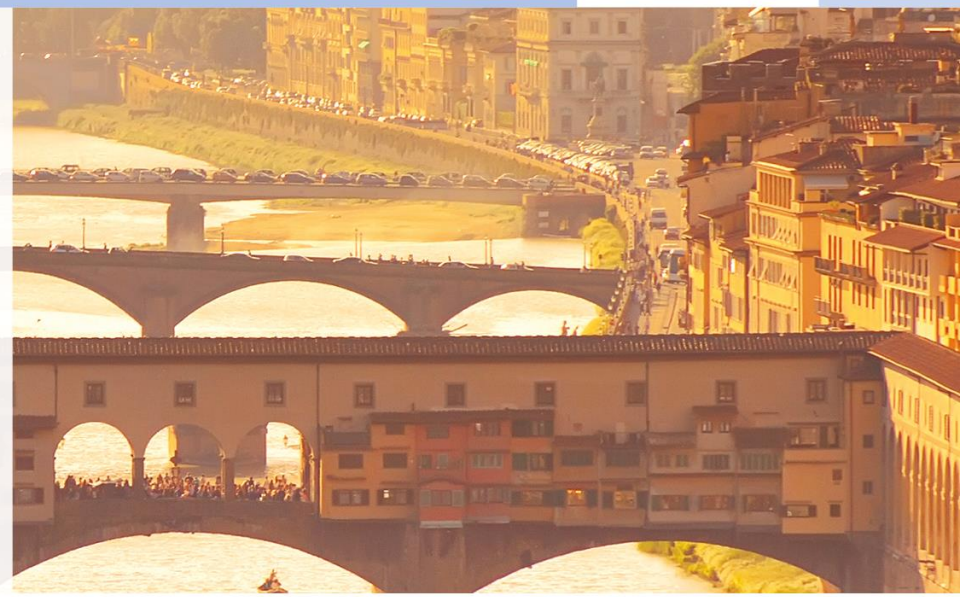
8° WORKSHOP
IN EMATOLOGIA TRASLAZIONALE

DELLA SOCIETÀ ITALIANA DI EMATOLOGIA SPERIMENTALE

Firenze - Auditorium CTO - A.O.U. Careggi, 22-23 giugno 2023



Meccanismi di progressione clonale e nuove prospettive terapeutiche per la leucemia mieloide acuta secondaria a NMP

Francesco Mannelli

Disclosures of Name Surname

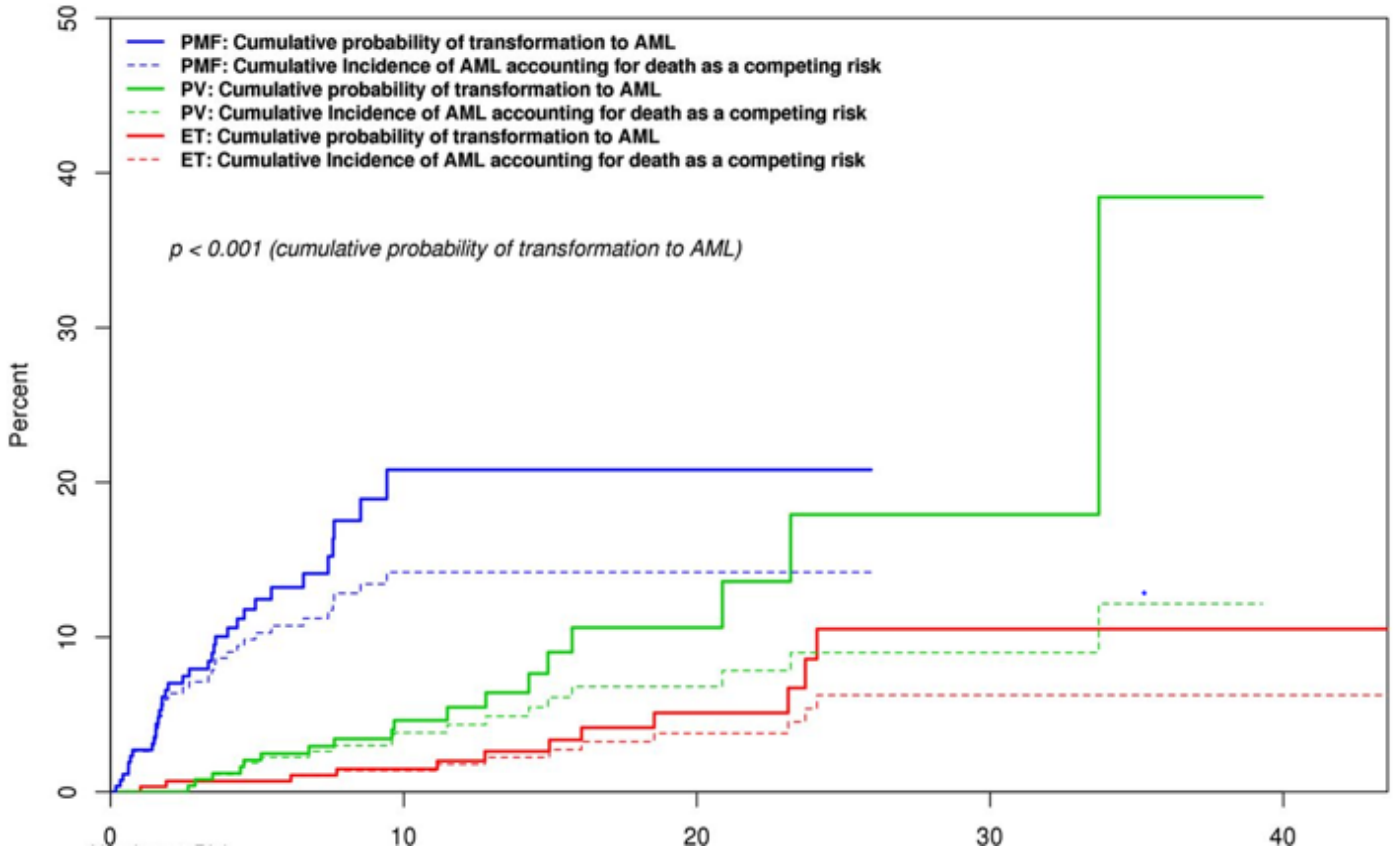
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					X		
Blueprint					X	X	
Novartis					X	X	

Progression to blast phase

- **Blast phase** is defined by the presence of ≥ 20% blasts in either peripheral blood or bone marrow
- **Accelerated phase** is defined by 10-19% blasts and sometimes can precede BP; should be considered separately in prognostic data

10-year risk of leukemic progression:

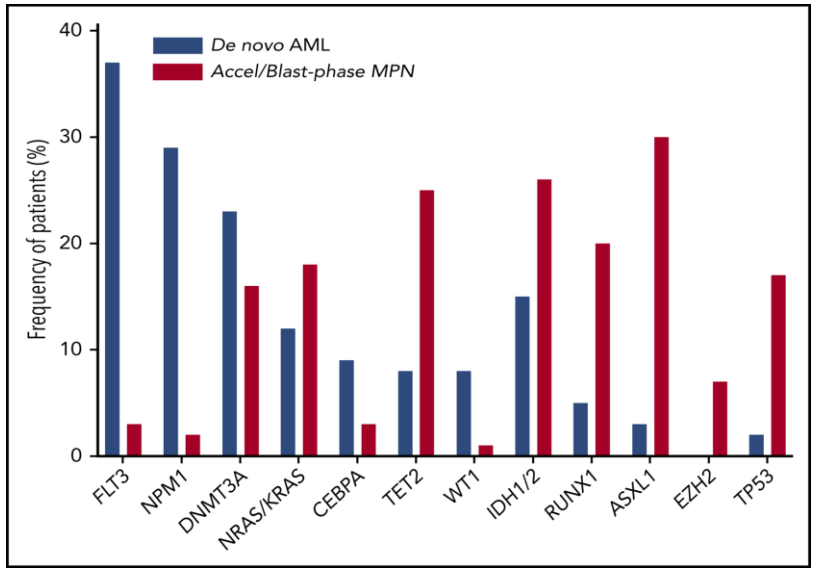
- PMF 10% to 20%
- PV 2% to 4%
- ET 1%



Tefferi A, Guglielmelli P, et al. Blood. 2014;124(16):2507-2615

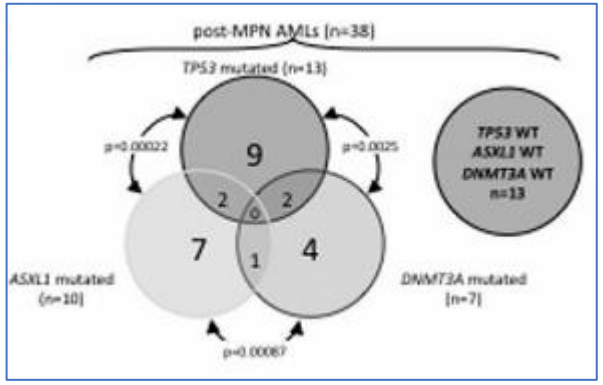
MPN blast phase molecular genetics

✓ Over-representation for *TP53*, *RUNX1*, *EZH2*, *ASXL1*, *IDH1/2* gene mutations



Dunbar, et al. Blood. 2020; 136:61-70

✓ Highly heterogeneous mutation profile at blast phase onset



Courtier, et al. Haematologica. 2016; 102(1):e11-e14

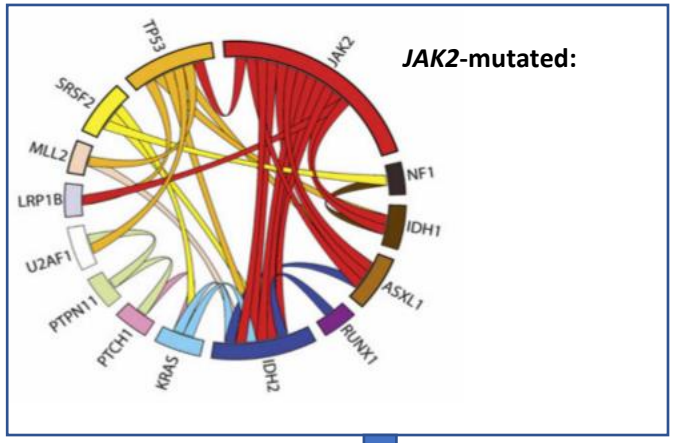
Rare co-occurring mutations *DNMT3A - ASXL1 - TP53* suggests different mechanisms of transformation:

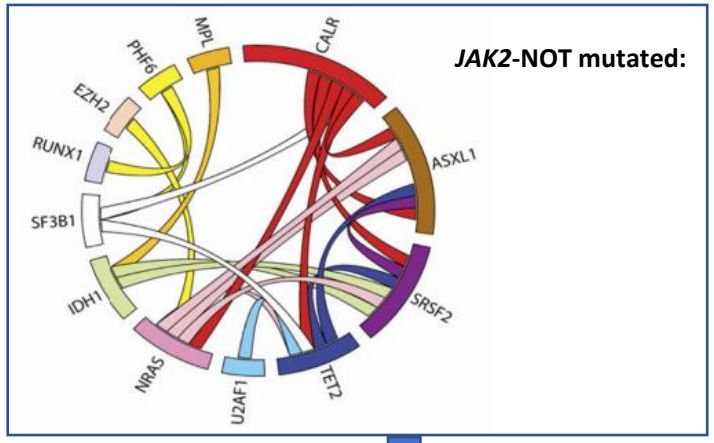
✓ *TP53* o *DNMT3A* especially in AML post PV/ET

✓ *ASXL1* in post MF

Progression to blast phase

✓ 2 main mutational *patterns* at transformation:





JAK2*+ and *TP53:
often elevated VAF: potentially sinergic

***TP53*:** increase of VAF concomitant with leukemic transformation with selection of homozygous clones

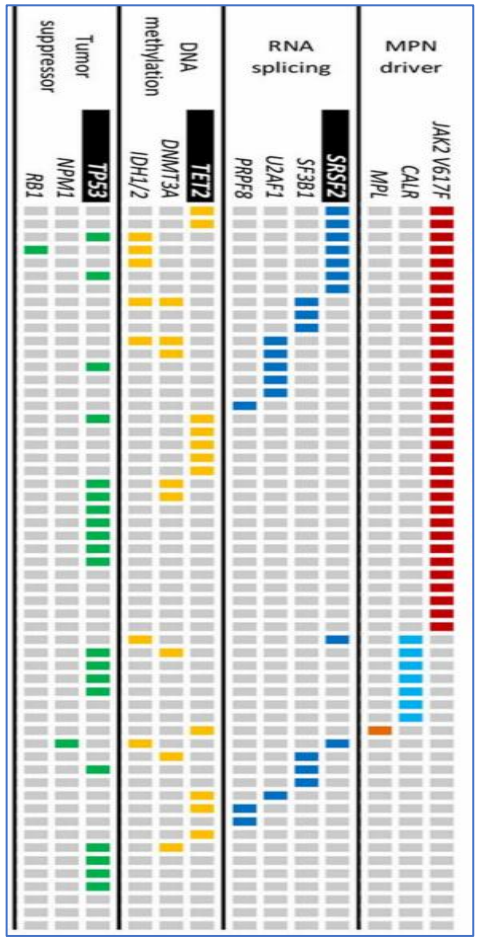
***JAK2* wild type**:

✓ Antecedent clone

✓ De novo AML

Rampal, et al. PNAS 2014;111, E5401–E5410

✓ A unifying model of clonal evolution can't be drawn; rather there are several patterns

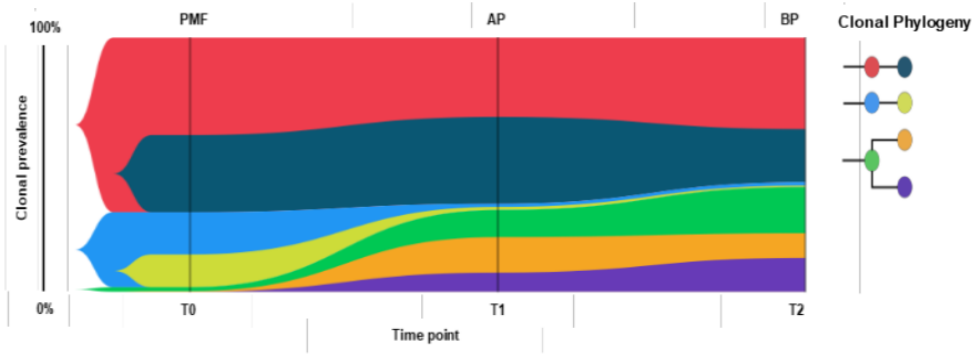


Venton, et al. AJH 2018;93, 330–338

Progression to blast phase

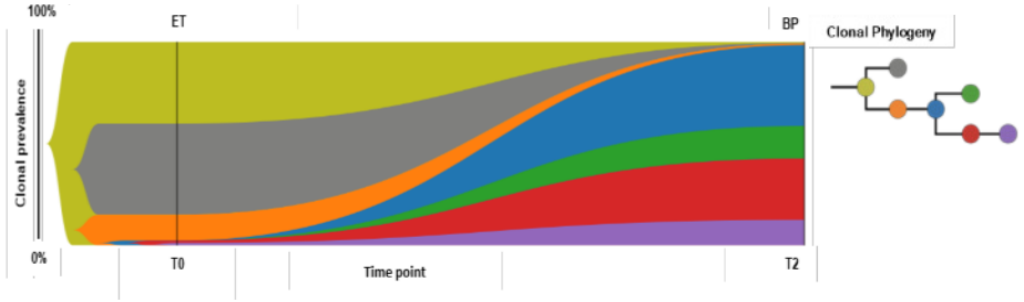
- Novel opportunities of insight from **single-cell sequencing**:
  - ✓ Detection of additional low-frequency variants (VAF < 2%) that were missed on bulk analysis
  - ✓ EZH2 frequently affected by CNVs in the leukemic clones

Patient #8



	Subclones	T0 (%)	T1 (%)	T2 (%)
	ASXL1_Het/EZH2_Het (a)/EZH2Het (b)/NRAS_Het (a)	37.2	30.03	35.97
	ASXL1_Het/EZH2_Het (a)/EZH2Het (b)/NRAS_Het (a)/CALR_Het	31.27	36.01	20.96
	ASXL1_Het/EZH2_Hom (b)/NRAS_Het (b)	16.44	1.19	1.32
	ASXL1_Het/EZH2_Hom (b)/NRAS_Het (b)/CALR_Het	13.48	1.37	0.66
	ASXL1_Het/KRAS_Het	1.35	10.24	17.49
	ASXL1_Het/KRAS_Het/CALR_Het	0.27	13.65	10.07
	ASXL1_Het/KRAS_Het/WT1_Het	0.27	7.51	13.53

Patient #9

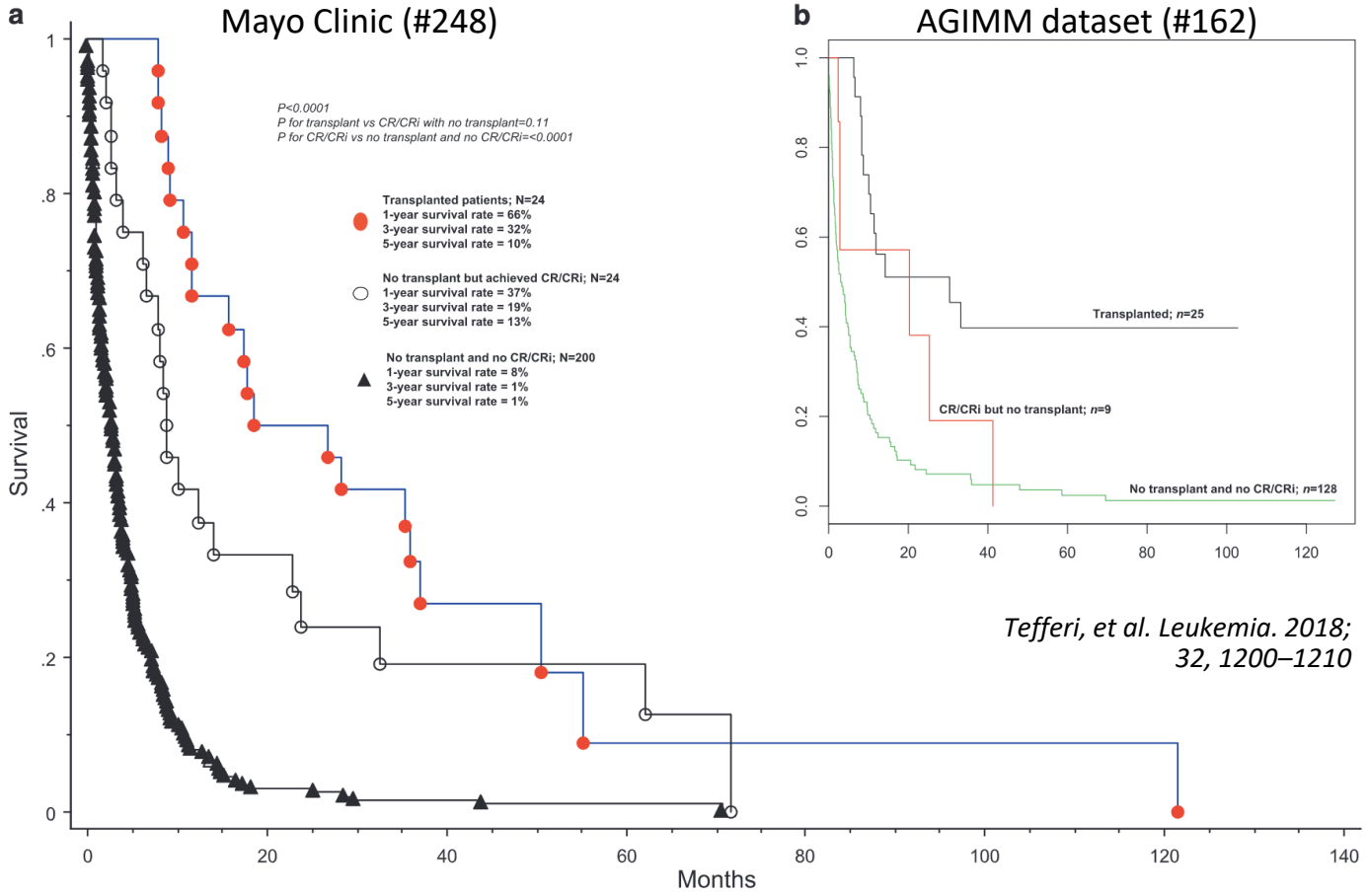


	Subclones	T0 (%)	T2 (%)
	TET2_Het	40.7	0.51
	TET2_Het/CALR_Het	45.35	0.37
	TET2_Het/TP53_Het	11.63	0.74
	TET2_Het/TP53_Hom	0.1	39.89
	TET2_Hom/TP53_Hom	0	15.89
	TET2_Het/TP53_Hom/CALR_Het	1.16	31.32
	TET2_Het/TP53_Hom/CALR_Hom	1.16	11.19

Calabresi, et al. Am J H 2023; in press

Prognosis at transformation

- **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



Tefferi, et al. Leukemia. 2018; 32, 1200–1210

Curative intent: eligibility for allogeneic transplant

Non intensive treatment approach

Principles of Treatment – Curative intent

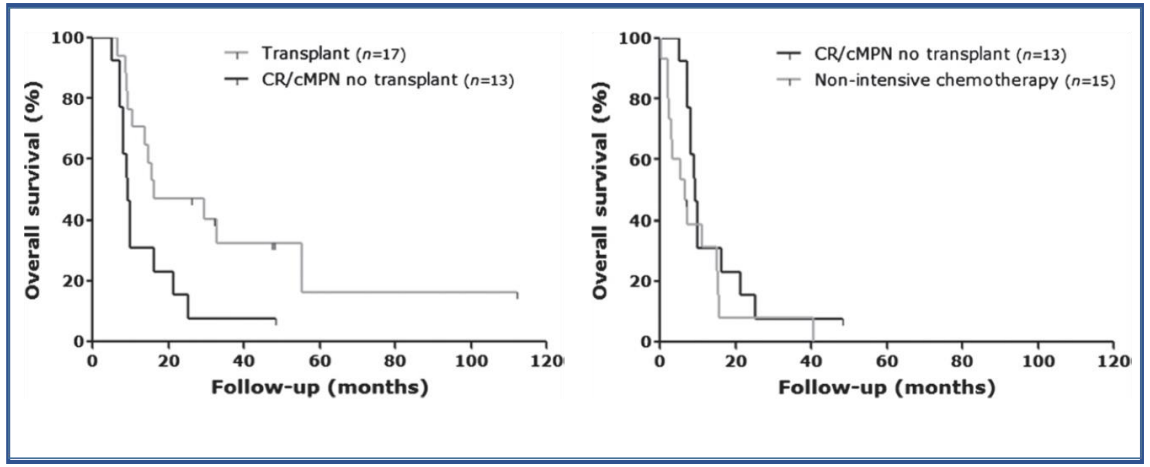
- **No established standard** of care for MPN-BP
- The only probability of long-term survival relies on **allogeneic transplant**

Reference	Induction chemotherapy					Allogeneic transplant						
	#	Type	Response	TRM	OS, mo	#	Conditioning	Disease status	Donor	CIR @ 2y	NRM @ 2y	OS @ 2y
Mesa, Blood 2005	24	"3+7" 75% HDAC 13% MEC 13%	CR 0%	33%	3.9	-	-	-	-	-	-	-
Tam, Blood 2008	41	Ida-HDAC 54% "3+7" 15%	CR/CRi 46%	15%	NR	8	NR	CR 12.5% CRi 50% NR 37.5%	Sib 62.5% MUD 37.5	12.5%	12.5%	37.5%
Ciurea, Biol Blood Marrow Transpl 2010	-	-	-	-	-	14	MAC 36% RIC 64%	CR/CRi 43% NR 57%	Sib 57% MUD 43%	38%	29%	33%
Kennedy, Blood 2013	38	"3+7" 66% MEC 32%	CR 32% CRi 5% c-MPN 26% NR 24%	-	9.2	17	MAC 47% RIC 53%	CR/CRi 59% c-MPN 41%	Sib 70% MUD 30%	24%	47%	29%
Alchalby, Biol Blood Marrow Transpl 2014	-	-	-	-	-	38	MAC 53% RIC 47%	CR 23% NR 77%	Sib 45% MUD 55%	47%	28%	33%
Takagi S, Biol Blood Marrow Transpl 2016	-	-	-	-	-	39	MAC 38% RIC 62%	CR 18% NR 52% Untreated 30%	Sib 21% MUD 38% CB 41%	34%	34%	29%

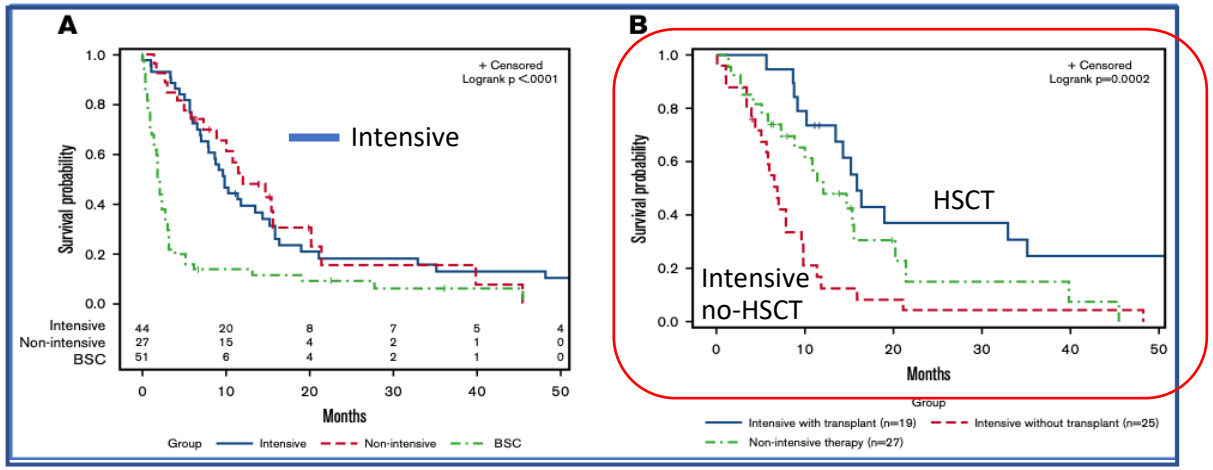
Principles of Treatment – Eligibility for Allogeneic Transplant Program

- Response to chemotherapy:
  - **very low** according to standard criteria and **short-term**
  - beyond primary resistance, the clinical management is often complicated by underlying MPN (splenomegaly, long-lasting aplasia, high TRM)

- Intensive chemotherapy **does not improve survival** compared to supportive care **if not followed by allogeneic transplant**



Kennedy, et al. Blood. 2013; 121, 2725–2733



McNamara, et al. Blood Adv. 2018; 2, 2658–71

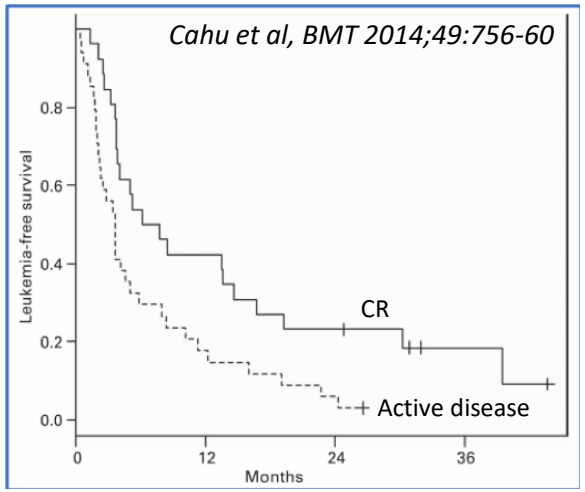
If NOT **eligible for allogeneic transplant,** the patient should be spared from toxicity of intensive chemotherapy and managed with clinical trials (if available), supportive/care or low-doses approaches

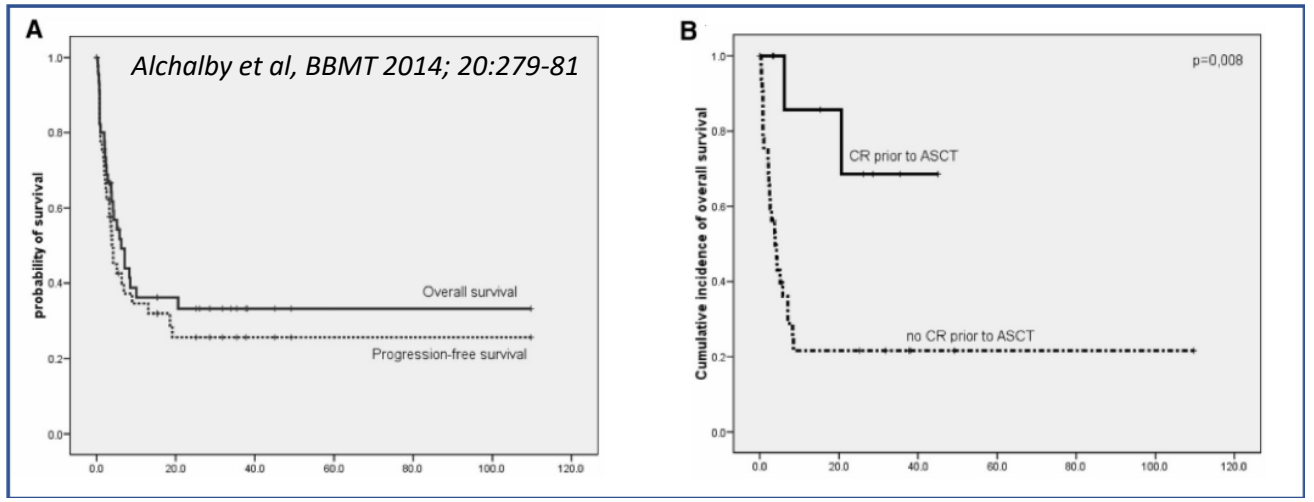
Eligibility for Allogeneic Transplant – Disease status at HSCT

- Remission at HSCT **tends to improve HSCT outcome** but it occurs only **in a minority of cases**

- Retrospective data demonstrate **high rate of engraftment** and early achievement of full **chimerism** , also with reduced intensity conditioning

- HSCT is able to induce long term **RFS in about 20%** of patients even when transplanted with active disease





In **eligible patients**, HSCT is the main target; its delivery should **NOT** be subordinated to complete remission achievement

Bridge to transplantation – Disease control

64th ASH Annual Meeting Abstracts

PLENARY SCIENTIFIC SESSION

PLENARY ABSTRACTS

In Patients with Relapsed/Refractory AML Sequential Conditioning and Immediate Allogeneic Stem Cell Transplantation (allo-HCT) Results in Similar Overall and Leukemia-Free Survival Compared to Intensive Remission Induction Chemotherapy Followed By Allo-HCT: Results from the Randomized Phase III ASAP Trial

Matthias Stelljes, Prof. Dr. MD[1], Jan Moritz Middeke, MD[2,], Gesine Bug, MD[3,*], Eva-Maria Wagner, MD[4,*], Lutz Peter Mueller, MD[5,*], Schmid Christoph[6,*], Stefan W. Krause, MD[7,*], Wolfgang Bethge, MD[8,*], Edgar Jost[9,*], Uwe Platzbecker, MD[10,*], Stefan Klein, MD[11], Jörg Schubert[12,*], Judith Niederland[13,*], Martin Kaufmann, MD[14], Kerstin Schäfer-Eckart[15,*], Markus Schaich, MD[16,*], Henning Baldauf[17,*], Friedrich Stölzel[18,*], Cathleen Petzold, PhD[17,*], Christoph Röllig, MD MSC[19,*], Nael Alakel, MD[20,*], Björn Steffen, MD[21,*], Beate Hauptrock[22,*], Christian Reicherts, MD[23,*], Christoph Schliemann, MD[24,*], Hubert Serve, MD[21], Alexander H. Schmidt, MDPhD[25], Martin Bornhäuser, MD[26,*], Jan-Henrik Mikesch, PD, MD[24,*], Johannes Schetelig, MDMSc[20,17]*

Non-inferiority trial

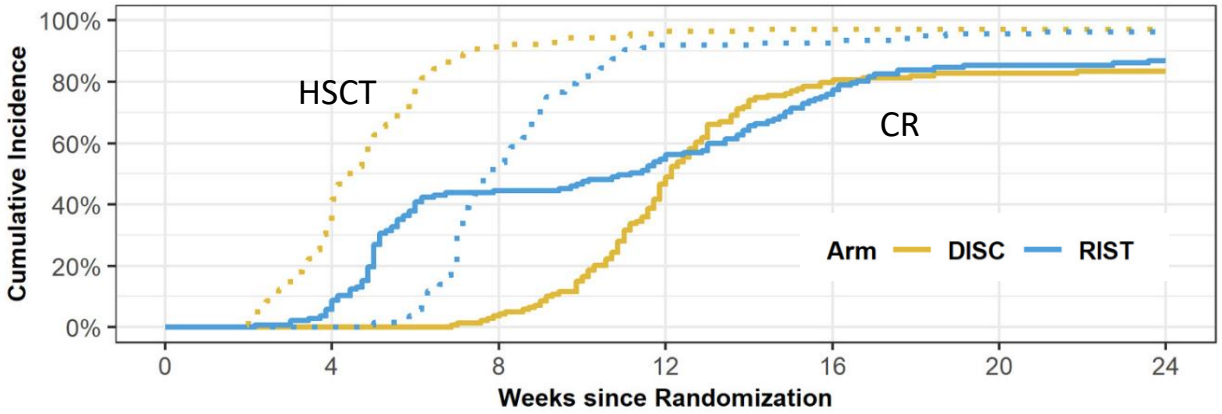
Inclusion criteria:

281, unfavorable R/R AML, eligible for HSCT

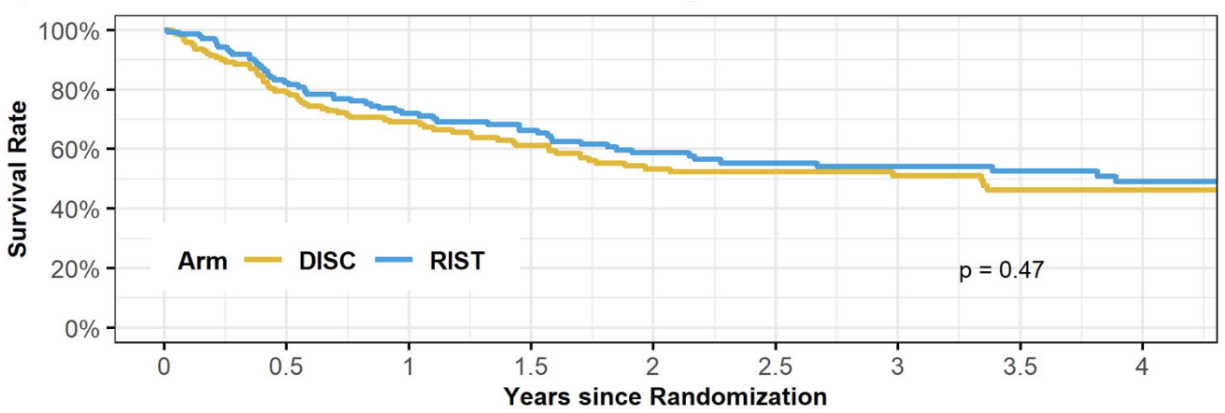
1:1 randomization:

- HAM salvage therapy (**RIST**-arm)
- Watchful wait and sequential conditioning (**DISC**-arm)

Cumulative incidence of HSCT and CR



Overall survival



Principles of Treatment – Bridge to allogeneic Transplant

➢ Bridge to transplantation

- No definite standard, generally based on **«3+7»/like induction** chemotherapy

- Proposed **comprehensive approaches** (CHT + HSCT) embedding clofarabine and RIC conditioning

A multicenter trial of myeloablative clofarabine and busulfan conditioning for relapsed or primary induction failure AML not in remission at the time of allogeneic hematopoietic stem cell transplantation

J Magenau[1], P Westervelt[2], S Khaled[3,4], J McGuirk[4], P Hari[5], M Eapen[5], PS Becker[6], B Parkin[1], T Braun[7], B Logan[8], H Wang[8], M Jagasia[9], SD Rowley[10], DDH Kim[11], T Schechter[12], N Frey[13], B Scott[6], T Churay[1], S Lieland[1], S Forman[3,4] and S Mineishi[14]

Bone Marrow Transplantation (2016), 1–7

Magenau et al, BMT 2016; 52:59-65

haematologica
Journal of the European Hematology Association

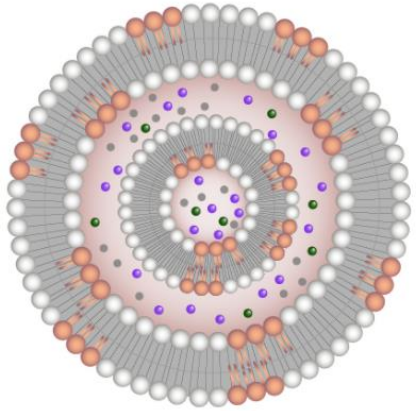
Sequential regimen of clofarabine, cytosine arabinoside and reduced intensity transplantation for primary refractory acute myeloid leukemia

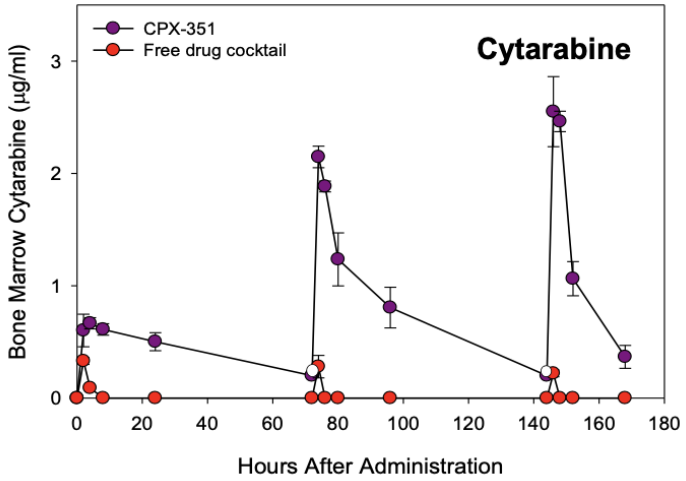
by Mohamad Mohty, Florent Malard, Didier Blaise, Noel Milpied, Gerard Socie, Anne Huynh, Oumedaly Reman, Ibrahim Yakoub Agha, Sabine Furst, Thierry Guillaume, Reza Tabrizi, Stephane Vigouroux, Pierre Peterlin, Jean El-Cheikh, Philippe Moreau, Myriam Labopin, and Patrice Chevallier

Mohty et al, Haematologica 2017; 102(1):184-191

Bridge to transplantation – CPX-351

- Liposomal formulation of cytarabine and daunorubicin with fixed 5:1 molar ratio





- Synergistic and prolonged effect
- BM accumulation
- Preferential uptake by leukemic cells independent from PgP expression

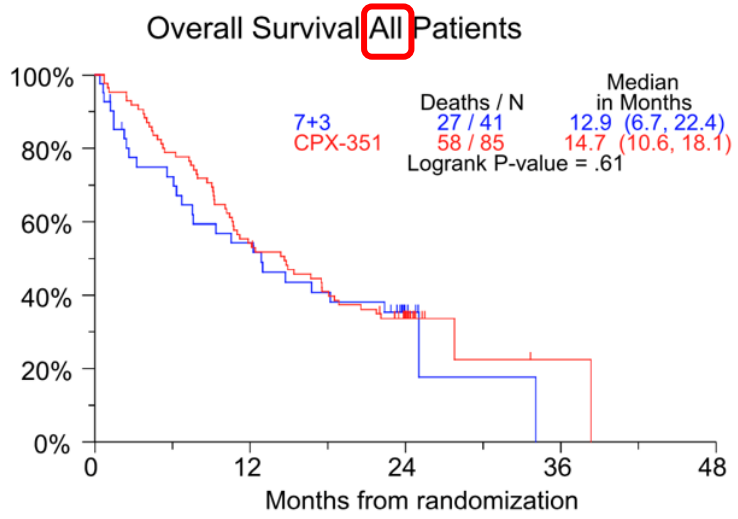
- <u>Phase 2 randomized trial</u>

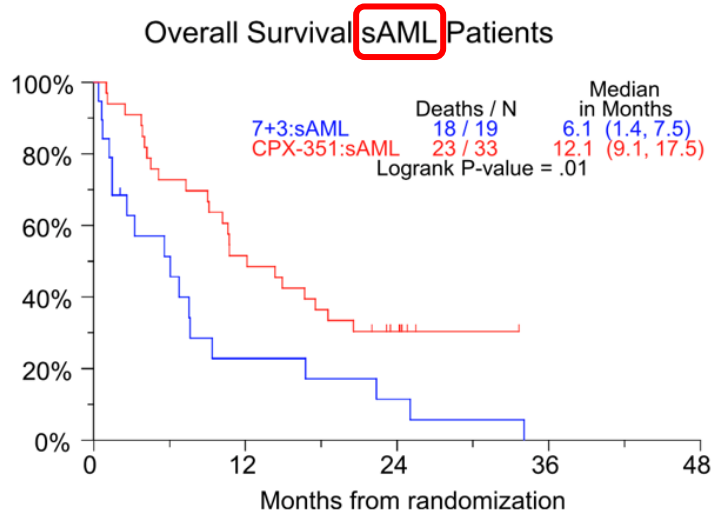
Inclusion criteria:

127, age > 60 y

Primary endpoint (CR + CRi):

- CPX: 66.7% (CR 48.8%)
- 3+7: 51% (CR 48.8%)





3:2

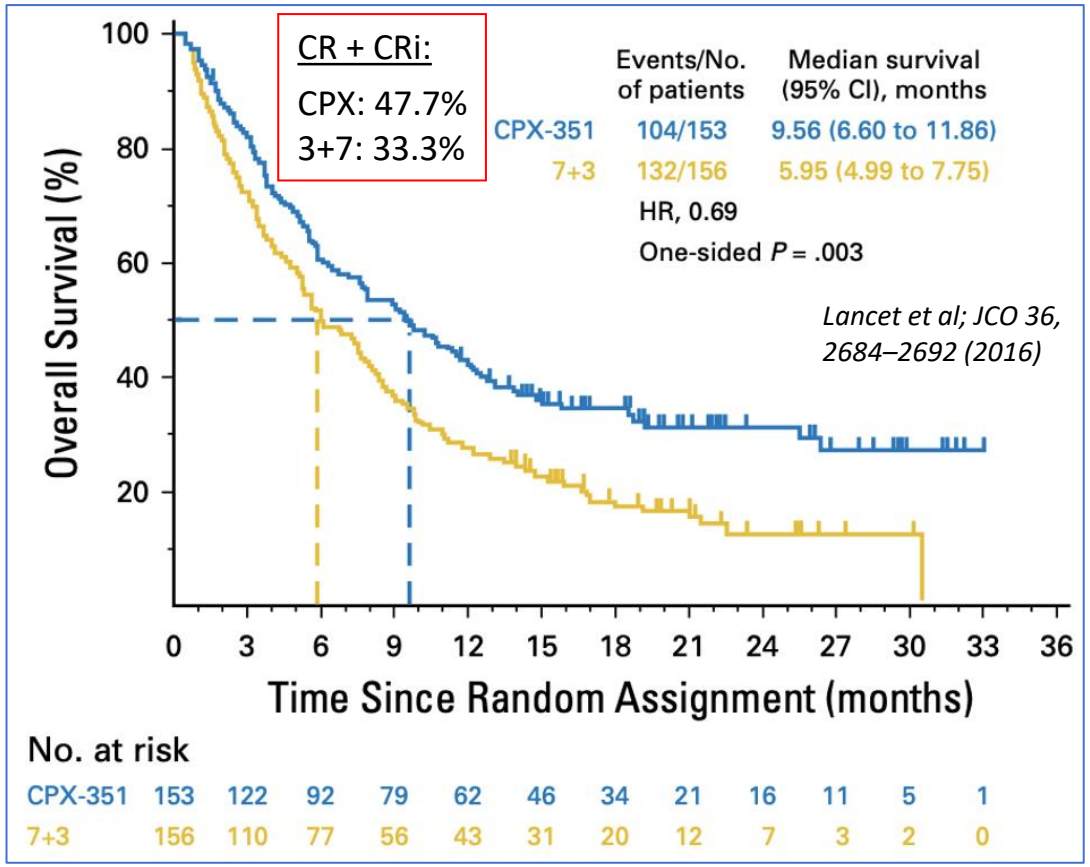
Lancet et al; Blood 123, 3239 (2014)

Bridge to transplantation – CPX-351

➢ Phase 3 randomized trial

309 randomly assigned, age 60-75 y, stratified for type of secondary disease:

- ✓ therapy-related
- ✓ post MDS (with/out prior HMA)
- ✓ CMML
- ✓ de novo with MDS-related cytogenetic abnormalities



Lancet et al; JCO 36, 2684–2692 (2016)

➢ **MPN-BP excluded** from registrational trial

CORRESPONDENCE OPEN

CPX-351 treatment in blast-phase myeloproliferative neoplasm (MPN-BP): real-world experience in 12 consecutive cases

Ilyas et al; Blood Cancer Journal 13:2 (2023)

12, CR 25% (3/12), PR 8% (1/12)

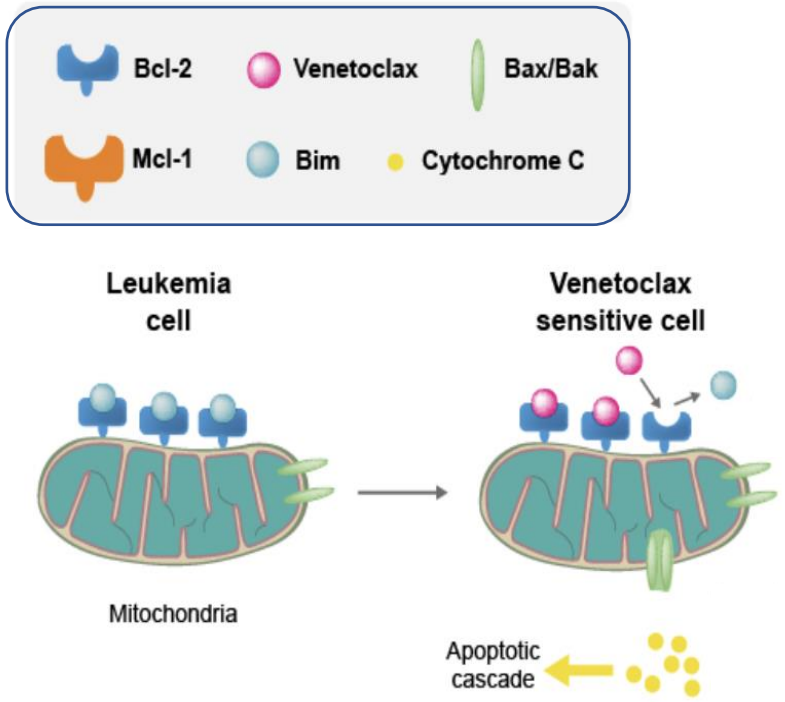
FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

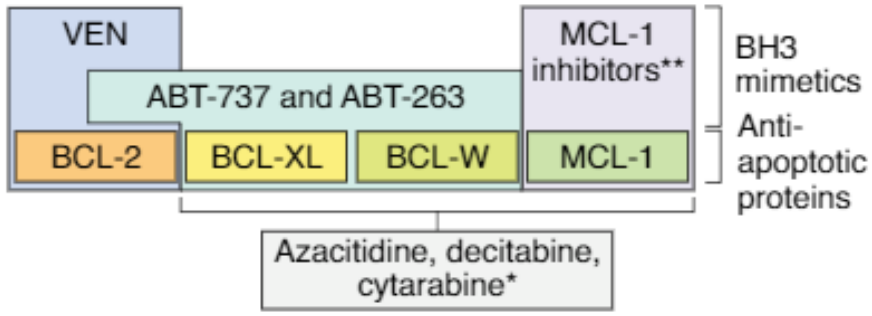
Phase II Study of CPX-351 Monotherapy in MPN-BP

ClinicalTrials.gov Identifier: NCT04992949

Non intensive treatment approach

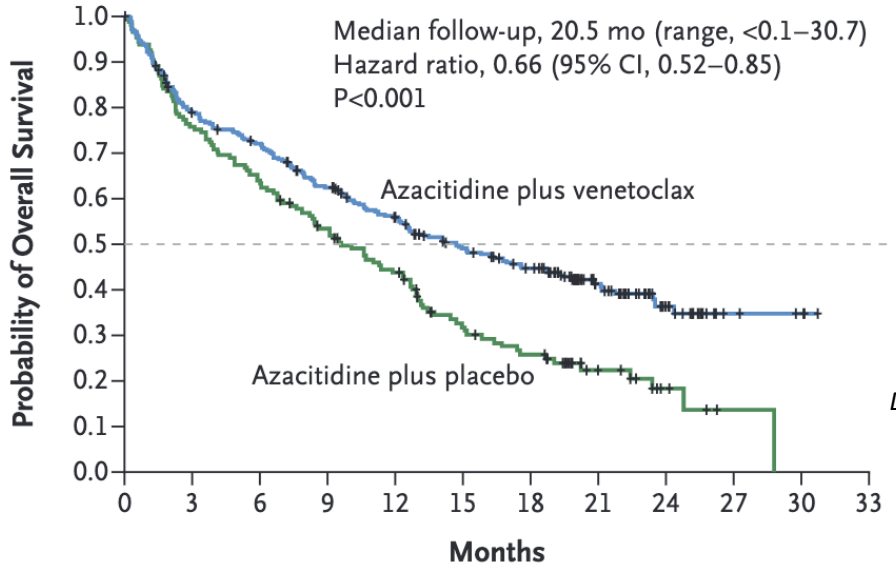
➢ **Hypometilating agents plus venetoclax**





Konopleva et al, Cancer Discovery 2016; 6:1106-1117

➢ **VIALE-A trial**: phase 3 randomized, double-blind placebo-controlled trial



DiNardo C et al; NEJM 383, 617–629 (2020)

✓ Preclinical evidence of dependence on other antiapoptotic BCL2 family members (MCL1, BCL-XL)

✓ MPN-BP **excluded** from registrational trials

Non intensive treatment approach

➢ Hypometilating agents plus venetoclax

✓ Low extra-hematological toxicity

✓ Potentially effective in selected subsets (i.e., *IDH1/2*)

Study	Design	Subset	Combination	Pt n	Outcomes
Gangat et al 2021	Retrospective	MPN-BP	HMA	32	CR/CRi 44%, OS 8 months
Tremblay et al 2020	Retrospective	MPN AP/BP	HMA	AP # 1, BP # 8	CR/CRi 33%, OS 4.2 months
Masarova et al 2021	Retrospective	MPN-BP	HMA, IC, cladribine, LDAC	31	ORR 50%
King et al 2022	Retrospective	MPN AP/BP	HMA, LDAC	AP # 6, BP # 21	ORR 52% in MPN-BP and 50% in MPN-AP

Gangat, et al. Am J Hematol 2021;96(7):781–9
Tremblay, et al. Leuk Res 2020;98:106456
Masarova, et al. Blood Adv 2021;5(8):2156–64
King, et al. Am J Hematol 2022;97(1):E7–e10

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 combination including decitabine and venetoclax

ENABLE (vENetoclax plus decitAbine treatment in Blastic phase of myeLoproliferative nEoplasms)

GIMEMA AML2420

EudraCT number 2020-006114-20
Clinical Trial number NCT04763928

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

Perspectives:

✓ Profound clonal responses

✓ Potential bridge to HSCT in fit pts

Caveat:

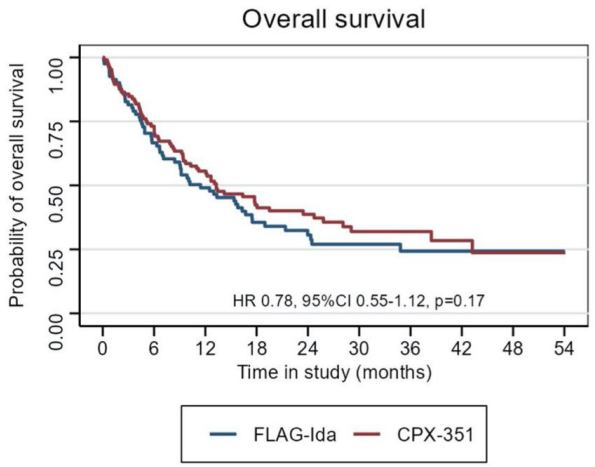
✓ Hematological toxicity

Bridge to transplantation - Summary

- ✓ **Induction** chemotherapy (including CPX-351)
- ✓ **Venetoclax**-based regimens
- ✓ **Frontline** transplant

UK NCRI AML19 Trial

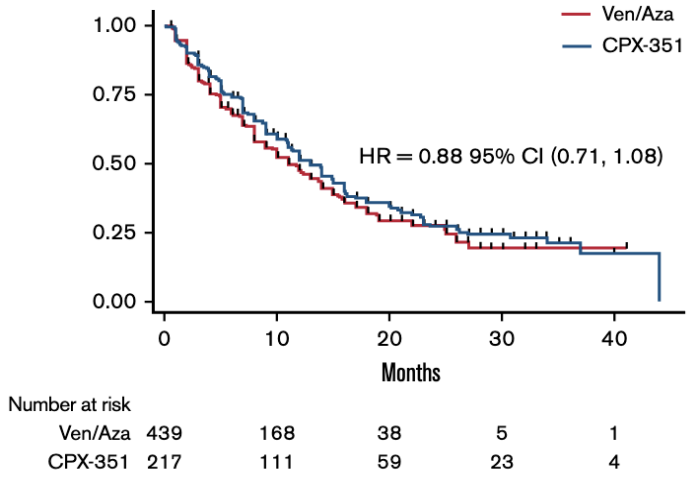
- Adverse risk AML and MDS
- 20% of secondary AML
- R 1:1 **FLAG-Ida vs CPX-351**



Othman; Blood Adv 2023

US retrospective real-world trial

- # 656 AML pts
- 38% of secondary AML
- # 439 **Ven-Aza**; #217 **CPX-351**

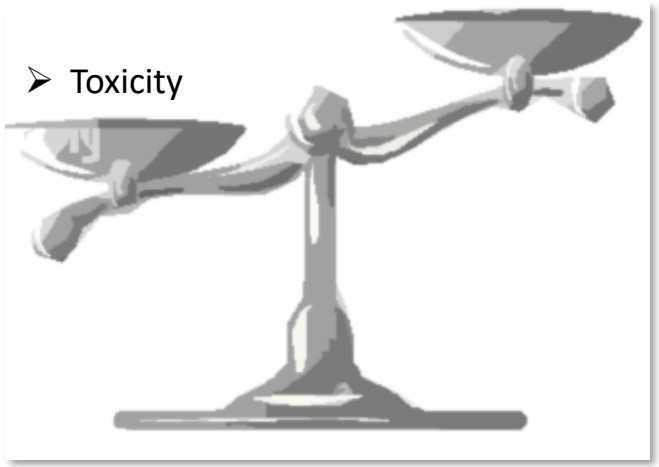


Matthews; Blood Adv 2022 (6);13:3997

Venetoclax-based regimens

➢ Pre-HSCT disease status

➢ Toxicity



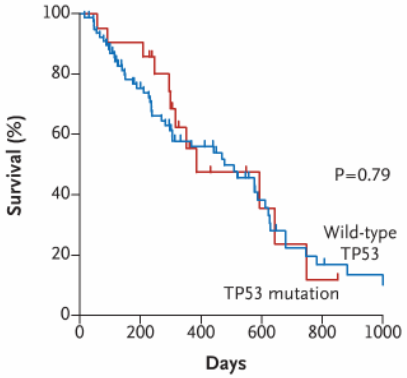
Tefferi & Bacigalupo; AJH 98(4):553-5 (2023)

Non intensive treatment approach

➢ **Hypometilating agents**

✓ Rationale for HMA in MPN-BP derived from the demonstrated efficacy in MDS and pauciblastic AML

TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes



✓ 10-days Decitabine 20 mg/sqm

✓ Transient bone marrow blast clearance

Welch et al, NEJM 2016; 375, 2023–36

✓ Complete responses generally scarce (about 10%) in blast phase

Study	Design	Subset	Treatment	Pt n	Outcomes
Andriani et al 2015	Retrospective	MPN-BP	AZA	19	OS 8 months
Badar et al 2015	Retrospective	MPN-BP	DEC	21	OS 7 months
Thepot et al 2010	Prospective	MPN-BP	AZA	26	ORR 38%; CR/CR1 12%

Andriani, et al. Leuk Res 2015;39(8):801–4
Badar, et al. Leuk Res 2015;39(9):950-6
Thepot, et al. Blood 2010;116(19):3735–42

→ Potential therapeutic option in unfit patients

Non intensive treatment approach - Other treatment options

- **Combination of RUXOLITINIB with chemotherapy or HMA**

Chemotherapy	○ *Devillier et al BJH 2016*: # 5; combination of Rux 10 mg bid with 3+7; ORR 4/5 pts
Decitabine	○ *Rampal et al Blood Adv 2018*: Phase 1 (#14) dose escalation trial; Phase 2 (#15): Rux 25 mg bid; ORR 45%
Azacitidine	○ *Drummond et al ASH 2020*: Phase 1b trial (PHAZAR); #34 (20 evaluable for response); ORR 50%
Ven + Azacitidine	○ *Systchenko et al BJH 2023*: #5; ORR 80% (4/5), median OS 13.4 months

  - ✓ Overall, limited single-center experiences and case reports
  - ✓ Often patients **evolved to BP upon ruxolitinib**; feasible in combination with chemotherapy

- **IDH1/2 inhibitors:**
  - ○ Ivosidenib, Enasidenib in presence of *IDH1/2* mutations, respectively
    - ✓ Ongoing trials in combination with VEN +/- HMA

Conclusions

- **In eligible patients**, allogeneic **HSCT** is the only curative option in blastic phase of MPN

- Intensive chemotherapy **does not improve survival** compared to supportive care **if not followed by allogeneic transplant**

  → unuseful in pts not eligible for HSCT

- **Bridge to transplant:**
  - Standard chemotherapy or CPX-351
  - Frontline HSCT
  - **Venetoclax plus HMA** could ameliorate outcome in some subsets and potentially represent the most suitable strategy

- In **elderly/not eligible** patients: non intensive approaches (HMA +/- Ven) or supportive care