LEUKEMIA2022

Rome, Hotel NH Collection - Vittorio Veneto

May 5-6, 2022

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UNDER THE AUSPICES OF:

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

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Post-MPN acute leukemia: a persistently unmet need

Paola Guglielmelli

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Università di Firenze

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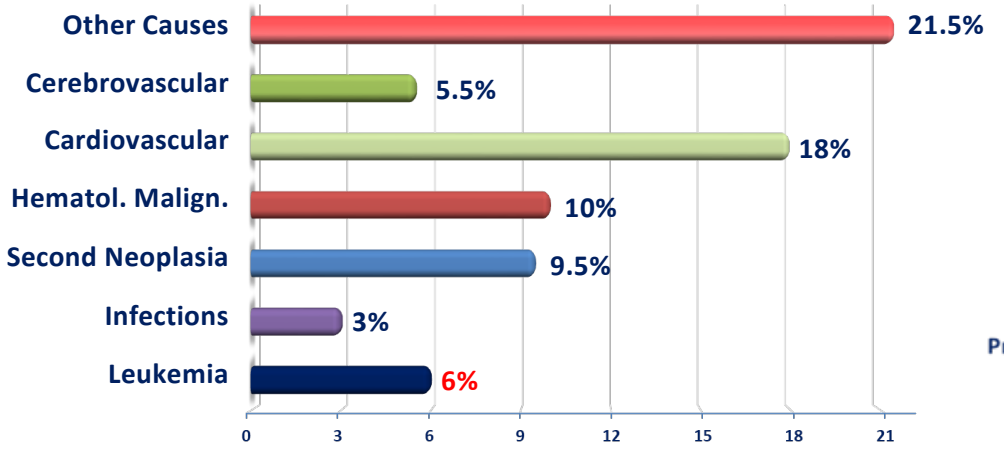
Disclosures
Paola Guglielmelli

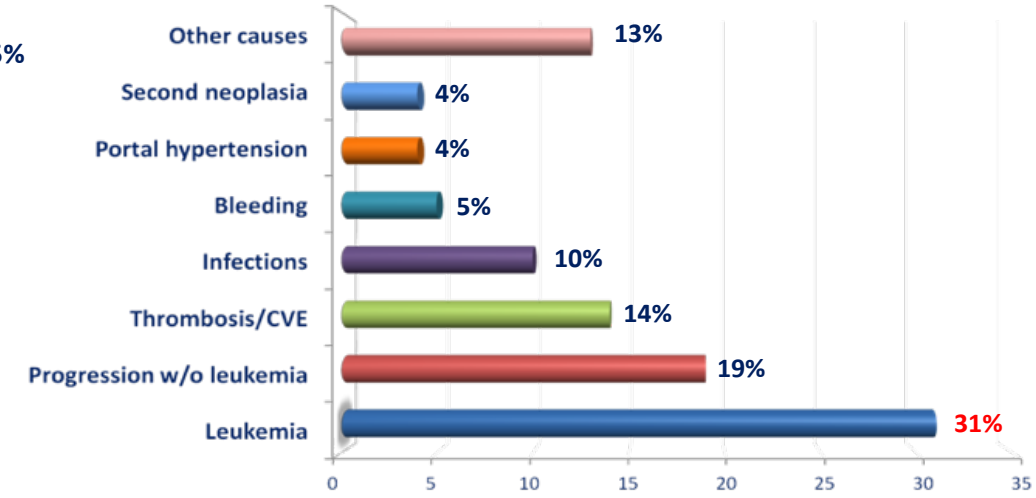
- Relevant financial relationships with a commercial interest:
  - **Novartis:** Advisory board. Speaker fee.
  - **AbbVie:** Advisory board.

Cause of Death in MPNs

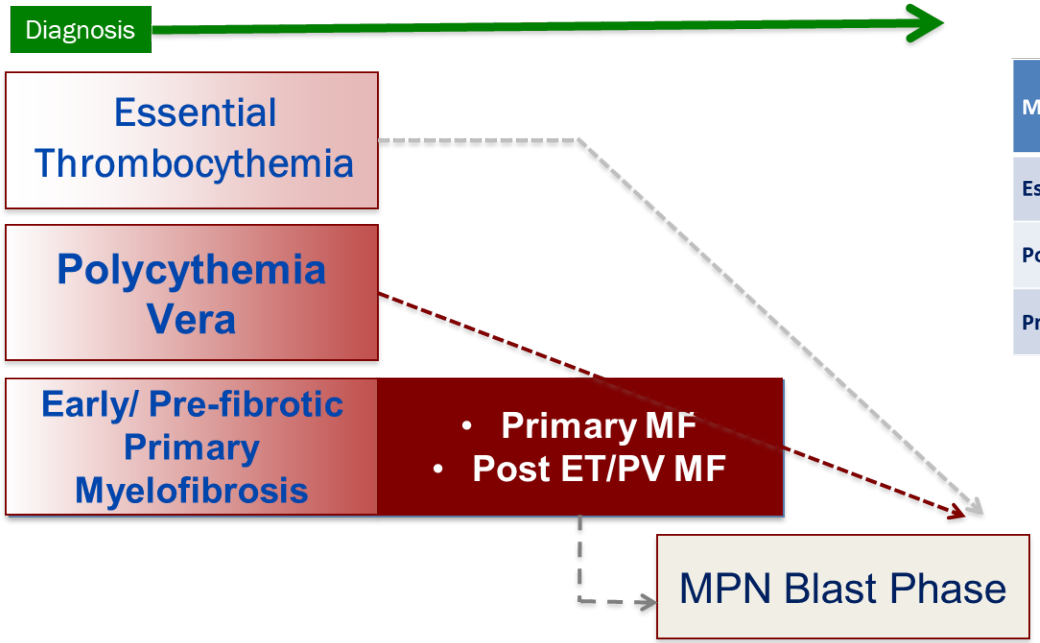
Essential Thrombocythemia
Polycythemia Vera



Primary Myelofibrosis
Post ET/PV Myelofibrosis



Leukemic Transformation in MPN



MPN subtype	Incidence after 10yrs	Overall Risk of AML Transformation (95%CI)
Essential Thrombocythemia	2-5%	24.7 (17.3-34.2)
Polycythemia Vera	5-10%	33.0 (27.8-38.9)
Primary Myelofibrosis	8-20%	63.8 (42.7-91.6)

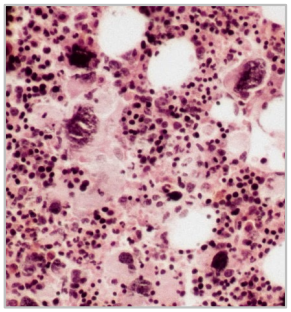
- Blasts from AML secondary to MPN most often show myeloid phenotype with erythroid or megakaryocytic
- lineage differentiation (higher frequency of M6 and M7, ALL exceptional)
- Evolution to AML usually, but not obligatory, through transition to PPV-/PET-MF

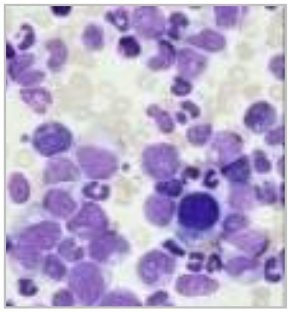
Bjorkholm M, JCO 2011; Abdulkarim K, et al. Eur J Haem 2009;82(2):106–11; Mesa RA.et al. Blood 2005;105(3):973–7.

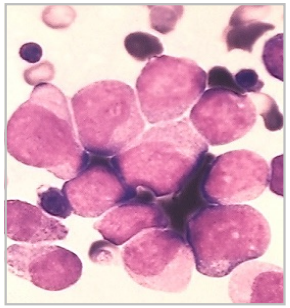
Let's Start From Current knowledge…

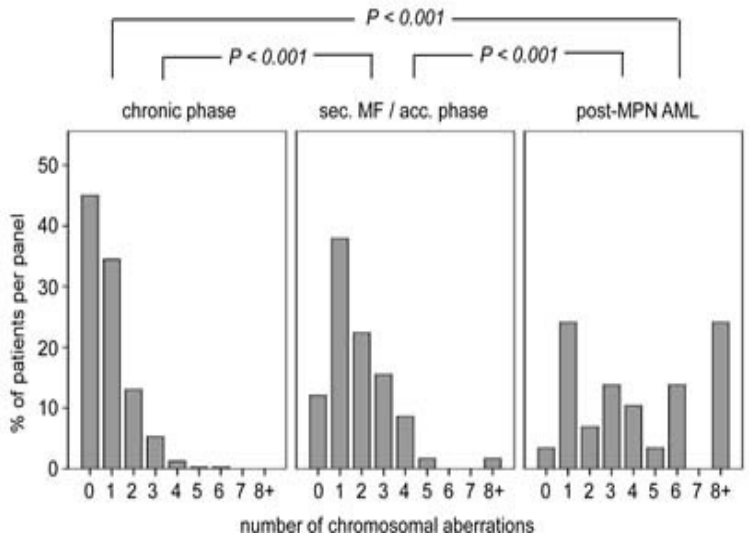
Disease Progression is Associated with Accumulation of Genetic Aberrations

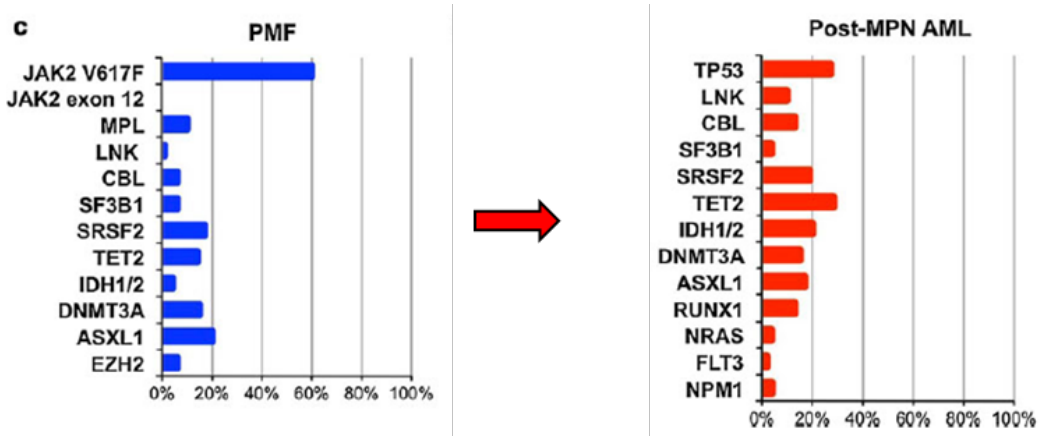
Chronic → **Accelerated** → **Leukemic**







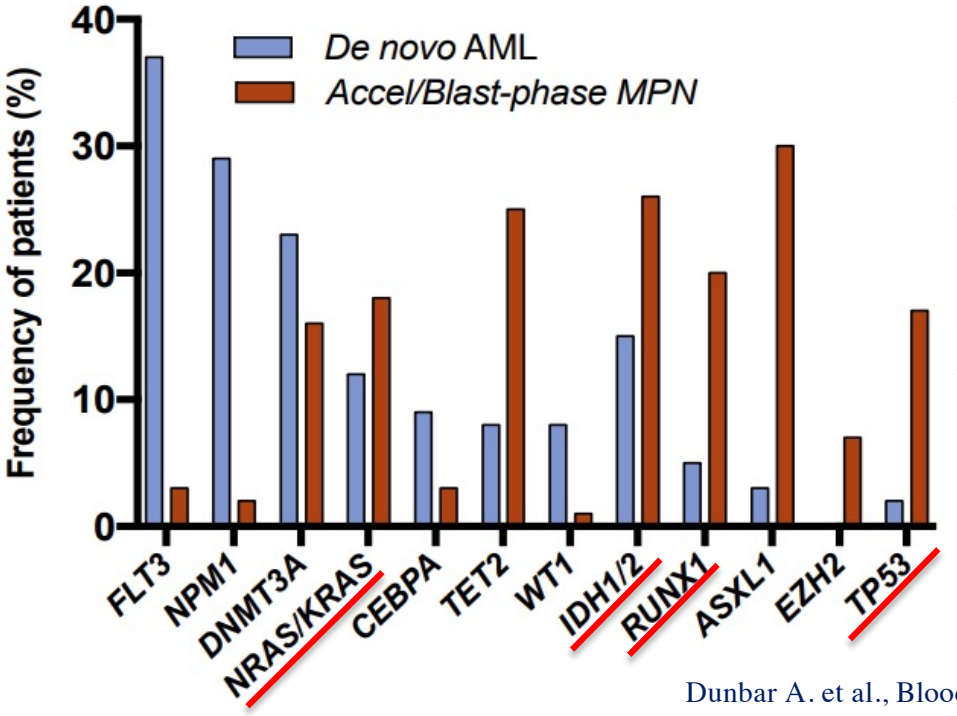




Klampfl T, Blood 2011; 118:167-76. Milosevic and Kralovics, Int J Hematol 2013; Venton et al AJH 2017

Molecular Landscape of post-MPN Blast Phase Differs from De Novo AML

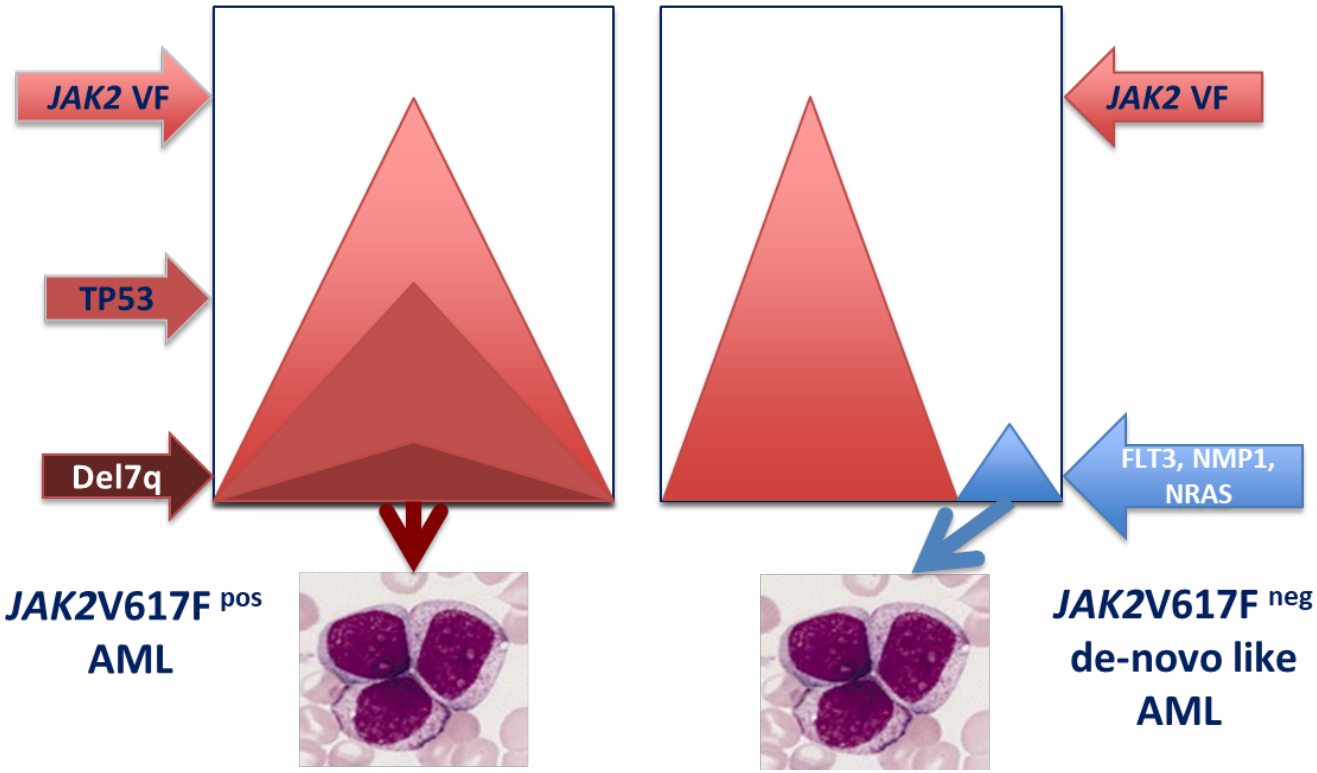
The molecular features of post-MPN BP are strikingly different from de novo disease suggesting an unique path to leukemogenesis.



- *FLT3*, *NPM1*, and *CEBPα* mutations are frequently absent in BP.
- Mutation in genes involved in the epigenetic regulation -*IDH1, IDH2*, *TET2, ASXL1*, *EZH2*- and spliceosome -*SRSF2.*- are enriched in BP.
- *TP53* mutations are enriched in BP.

Dunbar A. et al., Blood. 2020; Milosevic JD. et al., Am J Hematol. 2012; Milosevic and Kralovics, Int J Hematol. 2013; Harutyunyan A. et al., N Engl J Med. 2011; Marcellino BK. et al., Blood Adv. 2018; Lundberg P. et al., Blood 2014; Kubesova B. et al., Leukemia 2018; Vannucchi AM. et al., Leukemia. 2013; Guglielmelli P. et al., Leukemia 2014; Tefferi A. et al. Blood Adv. 2016. ; Lasho Blood Adv. 2018 Feb 27; 2(4): 370–380.

Models of Leukemic Transformation in MPN



Rare co-occurring mutations *DNMT3A-ASXL1-TP53* suggests 3 different mechanisms of transformation:

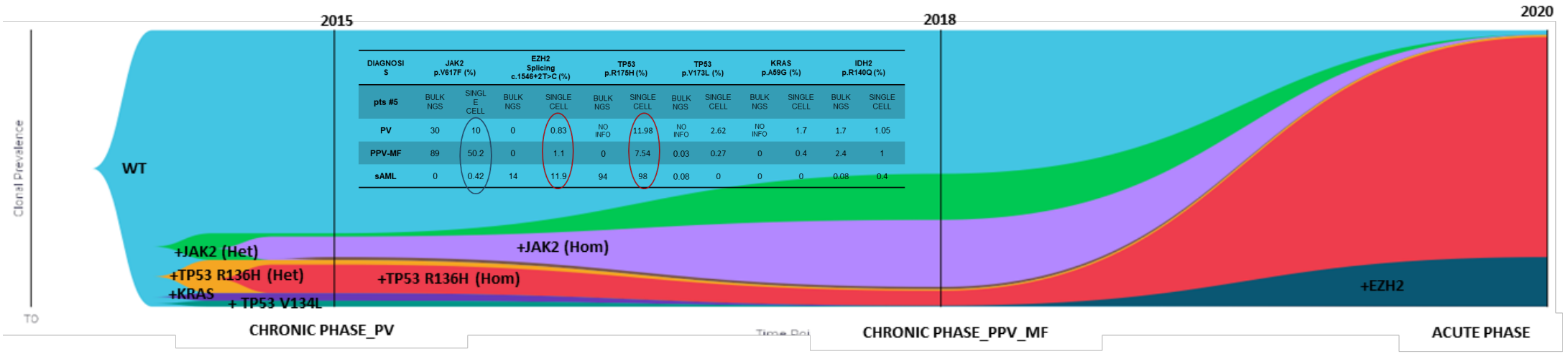
- TP53 o DNMT3A especially in AML post PV/ET
- ASXL1 in post MF

Courtier et al Haematologica 2016

Mutation Complexity Detected by SCS at CP and BP

- Clonal hematopoiesis preceded the acquisition of driver mutation in 6 pts (3 ASXL1; 1 EZH2, 1 IDH1+RUNX1, 1 TET2)
- At CP, all pts showed 2 to 3 mutated clones, at BP from 2 to 5 clones.
- In 7/10 pts, the dominant leukemic clone(s) were already detectable at low frequency (<2%) at CP by SCS, that were missed by bulk sequencing.
- SCS revealed greater clonal heterogeneity that bulk sequencing:
  - 36% more variants identified in CP
  - 17% more variants in BP
- CNV profile at BP differed significantly from CP due to preferential occurrence of region amplification.

Fishplot



DIAGNOSIS	JAK2 p.V617F (%)		EZH2 Splicing c.1546+2T>C (%)		TP53 p.R175H (%)		TP53 p.V173L (%)		KRAS p.A59G (%)		IDH2 p.R140Q (%)	
pts #5	BULK NGS	SINGLE CELL	BULK NGS	SINGLE CELL	BULK NGS	SINGLE CELL	BULK NGS	SINGLE CELL	BULK NGS	SINGLE CELL	BULK NGS	SINGLE CELL
PV	30	10	0	0.83	NO INFO	11.98	NO INFO	2.62	NO INFO	1.7	1.7	1.05
PPV-MF	89	50.2	0	1.1	0	7.54	0.03	0.27	0	0.4	2.4	1
sAML	0	0.42	14	11.9	94	98	0.08	0	0	0	0.08	0.4

Guglielmelli P, ASH 2021

Risk Factors for Leukemia Transformation in MF

Risk Factors		
Clinical	• Age • Anemia • RBC-transfusion dependence • Thrombocythopenia • Thrombocythosis	• Leukocytosis • PB blasts • Prior thrombosis • Weight loss • Cytotoxic drugs
Biological	• Circulating $CD34^+$ cells (≥ 300/ml) • Original diagnosis (consider ET *vs* pre-fibrotic MF) • *JAK2*V617F VAF	
Genetic	• Unfavorable Karyotype [monosomal karyotype, Chr17 abnormalities, Inv3/I(17q)] • Absence of driver mutations (only in MF pts) • Non Driver Gene mutations (HMR, TP53,..)	

Barbui T, JCO 2011; Passamonti F, Haematologica 2008 ; Tefferi A, Eur J Haematiol 2008; Gangat N, BJH 2007; Kiladjian JJ, Semin Thromb Hemost 2006; Finazzi G, Blood 2005; Bjorkholm M, JCO 2011; Rago A et al.Leuk Res. 2015 Mar;39(3):314-7; Passamonti F Am J Med 2004;Barosi G, Blood 2001;Morel P, Blood 2010; Passamonti F, BJH 2010; Tefferi A, BJH 2001; Grinfeld JG et al. N Engl J Med 2018; 379:1416-1430; Paz DL et al Blood Adv (2020) 4 (19): 4887–4897; Gupta V et al. Blood Adv (2020) 4 (21): 5562–5573.

Clinical Risk factors for Leukemic Transformation

Table 2. Multivariate analysis

	Patients with AML/MDS N = 22	Patients without AML/MDS N = 1616	HR (95% CI) *[P]*
Treatment at registration (%)			
Phlebotomy	13 (59.09)	1027 (63.55)	0.91 (0.37-2.21) [.8261]
Hydroxyurea	10 (45.45)	783 (48.45)	1.09 (0.42-2.80) [.8654]
Interferon	1 (4.55)	63 (3.90)	1.24 (0.16-9.80) [.8397]
Busulphan	4 (18.18)	57 (3.53)	8.64 (2.44-30.60) [.0008]
Pipobroman	4 (18.18)	102 (6.31)	4.32 (1.27-14.68) [.0191]
P32	3 (13.64)	41 (2.54)	8.96 (2.13-37.58) [.0027]
Chlorambucil	0 (0.00)	5 (0.31)	NA
Treatment at registration, grouped (%)			
No treatment, phlebotomy only, interferon only†	5 (22.73)	664 (41.09)	1.00
Hydroxyurea as only cytoreductive drug	6 (27.27)	736 (45.54)	0.86 (0.26-2.88) [.8021]
Any other cytoreductive drug, alone or in combination	11 (50.00)	216 (13.37)	5.46 (1.84-16.25) [.0023]

Finazzi et al. *Blood* 2005

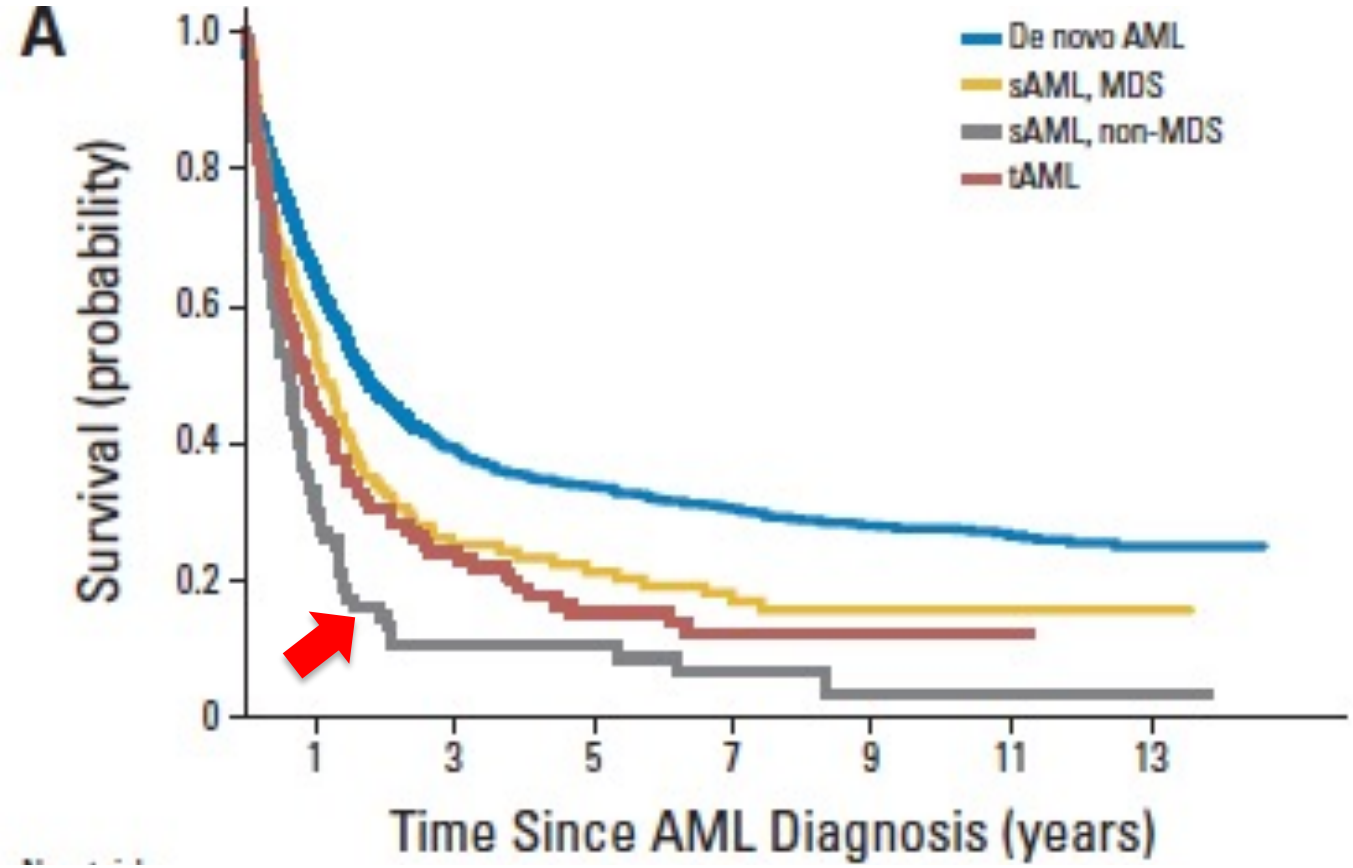
Acquisition of genetic abnormalities in MPN

Gene	Chr location	PV (%)	ET (%)	MF (%)	Blast phase (%)
TET2	4q24	10-16	4-5	7-17	17-32
IDH1/2	2q33.3 / 15q26.1	2	1	4	9-22
DNMT3A	2p23	3-7	<1	2-15	14-17
EZH2	7q36.1	3	<1	7-13	---
ASXL1	20q11.1	2-7	0-3	13-32	18-33
SRSF2	17q25.1	---	---	≈15%	≈20%
SF3B1	2q33.1	---	---	7%	---
CBL	11q23.3	rare	rare	6%	---
TP53	17p13.1	---	---	4%	**27%**
U2AF1	21q22.3	---	---	16%	---

- *TP53* mutations or 1q gains in 45.5% of post-MPN AML
- TP53 mutations were detected at a low allele burden in CP, whit a clonal expansion only after loss of the WT allele

Harutyunyan A et al. N Engl J Med 2011;364:488-490; Vainchenker W et al, Blood. 2011; 18;118(7):1723-35;
Vannucchi AM et al, Leukemia 2013; 27:1861-9; Lundberg P et al. Blood 2014;123:2220-2228.

Leukemic transformation carries a poor prognosis



Granfeldt et al. *JCO* 2015;105:973-977

Post-MPN AML demonstrates limited response to conventional AML therapy

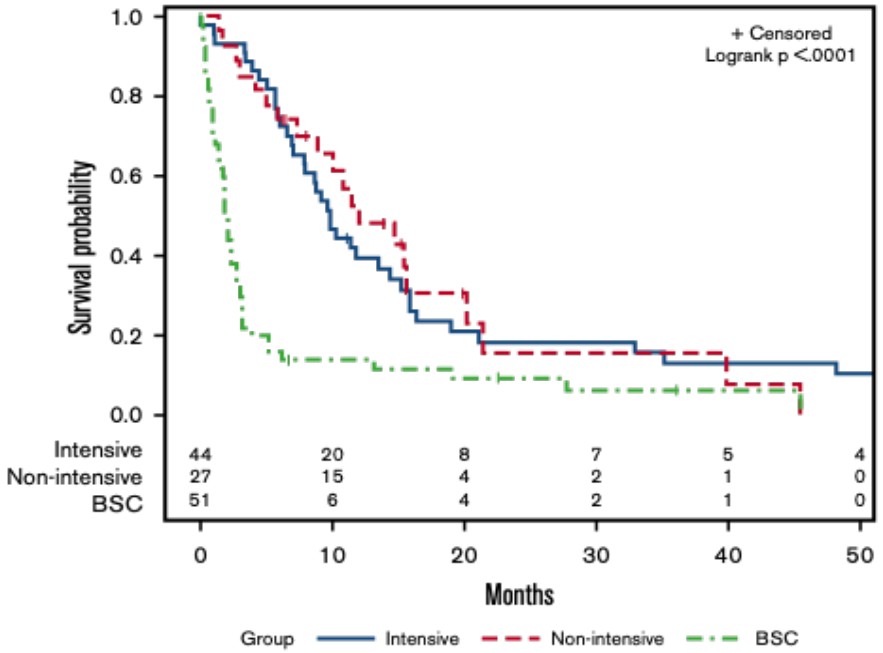
Table 2. Summary of reports about intensive therapeutic approaches (including allogeneic hematopoietic stem cell transplant (HSCT)) in secondary acute myeloid leukemia (sAML).

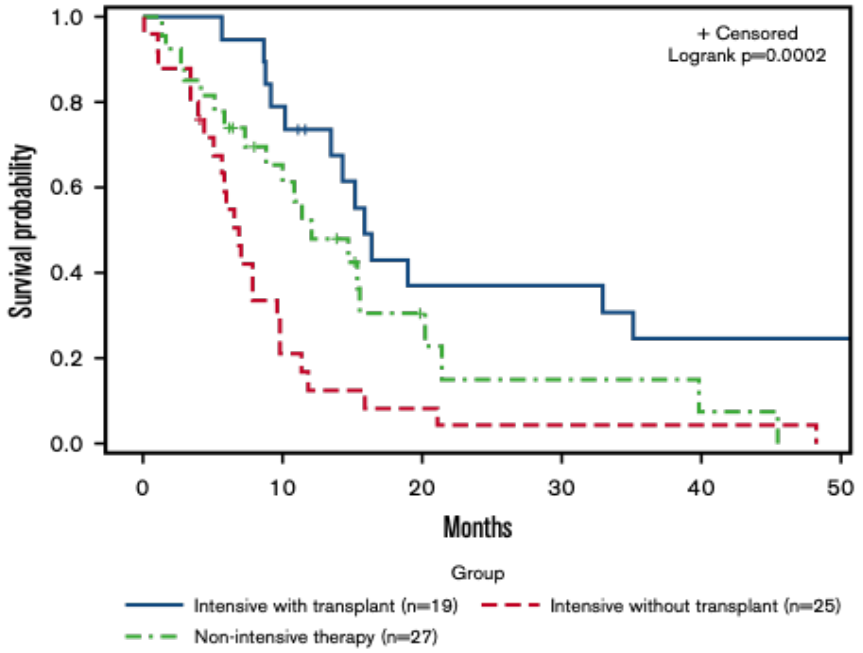
Reference	Induction Chemotherapy				Allogeneic Transplant						
	n	Type	Response	OS, mo	*n*	Conditioning	Disease status	Donor	CIR @ 2y	NRM @ 2y	OS @ 2y
Mesa, 2005 [16]	24	"3 + 7" 75% HDAC 13% MEC 13%	CR 0%	3.9	-	-	-	-	-	-	-
Tam, 2008 [4]	41	Ida-HDAC 54% "3 + 7" 15%	CR/CRi 46%	NR	8	NR	CR 12.5% CRi 50% NR 37.5%	Sib 62.5% MUD 37.5	12.5%	12.5%	37.5%
Ciurea, 2010 [22]	-	-	-	-	14	MAC 36% RIC 64%	CR/CRi 43% NR 57%	Sib 57% MUD 43%	38%	29%	33%
Kennedy, 2013 [19]	38	"3 + 7" 66% MEC 32%	CR 32% CRi 5% c-MPN 26%	-	17	MAC 47% RIC 53%	CR/CRi 59% c-MPN 41%	Sib 70% MUD 30%	24%	47%	29%
Alchalby, 2014 [21]	-	-	-	-	38	MAC 53% RIC 47%	CR 23% NR 77%	Sib 45% MUD 55%	47%	28%	33%
Takagi, 2016 [30]	-	-	-	-	39	MAC 38% RIC 62%	CR 18% NR 52% Untreated 30%	Sib 21% MUD 38% CB 41%	34%	34%	29%
Tefferi, 2018 Mayo cohort [24]	66	"3 + 7"/like 90% Other 10%	CR 35% CRi 24%		24	NR	CR/CRi 67% NR 33%	NR	NR	NR	41%
Tefferi, 2018 AGIMM cohort [24]	48		CR 27% CRi 8%		25	MAC 76% RIC 24%	CR/CRi 40% NR 60%	Sib 40% MUD 44% Haplo 16%	39.5%	21.7%	41.5%

n, number of patients; HDAC, high dose cytarabine; MEC, mitoxantrone, etoposide, cytarabine; CIR, cumulative incidence of relapse; NRM, non-relapse mortality; OS, overall survival; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; MAC, myeloablative condition; RIC, reduced intensity conditioning; Sib, sibling donor; MUD, matched unrelated donor; Haplo, haploidentical donor.

Mannelli F . J. Clin. Med. 2021, 10, 436.

Post-MPN AML demonstrates limited response to conventional AML therapy



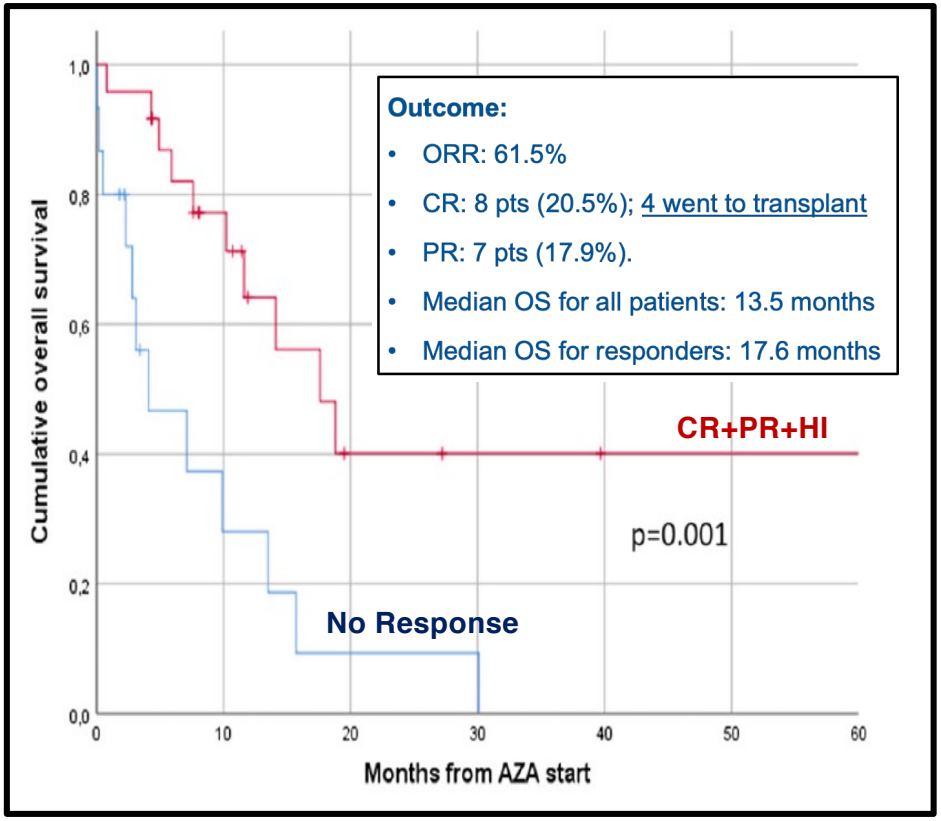


CR status at the time of conditioning regimen starting was associated with favorable outcome

Kennedy JA et al. Blood 2013; Cahu X et al. Bone marrow transplantation 2014;49(6):756–60; McNamara CJ et al. Blood Advances 2018;2(20):2658–71.

Clinical Experience with Hypomethylating agents in post-MPN AML

Azacitidine



Ruxolitinib + Decitabine

N = 25

Treatment: up to 25 mg Ruxolitinib BID for induction, then 10 mg BID + decitabine (20 mg/m^2 IV for 5 days on a 4 week schedule)

Median # of cycles given: 4

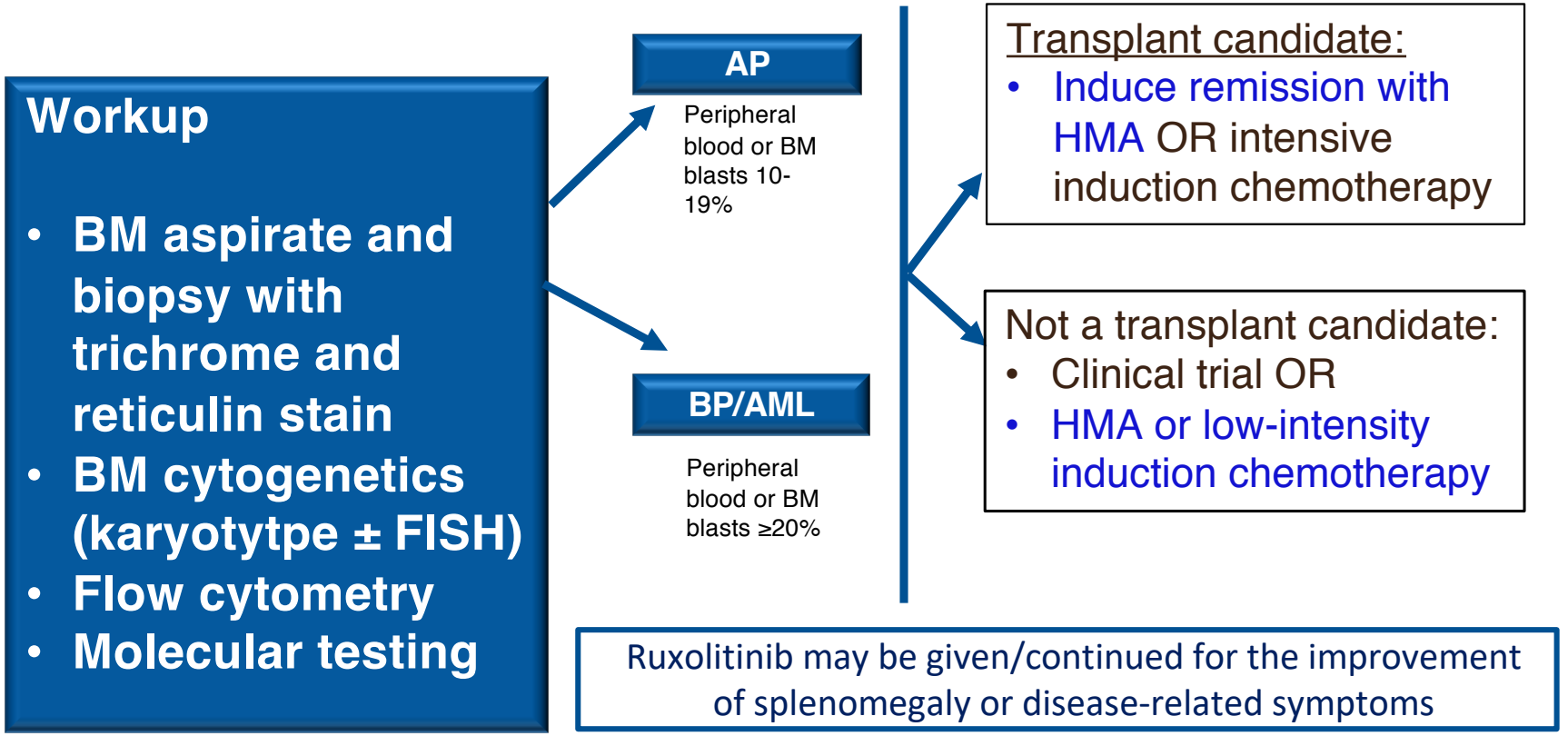
Response (CR + CRi + PR): 44% overall (11/25)

Survival: 9.5 months for responders (median OS 9.5 months)

Median reduction of spleen size: 70.5%

Thepot et al. *Blood*. 2010;116(19):3735-3742; Andriani A, et al. Hematol Oncol. 2019;;37(3):291-295; Mascarenhas et al. *Blood Adv.* 2020;4(20):5246–56.

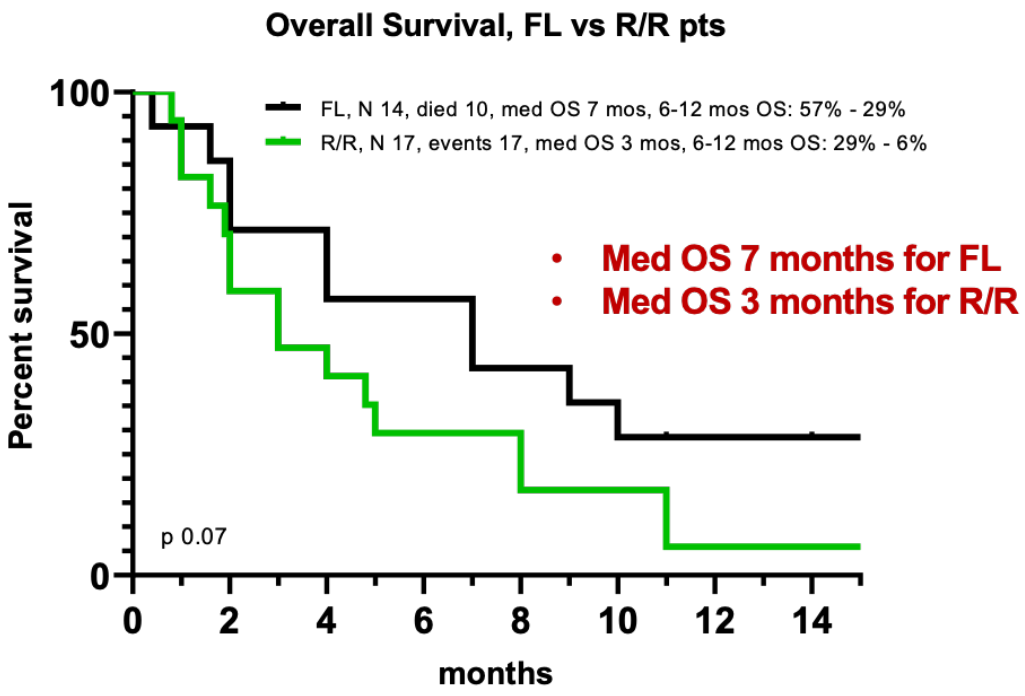
NCCN Guideline for Treatment of post-MPN AP/BP AML



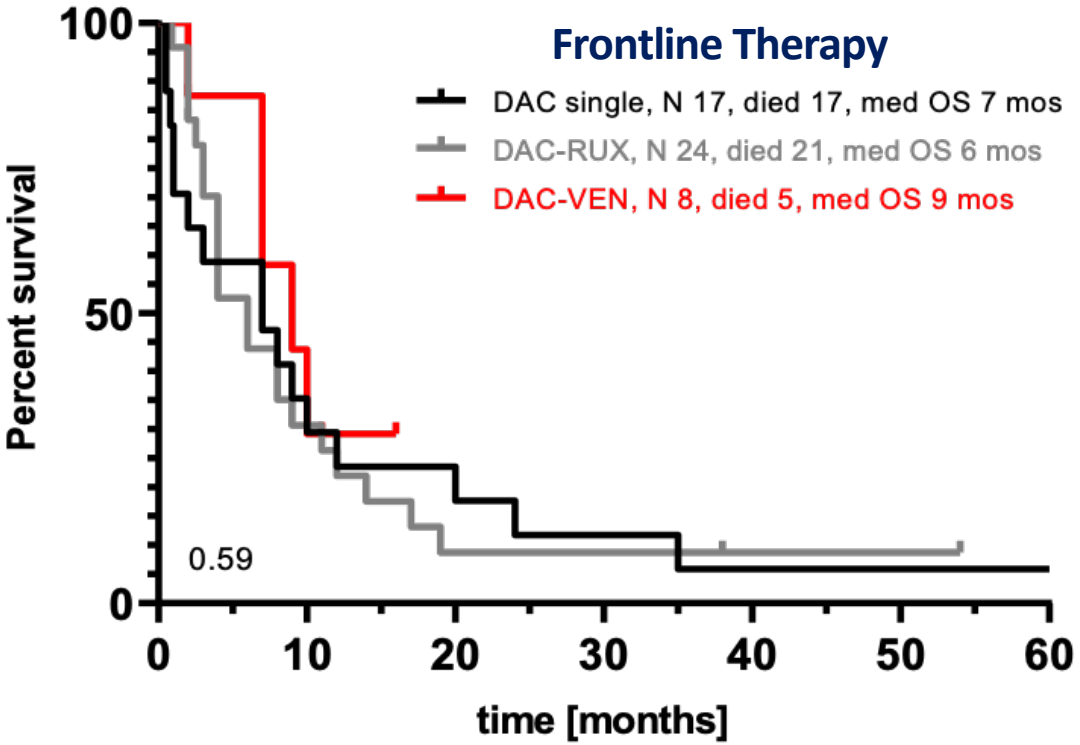
Adapted from NCCN. Myeloproliferative Neoplasms (Version 1.2021), https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Accessed May 12, 2021.

No Apparent Benefit on Survival from Venetoclax-Based Combinations in MPN-BP

Preclinical data provide rationale for clinical study: Bcl-xL expression is high in MPN cells; Sensitivity of AML cells to Venetoclax correlates positively with BCL-2 levels; Synergistic Targeting of Bcl-xL and JAK2 in JAK2-Driven MPN cells shows high apoptotic rate



31 MPN-BP ; Med OS 4 months for all Pts



Masarova L, et al.Blood Adv. 2021 Apr 27;5(8):2156-2164. Tremblay D, Leuk Res. 2020;98:106456.

IDH1/2 Mutations Confer Sensitivity to Venetoclax in AML

Regimens: VEN + Decitabine (20 pts), VEN + AZA (12 pts)

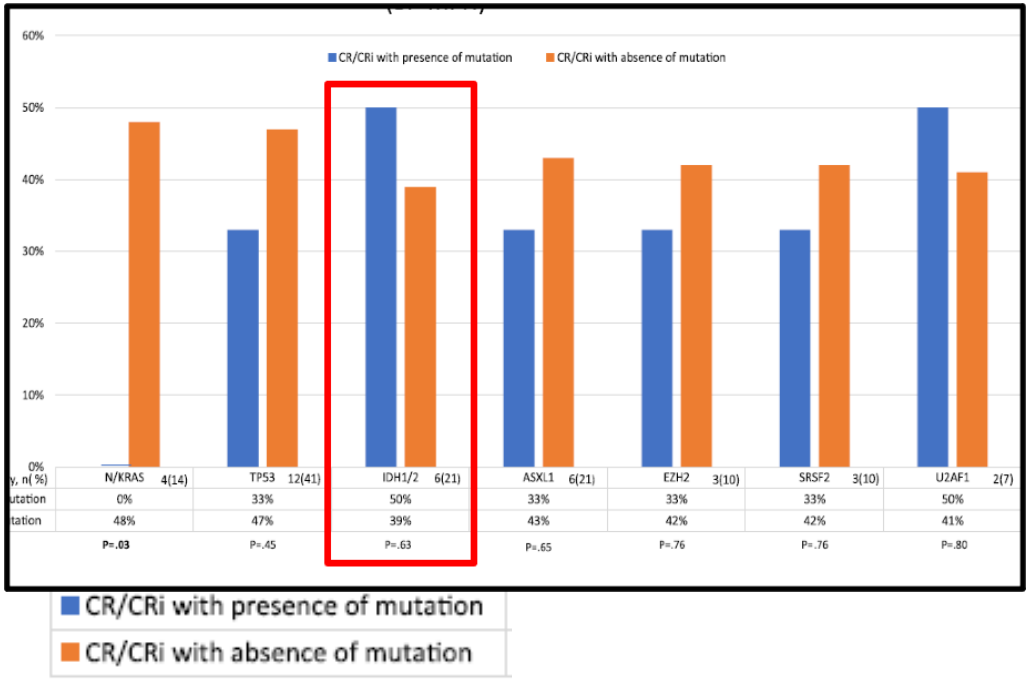
Median age: 69 years (47-81)

CR/CRi: 44% (14 patients; 10 CR and 4 CRi); median duration 3.5 months

6 patients in CR/CRi underwent allo-SCT

Neutropenic fever or sepsis: 10 patients (31%); 1 death related to intracranial hemorrhage

Median OS: 8 months (1-24)



CR/CRi was more likely in the absence of pre-leukemic PV/post-PV MF phenotype, complex karyotype and *K/NRAS* mutations

DiNardo CD, et al. Blood 2020;135(11):791-803. Gangat N. et al. Am J. Hematol. 2021;1-9

Targeted IDH1/2 Inhibitor-based Treatments in *IDH1/2*-Mutated post-MPN AML Patients

- N=12, 7 with *IDH1*, and 5 with *IDH2* mutation
- 7 in first line (FL) setting, 5 with R/R
- 3 CR in FL setting:
  - Given combination IDH1/2-inhibitor-based therapy
  - All 3 patients with CMR
  - Median response duration 17.5+ months
- 2 with SD in FL, and 3 with SD in R/R
  - Duration of SD for 8+ months
- Well tolerated
  - 5 with differentiation syndrome
  - 1 discontinued Rx due to N/V
  - 60 day mortality: 2 patients

Chifotides HT, et al. Blood Adv. 2020 Nov 10;4(21):5336-5342.

Why post-MPNs Leukemia is Still a Challenge and an Unmet Need?

- Leukemogenic mechanisms not fully understood; data from NGS on paired (chronic and blast phase) do not display homogeneous patterns of transformation with different representation for recurrent gene mutations in published reports
- Conventional prognostic risk model (age, Karyotype, ELN2017) fail to predict the pts outcome and a validated predictive model for AL progression is still lacking
- Median survival 3-6 months
- Often advanced age: just a minority of pts are eligible for intensive treatment.
- Available data mainly retrospective and on small groups of pts

Why post-MPNs Leukemia is Still a Challenge and an Unmet Need?

- Efficacy of standard induction therapy is limited in post-MPN AML.
- Intensive chemotherapy does not improve survival compared to supportive care if not followed by allogeneic transplant.
- beyond primary resistance, the clinical management is often complicated by underlying MPN (splenomegaly long aplasia, high TRM).
- Limited prospective therapeutic trials, no prospective randomized studies

A Phase 2, prospective, multi-center intervention trial in patients with acute myeloid leukemia secondary to myeloproliferative neoplasms unfit for intensive chemotherapy investigating a treatment combinationincluding decitabine and venetoclax.

GIMEMA AML 2420– Mynerva study

Trial ENABLE (v**EN**etoclax plus decit**A**bine treatment in **B**lastic phase of mye**L**oproliferative n**E**oplasms)

Sponsor
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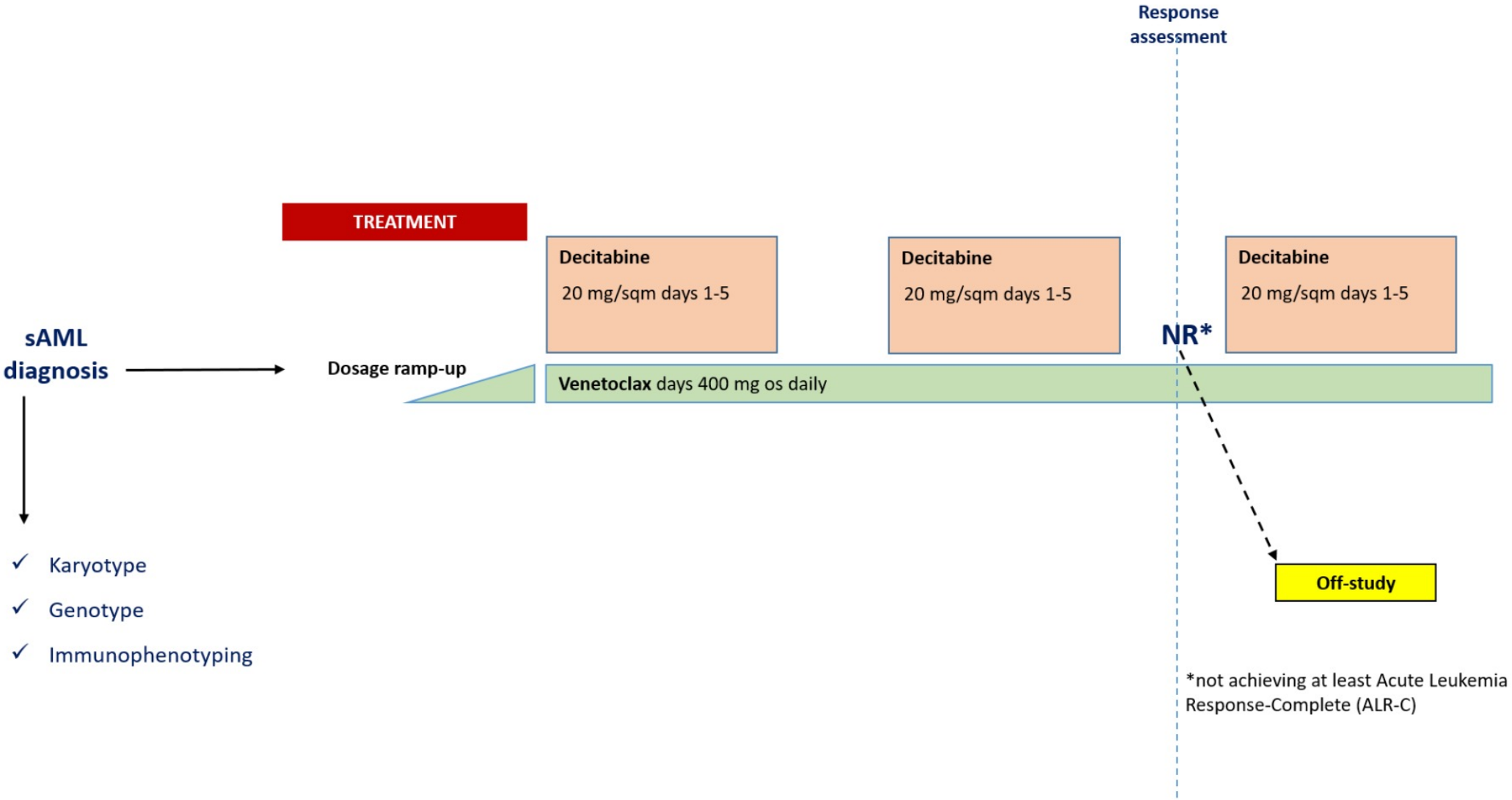
fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

AIRC Metastatic disease: the key unmet need in oncology
Mynerva
MYeloid NEoplasm Research Venture Airc

sAML ENABLE trial – treatment plan



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