FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

CONVEGNO FISiM

Firenze, CSF Montedomini
"Il Fuligno"
24-25 ottobre 2025

International clinical studies in CMML

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Disclosures of Francesco Onida

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda					√	√	
Kyowa kirin					√		
Menarini StemLine					√		
Johnson & Johnson					√		

Approved drug therapies in CMML

US FDA

- Azacitidine
- Decitabine
- Decitabine + Cedazuridine

EMA

- Azacitidine, only in dysplastic CMML with 10-19% blasts/promonocytes (CMML-2)

- Hydroxyurea: *Not formally approved as a "disease-modifying drug" but standard of care for proliferative CMML* with leukocytosis or splenomegaly

- ESAs: may be beneficial in low-risk, anemic patients.

DACOTA randomized phase 3 study of decitabine ± HY vs HY in advanced proliferative CMML

CMML
WBC > 13 G/L

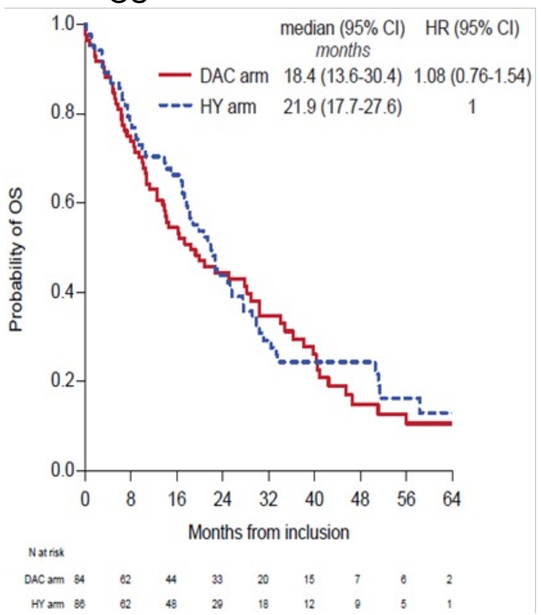
≥2 criteria:
Marrow blasts 5%
Abnormal K (except –Y)
ANC >16 g/L
Hb <10 g/dL
Platelets <100 g/L
Splenomegaly >5 cm
Or extramedullary localization

Decitabine 20mg/m²/d x5d q.28d **N=84**
± HY during the first 3 cycles

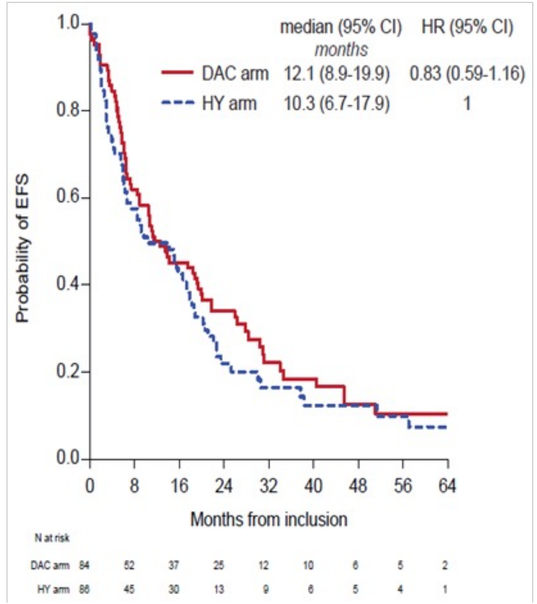
HY **N=84**

Primary Endpoint: Event-free Survival
- Disease Progression
- Transformation to AML
- Death

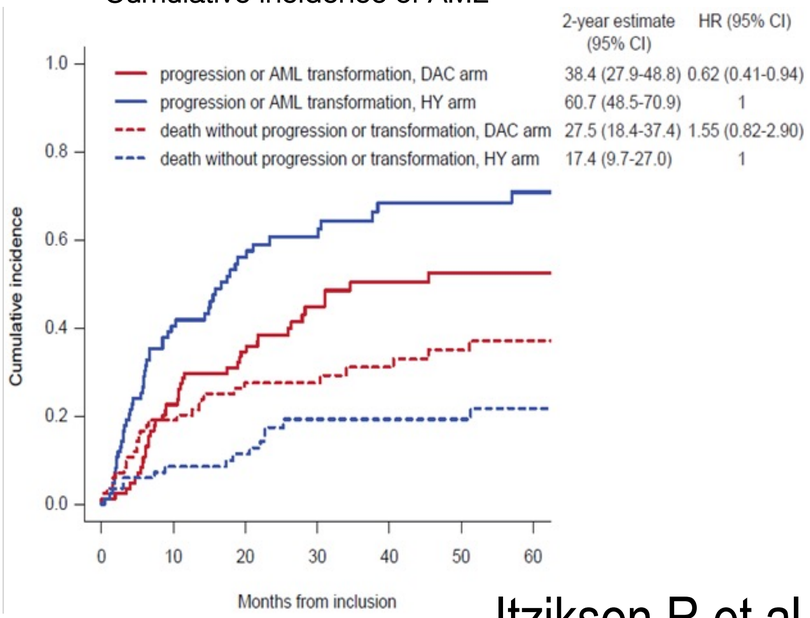
OS



EFS



Cumulative incidence of AML



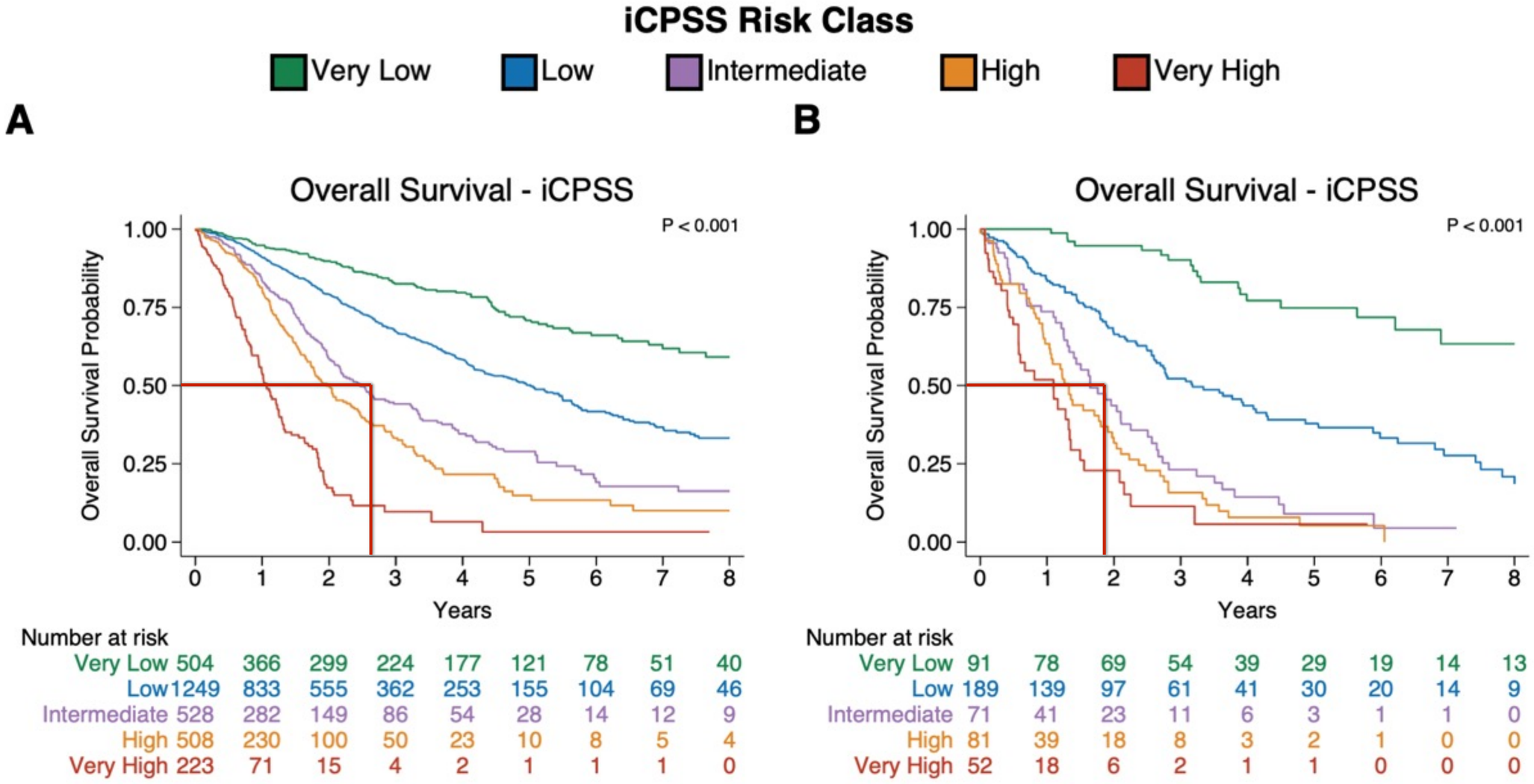
Itzikson R et al. JCO 2023

DNMTi – Clinical Pearls

- ORR rates 45-50%
- CR rates 7-17%
- Time to response: 3-4 cycles
- Median duration od response: 12-18 months
- Survival after progression: 3-6 months

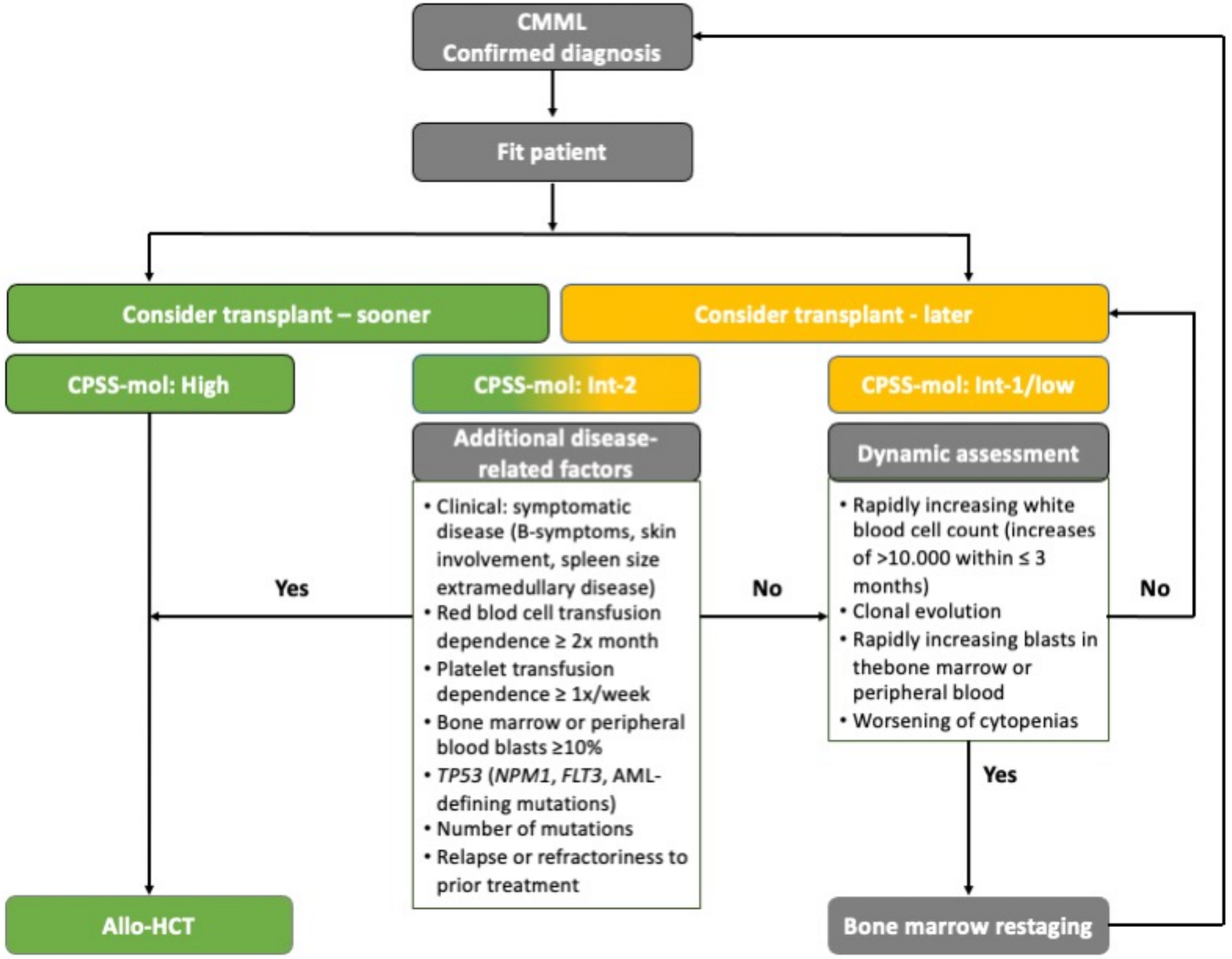
Fenaux P et al. Lancet Oncol 2009; Garcia-Manero G et al. Blood 2006; Tucker & Patnaik AJH 2019

CMML: Life expectation



Lanino L. ASH 2024/Submitted

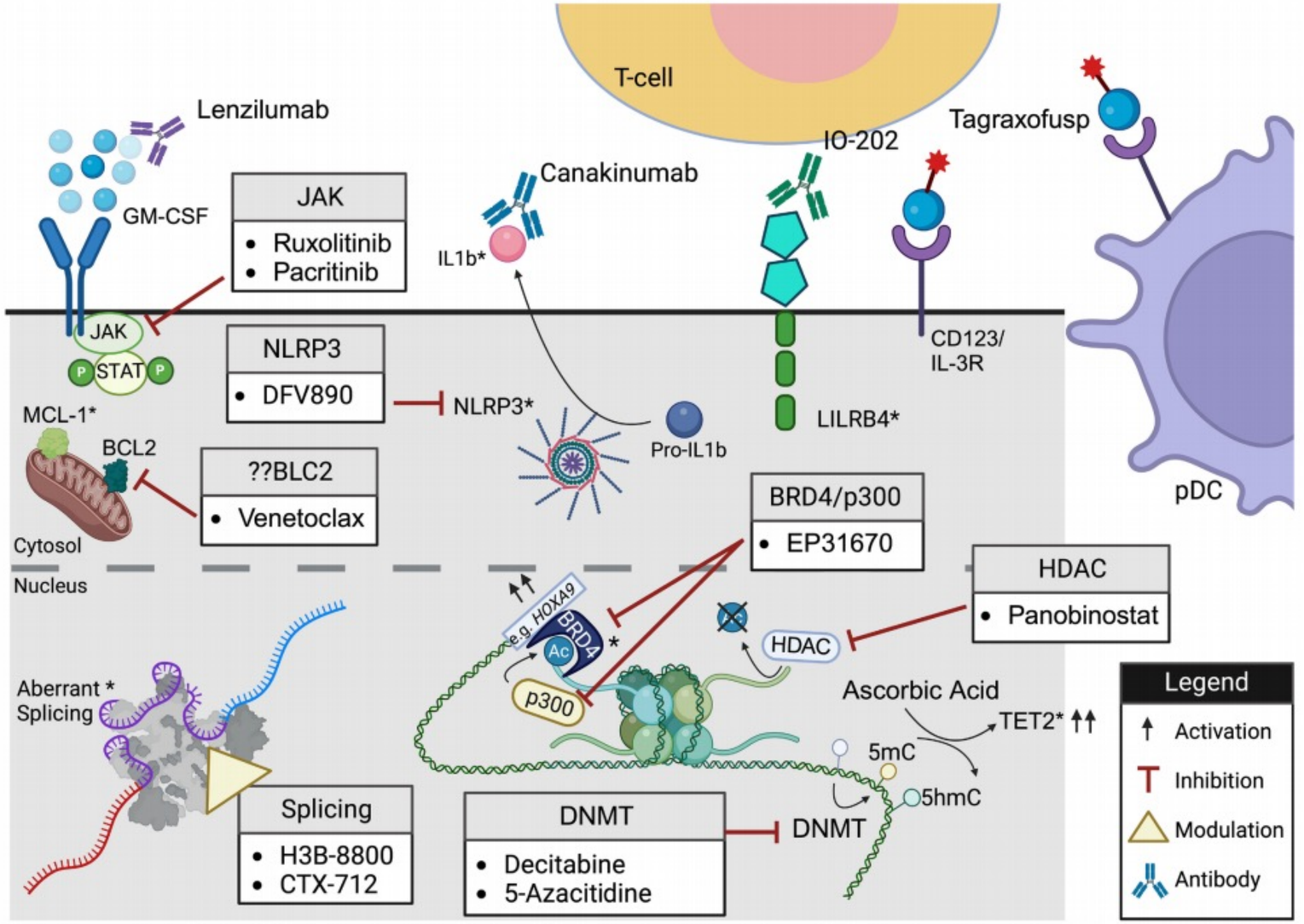
Allo-SCT in CMML: recommendations from the EBMT PH&G Committee



- In absence of data from RCT, remains unclear whether debulking and/or CR status is advantageous for allo-HCT outcomes
- Pre-HCT debulking strategies may result in worsening cytopenias, increased transfusion dependence with ensuing complications and/or infections that may preclude proceeding to transplant
- **Upfront transplantation** without prior disease-modifying treatment **should be preferred whenever possible irrespective of BM blast count** (to maximize chances of reaching allo-HCT)

Onida F. et al, Blood 2024; 143 (22) 2227-2244

Established and investigational therapeutic targets in CMML



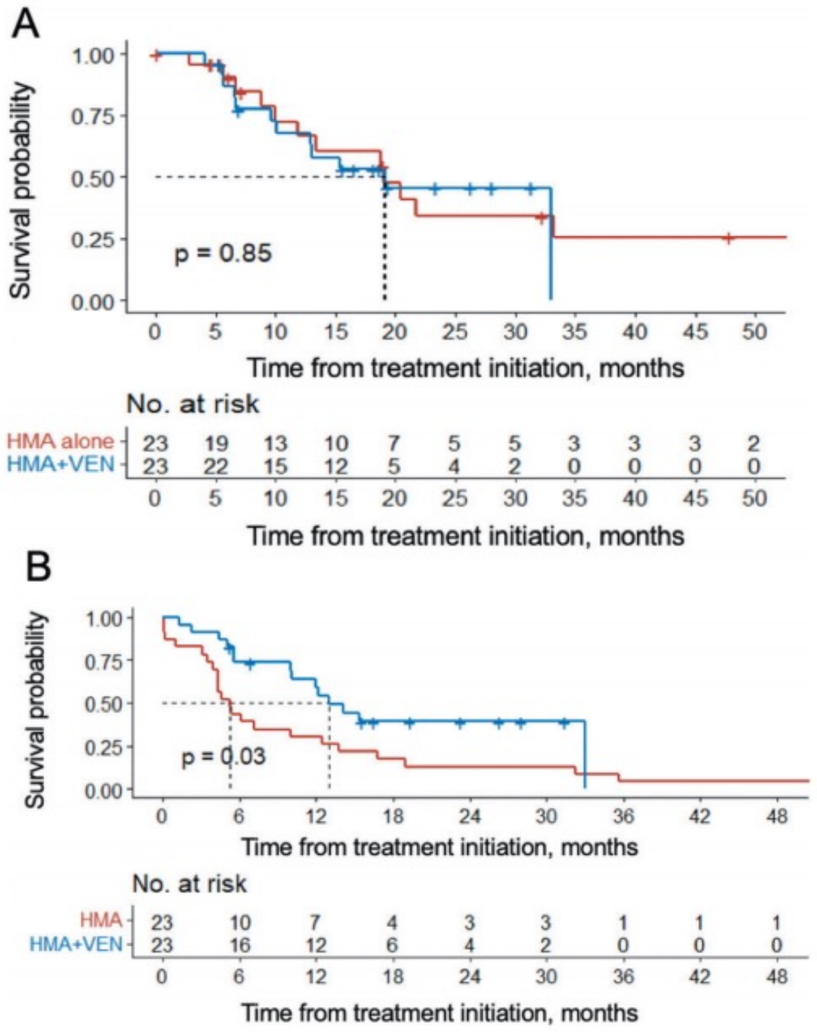
Marando L et al Haematologica 2025

Venetoclax + HMA: a PS matched multicenter cohort study

	Overall (*n* = 89)	CMML (*n* = 51)	CMML-BT (*n* = 38)
Age (years), median (IQR)	71 (64, 76)	70 (63, 75)	73 (67, 78)
Gender, *N* (%)			
Female	27 (30%)	12 (24%)	15 (39%)
Male	62 (70%)	39 (76%)	23 (61%)
ECOG performance status, *N* (%)			
0	7 (13%)	4 (16%)	3 (10%)
1	38 (70%)	19 (76%)	19 (66%)
2	6 (11%)	2 (8.0%)	4 (14%)
3	3 (5.6%)	0 (0%)	3 (10%)
Hemoglobin (g/dL), median (IQR)	10.70 (8.70, 12.20)	10.30 (8.10, 12.10)	10.95 (9.05, 12.53)
Platelet (x 10^9/L), median (IQR)	93 (51, 155)	82 (55, 168)	100 (45, 139)
WBC (x 10^9/L), median (IQR)	13 (7, 34)	14 (8, 33)	11 (6, 36)
AMC (x 10^9/L), median (IQR)	3.1 (1.6, 7.0)	3.8 (1.7, 7.9)	2.6 (1.3, 5.7)
Peripheral blasts (%), median (IQR)	1.00 (0.00, 7.00)	1.00 (0.00, 4.50)	1.00 (0.00, 14.00)
BM blasts (%), median (IQR)	12.0 (5.0, 18.8)	10.0 (5.5, 14.5)	20.0 (4, 47)
Complex karyotype (%), median (IQR)	6 (7%)	4 (11%)	2 (8%)
CMML subtype, *N* (%)[a]			
Myelodysplastic	–	23 (45%)	–
Myeloproliferative	–	28 (55%)	–
CMML stage, *N* (%)[b]			
CMML–1	–	18 (35%)	–
CMML–2	–	33 (65%)	–
CPSS–Mol, *N* (%)			
Low	–	0 (0%)	–
Intermediate 1	–	6 (12%)	–
Intermediate 2	–	15 (30%)	–
High	–	29 (58%)	–
CMML response, *N* (%)			
CB	–	6 (12%)	–
PMR	–	3 (6%)	–
OMR	–	25 (50%)	–
CR	–	11 (22%)	–
CMML ORR (%)	–	90%	–
CMML-BT response, *N* (%)			
MLFS	–	–	8 (23%)
PR	–	–	4 (11%)
CRi	–	–	10 (29%)
CRh	–	–	1 (3%)
CR	–	–	6 (17%)
CMML–BT ORR (%)	–	–	83%

CONCLUSIONS

- higher response & LFS, but no OS gain
- May facilitate **bridging to HSCT** in eligible patients
- **Toxicities & optimal VEN schedule** require further prospective study



Tremblay D et al. Leukemia 2025

Recruiting

Azacitidine Combined With Venetoclax in Patients With Higher-risk Chronic Myelomonocytic Leukemia (AVENHIR) (AVENHIR)

ClinicalTrials.gov ID NCT05768711

Sponsor Groupe Francophone des Myelodysplasies

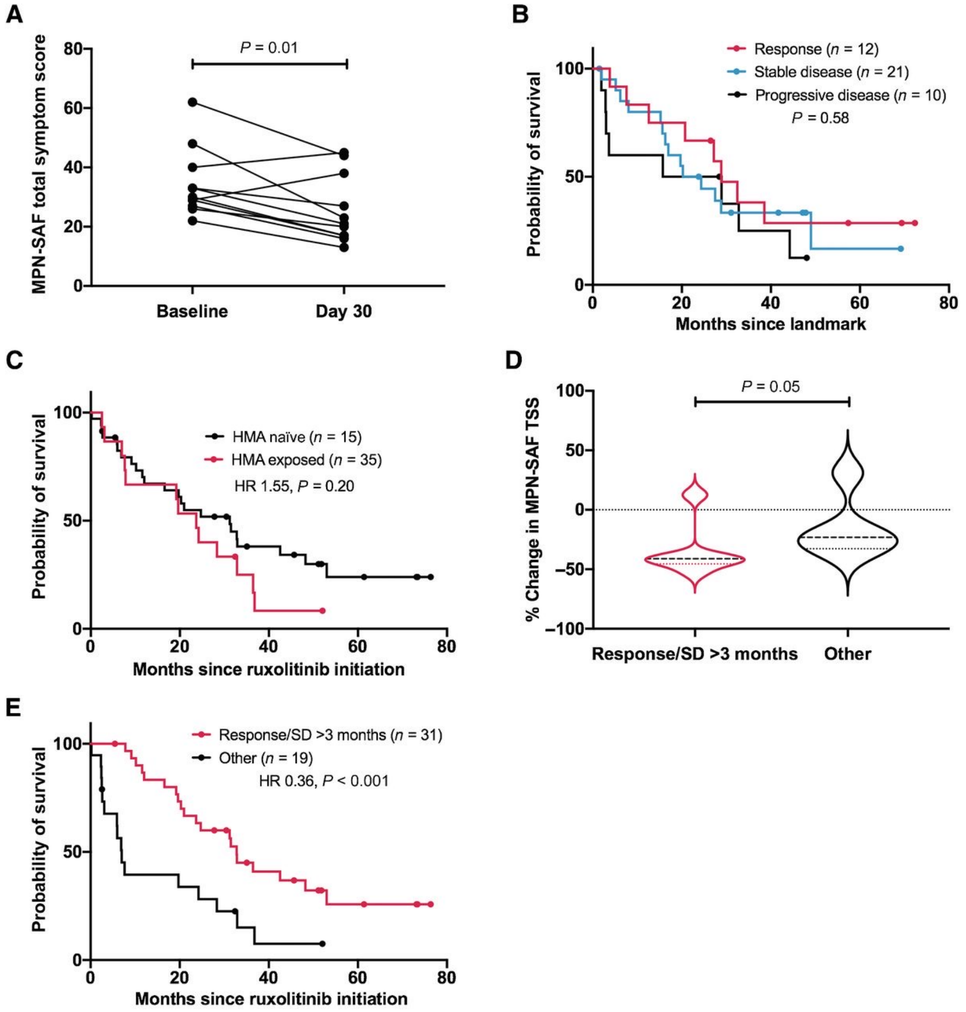
Information provided by Groupe Francophone des Myelodysplasies (Responsible Party)

Last Update Posted 2025-05-09

Ruxolitinib in CMML: a phase I/II study

Table 2. Summary of best response to ruxolitinib.

Response	Phase I ($n = 20$)	Phase II ($n = 30$)	Total ($n = 50$)
Complete remission	0	1	1
Partial remission	0	2	2
Optimal marrow response	0	3	3
Partial marrow response	1	0	1
Clinical benefit (total patients)	**6**	**6**	**12**
Erythroid	0	1	1
Platelet	1	0	1
Spleen	2	5	7
Erythroid + spleen[a]	1	0	1
Platelet + spleen[a]	2	0	2
Spleen response (% of eligible)[b]	5 (55.5%)	5 (35.7%)	10 (43.5%)
Stable disease	11	11	22
Progressive disease	2	7	9
Overall response rate	7 (35%)	12 (40%)	19 (38%)

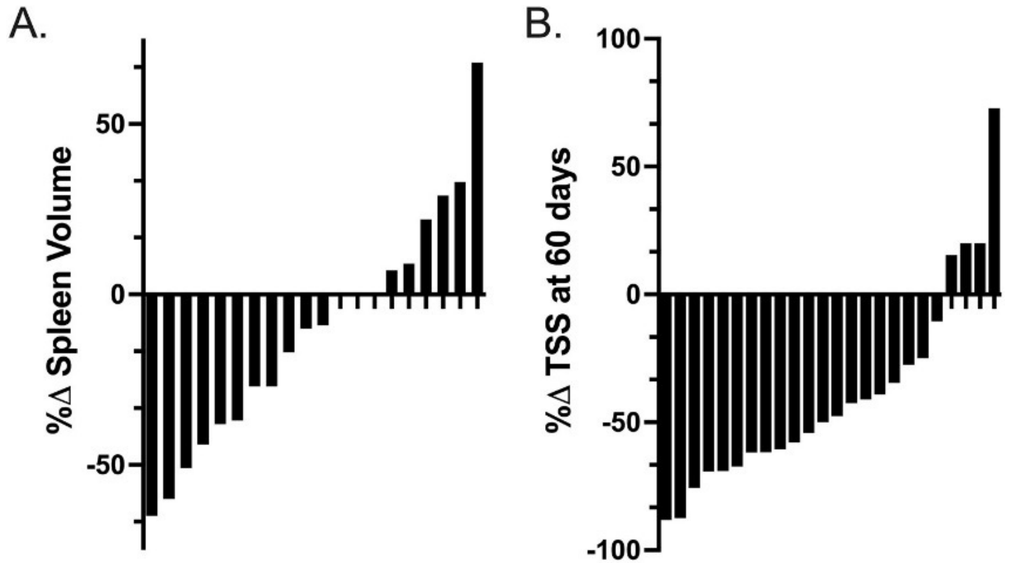


Hunter HM et al. Clin Cancer Res. 2021;27(22):6095-6105

Efficacy and Safety of Ruxolitinib for Treatment of Symptomatic CMML: Results of a Multicenter Phase II Clinical Trial

Eligibility criteria: symptomatic splenomegaly and/or MPN-SAF total score (TSS) >17

- 29 pts (9/2019-6/2022)
- Ruxo 20 mg BID
- ORR by MDS/MPN IWG criteria: 17% (10%PR, 7% mR)
- 69% SD, 14% NE
- Clinical benefit 66% (19/29)
- 30% (6/20) achieved ≥ 35% SVR
- 50% (10/20) had 10% or more SVR
- 54% MPN-SAF TSS >50% reduction at 60 days
- all but four patients demonstrated an improvement in MPN-SAF TSS

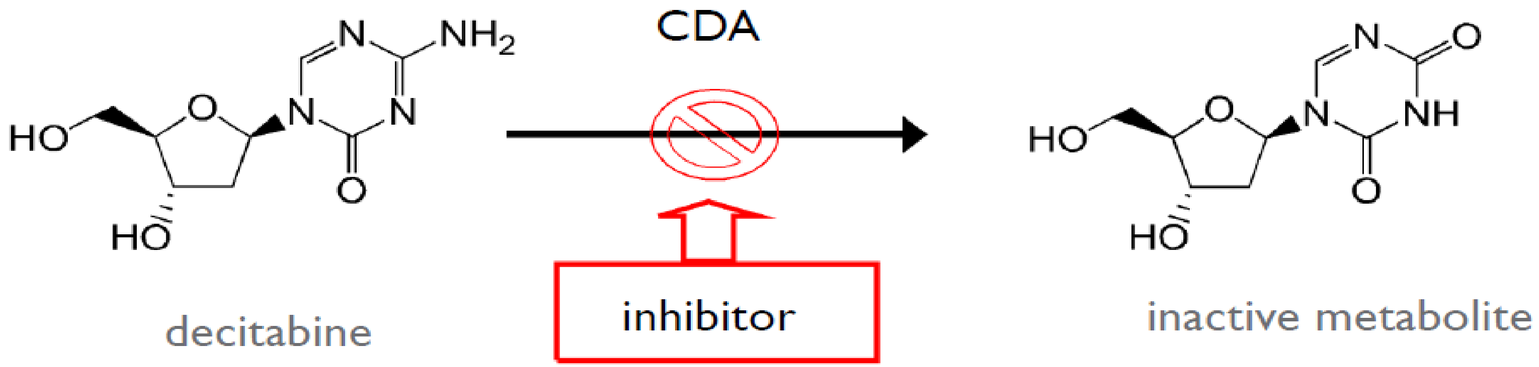


American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Padron E et al. Blood (2022) 140 (Supplement 1): 1101–1103.

ASTX727 (Oral decitabine + cytidine deaminase inhibitor cedazuridine) provides oral HMA option

- DNMTi's when administered orally are rapidly degraded by Cytidine Deaminase (CDA) upon first-pass in GI tract and liver
- Administering decitabine orally with a CDAi allows greatly enhanced bioavailability of decitabine at low doses
- May avoid potential GI toxicities associated with high oral doses
- Potential for improved efficacy because of increased systemic exposure due to systemic CDA inhibition, and more convenient chronic administration



OS and LFS with ASTX727 in CMML

Oral Decitabine/Cedazuridine in Chronic Myelomonocytic Leukaemia (CMML)

Retrospective Subset Analysis of Phase 2 & 3 Trials

Dysplastic-type CMML (n=25)
Proliferative-type CMML (n=8)

+

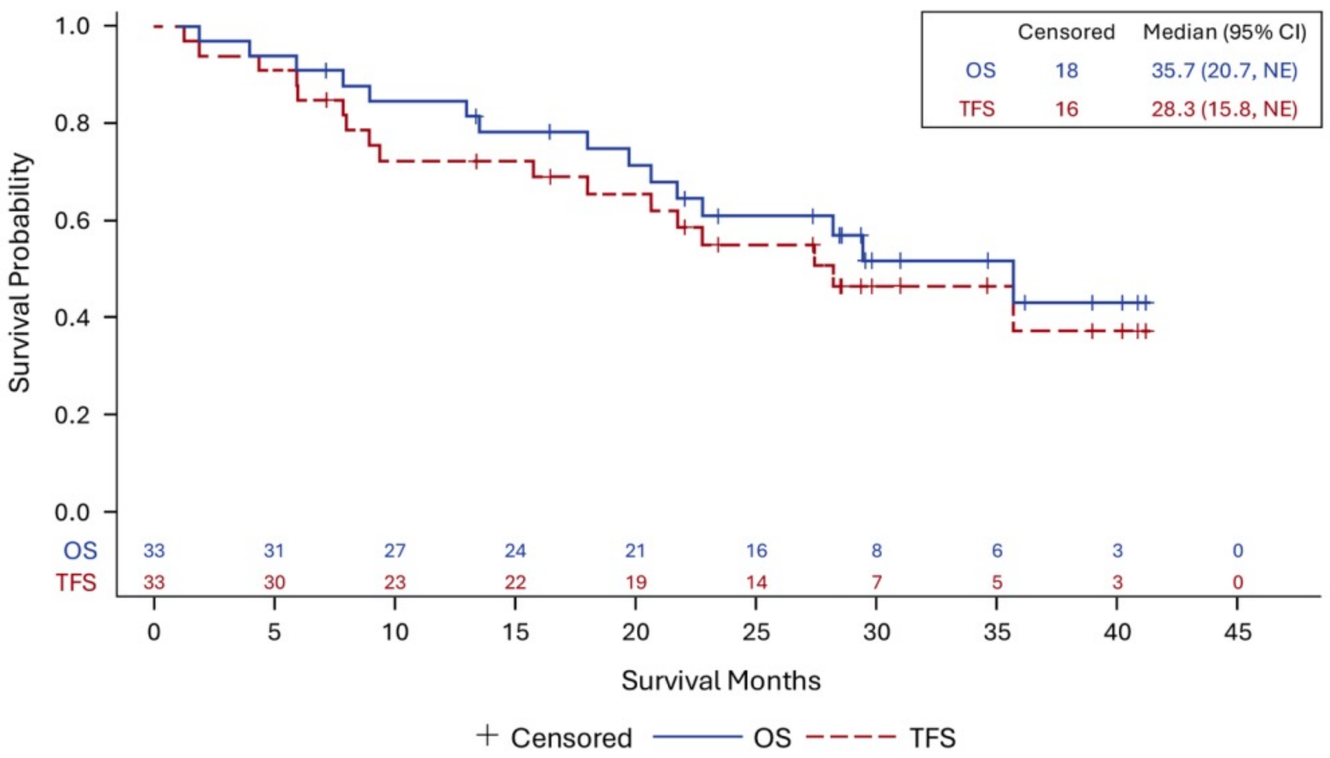
Oral decitabine 35 mg
+ cedazuridine 100 mg

Key Findings

- Overall response rate: 76%
  Complete response rate: 21%
- Median overall survival: 35.7 months
  Median transformation-free survival: 28.3 months
- Nearly 1/2 of transfusion-dependent patients attained transfusion independence for ≥12 weeks

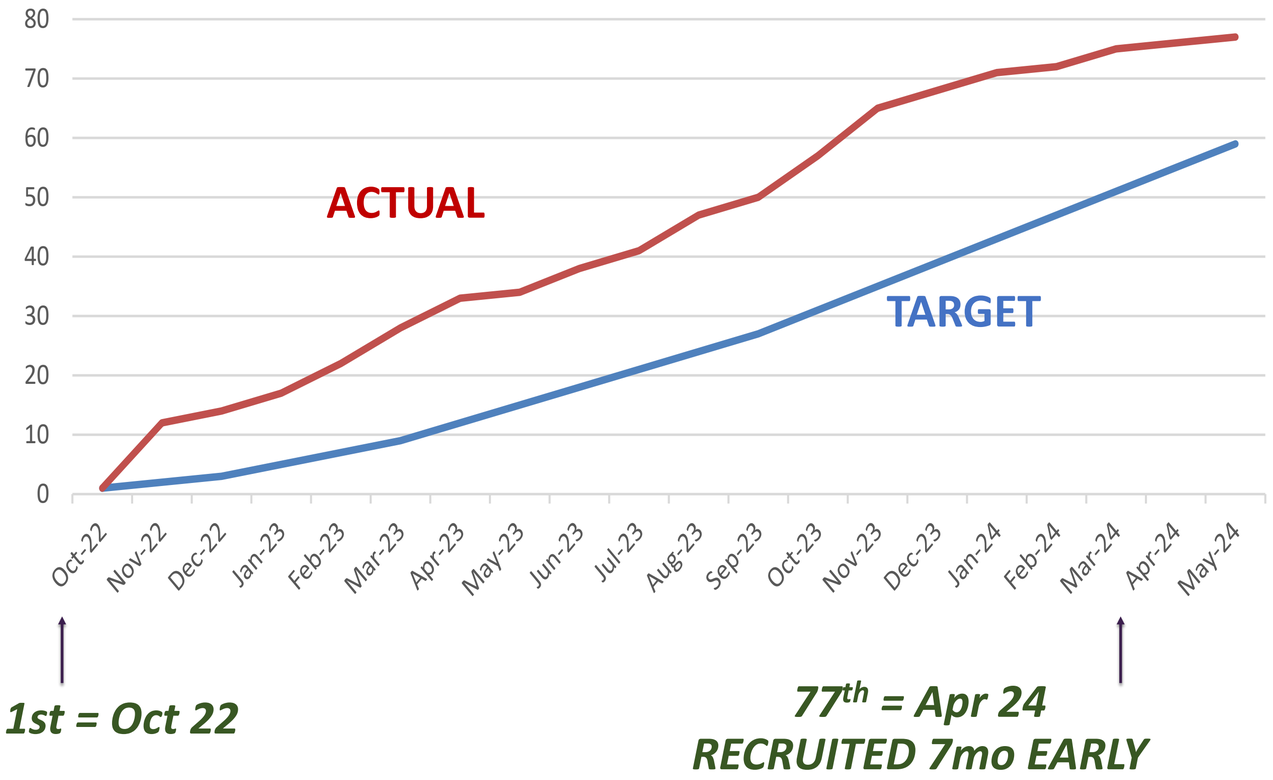
Study Impact

Oral decitabine/cedazuridine showed durable responses and was well tolerated in high-risk CMML, supporting future dedicated trials to identify patients most likely to benefit



Savona et al. *BJH* 2025.

*A*STX727 vs HU/BSC in *M*DS/*M*PN *O*verlap Syndromes (AMMO)



Chief Investigator - Dr Daniel Wiseman

- ASTX727 vs HU 2:1
- Enrolled 77 patients in 18 months

Results: ASH ORAL – December 2025

MDS/MPN INTERNATIONAL WORKING GROUP

ABNL MARRO
A BASKET STUDY OF NOVEL THERAPY FOR UNTREATED MDS/MPN AND RELAPSED/REFRACTORY OVERLAP SYNDROMES

ABNL MARRO – A MDS/MPN IWG Study

A Basket Trial of *Novel* therapy combinations in untreated *M*DS/MPN *A*nd *R*elapsed/*R*efractory *O*verlap Syndromes (*ABNL-MARRO*)

By courtesy of Michael Savona

MDS/MPN INTERNATIONAL WORKING GROUP

ABNL MARRO
A BASKET STUDY OF NOVEL THERAPY FOR UNTREATED MDS/MPN AND RELAPSED/REFRACTORY OVERLAP SYNDROMES

ABNL MARRO Objectives

1. To test new therapies in MDS/MPN
2. To validate / update the MDS/MPN IWG Response Criteria
3. To develop biomarkers for response to therapy in MDS/MPN
4. To improve understanding of MDS/MPN

By courtesy of Michael Savona

MDS/MPN INTERNATIONAL WORKING GROUP

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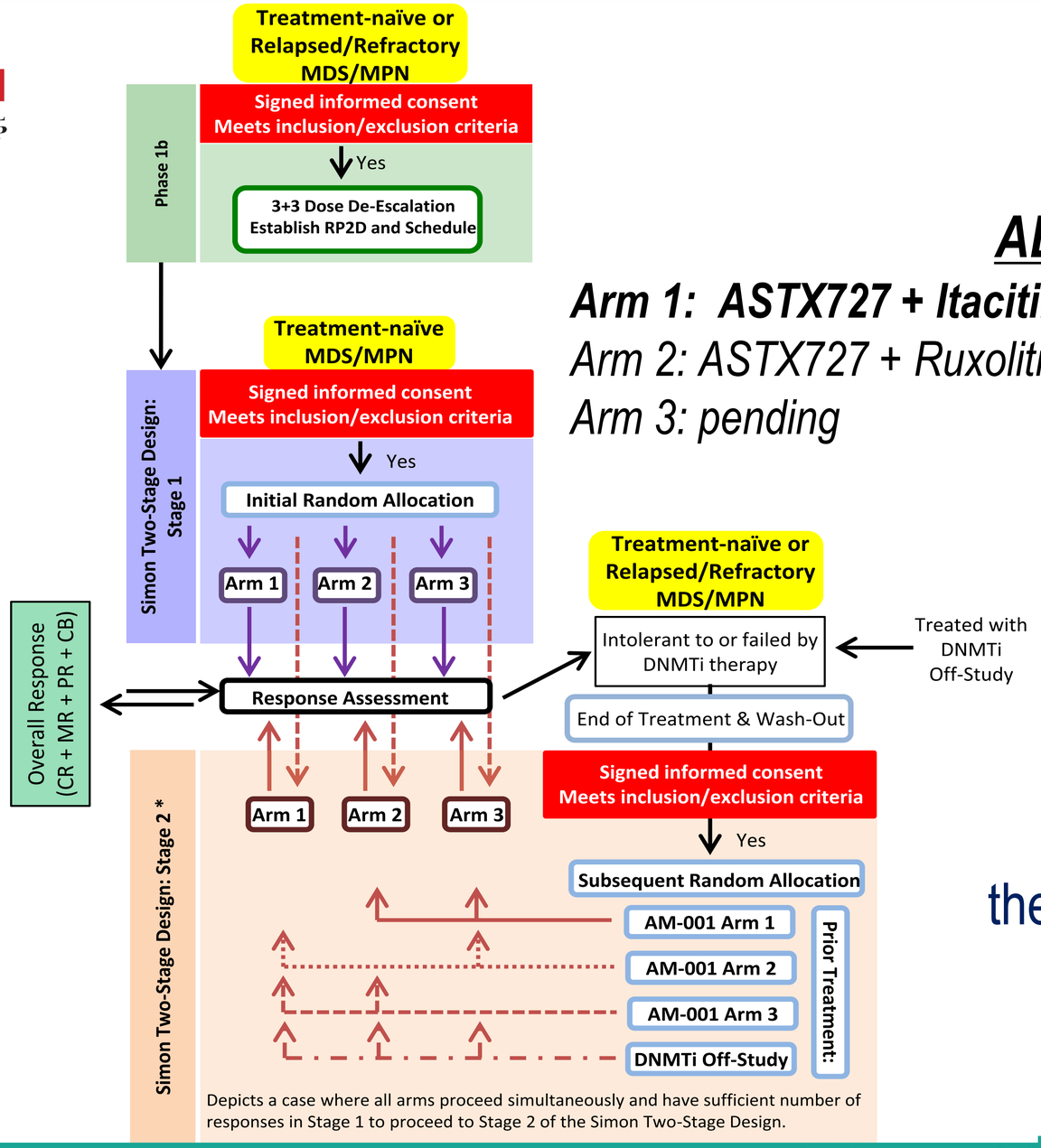


ABNLMARRO-001

Arm 1: ASTX727 + Itacitinib (JAK1-i) – closed to enrollment

Arm 2: ASTX727 + Ruxolitinib (opens q3 2025)

Arm 3: pending

ABNLMARRO 001

A Phase Ib-II Trial of Novel Combination Therapies in MDS/MPN patients naïve to therapy or who fail primary therapy with DNMTi (DNA methyltransferase inhibitors)

Moyo et al. *BMC Cancer 2022.*

MDS/MPN INTERNATIONAL WORKING GROUP

ABNL MARRO
A BASKET STUDY OF NOVEL THERAPY FOR UNTREATED MDS/MPN AND RELAPSED/REFRACTORY OVERLAP SYNDROMES

ABNL MARRO-002 (PROSPERA)

CLINICAL STUDY PROTOCOL

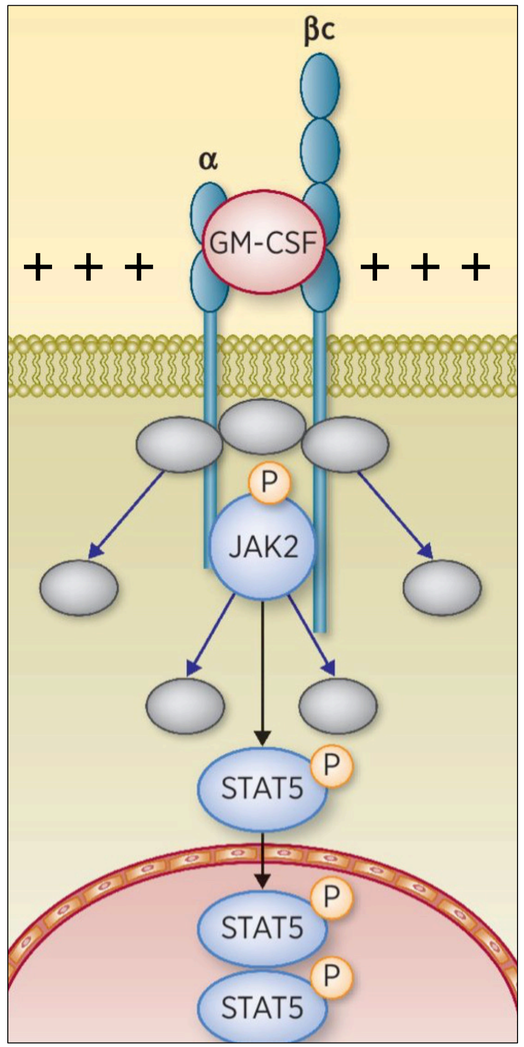
PROSPERA: A Randomized Phase 2 Study of Pacritinib vs. Hydroxyurea in Patients with Advanced Proliferative Chronic Myelomonocytic Leukemia (CMML)

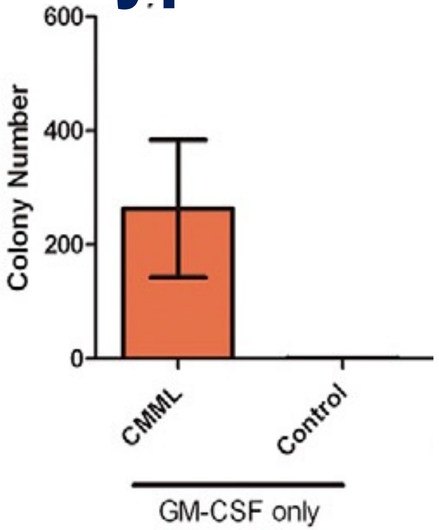
Main targets of Pacritinib:

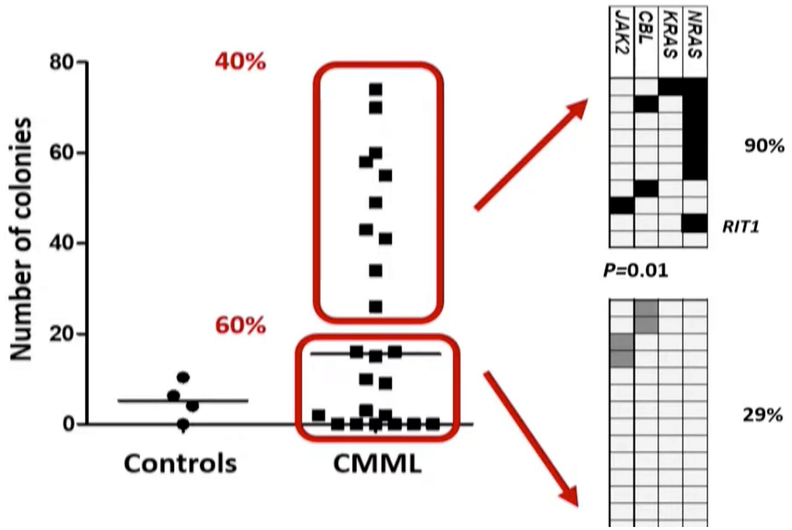
- **JAK2**
- **FLT3**
- **IRAK1 (*Interleukin-1 Receptor–Associated Kinase 1*)**
- **CSF1R**

By courtesy of Michael Savona

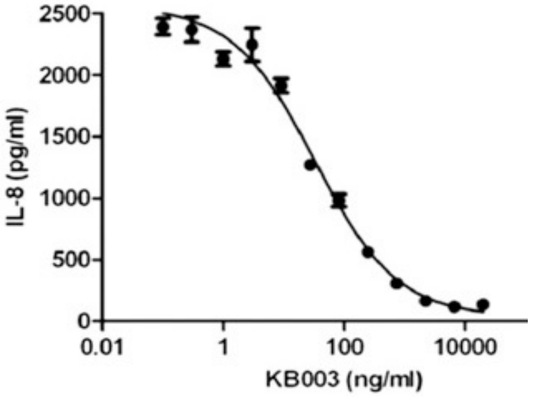
Targeting GM-CSF Hypersensitivity: LENZILUMAB





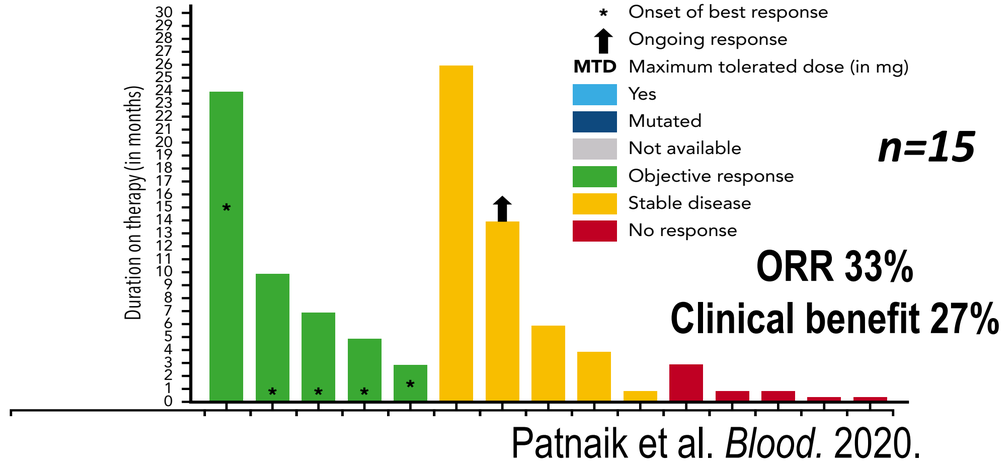


- **moAb v GM-CSF**
- E*x vivo* efficacy:



blood **Letter to *Blood***

Phase 1 study of lenzilumab, a recombinant anti–human GM-CSF antibody, for chronic myelomonocytic leukemia



Patnaik et al. *Blood.* 2020.

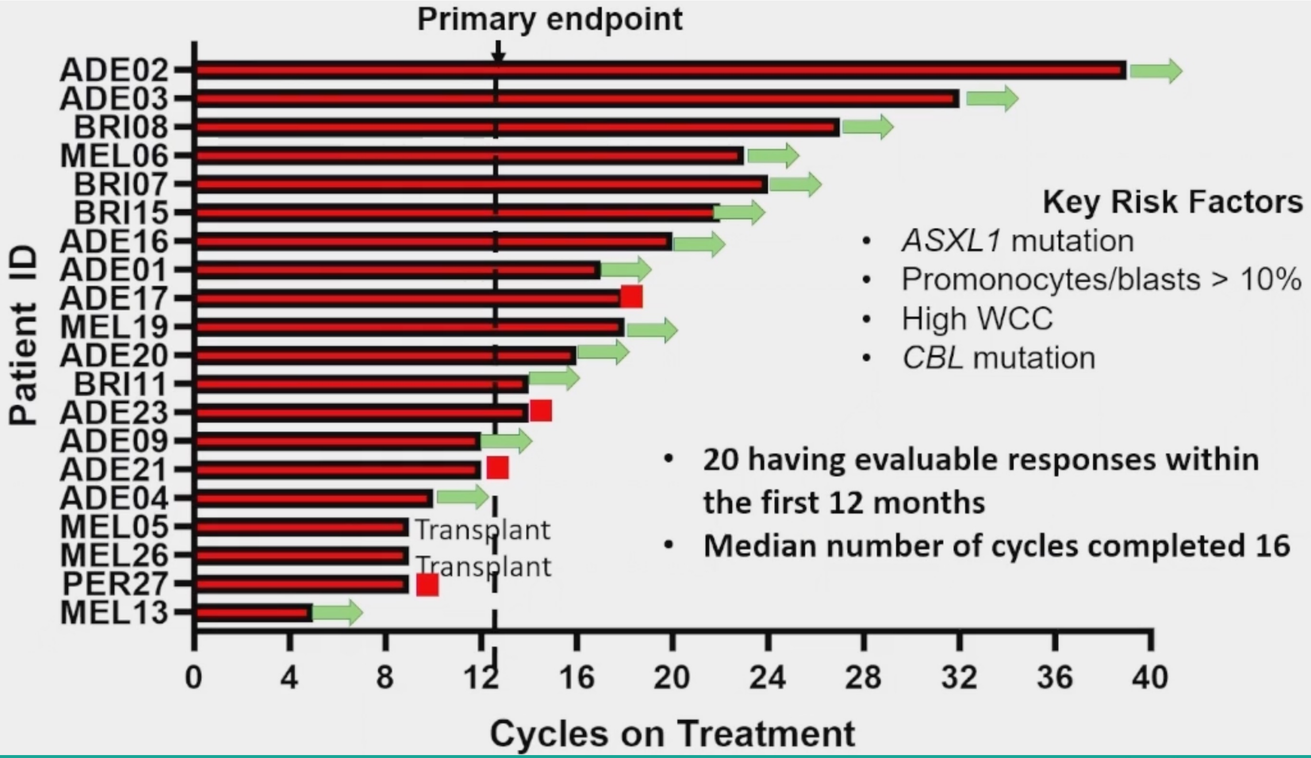
Padron et al. *Blood.* 2013. Geissler et al. *Leukemia.* 2016. Solary E. *Clin Cancer Res.* 2016.

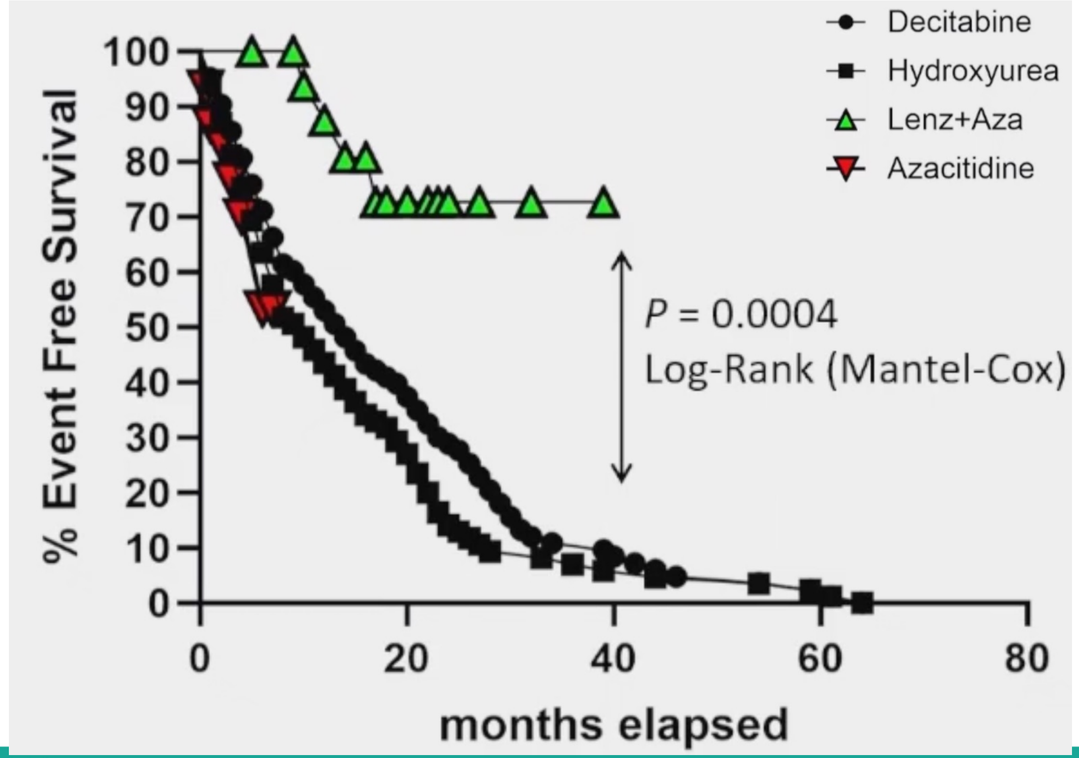
Combination therapy with lenzilumab and azacitidine

PREACH-M:
- **PRE**cision Approach to **CH**ronic **M**yelomonocytic Leukaemia
- Ph2 (2022→)

R
- TET2 mut ***(Low risk)*** → AZA + VIT C
- RAS mut ***(High risk)*** → AZA + **LENZILUMAB**

- N = 32 (May 2025)
- 55% *ASXL1*-mutated
- CR 41% ORR 95%
- Durable responses (esp in CBL/TET2 mut)



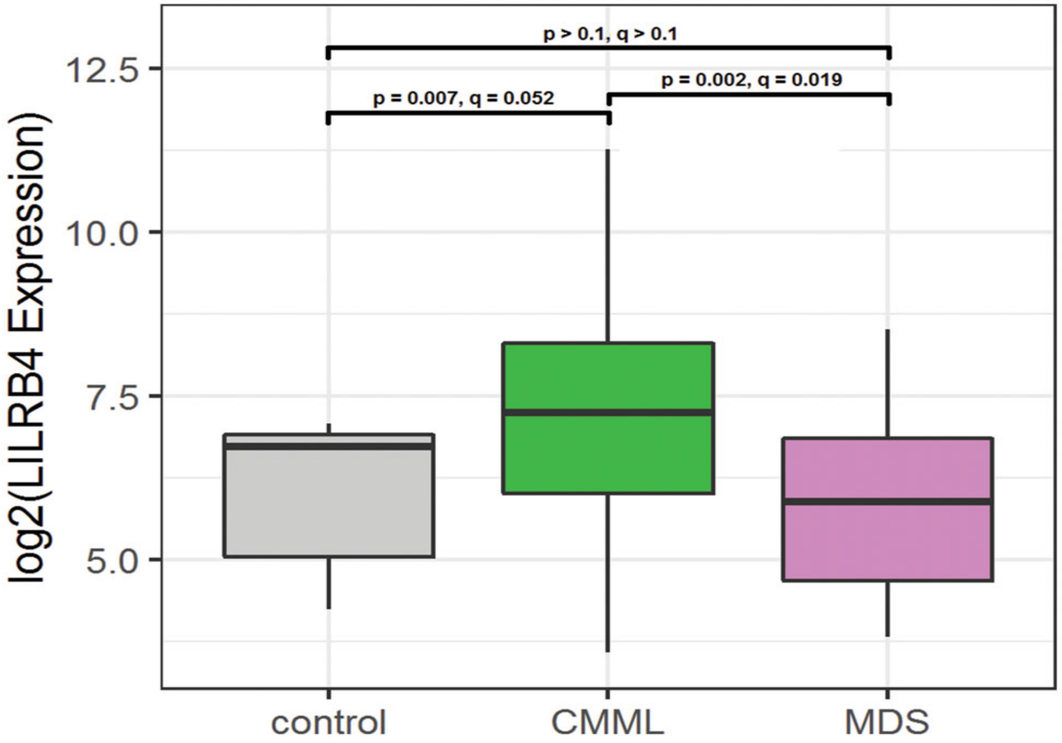


Hiwasi et al. ASH. 2024 / Thomas et al. EHA 2025.

IO-202 mAB targets LILRB4 - upregulated on monocytes

LILRB4 (ILT3): inhibitory receptor on monocytic cells → immune evasion and T-cell suppression.

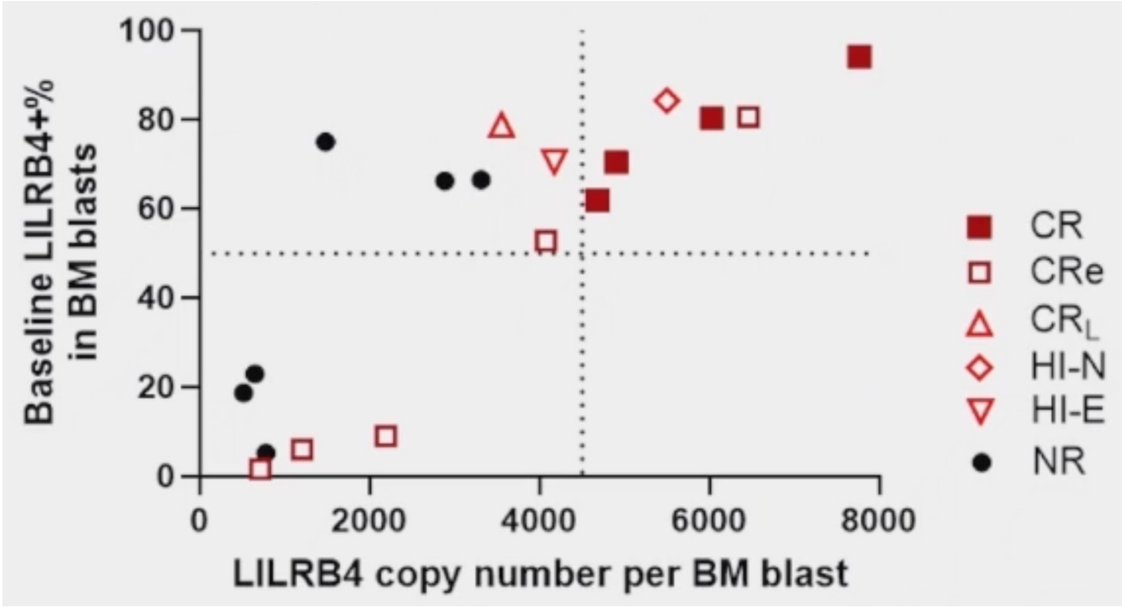
Highly expressed in CMML (& monoblastic AML)



IO-202 + AZA ± VEN in R/R CMML

[Ph1; NCT04372433; US Multicenter]

Ph1: IO-202 + AZA: *First 18 pts*



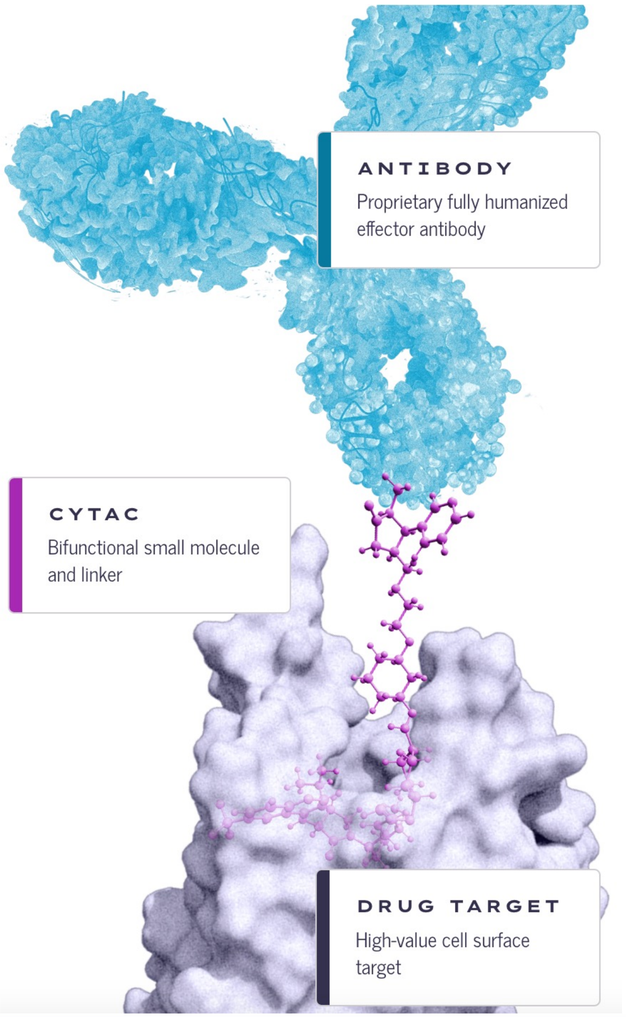
CR 50%
ORR 67%

All high expressors responded

Chien et al. *Leuk Lymphoma.* 2020

Mannis et al. *ASH.* 2024.

CCL2 is upregulated only on abnormal monocytes and can be exploited

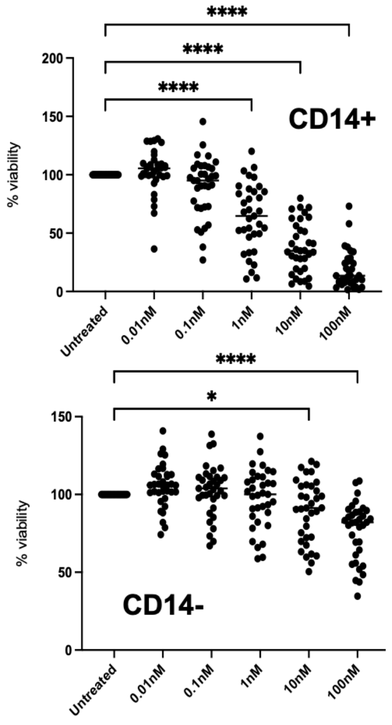


Small molecules bound to antibodies

CCL2 present in 95% of malignant monocytes and <5% normal monocytes

STX0712 depleted 60-90% CD14+ monocytes with average 3nM potency

Synthetic CCL2 peptide conjugates to warhead

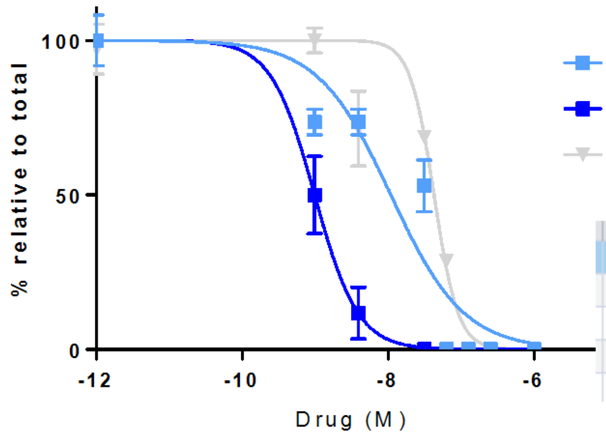


Sam Butterworth

Dan Wiseman

MC210807 – Onvansertib in RASmut CMML (Phase 1)

- R/R/Intolerant MPN-CMML
- Three dose levels 6 mg/m2, 9mg/m2 and 12 mg/m2
- Dosed day 1-21, every 28 days
- Six patients currently enrolled



TEST	RESU	SC	BURL	MUTATION	TR
SRSF2	POS		48%	SRSF2 P95L	
SETBP1	POS		47%	SETBP1 D868N	
ASXL1	POS		48%	R693*	
NRAS	POS		43%	G12D	

Sample	Drug	IC50
L-010	O	6.9nM
	O+D	977pM
Normal	O	86.2nM
	O+D	20nM
L-023	O	56nM
	O+A	32nM
L-040	O	10.8nM
	O+D	977pM
	O+A	42.3nM

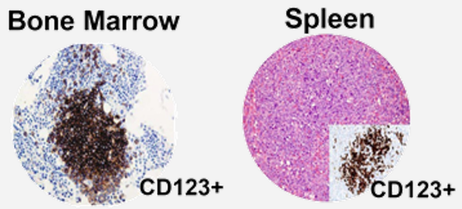
NCT05549661

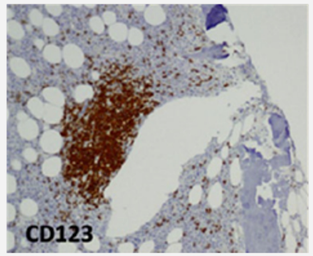
By courtesy of M. Patnaik

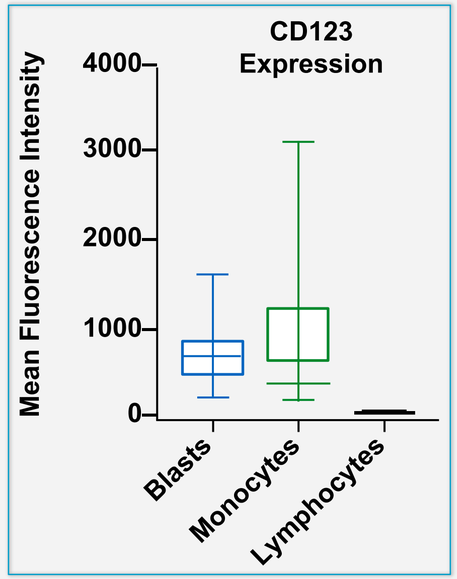
CD123 in CMML

CD123⁺ cell populations in CMML

- **Expressed in key disease compartments[1,2]**
- **Present on both CMML blasts and monocytes[3]**
- **Clonal pDCs in BM and tumor microenvironment[4]**







blood neoplasia

Tagraxofusp, a CD123-targeted therapy, for chronic myelomonocytic leukemia: final results of a phase 1/2 study

- Design: Non-randomized, multicenter, open-label; 42 pts (15 treatment-naïve, 22 R/R)
- Dose: RP2D = 12 μg/kg IV days 1–3 (21/28-day cycles)
- Safety:
  - Manageable, no new safety signals
  - Frequent AEs: fatigue (49%), hypoalbuminemia (46%), nausea/hypokalemia (44%)
  - Capillary leak syndrome: 23% (G3-4: 13%); tumor lysis: 13%
  - Hematologic G3-4 AEs: thrombocytopenia (28%), anemia (13%), neutropenia (13%)

Phase 1/2 study of tagraxofusp in CMML: Efficacy

- No CR/PR; 1 CCyR + marrow response in each cohort
- Stable disease: 40% (naïve) / 59% (R/R)
- Clinical benefit: 27% (naïve) / 23% (R/R)
- 2 R/R patients bridged to allo-HCT
- Median OS: 11.2 mo (naïve), 15.6 mo (R/R)

Conclusions: Tolerable, modest single-agent efficacy. Future role in combinations

Patnaik MM et al. Blood Neoplasia 2025

NCT05038592 Recruiting

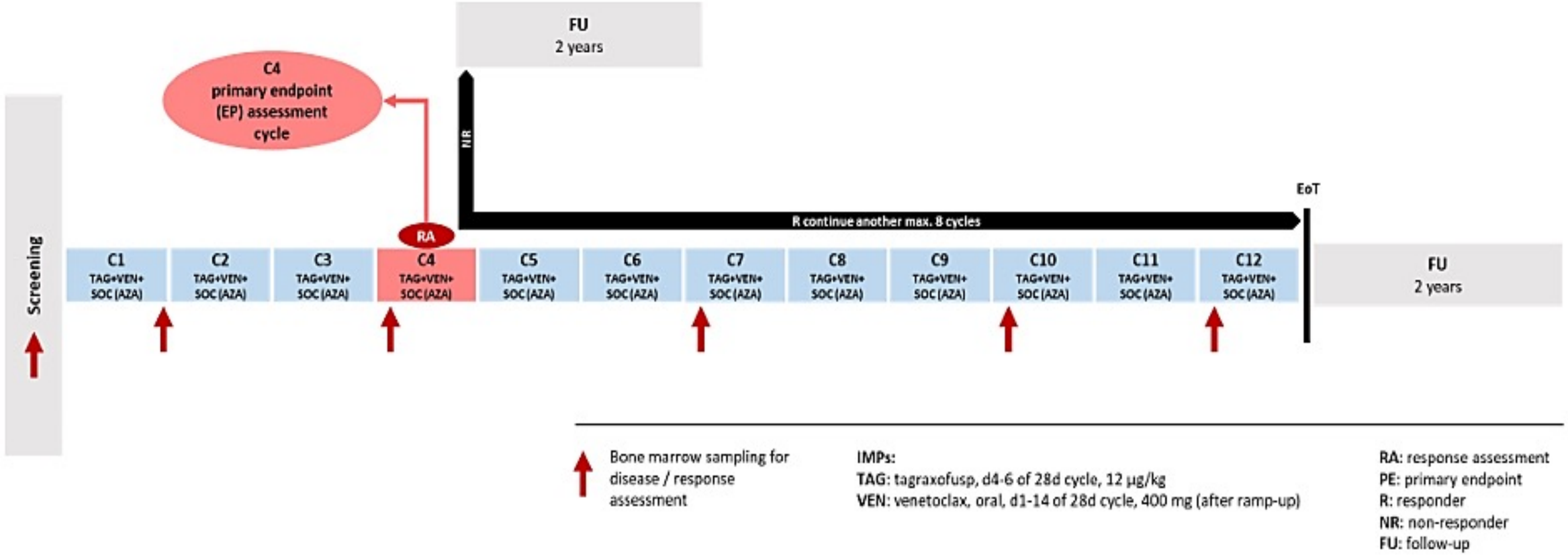
Phase I/II Study of Tagraxofusp in Combination With Decitabine for Patients With Myelomonocytic/Myeloproliferative Neoplasm and High Risk Myelodysplastic Syndromes

EMSCO
European
Myelodysplastic Syndromes
Cooperative Group

Phase II study of standard of care therapy AZA combined with VEN and TAG in patients with higher-Risk CMML (PATROL)

PATROL: Study Summary

Design: Open-label, single-arm, multicenter, phase II study



EBMT: New Proposal

Observational Non-Interventional Study on the Role of Allogeneic Hematopoietic Cell Transplantation (allo-HCT) in Chronic Myelomonocytic Leukemia (CMML)

"ChroMMAllo Study"

- Francesco Onida - EBMT-CMWP

ChroMMAllo Study Objectives

Primary Objectives:
- OS at 1 & 3 years
- % patients transplanted
- Bridge vs upfront transplant

Secondary Objectives:
- PFS, relapse, NRM
- GVHD, engraftment, infections
- Impact of disease biology & pre-HCT therapy
- Post-HCT relapse management
- Cause of death analysis

ChroMMAllo Study Design

Recruitment: Patients will be enrolled at the time of their referral to the BMT center, regardless of whether they proceed with transplantation

Referral for allo-HCT

Pre-transplant evaluation

Allo-HCT

Post-HCT follow-up (3, 6, 12 mo, annually)

Relapse management

Cause of death analysis

Conclusions and take-home messages

- CMML is an **aggressive hematopoietic stem cell malignancy** of older adults, with a **median survival of <36 months**
- **Integration of genetic and clinical variables** appears to provide the maximal information **for clinical decision making**, and is therefore highly recommended
- **HMAs** in CMML have limited efficacy in a minority of patients, with short duration of response
- **Ruxolitinib** may be helpful in symptomatic patients and/or in case of large splenomegaly
- **Allo-HSCT** may provide **durable remission for selected patients with CMML,** but it is still associated with a **high relapse rate and mortality risk**
- **New agents** are currently under active **development** in CMML-specific trials
- **Combination strategies** including drugs with different mechanisms of action **should also possibly be investigated**

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