FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE



CONVEGNO FISiM

Firenze, CSF Montedomini
"Il Fuligno"
23-24 ottobre 2026

Terapia della LMMC e trapianto

Francesco Onida

ASST Fatebenefratelli-Sacco
Università degli Studi di Milano

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.

Hypomethylating agents in CMML: key clinical studies

Study	n	Design	Treatment	ORR (CR)	Median OS (mo)	Key finding
RETROSPECTIVE / POOLED ANALYSES						
Aribi (2007)	19	Retrospective, pooled trials	DEC	69% (58%)	19	MD Anderson decitabine studies; CMML subset
Wijermans (2008)	31	Retrospective, pooled trials	DEC	26% (10%)	15	CMML subset from three decitabine trials
Costa (2011)	38	Retrospective, single centre	AZA	39% (11%)	12	Mixed on/off-protocol azacitidine cohort
Duchmann (2018)	174	Retrospective, multicentre	AZA / DEC	52% (17%)	23	Large real-world HMA cohort
Coston (2019)	121	Retrospective	AZA / DEC	41–56% (<20%)	31 (vs 18*)	Response depends on assessment criteria
COMPARATIVE REAL-WORLD COHORTS						
Pleyer (2021)	949 (412 HMA)	Retrospective, multicentre	HMA vs HU	—	20.7 vs 15.6†	Adjusted OS favoured HMA
Mayo (2026)	457 (78 HMA)	Retrospective, single centre	HMA vs other	Not reported	No significant difference	OS from diagnosis: 35 mo (HMA) vs 23 mo (HU); NS
PROSPECTIVE CMML TRIALS						
Drummond (2014)	32	Phase II, UK multicentre	AZA	17% (7%)	16	Dedicated CMML trial; limited activity
Santini (2018)	43	Phase II, single arm	DEC	47.6% (16.6%)	17	Prospective CMML-specific study
DACOTA (2023)	170	Randomised phase III	DEC vs HU	63% vs 35%	18.4 vs 21.9	First randomised CMML trial; EFS 12.1 vs 10.3 mo

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

CMML
WBC > 13 G/L

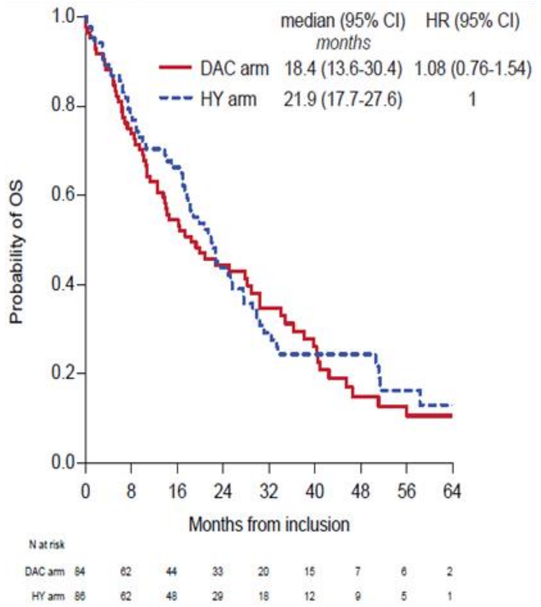
≥2 criteria:
Marrow blasts 5%
Abnormal K (except –Y)
ANC <16 g/L
Hb <10 g/dL
Platelets <100 g/L
Splenomegaly >5 cm
Or extramedullary localization

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

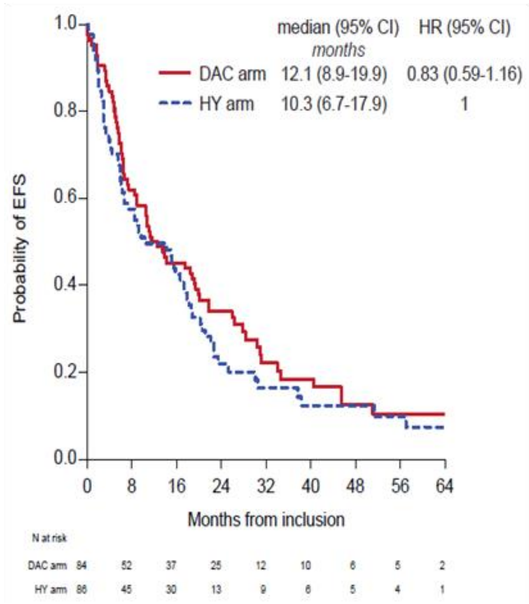
HY **N=84**

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

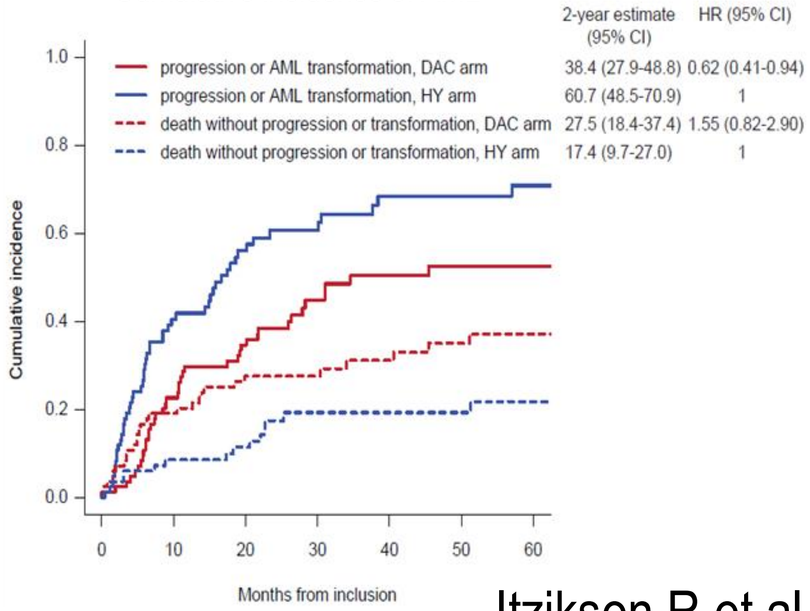
OS



EFS



Cumulative incidence of AML



Itzikson R et al. JCO 2023

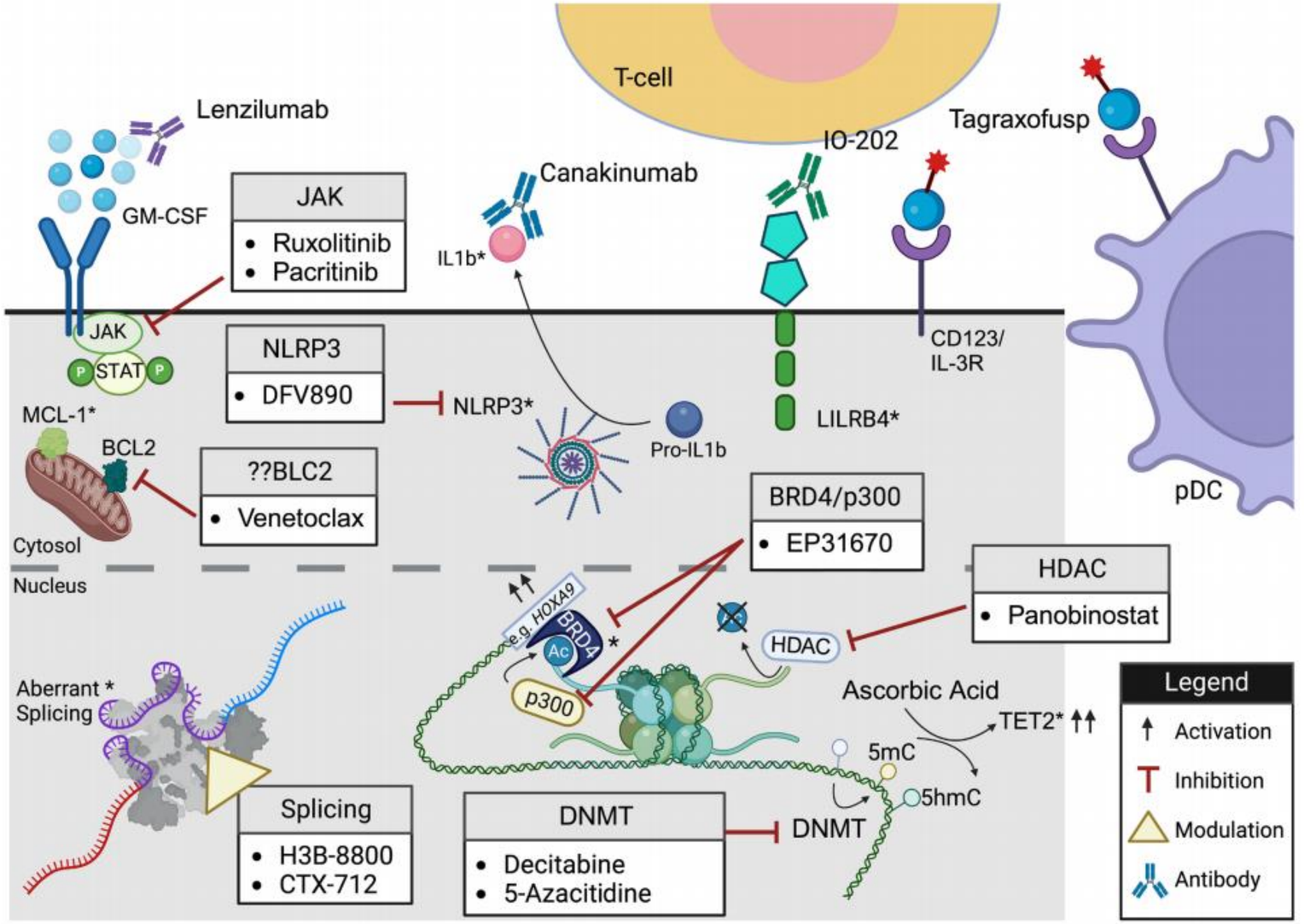
HMAs in CMML: What Can We Expect?

- ORR: approximately 40–50%
- CR: generally below 20%
- Time to response: usually 3–4 cycles
- Median duration of response: approximately 12–18 months
- Survival after HMA failure: often less than 6 months

Higher response rates do not necessarily translate into improved overall survival

Santini V et al. Leukemia 2018;32:413–418; Duchmann M et al. 2018; Itzykson R et al. J Clin Oncol 2023;41:1888–1897; Patnaik MM, Tefferi A. Am J Hematol 2024

Established and investigational therapeutic targets in CMML



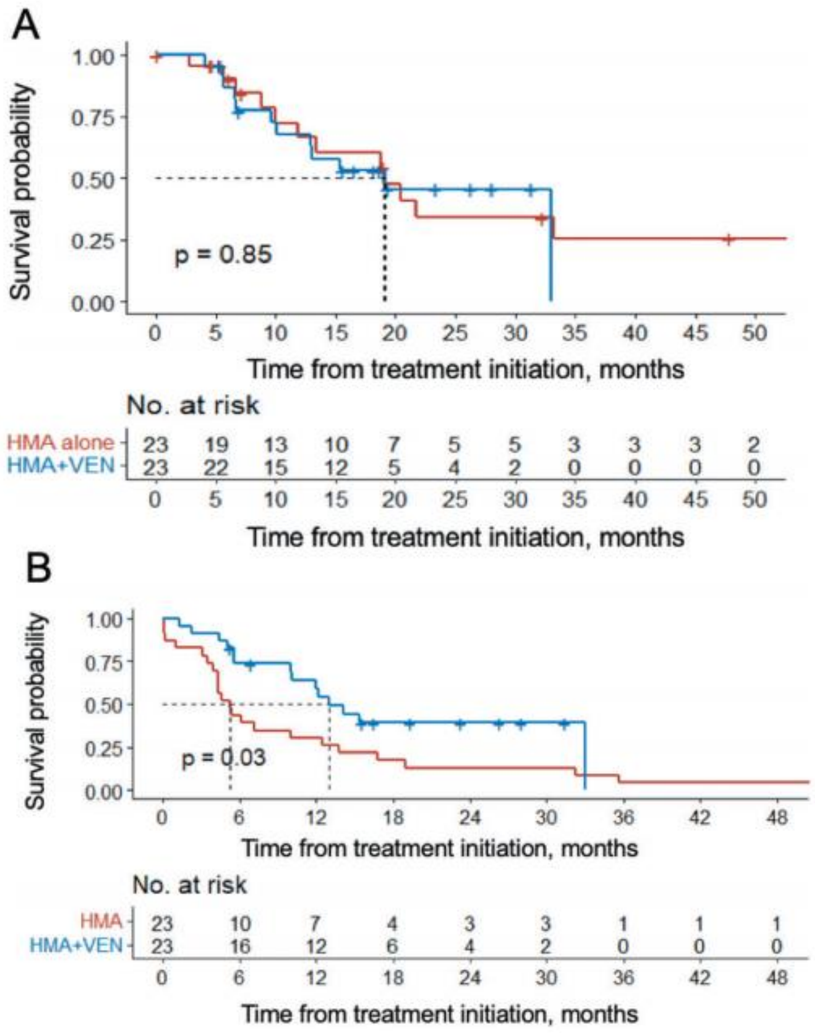
Marando L et al Haematologica 2025

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

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 2026-09-29

Active, not recruiting

No longer looking for participants

Study Start (Actual)

2023-10-04

Primary Completion (Actual)

2026-06-16

Study Completion (Estimated)

2028-10

Enrollment (Estimated)

44

Brief Summary

Open-label phase II, single arm, multicenter study with safety run-in to evaluate the efficacy and safety of Azacitidine combined with Venetoclax in patients with higher-risk chronic myelomonocytic leukemia

www.clinicaltrials.gov

MDS/MPN INTERNATIONAL WORKING GROUP

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

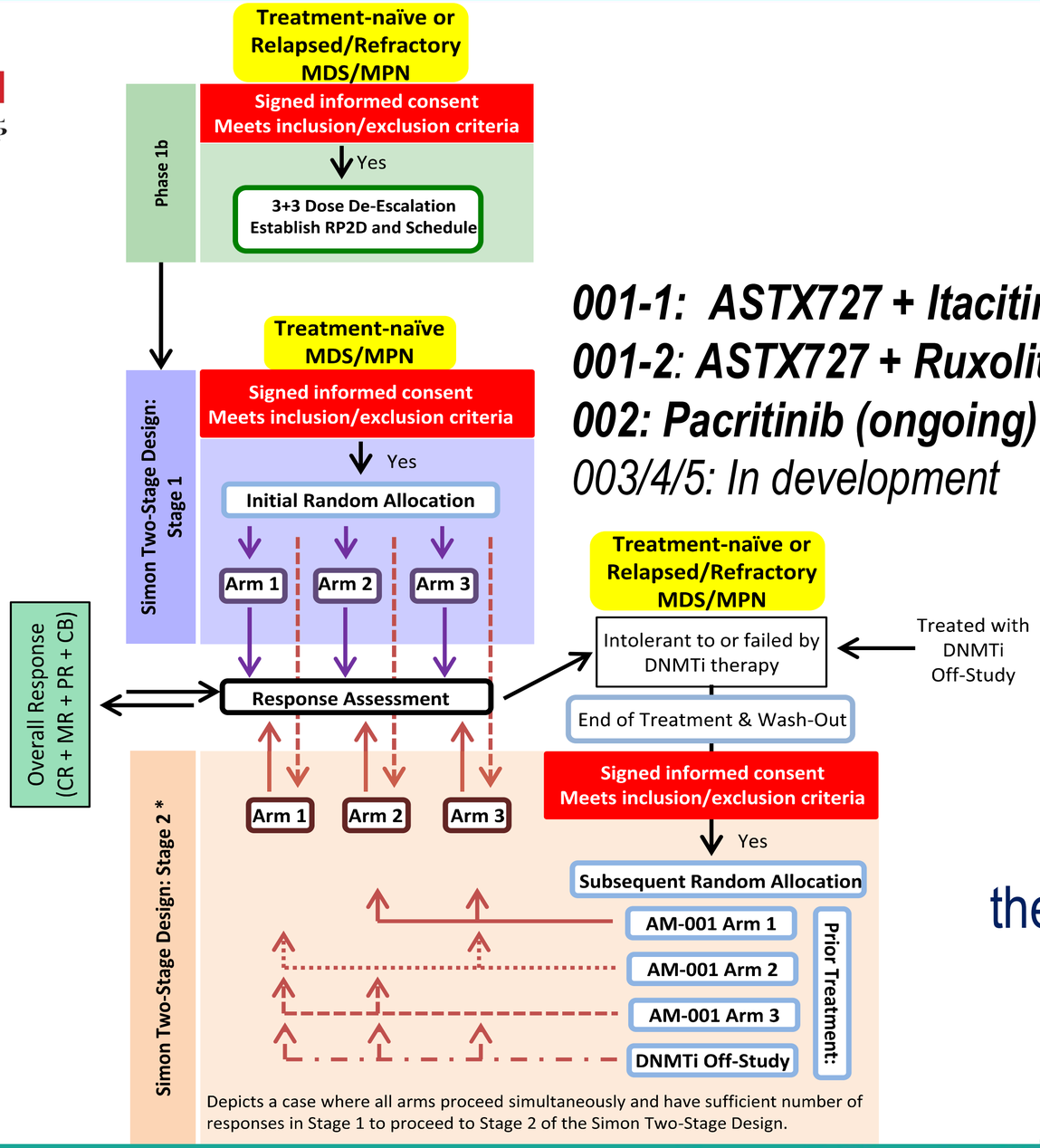
ABNL MARRO – A MDS/MPN IWG Study

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



ABNLMARRO-001

001-1: ASTX727 + Itacitinib (JAK1-i) – closed to enrolment → ASH 2026

001-2: ASTX727 + Ruxolitinib (ongoing)

002: Pacritinib (ongoing)

003/4/5: In development

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

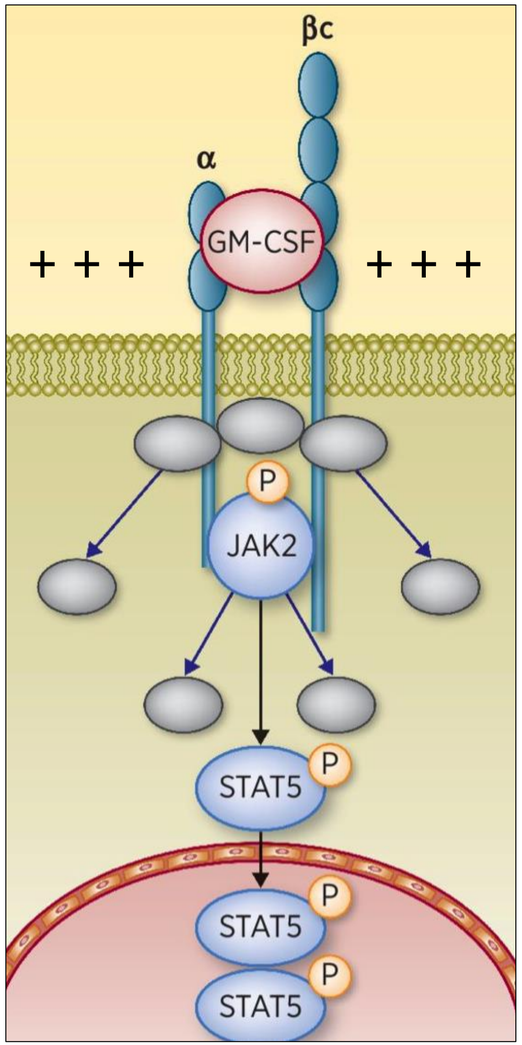
PROSPERA: A Randomized Phase 2 Study of Pacritinib vs. Hydroxyurea in Patients with Advanced Proliferative Chronic Myelomonocytic Leukemia (CMML)

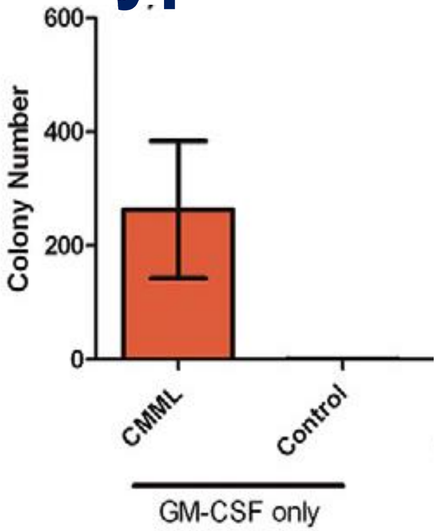
Main targets of Pacritinib:

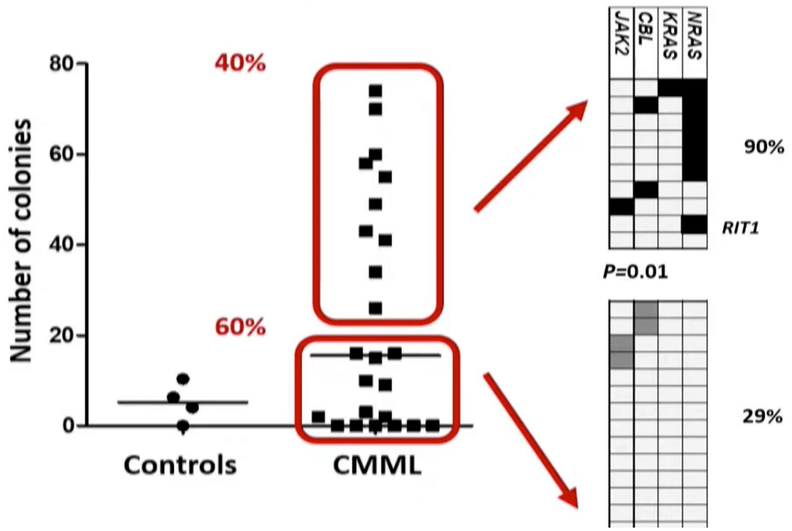
- **JAK2**
- **FLT3**
- **IRAK1 (*Interleukin-1 Receptor–Associated Kinase 1*)**
- **CSF1R**

By courtesy of Michael Savona

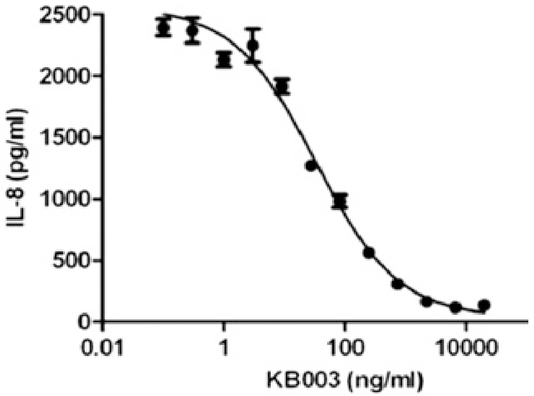
Targeting GM-CSF Hypersensitivity: LENZILUMAB





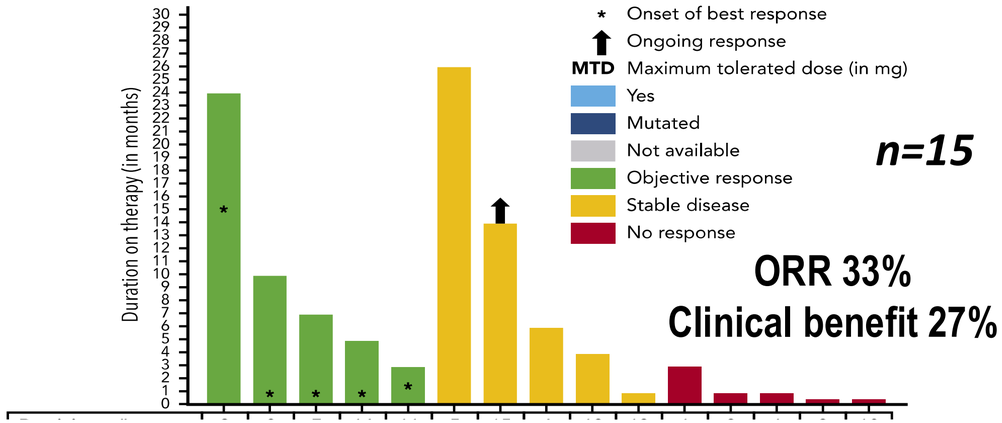


- **moAb v GM-CSF**
- E*x vivo* efficacy:



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.

PREACH-M Trial Design: Molecularly Informed Phase IIb

Newly diagnosed CMML with no prior treatment
- Cytopenia
- Constitutional symptoms or
- Proliferative CMML

BM sample sent to central laboratory for **mutation profiling**

NRAS, KRAS, PTPN11, NF1, CBL mutation

Lenzilumab with Azacitidine
- s/c Azacitidine 75 mg/m2 d1-5,8-9 or d1-7
- IV Lenzilumab 552 mg days 1 & 15 of cycle 1, day 1 only of all subsequent cycles

(continue for 24 x 28-day cycles)

Confirmed **TET2** mutation

High Dose Sodium Ascorbate with Azacitidine
- s/c Azacitidine 75 mg/m2 d1-5,8-9 or d1-7
- IV Ascorbate 30 g d1-5, 8-9 or d1-7
- PO Ascorbate 1.1 g on days where IV not scheduled

(continue for 24 x 28-day cycles)

No mutation in either category

Screen fail

By courtesy of Daniel Thomas - modified

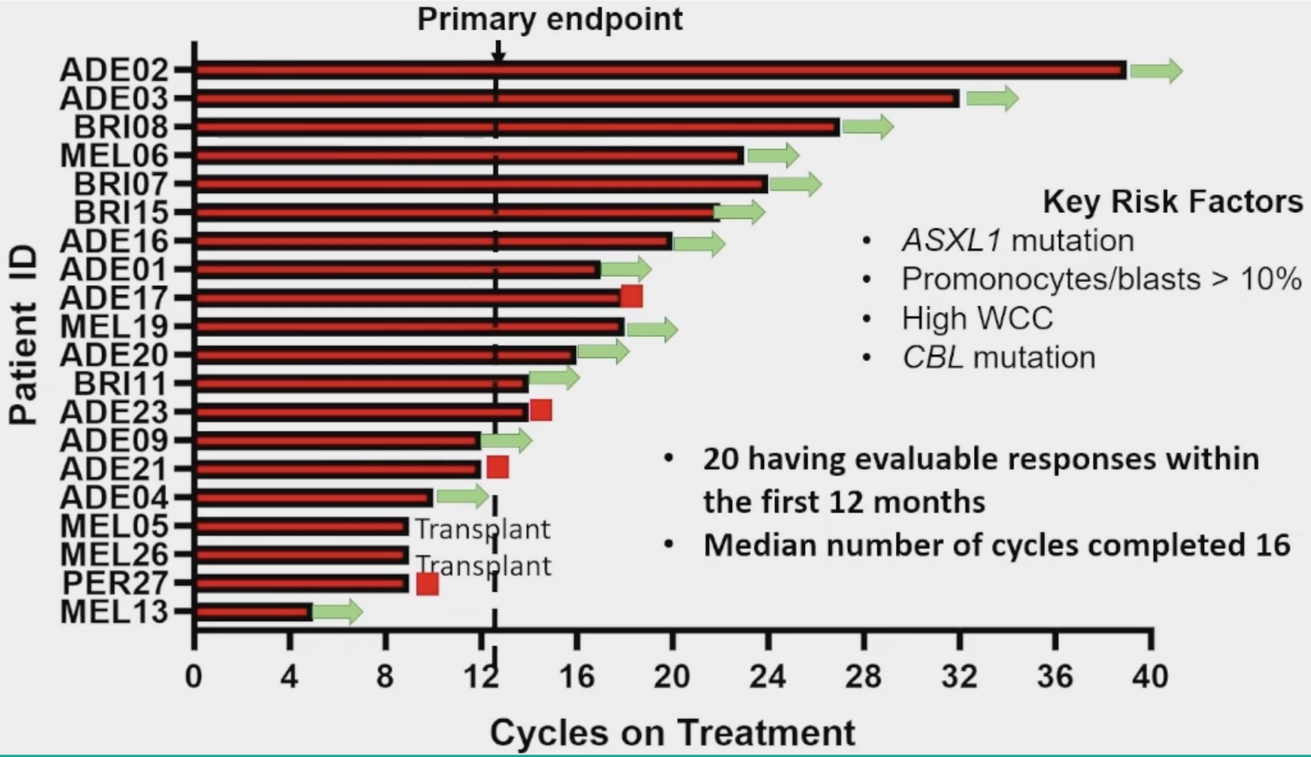
Hiwasi et al. ASH. 2024 / Thomas et al. EHA 2025.

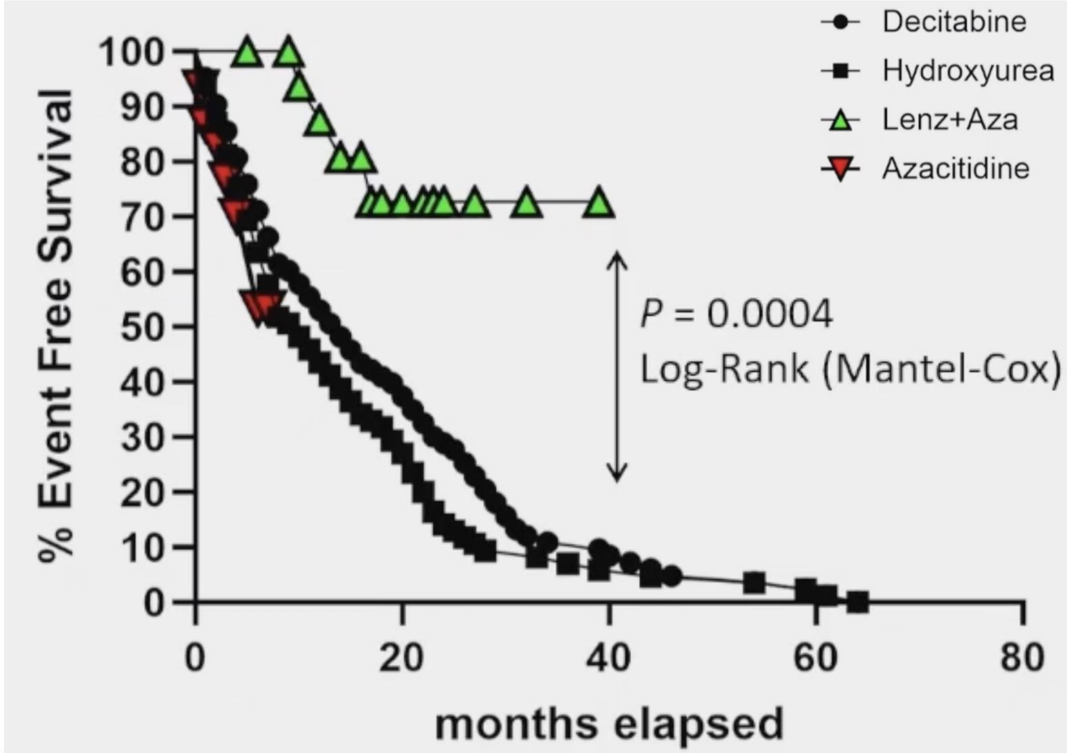
Combination therapy with lenzilumab and azacitidine

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

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)



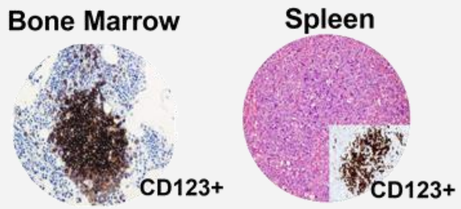


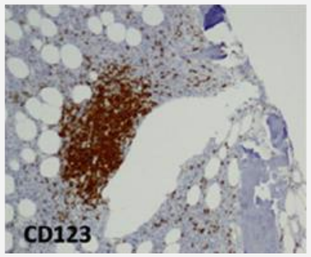
Hiwasi et al. ASH. 2024 / Thomas et al. EHA 2025.

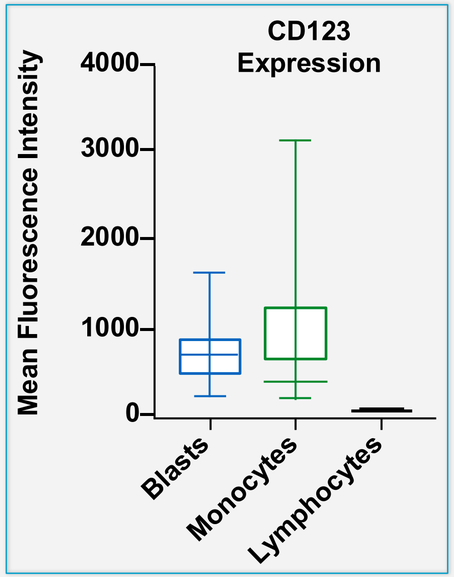
CD123 in CMML

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]







NCT05038592

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

Active, not recruiting

No longer looking for participants

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)

ASTX727 in CMML

Pooled Phase II/III analysis (Savona et al, 2025)

n = 33 CMML
25 dysplastic / 8 proliferative

Ascertain MDS, CMML, and AML

Key responses

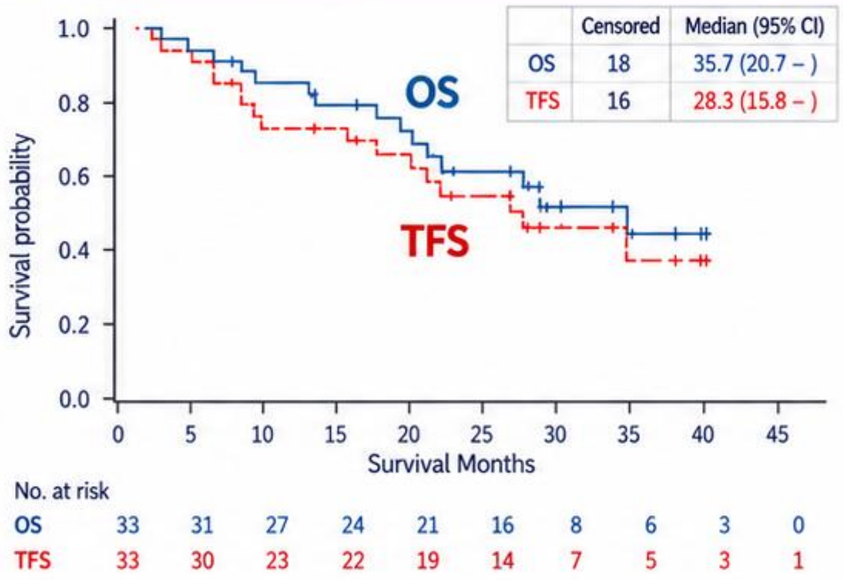
Overall response rate
(CR + PR + mCR + HI)
76% (25/33)

Complete remission
21% (7/33)

RBC transfusion independence
(≥12 weeks)
46% (5/11)

Responses seen in both dysplastic and proliferative CMML

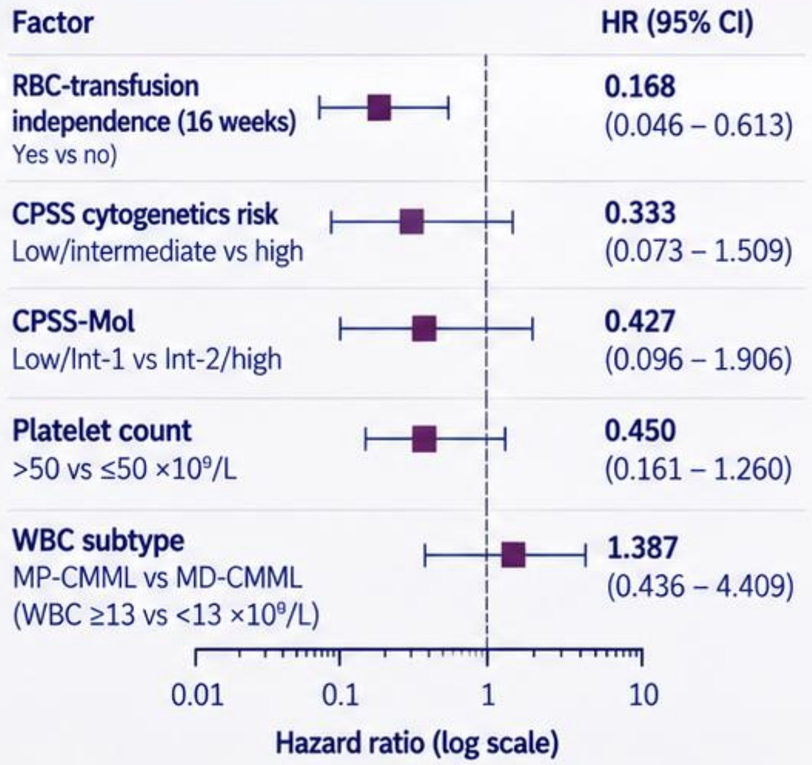
Overall survival



Median OS
35.7 months
(95% CI 20.7 –)

Median TFS
28.3 months
(95% CI 15.8 –)

Prognostic factors for overall survival



ASTX727 demonstrates high response rates and durable activity in CMML, with encouraging long-term outcomes and RBC-TI associated with survival.

Savona et al.
Br J Haematol. 2025.
(Phase II/III pooled analysis; CMML n = 33)

ASTX727 in MDS/MPN Overlaps (AMMO)

Any MDS/MPN (excl JMML)
- CMML-2 / blasts ≥10%
- CPSS-Mol: INT2/HIGH
- Adverse cytogenetics
- WCC ≥50 (≥30 if symptoms)
- Transfusion-dependency
- Symptomatic thrombocytopenia
- Symptomatic splenomegaly
- Severe systemic symptoms
- Extramedullary disease

Treatment-naïve (except HC)
ECOG ≤2

R

2 → **ASTX727** d1-5 (/28d) → x6 cycles → **CB+**

+HC during C1 only

Y → Continue until progression

N → (No crossover)

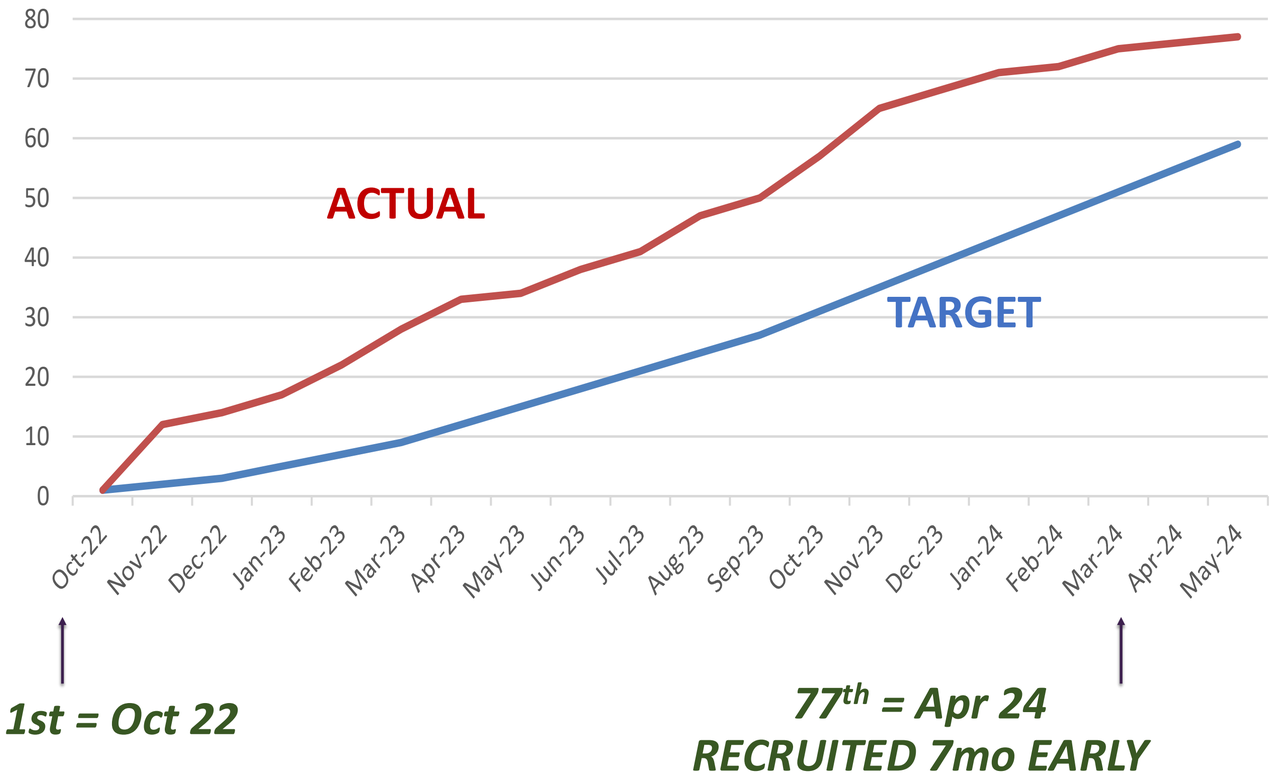
1 → **Hydroxycarbamide Supportive Care** → x6 cycles → Continue HC/BSC

- **Primary EP:** Best ORR @C6*
- **Secondary:** CR/mCR
  PFS/OS/TFS
  Safety/tolerability
  QoL (pilot MPN-SAF)

**IWG (Savona)*

By courtesy of Daniel Wiseman (ASH Oral 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

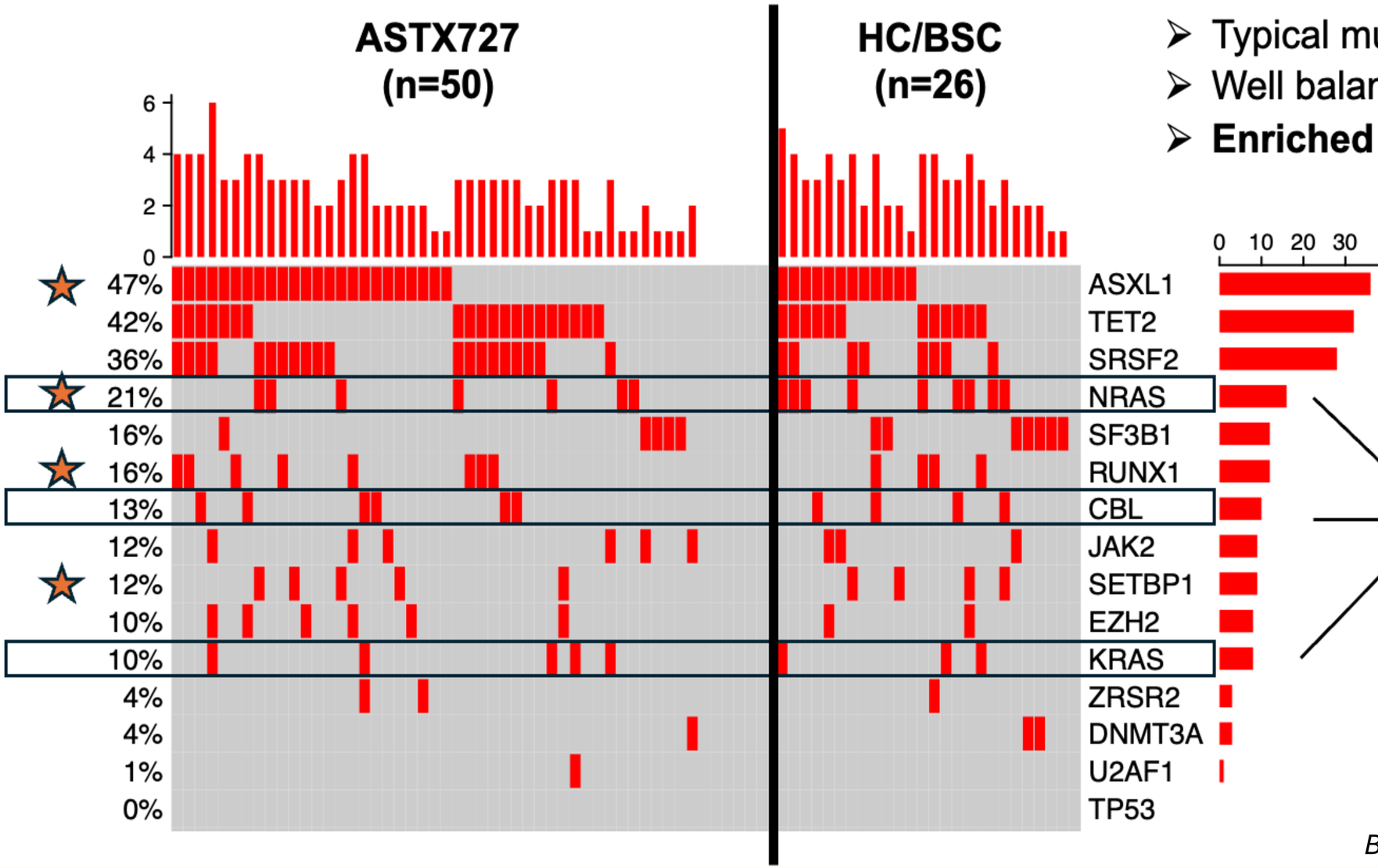
Well balanced across arms (~70% CMML)

	ASTX727 n=50	HC/BSC n=26	TOTAL n=76
Age (y)	73 (63-86)	72 (58-83)	73 (58-86)
Male	30 (60%)	19 (79%)	49 (64%)
CMML aCML MDS/MPN-RS-T MDS/MPN-U	34 (68%) 0 (0%) 6 (12%) 10 (20%)	18 (69%) 1 (3.8%) 4 (15%) 3 (12%)	52 (68%) 1 (1.3%) 10 (13%) 13 (17%)
Stratification parameters: "Cytoreduction indicated"	37 (74%)	19 (73%)	56 (74%)
Stratification parameters: > 6mo from diagnosis	34 (68%)	19 (73%)	53 (70%)
CPSS-Mol Low Int-1 Int-2 High	1 (2.1%) 7 (15%) 25 (53%) 14 (30%) 83%	0 4 (18%) 11 (50%) 7 (32%) 82%	1 (1.5%) 11 (16%) 36 (52%) 21 (30%)
Haemoglobin (g/L)	99 (71-158)	97 (59-144)	99 (59-158)
Platelets (x10^9/L)	104 (9-1000)	89 (6-543)	104 (6-1000)
WCC* (x10^9/L)	11 (1-67)	22 (3-133)	13 (1-133)
Creatinine (umol/L)	81 (50-197)	86 (38-167)	83 (38-197)

**Most already on prior cyto-reduction*

By courtesy of Daniel Wiseman (ASH Oral 2025)

Well balanced across arms (adverse genetic risk)



- Typical mutation profile for MDS/MPN
- Well balanced across arms
- **Enriched for adverse risk mutations:**

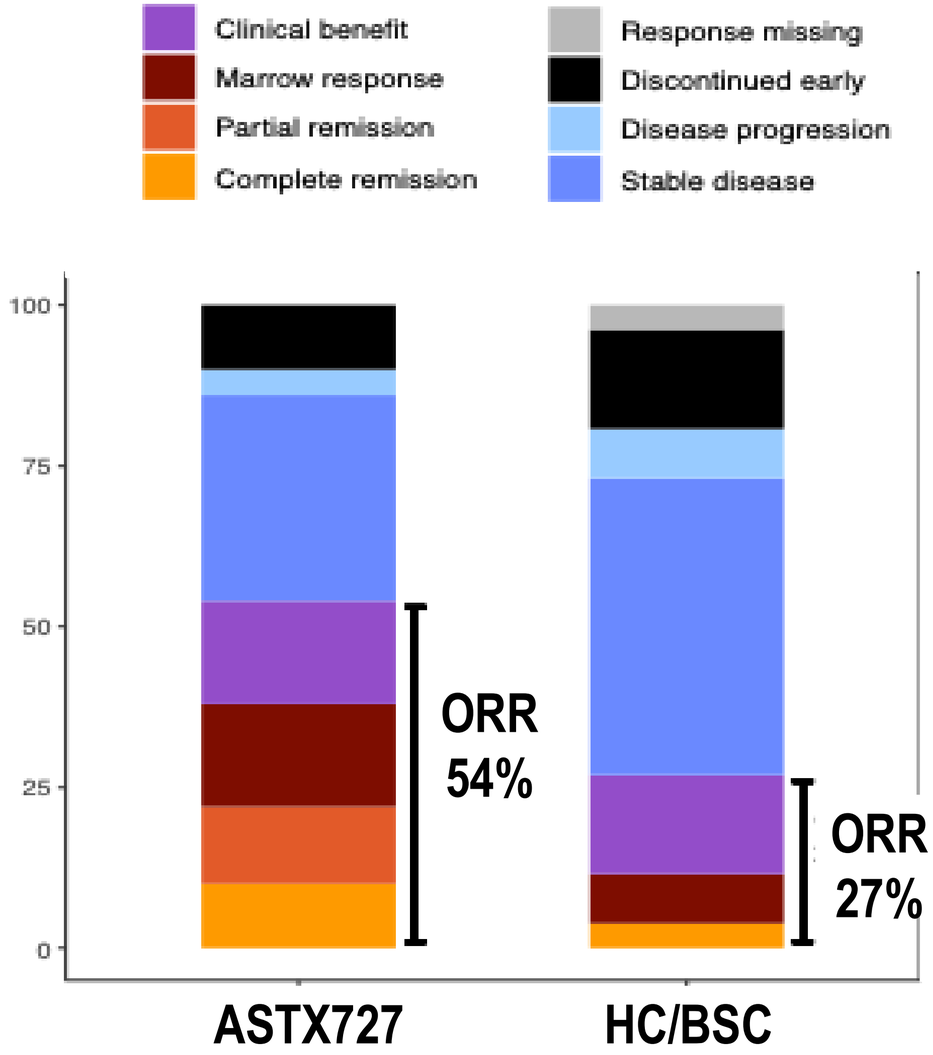
ASXL1= most common (47%)
TET2 under-represented

RAS mutations in 41%(+)

By courtesy of Daniel Wiseman (ASH Oral 2025)

ASTX727 delivered improved response by cycle 6

	ASTX727 n=50	HC/BSC n=26	TOTAL (n=76)
Overall Response (CR+PR+MR+CB)	**27 (54%)**	**7 (27%)**	**34 (45%)**
Best Response:			
•Complete remission	5 (10%)	1 (3.8%)	6 (7.9%)
•Partial remission	6 (12%)	0	6 (7.9%)
•Marrow response	8 (16%)	2 (7.7%)	10 (13%)
•Clinical benefit	8 (16%)	4 (15%)	12 (16%)
•Stable disease	16 (32%)	12 (46%)	28 (37%)
•Progressive disease	2 (4.0%)	2 (7.7%)	4 (5.3%)
•Discontinued early	5 (10%)	4 (15%)	9 (12%)
•Missing data	0	1 (4.2%)	1 (1.4%)

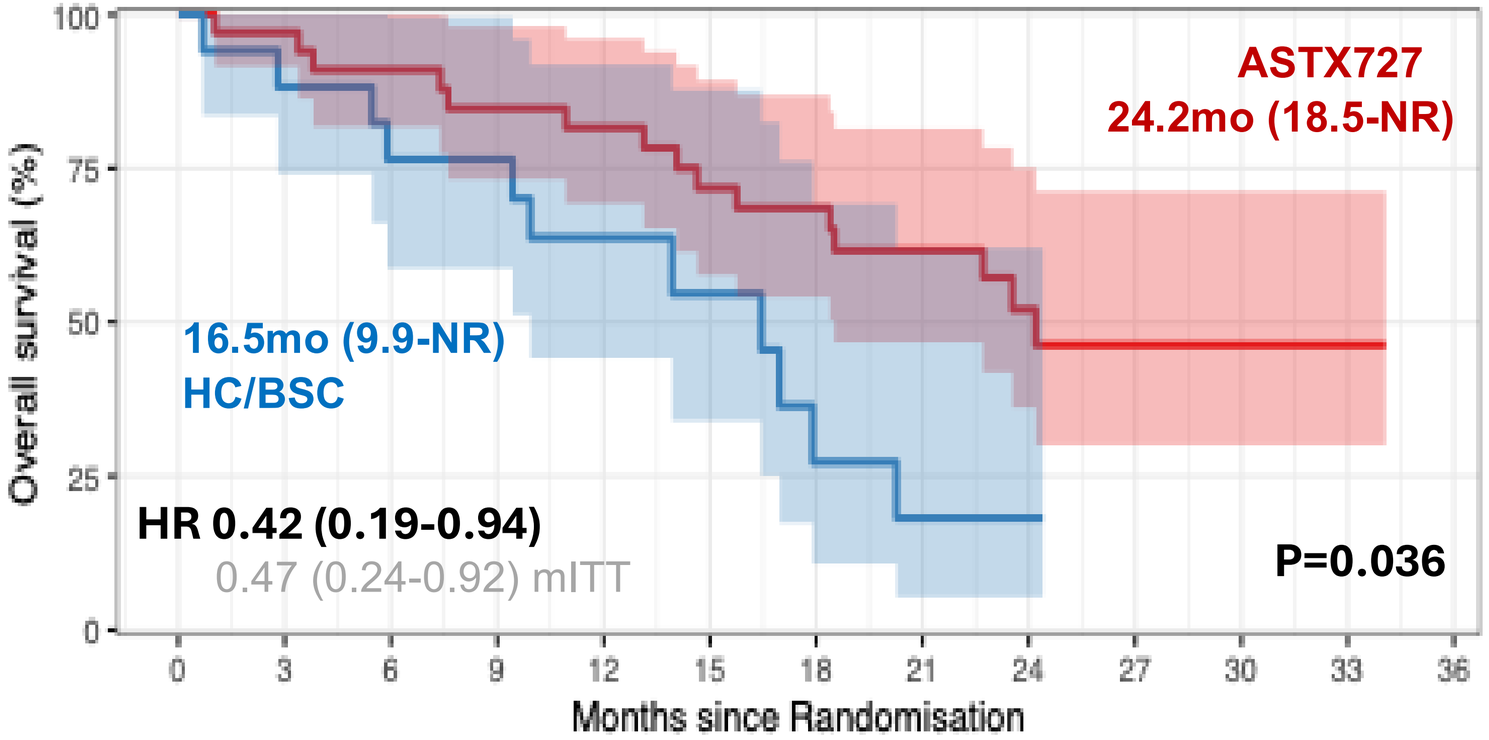


By courtesy of Daniel Wiseman (ASH Oral 2025)

ASTX727 delivered improved survival outcomes

CMML SUBGROUP (DACOTA-E; n=52)

OS



Number at risk (number of events)

34 (0)	33 (1)	30 (3)	27 (5)	26 (6)	22 (9)	20 (10)	14 (12)	10 (14)	5 (15)	4 (15)	1 (15)	0 (15)
18 (0)	15 (2)	12 (4)	12 (4)	9 (6)	6 (7)	3 (10)	2 (11)	1 (11)	0 (11)	0 (11)	0 (11)	0 (11)

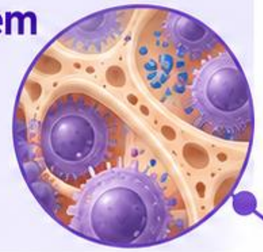
Median FU: 24mo

By courtesy of Daniel Wiseman (ASH Oral 2025)

Targeting CMML biology: conceptual strategies with oral HMA

Clonal niche and ecosystem

- **plerixafor** (CXCR4)
- **magrolimab** (CD47)
- CXCL12/CXCR4 axis targeting



RAS pathway dependence



- **trametinib** (MEK1/2)
- **daraxonrasib / RMC-6236** (multi-RAS(ON))
- SHP2 / SOS1 inhibitors
- ERK inhibitors

Cytokine/GM-CSF addition



- **lenzilumab** (GM-CSFR)
- **ruxolitinib, itacitinib**
- selective JAK2 inhibitors

Replicative immortality

- **imetelstat** (telomerase)
- shelterin/ALT pathway targeting



Oral HMA in CMML



- Epigenetic reprogramming
- Increased antigenicity

Monocyte identity and function



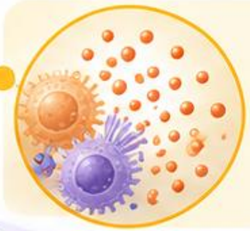
- **pexidartinib** (CSF1R)
- **venglustat** (GCase)
- CCR2 moAb/CCL2 conjugates

Metabolic addiction



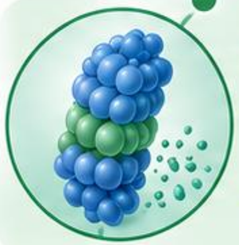
- **ivosidenib** (IDH)
- **etomoxir, ranolazine** (FAO)
- **IACS-010759** (OXPHOS)

Inflammatory ecosystem



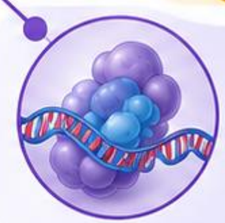
- **emavusertib** (IRAK4)
- **dapansutrile** (NLRP3)
- **anti-cytokine** approaches (anti-IL-1β, anti-IL-6)

Proteotoxic stress



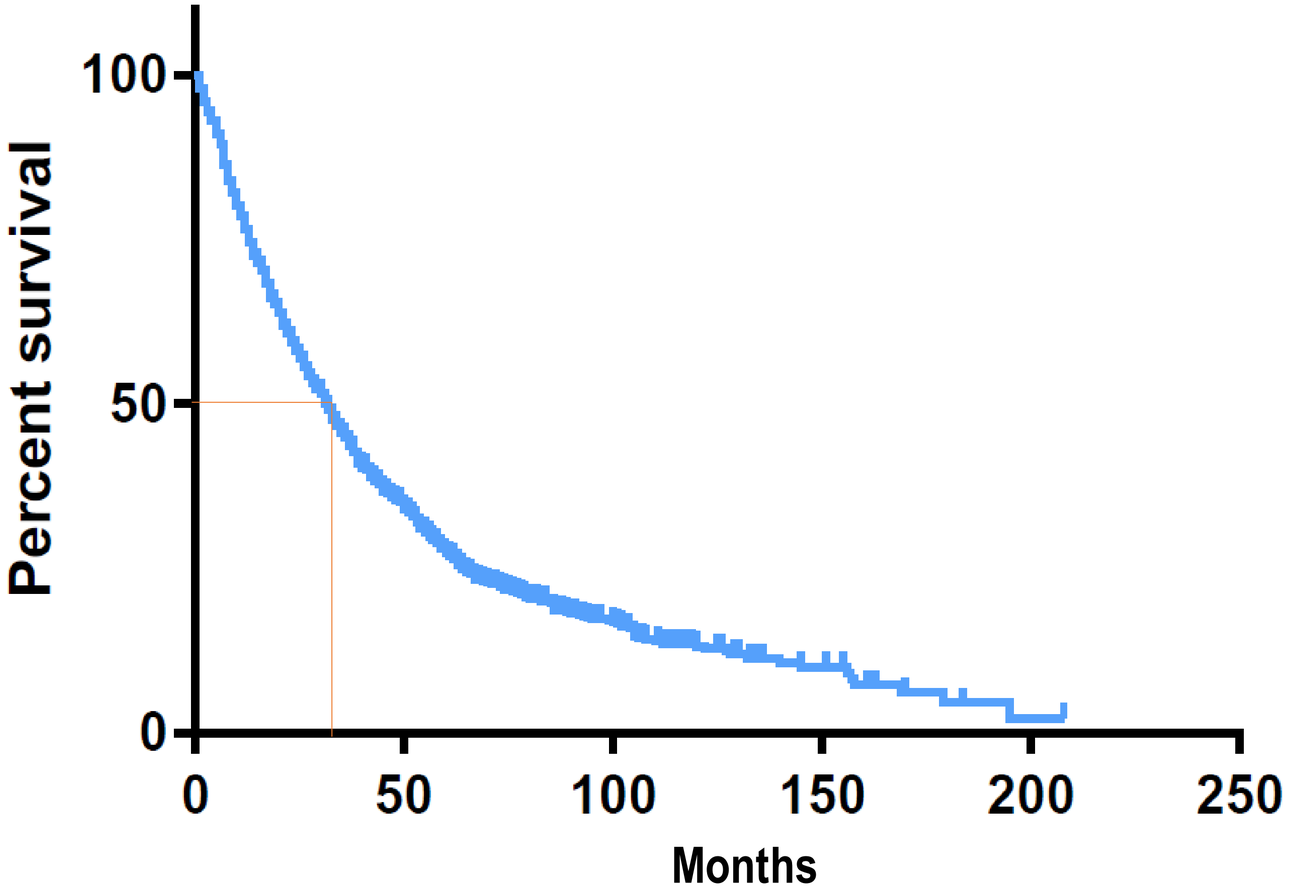
- **bortezomib, carfilzomib** (proteasome)
- **ganetespib** (HSP90)

Spliceosome stress



- **H3B-8800** (SF3B1)
- **GSK3326595** (PRMT5)
- combinatorial splicing / R-loop targeting

CMML: a disease associated with a dismal prognosis



International CMML Consortium

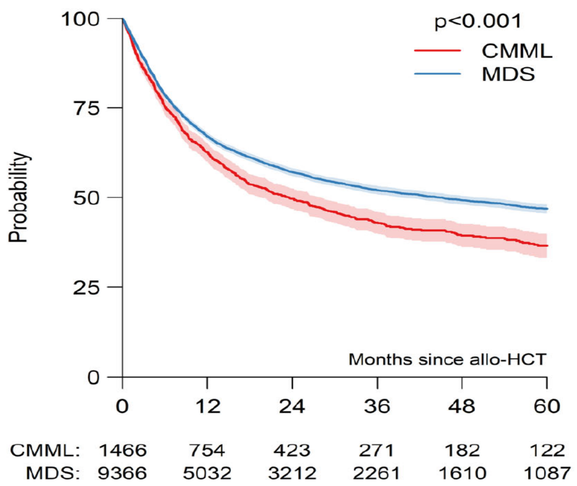
Characteristic	N=1832
Median age, years (range)	70 (16–93)
Median survival, months (range)	32 (0–206)
Estimated survival: <1 year	33%
Estimated survival: >8 years	17%

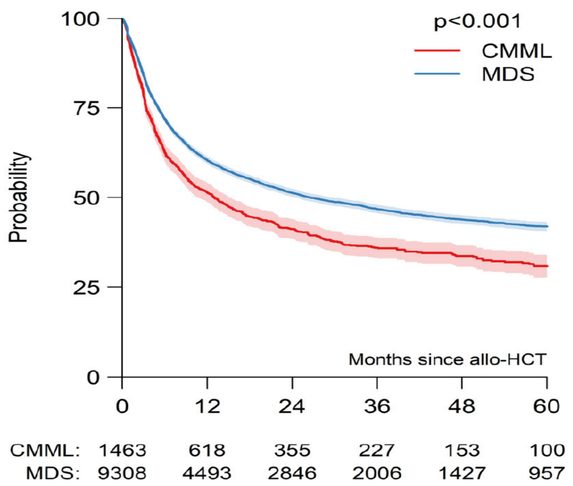
- Life expectancy in CMML varies greatly depending on several patient- and disease-specific factors

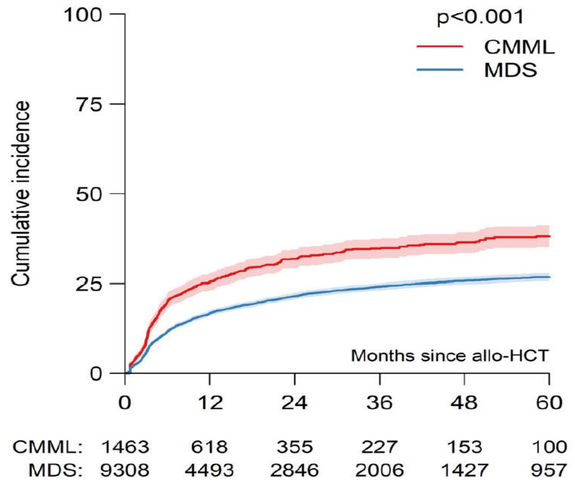
Padron E, et al. *Blood Cancer J* 2015;5:e333.

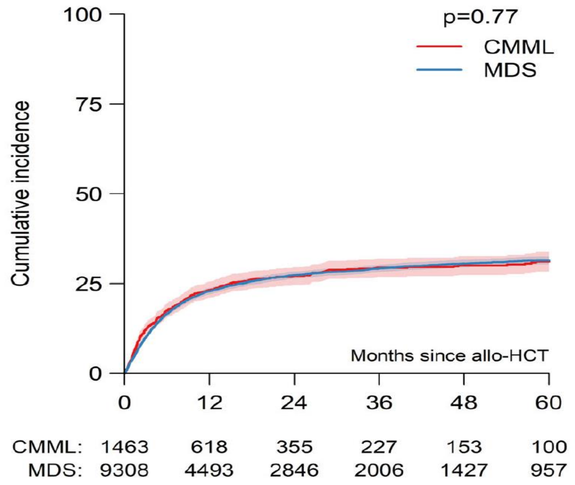
Allo-HCT in CMML: relapse remains a major challenge

EBMT 2010-2018: **1466 CMML pts / 9366 MDS pts**
(transformed to AML excluded)





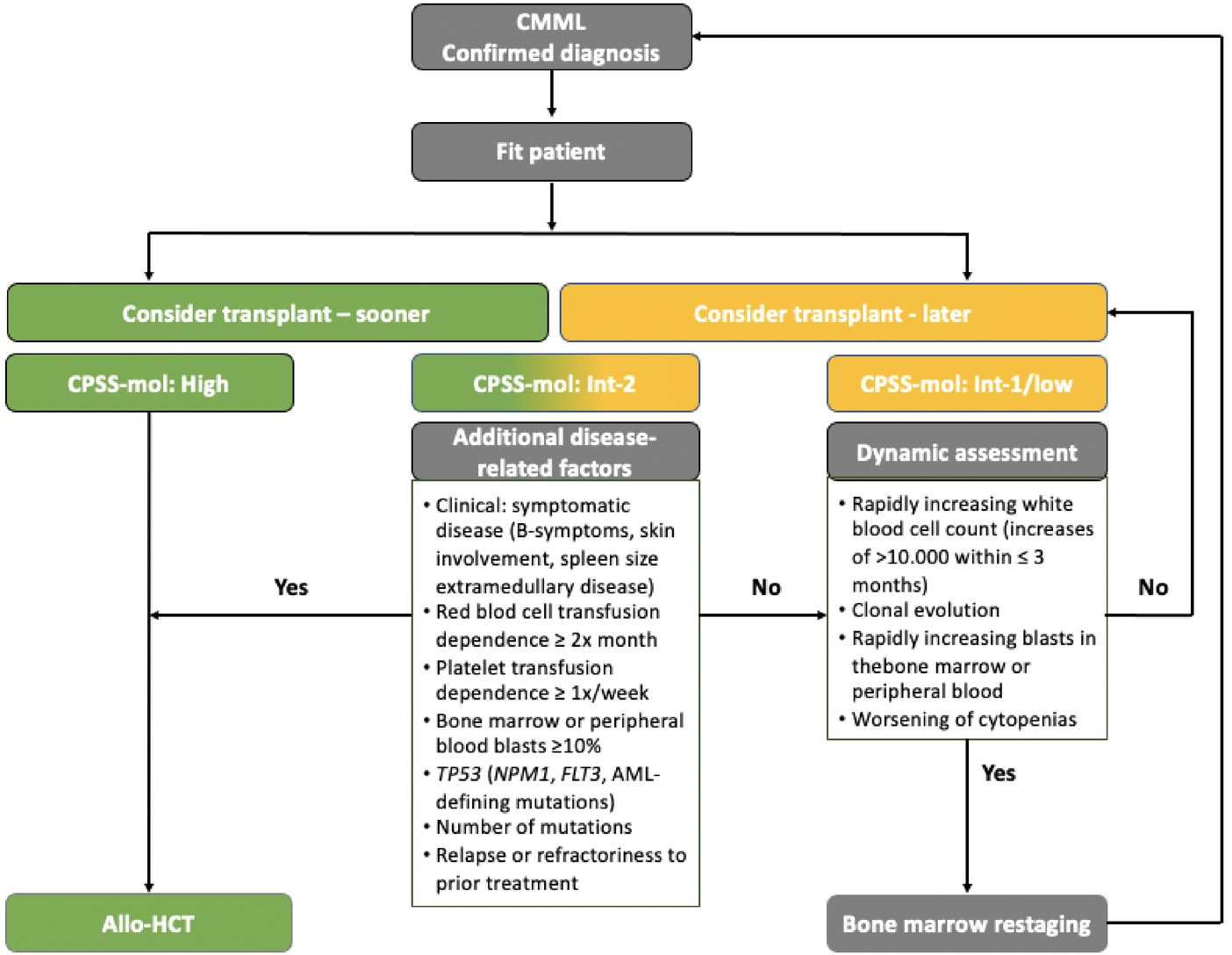




CMML	**5-yr OS: 37%**	**5-yr DFS: 31%**	**5-yr Rel: 37%**	**5-yr NRM: 32%**
MDS	5-yr OS: 47%	5-yr DFS: 42%	5-yr Rel: 27%	5-yr NRM: 31%

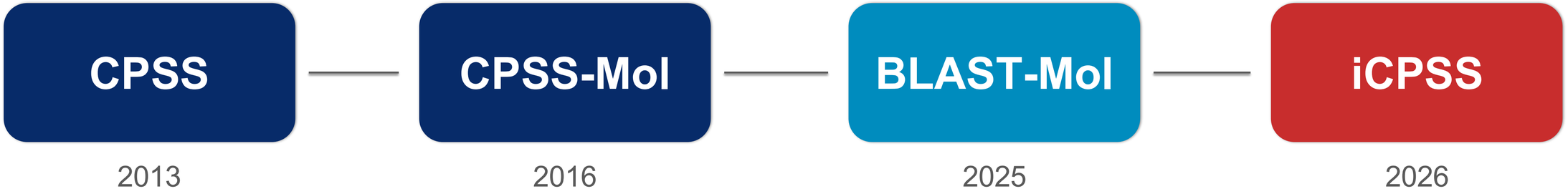
Rovò A et al. Am J Hematol 2024

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



Onida F. et al, Blood 2024

Risk stratification in CMML: a moving target



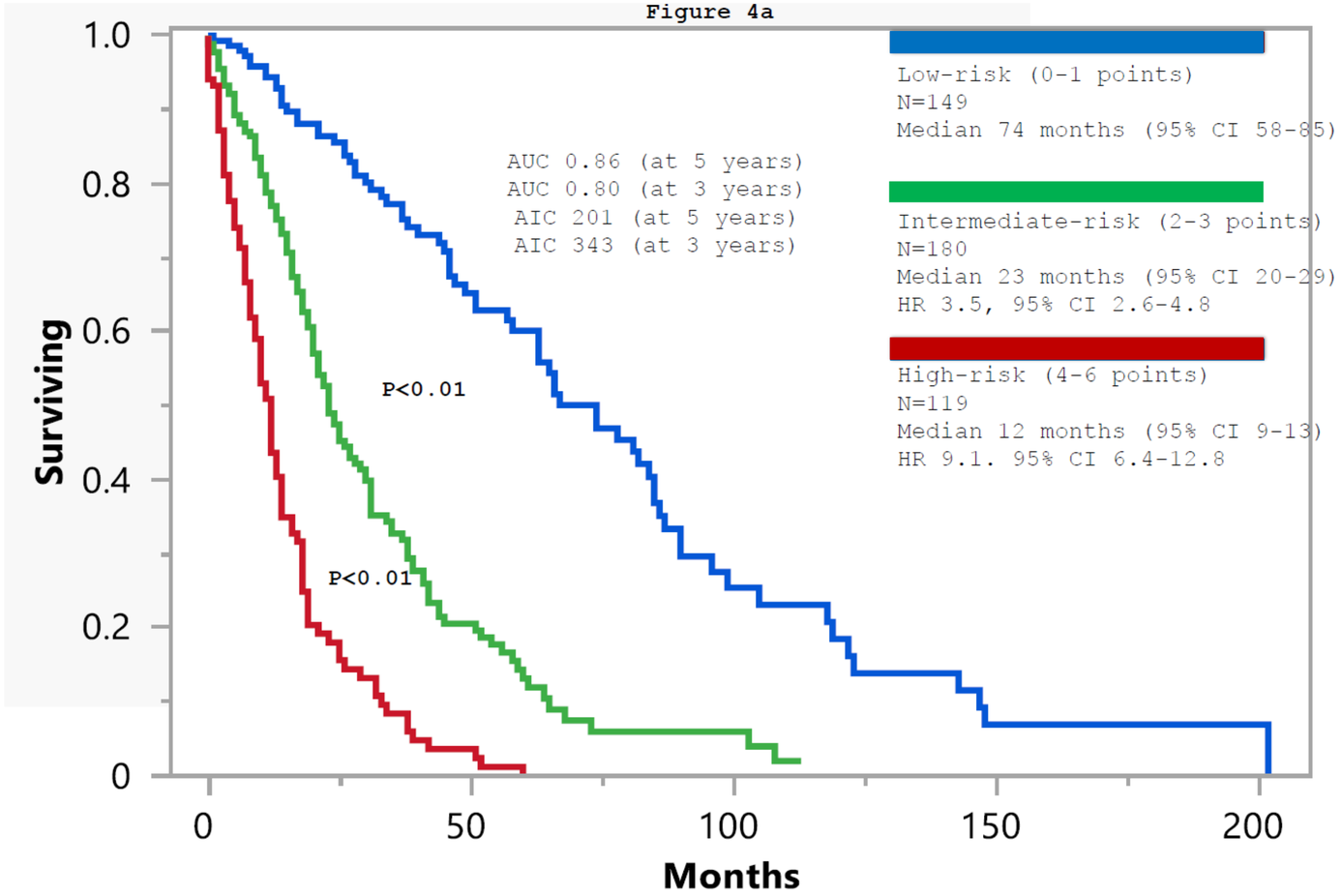
From fixed clinicogenetic scores → more refined clinical-molecular prediction

Transplant recommendations based on CPSS-Mol should now be interpreted in the context of contemporary risk models.

Elena et al. Blood 2016; Tefferi et al. Blood 2025; Lanino et al. JCO 2026

BLAST-mol: A Combined Clinical-Molecular Risk Model for Survival in CMML (N=448)

https://sudheshk.com/projects/blast-model



Molecular high risk¥ – 2 points
Severe anemia – 2 points**
Molecular intermediate risk – 1 point
Circulating blasts ≥2% – 1 point
WBC ≥13 × 10^9/L – 1 point
Moderate anemia* – 1 point

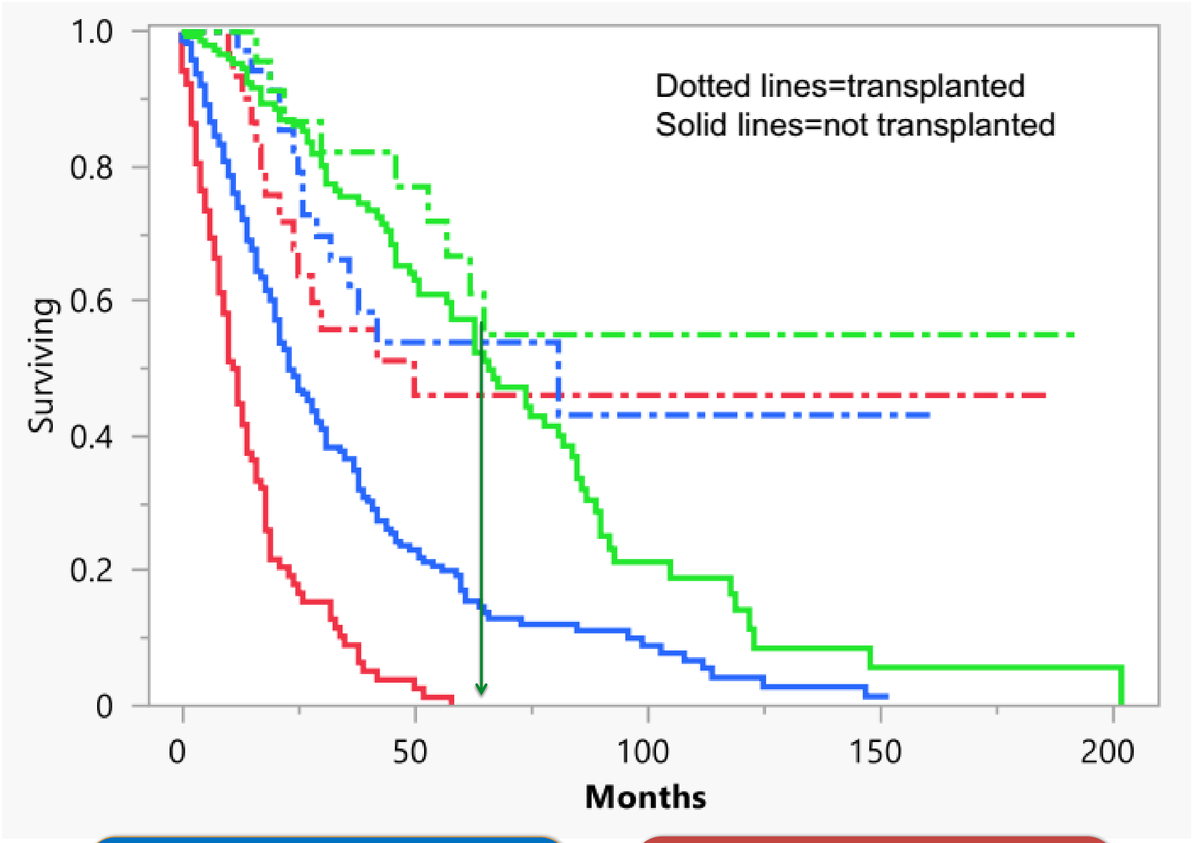
¥***Unfavorable genetic risk factors***: *$DNMT3A^{MUT}$; $U2AF1^{MUT}$; $BCOR^{MUT}$; $SETBP1^{MUT}$; $PTPN11^{MUT}$; $NRAS^{MUT}$; $RUNX1^{MUT}$; $TP53^{MUT}$; $ASXL1^{MUT}$;*
and adverse karyotype defined by cytogenetic abnormalities other than sole loss of Y chromosome or trisomy 8
Favorable genetic risk factors: *$TET2^{MUT}$; $PHF6^{MUT}$*

**Severe anemia: transfusion-requiring or hemoglobin <8 g/dL for women or <9 g/dL for men
*Moderate anemia: hemoglobin 8 to <10 g/dL in women and 9 to <11 g/dL for men

Tefferi A et al. Blood 2025

Does allo-HCT improve survival in the molecular stratification era?

Overall survival of 593 Mayo Clinic CMML pts stratified by BLAST-Mol score and transplant status



BLAST Intermediate 81 vs 23 mo

BLAST High 50 vs 14 mo

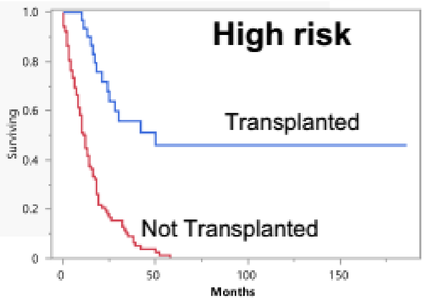
High risk

N=104 Median OS: 12 m

N=31 Median OS: 50 m

P<0.01

HR 0.15, 95% CI 0.08-0.2



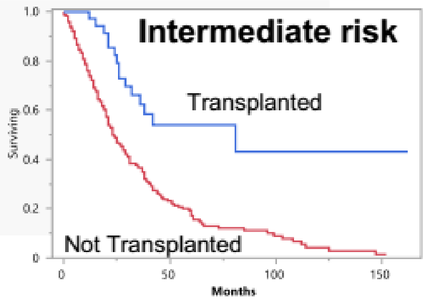
Intermediate risk

N=243 Median OS: 23 m

N=36 Median OS: 81 m

P<0.01

HR 0.3, 95% CI 0.2-0.5



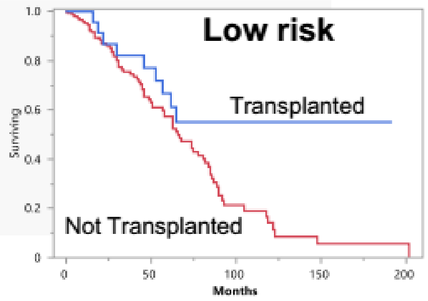
Low risk

N=155 Median OS: 66 m

N=24 Median OS: NR

P=0.08

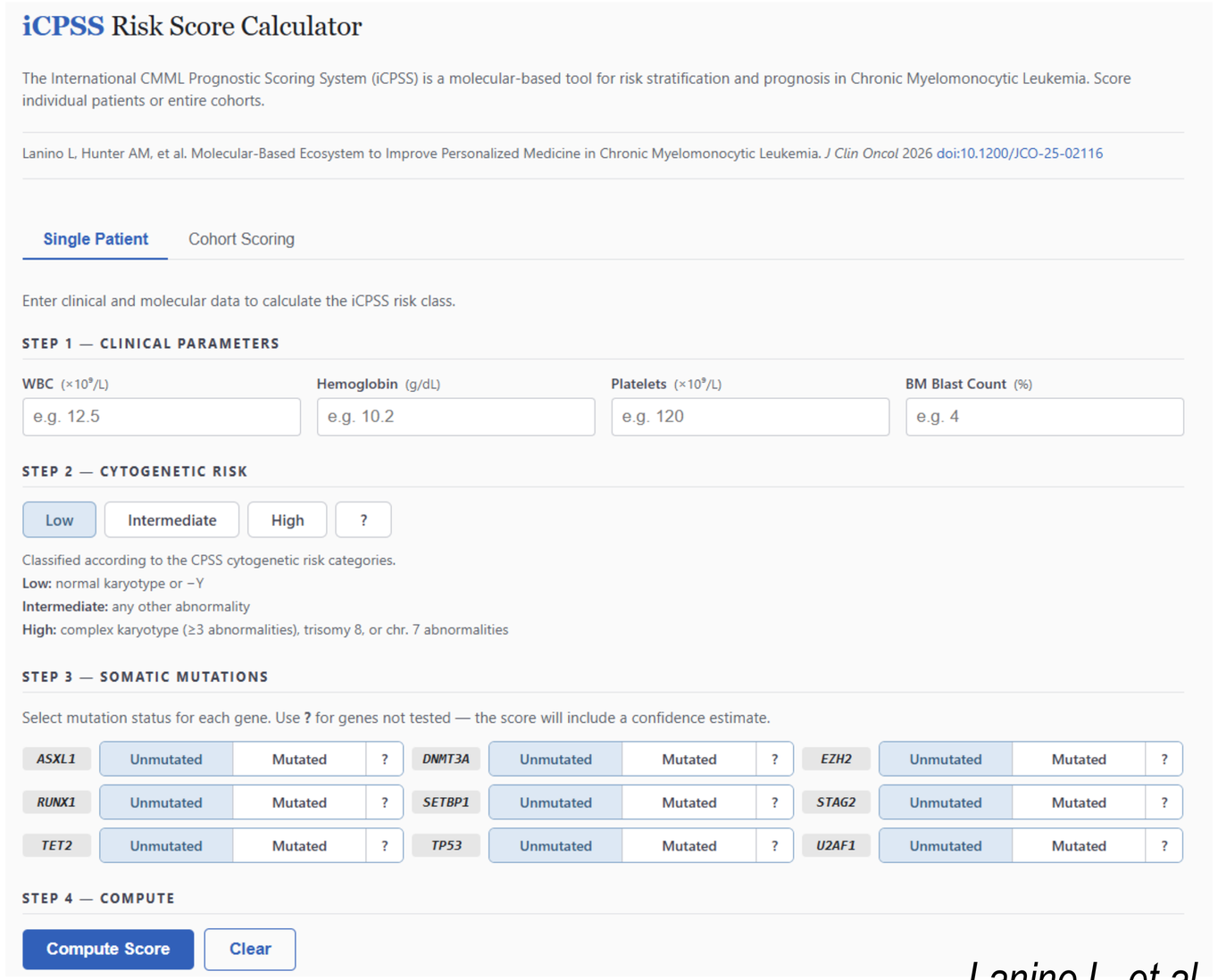
HR 0.5, 95% CI 0.2-1.1



Alsugair et al. AJH 2026

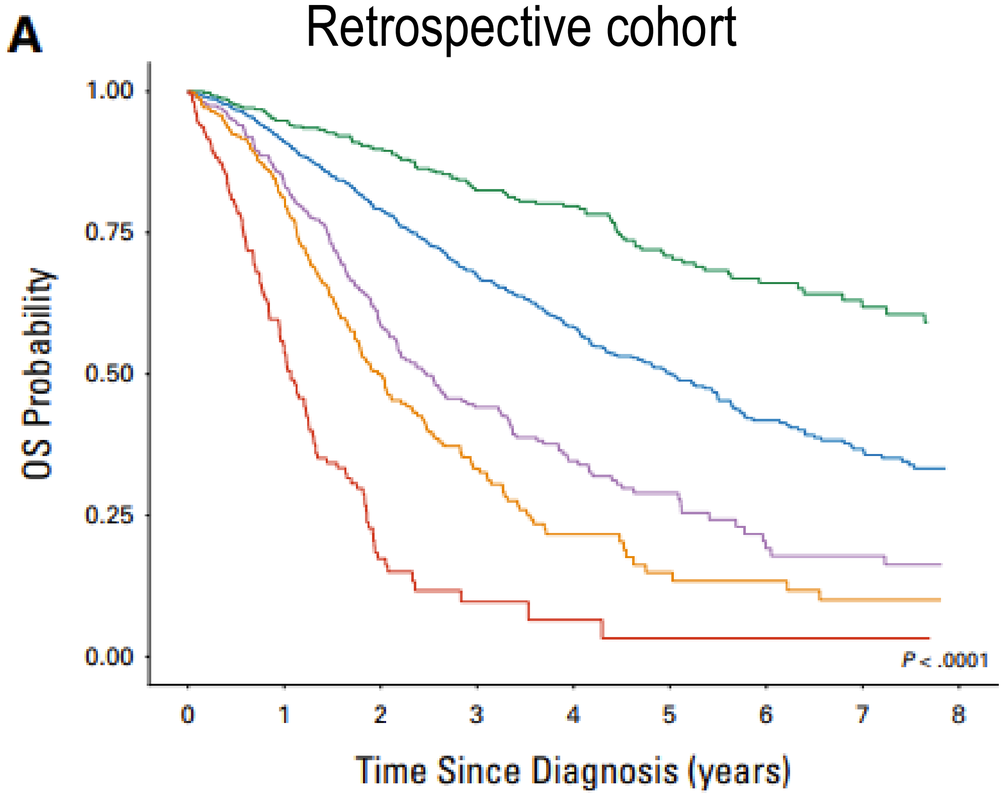
International CMML Prognostic Score (iCPSS): Website

https://icpss-risk.com/



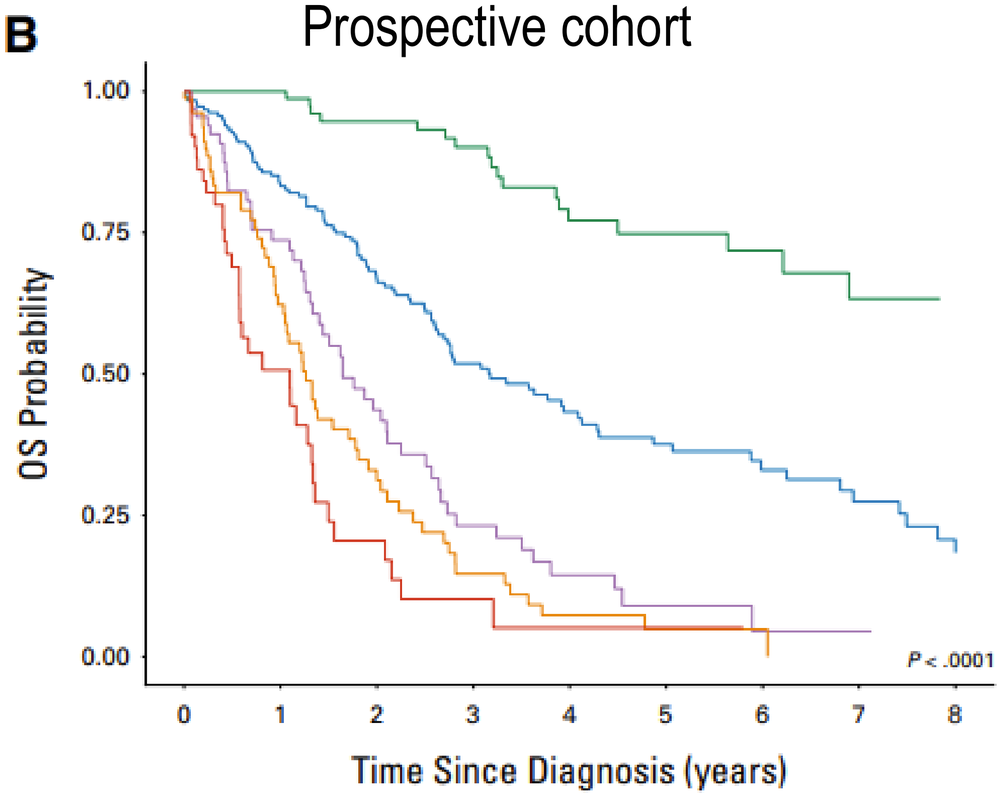
Lanino L. et al. JCO 2026

iCPSS: toward individualized CMML risk prediction



Number at risk (censored)

Very low	504 (0)	366 (116)	299 (49)	224 (53)	177 (40)	121 (39)	78 (36)	51 (23)	40 (9)
Low	1250 (0)	834 (322)	556 (183)	363 (120)	254 (66)	155 (67)	104 (28)	69 (24)	46 (17)
Intermediate	528 (0)	282 (177)	149 (61)	86 (30)	54 (15)	28 (18)	14 (6)	12 (1)	9 (2)
High	508 (0)	230 (205)	100 (55)	50 (21)	23 (12)	10 (8)	8 (1)	5 (1)	4 (1)
Very high	223 (0)	71 (72)	15 (15)	4 (6)	2 (1)	1 (0)	1 (0)	1 (0)	0 (1)

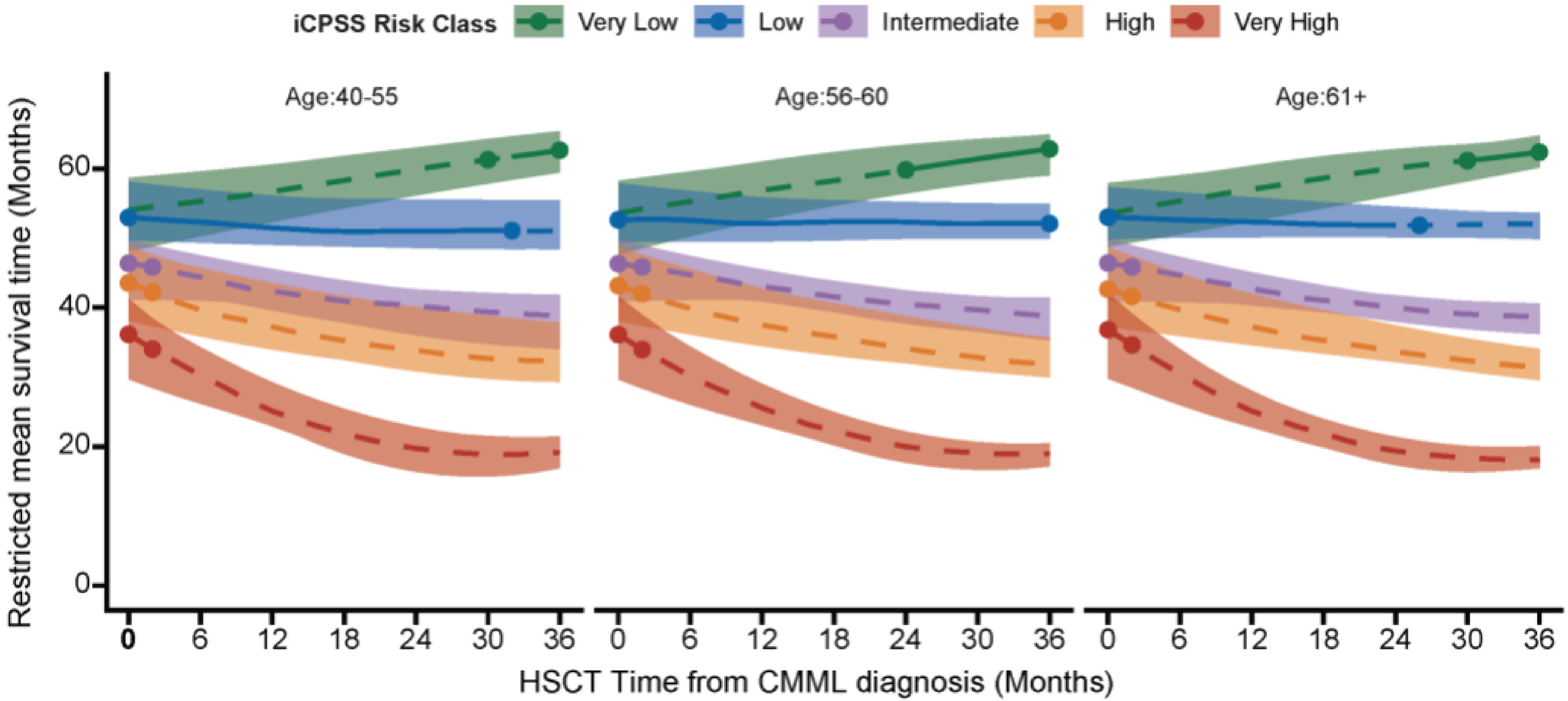


Number at risk (censored)

Very low	91 (0)	78 (13)	69 (5)	54 (12)	39 (8)	29 (9)	19 (9)	14 (3)	13 (1)
Low	188 (0)	138 (21)	96 (17)	60 (17)	41 (10)	30 (6)	20 (7)	14 (3)	9 (2)
Intermediate	71 (0)	41 (14)	23 (2)	11 (2)	6 (1)	3 (1)	1 (1)	1 (0)	0 (1)
High	79 (0)	37 (16)	17 (2)	8 (0)	3 (1)	2 (0)	1 (1)	0 (0)	0 (0)
Very high	51 (0)	17 (12)	6 (2)	2 (1)	1 (0)	1 (0)	0 (1)	0 (0)	0 (0)

Lanino L. et al. JCO 2026

Optimal timing window for allo-HCT with a iCPSS strategy



Lanino L. et al. JCO 2026 suppl.

Who should be considered for allo-HCT?

PATIENT «fit for allo-HCT»	DISEASE	HIGH-RISK FEATURES
Age ≤70 years* ECOG PS<2 No major comorbidities§ HCT-CI <3	CPSS-Mol → BLAST-Mol/ iCPSS Disease kinetics → Dinamic assessment (worsening cytopenias, rapid ↑ of WBC or blasts, clonal evolution)	Transfusion dependence • blasts ≥10% Proliferative / symptomatic disease Adverse cytogenetics / mutations Relapse or refractoriness to previous treatments

*in selected cases ≤75

§Ferrara F et al. Leukemia 2013

EARLY REFERRAL FOR ALLO-HCT

Early referral ≠ immediate transplantation in every patient:
The goal is not "transplant as early as possible" - but transplant before the window of opportunity is lost

Adapted from Onida et al. Blood 2024; contemporary risk models incorporated

Should we debulk before transplantation?

Recommendations from the EBMT PH&G Committee

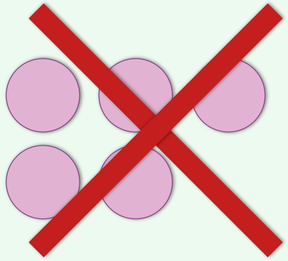
No randomized evidence demonstrates that **pre-HCT debulking** or **achievement of CR** improves transplant outcomes.



Pre-HCT treatment may **worsen cytopenias, transfusion dependence and infections**, potentially preventing transplantation.



Upfront allo-HCT without prior disease-modifying treatment **should be preferred whenever possible**, irrespective of BM blast count.



Onida et al. Blood 2024

What if bridging therapy is needed?

UPFRONT HCT

Preferred whenever feasible

BRIDGING IF NEEDED

- **donor / logistic delay**
- **rapid progression**
- **high disease burden**

HMA-BASED THERAPY*

± cytoreduction according to phenotype

* Clinical trial → prioritize whenever available

Proceed to allo-HCT at the best achievable response without unnecessary delay

AMMO Trial provides new randomized evidence for ASTX727 vs HC/BSC, but its role as transplant bridging remains to be defined

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)

Onida et al. Blood 2024; Wiseman D. et al. ASH 2025

How should we transplant?

CONDITIONING

MAC or RIC according to age, fitness and comorbidities

No clearly superior regimen

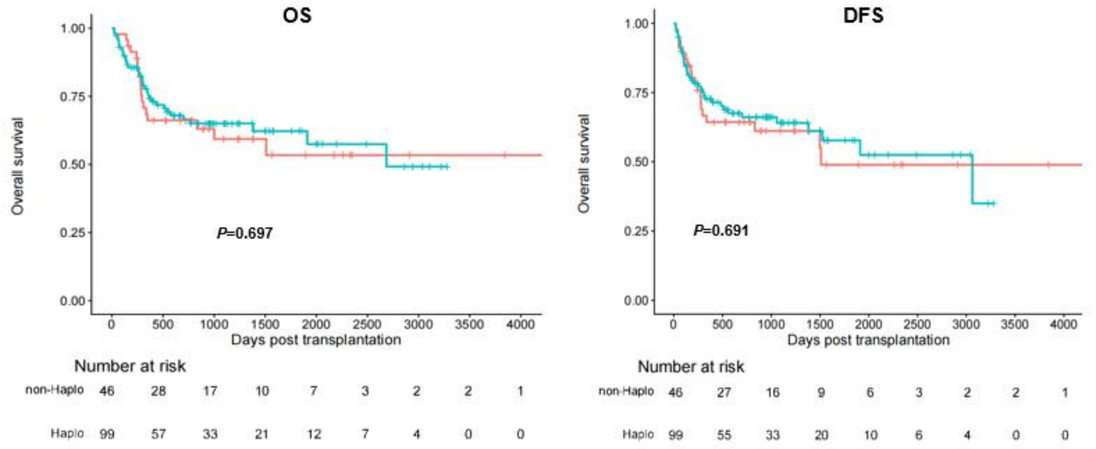
DONOR

MSD / MUD
Alternative donors increasingly feasible

Haplo-HCT: reassuring emerging data*

GRAFT SOURCE

PBSC generally preferred in adult CMML transplantation



Ma et al. Cancer Lett 2026

Onida et al. Blood 2024

Post-transplant monitoring and relapse: can we intervene earlier?

CHIMERISM	MOLECULAR MONITORING	EARLY WARNING	INTERVENTION
backbone of surveillance	qPCR / NGS when informative	mixed chimerism / molecular persistence	taper IS → DLI → HMA-based therapy

Molecularly triggered pre-emptive strategies are attractive — but robust CMML-specific evidence is still lacking.

Second allo-HCT / clinical trial / supportive care according to relapse context and patient fitness

Onida et al. Blood 2024

EBMT: From Approval to Implementation

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

“ChroMMAllo Study”

P.I. Francesco Onida – Chair MDS/MPN Subcommittee EBMT-CMWP

Co-P.I. Marie Robin – Chair of the EBMT-CMWP

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

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

Conclusions and take-home messages

- **CMML** remains a challenging myeloid malignancy, with **heterogeneous clinical behavior** and generally **poor outcomes in higher-risk disease**.
- **Conventional HMAs** provide responses in a subset of patients, but **responses** are often **transient** and **survival benefits** remain **uncertain**.
- The randomized AMMO trial has shown **promising results with oral decitabine/cedazuridine** (ASTX727), including improved response rates and survival outcomes versus hydroxyurea/best supportive care in MDS/MPN overlap syndromes.
- **Novel targeted agents and rational combination strategies are expanding** the therapeutic landscape, although prospective validation is needed.
- **Allo-HSCT remains the only potentially curative treatment** for eligible patients, despite substantial risks of relapse and non-relapse mortality.
- **Integrated clinical and molecular risk assessment is essential** to guide treatment decisions and **transplant referral**.



francesco.onida@unimi.it