable remissions and clinically meaningful survival outcomes in high-risk pts with heavily pre-treated R/R FL. Safety was manageable and consistent across subgroups, supporting outpatient administration.

Table 1. Efficacy outcomes across subgroups.

Subgroup	POD24 status		Line of therapy		Age		Overall population (N=90)
Efficacy endpoints	POD24 (n=47)	Non-POD24 (n=43)	3L therapy (n=35)	4L+ therapy (n=55)	<65 years (n=60)	≥65 years (n=30)	
ORR, n (%) [95% CI]	38 (80.9) [66.7–90.9]	32 (74.4) [58.8–86.5]	30 (85.7) [69.7–95.2]	40 (72.7) [59.0–83.9]	45 (75.0) [62.1–85.3]	25 (83.3) [65.3–94.4]	70 (77.8) [67.8–85.9]
CR, n (%) [95% CI]	28 (59.6) [44.3–73.6]	26 (60.5) [44.4–75.0]	24 (68.6) [50.7–83.2]	30 (54.5) [40.6–68.0]	34 (56.7) [43.2–69.4]	20 (66.7) [47.2–82.7]	54 (60.0) [49.1–70.2]
Median DOR, months (95% CI)	NR (10.6–NE)	35.9 (20.7–NE)	NR (11.9–NE)	34.5 (16.5–NE)	NR (16.5–NE)	35.9 (13.7–NE)	35.9 (18.7–NE)
Median DOCR, months [95% CI]	NR (18.7–NE)	NR (31.5–NE)	NR (NE–NE)	33.0 (18.7–NE)	NR (33.0–NE)	NR (18.7–NE)	NR (33.0–NE)
Median PFS, % (95% CI)	17.8 (12.0–NE)	26.3 (11.8–NE)	NR (12.0–NE)	18.1 (11.8–37.3)	17.8 (9.4–NE)	25.8 (15.2–NE)	24.0 (12.0–NE)
36-month PFS, % (95% CI)	43.9 (28.2–59.5)	42.0 (25.0–59.0)	54.3 (37.0–71.5)	36.3 (21.8–50.7)	41.5 (27.3–55.8)	46.9 (28.1–65.8)	43.2 (31.8–54.7)
Median OS, months (95% CI)	NR (NE)	NR (NE)	NR (NE)	NR (NE)	NR (NE)	NR (NE)	NR (NE)
36-month OS, % (95% CI)	84.2 (72.1–96.3)	81.0 (69.1–92.9)	84.9 (72.7–97.2)	81.7 (70.5–92.8)	81.2 (70.6–91.9)	86.4 (74.0–98.8)	82.9 (74.6–91.2)
Median TTNT, months (95% CI)	NR (16.2–NE)	NR (16.0–NE)	NR (18.1–NE)	NR (13.9–NE)	19.4 (9.7–NE)	NR (NE)	NR (19.4–NE)

3L, third line; 4L+, fourth or later line; CI, confidence interval; CR, complete response; DOCR, duration

P010

ABSTRACT NOT PUBLISHABLE

P011

BASELINE WHOLE BODY PET METRICS PREDICT PROGRESSION FREE SURVIVAL AFTER CAR T-CELL THERAPY IN RELAPSED/REFRACTORY AGGRESSIVE B-CELL LYMPHOMA

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In patients with relapsed or refractory aggressive B-cell lymphoma undergoing treatment with CAR-T cell therapy, sustained benefit is observed in only approximately 40% of cases. This study aims to identify prognostic biomarkers in patients receiving CAR-T cell therapy for aggressive B-cell lymphomas.

Methods. Consecutive patients who underwent CAR-T cell infusion for aggressive B-cell lymphoma were retrospectively enrolled in this single-center study. All patients underwent FDG PET/CT scans before CAR-T infusion, and at 1 (PET-1) and 3 months post-infusion. Total metabolic tumor volume (TMTV) and whole-body total lesion glycolysis (WB-TLG), were quantified using an AI-based automated segmentation algorithm (Lesion Scout with Auto ID, Siemens Healthineers). Treatment response was assessed clinically and radiologically every 3 months post-CAR-T or upon clinical progression.

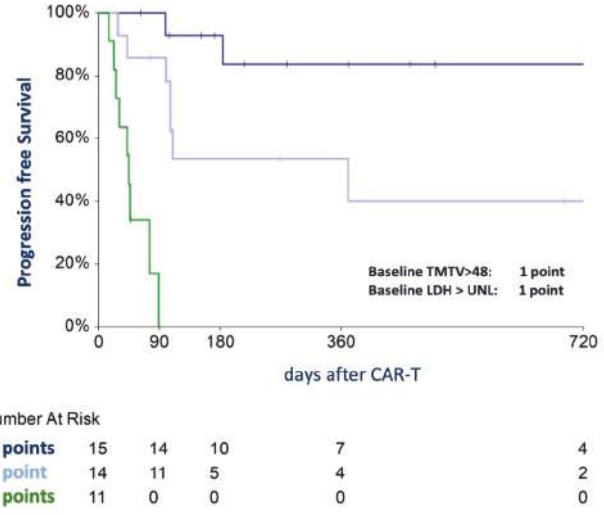

Figure 1.

Results. Forty patients were included (median age 55 years, range 28-75). Most patients (65%) presented with advanced stage (III-IV) disease. Baseline parameters including the International Prognostic Index (IPI), lactate dehydrogenase (LDH) levels, and extranodal involvement were also analyzed. Median baseline TMTV and WB-TLG were 28.34 cm^3 (range 0-1306) and 222.36 (range 0-12318), respectively. With a median follow-up of 8 months, 22 patients (55%) showed a response to CAR-T cell infusion. The median

progression-free survival (PFS) was 12 months, with an overall PFS rate of 48% at 2 years. Baseline TMTV and WB-TLG were predictive of PFS (p<0.001), with higher baseline TMTV (≥48) and WB-TLG (≥407) associated with lower PFS (median PFS, 1.4 months *vs.* not reached and 2.5 months *vs.* not reached; p<0.001, respectively). On multivariate analysis, baseline TMTV (cut-off 48.4) and LDH above the upper normal limit were independent prognostic factors for PFS (p<0.001 and p=0.003, respectively). We assigned 1 point each for TMTV ≥48 and LDH above normal, distinguishing 3 groups with 0 (15 patients), 1 (14 patients), or 2 (11 patients) points each. Patients with 0, 1, or 2 points had increasingly worse responses to CAR-T cell therapy (median PFS not reached *vs.* 12 months *vs.* 1.5 months, p<0.001) (Figure 1).

Conclusion. Baseline PET metrics hold promise for early identification of patients likely to benefit most from CAR-T cell infusion. Integrating clinical variables with baseline and PET-1 metrics could enhance patient stratification, enabling timely adaptation of clinical management strategies.

P012

ANALYSIS OF TREATMENT OUTCOMES AND CART ELIGIBILITY IN ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA AGED BETWEEN 65 AND 75 YEARS.

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Diffuse large B-cell lymphoma (DLBCL), a potentially curable disease also in the elderly, poses challenges in the treatment due to concurrent comorbidities. CAR-T therapy has been approved in Italy for DLBCL patients (pts) up to 75 years, more recently also as a second-line for relapse within 12 months from first-line. This study aimed to assess, in a real-life setting, clinical outcomes, feasibility of different chemotherapies, and second-line strategies in this particular group, with a focus on potential eligibility to CAR-T. We included 127 pts aged 65-75 out of 447 DLBCL diagnosed between January 2017 and December 2021 into this single-center study. The majority of pts (75.6%) had advanced-stage disease, with 67.7% having an IPI of 3-5. All pts received R-CHOP based regimen, with full dose anthracycline (AC) in 98 pts (77.2%, using liposomal AC in 61 pts), AC reduction in 22 pts (17.3%) ("R-miniCOMP"), and AC omission in 7 pts (5.5%) ("R-CVP"). As expected, at a median follow-up of 43 months, PFS varied significantly between AC-containing regimens and R-CVP, (70% in R-CHOP, 51% in R-miniCOMP and 28% in R-CVP, p<0.005). Thirty-six (28%) pts had disease recurrence, including 7 progression to the central nervous system (CNS). Sixteen pts were refractory, 12 relapsed within 12 months, while only 8 relapsed beyond 1 year. Among recurrences, 7/36 (19.5%) died early due to rapid progression, 7/36 (19.5%) received oral chemotherapy with palliative intent and 22/36 (61%) intravenous second line therapy (mostly platinum-based, in 6 cases with intention-to-transplant). Only 9 pts (all treated with a full-dose AC regimen) would have met the eligibility criteria for CAR-T as a second-line therapy based on current regulations in Italy. This translates to just 25% of relapsed pts and 7% of the entire population. The other 27 pts presented characteristics that would have been considered exclusion criteria from CAR-T: ECOG > 1 (10/36), late relapse (8/36), CNS involvement at relapse (7/36), age at relapse (1/36), severe cytopenia (1/36). Overall, 76.1% of recurrent pts died. Relapse in elderly DLBCL aged 65 -75 is associated with poor risk characteristics, rendering the vast majority of pts ineligible for CAR-T, and with a dismal outcome with chemotherapy-based approaches, representing an unmet clinical need. These real-world data underscore the importance of optimizing the risk-benefit ratio in the first line setting to improve overall outcome in elderly DLBCL.

P013

EPCORITAMAB LEADS TO DEEP RESPONSES IN RELAPSED OR REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL): SAFETY AND POOLED EFFICACY FROM THE PIVOTAL AND CYCLE (C) 1 OPTIMIZATION (OPT) FL COHORTS OF EPCORE NHL-1

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In the pivotal cohort of EPCORE® NHL-1 (phase 1/2; NCT03625037), epcoritamab treatment (tx) led to deep, durable responses per independent review committee in patients (pts) with multiply R/R FL (overall response rate [ORR], 82%; complete response [CR] rate, 63%). Most CRS events were low grade (Table), all resolved, and none led to tx discontinuation. Enhanced CRS mitigation strategies without mandatory hospitalization for CRS monitoring are being evaluated in a C1 OPT cohort of EPCORE NHL-1. In this cohort, pts with $CD20^+$ R/R FL grade (G) 1–3A and ≥2 prior lines of systemic tx received subcutaneous epcoritamab (28-d Cs) with a third step-up dose in C1 (D1, 0.16 mg; D8, 0.8 mg; D15, 3 mg), followed by 48-mg full doses (QW, C1–3; Q2W, C4–9; Q4W, C≥10) until disease progression. Adequate hydration and dexamethasone as the preferred steroid for mandatory CRS prophylaxis were recommended in C1. Rates of any-grade and G≥2 CRS events were the primary endpoints. Secondary endpoints included response per Lugano criteria, minimal residual disease (MRD) negativity in peripheral blood (clonoSEQ®; 10^{-6} cutoff), and safety/tolerability. Efficacy analyses for the pooled pivotal and C1 OPT cohorts were conducted. As of Jan 8, 2024, 86 pts had received epcoritamab in this C1 OPT cohort. Median follow-up was 5.7 mo. Demographic and disease characteristics were similar between the pivotal and C1 OPT cohorts (C1 OPT:

median prior tx lines, 2 [range, 2–9]; stage III–IV FL, 92%; double refractory, 63%; primary refractory, 44%; POD24, 42%). All CRS events were low grade (49% overall; 40% G1, 9% G2; Table 1); most events occurred in C1, and none led to tx discontinuation. No pts had ICANS or clinical tumor lysis syndrome. Of the 82 pts in C1 OPT who received the first full dose, 44 (54%) received outpatient CRS monitoring. ORR was 84% and CR rate was 65% among the 214 pts in the pivotal and C1 OPT cohorts (per investigator). In each cohort, median times to response/CR were 1.4/1.5 mo. Of the 135 MRD-evaluable pts in both cohorts, 89 (66%) had MRD negativity. CR, MRD negativity overall, and MRD negativity at C3D1 (prespecified time point) were associated with improved progression-free survival. In the largest R/R FL population receiving a T cell–engaging tx to date, epcoritamab led to early, deep responses with manageable safety. Rate and severity of CRS were substantially reduced with C1 OPT. These results support continued evaluation of epcoritamab tx in the outpatient setting.

Table 1. CRS events in the pivotal and C1 OPT cohorts.

n (%)	Pivotal cohort[a] N=128	C1 OPT cohort N=86
Any-grade CRS	85 (66)	42 (49)
G1	51 (40)	34 (40)
G2	32 (25)	8 (9)
G3	2 (2)	0
G≥4	0	0

[a]Data cutoff: April 21, 2023.

P014

OUTCOME OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS ACCORDING TO RISK STRATIFY SEQUENTIAL TREATMENT: A SINGLE CENTRE ITALIAN EXPERIENCE

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Post-transplant lymphoproliferative disorders(PTLD) are a severe complication related to immunosuppression occurring after solid organ transplantation. We present a retrospective monocentric real-world analysis encompassing 20 cases of CD20+ PTLD(16 Diffuse Large B-Cell Lymphoma and 4 Burkitt Lymphoma) managed at Niguarda Hospital in Milan from 2015 to 2023. Patients(pts) were treated according to modified Risk Stratify Sequential Treatment(RSST) criteria. Each pt received induction therapy with 4 cycles of weekly intravenous Rituximab(R), followed by interim response evaluation via computed tomography/positron emission tomography(CT/PET) between days 42-49. Risk stratification for subsequent therapy was based on interim CT/PET response. Pts were categorized into low-risk(LR) group if they attained a complete response(CR) on interim CT/PET, regardless of their International Prognostic Index (IPI) score, or if they achieved a partial response(PR) with IPI score<3. Conversely, pts with PR and IPI score>3, or those with stable or progressive disease (SD,PD), were classified into high-risk (HR) group. LR group received consolidation with 4 further 3-weekly doses of R iv,while HR pts received intensification with immuno-chemotherapy R-CHOP21(CIT). Overall survival(OS) and event free survival(EFS) were analysed for the entire group, LR and HR pts. After R-induction the ORR was 65%(13/20,95%CI: 41-85%):5 CR, 8 PR(1pt died after CT evaluation),2 SD and 2 PD. During induction 4 pts died because of infection/organ failure. Applying RSST criteria, we identified 8 LR and 8 HR pts. The ORR at the end of treatment was70%(14/20,95%CI:46-88%). The OS at 1 and 2years(y) was 70%(95%CI: 50-90%). 6 deaths at 5y. For LR pts OS at 1 and 2y was100%, at 5y all LR pts were alive. In HR group OS at 1y and 2y was 75%(95%CI: 45-100%). HR pts, who reached CR after CIT, were still in remission at 5y. EFS was 60%(95%CI: 38-81%)at 1y and 47%(95%CI: 24-70%)at 2y. We observed:3 relapses, 3 progressions and 4 deaths not related to PTLD. EFS in the HR group at 1y and 2y was 62.5%(95%CI: 29-96%). EFS of LR pts was 70%(95%CI: 34-100%) at 1y and decreased to 52.5%(95%CI: 12.5-92.5%)at 2y. In our study, we reaffirmed the efficacy and safety of RSST based on response to R-induction and IPI score. The analyses demonstrated a 5-y OS rate of 100% for LR pts and 75% for HR pts, comparable to PTLD-2 trial results, highlighting the importance of risk stratification in guiding therapeutic decisions.

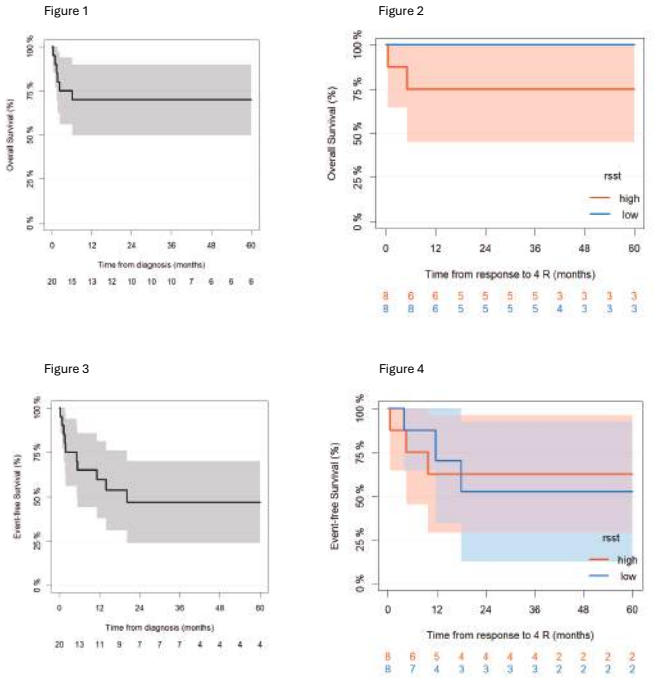

Figure 1) Overall survival, time from diagnosis. Figure 2) Overall survival by RSST on patients alive after 4 Rituximab; from time to response to 4 R. Figure 3) Event free survival, time from diagnosis to progression, relapse or death. Figure 4) Event free survival by RSST, on patients alive after 4 rituximab; from time to response to 4 R.

Figure 1.

P015

FEATURE AND EARLY IDENTIFICATION OF IMMUNE EFFECTOR CELL ASSOCIATED NEUROTOXICITY (ICANS) IN CHIMERIC ANTIGEN RECEPTOR (CAR) T - CELL TREATED NON HODGKIN LYMPHOMA: A MONOCENTRIC EXPERIENCE

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ICANS is the most clinically challenging complication of CAR-T cell therapy, reported in 20–60% of patients (pts), 12–30% with severe symptoms, and up to 30% with seizures. The indications and

utility of the electroencephalogram (EEG) for an early identification of ICANS remain poorly defined, and EEG findings have been reported anecdotally. Here we describe a monocentric population of patients with non Hodgkin lymphoma, treated with CAR-T cells between 2020 to 2024. All pts had per protocol EEG and magnetic resonance imaging (MRI) before CAR-T infusion, MRI screening between 7-10 days from infusion and pts with ICANS repeated EEG during the acute phase. Toxicity was graded according to the ASTCT Consensus Grading. Seizure prophylaxis with levetiracetam was administered only in case of history of seizures or previous secondary central nervous system (CNS) lymphoma. A total of 53 pts affected from DLBCL or high grade lymphoma (n=46), PMBCL (n=5), MCL (n=2), were infused with CAR-T products (26 Axi-Cel, 25 Tisa-Cel, 2 Brexu-Cel). One month PET-CT response was 25 CR (51%), 15 PR (31%) and 9 PD (18%). Four pts died before the first response evaluation for progressive disease or infectious complications. Forty-four pts (83%) were complicated with CRS G1-2, and 3 pts (5%) experienced CRS G>2. Four pts received seizure prophylaxis, and 6 pts (11%) had ICANS G1-2, ICANS G>2 in 3 patients (6%). Among the 4 pts with previous history of seizures or CNS lymphoma, we observed only one case of ICANS G3. Median time to ICANS onset was 10 days, with a median duration of 6 days; all pts with ICANS had a preceding diagnosis of CRS. No late neurologic toxicity was reported. Baseline EEG was normal in the whole population. In the acute phase, 6 pts with ICANS performed EEG, and they were all abnormal (Table 1). Only 2 pts with ICANS had MRI alterations concomitant to impaired consciousness (Table 1). Post infusion MRI showed radiologic alterations (2 new ischemic lesions and 1 DWI mild restriction in the corpus callosum splenium) in 3 pts without ICANS or specific clinical symptoms. The frequency of ICANS in our population is quite low, and there was not an increase of seizures even in the absence of primary prophylaxis. All pts who performed EEG in the acute phase of ICANS had EEG alterations, and the severity of EEG findings correlated with the clinical severity of the neurotoxicity. EEG can be a useful tool for the early diagnosis of ICANS, prospective studies are needed.

Table 1. Clinical, EEG and MRI findings of ICANS patients.

Number of patients	Severity of ICANS	ICANS findings	EEG findings	MRI findings
2	G1	Tremor and dysgraphia	Diffuse and irregular theta activity	None
2	G1	Mild consciousness impairment	Mild slowing of background rhythm, anterior delta waves, occasionally with triphasic morphology	1 pt with pachymeningeal enhancement* 1 pt without alterations
1	G2	Severe consciousness impairment	Mild slowing of background rhythm, anterior delta waves, occasionally withtriphasic morphology	Alterations compatible with PRES
1	G3	Bilateral tonic-clonic seizures**	Electrographic seizures	None

ICANS: Immune effector cell associated neurotoxicity syndrome; EEG: electroencephalogram; MRI: magnetic resonance imaging; PRES: posterior reversible encephalopathy syndrome
**clinical findings appeared after the EEG findings

P016

REAL-LIFE T-CELL PHENOTYPE MONITORING AFTER ANTI-CD19 CAR-T CELL THERAPY MAY BE INFORMATIVE OF CAR-T FITNESS AND IMMUNE RECONSTITUTION.

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Background. Chimeric antigen receptor T (CAR-T) cell therapy has emerged as promising treatment for Diffuse large B-cell Lymphoma (DLBCL), Primary mediastinal B-cell lymphoma (PMBCL) and Mantle cell Lymphoma (MCL). However, more than half of patients (pts) still relapse, and prolonged cytopenias and infections have been increasingly reported. This study aimed to characterize immune reconstitution following CAR-T cell therapy.

Methods. Immune phenotype was assessed at various time points (day +10, +30, +90, and +180) post CAR-T cells infusion at Spedali Civili in Brescia. Since December 2021, 24 pts have been evaluated: 15 DLBCL (8 Tisa-cel; 7 Axi-cel), 3 PMBCL, and 6 MCL. 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-), and HLA-DR+ CD4+/CD8+ cells. CAR-T cells expansion was evaluated using a specific CD19 CAR reagent.

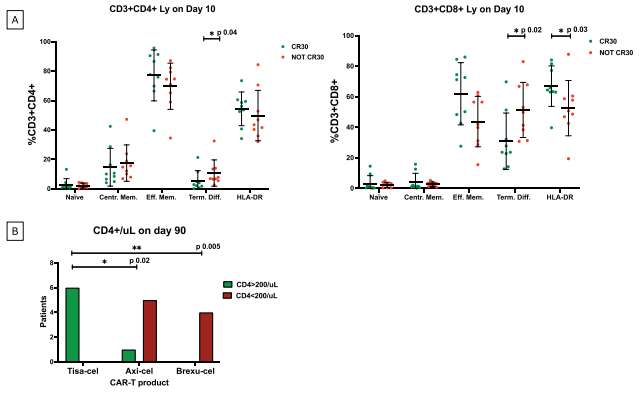

Figure 1: (A) Analysis of CD4+ and CD8+ T-cell subsets on day 10 following CAR-T cell infusion. Patients who achieved complete remission at 30 days are shown in green, while those who did not are shown in red. (B) Patients who attained 200 CD4+ cells/μL are depicted in green, compared to those who did not in red, categorized by the different CAR-T cell products.

Figure 1.

Results. Lower levels of CD4+ and CD8+ Terminally Differentiated T-cells on day 10 were associated with a higher complete remission (CR) rate at day 30 (p 0,04 and p 0,02, respectively; Figure 1).

Additionally, higher levels of HLA-DR expression on CD8 cells on day 10 were correlated with CR at day 30. This data highlights how having more exhausted T-cells at the peak of the CAR-T cells expansion results in a lower response rate. We then assessed the immunological recovery over time, determining when pts exceeded the threshold of 200 CD4+ cells per microliter. Remarkably, all pts treated with Tisa-cell achieved over 200 CD4+ cells/uL at +90 days, compared to 16 % of those treated with Axi-cell (p 0,02) and none of the pts treated with Brexu-cell (p 0,005). The expansion of CAR-T cells also seems to affect CD4+ recovery. Specifically, only 22 % of pts in the "expander" group have over 200 CD4+ cells/uL at +90 days, compared to 100 % of pts who did not undergo expansion (p 0,045). Conversely, the type of disease, experiencing CRS or ICANS, CR at day 30, or receiving high doses of steroids, do not affect CD4+ recovery at 3 and 6 months. Of the patients with <200 CD4/uL at 3 months, 55,6 % subsequently developed an infection, compared to 14,3 % of those with >200 CD4/uL.

Conclusions. The T-cell phenotype at day 10 post CAR-T cells infusion impacts on outcome at 30 days, while the type of product and CAR-T cells expansion influence CD4+ recovery.

P017

ASSESSING THE COST-EFFECTIVENESS OF MOSUNETUZUMAB VERSUS TISAGENLECLEUCEL FOR RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA: AN ITALIAN HEALTH SERVICE PERSPECTIVE

M. Bellone, A. Sabinot, L. Pradelli

AdRes, Health Economics & Outcome Research

Objective. To assess the cost-effectiveness of mosunetuzumab versus tisagenlecleucel for the treatment of adult patients with relapsed/refractory follicular lymphoma after two or more lines of systemic therapy (R/R 3L+ FL) from the perspective of the Italian National Health Service (NHS).

Methods. A partitioned survival model of three mutually exclusive health states-progression-free, post-progression, and death-was developed to project lifetime costs and benefits associated with mosunetuzumab and tisagenlecleucel. Data from the GO29781 and the ELARA studies informed treatment effectiveness. A matching-adjusted indirect comparison (MAIC) approach was used to account for differences in trial population characteristics on the relative efficacy of mosunetuzumab to tisagenlecleucel. Progression-free survival (PFS) and overall survival (OS) were extrapolated beyond the trial period by applying the hazard ratios from the MAIC to mosunetuzumab's parametric survival curves (OS=0.86 with 95%CI: 0.15-1.93; PFS=1.73 with 95%CI: 1.10-2.75). Direct healthcare costs, including drug acquisition and administration, disease monitoring, adverse event management and post-progression therapy, were collected from Italian sources. Total costs, life-years (LYs), and quality-adjusted life-years (QALYs) were the outcome measures used in the estimation of cost-effectiveness. Scenario and probabilistic sensitivity analyses (PSA) were conducted to assess the robustness of the findings.

Results. The base-case analysis indicated that mosunetuzumab dominates tisagenlecleucel in patients with R/R 3L+ FL, demonstrating both positive effects (QALYs: 0.70) and substantial lower costs (approximately -€140,000). The PSA confirmed consistent results despite clinical parameter input uncertainty, with mosunetuzumab maintaining cost-effectiveness over tisagenlecleucel in >90% of iterations, at the Italian willingness-to-pay (WTP) threshold of €40,000/QALY. In a scenario analysis assuming equal OS between treatments (HR=1), mosunetuzumab remained an economically efficient option.

Conclusion. Mosunetuzumab results a cost-effective treatment option compared to tisagenlecleucel for adult patients with R/R 3L+ FL, presenting favorable outcomes from the perspective of the Italian NHS. Future research and data collection efforts will be crucial to confirm these findings and reduce uncertainties regarding long-term clinical and economic implications.

P018

CENTRAL NERVOUS SYSTEM RELAPSE IN DIFFUSE LARGE B-CELL LYMPHOMA AND ROLE OF CNS PROPHYLAXIS: A SUB-ANALYSIS OF THE RETROSPECTIVE OBSERVATIONAL STRIDER STUDY

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Central nervous system (CNS) relapse of diffuse large B-cell lymphoma (DLBCL) is a rare event and correlates with a dismal prognosis. The efficacy of strategies to avoid CNS disease recurrence, such as high-dose intravenous methotrexate (HD-MTX) and intrathecal prophylaxis (IT), is controversial. Our study focuses on patients (pts) with CNS relapse of DLBCL in order to evaluate clinical features, the validity of prognostic scores and the efficacy of CNS prophylaxis. Three hundred and forty two pts (excluding primary testicular lymphoma or CNS disease at diagnosis) with DLBCL included in the retrospective observational STRIDER study (full paper in press), diagnosed between January 2010 and December 2019 at AOU Città della Salute e della Scienza di Torino and treated with curative intent were selected.

Figure 1. Above: Multivariate analysis for the risk of CNS recurrence. Below: Cumulative incidence of CNS relapse by ECOG PS ≥ 2 (dotted line).

	HR	95% CI	p-value
ECOG PS ≥ 2	2.83	1.04, 7.69	0.042
CNS IPI ≥ 4	1.26	0.36, 4.39	0.712
IT OR MTX prophylaxis	0.62	0.10, 3.95	0.613

Figure 1.

Mean age was 67 years, 51/342 had ECOG PS ≥ 2 (15%), 199/341 elevated LDH (58%), 211/341 were stage IV (62%), 180/339 IPI score ≥ 3 (53%), 168/339 CNS-IPI 2-3 (49.5%), 85/339 CNS-IPI 4-6 (25%). 95/342 pts received CNS prophylaxis (28%): 59 by IT route only (17%) (25 CNS-IPI 2-3; 28 CNS-IPI 4-6), 14 by intravenous (iv) MTX only (4%) (9 HD-MTX ≥3 g/mq; 1 CNS-IPI 2-3; 12 CNS-IPI 4-6), and 11 by combined route (3%) (5 CNS-IPI 2-3, 6 CNS-IPI 4-6). Eleven pts experienced CNS relapse (8 CNS only, 3 CNS + systemic recurrence). The cumulative incidence at 3 years was 2.6%. In univariate analysis, CNS relapse risk was influenced by elevated LDH levels but not by the use of CNS prophylaxis. However, none of the pts receiving iv MTX had CNS recurrence while 2/59 pts receiving exclusive IT experienced this event (3.4%). In multivariate analysis, only ECOG PS confirmed significant correlation with the risk of CNS recurrence (Figure 1). The 1-year overall survival for pts with SNC recurrence was 37%. With the limit of a retrospective study and a small sample size our data did not show

benefit of IT prophylaxis. Although a statistically significant benefit from the use of HD-MTX prophylaxis is not shown, probably due to the low number of overall events, omitting 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 population with very high-risk of CNS relapse.

P019

MONOTHERAPY WITH SECOND-GENERATION BCL2 INHIBITOR SONROTOCLAX (BGB-11417) IS WELL TOLERATED, WITH HIGH RESPONSE RATES IN RELAPSED/REFRACTORY (R/R) MARGINAL ZONE LYMPHOMA (MZL): DATA FROM AN ONGOING PHASE 1 STUDY

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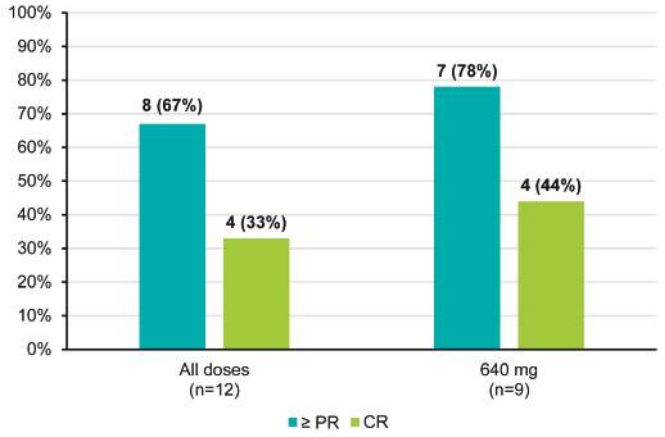
Background. Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and potent inhibitor of BCL2 than venetoclax in biochemical assays. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study in pts with B-cell malignancies. Presented here are safety and efficacy data for sonrotoclax in pts with R/R MZL.

Methods. Pts received sonrotoclax (dose escalation: 40, 80, 160, 320, or 640 mg QD) with a 3-day dose ramp-up. Expansions at 640 and 320 mg followed. DLTs were evaluated from ramp-up through day 21 at the intended dose. The primary endpoint was safety per CTCAE v5.0; a secondary endpoint for dose-expansion was ORR (defined as partial response [PR] or better) per Lugano 2014 criteria. TLS was assessed per Howard 2011 criteria.

Results. As of April 24, 2023, 13 pts with MZL had received sonrotoclax across the dose-escalation and -expansion cohorts (40 mg, n=1; 160mg, n=2; 640 mg, n=10). Overall, median age was 73 years (range, 54-85); the median number of prior tx was 1 (range, 1-3). Four pts progressed on BTK inhibitors (BTKi); 3 had BTKi as their last therapy. Dose escalation occurred per protocol at all defined doses. MTD was not reached up to 640 mg. One DLT of febrile neutropenia was observed at 160 mg. Expansion was completed with the recommended phase 2 dose of 640 mg. Median follow-up was 7.8 mo (range, 2.6-36.6). TEAEs occurring in ≥20% of pts were nausea (39%) and pyrexia, diarrhea, and constipation (31% each). The most common grade ≥3 TEAEs were neutropenia, febrile neutropenia/neutropenic sepsis, and TLS (n=2, 15% each). Five pts discontinued tx (progression, n=3; AE [infection], n=1; withdrawal, n=1). No TEAEs led to death. Two pts in the 640-mg cohort had laboratory TLS after initial ramp-up doses: 1 after 160 mg and 1 after initial doses of 40 and 80 mg. All TLS events resolved within 24 hrs without sequela or dose change. Of 12 response-evaluable pts, the ORR was 67%, including 4 CRs (33%). Of 9 response-evaluable pts treated at 640 mg, the ORR was 78%, including 4 CRs (44%; Figure 1). Responses were observed in all 4 pts with prior progression on BTKi (CR, n=3; PR, n=1).

Conclusions. Sonrotoclax monotherapy had a tolerable safety profile and encouraging antitumor activity across tested doses in pts with MZL. Two pts had laboratory TLS following initial doses that resolved. No clinical TLS was observed. An exploratory 320-mg cohort is currently enrolling.

Figure: Overall Response Rates by Lugano Criteria in Patients With R/R MZL Treated With Sonrotoclax Monotherapy



CR, complete response; MZL, marginal zone lymphoma; PR, partial response; R/R, relapsed/refractory.

Figure 1.

P020

SINGLE CENTER EXPERIENCE OF DA-EPOCH AS FRONTLINE TREATMENT FOR AGGRESSIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Background. Diffuse Large B-cell Lymphoma (DLBCL) is the most common large B-cell Lymphoma. Unfortunately, only 60% of DLBCL can be cured with standard therapy and patients with aggressive features (such as mutation in c-MYC, BCL2 or BCL6, elevated proliferation index (i.e. Ki67), ABC type and high IPI score) have a poor outcome. CALGB 503 randomized study show no survival advantage of R-DA-EPOCH over R-CHOP in DLBCL, but most of the patients enrolled had favorable prognostic features. The aim of our study is to investigate the tolerability and efficacy of R-DA-EPOCH regimen in patients with DLBCL with poor prognostic factors.

Methods. We have retrospectively analyzed the outcome of 50 patients affected by DLBCL and treated in first line with R-DA EPOCH from 2016 to 2023. The median age was 62 years (range: 33-74 years) and the median FUP was 40.5 months. 40% of patients had more than 65 years, 52% had Ann Arbor stage IV, 46% had a ki67>90%, 54% were ABC type. CNS IPI and IPI score were high (>3) in 62% and 24% of patients, respectively. Only 3 patients had double/triple hit lymphoma.

Results. Therapy was well tolerated, also among older patients: nine patients needed hospitalization for adverse events and no treatment-related deaths were recorded. Only one patient died during treatment due to disease progression, while 96% of patients (47/50)

were able to receive at least one dose escalation. The ORR was 82% (with a CRR 76%) and the OS and PFS at 2 years were 76.5% and 67%, respectively. No differences in 2-years OS were seen according to age (73% *vs* 71%, for patients with ≥ or<65 years, Figure 1), elevated IPI score (72% *vs* 83% for IPI ≥ 3 and<3), elevated CNS-IPI score (79% *vs* 77% for CNS-IPI ≤ 3 or > 3), cell-of-origin (75% for both GC type and non-GC type), advanced stage (72% *vs* 82% for stage IV or lower) and very high ki67 (81% *vs* 69% for patients with ki67 ≥ or<90%). P-value were n.s. in all subgroups.

Discussion and Conclusions. Our data showed that R-DA-EPOCH is well tolerated and results in a favorable CRR, despite the unfavorable characteristics of our cohort, and the adverse prognostic features analyzed didn't impact on CRR or OS. Notably, the regimen was effective and feasible also in older patients, usually considered ineligible to intensive therapy. In conclusion, R-DA-EPOCH may be a good backbone chemotherapy for patients with aggressive DLBCL which may be further improved in the future with the inclusion of novel targeted agents.

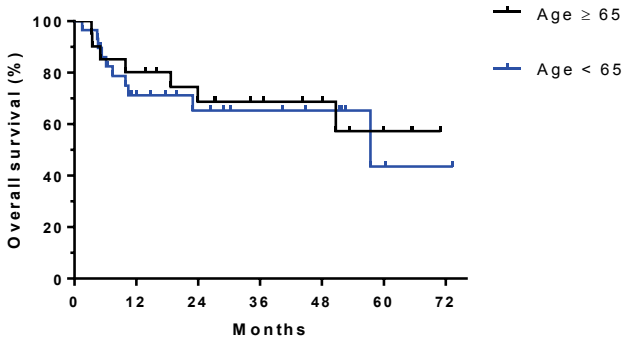

Figure 1.

P021

A REAL-LIFE MULTICENTER STUDY ON BEHALF OF THE FONDAZIONE ITALIANA LINFOMI INVESTIGATING RENAL DYSFUNCTION IN WALDENSTRÖM MACROGLOBULINEMIA: CLINICAL OUTCOMES AND MANAGEMENT STRATEGY

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Renal impairment in Waldenström Macroglobulinemia (WM) may be lymphoma-related or unrelated. We have retrospectively analyzed a cohort of 464 WM patients - from 17 Italian Fondazione Italiana Linfomi-affiliated centers - who received a first-line treatment from year 2000 to 2023. We compared the clinical characteristics and outcomes of patients without and with renal dysfunction, defined as creatinine clearance at diagnosis<60 ml/min/1,73m^2. A sub-analysis was done distinguishing cases with and without biopsy-proven renal involvement. The 116/395 WM patients with renal dysfunction displayed advanced median age (76 *vs* 67 y, p<0.0001), lower median Hemoglobin (10.8 *vs* 11.8 g/dL, p=0.008) and higher median 24h proteinuria levels (0.29 *vs* 0.20 g, p=0.04). Cumulative Illness Rating Scale (CIRS), comorbidities such as hypertension, diabetes, urothelial malignancies and therapy regimens and responses did not differ between the two subgroups. The histopathological patterns identified in 25 renal biopsies out of 116 cases were: amyloidosis (40%), tubulo-interstitial infiltration (20%), other lesions (16%), non-cryoglobulinemic-glomerulonephritis (GNF) (12%), combined non-cryoglobulinemic-GNF and light chain deposition disease (8%), cryoglobulinemic-GNF (4%). The biopsied subgroup did not present different outcomes as compared to not biopsied one. Patients with renal dysfunction showed an inferior median overall survival (OS) (139 *vs* 203 months, p<0.0001) and median progression free survival (PFS) (80 *vs* 106 months, p=0.0018) (Figure1). The cumulative incidence of progression events was higher in the subgroup with renal dysfunction both at 100 (38% *vs* 28%) and 200 (58% *vs* 52%) months (p=0.049). In univariate Cox-regression analysis, older age (HR 1.03, p=0.04), first line therapy with Bendamustine-Rituximab (BR) alone (HR 0.4, p=0.002) and first line therapy with both Rituximab-Cyclophosphamide-Dexamethasone and BR taken together (HR 0.58, p=0.04) were prognostic factors for PFS in patients with renal dysfunction. In renal dysfunction subgroup BR as first line therapy displayed higher median PFS as compared to other regimens (109 *vs* 53 months, p=0.002). In conclusion, renal dysfunction portends a worse PFS and OS outcomes in WM. BR seems to be a valid first-line therapeutic option in this setting. Prospective multicenter studies, including larger cohorts of renal-biopsied patients, are needed to confirm these findings.

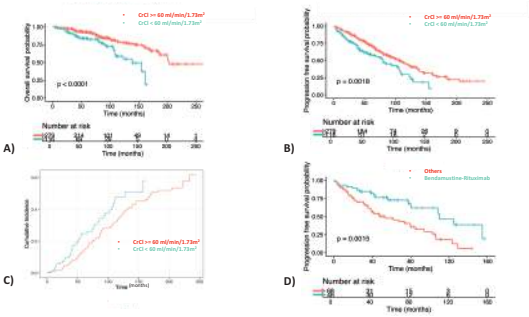

Figure 1. A) Overall survival B) Progression Free survival C) Cumulative incidence of relapse events, comparing WM patients with CrCl < 60ml/min/1.73m^2 and CrCl > = 60 ml/min/1.73m^2 D) Progression Free Survival comparing WM patients with CrCl < 60 ml/min/1.73m^2 treated with or without Bendamustine-Rituximab as first line therapy

Figure 1.

P022

METHOTREXATE MONOTHERAPY AND COMBINATION THERAPY IN MYCOSIS FUNGOIDES AND SEZARY SYNDROME: A MULTICENTER, RETROSPECTIVE STUDY FROM THE 'FONDAZIONE ITALIANA LINFOMI CUTANEOUS LYMPHOMAS TASK FORCE'

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Low-dose methotrexate (MTX) is advocated as a secondary treatment for stage IA-IB-IIA Mycosis Fungoides (MF) and as a primary treatment for stage IIB, IIIA, IIIB MF, and Sezary syndrome (SS). Despite its common usage in MF, folliculotropic MF (fMF), and SS, the existing scientific evidence primarily stems from studies conducted before the implementation of the ISCL/EORTC/WHO standardized criteria for MF/SS staging and outcome assessments, resulting in a low level of recommendation. This multicenter, retrospective, observational study aims to present real-world data on Overall Response rates (OR), Relapse-Free Interval (RFI), time to next treatment (TTNT), and the incidence of severe adverse events in patients with MF, fMF, and SS treated with subcutaneous methotrexate either as a monotherapy or in combination with any other systemic agent. Data analysis encompassed 72 patients (45 males, 27 females): 44 with MF, 10 with fMF, and 18 with SS. The staging at the time of treatment was distributed as follows: IA=1, IB=25, IIA=5, IIB=12, IIIA=7, IIIB=4, IVA1=12, IVA2=5, IVB=1. The median age at treatment initiation was 72 years (range: 44-93), with a median follow-up of 720 days (range: 30-3285). The Overall Response Rate (ORR) in patients treated with low-dose methotrexate monotherapy was 55% (13 complete responses, 21 partial responses), while it was 61% (3 complete responses, 8 partial responses) in patients treated with combined therapies including methotrexate. The Relapse-Free Interval (RFI) in patients receiving single-agent MTX was 377 days, whereas it was 466 days in patients treated with combination therapies including MTX. The median Time to Next Treatment (TTNT) in patients treated with single-agent MTX was 371 days (range: 30-3271), compared to 287 days (range: 22-1649) in the combination cohort. Only one patient in the MTX monotherapy group discontinued treatment due to a grade III hepatic adverse event. In the combination cohort, three patients had to discontinue treatment due to toxicity: one due to a grade III hepatic adverse event, one due to renal adverse events, and one due to unbearable grade II fatigue, respectively. Based on our data, low dose mtx confirms its effectiveness both as single agent and in combination in MF, fMF and SS. Combination treatments may allow to induce clinical remissions in cases relapsed/refractory after low dose mtx monotherapy, likely at a cost of increased rate of severe adverse events.

P023

CNS RELAPSE RISK IN HIV-POSITIVE PATIENTS AFFECTED BY DLBCL AND HGBL - A RETROSPECTIVE STUDY OF THE MUSTHAL COHORT

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Background. HIV+ patients (pts) with aggressive lymphoma are at higher risk of central nervous system (CNS) relapse, but data from randomized and controlled studies on efficacy of CNS-directed prophylaxis are lacking. A CNS relapse risk score (CNS-IPI) has been validated in HIV- pts.

Material and methods. Data on clinical and virological features, treatment, and outcomes of 96 HIV+ pts affected by diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL) from 1996 to 2023 in Northen Italy were recorded. Survival, the impact of lymphoma-related and HIV-related features, first line treatments and CNS-directed prophylaxis on survival and relapse risk were evaluated, with focus on CNS relapses. We tested whether CNS-IPI is valid in HIV+ pts.

Results. 82 DLBCLs and 14 HGBLs were evaluated. 90% of pts had an advanced stage at diagnosis. CNS involvement was observed in 8 pts (8%) at diagnosis. Two thirds of pts were already on cART at the time of lymphoma diagnosis. Pts received CHOP-like regimens (74%), EPOCH (12%) and intensive chemotherapy (10%) in first line. 57 pts (61%) achieved complete response (CR). 23 pts progressed during chemotherapy and 10 pts relapsed after obtaining a first remission. 8 CNS relapses were recorded, mostly in high-risk CNS-IPI population. 46 pts are currently alive in CR. After a median follow-up of 43 months, 5-years OS is 57% and PFS is 59%. Pts who responded to first line treatment showed an OS of 78% at the last follow-up. Only 4 deaths were due to infective complications during chemotherapy. A CD4+ count at lymphoma diagnosis > 200/microliter has a borderline association with a longer OS (p=0.072). Multivariate analysis showed that PFS, but not OS, was significantly influenced by HIV viral load at its zenith, by CD4+ count at lymphoma diagnosis and by the presence of a cART at lymphoma diagnosis. Neither HIV and lymphoma-related features, therapeutic regimens nor CNS directed prophylaxis seem to influence CNS relapse risk in our cohort.

Conclusions. CNS-IPI seems effective also in HIV+ DLBCL and HGBL, which still display higher risk of CNS involvement than HIV- pts. HIV+ pts who achieve a stable CR after first line therapy show a significantly higher and longer survival. The main cause of death in our cohort is progressive disease and not infective or therapy-related complications. A larger sample and further studies to clarify which CNS-directed prophylactic approach is the most effective are needed.

P024

THE ROLE OF RADIOTHERAPY ON SINGLE RESIDUAL PET POSITIVE LESION AFTER FRONTLINE CHEMIOIMMUNOTHERAPY IN PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA: A SINGLE CENTER RETROSPECTIVE ANALYSIS

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Background. Front line chemoimmunotherapy with R-CHOP in Diffuse Large B Cell Lymphoma (DLBCL) yields a complete response (CR) in 80% of patients (pts). Among those who achieve a partial response (PR), the role of radiotherapy (RT) on single residual PET positive lesion at end of treatment (EOT) evaluation has not been fully evaluated, even if modern studies report encouraging results.

Aims. To evaluate the efficacy of RT on single residual PET positive lesions at EOT evaluation after frontline therapy.

Methods. We included pts aged> 18 years with a diagnosis of DLBCL, both limited and advanced stage, who underwent RT after frontline therapy on a single residual PET positive lesion from 2014 to 2024 at our institution.

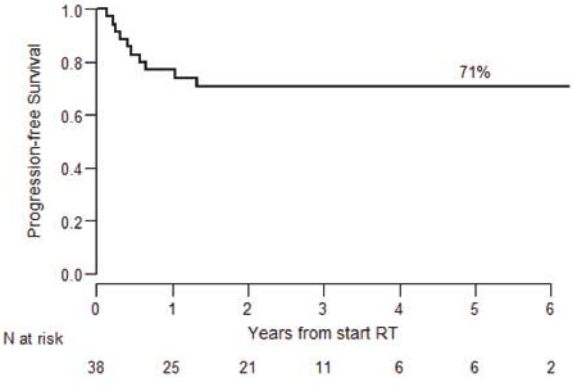

Figure 1.

Results. We identified 38 patients who met the study criteria. Median age at diagnosis was 70 years (range 25-85). Thirteen (34.3%) pts had limited stage disease stage (I-II), 25 pts (65.7%) had advanced (III-IV) stage disease. Most pts (n=35, 92.1%) underwent R-CHOP or R-COMP chemotherapy, 2 pts (5.2%) received R-GMALL (due to high tumor burden) and 1 patient (2.6%) received R-CVP (due to concomitant heart failure at diagnosis). A RT dose of 30-39.6 Gy was delivered to 12 (31.5%) pts and a dose of 40-50 Gy to 26 (68.5%) pts, with 1.8-2.0 Gy per fraction. After a median follow up of 2.1 years (range 0.08-11.1), 28 patients (73.6%) maintained a prolonged clinical response after RT: 17 patients after a PET-proven CR (60.3%), 3 pts after PET-proven SD (7.8%), and 8 pts (21%) not experiencing relapse/progression in absence of a PET scan after RT. Five pts had a progressive disease (PD) at post RT PET scan. At the latest follow up, 7 pts (18,4%) were dead. Among those who achieved CR, only one patient relapsed, and died of disease progression. Among those who did not respond to RT, all pts who had a proved PD died of disease progression, while only 3 pts among those who achieved SD died due to disease progression. Overall survival (OS) and progression-free survival (PFS) at 5 years were 78% and 71% respectively. At univariate analysis, among pts with an available post RT PET evaluation, achieving a CR status was related to improved OS (p=0.02) and PFS (p=0.006), while RT dose wasn't related to outcome.

Conclusions. Our data confirm the curative potential of RT in DLBCL pts with single residual PET positive lesion after front line therapy. A CR to RT predicts for better outcome.

P025

ABSTRACT NOT PUBLISHABLE

P026

INTENSIFIED R-CODOX-M/IVAC THERAPY FOR BIOLOGICALLY UNFAVOURABLE DIFFUSE LARGE B-CELL LYMPHOMA: EFFICACY, TOXICITY, AND CNS RELAPSE

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Background. Diffuse Large B-cell Lymphoma (DLBCL) is a heterogeneous disease. R-CHOP is noncurative in 40% of cases. High-grade B-cell lymphomas may be treated with high dose-intense chemotherapy such as R-CODOX-M/R-IVAC, the most used treatment for Burkitt's Lymphoma.

Aims. To report a monocentric series of patients affected by DLBCL with aggressive features, including a high risk of central nervous system (CNS) involvement, treated with R-CODOX-M/R-IVAC.

Methods. Fourty-six patients with DLBCL were treated in first line with R-CODOX-M/R-IVAC from 2008 to 2023. Treatment inclusion criteria were: eligibility for intensive chemotherapy, ECOG<3, histological diagnosis of DLBCL, at least one unfavorable features: IPI score ≥4; Ki67>90%; non-GC type; Double or Triple Hit Lymphomas (DHL or THL); Double Expressor Lymphoma (DEL). The median age was 52 years (range: 23-63). The median follow up was 49 months. Twenty percent of patients had IPI score ≥4, 45% of patients had a ki67>90%, 80% had Ann Arbor stage 4, 45% of patients had non-CG type, 23% had high risk CNS-IPI. Three patients had DHL/THL; 7 patients had DEL. Three patients had CNS involvement at diagnosis.

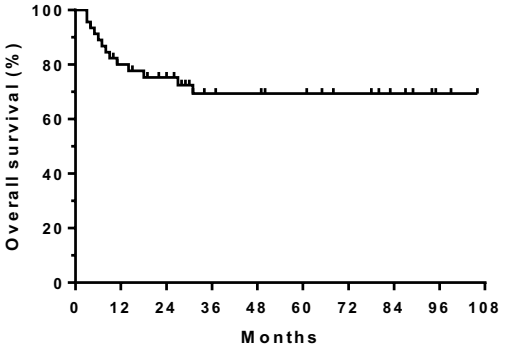

Figure 1.

Results. The most common side effect was mucositis (87%), never > grade 3. Platelets <50.000/mmc was the predominant hematologic toxicity (63% > 10 days). There were not cases of severe

(grade > 2) renal impairment. Only 3 patients discontinued therapy for adverse events (AEs). Treatment-related deaths did not occur. Overall response rate was 89.1% (complete response rate CRR 84.8%). 2-year OS and PFS were 75% and 70%, respectively. No significative differences in 2-year OS were seen according to IPI score (80% *vs* 66% for IPI ≤3 or >3, p=n.s.), non-CG type (79% *vs* 80% for non-CG or GC type, p=n.s.), ki67 (78% *vs* 82% for patients with ki67>90% or lower, p=n.s.), DH/TH (66% *vs* 76% for DH/TH or non-DH/TH, p=n.s.), DEL (83% *vs* 70%, for DEL or non-DEL, p=n.s.). 2-year-OS was inferior for patients aged >55 (57% *vs* 88%, for age >55 or 50 or (71% *vs* 85%, p=n.s.). 1 CNS relapse occurred in a patient who did not exhibit CNS localization at diagnosis.

Summary/Conclusion. R-CODOX-M/R-IVAC results in favourable CRR, OS and PFS irrespective of unfavourable prognostic features, in a manageable toxicity and in effectiveness in preventing CNS relapse. In summary, R-CODOX-M/R-IVAC may be a firstline treatment for patients aged <55 with biologically unfavourable DLBCL.

P027

CLINICAL APPROACH TO DIFFUSE LARGE B CELL LYMPHOMA WITH PERSISTENT POSITRON EMISSION TOMOGRAPHY (PET) POSITIVITY AFTER FRONTLINE TREATMENT: A SUBGROUP ANALYSIS OF THE RETROSPECTIVE OBSERVATIONAL STRIDER STUDY

M. Bisio[1,2], I. Dogliotti[3], V. Peri[2,3], E. Califaretti[4], G. Rovera[4], A. Evangelista[5], L. Legato[1,2], F. Cavallo[3,6], M. Levis[7], M. Clerico[3], C. Consoli[2,3], S. Ragaini[3], B. Botto[1], U. Ricardi[7], B. Bruno[3,6], R. Freilone[1], S.D. Morbelli[4], M. Novo[1]

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Diffuse large B cell lymphoma (DLBCL) is curable in approximately 60% of cases with frontline R-CHOP. Best clinical approach in patients (pts) showing a partial metabolic response [Deauville score (DS) ≥ 4] (PETpos) at the end of frontline treatment (EOT) is unclear. We aimed to analyse the clinical decisions adopted and subsequent outcomes for pts with DLBCL showing PETpos at EOT in the context of the retrospective STRIDER study (full paper in press). An independent radiological revision of all EOT-PET available has been performed. DS classification and quantitative PET parameters such as residual SUVmax and differential SUVmax between baseline and EOT-PET (DSUVmax) have been analysed. Between January 2010 and December 2019 105/403 consecutive pts with newly diagnosed DLBCL treated at AOU Città della Salute e della Scienza di Torino resulted PETpos at EOT. EOT-PET images were available for 41/105 pts, 12/41 pts had progressive disease and were excluded, thus 29 pts were included in the subsequent analyses. Median age was 71 years (62-78), 22/29 (76%) had stage IV, 19/29 (65%) were IPI ≥3, 16/29 (55%) had bulky disease. Nineteen out of 29 pts were DS4 at EOT-PET, 10/29 were DS5 (9 partial responses, 1 stable disease). Among pts with DS4 3 were biopsied on the PETpos lesion none revealing lymphoma disease; 10/19 pts underwent consolidative radiotherapy (RT) (5/10 on initial bulky disease) and 5/10 subsequently progressed or relapsed; 6/19 underwent salvage therapy. Among pts with DS5 2 were observed and both subsequently progressed, 6 underwent RT (5/6 on initial bulky disease) and 3/6 progressed thereafter (all had EOT-PET DSUVmax ≤ 3), 2/10 underwent salvage therapy (both had EOT-PET residual SUVmax > 20). Three-year (y) progression-free survival (PFS) for the 29 pts was 34.1% and 3-y overall survival (OS) was 47.1%. Pts with DS4 showed an improved OS over DS5 pts (3-y OS 55.0% *vs.* 30.0%, p=0.028) and a non-statistical trend of better PFS (3-y PFS 41.5% *vs* 20.0%, p= 0.30). With the limit of a small sample size and the retrospective nature of the study our data confirm the heterogeneity of clinical approaches adopted on DLBCL pts with PETpos at EOT. Consolidative RT may represent a curative option for DS4 cases with bulky disease or focal residual uptake and can be considered for very selected cases of DS5 with high DSUVmax and limited disease while salvage treatment is otherwise recommended for these pts.

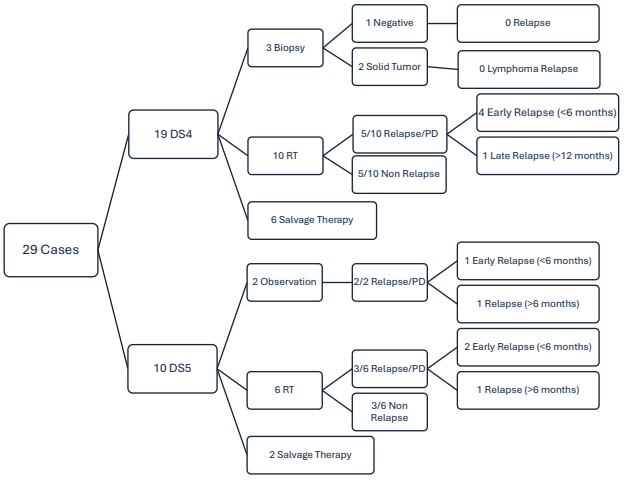

Figure 1.

P028

THE EVALUATION OF THE CYTOKINE PROFILE IN PATIENTS AFFECTED BY B-CELL LYMPHOMAS TREATED WITH CAR-T CELLS CAN PREDICT CELLULAR EXPANSION AND THE ONSET OF ICANS?

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Background. CD19-CAR-T cell therapy has demonstrated remarkable efficacy in patients with B-cell lymphomas, especially in those with greater cellular expansion. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are the main toxicities associated with CAR-T cell therapy.

Aim. The aim of the study is to evaluate the trend of circulating cytokines during CAR-T cell therapy, assessing their association with cellular expansion and neurological toxicity.

Methods. We evaluated all B-cell lymphomas patients treated at our center with commercial CAR-T cells (Axi-cel, Brexu-cel, and Tisa-cel) from December 2021 to March 2024. Circulating cytokine levels (IL-1beta, IL-6, IL-8, TNFα, IL-2RA, IL-10, IP10, IFN-γ, IL-15, Nfl, IL-17, Fractalkine) were measured using a commercial kit on days 0, 4, 7, 10, 14, 21, and 30 post-CAR-T cell infusion. Additionally, CAR-T cells were quantified by flow cytometry. A threshold of 40 CAR-T cells/μL was used to define patients as poor or strong expanders.

Patients. 24 patients were treated with CAR-T cells, including 11 males and 13 females, with a median age of 63 years (range 42-78). 63% (15/24) of patients were affected by diffuse large B-cell lymphoma, 17% (4/24) follicular lymphoma, 12% (3/24) mantle-cell lymphoma, and 8% (2/24) PMBCL. Tisa-cel was infused in 46% (11/24) of cases, Axi-cel in 41% (10/24), and Brexu-cel in 13% (3/24). ICANS was observed in 25% (6/24) of patients, with grade ≥3 in a single case.

Results. Patients defined as strong expanders had higher levels of IL-2RA at the time of infusion (day 0) compared to poor expanders (mean IL-2RA 5120 *vs* 2000 pg/ml, p=0.05). Poor expander patients showed a lower peak of IL-2RA, although it was not significant (p=0.11). Elevated levels of IL-15 and fractalkine on day 0 were correlated with the development of ICANS (p=0.007 and p=0.01, respectively), unlike Nfl and IFN-γ levels (p=0.66 and p=0.56, respectively). Peak levels of IL-15, fractalkine, Nfl, and IFN-γ in the days following infusion were correlated with the development of any-grade neurological toxicity (p<0.0001, p<0.0001, p=0.05, p=0.01, respectively).

Conclusion. The evaluation of the cytokine profile within our cohort of patients with B-cell lymphomas treated with CAR-T cells has proven to be an effective tool in predicting cellular expansion (IL-2RA) and neurological toxicity (IL-15, fractalkine, Nfl, and IFN-γ).

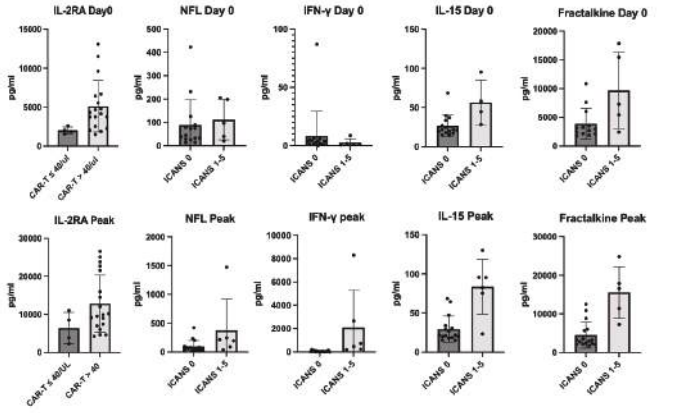

Figure 1.

P029

T CELL IMMUNOGLOBULIN AND ITIM DOMAIN (TIGIT) EXPRESSION IN HODGKIN DISEASE CORRELATES WITH AGE AND ADVANCED STAGE

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TIGIT, an inhibitory receptor present on lymphocytes, has emerged as a promising target for cancer immunotherapy. Recently We demonstrated the presence of TIGIT in the microenvironment of HL (Annibali O et al, Sci. Rep 2021). The aim of this study is to confirm the presence of TIGIT in a larger group of patients and to correlate its expression with clinical characteristics and outcomes (OS and EFS). We also assessed correlations with viral latent infections (EBV and CMV). We evaluated all patients treated for HL from 2010 to 2023 and collected clinical data (age, sex, bulky disease, extranodal sites, B symptoms, and stage). TIGIT expression was determined by immunohistochemical analysis. CMV and EBV viral infection was assessed through IgG and IgM serology at onset moreover the detection of Epstein–Barr encoding region (EBER) and/or Epstein–Barr latent membrane protein 1 (LMP1) in Reed-Sternberg cells was performed. We analyzed a total of 56 patients with a median age at diagnosis of 42 years (range 16-82 years). CMV and EBV serology at diagnosis were available for 38 and 41 patients, respectively. Among them, 32 (84%) tested positive for CMV IgG and 24 (59%) for EBV IgG. Latent EBV infection was investigated in 42 out of the 56 histological samples, with 14 out of 42 (33%) testing positive for one or both markers. Twenty-five (45%) patients showed negative expression of TIGIT in peritumoral lymphocytes, with a score of 0, while 31 patients (55%) exhibited TIGIT positivity. Correlating TIGIT expression with IPS score, B symptoms, and bulky disease revealed no differences among different subgroups. However, TIGIT positivity correlated with the stage of disease at onset: 19 out of 28 (68%) patients in stage III-IV showed TIGIT positivity compared to 12 out of 28 (42%) TIGIT-positive patients in stage I-II (P=.05). Patients were divided into two groups according to age at onset, showing a higher expression of TIGIT (70%) in older patients compared to 38% in younger patients (P=.01). TIGIT expression was not correlated with EBV-positive biopsies and positive CMV serology, but we observed that 20 patients tested positive for both viruses (EBV/CMV), with 70% of them being TIGIT positive. The OS and EFS were 86% and 62% at 67 months of follow-up, respectively, and we observed a trend towards EFS in favor of TIGIT 0 patients (75% *vs.* 53%).In conclusion, our data confirm the presence of TIGIT in HL, showing a correlation with age and advanced stage.

P030

THE CARCHAT PROJECT AND THE REGIONE LAZIO LYMPHOMA NETWORK 'RELLI' HUB-AND-SPOKE MODEL FOR MANAGING CAR-T PATIENTS JOURNEY

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[18]Uosd Ematologia, ASL Roma1; [19]Nuclear Medicine Unit, Department of Medical-Surgical Sciences and of Translational Medicine; "Sapienza" University; [20]Hematology, Department of Biomedicine and Prevention, University Tor Vergata, Italy

Background. CAR-T are innovative immunotherapies representing a significant breakthrough for treating hematologic malignancies. These therapies require careful coordination and a multidisciplinary team effort, from the manufacturing to the administration phases. The emergence of various needs and challenges for enabling pts to be treated has called for creating a regional organization. For these reasons, the RELLI has promoted a pilot organizational project named"CARchaTprogram".

Aims. To optimize the pt journey for CAR-T between hub and spoke centers of the Lazio region, improving access to care, enhancing treatment outcomes, and maximizing the efficient use of healthcare resources.

Methods. The CARchaT project is designed as a region-wide management system pivoting around a hub-and-spoke model. The project is based on the organization of periodic online meetings to discuss pts' cases and treatment plans. A multidisciplinary team composed of haematologists, nuclear medicine physicians and case managers from the various centers attend the meeting. A standardized evaluation form considering the AIFA criteria was used to implement streamlined referral processes.

Results. The CARchaT project started in December 2023 involving 2 CAR-T centers (AOU Umberto 1 and Policlinico A. Gemelli) and 11 hematological referral centers in Lazio. Until 22nd April, we had 7 online meetings, participated by hematologists from all regional centers. Among a total of 20 pts (14 LBCL, 3 FL, 2 PMBCL, 1 MCL) discussed for CAR-T, 15 were eligible for treatment (12 LBCL, 2 PMBCL, 1 MCL) and assigned to CAR-T centers, which confirmed the eligibility in 15/15 (100%) pts. The median time for arranging in-person appointments for eligible pts was of only 5 days. After clinical discussion, 3 pts with R/R FL in 4th line and 2 with R/R DLBCL were considered ineligible, because of less 6 months wash-out from bendamustine and ECOG >2, respectively: for those pts, the team proposed alternative rescue strategies. Furthermore, there was the opportunity to discuss which bridging therapy in 7/14 pts and the treatments outcomes in a pt in PR after 3 months from the infusion.

Conclusion. Considering the increasing number of pts accessing CAR-T therapies, implementing a hub-and-spoke model has helped overcome obstacles and improve success rates and cost-effectiveness. Collegial discussions in regular online meetings are strategic to examine eligible pts and produce a regional waiting list.

P031

GLOBRYTE: A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED TRIAL EVALUATING GLOFITAMAB MONOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA

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There is a high unmet need for new treatment options for pts who do not respond to, or progress through Bruton tyrosine kinase inhibitors (BTKi) therapy. Glofitamab is a CD20xCD3 T-cell-engaging bispecific antibody that redirects T cells to eliminate B cells. A Phase I/II trial of glofitamab monotherapy and obinutuzumab pretreatment (Gpt, 1000/2000 mg) to mitigate the risk of CRS showed high and durable complete response (CR) rates (73.0%) and manageable, mostly low-grade CRS in heavily pretreated pts with R/R MCL (n=37), most of whom had failed prior BTKi therapy (Phillips et al. ASH 2022).The GLOBRYTE study (GO43878) is a Phase III, open-label, multicenter, randomized, controlled trial that will evaluate glofitamab monotherapy in pts with R/R MCL in comparison with an investigator's choice of rituximab + bendamustine (BR) or rituximab + lenalidomide (R-Len). Pts with histologically confirmed R/R MCL who have received ≥1 prior line of systemic therapy (including a BTKi) are eligible for enrollment. Eligible pts will be randomly assigned (1:1) to receive glofitamab or investigator's choice of BR or R-Len. Pts will receive intravenous (IV) Gpt (2000 mg) on Day (D)1 of Cycle (C)1, 7 days prior to the first glofitamab dose. Pts will receive glofitamab for a fixed duration of 12 cycles, unless progressive disease (PD) or unacceptable toxicity occurs earlier. Glofitamab IV will be given on C1D8 (2.5mg), C1D15 (10 mg), and then the target dose (30 mg) on D1 of C2-12 (21-day cycles). Pts randomized to the investigator's choice will receive 375mg/m^2 IV rituximab on D1 in combination with either 90 mg/m^2 IV bendamustine on D1-2 of each cycle (BR for 6 cycles) or 20 mg/day oral lenalidomide on D1-21 of each cycle (R-Len until PD); the cycle length for BR or R-Len is 28 days. Crossover to glofitamab from the investigator's choice is permitted in pts with radiologic confirmation of PD. The primary endpoint is progression-free survival (PFS) determined by an independent review committee (IRC). Secondary endpoints include overall survival (OS), CR rate and duration, safety, health-related quality of life, PK and immune response to glofitamab. An estimated 80 sites globally will enroll approximately 182 pts with R/R MCL. The trial started globally as of October 2023 and has enrolled 17 patients, so far; in Italy, 4 sites have been activated, 1 is still to be opened and 1 patient has started treatment at the present abstract submission.

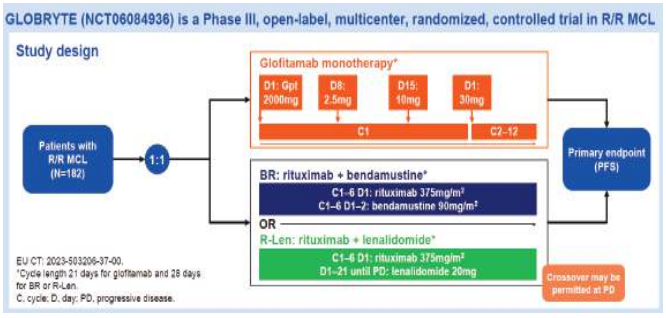

Figure 1.

P032

LIPOSOMAL-ENCAPSULATED DOXORUBICIN SUPERCHARGE-CONTAINING FRONT-LINE TREATMENT IMPROVES RESPONSE RATES IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMBL) AND MEDIASTINAL GRAY ZONE LYMPHOMA (MGZL)

C. Giordano[1], M. Picardi[1], N. Pugliese[1], M. Mascolo[2], S. Varricchio[2], G. Troncone[3], E. Vigliar[3], C. Bellavicine[3], M. Lamagna[1], D. Lisi[1], A. Vincenzi[1], F. Pane[1]

[1]Department of Clinical Medicine and Surgery, Federico II University Medical School; [2]Department of Advanced Biomedical Sciences, Federico II University Medical School; [3]Department of Public Health, Federico II University Medical School, Italy

PMBL and MGZL are characterized by poor prognosis when adequate responses are not rapidly achieved or if the disease recurs. Tumor-infiltrating macrophages (TIMs) are ≥5% staining at immunohistochemical analysis on biopsy specimens of tumor masses, in PMBL and MGZL. Non-pegylated liposomal-encapsulated doxorubicin (NPLD), Myocet, rapidly accumulates within the CD68-positive TIMs acting as slow-release reservoir with prolonged tumoricidal effects. For this reason, in our Hematology Unit of the Federico II University of Naples a retrospective study was conducted on consecutive patients with PMBL or MGZL receiving the R-COMP-Dose intensifiedx6 (DI) scheme from 1 March 2016 to 31 January 2022, with ≥18 and ≤60 years, Ann Arbor stage I-IV, heart Global Longitudinal Strain (GLS) ≥−20% and LVEF ≥50 at baseline echocardiography assessment. The R-COMP-DIx6 schedule consisted of 1-day outpatient intravenous infusions of Myocet™ at an escalated dose of 70 mg/m^2 with dose-intensity for all cycles increased to 140% of standard dosage (<785 mg/m^2, ceiling dose for cardiological toxicity risk) plus rituximab, cyclophosphamide, vincristine and prednisone at standard dosages, at a 3-week interval for a total of six cycles. The primary endpoint was EoT-FDG-PET negativity. Secondary endpoints were hematological and cardiological toxicity and PFS. CD68 stains were scored as 1+ (5% to 25% positive cells observed), 2+ (26% to 50%) and 3+ (>50%) at lymph node microenvironment immunohistochemistry and the optimum cutoff point which correlated with better outcome was explored. A total of 14 patients were enrolled, 9 were PMBL and 5 MGZL (Figure 1).

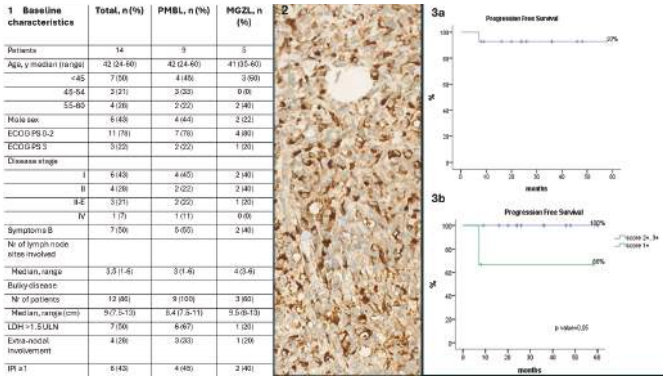

Figure 1.

12 patients received full dose (100%), and two patients (PMBL) received a dose-intensity between 85% and 99%. Complete metabolic remission rate at EoT-PET, was 92.8% (95% CI, 0.5-1.58) since only one patient with PMBL (11%) had positive EoT imaging scans . No patient received consolidation radiotherapy. A complete echocardiography evaluation (GLS and LVEF evaluated at baseline, interim, EoT and 6 months later) was performed: in 3 patients <10% point reduction in values of GLS (and <5% point reductions in values of LVEF) at interim, EoT and/or 6-month follow-up, compared with the median values at baseline (GLS of −21%, LVEF of >50%), was observed. None of the patients required hospitalization to manage treatment-related adverse events (grade 3). At a median follow-up of 24 (range,1-55) months the PFS was 92.8% (95% CI, 52-98) and according to CD68 stains subgroups the 2-year PFS was 66% (score 1+ group) and 100% (score 2+ and 3+ group) respectively (P= .05; Figure 2). This suggests a trend that many TIMs (cutoff point, >25%) had a favorable prognostic impact when R-COMP-DIx6 regimen was administered (Figure 3). Because of the limited number of patients, these results need to be assessed in a larger series.

P033

FIRST INTERIM ANALYSIS OF A REAL-WORLD INTERNATIONAL OBSERVATIONAL STUDY OF MOGAMULIZUMAB IN ADULT PATIENTS WITH MYCOSIS FUNGOIDES AND SEZARY SYNDROME (PROSPER STUDY NCT05455931)

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CTCLs are rare heterogenous group of NHLs that present primarily in the skin as plaques, patches, tumours, or erythroderma. MF and SS are two well-known subtypes of CTCL. Symptom burden in patients can be extensive with pruritis, pain, disfiguring lesions and sleep disturbance being frequently reported and greatly impact HRQoL. In phase 3 MAVORIC study, mogamulizumab, an anti-CCR4 monoclonal antibody, significantly prolonged PFS and significantly improved HRQoL compared to vorinostat. PROSPER aims to evaluate patient-reported changes in disease symptoms and HRQoL following initiation of mogamulizumab in a real-world clinical setting. Using a novel symptom diary, patients rate symptom severity at its worst in last 24-hours using an NRS scale for skin pain, flaking skin, itchy skin, and skin redness weekly for first 16-weeks. Using a 5-point Likert scale, patients also report the frequency of sleep problems and difficulties in body temperature regulation in last 7 days weekly for the first 16-weeks.

Table 1.

Symptom	Baseline	W4	W8	W12	W16
Skin Itch *(0-10)*					
- mean (SD)	6.63 (3.02)	4.44 (2.99)	4.72 (2.65)	4.18 (2.70)	3.88 (2.71)
- *n*	*19*	*16*	*18*	*17*	*17*
Skin Pain *(0-10)*					
- *mean(SD)*	4.00 (3.25)	3.38 (2.39)	3.35 (2.52)	1.82 (1.88)	1.88 (2.13)
- *n*	*19*	*16*	*17*	*17*	*16*
Redness (0-10)					
- *mean(SD)*	6.21 (3.05)	4.27 (2.52)	4.78 (2.67)	3.88 (2.31)	3.29 (2.42)
- *n*	*19*	*15*	*18*	*16*	*17*
Flaking *(0-10)*					
- *mean(SD)*	5.89 (2.92)	3.75 (2.41)	3.89 (2.81)	3.82 (2.32)	3.35 (2.37)
- *n*	*19*	*16*	*18*	*17*	*17*
Sleep problems					
- *Frequently or Every night, n(%)*	10 (55.56)	8 (53.33)	3 (17.65)	5 (29.41)	3 (17.65)
- *n*	*18*	*15*	*17*	*17*	*17*
Regulating body temperature					
- *Frequently or Always, n(%)*	9 (47.37)	3 (20.00)	5 (27.78)	2 (11.76)	3 (17.65)
- *n*	*19*	*15*	*18*	*17*	*17*

Table 1. Patient reported symptom scores at baseline, week 4, week 8, week 12 and week 16.

This first interim analysis presents symptom data for the first 20 patients enrolled for up to 16-weeks of follow-up following treatment initiation, from Italy, UK, Spain, Netherlands and US. Both MF (8) and SS (12) patients were included, 90% with advanced disease at the start of treatment and 65% with blood involvement. At baseline (Table 1), skin itch scored highest followed by skin redness and flaking skin with skin pain scoring lowest. Over 50% of patients reported having sleep problems either frequently or every night while 47% reported difficulties regulating body temperature at baseline. There was improvement for all symptoms within 4 weeks of treatment initiation of mogamulizumab with flaking skin, skin itch, and body temperature regulation showing the most rapid onset of symptom improvement. By W16, symptom severity decreased considerably with greatest improvements in skin redness (-2.92) closely followed by skin itch (-2.75), flaking skin (-2.54) and skin pain (-2.12). At W16 patients reporting sleep problems or difficulties regulating body temperature frequently or always decreased to 17.65%. Patients receiving mogamulizumab in a real-world clinical setting reported high symptom burden at baseline across all 6 symptoms, with approximately half of patients reporting frequent sleep problems and difficulties regulating body temperature. All recorded symptoms showed considerable improvement over the first 16 weeks following initiation of mogamulizumab.

P034

ZUMA-23: A GLOBAL, PHASE 3, RANDOMIZED CONTROLLED STUDY OF AXICABTAGENE CILOLEUCEL VERSUS STANDARD OF CARE AS FIRST-LINE THERAPY IN PATIENTS WITH HIGH-RISK LARGE B-CELL LYMPHOMA

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Introduction. Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved to treat patients (pts) with relapsed/refractory (R/R) LBCL (Large B-cell lymphoma) after demonstrating significant clinical benefit as 2L (ZUMA-7; Locke FL, *et al.* N Engl J Med. 2022) and ≥3L (ZUMA-1; Neelapu SS, *et al.* N Engl J Med. 2017) therapy. In the Phase 2 ZUMA-12 study in pts with refractory 1L LBCL, axi-cel showed durable responses with an objective response rate of 89% (complete response rate, 78%) and an ongoing response rate of 73% (median follow-up, 15.9 mo). ZUMA-23 is the first Phase 3, randomized controlled study to evaluate CAR T-cell therapy as a 1L treatment for any cancer and will assess axi-cel versus standard of care (SOC) in pts with high-risk LBCL (IPI 4-5).

Methods. ZUMA-23 will enroll ≈300 adult pts with high-risk, histologically confirmed LBCL (2016 WHO classification), including diffuse large B-cell lymphoma (DLBCL), HGBL, and transformed lymphoma. Eligible pts after 1 cycle of R-chemotherapy will be randomized 1:1 to receive axi-cel or continue with SOC. Pts in the axi-cel arm will undergo leukapheresis followed by R-CHOP or DA-EPOCH-R as bridging therapy, followed by lymphodepleting chemotherapy (fludarabine/cyclophosphamide), and a single axi-cel infusion (2×106 CAR T cells/kg). Prophylactic corticosteroids may be administered to reduce the incidence and severity of cytokine release syndrome at the investigator's discretion. Pts in the SOC arm will receive 5 additional cycles of R-CHOP or DA-EPOCH-R (investigator's choice). The primary endpoint is event-free survival. Key secondary endpoints are OS and PFS. Key exclusion criteria include LBCL of the central nervous system. ZUMA-23 is open for enrollment (NCT05605899).

P035

TREATMENT WITH 5-AZACITIDINE IN RELAPSED OR REFRACTORY PERIPHERAL T-CELL NON-HODGKIN LYMPHOMAS: A MULTICENTER RESTROSPECTIVE ANALYSIS

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Peripheral T-cell Lymphoma (PTCL) still has a suboptimal response to classical chemotherapy regimen and also common relapses and poor survival rates after progression with a median OS of 5.5 months. Even the use of the anti-CD30 monoclonal-antibody Brentuximab Vedotin has only partially improved the results, since some lymphomas are histologically CD30 negative. As such, the treatment of PTCL is still an unmet medical need.

Table 1.

Table 1. Patients' clinical features

Characteristic	n (%)
Total patients	8
M	7 (88%)
F	1 (22%)
Age	
Mean	64.8 ± 7.3
Median	64.5
Range	60.9 -75.3
Histotype	
Angioimmunoblastic T	5 (63%)
T not otherwise specified	2 (25%)
Follicular T helper	1 (12%)
CD30+	
No	8 (100%)
Ann Arbor Stage	
3	2 (25%)
4	6 (75%)
Extranodal	
Yes	7 (88%)
No	1 (12%)
IPI score	
1	0 (0%)
2	1 (12%)
3	3 (38%)
4	3 (38%)
5	1 (12%)
Previous line of treatment	
1	1 (12%)
2	3 (38%)
3	3 (38%)
>3	1 (12%)
ASCT	
Yes	3 (38%)
No	5 (62%)
HSCT	
Yes	1 (12%)
No	7 (88%)

A few studies showed the potential benefit of a treatment using Azacitidine or other hypomethylating agents in relapsed or refractory (R/R) PTCL, with results varying: some are poor, with a PFS of 8 months, while other are particularly promising, with an overall response rate of 61% and complete response of 48%. The aim of this retrospective study was to analyse the clinical characteristics and outcomes in patients with relapsed or refractory PTCL collected in some Italian centres and authorized by the Internal ethical committee and General affair committee from 2020 to 2024. We collected data of 8 patients who received 5-azacitidine 75 mg/m^2 daily, subcutaneously, for 7 consecutive days, every 28 days, until progression or unacceptable toxicity. All patients showed CD30 negative lymphomas and advanced-stage lymphomas, all but one were extranodal. Five were classified as T angioimmunoblastic, two as T not otherwise specified, one as T–follicular helper. Three patients had undergone a previous autologous stem cell transplant. All clinical features are listed in Table 1. Patients had undergone a median of 3 cycles of treatment, with a range of 1 to 46. The ORR at the first evaluation was 25%. Five out of eight patients died, the median OS was 6.83 months (range 0.67 to 47.03 months). Five out of the eight patients had grade 4 neutropenia, four had adverse effects that required hospitalization, with three of them being for an infectious episode. The overall median PFS was 4.10 months (range, 0.47 to 47.3). Two patients obtained a sustained CR, with a longer PFS compared to the remaining patients (12.47 and 47.03 months, respectively). In conclusion, 5-azacitidine has a therapeutic role in patients with R/R PTCL particularly considering patients who are unable to sustain intensive chemotherapy regimen or are ineligible for treatment with BV. The ORR was not encouraging but our data showed that patients who responded have long duration of response. Furthermore, more data are required to know the feasibility of this treatment.

P036

A RETROSPECTIVE STUDY ON THE USE OF R-COMP IN TREATMENT OF DLBCL PATIENTS: WHEN A SAMPLE IS NOT BIAS SELECTED

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A retrospective study is often burdened by possible case selection bias compared to a prospective study that includes all patients (pts) consecutively. We compare in this study data of a retrospective study (946 pts) with a prospective study (308 pts). The aim of this study was to evaluate from a statistical point of view if the sample of the retrospective study and the sample of pts of the prospective study were drawn from the same population. It was used a statistical test of hypothesis called "Anderson-Darling test", a non-parametric statistical test, and it is used to test whether a number of random samples with possibly different sample sizes may have arisen from the same distribution, where this distribution is unspecified may have arisen from the same distribution, where this distribution is unspecified. The concept of distribution implies the use of a continuous variable in the test. The "overall survival", computed as the difference in months between the follow-up date and the diagnosis date, was employed in the test. The application was done using the statistical software R, specifically the function "ad.test.combined" of the package "kSample". This test is usually useful in analyzing treatment effects in randomized block experiments and in examining performance equivalence of several laboratories when presented with different test materials for comparison. To adapt this use in our scenario, we can assume that the different laboratories (blocks) are our two studies, while as treatment (levels) we used the stage of cancer. The assumption in randomized block experiments is that treatments, in each block, are assigned to samples randomly. For this reason, we chose the stage of cancer as the treatment variable since the stage of the lymphoma can be assumed to be assigned randomly to patients. Finally, as the age could be a confounding variable, we compared the overall survival of patients of age greater than 64. The following results show the outcome of two hypothesis tests. Based on the results we have obtained, in both tests, we can not reject the null hypothesis. Focusing our attention on the second case, we can say that the overall survival of the samples in the two studies comes from the same population, leading us to affirm that the patients of the two studies are similar. In conclusion, this study confirms that the data from the large retrospective study are reliable from a population that is neither positively nor negatively selected.

P037

THERAPEUTIC APPROACH TO PATIENTS WITH EARLY STAGE DIFFUSE LARGE B CELL LYMPHOMA: RETROSPECTIVE, MULTICENTER, REAL-LIFE STUDY OF THE "TUSCAN LYMPHOMA NETWORK

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Introduction. Early stage diffuse large B-cell lymphoma (ES-DLBCL) could represent 25-30% of cases (ES-DLBCL) and it is characterized by excellent prognosis. Treatment strategies include rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) with a similar schedule to that used in advanced stage, or a reduced number of cycles followed by radiation therapy (RT). Due to the lack of agreement about first-line regimen, real-life studies are needed.

Methods. We retrospectively analyzed a cohort of 179 consecutive ES-DLBCL patients, managed in 6 Tuscan onco-hematological centers between 2011 and 2021. All patients received first-line treatment according to the local clinical practice. Treatment regimens include chemoimmunotherapy 4-6 cycles +/- RT as consolidation. Progression-free survival (PFS) was our primary 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).

Results. Median age was 67 years (range 23-88) as represented in Table 1. CT-PET scan was performed at diagnosis for 61.6% of patients. Ann Arbor stage was I and II in 36.8% and 63.2% of patients, respectively. Stage modified (sm) IPI was 0, 1, 2 and ≥3 in 10.6%, 31.3%, 40.2% and 17.9% patients. First-line therapy was R-CHOP or CHOP-like in 88.8% of cases; the remaining cases received low-dose anthracyclines or regimens without anthracyclines. RT as

consolidation was administered to 29.9% of cases. Complete response (CR) rate was 87.2% and only 13.9% had a disease relapse. Median PFS and OS were not reached in the entire cohort. In univariate analysis, inferior PFS and OS were associated with age >75, ECOG 2, first-line regimen other than R-CHOP/CHOP-like, first-line regimen with 3-4 cycles of R-CHOP without RT, IPI 2-3, smIPI 3-4, stage II *vs* I and stage I extranodal *vs* nodal (in these latter two subgroups, only if PET-staged). Interestingly, IPI 2-3 and first-line regimen with 3-4 cycles of R-CHOP without RT were the only 2 prognostic variables for OS in multivariate analysis. After a median follow-up of 48 months, 31 patients died (17.3%) and only 11/179 (6.1%) died due to progressive disease.

Conclusions. We confirm the excellent prognosis for ES-DLBCL patients even if late relapse was possible. R-CHOP for 6 cycles has the same efficacy as R-CHOP for 3-4 cycles followed by RT as consolidation, while an abbreviated strategy without RT showed worse prognosis.

Table 1.

Characteristic	Number of patients
M	52% (n = 93)
F	48% (n = 86)
Age (range)	**23 – 88 years**
Median	67 years
< 65	44.1% (n = 79)
65-75	33% (n = 59)
≥ 75	22.9% (n = 41)
ECOG	**n = 165**
0	50.3% (n = 83)
1	41.2% (n = 68)
2	8.5% (n = 14)
PET-staged	61.6% (109/179)
Ann Arbor stage	
I/IE	12.2% (n = 22) /24.6% (n = 44)
II/IIE	34.1% (n = 61) /29.1% (n = 52)
IPI	
0	17.3% (n= 31)
1	58.6% (n= 105)
2	21.2% (n= 38)
3	2.9% (n= 4)
SmIPI	
0	10.6% (n = 19)
1	31.3% (n = 56)
2	40.2% (n = 72)
3	16.2% (n = 29)
4	1.7% (n = 3)
GCB	59.5% (75/126)
nonGCB	40.5% (51/126)
Double hit	1.7% (2/121)
Double expressor	33.1% (40/121)

P038

IDENTIFICATION OF AN ONCOSUPPRESSIVE SERUM THREE-MIRNA SIGNATURE AS A PREDICTIVE BIOMARKER AND POTENTIAL THERAPEUTIC TARGET IN DIFFUSE LARGE B-CELL LYMPHOMA

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Diffuse large B-cell lymphoma (DLBCL) is an aggressive hematological malignancy. Despite the R-CHOP immunochemotherapy, ≈35% of patients are refractory/relapsing. Up to date, none of the prognostic factors such as genomic alterations, gene expression profiles as well as the international prognostic index can entirely predict treatment response. MiRNAs, small non-coding RNA with an epigenetic function, impact on several cancer processes including drug resistance. They are deregulated both in tumor tissues and patient blood. We previously identified the serum miR-22-3p as a circulating prognostic biomarker being its levels related to patient survival, supporting the usefulness of miRNAs as non-invasive biomarkers candidates. Thus, the identification of new prognostic biomarkers as a useful source of information that might complement the existing ones currently in use, is demand. Here we show the identification, by a genome-wide approach, of a three-serum miRNAs signature, as differentially expressed according to treatment response. Depending on the tumor context, each member of the signature can act as well as an oncomiR or oncosuppressor. Moreover, everyone is scarcely studied in the DLBCL setting, representing a novelty in the liquid biopsy field. We found that the overexpression of these miRNA signature induced a proliferation decrease in the GCB-COO DLBCL but not in ABC subtype. Moreover, in GCB double-hit cMYC and Bcl2 translocated cells, only two out of three miRNAs have an antiproliferative effect. These data suggest an oncosuppressive role of the signature depending both on the COO and the genetic tumor context. Moreover, by in silico target analysis, we found novel direct targets of each miRNA of the signature. Of note, all of them belong to a protein interaction network which is related to the redox homeostasis. The biological processes involved in redox homeostasis are frequently altered in DLBCL and are reported to impact on tumor cell survival and response to treatment. Altogether, these data show the potential value of a restricted miRNA signature as non-invasive predictive biomarker in DLBCL. Moreover, its oncosuppressive role suggests a possible application for miRNA-based therapeutic approaches, particularly in the GCB-DLBCL subtype.

P039

CEREBROSPINAL FLUID INVESTIGATION IN DIFFUSE LARGE B-CELL LYMPHOMAS AT DIAGNOSIS: STILL AN USEFUL PROCEDURE?

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Background. Central nervous system (CNS) involvement in patients with diffuse large B-cell lymphoma (DLBCL) is a rare condition associated with poor outcomes. It is not clear which criteria may be used to identify patients with higher risk of leptomeningeal involvement at diagnosis or those at highest risk of late CNS relapse.

Methods. In this study, to evaluate the risk of CNS recurrence, we collect data on patients with DLBCL who received a diagnostic lumbar puncture. From 2008 to 2023, we performed 215 new diagnosis of DLBCL. Of those, 87 (40%) received, according to CNS-IPI, a diagnostic lumbar puncture. Old patients or those with significant comorbidities (UNFIT or FRAIL patients) were excluded. Median age was 61 years (range 27-78). In our population, 13 patients (15%) had a very low IPI (0-1); 23 (27%) a low IPI (2); 33 (38%) an high IPI (3) and 17 patients (20%) a very high IPI (4-5). According to CNS-IPI, 20 patients (22.9%) had a low risk (CNS-IPI 0-1); 47 patients (54%) an intermediate risk (CNS-IPI 2-3) and 19 patients (21.8%) an high risk (CNS-IPI 4-6). Prophylaxis with methotrexate (intrathecal administration, high dose therapy or both) was carried out in 40 patients (45%) according to CNS-IPI risk. CSF immunophenotype resulted negative in all patients except for 1 patient, morphology was positive in 2 patients and chemical-physical examination showed cellularity over 10 elements in only 1 but with a negative morphology. A systemic relapse was reported in 17 patients (19.5%) and a CNS relapse was reported in 3 patients (3.44%). Patients who relapsed in CNS received prophylaxis, 2 with intrathecal methotrexate and the other with high dose methotrexate at the end of R-CHOP. OS, with a median follow-up of 32 months, was 76% while PFS, with a median follow up of 25 months, was 63%. Our results showed that CNS-IPI is statistically associated with an higher risk of systemic relapse (p:0.013) but not with an increased risk of CNS relapse (p:0.062). CSF immunophenotype, morphology and chemical-physical exam are not associated with CNS relapse.

Summary/Conclusion. Our results, in line with literature data, confirm a low incidence of CNS relapse (3.5%) and show that CSF analysis at diagnosis is not predictive of future recurrence in CNS and it is not indicated in staging work-up. More studies are needed to evaluate new parameters to predict CNS relapse and to identify patients who really benefit from a CSF analysis at diagnosis.

P040

BRENTUXIMAB VEDOTIN (BV) COMBINED WITH BENDAMUSTINE SUPERCHARGE (BS), A LOW-TOXICITY AND EFFICIENT SALVAGE REGIMEN FOR EARLY REFRACTORY, LATE REFRACTORY OR FIRST-RELAPSED CLASSIC HODGKIN LYMPHOMA: LONG-TERM RESULTS OF A RETROSPECTIVE MONOCENTER STUDY

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Salvage treatment with high-dose chemotherapy and autologous stem cell transplantation (ASCT) is the best course of action for patients with refractory or relapse (R/R) classical HL to first-line therapy with ABVD. We carried out a retrospective study enrolling all patients (18-60 years) with CD30+ c-HL at first R/R receiving four 3-week courses of sequential Bv and Bs (Bv+Bs21) as first salvage regimen. The primary endpoint was OS and secondary endpoints were PFS, response to treatment and safety and PBSC mobilization. 35 patients with R/R c-HL receiving the Bv+Bs21 regimen from 1 September 2013 and 1 September 2023 at a median time of 6 months (range 2-67) since diagnosis were enrolled (Table 1 and Figures 2 and 3).

Table 1. Patients characteristics at Bv-Bs start. Refractory patients, late primary refractory patients and relapsed patients.

Characteristics at Bv-Bs start	n	%
Total population	35	100
Age, median (range)	37 (19-60)	
Male sex, n (%)	18	51
Characteristics of disease		
Hystological subtype		
nodular sclerosis	28	80
mixed cellularity	6	17
lymphocyte rich	1	3
≥3 nodal sites involved	22	63
Extranodal involvement	5	14
Mediastinal bulky	8	23
Bone marrow involvement	1	3
LDH > normal limits	11	31
ESR > 50	15	43
Ann Arbor/Cotswold staging		
I-II	12	34
III-IV	23	65
B symptoms	19	54
Frontline ABVD n°cycles received		
2	10	34
6	25	66
Response to frontline ABVD		
Primary refractory	24	69
early PR	10	29
late PR	14	40
Relapsed	11	31
CR<3ys	6	17
CR>3ys	5	14

Induction treatment consisted in ABVD: 10 patients were early primary refractory (EPR) progressing after 2 cycles according to the interim FDG-PET, 14 patients were late primary refractory (LPR) after 6 cycles according to EOT FDG-PET, and finally 11 patients relapsed after 6 cycles at a median time of 29 months from EOT. All patients received 4 courses of Bv+Bs21 as 3-day outpatient i.v of 1.8 mg/kg Bv on Day 1 and bendamustine (day 2 and 3) at a fixed dose of 120 mg/m^2/day i.v and were all routinely prophylaxed with methylprednisolone at 200 mg i.v, diphenhydramine at 50 mg i.v and febuxostat at 80 mg orally on days 1 to 5 and with peg-filgrastim 6 mg s.c on day 6. The median-dose intensity was 100% (range, 88.6%-102.4%) for Bv and 100% (range, 88.7%-102.4%) for Bs. Finally, 29 patients (82.8%) obtained a complete metabolic remission (CMR) and 6 a partial remission (PR) with an ORR of 100%. Thirty-five (100%) patients underwent PBSC mobilization (after 2 courses of Bv+Bs21) with a median CD34+ cells/kg yield of 3.8×106 (per-

formed with GCSF and endoxan or plerixafor, if necessary); 31 (89%) proceeded to ASCT but four refused. With a median FUP of 56 months from Bv+BS21, the overall 5-year OS rate was 89% (100% for EPR patients, 81% for LPR and 90% for those relapsing): 4 died at a median time of 15 months with 3 patients in CMR (1 death for ASCT-related infection, 1 for committed suicide, 1 secondary neoplasm) and 1 for disease progression. The overall 3-year PFS rate at median FUP of 36 months was 77% (100% for EPR, 72% for LPR, 60% for relapses). The most common grade 3-4 extra-hematologic toxicity was CMV reactivation with viremia and fever (5 patients) successfully treated with preemptive valganciclovir except for one grade 5 (CMV-related pneumonia). Our OS and PFS results are consistent with data reported on the same subset of patients from La-Casce (3-y OS of 92% and 3-y PFS of 60.3%) and Broccoli (3-y OS of 88.1% and PFS of 67% [median FUP: 23 months]). Our study reported not only longer FUP data but better results were specially recorded in the EPR patients (5-y OS of 100%) demonstrating that an earlier (at interim) salvage regimen with Bv+Bs21 and ASCT can obtain excellent outcome in first R/R cHL patients.

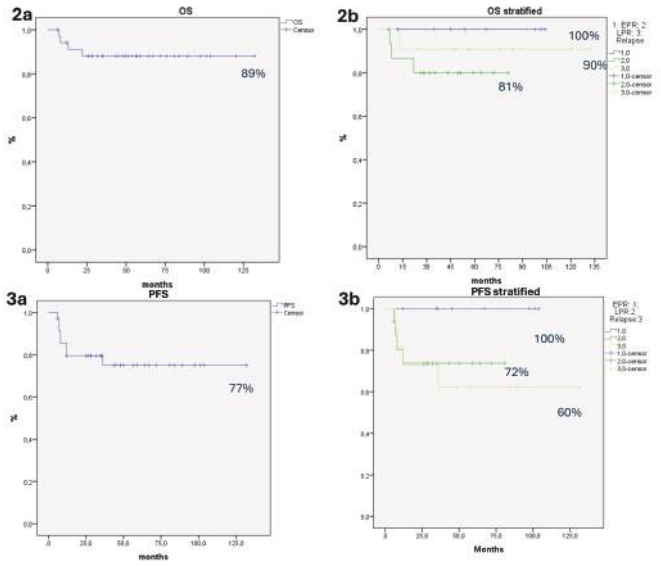

Figure 2a. Total population OS; Figure 2b Subgroup Os stratified for early primary refractory patients, late primary refractory patients and relapsed patients; Figure 3a. Total population PFS; Figure 3b Subgroup PFS stratified for early primary refractory patients, late primary refractory patients and relapsed patients.

P041

R-DA-EPOCH AS FRONTLINE TREATMENT FOR AGGRESSIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL). A SINGLE CENTRE EXPERIENCE

G. Francia[1], E. Montanari[1], C. Salvetti[2], M. Schirru[1], E. Fioribello[1], F. Santoro[1], A. Incorvaia[1], C. Martellossi[1], E. Granero[1], F. Guolo[1,2], A. Todiere[2], F. Ballerini[2], R.M. Lemoli[1,2]

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Background. Diffuse Large B-cell Lymphoma (DLBCL) is the most common large B-cell Lymphoma. Unfortunately, only 60% of DLBCL can be cured with standard therapy and patients with aggressive features (such as mutation in c-MYC, BCL2 or BCL6, elevated proliferation index (i.e. Ki67), ABC type and high IPI score) have a poor outcome. CALGB 503 randomized study show no survival advantage of R-DA-EPOCH over R-CHOP in DLBCL, but most of the patients enrolled had favorable prognostic features. The aim of our study is to investigate the tolerability and efficacy of R-DA-EPOCH regimen in patients with DLBCL with poor prognostic factors.

Methods. We have retrospectively analyzed the outcome of 50 patients affected by DLBCL and treated in first line with R-DA EPOCH from 2016 to 2023. The median age was 62 years (range: 33-74 years) and the median FUP was 40.5 months. 40% of patients had more than 65 years, 52% had Ann Arbor stage IV, 46% had a ki67>90%, 54% were ABC type. CNS IPI and IPI score were high (>3) in 62% and 24% of patients, respectively. Only 3 patients had double/triple hit lymphoma.

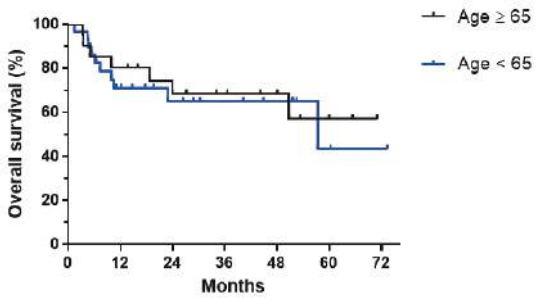

Figure-1:-Overall-Survival-according-to-age.¶

Figure 1.

Results. Therapy was well tolerated, also among older patients: nine patients needed hospitalization for adverse events and no treatment-related deaths were recorded. Only one patient died during treatment due to disease progression, while 96% of patients (47/50) were able to receive at least one dose escalation. The ORR was 82% (with a CRR 76%) and the OS and PFS at 2 years were 76.5% and 67%, respectively. No differences in 2-years OS were seen according to age (73% *vs* 71%, for patients with ≥ or<65 years, Figure 1), elevated IPI score (72% *vs* 83% for IPI ≥ 3 and<3), elevated CNS-IPI score (79% *vs* 77% for CNS-IPI ≤ 3 or > 3), cell-of-origin (75% for both GC type and non-GC type), advanced stage (72% *vs* 82% for stage IV or lower) and very high ki67 (81% *vs* 69% for patients with ki67 ≥ or<90%). P-value were n.s. in all subgroups.

Discussion and conclusions. Our data showed that R-DA-EPOCH is well tolerated and results in a favorable CRR, despite the unfavorable characteristics of our cohort, and the adverse prognostic features analyzed didn't impact on CRR or OS. Notably, the regimen was effective and feasible also in older patients, usually considered ineligible to intensive therapy. In conclusion, R-DA-EPOCH may be a good backbone chemotherapy for patients with aggressive DLBCL which may be further improved in the future with the inclusion of novel targeted agents.

P042

R-DA-EPOCH AS FRONTLINE TREATMENT FOR DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) WITH POOR PROGNOSTIC FACTORS: A SINGLE CENTRE EXPERIENCE

G. Francia[1], E. Montanari[1], C. Salvetti[2], M. Schirru[1], E. Fioribello[1], F. Santoro[1], A. Incorvaia[1], C. Martellossi[1], E. Granero[1], F. Guolo[1,2], A. Todiere[2], F. Ballerini[2], R.M. Lemoli[1,2]

[1]Clinic of Hematology, Department of Internal Medicine (DiMI),

University of Genoa; [2]Department of Oncology and Hematology (DIPOE), IRCCS Ospedale Policlinico San Martino, Italy

Background. Diffuse Large B-cell Lymphoma (DLBCL) is the most common large B-cell Lymphoma. Unfortunately, only 60% of DLBCL can be cured with standard therapy and patients with aggressive features (such as mutation in c-MYC, BCL2 or BCL6, elevated proliferation index (i.e. Ki67), ABC type and high IPI score) have a poor outcome. CALGB 503 randomized study show no survival advantage of R-DA-EPOCH over R-CHOP in DLBCL, but most of the patients enrolled had favorable prognostic features. The aim of our study is to investigate the tolerability and efficacy of R-DA-EPOCH regimen in patients with DLBCL with poor prognostic factors.

Methods. We have retrospectively analyzed the outcome of 50 patients affected by DLBCL and treated in first line with R-DA EPOCH from 2016 to 2023. The median age was 62 years (range: 33-74 years) and the median FUP was 40.5 months. 40% of patients had more than 65 years, 52% had Ann Arbor stage IV, 46% had a ki67>90%, 54% were ABC type. CNS IPI and IPI score were high (>3) in 62% and 24% of patients, respectively. Only 3 patients had double/triple hit lymphoma.

Results. Therapy was well tolerated, also among older patients: nine patients needed hospitalization for adverse events and no treatment-related deaths were recorded. Only one patient died during treatment due to disease progression, while 96% of patients (47/50) were able to receive at least one dose escalation. The ORR was 82% (with a CRR 76%) and the OS and PFS at 2 years were 76.5% and 67%, respectively. No differences in 2-years OS were seen according to age (73% *vs* 71%, for patients with ≥ or<65 years, Figure 1), elevated IPI score (72% *vs* 83% for IPI ≥ 3 and<3), elevated CNS-IPI score (79% *vs* 77% for CNS-IPI ≤ 3 or > 3), cell-of-origin (75% for both GC type and non-GC type), advanced stage (72% *vs* 82% for stage IV or lower) and very high ki67 (81% *vs* 69% for patients with ki67 ≥ or<90%). P-value were n.s. in all subgroups.

Discussion and conclusions. Our data showed that R-DA-EPOCH is well tolerated and results in a favorable CRR, despite the unfavorable characteristics of our cohort, and the adverse prognostic features analyzed didn't impact on CRR or OS. Notably, the regimen was effective and feasible also in older patients, usually considered ineligible to intensive therapy. In conclusion, R-DA-EPOCH may be a good backbone chemotherapy for patients with aggressive DLBCL which may be further improved in the future with the inclusion of novel targeted agents.

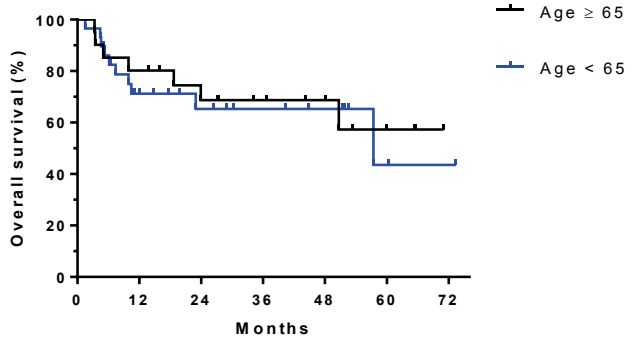

Figure 1.

P043

ABSTRACT NOT PUBLISHABLE

Acute leukemia

P044

β3-AR ANTAGONIST SR59230A REPROGRAMS LIPID METABOLISM IN T-ALL AND FLT3-MUTATED AML BY TARGETING CD36: A NOVEL THERAPEUTIC STRATEGY

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Background. Several recent studies have shown that Beta-adrenergic receptors (β-ARs) sustain the pathogenesis of various malignant cancers. Furthermore emerging evidences demonstrated the potential therapeutic role of a selective β3-AR antagonist (SR59230A) which exhibits a direct anti tumor activity. β3-AR is also involved in the regulation of lipid metabolism and glucose homeostasis in cancer cells. Therefore, high levels of β3-AR in different T-ALL subset and in FLT3-mutated AML cells reveals a promising therapeutic target for not-responder. Despite SR primary action on β3-ARs it also exhibits an off-target effect on lipid metabolism, potentially by down-regulating the fatty acid uptake glycoprotein CD36.

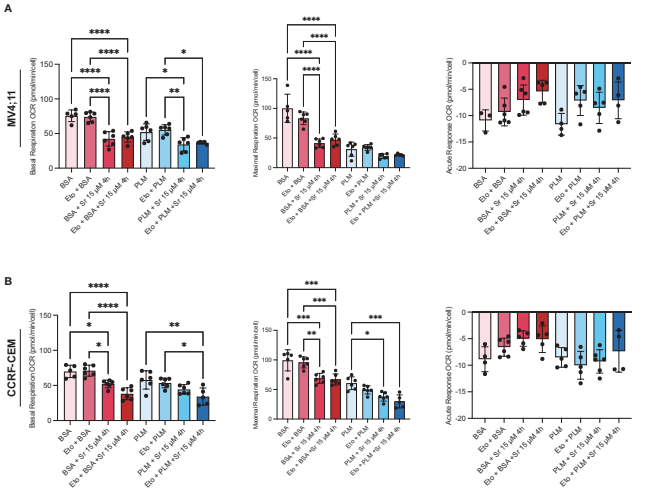

Figure 1.

Aims. This study aimed to identify novel targets for innovative therapies, which are strictly needed to overcome resistance in hematological malignancies.

Methods. Cytofluorimetric analysis of β3-AR and CD36 expression levels was assessed in normal peripheral blood mononuclear cells (PBMCs), T-ALL and FLT3-mutated acute myeloid leukemia (AML) cell models. The metabolic profile after administration of SR59230A (SR), were examined in these cell models through the Seahorse XFe Analyzer. Cell viability was evaluated using MTS assay.

Results. Our findings revealed a significant upregulation of β3-AR expression in T-ALL Molt-3 (40%), in Molt-4 (63%), in CCRF-CEM (75%) and in FLT3-mutated MV4;11 (92%) cellular models when compared to healthy PBMCs (4-7%). This made these cells a good target for treatment with SR. The MTS assay showed a decrease

in cell viability in a dose-dependent manner, but it was more effective when cells were starved and supplement with carnitine. Analysis of fatty acid oxidation (FAO) conducted through the Seahorse XFe Palmitate Oxidation Stress Test after 4h starvation and treated with SR revealed a decrease in endogenous FAO in MV4;11 ($p<0.0001$) and a decrease in both endogenous ($p=0.0001$) and exogenous ($p=0.05$) FAO in CCRF-CEM, suggesting a possible off-target of SR (Figure 1). Cytofluorimetric analysis of CD36 after stimulation with BSA/Palmitate revealed a decrease of 50% in CD36 expression after 4h of treatment with SR.

Conclusions. These results indicate a possible off-target action of the ADRB3 receptor antagonist on the lipid metabolism of T-ALL and FLT3-mutated AML cells, leading to metabolic reprogramming. Moreover, the common response of these models suggests a possible common mechanism that would be worth investigating.

P045

USE OF PRIMARY PROPHYLAXIS WITH G-CSF IN ACUTE MYELOID LEUKEMIA PATIENTS UNDERGOING INTENSIVE CHEMOTHERAPY DOES NOT AFFECT QUALITY OF RESPONSE

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Intensive chemotherapy remains the gold standard for achieving remission in Acute Myeloid Leukemia (AML). However, myelosuppression-related complications, particularly infections, contribute to prolonged hospitalization, morbidity, and mortality. Granulocyte-colony stimulating factor (G-CSF) plays a crucial role in increasing myelopoiesis and may be helpful to shorten neutrophil recovery. While some studies, including randomized, have shown its safety on long-term outcomes of AML, numerous controversies still exist on its effectiveness and clinical value, especially in patients undergoing induction therapy. In fact, some studies even suggest its potential ability to promote AML blasts *in vitro*. Besides, the 2022 ELN guidelines do not recommend routine G-CSF use. In this retrospective study, we evaluated 112 consecutive AML patients treated with intensive chemotherapy at the Hematology Unit of Policlinico Tor Vergata in Rome between January 2014 and December 2023. G-CSF was administered to 31 out of 112 patients from day +8 until achievement of an absolute neutrophil count (ANC) $>1x10^9$/L. We analyzed incidence of neutropenia, its severity and duration, as well as hospitalization duration (HD), incidence of febrile neutropenia and septic shock, intravenous antibiotic therapy (ABT) and antifungal therapy (AFT) duration, complete remission (CR) and relapse rates, overall survival (OS), and minimal residual disease (MRD) negativity rate after the first consolidation cycle in CR patients. Our results showed that the G-CSF group and non-G-CSF group were comparable in terms of sex, age, and ELN risk classification (Table 1). CR was achieved in 69% of patients, of whom 60% experienced relapse. Patients treated with G-CSF had a significantly shorter neutropenia phase (ANC$<0.1x10^9$/L: 12 *vs.* 16 days, $p=0.002$; ANC$<0.5x10^9$/L: 18 *vs.* 24 days, $p<0.001$; ANC$<1x10^9$/L 21 *vs.* 28 days, $p<0.001$) and HD (38 *vs.* 41 days, $p=0.041$). Finally, no significant differences were noticed in ABT or AFT duration, septic shock, CR rate (73% *vs.* 67%), 3-year OS (34% *vs.* 33%) or MRD negativity rate (30% *vs.* 47%) between patients receiving G-CSF or not. In conclusion, our findings support G-CSF safety, with no detrimental impact on response quality or duration. The potential benefits of reducing hospitalization and neutropenia duration highlight G-CSF's value in clinical practice, encouraging a broader utilization in AML patients undergoing induction chemotherapy.

Table 1.

	Patients treated with intensive chemotherapy 2014-2023 (n=112)		
	G-CSF (n=31)	n-G-CSF (n=81)	p value
Sex (%) Male Female	 13 (41.93) 18 (58.06)	 45 (55,56) 36 (44,43)	 0.21
Age at diagnosis, median	57	57	0.68
2022 ELN risk group (%) Favorable Intermediate Adverse Not assessable	 5 (16.12) 14 (45.16) 8 (25.8) 4 (12.9)	 16 (19.75) 43 (53.08) 19 (23.45) 3 (3.7)	 ref. 0.94 0.65 1
HD in days, median	38	41	**0.041**
Duration of ANC < 0.1 x 109/L in days, median	12	16	**0.002**
Duration of ANC < 0.5 x 109/L in days, median	18	24	**< 0.001**
Duration of ANC < 1 x 109/L in days, median	21	28	**< 0.001**
ABT duration in days, median	15	18	0.12
AFT therapy duration in days, median	0	0	0.89
Septic shock, %	9.6	12.3	1
CR, %	73.3	67.1	0.64
MRD negativity, %	30	47	0.35
Relapse, %	61	60	1
OS at 3 years, %	34.4	32.6	0.3

Legend: G-CSF, granulocyte - colony stimulating factor; ELN, European LeukemiaNet; HD, duration of hospitalization; ANC, absolute neutrophil count; ABT, antibiotic therapy; AFT, antifungal therapy; CR, complete remission; MRD, minimal residual disease; OS, overall survival.

P046

FLT3-ITD MUTATION: TIME FOR MOLECULAR RISK STRATIFICATION IN ACUTE PROMYELOCYTIC LEUKEMIA?

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Background. Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia with a distinctive molecular pathophysiology and clinical manifestations. ATRA and ATO therapy has improved the outcome of APL patients (pts). The long-term survival rate is now greater than 95, yet refractory/relapsed disease is still seen in around 5% of pts. A high white blood cell (WBC) count ($>10\times10^9$/L) is supposed to be the main factor associated with relapse. The Sanz score subdivides APL pts according to peripheral blood counts into three risk groups. The most suitable parameters for risk stratification in APL are still under debate. FLT3-ITD mutations have a significant incidence rate of about 12-38% in APL. The role of FLT3-ITD mutations in APL as a prognostic factor has not yet been clarified, and the significance of these genetic alterations remains controversial.

Purpose. In this monocentric study, we investigated the impact of FLT3-ITD mutations on relapse-free survival (RFS) and overall survival (OS) of newly-diagnosed pts with APL treated with all-trans retinoic acid and arsenic trioxide.

Methods. The study was based on 25 newly-diagnosed APL pts (13 male and 12 female, median age 50 years, range 15-83 years) The FLT3-ITD mutation was assayed by PCR and gel electrophoresis

analysis. Its impact on RFS and OS was investigated in pts with and without the mutations.

Results. The FLT3-ITD mutation rate in newly-diagnosed APL pts was 40% (10/25). The WBC count at diagnosis in pts with mutations was higher than that in pts without mutations and the FLT3-ITD mutation rate was significantly higher in the high-risk group than in the low/intermediate-risk group (P= 0.001). Pts with FLT3-ITD mutations had a significantly higher early death rate (40% *vs* 0%) than those lacking the mutation (P =0.007), all of them showed PML-RARA transcript bcr3 and a high WBC count. OS analysis showed a significant difference between the pts stratified by FLT3-ITD mutation status (P =0.007) while survival outcome in terms of RFS did not differ significantly in our study.

Conclusion. Our study confirms that APL pts with FLT3-ITD mutations showed a higher WBC count than pts with FLT3 wild-type. Pts carrying mutations had a higher early death rate compared to those without mutations and reduced OS rates. Prospective trials should further investigate the clinical impact of the FLT3-ITD mutation aiming to evaluate whether this parameter might be included in risk stratification in APL.

Table 1.

Table 1. Baseline demographics and clinical characteristics of 25 APL patients.

Characteristics	Patients (N = 25)
M/F	13/12
Age at APL diagnosis (years), median (range)	50 (15 - 86)
Sanz risk, n (%)	
Low	9 (36.0)
Intermediate	6 (24.0)
High	10 (40.0)
FLT3-ITD status, n (%)	
Wild-type	15 (60.0)
Mutated	10 (40.0)
PML RARα transcript type, n (%)	
Bcr1	15 (60.0)
Bcr2	0
Bcr3	10 (40.0)

P047

GEMTUZUMAB OZOGAMYCIN PLUS 3 + 7 IN UNTREATED ACUTE MYELOID LEUKEMIA PATIENTS: UPDATES ON A REAL-LIFE EXPERIENCE

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Background. Gemtuzumab-ozogamycin (GO) is approved in combination with high-dose chemotherapy (3+7) 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.

Methods. A total of 31 fit low- and intermediate-risk AML patients treated with GO-based plus chemotherapy were retrospectively included in this real-life multicenter study, and results were compared with a control cohort treated with 3 + 7 alone.

Results. Complete remission (CR) rate after induction was 77%, and most responders (45%) underwent two GO-based consolidation cycles. Minimal residual disease (MRD) negativity was observed in 17 cases (55%) after the end of consolidation. Low genetic risk was associated with increased CR rate compared with intermediate-risk AML (88% *vs.* 33%; p<0.001), as well as prolonged overall survival (OS; hazard ratio, 0.16; 95% confidential interval, 0.02-0.89; p<0.001). Moreover, GO addition resulted in a survival benefit for low-risk AML (median OS not reached *vs.* 25 months; p=0.19) while not for intermediate-risk subjects (10 *vs.* 13 months; p=0.92), compared with the control group. Finally, GO-treated patients experienced fever of unknown origin or sepsis (42% or 36% of cases, respectively, with one death during induction due to septic shock) with similar rates compared to the control group (p=0.3480 and p=0.5297, respectively). No cases of veno-occlusive disease after allogeneic transplantation were observed.

Conclusions. In conclusion, our real-life multicenter study confirmed GO-based treatment efficacy with high MRD negativity rates in fit newly diagnosed untreated AML patients, especially in those with low genetic risk, with a less significant benefit in intermediate-risk AML. Infections could be frequent, because of chemotherapy-induced neutropenia, and require prompt clinical management.

Table 1.

Characteristics	GO-treated N = 31	Control N=15	P value
Median age, years (range)	50 (19-68)	59 (46-68)	0.2
Gender, n (%)			0.11
Male	13 (42)	10 (67)	
Female	18 (58)	15 (33)	
ELN risk stratification, n (%)			0.1
Low	22 (71)	7 (47)	
Intermediate	9 (29)	8 (53)	
AML type, n (%)			0.2
NPM1 mutated	15 (48)	5 (27)	
FLT3 mutated	2 (6)	1 (7)	
inv(16)	4 (12)	2 (13)	
t(8;21)	1 (3)	2 (13)	
BM blasts, % (range)	58 (17-90)	69 (22-90)	0.36
Induction, n (%)			0.5
3+7	30 (97)	15 (100)	
2+5	1 (3)		
CR post-induction, n (%)	24 (77)	11 (73)	0.52
Consolidation cycles, n (%)			0.15
0	3 (10)		
1	6 (20)	5 (27)	
2 – only one with GO	4 (13)		
2 – both with GO	14 (45)		
Others	4 (13)		
≥2 without GO	-	6 (40)	
Allogenic HSCT, n (%)	8 (26)	5 (33)	0.4
Autologous HSCT, n (%)	1 (3)	5 (33)	0.03
Refractory/Relapsed, n (%)	11 (35)	4 (27)	0.31
Median OS, months (range)	N.R. (1-32)	19 (4-83)	0.23
1-year OS, %	77	72	
Safety, n (%)			0.1
Neutropenia with FUO	13 (42)	9 (60)	
Sepsis	11 (36)	7 (47)	
Pneumonia	1 (3)	2 (13)	
Typhlitis	1 (3)	-	
Persistent thrombocytopenia	1 (3)	-	
Death due to toxicity	1 (3)	-	
MRD monitoring, n (%)			0.47
Flow cytometry	11 (35)	6 (40)	
Low-risk AML	3 (27)		
Intermediate-risk AML	8 (73)		
Real-time PCR	20 (65)	9 (60)	
Low-risk AML	19 (95)		
Intermediate-risk AML	1 (5)		
MRD post-consolidation, n (%)			0.4
Negative	17 (55)	8 (53)	
Flow cytometry	4 (36)		
Real-time PCR	11 (55)		
Positive	7 (23)	3 (20)	
Flow cytometry	4 (36)		
Real-time PCR	5 (25)		
Not available	7 (23)	4 (27)	
Flow cytometry	3 (27)		
Real-time PCR	4 (20)		

P048

USE OF GRANULOCYTE GROWTH FACTOR (G-CSF) IMPROVES SURVIVAL OF PATIENTS UNDERGOING VENETOCLAX HYPOMETHYLATING THERAPY IN A MONOCENTRIC EXPERIENCE

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Hypomethylating agents (HMA) and venetoclax (Ven) are the golden standard treatment of AML patients aged >75 years or unfit for intensive chemotherapy. We analyzed the characteristics and outcomes in terms of overall and event-free survival (OS, EFS) and predictive factors for OS in our case series of 41 patients, treated with HMA-VEN as first-line since 2020 to 2023, 20 aged <75 years and 21 aged ≥75 years, with 2017 ELN risk unfavorable in 19, intermediate in 15 and favorable in 4 patients. NGS data were available in 10 patients, 2 of whom had the TP53 mutation. We performed geriatric multidimensional assessment (GMA), adapted according to Balducci (1), identifying 12 frail, 19 unfit and 10 fit patients. The rate of CR+CRi was 61%, that of relapse 36%, with a median follow-up of 14 months. We observed a median OS of 10.4 and a median EFS of 10 months. The 100-day mortality was 12.3%. Multivariate analysis of OS identified G-CSF use as the sole predictor of survival with a HR of 4 (95% CI: 1,6-10,4), p=0,003, for patients who did not use G-CSF compared with those who did. The GMA had a trend of significance in univariate, which was not confirmed on multivariate analysis. G-CSF, included in the data sheet at the physician's discretion, was used in the first cycles after bone marrow (BM) evaluation or in 7 cases of febrile neutropenia, even before bone marrow reassessment, and in subsequent cycles to facilitate recovery of neutrophil counts. The patients who did not receive G-CSF were those who had persistent blastosis or absence of neutropenia in the initial courses. This result suggests the importance and safety of using G-CSF to maintain adequate dose intensity in patients with AML, candidates for HMA-Ven therapy, which is known to be associated with hematologic toxicity both in the first courses and in the long term treatment.

Table 1. Patients charactheristics and outcome of the 41 patients receiving HMA-Ven.

VARIABLES	HMA-VEN	VARIABLES	HMA-VEN
Age		**First courses hospitalization**	
< 75 anni	20 (49%)	No	19 (48%)
≥ 75 anni	21 (51%)	Yes	21 (52%)
Gender		**G-CSF administration**	
Male	18 (44%)	None	17 (43%)
Female	23 (56%)	First courses (prior to bone marrow aspirate)	7 (17%)
		After bone marrow aspirate	16 (40%)
ECOG PS		**Antifungal prophylaxis**	
0-1	31 (76%)	No	9 (23%)
2-4	10 (24%)	Yes	31 (77%)
ELN 2017		**Final response**	
Favorable	4 (10%)	CR	23 (56%)
Intermediate	15 (37%)	CRi	2 (5%)
Unfavorable	19 (46%)	PR	7 (17%)
Not evaluable	3 (7%)	SD	5 (2%)
		PD	0 (0%)
		Too early	4 (10%)
Albumin		**Relapse**	
3,5-5,5 g/dl	23 (59%)	No	16 (64%)
3,5-2,5 g/dl	13 (33%)	Yes	9 (36%)
<2 g/dl	3 (8%)		
SORROR		**GMA**	
0-2	12 (29%)	Fit/unfit	10/19
2-8	29 (71%)	frail	12
De novo AML	18 (43.9%)		
Secondary AML	23 (56.1%)		

P049

VENETOCLAX PLUS HYPOMETHYLATING AGENTS OR LOW-DOSE CYTARABINE IN RELAPSED/REFRACTORY OR MRD POSITIVE NPM1-MUTATED AML-A MONOCENTRIC EXPERIENCE

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Background. *NPM1* mutations are found in ~30% of adult acute myeloid leukemia (AML). From a clinical perspective, *NPM1*mut AML displays heterogeneous behavior including patients with rapid clearance of measurable residual disease (MRD) and others experiencing early relapse or refractoriness. While first-line treatment of *NPM1*mut AML is well established, the management of relapsed/refractory (R/R) disease is still a matter of debate and outcomes remain unsatisfactory. Moreover, as molecular MRD monitoring has become the standard of care in this molecular subset, the use of updated treatment strategies as early MRD-directed interventions could provide a convenient bridge-to-transplant platform. Recently, favorable toxicity profile and efficacy of venetoclax (VEN) in combination with hypomethylating agents (HMAs) or low-dose cytarabine (LDAC) in *NPM1*mut AML was reported both in the first line and the R/R setting.

Methods. We evaluated the outcomes of 24 pts treated with VEN in combination with HMAs (n=18) or LDAC (n=6) for R/R (n=15) or MRD positive (n=9) *NPM1*mut AML at AOU Careggi between 2017 and 2023.

Results. In the R/R setting, overall response rate (ORR) was 47% (71% MRD negative), median OS was 9.5 m, mEFS was 9.4 m. Compared to *FLT3*-ITD neg pts, *FLT3*-ITDpos pts had inferior ORR (17% *vs* 75%, p=0.019) and outcomes (mOS, 2.3m *vs* not reached; p=0.009; mEFS 2.4m *vs* 23.2m, p=0.006). HSCT was performed in 3/7 (43%) of the intention-to-transplant pts. Three pts are in treatment-free remission w/o HSCT at 65, 46 and 42 months from VEN initiation. In the MRDpos setting (molecular relapse, n=6; MRD persistence after consolidation, n=3) 8/9 patients achieved complete bone marrow MRD clearance after a median of 2 cycles (1-4), while one pt achieved a 1.8 log MRD reduction. All patients were bridged to consolidative HSCT. Seven out of 9 are currently alive in CR. Median OS was 19.1m, mEFS was 13.9 m. Myelosuppression and constipation were the most common adverse events. In the MRD setting cytopenias occurred less frequently and were lower in grade. Six out of 24 pts experienced infectious complications, none of them was graded >3.

Conclusions. Our data is confirmatory of the clinical activity and overall favorable toxicity profile of VEN+HMA/LDAC in *NPM1*mut AML with particularly remarkable results in the MRDpos setting. Patients with concomitant *FLT3*-ITD mutations have inferior outcomes and treatment with *FLT3* inhibitors should be prioritized.

P050

EFFICACY AND TOLERABILITY OF TREATMENT WITH VENETOCLAX AND AZACITIDINE FOR 5 DAYS IN PATIENTS WITH ACUTE MYELOID LEUKEMIA: A SINGLE CENTER EXPERIENCE

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Background. Acute Myeloid Leukemia (AML) in elderly patients has a dismal prognosis as intensive chemotherapy and allogeneic hematopoietic stem cell transplantation are not feasible. Recently, Venetoclax (VEN) combined with hypomethylating agents (HMA) such as azacitidine (AZA) and decitabine (DAC) has been shown to be effective in AML in both treatment-naïve and relapsed or refractory settings. However, this therapy may induce severe marrow-suppression that could affect the outcome of these patients.

Aims. We aimed at retrospectively evaluate AML patients ≥ 60-year-old treated with HMA+VEN, investigating if the reduced administration of AZA for 5 days, can affect the treatment response, the prognosis and the hematological toxicity profile.

Methods. 27 consecutive newly diagnosed AML patients treated with HMA (7 DAC and 20 AZA) + VEN from Feb 2022 to Feb 2024 were included. Median age at diagnosis was 74 years, ranged between 62-84 years with 8 patients ≥ 80 years. The drug schedule for DAC was 20 mg/m^2 daily for 5 days (8 pts), for AZA was 75 mg/m^2 daily for 7 days (5 pts) or 5 days (14 pts) every 4 weeks, according to pts fitness; VEN starting dose was 400 mg daily (dose reduced to 25% in case of combination with azoles fungal prophylaxis) 14 to 28 days every 4 weeks (treatment duration was modulated on hematological toxicity and was stopped at complication onset).

Results. 26 pts were evaluable for response. The Overall Response Rate (ORR=CR+PR) was 81%, with 81% CR and 19% PR; CR was obtained after a mean of 1.09 cycles. Although the small samples size, we found no differences in terms of pts age, rate of CR, time to CR and rate of relapse according to HMA used (DAC or AZA for 7 or 5 days). The median follow up was 9 months; at last follow-up 14 pts (54%) are still alive and 12 (46%) had died. The main cause of death was disease progression (80%). The most common toxicities were myelosuppression (100%) and documented infectious complications (56%). Notably, the 5 days-AZA+VEN group had a lower rate of neutropenic fever (30% *vs* 42%), grade ≥3 thrombocytopenia (28% *vs* 40%) and gastrointestinal toxicities (22% *vs* 43%) compared to standard regimens.

Conclusions. Our findings suggest that the reduced administration of AZA for 5 days combined with VEN shows comparable efficacy to the standard regimens and relatively less toxicity. Further studies on a higher number of patients with a longer follow-up is necessary to confirm these results.

P051

WOULD IMMUNOPHENOTYPE AT ACUTE MYELOID LEUKEMIA DIAGNOSIS BE PREDICTIVE OF FLT3-ITD AND NPM1 MUTATIONS? A PILOT STUDY

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Background. Patients with a new diagnosis of acute myeloid leukemia (AML) harbor mutations in the fms-like tyrosine kinase 3 gene (FLT3) in 30% of cases, and in the nucleophosmin gene (NPM1) in another 30% of cases. Frequently, both mutations are present.

Aims. The purpose of our study was to determine if a specific immunophenotype at AML diagnosis would be predictive for FLT3-ITD and/or NPM1 mutation.

Materials and Methods. we retrospectively analyzed all non-promyelocytic AML cases diagnosed at our center between June 2018 and August 2022 (n=148). We recorded all data on AML diagnosis: full blood count, AML subtype, karyotype, molecular markers, and immunophenotype. Eight-colors flow cytometric panels on bone marrow samples were acquired using BDFACS Canto II Instrument. Antigen expression on blast population was evaluated both as percentage of expression (positive >20%) and as median fluorescence index (MFI). According to FLT3-ITD and NPM1 mutational status, patients were divided into 4 groups: double negative (DN) AML (n=48), FLT3-ITD+ AML (n=24), NPM1+ AML (n=47), and double positive (DP) AML (n=29). Statistical analysis was realized using SPSS10 Software. The comparison between groups for each antigen was made using the Kruskal-Wallis test. The antigens resulting significantly associated with a mutation were tested with the receiver operating characteristic (ROC) curve to identify an optimal cut-off. Significant variables were included in the logistic regression model for multivariate analysis on predictive antigens for FLT3-ITD and/or NPM1 mutations.

Results. The FLT3-ITD+ group presented a high CD7MFI (OR 3.37, p=0.01) compared with other groups. The optimal cut-off value was 145 (AUC 0.686, p<0.0001, PPV 75.8%, NPV 74.3%). The NPM1+ group presented a high CD33MFI (OR 3.11, p=0.03) and a low CD34MFI (OR 8.05,p=0.00005) compared with other groups. The optimal cut-off values were 4560 (AUC 0.837, p<0.00001, PPV 71.7%, NPV 92%) for CD33 and 1570 (AUC 0.903, p<0.00001, PPV 86.6%, NPV 81.8%) for CD34. Finally, the DN group showed negativity for CD15 (OR 15.17, p=0.01) and CD64 (OR 10.16, p=0.03) antigens.

Conclusion. Flow Cytometry may be considered a rapid tool to predict molecular alteration in this setting. However, the main limitation of our study is that it was retrospective. Currently, we have begun a prospective study of newly diagnosed AML cases at our center to confirm or refuse the results of the present study.

P052

OPTICAL GENOME MAPPING REVEALS MUTIPLE STRUCTURAL VARIANTS IN EPIGENETIC FACTORS AND CELL CYCLE REGULATORS IN ACUTE LYMPHOBLASTIC LEUKEMIA

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B-Acute Lymphoblastic Leukemia (ALL) includes over twenty subtypes defined by somatic genetic alterations, including aneuploidy, chromosomal rearrangements and/or known gene fusions, that converge on distinct gene expression profiles. Optical Genome Mapping (OGM) is a new genome-wide technology that allows the

detection of structural genomic variants (SVs) from 500 bp to 1 Mbp, copy number variations (CNVs), and whole chromosome aneuploidies in a single assay. Here, we report the results of OGM analysis performed at the Hematological Genomics Laboratory of University of Modena and Reggio Emilia and Modena University Hospital on leftover bone marrow (BM) samples from a 71-years old adult patient with Ph- ALL relapsed after 14 months during follow-up. Sample was inspected by OGM to detect structural variants, by Lymphotrack IGH/TCR NGS assay to define clonal rearrangements of IG and TCR genes, and by Archer FusionPlex ALL assay to evaluate SNVs, fusions and indels in 81 genes, following the manufacturers' instructions.

We did not detect IG or TCR rearrangements by clonotype analysis and any genetic variants by Archer FusionPlex ALL assays. Then, we applied OGM approach on ultra-high-molecular weight (UHMW) DNA, extracted from BM sample at relapse. DNA was labelled with DLE-1 enzyme, loaded onto a chip, and run on Saphyr instrument. Rare variant analysis algorithm on BionanoSolve software was applied on Saphyr data. OGM analysis identified several structural variants, comprising hyperdiploidy (57 chromosomes), intra- and inter-chromosomal translocations and multiple deletions and insertions (Figure 1). In particular, we found a novel translocation, t(7;22) (q21.11;q13.2), juxtaposing EP300 gene, an histone acetyltransferase essential for the maintenance of normal hematopoiesis, and CD36 gene. In addition, a 209kbp deletion of chromosome 1, including loss of CDKN2C gene, and a large 2200kbp deletion of chromosome 11, including loss of WT1 gene, was found by OGM. Loss of function mutations or deletions of WT1 are reported in about 10% of T-ALL, implying resistance to DNA damaging agents due to impairment of TP53 function and XIAP upregulation. In conclusion, OGM analysis detected several structural variants in BM sample at relapse from a patient with Ph- B-ALL, comprising alterations that disrupt epigenetic mechanisms, proliferation, and apoptosis, confirming that a more extensive evaluation of ALL patients by OGM may identify novel pathogenetic events.

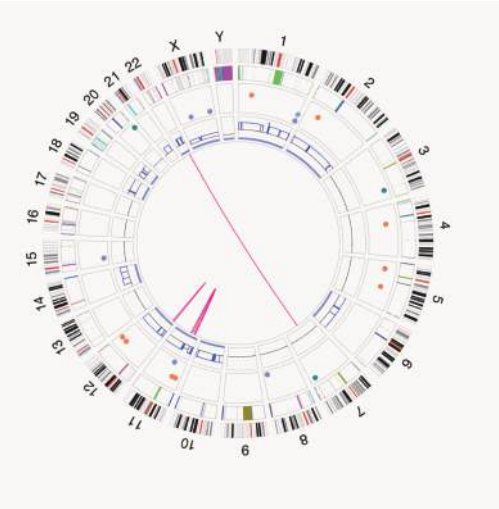

Figure 1. Circos plot depicts structural variants in ALL patient.

P053

THE BENEFIT OF THERAPY WITH HYPOMETHYLATING AGENTS + VENETOCLAX IN LATE ELDERLY AML: AN OPEN QUESTION?

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Background. Approximately one-third of patients (pts) with acute myeloid leukemia (AML) are ≥75 years (y) old, therefore unfit for conventional chemotherapy. Since 2020, hypomethylating agents (HMA) with venetoclax has shown increased effectiveness in less-intensive treatment. However, real-world data concerning this combination in late elderly individuals are lacking, despite their critical significance in refining therapeutic strategies.

Methods. We retrospectively collected data from all ≥75 y AML pts treated with HMA+venetoclax at our center from 2020, outside clinical trials. Overall Survival (OS) and Event-free Survival (EFS) were obtained using Kaplan-Meier method. Significant p-value was expressed as <0.05.

Results. We considered 29 pts with a median age of 80.4y (range 75.6-90.1). All other clinical features are summarized in Figure 1A.

Best response (BR) was not evaluable in 3 pts: 8 pts (28%) obtained a complete response (CR), 3 a CR with partial hematologic recovery (CRh) (10%), 2 a Morphologic Leukemia-Free State (MLFS) (7%), 2 had only a partial response (PR) (7%) and the other 11 pts had no response (38%). Mean follow-up was 8 months (range 1-37.6). Figure 1B-C represents EFS (as death or progression) and OS. The median EFS and OS was reached at 6.2 and 7.2 months, respectively. In a sub analysis age ≥80 y didn't influence outcome (p=0.594). Hematological improvement (HI), as transfusion independence, was perfectly correlated with a better BR (p <0.001). Regarding other variables: risk class, previous HMA therapy and BR (according to ELN2022), as expected, the favorable risk, the absence of previous therapy and the CR showed a positive impact, in fact the median OS in these subgroups was not reached (p=0.02, 0.04 and 0.008, respectively). (Figure 1D-F).

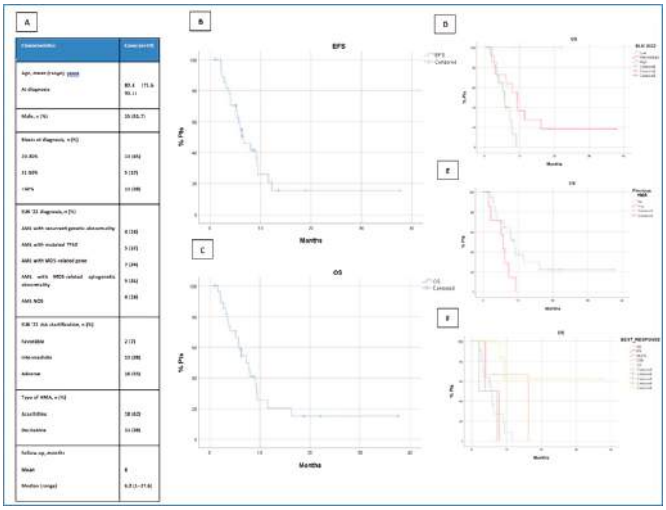

Figure 1.

Conclusions. No real-world series have yet been published for late elderly treated with HMA+venetoclax. With the limitations of

retrospective analysis, we can say that this approach is feasible for this group of pts. Age should not be a limiting factor in the choice of this combination, since the group of pts ≥80 years had a response comparable to those <80y. Remarkably, similar trends for EFS and OS underlines the importance of first line therapy because, at the disease progression, there is no concrete time for second line treatment. Obviously, only further studies, possibly prospective, will highlight the advantage of regimens based on HMA+venetoclax compared to best supportive care.

P054

GILTERITINIB:MORPHOLOGICAL EVALUATION OF A NOVEL DIFFERENTIATING THERAPY IN ELDERLY PATIENTS WITH REFRACTORY RELAPSED FLT3 POSITIVE ACUTE MYELOID LEUKEMIA. MONOCENTRIC EXPERIENCE

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Background. Gilteritinib is a potent FMS-like tyrosine kynase3 inhibitor approved in the treatment of refractory relapsed acute myeloid leukemia withFLT3mutation.This differentiation drug promotes leukemic blasts differentation,inducing cell apoptosis,as all-trans retinoic acid (ATRA)and arsenic trioxide(ATO). Drug-induced differentiation syndrome (DS) is a clinical rare adverse drug reaction,potentially fatal, occurring in about1%of pts,characterized by several organ manifestations, including non-infectious leukocytosis. Leukocytosis not necessarily predict DSdevelopment. The response pattern of gilteritinib may or not include hematopoietic differentiation,which can be assessed by morphological examination of both bone marrow and peripheral blood smear.Aim:To evaluate the aspects of morphological differentiation during therapy and the possible correlation with the response type to treatment.

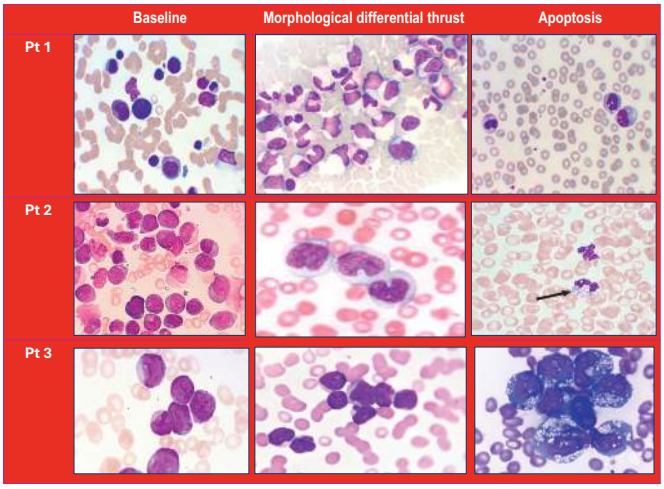

Figure 1.

Methods. Two internal observers (S.F.&A.L.P.) performed a morphological revision of bone marrow and peripheral blood smears at baseline then at each therapy cycle. 7patients (pts) treated with gilteritinib were retrospectively evaluated from March 2022 to March 2024.3/7 pts were evaluated for morphological features at baseline and at each cycle of therapy. Pts median age was 82y(range 69-83). Risk category was intermediate(ELN 2017). Median number of cycles was 4.Results:Gilteritinib treatment resulted in myeloid differentation in5/7pts(71.4%)with granulocytic hyperplasia without dysplastic changes. 3/7pts (42.8%) was analized based on the timing and characteristics of the morphological response to drug (Figure 1). All pts manifested DS:2 pts as non-infectious leukocytosis,1 pt after the first cycle and 1 pt after the second, the third pt as dermatitis spread to the four limbs and trunk to the fifth cycle. All pts experienced a drug response associated with signs of hematopoietic differentiation on peripheral venous blood smear assessed at each cycle.The morphological response to therapy was obtained in1/3 pts(33.3%) after the second (PR) and sixth cycle (CR).

Conclusions. An evaluation of to the gilteritinib response based on morphological analysis of peripheral blood smears is possible because a good correlation between the morphological data and the response to therapy. Morphological differentiation signs were indipendent by bone marrow blasts burden and by response type to treatment.Ongoing the evaluation a greater population including the citogenetics and molecular data.

P055

A NETWORK META-ANALYSIS COMPARING FIRST AND SECOND GENERATION FLT3 INHIBITORS IN ACUTE MYELOID LEUKEMIA DOES NOT SHOW OVERALL SURVIVAL DIFFERENCES

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FLT3 inhibitors combined with chemotherapy are now the standard of care for newly diagnosed FLT3-mutated acute myeloid leukemia (AML). Despite this, there is a lack of head-to-head studies comparing the efficacy of different FLT3 inhibitors. To determine whether specific FLT3 inhibitors yield superior outcomes, we conducted a network meta-analysis (NMA) focusing on overall survival (OS). Studies selected met these criteria: (1) randomized controlled trials (RCTs) with patients diagnosed with *de novo* AML and positive FLT3 mutations; (2) trials designed to evaluate the efficacy of FLT3 inhibitors against a control arm; (3) trials that reported data on OS. We employed a graphical representation approach to visually synthesize the evidence, presenting relative risk (RR) values for both direct and indirect comparisons. A treatment was considered superior if the 95% confidence interval (CI) for HR did not include the value 1.0, corresponding to a probability of exceeding 97.5% in this pairwise comparison. Among the relevant RCTs, three were suitable for our base-case analysis, involving a total of 1358 patients. These trials assessed the combination of sorafenib plus standard chemotherapy (SC) versus SC alone (Australian Leukaemia and Lymphoma Group Study; n=102), midostaurin plus SC versus SC (RATiFY study; n=717), and quizartinib plus SC versus SC (QUANTUM-first study; n=539). Both midostaurin (Hazard Ratio [HR], 0.70; 95% CI, 0.63–0.96) and quizartinib (HR, 0.78; 95% CI, 0.62–0.98) were associated with significant improvements in OS compared to SC alone. Conversely, sorafenib did not show OS improvement (HR, 0.76; 95% CI, 0.43–1.39), possibly due to the smaller sample size in its trial. Fixed-effects analysis showed no significant differences in OS between midostaurin and quizartinib (HR, 1.00; 95% CI, 0.73–1.36), midostaurin and sorafenib (HR, 0.97; 95% CI, 0.52–1.84), or quizartinib and sorafenib (HR, 0.97; 95% CI, 0.51–1.85), with the upper limits of the 95% CI for all comparisons crossing 1.0. This NMA

suggests no significant differences in OS among the first-generation FLT3 inhibitor midostaurin and the second-generation FLT3 inhibitor quizartinib. Patient selection bias may have influenced these results, indicating the need for cautious interpretation.

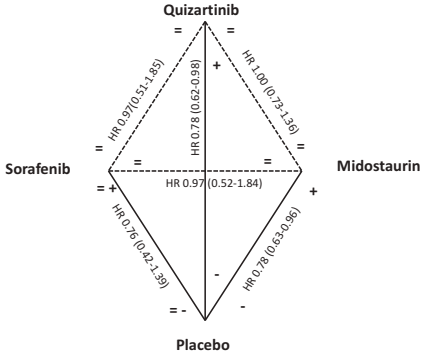

Figure 1.

P056

DOSE-REDUCED VENETOCLAX COMBINED WITH ANTIFUNGAL PROPHYLAXIS SHOWS SIMILAR EFFICACY WITHOUT INCREASING FUNGAL INFECTION INCIDENCE IN ELDERLY ACUTE MYELOID LEUKEMIA: A SINGLE-CENTER REAL-LIFE EXPERIENCE

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Background. Acute myeloid leukemia (AML) in elderly patients with comorbidities is associated with poor prognosis, and combination of azacitidine (AZA) with BCL-2 inhibitor venetoclax (VEN) has significantly improved their clinical outcomes compared to AZA alone. AZA/VEN induce severe neutropenia as hematological toxicity, and expose patients to invasive fungal infections (IFI). However, anti-fungal prophylaxis has pharmacodynamics interactions with VEN, and its use might impact on drug effectiveness. Therefore, we aimed to evaluate fungal infection incidence and hematologic response in AML patients treated with VEN-based regimen and antifungal prophylaxis.

Methods. A total of 19 AML patients treated with VEN/AZA (median age, 75 years old; range, 68-80; M/F, 13/6) were enrolled in this retrospective observational study conducted at the Hematology and Transplant Center, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy, from March 2022 to March 2024. Patients with history of prior IFI were excluded. Primary endpoint was IFI incidence during VEN/AZA therapy with antimycotic prophylaxis. Secondary endpoint was Overall Response Rate (ORR). Fungal infections were evaluated by CT scan imaging and/or bronchoscopy, aspergillus DNA and galactomannan antigen levels, and clinical evaluation.

Results. In our cohort, 88.8% of patients had an intermediate or adverse risk AML, according to ELN-2022 risk stratification system. Antifungal prophylaxis was administered in 18 subjects (94.7%) using posaconazole (68.4%), isavuconazole (21%), or caspofungin (5.26%). In almost all prophylaxed patients (94.4%), VEN dose was reduced to 70 mg in 47% (N=8) or 100 mg in 53% of them (N=9). ORR was 84% (8 complete remission, and 8 complete remissions with incomplete count recovery). In 36.8% of cases, at least 1 episode of fever occurred, and one of them was associated with galactomannan positivity. Median overall survival was 9.6 months and median progression-free survival was 9.1 months. Three patients died for disease progression, while no deaths associated to neutropenic fever or IFI were observed.

Conclusions. Based on our single-center real-life experience results, we added evidence to the efficacy of dose-reduced VEN in combination with AZA and anti-fungal prophylaxis in elderly AML without increasing IFI incidence or severe neutropenic fever .

P057

TREATMENT OPTIONS FOR FRAIL PATIENTS WITH AML: GLASDEGIB, HMAS OR BEST SUPPORTIVE CARE? A RETROSPECTIVE MULTICENTER EXPERIENCE

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In acute myeloid leukemia (AML), intensive chemotherapy ineligible patients face poor outcomes, with limited treatment options. Glasdegib with low-dose cytarabine (LDAC) is emerging as an alternative to Venetoclax and hypomethylating agents (HMA) combination in selected cases. Our analysis compares survival outcomes among patients receiving Glasdegib+LDAC, Azacytidine monotherapy, and best supportive care (BSC). We analyzed data from 40 newly diagnosed AML patients across three Italian Centers (Verona, Catania, and Padova) until March 2024, all considered ineligible for intensive chemotherapy due to age or comorbidities. The median age was 79 years (range 60-92), and 25 patients (62.5%) were male. Ten patients (25%) received Glasdegib+LDAC, 11 (27.5%) Azacytidine and 19 (47.5%) only BSC. Clinical characteristics and outcomes are summarized in Table 1. In our series, 90% of patients treated with Glasdegib+LDAC had AML secondary to MDS, compared to 26.3% of patients in the BSC group and 27.3% of patients treated with Azacytidine (p=.01). Four patients treated with Glasdegib+LDAC (40%) had previously received Azacytidine for primary MDS (p=.02). With a median follow up of 3 months, median OS was similar for patients treated with Glasdegib+LDAC and Azacytidine (6 months; p=.02), but higher than BSC group (2 months; p=.01 *vs* Glasdegib; p=.07 *vs* Azacytidine). The survival advantage was confirmed in univariate analysis for both Azacytidine (HR 0.49; p=.03) and Glasdegib+LDAC (HR 0.39; p=.03). In multivariate analysis involving age, ECOG ≥2, and secondary AML, only Azacytidine showed an advantage versus BSC (HR 0.30; p=.01). Hospitalization rates were slightly higher, though not statistically significant for Azacytidine (6/11, 54.5%), and Glasdegib+LDAC (8/10, 80%) compared to BSC (7/19, 37%) (p=.08). Hospitalizations due to infectious complications were significantly higher for Glasdegib+LDAC (70%) compared to Azacytidine (45.5%) or BSC (21.1%) (p=.003). In our study, although in a limited number of patients, both Glasdegib+LDAC and Azacytidine showed survival benefits over BSC. Nevertheless, Glasdegib+LDAC's advantage over BSC was not confirmed in multivariate analysis, possibly due to more unfavorable characteristics of patients in this group. Further studies in a larger cohort of patients

are needed to validate these findings and elucidate the optimal treatment approach for AML patients ineligible for intensive chemotherapy and Venetoclax-based therapies.

Table 1. Patients' baseline characteristics and outcomes according to treatment.

Parameters		BSC (n = 19)	Azacytidine (n = 11)	Glasdegib+ LDAC (n = 10)	p-value
Age years, median (range)		79,5 (66-92)	72,5 (60-84)	78,2 (70-87)	0.07
PS-ECOG status, median (range)		2 (1-4)	2 (2-3)	2 (1-3)	0.06
Sex, n (%)	Male	13(68)	5(46)	7(70)	0.38
WHO 2022, n (%)	AML defined by differentiation	10 (52)	6 (54)	4(40)	0.22
	AML myelodysplasia related	5(26)	4(36)	3(30)	
	AML with defining genetic abnormalities	0	1(9)	3(30)	
Karyotype, n (%)	Normal	5(26)	3(27)	2(20)	0.58
	Complex*	2(11)	2(18)	4(40)	0.31
	Recurrent alterations#	0	1(9)	1(10)	0.31
	Other alterations	2(11)	1(9)	0	0.42
	Not available	10(52)	4(36)	3(30)	
Mutational status, n (%)	FLT3	0	0	0	
	NPM1	1 (5)	0	1(10)	0.69
	IDH1	0	0	2(20)	0.22
	Not available	12(63)	6(54)	1(10)	
AML type n (%)	De novo	10(53)	5(46)	1(10)	0.07
	Secondary to MDS	5(26)	3(27)	9(90)	**0.002**
	Secondary to MPN	4(21)	3(27)	0	0.21
Previous therapy with Azacytidine		0 (0)	0 (0)	4 (40)	**0.02**
Hospitalization rate, n (%)	Overall	7(37)	6(54)	8(80)	0.08
	For sepsis	4(21)	5(46)	7(70)	**0.03**

BSC: Best supportive care, Glasdegib-LDAC: Glasdegib in combination with low-dose cytarabine, ECOG: Eastern Cooperative Oncology Group, AML: Acute myeloid leukemia, MDS: Myelodysplastic syndrome, MPN: Myeloproliferative neoplasms, FLT3 mut: Fms-like tyrosine kinase 3 gene mutation, NPM1 mut: Nucleophosmin 1gene mutation, IDH1 mut: Isocitrate dehydrogenase 1 gene mutation

***Complex**: more than or equal to 3 independent abnormalities

 # Recurrent alterations: two patients with inv(16)(p13.1q22)

P058

EVOLVING "INTENTION TO TRANSPLANT" POLICY FOR ELDERLY PATIENTS WITH ACUTE MYELOID LEUKEMIA: PRELIMINARY ANALYSIS OF A METROPOLITAN TRANSPLANT PROGRAM

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Background. Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative therapy for patients (pts) diagnosed with Acute Myeloid Leukemia (AML), nonetheless age per se may represent a limitation to the referral of older patients for transplantation. Thanks to the introduction of RIC regimens and to the use of fitness assessments, rather than chronologic age, the number of allogeneic SCTs among elderly patients has increased.

Aim. To evaluate percentage of AML pts aged 65-75 years who were referred for HCT and actually transplanted. To evaluate HCT policy in older AML pts, we discerned: the physician's indication to transplant at diagnosis or during treatment, the assessment of eligibility for transplant at transplantation unit and the transplant procedures actually performed.

Results. 105 patients aged 65 to 75 diagnosed with AML from 2013 to 2023 in 3 Hematology Units belonging to Rome Transplant Network, were retrospectively analyzed. Baseline characteristics are reported in Table 1. Pts were stratified according to ELN risk classification at time of diagnosis. According to exclusive AML characteristics, 96 pts were eligible to transplant. Of these, 35 (36,5%) were declared eligible to transplant by clinicians with no difference before and after 2020 (16/43 *vs* 19/53 , p=0,89). After 2020 we observed an increasing number of pts referred to the transplant team (4/43 before 2020, 13/53 after 2020, p=0.05). Eight out 35 pts (23%) received HCT in CR. Six of them are still alive and 2 died due to disease relapse, with a median of overall survival not reached at 2 years. The proportion of pts who underwent SCT has not increased over the years (4/43 before 2020 *vs* 4/53 after 2020, p=0,76). Furthermore, after 2020 we noted an increase rate of infectious complications leading to patient's death (18% *vs* 45%, prior and starting from 2020 respectively, p=0,016) (Table 1).

Conclusion. Despite a high proportion of elderly pts who could benefit from allogeneic HCT, only a minority of pts were actually transplanted with a favorable outcome. Our analysis confirms that elderly pts remain difficult to bring to transplant. Hypothesizing that introduction of Venetoclax may be helpful to bridge elderly pts to transplant, no difference in terms of transplants performed was observed despite an increased rate of transplant evaluations. This could be explained by the higher incidence of severe infectious events, however more data are needed to confirm these findings.

Table 1. CR= Complete Response, PR= Partial response, SD= Stable Disease, PD= Progression Disease, ED= Early Death.

N° of patients	**105**
M/F, n° (%)	63/42 (60/40)
Median age, years	70 (65-75)
Year of diagnosis, n° (%)	
Before 2020	49 (47%)
After 2020	56 (53%)
AML Category, n° (%)	
De novo AML	47 (45%)
Secondary AML (after MDS/MPN)	28 (27%)
AML with MRC	27 (26%)
t-AML	3 (3%)
Pre-treatment with AZA	
Yes	7 (7%)
No	98 (93%)
Treatment, n° (%)	
Intensive cht	57 (54%)
Hypomet agent (HMA)	27 (26%)
HMA + Venetoclax	21 (20%)
Type of response, n° (%)	
CR	56 (53%)
PR	10 (10%)
SD	10 (10%)
PD	13 (12%)
ED	12 (11%)
Interrupt for complication	4 (4%)
Deaths, n° (%)	78
Infection	24 (31%)
Relapse	35 (45%)
Refractory	14 (18%)
Other causes	5 (6%)

P059

SUCCESSFUL PONATINIB TREATMENT IN BCR/ABL1-POSITIVE ACUTE MYELOID LEUKEMIA (PH+ AML): TWO CASE REPORTS

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BCR/ABL1 mutation is observed in less than 1.5% of acute myeloid leukemia patients (Ph+AML) and is associated with high risk of refractoriness and early relapse after conventional chemotherapy. We report 2 cases of Ph+AML treated with BCR/ABL1-tyrosine kinase inhibitor Ponatinib (PON) for off-label use. Case 1 is a 34-years-old female who was admitted to our unit in November 2022 after an occasional finding of leukocytosis with anemia and thrombocytopenia. The peripheral blood smear showed 85% blasts. Bone marrow morphological and flow cytometry analysis confirmed the diagnosis of AML. Cytogenetic was positive for t(9;22)(q34;q11) in 1/20 methaphases. Molecular analysis revealed the simultaneous presence of the FLT3-ITD mutation and the p190 fusion protein (BCR/ABL1:3,2805%). The patient was enrolled in GIMEMA AML1919 protocol resulting in a refractory disease after induction therapy with Daunorubicin and Cytarabine ("3+7") chemotherapy plus Midostaurin and salvage therapy with high dose Cytarabine. Furthermore, molecular analysis displayed the disappearance of FLT3 and the persistence of BCR/ABL1. In March 2023, patient started therapy with PON (45 mg/day) and achieved a CR MRD+ with MR4 molecular responce after 3 courses. PON was well tollerated and patient underwent to haploidentical stem cell transplant (haplo-SCT). Maintenance therapy with PON was administered post-transplant and is still ongoing. The patient, after one year follow-up, shows a CR MRD- and complete molecolar responce (CMR). Case 2 is a 63-years-old male who was referred to our unit due to pancytopenia and fever in November 2021. The bone marrow aspiration and immunophenotype were diagnostic of AML. Furthermore, MDS-related abnormalities were found in both myeloid and megakaryocytic lineages. Karyotipe was complex in all examinated metaphases. Both qualitative and quantitative molecular tests confirmed the presence of BCR/ABL1 p210 (89,9687%). No other AML molecular markers were found. The patient resulted refratory to two lines of therapy (CPX-351 and Decitabine plus Venetoclax). In June 2022, PON (30 mg/day) was started and a CR MRD- with MR4 molecolar response was obtained after 4 mounth of continuous therapy. PON was discontinued due to the onset of critical coronary stenosis and replaced with Bosutinib. The molecular monitoring showed a progressive loss of response which led us to resume PON. The patient underwent haplo-SCT and shows a CR MRD- with CMR after 6 mounth from the transplant. In conclusion, PON represents a valid bridge to allogeneic-SCT in Ph+AML setting. However, studies conducted on larger series of cases are necessary to validate these results.

P060

PONATINIB INDUCED GRAFT VERSUS HOST DISEASE AND MOLECULAR RESPONSE IN A PATIENT WITH PHILADELPHIA POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA RELAPSED AFTER ALLOGENEIC TRANSPLANT

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Introduction. The Philadelphia cromosome (Ph+) is the most common chromosomal abnormality in adult acute lymphoblastic leukemia (ALL). With the 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.

Case Report. A 29 years old caucasian woman has been admitted to hematology unit in August 2014. The blood count showed white blood cell count of 7000 x 10^9/l with 87% of blasts, severe anemia and thrombocytopenia. Bone marrow examination showed 91% lymphoid blasts with immunophenotype CD19+, CD10+, Cd22+, cyCd79a+. The BCR ABL 1 rearrangement was identified with RT-PCR tecniques (PCR-RT), with the presence of p190 transcript. The patient underwent induction treatment with dasatinib, steroid and intratechal therapy obtaining a molecular response (day+60). During dasatinib treatment, the minimal residual disease (MRD) remained persistently negative. In December 2014, the patient underwent a matched, related donor allogeneic transplant (after conditioning regimen with total body irradiation, cyclophosphamide and ATG 2.5 mg/kg/day, days -3 and -2). A major molecular response (MMR) was achieved at day+100 with a complete chimerism (100%). In December 2022, the patient experienced a disease relapse (bone marrow examination showed 90% lymphoid blasts; no evidence of T315I mutation). The patient underwent a salvage chemotherapy regimen with steroids and ponatinib (45 mg p.o.) After starting ponatinib (at day +20), the patient experienced skin graft-versus-host disease (diffuse erythema, xerosis, alopecia). A rapid decrease of minimal residual disease has been observed with a MMR confirmed by bone marrow evaluations and full donor chimerism on days +30, +60, +100, +130, +200, +260, +320, +380 [Figure 1].

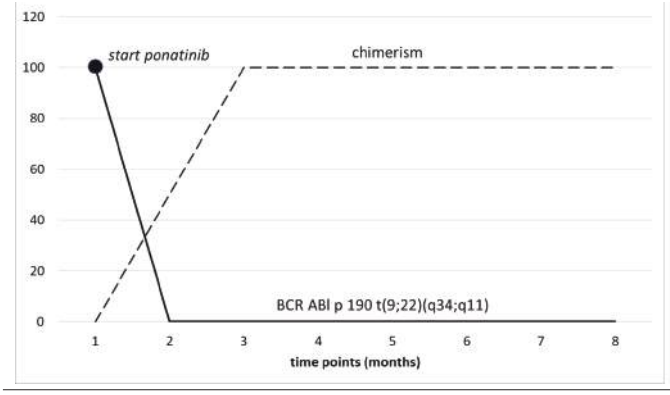

Figure 1.

Discussion. This case shows that a "chemo free therapy" with ponatinib is highly effective in the treatment of a patient with Ph+ ALL without the T315I mutation who relapse after allogenic stem cell transplantation. First of all, ponatinib demonstrates a significant antileukemic actions causing a deep and persistent molecular response. Moreover, a single agent ponatinib could produce an indirect immunologic graft-versus-leukemia (GVL), promoted by restoring

of donor-derived T cell. However, the molecular mechanism involved in this response remains unclear, and there are not extensive data available in the medical literature.

P061

IS VENETOCLAX PLUS AZACITIDINE (VEN-AZA) A VALID OPTION AS SALVAGE THERAPY PRIOR TO HSCT IN YOUNG AND FIT PATIENTS WITH IDH2 MUTATED AML REFRACTORY TO INDUCTION THERAPY?

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Despite the greater biological understanding and the new drugs available, R/R Acute Myeloid Leukemia represents an unmet clinical need, especially in young patients in good clinical condition who are eligible for bone marrow transplantation. Hypomethylating agents (Azacitidine or Decitabine) in addition to Venetoclax represent the standard of care for elderly patients or for ineligibles to conventional intensive chemotherapies. Whether this strategy can be considered in other patient cohorts outside the elderly or unfit patients is a matter of debate. Based on the recent evidence that VEN-AZA provides excellent response rates in specific genetic subgroups of AML, as *NPM1* or *IDH2*-mutated AML, we decided to treat with this low intensity regimen 3 patients younger than 60 years, with *IDH2*-mutated AML refractory to standard chemotherapy, as salvage therapy and bridge to transplant. Characteristics of patients and previous treatments are illustrated in Table 1.

Table 1.

	Sex	Age	NGS	FLT3	Karyotype	I line therapy	II line therapy	ELN 2022	AML status before VEN-AZA	AML status after VEN-AZA	FU after HSCT (months)
Pt 1	F	33	*DNMT3A, IDH2, NPM1*	ITD	46, XX	7+3 plus Mido	Gilteritinib	Intermediate	Refractory	PR	22
Pt 2	F	33	*DNMT3A, IDH2*	Wild type	46, XX	7+3 plus GO	FLAIE	Intermediate	Refractory	CR	20
Pt 3	F	56	*DNMT3A, IDH2, RUNX1, TET2, FLT3*-TKD	TKD	+8	7+3 plus Mido	/	Adverse	Refractory	CR	8

The three patients are all females aged 33, 33 and 56, respectively, who was diagnosed with *NPM1* and *FLT3*-ITD mutated AML (pt.1), AML-NOS (pt.2), and AML with MDS-related gene mutations and *FLT3*-TKD (pt.3) according to ICC 2022. Previous treatment included 3+7 plus Midostaurine followed by Gilteritinib (pt.1), 3+7 plus GO followed by FLAIE regimen (pt.2), and 3+7 plus Midostaurine (pt.3). Upon VEN-AZA, 2 out 3 patients (pt. 2, pt.3) achieved CR after the first cycle and underwent a second cycle before transplant. The other patient (pt.1) with *NPM1* and *FLT3*-ITD mutated AML, in progression during gilteritinib treatment, achieved PR (15-20% blasts in bone marrow biopsy with >50% blast reduction) after 1 cycle and underwent directly to transplant. In all cases TMI/TLI+Treg/Tcon bone marrow transplantation was performed from either HLA-haploidentical (pt. 1, pt. 3) or HLA-matched donor (pt.2) according to Pierini *et al* (Blood Adv 2021). The transplant procedures was very well tolerated by all three patients without any relevant extra-hematological toxicity. Currently, all three patients are in CR and in excellent clinical condition at 22 (pt.1), 20 (pt.2) and 8 (pt.3) months since transplant. Our experience suggests that the choice of VEN-AZA as salvage and bridge to transplant treatment can be driven by the genetic assessment of the disease, allowing achievement of CR even in high risk chemorefractory patients while sparing toxicity before allogeneic HSCT.

P062

ATYPICAL FLT3 MUTATION TREATED WITH SALVAGE GILTERITINIB IN RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA

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The FLT3 mutations (ITD or TKD) account for nearly 30% of the novo cases of acute myeloid leukemia (AML); as the concept of FLT3 inhibition is nowadays part of common clinical practice, little is known about the efficacy of available drugs in presence of atypical FLT3 mutation. Herein we report the efficacy of single agent Gilteritinib (Xospata, Astellas) in a case of refractory AML. A 60-year-old man was referred in May 2023 to the hematology department for major hyperleucocytosis (460 x 10^9/L), grade 4 anemia (6.7 g/dL) and thrombocytopenia. Peripheral blood smear showed 97% of myeloid blasts and the subsequent bone marrow evaluation confirmed the diagnosis of acute myeloid leukemia. Karyotype at diagnosis was not evaluable due the absence of analyzable mitosis; no extra medullary leukemia involvement was detected. A wild type state of NPM1, FLT3-ITD/TKD, CEBPA, IDH1 and IDH2 mutations was assessed with PCR/capillary electrophoresis. As per local clinical practice, the patient was started on standard induction chemotherapy according to the classic 3+7 regimen; at the re-evaluation one month later, the patient's blood count showed persistent hyperleucocytosis (WBC 30 x 10^9/L) with > 90% of myeloid blasts in the peripheral blood. After salvage chemotherapy according to the standard FLAG-Ida regimen, we received the results of the Next Generation Sequencing (NGS) panel sent at diagnosis, which revealed the presence of two non-canonical FLT3 mutations along with IDH1, DNMT3A, JAK2 and RUNX1 mutations, whose variant allele frequencies (VAF) were respectively 3%, 39.9%, 49.9%, 50.5%, 49.7%, 50.6%. In particular, the two mutations affecting the FLT3 gene were: c.1735_1736delinsCC p.(Val579Pro), never described before, and a missense c.2533A>G p.(Arg845Gly) located in a mutational hotspot in which pathogenic variants have been already reported. At the interim evaluation done at day +14 of FLAG-Ida circulating peripheral blasts were still present and the patient was started on daily Gilteritinib 120 mg. After experiencing grade 2 differentiation syndrome, the patient achieved complete remission with 1% level of MRD positivity at flow cytometry. At this point, the patient underwent haploidentical stem cell transplantation and he is still alive and in remission after 11 months from diagnosis. This experience adds to the reports of successful FLT3 inhibitors use in the context of refractory AML carrying an atypical FLT3 mutation.

P063

IMPACT OF DARATUMUMAB/BORTEZOMIB/THALIDOMIDE/DEXAMETHASONE (DVTD) INDUCTION THERAPY ON CHEMO-FREE STEM CELL MOBILIZATION IN TRANSPLANT-ELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: A MULTICENTRIC REAL LIFE EXPERIENCE

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Background. Daratumumab-based induction followed by autologous stem cell transplantation (ASCT), is the standard of care for transplant-eligible newly diagnosed multiple myeloma patients (NDMM). Daratumumab (Dara) adversely affects stem cell mobilization, and this is clearly reported in prospective clinical trials. Here, we described a real-life experience on peripheral blood stem cell (PBSC) mobilization in patients treated with Dara-based induction.

Methods. From 2022 to 2024, NDMM patients treated with Dara, bortezomib, thalidomide and dexa (DVTD) were mobilized using G-CSF 10 µg/kg/day, in 2 centres. PBSC minimum target was $2.5x10^6$ cells/kg for 1 ASCT and $5x10^6$ cells/kg for 2 ASCT. Plerixafor (Plx) 240 µg/kg was used on demand when circulating CD34+ was less than 20/µL at day +5. Categorical variables were reported as count with percentage and continuous variables as median with range. Chi-square tests were used to compare categorical variables and p value <.05 was considered for statistical significance.

Results. 100 patients were included. Median age was 61 years (range 42-71). Median induction cycles were 4 (3-6); 63% of patients mobilized after fourth cycles, 37% after third cycle; median time from last Dara to G-CSF start was 25 days (9-109). Responses to induction were: CR 16%, VGPR 60%, PR 16%, SD 1%. PBSC mobilization was successful in 90% of cases. Plx was added in 36%. The median CD34+ peak was 39/µL (0-490); the median of CD34+ cells harvested was $6.7x10^6$/kg (2.5-23.9) with 66% of patients harvesting more than 5×10^6/kg. The median number of apheresis was 1.7 (range 1-3). 10 patients failed first mobilization, and 9/10 were subsequently mobilized with chemo-based regimen. In univariate analysis, age (>60y *vs* <60y), response after induction (≥VGPR *vs* <VGPR) and days from last Dara (>25 *vs* <25) did not affect Plx use and number of apheresis. The number of apheresis' day was longer in pts mobilized after 4 *vs* 3 induction cycles (p=0.049). All patients received ASCT. The median time to absolute neutrophils count >0.5 and platelets count more than 20 was 11 (6-24) and 13 days (7-30) respectively.

Conclusions. our study showed that chemo-free PBSC mobilization is feasible and effective even after DVTD induction. However, the use of Plx seems to be higher. 10% of patients failed to mobilize, and a second round of mobilization was effective for harvesting stem cells.

Myeloma and monoclonal gammopathies

P064

EXPLORING THE ROLE OF THE COMBINATION OF FDG PET PLUS WHOLE BODY MRI FOR STAGING NEWLY DIAGNOSED AND RELAPSED/REFRACTORY MULTIPLE MYELOMA: A PROSPECTIVE TRIAL

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Background. The integration of FDG-PET/TC and WB-MRI in the diagnosis of MM may results in higher accuracy to detect bone lesion compared to them alone. This could be translated into better outcomes if early detection of myeloma defining events leads to earlier induction or re-induction treatments.

Methods. In our Institution, from January 2021 to January 2023, we performed a prospective trial enrolling 73 consecutive newly diagnosed and relapsed/refractory MM (median age 63 years - range 85-35), according to IMWG, in which WB-MRI was performed according to MY-RADS criteria in combination with FDG PET/CT. 31/73 (42%) had a newly diagnosed MM, 25/73 (34%) were in follow-up after autologous stem cell transplantation and 17/73 (23%) patients were affected by relapsed/refractory MM. Subsequently, in 2 cases WB-MRI were aborted and not diagnostic so patients were excluded from the final analysis.

Results. In these 71 patients: 52/71 (73%) cases of concordance of WB-MRI and 18F PET-CT, 18/71 (25%) cases of discordance. In this group 15/18 (83%) cases FDG-PET/CT was negative and WB-MRI showed positive findings according to MYRADS criteria (5 micronodular pattern, 9 diffuse pattern e 1 focal pattern) (Figure 1 Newly diagnosed MM-diffuse pattern in WB-MRI, PET negativity), in 3/18 (17%) FDG-PET/CT was positive for focal lesions and WB-MRI was negative.

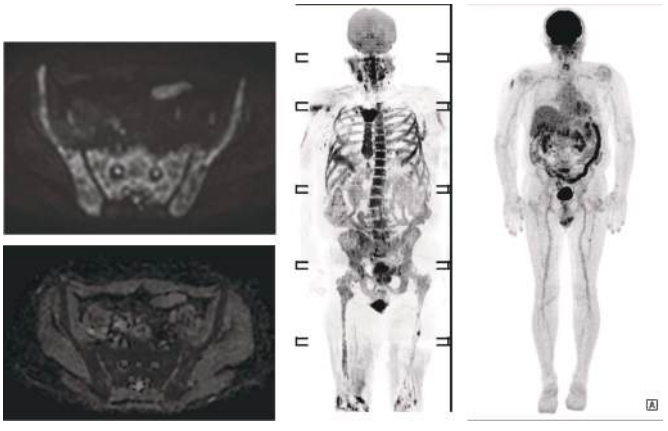

Figure 1.

Conclusions. Our preliminary results support a potential complementary role of WB-MRI and FDG PET/CT findings, on the management of patients with MM at both diagnosis and relapse. To date, there is no wide availability of WB-MRI because in concerning about costs and technical issues, but data are consistent with its possible future leading role in MM diagnostic work-up.

P065

POMALIDOMIDE-CYCLOPHOSPHAMIDE-DEXAMETHASONE AND ANTI-MULTIPLE MYELOMA (MM) T-CELL RESPONSES IN RELAPSED/REFRACTORY MM: A SINGLE CENTER RETROSPECTIVE STUDY IN A REAL LIFE SETTING

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Background. The combination of Pomalidomide and Dexamethasone (Pd) is a recognized therapy for relapsed and refractory multiple myeloma (RRMM) after at least two prior lines of treatment, including lenalidomide and a proteasome inhibitor (PI). While earlier trials showed modest efficacy with Pd over 4-5 months, other studies have explored the beneficial addition of Cyclophosphamide.

Methods. This retrospective analysis examined 24 consecutive patients treated at our institution from May 2018 to March 2024 with a Pomalidomide, Cyclophosphamide, and Dexamethasone (PCD) regimen. By using the IFNy-Elispot assay, we assessed T-cell responses against specific antigens of MM cells, namely WT1, Melan-A/MART-1, NY-ESO-1, MAGE-A1, hTERT, SOX-2, DKK1, JAM-1, SLAMF7 and BCMA.

Results. The study included 24 patients, evenly split between genders, with a median age of 74 years (range 55-84). Half of whom were over 75 years old. Eleven patients (45%) had high-risk cytogenetics. Patients had received a median of 3 prior treatment lines (ranging from 2 to 6), all previously exposed to lenalidomide and a PI. Of these, 91% were lenalidomide refractory, and 54% were double refractory (IMiDs and IP). The overall response rate (ORR) was 79%, with 37% achieving a very good partial response. With a median follow-up of 11.5 months (range 3-59), the median progression free survival (PFS) was 13 months (95%CI 4.8-21.2), and the median overall survival (OS) was 13 months (95% CI 2.5-23.5), consistent with prior studies. Patients maintaining a response for 4 months showed improved PFS (19 months 95% CI 4.5-33.5). No PFS or OS difference was observed between high and standard-risk cytogenetics. The most common adverse events were hematologic toxicities, with 70% experiencing grade 3-4 cytopenia. T-cell responses were analyzed by using the IFNy-Elispot assay in 9 of 24 patients. Three patients resulting unresponsive to therapy for over 4 months showed no anti-MM T-cell responses. Conversely, all the other patients with anti-MM T-cell responses maintained their response to therapy for more than 4 months.

Conclusions. In summary, our study supports the safety and efficacy of triple therapy in a challenging patient population (particularly elderly, heavily pretreated and lenalidomide refractory). Furthermore, the addition of cyclophosphamide may enhance anti-MM T-cell responses, possibly contributing to an extended PFS duration.

P066

MULTPLE MYELOMA IN PATIENTS WITH HCV-RELATED DISEASE: SINGLE CENTRE REAL WORD EXPERIENCE

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Introduction. Hepatitis C virus (HCV) is a global health infection that affects about 170 million persons. HCV encodes a virus-specific helicase, protease, and polymerase, and because of the critical function of these proteins in the viral life cycle, they represent attractive targets for antiviral therapy worldwide. In Multiple Myeloma (MM), solid tumors and other pathologies, the adverse hepatic effects during treatment with Lenalidomide have been described. Some case reports have described the use of lenalidomide in MM patients with decreased hepatic function and pre-existing hepatotoxicity. In literature, there are no case study of patients affected by MM and Hepatitis C treated with Daratumumab-Bortezomib-Melphalan-Prednisone (DARA-VMP) or Daratumumab-Lenalidomide-Dexamethasone (DARA-RD) scheme.

Methodology. In this study we report 20 cases: 16 women and 4 men affected by MM with average age 67-81. IgG 14 pts stage III ISS. IgA 6 pts stage I ISS. 8/20 pts had high risk karyotype. 8/20 pts treated with DARA-VMP (5 pts relapsed / 3 pts previous). 10/20 pts treated with DARA-RD (5 pts relapsed / 5 pts previous). 2/20 pts treated with Dara VD (1 pt relapsed/1 pt previous). Liver structure and function were monitored. We report that they have maintained stable parameters over the six-month cycle. Antiviral therapy with Acyclovir has not been prescribed. Prophylaxis with Bactrim was carried out only in patients affected by previous hepatitis. As for the treatment for hepatitis, we have used Epclusa which is composed of Sofosbuvir and Velpatasvir, that block the action of two proteins ("NS5A") which are essential for the multiplication of the hepatitis C virus. The viral load was monitored in all patients for 3 months.

Results. During therapy, a clear reduction in viral load was observed in all patients (>50%) compared to the initial values of the HCV virus. Liver function parameters were always stable during the therapy with Dara, which was administered according to the scheme Dara-VMP, Dara-RD, Dara-VD. The average number of platelets was 120,000 (range 60,000 -140,000). Currently, all patients are alive and receiving therapy monthly.

Conclusion. We have shown that although some patients have been affected by HCV-related liver disease and MM for many years, treatment with Dara-VMP or Dara-RD allows us to obtain a very good partial response (VGPR).

P067

SIGNIFICANCE OF DIFFUSION-WEIGHTED WHOLE-BODY MRI (DW-MRI) IN STAGING AND RESPONSE ASSESSMENT IN MULTIPLE MYELOMA PATIENTS: A RETROSPECTIVE STUDY.

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Diffusion-weighted whole-body MRI (DW-MRI) is increasingly used in the management of multiple myeloma (MM) patients in staging and in response evaluation. However, comparison data with other functional imaging methods and on the combination with other laboratory-based response assessment methods are lacking in the literature. The purpose of this retrospective single-centre study is to describe the use of DW-MRI in staging of MM and at evaluation of response after therapy in a real-world contest. We enrolled all MM patients with at least one DW-MRI for staging or response assessment in this study. A total of 23 patients with MM were staged with DW-MRI. DW-MRI showed bone lesions in 87% of cases; 13% of cases didn't have therapeutic criterion other than DW-MRI lesions. A comparison with PET-CT scan was possible in 12 cases. PET-CT scan was positive for disease localization in only 6 cases. In 2 cases, both PET and DW-MRI were negative, and 4 patients had a negative PET-CT scan despite the positivity of DW-MRI. Considering the disease re-evalution setting after therapy, as per clinical practice, we performed DW-MRI only in patients with a serologic response to at least very good partial response (VGPR): a total of 22 patients was included in the analysis. For all cases a comparison with detection of minimal residual disease (MRD) in bone marrow samples by next-generation flow cytometry (NGF) was possible. Of these, 13 patients had negative MRD on bone marrow aspirate but 6 of them still showed positive DW-MRI for myeloma localizations; in the group of patients with positive MRD on bone marrow aspirate (9 patients), only 2 had a negative DW-MRI.

Conclusions. this small retrospective study confirms that DW-MRI is a valid option for staging myeloma patients and appears to have greater accuracy than PET-CT in identifying disease localizations. Recently, in multiple myeloma patients MRD negativity on bone marrow aspirate has been approved by the FDA as an endpoint for therapy, and new clinical trials are exploring an MRD-based therapeutic approach. The discordance between DW-MRI and bone marrow analysis by NGF showed in our study, suggest that MRD assessment needs to be multiparametric and not just based on a single technique.

P068

ROLE OF THE COMBINATION OF FDG PET PLUS WHOLE BODY MRI FOR STAGING PATIENTS IN HIGH RISK SMOLDERING MYELOMA: A PROSPECTIVE TRIAL

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Background. It is really important to clarify in SMM setting the best imaging analysis in order to perform a correct diagnosis, and particularly it is necessary to define if the combination of FDG-PET/TC and WB-MRI could improve the assessment of lytic lesions and so the discrimination between high risk SMM and symptomatic MM.

Methods. In our Institution we are currently conducting a prospective multicenter trial, based on integrated new generation imaging (PET/CT + Whole body MRI), aiming to improve patients' stadiation and to define its prognostic implications. From January 2021 to January 2023, we performed a prospective trial enrolling 26 consecutive newly diagnosed high risk SMM, according to IMWG, in which WB-MRI was performed according to MY-RADS criteria in combination with FDG PET-CT (median age 56; range 36-85).

Results. Interim analysis of the comparison between WB-MRI and FDG PET-CT, showed a discordance between the two imaging modalities in 4/26 (15%) cases. In particular, in 3/26 (12%) cases WB-MRI showed bone lesions that have lead to symptomatic MM diagnosis according to IMWG criteria, while PET-CT was negative. In one case, PET-CT showed a diffuse uptake, not diagnostic for MM, while WB-MRI was negative. WB-MRI showed a 100% of accuracy in detecting SMM and MM. Therefore, WB-MRI has lead to a modification of the prognosis and treatment approach (observation in SMM *vs* treatment in symptomatic MM) in 3/26 patients (11%) (*i.e.* Figure 1, with DWI of C2 lesion). Furthermore, in 5/23 (22%) cases of confirmed SMM WB-MRI showed a slight diffuse alteration pattern of bone marrow without any overt lytic bone lesion, which could be a potential prognostic evidence.

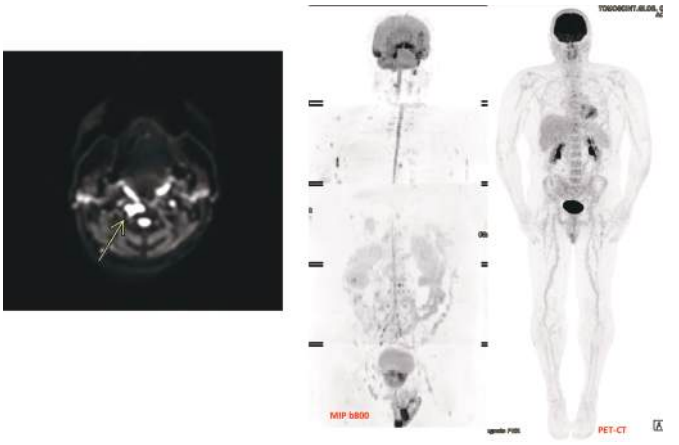

Figure 1.

Conclusions. Our preliminary results support a fundamental role of WB-MRI in combination with FDG PET/CT in the stadiation of patients with newly diagnosed high risk SMM, which could modify prognosis and treatment approach, improving the differentiation with symptomatic MM. In particular, combination of WB-MRI plus FDG PET/CT could be more accurate in the detection of bone lesions (myeloma defining events) than FDG PET/CT alone, being able to anticipate symptomatic MM diagnosis and consequently its treatment. Moreover, a diffuse pattern of marrow involvement could be detected in some HR-SMM patients without any overt lytic lesions: it is questionable if this group of patients is associated with a rapid progression in lytic lesions and so in symptomatic MM diagnosis. Prospective data on evolution of these patients are pending.

P069

PHENOTYPE OF BONE MARROW MONOCYTES IN PATIENTS WITH PLASMA CELL NEOPLASMS

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In the development and pathogenesis of Multiple Myeloma (MM), the micro-environment is considered fundamental both for disease progression. Different types of cytokines, proteins and cells contribute to the MM micro-environment; among them, monocytes are vital in fostering the inflammation and in contributing to bone lesions. Monocytes can be classified into classic, intermediate and non-classic. In particular, the latter corresponds to M2 macrophages, which are involved in anti-inflammatory and pro-angiogenic mechanisms; furthermore, osteoblastic cells are often evolved from non-classic monocytes. To understand the variability of monocyte phenotype in MM patients we analyzed the monocyte phenotype by multiparameter flow cytometry (MFC). We differentiated between monocyte subtypes based on their phenotype: classic monocytes express CD14 but not CD16, non-classic monocytes express CD16 and low level of CD14, while intermediate monocytes are in between. The analyses was performed on 49 bone marrow samples of patients with plasma cells dyscrasia (39 MM, 3 smoldering MM, 6 Monoclonal Gammopathy of Undetermined Significance 1 plasmacytoma). 36 samples were obtained from onset patients, 4 from relapse/refractory patients, 9 from post therapy follow-up patients. We found a significant relative reduction of classic monocytes (p 0,027) and an increase of non-classic monocytes (p 0,005) paralleling the increased degree of plasma cell infiltration observed in the morphological bone marrow examination. We did not find any significant correlation between monocyte phenotype and plasma cell phenotype. As collateral analysis we analyzed plasma cell phenotype. We found a relative decrease in CD19+/CD56- plasma cells (p 0,003), and an increase in CD19-/CD56+ plasma cells (p 0,045) once again paralleling the increased degree of plasma cell infiltration observed in the morphological bone marrow examination. From our results, a change of monocyte phenotype towards the non-classic type mirroring the increase of the bone marrow plasma cell population emerged. Although we did not find a direct link between this tendency and plasma cells phenotype, a significant positive relationship was found between the frequency of CD19-/CD56+ plasma cells, usually associated to malignancy, and the global amount of plasma cells. Overall, our work, by demonstrating an atypical pattern of monocyte phenotype, supports the hypothesis of their potential role in the MM micro-environment and pathogenesis.

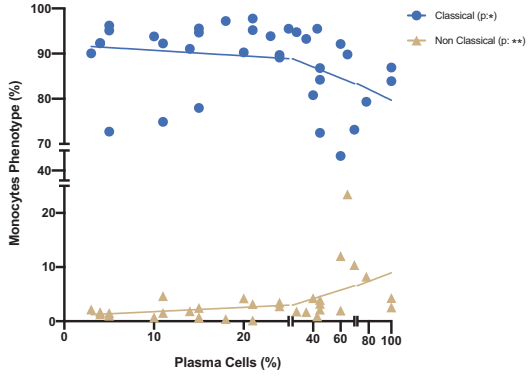

Figure 1.

P070

PROGNOSTIC IMPACT OF 1Q21+ ON RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS TREATED WITH ELOTUZUMAB-BASED CONTAINING REGIMENS: A MULTICENTER, RETROSPECTIVE REAL-WORLD EXPERIENCE WITH 192 CASES OUTSIDE OF CONTROLLED CLINICAL TRIALS

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Extra copies of chromosome 1q21 (1q21+) are associated with worse outcomes in multiple myeloma (MM). Elotuzumab-based treatments' impact on RRMM patients with 1q21+ has been documented. ELOQUENT-2 trial unveiled a significant improvement in progression-free survival (PFS) for 1q21+ patients treated with elotuzumab-lenalidomide-prednisone (EloRd) combination compared with Rd, although this did not extend to overall survival (OS). Similarly, the ELOQUENT-3 trial exhibited PFS improvements in the 1q21+ subgroup with elotuzumab-pomalidomide-dexamethasone (EloPd), albeit not reaching statistical significance. This study explores the prognostic implications of 1q21+ in RRMM patients undergoing Elo-based therapy. Out of 640 cases of EloRd (319 cases) or EloPd (321 cases) from two Italian real-world cohorts, cytogenetic data were available for 192 patients, divided into 1q21+ (61 cases) or and 1q21- (131 cases) subgroups. Subgroup analysis identified a significant association (P<0.0001) between 1q21+ and the presence of t(14;16), while clinical and biological parameters while other clinical and biological characteristics remained well balanced between the 1q21+ and 1q21- cohorts. Importantly, a significantly higher proportion of 1q21+ patients received EloRd compared to EloPd (36% *vs* 22%; P=0.047). After a median follow-up of 33 months, patients with 1q21+ showed a significantly shorter PFS (6.8 months) compared to 1q21- counterparts (16.6 months; HR 1.79; P=0.003) (Figure 1).

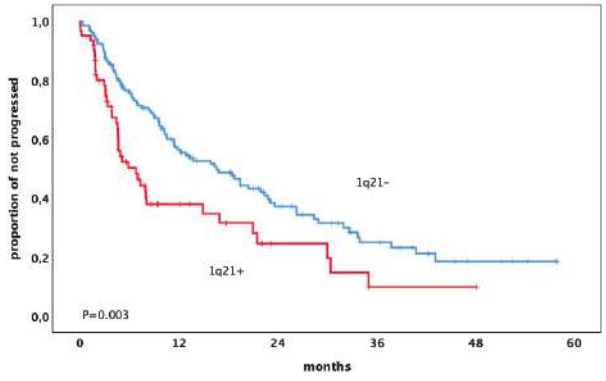

Figure 1.

Univariable analyses underscored several prognostic factors significantly associated with shorter PFS, including ISS stage II (HR=1.33; P=0.009), ISS stage III (HR=1.71; P<0.0001), number lines of therapy >2 (HR=2.04; P<0.0001), del17p+ (HR=2.33; P=0.001), t(4;14) (HR=1.72; P=0.03), and EloPd schedule (HR=2.15; P<0.0001). When all univariate correlates of progression and all variables, which significantly differed between the two 1q21 subgroups, were jointly introduced into multiple Cox model, 1q21+(HR=2.17; P<0.0001), ISS II stage (HR=1.93, P=0.002), ISS III stage (HR=4.46, P<0.0001), del17p+ (HR=2.1; P=0.004), and EloPd schedule (HR=2.56; P<0.0001) maintained an independent prognostic impact on PFS. No significant differences in OS between 1q21+ and 1q21- groups were observed. In conclusion, this analysis underscores an independent adverse impact on PFS of 1q21+ in Elo-based treated RRMM patients, indicating a pressing need for new therapeutic strategies for this subset of patients.

P071

MANAGEMENT OF ADVERSE EVENTS ASSOCIATED WITH THE USE OF BISPECIFIC ANTIBODIES IN MULTIPLE MYELOMA: A MULTIDISCIPLINARY INTRAREGIONAL CONSENSUS

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Despite many new developments in the therapeutic armamentarium available for multiple myeloma (MM), the management of relapsed/refractory disease remains a major challenge for clinicians. Therapies including Chimeric Antigen Receptor-modified (CAR)-T-cells and Bispecific Antibodies (BsAbs) have been approved for this specific setting. In Italy, two BsAbs are currently available: Teclistamab, who targets the B-cell maturation antigen (BCMA) and Talquetamab, directed against GPRC5D protein. Since BsAbs are very recent, the management of the various and different toxicities has been emerging as an important and new issue to face. The most frequent adverse events are similar to the ones observed for CAR-T: cytokine release syndrome (CRS), neurotoxicity, infections, and cytopenia. Moreover, peculiar on-target/off-tumor effects have been noticed, above all with Talquetamab, with a specific toxicity on cutaneous cells, expressing GPRC5D protein. Since the clinical scenarios can be very different for each adverse event, both in term of clinical manifestations and in timing of presentation, it looks fundamental to better understand how to manage toxicities, whereas BsAbs would possibly become more and more available as treatment for MM. Considering the different specialties possibly involved in the management of BsAbs-related toxicity, it looks necessary to collect high specialty advice from several scientific voices. With this purpose, a multidisciplinary intraregional consensus was born from the collaboration of several experts (hematologists, infectious disease specialists, dermatologists, anesthesiologists, and neurologists) working in the same region, who compare their own expertise and their scientific knowledge. Using as a fundamental starting point the guidelines updated to 2023 proposed by the European Myeloma Network, this group aims to provide a guide to evaluate clusters of patients at higher risk of developing a certain adverse event, looking for possible prevention strategies, but also to find markers suitable as early predictors and, eventually, to manage BsAbs-related toxicity once it has occurred. With specific regards to infections, in this consensus we also discuss the most suitable and possibly successful pre-

vention strategies, such as vaccinations and prophylaxis, of the major complications, considering that BsAbs are administered until progression of disease, with this being a great issue given the prolonged state of immunodepression caused.

P072

IMPACT OF DARA-VTD INDUCTION THERAPY ON STEM CELL MOBILIZATION OUTCOMES IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS (NDMM) UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT): A MULTICENTER STUDY

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Background. There are few data about stem cell mobilization in the era of anti-CD38 as standard of care in NDMM.

Aims and Methods. This retrospective study aimed to analyze the outcomes of hematopoietic stem cell mobilization and collection in 81 consecutive patients with NDMM who underwent Dara-VTD induction therapy before ASCT, comparing the outcome with VTD-treated NDMM. In the Dara-VTD cohort, data were collected in four hospitals in the Campania Region, Italy, from November 2021 to June 2023 and were compared with the historical cohort of 93 VTD-treated patients matched for baseline characteristics. Statistical analysis was performed using R Statistical Software.

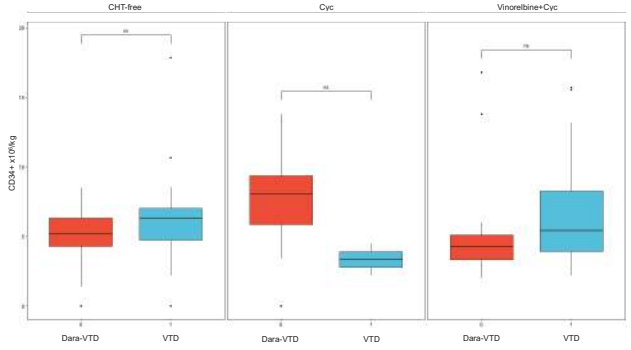

Figure 1.

Results. The Dara-VTD cohort included 81 patients, 38 females (40.5%) and 43 males (49.5%) with a median age of 59 years. According to the International Staging System (ISS), 48,1% were at stage I, 30,9% at stage II, and 21% at stage III. Regarding the Revised ISS (R-ISS), 28,4% were at stage I, 58% at stage II, 12,3% at stage III. Mobilization therapies included cyclophosphamide (28.4%), vinorelbine + cyclophosphamide (33.3%), and chemotherapy-free regimens (38.3%), all with G-CSF, and 56.2% received plerixafor. The median CD34+ cells collected were $5.1x10^6$ cells/kg. 96.3% of patients mobilized $\geq 2x10^6$ cells/kg, 1.2% mobilized poorly, and 2.4% failed to mobilize. Stem cell collection efficacy correlated significantly with the ISS stage (p=0.048). Patients who received cyclophosphamide + G-CSF had notably higher CD34+ cells yields than those treated with the other regimens (p=0.01). Furthermore, a greater proportion of patients undergoing cyclophosphamide or chemo-free regimens received plerixafor and the introduction of plerixafor, irrespective of the treatment regimen, enhanced the quality of stem cell collection (p=0.007). Comparing the Dara-VTD and VTD groups, the use of cyclophosphamide regimen was significantly higher in the Dara-VTD group (p<0.0001). CD34+ cells collection outcomes were similar between the groups (p=0.43), but in the DARA-VTD group plerixafor was administered in a greater proportion of patients (p<0.0001).

Conclusions: In NDMM patients post-Dara-VTD, stem cell collection correlates with ISS stage. Cyclophosphamide followed by G-CSF yields more CD34+ cells, and plerixafor enhances collection quality regardless of mobilization regimen. Moreover, the Dara-VTD group had higher plerixafor use than the VTD cohort, with no significant difference in stem cell collection.

P073

ABSTRACT NOT PUBLISHABLE

P074

IMPACT OF DARATUMUMAB-BASED REGIMEN ON INFECTIOUS RISK IN TE-NDMM TREATED WITH D-VTD FOLLOWED BY HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANT: A MONOCENTRIC EXPERIENCE

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The addition of daratumumab to VTD (bortezomib-thalidomide-dexamethasone) as induction and consolidation therapy post-autologous stem cell transplant (ASCT) in transplant-eligible newly diagnosed myeloma (TE-NDMM) was proven to be safe and effective in CASSIOPEIA trial. Overall, toxicity was not increased when adding daratumumab to VTD, but infections (any grade) were more common in the D-VTD group (65% versus 57%), whereas the rate of grade 3-4 infections was similar [Moreau P et al Lancet. 2019 Jul 6;394(10192):29-38]. The aim of this study is to retrospectively evaluate the incidence and severity of infections in TE-NDMM patients who received D-VTD followed by high-dose melphalan and ASCT in a real-world setting. Each patient received 4 cycles of D-VTD as induction followed by ASCT, then 2 D-VTD cycles as consolidation. CD34+ stem cells were collected using cyclophosphamide with granulocyte colony stimulating factor. During treatment, patients were given antimicrobial prophylaxis as per clinical practice. High-risk CAs (HRCAs) patients (including ≥1 among del(17/17p), t(4;14), t(14;16) and gain/amp(1q)) were treated with tandem ASCT. From December 2021 to April 2024, 49 NDMM patients (median age 57 years; 53% males) were treated at Careggi Hospital; 45% were stage ISS-I, 23% ISS-II, 32% ISS-III. During induction, 5 infections were reported, mostly G3-4, including 1 pneumonia requiring hospitalization and 1 SARS-CoV2 infection causing death. Among 46 patient proceeding to mobilization, infections occurred in 4 (9%), 3 of them requiring hospitalization. A first ASCT was performed in 39 patients; 40 infectious complications were seen in 26 patients (67%) including fever of unknown origin (FUO) (50%), sepsis (30%) mainly sustained by Gram negative agents (70%), pneumonia (10%) and UTIs (7%); all of them required broad-spectrum antibiotic therapy (mainly piperacillin/tazobactam) for a median of 5,5 days (range 4-15 days) but none demanded for treatment intensification. Infectious events prolonged median hospitalization length of 1,5 days. Of 16 (35%) patients harbouring HRCAs, 5 underwent second ASCT. Infection rate was similar among first and second ASCT (67% and 60% respectively). Among

4 infection episodes occurring in 3 patients, 3 of them were FUO (75%), 1 pneumonia and 1 sepsis and UTI. None infection-related deaths were seen during the ASCT procedures. In our experience the quadruplet D-VTD appeared safe and tolerable.

P075

THE ROLE OF IMAGING IN MULTIPLE MYELOMA: LOW-DOSE WHOLE-BODY CT (WBLD-CT) AND WHOLE-BODY MRI (WB-MRI) IN BONE INVOLVEMENT ASSESSMENT IN MULTIPLE MYELOMA

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Abstract. MM is one of the most common hematological malignancies, with bone involvement being one of its most common features and representing the main cause of morbidity. Recent diagnostic innovations achieved significant impact on patients' overall survival and quality of life: low-dose whole-body CT (WBLDCT) and whole-body MRI (WBMRI) could be a useful radiological combination to detect the presence of early bone involvement.

Methods. We restrospectively identified 63 patients from 2021 to 2023 in our Centre, with newly diagnosed SMM or MM, who performed both WBLDCT and WBMRI at diagnosis. The WBLDCT was considered positive in case of more than one lytic bone lesion > 5 mm, according to IWMG Criteria. The WBMRI was considered positive in case of more than one restricted focal bone lesion > 5 mm, according to MYRADS Criteria. Subsequently we combined serological data with the evidences from the multimethod imaging.

Results. We identified 63 patients (37 male and 26 female) with a median age of 68 years (range: 34-86y) that performed both WBLDCT and WBMRI at the diagnosis. The 68% (43 patients) had SMM, while the 32% (20 patients) had MM. Among the 43 patients with SMM who performed both WBLD-CT and WB-MRI at the diagnosis, most of them showed no sign of bone involvement disease both in CT and MRI, although in 9 patients the WB-MRI detected a single focal lesion > 5 mm previously reported as negative for bone involvement on WBLDCT. According to our internal guidelines, these 9 patients received additional radiological follow-up, in order to detect early bone disease progression. Among the 20 patients affected by MM, 3 of them met the SlimCRAB criteria without any bone involvement (1 with more than 60% BMPCs, 2 with FLCr more than 100 and more than 60% BMPCs). The bone involvement was always present in the others 17 patients: one or more restricted bone lesions were reported on WBMRI in 4 of them, with no lytic lesion on WBLDCT. The other 13 patients showed both WBLDCT and WBMRI positive for bone involvement.

Conclusions. The role of imaging techniques has increased in significance for the diagnosis, staging, and treatment monitoring of MM. In our experience the multidisciplinary approach including multimethod imaging (WBLDCT and WBMRI) is recommended to early detect and monitor the bone disease in MM. WBMRI showed more accuracy in revealing bone involvement instead of WBLDCT.

P076

FEASIBILITY OF THE TRIPLE REGIMEN DARATUMUMAB-LENALIDOMIDE-DEXAMETHASONE (DARA-RD) IN ELDERLY FRAIL PATIENTS WITH MULTIPLE MYELOMA (MM)

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In recent years, the outcome of elderly MM patients has significantly improved due to the availability of more effective and less toxic drug combinations. Some of these combinations could be offered even to elderly frail patients, in case their comorbidities could potentially predict an acceptable survival duration and a good quality of life. The present analysis includes 28 consecutive MM patients > 72 yrs that have been treated with DARA-RD regimen at our Institution. Seventeen patients (61%) had newly diagnosed MM while 11 had relapsed/refractory disease. Patients have been treated with a median of 10.5 cycles (range 1-29) Results obtained in frail patients (N= 14, median age 84 yrs, range 80-89) do not differ significantly from those observed in unfit patients (N=14, median age 77 yrs, range 72-79), both in terms of response (≥ VGPR observed in 10 *vs* 9 patients) and response duration (9 *vs* 12 mos). Remarkably, DARA-RD triplet was extremely well tolerated, as permanent treatment interruption occurred in the same percentage of patients (20%), both in frail and unfit group. Major toxicity included neutropenia and infections. Our results, although preliminary, suggest that DARA-RD combination could be proposed even in selected (limited comorbidities, availability of a caregiver) unfit MM patients.

P077

EFFICACY AND SAFETY OF TALQUETAMAB IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): RESULTS FROM A REAL-LIFE EXPERIENCE IN CAMPANIA.

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Background. Multiple Myeloma (MM) presents significant challenges in treatment due to its complexity and potential for relapse. Talquetamab, a bispecific antibody construct, targets both G protein-coupled receptor class C group 5 member D expressed on myeloma cells and CD3 expressed on T cells, stands out as a promising advancement in the field.

Methods. Here we evaluated the use of Talquetamab in a real-life experience through Early Access Program (EAP) in Hematology of AOU Federico II, in Naples.

Results. From December 2022 to January 2024, 5 patients were enrolled through the EAP program. The median age was 65 years (range 64-73). Of 5 patients, 3 were classified stage ISS I (60%), 1 was stage ISS II (20%) and 1 was stage ISS III (20%). One patient (20%) had extramedullary disease. Their median prior lines of therapy stood at 7 (range 7-15). Notably, 60% of the cohort had undergone previous stem cell transplantation, highlighting the advanced nature of their disease. Furthermore, 80% were triple refractory and 20% of the patients were classified as penta-refractory. In the entire sample, the median follow-up was 4 months (range: 2-9), with a median number of administrations received of 10 (range 5-20). The ORR was found to be 80% (4/5 patients), with 60% achieving complete response (3/5 patients), 20% achieving very good partial response (1/5 patients), and one patient showing no response to treatment, leading to progression of disease and subsequent death. The median PFS at 4 months was 80% and the median OS at 4

months was also 80% (Figure 1). Furthermore, the median time to response was 8 weeks (rang: 8-13), and the time to best response was 8 weeks (range 8-13). Cytokine release syndrome (CRS) occurred in 60% of patients, and all three patients with grade 2 CRS received tocilizumab. Hematologic toxicity occurred in 60% of the patients (neutropenia 20%, anemia in 20% and thrombocytopenia in 20%). All 5 patients experienced skin toxicity. During follow-up, common adverse events all resolved with specific therapy. No infectious events occurred in the examined population. The management of adverse events requires a multidisciplinary approach to ensure a good quality of life for heavily treated MM patients.

Conclusions. The data from our real-life experience with Talquetamab, although from a small population with a short follow-up, confirm those from the MajesTec-1 study. Further follow-up is certainly required.

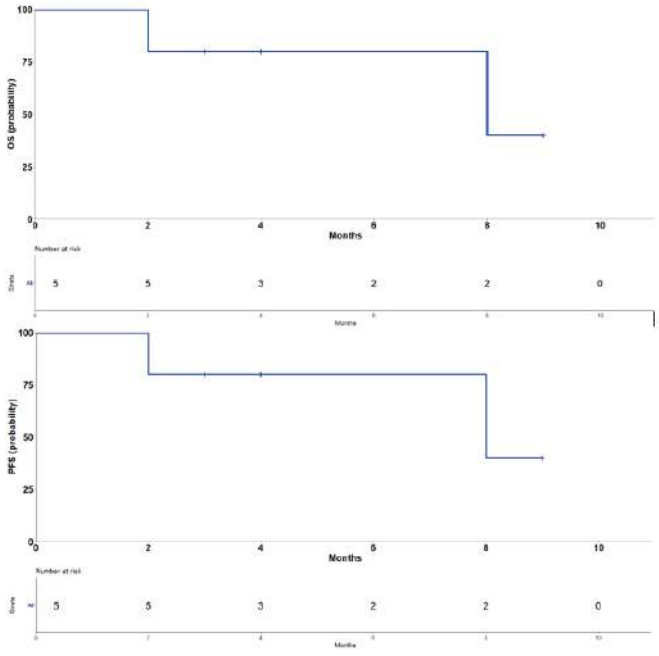

Figure 1.

P078

DOES THE NEUTROPHIL-TO-LYMPHOCYTE RATIO IN MULTIPLE MYELOMA STILL HAVE A ROLE IN THE ERA OF IMMUNOTHERAPY?

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Raised neutrophil-to-lymphocyte ratio (NLR), a biomarker for systematic inflammation, has been linked with a poor prognosis in patients affected by Multiple Myeloma (MM) treated with standard chemotherapy. However the introduction of monoclonal antibodies have revolutionized MM therapy in the latest years improving the ORR, PFS and OS. Actually, monoclonal antibody-based therapies are standard induction therapies for transplant-eligible and ineligible patients with newly diagnosed multiple myeloma (NDMM) and in patients with relapsed and/or refractory multiple myeloma (RRMM). This study aims to examine the evolving role of NLR in the context of MM treatment, particularly in the anti-CD38 antibodies era. In this study we included 61 patients with diagnosis of MM performed between 2012 and 2024 at the Fondazione Policlinico Universitario Campus Bio-medico. All patients were treated with anti-CD38 antibodies-based regimens as first (43/61) or second line (18/61). We collected and analyzed data on demographics, prognostic markers and laboratory parameters. The median age at diagnosis was 69 years (38-86).

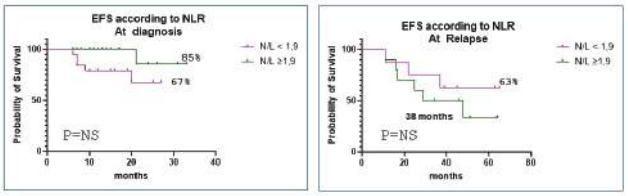

Figure 1.

According to cutoff value 1.9 from the Receiver Operating Characteristic curve (ROC), patients were separated into two groups: high-NLR group (H-NLR, n=28/61) and low-NLR group (L-NLR, n=33/61). In our study, we observed no meaningful divergence between the two groups regarding age, albumin levels, hemoglobin levels, ISS stage, plasma cell percentage, or cytogenetics. In terms of hematological response (HR), we find a major incidence of a very good partial response or better (≥VGPR) in H-NLR group compared with the L-NLR group (31 *vs.* 20; log-rank P-value 0.017). The median EFS and OS were 48 and 67 months, respectively. According to the NLR, we observed a positive trend in EFS in H-NLR group (85% versus 67%, P=NS) at diagnosis, whereas we observed an opposite behavior at first relapse. (Figure 1). In our study population, treatment with anti-CD38 antibodies appears to counteract the negative impact of NLR on the EFS and OS of MM patients at diagnosis. However, these results do not seem to be confirmed at relapse. Given the limitations of our cohort, further data are needed to validate these findings and to elucidate their biological underpinnings in the era of evolving MM therapeutics.

P079

EFFICACY AND SAFETY OF TECLISTAMAB IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): RESULTS FROM A REAL-LIFE EXPERIENCE IN CAMPANIA.

A. Perrotta[1], M.L. Giannattasio[1], L. Elefante[1], R. Spisso[1], I. Conversano[1], F. Grimaldi[1], S. Avilia[1], S. Palmieri[2], S. Rocco[2], N. Pugliese[1], A. Leone[1], R. Della Pepa[1], A. Picardi[2], F. Pane[1]

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Background. Teclistamab is the first approved T-cell redirecting bispecific antibody for adult patients with relapsed/refractory MM (RRMM), targeting both CD3 receptor on T cells and BCMA on MM cells and leading T-cell activation and subsequent lysis of myeloma cells.

Methods. We conducted a real-life study comparing the efficacy and safety of Teclistamab with the MAJESTEC-1 study. Six RRMM patients, who had failed four prior lines of therapy (PIs, IMiDs, anti-CD38 mAbs and anti-BCMA), were enrolled from December 2022

to March 2024, treated under an expanded access program at A.O.U. Federico II and A.O.R.N. A. Cardarelli of Naples.

Results. Average age was 62 y.o. (range 53-70), median time from diagnosis was 10 years (range 6-22). Of 6 patients, one had diagnosis of extramedullary plasmacytoma, 5 of diagnosis of multiple myeloma stage II and 1 stage III according to ISS. One patient had high cytogenetic risk. 80% of patients received prior autologous hematopoietic stem cell transplantation, 80% of patients were triple-refractory and 20% were penta-refractory. CRS occurred in all patients, treated either with tocilizumab or steroids and paracetamol. Hematologic toxicity affected 83.3% of patients, including neutropenia in 3 patients (2 of grade 3/4), anemia in 4 patients (2 of grade 3/4), and thrombocytopenia in 3 patients (2 of grade 3/4). Infections occurred in 4 of 6 patients, with pneumonia being the most common, affecting 33.3% (2 patients) and caused by various pathogens (Klebsiella Pneumoniae, Acinetobacter, E. Faecalis, Covid-19). One patient developed grade 4 pneumonia with sepsis, resulting in death. Supportive therapy with immunoglobulins significantly reduced all infectious events. The median follow-up was 8 months (range 3-9), with a number of administrations equal to 27 (range 11-32). Primary endpoint was the ORR, that was 100%, with RC 50% (3/6), PR 16.6% (1/6), VGPR 16.6% (1/6) and 16.6% not available. In our study median PFS and median OS at 4 months were, respectively, 60% and 80% (Figure 1). Furthermore, the median time to response was 6 weeks (range: 6-12), and the median time to best response was 9 weeks (range: 7-12).

Conclusions. In our real-life experience, Teclistamab demonstrates a feasible profile, representing a new frontier in MM therapeutic strategies. The toxicity profile of Teclistamab underscores the importance of vigilance towards infections, with management strategies closely tied to neutropenia and hypogammaglobulinemia.

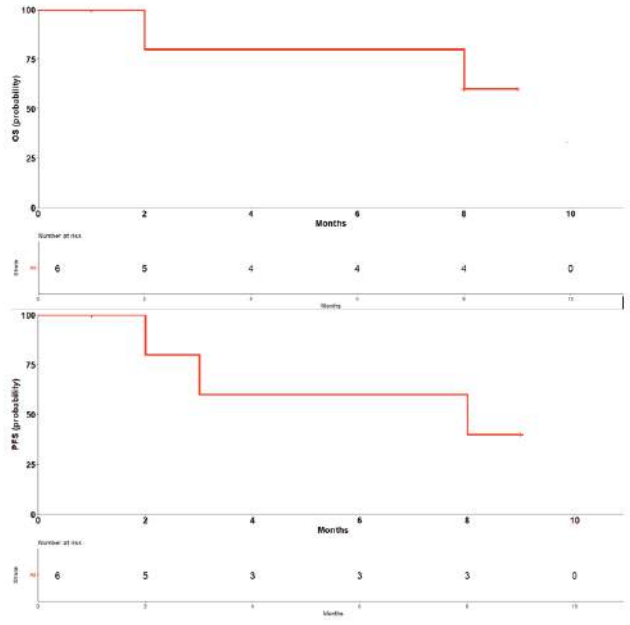

Figure 1.

P080

PATHOLOGICAL PLASMA CELLS/NORMAL PLASMA CELLS RATIO AS A PREDICTOR OF PFS IN MRD-POSITIVE MULTIPLE MYELOMA PATIENTS - A MONOCENTRIC EXPERIENCE

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Aims. Since 2018 in our center we monitored the MRD at various checkpoint in transplant eligible Newly Diagnosed Multiple Myeloma patients. Given the limited number of patients treated at our center, we had no negative MRD patients at the given timepoints (after 4 and 6 cycles of induction, after autologous hematopoietic stem cells transplantation). Therefore we tried to explore retrospectively the possible role of pathological/normal plasma cells ratio as predictor of relapse.

Table 1.

	VTD (N = 37)	D-VTD (N = 11)
Median Age (Range)	61 (43-71)	57 (39-74)
Sex		
Male (%)	21 (56.8)	6 (54.5)
Female (%)	16 (43.2)	5 (45.5)
M-Protein Type (%)		
IgG k/l	20/3 (54/8.1)	7/2 (63.6/18.2)
IgA k/l	3/5 (8.1/13.5)	1/0 (9.1)
IgM k/l	0/0	0/0
Light chain kappa	2 (5.4)	0
Light chain lambda	3 (8.1)	0
ISS (%)		
1	10 (27)	3 (27.3)
2	3 (8.1)	0
3	10 (27)	6 (54.5)
Not evaluable	14 (37.8)	2 (18.2)
Poor Cytogenetic (%)		
t(4 ;14), t(14 ;16) ; del17p ; amp/gain 1q		
1	5 (13.5)	1 (9.1)
> 2	2 (5.4)	3 (27.3)
R-ISS (%)		
1	5 (13.5)	2 (18.2)
2	9 (24.3)	2 (18.2)
3	2 (5.4)	5 (45.5)
Extramedullary Disease (%)	6 (16.2)	3 (27.3)
Number of ASCTs (%)		
1	16 (43.24)	9 (81.8)
2	21 (56.76)	2 (18.2)
Median Follow Up (Months)	122.75	28.92
Median PFS	Not reached	Not reached
Patients switched to second-line therapy (%)	10 (27)	0
Deaths (%)	2 (5.4)	0

Methods. The study population is composed of 48 patients. 37 patients were treated with VTD, 11 with Dara-VTD. Median follow up was of 122.75 months for the VTD group and 28.92 months for the Dara-VTD one. 2 patients in the VTD group were R-ISS 3, 5 in the Dara-VTD one. 2 patients had two or more high risk cytogenetic alterations in the VTD group, 3 in the Dara-VTD one. 6 patients had extramedullary disease in the VTD group, 3 in the Dara-VTD one. All patients reached at least a Very Good Partial Response after the induction, except for 8 patients in the VTD group that reached a Partial Response. The number of autologous hematopoietic stem cells transplantation (ASCT) received was determined by the cytogenetic risk and the response after the first ASCT: tandem-ASCT was performed in patients with high cytogenetic risk and/or without improvement of the response after the first ASCT. 16 patients received one ASCT in the VTD group, 9 in the Dara-VTD one; while tandem-ASCT was received respectively by 21 and 2 patients. Median PFS wasn't reached in either group. MRD was evaluated by NGF with a

sensitivity of 10-5, following the Euroflow group consensus. A ROC curve was performed to determine which cut-off of ratio pathological/normal plasma cells had the best sensitivity and specificity in predicting relapse. The analysis was performed based on values obtained at each time-point. A Kaplan-Meier curve was performed to determine difference in terms of progression free survival between patients with different cut-off of pathological/normal plasma cells ratio.

Results. With the limits linked to the retrospective analysis, the number of patients and the length of the follow up no statistically significative cut-off of pathological/normal plasma cells ratio was found to be predictive of relapse at the given timepoints.

P081

LENALIDOMIDE EFFECTS ON PERIPHERAL BLOOD STEM CELL COLLECTION IN PATIENTS WITH 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-arm bi-center experience, we investigated PBScC efficiency and autologous stem cell transplant (ASCT) engraftment after lenalidomide-based regimens, and results were compared to thalidomide-treated control population.

Methods. A total of 34 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). PBScC failure was defined as a CD34+ cell count<2 x 10^6/kg.

Results. PBScC was performed after more than 12 months from diagnosis in 41% *vs* 17% (P<0.005) of LT and TT cohorts, respectively. PBScC was performed for LT and TT arms in complete (CR; 50% versus 8%), very good partial (VGPR; 36% versus 75%) and partial response (PR;14% versus 17%) (P=0.04). Stem cell mobilization was performed using G-CSF, plerixafor or cyclophosphamide in 95% *versus* 17%, 41% versus 0, 23% versus 100% (P<0.005) subjects for LT and TT populations, respectively. 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), and delayed mobilization was more frequent in LT patients (77% versus 42%; 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 employed for 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 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 (%)			NS
-Male	10 (45)	7 (58)	
-Female	12 (55)	5 (42)	
M-protein type, n (%)			NS
-IgG	14 (64)	11(92)	
-IgA	10 (22)	-	
-Micromolecular	2 (9)	1 (8)	
-Not secement	1 (5)	-	
Light chain type, n (%)			NS
- Kappa	15 (68)	11 (92)	
- Lambda	7 (32)	1 (8)	
Body weight, n (%)			NS
- ≤ 65 kg	5 (23)	2 (17)	
- > 65 kg	17 (77)	10 (83)	
Median body weight, kg, (range)	76 (49-96)	70(49-94)	
Median previous treatment, n (range)	1 (1-3)	1 (1-1)	NS
What lenalidomide/thalidomide-based treatment, n (%)			
-Bortezomib-lenalidomide-dexamethasone (VRD)	18 (82)	-	
-Carfilzomib-lenalidomide-dexamethasone (KRD)	4 (18)	-	
- Bortezomib-thalidomide-dexamethasone (VTD)	-	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 (%)			**0.04**
-Complete response	11(50)	1 (8)	
-Very good partial response	8 (36)	9 (75)	
-Partial response	3 (14)	2 (17)	
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

P082

REAL-WORLD EXPERIENCE ON MULTIPLE MYELOMA TREATMENT IN A SINGLE INSTITUTION: EVALUATION OF DIFFERENT RESPONSE RATE BY THERAPY APPLIED

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Introduction. Despite its incurability, multiple myeloma (MM) has a wide therapeutic range that changed significantly over the decades. This evolution is evident also from small patient case studies. We conducted a retrospective analysis, in a single-center, on 111 MM patients diagnosed in our center from 2009 to date. Median age was 62 years and 55% of patients were male. Notably, the 54,95% patients were under 70 years old, and 15 of them were under 50 years old.

Results. Our study focused on genetic, cytogenetic, and molecular alterations. Strikingly, the subgroup of patients under 50 exhibited a threefold higher frequency of these alterations compared to the rest of the cohort. Additionally, 77% of the patients were classified as stage 3 according to the International Staging System (ISS). Regarding therapies, 35% of patients received the DRD regimen, 18.9% were treated with DVTD, 14.3% with VTD, 11.7% with VD, 10.2% with RD, 6.3% with VMP and finally, 3.6% with PAD. Regarding treatment, 38 patients discontinued first-line therapy. Among this group: 23 patients discontinued due to disease progression (60%). 14 patients stopped treatment due to complications, including 9 cases of cardiovascular complications (88% of these were on Lenalidomide

therapy). One patient discontinued treatment due to toxicity. Despite many patients being treated in the pre-daratumunab era, we obtained a median progression-free survival 2 (PFS2) of 67,5 months. Progression-free survival 2 (PFS-2), defined as the time from randomization to progression on first subsequent therapy, has been proposed as a surrogate for OS.

Conclusions. The therapeutic landscape of MM drastically changed in recent years and the optimal therapeutic algorithm, considering both characteristics of the disease and the patient, is fortunately destined to further evolve. We obtained a remarkable PFS2 indeed, regardless of treatment, risk stage and a significant first-line discontinuation rate. CAR-T and bi-specific antibodies will be soon embodied in our therapeutic strategies, while some therapeutic agents may become obsolete or unusable, but, in our clinical practice, they will exceptionally help when the most innovative therapies cannot be used, contributing to prolong survival and move on to a subsequent therapeutic line.

Chronic lymphocytic leukemia and lymphoproliferative syndromes

P083

COMPARATIVE INCIDENCE OF ATRIAL FIBRILLATION (AF) IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) PATIENTS TREATED WITH ACALABRUTINIB AND IBRUTINIB: A RETROSPECTIVE REAL-WORLD ANALYSIS FROM TWO ITALIAN CENTERS

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Background. Bruton tyrosine kinase inhibitors (BTKi), such as ibrutinib first in class, and acalabrutinib second generation BTKi, are pivotal in treating CLL but exhibit differing associated risk of AF. This study aimed to compare the incidence of AF between these drugs in a real-life setting, assessing the impact of treatment duration and patient characteristics on AF risk.

Methods. A retrospective analysis was conducted on 170 CLL patients treated for at least six months with ibrutinib (n°104) and acalabrutinib (n° 66) between 2014 and 2023. Demographic, biologic, and clinical data at baseline were collected, including baseline echocardiographic findings (Table 1). Cumulative incidences of AF at 12, 24 and 36 months were calculated, and Cox proportional hazards were utilized to obtain hazard ratios (HR).

Table 1. Patients's characteristics according to BTKi.

		Total	Acalabrutinib	Ibrutinib	p
Total N (%)		170	66 (38.8)	104 (61.2)	
Males		108 (63.5)	47 (71.2)	61 (58.7)	0.135
Months from diagnosis to BTKi: Median (IQR)		46.0 (12.5 to 90.8)	32.6 (6.4 to 65.2)	55.7 (20.4 to 98.0)	0.022
Previous Lines: Median (IQR)		0.0 (0.0 to 1.0)	0.0 (0.0 to 0.0)	1.0 (0.0 to 2.0)	<0.001
IGHV Unmutated		94 (72.3)	43 (72.9)	51 (71.8)	>0.999
NOTCH1 Mutated		40 (30.8)	23 (42.6)	17 (22.4)	0.023
TP53 Disrupted		59 (34.7)	14 (21.2)	45 (43.3)	0.005
del11q		24 (15.1)	13 (21.7)	11 (11.1)	0.116
del13q		57 (36.1)	26 (44.1)	31 (31.3)	0.149
Tris12		29 (18.4)	12 (20.3)	17 (17.2)	0.776
FISH neg		67 (42.1)	19 (32.2)	48 (48.0)	0.075
Age at start BTKi: Median (IQR)		71.8 (64.4 to 77.0)	73.5 (65.5 to 79.1)	71.4 (62.9 to 76.0)	0.061
Hb mg/dl: Median (IQR)		11.4 (9.5 to 12.7)	11.4 (9.5 to 12.7)	11.4 (9.5 to 12.6)	0.716
PLT/ul: Median (IQR)		150000 (100000 to 197500)	141000 (102500 to 219500)	151000 (99000 to 195000)	0.657
Valvular Insufficiency		29 (17)	12 (18.2)	17 (16.3)	0.920
Atrial Dilation		20 (11.8)	9 (13.6)	11 (10.6)	0.719
Other Ecochardiographic Abnormalities		73 (42.9)	28 (42.4)	45 (43.3)	>0.999
Any Ecochardiographic Abnormalities		78 (45.9)	28 (42.4)	50 (48.1)	0.573
Rai Stage at start BTKi	0-II	82 (49.4%)	34 (41.5%)	48 (58.5%)	0.822
	III	45 (27.1%)	17 (37.8%)	28 (62.2%)	
	IV	39 (23.5%)	14 (35.9%)	25 (64.1%)	
ECOG >1		10 (7.4)	7 (4.5%)	3 (5.5%)	0.192
Creatinine Clearance: Median (IQR)		67.4 (53.1 to 85.3)	68.2 (54.0 to 79.3)	67.0 (52.7 to 86.8)	0.919
CIRS: Median (IQR)		4.0 (2.0 to 6.0)	3.0 (2.0 to 6.0)	5.0 (2.0 to 6.0)	0.208
CIRS 3+		63 (37.1)	0 (0.0)	63 (60.6)	<0.001
Prior History of Arrhythmia		18 (10.7)	7 (10.6)	11 (10.7)	>0.999
Hypertension		76 (45.5)	28 (42.4)	48 (47.5)	0.625
Smoking Status		67 (39.4)	21 (31.8)	46 (44.2)	0.146

Results. The median follow-up was 36.8 months for ibrutinib and 8.29 months for acalabrutinib. At 12 months, the cumulative incidence of AF was 7.4% for acalabrutinib and 8.9% for ibrutinib, increasing to 11.9% and 15.9% and to 11.9 and 19.9% at 24 and 36 months, respectively. The hazard ratio for ibrutinib compared to acalabrutinib at 12 months was 1.33 (0.36-4.97, p=0.667), showing no

significant adjusted difference. For treatment-naïve patients, cumulative incidence of AF was 2.1% for acalabrutinib both at 12, 24 and 36 months, while for ibrutinib were 5.1%, 11.4 and 14.8%, respectively. Overall incidence rates per 100 patient-years were 7.59% for acalabrutinib and 6.6% for ibrutinib; in the treatment-naïve subgroup these rates were 2.3% and 4.5%, respectively. Significant predictors for AF included dilated atria and a previous history of arrhythmia, which markedly increased AF risk and retained their significance in multivariable analysis (p=0.005, p=0.002, respectively).

Conclusions. Although cumulative incidence and per-person-year incidence rates of AF were higher in the ibrutinib group at later time points, the lack of significant differences in adjusted hazard ratios suggests that the inherent risk of AF may be comparable for both drugs, according to a specific class-effect profile. This study highlights the need for further research with balanced follow-up periods and larger sample sizes, to fully understand the long-term risks of AF associated with BTKi and to guide more personalized patient management strategies.

P084

THE 10-5 CUT-OFF IN BONE MARROW-MEASURED MRD CORRELATES WITH POSITIVE SURVIVAL OUTCOMES IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction. Measurable residual disease (MRD) proved itself as a powerful prognostic factor in CLL clinical trials and is set out to reshape CLL treatment strategies by acting as a surrogate endpoint in clinical trials and allowing the development of MRD-guided treatment strategies. In this study, we aimed to explore the value of a lower MRD threshold of 10^{-5} (uMRD5) and its correlation with survival outcomes compared to 10^{-4} (uMRD4).

Methods. We retrospectively reviewed the electronic medical records of 97 patient with CLL treated at Hematology Unit of Padua University Hospital who underwent MRD evaluation in bone marrow (BM) or peripheral blood (PB) through multiparametric flow-cytometry after treatment with chemo-immunotherapy (CIT) or targeted agents. Patients were stratified according to MRD status at the end of treatment, those achieving MRD $<10^{-5}$ were categorized as uMRD5 and those with MRD $\geq 10^{-5}$ as dMRD5.

Results. A total of 97 patients had a MRD measurement either from BM (n=64; 66%), PB (n=78; 80.4%) or both (n=45; 46.4%). Median age was 69 years, 29 patients were treated with CIT (29.9%) and 70 with target therapies (70.1%). uMRD4 was achieved in 39 (50%) in PB and 21 (32.8%) in BM, while uMRD5 in 28 (35.9%) in PB and 12 (18.8%) in BM. Obtaining a uMRD5 in PB was significantly associated with uMRD4 in BM (p<0.001). There were no statistically significant differences in terms of clinical and biological variables (treatment type, rate of IGHV status, FISH abnormalities and *TP53*/*NOTCH1* mutations) between uMRD5 and dMRD5 patients. BM uMRD5 correlated with better 5-year time to next treatment (TNTT) (100% *vs.* 50%; p=0.003) (Figure 1A) and 5-year overall survival (OS) (100% *vs.* 65%; p=0.02), unlike PB uMRD5 (5-year TTNT: 66% *vs.* 65%; p=0.4; 5-year OS: 82% *vs.* 72%; p=0.8). Overall, BM MRD was a better predictor of TNNT than PB MRD (AUC: 0.81 *vs* 0.71) (Figure 1B). Moreover, the uMRD5 threshold conferred better sensitivity (100% *vs.* 90.9%) and NPV (100% *vs.* 90.5%) to identify patients who will ultimately relapse compared to the uMRD4 threshold (Figure 1C).

Conclusion. In this study we explored the role of a lower MRD threshold of 10^{-5} to predict outcome in CLL patients. This exploratory work paves the way for the possible consideration of a lower MRD threshold in trials, enabling the identification of a patient population with even better outcomes than that identified by higher thresholds.

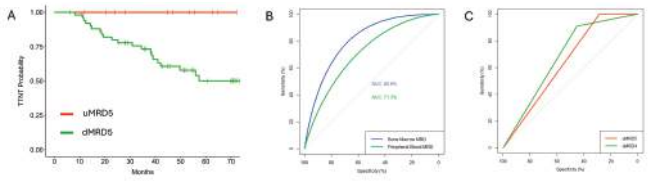

Figure 1.

P085

ADIPONECTIN'S SERUM LEVEL CORRELATION WITH KNOWN PROGNOSTIC FACTORS IN B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): A PROSPECTIVE STUDY IN TREATMENT NAÏVE CLL PATIENTS

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Adiponectin is an adipokine with anti-inflammatory properties that has been linked mainly to the risk of myeloid hematological malignancies while there're controversial data regarding its role in CLL. Adiponectin level (norm. range: 2-30 ug/ml) are determined by various genetic, anthropometric, hormonal, inflammatory, dietary, and pharmacological factors. The aim of our study was to prospectively assess serum levels of adiponectin in consecutively admitted patients with treatment naïve CLL to the Hematology department of Federico II University from January 2023 until March 2024 and correlate the values with disease characteristics and known prognostic factors. Serum and total adiponectin concentration was analyzed in triplicate by an enzyme-linked immunosorbent assay using a polyclonal antibody produced entirely against a human adiponectin aminoacid fragment. Routine laboratory studies consisted of complete blood count and blood chemistry, as well as NGS analysis for IGHV (MUT or UNMUT) and TP53 mutational assessment (MUT or WT), karyotype analysis and FISH analysis. Biometric data analysis (BMI and waist circumference) and pharmacological anamnesis was also performed. A total of 40 patients were enrolled with median age 56 (range, 48-72), the 70% (28/40) was male; BMI was under 30 in all patients, median waist circumference was 95 cm (range, 75-112). The 37% (15/40) had RAI stage I and the 30% RAI Stage IV. The 20% of patients were TP53-MUT and the 55% IGHV-UNMUT. At cytogenetic and FISH analysis: 7 patients had del13 (2 of them with concomitant del11), one single del11 and 3 del17. Overall 7 patients had complex karyotype with≥ 3 alterations. Median white blood cell count at enrolment was 58.390/mmc (range, 2870-378000/mmc). Overall, a total of 24 patients (65%) had indication to start treatment for either lymphoadenomegaly (>10 cm at ultrasound exam), severe splenomegaly or cytopenia. Adiponectin serum median level was 14.38 ug/mL (range, 5.56-24.16 ug/ml). At t-student test, lower circulating level of adiponectin were found in patients with TP53-MUT versus TP53-WT (P=0.005; 95%CI: 1.8-8.8), in IGHV-UNMUT ver-

sus MUT (P=0.03; CI: 0.42-6.93) and in patients with indication to start treatment for bulky lymphoadenomegaly or severe splenomegaly (P=0.05; CI: 0.10-6.5) versus no indication. No difference were found for sex, age, smoke, drugs, biometrical data and cardiovascular comorbidities. At Pearson correlation, a significant inverse association between adiponectin and absolute peripheral blood lymphocyte count (r=-0.445; P=0.05) was found. We were able to demonstrate that serum adiponectin is an easy and relatively economic test to perform that inversely correlate with absolute peripheral blood lymphocyte count, disease severity in terms of splenomegaly, lymphoadenomegaly or cytopenia; moreover, with TP53-MUT CLL cells and IGHV-UNMUT cells, all markers of disease severity.

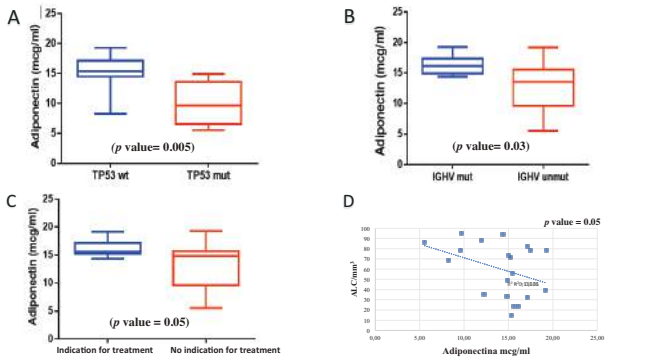

Figure 1.

P086

CONSENSUS-BASED BEST PRACTICE RECOMMENDATIONS FOR CLL MANAGEMENT IN ROUTINE CLINICAL PRACTICE IN CAMPANIA: SYSTEMATIC LITERATURE REVIEW AND CLINICAL PRACTICE RECOMMENDATIONS FROM A LOCAL CONSENSUS GROUP

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Background. A strategy was developed to standardize the management of Chronic Lymphocytic Leukemia (CLL) across academic and community hospitals in Campania, a region in southern Italy with around 6 million residents, through local consensus recommendations. This approach is critical in scenarios with incomplete evidence.

Methods. The initiative used a three-step adapted Delphi consensus process that began with a meeting on October 27th, 2023, to address CLL management. This meeting identified three main factors influencing therapy selection: patient characteristics (*e.g.*, specific comorbidities), disease-related factors (*e.g.*, high or low-risk genetic profile), and treatment regimen variables (*e.g.*, continuous *vs* fixed-duration therapy, all oral *vs* combined oral/infusional therapy, patient feasibility). Across these domains, the panel recognized 12 clinically critical questions. Notably, at the time of the first expert group meeting (October 27th, 2023), the Italian Medicines Agency had granted approval for three Bruton kinase inhibitors (BTKis) for continuous duration therapy—namely, ibrutinib, acalabrutinib, and zanubrutinib as well as the combination of Venetoclax and Obinutuzumab (VO) for fixed-duration (FD) therapy. A systematic literature review (SLR) was conducted adhering to the PICO framework, followed by two rounds of voting using an online platform to measure consensus among the panel members expressing their opinions anonymously on a 4-point Likert scale.

Results. High consensus (at least 85% agreement) was achieved for 9 of the 12 critical questions, which emphasized the necessity of genetic profiling and comorbidity assessment before therapy, the limited current role of chemo-immunotherapy (CIT), and preferred therapies based on patient genetic mutations (patients with del(17p) or TP53 aberrations and unmutated IGHV CLL patients), comorbidities, and intolerances to previous treatments. There was intermediate consensus for one question, and low consensus for two questions, with no statements falling into the lowest category of evidence (less than 25% agreement).

Conclusions. These consensus-based recommendations are intended to provide guidance for CLL management in Campania, reflecting a collaborative effort to update practices based on emerging evidence and clinical experience. The final meeting on February 27th, 2024, reinforced the need for ongoing updates and collaboration among CLL specialists in the region.

P087

CLINICAL BIOLOGIC CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH T-PROLYMPHOCYTIC LEUKEMIA (T-PLL): A SINGLE INSTITUTION REPORT

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T-cell prolymphocytic leukemia (T-PLL) is a rare lymphoproliferative disorder associated with an aggressive outcome and dismal prognosis. To better define factors affecting the survival of patients with T-PLL, we carried out a retrospective study on 31 patients diagnosed at our institution between July 1991 and September 2023. We analyzed the patient's clinical and biological profile at diagnosis, the immunophenotype pattern (CD4+CD8-or CD4+CD8+), treatment, and response to treatment. The patients' median age was 65 years (range, 32-85), the median lymphocyte count 36.2x10^9/L (range, 6.4–217 x10^9/L), and 21 patients (68%) showed marked splenomegaly. TP53 mutation was recorded in 1/14 (7%) of evaluated patients and complex karyotype (>3 aberrant clones) in 8/12 (62%) (Table 1). T-PLL cases with CD8+/CD4+ immunophenotype compared to those with CD8-/CD4+ immunophenotype were rarer (24% *vs.* 76%), involved more frequently younger age-patients (p=0.004), patients with B-symptoms (p=0.053) and complex karyotype (p=0.08). The most commonly used front-line treatments included fludarabine in 12 patients (39%), bendamustine in 4 (12%), and alkylating agents in 4 (13%). Palliative therapy was given to 3 patients, and a watch-and-wait approach was considered in a patient with a recent diagnosis. The response was assessed in 27 patients (ORR, 59%; CR, 41%; PR, 18.5%). Twenty-two (71%) patients died, mostly due to disease progression (55%) or infections (41%). The 24-month PFS was 16.6% and, 22.2%, for the 9 patients who underwent allogeneic stem cell transplantation after response. At univariate analysis, the only baseline factor with a significant impact on survival

was age >60 (p=0.05), with a trend to significance (p=0.076) for the lymphocyte count >30x10^9/L. Other factors, the immunophenotype, elevated LDH, B-symptoms, and complex karyotype had no effect on survival. CR (p=0.018) emerged as the only factor with a favorable impact on PFS. Our data confirm the very poor prognosis of patients with T-PLL and highlight the younger age of patients with CD8+/CD4+ phenotype. When possible, allogeneic stem cell transplantation should be considered for less young but still fit patients in the absence of a therapeutic approach capable of giving prolonged responses.

Table 1.

Table.1. Clinical and biologic characteristics of patients at diagnosis

	All patients	Immunophenotype of T-PLL cells		p value
		CD8-/CD4+	CD8+/CD4+	
	N (%)	N (%)	N (%)	
No patients	31 (100)	22 (71)	7 (23)	
Sex, M/F, n (%)	20/11 (65 – 35)	15/7 (68-32)	4/3 (57-43)	0.93
Median age, years (IQR)	65 (59 – 74)	70 (63-76)	49 (48 – 53)	0.004
Median follow-up, months (IQR)	86.4 (9.4 – 163)	72.7 (31.3-113)	86.4 (NA)	
Median overall survival, months (95% CI)	18.2(11.6–24.8)	13,4 (9.3 -17.6)	28.5 (0.5-58.4)	0.12
Median lymphocyte count x10^9/L (IQR)	36.2 (22.7-72.6)	48.4 (31-175.4)	34 (18.7-79.7)	0.40
Increased LDH, n (%)	23/28 (82)	16/21 (76)	6/7 (86)	1
Prominent nucleoli, n (%)	21/23 (91)	15/17 (88)	6/7 (86)	0.61
Median % positive CD38 cells	95 (70.7 – 99.3)	89 (70.7 – 96.5)	99 (13 - 100)	0.22
*TP*53 gene mutation, n (%)	1/14 (7)	1/10 (10)	0/4(0)	0.98
Complex karyotype (>3 aberrant clones), n (%)	8/12 (67)	3/7 (43)	5/5 (100)	0.08
B symptoms, n (%)	4/31 (13)	1/21 (5)	3/7 (43)	0.05
Splenomegaly (>13 cm) , n (%)	21/31 (68)	14/21 (67)	5/7 (71)	0.81
Skin involvement, n (%)	3/31 (9.6)	1/21 (5)	1/7 (14)	0.97
Ocular involvement, n (%)	3/31(9.6)	3/20 (15)	0/7(0)	0.54
SNC involvement, n (%)	0/31 (0)	0/22 (0)	0/24 (0)	-
Front-line treatment, n (%)				
Bendamustine	4/31 (13)	3/22 (14)	1/7(14)	-
Fludarabine-based treatment	12/31 (39)	7/22 (32)	3/7 (43)	-
Alkylating agents	4/31 (13)	4/22 (19)	0/7 (0)	-
CHOP	3/31 (10)	3/22 (14)	0/7 (0)	-
Campath-1H only	3/31 (10)	1/22 (5)	2/7 (29)	-
Pentostatine	1/31 (3)	1/22 (5)	0/7 (0)	-
Palliative treatment	3/31 (10)	3/22 (14)	0/7 (0)	-
Watch and wait	1/31 (3)	0/22 (0)	1/7 (14)	-
Hematopoietic stem cell transplant, n (%)	9/31 (29)	3/19 (16)	5/6 (83)	0.01
ORR, n (%)	16/27 (59)	11/19 (58)	5/6 (83)	0.51
RC	11/27 (41)	7/19 (37)	4/6 (67)	-
RP	5/27 (18.5)	4/19 (22)	1/6 (16)	-
NR	10/27 (37)	8/19 (42)	1/6 (16)	-

P088

ABSTRACT NOT PUBLISHABLE

P089

FIRST LINE TREATMENT WITH OBINOTUZUMAB AND VENETOCLAX (VO) IN CLL PATIENTS FROM THE CAMPANIA CLL GROUP: A REAL LIFE EXPERIENCE

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Aim. A retrospective real life study aimed to evaluate tolerability and safety of combination treatment with VO as first line therapy in CLL patients (pts) was conducted in 11 Campania Hematology Units

Primary endpoints. Efficacy in terms of Overall Response Rate (ORR) e Complete response rate(CR). Safety evaluated as rate of discontinuation due to AE

Secondary endpoints. Role of G-CSF Prophylaxis (PPx) to prevent infectious AE. Adherence to treatment schedule

Pts and methods. From June 2019 to March 2024 71 Pts were enrolled. Basal characteristics of pts were summarized in Table1. Treatment was started for all Pts according to current guidelines and therapy was selected by physician choice and administered following registered dose and schedule. Neutrophil counts were evaluated monthly and G-CSF administration was suggested for counts in between 1000-1500/mmc. Dose reduction and treatment discontinuation for hematological and/or extra hematological toxicities were evaluated at any time of occurrence.

Results. At a median follow-up of 12months, 59 out of 71pts(83%) were evaluable for response and 38 (53%) completed the treatment. 57 of 59 evaluable pts (96%) obtained a CR, confirmed by peripheral blood flow cytometry and imaging scan and only 2 (3.4%) a PR. A dose reduction (200mg) was observed in 9% of pts and treatment was definitively interrupted in 8 (11%) due to sAE>G3 (7 infection diseases and 1 tumor lysis syndrome). Despite all 71 Pts received Sars-Cov2 vaccination and 23% got also Tixagevimab al last 2 weeks prior treatment, 4 COVID infections were observed. All pts received cotrimoxazole/acyclovir PPx. G-CSF PPx was performed in 32 pts (45.7%) with no bacterial infections observed. The only 1 case of bacterial pneumonitis was showed in the non-PPx group. Only 4 deaths (5.6%) were observed due to COVID pneumonitis (N=2), thrombotic event (N=1) and not related cause (N=1 complication of a pre-existing SLA).

Conclusions. Our data confirmed the efficacy of VO treatment as already reported in clinical trials data and other real life experiences. The safety results seem to be better than the reported ones and this evidence could be in part related to infection PPx for both virus and bacteria. Of course a longer follow-up and an increase number of pts are needed to confirm such hypothesis. The VO treatment shows a hypothetical pharmacoeconomic advantage *vs* continuing therapy even if we correct the costs for the PFS reported for each treatment in the registration studies.

Table 1.

Sesso	M/F	29/42	
Età mediana	66 years	(40-89)	
Stato mutazionale	IgVH unmutated	34/71	49%
	IgVH mutated	35/71	50%
Fish	17 del	1/71	1%
	Complex katyotype	3/71	4%
Stage	Stage IV	27/71	38%
	Stage III	13/71	22%
	Stage II	22/71	30%
Bulky disease		2/71	2%

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CONCOMITANT USE OF BRUTON TYROSINE KINASE INHIBITORS (BTKI) AND DIRECT ORAL ANTICOAGULANTS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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The concomitant use of BTKi and anticoagulants is challenging in patients with CLL, given the well-known antiplatelet effects of BTKi. Direct Oral Anticoagulants (DOACs) are the preferred antithrombotic prophylaxis in patients receiving BTKi. However, safety data on the co-administration of BTKi and DOACs are limited. We retrospectively analyzed the outcomes of 135 patients with CLL who

required treatment with BTKi (ibrutinib, 121, 90%; acalabrutinib, 12, 9%; zanubrutinib, 2,1%) at the Hematology Unit of Sapienza, University of Rome, between September 2014 and April 2024. With a median follow-up of 60.5 months (95CI% 48-73), 22 (16.2%) patients, all on ibrutinib, developed AF (18 patients) or a thrombotic event (4, arterial thrombosis, 2; myocardial infarction,1; stroke, 1), after a median time of 4 months (IQR 2.5-30.5) from the start of BTKi. Fourteen (14/22, 63.6%) patients permanently discontinued ibrutinib. Of them, 9 received DOACs, 2 antiplatelet agents, and 2 low molecular weight heparin. None of these patients experienced severe bleeding. Eight out of 14 (57%) patients died due to disease progression [Richter transformation (RT), 4; CLL, 4]. Eight (8/22, 36.3%) patients continued ibrutinib at a lower dose (280 mg daily), and all received DOACs (rivaroxaban, 3; edoxaban,3; apixaban,1; dabigatran,1). Four patients continued ibrutinib with DOACs without adverse events. Three (37.5%) patients experienced a severe bleeding (gastrointestinal, 2; hematoma, 1), and 2 with stable CLL discontinued permanently ibrutinib. An alternative DOAC was given in 2 (edoxaban, 2), while 1 received fondaparinux. In addition, a patient on apixaban recovered from thrombocytopenia after switching from ibrutinib to acalabrutinib. Five patients died: 1 (12.5%) due to RT, and 4 (50%) due to not CLL-related causes. The median survival probability from the start of anticoagulation for patients who received ibrutinib with concomitant DOACs *vs* anticoagulation alone was 72.6 months (95% CI, 55.2-88.9) versus 54.3 months (95% CI, 2.8-105.8), respectively (p=0.380, Figure 1). Although the number of patients is small, our data demonstrate that 6/8 patients with CLL who received ibrutinib and concomitant DOACs were able to continue treatment without fatal bleeding events. Further studies are needed to better define the safety profile of the co-administration of BTKi and DOACs.

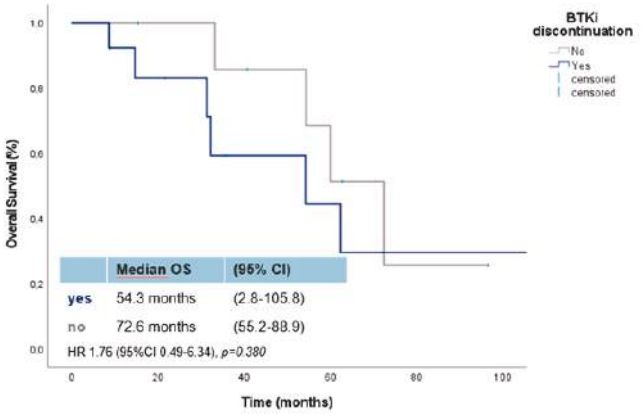

Figure 1.

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REAL WORLD EFFECTIVENESS AND SAFETY OF VENETOCLAX IN COMBINATION WITH OBINUTUZUMAB IN PREVIOUSLY UNTREATED CLL PATIENTS: A SINGLE CENTRE EXPERIENCE

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Introduction. Data from the two Phase-III studies, the CLL14 for elderly and unfit patients with chronic lymphocytic leukemia (CLL), and the CLL13 study, recruting younger and fit patients, showed promising efficacy and good tolerability of fixed-duration combination therapy with Venetoclax and Obinutuzumab (VenO). Fixed duration venetoclax-obinutuzumab (VenO) is approved for treatment of naïve (TN) chronic lymphocytic leukemia (CLL) patients with coexisting conditions. However, real-life experience with this regimen are limited.

Aim. The purpose of this retrospective observational monocentric study is to evaluate the efficacy, the quality of response and the tolerability in TN CLL patients receiving VenO in a real life setting.

Table 1.

Tab 1. VenO: pts characteristics

Median Age	68 (58-76)
Median Age < 65 yrs	6 (46%)
M/F	9/4
Stadio Binet:	
A	0/13
B	7/13
C	6/13
Tumor lysis syndrome risk category:	
Low	0/13
Intermediate	9/13
High	4/13
Median CIRS SCORE	10 (5-13)
CIRS > 6	7/13
Clearance creatinine <70ml/min	7/13
Cytogenetic subgroup	del(11q) = 2 del(17p) = 0
TP53:	
Mutated	0/13
Unmutated	13/13
IGHV mutational status:	
Mutated	7/13
Unmutated	6/13

Methods. Adult patients with CLL requiring first line therapy and treated with VenO in a single institution were included. Patient's visits were scheduled based on clinical practice and at a physician discretion. Adverse event were reported according to CTCAE 5.0. Response assessment were evaluated in line with iwCLL criteria at the end of treatment. A total of 13 patients receiving at least one dose of VenO, between July 2022 and December 2023, were included in this analysis and 6 patients completed the fixed duration treatment as planned at the time of evaluation. Median age at the timepoint of diagnosis was 64 years (range 58-76). Median age at the start of treatment with VenO was 68 years (range 58-76). 6 pts (46%) were IGHV unmutated; no pts with del (17p) and/or TP53 mutation were included. Six pts (46%) was younger than 65. Median Cumulative Illness Rating Scale (CIRS) score was 10 (range 5-13). In particular 7 pts (54%) had a CIRS score > 6 and/or creatinine clearance <70ml/min; median Charlson Comorbidity Index (CCI) was 5 (range 4-7). Cardiovascular disease was the main comorbidity. Pts' characteristic are shown in Table 1.

Results. Overall Response Rate (ORR) was 100% in the cohort

of 6 pts who completed VenO as planned; all pts achieved a complete remission (CR) at the end of treatment in both fit and unfit patients; the scheduled treatment was well tolerated without serious adverse event (SAE). In the total population of 13 pts early VenO discontinuation occurred in 3 pts (20%) due to infection toxicity. Obinutuzumab doses were not completed in 3 pts (20%) due to infections (g2-3) and hematological toxicity (g4); venetoclax dose reduction occurred in 2 patients (15%) for hematological toxicity (g4) and gastrointestinal toxicity (g2). Infusion-related reactions (all g 1-2) occurred in 8 pts (61%). No laboratory or clinical TLS occurred with VenO (Howard criteria). Treatment was administered on an inpatient basis in 4 pts (30%) with high risk TLS. Adverse events (any grade) occurred in 12 pts (92%). Grade 3-4 AEs of clinical interest were pneumonia and hematological toxicity. Three pts died due to infection (aspergillus spp, acinetobacter baumannii spp, pneumonia), 2 of them during the ramp-up phase. Covid-19 infection occurred in 5 pts (33%), 2 of them were not vaccinated for SARS-CoV-2 (0 fatal). No disease progression was documented so far.

Conclusions. In summary, this real-world, small retrospective study demonstrated that VenO treatment achieves an high response rate in both fit and unfit TN CLL/SLL pts and can be safely administered outpatient.

Haemostasis, thrombosis, thrombocytopenia and platelet disease

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TREATMENT AND SECONDARY PROPHYLAXIS WITH DIRECT ORAL ANTICOAGULANTS IN CANCER PATIENTS WITH CATHETER-RELATED THROMBOSIS

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Background. Upper extremity deep vein thrombosis (UEDVT) constitutes approximately 5-10% of all deep vein thrombosis (DVT). UEDVT is mostly secondary to triggering factors. Central venous catheters (CVCs) are a relevant thrombotic risk factors in cancer patients, with catheter-related thrombosis (CRT) being one of the most common non-infective complications in this population. Currently, there are limited data on the choice of the best anticoagulant therapy for UEDVT. General recommendations for UEDVT management have been extrapolated from data on lower extremity DVT treatment. Current guidelines recommend maintaining a functional, non-infected catheter in place, and suggest low-molecular-weight heparins (LMWHs) as the first-choice anticoagulant therapy to be continued for a minimum of three months and as long as the catheter remains in place. Cancer-associated venous thromboembolism (VTE) guidelines suggest full-dose anticoagulant therapy, with no data supporting low-dose anticoagulation for secondary prophylaxis. Additionally, data on the use of Direct Oral Anticoagulants (DOACs) in the CRT context for cancer patients are lacking.

Objectives. To assess DOAC efficacy and safety in the treatment and secondary prophylaxis of CRT.

Patients/Methods. We conducted a single-center retrospective and prospective observational study involving 25 patients with CRT, including 18 cancer patients, 16 undergoing chemotherapies. Among these 18, 9 patients received LMWHs, 2 patients received LMWHs followed by vitamin K antagonists, while 7 patients, due to non-compliance with subcutaneous therapy, were subsequently administered DOACs after a short period of LMWHs (3 treated with Edoxaban, 3 with Rivaroxaban, and 1 with Apixaban).

Results. We observed that treatment outcomes between patients treated with LMWHs and those treated with DOACs were comparable with a vein recanalization rate of 77.8% (95% CI: 52-100%) and 71.4% (95% CI: 37.2-100%), respectively. No clinically relevant non-major bleedings were detected in the DOACs-treated population. Of the 13 patients who achieved recanalization and maintain the catheter, 11 received thromboprophylaxis with DOAC. After a follow-up of at least six months, no thrombotic recurrences were recorded.

Conclusion. DOACs exhibit an efficacy and safety profile comparable to LMWHs. Further studies are needed to investigate the use of prophylactic dose anticoagulation therapy in the oncologic population.

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USE ON DEMAND OF EHLS IN WITH MILD-TO-MODERATE HEMOPHILIA PATIENTS: A SINGLE CENTER EXPERIENCE

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Background and aims. For patients (pts) affected by severe hemophilia A (HA) and B (HB), the use of extended half-life clotting factor concentrate (EHL CFC) is well established, both in the prophylaxis setting and for invasive procedures/surgery. In contrast, for pts with mild-to-moderate hemophilia, evidence is still limited. These pts could benefit from the use of EHL CFCs for the treat-ment of bleeding and pre- and post-surgical prophylaxis by maintaining prolonged hemostasis with a limited number of infusions.

Table 1. EHL CFC: extended half-life clotting factor concentrate; SHL CFC: short half-life clotting factor concentrate; FVIII: factor VIII of coagulation; HA: hemophilia A; HB: hemophilia B; LAAC: Left atrial appendage closure; D: day. *According with World Federation of Hemophilia (WFH) guidelines for the management of hemophilia – 3rd Edition.

	Hemophilia (basal level)	*Type bleeding/surgery*	*N° of infusions (EHL CFC)*	*N° predicted infusions (SHL CFC)**	*FVIII trough*	*Inhibitors after EHL*
Case 1	HA (8%)	Right elbow hemarthrosis; hemorrhoids bleeding	2;1		9% (72h)	No
Case 2	HB (20%)	Gastroscopy with biopsy	1	2	30%	No
Case 3	HA (10%)	Multiple dental extraction and implantology	1	6	20%	No
Case 4	HB (6%)	Dental extraction and removal of stitches	1	4	21%	No
Case 5	HA (13%)	Multiple dental extraction	3	7	18%	No
Case 6	HB (14%)	Dental extraction and removal of stitches	1	3	20%	No
Case 7	HB (11%)	LAAC + DAPT	1/week	3/week	20%	No
Case 8	HB (3%)	Left hip replacement	15 (since D +40)	34 (since D +40)	50% (D 1-11) 20% (D 12-40)	No

Case report. We report 8 pts with mild-to-moderate hemophilia treated with an EHL CFC (Table 1). Median age was 49 years (range 19-78), 1/8 was female, 3/8 suffers from HA and 5/8 suffers from HB. Mean basal FVIII was 10%, mean basal FIX was 11% and all were treated on demand and were not sufficient at self-infusion. First pt arrived at our attention for right elbow hemarthrosis on Friday afternoon; pt was infused with EHL CFC in order to treat bleeding and avoid weekend hospital admission. Another infusion was performed after 72 h with resolution of hemarthrosis. Pt returns 1 month later with hemorrhoidal bleeding and 1 EHL CFC infusion was performed with bleeding interruption. 3 pts underwent dental extraction (plus implantology in 1 pts) with removal of stitches using a single EHL CFC infusion. Another pts for multiple dental extractions received 3 infusions every 72h of EHL CFC to ensure trough level above 20% for 1 week. The pt had the same procedure after DDAVP complicated by major bleeding a few months earlier. Esophagogastroduodenoscopy with biopsy was performed under EHL CFCs coverage in a woman affected by HB and erosive duodenitis, without complications. Left hip replacement was performed using an EHL CFC in a pt who had previously undergone knee replacement; a comparison between the two surgeries in terms of burden of infusion was made. Last pt had a left atrial appendage closure for atrial fibrillation with subsequent need for dual antiplatelet therapy (DAPT) for 1 month. In this period to achieve trough above 20% to allow DAPT was administered EHL CFC weekly. Nor hemorrhagic complications neither inhibitor were observed.

Conclusions. In conclusion in our case series, the use of EHL CFCs in pts affected by mild-to-moderate hemophilia A and B has been shown to be safe and effective, allowing reduction in intensity of care with fewer infusions compared to standard CFC. In pts who are not able to self-inject means a saving hospital access.

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SPLANCHNIC VEIN THROMBOSIS DIAGNOSIS AND MONITORING: CLUES FOR FURTHER APPROACHES?

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Splanchnic vein thrombosis (SVT) cause remains unidentified in about 20% of cases. This retrospective study analyzed 47 patients with SVT and assessed clinical/laboratory data, veins involvement, occlusion degree, cavernoma or varices presence, spleen size, thrombophilia state, liver and spleen stiffness and therapies. Histological data from bone marrow biopsy were collected when available. The cohort consisted of 25 males and 22 females (mean age 58.6 years). Idiopathic cases were reduced to 23%. CHIP was identified in 9 cases, but no clinical differences correlated with mutations were identified. Overall, SVT was attributed to myeloproliferative neoplasms (MPN) in 10 patients. One patient was initially diagnosed with CHIP, and after a four-year interval met the criteria for MPN. A slight increase in the basophil count (mean difference [MD] +50/uL, p=0.004) was identified in patients with CHIP and a post-hoc analysis revealed that a basophil count >40/uL may be a risk factor for CHIP (OR 15, p=0.019). 21% of patients developed portal cavernomatosis, with an average onset of 6 months. Those with portal thrombosis in conjunction with mesenteric or splenic thrombosis had an increased risk for cavernoma development at the limit of significance (OR 4.9, p=0.052). Conversely, when the three veins were involved, a significant increased risk of developing cavernoma was observed (OR 13.5, p=0.003). 10 patients underwent liver and spleen elastography. Both liver (MD 2.5 kPa, p=0.011) and spleen (MD 67.3 kPa, p=0.005) stiffness were lower in patients with SVT resolution. In a post-hoc analysis, liver stiffness >6 kPa (OR 25, p=0.048) and spleen stiffness >60 kPa (OR 77, p=0.018) were associated with a risk of persistent thrombosis. Similarly, liver stiffness was greater in patients who developed portal cavernomatosis (MD 2.13 kPa, p=0.016), while both stiffnesses were greater in patients who developed esophageal varices (liver: MD 2.36 kPa, p=0.003; spleen: MD 64.6 kPa, p=0.001). Our study suggests that a significant proportion of SVTs has an underlying hematologic disorder that requires closer monitoring. Basophils count may identify suitable patients for hematologic investigation. The stratification of patients at risk for chronic complications is crucial. Consistent with this, liver and spleen elastography may be beneficial in clinical monitoring of SVT patients limiting exposure to more invasive investigations.

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THE THERAPY OF RELAPSED/REFRACTORY CHRONIC IMMUNE THROMBOCYTOPENIA PATIENTS WITH NOVEL AGENTS: A MONOCENTRIC EXPERIENCE

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Background. Fostamatinib and Avatrombopag are novel agents approved as therapy in chronic immune thrombocytopenia (ITP) patients refractory to other therapies, but is unclear which is the best terapeutic paradigm of therapy after the second line. Aim: to observe the efficacy, safety of novel agents and to identify predictive factor of response and tolerability in order to choose the optimal therapy for each ITP patient.

Patients and Methods. we retrospectively evaluated 22 patients (pts) treated from February 2022 to April 2024: 17 pts (14F/3M) were treated with Fostamatinib(F), 5 pts (5 F) with Avatrombopag(A), 3 pts (5F) received F and A (25 total treatments). The median age at the start of treatment was 57 years (range 29-85) in F treatment and 60 years (range 45-85) in A treatment. In F group the median of previous lines of therapy was 4 (range 2-11):15 pts were previous treated with Eltrombopag, 6 with Romiplostim, 9 with Rituximab, 5 pts were splenectomized, 3 pts were on antiplatelet or anticoagulant prophylaxis. At start time, 8 pts received a concomitant short course of steroids for 10-20 days for platelet count<20 x 10^9/L, 2 pts were on low dose steroid therapy for other disease. In the group of A treatment the median of previous lines of therapy was 4 (range 2-12),including Eltrombopag in whole court, Romiplostim in 4 pts, splenectomy in 2 pts and Rituximab in 4 pts. 4 pts treated with Avatrombopag were steroid-refractory and at the start they underwent to high dose immunoglobulin for platelet count less than 20x 10^9/l , 2 pts received a concomitant short course of steroids for 10-20 days ,1 pt was on low dose steroid therapy for Sjogren's syndrome. The reason of beginning Fostamatinib or Avatrombopag were refractory disease (3 pts), platelet count fluctuation or suboptimal response with high dose of TPO RAs (6 pts), loss of response to TPO RAs (3), relapse (10 pts)

Results. In F treatments 9 pts obteined a complete response (CR) in a median time of 30 days (range 6-90), 4 pts achieved a response(R) in a median time of 50 days, 3 pts were refractory, 11 treatments are ongoing after a median therapy time of 170 days (range 40-380) with persistent response, 1 pt died for other cause, 1 pt discontinued the drug for diarrhea (grade 3), 1 for hypertransaminsemia,1 for allergic reaction, 2 for no response. We observed 1 case of hypertension (grade 2), 2 cases of diarrhea (1 pt discontinued, 1 pt started a tapering with improvment), 1 pt experienced neutropenia (grade 3). In A treatmttent 6 pts obtained a CR ,1 pt a R in a median time of 23 days(range 6-40), the median time of follow up from the start of therapy was 145 days (range 13-375),7 treatments are ongoing with persistent response, 1 pt stopped the drug for no response. 3 pts experienced platelet count fluctuation. We observed no trombotic events in both groups of treatment,10 pts discontinued concomitant steroid therapy, 3 pts takes low dose of steroids for other disease

Conclusion. Fostamatinib ed Avatrombopag showed good efficacy (ORR 82% and 87% rispectively) and optimal safety (no severe adverse events) in relapsed/refractory ITP pts, in patients with suboptimal response to second line of therapy, in steroid-refractory patients, but we need a longer observation time to define the duration of the response and the possibility of a sustained response

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12 MONTHS JOINT HEALTH EVALUATION IN HEMOPHILIA A PATIENTS TREATED WITH EMICIZUMAB: A SINGLE CENTRE EXPERIENCE

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Background and Aims. Severe hemophilia patients commonly experience regular bleeding into joints, which may result in joint damage and degenerative arthropathy. Emicizumab has previously demonstrated efficacy in reducing the occurrence of joint bleeds and target joints, along with having a favorable safety profile; however, data on long-term effects on joint health are lacking. The aim of this study is to evaluate joint health in adult severe hemophilia A patients treated with Emicizumab through US HEAD US score (Hemophilia Early Arthropathy Detection with Ultrasound), HJHS (Hemophilia Joint Health Score), ABR (Annualized Bleeding Rate) and NRS (Numeric pain Rating Scale) evaluated at baseline, after 6 months (T1) and after 12 months (T2) of regular Emicizumab prophylaxis.

Methods. Adult severe hemophilia A patients treated with Emicizumab were included. FVIII inhibitors patients were excluded. At each visit (baseline, after 6 months and after 12 months) articular function was evaluated with HJHS and HEAD US score. Joint pain (NRS), through level and prophylaxis efficacy whit ABR were monitored, as well as target joints.

Results. We evaluated 9 patients. Median age was 24 years old (IQR1-3 22-56), median target joints value was 2 (IQR1-3 2.00-6.00). ABR was 0 for all patients at each timepoint. Median HEAD US, NRS and HJHS at baseline, at T1 and at T2 are shown in Table 1. As reported, no significant differences were found within the 3 timepoints. A univariate correlation analysis was performed and no significant correlations within variables was found; furthermore, no significant variations during observation period was found.

Conclusion. Emicizumab has demonstrated safety and efficacy in prevent bleeding, but data regarding evaluation of long-term joint health are still lacking. Despite reduced sample size, our analysis suggests that a 12 months treatment evaluation no significant differences in HEAD US score, HJHS and NRS were found. These data are in accordance with a good protection on articular bleeding (especially regarding microbleeds that are responsible of arthropathy progression), but 12 months observation may be too early to detect significant intrarticular changes. Longer follow up is needed to confirm this preliminary data.

Table 1.

VARIABLES	T0			T1			T2			FRIEDMAN TEST P.VALUE
	Median	q1	q3	Median	q1	q3	Median	q1	q3	
HEADUS	9.00	3.00	15.00	9.00	6.00	19.00	5.00	2.00	17.00	0.607
NRS	1.00	0.00	1.00	1.50	0.00	3.00	2.00	0.00	4.00	0.223
HJHS	6.00	0.00	15.00	9.00	2.50	23.00	12.00	0.00	13.00	0.497

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ABSTRACT NOT PUBLISHABLE

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PROPHYLACTIC USE OF DANAPAROID AFTER LIVER TRANSPLANT IN HEPARIN-INDUCED THROMBOCYTOPENIA (HIT): A CASE REPORT

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Background. Heparin-induced thrombocytopenia (HIT) is an immune-mediated disorder of platelet caused by antibodies against a platelet factor 4 (PF4)-heparin complex and may lead to life threatening thrombosis. The diagnosis of HIT is based on a clinical pretest probability (4T-score) confirmed by an immunoassay (ELISA) and, if available, a functional test. In all cases of suspected or proven HIT, any form of heparin should be avoided and an anti-coagulation therapy (ACT) with an alternate drug like as argatobran and recently danaparoid (DA). Furthermore DA is the first drug approved for use on prophylaxis (750 U twice daily) in patients at thrombotic risk with previous HIT.

Case report. We report a case in which was used DA at prophylactic dose in a non-conventional way. A 63-year-old patient with previous hemorrhagic stroke, hypertension, a treated HCC and liver cirrhosis requiring TIPS placement, had an acute myocardial infarction (requiring PTCA) complicated by two episodes of cardiac arrest. Dual antiplatelet therapy and LMWH at prophylactic dose (4000U daily) was started. From initial values of 124.000/mmc platelets, a progressive thrombocytopenia was observed until 4T-score was performed (5-intermediate probability)(IP) and heparin/PF4 antibody positivity was found (first positivity 10/08/22-last positivity 9/9/22). A switch from LMWH to fondaparinux (FO) (2.5 mg daily) was opted for. Following the finding of DVT, the dosage of FO was increased to 7.5 mg. At 1-month follow-up, the DVT had resolved, but given the need for ACT to maintain flow in the TIPS in view of liver transplantation (LT), a switch to a treatment with DAPT + Warfarin and then only with Clopidogrel. Due to the IP of HIT and the high thrombotic perioperative risk (LT with mesenterico-portal anastomosis using interposition venous graft), LMWH therapy was not administered during surgery on 12/27/23. Instead, immediately after LT, antithrombotic prophylaxis with DA was started and continued for 30 days. Prophylaxis was continued for another two months with FO (2.5 mg daily) and, at the end of two months, acetylsalicylic acid (75 mg daily) was started. During follow-up, there were no thrombohemobolic complications while there was a progressive recovery of platelet levels.

Conclusions. We report the first case of successful and prolonged use of DA at prophylactic dose in prevention of thrombotic complications after LT in a patient with previous diagnosis of HIT.

P099

UPDATE ON ITP PATIENTS TREATED WITH AVATROMBOPAG: A REAL-LIFE MONOCENTRIC EXPERIENCE

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Background. Avatrombopag(AVA),a second-generation thrombopoietin receptor agonist (TPO-RA),is part of the second-line treatment of chronic idiopathic thrombocytopenic purpura(ITP). Post-hoc analyses of the Phase III study showed that patients(pts) younger, males and with fewer than 3 prior ITP therapies had longer treatment responses. In addition, prior use of TPO-RAs such as eltrombopag and romiplostim had a minimal effect on durability of response.

Aims. The aim of this study was to evaluate the efficacy and treatment duration of AVA in pts with ITP treated at our centre in a real-world setting.

Materials and Methods. We performed a retrospective analysis of data from a single-centre cohort of 21 ITP pts(15 women,6 men)with a median age of 55 years (24-79) at the start of AVA therapy. All pts were in the chronic phase of ITP. The median plt count at baseline(BL) was 34000/μL(1000-146000/μL). Blood samples were taken weekly during the first month of treatment and then at variable intervals depending on the plt count. Data were collected between August 2022 and April 2024.

Results. After 1 week of treatment, the median plt value was 89000/μL (1000-1000000/μL); the median time to reach a plt count higher than BL was 7 days(5-21).3 pts (14%) never reached a plt count>50000/μL.The starting dose of AVA was 20 mg/die. At 1 month, only 5 pts (24%) were on concomitant therapy. 16 pts(76%)switched from another TPO-RA to AVA for different reasons:7(43%) loss of response, 3 (19%)no response(NR), 3(19%) pts preference, 3 (19%)adverse events (AE). 9 pts(43%) received both first generation TPO-RAs. After one month of treatment,we observed no difference in terms of response(PLT>50000/μL)between pts with less or more than 50 years(p=0.67)and in pts treated with >or≤3 previous lines(p=0.6); or between males and females(p=0.33).No differences were observed even between pts with plt values more or less than 15000/μL at the start of AVA(p=1)or more or less than 30000/μL at the start of AVA(p=0.38). Treatment was discontinued in 8 pts(38%):6(28%)NR,1(5%)fluctuating plt values,1(5%)AE.3 pts(14%)had to be temporarily stopped because of thrombocytosis. Currently 13 pts(62%)are on AVA with a median duration of therapy of 314 days(30-621);median number of tablets/weekly taken is 4(2-21).

Conclusions. In our analysis demonstrate the efficacy of AVA with a durable response despite multiple previous treatments including other TPO-RAs.Moreover,the efficacy is confirmed by the possibility to reduce the dose of the drug.

P100

PROGNOSTIC ROLE OF PLATELET-TO-LYMPHOCYTE RATIO (PLR) IN IMMUNE THROMBOCYTOPENIA (ITP): A RETROSPECTIVE, MONOCENTRIC STUDY

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Background. Immune thrombocytopenia (ITP) is an immune-mediated acquired disease characterized by a repeatedly reduced platelets (PLTs) count (PLTs<100000/mmc). ITP is distinguished from secondary forms that are generally iatrogenic or related to an underlying medical condition (e.g., autoimmune, infectious, or haematological disease). PLR is an inflammatory biomarker studied as a potential prognostic factor in cardiovascular, autoimmune disease and sepsis. Recent studies have investigated the association between platelets, lymphocytes count and ITP clinical characteristics. Currently, guidelines standardize ITP diagnosis and treatment, but they do not provide prognostic factors able to predict the disease course.

Aims. To investigate the role of platelet to lymphocyte ratio (PLR) as an ITP prognostic factor in a retrospective cohort of patients.

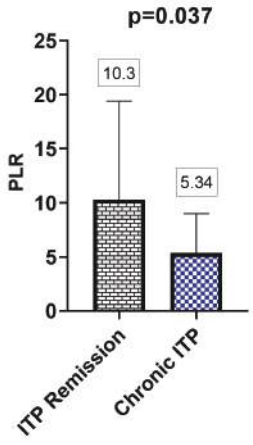

Figure 1.

Methods. Our historical cohort enrols 32 newly identified ITP, 18 female and 14 male, median age 52,5 (range 22-82) diagnosed from December 2009 to August 2022. We collect data of complete blood cell count (CBC) and evaluate the PLR values at diagnosis. According to national guidelines, we record CBC values during patient follow-up to describe treatment response and, particularly, durable response and remission respectively at 6 and 12 months from diagnosis. The study population was divided in two groups: Chronic ITP (CI, ITP duration longer than 12 months; 22 patients 14 female and 8 male) and ITP Remission (IR, 10 patients 4 female and 6 male) composed by patients with a PLTs count greater than 100000/mmc at 12 months from diagnosis. All patients receive at least corticosteroids, in the CI subgroup the median number of treatment's lines was 2 (range 1-3). The PLR and PLTs count values of these subgroups were analysed performing a Student t-test (statistically significant p value <0.05).

Results. The IR group shows a PLR mean value of 10.3 (range 3-30), mean PLR in CI subgroup was 5.34 (range 0.43-14.67). The statistical analysis demonstrates a significant difference between the groups (p=0.037). The same comparison does not show a difference between PLTs count: mean PLTs value was respectively 16667/mmc and 10773/mmc in IR and CI group (p=0.11).

Conclusions. Our findings highlight the value of PLR as an ITP prognostic factor. Further investigations are necessary to validate the PLR role in clinical practice: to predict the course of disease and guide treatment decisions.

P101

DARATUMUMAB FOR RAFRACTRY IMMUNE-MEDIATED THROMBOTIC THROMBOCTOPENIC PURPURA: 2 CASE REPORTS

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Immune thrombotic thrombocytopenic purpura (iTTP) is a life threatening condition resulting from severe ADAMTS13 (A13) deficiency caused by antibody-mediated destruction. Despite current acute treatments have improved outcomes, relapses remain common. Rituximab (RTX) is the main treatment for relapsing/refractory iTTP, but additional immunosuppressive therapy like mycophenolate, azathioprine, bortezomib and anti-CD38 antibody daratumumab may be necessary for normalizing A13 activity. Relapses are due to continued production of anti-A13 antibodies (AbA13) by plasma blasts and long-lived plasma cells expressing CD38, but not CD20. We present 2 cases of multirefractory iTTP.

Table 1.

Tab.1 Patients clinical history

	Patient 1	Patient 2
Age at diagnosis/Sex	54/F	24/F
N. iTTP relapses	5	9
Teraphies prior to bortezomib	PE, PDN RTX Aza CSA Capla	PE, PDN RTX Capla MMF
Therapy(ies) during bortezomib	None	PE,PDN Capla
A13/AbA13 prior to bortezomib	0% 145.5 U/ml	0% 28.7 U/ml
N. bortezomib cycles	2	2
Best Response (A13/ AbA13 titre)	0% 57.8 U/ml	41% 3.6 U/ml
Toxicity related to bortezomib	Neuropathy G2	None
Time to next treatment (months)	4	1
Therapy(ies) during daratumumab	None	PE,PDN FFP Capla
A13/AbA13 prior to daratumumab	0% 82.4 U/ml	4% 7.5 U/ml
N. daratumumab cycles	3	4
Best Response (A13/ AbA13)	0% 0 U/ml	100% 0.93 U/ml
Month to A13 relapse post daratumumab (A13, AbA13 titre)	1 (0% 118.3 U/ml)	3 (3% 19.7 U/ml)

Legenda:
PE: plasma exchange; PDN: prednisone; RTX: rituximab; Aza: azathioprine; CSA: ciclosporin; Capla: caplacizumab; MMF: mycophenolate mofetil; FFP: Fresh Frozen Plasma

Both patients received plasma exchange (PE) and steroids as

acute treatment. Relapses were treated with caplacizumab, RTX, immunosuppressants agents, bortezomib (Bor) and daratumumab (Dara). Patient 1. A 54-year-old woman, first experienced iTTP in 2013, followed by several relapses treated with the addition of RTX. Despite achieving clinical remission, severe A13 deficiency persisted leading to treatment with multiple lines of immunosuppressive therapy. Despite these efforts, normalization of A13 was not achieved and high inhibitor titre persisted. Treatment with 2 cycles of Bor yielded no response and subsequent treatment with 3 cycles of Dara led to AbA13 reduction with persistent undetectable A13 activity. One month post-Dara therapy, A13 activity was still 0%, with a return of high AbA13 titre (Table 1). Patient 2. A 24-year-old woman, experienced 9 relapses since 2009, with severe neurological symptoms presenting from the 5th episode. Various treatments including PE, steroids, RTX, caplacizumab and immunosuppressants agents were administered. At the 8th relapse the patient was then treated with Bor, achieving A13 normalization after the 1st cycle, but observing a new A13 relapse after the 2nd. The patient experienced the 9th clinical recurrence 1 month post-Bor therapy, then treated with 4 doses of Dara that led to A13 recovery. 3 months post-Dara therapy A13 activity was again undetectable, necessitating plasma transfusions (Table 1).

In summary, Dara induced rapid but temporary AbA13 eradication in both patients, with A13 recovery observed only in one patient. The optimal treatment strategy for RTX and immunosuppression refractory iTTP remains unclear, but targeting inhibitor-producing plasma cells with dara appears promising. Our experience shows that some patients may have a rapid, but only transient response. Further studies are needed to assess the long-term efficacy and safety of daratumumab in iTTP patients

P102

ABSTRACT NOT PUBLISHABLE

P103

REAL WORLD DATA ON THE IMPACT OF CAPLACIZUMAB IN THE MANAGEMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA

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Introduction. Caplacizumab (CPL) is a monoclonal antibody approved for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP), both as first-line and subsequent lines of treatments. This study aimed to evaluate the advantages of CPL with reference to hospital length of stay and number of plasma exchanges (PEX) needed in real life.

Patients and Methods. The study cohort comprises 13 patients (6 males, 7 females, median age 42 years), treated for aTTP at our department in the last ten years. Three were terated with CPL at diagnosis, 4 during relapse, and 6 were never treated with CPL as their diagnosis was made before 2019. All patients were hospitalized at diagnosis, and some required additional admissions. The aim of our analysis was to compare patients who received CPL as first-line therapy, in addition to PEX, with those who never received it or received CPL in subsequent lines, in terms of relapses, evaluating the PEX required to achieve an initial platelet count of at least $100*10^3/\mu L$, the PEX needed to achieve remission, and the duration of hospital stay.

Results. The mean maximum length of hospital stay for patients treated with CPL as first line was 17 (14-21) days, while for patients treated in subsequent lines or not treated, it hospital stay lasted 21 (11-36) days. The mean number of PEX required to achieve remission at the last relapse for patients treated in the first line was 6 (4-10), while for patients treated in subsequent lines or not treated, it was 8 (4-21). The mean number of PEX required to achieve an initial platelet count of at least $100*10^3/\mu L$ for patients treated in the first line was 6 (4-10), while for patients treated in subsequent lines or not treated, it was 7 (4-9).

Conclusions. The analysis, conducted at a Regional Reference Center for the diagnosis and treatment of aTTP, confirms in a real life setting a reduction in the number of PEX required to achieve complete remission and duration of hospital stay after the availability of CPL ,compared to the pre- CPL era, as well as a shorter hospital stay when CPL is adopted as first-line therapy.

P104

SINGLE-CENTER RETROSPECTIVE DESCRIPTIVE STUDY FOCUSING ON IMMUNOSUPPRESSIVE THERAPY IN THROMBOTIC THROMBOCYTOPENIC PURPURA

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Idiopathic thrombotic thrombocytopenic purpura (iTTP) is characterized by decreased ADAMTS13 protein due to the presence of autoantibodies. Initial therapy involves starting the plasma-exchange procedure associated with caplacizumab as soon as possible. It's necessary, however, to achieve eradication of autoantibodies with immunosuppressive therapy. The most studied and used drugs for this purpose are corticosteroids and rituximab. In most recents SIE guidelines the use of rituximab was limitated only in the relapse setting.

Objective. Retrospective descriptive study of the iTTP case series afferent to our Center focusing on immunosuppressive therapy used at onset and relapse.

Results. 4 patients, all males, with a median age of 51 years were enrolled from 2013 to 2023. All patients presented with thrombocytopenia (mean values 26000/mmc), anemia (mean values 9.87g/dl), hemolysis parameters, leukocytosis with suppressed ADAMTS13 and presence of autoantibodies. All our patients were treated with steroids at a dosage of 1mg/kg/day and received in combination rituximab 375mg/mq for 4 weekly infusions obtaining complete response. With a mean follow-up of 65 months, only 1 patient relapsed. A first relapse without hemolysis but with reduction of ADAMTS13 occurred at 42 months after the last plasma-exchange and was treated with steroids for three months and only two rituximab administrations; the drug was discontinued for mixed type I and III immune-mediated reaction. One year after the end of steroid therapy, the patient had a clinical relapse with thrombocytopenia and hemolysis with the need for caplacizumab and only 2 plasma-exchange procedures. He was treated with prednisone 1mg/kg/day and obinutuzumab 1000mg/ev weekly for 4 administrations, achieving normalization of ADAMTS13 levels 20 days after the start of immunosuppressive therapy. The patient is now in follow-up and is maintaining a complete response.

Conclusions. This retrospective analysis of our TTP case series raises the question of how to treat patients who initially received rituximab treatment in case of relapse. In our experience, retreatment

with the same immunosuppressant has not resulted in long-term benefit, with early relapse and risk of developing immune-mediated reactions. Obinutuzumab therapy appears to be a viable therapy in this setting of patients, but data on its efficacy derived from case report or cases series and it's necessary more data and prospettic studies.

P105

SPLENIC EMBOLIZATION AS TREATMENT OF EVANS SYNDROME WITH MASSIVE SPLENOMEGALY

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Here we present a case of a patient diagnosed with Evans syndrome who suffered for almost 40 years, since childhood, of immune hemolytic anemia and thrombocytopenia. He was transferred to our hospital with relapse or Evans Syndrome, with severe hemolytic anemia (hemoglobin 3.4g/dl), in poor condition, unstable with low blood pressure, hypoxia. He has been treated with 2 rounds of high-dose immunoglobulins, steroid therapy and transfusion of incompatible erythrocyte concentrates. After a few days therapy with 4 weekly Rituximab, 375 mg/m^2, was started, with slow and progressive normalization of hemoglobin and platelets values. Considering the severity of the last relapse and the possible fatal course of the disease, it was proposed to proceed with interventional radiology and a selective embolization of the splenic artery was carried out, leaving the possibility of performing a splenectomy to a subsequent moment. The following clinical course was characterized by the appearance of a reversible post-embolization syndrome with several episodes of transient abdominal pain. The patient has been in complete remission for a year and a half with reduction of the spleen to normal volumes and disappearance of the hemolytic and thrombocytopenic component. After this period there was a recurrence of ITP for which resumed steroid therapy in association with immunoglobulins and subsequently therapy with eltrombopag. Clinical evaluation at this time point showed absence of the autoimmune hemolytic component and size of the spleen within normal range. This case report focus the attention on the possibility of opting for an interventional procedure such as selective embolization of the splenic artery in the context of severe splenomegaly associated with autoimmune hemolytic anemia and chronic ITP as an alternative to splenectomy. This procedure can be safely used also in other situations such as splenic lymphoma, chronic lymphocytic leukemia, myelofibrosis, leukemia hairy cells, polycythemia vera, hereditary spherocytosis, idiopathic hypersplenism and Felty syndrome, as well as in patients with hypersplenism and cytopenia induced by anticancer chemotherapy, those ad high operational risk and those who refuse blood transfusion (Jehovah's Witnesses).

P106

INHERITED PLATELETS DISEASE AND ACQUIRED THROMBOCYTOPENIA MAY COEXIST: THE INTRIGUING HISTORY OF A THREE-YEAR-OLD CHILD

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Inherited platelet disorders, including platelet storage pool diseases (SPDs) may lead to several bleeding symptoms, their severity is often categorized based on their effects on either the surface receptors or internal structures of platelets. This rare condition, characterized by defects in platelet granules, exhibits broad phenotypic variability, ranging from mild bruising to severe hemorrhages. SPDs diagnosis requires specialized analyses such as platelet aggregation assays and genetic studies, it furthermore requires a multidisciplinary approach for an accurate management. Our case report describes a three-year-old child with recurrent episodes of profuse epistaxis and thrombocytopenia. Initially diagnosed with immune thrombocytopenia, the patient's condition worsened over time, leading to further investigations. Despite ruling out von Willebrand disease, subsequent tests indicated a platelet function disorder. Genetic analysis ultimately revealed mutations in ANKRD26, ITGA2B, and ITGB3 genes, confirming a diagnosis of "storage pool disease." Treatment options of SPDs include desmopressin, antifibrinolytic agents, and platelet transfusions, tailored to individual needs. The discussion underscores the diverse manifestations of SPD, emphasizing the importance of thorough diagnostic assessments. Treatment strategies aim to alleviate bleeding symptoms and mitigate associated risks, with a strong focus on personalized care. Challenges in managing SPD include missed diagnoses and the influence of genetic variations on disease severity. Ultimately, early detection and individualized therapies are essential for effectively managing SPD, underscoring the ongoing need for research to enhance outcomes for affected individuals.

Chronic myeloid leukemia and cytogenetic

P107

THE DIGITAL PCR IS A SENSITIVE TOOL FOR THE DETECTION OF KITD816V MUTATION IN MASTOCYTOSIS

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Mastocytosis is a rare and heterogeneous disease characterized by the abnormal accumulation of mast cells in various tissues, leading to a broad spectrum of symptoms from mild to severe. Activation of the KIT receptor kinase due to mutations in c-*KIT* is associated with mastocytosis. According to WHO classification, the presence of the *KIT*^{D816V} mutation in the bone marrow and/or peripheral blood is considered one of the minor criteria for diagnosing systemic mastocytosis (SM). From a diagnostic perspective, highly sensitive molecular techniques capable of detecting mutations even when the mast cell burden is low, as well as monitoring efficacy after tyrosine kinase inhibitor treatments, are of significant importance. Aim is to evaluate a plate-based digital PCR assay as a promising alternative to ASO-qPCR for D816V mutation testing. A commercial dPCR assay for the detection of *KIT*^{D816V} was used on the Absolute Q digital PCR platform (Thermofisher^{TM}), where all the necessary steps for dPCR are performed on a single instrument. DNAs samples obtained from 59 peripheral blood of subjects with suspected mastocytosis were analyzed, retrospectively. Ten DNAs from healthy donors were used as negative controls. A patient sample with 40% D816V mutation-positive *KIT* alleles detected by NGS was mixed in decreasing amounts of wild-type DNA. Dilutions with different allele burdens (from 40% to 0.006%) were tested to determine the limit of detection (LoD). Regression analysis showed a high correlation between the expected and detected ratios (R2=0.999). The LoD was determined to be 0.01% mutated allele frequency (MAF). Assay accuracy was assessed by testing 59 DNA samples with suspected or confirmed mastocytosis (15 suspected, 5 MC, 2 MCAS,6 MIS,7 MS,24 MC+MS) that had previously been analyzed using ASO-qPCR. Thirty out of 59 samples (51%) resulted mutated by both dPCR and ASO-qPCR with MAFs from 0.09% to 31.5%. Concordance in mutation detection and quantification was high, with only one discordant sample (p=0.048). We demonstrated the utility of the Absolute Q digital PCR system as a sensitive and reliable tool for *KIT*^{D816V} detection. Compared to ASO-qPCR, dPCR offers the advantages of allowing quantification without the need for standard curve and simplifying the laboratory workflow. Quantification of *KIT*^{D816V} allele burden detection using digital PCR may help clinicians in diagnosis and monitoring therapeutic responses in patients with SM.

P108

IN CHRONIC-PHASE CHRONIC MYELOID LEUKEMIA (CP-CML) PATIENTS (PTS) IS A SECOND TREATMENT FREE REMISSION (TFR2) ATTEMPT A FEASIBLE AND SAFE OPTION?

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The vast majority of pts with CML-CP who fail a 1st tyrosin kinase inhibitors (TKIs) discontinuation re-achieve a deep molecular response (DMR), but in literature few data are available about pts who re-gain a durable DMR, after a 1st treatment free remission (TRF1) failure, and attempt a 2nd TKIs stopping. To describe the results of TFR2 in CML-CP pts followed in our center, we evaluate all consecutive pts with CML-CP diagnosis from 2000 to 2023. Pts with at least a 2-years of sustained DMR (sDMR), after resuming TKIs as a consequence of a 1st TKI failure discontinuation, attempting a 2nd TKIs withdrawn following a personal request or TKIs side effects, were here described.

Among 310 evaluated CML-CP pts, 121 reached a TFR1: molecular relapse (MR) was observed in 44 pts and 15/44, 10 female and 5 male, experienced TFR2. At TFR2 median age was 62y, (range 34-84) and median time from CML diagnosis 10 y (range 7-17). At their TFR1 attempt, median time to MR was 4 months (2-33); after MR all 15 pts were re-introduced to TKI treatment and all of them achieved a 2nd sDMR (sDMR2) with a median time of 2 months (1-38). The median duration of sDMR2 before TFR2 was 62 months (32-86), median time between TFR1 failure and TFR2 was 69 months (35-99). Before TFR2, 10/15 pts were receiving reduced TKI dose (2 imatinib, 1 bosutinib, 4 nilotinib, 3 dasatinib) and 5/15 pts were receiving full TKI dose (2 imatinib, 3 nilotinib). Median follow up from 2nd TKI discontinuation was 11 months (3-43), in particular only 3 pts have a follow up shorter than 6 months and 7 pts have a follow up longer than 12 months. Eleven out of 15 (73%) pts remain in TFR without therapy; 4 pts lost major molecular response, one after 12 months and 3 pts within 3 months from 2nd TKIs discontinuation: the 4 relapsed pts resumed TKIs treatment, 2 pts re-gained DMR quickly, within 4 months, and the other 2 are not yet evaluable because they resumed therapy less than 1 month ago. No disease evolution were observed in pts that experienced TFR2.

Our experience confirms that a 2nd TKI discontinuation in CML-CP pts is a safe and feasible option in a real-life setting. The high percentage of pts that remains in TFR after 2nd TKI discontinuation should be confirmed with longer follow up. The duration of TKIs treatment after TFR1 failure (longer than the one reported in other series) could represent a favorable factor for a 2nd successful TRF.

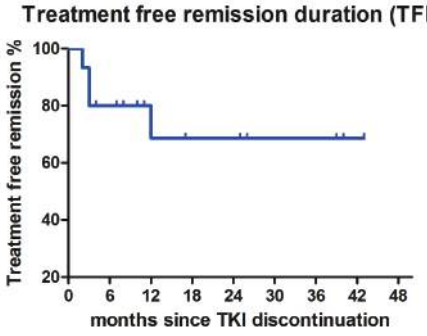

Figure 1.

P109

A SENSIBLE AND SPECIFIC AUTOMATED SYSTEM FOR THE DETECTION OF DIFFERENT BCR:ABL1 REARRANGEMENTS IN PHILADELPHIA-POSITIVE LEUKEMIAS AT DIAGNOSIS

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The growing request for molecular detection of *BCR::ABL1* fusion transcripts in CML and ALL patients makes it mandatory to explore new laboratory tools, for detecting and discriminating the different *BCR::ABL1* rearrangements. The BCR-ABL Dx - ELITe InGenius® System solution (ElitechGroup) performs RNA extraction, retrotranscription amplification and isoform discrimination in an automated manner, and with its short time-to-result could answer this need. Here we compared the new BCR-ABL Dx one-step RT-PCR automated assay with our BIOMED-1 PCR routine homemade assay in detecting different *BCR::ABL1* rearrangements at diagnosis. We first assessed the diagnostic performance using 100 mRNA samples from 106 peripheral mononucleated cells (PBMC) by QIASymphony. The mRNAs were tested in parallel with the BIOMED-1 PCR technique and the One-step BCR-ABL Dx assay on the ELITe InGenius® System. The BCR-ABL Dx kit showed good agreement in detecting the p190, p210 and p230 isoforms (k=0.77; 95%IC0.68-0.88). In a few samples (29%), the BCR-ABL Dx kit detected co-expressed variants at a high Ct -(Ct>36). To standardise the result interpretation according to ELN guidelines, we calculated a positivity cut-off at Ct=35 by ROC curves (AUC 0.94; 95% IC=0.8-0.99; p<0.0001). Applying the cut-off, the agreement of the two detection methods was excellent (AUC=1; 95%CI: 0.96-1) with 100% specificity and sensitivity, and diagnostic accuracy higher than 96.3%. We then investigated the Elite InGenius® extraction and full-automated workflow. The mRNA from 22 samples were isolated in parallel with ELITe InGenius® using ELITe InGenius SP RNA extraction kit and the routine QIASymphony system, following the respective procedures. The extracted mRNAs were evaluated in quality and tested to detect the *BCR::ABL1* transcripts by the homemade assay based on PCR technique and BCR-ABL Dx kit on InGenius®, respectively, from extraction to interpretation of results. The quality of the RNA extracted by the ELITe InGenius ® was good: mean concentration= 12.8 µg/sample, mean A260/280 =1.68, and A260/230 =1.46. The ELITe InGenius ® results were 100% concordant in the isoform detection. In conclusion, the BCR-ABL Dx is a highly sensitive new assay to detect and discriminate all the BCR::ABL1 variants. It can be used with the ELITe InGenius or QIAGEN extraction systems. In association with ELITe InGenius full-automated workflow is a valid alternative to the gold standard qualitative BIOMED-1 PCR technique.

P110

TKI DOSE REDUCTION IN CML PATIENTS WITH A SUSTAINED DEEP MOLECULAR RESPONSE. REAL LIFE MONOCENTRIC EXPERIENCE

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Background. The introduction of the tyrosine kinase inhibitors (TKI) has revolutionized the treatment of chronic myeloid leukemia (CML) and most patients can live a near-normal life expectancy. However, long-term TKI use is frequently accompanied by adverse events,impact on quality-of-life (QoL), poor adherence, and high treatment costs. Several clinical trials and real-world studies have shown that 40–60% of patients with a sustained, stable deep molecular response (DMR) can successfully discontinue TKI and achieve treatment-free remission (TFR). However,it is worth noting that only a proportion of patients can reach the threshold for TKI discontinuation. Recently, TKI dose optimization is also being increasingly emphasized as an important part of individualized therapy.Several studies have confirmed that low-dose TKI can effectively maintain molecular response and also reported that dose reduction before discontinuation did not impact the attainment of TFR.

Methods. We conducted a monocentric,retrospective study on the possibility of CML patients receiving lower than standard dose TKI after at least 3 years of treatment and the achievement of major molecular response.Clinical characteristics of patients were summarized in Table 1.

Table 1. Clinical characteristics of patients.

	Dose reduction	Original dose
No	42	26
Age, median (range)	62 (25-84)	44 (15-60)
Male/Female	21/21	19/7
Type of Tyrosine kinase inhibitors		
Imatinib	24 (57)	14 (54)
Dasatinib	4 (9.5)	3 (11)
Nilotinib	8 (19)	8 (31)
Ponatinib	4 (9.5)	1 (4)
Bosutinib	2 (5)	0
Type of Molecular Response		
≤ MMR	10 (31)	15 (58)
DMR	32 (69)	11 (42)
Duration of TKIs therapy, median (range, years)	9 (3-25)	7 (3-27)
Daily dose of TKIs (%)		
Imatinib	62.5	
Dasatinib	57.5	
Nilotinib	60	
Ponatinib	41	
Bosutinib	50	

Results. 42 of 68 CML patients (62%) treated at the San Carlo Hospital of Potenza experienced dose reduction,5 because of intolerable adverse events,7 for pre-existing comorbidities and in 30 dose modifications is used to prevent the toxicities of TKIs.After dose reduction, molecular response has been monitored every two months during first year and then every 3 months.Molecular response was maintained at median follow up of 21 months (3-84),therefore in none of them it was necessary to return to the original dose.Molecular response was

maintained even in 5 patients who experienced dose reduction once a new MMR was achieved after loss of TFR.All patients appear to be safely managed with low dose TKI, none of them had new toxicities.

Conclusions. Our retrospective study evaluated the outcome of TKI dosage reduction,according clinical decision, in patients who had achieved stable MMR after at least 3 years of treatment. The observation period is still short, so no definitive conclusions can be drawn. However, it seems possible to confirm the indication, as shown in the literature, on the possibility of using this strategy to prevent or limit the toxicity of TKIs, when TFR is not possible and, probably, even after the loss of the TFR.

P111

TIME TO TREATMENT FREE REMISSION (TFR) IS DIRECTLY RELATED TO LONGITUDINAL DIAMETER OF THE SPLEEN AT THE DIAGNOSIS IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA (CML)

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Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of BCR-ABL1 protein, classically deriving from the 9;22 chromosomal translocation. Tyrosine kinase inhibitors (TKIs) represent the standard of care since 2001, when the Food and Drug Administration (FDA) approved imatinib. Other drugs from the same family approved include nilotinib, dasatinib and ponatinib, the last used from the second line therapy and the only molecule for CML patients with ABL T315I mutation. Using TKIs, the mortality is 1-2% per year, while the 10-year survival rate is 80-90%. Patients achieving a molecular response 4.0 (MR4.0), characterized by a 4-log reduction of BCR-ABL1 levels, are defined as in deep molecular response (DMR). Basing on the recommendations of the National Comprehensive Cancer Network (NCCN), patients with a stable DMR for almost two years could discontinue the TKI therapy, reaching the so-called Treatment-free remission (TFR). There are not previous reports about the correlation of the longitudinal diameter of the spleen at the diagnosis in patients with CML and the time to the discontinuation of TKI therapy due to the attainment of TFR. Basing on European LeukemiaNet (ELN) 2020 recommendations for treating chronic myeloid leukemia, mandatory criteria for the discontinuation of TKIs are the possibility to perform high quantitative Protein-Chain Reaction (PCR) test using the International Scale (IS) with rapid turn-around of PCR test results, CML in first chronic phase and the patient's accordance to more frequent monitoring after stopping therapy, in detail once a month for the first six months, then every two months for one year and finally every three months. Since Sokal Score is based on age of the patient, spleen dimensions, blasts and platelet count, it is possible to have a high risk just because there is the influence of the age. In order to overcome this bias, we isolated a clinic parameter (longitudinal diameter of the spleen) with the aim to make a correlation with the TFR achievement. We evaluated 48 patients with CML, both males and females, treated with TKIs and focused our attention on clinic parameters like white blood cell (WBC) count and platelet count, lactate dehydrogenase (LDH) and longitudinal diameter of the spleen at the onset of the disease: in detail, we used the multiple linear regression (MLR) as statistical method and noticed for the first time in scientific literature that longitudinal diameter of the spleen measured in centimetres from the costal arch at the time 0 (at the diagnosis) is directly proportional to the time needed to achieve the TFR in patients with CML. Obviously, the numerousness of the examined sample does not allow us to state with certainty a statistical significative correlation between the above parameters (longitudinal diameter of the spleen and time needed to achieve the TFR), therefore further studies that take into consideration a greater number of patients are fundamental.

P112

DEEP MOLECULAR RESPONSE RATE IN CHRONIC PHASE CHRONIC MYELOID LEUKEMIA. ELIGIBILITY TO DISCONTINUATION RELATED TO TIME TO RESPONSE AND DIFFERENT FRONTLINE TKI: THE LABNET CML NATIONAL NETWORK

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The outcome of patients affected by chronic myeloid leukemia (CML) has drastically changed after the introduction of specific tyrosine kinase inhibitors (TKIs). In the last decade, TKIs improved the overall survival (OS) and patients who achieved a deep and sustained deep molecular response (DMR, defined as stable MR4 and MR4.5) may attempt therapy discontinuation, namely treatment-free remission (TFR). In our analysis, we report the differences in eligibility criteria due to time of response and different TKI used as frontline treatment analyzed in a large cohort of CP-CML patients. Data were exported by LabNet CML, a network founded by GIMEMA in 2014, with an unconditional grant from Novartis. The network standardized and harmonized the molecular methodology among …laboratories distributed all over Italy for the diagnosis and molecular residual disease (MRD) monitoring. To participate in the network, laboratories fulfilled quality controls and regularly undergo standardization procedures. The connection between the hematology centers and laboratories is managed by a web-based GDPR compliant platform. Out of 1777 patients analyzed, 774 had all evaluable timepoint (3, 6, and 12 months). At 3 months, 40 patients obtained ≥MR4: of them 14 (3.6%) with imatinib, 8 (5.8%) with dasatinib, and 18 (7.4%) with nilotinib (p=0.093). At 6 months, 146 patients achieved ≥MR4: 42 (11%) with imatinib, 38 (28%) with dasatinib, and 66 (27%) with nilotinib (p<0.001). At 12 months, 231 patients achieved a DMR: 85 (22%) with imatinib, 55 (40%) with dasatinib and 91 (38%) with nilotinib (p<0.001). Achieving at least ≥MR2 at 3 months, was predictive of a DMR at any timepoint of observation with any frontline TKI: with imatinib 67% *vs* 30% of patients with <MR2, with dasatinib 66% *vs* 28% of patients with <MR2 and similar results reported with nilotinib 75% *vs* 30% of patients with<MR2 at 3 months (p<0.001). At the same time point, as already reported, achieving at least ≥MR3 is even more predictive of a DMR at any timepoint: 89% *vs* 38% of patients with <MR3 with imatinib (p<0.001), 84% *vs* 40% of patients with <MR3 with nilotinib (p<0.001), and 89% *vs* 49% of patients with <MR3 with dasatinib (p<0.001). Of 908 patients who reached a DMR, 461 (51%) lost it: the loss of response after >2 years was significant for patients who at 3 months had ≥MR2 (18% *vs* 9.9% of pts with <MR2, p=0.038). No differences were revealed in patients who maintained a DMR and were considered eligible for TFR considering the different type of TKIs: 106 (27%) with imatinib, 49 (26%) with dasatinib, and 105 (32%) with nilotinib. In a large cohort of CML patients analyzed, reaching ≥MR2 and an MR3 at 3 months it seems predictive of a DMR at any time point. Considering the pre-requisite for a discontinuation with a sustained DMR only a

minority of patients can be eligible for the discontinuation, regardless the frontline treatment received. The results suggested that in order to improve the rate of TFR, new treatment options or investigational approaches should be applied.

P113

HOW MANY PATIENTS CAN BE RESCUED FROM IMATINIB TO A SECOND GENERATION TKI TO INCREASE THE DEPTH OF MOLECULAR RESPONSE? THE EXPERIENCE OF GIMEMA LABNET CML NATIONAL NETWORK

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Imatinib can induce long-term favorable outcome, but about 25-30% of patients require a switch to another line of therapy for resistance and/or intolerance. In sponsored trials, a second-generation tyrosine kinase inhibitor (TKI) can rescue about 45-50% of patients who failed frontline imatinib. What about the real-life evidence? In our analysis we report a large cohort of patients initially treated with imatinib who changed after the occurrence of resistance and/or intolerance and analyzed the kinetic of molecular responses. Data were extracted from LabNet CML database, a network of hematology centers and reference laboratories founded by GIMEMA, with an unconditional grant from Novartis. The network currently includes 51 laboratories and 120 hematology centers distributed all over Italy and it provides a standardized and harmonized evaluation of diagnosis and molecular residual disease (MRD). For the current project, 668 patients were evaluable. Patients' median age was 54 (IQR 41-65); 59% were male and 41% female. Patients were registered from 2008. Out of 668, 313 initially treated with imatinib were switched to dasatinib after a median time of 25 months. The MR3 rate with imatinib (17%) became 21% with dasatinib, but the percentage of patients with a deep molecular response (DMR, MR4 to MR5) improved from 16.2% to 49% ($p<0.001$) after a median follow-up of 43 months. With nilotinib second line, 316 patients were evaluable: MR3 rate remained stable after switching from imatinib to nilotinib (25%), whereas the DMR rate improved from 20.7% to 55% ($p<0.001$) after a median follow-up of 54 months. Thirty-nine patients were switched to bosutinib: the MR3 rate improved from 28% to 33%, whereas the DMR rate change from 12.9% to 41.1% ($p=0.01$) after a median follow-up of 28 months. At the last follow-up, in the whole cohort, 22% of patients obtained an advantage switching from imatinib to a second generation TKIs. A limitation of this analysis is the lack of information (not collected in the database) regarding baseline characteristics of the patients and the reason of switch. In sponsored trials, about 30% of patients were rescued with a switch from imatinib to nilotinib and all were initially in complete cytogenetic response (CCyR). In our analysis, 61% of patients treated with imatinib were not in CCyR at the time of switch, and this percentage decreased to 25% after the switch. The percentage of those with an optimal response increased from 39% to 75%; of note, 51% obtained a DMR. In conclusion, in the real-life a switch from imatinib to a second generation TKIs in case of failure can rescue about 35% of patients, as already reported in sponsored trials. Indeed, a switch in patients already in optimal response can deepen the molecular response, increasing the rate of eligible patients for a possible discontinuation.

Allogenic and autologous transplant

P114

COMPARISON BETWEEN GVHD PROPHYLAXIS WITH THREE VERSUS FIVE DRUGS COMBINATION IN AML PATIENTS UNDERGOING ALLOGENEIC TRANSPLANT FROM HLA MISMATCHED UNRELATED OR HAPLOIDENTICAL RELATED DONOR

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Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is the only curative option for high risk hematological malignancies, but the onset of acute and chronic GVHD remains the major obstacle to long terms benefits. Currently, in the setting of mismatched donors, a comparison between GVHD prophylaxis with 5 drugs (CSA, MTX, MMF, ATG, and Basiliximab) and the Baltimore like protocol (CSA, MMF and PT-CY, 3 drugs combination) is still undiscovered. Here we retrospectively evaluate the impact of these 2 different GVHD prophylaxis strategies on the engraftment and GVHD incidence in AML patients transplanted from a mismatched unrelated or haploidentical related donor.

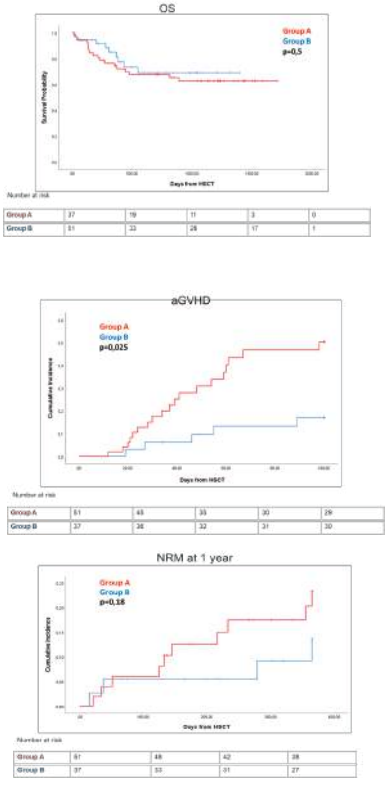

Figure 1.

Data were collected from January 2019 to date at AORN Cardarelli, Tor Vergata University, Ospedale Civile in Pescara, Ospedale Metropolitano in Reggio Calabria. Inclusion Criteria were: adult age, AML diagnosis, Complete Remission at transplant, Thiotepa, Busilvex and Fludarabine conditioning regimen, 7/8 HLA mismatched from unrelated or haploidentical related donor, GVHD prophylaxis according to 5 (group A) or 3 drugs (group B) combination. 88 patients were included: 51 and 37 in group A and in group B, respectively. The two patient series do not showed any significant differences in clinical characteristics, except for the stem cell source that was G-CSF priming BM in 93% of Group A and PB in 70% of Group B (p<0.001). The cumulative incidence of neutrophil engraftment was 97% with a median of 19 days (group A=13-31; group B=13-46) in both series (p=0.1). Acute and chronic GVHD occurrence were 37% and 27% in the Group A and 13% and 13% in the Group B (respectively, p=0.025 and P=0.08). With a median follow up of 28.47 months (0.7-57) in the group A and 14.43 (0.5-46.46) in the group B, the 100days and 1-year Non Relapse Mortality (NRM) were 8% and 19.8% versus 5% and 8.1% (respectively, p= 0.69 and p=0.18). OS and Relapse Incidence were 65% and 20% in the group A and 76% and 16% in the group B (respectively p=0.5 and p=0.68). In summary, these preliminary data on homogenous AML patients transplanted from HLA mismatched donor receiving TBF as conditioning regimen shows that both GVHD prophylaxis schedules are effective in terms of incidence and timing of PMN engraftment. Although no significative impact on 100days, 1year-NRM and OS, the 3 drugs combination seems more protective against aGVHD occurrence. However, an in depth-extension of the analysis is in progress.

P115

REDUCED INTENSITY TREOSULFAN-BASED CONDITIONING REGIMEN IN ACUTE MYELOID LEUKEMIA AND MYELODISPLASTIC SYNDROME: COMPARISON BETWEEN TREOSULFAN-FLUDARABINE VS THIOTEPA-TREOSULFAN-FLUDARABINE IN A SINGLE CENTER COHORT

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Background. Reduced intensity Treosulfan-based conditioning regimen represents the standard of care in elderly and unfit patients (pts) affected by Acute Myeloid Leukemia (AML) or Myelodisplastic Syndrome (MDS) undergoing allogeneic hematopoietic transplant (HSCT). Intensification via Thiotepa addition to Treosulfan-Fludarbine (Treo-Flu) combination might be useful in case of active disease at HSCT.

Methods. A total of 53 (47AML, 6MDS) pts underwent HSCT harnessing Treosulfan (30g/m^2)-based conditioning from January 2020 to December 2023 at Hematology Division of Udine. Thiotepa (5 mg/kg) was added to Treosulfan-Fludarbine (Treo-Flu) combination by clinical decision based on fitness, age and disease status at HSCT. OS and PFS were calculated from HSCT to death/disease progression and last contact, respectively.

Results. At HSCT, median age was 67(43-76) years (yrs), 29(54%) pts had HCT-CI>2, 41(77%) pts were in complete response (CR), 14(26%) in molecular response (MR). HSCT was performed from matched unrelated donor in 28(53%), haploidentical donor in 18(34%), and matched related donor in 7(13%) pts. Graft source was peripheral blood in all cases and 29(55%) pts received ATG as GVHD prophylaxis. All pts engrafted and acute GVHD grade 2-4 was observed in 24 (45%) pts. Overall, post-HSCT median follow up was 14 (0-56) months, with 2-yrs PFS of 44%(31-62) and 2-yrs OS of 60% (46-79). Conditioning regimen was Treo-Flu in 35(66%) pts and Treosulfan-fludarabine-thiotepa (TTF) in 18(34%) pts. Non-CR rate was higher in TTF group, compared to Treo-Flu (45%vs11%, p= 0,007). Besides, MR rate was higher in Treo-Flu group than TTF group (46% *vs* 6%, p=0.006). Other characteristics were similar between two groups. As shown in Figure 1, no difference between Treo-Flu and TTF was noted in neither in 2-yrs PFS (43%vs50%, p=0,936), nor in 2-yrs OS (62%vs62%, p=0,831). Moreover, aGVHD grade 2-4 rates (51%vs33%, p=0,210), NRM rates (17%vs17%, p=0,965), relapse rates (34%vs22%, p=0,365) were similar in Treo-Flu and TTF groups, respectively.

Conclusions. This study showed Tresulfan-based regimens use in elderly and unfit pts is safe and effective. Indeed, no differences between Treo-Flu and TTF was noted in terms of NRM, OS and PFS despite a higher proportion of non-CR pts at HSCT was noted in the TTF group. Low-dose Thiotepa addition is feasible and could be useful in elderly pts with active disease at HSCT even if larger prospective studies are needed to confirm this data.

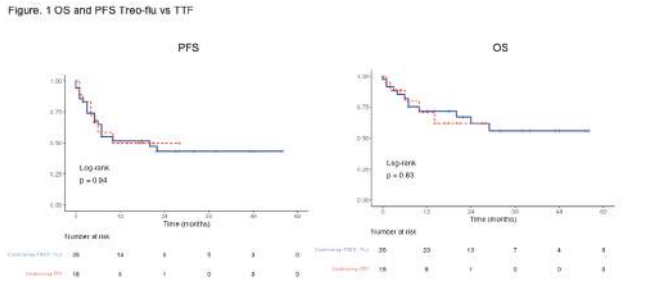

Figure 1.

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EXTRACORPORAL PHOTOPHERESIS (ECP) IN STEROID REFRACTORY CHRONIC GRAFT-VERSUS-HOST DISEASE (CGVHD): A MONOCENTRIC EXPERIENCE

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Background. The most important late complication after allogeneic hematopoietic stem cell transplantation is chronic graft-versus-host disease (cGVHD); its incidence is 50% and mortality is approximately 25%. First-line treatment depends on the grade of cGVHD, mild or moderate/severe, and varies from topical to systemic steroids. Extracorporeal photopheresis (ECP) plays a role from second line in steroid refractory patients.

Aim and Methods. The aim of our study is to assess the efficacy and safety of ECP in refractory patients. We evaluate between January 2016 and April 2023, 59 patients who developed steroid-refractory cGVHD and received ECP from the second-line treatment. Before starting ECP, 31 patients presented with moderate cGvHD, 28 with severe cGvHD. Among them 37 had an oset as acute GVHD. The patients underwent 2 consecutive treatments every 15 days as an induction phase and then 2 treatments per month. Response was evaluated as follows: CR (complete resolution with suspension of IS), PR (partial resolution and/or tapering of immunosuppressive therapy (IS)), SD (no response and no tapering) and PD (worsening of cGvHD).

Results. Among 59 patients, we evaluated those who reached at least one year of ECP treatment (n=46), at two different time-points: at 6 months from the first ECP, 9% of patients achieved CR, 67% PR, 15% SD and 9% experienced PD; at 1 year 28% achieved CR, 52% PR, 9% SD and 11% experienced PD. In addition, we evaluated the responses obtained in all patients at the last ECP (median of observation 15.5 months, range 2-72) with 33 CR, 16 PR, 5 SD, 4 PD; one patient discontinued treatment due to relapse after 15 months of ECP. Among them, six patients experienced disease relapse after stopping ECP for CR and died of progressive disease. All 4 patients with PD died of cGvHD, 2 of the 5 patients with stable disease died of cGvHD. At the last ECP, 68% of the patients had interrupted IS. Comparing overall response (CR + PR), no statistically significant difference was observed at 6-month and 12-month. However, we observed a statistically significant difference (p=0.02) when comparing CR at the two time points.

Discussion. In our experience, emerged ECP main role in improving cGVHD grade and in leading to interruption of IS, reducing the collateral effects associated with prologued IS. Additionally, in patients who achieved an early response, a longer duration of treatment seems to increase the depth of response.

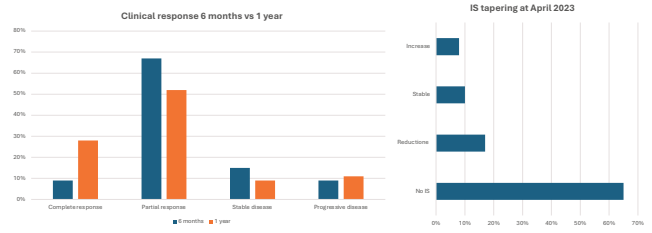

Figure 1.

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TOTAL BODY IRRADIATION-BASED MYELOABLATIVE CONDITIONING FOR ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: IMPACT ON RELAPSE IN A SINGLE CENTER EXPERIENCE

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Background. The total body irradiation (TBI)-based myeloablative conditioning regimen in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered the standard backbone in acute lymphoblastic leukaemia (ALL) patients. However, the TBI-driven efficiency benefit has been not clearly demonstrated when allo-HSCT was performed in ALL-patients with diagnostic standard-risk features and in first complete remission (CR1) using <12 Gy-TBI [Zhang H, et al. J Clin Oncol. 2023; 41(2):343-353]. It was also recently reported that 12Gy-TBI was associated with better survival and lower relapse rate if compared with busulfan-based conditioning regimen [Peters C, et al. J Clin Oncol. 2021;39:295-307]. Therefore, in a real-world scenario, we retrospectively collected data from allotransplanted ALL-patients comparing those who performed a high dose (i.e. 12 Gy) TBI-based allo-HSCT, so excluding a possible confounding TBI-dose variable, with those who underwent a TBI-free myeloablative conditioning in order to investigate the TBI impact on adult ALL allotransplanted patients' outcomes

Patients and methods. Data from all patients who underwent myeloablative conditioning regimen allo-HSCT from November 2009 to April 2019 were retrospectively collected. All patients underwent allo-HSCT in complete remission (CR, <0.1% by cytometry) Patients' characteristics are detailed in Table 1.

Results. According to disease status (CR1 *vs* second and subsequent CR (CR≥2)) at allotransplantation, the median OS was not reached (NR) and 194 days (d) in CR1- and CR≥2-allotransplants (p=0.006), respectively. The 3-year cumulative incidence of relapse (CIR) in TBI- and non-TBI-allotransplanted patients was 32% and 66% (HR=0.516), respectively. In particular, the subanalyses of the effects of TBI on relapse-risk showed a 3-year-CIR rate of 12% and 48% in CR1- and CR≥2-allotransplanted patients, respectively. Multivariate analysis of factors (age, CR1 *vs* CR≥2, donor-type, TBI, cell lineage, disease-risk) with impact on OS, relapse and TRM showed that CR1 (HR=0.378; p=0.032) and TBI (HR=0.349; p=0.039) were the variables impacting on OS and relapse, respectively.

Conclusions. TBI-based conditioning regimen was protective against relapse both in CR1 and in CR≥2-patients. Obviously, the optimal results in terms of 5-year CIR rate in CR1 (12%, in TBI-based allotransplants) should be cautiously considered bearing in mind the retrospective nature of our study

Table 1.

Table 1. Patient characteristics

		Conditionin regimen	
	Whole population n=50	TBI-based n=21	Bu-based n=29	p*
Age years, median value, (range)	32 (17-64)	30 (18-53)	33 (17-64)	0.650
Sex, n (%)				0.950
Male	30 (60)	12 (57)	18 (62)	
Female	20 (40)	9 (43)	11 (38)	
Lineage, n (%)				0.937
B-ALL	31 (62)	13 (62)	18 (62)	
T-ALL	15 (30)	6 (29)	9 (31)	
Mixed Phenotype	4 (8)	2 (9)	2 (7)	
Risk at diagnosis, n (%)				0.979
Standard Risk	13 (26)	6 (28)	7 (24)	
High or very high Risk	37 (74)	15 (72)	22 (76)	
Ph, n (%)				0.893
Positive	16 (32)	7 (33)	9 (31)	
Negative	34 (68)	14 (67)	20 (69)	
Therapy before HSCT, n (%)				0.984
Chemotherapy	29 (58)	12 (57)	17 (59)	
Chemotherapy + immunotherapy[#]	5 (10)	2 (10)	3 (10)	
TKIs-based[§]	16 (32)	7 (33)	9 (31)	
Disease status at transplant, n (%)				0.908
CR1	21 (42)	9 (43)	12 (41)	
CR2	18 (36)	8 (38)	10 (35)	
CR>2	11 (22)	4 (19)	7 (24)	
Donor HSCT, n (%)				**0.045**
Matched Related	18 (36)	6 (29)	12 (41)	
Matched Unrelated	27(54)	15 (71)	12 (41)	
Haploidentical	5 (10)	0 (0)	5 (18)	
Graft source, n (%)				0.129
BM	4 (8)	0 (0)	4 (14)	
PB	46 (92)	21 (100)	25 (86)	
GVHD prophylaxis, n (%)				0.066
Csa + MTX	45 (90)	21 (100)	24 (82)	
PT-CY + MMF + CsA	5 (10)	0 (0)	5 (18)	

TBI indicates total body irradiation; ALL, acute lymphoblastic leukemia; Ph, Philadelphia chromosome ALL; Bu, busulfan; CR, complete remission; CR1, first CR; CR2, second CR; CR>2, third or subsequent CR; HSCT, hematopoietic stem cell transplantation; BM, bone marrow; PB, peripheral blood; GVHD, graft versus host disease; CsA, cyclosporine A; PT-CY, post-transplant cyclophosphamide; MTX, methotrexate; MMF, mycophenolate mofetil; [#]blinatumomab and/or inotuzumab; [§]TKIs, Tyrosin kinase inhibitors; *The χ2-test (or Fisher exact test) was used to compare categoric variables and the Mann-Whitney U test for continuous variables.

P118

BLINATUMOMAB IS AN EFFECTIVE AND LOW TOXICITY BRIDGE TREATMENT TO HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ACUTE LYMPHOBLASTIC LEUKEMIA ASSOCIATED WITH SHWACHMAN- DIAMOND SYNDROME

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Background. Shwachman- Diamond Syndrome (SDS) is a rare multisystem disease characterized by skeletal abnormalities, pancreatic exocrine insufficiency and bone marrow dysfunction. Patients affected by SDS are at risk for severe cytopenia and predisposition for myeloid malignancies.

Methods. We report our experience of a young girl diagnosed with SDS who developed ALL at the age of 15-years.

Results. At the age of 14-months the patient was diagnosed with SDS. Therefore, hematological follow up was performed in order to exclude myelodysplastic/AML evolution and treatment for gastroenterological-nutritional complications was started. In September 2020, the patient was diagnosed with B-Cell-ALL. She started treatment with the dose reduced AIEOP-BFM ALL 2017 protocol, consisting of vincristine and daunoblastin without asparaginase to avoid pancreatic toxicity. She received just day 8 dose of chemotherapy due to prolonged cytopenia after only one vincristine and daunoblastin administration. Therefore, chemotherapy was discontinued and Blinatumomab was administered for 2 cycles. A complete remission (CR) with undetectable MRD was achieved and patient was consolidated with allogeneic SCT. The conditioning regimen consisted of 12 GY-TBI plus etoposide and GVHD prophylaxis consisted of Cyclosporin A without short course MTX, omitted to reduce toxicities. In September 2021, the patient had a molecular relapse demonstrated by two consecutive bone marrow evaluation. She received treatment with blinatumomab (1 cycle) and 4 DLI again achieving a CR. She is currently in CR 34 months after SCT.

Conclusions. SDS is associated with predisposition to develop MDS or AML. Children with SDS develop AML in 12-25% of cases, while ALL rarely occurs. Only two cases of lymphoid malignancies in patients with SDS have been described: 1 patient in 1978 with ALL and a postmortem SDS diagnosis based on pancreatic histology and 1 patient with primary mediastinal B cell lymphoma. The latter was treated with the R-CHOP regimen and he was in remission at last follow up 15 months after diagnosis. Our case is the third ever described lymphoid malignancy in patients with SDS, and the only case with ALL currently alive and in CR. Second ALL can be very aggressive disease with poor prognosis. There is no experience in the treatment of ALL in patients with SDS. The BFM inspired protocols showed the importance of the dose density and dose intensity in the treatment of ALL. In order to achieve the CR, an ALL patient should receive on time the entire treatment. These aspects represented the problems for the treatment of ALL in our "unique/rare" case. She, in fact, could not receive asparaginase due to pancreatic toxicity and she could not strictly adhere to the treatment schedule. Besides, blinatumomab was the best treatment option for lower risk for toxicity and is a well tolerable treatment with no gastrointestinal/pancreatic side effects and low-grade hematological toxicities (no prolonged neutropenia) that allowed the treatment administration and adherence to treatment schedule and a bridge to transplant. Allogeneic-SCT was performed to consolidate the CR based on the consideration that our case was a secondary ALL and because of high efficacy of combination therapy of blinatumomab and SCT in pediatric ALL.

P119

A RAPID FLOW CYTOMETRY METHOD TO RAPIDLY DETERMINE THE STEM CELL CLONAL POTENCY IN FRESH APHERESIS UNITS

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The clonal potency is the potential capacity of stem cells to differentiate into different mature cell types. The clonal potency is usually measured by colony-forming unit (CFU) methods,. which evaluates the number of Granulocyte–Monocyte progenitor colony (CFU-GM) and Erythroid burst-forming units (BFU-E) in culture. However, these assays are poorly standardized and require 14 days to obtain the result. To rapidly determine the stem cell clonal potency, a fast flow cytometric method based on the measurement of intracellular phosphorylated STAT5 (pSTAT5) in CD34+ cells in response to IL-3 stimulation was developed. Aim of this study was the comparison of the pSTAT5 assay with the CFU method in ten units of fresh stem cell collections. Briefly, 25 µl of fresh stem cell apheresis suspension was diluted in 85 µl of Iscove's modified Dulbecco's Medium. For each sample two wells were used, one as the unstimulated control, and the other one as the stimulated sample by adding 1 mL of 10 mg/mL IL-3. After an incubation for 20 min at 37°C and 5% CO2 the cells were fixed and permeabilized with 70% of methanol and stained with anti-CD45-FITC/CD34-PE mix and anti-STAT5 (pY694) Alexa Fluor 647 overnight at 4°C. The results were expressed as the percentage of pSTAT5+CD34+CD45+ cells in the IL-3-stimulated well. The stimulated cell quadrant was set according to the unstimulated control sample. We obtained respectively a median of 46,7% of pSTAT5+CD34+CD45+ cells, 56,5 CFU-GM x10^4 Kg and 42,2 BFU-e x10^4 Kg. We didn't find significantly differences in potential capacity of stem cells evaluated by both methods in patients with multiple myeloma treated with DaraVTD (Daratumumab, Bortezomib, Thalidomide, Dexamethasone), among 50% of cases, versus VTD. We did not find significant differences in 4 patients treated to plerixafor *vs* untreated patients. We did not find differences of %pSTAT5+CD34+CD45+ cells in patients aged <55 years (42%) *vs* patients aged >55 years (47.7%). The median CFU GM count in patients aged <55 years was 69.42 x10^4 Kg *vs* 44.82 x10^4 Kg in patients aged >55 years (p-value n.s.). Our preliminary results indicate that the pSTAT5 flow cytometric assay is complementary to the CFU method. This innovative method is faster and more standardized than the CFU method. The limitation of our preliminary study is the small number of samples analyzed. Further studies including more cases are necessary to confirm our data.

P120

GRAFT VERSUS HOST DISEASE PROPHYLAXIS WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE VERSUS ANTI-THYMOCYTE GLOBULIN IN PATIENTS RECEIVING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM HAPLOIDENTICAL AND MATCHED UNRELATED DONORS: A REAL-LIFE REPORT

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Background. Post-transplant cyclophosphamide (PTCY) is widely used as graft versus host disease (GvHD) prophylaxis in allogeneic hematopoietic stem cell transplant (HSCT) recipients, with reported clinical benefits in matched unrelated donor (MUD) HSCT. However, real-life data on clinical efficacy and safety of PTCY are still poor.

	PTCY cohort N = 24	ATG cohort N= 16	*P* value
Median age, years (range)	51 (20-71)	45 (21-61)	0.39
Gender, n (%)			0.25
Male	11 (46)	5 (31)	
Female	13 (54)	11 (69)	
Hematologic malignancy, n (%)			0.63
AML	15 (63)	12 (75)	
ALL	5 (21)	4 (25)	
MM	3 (12)	-	
Other	1 (4)	-	
Stem cell source, n (%)			0.05
Peripheral blood	11 (46)	12 (75)	
Bone marrow	13 (54)	4 (25)	
Time to transplant, months, median (range)	11 (1-55)	9 (1-44)	0.23
Stem cells infused, x10⁶/kg, median (range)	3.70 (0.60-7.90)	4.78 (1-8.29)	0.05
Type of donor, n (%)			
Sister/brother	7 (30)	13 (72)	
Mother/father	2 (8)	2 (12)	0.001
Son/daughter	13 (54)	1 (6)	
MUD	2 (8)	-	
Conditioning regimen, n (%)			
TBF	22 (92)	5 (31)	
BU-FLU	1 (4)	9 (56)	0.001
FLU-NPAM	1 (4)		
R-TBF	-	2 (13)	
Type of conditioning, n (%)			
Myeloablative	17 (71)	15 (94)	0.07
Reduced intensity	7 (29)	1 (6)	
Engraftment failure, n (%)	2 (8)	3 (19)	0.32
Neutrophil engraftment, days, median (range)	20 (11-36)	16 (10-25)	0.01
Platelet engraftment, days, median (range)	29 (11-184)	16 (10-37)	0.03
Acute GvHD, sites, n (%)	11 (46)	6 (37)	0.72
Skin	8 (32)	4 (25)	
Intestine	6 (24)	1 (6)	
Liver	4 (16)	2 (13)	
Acute GvHD grading, n (%)			0.8
Grade I-II	10 (40)	5 (31)	
Grade III-IV	1 (4)	1 (6)	
Chronic GvHD, sites, n (%)	10 (42)	5 (31)	0.8
Skin	7 (28)	5 (31)	
Intestine	2 (8)	2 (13)	
Liver	4 (16)	1 (6)	
Lung	1 (4)	1 (6)	
Eyes	1 (4)	-	
Chronic GvHD grading, n (%)			0.7
Mild	6 (24)	3 (19)	
Severe	4 (16)	2 (13)	
Donor lymphocyte infusion, n (%)	3 (12)	2 (13)	0.97
Hematological relapse, n (%)	4 (16)	8 (50)	0.02
All-cause deaths, n (%)	9 (36)	12 (75)	0.02
Transplant-related mortality, n (%)	4 (17)	4 (25)	0.56
2-year relapse free survival	30%	51%	0.04
2-year overall survival	61%	42%	0.26

Abbreviations. PTCY, post-transplant cyclophosphamide; ATG, anti-thymocyte globulin; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; MM multiple myeloma; MUD, mismatched unrelated donor; TBF, thiotepa-busulfan-fludarabine; BU-FLU, busulfan-fludarabine; FLU-NPAM, R-TBF; GvHD, graft *versus* host disease.

Table 1.

Methods. In our real-life retrospective observational study, we included a total of 40 consecutive adult patients who underwent haploidentical or MUD HSCT and who received PTCY (n=24) or anti thymocyte globulin (ATG, n=16) as GvHD prophylaxis at Hematology Units from Salerno and Avellino, Italy, between 2009 and 2021.

Results. Patients received a diagnosis of acute myeloid leukemia (AML) in 63% and 75%, acute lymphoblastic leukemia (ALL) in 21% and 25%, and multiple myeloma (MM) in 12% and 0% of cases in PTCY and ATG arms, respectively. Patients who had PTCY more frequently received bone marrow stem cells (54% *vs.* 25%; p=0.05), and son/daughter or brother/sister were the most represented source of donor (54%) (p=0.001). Incidence of acute (46% *vs.* 37%; p=0.72) and chronic (42% *vs.* 31%; p=0.8) GvHD was similar between groups, while graft failure rate was lower in the PTCY group (8% *vs.* 19%; p=0.32). Time to engraftment was longer in the PTCY group for neutrophils (20 *vs.* 16 days; p=0.01) and platelets (29 *vs.* 16 days; p=0.03) compared to ATG-treated patients. Furthermore, relapse rate after transplantation was lower in the PTCY compared to ATG arm (16% versus 50%; p=0.02). All-cause mortality was lower (36% *vs.* 75%; p=0.02) and the 2-year overall survival was slightly superior in patients who received PTCY (61% *vs.* 42%; p=0.26).

Conclusions. We support the use of PTCY, even in a real-life setting; however, the optimization of this protocol should be further investigated to better balance relapse prevention and GvHD prophylaxis.

Myeloproliferative neoplasms

P121

THE PROGNOSTIC NUTRITIONAL INDEX (PNI) AT DIAGNOSIS IS A PREDICTIVE MARKER OF POOR OUTCOME IN PATIENTS WITH PRIMARY MYELOFIBROSIS: A MONOCENTRIC REAL-LIFE EXPERIENCE

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Background. Primary Myelofibrosis (PMF) is a myeloproliferative neoplasm characterized by bone marrow fibrosis, cytopenias, splenomegaly and constitutional symptoms. Laboratory biomarkers, such as albumin (ALB) and absolute lymphocyte counts (ALC) can provide information regarding the prognosis of PMF. The Prognostic Nutritional Index (PNI) combines ALB and ALC data to provide insight into patients (pts) inflammatory, nutritional, and immune status.

Aims. The aim of this study was to investigate the role of the PNI as a predictor of outcome in pts with PMF, in term of overall survival (OS) and thrombosis-free-survival (TFS).

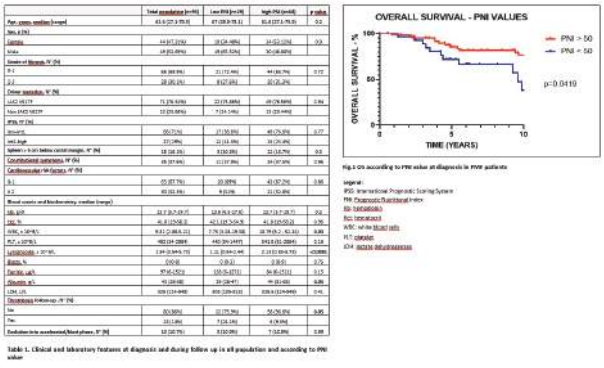

Figure 1.

Methods. A total of 93 pts, affected by PMF, followed in our Center from 2004 to 2024, were retrospectively evaluated. PNI value is obtained by adding the serum ALB level (g/L) to the ALC ($*10^9$/l) multiplied by 0.005. Pts were dichotomized using the best threshold of PNI identified by ROC analysis. TFS and OS were estimated using Kaplan-Meier analysis; other analyses were conducted using common statistical methods.

Results. Overall, 93 pts were enrolled into this study; 49 (52.7%) were male. The median age at diagnosis was 63.6 years (range 27.1-79.9). Majority presented into prefibrotic phase (68.9%), according to 2022 WHO classification. Features of pts were showed into Table 1. The median value of ALB levels at diagnosis was 43 g/l (range 26-68), while the median value of ALC was 1940/uL (range 540-5730). No significant differences were reported at diagnosis between low (n=29) and high (n=63) PNI groups, except for a lower white blood count and ALC (p=0.03 and p<0.01) in the low PNI group. After a median follow-up of 6.9 (range 0.5-19.6) years, 29 pts (31.2%) died. 10 pts (10.7%) had a disease progression into an accelerated or blast (A/B) phase. Pts with low PNI at diagnosis had a significant shorter OS compared to the other group (Figure 1, p=0.04). In pts with PNI > 50, a lower number of thrombotic events was observed (p=0.05), with a significant better TFS (p<0.01) compared to low PNI group. No correlation between PNI value and transformation in A/B phase was observed (p=0.7).

Conclusion. Our study firstly describes a potential predictive role of PNI, a marker of nutritional and inflammatory status, for poor outcome in PMF; in particular pts with a PNI value<50 at diagnosis seem to have a significant worse survival and higher incidence of thrombosis. Further studies on larger scale are needed to confirm these data.

P122

DISEASE SPECIFIC AND NON SPECIFIC RISK FACTORS FOR THROMBOSIS AT UNUSUAL SITES IN CHRONIC MYELOPROLIFERATIVE NEOPLASMS: ROLE OF JAK2V617F ALLELIC BURDEN AND LEUKOCYTOSIS IN OUR MULTICENTRE RETROSPECTIVE COHORT OF 66 CONSECUTIVE CASES

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Background. Thrombosis at unusual sites represent understudied illnesses with unique presentation, pathophysiology and often not clear provoking factors. The occurrence of atypical venous thrombosis suggests itself a possible MPN, even in case of a normal blood count and in absence of organomegaly. The detection of a JAK2V617F allele burden at least equal to 50% has been shown to be a risk factor for thrombosis. The direct link between leukocytosis and thrombotic risk in MPN is still challenging. The role of other risk factors needs to be better clarified. Aim: The aim of our multicentre retrospective study is to identify disease specific and non specific risk factors for thrombosis at unusual site in MPN.

Methods. Our study included n 66 consecutive patients with atypical venous thrombosis and previous or concomitant diagnosis of MPN according to WHO 2008 and 2016 diagnostic criteria; all cases of cerebral and splanchnic venous thrombosis (CVT and SVT) were confirmed by imaging studies and treated according to current guidelines.

Results. In our cohort 43.9% of all patients were male, 56.06% female (p:0.584). Most patients experienced SVT (77.3%), followed by CVT (22.7%). MPN diagnosis were distributed as follows: 24.2% of PV, 31.8% of ET, 31.8% of MF, and 12.1% of MPN-U. The most prevalent driver mutation was JAK2V617F (85.9%), followed by CALR type I and II (9.4%), and MPL 3.1%. At diagnosis of thrombosis median white blood cell count is 9.140/μL-1 and median absolute neutrophil count (ANC) is 5.455 /μL-1. Median platelet count is 359.000/μL-1. JAK2V617F allelic burden is available for 34 patients. Median JAK2 allelic burden is 25.6%. Among JAK2V617F patients only 6/34 showed an allele burden superior to 50% (17.6%). Thrombophilia conditions, detected in 57.1% of 49 patients studied, the presence of traditional risk factors, detected in 33.3% of patients, and previous thrombotic history, reported in 13.6%, do not significantly affect the occurrence of thrombosis (p: 0.263, p: 0.193 and p: 0.801 respectively).

Conclusions. Among disease specific associated prothrombotic conditions median platelet count, total white blood count as well as ANC appear within the normal range; just a minority of JAK2V617F positive patients show an homozygous allelic burden; among non-disease specific conditions sex, previous thrombosis, thrombophilia and traditional risk factors for thrombosis do not affect the risk of atypical venous thrombosis.

P123

RED CELLS DISTRIBUTION WIDTH (RDW) MAY PREDICT PROGNOSIS IN MYELOFIBROSIS PATIENTS TREATED WITH RUXOLITINIB

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In myelofibrosis, fibrosis in the bone marrow and development of extramedullary haematopoiesis may lead to the production of red blood cells (RBC) of often bizarre shape, increasing variability in RBC volume. The increased anisocytosis, measured in terms of red cells distribution width (RDW) showed a negative prognostic role in MF patients. In our retrospective single center analysis, we evaluated 182 patients diagnosed with DIPSS ≥ intermediate-1 risk PMF/SMF treated with ruxolitinib (ruxo) from 2011 to 2024. At baseline before ruxo start, the median RDW was 19.35% (IQR 18.0-21.7). A higher baseline RDW was associated with higher DIPSS risk (p<0.001) and overt-MF (p<0.001). A ROC analysis for survival found 20.5% as an optimal cut-off RDW value to predict longer OS. Both baseline RDW as a continuous value (lower values) and RDW<20.5% was significantly associated with better spleen response (p<0.001 - p<0.001). After a median follow up of 65.7 months, 74 patients died (40,4%). Patients with a baseline RDW <20.5% *vs* ≥20.5% had a median overall survival OS of 84.2 months *vs* 34.6 months (p<0.001) [HR 3.4 (95%CI 2.1-5.4)]. For patients with a baseline Hb≥10g/dl, RDW <20.5% *vs* ≥20.5% had a median overall survival OS of 93.5 months *vs* 69.2 months (p=0.016) [HR 2.5 (95%CI 1.2-5.2)]. For patients with a baseline Hb<10g/dl, RDW <20.5% *vs* ≥20.5% had a median overall survival OS of 61.8 months *vs* 27.8 months (p<0.001) [HR 2.5 (95%CI 1.2-5.2)]. Therefore, patients with Hb≥10g/dl and RDW≥20.5% had a comparable median OS to patients with HB<10g/dl and RDW <20.5%. For patients with a baseline DIPSS=Int-1, there was no difference median OS between RDW <20.5% *vs* ≥20.5% (p=0.99) and for DIPSS=high, the median OS difference between RDW <20.5% *vs* ≥20.5% did not reached the statistically significance (39.0 *vs* 25.9 months) (p=0.178). In patients with a baseline DIPSS=Int-2, RDW <20.5% *vs* ≥20.5% had a median overall survival OS of 79.0 months *vs* 29.8 months (p<0.001) [HR 5.8 (95%CI 2.8-12.0)]. In particular, DIPSS=int-2 patients with RDW ≥20.5% presented a comparable median OS to patients with DIPSS=high (29.8 *vs* 26.6 months). In the univariate and multivariate analyses, both baseline RDW as a continuous value and RDW≥20.5% were significantly associated with a shorter OS, along with other known negative prognostic factors. Moreover, both baseline RDW as a continuous value and RDW≥20.5% were associated with higher RR6 risk (p<0.001-p<0.001).

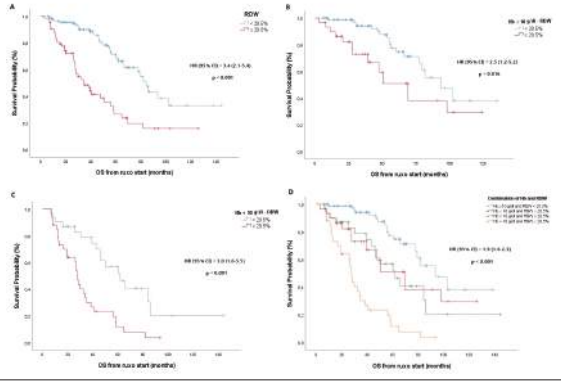

Figure 1.

P124

ABSTRACT NOT PUBLISHABLE

P125

"SECONDARY" ESSENTIAL THROMBOCYTHEMIA OCCURRING IN NPM1-MUTATED AML DURING LONG-STANDING COMPLETE REMISSION. A NEW DISEASE ENTITY POTENTIALLY LINKED TO THE PRESENCE OF JAK2 V617F MUTATION AT AML DIAGNOSIS

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NPM1-mutated Acute Myeloid Leukemia (AML) is a good prognosis molecular subgroup, with a high rate of complete remission and 5-y survival of 60%. With extended follow-up of NPM1 AML in continuous remission, we observed the development of thrombocytosis in 5 patients (pts). A diagnosis of Essential Thrombocythemia (ET) was made in all pts. They represent 3.2% of the entire *de novo* AML NPM1 population diagnosed at our Center from 2006 to 2023. Their biological and clinical features both at *de novo* AML and at ET diagnosis are showed in Table 1. At AML diagnosis, median age was 62 years (51-73), median WBC was 44.76x10^3/µl, median platelets count was 223x10^3/µl (27-372) and median bone marrow blasts was 79%. All pts had a normal karyotype with NPM1-A mutation and three had FLT3-ITD.

Table 1.

Pt sex	AML DIAGNOSIS									ET DIAGNOSIS					SURVIVAL	
	AGE	CBC AML DIAGNOSIS			MOLECULAR BIOLOGY	INDUCTION	COMPLETE REMISSION	CONSOLIDATION	RELAPSE	EFS (MONTHS)	AGE	CBC			MOLECULAR BIOLOGY	MONTHS	STATUS
		HB (g/dL)	PLT (10^3/µL)	WBC (10^3/µL)								HB (g/dL)	PLT (10^3/µL)	WBC (10^3/µL)			
F	51	13	372	85.9	NPM1-A, FLT3-ITD, JAK2 V617F (VAF 3,7%), TET2	Midostaurin 3+7	Yes	HD-AraC	No	14.2	52	13.5	656	7.8	JAK2 V617F (VAF 41,2%), TET2	30.2	Alive
F	51	8.2	27	73.4	NPM1-A, FLT3-ITD, NGS not done	ICE	Yes	HD-AraC	No	83.5	57	14	337	5.3	JAK2 V617F, NGS not done	214.3	Alive
M	59	8.7	116	6.1	NPM1-A, FLT3-ITD, NGS not done	ICE	Yes	HD-AraC	No	155.2	71	14.9	672	10.5	JAK2 V617F, NGS not done	154	Alive
M	69	9.7	165	13	NPM1-A, IDH1, JAK2 V617F (VAF 0,6%), DNMT3A	ICE	Yes	HD-AraC	No	53.6	73	15.8	702	5.5	JAK2 V617F (VAF 12,6%), DNMT3A, TET2	126	Dead
F	73	6.7	74	3.5	NPM1-A, NGS not done	ICE	Yes	HD-AraC	No	70.3	78	12.3	717	4.6	JAK2 V617F, NGS not done	77.6	Alive

The genetic landscape was analyzed by NGS in two pts, showing in addition to NPM1 and FLT3-ITD, also JAK2 V617F and epigenetic gene mutations (TET2, DNMT3A and IDH1). All pts were treated with intensive chemotherapy (ICE cycle followed by high dose AraC) plus midostaurin in one. Complete remission was achieved in all pts. None underwent allo-SCT in first complete remission. With a median follow-up of 117 months, no relapses were observed, and four pts were alive. Median survival was 125 months (30-214) and median time to ET onset from AML was 42 months (14-155). At ET diagnosis, median age was 65 years (52-78), median WBC was 6.2*10^3/µl and median platelets count was 687x10^3/µl (537-717). All pts had JAK2 V617F mutation, with a median VAF of 19.8% (5.09-34.46). No splenomegaly and no major thrombotic or hemorrhagic events were recorded. Treatment included aspirin in 5 and hydroxyurea in 4 pts. The overall prognosis of "secondary" ET seems good with no evolution to myelofibrosis or AML. The pathogenetic significance of JAK2 mutation at NPM1-AML diagnosis in

the subsequent development of ET needs to be further confirmed by ongoing analyses of the mutational landscape of all five patients. The investigation of co-mutations to AML and ET diagnosis could help to define mutational trajectories, allowing to understand the development of AML followed by ET in this subgroup of interesting patients.

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RUXOLITINIB TREATMENT IN MYELOFIBROSIS IN THE LAST 10 YEARS: A SINGLE CENTER EXPERIENCE: HIGH EFFICACY AND SAFETY

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Background. Myelofibrosis (MF) is a chronic myeloproliferative neoplasm with constitutive activation of the Janus kinase (JAK) . Ruxolitinib, an oral JAK1 and JAK2 inhibitor, showed efficacy in reduction of spleen volume, total symptoms score and lower risk of mortality compared to placebo. Aim of this study was to describe the efficacy of ruxolitinib treatment in a single center retrospective experience and its safety.

Methods. We evaluate characteristics and outcome of all consecutive patients (pts) diagnosed with MF, including primary (PMF), post polycythemia vera (post-PV MF) and post essential thrombocytemia (post-ET MF), treated with ruxolitinib in our center from January 2013 to December 2023.

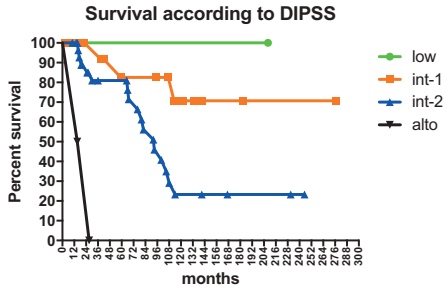

Figure 1.

Results. We observed 145 patients (pts) with MF and 56 (39%) were treated with ruxolitinib. Median age was 65 yo (range 26-85), M/F ratio was 32/24, 29 (39%) had PMF, 8 (14%) post-PV and 19 (34%) post-ET MF. DIPSS at diagnosis was int/high risk for 57% of patients. Splenomegaly was observed in 93% of pts and systemic symptoms in 43% at diagnosis. JAK2 mutation was positive in 39 pts (70%), CALR in 10 pts (18%), MPL in 4 (7%) and 3 patients were triple negative. Forty-two pts (75%) showed a reduction of almost 50% in spleen volume from baseline and 34 pts (61%) are alive with a median follow up of 62 months (range 3-277), 22 pts of 56 (39%) are still on ruxolitinib therapy with a median duration of 19 months. Median survival was 92 months (not reached in DIPSS low and Int-1) (v. Figure 1). Nine pts (16%) underwent an allogenic bone marrow transplantation. The rate of discontinuation was low (14%), mainly due to disease progression. Twelve pts (21%) experienced a second cancer during follow up, including 7 non-melanoma skin cancer (NMSC). Notably, 5 of this 7 pts had been previously treated with hydroxyurea for almost 5 years.

Conclusions. This retrospective study confirms the efficacy of ruxolitinib use in these setting, including spleen reduction and OS benefits. Our data confirm the need to consider regular skin cancer monitoring in pts treated with ruxolitinib, in particular if previously exposed to hydroxyurea. The outcome remains poor for high-risk DIPSS pts. Future directions will be probably based on optimizing therapeutic strategies, including ruxolitinib use as earlier as possible, dose-adjusting or combination with other agents.

Keywords: myelofibrosis, ruxolitinib, second neoplasm

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CARDIOVASCULAR RISK IN PATIENTS WITH POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA: FOCUS ON THE POTENTIAL ROLE OF LIPOPROTEIN(A)

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Background and Aims. Cardiovascular disease represents the main cause of mortality in Polycythemia Vera (PV) and Essential Thrombocythemia (TE) pts. The objectives of this study are to assess the potential role of cardiovascular (CV) risk factors, including LDL cholesterol (LDL-C) and Lipoprotein(a) [Lp(a)], in thrombotic events; to evaluate if altered levels of Lp(a) may modify CV risk stratification according to the European Society of Cardiology (ESC) and to compare ESC CV stratification with prognostic stratifications in use.

Methods. We analyzed 48 pts (16 PV and 32 TE), assessing hematologic parameters and ESC CV risk, including LDL-C and Lp(a). Lp(a) targets followed the Italian Atherosclerosis Society consensus (pathological >125 nmol/L, intermediate 75-125 nmol/L).

Results. Lp(a) values above 75 nmol/L were present in 6.25% of pts with PV and 3.1% of pts with moderate ESC CV risk. Thrombotic events occurred in 8 PV pts (75% venous) and 14 TE pts (79% arterial). Among pts with thrombotic events, Lp(a) levels were >75 nmol/L in 1 PV pt with acute coronary syndrome (ACS), in 1 TE pt with ACS, in 1 TE pt with 3 coronary artery diseases, in 1 TE pt with peripheral arterial disease (PAD), in 1 TE pt with stroke, and in 1 TE pt with PAD and deep vein thrombosis. In PV and TE pts, arterial hypertension was present in 66% and 37% of cases, diabetes mellitus in 6.25% and 12.1%, dyslipidemia in 75% and 87.5% and smoking habit in 25% and 15.6%, respectively. In pts cohorts with PV and TE, 78.6% and 40.6% of pts, respectively, had more than one risk factor, and within these two subgroups, 100% and 93% of the recorded thrombotic events occurred, respectively. 31% and 15.6% of PV and TE pts had LDL-C values at therapeutic goal. There was incongruity between hematologic prognostic stratification and ESC CV stratification in the case of 1 low-risk PV pt with moderate ESC risk with Lp(a) 136 nmol/L and 2 pts respectively low and intermediate r-IPSET-t risk with high ESC risk with Lp(a) values of 123 nmol/L and 215 nmol/L.

Conclusions. Classic CV risk factors, though common and associated with thrombotic events, are inadequately identified and managed. Prognostic scores should be integrated with ESC cardiovascular risk stratification to predict thrombotic risk more accurately. Lp(a) testing should be considered as a baseline screening due to its correlation with increased CV risk, potentially impacting ESC risk classification and expected mortality.

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MYDOSTAURIN PLUS AZACITIDINE FOR TREATMENT OF ADVANCED SYSTEMIC MASTOCYTOSIS ASSOCIATED TO HAEMATOLOGICAL NEOPLASMS: A SINGLE CENTER EXPERIENCE

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Outcome of Systemic Mastocytosis Associated Hematologic Neoplasm (SM-AHN) is dismal and primarily determined by the associated disorder. We have reviewed 15 SM-AHN cases diagnosed and followed in our center. 3 patients received contemporary treatment for the hematological disorder and SM based on midostaurine (mido) and azacytidine (aza). Pt#1: 31-yrs female, affected by HES (FIP1L1-PDGFR-α mut) and ASM (c-KIT D816V, VAF<0.1%), low MARS score, TET-2 mutated, received up-front imatinib100mg/day developing a secondary heparin-like coagulative disorder with life-threatening retroperitoneal hemorrhage. 2ndline treatment was started with Cladribine (7.8mg sc for 5 days) with improvement of clinical symptoms. After one month, cytopenias, flushing and hypotension occurred. BM evaluation confirmed diagnosis of mast-cell leukemia (c-KIT D816V VAF 40%), and a combination of mido 200 mg/die, aza75mg/m^2 s.c. for 7 days, Venetoclax (200 mg/day for 14 days) was started. After initial clinical benefit, the pt developed multi-resistant opportunistic pneumonia and died. Pt#2: 68-yrs male, affected by ISM (c-KIT D816V, VAF<1%) and CNL (CSF3R wt) received 1st line therapy with Hydroxyurea 1000mg/day. After 6 yrs, at onset of ASM, c-KIT D816V VAF increased (50%) associated to the of occurrence of RUNX-1-I342-K mutation (VAF:5%). A 2nd line treatment was offered, consisting in 20 mg/m^2 decitabine for 5 days/cycle, venetoclax 400mg/day and mido 200mg/day achieving hematological improvement with persistence of mast cells in the BM. During the 3rd cycle of treatment further progression in AML occurred and HAM regimen was given as bridge to allo-transplant, but death occurred for sepsis. Pt#3: 82-yrs unfit male, affected by ASM (c-KIT D816V, VAF 10%), high MARS score, and high-risk MDS (del7) received up-front mido 200 mg/day and aza 75mg/m^2 s.c. for 7 days, venetoclax was postponed for unfitness. After first two months of treatment, pt achieved blasts clearance in peripheral blood with hematological improvement. Treatment was interrupted at month 6 for pneumonia, with occurrence of progressive refractory thrombocytopenia, until death for intracranial bleeding. SM-AHN can require contemporary treatment of both hematological neoplasms. In real life, the combination of mido, aza and venetoclax is feasible but not curative, leading to short-term responses. Further studies are required to establish the clinical benefit of this combination as bridge-to-transplant strategy.

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ANEMIA IN PATIENTS WITH MYELOFIBROSIS: A SINGLE-CENTRIC REAL-LIFE EXPERIENCE OF MOMELOTINIB FOR COMPASSIONATE USE

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Background. Momelotinib (MMB) is a small oral molecule effective against symptoms and splenomegaly in myelofibrosis (MF). In addition to targeting JAK, it has a significant inhibitory effect on the ACVR1/ALK2 activation pathway, which plays an important role in hematopoiesis and anemia, which regulates the expression of hepcidin, the master regulator of iron homeostasis. Based on SIMPLIFY-1/-2 and MOMENTUM trials, it is the fourth JAKi FDA-approved, indicated for MF anemic patients, where ruxolitinib (RUX) or other JAKi are not very effective, considering the well-known cytopenic side effects.

Aims. We report the first unicentric real-life data of MMB in patients treated through the compassionate use program in our experience. Data were collected at baseline and during follow-up, with a data cut-off in April 2024 and a last time point at 6 months.

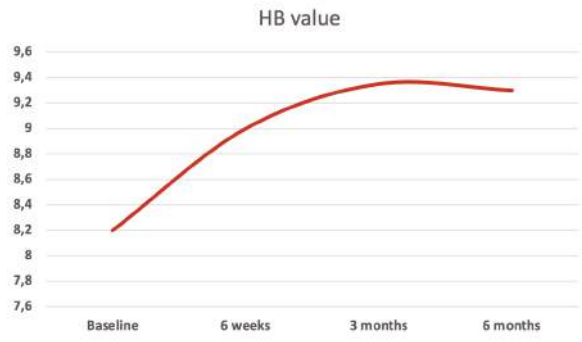

Figure 1A. Improvement in hemoglobin value, as described in text (p<0.001).

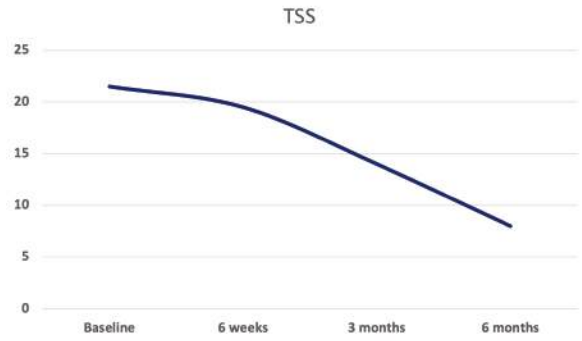

Figure 1B. Reduction in symptom burden during MMB treatment (p<0.001). TSS: total symptom score).

Results. 7 MF patients (6 primary MF, 1 secondary to ET; DIPSS/MYSEC-PM: intermediate-2 in 5 cases, intermediate-1 in 2), with a median age of 74 years [62-84], started MMB at a dosage of 200 mg daily after 134 median months from diagnosis [17-109]. 6 were previously exposed to RUX (for a median of 86 months), and 1 was treated with hydroxycarbamide. They all interrupted the prior treatment for hematological side effects (anemia in 5, associated with thrombocytopenia in 2). 3 patients were transfusion dependent (3 RBC units/months), and 3 splenomegalic. During the treatment, the median Hb value improved from a median of 8.2 g/dL to 9, 9.4, and 9.3 g/dL (Figure 1A, p<0.001 through one-way ANOVA), and only 1 patient required 2 RBC units between baseline and 6 weeks. Spleen size was reduced by about 40% in 2 cases. TSS was decreased in all of them, from a baseline of 22 to 8 at 6 months (Figure 1B, p<0.001). The most frequent non-hematological adverse events (57% of patients) were limited to grade 1 infections (2 urinary, 1 upper respiratory system), constipation, and myalgia, without any hematological side effects. At the data cut-off, 100% of patients continued therapy and achieved a median treatment time of 10 months.

Conclusion. MMB showed a favorable hematological response with improved hemoglobin value, reducing (until suspending) trans-

fusion support without noteworthy side effects, and associated with an improvement in symptom burden, considering the possibility of using JAKi at full dose. Further real-world analyses are required to confirm the trial results and identify the patients who could benefit from early MMB treatment.

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DASS: A NEW PROGNOSTIC SCORE FOR MYELOFIBROSIS INCLUDING INFLAMMATION

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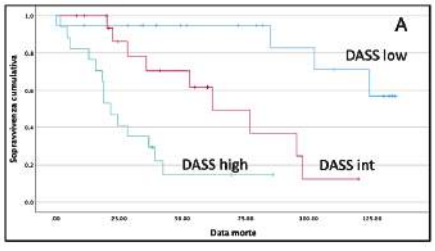
Background. The role of inflammation in myelofibrosis (MF) has emerged as an important pathogenetic and prognostic factor.

Aim. To set a new prognostic score by adding to DIPSS some inflammatory parameters: PLT/Ly (PLR), N/Ly(NLR), WBC/Ly(WLR); Ferritin/Ly(FLR), Ly/LDH(LLR), immuno-systemic inflammation index SII((PLT x N)/Ly), and the systemic inflammatory response index SIRI(NxMo/Ly).

Patients and Methods. This retrospective study involved 96 MF patients followed in our center, treated with Ruxolitinib (56 patients) or BAT (40 patients), with diagnosis between January 2010 and May 2023. The median age was 70 years, 59 were male and 37 females; 57% carried mutations of JAK2, 16% of CALR, and 3% of MPL. For 80 patients it was possible to calculate DIPSS based on age, symptoms, WBC count, Hb, blasts, karyotype, transfusion dependence and PLT: 12% were at low, 30% at intermediate-1, 43% at intermediate-2, and 15% at high risk.

OS according to the DASS score.



P<0.01

	low	int	high
OS 60mesi	95%	62%	15%

Figure 1.

Results. The median OS of the entire cohort was 62 months; 52% of patients was alive at 5 years and 30% at 10 years, with longer OS for patients younger than 65 years (5-year OS: 72% *vs* 38%; p=0.006), for patients with low/intermediate-1 *vs* intermediate-2/high DIPSS (5-year-OS: 81% *vs* 26%; p<0.001), and for patients without systemic symptoms (5 years-OS: 68% *vs* 39%; p=0.019). The 5-year OS was 76% for subjects with low *vs* 45% for those with high SIRI (p=0.015). Based on the parameters significant in univariate analysis, we created a new prognostic score called DASS (DIPSS, Age, Symptoms, SIRI) which assigns 1 point to age >65 years, 2 points to SIRI>2.7 and 3 points for systemic symptoms. According to this score, we distinguished 3 populations: one at low risk, with 5-year OS of 95%, one at intermediate, with OS of 62%, and one at high risk, with 5-year OS of 15%. According to DIPSS, the 5-year OS was 81% for the low/intermediate-1 risk and 26% for the intermediate-2/high risk subgroup. In the cohort of the 35 patients treated with ruxolitinib, the DASS identified 3 subgroups with significantly different median OS: low risk=102 months; intermediate risk=95 months; high risk=19 months (p<0.001).

Conclusions. DASS is a new good prognostic score that could allow better selecting patients candidate to allogeneic transplantation. The validation on a further independent cohort is ongoing.

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ASSISTED REPRODUCTIVE TECHNOLOGY IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA: A NEW CLINICAL CHALLENGE

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Essential thrombocythemia (ET) is the most common myeloproliferative neoplasm in young women, with over 20% being under 40 years old. Women with ET face a 3.4-fold increased risk of fetal loss compared to their healthy counterparts, mainly due to spontaneous abortion. As women delay childbearing and opt for assisted reproductive technology (ART), such as *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI), they face additional challenges. ART procedures, including controlled ovarian hyperstimulation (COH), lead to elevated estradiol levels, compounding the procoagulant state seen in ET. However, practice guidelines addressing clinical management as well as maternal and fetal outcomes in ET women undergoing ART are lacking. Here, we retrospectively evaluated cases of ART in a monocentric cohort of ET women in childbearing age. During a median follow up of 8 years (range 5-17), 28 pregnancies were recorded in 154 women, among which four (3%) pursued ART. The median age at diagnosis was 33.5 years (range 28-36). Median platelet count at diagnosis was $521x10^9$/L (range 500-786), with no personal history of thrombotic events or cardiovascular risk factors recorded. One patient carried JAK2 V617F mutation, whilst the others tested negative for driver mutations; 2 patients were on anti-platelet therapy. Two out of four women had successful ART. In the first one, after a failed first attempt, ART was successful with LMWH prophylaxis during COH. In the second patient, ART was successful but complicated by retroperitoneal hematoma after ovarian pick up. Both used aspirin during pregnancy, had full-term deliveries via cesarean section, with neither maternal nor fetal complications. The remaining two patients had ART failure. One underwent 3 unsuccessful IVF cycles, and one year after COH experienced a severe increase of platelet count ($4.331x10^9$/L) which required low dose cytarabine therapy. The other one, JAK2 mutated, sustained 4 ART attempts followed by recurrent implantation failure. No thrombotic events or ovarian hyperstimulation syndrome (OHSS) occurred in any patient. In conclusion, our data show that ART in ET patients can be pursued, but women must be aware of the consistent thrombotic risk related to this procedure. A multidisciplinary approach to control potential risks, optimizing treatment outcomes is of fundamental importance.

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BOMEDEMSTAT, A LYSINE-SPECIFIC DEMETHYLASE 1 (LSD1) INHIBITOR, FOR THE TREATMENT OF ESSENTIAL THROMBOCYTHEMIA (ET): AN OPEN-LABEL PHASE 3 STUDY

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[1]University of Florence, DMSC, AOU Careggi; [2]Hadassah Medical Center; [3]Sheba Medical Center–Tel HaShomer; [4]Tel Aviv Sourasky Medical Center, School of Medicine, Faculty of Medical and Health Sciences, Tel Aviv University; [5]Merck & Co., Inc; [6]Royal Adelaide Hospital and SA Pathology

ET is a myeloproliferative neoplasm characterized by clonal thrombocytosis. Currently available treatments prevent thrombotic complications but do not alter disease course. LSD1 is an enzyme that regulates hematopoietic stem cell and progenitor cell proliferation. In a phase 2 study, bomedemstat, an irreversible inhibitor of LSD1, improved symptoms, durably reduced platelet and white blood cell counts, and reduced mutation burden in patients with ET. Here, we present the methodology for a randomized, open-label, phase 3 study (NCT06079879) designed to evaluate the efficacy and safety of bomedemstat versus best available therapy in patients with ET with an inadequate response to or intolerance of hydroxyurea. Eligibility criteria include age ≥18 years, ET per WHO 2016 diagnostic criteria, bone marrow fibrosis score of 0 or 1, platelet count of >450 x 10^9/L, and absolute neutrophil count of ≥0.75 x 10^9/L. Patients must have a history of inadequate response to or intolerance of hydroxyurea per modified ELN criteria and an inadequate response or loss of response to their most recent therapy. Approximately 300 patients will be randomly allocated 1:1 to bomedemstat 50 mg/day by mouth (starting dose; titrated to target platelet count of ≥150 x 10^9/L to ≤350 x 10^9/L) or investigator's choice of anagrelide, busulfan, interferon alfa/pegylated interferon alpha, or ruxolitinib (best available therapy). After 52 weeks, patients receiving best available therapy will be eligible to cross over to bomedemstat. Maximum time on study treatment is 156 weeks. Randomization will be stratified by hydroxyurea history (inadequate response *vs* intolerance) and MFSAF v4.0 baseline score (≥4 *vs* <4). Clinic visits will occur every 2 weeks until week 12 and monthly thereafter. Primary end point is durable clinicohematologic response rate per modified ELN criteria. Secondary end points are change in fatigue and total symptom per the MFSAF v4.0, change in total fatigue score per the PROMIS Fatigue SF-7a scale, duration of clinicohematologic response, duration of hematologic remission, incidence of thrombotic and major hemorrhagic events, transformation to post-ET myelofibrosis or myelodysplastic syndrome/acute myeloid leukemia, event-free survival, and safety. Recruitment is ongoing.

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REAL-WORLD ITALIAN EXPERIENCE WITH ROPEGINTERFERON ALFA-2B (BESREMI) IN POLYCYTHEMIA VERA

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Background. Ropeginterferon alfa-2b, a novel interferon-formulation, has recently been approved in Italy for Polycythemia Vera (PV) treatment. Despite clinical trial data availability, the real-world effectiveness and safety profile of Ropeginterferon alfa-2b remains unexplored.

Methods. In this observational study, we evaluated the therapeutic impact of Ropeginterferon alfa-2b in 14 PV patients at Azienda USL-IRCCS of Reggio Emilia between November 2022 and March 2024, focusing on tolerance, safety and treatment responses.

Results. The study included 14 patients with PV, with a median age of 52 years. Among these patients, 21% were female and 79% male.The patient group was evenly split into two categories: low-risk (LR) and high-risk (HR). Among HR patients, classification was primarily by age for 71% and by vascular events for 29%. Ropeginterferon alfa-2b therapy initiation was driven by hydroxyurea resistance in 57% of patients, intolerance to hydroxyurea in 35%, and 7% of patients were women of childbearing age. Notably, 71% of the patients maintained the treatment for a minimum of 12 months, with 80% of these patients still on therapy. At the onset of therapy, 57% of the patients exhibited non-symptomatic splenomegaly, with spleen sizes exceeding 12 cm (range 9-15).Overall, the complete blood count remission rates amounted to 50%. The side effects observed were predominantly mild and manageable. A single patient developed mild flu-like symptoms, which were successfully treated with premedication using paracetamol. However, 28% of the patients ceased treatment. Within this subset, only one individual discontinued due to adverse effects (Raynaud's disease), which subsided after stopping the therapy. The remaining patients halted treatment mainly because of disease progression or difficulty in drug administration (85-year-old patient).

Conclusions. This study demonstrates the safety, tolerability, and effectiveness of the Ropeginterferon alfa-2b formulation for PV patients in a real-world clinical setting, supporting its utilization as a strategic therapeutic option. While the findings are promising, they are derived from a modest sample size and short follow-up period, suggesting the need for further research to consolidate these findings, especially regarding long-term and molecular effects.

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REAL-LIFE EXPERIENCE WITH ROPEGINTERFERON ALFA-2B IN THE TREATMENT OF PATIENTS WITH POLYCYTHEMIA VERA: A REPORT FROM THE RETE EMATOLOGICA PUGLIESE (REP)

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Rogpeginterferon alfa-2b, a polyethylene glycol-conjugated proline-interferon, is a new-generation long acting formulation allowing a two weeks administration interval; its robust and sustained efficacy in polycythemia vera (PV) patients has been demonstrated in large clinical trials. However, few data are available about the use of this drug in the real-life setting. We describe ropeginterferon alfa-2b effects on blood count and clinical changes in 19 patients affected by PV, diagnosed according to WHO 2022 criteria and treated in-label at 5 hematological REP centers in Puglia. All the patients received

acetyl salicylic acid prophylaxis and 16 of them were resistant to hydroxyurea. Bone marrow histology consistent with PV and JAK2V617F mutation were present in all cases. Complete blood count at baseline and at 3, 6, 12, 18 months, necessity of phlebotomy, change in JAK2 allele burden and PV-related symptoms, as well as adverse events, were collected. Of the 19 patients, 14 were male (74%) and 5 female (26%); median age at diagnosis was 59 years (range 37-81). Median follow up was 13 months (3-19). Data at baseline were as follows: median splenic length by CT scan 14 cm (9.5-18), median HCT 49% (43-60.2), median Hb 17 g/dl (12.5-21.4), median platelet count 324x10^9/L (169-1246), median leucocyte count 8.1x10^9/L (4.5-17.4). All, except three patients, had symptoms: headache, itching (also associated with anxiety), weakness (associated with iron deficiency), fatigue, night sweating, scotoma, vertigo. At last follow up (April, 2024), 8 patients were in complete hematological response (HR) (Hct<45%, platelet count <400 × 10^9/L, and leucocyte count <10 × 10^9/L), and 7 were in partial HR. All patients had complete resolution of symptoms. JAK2V617F allele burden changes at 12 months from baseline were available in 5 patients: -33%, -27%, -21%,-15%, -10%, respectively. Such a decrease seemed to be deeper in those patients who had baseline VAF >50%. No grade 3-4 toxicity were reported. This preliminary real-life REP experience confirms efficacy and safety of ropeginterferon alfa-2b in PV patients outside of clinical trials.

P135

PACIFICA: RANDOMIZED, PHASE 3 STUDY OF PACRITINIB VERSUS PHYSICIANS`S CHOICE IN PATIENTS WITH MYELOFIBROSIS

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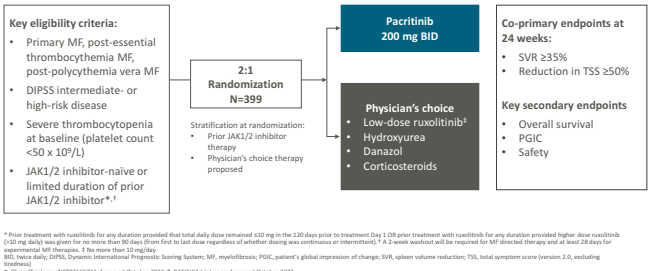
Background. As the treatment landscape continues to evolve in myelofibrosis, there remains an unmet need for patients with cytopenic myelofibrosis who have thrombocytopenia, leukopenia, and/or anemia (Palandri et al. Cancer; 2023). Pacritinib is an oral JAK2/IRAK1/ACVR1 inhibitor with demonstrated clinical activity in myelofibrosis in two phase 3 studies and a phase 2 dose-finding study, all inclusive of patients with severe thrombocytopenia and anemia. The PACIFICA trial (NCT03165734) is designed to confirm the efficacy and safety of pacritinib 200 mg twice daily (BID) *vs* physician's choice (P/C) therapy in patients with myelofibrosis and severe thrombocytopenia.



* Prior treatment with ruxolitinib for any duration provided that total daily dose remained ≤10 mg in the 120 days prior to treatment Day 1 OR prior treatment with ruxolitinib for any duration provided higher dose ruxolitinib (>10 mg daily) was given for no more than 90 days (from first to last dose regardless of whether dosing was continuous or intermittent). † A 2-week washout will be required for MF directed therapy and at least 28 days for experimental MF therapies. ‡ No more than 10 mg/day.
BID, twice daily; DIPSS, Dynamic International Prognostic Scoring System; MF, myelofibrosis; PGIC, patient's global impression of change; SVR, spleen volume reduction; TSS, total symptom score (version 2.0, excluding tiredness)
1. ClinicalTrials.gov NCT03165734. Accessed October 2023. 2. PACIFICA trial page. Accessed October 2023.

Figure 1.

Study Design. PACIFICA is an international, multicenter, randomized, controlled phase 3 trial of pacritinib *vs* P/C in adults with myelofibrosis with DIPSS intermediate- or high-risk disease, ECOG performance status 0-2, platelet counts <50 x 10^9/L, not candidates for stem cell transplant and either JAK2 inhibitor (JAK2i) naïve or have had prior JAK2i therapy. Patients with prior ruxolitinib exposure may enroll provided that the daily dose did not exceed 10 mg in 90 of the 120 days prior to Day 1. Patients with other (non-ruxolitinib) prior JAK2i exposure may enroll provided that the total duration of therapy was <90 days. Patients may not have had exposure to >1 prior JAK2i. Additional exclusion criteria include recent grade ≥2 cardiac or hemorrhagic events, left ventricular ejection fraction <50%, QTcF >450 msec, or use of medications that increase risk of hemorrhage or QTc prolongation. Patients are randomized (2:1) to continuous pacritinib 200mg BID or P/C (low-dose ruxolitinib [≤10mg/day], danazol, corticosteroids, or hydroxyurea). Coprimary endpoints include the proportion of patients achieving a ≥35% spleen volume reduction and the proportion achieving a ≥50% reduction in total symptom score (version 2.0, excluding tiredness) from baseline at week 24. A sample size of 399 provides 85% power to meet both primary endpoints. Secondary endpoints include overall survival, Patient Global Impression of Change response at week 24, and safety. Tertiary endpoints include leukemia-free survival, hematologic improvement, fatigue improvement, changes in biomarkers and gene expression, and proportion of patients who experience a major adverse cardiac event. PACIFICA is enrolling at approximately 100 sites globally.

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OXIDATIVE STRESS AND PLATELET ACTIVATION IN PRIMARY MYELOFIBROSIS: CALR VS JAK2

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Primary myelofibrosis (PMF) is a chronic myeloproliferative neoplasm associated with thrombotic risk. The PMF genotypes include JAK2V6717F and CALR. The impact of CALR *vs* JAK2V6717F on thrombotic risk is obscure. It is reported that CALR causes higher oxidative stress than JAK2V617F. Oxidative stress activates platelets. Therefore, we studied oxidative stress through lactate dehydrogenase (LDH) and platelet activation through P-selectin expression (P-selectin) and platelet adhesion and aggregation. As activated platelets assemble coagulation factors, we measured the FVIII. We studied 70 patients with PMF according to ICC/WHO-criteria. 20/70 were homozygous CALR-1 with mean age of 56 years (range 23-85 years), 50/70 were heterozygous JAK2V617F with mean age of 67 years (range 41-84 years). Of 20 CALR patients, 10 were Low-, 7 Intermediate-1-, and 3 Intermediate-2-IPSS, respectively. Of 50 JAK2 patients, 19 were Low-, 18 Intermediate-1-, 10 Intermediate-2, and 3 High-IPSS, respectively. Nobody had inherited or acquired thrombotic risk or comordidities (heart failure, heart attack, stroke, diabetes, cancer). The mutations were conducted by ARMS-PCR gel electrophoresis as described by Baxter et al. Platelets were measured by automated analyzer, P-selectin by flow cytometry, FVIII by chromogenic assay (HemosIL, IL, Lexington, MA, USA) and platelet adhesion and aggregation by method PFA-100 System (Siemens, Munich, Germany - Dade International Inc., FL, USA) using CADP and CEPI cartridges. LDH was measured by enzyme immunoassay (DxC700 AU Chemistry Analyzer, Beckman Coulter AU, Milan, Italy). Platelets were 430x10^9/L (range 100-965x10^9/L) and 317x10^9/L (range 20-940x10^9/L) in CALR-1 patients

and JAK2V6717F patients, respetively. CALR-1 patients had higher LDH (792±5 U/L) than the JAK2V617F patients (516±10 U/L) and higher P-selectin (28±0.5%) than JAK2V617F patients (12±0.2%). Interestingly, we found low FVIII (47±1%) and prolonged closure times (CTs) with CADP (202 sec (n.v. 68-121 sec) plus CEPI (>300 sec (n.v. 84-160 sec) in CALR-1 patients whereas we found normal FVIII (57±2%) and normal closure times (CTs) with CADP (100 sec) plus CEPI (120 sec) in JAK2V617F patients. A positive correlation there was between LDH and P-selectin as well as P-selectin and FVIII. We speculate that the high oxidative stress in CALR-1 patients could cause platelet activation which ultimately causes exhausted defective platelets and secondary storage pool disease.

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ASSOCIATION OF JAK2 HAPLOTYPE GGCC_46/1 WITH THE RESPONSE TO ONCODRUGS IN MYELOPROLIFERATIVE NEOPLASMS

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Polycythemia vera, essential thrombocythemia and primary myelofibrosis are myeloproliferative neoplasm (MPN), clonal blood diseases characterized by overproduction of differentiated peripheral blood cells. JAK2 is a gene that encodes for a non-receptor tyrosine kinase that is involved in the JAK-STAT pathway, fundamental in hematopoiesis and altered in many blood diseases. Genetic polymorphism of JAK2 has been associated with MPNs. In particular, it occurs in almost 95% of patients with polycythemia vera and 50-60% with essential thrombocythemia and primary myelofibrosis. Hematopoietic cells with JAK2V617F mutation are transformed into cytokine-independent growth, thus promoting tumorigenesis, tumor progression and inflammation. Recent findings indicate that JAK2V617F is associated with a specific haplotype, the germline GGCC (46/1) haplotype, in MPNs, because it precedes the acquisition of the JAK2V617F variant. This haplotype can be tagged with four SNPs, for instance rs10974944, that has been discovered to be strongly associated with JAK2V617F positive MPN patients when compared to controls. The C allele is the common allele, whereas the G allele rs10974944 (G) is a risk allele for MPNs. About ten years after its discovery, the possible pathogenic role of the JAK2 haplotype GGCC_46/1 in MPN patients, as well as in other myeloid malignancies, is not yet understood, thus the aim of this study is to evaluate the association between 46/1 haplotype in JAK2V617F patients and their response to the therapy with oncodrugs used to treat MPNs. We tested 50 patients V617F positive with MPN to evaluate the presence of the haplotype, finding 58% of the patients with C/G genotype in rs10974944 SNP and 6% of G allele. By data analysis, heterozygous conditions were discovered to be the most diffused but were not associated with the development of oncodrugs resistance. Among 3 patients with G allele, only one developed resistance to oncodrugs. Moreover, the presence of G allele was also associated with the evolution of polycythemia vera and essential thrombocytopenia in myelofibrosis, suggesting that G allele could be a risk allele for MPNs evolution to myelofibrosis condition but further studies are needed.

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PHASE 3 RANDOMIZED DOUBLE-BLIND STUDY EVALUATING SELINEXOR, AN XPO1 INHIBITOR, PLUS RUXOLITINIB IN JAKI-NAÏVE MYELOFIBROSIS

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Background. Myelofibrosis (MF) is a myeloproliferative neoplasm with common somatic gene driver mutations in JAK2, CALR, and MPL. Selinexor, an investigational oral XPO1 inhibitor, may inhibit MF-relevant JAK/STAT and non-JAK/STAT pathways and preclinical studies have shown potential synergy with ruxolitinib treatment. In the phase 1 portion of XPORT-MF-034 evaluating the combination of selinexor and ruxolitinib in JAK inhibitor (JAKi)-naïve patients with MF, the most common AEs in the 60 mg cohort were nausea (79%), anemia (64%), thrombocytopenia (64%), and fatigue (57%). Nausea events were predominantly Grade 1 and transient in nature. Treatment-related AEs leading to treatment discontinuation were thrombocytopenia (n=1) and neuropathy (n=1). SVR35 and TSS50 was achieved by 79% and 58% of the 60 mg cohort intent-to-treat population at Week 24, respectively. Response rates were consistent across subgroups, including sex and regardless of ruxolitinib starting dose. These data provide strong support to further evaluate selinexor (60 mg) and ruxolitinib in patients with JAKi-naïve MF.

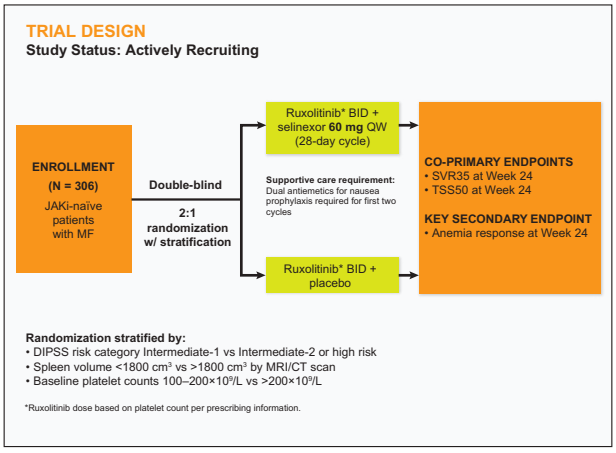

Figure 1.

Methods. The XPORT-MF-034 (NCT04562389) trial includes a global, Phase 3 randomized, double-blind, placebo-controlled study designed to evaluate selinexor and ruxolitinib. JAKi-naïve patients with MF will be randomized 2:1 to receive oral selinexor 60 mg or placebo once weekly (28-day cycle) and twice daily ruxolitinib. Randomization will be stratified by DIPSS risk category (intermediate-1 *vs* intermediate-2 or high-risk), spleen volume (<1800 cm^3 *vs* >1800 cm^3 by MRI/CT scan), and baseline platelet counts (100-200x10^9/L *vs* >200x10^9/L). Dual anti-emetics for nausea prophylaxis will be required for the first two cycles. Select eligibility criteria include ≥18 years of age, spleen volume ≥450 cm^3 by MRI or CT,

DIPSS intermediate-1, intermediate-2, or high-risk, active symptoms of MF (MFSAF v4.0), currently not eligible for stem cell transplantation, ECOG ≤2, and platelet count ≥100 x 109/L. Select exclusion criteria include >10% blasts in peripheral blood or bone marrow; previous treatment with JAKi for MF, or previous treatment with selinexor or other XPO1 inhibitors. The co-primary study endpoints are SVR35 and TSS50 at Week 24 and will be tested hierarchically. The key secondary endpoint is anemia response at Week 24 per the IWG-MRT and ELN criteria.

Results. The XPORT-MF-034 Phase 3 trial will enroll a total of 306 JAKi-naïve MF patients and is currently open for enrollment.

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CO-OCCURRENCE OF JAK2/CALR-POSITIVE MYELOPROLIFERATIVE DISORDER AND BCR-ABL-POSITIVE CHRONIC MYELOGENOUS LEUKAEMIA TREATED WITH COMBINATION OF TYROSINE KINASE INHIBITORS AND RUXOLITINIB: A CASE REPORT WITH REVIEW OF THE LITERATURE

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The concomitant presence of BCR-Abl1 and JAK2/CALR/MPL mutations in Myeloproliferative neoplasms (MPNs) is rare and its contribution to the clinicopathologic phenotype is unclear. The presence of two independent, competitive clones seems to represent the more common event. The contemporary availability of tyrosine kinase inhibitors (TKI) and the Jak2 inhibitors (Ruxolitinib) opens the question of whether a combination of these two drugs represents an optimal therapeutic strategy in terms of feasibility, safety and tolerance. We herein report a case we managed at our canter and we conduct a review of cases published where dual MPNs coexisted and were treated with a combination of TKI and Ruxolitinib. In a 55-years–old man with splenomegaly and leucocytosis, concurrent BCR-ABL rearrangement (b3a2 and b2a2) and Jak-V617F mutation was documented. The bone marrow biopsy (BM) confirmed the diagnosis of chronic myeloid leukemia (MLC) and early Myelofibrosis. Consequently, Dasatinib therapy was administered at 100 mg daily associated with aspirin. Deep molecular response (DMR) (MR 5.0) was rapidly achieved at 6 months. In March 2023, despite DMR during Dasatinib treatment, splenomegaly and persistent moderate anemia were documented. A new BM documented a significant increase in fibrosis (grade 3).

Table 1.

Table 1: Combination therapy of tyrosine kinase inhibitors (TKI) and the Jak 2 inhibitor (Ruxolitinib) in patients with concomitant or sequential Jak2/Calr-positive MPNs and CML

REFERENCES	N. PATIENTS	DRIVER MUTATIONS	DIAGNOSIS	TKI	RUXO DOSAGE	DOSE ADJUSTMENT	TIME of TKI and RUXO ASSOTIATION	OUTCOME
cho A et al 2016	Case 1	Bcl-Abl1 and Jak 2-V617F	CML and post-PV	Imatinib (400 mg/day)	15 mg BID	Reduction of Ruxo dosage at 10 mg and Imatinib at 300 mg for hematological toxicity (grade 4 anemia and grade 3 thrombocytopenia)	10 months	clinical and TKI response
	Case 2	Bcl-Abl1 and Jak 2-V617F	CML and post-PV MF	Imatinib (400 mg/day)	20 mg BID increased at 25 mg	discontinuation for hematological toxicity (grade 3 anemia and grade 3 thrombocytopenia)	2 months	alive in complete remission after allo-SCT
hou A et al 2016	Case 3	Bcl-Abl1 and Jak 2-V617F	CML and PV	Dasatinib (100 mg/die)	10 mg BID	Reduction of Ruxo dosage to 10 mg alternating with 5 mg	3 years	stable after 3 years of combination treatment
andarpa e al 017	Case 4	Bcl-Abl1 and Jak 2-V617F	CML and MF	Imatinib and Dasatinib	N.A.	N.A.	more than 1 year	clinical and TKI response
	Case 5	Bcl-Abl1 and Jak 2-V617F	CML and MF	Nilotinib	N.A	Alternating schedule of Nilotinib (4 days on/1 day off, then Ruxolitinib (1 days on/1 day off)	more than 1 year	clinical and TKI response
ddike P et al 018	Case 6	Bcl-Abl1 and CALR	CML and MF	Imatinib	N.A.	N.A.	2 months	alive in complete remission after allo-SCT
ora F et al 2021	Case 7	Bcl-Abl1 and CALR	CML and MF	Nilotinib (400mg)	10 mg BID	Dose Reduction of Ruxo and Nilotinib for hematological toxicity	4 years	died after allo-SCT for progression of symptom (hepatomegaly, transfusion requirement)
yu J et al 2022	Case 8	Bcl-Abl1 and Jak 2-V617F	CML in accelerated-phase and MF	Imatinib	N.A.	N.A.	1.5 months	Poor response
hao Y et al 2022	Case 9	Bcl-Abl1 and Jak 2-V617F	CML and MF	Imatinib, switched to Nilotinib, Sunitinib, Ponatinib, Dasatinib,	N.A.	N.A.	N.A.	alive in complete remission after allo-SCT
	Case 10	Bcl-Abl1 and Jak 2-V617F	CML and MF	Nilotinib	N.A.	N.A.	17	alive in complete remission after allo-SCT
	Case 11	Bcl-Abl1 and Jak 2-V617F	CML and MF	Nilotinib	N.A.	N.A.	26 months	Poor clinical response and TKI response
heng T. et al 022	Case 12	Bcl-Abl1 and Jak 2-V617F	CML in accelerated-phase and post-ET MF	Imatinib and Fumatinib	20 mg BID	Imatinib discontinued for toxicity	N.A.	Poor response to therapy, eligible for allo-SCT

BID: two times a day; ET: Essential Thrombocythemia; CML: Chronic myeloid leukaemia; N.A: no available; PV: Polycythemia Vera; MF: Myelofibrosis; Ruxo: Ruxolitinib; SCT: stem cell transplant; TKI:tyrosine kinase inhibitors

The cytogenetic analysis showed del(20) and next-generation sequencing detected several mutations (ETV6,IDH1,ZRSR2). On June 2023, Ruxolitinib was started at the dose of 15 mg twice a day and Dasatinib was maintained with a lowered dosage (50 mg/die) to manage the association of the two drugs. No hematological toxicity was reported and the DRM was maintained. In January 2024, the patient received an allo-stem cell transplant obtaining a stable full donor chimerism. Across literature, only 12 cases of coexistence of MLC and Ph-negative MPN disease treated with association of TKIs and Ruxolitinib are reported (Table 1). In all of the 7 patients with available data, the dosage of the TKI and Ruxolitinib required adjustment to manage the toxicity particularly hematological one. In these patients with double mutations, CML seems to be rather easy to manage, with an overall good response of Bcr-ABL 1 burden to different types of TKIs. The data suggests that the association of TKIs and Ruxolitinib for the treatment of patients with dual MPNs could be considered after a dosage adjustment of both TKIs and Jak2 inhibitors. Whether the two-drug association represents an optimal therapeutic strategy requires further evaluation.

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CYCLIC THROMBOCYTOPENIA IN MYELOPROLIFERATIVE NEOPLASM TREATMENT

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Background. Cyclic thrombocytopenia (CTP) is a rare disease, characterized by periodic platelet count oscillation. The pathogenesis is unknown, and CTP is associated with heterogeneous conditions. CTP may occur in patients with MPN during hydroxyurea (HU) treatment or spontaneously. CASE REPORT We report two patients who developed CTP during HU treatment and successive normalisation with Ruxolitinib. PATIENT 1 (F, 60y): post-ET MF diagnosed in 2011, JAK2+, treated with ASA; in 2013 splenomegaly (18 cm) and CTP onset (Plt range 18-524, 28d cycle) were observed, with recurrent SVT (LMWH) and PE (AVK); in 2014 she started therapy with HU at low dose (3t/w) due to thrombocytopenia, showing worsening of CTP oscillation (range 7-782), and once was transfused with one platelet pool (Plt 7, epistaxis). After 10 months she stopped HU therapy, and on March 2015 started Ruxolitinib, initially at 10 mg/d, then at 30 mg/d in two months, showing an initial increased fluctuation of platelets (range 123-1207) but with disappearance of thrombocytopenia; in ten weeks since Ruxolitinib at 30 mg/d no fluctuations of platelet count (range 251-372) nor CPT were observed anymore.

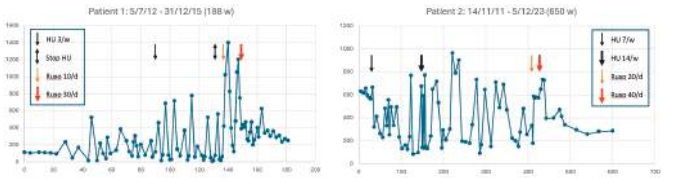

Figure 1.

PATIENT 2 (M, 48y): PV (JAK2 V617F) was diagnosed in 2011, treated initially with ASA and phlebotomy, with a stable platelet count at baseline (range 597-658). On June 2012 started therapy with HU (7t/w), showing CTP appearance (range 229-556, 28d cycle), and progressively increased fluctuations (range 94-996) as dosage was augmented to 14 t/w, without severe thrombocytopenia (nadir 94); in 2019 TVS (LMWH) then DVT (DOAC) occurred; in 2020

due to HU resistance, Ruxolitinib 20 mg/d was added, then increased to 40 mg/d in five months. Since 12w from maximum dose, reduction of platelet fluctuation (range 259-392) and disappearance of CTP were observed. CONCLUSIONS In our two cases CTP was induced or amplified by HU treatment. Platelet fluctuation was reduced and then disappeared in 10/12 weeks after Ruxolitinib therapeutic dose. Disappearance of CTP was independent of HU interruption. Both patients evidenced a high JAK2 allelic burden (Pt1 98%, Pt2 89%), that might facilitate the CPT onset after starting HU therapy (1). CPT may show very high platelet fluctuations, with possible thrombotic or hemorrhagic complications conditioning clinical outcomes in MPN patients.

Reference

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P141

UNUSUAL PRESENTATION OF EXTRANODAL ROSAI-DORFMAN DISEASE: A CASE REPORT

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Introduction. We report a case of an elderly woman with unusual presentation of extranodal Rosai-Dorfman disease (RDD), not associated with IgG4 syndrome, with ocular endobulbar nodulation, nasal and paranasal cavities involvement.

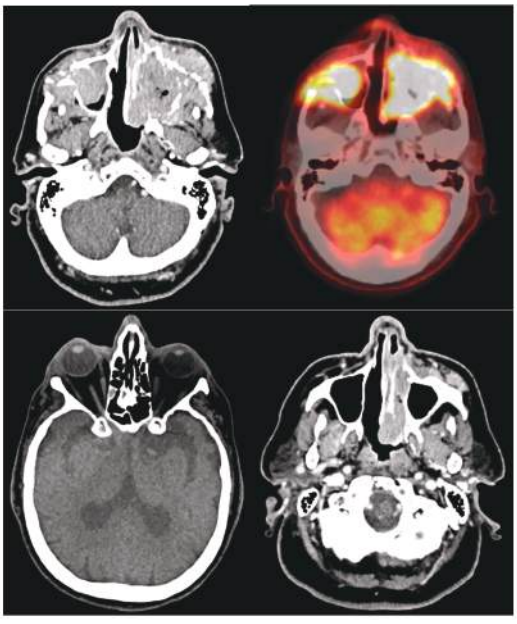

Figure 1.

Methods. An 80 y.o. woman was referred to our Center due to left genial swelling, bilateral epiphora and nasal congestion. CBC showed: WBC 4830/mmc (Ly 720/mmc),ESR 43 mm/h,CRP 11 mg/L, no serum electrophoresis abnormalities. TB CT scan revealed a scarcely measurable mass in the left and, with lower extension, in the right maxillary sinus, extending perimetrically to nasal cavity, infratemporal and pterygopalatine fossa, temporal and lateral pterygoid muscle, zygomatic process of the maxilla, maxillary alveolar ridge infiltrating the nasopalatine canal. 18FDG CT-PET scan revealed hypermetabolism in these masses, as well as in some skeletal segments. Diagnostic work-up included endoscopic paranasal sinus surgery, zygomatic,and BM biopsies. Liquid biopsy from PB samples, using digital droplet PCR (ddPCR)on cfDNA, was used to evaluate BRAF V600E mutation.

Results. Maxillo-facial biopsies showed inflammatory proliferation with multinucleated histiocytes, emperipolesis, a significant lymphocyte (CD3+ CD20+)and plasma cell (IgG4/IgG<30%) infiltration. Histiocyte immunohistochemistry showed S100+ OCT-2+ CD163+ Cyclin D1+ FXIIIa +/- and CD1a, CD21, BRAF V600E and EBV-EBER negativity, concluding for a diagnosis of extranodal RDD disease. BM biopsy was negative and liquid biopsy showed an absence of BRAF V600E mutation. Due to the patient's age and the unusual presentation, treatment approach included induction and maintenance therapy with Prednisone (PDN)and Vinblastine. CT scan re-staging revealed a right ocular endobulbar choroid nodulation (11x9 mm)and increased solid tissue in the left nasal cavity. Considering the disease progression and symptoms (lacrimation, exophthalmos, orbital pain, nasal congestion),a second-line therapy with PDN and MTX was performed. Stable disease was detected by CT scan but, due to persistent symptoms, a debulk approach involving surgery and radiotherapy was necessary.

Conclusions. Extranodal RDD is an uncommon condition and endobulbar localization is exceptionally rare, representing only 11% of RDD cases. Currently, there are no uniform treatment approaches for RDD. A combined treatment of surgical debulking, radiotherapy and chemotherapy is usually necessary, thus a multidisciplinary strategy is recommended.

Anemias and myelodysplastic syndromes

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BASELINE CHARACTERISTICS AND OUTCOMES FOR ITALIAN PATIENTS TREATED WITH LUSPATERCEPT IN THE PHASE 3 BELIEVE STUDY: A POST HOC ANALYSIS

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Background. In the phase 3 BELIEVE study, patients (pts) with transfusion-dependent β-thalassemia (TDT) achieved clinically meaningful reductions in transfusion burden (TB) with luspatercept. Pts were enrolled in 15 countries in Europe, Australia, the Middle East, North Africa, North America, and Southeast Asia. This post hoc analysis compared the baseline (BL) characteristics and efficacy outcomes of pts recruited and treated in Italy (Italian) *vs* other countries (non-Italian).

Table 1. BL characteristics of Italian and non-Italian pts in the BELIEVE study

	Italian pts			Non-Italian pts		
	Total (N=48)	Luspatercept + BSC (n=30)	PBO + BSC (n=18)	Total (N=288)	Luspatercept + BSC (n=194)	PBO + BSC (n=94)
Age, median (range), y	40.0 (21–66)	40.0 (24–66)	39.0 (21–59)	28.0 (18–58)	28.0 (18–56)	28.0 (18–58)
B^0/B^0 genotype, n (%)	24 (50.0)	15 (50.0)	9 (50.0)	79 (27.4)	53 (27.3)	26 (27.7)
BL TB category, n (%)[a]						
Low	4 (8.3)	3 (10.0)	1 (5.6)	54 (18.8)	38 (19.6)	16 (17.0)
Medium	14 (29.2)	9 (30.0)	5 (27.8)	128 (44.4)	83 (42.8)	45 (47.9)
High	30 (62.5)	18 (60.0)	12 (66.7)	106 (36.8)	73 (37.6)	33 (35.1)
Splenectomized, n (%)	33 (68.8)	21 (70.0)	12 (66.7)	161 (55.9)	108 (55.7)	53 (56.4)
MRI liver iron content, median (range), mg/g dw	3.16 (1.0–14.4)	3.67 (1.0–14.4)	2.90 (1.4–8.6)	6.97 (0.2–125.0)	7.09 (0.8–125.0)	6.41 (0.2–53.2)
SF, median (range), µg/L[b]	729.0 (136–3410)	751.5 (177–3410)	690.5 (136–2134)	1579.0 (88–6400)	1656.5 (88–6400)	1357.0 (171–6400)
24-wk pre-transfusion Hb threshold, median (range), g/dL[c]	9.61 (8.5–10.6)	9.50 (9.0–10.5)	9.86 (8.5–10.6)	9.10 (4.5–11.7)	9.19 (4.5–11.4)	8.97 (5.8–11.7)

[a]Based on 12 wk run-in data categorization II; low, medium, and high TB were defined as ≤5, >5 to ≤7, and >7 RBC U in the 12 wk prior to randomization; [b]BL SF is calculated as the mean of ferritin values during the 12 wk on or prior to dose 1 day 1/randomization; [c]24-wk pre-transfusion Hb threshold is defined as mean of a pt's all documented pre-transfusion Hb values during the 24 wk prior to dose 1 day 1.
dw, dry weight; MRI, magnetic resonance imaging.

Methods. Pts were aged ≥18 y, had TDT (6–20 units (U) of packed red blood cells (RBCs) with no transfusion-free period >35 d within 24 wk before randomization). Pts were randomized 2:1 to luspatercept (1.0–1.25 mg/kg) or placebo (PBO) subcutaneously Q3W plus best supportive care (BSC). The primary endpoint was the proportion of pts with TB reduction ≥33% *vs* BL and a ≥2 RBC U reduction (wk 13–24); other endpoints included TB reduction ≥33% and a ≥2 RBC U reduction during wk 37–48 and during any 12-wk period. Data were evaluated up to the last pt last visit date: Jan 5, 2021.

Results. In total, 48 Italian (30 luspatercept, 18 PBO) and 288 non-Italian pts (194 luspatercept, 94 PBO) were randomized. Italian pts were older, had a higher B^0/B^0 genotype prevalence, and higher pre-transfusion hemoglobin (Hb) threshold (Table). Greater proportions of Italian pts had high TB (>7 RBC U/12 wk) and prior splenectomy; Italian pts had lower liver iron content and serum ferritin (SF), possibly indicating differences in iron chelation therapy (ICT). Fewer Italian *vs* non-Italian luspatercept-treated pts had ≥33% TB reduction during wk 13–24 (primary endpoint, 13.3% *vs* 22.2%) and during wk 37–48 (13.3% *vs* 20.6%). Similar proportions of Italian *vs* non-Italian pts had ≥33% TB reduction during any 12-wk period (70.0% *vs* 78.4%); the median duration of the longest transfusion-free interval was 32.0 d in both groups. SF reduction from BL with luspatercept was greater in Italian *vs* non-Italian pts through wk 96 (median −412.50 µg/L *vs* −249.22 µg/L); however, the Italian subgroup was small (n=30).

Conclusions. Italian *vs* non-Italian pts had more severe BL characteristics and were treated with high adherence to transfusion guidelines and ICT. Fewer Italian *vs* non-Italian pts achieved TB reduction in wk 13–24 and 37–48; the proportion of Italian pts with TB reduction during any 12-wk period and duration of longest transfusion-free interval were similar to non-Italian pts, whereas SF reduction from BL was greater.

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LUSPATERCEPT IN LOWER-MYELODYSPLASTIC SYNDROMES (MDS): REAL-WORLD DATA FROM THE GRUPPO ROMANO-LAZIALE MIELODISPLASIE (GROM-L)

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Introduction. Luspatercept is a recombinant fusion protein that binds transforming growth factor β superfamily ligands, leading to red blood cells (RBC) maturation. The MEDALIST trial evaluated activity of this molecule showing encouraging results in terms of transfusion independence in lower-risk MDS with ring sideroblast.

Methods. We retrospectively analyzed patients treated in the Lazio Region, according to clinical practice, between 2021 and 2024. Eligible patients were 18 years of age or older affected by lower-risk MDS with ring sideroblasts, refractory to erythropoiesis-stimulating agents (ESA) and transfusion dependent. Responses were defined by the IWG 2006 criteria.

Results. We evaluated 40 patients (pts) (25 M, 15 F), with a median age at diagnosis of 70 years (range 56-85). According to IPSS-R classification 9/40 (22,5%), 24/40 (60%) and 7/40 (17.5%) pts were very low, low and intermediate risk, respectively. Median Hb at diagnosis and at treatment was 10.8 g/dL and 7.7 g/dL, respectively. All pts received ESA before treatment (median time 21 months, range 1-206 months). Concomitant iron chelation therapy was administered to 27/40 pts (67.5%). Baseline serum EPO level was <200 U/l in 13/40 pts (32.5%). Baseline transfusion burden was equal to or greater than 6 units every 8 weeks in 32/40 pts (80%), whereas it was less than 6 units every 8 weeks in 8/40 (20%). SF3B1 mutation was detected in 15/40 (37,5%) pts. NGS study was avail-

able in 21 patients; mutation of ASXL1, CSF3R, DNMT3A and JAK2 V617F were found in 4/21 (19%), 1/21 (5%), 5/21 (24%) and 2/21 (10%) patients, respectively. Median follow up was 14.6 months (range 1-87 months). Transfusion independence for 8 weeks or longer was observed in 13/40 pts (32,5%). Erythroid response occurred in 12/40 pts (30%) during the first 24 weeks. A dosage increase was required in 33/40 pts (82,5%), with the highest response found at 1.75 mg/kg. Median number of infusions was 13 (range 1-50). Median duration of response was 6 months (range 1.5-26). Overall, 14/40 (35%) pts stopped treatment due to no response (36%), lack of response (43%), toxicity (7%), and personal preference (14%). None of the pts progressed to acute myeloid leukaemia. Fatigue (7%) and arthralgia (10%) were the most frequent reported side effects.

Conclusion. Our study confirmed luspatercept efficacy in one third of cases in a cohort of heavily transfusion-dependent patients. It was well tolerated in absence of major side effects.

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LUSPATERCEPT IN MDS WITH RING SIDEROBLASTS: A REAL-LIFE EXPERIENCE

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Luspatercept is a recombinant fusion protein, which binds TGF-beta ligands in order to reduce SMAD2 and SMAD3 signaling, allowing erythroid maturation and erythroblastic differentiation, approved for transfusion dependent anemia in MDS with ring sideroblast patients refractory or ineligible at erythropoiesis stimulating agents (ESAs). Luspatercept's response rates varies across studies, especially between clinical trials and real world data. We collected data of 23 patients diagnosed with MDS with low blast count and SF3B1 mutation and/or ring sideroblasts treated with Luspatercept from January 2021 to date because of an ESA-refractory transfusion dependent anaemia. Both Revised International Prognostic Score (IPSS R) and Molecular International Prognostic Score (IPSS M) were calculated. Response was evaluated at both 24 weeks and 1 year applying haematological response criteria proposed by the IWG 2018. Statistical analysis was performed with IBM SPSS 26. With a median follow-up of 19,4 months (range: 6,16-36,9), 1 patient discontinued treatment after 3 doses due to non-compliance, 22 underwent treatment for 24 weeks and 16 for 1 year, without any evidence of side effects. Three patients discontinued treatment after 24 weeks due to loss of response (n=2) and disease progression to AML (n=1). At 24 weeks, 14 patients (63.5 %) achieved Hematological Improvement (HI), while 8 (36.5%) patients did not respond. At 1 year, 9 patients (56%) showed HI, while 7 (44%) did not respond. Eight (35 %) patients achieved transfusion independence (TI) at 24 weeks and 12 (51%) at 1 year of treatment. Fifteen patients are still in treatment, 1 stopped Luspatercept at 28 months due to loss of response. Neither TB nor IPSS R and IPSS M have a statistically significant impact on the response, both at 24 weeks and at 1 year. However, we found that a low TB correlates positively with the achievement of TI after 24 weeks (p=0.002). There was no difference between the responder group and the non-responder group in terms of VAF of the SF3B1 clone, nor any difference regarding the number and type of concomitant mutations assessed by NGS. No other characteristics appeared to have a significant impact on transfusion dependence response. Most patients took advantage from treatment, achieving HI with no evidence of side effects. To confirm these findings and to identify predictive factors of response, a larger number of patients need to be included.

Table 1.

Total number of MDS-RS patients treated with Luspatercept	23
Age	
Years, median (range)	72 (52-89)
Sex, n (%)	
Male	13 (56)
Female	10 (44)
Cytogenetic, n	
Normal	18
Trisomy 8	2
Trisomy 14	1
Monosomy Y	1
del 20q	1
IPSS-R Classification, n (%)	
Very Low Risk	2 (9)
Low Risk	14 (61)
Intermediate Risk	7 (30)
Mutation status, detected by NGS	
SF3B1, n (%)	21 (91)
Vaf , %, median (range)	41 (25-46)
N co-mutation, median (range)	0 (0-2)
IPSS M Classification, n (%)	
Very Low Risk	2 (9)
Low Risk	15 (64)
Moderatly Low Risk	4 (18)
Intermediate Risk	2 (9)
Duration of EPO traitment before Luspatercept	
Months, median, range	30, 6-106
Transfusion burden sec. IWG 2018	
Low Trasfusion Burden, n (%)	7 (31)
High transfusion burden , n (%)	16 (69)

P145

ENHANCING DIAGNOSIS AND REDUCING IDIOPATHIC ERYTHROCYTOSIS RATES WITH NEXT-GENERATION SEQUENCING PANELS

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Absolute erythrocytosis is defined by an increase in red blood cells, hemoglobin and hematocrit. It can be primary, involving defects in erythroid progenitor cells, or secondary, stemming from issues outside the erythroid compartment. However, around 70% of cases lack a known cause. The current study aimed to identify potential genetic contributors to erythrocytosis and to assess the true prevalence of idiopathic erythrocytosis. Between 2018 and 2024, 55 patients with unexplained erythrocytosis were clinically referred to investigate the underlying cause. All patients were negative for JAK2 V617F and exon 12 mutations and had no identified secondary causes of erythrocytosis. A NGS panel included *BPGM*, *EGLN1*, *EPAS1*, *EPOR*, *GATA1*, *GELSOLIN*, *HBA1*, *HBA2*, *HBB*, *JAK2*, *MPL*, *RUNX1*, *SH2B3*, *SRC*, *THPO*, *VHL* and *WAS*, was conducted by the CRIMM laboratory at Careggi Hospital in Florence. All pa-

tients provided informed consent. DNA extraction was performed from granulocytes in approximately 12 ml of peripheral blood collected at the Hematology Department of Federico II University of Naples. The median age was 40 years (range 17–74), the median Hb and Hct were 17 g/L (range 15.5–19) and 51% (range 42–63), respectively. Most patients were male (51/55, 93%), which aligns with prior studies indicating that men are more frequently affected by JAK2-negative erythrocytosis. Among the 55 patients, 15 (27.3%) displayed six distinct gene variants with one patient carrying two different mutations (table1). All the identified mutations have been previously described in the literature, suggesting a potential pathogenic role in erythrocytosis. Spontaneous erythroid colony cultures, in the absence of exogenous EPO, were performed for the four patients carrying mutation in the MPL gene, but no spontaneous erythroid colonies were observed. The remaining patients (40/55, 72.7%) without detectable mutations were consequently diagnosed as idiopathic erythrocytosis. This study explored the genetic landscape of 55 patients with unexplained erythrocytosis. A comprehensive NGS panel identified six different gene variants, demonstrating the NGS's value in identifying genetic causes in this setting. However, the majority of patients had no mutations, indicating that idiopathic erythrocytosis remains a significant challenge in clinical practice. Our results highlight the complexity of erythrocytosis and the need for continued research to elucidate unknown causes.

Table 1.

Patient	Age	Sex	Hb (g/dl)	Hct (%)	Epo (mU/mL)	Gene	Coding DNA Change	Allele frequency %	Protein Change
1	45	Male	15.8	49.5	1.0	EGLN1	380G>C	22	C127S
2	26	Male	15.3	51.1	19.3	EGLN1	380G>C	49	C127S
3	20	Male	18	50.8	3.3	EGLN1	380G>C	47	C127S
4	59	Male	15.6	46.8	24.2	EGLN1	380G>C	49	C127S
5	32	Male	19.2	62.9	7.1	EPAS1	c.466G>T	48	G156W
6	53	Male	17.4	51.2	7.2	HBB	c.371C>T	50	T124I
7	19	Male	17	51.3	11	MPL	117G>T	50	K39N
8	17	Male	16.7	49.8	8.3	MPL	117G>T	50	K39N
9	20	Male	17.5	19.6	12.4	MPL	1610G>A	47	R537Q
10	22	Male	16.9	45.6	5.9	MPL	209C>T	50	P70L
11	74	Male	17.9	58.6	6.0	MPL EGLN1	c.1610G>A c.380G>C	47 52	R537Q C127S
12	25	Male	17	52.6	9.9	SH2B3	1426C>T	48	L476F
13	50	Male	17.8	5..3	4.1	SH2B3	622G>C	50	E208Q
14	60	Male	14.7	52.4	4.3	VHL	598C>T	49	R200W
15	72	Female	15.8	50	5.2	VHL	598C>T	51	R200W

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RESPONSE TO BIOSIMILAR ERYTHROPOIETIN ALFA THERAPY IN ANEMIC PATIENTS WITH MYELODYSPLASTIC SYNDROMES: RETROSPECTIVE STUDY OF 58 PATIENTS

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Introduction. Biosimilar erythroid stimulating agents (ESAs) have recently been introduced into clinical practice in anemic patients (pts) with lower-risk myelodysplastic syndromes (MDS). However, information on their efficacy and safety in MDS patients is still scarce. Moreover, a recent retrospective study showed that in MDS there may be a difference in terms of response between different types of ESAs (Fattizzo, 2021). Therefor we retrospectively analyzed our clinical experience with biosimilar erythropoietin (EPO) alpha in lower-risk MDS pts, starting from its introduction in our Institution.

Methods. From June 2018 to December 2021, 28 pts (12 males), median age: 83.5 (72-95) yrs, previously treated with EPO alpha "originator" and responsive to treatment at the time of switch (group A), and 30 previously untreated pts (group B), were started on biosimilar EPO alpha, at the initial dose of 40-80,000 U/week subcutaneously (group B), or at the same dosage administered before switch (group A). Response to treatment was assessed according to IWG response criteria (Cheson, 2006). Results. In group A, with a median duration of previous therapy of 83.5 (2-165) months, 24/28 pts (85.7%) maintained the response after the switch, with a median duration of response of 27 (1-53) months, and a median duration of treatment of 28.5 (4-53) months. In 5/28 pts (17.9%) who had lost response shortly after the switch, the "originator" drug was restarted, with recovery of response in 3/5 cases (60%). The incidence of adverse events possibly related to the treatment was low (3.6%). With a median follow-up of 41 (9-53) months after the start of biosimilar drug, only one patient (3.6%) showed evolution into acute myeloid leukemia (AML). In group B, the overall response rate (ORR) was 66.6%, with a median duration of response of 26.5 (4-49) months, a median treatment duration of 27.5 (2-53) months and a median follow-up of 26 (3-53) months from the start of treatment. The incidence of adverse events possibly related to treatment was 13.3%, and 6/30 pts (20%) showed disease progression to higher-risk MDS (2 pts) or AML (4 pts). Conclusions. In our experience biosimilar EPO alpha proved to be effective and well tolerated both in pts previously treated with the "originator" drug and in subjects not previously treated, although in case of loss of response without disease progression a therapeutic attempt with the "originator" drug might be considered.

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REAL LIFE CASE SERIES OF HUMANIZED ANTIBODY ANTI-C1S OF COMPLEMENT PATHWAY, SUTIMLIMAB, FOR RELAPSED/REFRACTORY PATIENTS WITH COLD AGGLUTININE DISEASE (CAD)

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CAD is a rare chronic autoimmune hemolytic anemia caused by cold-type immunoglobulin (Ig)-M autoantibodies which exhibit greater titer at 0°C. Usually first line treatment consists in B-cell directed therapies as Rituximab, that can be further repeated at disease recurrence. Sutimlimab is a monoclonal humanized antibody, recently approved for patients with CAD relapsed/refractory to Rituximab, that selectively targets C1s component of the classical complement pathway preventing the classical complement pathway-mediated hemolysis, specific characteristic of cold CAD. Here we report two cases of relapsed/refractory CAD treated in the Hematology Unit of Federico II University, Naples, with sutimlimab. The first case is a 74-years old woman who came to our observation in January 2015 for acute severe anemia (Hb 8.0 g/dl, reticulocytes $0.130x10^6$/mmc, LDH 325 mU/l, bilirubin 1.3 mg/dl) and was initially treated with anti-CD20, rituximab, at dose of 375 mg/m^2 iv infusion weekly for 4 weeks, obtaining a complete remission. In October 2017, for disease recurrence, she repeated treatment with Rituximab, with same schedule maintaining a complete response for approximately two years. In 2019 the patient relapsed and was enrolled in a phase II study, available at our center, based on the oral administration of parsaclisib tb, an inhibitor of phosphatidylinositol-3 kinase (PI3Kδ), that discontinued after 7 weeks due to intolerance, albeit in partial remission. In November 2023, due to further recurrence with severe anemia (Hb 6 gr/dl), a third cycle of rituximab was administered but for persistence of severe anemia and positive biochemical hemolysis markers, she started treatment with azathioprine at a dose of 50 mg bis in die, without benefit. Therefore, in February 2024, she started treatment with Sutimlimab as compassionate use after 2 weeks from the completion of the required vaccination pro-

gram. Sutimlimab was administered according to schedule at day 0, 7, 14 and then every 2 weeks. No adverse events were recorded and a rapid and sustained increase in Hb level was achieved after only one week. The latest determination of hemoglobin was 12.5 g/dl and patient's still on treatment (Figure 1). The second case refers to a 75-year-old man, who came to our attention due to severe anemia (Hb 9.6 g/dl) and positive biochemical markers of hemolysis. In July 2016 he started treatment with rituximab at dose of 375 mg/m^2 weekly for 4 weeks, obtaining a complete remission despite the persistence of acrocyanosis symptoms. In February 2022, due to disease recurrence, he underwent further treatment with rituximab at same dose for 6 cycles, obtaining a partial recovery of red blood count, although positive hemolysis indices still persisted. In January 2024, due to rapid decrease of hemoglobin concentration (Hb 8.4 gr/dl), and cold-induced acrocyanosis associated with positive biochemical markers of hemolysis, he started treatment with sutimlimab as compassionate use after 2 weeks from the completion of the required vaccination program, according to schedule, with no side effects. He obtained increase in Hb level in 2 weeks, despite the persistence of cold-induced symptoms as acrocyanosis that respond to proper thermal protection. The latest determination of hemoglobin was 11.7 g/dl and patient's still on treatment (Figure 1). In our case series, sutimlimab achieved a rapid response in frail patients pluri-relapsed to rituximab treatment and demonstrated a favorable safety profile. More data from real life experience should be collected in order to assess the efficacy and the minimal toxicity related to this chronic treatment.

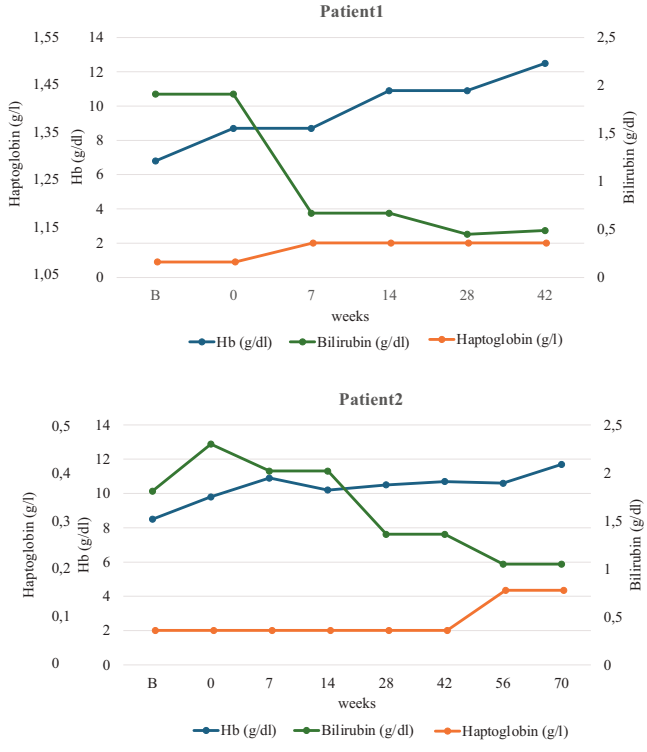

Figure 1. Effect of sutimlimab on Hb, haptoglobin and bilirubin level. *B: 30 days before Sutimlimab start.

Infections and quality of life

P148

COMMUNICATION AND DISTRESS IN HEMATOLOGY: WHAT CORRELATIONS EXIST?

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Introduction. People with hematological malignancies face a unique and unpredictable disease trajectory. Thus, they often require long-lasting and intensive therapies which carry a significant risk of morbidity, mortality, and prognostic uncertainty. Due to the acute onset and the clinical course, people with hematological malignancies experience high levels of distress and develop close and long-term relationships with healthcare workers (HCWs). Studies on HCWs-patient relationships reported hematologists' difficulties communicating diagnosis information to their patients. However, literature on this topic is still scarce. The present study aims to investigate the satisfaction of people with leukemias and lymphomas regarding HCWs-patient communication, perceived support, and the effects of these aspects on distress.

Methods. We recruited 58 individuals (26F, 18-77 years), 6 were diagnosed with ALL, 24 with AML, 4 with APL, 1 with HCL, 6 with HL, and 17 with NHL. All patients filled out a questionnaire about perceived support, communication, and distress.

Results. The majority of patients defined themselves as very/mostly satisfied with the support received from HCWs (88%), felt they had received information about the disease (93%), and were able to ask questions about it (77%). Less than 50% of participants felt they had received information about the state and work-related assistance rights. Controlling for age and gender, received support from HCWs correlated with received information about the disease and the assistance rights, $p<.017$, $r > .44$. Finally, medical information, but not information about the assistance rights , nor HCWs' support predicted patients distress levels, $\beta=-.45$, $p=.007$.

Conclusions. The present study shows how hematological HCWs are perceived as supportive by their patients. Communication regarding the illness is also perceived as adequate, while communication of information regarding assistance rights is more critical. Finally, the present study emphasizes the importance of HCWs-patient communication about the disease, as it is the primary predictor of distress in people with leukemias and lymphomas. Communication courses for hematologic HCWs seem rare. Thus, it would be crucial to design specific training interventions on this topic. Additionally, it would be beneficial to implement not only communication about illness but also about assistance rights.

P149

IMPLEMENTATION OF INTERACTIVE NARRATIVE MEDICINE IN ONCOHEMATOLOGICAL PATIENTS CURE PROGRAM OF ASL BAT HEMATOLOGY UNIT

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The emerging paradigm of person-centered medicine has led to a change in the approach represented by the introduction of Patient Reported Outcomes (PRO), without the mediation of the clinical interview.The questionnaires for collecting PROs include both standardized tools specific to pathology that investigate the patient's perceived health status and quality of life,which can be detected with narrative methodologies. Emanar is a narrative medicine path dedicated to patients with oncohematologic disease promoted by the ASL BT psychologist in the hematology department with the aim of facilitating the processes personalizing the treatment path of each patient starting by listening to his experience.Objectives of the study are:- Facilitate the process of shared therapeutic decision-making;- Personalize treatment paths through multidimensional exploration of the patient's existential and emotional experience;- Promote the work of the multidisciplinary team by orienting it towards a bio-psychosocial vision of the patient;- Monitor the impact of therapy on quality of life through the integration of standardized quality of life questionnaires and patient narratives.The DNMLAB.IT platform is used which offers patients the opportunity to tell their story in a narrative digital diary in a protected environment oriented towards clinical objectives,divided into four digital rooms which respectively welcome patients and teams treating the following pathologies to offer dedicated psychological support: 1) Chronic Lymphatic Leukemia; 2) Multiple Myeloma; 3) Acute Myeloid Leukemia, 4) Lymphomas. SCENARIO 1 - PATIENT WITH NEWLY DIAGNOSED:the digital narrative diary is proposed to the patient or caregiver close to the diagnosis with the aim of better understanding their experience and, based on it, subsequently agree with the patient on the most appropriate therapy. SCENARIO 2-PATIENTS UNDER TREATMENT 2:the digital narrative diary is proposed to the patient with the aim of better understanding their experience and personalizing the therapy.The treating team will decide whether and which scale to send from the platform to each patient. Specifically, the following scales will be loaded:- Scale for assessing the patient's quality of life;- Pain rating scale;- Psychological comorbidity scale.Feedback is given to the patient and caregiver during subsequent meetings. It is important that members of the care team read the patient/caregiver narrative before the follow-up visit.

P150

WHAT ARE THE NEEDS OF PATIENTS UNDERGOING CAR-T CELL THERAPY?

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Background. Despite the extensive focus in recent literature on the medical aspects of Chimeric Antigen Receptor (CAR) T-cell therapy (Brudno *et al.*, 2019; Davila *et al.*, 2014; June *et al., 20*18), there remains a lack of research addressing the needs of patients undergoing this treatment. Understanding these needs is fundamental to develop personalized treatment pathways that account for patients' actual conditions, preferences, and desires. This study aims to identify the needs of patients at a leading center for CAR-T cell treatment: the Fondazione IRCCS Istituto Nazionale dei Tumori.

Method. This is a qualitative observational, cross-sectional and single center study.

Participants. Patients were recruited from a group of individuals who had either undergone CAR-T cell treatment or were eligible for such. They participate in semi-structured interviews. The sample size was determined based on achieving theoretical saturation (Weller et al., 2018). Interviews were audio-recorded with participants' consent, transcribed verbatim, and analyzed through thematic analysis (Braun & Clarke, 2006).

Results. Twelve patients participated, 50% male. 50% (n=6) have non-Hodgkin's lymphoma, 16.7% (n=2) have multiple myeloma.

25 needs were identified, grouped by summary need into 4 macro areas: needs during hospitalization, psychological, improvement of daily life and assistance (Table 1). Theoretical saturation was reached at the sixth interview.

Discussion. Twelve patients (50% male) participated in the study. 50% (n=6) were diagnosed with non-Hodgkin's lymphoma, while 16.7% (n=2) had multiple myeloma. 25 needs were identified and categorized into four macro domains: hospitalization-related needs, psychological needs, improvements for daily living, and patient assistance (see Table 1). Theoretical saturation was reached at the sixth interview. Patients expressed some common needs among other oncological pathologies (*e.g.*, certain psychological, assistance, and daily life improvement needs), while other needs were specific to CAR-T cell treatment and are absent from the existing literature (e.g., needs during hospitalization). Several needs reported by patients, though legitimate, were unattainable (e.g., prognostic certainty), meanwhile others remain actionable. Particularly, many needs categorized under "patient assistance" can be addressed by efforts to mitigate the tiring and/or traumatic experience of hospitalization.

Table 1.

Type of need	Examples
Needs during hospitalization	- During hospitalization, be able to receive visitors with all due precautions - During hospitalization, be able to have some entertainment to pass the time - During hospitalization, have staff available who are attentive to all my needs - ...
Psychological needs	- Thinking that CAR-T cell therapy will go well - Accelerate healing times - Need for coherence/continuity with my previous life - ...
Needs to improve daily life	- Slow down the rhythms of daily life - Have more energy - Don't feel physical pain - Sleep well at night - ...
Assistance needs	- Having someone to support me psychologically - Having someone to help me manage daily life - Get quick access to visits and exams - Have free access to visits and exams - Have healthcare personnel available who are adequately trained in relation to the pathology (expertise) and empathetic - ...

P151

ROLE OF MULTIDRUG RESISTANT ORGANISMS (MDRO) COLONIZATION IN THE OUTCOME OF PATIENTS WITH ACUTE LEUKEMIA: SINGLE-CENTER PROSPECTIVE/RETROSPECTIVE EXPERIENCE

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Introduction. Patients (pts) with disease or therapy related immunodeficiency are at higher risk for fatal infections caused by multidrug resistant organisms (MDRO). Despite the research of MDRO colonization is frequently performed in pts hospitalized for acute leukemia (AL) the impact of MDRO colonization on the clinical course and overall survival (OS) has not been systematically studied.

Table 1.

Table 1 – Clinical and Biological features

Pts = 84	N (%)
Male	36 (43)
Female	48 (57)
Median age at diagnosis (years) [range]	69 [23.1 – 87.5]
Diagnosis	
AML	72 (86)
ALL	12 (14)
Therapy	
Intensive	42 (50)
Non intensive	42 (50)
Outcome	
Alive	50 (58)
Dead (PD, sepsis, other)	34 (42)
Duration of neutropenia, median (days) [range]	26 [4-112]

*Therapies: Intensive therapy: 3+7 regimen, CPX-351, FLAI, HD-ARAC, Gimema ALL1913 scheme therapy; Non intensive: hypomethylating agents single agents, hypomethylating agents plus venetoclax

Methods. A retrospective/prospective, observational single-center study to assess the role of MDRO in the outcome of a cohort of 84 consecutive pts with acute leukemia (AL), was developed at the UCO Ematologia in Trieste. The assessment of colonization was performed weekly during the period of hospitalization, with rectal and nasal swab. Serial blood cultures were performed in case of fever or other suspect of infection. Primary objective of the study was the evaluation of OS comparing pts with and without MDRO colonization. Data were stratified by diagnosis and therapies received.

Results. Between January 2020 and December 2022, 84 pts were included: 72 (86%) acute myeloid leukemia (AML), 12 (14%) acute lymphoblastic leukemia (ALL). Median age was 69 years (range 23-87). Two subgroups of pts, equally represented, were identified according to the therapies received (intensive or non-intensive chemotherapy). Clinical and biological features of the pts are shown in Table 1. 45/84 pts (53%) were colonized by MDRO [nasal swab 1/45 (2.5%), rectal swab 43/45 (95%), both rectal and nasal swab 1/45 (2.5%)], in particular E. Faecium VRE (47%) and E. Coli ESBL (17%); 7/45 experienced a breakthrough bacteremia by the same colonizing MDRO. The 12 and 24-months OS of the colonized subgroup was significantly lower than non-colonized pts (65,3% *vs* 79,2% and 45,8% *vs* 68%, respectively; p=0.038). MDRO colonization influenced OS regardless the subtype of AL [HR 2.47 (1.17-5.2, p=0.018)] and the intensity of therapies received [HR 2.5 (1.2-5.2, p=0.014)]. The impact of MDRO colonization in the development of breakthrough fatal infections was low (9/45 pts, 20%).

Conclusions. In our experience MDRO colonization resulted to be a strong general predictor of OS in AL pts, even if associated with direct fatal breakthrough infection only in a minority of cases. Further studies should be performed to investigate other direct or indirect relationships between MDRO colonization and pts outcome and, in particular, the possible role of fecal microbiota.

P152

RESEARCH: 'THURSDAYS WITH HEMATOLOGY' BECOMES. "TRAVEL TOOLS FOR THE HEMATOLOGY JOURNEY" AND INFORMATION POINT

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The "Thursdays with Hematology" (GE) project stems from the psychological intervention that the UOC Psychology Continuity Hospital Territory operates at UOC Hematology of the Versilia Hospital Presidio with the support of "Comitato Versilia per l'Ematologia Odv" (CVE, an AIL National affiliated committee). From actively listening to the disease experience of patients and family members emerges the need for a relationship in which to stay beyond the specialist protocol as a time of care, which improves the quality of patient care and patient compliance with better efficacy even on drug treatment. The project refers to Law 219/2017, which promotes the relationship as time of care, values the patient's decision-making autonomy, and places information and psychoeducation as central in the contract of trust at the basis of taking charge. With this in mind, GEs have been structured as discussion spaces open to patients, family members, volunteers, and general pratictioner. All specialists involved in the hematology pathway addressed a different topic monthly (13 meetings). The discussion in dual mind-body perspective involved about 200 total users. Realizing that how we are in the body influences our thoughts and vice versa, the topics covered are: the diagnostic process, outpatient chemotherapy, chemotherapy-rehospitalization in the ward, the elderly patient, adaptation to the disease, disease remission, transplantation, integrated medicine, pain, palliative care, venous accesses and the body, psychiatry and the organic patient. The project is multidisciplinary, and specialists made their expertise available to the audience by answering questions from those present. The GEs' "reflections and critical issues" became an informational handbook, "Travel Tools for the Hematology Pathway," distributed free of charge at the outpatient sites of the UOC Hematology Azienda Toscana Nord Ovest. The data that emerged concern the disease, the relationship, the time of care, and the bureaucratic and practical aspects that inexorably impact the quality of life of the system in which the disease manifests itself. Also in collaboration with the local association "Comitato Versilia per l'Ematologia Odv" an information point for the hematology pathway dedicated to patients and family members will be opened.

P153

THE TRANSFUSION SUPPORT IN THE END OF LIFE: IT'S REALLY NECESSARY?

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It's known that patients with hematological malignancies HM are entrusted to Palliative Care Services PCS in a more advanced stage of the disease and in a lower percentage than those with solid tumours. The hematological patients present a big burden of symptoms, often underestimated.

Which are the reasons of this missed passage to the PCS?

• unpredictability of the course of the HM

• number of treatments

• difficulty of the haematologists in deciding to stop active treatments.

Haematologists admit as difficulty in entrusting their patients to PCS the problem of the transfusion support TS

It's really necessary to continue with TS at the end of life?

We retrospectively anaylized 412 consecutive patients admitted to our hospice dedicated only to the care of patients with cancer. Among 412 only 42 had a HM, almost 10%. The real number was 40, because 2 had a double hospitalization; discharged, returned to hospice at the end of life.

Characteristics of the 40 patients:

• 23 M and 17 F

• age: 52-100

• pathologies:

20 Acute Leukemias and Myelodisplastic Syndromes

7 Multiple Myeloma

13 Lymphoma

• days spent in hospice: 1 to 59

The most frequent symptoms were asthenia and fever, managed with steroids, in particular dexamethasone and hydrocortisone.

27 pateints had severe anemia and trombocytopenia.

We considered as severe: anemia<80 g/L and trombocytopenia<20000/ul, target values for blood transfusions.

As an alternative to TS, severe anemia was managed with intravenous infusion of iron and multivitamin.

Thrombocytopenia was managed only in the presence of haemorragic manifestations with intravenous infusion of tranexamic acid and vitamin K. Considering that many patients entered in hospice in the last days/ hours of their life, we have not seen differences in the clinical conditions of the stable patients since it was decided to stop transfusion support. Only few patients, among 8 that had a temporary recovery, were supported with red cells or platelets at the moment of leaving the hospice.

Conclusions.

• the majority of patients with HM entrusted to PSC are old and with many comorbidities that controindicate active treatments

• many patients with HM are entrusted to PCS in the end of life; those who died within a week of entering into our hospice were 12

• transfusion support in the patients in avanced stage of disesas does not improve the quality of life; in one case it was detrimental because the patient presented an acute pulmonary edema.

P154

HOW I TREAT SARS-COV-2 INFECTION DURING HEMATOPOIETIC STEM CELL TRANSPLANT BONE MARROW APLASIA: MONOCENTRIC EXPERIENCE

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Background. Hematological patients and hematopoietic stem cell transplant (HSCT) recipients have high risk of mortality and morbidity from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an infection with an estimated at least 2.5-fold increased risk of death. In HSCT patients, estimated mortality from Centers of European Group for Blood and Marrow Transplantation was approximately 25%, and similar for autologous and allogeneic-HSCT patients.

Method. In our Center we carried out 11 HSCTs from July 2023 to April 2024, all patients are subject to bi-weekly monitoring of the SARS-CoV-2 swab. Only one patient tested positive.

Results. The patient has a refractory Hodgkin lymphoma after first-line treatment, he was 24 years old, unvaccinated for SARS-CoV-2, had not comorbidities and he was a smoker. The patient had a negative SARS-CoV-2 nasopharyngeal swab molecular test (Abbot Resp- 4 -Plex) at the admittance to hematological ward. It was conditioned according to FEAM protocol (fotemustine, cytarabine, etoposide and mephalan) and was undergoing to infusion of CD34-positive cell dose 7.38 x10^6/kg, on day 0 . On day -2 he had the first positive SARS-CoV-2 swab, 30.77 amplification cycles. The chest CT scan was performed after the positive swab, and it showed no signs of interstitial pneumonia. The patient received antiviral therapy: remdesivir 200 mg on day -2 and 100 mg on day -1 and day 0. The patient has febrile neutropenia on day +7 and he received empirical antibiotic therapy with piperacillin tazobactam, the infectious agent could not be determined, and the fever disappeared within 24 hours. The antibiotic treatment was withdrawn after ten days. SARS-CoV-2 swab was performed every other days, and resulted always positive (with viral load range from 30.77 to 38.09 amplification cycles); on day +10 , it resulted negative. The we observed neutrophils engraftment on day +11, and the patient was discharged home on day +14.

Conclusion. cases of SARS-CoV-2 infection in aplasia after high-dose regimen for autologous stem cell transplantation are rare in the medical literature; in our experience, the low viral load, the absence of comorbidities, but also the promptly CT scan and the start of antiviral therapy have allowed us to have no complications from SARS-CoV-2.

PUBLISHED ONLY

PU01

COMBINED CONGENITAL HEMOGLOBIN AND RED BLOOD CELL DEFECTS: DEALING WITH PHENOTYPE

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Introduction. The main cause of hereditary anemia is represented by hemoglobinopathies, although other defects affecting the red blood cell (RBC), such as enzymatic and membrane defects, are often encountered. Contrary to what is known, inheriting multiple defects affecting the RBC is not rare. However, the limited data available in the literature expose us to the risk of under-diagnosing such conditions, especially when multiple heterozygous conditions are combined, and the phenotype might not be readily apparent. Here, we present three cases in which, starting from an intermediary phenotype, genetic diagnostics were expanded, revealing compound mutations that could account for the clinical presentation.

Materials and Methods. Main characteristics are reported in Table 1. Patient 1 (P1) presented clinical features compatible with thalassemia intermedia (TI), with a spleen size of 14.5 cm. Patient 2 (P2), a carrier of Beta-thal trait (confirmed in the father), presented symptoms of moderate anemia associated with hyperferritinemia. Patient 3 (P3) presented clinical features compatible with TI, moderate anemia, and symptomatic worsening splenomegaly (20 cm).

Table 1.

Tabella 1

	Caso 1 (P1), F 28 anni, caucasica	Caso 2 (P2), F 35 anni, caucasica	Caso 3 (P3), F 33 anni, asiatica
Indici laboratoristici	Hb basale: <9 g/dl MCV 68 fl MCH 21 pg, RDW 21% reticolociti 2,8% HbA2 6%, HbF 6.9%, bilirubina tot 1.04 mg/dl, diretta 0.54 mg/dl	Hb basale: 8-9 g/dl MCV 62 fl MCH 20 pg RDW 16% non reticolocitosi ferritina 2000-3000 ST 86% bilirubina nei limiti	Hb basale: 7-8 g/dl MCV 76 fl MCH 21 pg RDW 25% reticolociti 3,6% HbA2 4,7%, HbF 1,3% bilirubina diretta 0,77 mg/dl
Analisi Genetica	triplicazione gene alfa eterozigosi: • HBB:c.118C>T; • PKLR:c.17106G >A • G6PD:c.72T>A	trait B-talassemia; omozigosi TFR2; eterozigosi: • SPTB:c.610G> A • SLC4A1:c.539G >A	triplicazione gene alfa eterozigosi: • HBB:c.92+1G> A (IVSI1G>A) • SPTA1:c.1688G >A varSPTA1:c.6531-12C>T

Discussion. In the literature, the PKLR variant (associated with PK deficiency) seems to ameliorate beta-thalassemia phenotype, while the G6PD variant found in P1 has an uncertain significance. The mutations identified in P2 are classified as probably pathogenic and of uncertain significance, respectively.In P2, these mutations presented with a pathological phenotype, which, in conjunction with hemochromatosis (TRF2), limited therapeutic options by making phlebotomy impractical.The SPTA1 mutations, typically associated in the literature with spherocytosis/elliptocytosis/pyropoikilocytosis, led to a phenotype in P3 compatible with hereditary spherocytosis, justifying the rapid worsening of splenomegaly, which had always been present and was in line with the TI phenotype. However, the acute clinical deterioration remains unexplained.

Conclusions. Some of the variants found do not have a clearly pathological significance. However this does not exclude the possibility that they could worsen the phenotype, in the presence of other genetic defects affecting the RBC. Given the limited data available, it is advisable to always expand the analysis to search for multiple defects, collecting a greater number of cases to investigate their frequency and delineate the phenotypes of the most common combined defects.

PU02

IMPROVED QUALITY OF LIFE AND TRANSFUSION INDEPENDENCE IN A PNH PATIENT TREATED WITH PEGCETACOPLAN AFTER C5 INHIBITORS FAILURE

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Pegcetacoplan is the first proximal complement inhibitor approved for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) in Europe in patients who are anemic after at least 3 months of treatment with a C5 inhibitor, following the results of the PEGASUS phase III trial. Pegcetacoplan prevents the C3 deposition on red blood cells and therefore reduce extravascular hemolysis, which represent one of the major causes of non response to terminal complement inhibitors. Here we report the case of a 54 year-old female patient diagnosed with PNH in 2017.

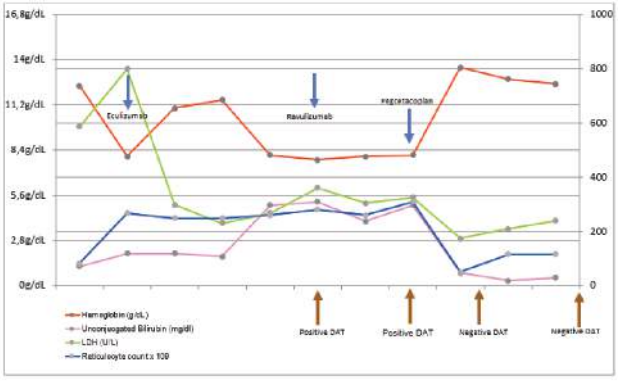

Figure 1. Hemoglobin value, hemolytic markers and DAT during the clinical course of disease.

Figure 1.

In March 2019 the patient was started on treatment with Eculizumab due to the development of an important asthenia and of a transfusion dependent hemolytic anemia. She achieved an optimal but transient response. In July 2020 the hemoglobin value started decreasing and she needed trasnfusion support. The transfusion need progressively worsened over time. A bone marrow evaluation was performed and showed a normal cellularity, a PNH clone of 92% and a normal karyotype. At this time, an allogeneic bone marrow transplant was considered. In November 2021 she was started on Ravulizumab, without any improvement. Direct antiglobulin test (DAT) detected C3 deposition consistent with C3-mediated extravascular hemolysis. In March 2023, she started therapy with the C3 inhibitor Pegcetacoplan at the dosage of 1080 mg subcutaneously twice a week. Hemoglobin value and hemolysis markers normalized within 2 weeks. DAT evaluation after one and two months of treatment confirmed negativity of C3 deposition on patient's red blood cells (Figure 1). Treatment was extremely well tolerated. Furhermore, the

patient reported a significant improvement in her quality of life. On the last follow up (one year from the start of treatment), the patient was asymptomatic and her laboratory exams showed an hemoglobin value of 12.5 g/dl with normal hemolysis markers and a negative DAT. This case confirm the beneficial effect of proximal complement inhibitors which are able to control both extra and intravascular hemolysis in PNH patients with persistent anemia and transfusion need in course of treatment with C5 inhibitors. This young patient was able to achieve transfusion independence with a normal hemoglobin level and, most importantly, she improved her quality of life.

PU03

FIRST ITALIAN PATIENT WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA TREATED WITH NOMINAL USE OF DANICOPAN AS ADD-ON THERAPY TO RAVULIZUMAB

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Extravascular hemolysis (EVH) remains a cause of persistent anemia in patients with paroxysmal nocturnal hemoglobinuria (PNH) receiving treatment with a C5 inhibitor. EVH is due to C3 deposition on PNH red blood cells (RBCs) surviving intravascular hemolysis (IVH) which were sequestered and destroyed in the liver and spleen. Danicopan (ALXN2040) is an oral factor D inhibitor that showed a positive profile as add-on therapy to C5 inhibitors for patients with PNH who experienced EVH. Our center was the first in Italy to join Danicopan (ALXN2040) nominal use program as add-on therapy to Ravulizumab.

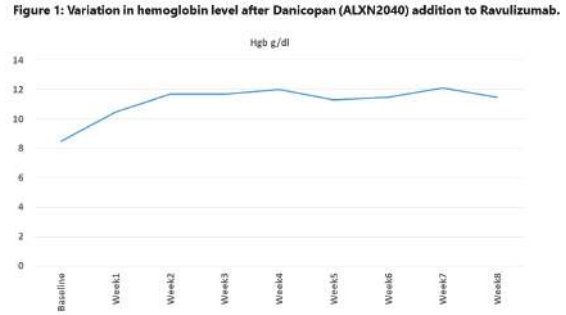

Figure 1.

This is the case report of the first Italian patient treated with this nominal use program of Danicopan (ALXN2040). The patient was an 82-year-old man with a diagnosis of PNH made in February 2021. Abnormal laboratory tests at diagnosis: white blood cell count 2.83x10^9/L, hemoglobin (Hgb) 8.3 g/dl, platelets 71x10^9/L, reticulocytes 181x10^9/L (n.v. 50-100), lactate dehydrogenase 760 UI/l (n.v.<250), and suppressed haptoglobin. Flow cytometry: PNH RBCs 18%, PNH monocytes 42%, and PNH neutrophils 0.5%. Once the appropriate vaccinations were received, the patient began therapy with Eculizumab. During this treatment, the patient occasionally required RBC transfusion, maintaining a good control of IVH (Hgb 8.5-9 g/dl), although he complained of asthenia. In March 2023 the patient was passed to Ravulizumab. Ravulizumab provided good control of IVH, and the patient did not require RBC transfusion anymore (Hgb 9g/dl). However, on November 2023 the patient experienced a breakthrough hemolysis (BTH) with severe anemia (Hgb 5 g/dl) that required hospitalization, antibiotic therapy, and RBC transfusions (n=4). Once BTH had resolved, the Hgb level remained above 9 g/dl and the direct antiglobulin test (DAT) was found to be positive for C3d deposition. On December 2023 we requested Danicopan (ALXN2040) under nominal use as add-on therapy to Ravulizumab. The pharmaceutical company accepted the request, and our ethics committee approved the treatment. In January 2024, the patient added Danicopan 150 mgx3/day to Ravulizumab. The Hgb level rapidly increased from 8.5 g/dl to 12 g/dl, as reported in Figure 1, demonstrating Danicopan (ALXN2040) efficacy in EVH while maintaining IVH control together with Ravulizumab. The patient had no side effects, showed a good adherence to the combined therapy, and experienced a significant improvement in his quality of life.

PU04

COVID EFFECTS ON HAEMATOCRIT

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The haematocrit analysis (HCT) is an evaluation that is part of the blood count, it indicates the percentage of the blood volume occupied by erythrocytes. HCT increases in smokers and in the course of haematological, pulmonary and renal pathologies; it is reduced in patients with anemia, particularly due to iron deficiency. To put in evidence the effect of Covid on HCT, were considered the test in male blood donors, in the four years preceding the start of the pandemic and in the following four years. The HCT analyzed were in the pre-Covid period from 01.07.2016 to 31.12.2019 and in the period from 01.01.2020 to 31.06.2023. There were 10978 donors in time pre-Covid with a median of 44,3% of HCT. There were 9983 donors in time postCovid with a median of 44,0% of HCT. Following the arrival of Covid the HCT in male donors decreased, according to Mann-Whitney test (P<0,0001). The cause could be due to the state of chronic anemia induced by the viral infection or autoimmune diseases Covid associated. The decreased should be probably also due to changes in eating habits, less introduction of iron, less smoking.

Sample 1	
Variable	2017_2019 2017-2019
Sample 2	
Variable	2020_2023 2020-2023

	Sample 1	Sample 2
Sample size	10978	9983
Lowest value	29,9000	33,3000
Highest value	58,4000	59,4000
Median	44,3000	44,0000
95% CI for the median	44,3000 to 44,4000	44,0000 to 44,1000
Interquartile range	42,6000 to 46,1000	42,2000 to 45,9000

Mann-Whitney test (independent samples)

Average rank of first group	776,9315
Average rank of second group	21152,2676
Mann-Whitney U	-51734577,00
Test statistic Z	-243,633
Two-tailed probability	P < 0,0001

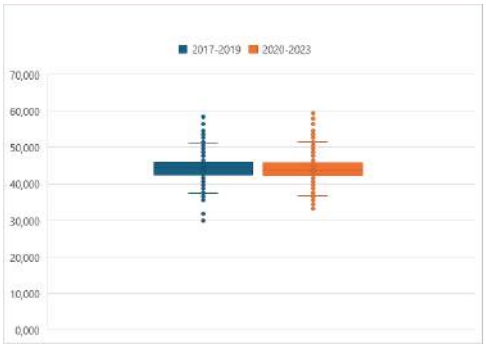

Figure 1.

PU05

COVID EFFECTS ON TCD

M. Piazza

ASL4 Transfusion Service

The direct Coombs Test (TCD) is used to show if agglutinating antibodies, determining autoimmune hemolytic disease or not, are present on the red blood cell membrane. Excluding the causes of maternal-fetal or transfusion incompatibility, the direct Coombs test is positive in the case of haematological pathologies, infections, use of drugs and autoimmune, rheumatic disease. To put in evidence the effect of Covid on the direct Coombs test, all tests carried out in the four years preceding the start of the pandemic and in the following four years. The patients analyzed were hospitalized or external; in the pre-Covid period from 01.07.2016 to 31.12.2019 and in the period from 01.01.2020 to 31.06.2023. There were a total of 745 pre-Covid TCDs of which 174 were positive (23%). There were a total of 968 postCovid TCDs of which 323 were positive (33%). Following the arrival of Covid, both the demand for testing and positivity increased. The increased demand is probably due to the increase in signs and symptoms of hemolysis. The grow of positivity could be linked to an high incidence of septic state and autoimmune diseases.

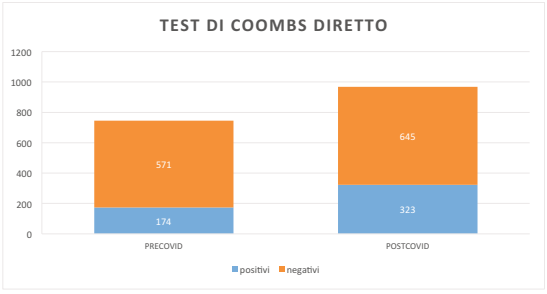

Figure 1.

PU06

EFFICACY OF EMICIZUMAB IN THE MANAGEMENT OF SEVERE HEMOPHILIA A: A CASE REPORT OF SUCCESSFUL THERAPY IN A PATIENT UNRESPONSIVE TO CONVENTIONAL TREATMENTS

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Recent advancements in severe hemophilia management have seen a paradigm shift with the advent of new extended half-life (EHL) molecules and emicizumab, approved in 2017 for hemophilia A. Emicizumab, administered weekly or biweekly subcutaneously, has shown remarkable efficacy in reducing bleeding episodes, irrespective of inhibitors, offering a more convenient treatment option. The growing emphasis on quality of life in healthcare, underscores the psychological, social, and emotional toll chronic diseases like hemophilia impose on patients and their families. The case study presented highlights the benefits of personalized therapies like tailored prophylaxis in enhancing the quality of life for hemophilic patients, considering the profound impact of hemophilia on various aspects of patients' lives. The case involves an 18-year-old male diagnosed with severe hemophilia A, with a history of unsuccessful inhibitor treatment and several immune tolerance induction attempts. Despite prior therapies, including recombinant Factor VIII and bypassing agents, the patient continued to experience severe bleeding episodes, leading to musculoskeletal complications and diminished quality of life. Transitioning to emicizumab, planned collaboratively with a specialized medical team, proved beneficial. Subcutaneous administration of emicizumab reduced treatment burden compared to previous therapies, leading to a significant reduction in bleeding episodes. Periodic quality of life assessments, including standardized questionnaires like SF-36 and EQ-5D, tracked improvements in treatment adherence, psychological well-being, and family relationships. Over the treatment period, bleeding episodes decreased significantly, with observed improvements in joint health. SF-36 and EQ-5D scores revealed challenges in movement-related functions and emotional well-being initially, but subsequent administrations showed improvements in health perception and slight enhancements in self-care and anxiety levels. The case underscores the efficacy of emicizumab in managing severe hemophilia A, particularly in patients with inhibitors unresponsive to conventional treatments. The multidisciplinary approach involving healthcare professionals ensured comprehensive support during treatment transition and long-term monitoring, highlighting the importance of innovative therapies like emicizumab in severe hemophilia management.

PU07

OCULAR RELAPSE POST HEMATOPOIETIC CELL TRANSPLANTATION OF B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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In November 2020, a 56-year-old women affected by relapsed and refractory Philadelphia chromosome-positive B acute lymphoblastic leukemia (B-ALL) harbored T315I-BCR-ABL mutation, and with CNS involvement at the time of diagnosis, underwent at hour hospital to myeloablative sibling-matched allogeneic peripheral blood stem cell transplantation (allo-PBSCT) , with MRD negative status. On day 116 after allo-PBSCT, the patient presented concurrent hepatic and cutaneous graft-versus-host disease (GVHD) responsive to administration of high-dose immunosuppressive therapy, but on day 155, despite the use of cyclosporin A and steroid therapy, the patient presented also ocular GVHD with central corneal ulcer in the left eye and severe lung GVHD. Therefore, she was started on extracorporeal photopheresis and treatment with ruxolitinib with regression of corneal ulcer and improvement of ocular and pulmonary simptoms. In August 2021, on day 271 after allo-PBSCT, she presented with sudden ocular pain and decreased visual acuity in both eyes. A diagnostic aspiration from the both anterior chambers was performed, and a flow cytometry test revealed abnormal lymphocytes phenotyped as CD19+ CD20+ CD22+ CD10+ CD34+ CD45+, compatible with B-ALL. A diagnosis of an ocular relapse of B-ALL was established. Therefore, the patient underwent a lumbar puncture that was found normal with no evidence for blast cells. Magnetic resonance imaging (MRI) of the brain was normal with no CNS involvement. Bone marrow aspiration excluded recurrence of the disease and BCR-ABL molecular test showed complete molecular remission. Furthermore, a whole marrow chimerism showed 100% of donor cells. Local treatment in both eyes with intravitreal injections of

methotrexate (400 µg/0.1 ml) was started on a schedule of once weekly for 8 weeks for the induction phase, and once monthly for 8 months for the maintenance phase, until therapy was discontinued because of sudden vision loss due to methotrexate toxicity. During follow up, the patient partially recovered the visual acuity. In September 2023, a MRI of the brain and orbits showed a left orbital relapse with partial involvement of the optic nerve. Since the diagnostic medullary work-up did not reveal a B-ALL relapse and cerebrospinal fluid exam was normal, the patient was referred for an eye irradiation (22 Gy into 12 daily fractions). The control MRI after radiotherapy showed a complete ocular remission. Currently, the patient is continuing regular follow up.

PU08

COEXISTENCE OF TWO RARE NEOPLASMS: CLONAL PROLIFERATION OF PLASMACYTOID DENDRITIC CELLS AND ACUTE LYMPHOBLASTIC LEUKEMIA/LYMPHOBLASTIC LYMPHOMA OF EARLY PRECURSORS OF T CELLS

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T-cell precursor acute lymphoblastic leukaemia (ETP/ALL) is a subtype of T/ALL distinguished based on a unique immunophenotypic and genomic profile characterized by a worse prognosis than the other subgroups. The definition of ETP/ALL is based on the immunophenotype of the blasts characterized by the expression of T-lineage antigens CD7, CD2 and cCD3, the absence or low expression of CD5 (<75% positive cells) and the absence of CD8 and CD1a. ETP blasts retain differentiation potential in myeloid/dendritic cells and therefore express myeloid and/or stem lineage-associated antigens such as CD34, CD117, CD13, CD11b, HLA-DR. The concomitant neoplastic proliferation of a population of plasmacytoid dendritic cells (pDCs) with specific morphological and immunophenotypic characteristics has been rarely described in the literature. Dendritic cells (DCs) are antigen-presenting cells involved in the immune response. DCs express CD4, CD123, CD303 and HLA-DR and are negative for CD56 and CD11c. The two types of hematologic neoplasms related to pDCs are clonal proliferations of mature pDCs (MPDCP) and blastic pDC neoplasms (BPDCN). MPDCPs with a nonmalignant clinical course are rare and mostly associated with myeloid neoplasms with which they share clonality. In contrast, cases of MPDCP neoplasms associated with lymphoid neoplasms are rare and no common genetic abnormalities were found in the described cases suggesting coexistence due to chance and not a common clonal origin. We describe the case of a 37-year-old male presenting with pancytopenia, splenomegaly, lymphadenopathy, anemia, and thrombocytopenia. Morphological examination of bone marrow blood smears revealed blasts of heterogeneous size partly with high N/C ratio, scant basophilic agranulated cytoplasm and partly with pseudopodial expansions indicative of BPDCN. Cytofluorimetric analysis shows a population of blasts with CD34+TdT+ cyCD3+CD7+CD5+dimCD33+CD13+CD123+/- immunophenotype indicative of ETP/ALL and a CD34-CD304+CD123+CD4+CD56- population indicative of mature pDCs. Considering the data, a diagnosis of ETP/ALL associated with proliferation of pDCs with mature phenotype and blastic morphology is made. The diagnosis is consolidated by the bone marrow biopsy report. The patient undergoes Hypercvad scheme and allogeneic hematopoietic stem cell transplantation. Integration of the morphologic, immunophenotypic, and bone marrow biopsy findings made it possible to make a correct diagnosis and guide appropriate treatment choices.

PU09

EFFICACY OF RITUXIMAB FOR MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS IN A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction. Chronic Lymphocytic Leukemia (CLL) is the most common leukemia in western countries, with an incidence aged-related and high clinical variability. Membranoproliferative glomerulonephritis (MPGN) can represent an uncommon extramedullary presentation of CLL, the only manifestation of an asymptomatic CLL or complicate an active disease, and it can present with either proteinuria or renal failure. There are no standard therapies for treating extramedullary/extranodal manifestations only, if CLL does not meet the criteria to start a specific treatment, so each case must be evaluated individually, weighing the organ damage and balancing the risks and benefits of an unconventional treatment. In such patients the anti-CD20 monoclonal antibody rituximab can offer a good treatment option, with an excellent safety profile even in patients with renal impairment. Its efficacy is demonstrated in numerous MPGN with monoclonal Ig deposit with cryoglobulinemia or monoclonal gammopathy of undetermined significance (MGUS) or idiopathic. However, to our knowledge, no cases are reported in the literature of patients with underlying CLL, but only one treated with obinutuzumab.

Patients and Methods. We describe the case of a 55-year-old woman, diagnosed in January 2022 with asymptomatic standard-risk classical CLL, that developed in February 2023 a MPGN-related mild renal failure with proteinuria, treated with rituximab administered as 4-weekly doses of 375 mg/m^2.

Results. After 4-weekly doses of rituximab the patient achieved complete remission, with normalization of renal indices and proteinuria. At the same time, there was a reduction in peripheral lymphocytosis compatible with a very good hematological response, but positive minimal residual disease (MRD). After 6 months from the treatment, the patient remaining to date in good renal function, suggesting a complete response of her underlying MPGN.

Conclusion. Rituximab has shown excellent efficacy in the treatment of an immune-mediated complication of CLL, as well as in other autoimmune diseases. So, we consider it useful to provide short-term therapy in immune complex-mediated MPGN in CLL patient that not meet the criteria to start a systemic treatment.

PU10

EXCELLENT COMPLIANCE AND EFFICACY IN PATIENT AFFECTED BY MYCOSIS FUNGOIDES UNDER TREATMENT WITH PEGASYS-PEGYLATED INTERFERON ALFA-2A

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Introduction. Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) observed in the general population. It primarily affects the skin and occasionally involves lymph nodes. The disease course is chronic, often insidious, and challenging to diagnose due to its resemblance to benign chronic dermatoses.

Case Presentation. A 65-year-old male presented with recurrent erythematous patches and plaques on his trunk and extremities. The

lesions were pruritic and resistant to topical treatments. Five previous biopsies had shown atypical lymphocytes consistent with MF. The patient had experienced multiple relapses despite various therapies (chemotherapy, immunotherapy, local teraphy, UV therapy).

Treatment Strategy. Pegasys (Pegylated Interferon-alpha 2A): given the patient's refractory disease, Pegasys was initiated. Pegasys is an immunomodulatory agent that has shown promise in CTCL management. The patient received subcutaneous injections weekly.

Clinical Response. Within 2 months of Pegasys therapy, the patient's lesions began to regress. Pruritus subsided, and skin texture improved. Regular follow-up visits monitored treatment response and adverse effects.

Histopathological Findings. Repeat skin biopsies demonstrated reduced epidermotropism and lymphocytic infiltrates. Immunohistochemistry confirmed decreased CD4+ T-cell infiltration. Pegasys appeared to modulate the immune microenvironment. Pegasys offers an alternative for patients with refractory MF. Its mechanism of action involves enhancing antitumor immunity. Close collaboration between dermatologists, hematologists, and pathologists is crucial for accurate diagnosis and treatment monitoring.

Conclusion. This case highlights the successful use of Pegasys in managing recurrent mycosis fungoides. Further studies are warranted to explore its long-term efficacy and safety profile.

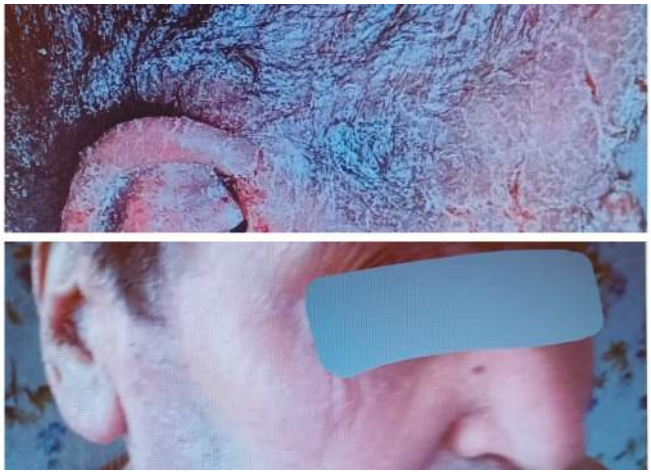

Figure 1.

PU11

A CASE OF MULTIPLE MYELOMA IN A PATIENT IN TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKEMIA

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Synchronous and sequential diagnosis of MM and CLL/SLL is a rare event with a few cases reported in literature and no case, to our knowledge, in need of concomitant treatment. Hereby we describe the case of a 58 years old male patient who was diagnosed with CLL in 2016 and MM in 2022. In April 2021, the criteria for CLL treatment were met for progressive lymphocytosis, splenomegaly and increasing dimensions of lymphadenomegalies. Therefore, Interphase FISH and NGS analysis for CLL were performed (unmutated-IGHV, absence of del17p, wt-TP53 and cr12 trisomy) and therapy with Acalabrutinib was started, after debulking with Chlorambucil and Prednisone, obtaining a Partial Response. In the beginning of February 2022 Acalabrutinib was discontinued for SARS-CoV2 pneumonia requiring non-invasive ventilation. Then the patient was lost to follow up and returned to our attention in May 2022, when he was revaluated for status of disease. At CT scan resulted increased lymphadenomegalies and multiple osteolytic lesions. Therefore, after further examination, the patient was diagnosed with Multiple Myeloma IgG-k, III R2-ISS, with positive CRAB criteria for osteolytic lesion. Interphase FISH analysis showed t(11;14) and 1q21 amp in pathological plasma cells. Considering the patient transplant ineligible for comorbidities and poor compliance, we started off-label treatment with Venetoclax-Bortezomib-Dexamethasone on the basis of the phase III Bellini trial for relapsed/refractory MM, targeting both diseases. Venetoclax was administered, CLL-like, orally at the dosage of 400 mg/die for 28 days per cycle, after 5 weeks rump-up; Bortezomib subcutaneously at the dosage of 1.3 mg/m^2 on days 1, 4, 8, and 11 and Dexamethasone at the dosage of 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for the first 8 cycles. From the ninth cycle, Bortezomib was administered on days 1, 8, 15, and 22 and Dexamethasone on days 1, 2, 8, 9, 15, 16, 22, 23 of each 35-days cycle. The therapy was well tolerated and effective on both diseases, achieving a Very Good Partial Response for MM and a Complete Response for CLL after 8 courses of therapy. After 14 cycles of therapy completed in February 2024, we decided to continue the therapy only with Venetoclax for the CLL, waiting for progression of disease for MM retreatment.

Conclusions. Our report aims to propose therapy for cases like this, needing concomitant treatment for both malignancies, with the limitations of a case-report.

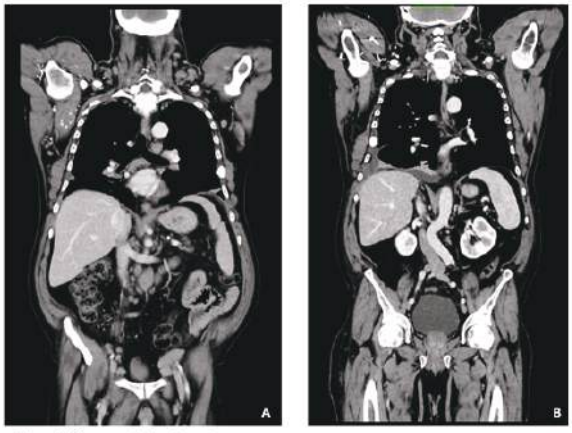

Figure 1: Response to treatment.
A: Coronal TC scan pre-therapy. **B**: Coronal TC scan post eight cycles of therapy.

Figure 1.

PU12

TAGRAXOFUSP IN ELDERLY BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM (BPDCN): A CASE REPORT

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[1]UOC Ematologia Aziendale, azienda USL Toscana Nordovest; [2]Centro Polispecialistico "Achille Sicari", Anatomia Patologica; [3]Azienda USL Toscana Nordovest-Dipartimento delle Diagnostiche-Laboratorio Analisi Chimico Cliniche, Italy

Background. Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) is a rare, aggressive hematologic malignancy. Tagraxofusp, a CD123-targeting cytotoxin, was approved for BPDCN treatment.

Case Report. A 78-year-old pt presented with fatigue and hematochezia. Medical history included hypertension, impaired vision, left adrenal swelling, and thyroid nodule. Blood tests showed pancytopenia (Hb 7.2 g/dL, PMN 300/mmc, plt 15,000/mmc) with peripheral blastosis of 9.5%. The marrow assessment revealed BPDCN (80%CD123+CD4+CD56+CD43+TdT+E-cadherin+CD14-lysozyme-CD19-MPO-CD3- blasts).A CT scan revealed rectal wall thickening and multiple lymph nodes. Antibiotic therapy was initiated for fever and positive blood cultures (S. hominis). Due to hematuria, a repeat CT scan was performed, showing thickening of the bladder walls. Positive urine culture (C. urealyticum, E. faecium) led to antibiotic therapy escalation. Fever was complicated by respiratory failure (nasal cannula 2 L/min) with interstitial lung disease and pulmonary consolidations. The pt received intravenous diuretics and albumin (120 g/day) with benefit. Subsequently, treatment with Tagraxofusp was started at 12 mcg/kg, administered over two consecutive days, followed by a three-day consecutive regimen. Poor blood pressure control was managed with intravenous clonidine. At G6, grade 2/3 transaminitis was evident, along with worsening dyspnea, prompting the addition of methylprednisolone 2 mg/kg and optimization of diuretic therapy. At g7, due to rapid respiratory failure worsening with weight gain (without hypotension), she was transferred to intensive care and started oxygen therapy with progressive improvement. On day 11, right vocal cord paralysis was diagnosed, followed by hearing loss on day 14. At day 21, there was a hematological improvement (hb 9.1 g/dL, plt 31,000/mmc, PMN 450/mmc). Steroid dosage was reduced. Complete cytometric remission was confirmed on day 22. Atrial fibrillation (AF) occurred on day 23, necessitating beta-blocker therapy. The pt became drowsy on day 24, with AF (heart rate 150 bpm), hypotension, oligoanuria and acute respiratory failure requiring circulatory support, oxygen therapy (CPAP helmet) and esmolol. Thoracic ultrasound revealed lung consolidation and blood cultures were positive for S. epidermidis. The pt died same day.

Conclusions. It's unclear if heart failure partly resulted from drug toxicity. Despite complications (some predating therapy), Tagraxofusp proved effective.

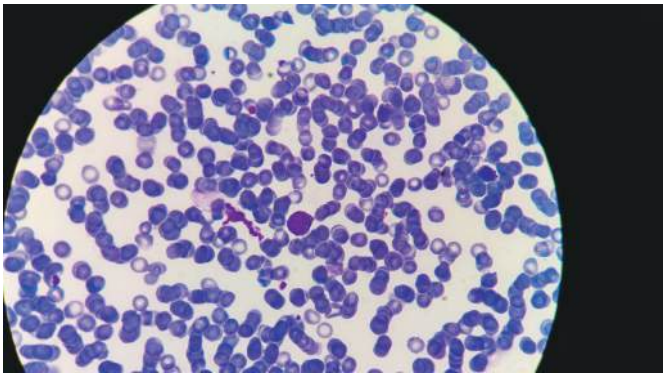

Figure 1.

PU13

DIAGNOSIS OF AGGRESSIVE SYSTEMIC MASTOCYTOSIS IN A PATIENT WITH ANEMIA, THROMBOCYTOPENIA, AND HEPATOSPENOMEGALY

D. Avino, M. Langella, K. Ferrara, M. Di Rosa, A. Di Palma, C. Califano

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Mastocytosis is a rare clonal disease caused by neoplastic proliferation of mast cells (MCs) within one or more organs, most frequently skin and bone marrow.Clinical manifestations are extremely heterogeneous including forms with only skin involvement (cutaneous mastocytosis) prevalent in pediatric age, to systemic forms (MS) typical of adult age in which at least one organ other than skin is involved.The WHO 2016 establishes as a major criteria for the diagnosis of MS the presence of dense multifocal infiltrates of MCs in bone marrow biopsies and/or other extracutaneous organs. Minor criteria include: infiltration>of 25% in the bone marrow or other extracutaneous organs of atypical or immature MCs, finding of KIT mutation at codon 816 in the bone marrow or another organ, presence of MCs expressing CD2 and/or CD25,and tryptase concentration>20ng/mL in the absence of other clonal myeloid neoplasms.The diagnosis of MS can be established if the major criteria and at least one minor criteria or three minor criteria are met. MS is subclassified into indolent (SMI),"smouldering" or aggressive (ASM) on the basis of the presence or absence of signs and symptoms of organ infiltration without (B-findings) or with (C-findings) altered function.In ASM, one or more C-findings (cytopenias, osteolysis, hepatosplenomegaly with altered function and malabsorption) are present. 71-year-old patient admitted to internal medicine for fever comes to hematology consultation for severe anemia and thrombocytopenia.On E.O., he presents with asthenia, hepatosplenomegaly, skin free; denies allergies. On hematochemical examination there is hyperferritinemia, increased indices of inflammation, β-2 microglobulin and GGT, decreased pseudokolinesterase, normal transaminases. On Tc TB with mdc there is pleural and pericardial effusion, mediastinal and axillary lymph nodes, peritoneal free fluid and marked hepatosplenomegaly.The patient practices bone marrow aspiration.On morphological examination, scattered atypical type 2 MCs with bilobated nuclei are observed. Serum tryptase is>200 µL and KIT mutation detection is mutated at codon 816. On bone biopsy, MC aggregates are present. Criteria for MS being met, a diagnosis of ASM is made in the presence of C findings. Skin lesions are present in most patients with MS; forms without skin involvement are likely to be underestimated and characterized by peculiar onset symptoms such as anaphylaxis, osteoporosis, or gastrointestinal symptoms.Cytopenias and organomegaly with or without unexplained organ damage should raise the suspicion of MS.

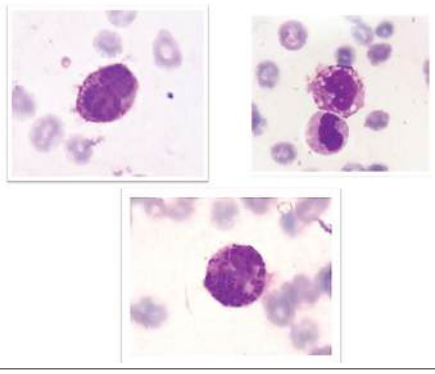

Figure 1.

PU14

R DA EPOCH AS FRONTLINE TREATMENT FOR DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) WITH POOR PROGNOSTIC FACTORS: A SINGLE CENTRE EXPERIENCE

G. Francia[1], E. Montanari[1], C. Salvetti[2], M. Schirru[1], E. Fioribello[1], F. Santoro[1], A. Incorvaia[1], C. Martellossi[1], E. Granero[1], F. Guolo[1,2], A. Todiere[2], F. Ballerini[2], R.M. Lemoli[1,2]

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Background. Diffuse Large B-cell Lymphoma (DLBCL) is the most common large B-cell Lymphoma. Unfortunately, only 60% of DLBCL can be cured with standard therapy and patients with aggressive features (such as mutation in c-MYC, BCL2 or BCL6, elevated proliferation index (i.e. Ki67), ABC type and high IPI score) have a poor outcome. CALGB 503 randomized study show no survival advantage of R-DA-EPOCH over R-CHOP in DLBCL, but most of the patients enrolled had favorable prognostic features. The aim of our study is to investigate the tolerability and efficacy of R-DA-EPOCH regimen in patients with DLBCL with poor prognostic factors.

Methods. We have retrospectively analyzed the outcome of 50 patients affected by DLBCL and treated in first line with R-DA EPOCH from 2016 to 2023. The median age was 62 years (range: 33-74 years) and the median FUP was 40.5 months. 40% of patients had more than 65 years, 52% had Ann Arbor stage IV, 46% had a ki67>90%, 54% were ABC type. CNS IPI and IPI score were high (>3) in 62% and 24% of patients, respectively. Only 3 patients had double/triple hit lymphoma.

Results. Therapy was well tolerated, also among older patients: nine patients needed hospitalization for adverse events and no treatment-related deaths were recorded. Only one patient died during treatment due to disease progression, while 96% of patients (47/50) were able to receive at least one dose escalation. The ORR was 82% (with a CRR 76%) and the OS and PFS at 2 years were 76.5% and 67%, respectively. No differences in 2-years OS were seen according to age (73% *vs* 71%, for patients with ≥ or<65 years, Figure 1), elevated IPI score (72% *vs* 83% for IPI ≥ 3 and<3), elevated CNS-IPI score (79% *vs* 77% for CNS-IPI ≤ 3 or > 3), cell-of-origin (75% for both GC type and non-GC type), advanced stage (72% *vs* 82% for stage IV or lower) and very high ki67 (81% *vs* 69% for patients with ki67 ≥ or<90%). P-value were n.s. in all subgroups.

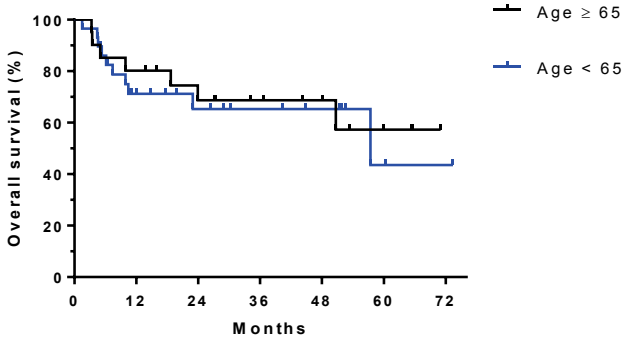

Figure 1.

Discussion and conclusions. Our data showed that R-DA-EPOCH is well tolerated and results in a favorable CRR, despite the unfavorable characteristics of our cohort, and the adverse prognostic features analyzed didn't impact on CRR or OS. Notably, the regimen was effective and feasible also in older patients, usually considered ineligible to intensive therapy. In conclusion, R-DA-EPOCH may be a good backbone chemotherapy for patients with aggressive DLBCL which may be further improved in the future with the inclusion of novel targeted agents.

PU15

EFFICACY AND SAFETY OF ZANUBRUTINIB IN RELAPSED/REFRACTORY WALDENSTRÖM MACROGLOBULINEMIA: A SINGLE-CENTER EXPERIENCE

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Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma characterized by monoclonal immunoglobulin M (IgM) gammopathy, with aberrant Bruton tyrosine kinase (BTK) signaling. Selective BTK inhibiting therapies have emerged as an attractive option for treatment within the therapeutic landscape, which also comprises chemotherapy, monoclonal antibodies, proteasome inhibitors and B-cell lymphoma 2 (BCL2) inhibitors. The next-generation highly selective agent, zanubrutinib, was developed to address concerns regarding toxicity and tolerance related to ibrutinib therapy, and has demonstrated strong efficacy in treating a multitude of B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and WM. Herein, we discuss the available data regarding the use of zanubrutinib in relapse/refractory (R/R) WM based on our experience. Between February 2023 and March 2024, nine R/R patients initiated treatment. At a median follow-up of 9.0 months, 78% remained on treatment (Figure 1).

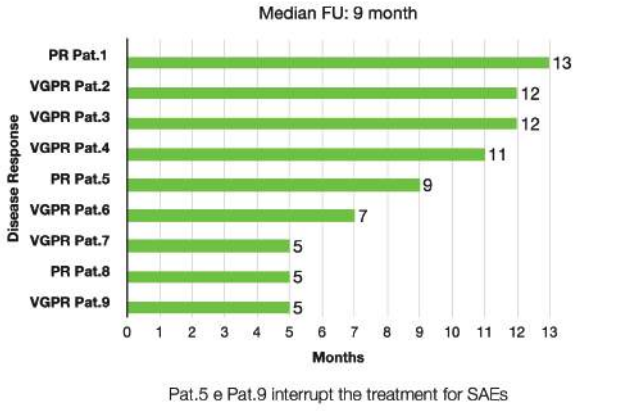

Figure 1.

Reasons for treatment discontinuation included severe adverse events in two of nine patients (one with arteria hypertension, one with vasculitis). The overall response rate (ORR) was 100%, with a very good partial response (VGPR)/complete response (CR) rate of 67%, of these, 50% at 6 months. In 3 patients resistant to first-line therapy with bortezomib, zanubrutinib elicited a favorable response after just 3 months of treatment. The estimated 2-year progression-free survival rate and overall survival rate were not available. Other adverse events of interest included neutropenia (one patient), atrial fibrillation/flutter (one patient), and pulmonary infection disease in

one patient. Long-term treatment with single-agent zanubrutinib resulted in deep and durable responses in some WM patients. The safety profile of long-term zanubrutinib therapy in these patients was deemed acceptable.

PU16

THE FOLLOWING CASE SUGGEST THAT CHLORMETINE IN COMBINATION WITH GEMCITABINE IS A SAFE AND HIGHLY EFFECTIVE TREATMENT OPTION IN FOR PATIENTS WITH MF

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Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphoma (CTCL) and it is usually characterized by skin-limited patches and plaques in sun-protected sites with indolent behavior. In advanced disease, there can be involvement of lymph nodes, blood, and/or visceral organs. A variety of therapeutic approach are available raging from phototherapy (PUVA), topical coritocosteroids and systemic chemo- or immunotherapy. However, there is a lack of clear a treatment sequencing. Herein, we describe a successful combination of chlormethine and gemcitabine in a relpades/refractory patient with MF. 72 -year-old patient presented in our department in 2021 suffering from diffuse skin patch and plaque lesions for about 4 years. A skin biopsy reveald a (descrivere l'infiltrato in microscopia) at microscopy examination. Immunohistochemical study demonstrated that tumor cells were positive for CD3, CD5, CD4, CD7, PD-1, and negative for CD20, CD8, CD30. No enlargement was found in the lymph nodes, liver, and spleen at CT scan. Pheriferal blood immunophenotype was negative for Sesary sindrome. Thus, a diagnosis of MF stage T2b N0M0B0 was established. The patient started treatment with PUVA (October 2020), he completed cycles attaining a remission. In October 2022 patient experienced a disease relapse with the appearance of patch lesions on more than 10% of the skin surface. Thus, a 2nd line treatment with Mogamulizumab was started in October 2022 for 4 cycles concluded frebrary 2023 Patient did not achieve a satisfactory response and a total skin irradiation in combination with targretin was started on April 2023 (12 Gy in 12 sessions) achiving a very good partial response. The patients maintained hematologic response until December 2023 when an hematologic replase occurred. Thus, a combination therapy with chlormethine and gemcitabine was started and the patient achieved a comple remission at 2 months from treatment initiation and he maintained the response until last follow-up (April 2024). The present report suggest that chlormetine in combination with gemcitabine is a safe and highly effective treatment option in for patients with MF who had received prior therapies that had proved ineffective.

Reference

Chlormethine gel in combination with other therapies for treatment of mycosis fungoides: a review with patient cases:
Marco Ardigò, Miriam Teolil, Liliana Crisan, Neda Nikbakht, Laura Gleason, Christiane Querfeld

PU17

CHALLENGES IN THE DIAGNOSIS OF ALK-POSITIVE LARGE B-CELL LYMPHOMA: A CASE REPORT

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Background. Alk-positive Large B-Cell Lymphoma (ALK+ LBCL) is a rare and aggressive lymphoma with ALK fusion genes and a plasma cell-like immunophenotype, which was first described in 1997 and since then very few cases have been reported in the literature. Diagnosis of ALK+ LBCL can be quite challenging because of its rarity and morphologic and immunophenotypic characteristics, which significantly overlap with other hematologic and nonhematologic neoplasms, requiring careful consideration of its molecular characteristics.

Case report. A 45-year-old female patient presented asymptomatic, with incidental finding of multiple lymph node swellings and evidence of an expansive neoformed process apically in the upper lobe of the right lung at the CT scan, and a 3 cm mass involving the right adrenal gland at MRI. At the blood tests: LDH 334 UI/L, seric beta-2 microglobulin 2.65 mg/L. The excisional biopsy of a right lateral cervical lymph node had been analyzed by three different hospital centers: the first made diagnosis of Histiocytic Sarcoma, but, later, the second one made diagnosis of ALK+ LBCL, also confirmed by the third opinion. Before starting treatment, a bone marrow biopsy resulted negative for disease localization, and a CT-guided biopsy of the lung lesion led to diagnosis of ALK+ Non-Small Cell Lung Cancer (NSCLC). Considering the peculiarity of two concurrent ALK+ neoplasms, further investigations have been initiated. The transcriptomic analysis by Next Generation Sequencing (NGS) (Ion Ampliseq RNA Fusion Lung Cancer Research Panel) of the histological specimens of the lymph node and the lung resulted positive for EML4-ALK(E13;A20) for both the specimens, while the mutational NGS analysis (Ion Ampliseq Colon and Lung Cancer Research Panel v.2) of the lymph node specimen did not detect ALK mutations. Moreover, the molecular analyses of the VDJ segment of the IgH gene in the Fr1-2-3/J region and the VJ segment of the TCRγ chain using PCR resulted in both negative on the lymph node for clonal rearrangements, leading to the exclusion of a concurrent ALK-positive large B-cell lymphoma diagnosis. After three years of treatment with the TKi Alectinib under the care of the Oncologists, the patient was re-evaluated by excisional biopsy of a right upper paratracheal lymph node, which confirmed the diagnosis of a primary lung tumor.

Conclusion. More studies need to be initiated to address the challenge of recognizing this rare lymphoma in time, but, in this case, molecular biology has been fundamental for the final diagnosis, excluding the initial hypothesis of two concurrent neoplasms and leading to an adequate and timely treatment of the pathology

PU18

VISCERAL LEISHMANIASIS IN MULTIPLE MYELOMA PATIENT TREATED WITH DARATUMUMAB, LENALIDOMIDE AND DEXAMETASONE

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New-generation agents such as Daratumumab, are dramatically improving the prognosis of multiple myeloma (MM), but the infectious impact of innovative agents remains to be defined. Leishmania is a parasitic infection endemic in india, Brazil and in the Mediterranean areas. A case of visceral leishmaniasis (VL) has been recently reported by a Greek group in a patient with MM receiving anti-CD 38 therapy. Two other cases of VL occurred at our center and below we describe the most relevant. A 73 y.o. man was diagnosed with syntomatic MM in June 2022 and underwent first line therapy with daratumumab, lenalidomide and dexamethasone. In August 2022, during his 3rd cycle, the patient was diagnosed with Kaposis sarcoma by skin biopsy of foot lesions. Considering the only cutaneous localization (EGDS, colonoscopy and CT-PET were negative, HHV8 DNA showed low positivity) the patient did not start any specific tretment. During cycle VI, the patient developed progressive trilinear cytopenia and fever, with negative chest CT and culture on blood and urine. Leishmania serology and PCR were performed resulting, respectively, negative and positive. A bone marrow aspirate showed hemophagocytosis but no Leishmania parasites, while a PCR assay was positive. The patient started the treatment with ambisome for the diagnosis of VL and after six weeks of therapy the PCR for Leishmania was negative both on medullary and peripheral blood. VL is a protozoan infection endemic in Mediterranean areas where dogs are the most common reservoir and frequently causes subclinical infections. In immunocompromised patients, VL usually presents as a reactivation favored by immunosuppresion caused by low CD4+ in HIV patients or Th1 suppression due to corticosteroids or chemoimmunotherap. NK cell reduction was first described in patients with MM treated with daratumumab monotherapy and was not associated with an increase in infectious adverse events. A subsequent retrospective review of patients receiving Daratumumab alone or in combination with other anti-myeloma agents (PI, ImiD, MEK) showed that patients who developed an infection during treatment had fewer NK cells than patients without infectious complications. It has recently been shown that Leishmania itself causes a reduction in NK cells to promote its own spread. In case of unexpected fever or cytopenia before starting and during Daratumuab therapy it is important to exclude an infection with Leishmania in the endemic area.

PU19

MONOCLONAL GAMMOPATHY OF NEUROLOGICAL SIGNIFICANCE - A CASE REPORT AND A NOVEL APPROACH

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Hereby we describe a case of a 61 years old male patient referred by the neurologist for a finding of monoclonal gammopathy IgM kappa and sensorimotor polyneuropathy (PN), unresponsive to high dose corticosteroids and high dose intravenous immunoglobulins (IVIGs), in February 2023. Cerebrospinal fluid (CSF) physical-chemical examination was negative. There were no alterations in blood count, renal function, calcium, kappa/lambda free light chain ratio and Bence-Jones proteinuria was absent. Total body CT scan with contrast medium was negative for osteolytic lesions and organomegaly, except for hepatomegaly (LD right lobe 18 cm) with steatosis, in absence of alterations of active pathological significance. However, there were high titre antibodies against myelin-associated glycoprotein (anti-MAG) (72142 BTU) and a positivity for anti-sulfatide IgM antibodies. Bone marrow needle aspiration and biopsy were performed, finding a small lymphoplasmacytic clone (< 5%), not diagnostic for Waldenstrom Macroglobulinemia (WM). We concluded, therefore, for a MGNS. Thereafter, in April 2023, four weekly doses of RTX were administered with improvement of the neurological symptoms and reduction of anti-MAG titre after two administrations of RTX (58773 BTU). However, at the end of the cycle of immunotherapy, there was a worsening of the symptoms and there was a slight increase in the titre of anti-MAG antibodies (75000 BTU). Thus, it was performed a new electroneuromyographic evaluation, which showed a worsening of the polyneuropathic picture. Therefore, in the view of the flare up of PN five sessions of PE were performed, exchanging a total of five volaemias (45058 BTU); then a novel protocol combining two sessions of PE preceding each one of four monthly RTX was administered, with a clinical improvement of sensory neuropathy, but not biochemical and electroneuromyographic response (59000 BTU).

Conclusions. MGNS represents a novel entity and an unmet clinical need, without a codified therapy, because of its rarity and misdiagnosis linked to its novelty. The available therapies have not been particularly effective. Hence, the need to investigate new approaches. Here we show our experience with an innovative approach combining plasmapheresis and RTX that showed a clinical benefit, but not a biochemical and electroneuromyographic one. Further studies will be needed to evaluate the possible application of this novel approach.

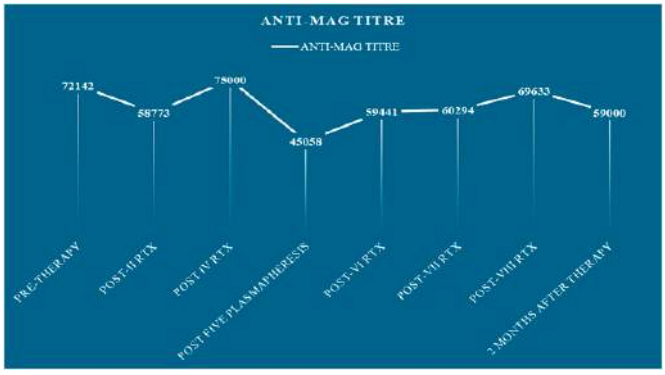

Figure 1.

PU20

A CORNEAL TRANSPLANT PATIENT IN BELANTAMAB-MAFODOTIN THERAPY

R. Bianco, G. Cetani, S. Iaccarino, M. Iovine, G. Farina, M. Troiano, G. Monaco, E. Vatiero, A. D'ambrosio, M. Di Palma, F. Frigeri

UOC Ematologia AORN Sant'Anna e San Sebastiano, Italy

Introduction. Belantamab-Mafodotin (BM) is a new drug used in the treatment (trt) of R/R MM. Clinical studies have shown promising responses, but ocular toxicity remains a major challenge with dose reduction or trt discontinuation being the only available trt option.

The most frequently (≥20%) reported adverse reactions grades

3-4 with BM were keratopathy (31%), thrombocytopenia (22%), and anemia (21%).

Results. In this case-report, one patient (pt), is underwent a bilateral corneal's transplant (trp) from 9 at 13 june 1994 for cheratocons. This pt is affected by IgG-K multiple myeloma, third stage, according to D&S classification, diagnosed in 2012, started on therapy according to the VTD and underwent a double ASCT, with subsequent consolidation therapy. In 2016, the patient presented a recurrence of the disease and was treated according to the Elo-RD, with a good response until 2018, when he was treated according to the KD56, suspended after two cycles for adverse event (in particular two episodes of pneumothorax). Daratumumab monotherapy (mt) was then rapidly started in the 2018, with best response of VGPR, but suspended due to PD in 2021. The extramedullary disease that was presented in the 2021 was caraterized from right omeral lesion, that was initially treated with radiotherapy and finally with PVD from september 2021 with partial response, until November 2022 for PD. This pt experienced episodes of pnx, arrhythmia, deep vein thrombosis, and bone pain. This pt has continuous oxygen therapy and does not walk independently, but with a wheelchair. This pt was extremely weak and had an ECOG III score. In December 2022 he was started on three-weekly mt with BM, with VGPR.

Conclusions. This pt is at XX cycles of BM without severe adverse ocular effected. Before starting the fifth-line trt and every month, he underwent an ophthalmological examination and prophylactic trt with eye drops. Currently, the pt has not been under trt since February 2024 due to the withdrawal of the medication by AIFA, but remains in CR and a stable eye condition.

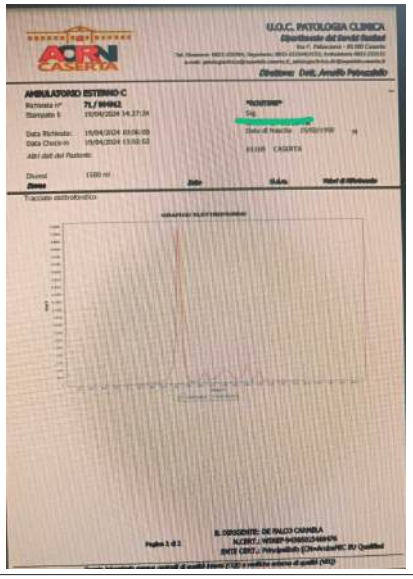

Figure 1.

PU21

ASCITES AS A COMPLICATION OF WALDESTROM'S MACROGLOBULINEMIA: CASE REPORT

D. Avino, M. Di Rosa, M. Rosania, A. Esposito, L. Ammirati, A. Di Palma, M. Lucignano, C. Califano

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Waldenström's macroglobulinemia (MW) is a rare indolent B-type lymphoproliferative disorder characterized by overproduction of monoclonal IgM proteins in serum and/or urine. The most common manifestations of MW are anemia, hepato-splenomegaly, and lymphadenopathy. Monoclonal immunoglobulins can cause hyperviscosity syndrome and hemorrhagic diathesis by interacting with coagulation factors and platelet function. A 54-year-old man comes to our attention for anemia (Hb 10.4 g\dL) and monoclonal IgM Kappa component (3 g\dL); he presents with mild renal insufficiency (creatinine 2.3 mg\dL), marked splenomegaly (DL 20 cm), palpable lymph nodes in submandibular and inguinal regions, and bilateral eyelid edema; he has no edema and cyanosis in the extremities, and neurological examination is negative. The patient performs an osteomidullary biopsy that deposes MW for finding interstitial infiltration equal to 20% of the total cellularity of atypical small lymphocytes and plasma cells. Approximately 15 days after the diagnosis, the patient enters the emergency room for asthenia and general malaise with finding of ascites. Morphologic examination of the paracentesis reveals the presence of numerous plasma cells sometimes with the presence in the cytoplasm of needle-like formations likely formed by precipitated immunoglobulin crystals. On cytofluorimetric examination, the neoplastic population consists mainly of plasma cells with CD138+CD38+CD19+CD56- immunophenotype and a small proportion of clonal B lymphocytes. The patient undergoes three plasmapheresis and starts chemotherapy with Bendamustine not followed by combination therapy with Rituximab due to onset of fever. Progressively there is reappearance of ascites whose fluid on cytometric examination does not detect B lymphocytes. Ascites is an uncommon manifestation in MW and has previously been considered a possible cause of hyperviscosity or peritoneal lymphomatosis in a case of evolution of pluritracted MW into immunoblastic lymphoma. In our patient, clonal lymphocytes and plasma cells were present in the ascitic fluid taken almost simultaneously at diagnosis but not after the start of chemotherapy, and this may suggest biological features and pathogenetic mechanisms of MW yet to be investigated.

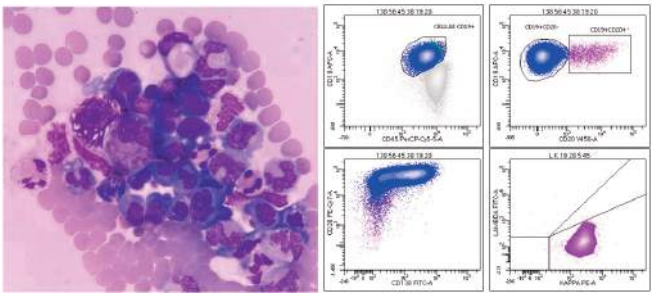

Figure 1.

PU22

THE FIRST CASE IN ITALY OF A PATIENT AFFECTED BY MULTIPLE MYELOMA AND UNDERGOING AN AUTOLOGOUS STEM CELL TRANSPLANT AFTER SECOND-LINE THERAPY ACCORDING TO THE DARAPD SCHEMA

R. Bianco, S. Iaccarino, M. Iovine, G. Farina, M. Troiano, G. Monaco, E. Vatiero, G. Cetani, A. D'ambrosio, M. Di Palma, F. Frigeri

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Introduction. We present a case report of a 60-year-old patient diagnosed with multiple myeloma (MM) who underwent autologous stem cell transplantation following second-line therapy using the Daratumumab, Pomalidomide, and Dexamethasone regimen.

Results. The patient had previously received treatment with this combination. Notably, the patient presented chronic cerebral vasculopathy. Given the challenges in treating extramedullary (homer left) relapse in patients progressing on proteasome inhibitors anti-CD38

monoclonal antibodies, and immunomodulatory drugs. This patient, initially eligible for transplantation, due to temporary denial of the transplant procedure, resulted in a extramedullary relapse of the disease. Therefore, considering the patient's previous denial of the transplant procedure and the underlying chronic cerebrovascular pathology, the patient is initiated on Daratumumab, Pomalidomide, and Dexamethasone. The results are immediately positive, and the patient achieves complete remission after the third cycle. This case highlights the importance of considering extramedullary relapse in MM patients and the potential efficacy of the Daratumumab, Pomalidomide, and Dexamethasone regimen in such cases. Further studies are warranted to explore its broader applicability and outcomes in similar scenarios.

PU23

A RARE CASE OF CHRONIC EOSINOPHILIC LEUKEMIA WITH TRISOMY 19 AND SRSF2 MUTATION SUCCESSFULLY TREATED WITH ALLOGENEIC BONE MARROW TRANSPLANTATION

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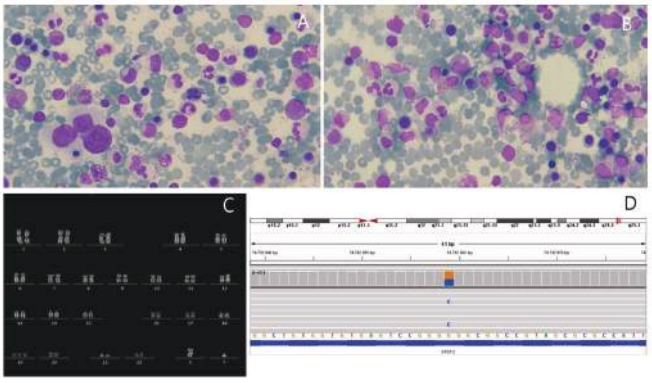
Chronic Eosinophilic Leukemia (CEL) is an extremely rare myeloproliferative neoplasm characterized by an aggressive clinical course with significant rates of acute leukemia transformation and end-organ damage. We report a case of a 58 year-old male patient referred to our center in June 2023 because of hypereosinophilia (7700/mmc).



(A-B) Medullary blood smears showing hypereosinophilia (B) and cells with dysplastic features: dyserythropoiesis, a dismorphic megakaryocyte and a blast cell with a prominent nucleolus (A).
(C) Abnormal kariotype revealing 47,XY, +19.
(D) Somatic mutation involving SRSF2 gene (c.284C>G, VAF 41%) located on Chromosome 17 identified by NGS.

Figure 1.

After the exclusion of secondary causes of hypereosinophilia, the following tests were performed: serum tryptase was normal and BCR-ABL fusion gene was not detected; rearrangement of FIPL1, PDGFRB, FGFR1, JAK2, ABL1 and FLT3 were negative by FISH; B cell or T cell clones were absent by flow cytometry; bone marrow evaluation showed increased cellularity (60%) with dysplastic megakaryocytes and dysplastic features of the erythroid lineage with an eosinophilic infiltrate (around 10%) and increased myeloid blasts (5%) in the absence of fibrosis; clonality was demonstrated as karyotype analysis showed a trisomy 19 and NGS showed the presence of a somatic mutation involving SRSF2 (c.284C>G, VAF 41%) (Figure 1). The patient presented with increased values of troponin and proBNP and a thickening of the left ventricle wall compatible with Loeffler's endocarditis. According to 5th edition of WHO and 2022 ICC diagnostic criteria, the patient was diagnosed with CEL. He was initially treated with Imatinib (200 mg/die), without achieving a response. Afterwards, he was treated with steroid therapy (1 mg/kg) obtaining only a partial response with a rapid increase of the eosinophil count at the reduction of the treatment. The addition of hydroxyurea was not useful in this case. The patient underwent an allogeneic bone marrow transplantation on February 2024 from a 10/10 matched unrelated donor conditioned with a reduced intensity regimen based on Fludarabine and Treosulfan and obtained a complete remission. In this case the presence of all the criteria listed by the 5th edition of WHO 2022 allowed us to differentiate CEL from hypereosinophilic syndromes: persistent hypereosinophilia for more than 4 weeks, the presence of clonality documented by cytogenetic analysis and NGS, the bone marrow morphological features compatible with a CEL diagnosis. The decision to proceed to an allogeneic bone marrow transplant was justified by the high risk of acute transformation of this entity, the presence of progressive eosinophilia-related end-organ damage and the refractoriness to other treatment.

PU24

G-CSF-INDUCED BLOOD COUNT ALTERATIONS IN RELATED DONORS OF PERIPHERAL BLOOD STEM CELLS ARE REVERSIBLE WITHIN 9 MONTHS AFTER THE DONATION: A MONOCENTRIC RETROSPECTIVE ANALYSIS

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Peripheral blood stem cell (PBSC) donation is a voluntary-based, widely employed strategy for harvesting hematopoietic stem cells (HSCs) to be transplanted into recipients with hematologic malignancies. Granulocyte-colony stimulating factor (G-CSF) is administered to donors to induce HSC pool expansion and subsequent mobilization from the bone marrow (BM) into the peripheral blood, which allows a convenient collection via an apheretic procedure. Since 2011, a vigilant post-donation follow-up (FU) is mandatory for related donors (RDs), as established by the FACT-JACIE Standards. Yet, to date, little is known about the outcomes of RDs, largely due to varied FU strategies employed among centers. Here, we report our real-world experience of PBSC donation FU during a 9-year period (2014–2023). Only 30 out of 96 individuals undergoing post-donation FU in our center (40 females, mean age 48 ±15.2 years; 56 males, mean age 40 ±13.9 years) had complete records available for analysis; the remaining 66 were consequently excluded due to incomplete data. This monocentric retrospective analysis sought to investigate any complete blood count alterations in RDs following G-CSF-induced BM stimulation. Monitoring occurred at standard intervals: pre-donation, donation day, +2 days, +7 days, +1 month, and +9 months post-donation. Mean hemoglobin, white blood cell, and platelet levels were calculated for each time point, stratified by sex. Pre-donation mean levels of these three parameters were compared with corresponding values at each FU time-point. Slightly reduced hemoglobin levels persisted for at least 1 month post-donation ($p<.001$). Following an initial surge post-G-CSF administration, white blood cells remained at lower levels for at least 1 month (p 0.03), reverting to baseline by the 9-month time-point. Platelet levels exhibited a significant decline on donation day ($p<.001$) but returned to pre-donation values after roughly 1 month. Notably, HSC mobi-

lization was not associated with lasting alterations in blood cell counts, and all the observed changes were reversible within 1 to 9 months after donation. This underscores the safety of PBSC donation for RDs but emphasizes the importance of long-term donor health monitoring. However, overall compliance with the FU scheme was low, with approximately 69% of RDs failing to attend each designated time-point, citing various reasons (*e.g.* recipient relative death, the COVID-19 pandemic, and logistical issues).

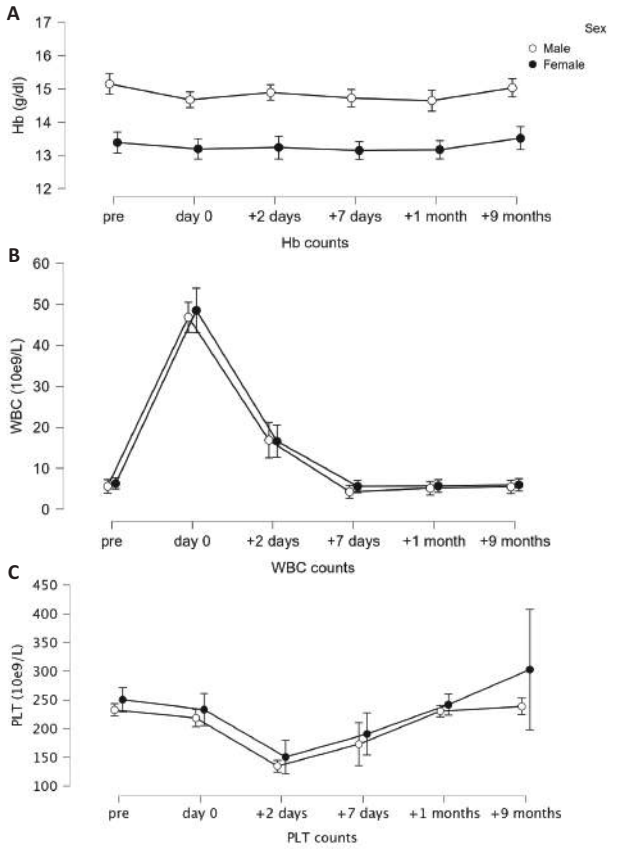

Figure 1. Blood cell counts across the different time-points, stratified by sex. **a.** Slightly lower levels of hemoglobin (Hb) persisted for at least 1 month (p <.001);**b.** White blood cell (WBC) counts remained at lower levels for at least 1 month (p 0.03);**c.** Platelet (PLT) counts declined on donation day (p <.001) but returned to pre-donation values after roughly 1 month.

Figure 1.

PU25

USE OF GRANULOCYTE COLONY-STIMULATING FACTOR IS FEASIBLE IN ALL DONOR SETTING WITHOUT INCREASING THE RISK OF ENGRAFTMENT SYNDROME

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Granulocyte colony-stimulating factor (G-CSF) may favor a more rapid neutrophil engraftment after allogeneic HSCT. This property reveals helpful in centres with reduced transplant room capacities, in order to fasten the sequence of transplants. However, concerns for an increased risk of engraftment syndrome prompt in some cases to limit its use only to patients with high risk of graft failure. We report a single-center experience with the use of G-CSF in patients undergoing allo-HSCT for hematologic malignancies from july 2020 to august 2023.

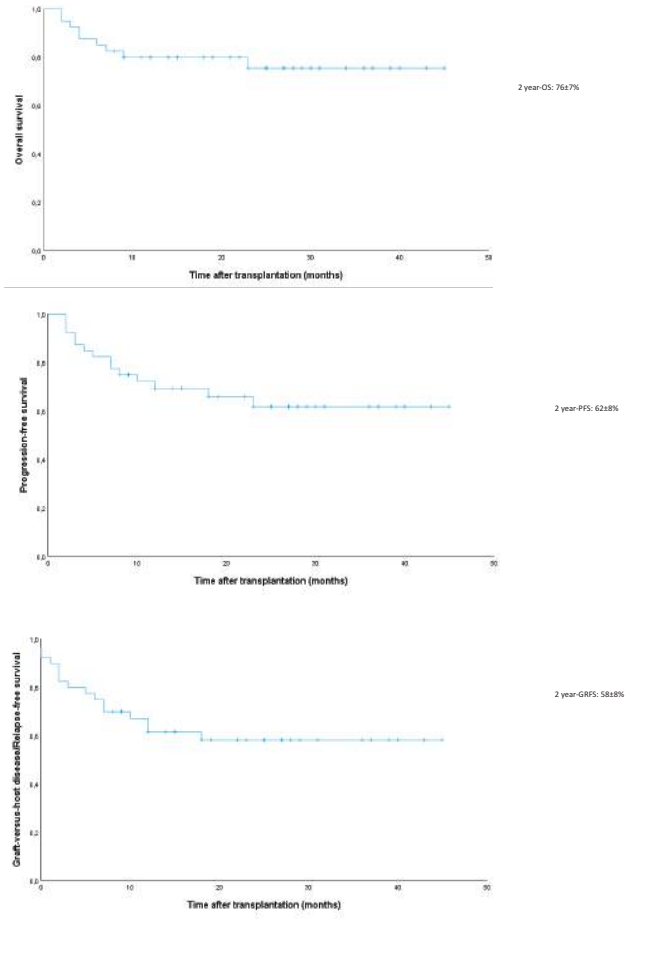

Figure 1.

When GVHD prophylaxis incorporated either methotrexate (MTX) or post-transplant cyclophosphamide (PTCy), G-CSF was started the day after the last administration of these drugs. Otherwise, it was started at neutropenia onset. Forty patients (15 M, 25 F) with a median age at transplant of 52 (range 25-71) years, underwent allo-HSCT for various hematological malignancies (AML [n=29], ALL [n=7], MDS [n=2], lymphoproliferative disease [n=2]). Peripheral blood was more frequently used as stem cell source (63%). Donors were HLA identical siblings for 14, unrelated for 18 (10/10 [n=12], 9/10 [n=6]) and haploidentical for 8 patients. 33 patients were transplanted in CR (CR1 [n=24]; CR2 [n=8], >CR2 [n=1]), 7 with active disease. Conditioning regimen was myeloablative in 19 (48%), reduced-intensity in 14 (35%) and sequential in 7 (17%) patients. GVHD prophylaxis consisted in cyclosporine A alone (n=2) or with either MTX (n=13) or mycophenolate mofetil (n=25). Addition of antityhmocyte globulin or PTCy was recorded in 27 and 12 patients, respectively. Median duration of G-CSF treatment was 9 (range 1-20) days. All patients achieved neutrophil engraftment in a median time of 14 (range 9-23) days. All but one patient experienced platelet engraftment in a median time of 17 (range 10-44) days. Median duration of hospitalisation was 30 (range 20-56) days. No cases of engraftment syndrome were observed. Acute GVHD of all grades occurred in 9 patients, including 4 grade 3-4. Chronic GVHD occurred in 2 patients, one being extensive. Ten patients experienced disease relapse. Death occurred in 10 patients, including 4 due to GVHD, 5 due to disease relapse and 1 due to unknown causes. With a median follow-up of 25 (range 8-45) months, 2-year GRFS, PFS and OS were 58±8%, 62±8% and 76±8%. In our experience G-CSF is feasible in all donor settings and does not result in increased incidence of engraftment syndrome.

PU26

NOVEL STRATEGIES FOR HEMATOPOIETIC STEM CELL (HSC) DIFFERENTIATION

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Background. Hematopoietic stem cells (HSCs) are precursors of all blood lineages, as erythroid, myeloid and lymphoid cells. In the last decades, hematopoietic stem cell transplantations (HSCTs) have been successfully applied as a form of cell therapy to patients for the treatment of hematological disorders such as lymphoma, leukemia and related bone/blood disorders. The major problem of the allogeneic HSCT procedure depends on donor–recipient matching that limits its use worldwide. The use of HSCs harvested from peripheral blood before transplantation and reinfused after myeloablation partly holds great promise for solving this issue for autologous HSCT. As a substitute, production of transplantable HSCs *in vitro* using embryonic or induced pluripotent stem cells represents a valid alternative to current procedures of isolation of HSCs from donors or patients. However, genetic manipulation required to induce HSCs differentiation limits its application in humans. Therefore, alternative ways to induce differentiation of HSCs precursors are needed.

Results. Mitogenic kinases are major downstream effectors of signaling cascades that control the initial steps of Haematopoietic stem cell (HSC) differentiation. Recent findings indicate that upregulation of mitogenic kinases is causally linked to HSCs differentiation. Kinase Suppressor of Ras 1 (KSR1) is an evolutionally conserved protein kinase that plays a fundamental role in mitogenic pathway. In response to Ras activation, KSR1 assembles a tripartite kinase complex that optimally transfers signals generated at cell membrane to downstream ERK signaling. We have identified a mechanism of ERK1/2 signal attenuation based on the ubiquitin-dependent control of KSR1 by the RING ubiquitin ligase praja2. Stimulation of membrane receptors by growth factor induced a rapid polyubiquitination of KSR1 by praja2, which paralleled the decay of ERK1/2 signaling. Treatment of embryonic stem cells with a designer peptide that selectively interferes with praja2 binding to KSR1 sustains ERK1/2 activity and induces epiblast differentiation.

Conclusions. This non-genetic approach represents a promising route to induce terminal differentiation of pluripotent stem cells. Using this approach, we expect to efficiently induce HSCs differentiation *in vitro* using adult pluripotent precursor cells isolated from mesenchymal tissue or endothelium.

PU27

A PROPOSAL FOR COMBINING AIFA'S DETERMINA REQUIREMENTS FOR PHASE 1 WITH FACT-JACIE GUIDELINES.

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The Trial Center of San Martino Hospital, located in Genova, is an establishment engaged in clinical trials and is closely affiliated with the Stem Cell Transplant Program, which holds FACT-JACIE accreditation. The Center is tasked with establishing a quality assurance system for Phase 1 trials in accordance with the Determina AIFA requirements (809/2015), while simultaneously adhering to the quality standards mandated for transplant programs.

In light of these dual obligations, it is imperative to:

- Define the alignment of the Transplant Program components (clinical unit, apheresis unit, and cell manipulation laboratory) within the Phase 1 Center, as stipulated by the Determina AIFA Requirements.
- Implement an organizational framework capable of satisfying both sets of requirements, thereby ensuring seamless integration of activities and compliance with both Determina AIFA regulations and FACT-JACIE standards.
- Minimize redundancy in documentation and maintain a streamlined and practical system.
- Identify specific aspects of the Determina AIFA regulations that may not fully accommodate the unique needs of a Cellular Therapy Center specializing in stem cell transplantation.

Consequently, the primary objective of this project is to elucidate the methodology for developing an integrated system that aligns with both FACT-JACIE and AIFA requirements, while also highlighting key elements and issues that necessitate resolution at the regulatory level.

To achieve the integration of the Clinical Trial Unit's organizational system, the following steps have been undertaken:

- Analysis of requirements outlined in the Determina AIFA.
- Analysis of requirements specified by the FACT-JACIE Transplant Program.
- Development of an integrated matrix reconciling FACT-JACIE and Determina AIFA requirements.
- Creation of a monitoring mechanism, focused on assessing the Center's compliance status with FACT-JACIE/Determina AIFA requirements.
- Design of an integrated organizational system for the Transplant Program, encompassing:

1. Organizational structure.
2. Document management.

3. Infrastructure requirements.
4. Enhancement initiatives.
5. Personnel requirements.

- Identification of critical issues inherent in the compliance requirements.

The ultimate deliverable of this project is an INTEGRATED organizational system that can be adapted for use in diverse centers, ensuring compliance with both FACT-JACIE and Determina AIFA standards.

PU28

POSSIBLE EFFECT OF LETERMOVIR ON EBV REACTIVATION IN PATIENTS UNDERGOING ALLOGENEIC TRANSPLANTATION: A SINGLE CENTER RETROSPECTIVE STUDY

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Background. The primary prophylaxis with letermovir has changed the management of cytomegalovirus reactivation within the first 100 days post-allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, the effect on Epstein-Barr virus (EBV) reactivation remains controversial. We report a single-center retrospective study evaluating the incidence of EBV reactivation and post-transplant lymphoproliferative disorders (PTLD) in two groups of patients receiving or not letermovir prophylaxis.

Method. A total of 36 patients who received allo-HSCT were included in this study. Of these, 16 received letermovir (L+) and 20 did not (L-). Clinical characteristics, transplant strategies and the incidence of EBV reactivation in each group are reported in Table 1.

Table 1.

		LET- (n=20)	LET+ (n=16)
Median age (range yrs)		43,5 (31-67)	45,6 (43-68)
Sex (M/F)		8/12	10/6
Disease	ALL	4 (20%)	4 (25,5%)
	AML/MDS	12 (60%)	10 (62%)
	Other	4 (20%)	2 (12,5%)
Status disease at HSCT	1CR	16 (80%)	3 (18%)
	CR>1	4 (20%)	13 (82%)
Median Time from diagnosis to HSCT (range mo)		7,5 (3-15,9)	10 (3-15)
Donor type	Sibling	17 (85%)	3 (19%)
	Haplo	3 (15%)	13 (81%)
Conditioning	MAC	13 (65%)	5 (31%)
	RIC	7 (35%)	11 (69%)
T-cell depletion	PTCy	0	7 (54%)
	ATG	3	6 (46%)
GvHD	Acute	4	8
	Chronic	10	7
EBV reactivation	viraemia	0	2
	PTLD	0	1
	Other	0	2 gastric

LET-: no letermovir prophylaxis; LET+: letermovir prophylaxis; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; CR: complete remission; MAC: myeloablative conditioning; RIC: reduced-intensity conditioning; PTCy: post-transplant cyclophosphamide; ATG anti-thymocyte globulin; GvHD: graft-versus-host disease; EBV: Epstein-Barr virus; PTLD: post-transplant lymphoproliferative disorders

Results. The two cohorts showed similar median age and diagnosis. However, in L- group 17/20 (85%) patients received HSCT from matched related donor, while in the L+ group 13/16 (81%) were transplanted with haploidentical-HSCT (haplo-HSCT) with post-transplant cyclophosphamide (PTCy) as T-cell depletion in 7/13 (53%). The EBV reactivation was observed in 5/36 (14%) patients allocated to the L+ group, while no EBV reactivation was seen in the L- group. In particular, 2 patients presented viraemia, 2 gastric localization and 1 PTLD, histologically documented in the last 3 patients. EBV reactivation occurred before day +100 from allo-HSCT in 3 patients. 4/5 patients received rituximab, while one died before treatment. Among the 4 patients treated, 2 are alive and 2 died for transplant complications or leukemia relapse.

Conclusion. In our retrospective experience, we observed 5 cases of EBV reactivation during the era of letermovir prophylaxis alongside the radical change in transplant strategies with the implementation of haplo-HSCT and PTCy. Therefore, it is challenging to establish which factors might have influenced EBV reactivation in the L+ cohort. Conversely, the absence of EBV reactivation in the L- group may be related not only to the predominant matched related transplant strategy but also to the fact that most of these patients were transplanted shortly after first complete remission. Certainly, letermovir in the early stages of transplantation has been a great achievement in recent years, but it would be necessary to establish its possible predisposition to EBV reactivation in order to prepare the proper therapies to control its severe complications.

PU29

THE ROLE OF THE IMMUNE SYSTEM IN PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY: A COMPARATIVE ANALYSIS OF TWO CASES FOLLOWING AUTOLOGOUS AND ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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Background. Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disorder of the central nervous system (CNS) caused by the JCV. Hematological patients, particularly post-transplant, presenting with worsening neurological symptoms should promptly consider PML in the differential diagnosis.

Aims. The rarity of PML after hematopoietic stem cell transplantation (HSCT) and the absence of an effective therapy represents a clinical challenge. Herein, we present two cases of PML developed after autologous and allogeneic HSCT.

Methods. Case 1. A 56-year-old man with relapsed diffuse large B-cell lymphoma underwent autologous HSCT. After five months, he developed neurological symptoms including dysphonia, dysarthria, and right upper limb hyposthenia. Brain MRI revealed hyperintense lesions in the left cerebellum, thalamic area, and fronto-parietal subcortical area associated with edema. After ruling out a recurrence of lymphoma with a PET/CT scan, a diagnostic lumbar puncture (LP) was performed, showing no evidence of lymphoma and no involvement of neurotropic viruses. Considering the absence of any diagnostic clue, we decided to perform a stereotactic brain biopsy. The histological exam revealed CD8+ T-lymphocytes infiltrates interpreted as a vasculitic reaction. High dose steroid treatment was then started with gradual neurological improvement and subsequent tapering due to complete resolution of MRI findings. A further definitive histological examination was acquired showing positivity for JCV viral antigens and DNA, configuring a CNS-Immune Reconstitution Inflammatory Syndrome (IRIS) in PML. The patient withdrew steroid therapy and preserved a radiological and clinical remission. Case 2. A 56-year-old woman with high-risk Acute Myeloid Leukemia underwent allogeneic HSCT. At 9 months after HSCT, the patient developed chronic GVHD and underwent steroid therapy. At the same time, she developed mild neurological symptoms which gradually worsened, including limbs hypostenia, dysarthria and agnosia. An extensive work up including MRI of the brain revealed hyperintense lesions, mainly on the right side, suspicious for PML, confirmed by JCV-DNA positivity on diagnostic LP. Efforts to obtain anti-JCV lymphocytes from an identical-HLA donor were unsuccessful, Cidofovir and Mirtazapine therapy did not yield improvement. The patient experienced worsening of neurological status leading to death.

Results. In case 1 the patient developed JCV infection as a result

of a reactivation in a post-transplant immunosuppressed setting with a prior anti-CD20 exposure. The gradual immunological reconstitution led to a rebound inflammatory reaction against brain infection, known as IRIS, resulting in the evidence of radiological findings and gradual viral clearance. The resolution of PML symptoms correlates with the immunological recovery, especially in the normalization of T-lymphocyte count. In case 2, the patient underwent an allogeneic HSCT highlighting a deeper immunogical suppression status, corroborated by initial steroid treatment for GVHD and a low T-cells count (CD4+ 97/mm^3), leading to PML progression and death.

Conclusion. PML poses a significant clinical challenge due to its rarity and lack of effective treatment. The absence of JCV in cerebrospinal fluid does not exclude PML, necessitating brain biopsy in cases of high suspicion. Deep immunosuppression is a primary driver of JCV infection, emphasizing the importance of immunological recovery in combating the disease. Case-specific interventions, including brain biopsy, may be necessary for accurate diagnosis and management in HSCT recipients.

PU30

USE OF MYCOPHENOLATE MOFETIL FOR GRAFT VERSUS HOST DISEASE PROPHYLAXIS IN PATIENTS UNDERGOING HEMATOPOIETIC STEM CELLS TRANSPLANTATION FROM UNRELATED DONORS

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Background. Graft versus host disease (GVHD) prophylaxis in unrelated donor transplantation (UD-HSCT) mainly relies on the use of a calcineurin inhibitor in association to either methotrexate or mycophenolate mofetil (MMF) when a myeloablative (MAC) or reduced-intensity (RIC) conditioning regimen is used, respectively. Concerns about the higher risk of GVHD with MMF compared to MTX exist. However, the implementation of GVHD prophylaxis through the addition of antithymocyte globulin (ATG) or post-transplant cyclophosphamide (PTCy) may reduce this complication.

Methods. We report transplantation outcomes in patients undergoing 9/ or 10/10 UD-HSCT and receiving cyclosporine A (CsA), MMF with the addition of PTCy or ATG as GVHD prophylaxis. MMF was administered at a total dose of 3 grams per day from day -3 when it was associated with CsA and ATG, and from day +6 when it was associated with CsA and PTCy. The drug was discontinued at day +35.

Results. We report 17 consecutive patients (6 males, 11 females) who underwent UD-HSCT (10/10, n=12; 9/10, n=5) in our center from July 2020 to November 2023. Median age at transplant was 51 (range 26-66) years. Main diagnosis were AML (n=13), ALL (n=3), MDS/MPN (n=1). All but 2 patients with active disease, were transplanted in CR (CR1, n=12; CR2, n=3). Sorror score was >2 in one patient. Stem cell source was peripheral blood in all but one patient. ATG was added in most cases (10/10, n=12; 9/10, n=1) to CsA and MMF, while PTCy was used in the remaining 4. Conditioning regimen was myeloablative in 12, reduced-intensity in 3, sequential in 2 patients. Thirteen patients (76%) experienced mucositis, including 5 grade 3. Neutrophil and platelet engraftment occurred in all patients with a median time of 14 (range 9-23) and 17 (range 8-44) days, respectively. Acute GVHD (aGVHD) of all grades occurred in 5 patients, including 1 grade 3-4. Chronic GVHD occurred in 2 patients, one being extensive. Relapse occurred in 4 patients, with one undergoing a second allo-HSCT after CR2 obtention. Four patients died, 2 due to GVHD, one due to disease relapse and one due to unknown causes. With a median follow-up of 22 (range 8-45) months, 1-year PFS, OS and GRFS, were 49±15%, 71±13% and 46±14%, respectively.

Conclusions. When adding ATG or PTCy to CsA, addition of MMF was feasible and resulted in no major toxicities and in acceptable GVHD incidence in UD-HSCT with both MAC and RIC regimens.

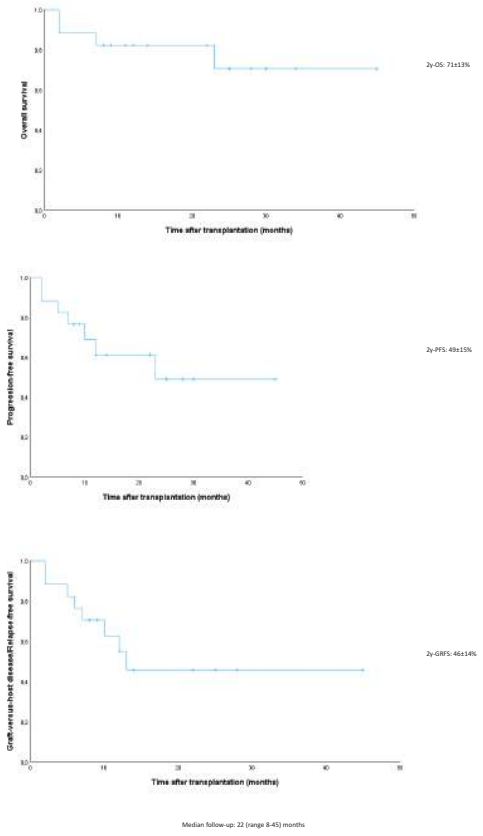

Figure 1.

PU31

REMISSION OF RELAPSED FLT3+ ACUTE MYELOID LEUKEMIA (AML) AFTER ALLOGENIC PERIPHERAL HEMATOPOIETIC STEM CELL TRANSPLANTATION (ALLO-HSCT) FROM AN HLA-IDENTICAL SIBLING DONOR AND TREATED WITH GILTERITINIB+DONOR LYMPHOCYTE INFUSION (DLI): A CASE STUDY REPORT

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Background. DLI is an allogeneic immunotherapy that can cause graft versus leukemia and has been used to treat relapses of acute and chronic myeloid leukemia after Allo-HSCT. Gilteritinib is a next-generation selective FLT 3 –inhibitor approved by the FDA for relapsed/refractory AML in 2018. We here report a case of morphological and cytogenetic remission after therapy with gilteritinib 120 mg/day and DLI in a patient with relapse of FLT3+ AML post Allo-HSCT from an HLA identical (sibling) familial donor.

Case report. In November 2020, a 42-year-old man underwent sibling Allo-HSCT (donor: sister) for FLT3+ acute myeloid leukemia. Myeloablative conditioning was administered which included: Fludarabine 40 mg/m^2/day for 4 days and Busulfan 130 mg/m^2/day for 4 days. Graft-versus-host-disease (GVHD) prophylaxis included: ciclosporin 3 mg/kg/day, anti-human thymocyte immunoglobulin 5 mg/kg and methotrexate 15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6 and +11. The engraftment of neutrophilic granulocytes was detected at day +16. Subsequent bone marrow evaluations highlighted 100% full donor chimerism. The cytogenetic examination on day +112 gave the following result: 46, XX [20]. This was also followed by the onset of a probable hepatic GVHD which regressed after steroid therapy. Approximately 18 months after the transplant, disease recurrence was documented and rescue therapy was started with gilteritinib 120 mg/day orally. Four months after treatment, the patient achieved complete remission of the disease and recovery of 100% full donor chimerism but the cytogenetic examination documented a complex karyotype in four metaphases. The aforementioned therapy was therefore associated with the administration of CD3+ as follows: DLI1= 1 x 10^6/kg, DLI2= 5 x 10^6/kg and DLI3= 10 x 10^6/kg. At the subsequent bone marrow re-evaluation both complete remission of the disease and 100% full donor chimerism were confirmed and the cytogenetic analysis gave the following result: // 46, XX [20].

Conclusion. Combined therapy with gilteritinib and DLI could be considered a possible bridge therapy to the second Allo-HSCT in a patient in relapse of FLT3+ AML post allogeneic transplant. However, studies on a large sample of patients in relapse after Allo-HSCT are necessary to evaluate the efficacy and safety profile of the aforementioned therapy, the number of DLIs to be performed and the risk of graft versus host disease (GVHD).

PU32

RARE EVENT OF CLOTS FORMATION IN HPCA PRODUCTS IN THE PREFREEZING PHASE IN THE GMP LABORATORY AND THAWING ON BEDSIDE OF THE PATIENT

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Introduction. Hematopoietic stem cells from apheresis and bone marrow are frequently used in transplantation therapies in hematological pathologies. HPCA, at now more frequent, but the management of stem cells in pre freezing stage and overall, at tawing in bedside of patient are very sensitive issues. At any time, the resolution of issues needs to be fast and strong to save the HPCA products for cell therapy. Aim of study: analyze 2 rare cases of clots formation, and see these adverse events, in positive way, for to understand the cause, but overall to find the effective resolution when happen and save the collection product continue the manipulation or save therapy product at tawing.

Materials and Methods. All 2 cases were referred from autologous collection, male patients. The first patient MM (case A), HPCA collection for 2 auto, Cobas Spectra, total dose 8,7 CD34x10^6/kg, TNC 3.9x10^8/kg, Neut. 80%, 4 bags, crio preserved in 10% of DMSO. The product was tawed in water bath at 37C, after tawed, numerous small clots are evident, was performed fast inoculation of 5 % of ACD but don't resolve the issue, was added other 5% of a ACD and the clots was dissolves. The HPCA product was filtered and given to the patient, at check of CD34 post tawed, the loss was low and inside the indicator of acceptability (75 to 100%, viability and recovery), the engraftment was good. Case B: Diffuse Large Cell Lymphoma, HPCA collection for 1 auto, HOPTIA, total dose 17,5 CD34x10^6/kg, TNC 3.3x10^8/kg, neut.46%, 4 bags, crio preserved in 10% DMSO. Before the manipulation after storage overnight, numerous clots were present Inside the bag, fast inoculation of 5 % of ACD don't resolve the issue, added other 5% of a ACD and the clots dissolved, to be continue the process for cryopreserved. The adverse evet was notified and one second collection 3 weeks after. The second mobilization was completed, and the product doesn't have evidence of any clots. The laboratory investigated, was sacrificed one bag, at Tawed in water bath at 37C, after tawed numerous small white clots were evident, HPCA was filtered and checked samples from primary bag and filtered product. Were performed slides and cd34 count.

Results. Case A: for MM patient, transplant therapy was completed, good engraftment (13day Neutr/21-day PLT), at check of CD34 post tawed, the loss was inside the range of acceptability and 85% of viability. Case B: for Diffuse Large Cell Lymphoma, HPCA of second mobilization will be used; was discovery the nature of clots after observation of slides and were WBC agglomerates, don't evidence of loss of CD34/kg, no evidence of clots inside of final bag after filtration with blood filter kit.

Conclusions. The event is rare, in our laboratories but not unfeasible, 1event/1500, (0.06%), for clots at thawing in 13 years of transplant activity, while for clots pre freezing 1event/215 (0.46%) in 9 year of transplant activity. The use of an emergency Kit, with clear procedure and bedside emergency kit proved to be essential to have a quick and effective solution; but also, a good quality system with an effective and rapid communication between the BMT, the Apheresis and the Laboratory and overall, the notify of adverse events made it possible to invest and understand the nature of the clots and make the correct therapeutic decisions.

MAIN PROGRAM

HIGH RISK MULTIPLE MYELOMA: BYOLOGICAL AND CLINICAL DEFINITIONS

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Multiple myeloma outcome is heterogeneous, with overall survival (OS) ranging from months to over 10 years. High-risk multiple myeloma refers to an aggressive biological and/or clinical manifestation of multiple myeloma associated with an inferior progression free survival and overall survival compared to standard-risk cases. Starting from the first definition in the International Staging System in 2014, based on beta-2 microglobulin and albumin levels, the risk classification has been challenged recently by emerging biological and clinical insights,[1] like LDH and cytogenetic aberrancies taken in account in the R2-ISS.[2]

The risk of inferior outcome in multiple myeloma should be based on a dynamic evaluation of several co-occurring factors, since a large analysis of serial samples showed that in up to 25% of patients transition to a high-risk expression subtype occurred at progression,[3] with a potential impact on front-line immunotherapy, including:

- ***genetic abnormalities***: presence of any two high risk chromosomal aberrancies is considered double-hit myeloma; three or more high risk factors is triple-hit myeloma[4]
- ***biological features***: like gene expression profile, recurrent mutations and engagement of compensatory pathways (*e.g.* TP53, K-RAS, B-RAF and APOBEC mutations), transcriptomics, epigenetics, enumeration of circulating tumor cells,[5,6] T-cell fitness and spatial immune types of MM that may provide an initial framework for the optimal application of specific immune therapies[7]
- ***the patient's overall fitness and clinical factors*** such as involvement of extramedullary sites, increased LDH, life-threatening bone disease and acute renal injury in the aggressive manifestation
- ***response to therapy*** regardless of baseline risk, early relapse occurring within 12-18 months of first-line therapy identifies a functional high-risk group with a median overall survival of less than 2 years.[8,9]

While a revised IMWG definition is awaited, at the last ASCO[10] meeting, the following features have been identified as consistent with definition of high-risk MM, leading to an overall survival within 36-60 months:

- Single-hit del(17p) or TP53 mutation
- Isolated del(1p), gain(1q), t(4;14), t(14;16), t(14;20)
- Circulating PCs, ≥0.07% but <2%
- High-risk according to ISS, R-ISS, R2-ISS, mSMART, etc but not satisfying criteria for uHRMM.

Taken together, the dynamic integration of genetic, biologic, and response variables requires the adoption of multidimensional evaluation of risk in multiple myeloma,[10] also based on new technological tools like neural networks and artificial intelligence.[4]

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MANAGEMENT OF HIGH-RISK PATIENTS AT DIAGNOSIS

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Despite therapeutic advances have led to unprecedented survival outcomes in newly diagnosed multiple myeloma (NDMM), high-risk (HR) subgroup continues to experience early disease progression and death. Numerous prognostic factors have been identified and included in the risk stratification models. However, no definition is consistently implemented in clinical practice and the revised IMWG definition is awaited. The heterogeneous risk definition, the limited number of studies designed for HR patients and the small HR subgroups in all studies, make it difficult to generate high-evidence recommendations. Despite treatment, achieving and maintaining measurable residual disease (MRD) negativity is now recognized as the main factor capable to mitigate the

adverse prognosis related to baseline HR features. Standard of care for frontline treatment of HRMM will continue to evolve. For transplant-eligible (TE) NDMM patients, quadruplet induction/consolidation regimen that includes anti-CD38 monoclonal antibodies plus proteasome inhibitor and immunomodulatory agents, and dexamethasone, and autologous stem-cell transplant and maintenance with, if available, at least a doublet combination could be the preferred option. Regarding non-TE NDMM, first-line quadruplet treatments are expected to provide the best treatment outcome; however, the balance between efficacy and potential toxicity requires even more careful consideration in this setting. Additionally, to further improve the treatment landscape in all NDMM patients with HR, new immunotherapies (*e.g*., chimeric antigen receptor [CAR] T cells and bispecific antibodies) might play a promise role. However, reliable and uniform identification of patients with HRMM remains the first step to enhance their outcomes.

MENAGEMENT OF DYNAMIC RISK IN MULTIPLE MYELOMA

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Multiple myeloma (MM) is characterized by a variety of biological and clinical features that confer a profound diversity in clinical courses and long-term prognosis. As consequence, there are patients with "low risk" disease and survival of more then 10 ten years, compared with subjects with an "high risk" profile and survival of maximum of 2-3 years, even when treated with intensive therapies.[1] Current prognostic models are based on baseline genetic, patient and disease-related factors [2-5] but can misclassify a group of them, because they do not consider their "functional high risk" profile, meaning the possibility of an early progression (12-18 months) or suboptimal response after initial treatment thus a shorter progression- free survival (PFS) and overall survival (OS). [6-7] The precise identification and definition of dynamic high-risk patients, as well as their management, currently represents an unmet medical need and different strategies are being explored to try to improve their outcome. First, the achievement of Minimal Residual Disease (MRD), both in and outside the bone marrow, is now considered the objective of MM treatment, particularly with the use of modern quadruplets with or without autologous transplant, intensive maintenance approaches and novel T-cell redirecting therapies; MRD allow to identify the most effective treatment up-front and at relapse at the highest possible sensitivity (aiming to 10^{-6}) to reduce the risk of early progression; can modulate the poor prognostic role of cytogenetic particularly when it is sustained overtime (1-2 year at least) and can be used as a dynamic tool to intensify or de-intensify treatment. Therefore, ongoing clinical trials are exploring a "response – adapted strategy" based on MRD response and other "high risk" features to try to improve the outcome of these MM patients, the use of modern T- cell treatments (CAR-T and bispecifics) in early phases of disease as well as the choice of the best salvage regimen at first MRD resurgence/biochemical relapse vs clinical relapse.[8]

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DIAGNOSI E TERAPIA DEI LINFOMI EXTRANODALI AD ORIGINE DALLA ZONA MARGINALE

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Extranodal marginal zone lymphomas (EMZLs) also known as MALT lymphomas represent the most frequent subtype of marginal zone lymphomas, accounting for 50-70% of cases.[1,3] They are usually diagnosed in the elderly (median age 65 years) and the most typically involved site is the stomach, although any organ in the body can potentially be involved. MALT lymphomas are typically associated with chronic infections, or autoimmune diseases. In addition to Helicobacter pylori, other microorganisms have been associated with site-specific EMZLs, although the evidence is less compelling. Several genetic alterations have been described including chromosomal translocations and gene mutations with a well-preserved association between anatomical sites, genetic changes, and infectious agents.[3] At presentation, MALT lymphomas are typically confined to a single organ, with the potential to remain localised for long periods. However, an involvement of regional lymph nodes and multiple mucosal sites or more disseminated disease may be evident at diagnosis, particularly in non-gastric EMZLs.[4] Clinical course of ENMZL is that of truly indolent neoplasms with a relapsing remitting course and with a risk of transformation into aggressive histotypes which however is lower compared to other low grade lymphomas. Several prognostic scores are currently available, and include the MALT-IPI[5] and the recently validated MZL-IPI[6] Regarding therapy, once a pathogenic infection is documented eradication therapy is required independent of stage and symptoms. In patients failing eradication therapy and in subjects without pathogenic infection, treatment choice is based on disease stage and symptoms, similarly to other indolent lymphomas.[7]. Involved-site radiotherapy at standard (or very low doses is recommended for stage I disease, while systemic therapy is only indicated for advanced-stage symptomatic cases and require the use of rituximab combined with several agents mainly alkylating[9] or purine analogues (*e.g.* bendamustine).[9] Patients with relapsed MZL require a highly individualised approach. Several agents have been confirmed as active in the treatment of MZL, mainly beyond first line. These include BTK inhibitors, immunomodulating agents, and promising data are being generated with bispecific antibodies and CAR-T therapies. Based on recently reported studies and those currently underway, the treatment landscape of MZL is expected to rapidly evolve towards multiple chemo-free options in the next few years.

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THE EVOLUTION OF TREATMENT OF PRIMARY MEDIASTINAL B-CELL LYMPHOMA

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Primary mediastinal B-cell lymphoma (PMBCL) is curable in nearly 70% of cases: anthracycline and rituximab-containing regimens remain an unsurpassed frontline approach.[1] The cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab combination given every 21 days (R-CHOP21) displays reduced efficacy in comparison to the same regimen delivered every two weeks (R-CHOP14).[2] Third-generation regimens, like the methotrexate/etoposide + doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin (MACOP-B/ VACOP-B), and the dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (DA-EPOCH) combination, both with the addition of rituximab, have outcomes similar to R-CHOP14.[3] According to the results of the randomized positron emission tomography-guided IELSG37 trial, consolidation radiotherapy can be safely omitted in patients achieving a complete metabolic response (Deauville score of 1-3) after induction chemoimmunotherapy.[4] However, the role of radiation therapy remains undetermined in case of an end-of treatment Deauville score of 4[5]: these patients may be managed conservatively, provided progression is excluded.[6] The extremely poor prognosis of refractory disease is nowadays mitigated by immunotherapy, which has definitely replaced salvage chemotherapy. The anti-programmed death-1 (PD-1) checkpoint inhibitor pembrolizumab yielded a response rate of 42% in the KEYNOTE-170 trial, with a complete response (CR) in up to 21% of cases and a progression-free survival (PFS) rate of 33% at 4 years. Patients in CR neither experienced progression nor required any further consolidation with transplant.[7] The combination of the anti-PD-1 nivolumab with the anti-CD30 drug conjugate brentuximab vedotin enhanced the response rate to 73%, including a CR in 40% of cases. Half of patients received consolidative transplant. More than 75% of treated patients were alive at 2 years, with 56% being progression-fre.[8] At present, no conclusion can be drawn about consolidation beyond CR in patients treated with checkpoint inhibitors. Chimeric antigen receptor (CAR) T-cells are an option in pretreated patients independently of prior checkpoint blockade: real life experience acknowledges high response rates (76%), mostly consisting of CR (67%), with 78% of patients being alive and 64% progression-free at 2 years.[9] PMBCL patients receiving CART-cells have better outcomes than those with diffuse large B-cell lymphoma.[10]

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PRIMARY BREAST LYMPHOMA

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Primary breast lymphoma (PBL) is a rare type of non-Hodgkin lymphoma (NHL), representing the 0.5% of all the malignant breast tumors, the 1% of NHL, and the 2% of extranodal NHL.[1] In 1972, Wiseman and Liao first defined PBL according to four criteria:[2]

1. mammary tissue and lymphoma must be in close anatomic proximity;
2. no preceding diagnosis of extramammary lymphoma;
3. no evidence of disseminated disease, other than ipsilateral axillary lymphadenopathy;
4. adequate quality of the histopathological specimen.

Usually, PBL occurs in female, but rarely cases are described in the male population; the median age at diagnosis is 62-64 years, but some cases, namely aggressive ones, are reported in younger females.[1]

Histologically, these lymphomas are heterogeneous and include diffuse large B-cell lymphomas (DLBCL), which are the most common form, in 40-80% cases, mucosa-associated lymphoid tissue (MALT), in 9-28%, follicular lymphomas (FL), in 10-19%, Burkitt's lymphomas (mainly occurring during pregnancy or lactation), in 1-5%; other (each < 1%) histological types include small lymphocytic lymphoma, mantle cell lymphoma, plasmablastic lymphoma, Hodgkin lymphoma, and peripheral T-cell lymphoma, namely anaplastic lymphoma kinase-negative T-cell lymphomas (BIA-ALCL), which are associated with breast implants.[3,4] The typical clinical presentation is a painless breast mass (median 4 cm diameter), slightly more frequently on the right side systemic symptoms present in <5% of patients, almost always those with disseminated disease. Approximately 70% of patients have stage IE disease,

with the other 30% having regional nodal involvement (stage IIE); from 4% to 13% of patients have bilateral breast involvement at presentation.[5,6] At relapse, PBL displays extranodal tropism; in particular, the ipsilateral and contralateral breasts are involved at relapse in 12-44%; central nervous system (CNS) recurrence is frequent (5-16%), expecially in bilateral PB-DLBCLs.[7] The standard treatment for newly diagnosed PB-DLBCL is R-CHOP for 6 cycles; a CNS prophylaxis is highly recommended.[5,7] A consolidation with ipsilateral radiotherapy 30 to 36 Gy should be considered, namely in cases with positive interim positron emission tomography.[8] BIA-ALCL is an uncommon and emerging T-cell lymphoma, most frequently arising around a textured surface breast implant. The clinical presentation is usually a delayed seroma around the breast implant, and manifests with breast pain, swelling or asymmetry, capsular contracture, but can also present with a breast mass, and lymph node or chest involvement.[9] The prognosis of BIA-ALCL is favorable; complete surgical excision for localized disease is an important part of the management of these patients.[9] In advanced stage, a combination therapy with Brentuximab-Vedotin plus CHP is recommended.[10]

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HIGH-RISK ACUTE MYELOID LEUKEMIA: FROM MICROENVIRONMENT IMMUNE LANDSCAPE TO IMMUNOTHERAPY

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Acute myeloid leukemia (AML) cell-intrinsic cytogenetic and molecular aberrations have always been considered the only determining factors in disease onset and progression. In recent years, this concept has been challenged, thus establishing that AML development also depends on BM microenvironment. Indeed, the interplay between leukemic cells and a variety of immune cells resulting in the dysregulation of both innate and adaptive immune response has been demonstrated to influence the disease outcome, being a crucial determinant of AML pathophysiology. In particular, an emerging body of evidence indicates that high-risk AML, especially TP53 mutated AML, may constitute a subset where such immune and inflammatory dysregulation is mostly pronounced and prominent. In this scenario, where cancer immunotherapy is rapidly changing the therapeutic armamentarium available to treat human solid and some hematological malignancies, a new era of immunological therapies has initiated also in the AML setting. Several immunological approaches have been tested, including antibody-based therapies and immune checkpoint/macrophage inhibitors, based on strong preclinical rationale and with promising early clinical results. However, further clinical interventions globally resulted in disappointing and dismals clinical data, despite some important exceptions. In this scenario, a possible explanation for these unsatisfactory results relies on a largely incomplete understanding of the interactions between AML cells and leukemia microenvironment and, very importantly, the lack of validated immunological targets, which represent major gaps and limitations for the advancement and optimization of effective and personalized immunological approaches in AML. The incorporation of immunotherapies within the backbone of AML therapy is certainly a mandatory step towards an optimization and full exploitation of such strategies. However, future immunotherapy studies should be designed in a way that immunologic and immunotherapy-specific biomarkers will be used to select those patients who have an increased probability to respond. In that, high-risk AML, whose treatment and clinical management represent an unmet medical need, should be considered a "fertile soil" for clinically developing a novel approach to immunotherapies, preferentially driven by the characterization of disease biology and immunological landscape.

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HOW CAN ALLOGENEIC STEM CELL TRANSPLANTATION BE OPTIMIZED IN PATIENTS WITH HIGH-RISK ACUTE MYELOID LEUKEMIA?

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Allogeneic stem cell transplantation (alloHSCT) is the most effective consolidation treatment modality for patients with acute myeloid leukemia (AML) since it decreases the risk of disease relapse in all cases. However, the risk of Non-Relapse Mortality (NRM) and Graft Versus Host Disease requires an accurate definition of disease and patient-re-

lated prognostic factors. Disease risk stratification utilizing genetic and measurable residual disease (MRD) technologies allows the identification of patients with high-risk acute myeloid leukemia (AML) with an estimated risk of relapse (>35%) if treated by chemotherapy alone. For all these patients an alloHSCT should be considered and eventually advised[1], at least in experienced transplant centers where the risk of NRM can be kept below the threshold of 20% at 2 years. Nonetheless, relapse occurs in a significant proportion of patients and remains the leading cause of transplant failure. Given the poor outcome of patients with relapsed disease, the development of new approaches to reduce the risk of post-transplant relapse is urgently needed. When considering all these variables, the improvement of the clinical outcome of patients undergoing alloHSCT will come from the following critical steps: 1. The initial treatment of each AML patient should start from the selection of the most appropriate induction/consolidation program taking into consideration the disease biology and patient's age.[2-4] Patients up to the age of 75 at diagnosis should be regarded as potential candidates for alloHSCT; 2. Immediate HLA typing and search activation for a donor (in the family and the registry including Cord Blood Units); 3. Increase the proportion of patients achieving a complete hematologic response after induction/early consolidation and optimize the supportive care to reduce the incidence of infectious complications; 4. Increase the remission quality by reducing MRD at conditionin;[5-6] 5. Selecting the most appropriate donor and keeping the time to transplant as short as possible; 6. Keeping a low NRM without compromising the antileukemic effect of the conditioning regimen; 7. Whenever possible and indicated, start an early post-transplant treatment with effective pharmacologic[7-9] or cell-based interventions.[10]

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SOLO LE CARATTERISTICHE BIOLOGICHE INFLUENZANO LA SCELTA TERAPEUTICA?

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Chronic lymphocytic leukemia (CLL) is usually a disease of the elderly, but chronological age does not accurately discriminate frailty status which instead describes the patient's resilience. Currently, we are in the era of targeted continuous and time-limed therapies, which have helped to control the disease and achieve long lasting remissions more effectively and to avoid the toxicity of chemoimmunotherapy (CIT).[1] However, these drugs are not free from side effects[2-3] and drugs interactions, comorbidities, or adherence to treatment should be considered when choosing between continuous or a time-limited therapy. The challenge we face is to balance the risk of toxicity and efficacy in a personalized way. In this line Geriatric assessment (GA) should be a standardized and reproducible tool used to evaluate the state of frailty beyond clinical observation[1]. Much of the evidence supporting the benefits of GA stems from the previous era in which CIT was predominant. One of the most used criteria for the assessment of fitness was presence of creatinine clearance <60ml/min and/or CIRS (Cumulative Illness Rating Scale) score ³6. Albeit several clinical trials have been designed specifically on these criteria, they failed to identify patients at higher risk of severe adverse events or treatment discontinuation since targeted therapies proved to be safe and effective also in "unfit" patients.[4-6] In a recent series of 712 patients with chronic lymphocytic leukemia (CLL) treated with BTKi outside clinical trials, baseline ECOG was the most accurate predictors of treatment feasibility and outcomes.[7] Age did not influenced survival and ibrutinib tolerance, indicating that not age per se, but age-related conditions, may affect drug management. The presence of a severe comorbidity was significantly associated with permanent dose reductions (PDRs), not translating into worse outcomes[7]. Instead, clinical outcome with venetoclax seems not influenced by CIRS or concomitant medications[8]. Among octogenarian patients PDRs were common but sustained and deep remissions were achievable.[9] Although most guidelines still suggest to select treatment according to the fitness status of the patients[10] no specific tool is recommended and treatment selection should be based on performance status, presence of specific comorbidities, availability of a caregiver, concomitant drugs and their interactions.

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MANAGMENT OF ACUTE PAIN IN SICKLE CELL DISEASE

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Sickle cell disease (SCD) is an inherited red cell disorder due to a single amino acid substitution at the sixth residue of the beta-globin subunit, resulting in the production of the pathological form of hemoglobin S (HbS). SCD is one of the most important hemoglobinopathies worldwide in terms of frequency and social impact.[1] The main clinical manifestations of SCD are chronic hemolytic anemia and recurrent acute vaso-occlusive crisis (VOCs), which are characterized by pain and ischemic/reperfusion organ damage. These are related to the entrapment of the sickled, dense red cells in the microcirculation associated with increased inflammatory response, vascular endothelial cell damage, and activation of the coagulation system.[2] Pain is a hallmark of VOCs and has different origins such as vascular or neuropathic. Pain and VOCs require early identification and a well-timed therapeutic intervention to halt the clinical course and abort the crisis, making patients with SCD high utilizers of emergency departments (EDs). The ED management of sickle cell-related VOCs consists of intravenous hydration and pain control with different molecules such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. The Scientific Italian Society for the study of Thalassemias and Hemoglobinopathies (SITE) has developed an algorithm to support ED healthcare professionals in the treatment of acute pain in patients with SCD.[3] The innovative aspect of SITE algorithm is the optimization of the pain management with multimodal analgesia. This is based on the administration of drugs with different pharmacological mechanisms of action and maximizing analgesia and minimizing their adverse events.[4-8] Ibuprofen and ketorolac are the most NSAIDs used for treating acute sickle cell-related pain. NSAIDs act at peripheral and central pain-mediated sites that are not involved in the opioid-mu receptor system pathways. When administered in conjunction with opioids such as morphine, NSAIDs are believed to have opioid-sparing effects, therefore, reducing the incidence of adverse events (*e.g.*: nausea/vomiting) in patients with acute, post-operative pain. Although morphine is the most widely used drug for pain management in ED, the parenteral route of administration, dosage, and the recurrency of the treatment may result in long-term drug addiction[9-10] and also in increased risk of chronic pain. Multimodal therapy is safe and effective during acute pain management in children and adults with SCD.

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VON WILLEBRAND FACTOR: A TWO-FACED JANUS

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Von Willebrand factor (VWF), a blood multimeric protein with a very high molecular weight, plays a crucial role in the primary haemostasis, the physiological process characterized by the adhesion of blood platelets to the injured vessel wall. Hydrodynamic forces are responsible for the VWF multiners conformational transitions from a globular to a stretched linear conformation. These characteristics render this protein a valuable object to be investigated by mechanochemistry, the biophysical chemistry branch that studies the effects of shear forces on protein conformation. This review will focus on the structural elements of the VWF molecule involved in the biochemical response to shear forces. The stretched VWF conformation favors the interaction with the platelet GpIb and at the same time with ADAMTS-13, the zinc-protease that cleaves VWF in the A2 domain, limiting its prothrombotic capacity. It is important to consider the level or the function of VWF or ADAMTS-13 always in relation each other, keeping in mind that in many thrombotic forms of microangiopathies the reduction of the ADAMTS-13/VWF ratio<0.5 can be a valuable parameter to predict a real thrombotic risk. Hence, a significant increase in VWF level alone, even without any reduction of ADAMTS-13 concentration, would still be responsible for a significant reduction of the ADAMTS-13/VWF ratio, which ultimately could reflect or predict a prothrombotic risk. This mechanism has been shown in some typical internal medicine diseases, such as liver cirrhosis and chronic thromboembolic pulmonary hypertension (CTEPH). Future studies will have to validate the concept whether ADAMTS-13/VWF ratio could a valuable and reliable biomarker to predict or confirm the presence of thrombotic risk in several morbid conditions.

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MANAGING BLEEDING COMPLICATIONS DURING ANTITHROMBOTIC THERAPIES

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In most Western countries, the number of patients taking antithrombotic agents (either oral anticoagulants, such as Vitamin K Antagonists, VKA and Direct Oral Anticoagulants, DOACs, or antiplatelet drugs) is steadily increasing, with an estimated prevalence of oral anticoagulant therapy (OAT) use around 1.5% of the general population.[1] A recent survey has demonstrated that the use of anticoagulant drugs is the leading cause of access to an emergency department because of outpatient adverse drug events.[2] We recently reported that the incidence of major bleeding in two Italian cohorts of patients taking OAT is 0.40 per 100 patient-years, meaning that every year, about one person in every 244 taking OAT is at risk of death or significant disability because of antithrombotic treatment. This figure may be even double when adding the burden of antiplatelet agents, however.[3] Consulting haematologists frequently face the dilemma of optimally managing bleeding complications in patients taking oral antithrombotic agents. This requires simultaneously assessing the bleeding severity, the need for drug reversal, and the optimal timing of antithrombotic resumption.

Appraising the bleeding severity. The degree of bleeding severity dictates the need for urgent interventions. As a practical rule, any cerebral or spinal bleeding requires immediate action, usually prompting the use of drug reversal with appropriate antidotes (if available). Drug reversal may be considered even before neurological imaging in the setting of a patient taking antithrombotic agents and a rapidly deteriorating consciousness state. Assessing the severity of gastrointestinal intestinal (GI) bleeding is more complex because, in most cases, the baseline haemoglobin level is unknown, and the dynamic of bleeding is consequently uncertain. Support with red blood cell concentrates, carefully monitoring the patient's life parameters, and endoscopic GI visualization are mandatory. Drug reversal should be considered in the face of rapidly falling haemoglobin values or in a frail patient with GI bleeding. Selective arterial embolization should also be considered in patients with retroperitoneal bleeding or in those patients with GI bleeding that could not be endoscopically treated. In patients with active bleeding, several clinical and laboratory parameters should be collected, such as standard clotting tests (PT, PTT, TT) and the plasma level of the assumed anticoagulant drug. The time of the last drug intake and the concomitant use of antiplatelet agents should also be obtained.

Drug reversal. While drug reversal should always be considered to control bleeding in high-risk patients, as previously discussed, it should be remembered that it simultaneously poses a thrombotic risk. This risk may be more relevant when using haemostatic-rebalancing agents (such as activated prothrombin complex concentrates or recombinant activated FVII [rFVIIa]) instead of specific drug antagonists. Stent thrombosis following platelet transfusion has been anecdotally reported, suggesting caution in the use of platelet concentrates as a reversal agent in patients receiving antiplatelet therapy.[4] The most specific antidote for each antithrombotic drug should be used for each patient (Table 1).

Vitamin K Antagonists. The most specific antagonist for this drug class is oral or intravenous vitamin K, generally at 5-10 mg.[5] Vitamin K is, however, too slow to obtain a prompt restoration of the acquired clotting deficiency induced by VKA. For this reason, prothrombin complex concentrates (PCCs) should be administered when immediate correction is required (*e.g.*, in patients with intracerebral hemorrhages). The usual suggested dose is 30-50 U/kg, administered as a single bolus infusion. Four-factor PCC concentrates more predictably normalize the INR and should be preferred when the INR is higher than three in bleeding patients. The thromboembolic risk following administration of PCCs appears to be reasonably low.[6]

Dabigatran. The monoclonal antibody idarucizumab specifically inhibits dabigatran, causing the complete disappearance of its antithrombin effect in >88% of patients immediately after the e.v. bolus infusion of two 2.5 g idarucizumab doses.[7] In the registration trial, one thrombotic event occurred within 72 hours after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated, suggesting the need for optimal antithrombotic resumption timing *(see below*).

Direct acting Factor Xa inhibitors (apixaban, edoxaban, rivaroxaban). The administration of an excess of 4-factors PCC (50 U/kg) has been traditionally suggested to restore thrombin generation in bleeding patients taking anti-FXa DOACs, mainly based on *ex vivo* studies. A more specific inhibitor, andexanet alpha - a modified recombinant FXa not exerting coagulant activity - may counteract the anticoagulant effects of DOACs by competing with endogenous FXa. In a recent trial comparing andexanet alpha to usual care (mostly PCC), andexanet alfa was associated with lower volume expansion of intracerebral hematomas but with an excess of thrombotic (particularly ischemic stroke) in those receiving andexanet alpha (10.3% *v*s 5.6%).[8] Therefore, the use of andexanet alpha may be considered in patients with an intracerebral haemorrhage, recent exposure to an anti-FXa drug, and a risk of neurological deterioration, provided that antithrombotic treatment is promptly resumed after bleeding control (*see below*). However, a recent meta-analysis failed to observe an improvement of 30-day mortality in patients receiving andexanet compared to those receiving 4-factors PCC.[9]

Optimal timing of antithrombotic resumption. As mentioned above, a common finding across several clinical studies is the recurrence of thromboembolic events in the first month after an antithrombotic agent's suspension and/or reversal because of a bleeding complication. There is no definite evidence about the optimal timing of resumption of the antithrombotic drug, and the decision should be weighed against the pre-existing thrombotic risk (*e.g.*, a high CHA_2DS_2-Vasc score in patients with atrial fibrillation, or a very recent thromboembolic event). Once bleeding control has been achieved, it is, however, mandatory to resume an antithrombotic treatment. This may require serial imaging of intracerebral or retroperitoneal hematomas and demonstration of the stability of their volumes. A suggested window for resumption after major bleeding events is after 7-14 days but no later than 6-8 weeks.[10]

Patients with concurring blood disorders. A particular case is the management of bleeding episodes in patients with blood disorders taking an anticoagulant therapy. Other than the previously mentioned measures, platelet count should be checked and maintained above a target value of at least 50 $x10^9$/L. Bruton-type tyrosine kinase inhibitors (BTKi) should be suspended until complete recovery of the bleeding episode, with sub-

sequent re-assumption of BTKi therapy at a lower dosage or a switch to another drug class.

Table 1. Main antidotes for DOACs.

Antidotes	Dabigatran	Apixaban, Edoxaban, Rivaroxaban	Dose, comments
Activated Charcoal	Yes	Yes	25-100 gr orally, if ingestion <2hr
Tranexamic Acid	Unclear	Unclear	10-15 mg/kg e.v., no studies on DOAC, but good safety profile
Haemodialysis	Yes	No	Urgent removal of dabigatran excess – may be considered if idarucizumab failure
aPCC	Unclear	Unclear	Probably beneficial for all DOACs; concerns about safety should discourage its use
4F-PCC	No	Unclear	50 IU/kg, possibly beneficial for Factor Xa inhibitors
rFVIIa	Unclear	Unclear	Possibly beneficial for all DOACs; concerns about safety should discourage its use
Idarucizumab	Yes	No	Specific antidote for reversal of dabigatran
Andexanet alfa	No	Yes	Specific antidote for anti-FXa drugs

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EMERGENCY MANAGEMENT OF ACQUIRED COAGULATION INHIBITORS

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The occurrence of acquired coagulation inhibitors (ACI) is a rare but potentially life-threatening syndrome, characterized by sudden bleed in patients without an history of hemorrhagic diathesis and previously normal hemostasis tests.[1,2] Table 1 summarizes the main steps to diagnose the specific factor defect.

Table 1. Diagnostic approach to a suspected case of acquired factor inhibitors.

- Perform accurate anamnesis to exclude inherited bleeding disorders and/or ongoing anticoagulant treatments.
- Perform baseline complete blood count, PT, APTT, fibrinogen, D-dimer (to exclude DIC).
- If the patient is taking a Direct Oral AntiCoagulant (DOAC) perform specific tests to assess its plasma concentration. DOAC can mask a bleeding diathesis due to acquired coagulation inhibitors.
- If PT and/or aPTT are prolonged, perform mixing studies, using a 1:1 mix of patient plasma with normal plasma. Whereas a correction of an initially prolonged test result will occur in the case of a factor deficiency, an inhibitor will not permit complete correction of the prolonged test result in the mixing test. FVIII inhibitors may show a time dependency for inhibition, so the mixing test should be performed after a two-hour incubation of the sample. Other inhibitors do not generally show such a dependency, and immediate mixing studies should still be effective for their identification.
- Assess abnormal results and findings of mixing tests to determine need for and type of factor and/or inhibitor assays.

The most common autoimmune acquired bleeding disorder is Acquired Haemophilia A (AHA), due to autoantibodies inhibiting factor VIII.[2] AHA is characterized by muscle and soft tissue hematomas, leading to severe anemia and compression of nerves and vessels up to compartment syndrome. Life-threatening hemorrhages (gastrointestinal bleeding, retroperitoneal hematoma, or intracranial hemorrhage) may also occur [Table 2]. Minor bleeds (*i.e*, gingival bleeding, epistaxis, and metrorrhagia) can be managed by local hemostatic measures, together with tranexamic acid (TXA), systemically or topically given. TXA should be avoided in case of urinary tract hemorrhages. Specific hemostatic treatment with bypassing agents, *i.e.* recombinant activated factor VII (rFVIIa) or Activated Prothrombin Complex Concentrates (APCC) is required in case of organ- or life-threatening bleeding 3]. Other options include Recombinant Porcine Factor VIII and emicizumab, a monoclonal antibody mimicking the function of activated FVIII.[3]

Immunosuppressive treatment with Prednisone, alone or in combination with cyclophosphamide, should be started along with the diagnosis of AHA.[3]

Immune Acquired Von Willebrand Syndrome [AVWS] is due to autoantibodies that increase VWF clearance, often associated with IgG/IgM MGUS or autoimmune diseases.[4] Bleeding in AVWS is usually mild and mainly mucocutaneous. In case of severe bleeding, the co-administration of VWF/FVIII concentrates and high-dose intravenous immunoglobulin (HDIVIG) increases the half-life of VWF/FVIII. HDIVIG alone require 24-48 hours to increase the endogenous VWF/FVIII:C levels; moreover, they have little effect in IgM MGUS-related cases.[4] Few cases of ACI to FV, FVII and FX have been described.[5-7] Clinical features and haemostatic and immunosuppressive treatments are reported in Table 2. Autoantibodies against coagulation factors II, IX, XI and XIII are extremely rare.[1] The principles of

management are the same of others ACI. Patients with ACI should be referred to specialized centers, to ensure the most appropriate treatment of bleeding along with the best global management.

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Table 2. Laboratory, Clinical Features and Management of Acquired Factor Inhibitors.

Coagulation Factor Defect	Baseline hemostasis tests*	Bleeding diathesis	Emergency management In case of Major Bleeding**	Notes
Acquired hemophilia A (Factor VIII)	↑↑ aPTT = PT	Muscle and soft tissue hematomas, leading to severe anemia and/or compartment syndrome Life-threatening hemorrhages (gastrointestinal bleeding, retroperitoneal hematoma, or intracranial hemorrhage) Joint bleeds are rare	Bypassing agents: rFVIIa 90-120 mg/kg every 2-3 hours APCC 50-100 U/kg every 8-12 h	Immunosuppressive therapy with prednisone (1-2 mg/kg daily) alone or with cyclophosphamide(1-2 mg/kg daily) ideally started immediately after the diagnosis Rituximab (375 mg/m^2 once weekly for 4 doses) can be also considered
Acquired Von Willebrand Syndrome (AVWS)	= / mildly ↑ aPTT = PT = / mildly ↓ vWF:Ag ↓↓ vWF:RCo	Usually mild , mainly mucocutaneous	HDIVIG 1g/kg per day for 2 days + Plasma-derived concentrates containing VWF, 30 - 100 VWF:RCo units/kg	Mainly due to Ab increasing factor clearance, rarely to inhibiting auto-antibodies HDIVIG ineffective in IgM MGUS-related cases.
Acquired Factor V inhibitors	↑ aPTT ↑ PT	Major bleeding rare Usually mild bleeding : muscle haematoma, epistaxis, gingival bleeding, haematuria, gastrointestinal bleeding, uterine bleeding	Fresh frozen plasma has little effect Platelet transfusion, APCC and rFVIIa..	Immunosuppressive treatment not required in drug-related cases If inhibitor eradication required: corticosteroids, cyclophosphamide, HDIVIG, rituximab
Acquired Factor VII inhibitors	= aPTT ↑ PT	Half of cases asymptomatic Severe bleeding also reported (vaginal bleeding, pulmonary and digestive tract haemorrhage, haematuria and intracerebral haematomas)	rFVIIa 90 g/kg daily for 2 days	Few cases reported Mainly due to Ab increasing factor clearance Acquired FVII deficiency does not respond to vitamin K therapy
Acquired Factor X Inhibitors	↑ aPTT ↑ PT	Bleeding often severe, involving subcutaneous tissues, lower intestinal (62%) and urinary (52%) tract	PCC ≈50 IU/kg	Mainly occurring in association with AL amyloidosis. Only few cases associated to circulating inhibitor Inhibitors eradication required

*Mixing test does not correct baseline hemostasis tests
**Always ensure local hemostatic measures, volume resuscitation, blood product transfusion when appropriate

aPTT: activated Partial thromboplastin Time; PT: Prothrombin Time; rFVIIa: recombinant activated Factor VII; APCC: Activated Prothrombin Complex Concentrates; vWF:Ag: von Willebrand Factor Antigen; vWF:RCo: von Willebrand Factor Ristocetin Cofactor; HDIVIG: high-dose intravenous immunoglobulin; MGUS: Monoclonal Gammopathy of Unclear Significance; PCC: Prothrombin Complex Concentrate

HEREDITARY DYSERYTHROPOIETIC ANEMIAS

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The hereditary dyserythropoietic anemias (HDAs), commonly referred to as congenital dyserythropoietic anemias (CDA), are a group of inherited blood disorders marked by abnormal erythroid development, resulting in ineffective erythropoiesis.[1] These conditions often present with anemia, signs of hemolysis, and a disproportionately low reticulocyte count. A frequent complication is secondary hemochromatosis due to increased iron absorption.[2] The severity of HDAs can range from severe cases in infancy to subtle or absent symptoms in adulthood. Consequently, the term "congenital" might be misleading, as clinical signs of the disease may not emerge until later stages of life. Diagnosing HDAs generally involves a multi-tiered approach, starting with basic assessments like complete blood counts and evaluation of hemolysis and iron overload. This is followed by a detailed morphological examination of the bone marrow and genetic testing to identify any relevant mutations. Traditionally, HDAs have been categorized into three main types - CDA I, II, and III - based on specific morphological features in the bone marrow.[1] However, such features are not exclusive to HDAs and can appear in other conditions that cause erythropoietic stress, complicating the diagnosis. Advancements in genomic sequencing have enhanced the understanding of HDAs.[3] Over ten genes involved in erythrocyte development have been linked to HDAs, underscoring the role of genetic testing in accurate diagnosis. This testing has led to diagnostic revisions in 10-40% of cases initially suspected to be CDAs, revealing other underlying conditions such as pyruvate kinase deficiency.[4-6] Moreover, research has expanded beyond the traditional types of CDAs to include transcription-factor-related and syndromic forms.[2] Recent studies have explored the specific impact of certain gene mutations on iron metabolism and erythroid differentiation, particularly mutations in *SEC23B* and *CDIN1,*[7,8] and have identified new HDA forms linked to variants in *VPS4A* and *RACGAP1* genes.[9,10] These findings are guiding the development of targeted treatments, which currently consist mainly of supportive care tailored to the severity and specific features of the disease. Comparisons with other erythrocyte disorders, such as pyruvate kinase deficiency, are shedding light on new potential therapeutic pathways by clarifying the underlying mechanisms of iron dysregulation and ineffective erythropoiesis.

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DEFICIT ENZIMATICI: NUOVE PROSPETTIVE

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Pyruvate kinase deficiency (PKD) is a rare congenital hemolytic anemia due to mutations in the *PKLR* gene, characterized by inefficient glycolysis, insufficient ATP levels and chronic hemolysis. The disease is inherited as autosomal recessive, and is diagnosed by a reduced PK enzyme activity, and by the identification of two causative mutations in the *PKLR* gene by molecular analysis. The clinical presentation is highly heterogeneous and includes variable degree of anemia, fatigue, jaundice, hepatosplenomegaly, cholelithiasis, and iron overload (both in transfused and not transfused patients). More rare manifestations are osteopenia and osteoporosis, aplastic crisis, extramedullary hematopoiesis, endocrine disease, lower extremity ulcerations, pulmonary hypertension, and thrombotic complications (all in splenectomized). All these manifestations deeply affect quality of life in patients with PKD. Therapy of PKD has been historically limited to supportive care with transfusions and splenectomy. The former are recommended based on anemia symptoms and complications rather than a universal hemoglobin threshold. Splenectomy is recommended in children older than 5 years and adults who require regular or frequent RBC transfusions, or who have symptomatic anemia after discussion of the individualized risks and benefits, particularly the lifelong risk of sepsis and thrombosis. Nowadays, mitapivat an oral allosteric PK activator, is available for adults with PKD (approved by the FDA and EMA). The open label and the randomized versus placebo clinical trials have demonstrated sustained improvements in anemia and quality of life, with reduced hemolytic features and ineffective erythropoiesis and in about 50% adults with PKD. Response is rapid and occurs through different doses but is observed only in patients with at least one-missense mutation. Mitapivat is also effective in transfusion-dependent patients (37% had a reduction of transfusions > 33%, and 22% became transfusion-free). Clinical trials in children are ongoing. Other PK activators are under investigation. An additional experimental treatment for PKD is gene therapy, which is currently under evaluation in clinical trials, with preliminary positive results. Allogenic hematopoietic stem cell transplantation has been performed in few severe cases, without encouraging outcomes (38% graft-versus-host disease grade 4, 65% three-year cumulative survival, and 31% transplant-related death).

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DIAMOND BLACKFAN SYNDROME (DBAS)

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DBAS is a pure erythroid dysplasia characterized by macrocytic anemia, reticolocytopenia and bone marrow erythroblastopenia. Sixty % of the patients present with congenital malformations. They also show an increased risk of cancer, including solid tumors. Because several patients do not show any symptoms, the main tool for diagnosis is the genetic test. Eighty % of the patients carry mutations in the 28 DBAS genes. In the others the diagnosis is made on clinical features, after exclusion of differential diagnoses. Twenty-four genes encode for ribosomal proteins (RP), 2 for chaperones involved in RP nuclear import (*TSR2, HEATR3*). *GATA1* and *TP53* are rarely mutated. The most common gene is *RPS19* (25%). Transmission is autosomal dominant for RP genes, X-linked for *GATA1* and *TSR2*, autosomal recessive for *HEATR3* .[1]

Loss of treatment dependence is shown by 20% of patients and in several cases is due to clonal hemopoiesis and the proliferative advantage of a revertant clone.[2]

Bone marrow failure is due to the hypoproliferative and proapoptotic phenotype of erythroid progenitors, that are sensitive to nucleolar stress, activated by the altered ribosome biogenesis, and resulting in p53 stabilization. The cells show a reduced number of active ribosomes, that differentially translate certain transcripts, *e.g.* the main erythroid transcription factor GATA1. The reduced general protein synthesis creates an imbalance between globin and heme synthesis. Consequently, the heme accumulates in erythroid precursors exerting a pro-oxidant effect.

Intriguingly, DBAS, that is characterized by hypoproliferation, shows a moderate cancer risk. The continuous activation of p53 may favor clones that somatically acquired an inactivating mutation of *TP53*. The loss of the second *TP53* allele may start tumor progression.[3]

Treatment includes chronic steroid administration or chronic transfusion with iron chelation for the patients who do not respond to steroids. HSCT shows a good outcome in transfusion-dependent children, but not in adults.[1] Gene therapy will be available soon, as an intense scientific effort is ongoing in preclinical studies.

The improvement in the treatment and follow-up of pediatric patients has posed new challenges for the adult hematologist, that provides lifelong care for these patients in adulthood. Multidisciplinary care is needed, and the main aims are prevention of the iron overload complications and cancer surveillance.[4]

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BLAST AND BLAST EQUIVALENTS IN THE MORPHOLOGICAL DIAGNOSIS OF MYELOID NEOPLASMS

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Despite advances in the molecular and genetic landscape, understanding of myeloid neoplasms (MNs), morphological evaluation still plays a crucial role in the diagnostic process. This is particularly true for major types of hematopoietic neoplasms, such as Acute Myeloid Leukemia (AML), Myelodysplastic Syndromes(MDS),and Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN). The diagnostic criteria outlined in the fourth and fifth editions of the WHO classification continue to emphasize morphological, cytochemical, and immunophenotypic characteristics of blast cells to determine their lineage, along with identifying genetic abnormalities. These newer criteria allow for an AML diagnosis with fewer than 20% blasts under certain genetic conditions or with more than 10% blasts according to the WHO fifth edition[1] or the International Consensus Classification[2] (ICC), respectively. Some criteria for defining blast cell morphology have been updated from previous classifications to provide a more precise definition of "blast cells". This precision is essential for categorizing MNs and predicting their prognosis. To improve the enumeration of blast percentages, the counting of "blast equivalents" has been introduced.

Morphology:

Promonocytes in acute monoblastic/monocytic leukemia and chronic myelomonocytic leukemia are characterized by slightly condensed nuclear chromatin, variably prominent nucleoli, and abundant, finely granular blue/gray cytoplasm, which may be vacuolated.

Megakaryoblasts in acute megakaryoblastic leukemia exhibit highly variable morphologic features. These cells often resemble lymphoid cells with a high nuclear-to-cytoplasmic ratio, fine to variably condensed nuclear chromatin, and cytoplasm that may be scant to moderate, usually agranular or containing few granules. Cytoplasmic blebbing or budding may also be evident.

Abnormal promyelocytes in acute promyelocytic leukemia typically have a reniform or bilobed nucleus. Their cytoplasm can range from heavily granulated with bundles of Auer rods to virtually agranular.

Erythroid precursors (erythroblasts) are not included in the blast count except in rare instances of "pure" erythroleukemia[3]

Conclusion The morphology should be considered as a kind of "gold-standard" starting point for the more accurate preliminary classification of MNs,pending integration with detailed genetic information according to the WHO 5th and the ICC.

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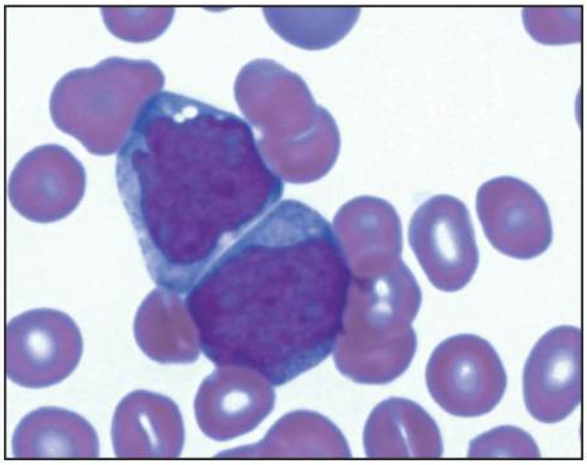

Figure 1. (MGG 1000x) Blast equivalent Promonocytes.

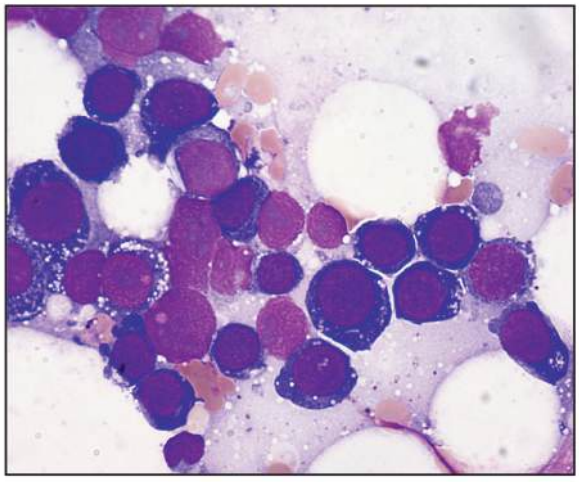

Figure 2. (MGG 5000x) Pure Erithrod Leukemia.

HOW TO IMPLEMENT EARLY PALLIATIVE CARE FOR PATIENTS WITH ACUTE MYELOID LEUKEMIAS/ MYELODYSPLASTIC SYNDROMES

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Acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) are largely incurable, with a 5-year survival rate that remains below 40% despite recent advances in treatment[1]. In addition, the course of these diseases remains physically and emotionally challenging. Patients often have a high burden of physical and psychological symptoms and a high use of avoidant coping strategies.[2,3] For patients with advanced solid tumours, the integration of early palliative care (EPC) into standard oncological care from the time of diagnosis has shown several benefits, including prolonged survival.[4] Recent studies have reported that EPC is feasible for AML patients in both inpatient and outpatient settings.[5-7] Specifically, the EPC intervention improves quality of life, promotes adaptive coping, reduces psychological symptoms, improves quality of care and reduces aggressiveness at the end of life.[5-7] It has been advocated that EPC should become the new standard of care for AML patients.[5] The results of these studies have been recognised by the Società Italiana di Ematologia (SIE), which in its latest guidelines for AML patients aged >60 years recommends that "...if possible, early involvement of the palliative care team...to promote simultaneous intervention by the haematologist and the palliative care specialist".[8] To implement such a model of care for all patients with AML/MDS and to extend it to patients with other haematological malignancies (HM), several steps are required. Firstly, haematologists need to recognise that EPCs are an additional layer of support for their patients and need to be involved in the care pathway in the same way as other specialties. Second, EPCs can help haematologists manage patients and support them throughout the disease process. Thirdly, the training of EPCs should be improved by increasing the number of master courses and speciality schools. In this regard, in Italy, the discipline of haematology should be recognised and included in the training network of the Italian School of Specialisation in Medicine and PC.[9] Finally, the extension of this model of care to a larger number of haematology patients, while training is still under development, could lead to demand exceeding supply. Therefore, it is necessary to identify criteria to determine the optimal timing for the integration of the EPC in the specific treatment pathways of different HM, in order to move from an early to a needs-based model.[10]

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RICHTER TRANSFORMATION: DIAGNOSIS, PROGNOSIS, CURRENT AND FUTURE THERAPEUTIC SCENARIOS

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Richter transformation (RT) is a complication of chronic lymphocytic leukemia (CLL) characterized by the development of an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).[1] It is a rare event that can occur at any point in the course of CLL, regardless of treatment status. Several risk factors for transformation have been identified, including chromosomal abnormalities, particularly the presence of high structural or numeric karyotype complexities, TP53 aberrations, NOTCH1 mutations, unmutated IGHV status, and stereotyped BCR usage. Currently, it is unclear whether treatment may favor transformation, and whether the incidence of RT has changed since the development of small molecule inhibitors is currently under investigation.[2,3] The diagnosis of RT typically involves a sudden clinical deterioration, with rapidly enlarging lymph nodes/asynchronous progression, systemic symptoms, and elevated lactate dehydrogenase levels.[4] Histopathological confirmation via biopsy is essential for diagnosis, as it distinguishes the histologic type of transformation and differentiates RT from other causes of disease progression, such as accelerated CLL or infections. FDG PET/CT is a helpful diagnostic tool in RT. In suspected cases, a SUVmax of ≥5 has high sensitivity, with increased specificity when the threshold is raised to ≥10, and may guide the biopsy to the area with the most intense uptake.[5,6] Prognostically, RT is associated with poor outcomes, with a median overall survival of less than 1 year.[7] Prognostic features include the presence of TP53 mutations, prior CLL treatment status, ECOG-performance status and response to treatment.[7,8] Determining the clonal relationship between DLBCL and CLL is crucial for assessing patients' prognosis and establishing treatment. About 80% of patients with RT are clonally related to the underlying CLL, exhibiting poor or no response to standard chemoimmunotherapy. In contrast, patients with clonally unrelated disease may benefit from DLBCL-directed therapies.[8] Recent advances in the treatment of RT have focused on targeted therapies and combination regimens. Novel agents such as pathway inhibitors, checkpoint inhibitors, bispecific antibodies, chimeric antigen receptor T-cell therapy are under investigation and show promise in improving outcomes.[9] Additionally, ongoing research is exploring the role of personalized medicine approaches, potentially offering new hope for patients with this challenging condition.

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LINFOMI PRIMITIVI CUTANEI DI DERIVAZIONE B LINFOCITARIA

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According to the WHO-EORTC classification 2018, included in the WHO 2023, primary B-cell lymphomas (CBCL) consist of indolent forma (follicle center ly. FCL; and marginal zone ly, MZ, with 60% 5- and 10-year survival) and more aggressive forms (diffuse large B-cell lymphoma, leg-type. DLBCL-LT, with <60% 5-year survival) the DLBC, NOS entity is discussed. Yet, their histogenetic profile (germinal center-like vs ABC-like) seems heavily conditioning prognosis. The prognostic significance of the primary site of localization (leg *vs* non-leg) and bcl2 protein expression is still debated. Concerning staging, bone marrow biopsy has to be considered optional in indolent entities, if not indicated by other work-up procedures, while it is always indicated in DLBCL. The treatment of choice in CBCL is radiotherapy in all patients with loco-regional extension of disease, with should be limited to pts. with single lesions and high risk of toxicity to systemic treatment in DLBCL. Systemic chemo(immuno)therapy is generally indicated in DLCBL, while in indolent forms it should be restricted to pts. with multiple lesions in non-contiguouos skin sites.

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THROMBOSIS IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA: A THORNY, NOT UNLIKELY CLINICAL CHALLENGE

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Immune thrombocytopenia (ITP) is a rare autoimmune disorder with potential dangerous bleeding risk, mainly but not only related to low platelet count. Nonetheless, in the last decades a closer observation of these patients has raised awareness of their somehow unexpected high risk of thromboembolic events (TE). Data published before the availability of Thrombopoietin receptor agonists (TPO-RA) showed that the annualized risk of venous thromboembolism (VTE) in ITP patients seems variable between 0.41 and 0.67, despite the different study designs, compared with a correspondent range in control population variable from 0.20 to 0.42.[1-5] Similarly, a mild but notable increase of arterial thrombotic events (ATE) has been also described in patients with ITP, with an incidence of 0.96 to 1.15 per 100 persons/years.[5] The increase of VTE and ATE in patients with chronic ITP is mainly related and modulated by additional factors such as age, cardiovascular risk factors and underlined comorbidities[5,8] but the impact of pharmacological and surgical treatment of ITP should be considered as not negligible. (Figure 1). In some retrospective cohort studies, splenectomized patients showed an increased risk (2 to 4 – fold) of TE. Moreover, patients presenting with antiphospholipid autoantibodies (APA) single, double or triple positivity seems to be at higher risk both of VTE and ATE in general population, but the role of these antibodies in increasing the TE risk in ITP patients is a matter of debate, because cohort studies[5,6,7] didn't show a close relationship between APA and TE in ITP patients. Recently a new class of drug has been used in patient with chronic ITP: fostamatinib, an inhibitor of spleen tyrosine kinase (Syk), unlike other treatments, has not demonstrated an increase in thrombotic risk in pivotal clinical trial[9] and may thus be considered for patients at higher thrombotic risk.[10] If fostamatinib, with its distinct mechanism of action, does not induce the prothrombotic state seen with TPO-RAs, has to be assessed collecting many data both in clinical trial and in real word clinical practice. With the help of real clinical cases we will focused on general consideration and suggestions about the management of acute TE in ITP patients (Figure 2) with ongoing treatment for their thrombocytopenia, but also about the role of prophylaxis of TE between bleeding and thrombotic risk, and how to select ITP treatment in patients at higher thrombotic risk.

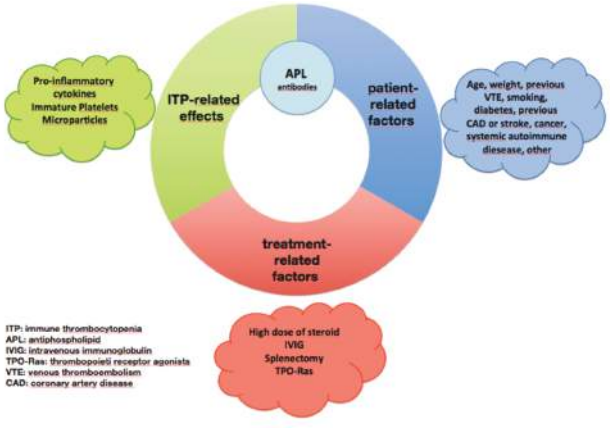

Figure 1. Thrombotic risk in ITP patients: main effectors.

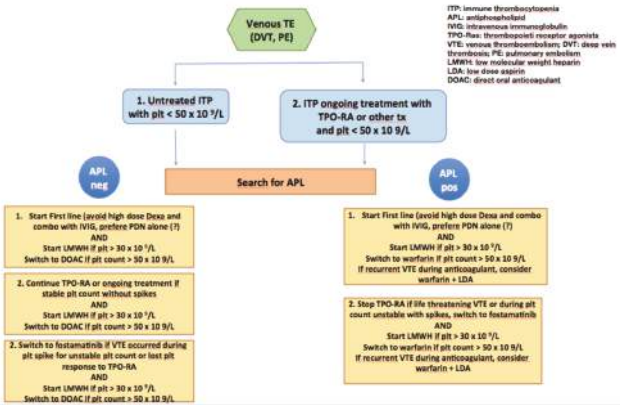

Figure 2. Prosposed management of Venous thromboembolism in ITP patients (personal view).

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HIGH RISK-AML. INTENSIVE CHEMOTHERAPY *VERSUS* NON-INTENSIVE THERAPY, WHICH CHOICE?

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High-risk acute myeloid leukemia (HR-AML), according to the ELN 2022 classification, accounts for approximately 35% of all AMLs worldwide and is associated with a poor prognosis, with a 5-year OS probability of 15% (9-10% if only patients older than 60 years are considered).[1-3] Nevertheless, there are no specific guidelines or recommendations for treatment of the fit patients with HR-AML subset. What is clear is that the efficacy of the 3+7 regimen in this HR population is unsatisfactory.[4,5] Comparative analyses between first-line intensive chemotherapy (IC)

and non-intensive therapy (NIT) in fit AML-HR are still very limited and are mainly derived from observational and retrospective studies in which the compared populations often differ in age, fitness, follow-up and AML biology, limiting the power of the results.[6] Regarding IC in fit HR-AML, one of the most tested and effective drugs is CPX-351 with a significant improvement in OS compared to 3+7 regimen, particularly in allogeneic SCT (Allo-SCT) recipients compared to those who did not receive transplant.[4] Other emerging IC regimens in this setting are FLAI+Venetoclax and CLAI+Venetoclax.[7] The therapeutic role of Allo-SCT is well established and the inclusion of Venetoclax in both IC and NIT regimens prior to allo-SCT is becoming increasingly important.[8-10] To date, the use of hypomethylating agents plus Venetoclax (HMA-VEN) in fit HR-AML patients who are also candidates for IC is being studied prospectively, but is not yet recommended outside of clinical trials. Retrospective studies suggest populations that may have a benefit from HMA-VEN over IC, but this is not yet prospectively confirmed.[6] The use of HMA-VEN prior to Allo-SCT is also under investigation, and some data indicate feasibility and ability to achieve pre-transplant measurable residual disease (MRD) negativity.[10] Upcoming prospective randomized clinical trials will evaluate HMA-VEN versus IC in fit HR-AML patients and its potential use as a standard pre-transplant induction regimen, particularly in patients older than 60 years. In this challenging setting of AML, work is in progress but we are hopeful that new and improved therapeutic options will be available in the near future.

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THE IMPACT OF GUT MICROBIOME IN HEMATOLOGIC MALIGNANCIES

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The gut microbiome (GM) has emerged as a key factor in the genesis and progression of many diseases. A large literature now supports the complex interlink between the GM and hematopoietic stem cells as well as differentiated myeloid and immune cells, both in steady-state and in pathological conditions. In particular, the microbiome communities have been suggested to influence the development and progression of hematologic malignancies, with specific GM configurations potentially contributing to the multistep developmental hypothesis for leukemogenesis and lymphomagenesis.[1] While causal evidence of microbial impacts on cancer biology is only beginning to be unraveled, enhanced biological understanding can potentially open up microbiome-based strategies for hematologic cancer prevention. Moreover, the intestinal bacterial composition also influences treatment-related side effects and even the efficacy of oncological therapies. GM alterations occur during chemotherapy course are associated with treatment-related complications, especially infections.[2] Moreover, growing literature is suggesting that GM configuration can be a predictor of response and toxicity to immunotherapy and cellular therapy, mainly immune checkpoint blockade with mono-clonal antibodies targeting PD-1 and CAR-T cells.[3,4] Allogeneic hemopoietic stem cell transplantation (allo-HCT) exerts a profoundly destructive effect on the composition and function of GM. Changes in GM influence the development of infections, graft versus host disease (GvHD) and endothelial complications, mediated mainly by the metabolites produced by the GM, such as short-chain fatty acids, secondary bile acids and indole derivates[5]. Lower ecosystem diversity prior to HCT at the time of neutrophil engraftment correlates with reduced overall survival in children and adults[6,7]. The reduction of commensal species, such as *Blautia*, and the growth of potential pathogens, such as *Enterococcus*, are correlated with the development of lethal graft versus host disease.[8,9] The GM also has a fundamental impact on post-transplant immune reconstruction and immune cell dynamics[10]. Growing evidence regarding the correlation between gut dysbiosis and transplant complications underscores the possible therapeutic implications of targeting the intestinal ecosystem (Figure 1). Potential strategies for modulating the GM are considered optimization of antibiotic administration, use of enteral nutrition and fecal microbiota transplantation.

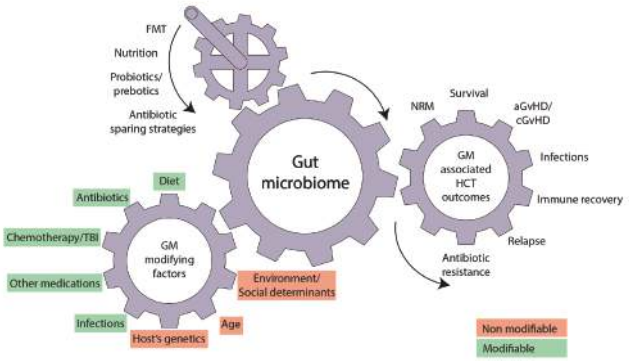

Figure 1. Factors implied in GM configuration during allo-HCT.

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SECONDARY CANCERS AFTER CAR-T

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Chimeric antigen receptor T cell (CART) immunotherapy is gene-modified cellular therapy, highly effective treatment for hematological malignancies. Nowadays six products are commercially available with a growing number of treatment indications. Thanks to this effective treatment a significant proportion of patients can be considered cured for their disease. However, this population is still at risk to develop short term and long term adverse events following this treatment. In particular, due to the genetic modification of the infused cells, people receiving CART are considered at risk to develop T cell lymphomas. Moreover, as a recently approved treatments, little is known about the potential risk to develop second primary malignancies after treatment infusion. Therefore understanding the risk of second primary malignancies development after CRAT, and the potential mechanisms facilitating them is mandatory to optimize this treatment and the follow up ot the treated patients.

In this lecture we will review the most updated data about the second primary malignancies development after CART. Up to date, very few T cell lymphoma cases after CART have been reported. Indeed, only in four cases CAR transgene was detected in neoplastic cells and no specific genetic lesions directly related to CAR insertion were identified to promote the malignant transformation. Also for CAR-negative T cell lymphoma cases, no specific risk factors have been identified, with a potential promoting role on inflammation or lymphocyte precursors abnormalities. Nevertheless, CART patients have higher incidence to develop hematologic and solid neoplasms. However, the rate of the incidence of these second primary malignancies seems similar to the rate expected in the same population after exposure to chemotherapy.

In conclusion, the analysis of second primary malignancies after CART is still an open research field and more studies are needed to fully understand the mechanisms behind this rare phenomenon.