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GRUPO ESPAÑOL DE SÍNDROMES
MIELODISPLÁSICOS

XIV Reunión Anual **GESMD**

V Curso Educacional en **SMD**

29 de febrero y 1 de marzo de 2024 | MADRID



Tratamiento de la leucemia mielomonocítica crónica

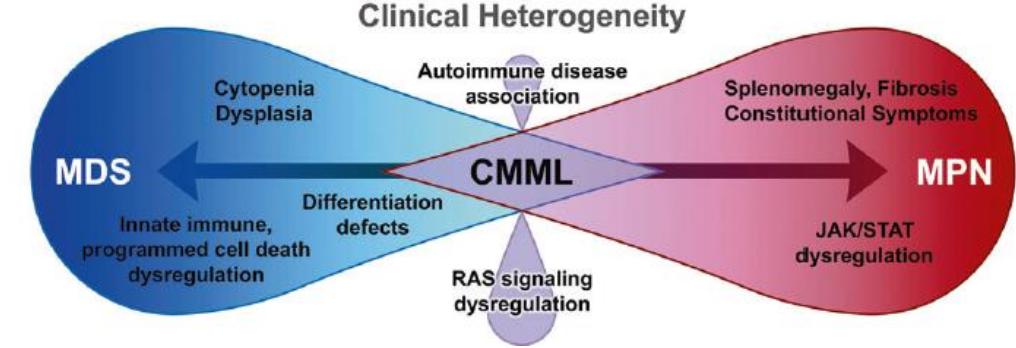
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Chronic Myelomonocytic Leukemia (CMML)

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder characterized by sustained peripheral blood monocytosis with features of both myelodysplastic syndromes and myeloproliferative neoplasm

The Chronic Myeloid Neoplasms Continuum



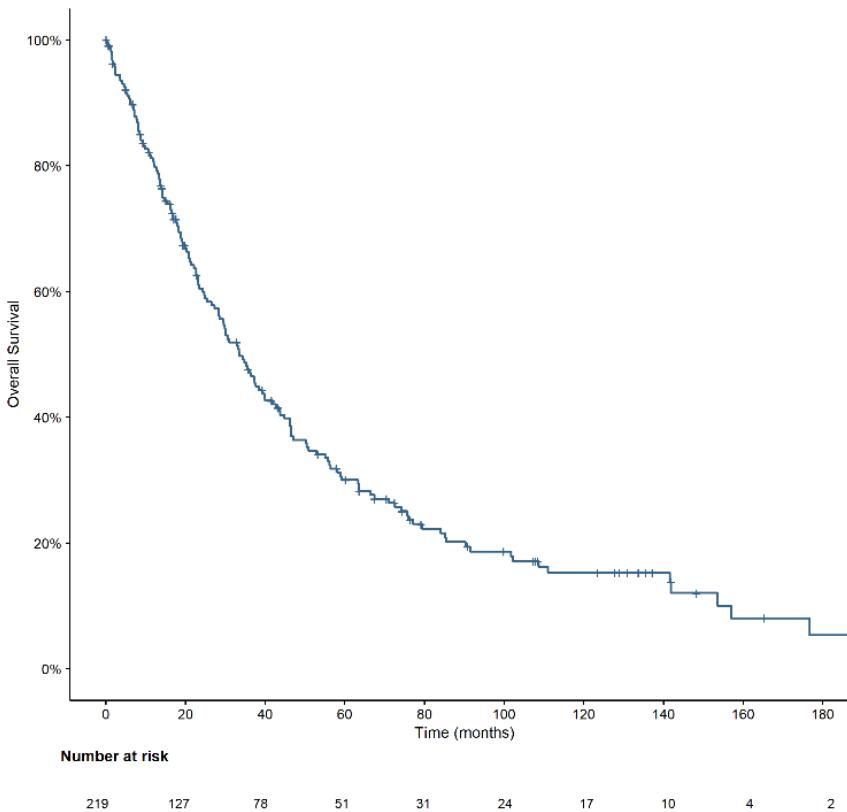
Proliferative component related to hypersensitivity of myeloid progenitors to activation of the GM-CSF/STAT5 pathway

Distinguishing factor	CMML	Steady-state hematopoiesis
Monocyte levels [60,61]	≥ 1000 cells/dL, $\geq 10\%$ differential	Normal range 1.9% differentiation
Classical monocyte levels [60,61]	Elevated ($\geq 94\%$)	Lower
Apoptosis [72*]	Resistant, MCL-1 dependent	Undergo spontaneous apoptosis with 1-7 days
Transcriptome [62]	Highly inflammatory	inflammatory
Inflammatory cytokine levels [67]	Elevated and Persistent	Lower except upon emergency monopoieses
Cytokine hypersensitivity [68]	Elevated in HSPC	Not present

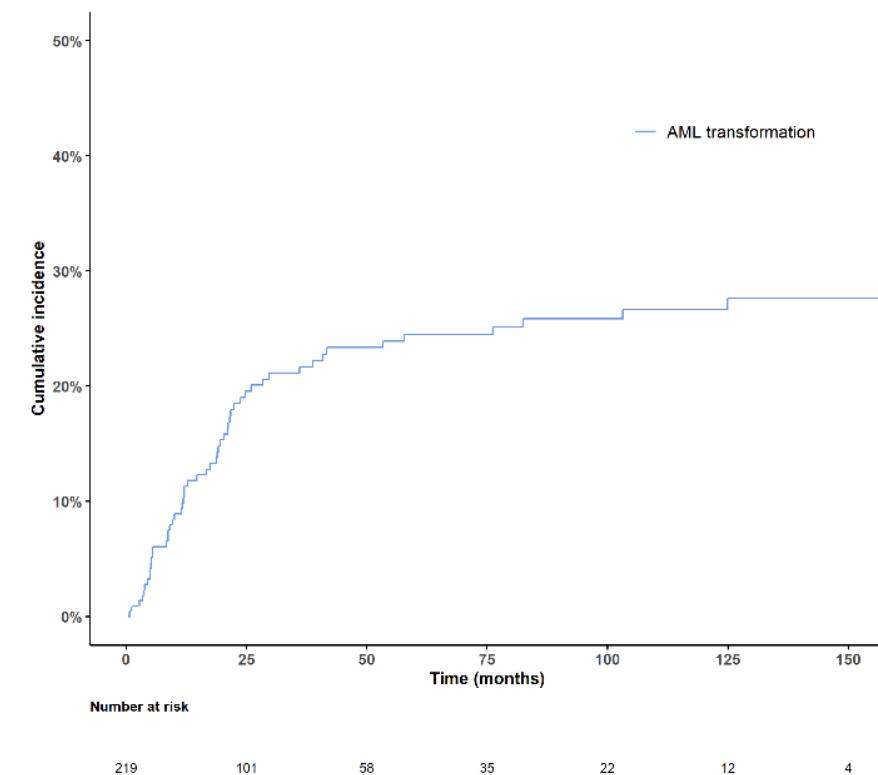
CMML, chronic myelomonocytic leukemia; HSPC, Hematopoietic stem and progenitor cell; MCL, Myeloid-cell leukemia.

CMMI Outcome

Median OS for the entire cohort was 34 months

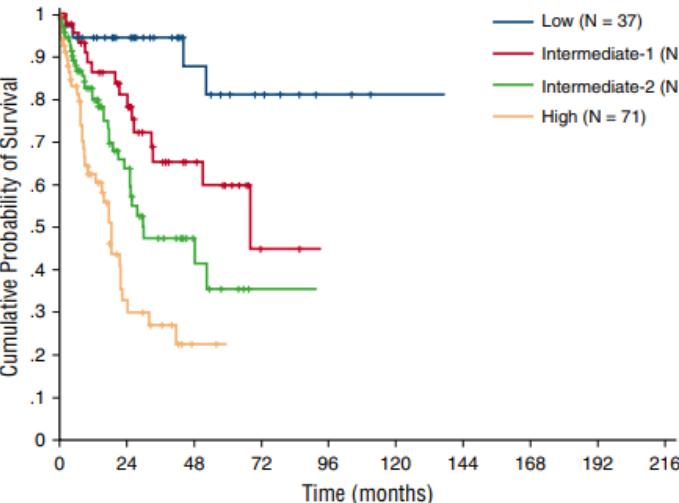


53pts (24.2%) progressed to AML
median time to transformation of 16.6 months
4-year CI of AML transformation 23.3%

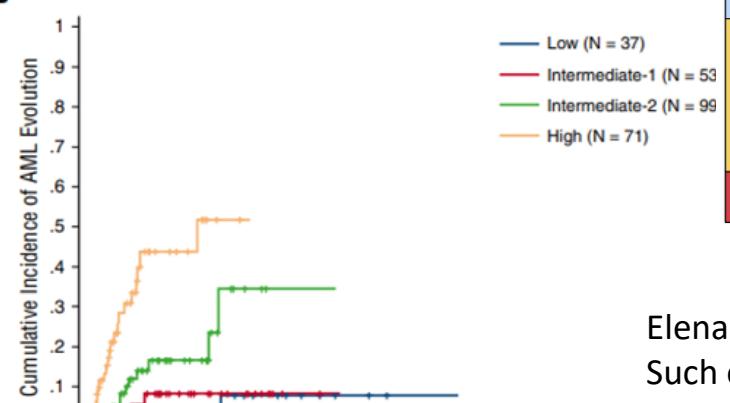


CML prognostic scores

ASXL1*, NRAS, RUNX1, SETBP1 Mutations described as a negative prognostic factors *Frame-shift and nonsense



Bone marrow blast $\geq 5\%$
RBC transfusion dependency
WBC $\geq 13 \times 10^9/L$



- Elena et al, Blood 2016;128:1408–17
Such et al, Haematologica 2011;96(3):375–383
Itzykson R, et al, J Clin Oncol.2013;31:2428–36
Such E, et al.Blood 2013;121:3005–15
Patnaik et al, Leukemia 2014;28:2206–12
Castaño-Díez et al, Cancers 2022, 14, 4107

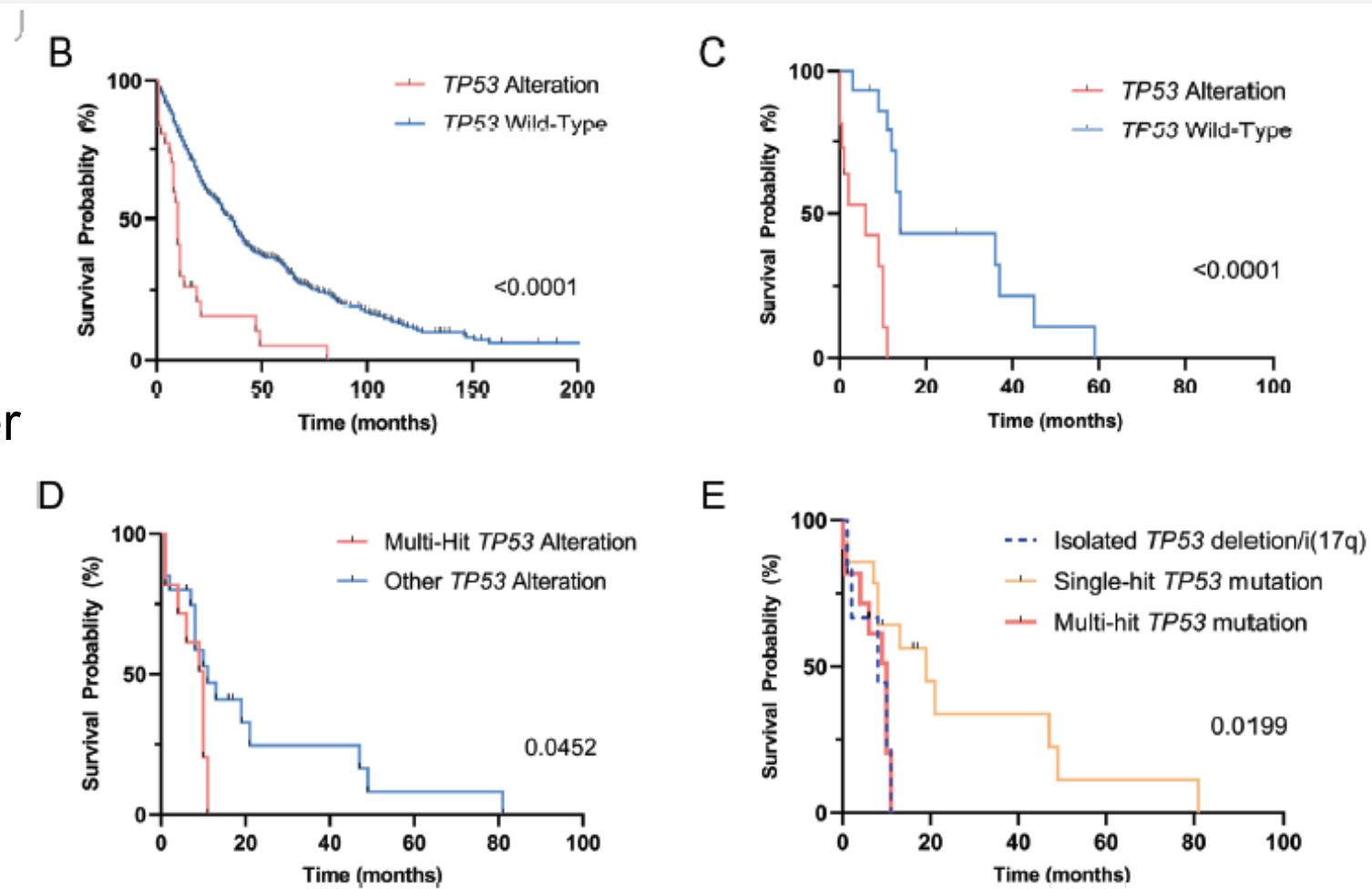
Model	Risk categories		Survival	Risk factors	
	MMM	GFM		CPSS Mol	Genetic risk* for CPSS Mol model
Mayo Molecular Model (MMM)	Low risk (0 points) Intermediate-1 risk (1.5 - > 2.5 points) Intermediate-2 risk (2.5-4.5 points) High risk (≥ 5 points)	Low risk (0 points) Intermediate risk (5-7 points) High risk (8-12 points)	97 mo MS 59 mo MS 31 mo MS 16 mo MS	• AMC $>10 \times 10^9/L$ (2 points) • Presence of circulating IMC (2 points) • Hemoglobin level <10 g/dL (2 points) • ASXL1 mutation (1.5 points) • Platelet count $<100 \times 10^9/L$ (1.5 points)	P
Groupe Francophone de Myelodysplasies (GFM)	Low risk (0-4 points) Intermediate risk (5-7 points) High risk (8-12 points)	65 mo MS 28 mo MS 17 mo MS	• WBC $>15 \times 10^9/L$ (3 points) • ASXL1 mutations (2 points) • Age >65 years (2 points) • Platelet count $<100 \times 10^9/L$ (2 points) • Hemoglobin <10 g/dL in females and <11 g/dL in males (2 points)	P	P
CPSS Mol	Points for mutation status WT MT ASXL1 0 1 NRAS 0 1 RUNX1 0 2 SETBP1 0 1	+ Points for karyotype status based on CPSS P Normal or -Y 0 All other abnormalities 1 Trisomy 8, Monosomal, Complex 2	= Low 0 Int-1 1 Int-2 2 High ≥ 3	Genetic risk* for CPSS Mol model	P
CPSS-Mol	Risk categories Low (0 points) Intermediate-1 (1 point) Intermediate-2 (2-3 points) High (≥ 4 points)	AML-TR 0% 8% 24% 52%	Median OS months Not reached 64 37 18	CPSS-Mol score 0 1 2 3 • Bone marrow blast $< 5\%$ • FAB subtype • Genetic risk* • RBC transf.	0 1 2 3 Bone marrow blast $\geq 5\%$ MDS-CMML MPN-CMML Low Int-1 Yes Int-2 High

TP53 alterations in CML are an adverse molecular prognostic factor

Incidence 1.9%

N=31

Their negative impact is further refined by consideration of TP53 allelic status



Chronic Myelomonocytic Leukemia (CMML) with AML Typical Mutations (NPM1, FLT3 or CEBPA) Identify a High-Risk CMML Group Independent of Molecular-Cpss

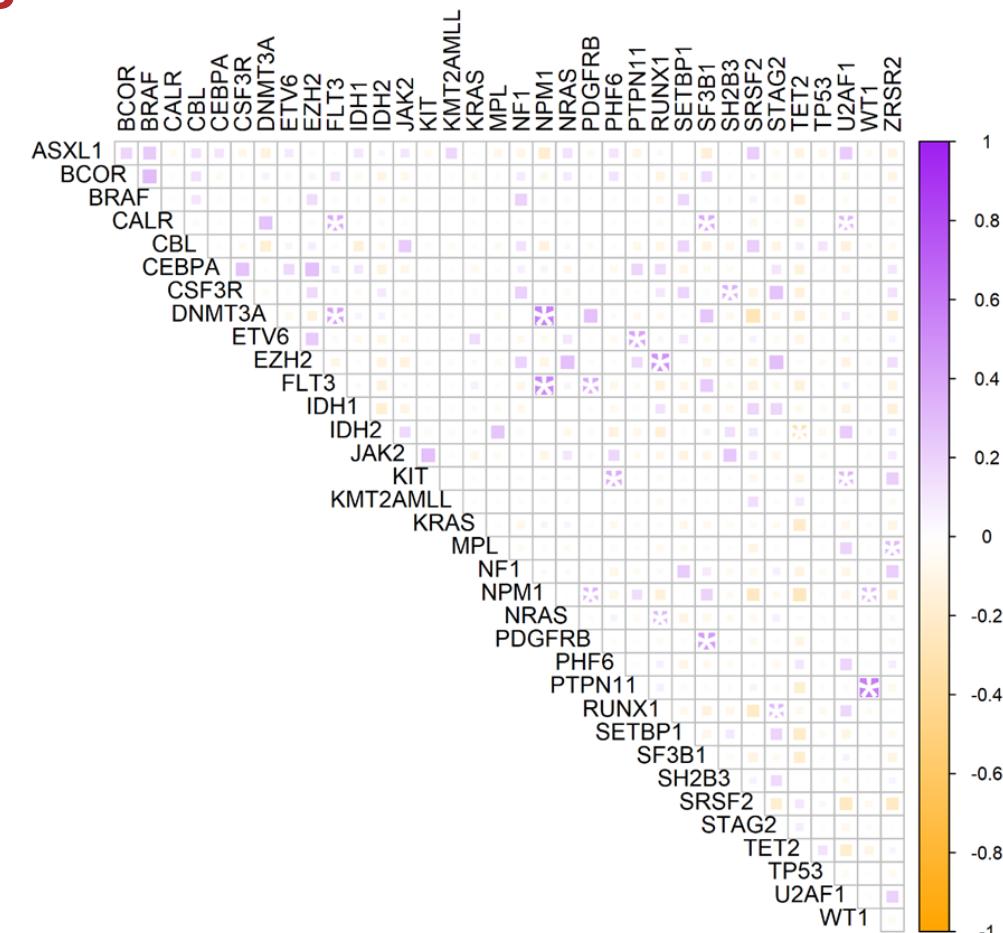
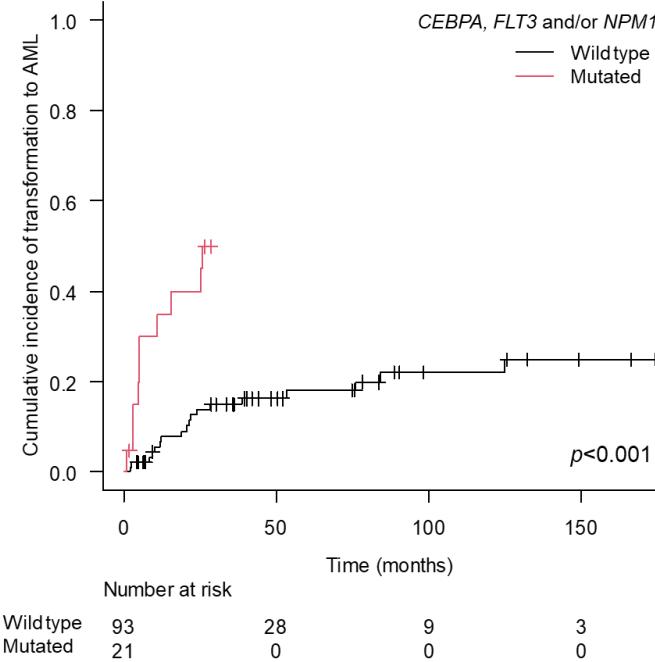
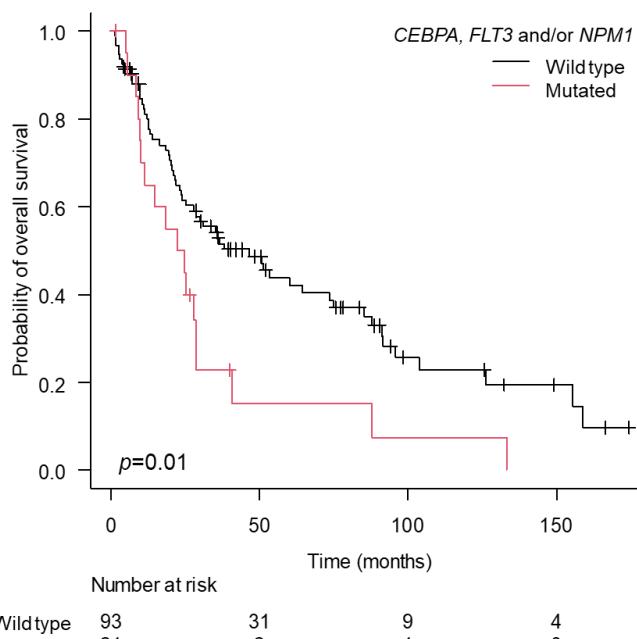


Table 5. Multivariate analysis

Variable	HR	95% CI	"p" value
Age at diagnosis	1.053	1.02-1.087	0.001
CPSS-Mol	1.566	1.203-2.039	0.001
mutCFN	2.452	1.237-4.86	0.01

Molecular Classification of Chronic Myelomonocytic Leukemia: Results of the Analysis of an International Cohort of 2,471 Patients

Subgroup	Cluster-defining abnormalities	Assigned patients	Median OS, years (95% C.I.)	Median LFS, years (95% C.I.)	Relevant Clinical Features
Splicing machinery	<i>SRSF2 + TET2</i>	7.9%	4.5 (3.4-7.5)	4.5 (3.3-7.5)	Dysplastic phenotype (by FAB criteria) in most cases; mild cytopenias; lower risk according to IPSS-R/CPSS-mol stratification; prolonged survival and low risk of AML evolution.
	<i>ZRSR2 + TET2</i>	3.1%	8.2 (4.3- NR)	8.0 (4.1-NR)	
Splicing and additional higher-risk mutations	<i>SRSF2 + TET2 + ASXL1/RUNX1</i>	22.2%	3.2 (2.8-3.5)	2.4 (2.1-3.0)	Overlap between dysplastic and proliferative features (FAB criteria); moderate cytopenias; intermediate risk according to IPSS-R/CPSS-mol stratification; lower probability of survival and AML evolution as compared with the first 2 clusters.
	<i>ZRSR2 + TET2 + EZH2/ASXL1</i>	8.9%	1.9 (1.7-2.5)	1.6 (1.1-2.3)	
Isolated SF3B1	<i>SF3B1 (often + TET2, DNMT3A)</i>	6.6%	4.2 (3.7-4.8)	3.3 (2.9-4.1)	Markedly dysplastic phenotype (FAB criteria); lower median hemoglobin concentration and higher prevalence of transfusion-dependent anemia with respect to the other clusters.
Signal transduction and tyrosine-kinase pathways	<i>CBL</i>	7.1%	3.9 (2.6-5.6)	3.8 (2.3-5.4)	Clinical phenotype mostly proliferative (FAB criteria), characterized by higher leukocyte and absolute monocyte counts; intermediate risk according to IPSS-R/CPSS-mol stratification; intermediate prognosis (overall survival and AML evolution). The presence of <i>JAK2</i> mutations appears to confer a better prognosis.
	<i>NRAS/KRAS</i>	11.7%	3.7 (2.6-4.5)	3.4 (2.3-4.0)	
	<i>SETBP1 (often +ASXL1/TET2)</i>	5.3%	2.4 (2.1-3.5)	2.0 (1.4-2.7)	
	<i>JAK2</i>	3.7%	4.9 (2.9-8.3)	4.3 (2.5-6.8)	
High-risk signatures	<i>TP53 (often biallelic) + Complex Karyotype</i>	2.1%	0.9 (0.7-1.3)	0.7 (0.6-1.1)	Dysplastic phenotype (FAB criteria); high rate of symptomatic cytopenias; high risk according to IPSS-R/CPSS-mol stratification; dismal outcome characterized by short overall survival and high rate of AML evolution
	<i>AML-like genotype (NPM1, FLT3, IDH1-2)</i>	2.5%	1.7 (1.0-2.6)	0.7 (0.5-1.2)	

Treatment

Low risk CMMI

mOS 60-80 m

High risk CMMI

mOS 30-15 m

Low risk CMML

MOS 60-80 m

Treatment

- Active W&W
- Anemia
 - EPO effective ER 64% IT 31% (consider avoid G-CSF)
 - Transfusion (consider iron chelating agent if needed)
 - Hypomethylating agents (HMA)
 - Standard dose
 - Low dose (CMML 16 pts; all MDS/CMML TI 33% for 22 mo)
 - SF3B1 mut (10%)- Luspatercept (off label). Completed Sotatercept CT phase 2 NCT01736683 (AEE failure, including MD-CMML)
 - Consider clinical trials
- Leukocytosis. Hydroxyurea (HU) when leukocytes are > 30-35 x10⁹/L as sustained high levels may be associated with a higher prevalence of renal disease. Also used for proliferative symptoms and splenomegaly

Renneville et al Leukemia (2021) 35:2739–2751

Xicoy B, et al, Europ haemat. 2016;97(1):33-8

Wudhikarn et al, Blood Adv (2020) 4 (22): 5716–5721

Sasaki et al NEJM Evid 2022;1(10))

Low risk CMML

MOS 60-80 m

Treatment

- **Splenomegaly**
 - Hydroxyurea
 - Ruxolitinib . Phil II 50 CMM (1L_R/R). 15mg/12 h. ORR 43% The median time to best response was 3.7 months. The median duration of response was 7.7 months
- **Trombocytopenia**
 - PDN. 20-30% of CMML patients immune-mediated thrombocytopenia
 - Hypomethylating agents (HMA)
 - Eltrombopag in CMML (NCT02323178) 46% achieving ORR duration 4 mo
Caution when prescribing eltrombopag for pCMML
- **Autoimmune manifestations/systemic inflammatory manifestations**

20-30% of CMML patients (sometimes preceding the diagnosis of CMML). Erythema nodosum, leukocytoclastic vasculitis, Sweet syndrome, polymyalgia rheumatica, seronegative arthritis, and mixed connective tissue disorder-like syndromes

- PDN
- HMA

Wattel et al, Blood, 88, 7 , 1996: pp 2480-2487
Hunter et al , Clin Cancer Res. 2021;27(22):6095-6105
Peker D, et al Acta Haematol. 2015;133(2):249-256
Zahid et al, Leuk Lymphoma. 2017;58(6):1488-1493.
Rabian et al Blood .2020;136:15-6

Treatment

Low risk CMM^L

mOS 60-80 m

High risk CMM^H

mOS 30-15 m

FIT (10%)

allo-SCT

Table 2. Proposed criteria for measurement of treatment response in adult MDS/MPN

CR (presence of all of the following improvements)*

Bone marrow: $\leq 5\%$ myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity*

Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (\leq grade 1 fibrosis)†

Peripheral blood‡

WBC $\leq 10 \times 10^9$ cells/L

Hgb ≥ 11 g/dL

Platelets $\geq 100 \times 10^9$ /L; $\leq 450 \times 10^9$ /L

Neutrophils $\geq 1.0 \times 10^9$ /L

Blasts 0%

Neutrophil precursors reduced to $\leq 2\%$

Monocytes $\leq 1 \times 10^9$ /L

Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly

Provisional category of CR with resolution of symptoms:‡ CR as described above, and complete resolution of disease-related symptoms as noted by the MPN-SAF TSS

Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia*

Complete cytogenetic remission

Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic, syndrome myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal of 20 metaphases or FISH§

Partial remission

Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining $>5\%$ of cellularity except in cases of MDS/MPN with $\leq 5\%$ bone marrow blasts at baseline

Marrow response

Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above.

Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining $>5\%$ of cellularity, or reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 mo apart

Clinical benefit

Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response (cord blood response must be verified at ≥ 8 wk) to be considered a clinical benefit

Erythroid response

Hgb increase by ≥ 2.0 g/dL

TI for ≥ 8 wk for patients requiring at least 4 packed red blood cell transfusions in the previous 8 wk

Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation||

Platelet response

Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 wk

Pretreatment $\leq 20 \times 10^9$ /L: increase from $<20 \times 10^9$ /L to $>20 \times 10^9$ /L and by at least 100%

Pretreatment $>20 \times 10^9$ /L but $\leq 100 \times 10^9$ /L: absolute increase of $\geq 30 \times 10^9$ /L||

Neutrophil response

Pretreatment $\leq 0.5 \times 10^9$ /L at least 100% increase and an absolute increase $\geq 0.5 \times 10^9$ /L

Pretreatment, $>0.5 \times 10^9$ /L and $\leq 1.0 \times 10^9$ /L At least 50% increase and an absolute increase $\geq 0.5 \times 10^9$ /L||

Spleen response

Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable

Symptom response

Improvement in symptoms as noted by decrease of $>50\%$ as per the MPN-SAF TSS scoring <20 were not considered eligible for measuring clinical benefit ¶

*Control proliferative features
constitutional symptoms*

Correct cytopenias

MYELOPROLIFERATIVE CMM^H

WBC count ≥ 13 G/L

Shorter survival

Splenomegaly

Constitutional symptoms

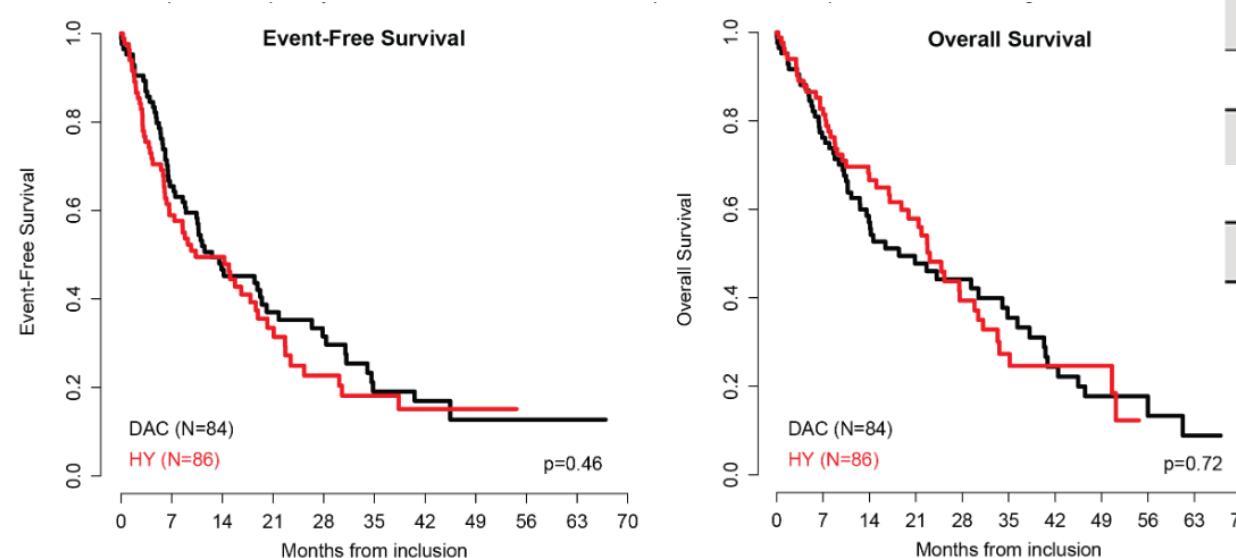
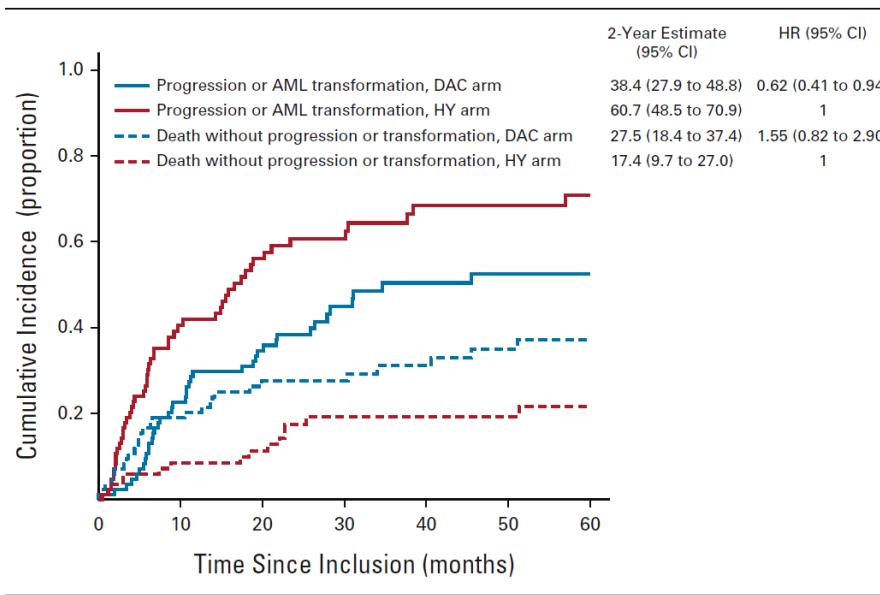
Clonal pDC (CD123+)

GM-CSF hypersensitivity

Signaling mutations

High risk CMML

Treatment



1L not eligible for SCT CMML WBC count $\geq 13 \times 10^9/L$ advanced disease:
extramedullary disease (except splenomegaly)
or ≥ 2 criteria: bone marrow blasts $\geq 5\%$, clonal cytogenetic
Hb < 10 g/dL, neutrophil $> 16 \times 10^9/L$, PLT $< 100 \times 10^9/L$ and Splenomegaly.

DAC N=84 HY N=86

ORR 63 % (DEC) vs 30% (HU) p=0.0004

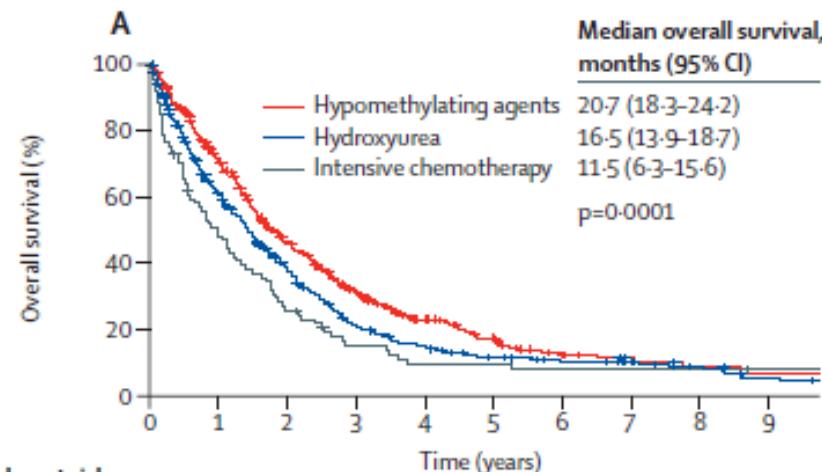
Response	Best Response (ITT)		P
	DAC	HY	
CR, No. (%)	10 (12)	2 (2)	.017
mCR with HI, No. (%)	22 (26)	4 (5)	
mCR without HI, No. (%)	3 (4)	4 (5)	
ORR, No. (%)	53 (63)	30 (35)	.0004
ORR excluding SD + HI-Pro, No. (%)	40 (48)	16 (19)	.00008
DOOR, months, median (95% CI)	16.3 (7.2 to 26.8)	17.4 (9.8 to 26.9)	.90

Wattel al, Blood 1996 Oct 1;88(7):2480-7

Itzykson, R. et al, J Clin Oncol 41:1888-1897 2022

High risk CMML

Treatment



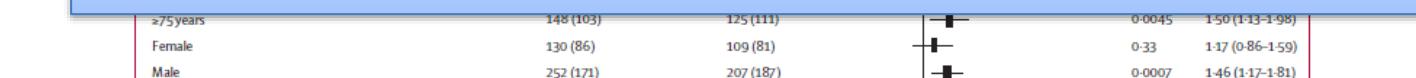
	Number at risk (number censored)									
Hypomethylating agents	412	267	159	92	50	27	14	9	5	3
	(0)	(26)	(44)	(61)	(81)	(91)	(98)	(102)	(104)	(105)
Hydroxyurea	391	218	123	64	42	29	22	15	11	5
	(0)	(23)	(37)	(41)	(43)	(48)	(52)	(58)	(60)	(62)
Intensive chemotherapy	83	38	20	10	6	6	5	5	5	4
	(0)	(2)	(2)	(4)	(4)	(4)	(4)	(4)	(4)	(5)

Outcomes by FAB and WHO classifications and CPSS risk group.

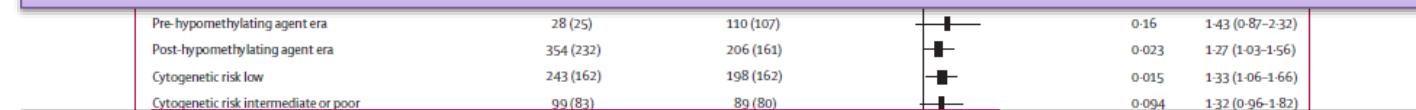
	Overall Response at C4-6	p	Median (95%CI) OS (years)	p	CIP (95%CI) to AML at 5 years	p
FAB classification	MD (n = 50)	30/50 (60)	0.707	3.1 (1.7, 4.5)	0.177 (19%, 51%)	0.367
	MP (n = 41)	23/41 (56)		1.6 (1.1, 2)	42% (25%, 58%)	
WHO classification (2017)	CMML-0/1 (n = 47)	24/47 (51)	0.151	1.7 (1.1, 2.2)	37% (21%, 52%)	0.929
	CMML-2 (n = 44)	29/44 (66)		2.8 (1, 4.6)	40% (23%, 56%)	
CPSS risk group	Low-Int 1 (n = 36)	22/36 (61)	0.653	2.6 (1.2, 4.1)	23% (9%, 41%)	0.034
	Int 2-High (n = 55)	31/55 (56)		1.8 (0.5, 3)	47% (32%, 61%)	

C6: sixth cycle of AZA treatment; OS: overall survival; CIP: cumulative incidence of progression; AML: acute myeloid leukemia; FAB: French-American-British; WHO: World Health Organization; CPSS: Chronic myelomonocytic leukemia-Prognostic Score System

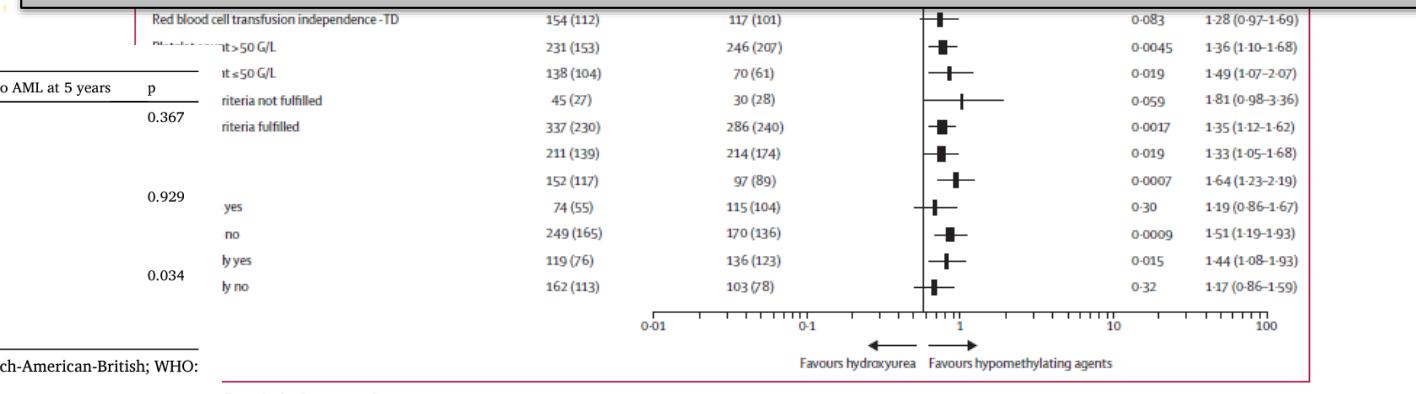
Hypomethylating agents did not confer an overall survival advantage for patients classified as having lower-risk disease:
Myelodysplastic CMML <10% blasts, CMML-0 or lower-risk CPSS



Better overall survival, time to next treatment, and time to transformation to acute myeloid leukaemia with hypomethylating



Myeloproliferative CMML median OS 12.6 mo(HU) VS 17.6 months (HMA) p=0.0027) 12.3 months (Chemo)



Treatment

Real Word data:
Aprox 40% treated with HMA
ORR 40-60% CR <20%

HMA have no impact on mutational allele burden or leukemic transformation, even in responding patients, and all responders ultimately relapse

Progression after HMA response median OS of 6-8 months

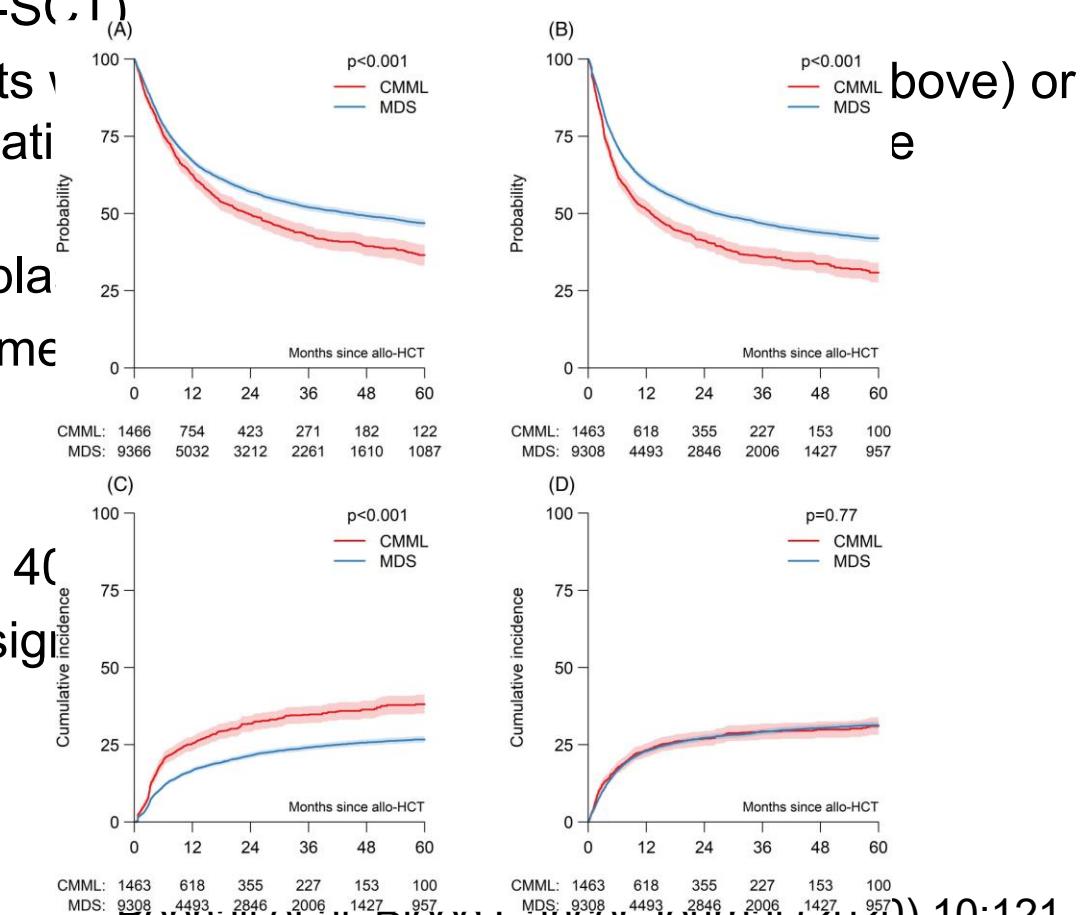
Consider clinical trial

- Santini V, et al. Leukemia.2018;32:413–8
Triguero et al, LeukemiaResearch116(2022)106836
Alfonso, et al., Am. J. Hematol. 92 (7) (2017) 599–606.
Castaño-Díez et al, Cancers 2022, 14, 4107.
MerlevedeNat Commun., 2016 Feb 24;7:10767.
Coston et al, Am J Hematol. 2019;94:767–779.

High risk CMML

Treatment alloSCT

- Only potential curative option (10% patients received an Allo-SCT)
- The ELN/EHA 2018 guideline for CMML recommends patients with selected lower risk (mainly intermediate-1 with poor-risk somatic mutations) considered for alloHCT
- Up-front intermediate-2 and high risk CMML pts with < 10% blasts
- Unclear if achievement of complete remission predicts outcome
- Controversial but seems better HMA pre allo-SCT
- AloTPH No OS advantage in low risk CMML patients
- Median OS post TPH ranged between 27-64 mo. 4 year-CIR 40%
- 1466 CMML, outcome of CMML patients after Allo-HCT are significant
5-year OS 37% , CIR 31%.



Itzykson R, et al. Hematology 2018;2:e150.

de Witte T, Blood. 2017;129(13):1753-1762

Symeonidis A, Br J Haematol. 2015;171(2):239-246.

Kongtim P, Biol Blood Marrow Transplant. 2016;22(1):47-53

Papadimitriou et al. Blood Cancer Journal (2020) 10:121

Robin , et al. Blood. 2022 Jun 6:blood.2021015173

Robó et al, Am J Hematol. 2024;99:203–215

Gagelmann, et al. Transplant and Cell Therapy 27 (2021) 95.e195.e4

Possible Future treatments HMA +VEN

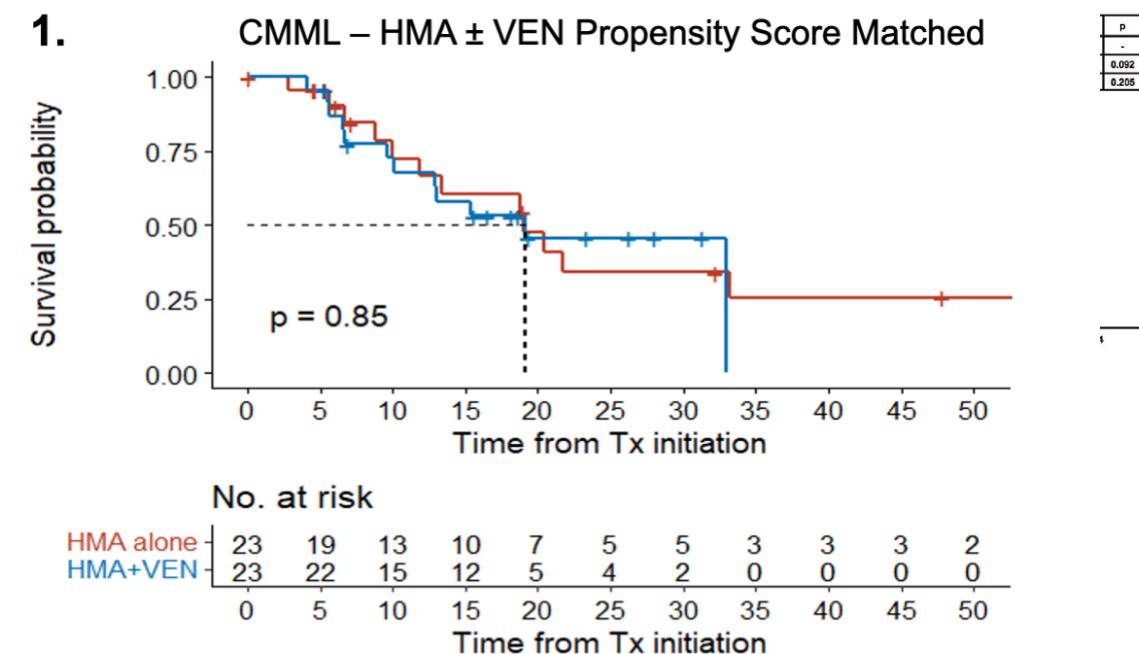
27 CMM, 74% failure HMA 26 AML post CMM.

LMMC ORR 68% Median to best response 1 cicle.

Median duration 4 mo.

5 CMM and 4 AML post CMM patients bridged to HSC

2 studies: 20 and 26 pts CMM or AML post CMM: ORR
CMM R/R ORR 54%, Median duration < 6 mo OS 1year



HMA-naïve 51 CMM and 38 CMM-BT. CMM patients, ORR was 90%,(vs 41% AZA) including complete remission (CR) in 22%, The OS of CMM patients was 25.1 mo (no differences AZA, propensity score population analysis of patients being treated with an HMA)

HSCT 22 (43%) with CMM The median OS after alloSCT was 26.7 mo.

Montalban-Bravo et al. Leukemia (2021) 35:1494–1499

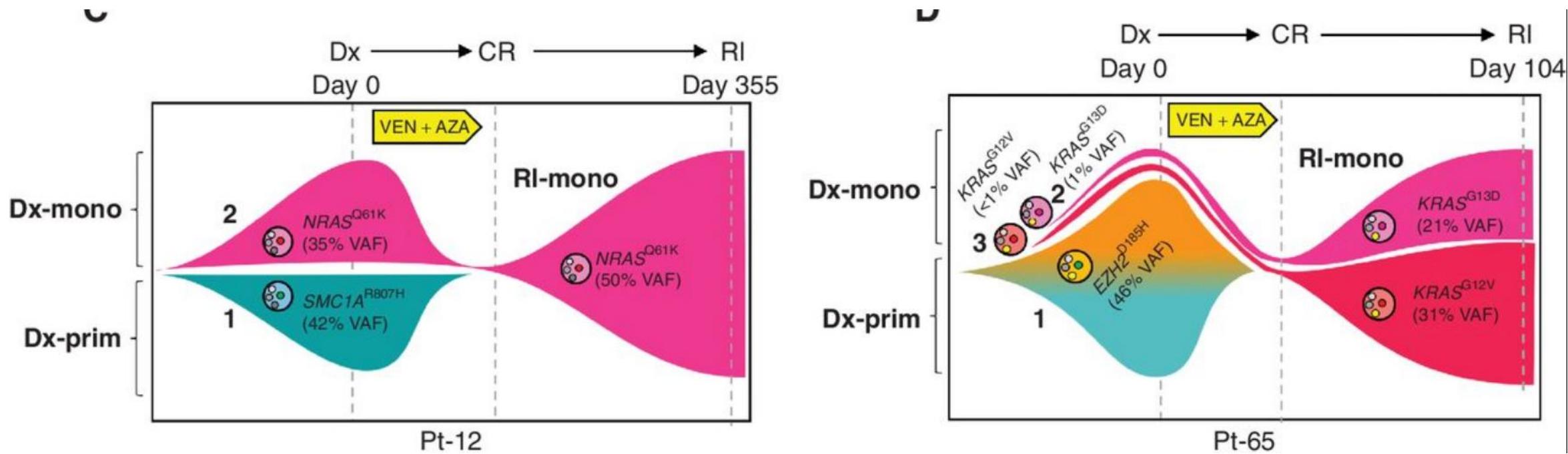
Ball S et al, American journal of hematology. 2022;97(5):E185-E8.

Ball S et al, Blood. 2021;138:4138.

Douglas Tremblay, et al ASH 2023 abstr 321

It could be an adequate option for CMM and post-CMM AML as a bridge to allo-SCT

Possible Future treatments



Resistant monocytic AML (sub)clones lose expression of the venetoclax target BCL2 and rely on MCL1 to mediate oxidative phosphorylation and survival. RAS mutations may contribute to venetoclax resistance either through epistatic mechanisms and/or by driving monocytic differentiation

Possible Future treatments. CPX-351

Phase II	Peterlin et al	Montalban-Bravo et al
Pts	31 (MDS/5 CMML) 1L	25 (6 CMML) R/R
Dose	100 mg/m cytarabine and 44 mg/m daunorubicin)	daunorubicin 22 mg/m ² and cytarabine 50 mg/m ²)
ORR	87%	56% (CMML 1 response)
4 and 8-week mortality	0% (30-day)	0-8%
HSCT	94%	3pts
OS	Median overall survival was also not reached, being 80·6% at 12 months	8.7

Peterlin P, et al. The Lancet Haematology. 2023. DOI:[https://doi.org/10.1016/S2352-3026\(23\)00090-X](https://doi.org/10.1016/S2352-3026(23)00090-X)

Montalban-Bravo G, et al. British Journal of Haematology. 2023;00:1–12. <https://doi.org/10.1111/bjh.19193>

Possible Future treatments targeted therapies

IDH1 (1%) IDH 2 (5%) FLT3 (4%)

- AZA with the IDH2 inhibitor **enasidenib**, in CMML patients (NCT03683433, NCT03383575)
- **Quizartinib** Previously untreated or HMA failure CMML with *CBL* or *FLT3* mutations In combination AZA Phase I-II FLT3 signaling inhibition NCT04493138

JGP 61-year-old CMML-2 and an IDH2 mutation relapsed 4.5 months after alloSCT → enasidenib from dic/2018 CR after 4.5 year

NRL 55y CMML-2 NPM1mut and *FLT3*-TKD chemotherapy plus midostaurin followed by alloSCT. She relapsed 2.5 months after alloSCT *FLT3*ITD emerged immunosuppressive therapy was reduced, and she started treatment with sorafenib. She achieved a complete remission for a year while continuing with sorafenib but died due to non-relapse mortality while still in complete remission

GJNV: 56 y CMML-2 and *TET2*, *NPM1*, and *FLT3*-ITD Chemo plus midostaurin followed by alloSCT. He relapsed 3 months after alloSCT, immunosuppressive therapy was reduced, and he achieved a complete remission with negative minimal residual disease (MRD). After 6 months, MRD reappeared, he started sorafenib, and he continues to be in complete remission+20m

Possible Future treatments

ASTX727: The FDA has approved ASTX727 the oral combination of decitabine and cedazuridine for myelodysplastic syndromes and CMML.

Safety and efficacy of ASTX727 have recently been reported in 33 patients with CMML from the Phase 2 and 3 ASCERTAIN studies with a 75% ORR and an mOS of 35 months.

Several trials are currently underway studying this agent in monotherapy or in combination (AMMO (ISRCTN30808508) and ABNL-MARRO 001 (NCT04061421).

Oral decitabine plus cedazuridine and venetoclax in patients with higher-risk myelodysplastic syndromes or chronic myelomonocytic leukaemia: a single-centre, phase 1/2 study

CMML= 6 Decitabine (35 mg) and cedazuridine(10mg) d 1-5 /VEN 400 (1-14)

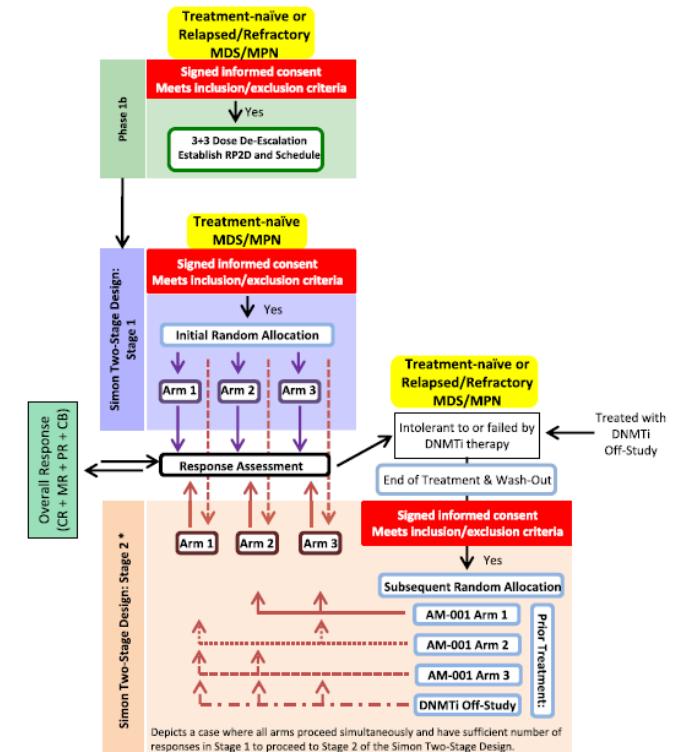
ORR (all) 95% (median 1 cycle to first and best response) 49% underwent SCT , mOS not reached. mEFS 17 mo

Garcia-Manero G, et al. Blood,. 2020;136(6):674-83; Savona et al. Clinical Lymphoma Myeloma and Leukemia. 2023;23:S375-S6.

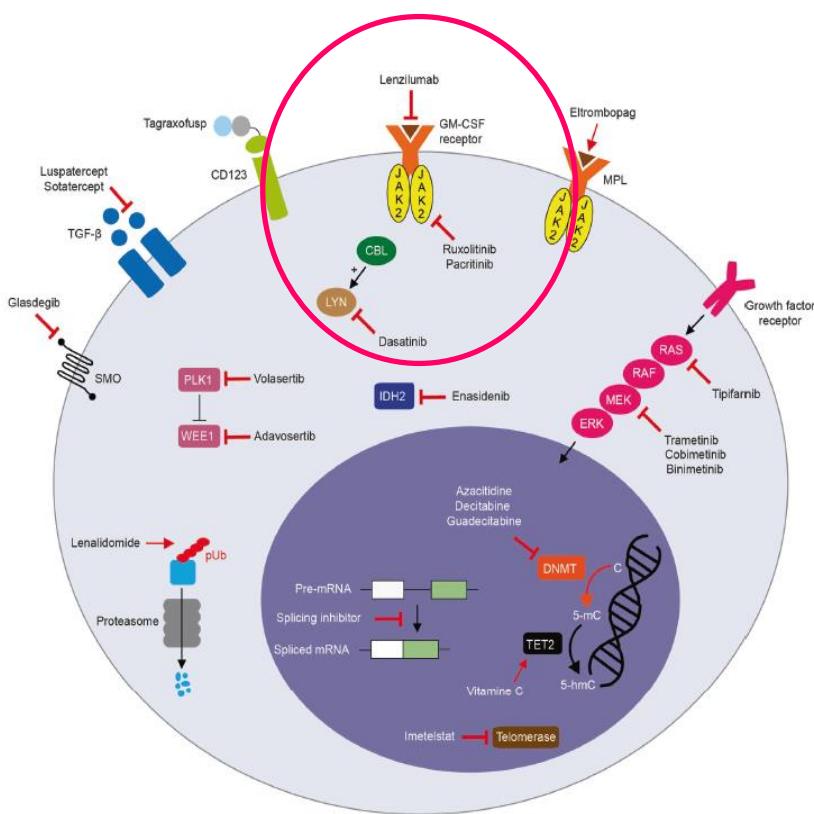
Moyo TK et.al BMC Cancer. 2022; Bataller et al , Lancet Haematol . 2024 Feb 2:S2352-3026(23)00367-8

Possible Future treatments

ABNL-MARRO (A Basket study of Novel therapy for untreated MDS/MPN and Relapsed/Refractory Overlap Syndromes) is an international cooperative effort that leverages the expertise of the MDS/MPN International Working Group (IWG) and provides a framework for collaborative studies around the world to advance treatment of MDS/MPN and to explore clinical and pathologic markers of disease severity, prognosis, and treatment. ASTX727 together with a series of active agents in myeloid disease for MDS/MPN. In arm A, ASTX727 is combined with itacitinib 300 mg (days 1-28), a selective JAK1 inhibitor



Novel targeted approaches



Myeloid progenitor hypersensitivity to granulocytemacrophage colony-stimulating factor (GM-CSF) → CMML proliferation cascade of downstream signaling and transcription factor activation Small molecules inhibitors of downstream components of the GM-SCF receptor signaling pathway

Lenzilumab (KB003) → human IgG1κ monoclonal antibody,
(high affinity for GM-CSF) phase 1, 15 patients safety ok, durable clinical benefit was achieved in four (33%) patients

RUXOLITINIB: safety ok, ORR 35% (ph2 20 pts) Ph 2 ongoing
Ruxo+AZA ORR 57% (NTC 01787487). Safety ok
Symptomatic CMML hig risk: ORR 17%, clinical benefit 66%.
6/20>35% spleen volumen reduction, 54% total symptoms score reduction >50% mOS 24 mo. NCCN guidelines to treat CMML-2

Pacritinib: JAK2/FLT3 inhibitor. CT Ph I/II +AZA

Padron E, et al Clin Cancer Res. 2016;22:3746–54. Padron et al, Blood (2022) 140 (Supplement 1): 1101–1103. Assi R, et al, Am J Hematol. 2018;93:277–85. Tremblay et al ASH 2023 abstr 3248

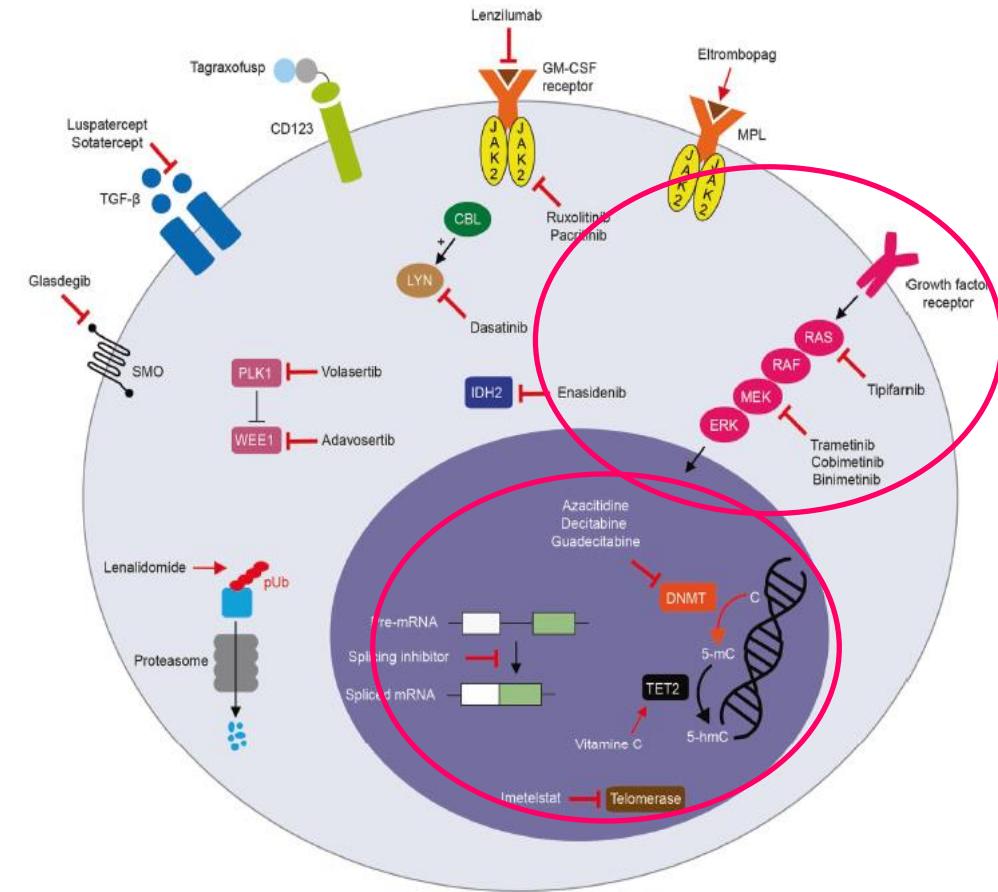
Renneville et al, Leukemia; (2021) 35:2739–2751;

Padron et al, Blood. 2013;121:5068–77

Patnaik et al, Blood. 2020;136:909–13..

Yoshimi A, et al. Blood, 2017;130(4):397-407.

Novel targeted approaches



Therapies targeting RAS-MAPK pathway

35% CML Oncogenic RAS pathway mut (NRAS, KRAS, CBL, PTPN11)

Tipifarnib: phase 2 trial in CML patients (NCT02807272)
but results were suboptimal and the study is now closed

MEK1/2 inhibitors, CML-specific phase 2 trial is ongoing to assess the efficacy of cobimetinib in newly diagnosed or HMA-treated CML patients with RAS pathway mutations (NCT04409639).

Targeting the spliceosome

50% CML mut spliceosome genes: SRSF2, SF3B1, and U2AF1
typically early events in CML pathogenesis cancer cells with
spliceosome mutations are preferentially susceptible to
additional splicing perturbation

H3B-8800: modulator of the SF3b complex phase 1 in AML, MDS,
and CML (NCT02841540) safety, disappointing response

Novel targeted approaches

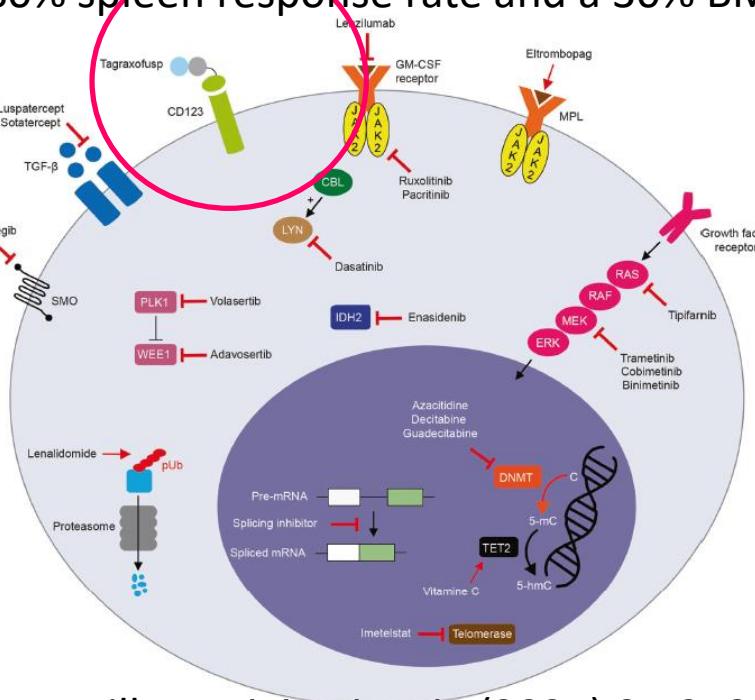
Tagraxofusp is a CD123-directed cytotoxin

consisting of recombinant human interleukin-3 (IL-3) fused to a truncated diphtheria toxin

Tagraxofusp was FDA-approved for the treatment of blastic plasmacytoid dendritic cell neoplasm

322 A Phase II Study of Vibecotamab, a CD3-CD123 Bispecific T-Cell Engaging Antibody, for MDS or CMML after Hypomethylating Failure and in MRD-Positive AML

A phase 2 trial of tagraxofusp in CMML (NCT02268253),
80% spleen response rate and a 30% BM CR rate



In the MDS/CMML cohort, 7 pts responded (64%)

Table 2: Responses

Response rates, N (%) / median [range]	MDS/CMML after HMA failure (N=11)	AML MRD (N=12)
MDS/CMML best response IWG 2006		
mCR	6 (55)	-
HI	1 (9)	-
Stable disease	1 (9)	-
Progressive disease	2 (18)	-
Not evaluable/Early death	1 (9)	-
IWG 2023 (MDS only)		
CR _L	5/9 (56)	-
No response	1/9 (11)	-
Progressive disease	2/9 (22)	-
Not evaluable/Early death	1/9 (11)	-
AML MRD best response		
MRD negativity	-	3 (25)
No response	-	9 (75)
Best response after 1 cycle	7/7 (100)	3/3 (100)
Median CD123 of responders	59% [43%-90%]	98% [95%-99%]
Median CD123 of non-responders	79% [77%-94%]	87% [66%-96%]
Median MRD of responders	-	0.2% [0.1%-0.2%]
Median MRD of non-responders	-	1.8% [0.5%-3.9%]

Abbreviations: IWG, International Working Group; mCR, marrow complete remission; HI, hematologic improvement;

En resumen

- LMMC neoplasia clínicamente heterogénea
- Tratamiento estratificado al riesgo. Imprescindible el seguimiento cercano
- Escasas respuestas a tratamientos actuales
- En pacientes de alto riesgo candidatos el alotrasplante es el único tratamiento potencialmente curativo
- Estudio molecular al diagnóstico y en la progresión nos puede identificar pacientes tributarios a tratamientos dirigidos
- Es imprescindible esfuerzo/collaboración internacional para poner en marcha estudios dedicados a LMMC y desarrollar arsenal terapéutico eficaz



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XIV Reunión Anual GESMD V Curso Educacional en SMD

29 de febrero y 1 de marzo de 2024
MADRID



Gracias por vuestra atención!!

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A los pacientes y a sus familias



CETLAM

Grupo Cooperativo de estudio y tratamiento de las leucemias agudas y mielodisplásicas



Organizado por:



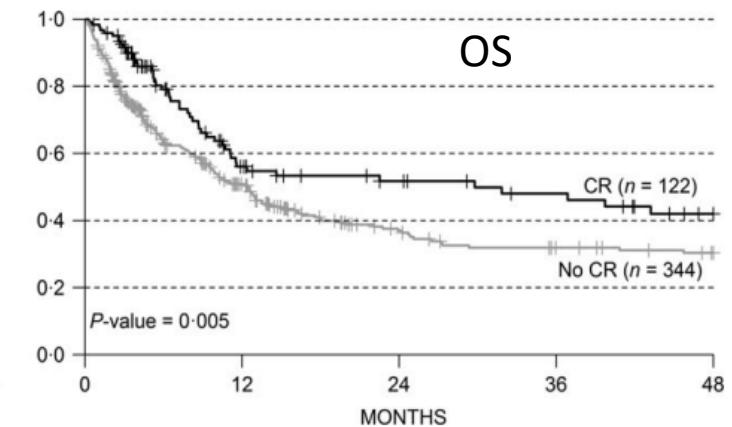
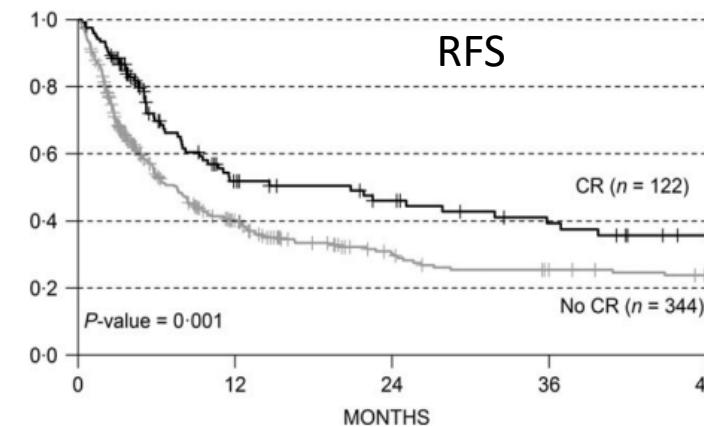
GRUPO ESPAÑOL DE SÍNDROMES
MIELODISPLÁSICOS

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MADRID



- Only potential curative option (10% patients received an Allo-SCT)
- The ELN/EHA 2018 guideline for CML recommends patients with higher-risk (intermediate-2 and above) or selected lower risk (mainly intermediate-1 with poor-risk somatic mutations or severe cytopenia) to be considered for alloHCT
- Up-front intermediate-2 and high risk CML pts with < 10% blast
- Unclear if achievement of complete remission predicts outcome
- Controversial but seems better HMA pre allo-SCT



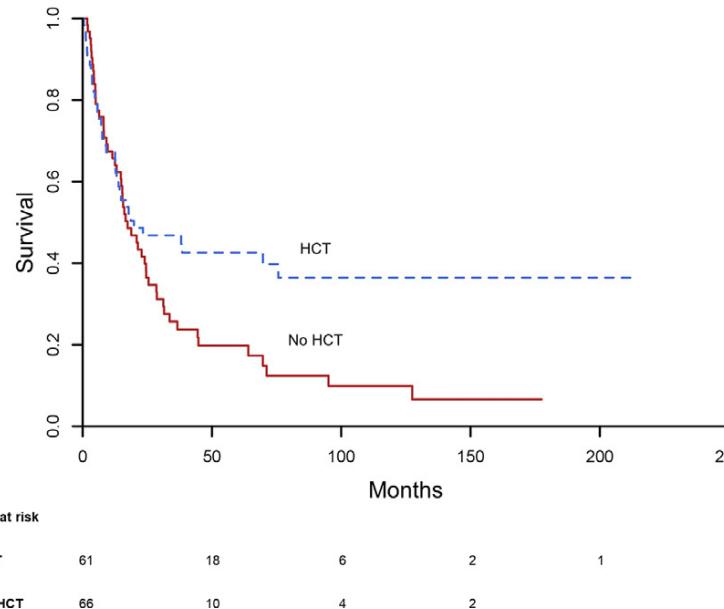
Itzykson R, et al. Hemasphere 2018;2:e150.

de Witte T, Blood. 2017;129(13):1753-1762

Symeonidis A, Br J Haematol. 2015;171(2):239-246.

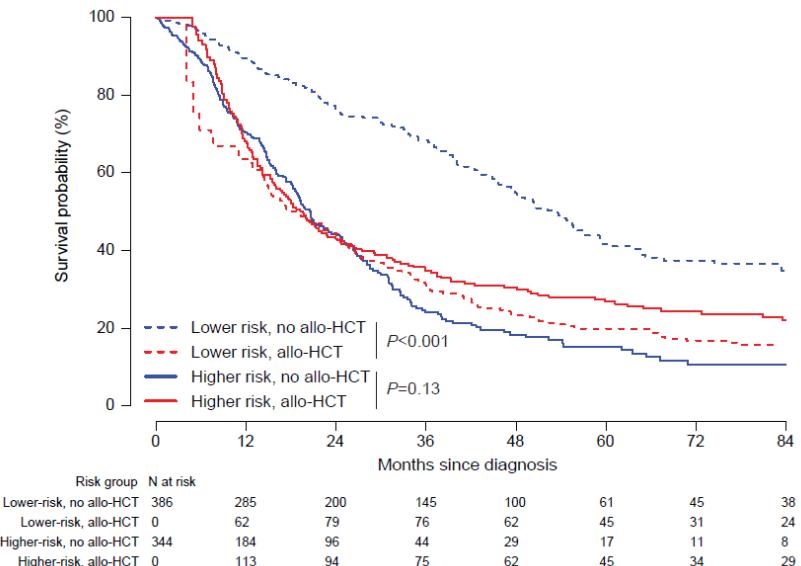
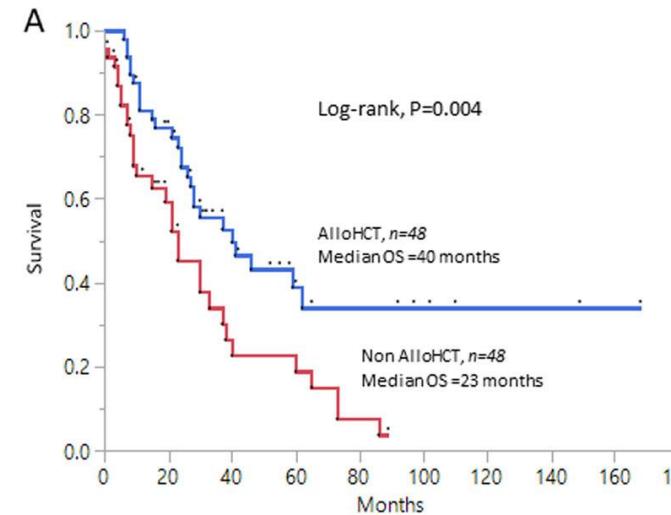
Kongtim P, Biol Blood Marrow Transplant. 2016;22(1):47-53.

High risk CMML



No OS advantage in low risk patients

Treatment allo SCT

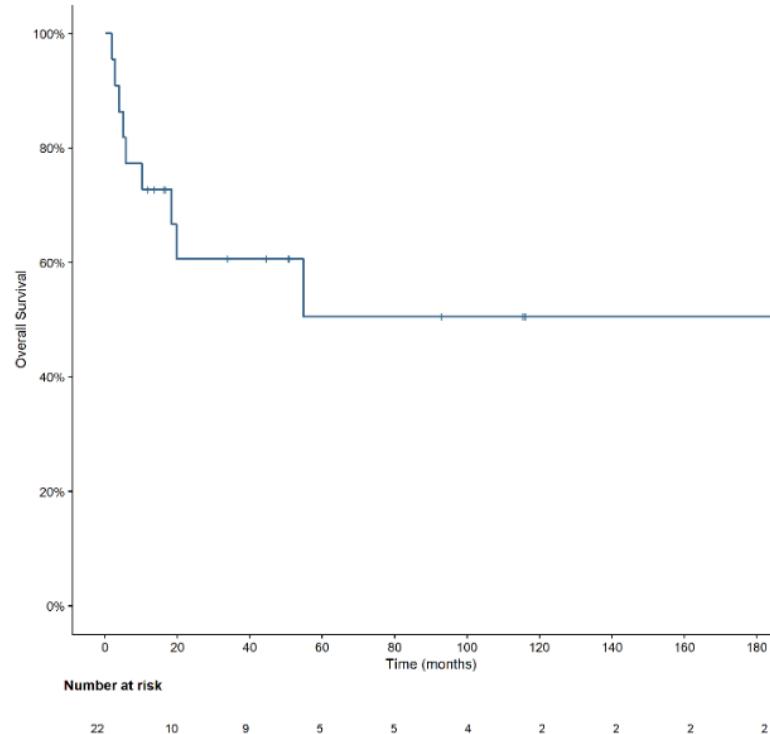


Retrospective N= 1114 (2000-2014)

Gagelmann, et al. Transplantation and Cellular Therapy 27 (2021) 95.e195.e4

Pophali et al. Blood Cancer Journal (2020) 10:121

Robin , et al. Blood. 2022 Jun 6:blood.2021015173
doi: 10.1182/blood.2021015173.

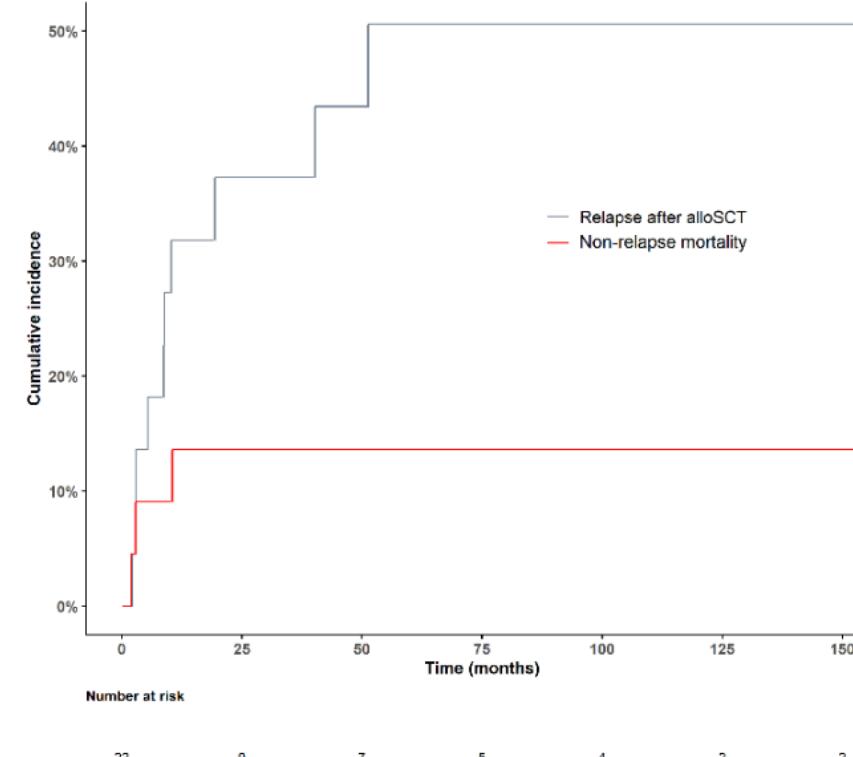


N= 22

2- and 4-year OS after alloSCT 60.6%

Non-relapse mortality at both 2 and 4 years after alloSCT was 13.6%

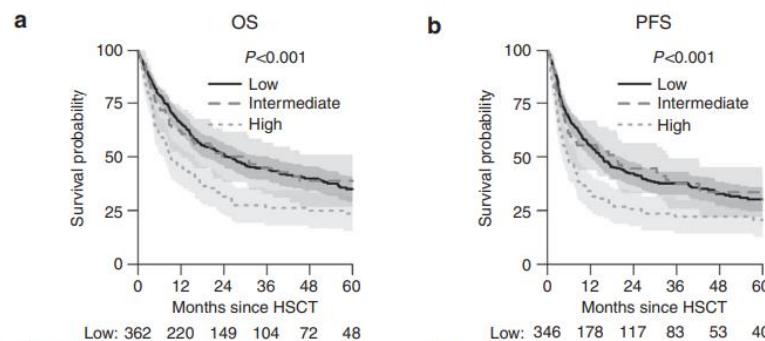
2- and 4-year cumulative incidence of relapse after alloSCT of 37.6 % and 43.7%



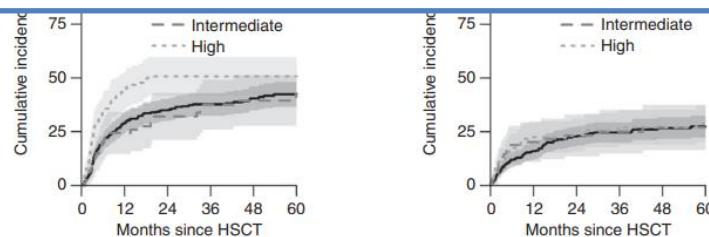
High risk CMML

Treatment allo SCT prognostic factors (allo-SCT setting)

- Retrospective N= 347 (2000-2015)EBMT
- 2-OS 39% and 5-OS 29%
- 2-yCIR 35% and 5-CIR-41%

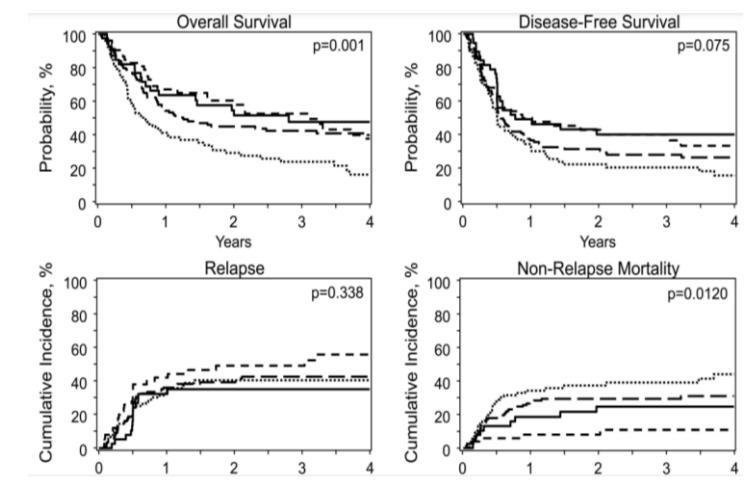


CPSS-cytogenetics risk as a prognostic factor post allo-SCT



- Retrospective N= 313 (2001-2017) CIBMTR
- Available PH blood sample before conditioning
- DNMT3A and TP53 mutations were associated with decreased OS and LFS (+JAK2)

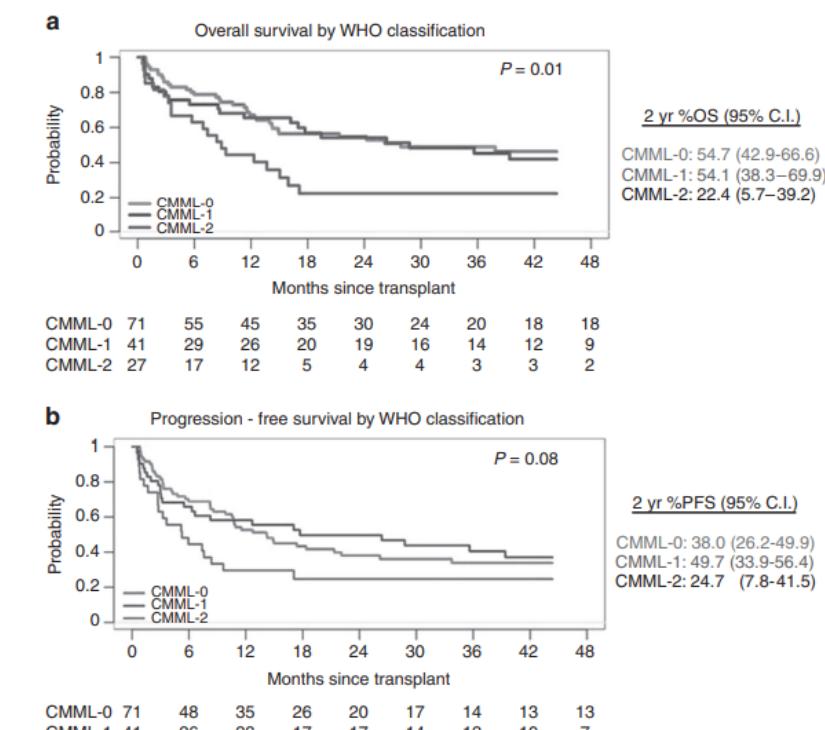
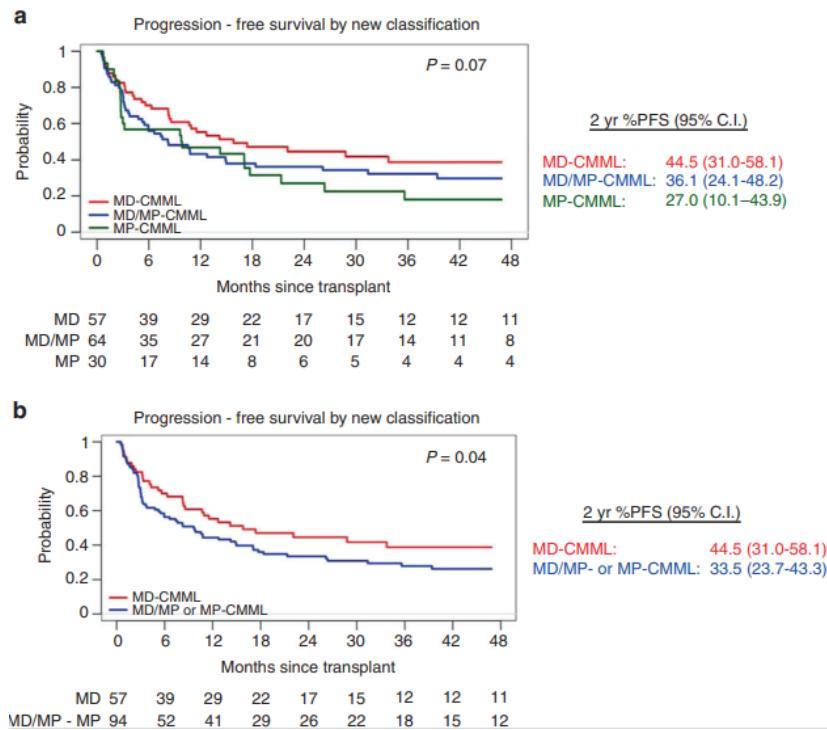
Univariate analysis, both the CPSS and CPSS-Mol scores significantly correlated OS, DFS and TRM



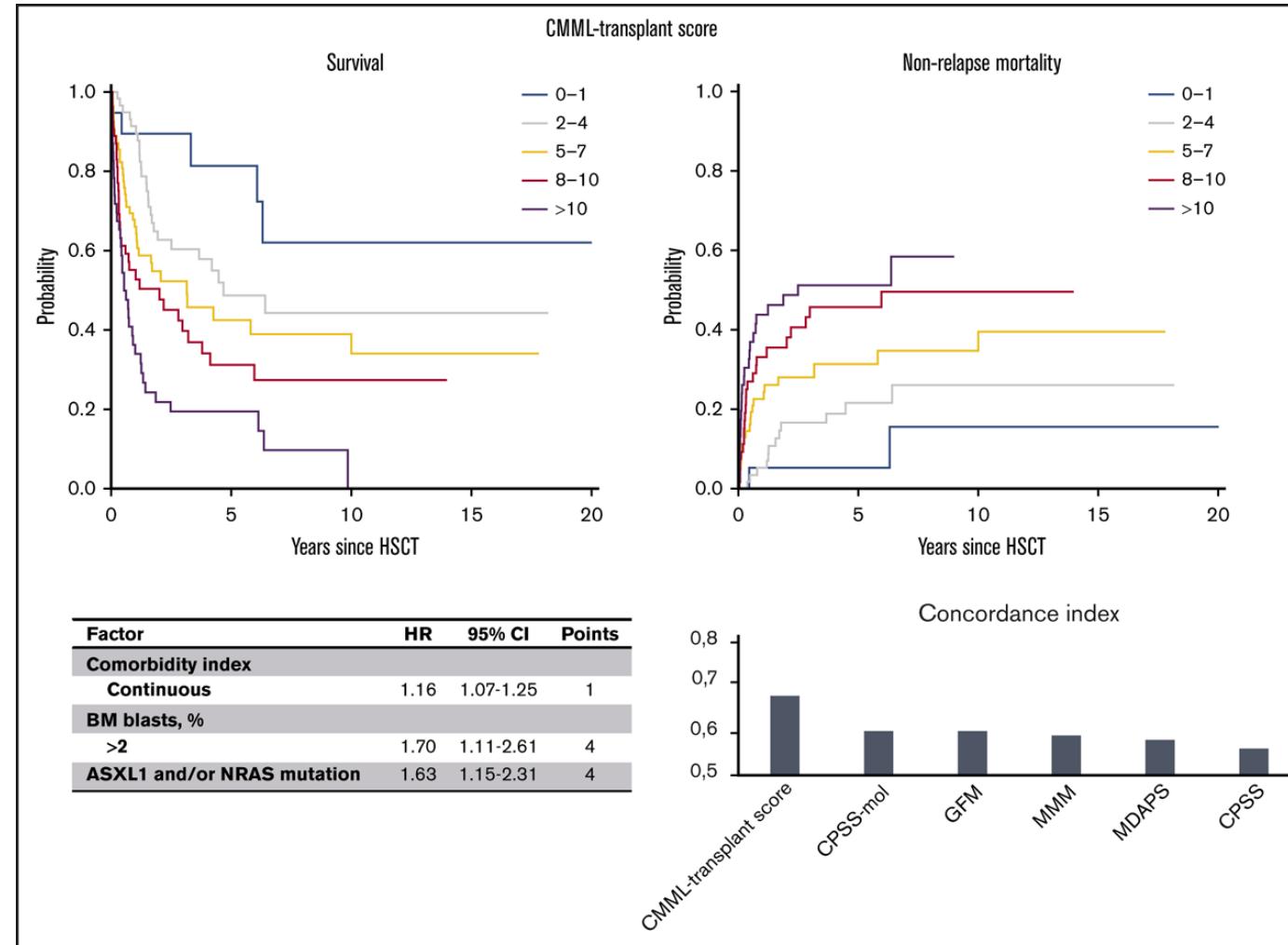
NO scoring system predictive for disease progression/relapse

Mei et al Haematologica . 2022 Apr 21. doi: 10.3324/haematol.2021.280203.

- Retrospective N= 151 1997 and 2016 EBMT OS at time allo-SCT
- MD-CMMML as a low-risk group with higher CR rate at transplant and a longer post-transplant 2-year LFS (44.5% vs 33.5%) .
- The WHO classification was superior in identifying high-risk patients (CMMML-2) with inferior survival outcomes.



A prognostic score including mutation profile and clinical features for patients with CMML undergoing stem cell transplantation



Gagelmann Blood Adv (2021) 5 (6): 1760–1769.

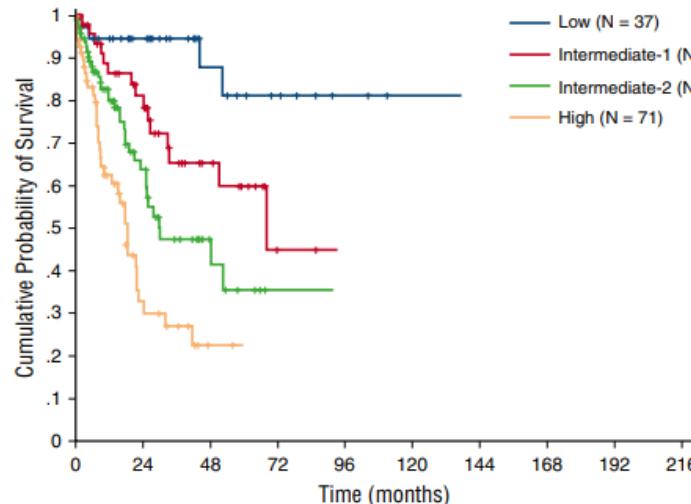


American Society of Hematology
Helping hematologists conquer blood diseases worldwide

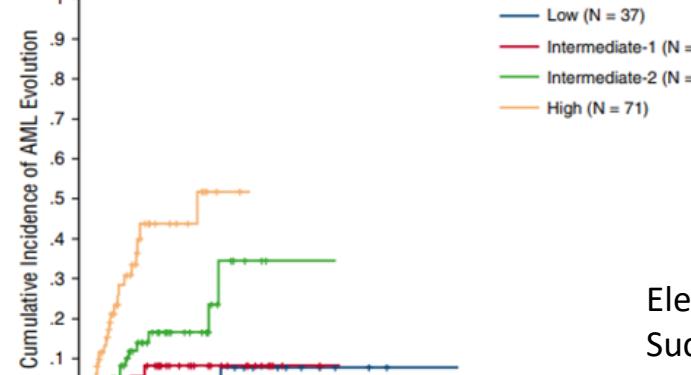
- Retrospective N= 240 10 centers
- 1996 and 2019
- Mutation before TPH
- Citogenetics no predictive
- WHO CMML classification no predictive
- CPSS-mol no predictive
- ASXL1 mut or NRAS mutation

CMMML prognostic scores

ASXL1*, NRAS, RUNX1, SETBP1 Mutations described as a negative prognostic factors *Frame-shift and nonsense



Bone marrow blast \geq 5%
RBC transfusion dependency
WBC $\geq 13 \times 10^9/L$



- Elena et al, Blood 2016;128:1408–17
Such et al, Haematologica 2011;96(3):375–383
Itzykson R, et al, J Clin Oncol.2013;31:2428–36
Such E, et al.Blood 2013;121:3005–15
Patnaik et al, Leukemia 2014;28:2206–12
Castaño-Díez et al, Cancers 2022, 14, 4107

Model	Risk categories		Survival		Risk factors	
	MMM	GFM	Low risk (0 points)	97 mo MS	• AMC >10x10 ⁹ /L (2 points)	• Presence of circulating IMC (2 points)
Mayo Molecular Model (MMM)			Intermediate-1 risk (1.5 - > 2.5 points)	59 mo MS	• Hemoglobin level <10 g/dL (2 points)	
			Intermediate-2 risk (2.5-4.5 points)	31 mo MS	• ASXL1 mutation (1.5 points)	
			High risk (\geq 5 points)	16 mo MS	• Platelet count <100x10 ⁹ /L (1.5 points)	
Groupe Francophone de Myelodysplasies (GFM)			Low risk (0-4 points)	65 mo MS	• WBC >15x10 ⁹ /L (3 points)	
			Intermediate risk (5-7 points)	28 mo MS	• ASXL1 mutations (2 points)	
			High risk (8-12 points)	17 mo MS	• Age >65 years (2 points)	
					• Platelet count <100x10 ⁹ /L (2 points)	
					• Hemoglobin <10 g/dL in females and <11 g/dL in males (2 points)	
CMMML-Specific Prognostic Scoring System (CPSS-Mol)	Points for mutation status		Points for karyotype status based on CPSS		Genetic risk* for CPSS Mol model	
	WT	MT	P		P	
	ASXL1	0 1	Normal or -Y		Low	0
	NRAS	0 1	All other abnormalities		Int-1	1
	RUNX1	0 2	Trisomy 8, Monosomal, Complex		Int-2	2
	SETBP1	0 1			High	≥ 3
CPSS-Mol		Risk categories		AML-TR	Median OS months	CPSS-Mol score
		Low (0 points)		0%	Not reached	0
		Intermediate-1 (1 point)		8%	64	1
		Intermediate-2 (2-3 points)		24%	37	2
		High (\geq 4 points)		52%	18	3
		<ul style="list-style-type: none"> • Bone marrow blast < 5% • FAB subtype • Genetic risk* • RBC transf. 				
		<ul style="list-style-type: none"> • Bone marrow blast \geq 5% MDS-CMML MPN-CMML No Yes 				