Diagnosi, classificazione e trattamento della LMMC

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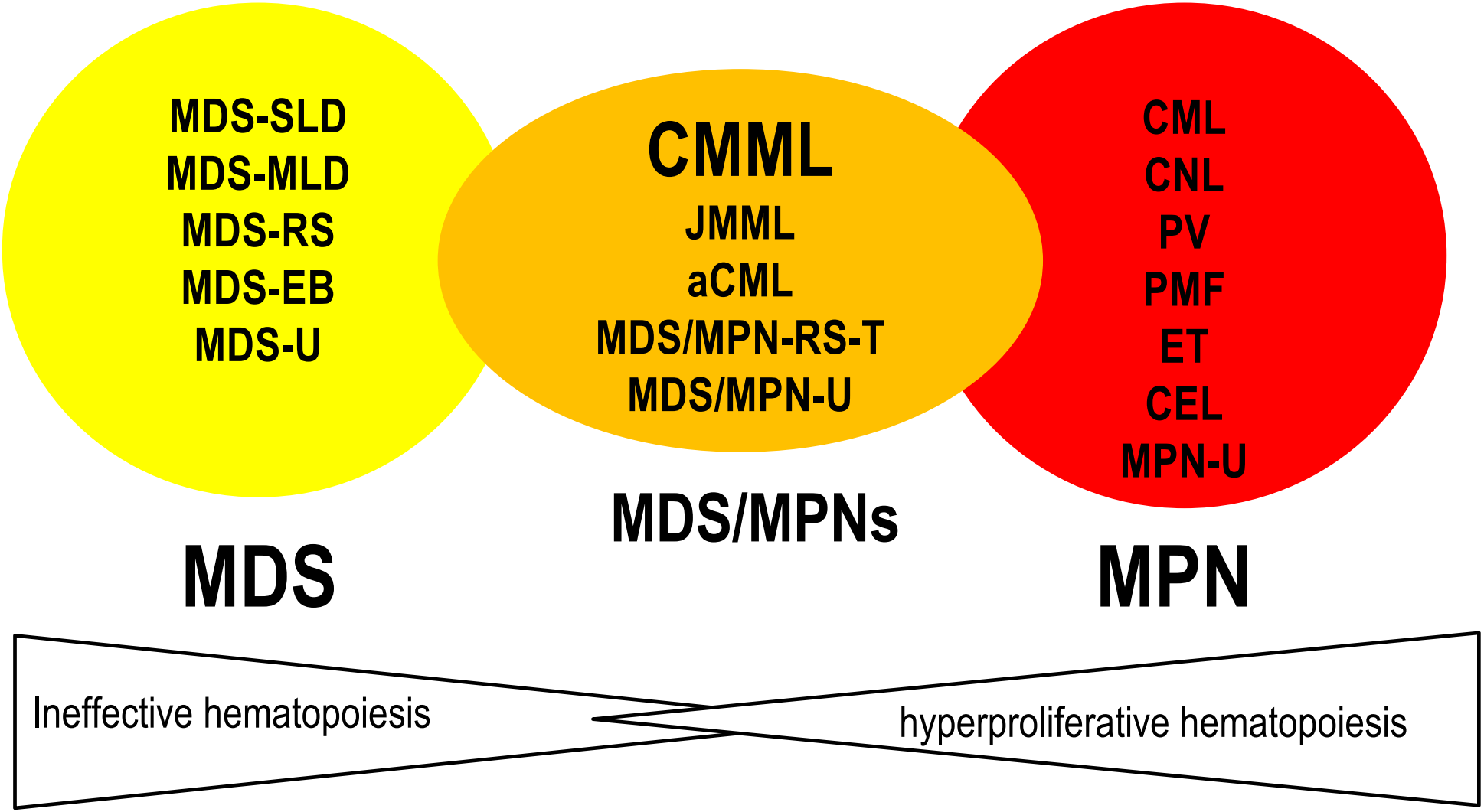
OVERLAP chronic myeloid malignancy

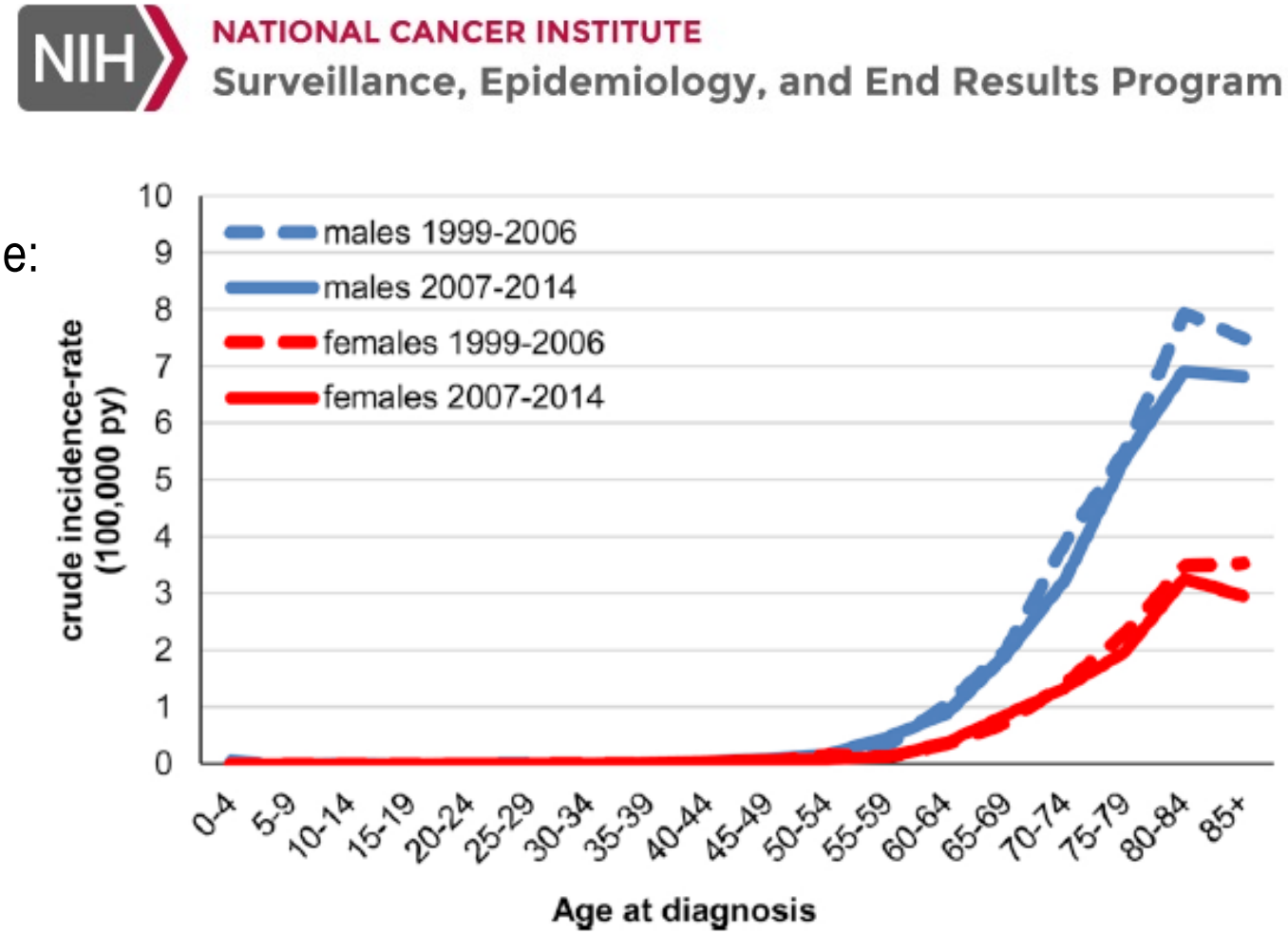


CMML: INCIDENCE

4144 pts (1999-2014)

Age-standardized incidence rates stable: 0.32-0.38/100,000 py

Age ≥ 75yrs = 55%



Benzarti S. et al. Cancer Epidemiology 2019

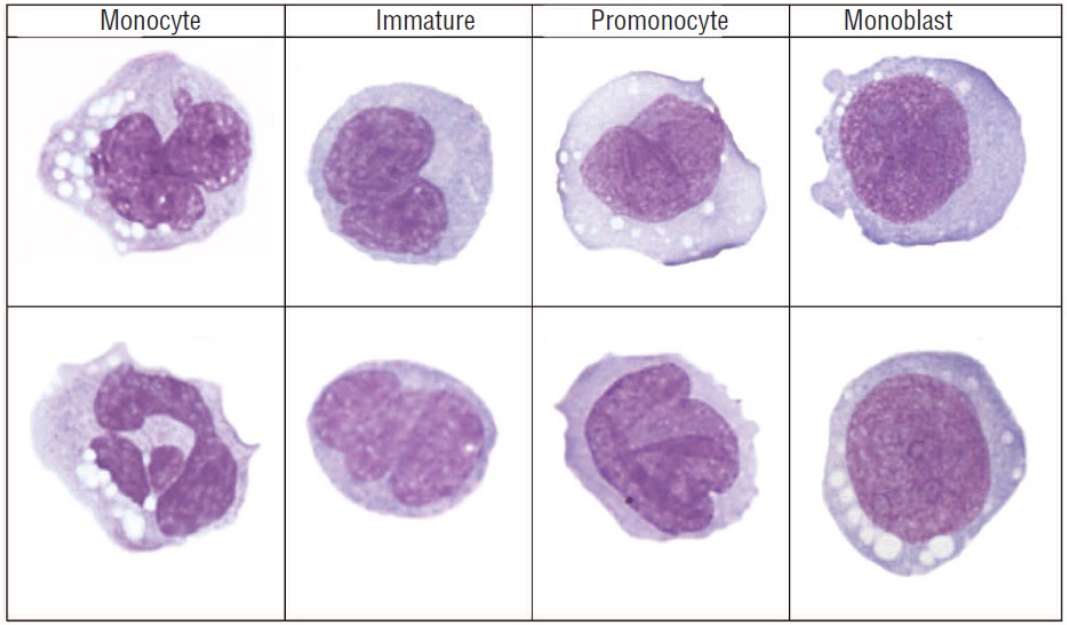
CMML: WHO 2016 DIAGNOSTIC CRITERIA

1. Persistent peripheral blood monocytosis >1x10^9/L, with **monocytes accounting for ≥10%** of the WBC count
2. **Not meeting WHO criteria for BCR-ABL1 CML, PMF, PV, or ET**
3. **No evidence of PDGFRα**, PDGFRβ, or **FGFR1 rearrangement or PCM1-JAK2** (should be specifically excluded in cases with eosinophilia)
4. Fewer than 20% blasts* in the blood and in the bone marrow
5. Dysplasia in 1 or more myeloid lineages. If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met and:
   - ✓ an acquired, clonal cytogenetic or molecular genetic abnormality is present in the haemopoietic cells, *or*
   - ✓ the monocytosis has persisted for at least 3 months *and*
   - ✓ all other causes of monocytosis have been excluded

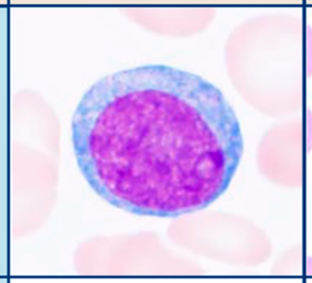
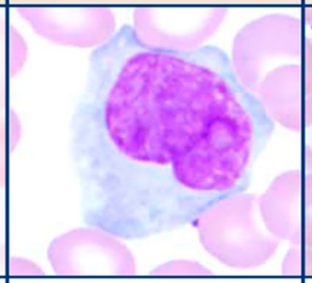
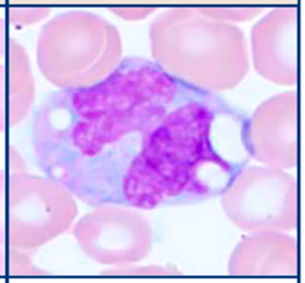
***Blasts include myeloblasts, monoblasts and promonocytes.**

Arber DA et al. Blood 2016; 127(20):2391-2405

Monoblasts, Promonocytes and Monocytes: morphology

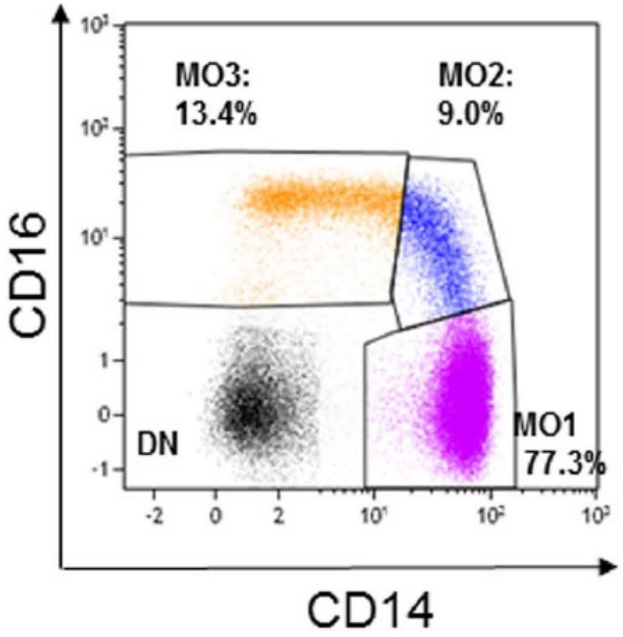


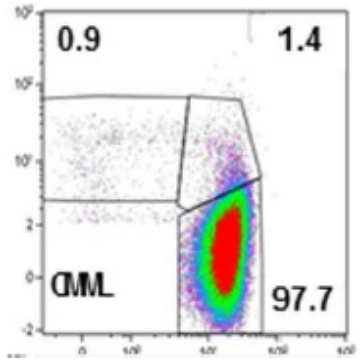
Guasguen JE et al. Haematologica 2009

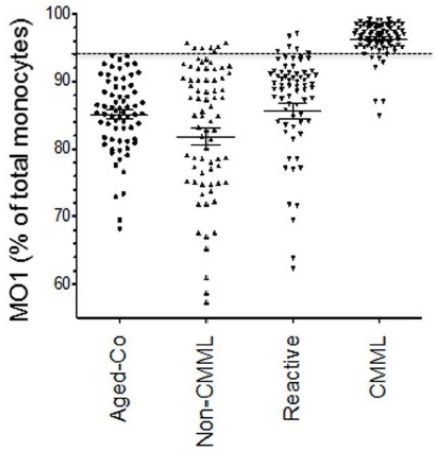
	Monoblast	Promonocyte	Monocyte
Cells without mask applied to background			
N:C ratio	7:1 to 3:1	7:1 to 3:1	4:1 to 2:1
Cell shape	Round to oval	Round to oval	Round with smooth edges, may have pseudopod-like extensions
Nuclear shape	Round, more regular	Indented or lobulated, more irregular than monoblast	Indented, often reniform or folded resembling three-pointed hat, but may be rounded, oval or lobulated
Nucleoli	1 or 2, distinct	1 or 2, less distinct than monoblast	Generally absent, but occasionally small and inconspicuous
Cytoplasm	Grey to cloudy blue, few red granules	Grey to cloudy blue, few red granules	Abundant grey or grey-blue, may contain fine azurophilic granules

Osman M et al. J. Clin. Med. 2021

Flow cytometry as a diagnostic tool in CMML







CMML: MO1 >94%

Non-CMML: MO1 ≤94%

Classical	$CD14^{++}CD16^{-}$	$CCR2^{hi}CX_3CR1^{low}$	Resemble $LY6C^{hi}$ monocytes based on gene-expression arrays[7,17,140]
Intermediate	$CD14^{++}CD16^{+}$	$CX_3CR1^{hi}CCR2^{low}$	Pro-inflammatory roles[12,15]
Non-classical	$CD14^{+}CD16^{++}$	$CX_3CR1^{hi}CCR2^{low}$	Patrolling[14]; antiviral roles[14]

Selimoglu-Buet et al. Blood 2015

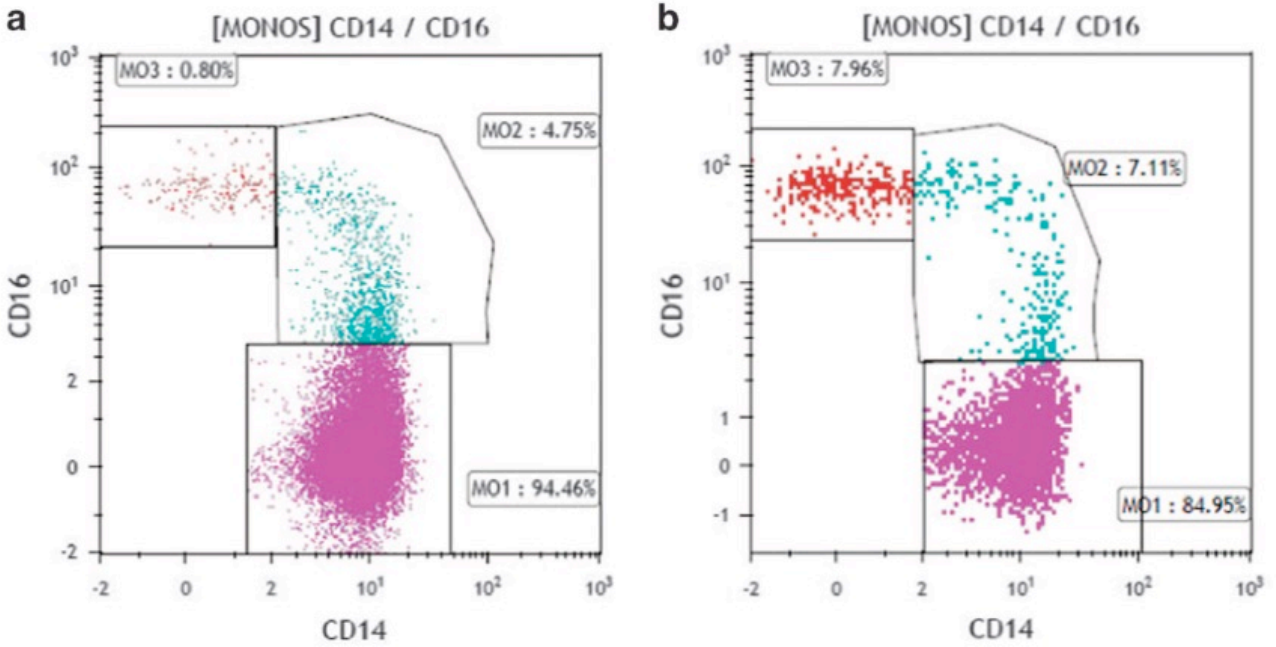
Talati C et al. Blood 2017

Shi C & Pamer Eg. Nat Rev Immunol. 2011

Monocyte subsets analysis for distinction of CMML from MPN with monocytosis

CMML

PMF with monocytosis



Patnaik MM et al. Blood Cancer Journal 2017

CMML: current subclassification

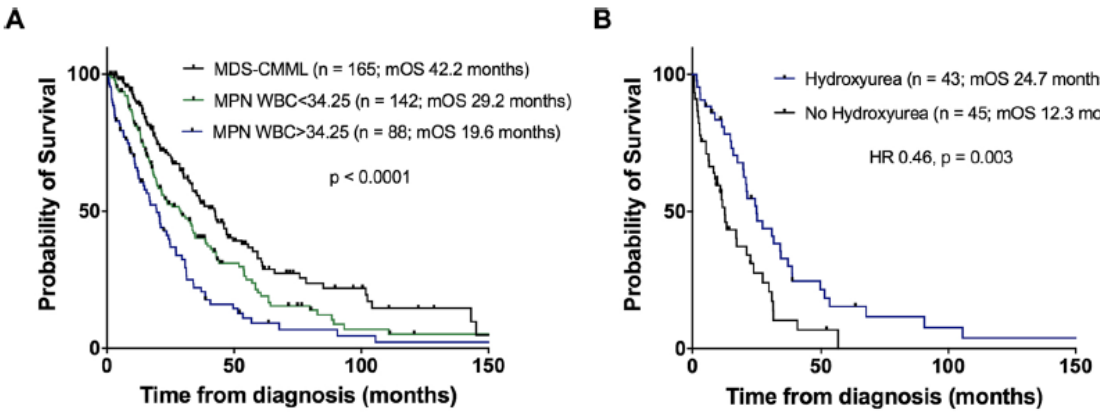
WHO 2016	BP Blasts	BM Blasts
– CMML-0	<2%	<5%
– CMML-1	2-4%	5-9%
– CMML-2	5-19% or Auer rods	10-19% or Auer rods

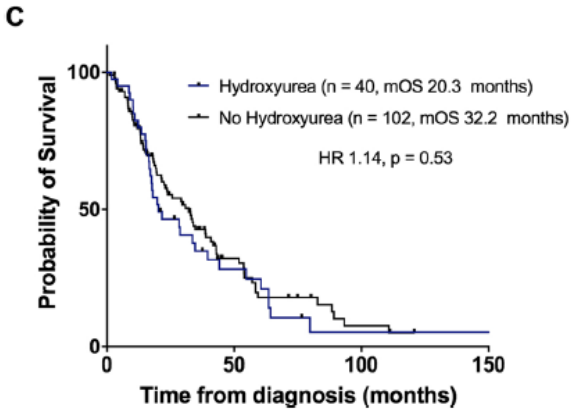
FAB 1994 (endorsed by the WHO 2016)

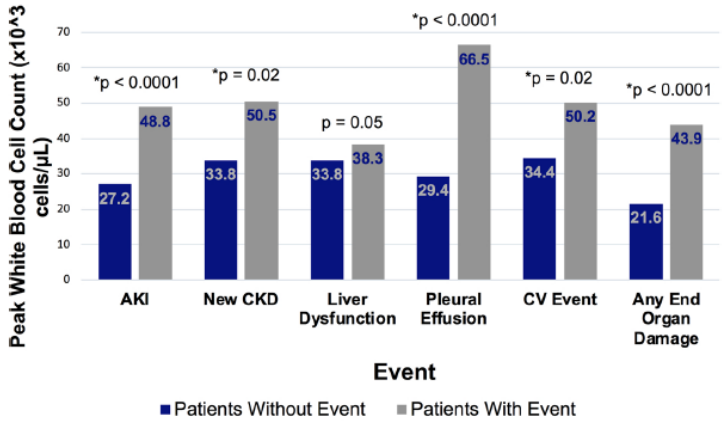
- Myelodysplastic (MD)-CMML	WBC ≤13x10^9/L
- Myeloproliferative (MP)-CMML	WBC >13x10^9/L

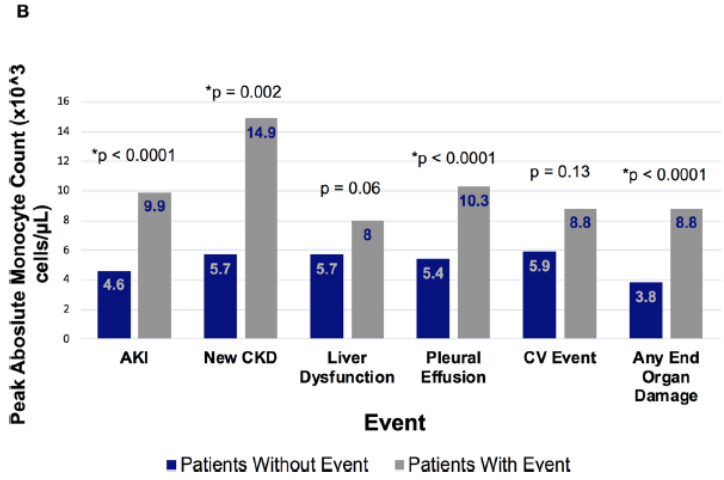
Arber DA et al. Blood 2016
Bennett JM et al. Br J Haematol 1994

CMML: prognostic impact of leukocytosis









Hunter AM et al. Leukemia Research 109 (2021)

Oligomonocytic CMML: a new entity

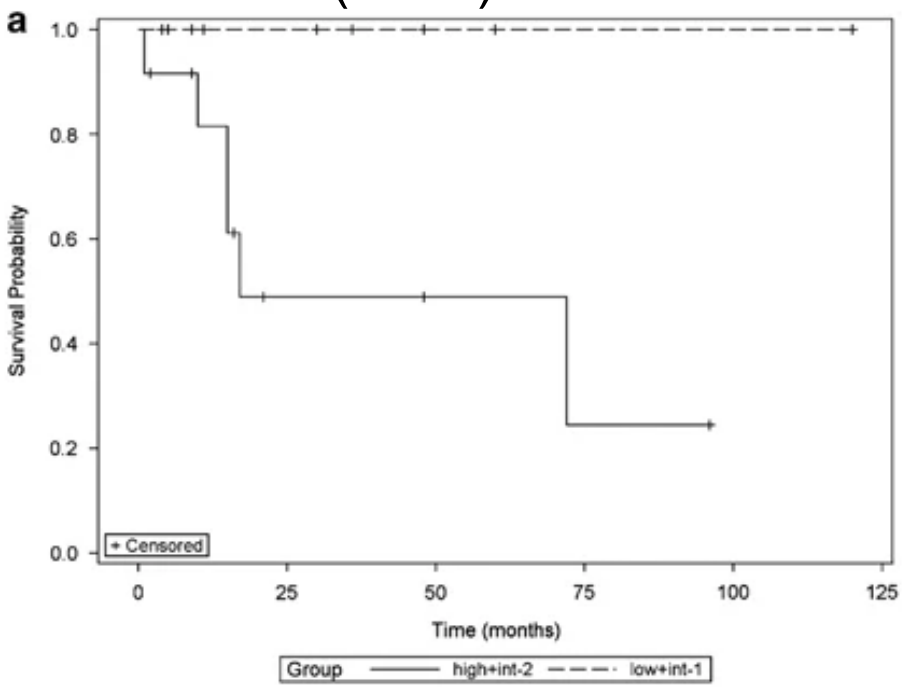
O-CMML: ≥10% peripheral blood monocytes with absolute monocyte count of 0.5–1 × 10^9/L

	OM-CMML	*Control CMML*	*Significance*
Age (range)	65 (31–87) years	72 (58–88) years	*P*=0.004
WBC, mean (range)	3.9 (1.8–9.4) × 10^9/l	17.2 (3.0–69.0) x10^9/l	*P*<0.001
PB, AMC	0.75 (0.52–0.97) × 10^9/l	4.15 (1–19) x10^9/l	*P*<0.001
PB monocyte %	16.8 (10–48)%	25.2 (10–47)%	No
Hb, mean (range)	10.0 (6.8–14.7) g/dl	10.9 (6.4–14.7) g/dl	No
MCV, mean (range)	97 (80–121) fl	92 (62–113) fl	No
Plt, mean (range)	138 (10–477) x10^9/l	103 (23–239) x10^9/l	No
Progression to CMML	16/42 (38%)	—	—
Progression to AML	11/42 (26%)	5/28 (18%)	No
Year 5±s.e. (%)[a]	57.8±7.9	80.1±11.9	*P*=0.027

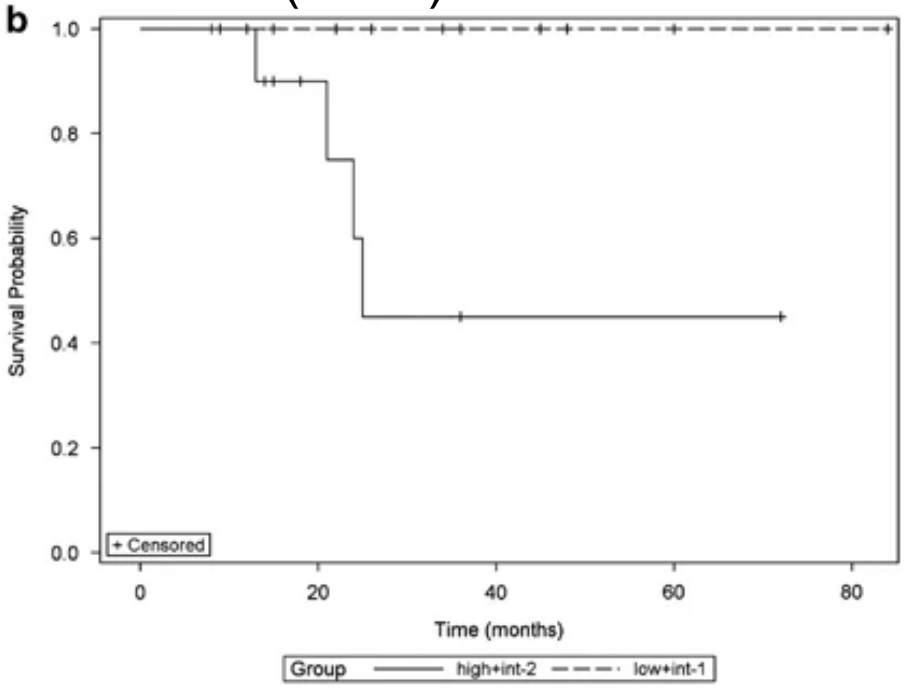
Geyer JT et al. Modern Pathology (2017) 30, 1213–1222

Survival according to CPSS-Mol

O-CMML (n=44)



CMML (n=28)

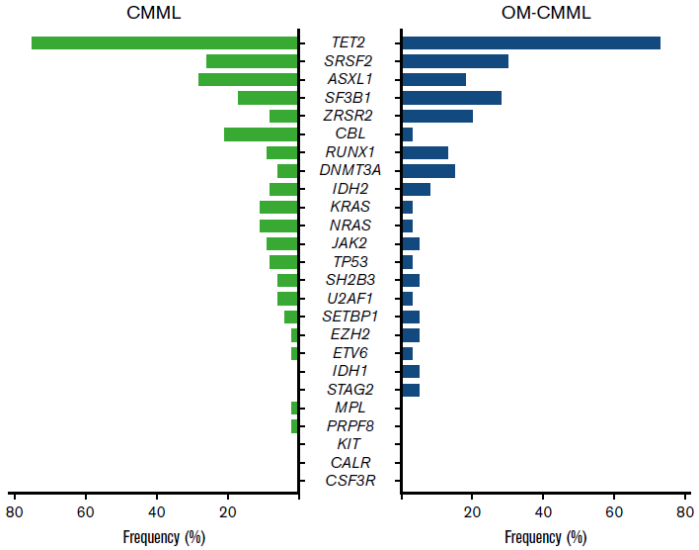


Geyer JT et al. Modern Pathology (2017) 30, 1213–1222

International Working Conference on CMML diagnostic criteria

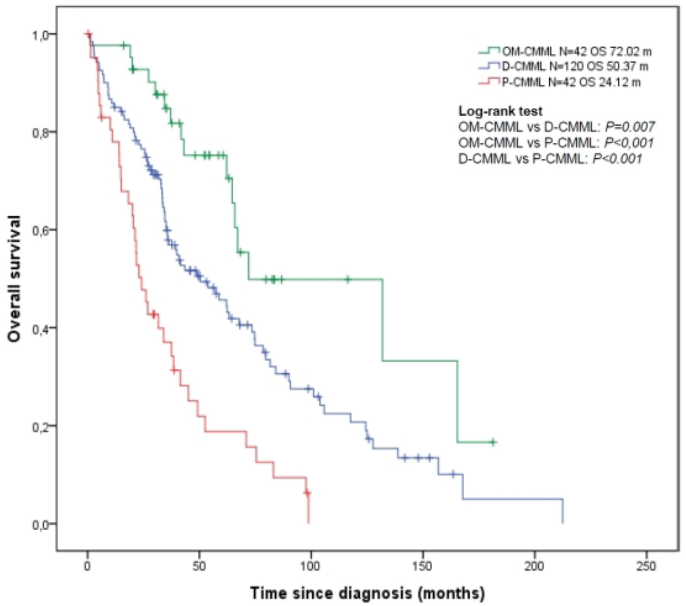
Table 2. Overview of special variants of chronic myelomonocytic leukemia.

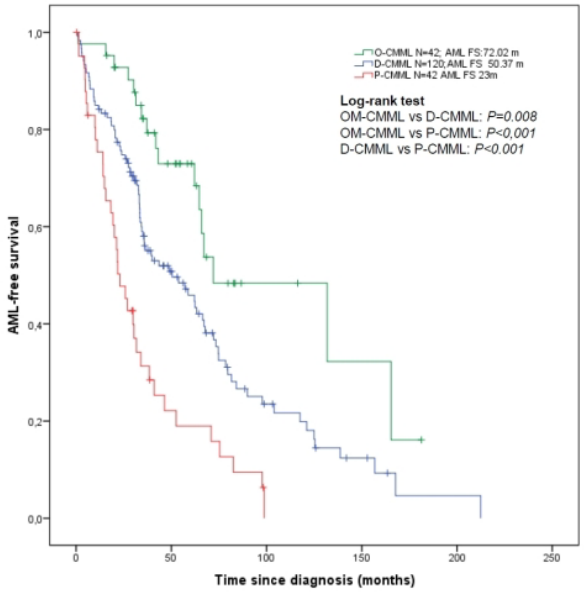
Special variant	Key diagnostic features that discriminate the variant from classical CMML
Oligomonocytic CMML	Absolute PB monocyte count <1x10⁹/L
SM with concomitant CMML = SM-CMML	WHO criteria for SM fulfilled; in most patients CMML monocytes exhibit *KIT* D816V
CMML with a concomitant myeloid neoplasm* expressing a classical MPN- driver, such as *JAK2* V617F, *BCR-ABL1* or rearranged *PDGFRA/B**** or *FGFR1*.	WHO criteria for a classical MPN, such as CML**, PMF, or a myeloid neoplasm with rearranged *PDGFRA/B* are fulfilled in addition to the criteria for CMML.
CMML with expression of a molecular MPN-driver – examples: CMML with *JAK2* V617F or CMML with a rearranged *PDGFRA/B* or CMML with rearranged *FGFR1*.	Molecular drivers of classical MPN, such as *JAK2* V617F***** or rearranged *PDGFRA/B**** are found but diagnostic criteria for such classical MPN are not fulfilled (only criteria for CMML are met)
CMML with a concomitant lymphoid/lymphoproliferative neoplasm	WHO criteria for a lymphoid neoplasm are fulfilled

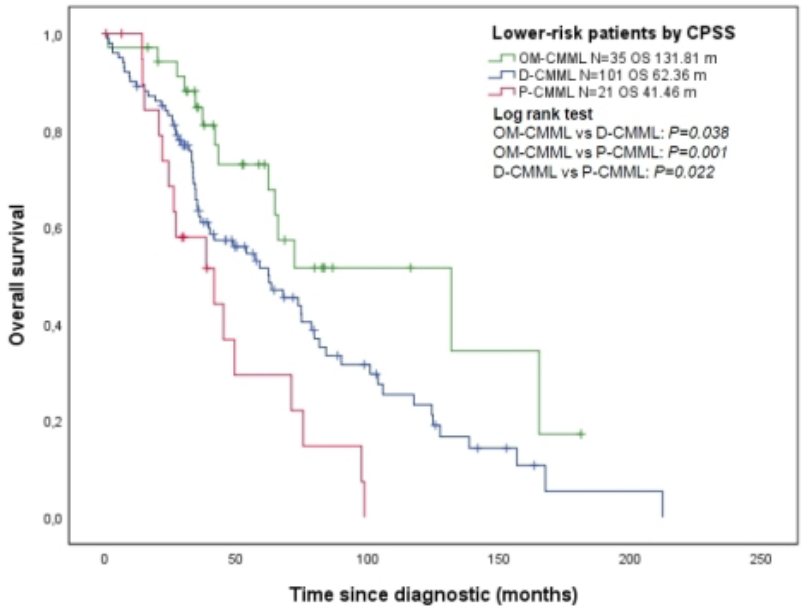


Valent P et al. Haematologica 2019 - Calvo X et al. Blood Adv 2020

OM-CMML, D-CMML and P-CMML: an evolutionary continuum?





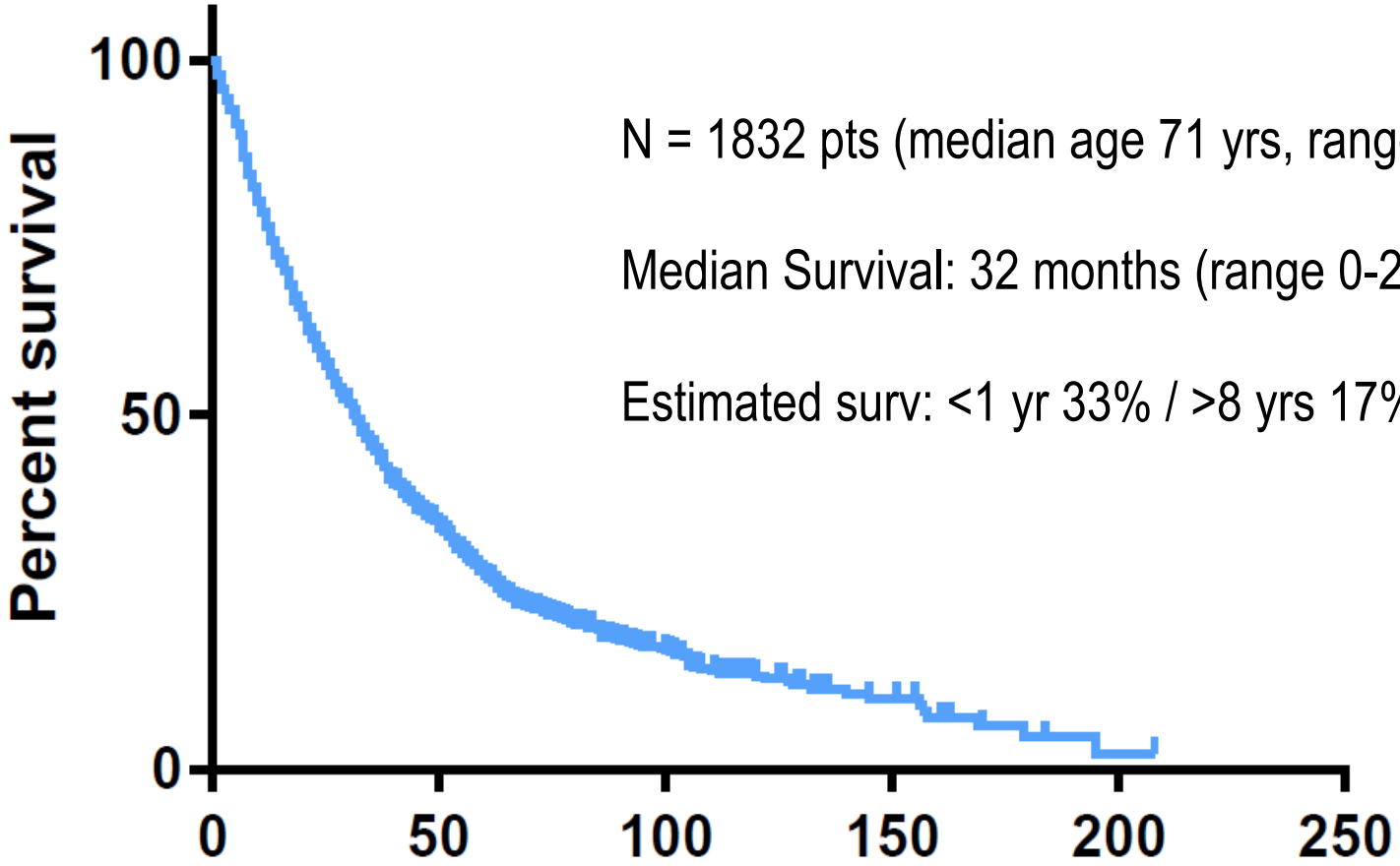


- 29.3% of OM-CMML patients progressed to D-CMML (median f-up 53 months)
- 28.6% of D-CMML patients progressed to P-CMML (median f-up 46 months)
- Gene mutations associated with increased proliferation (ASXL1, CBL and RAS pathway)

Calvo X. et al. Submitted

CMML: Prognosis [International CMML Consortium]

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



N = 1832 pts (median age 71 yrs, range 16-93)

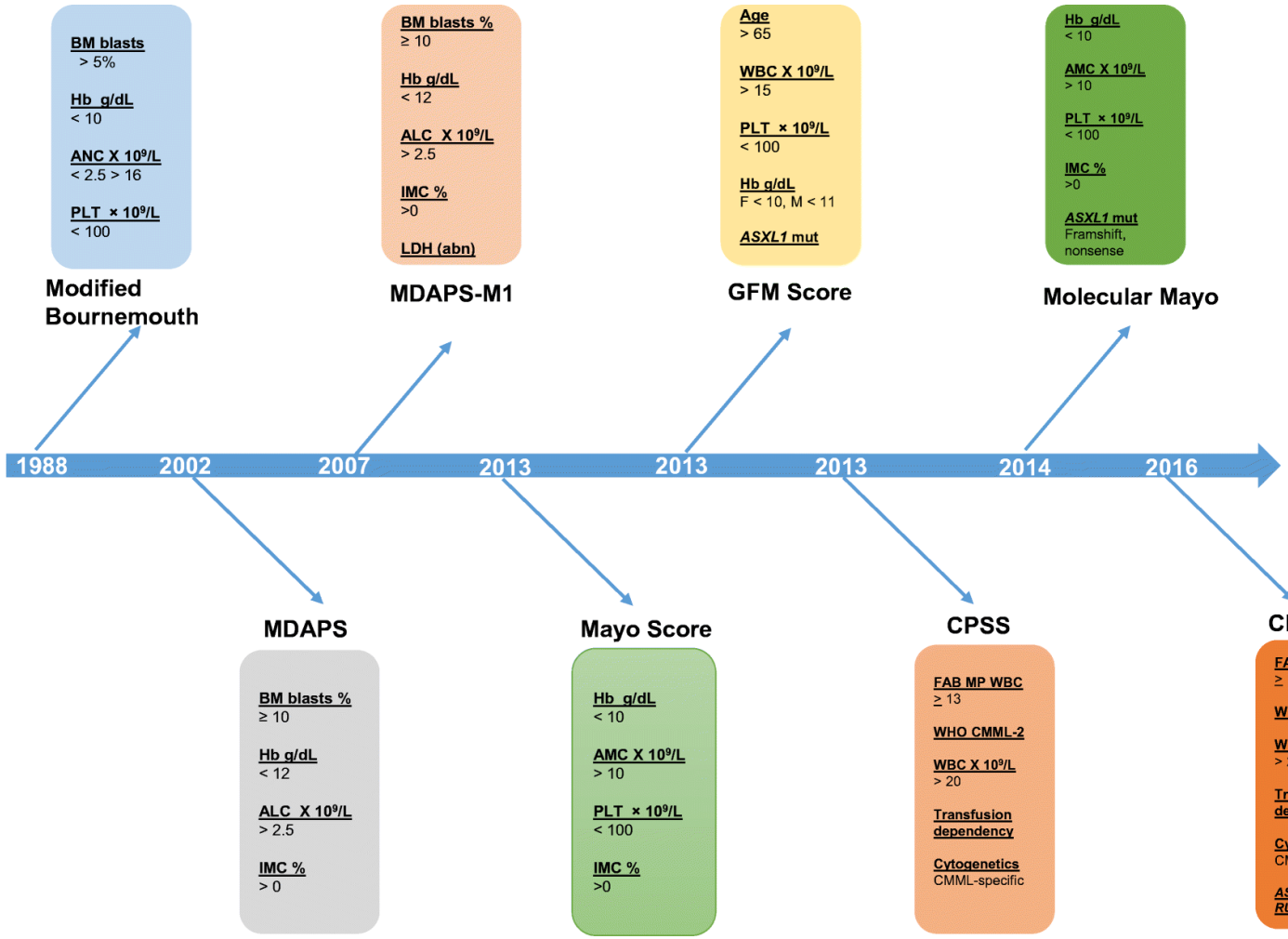
Median Survival: 32 months (range 0-206)

Estimated surv: <1 yr 33% / >8 yrs 17%

Padron E et al. Blood Cancer J. 2015

Prognostic scoring systems in CMML

CMML-Specific Models



Common risk factors

Hb level
WBC counts
Blasts burden

Gene mutations

ASXL1 (frameshit or nonsense)
N-RAS
RUNX1
SETBP1

Nazha A et al. Curr Hematol Malig Rep 2018

Cytogenetic risk stratification in CMML

Abnormal karyotype: 110/414 (27%)

- Trisomy 8 (n=30; 27%)
- -Y (n=18; 16%)
- Complex (n=12; 11%)
- Monosomy 7 (n=6; 5%)

Low risk:
- normal or –Y (single)

High risk:
- abn chr 7, complex, +8

Intermediate risk:
- all others

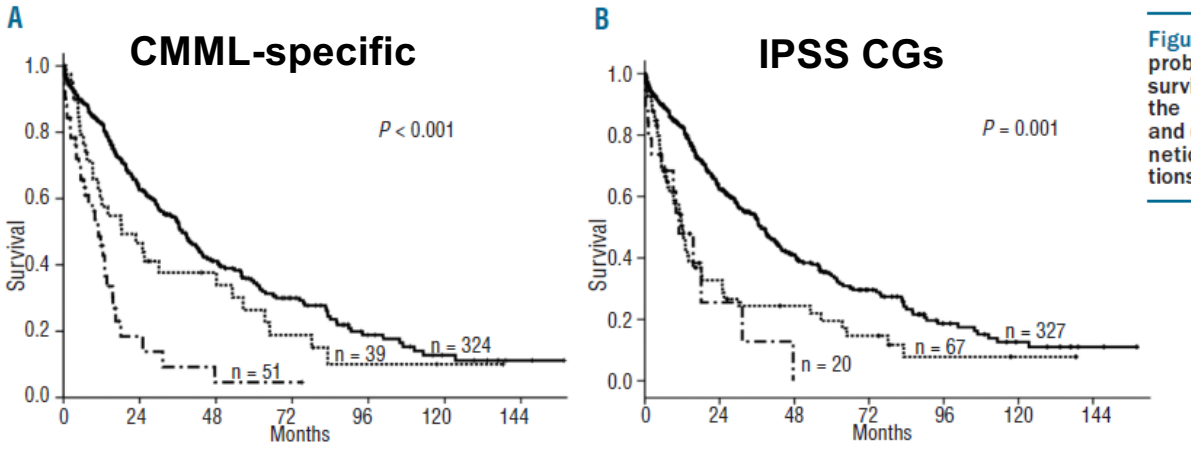


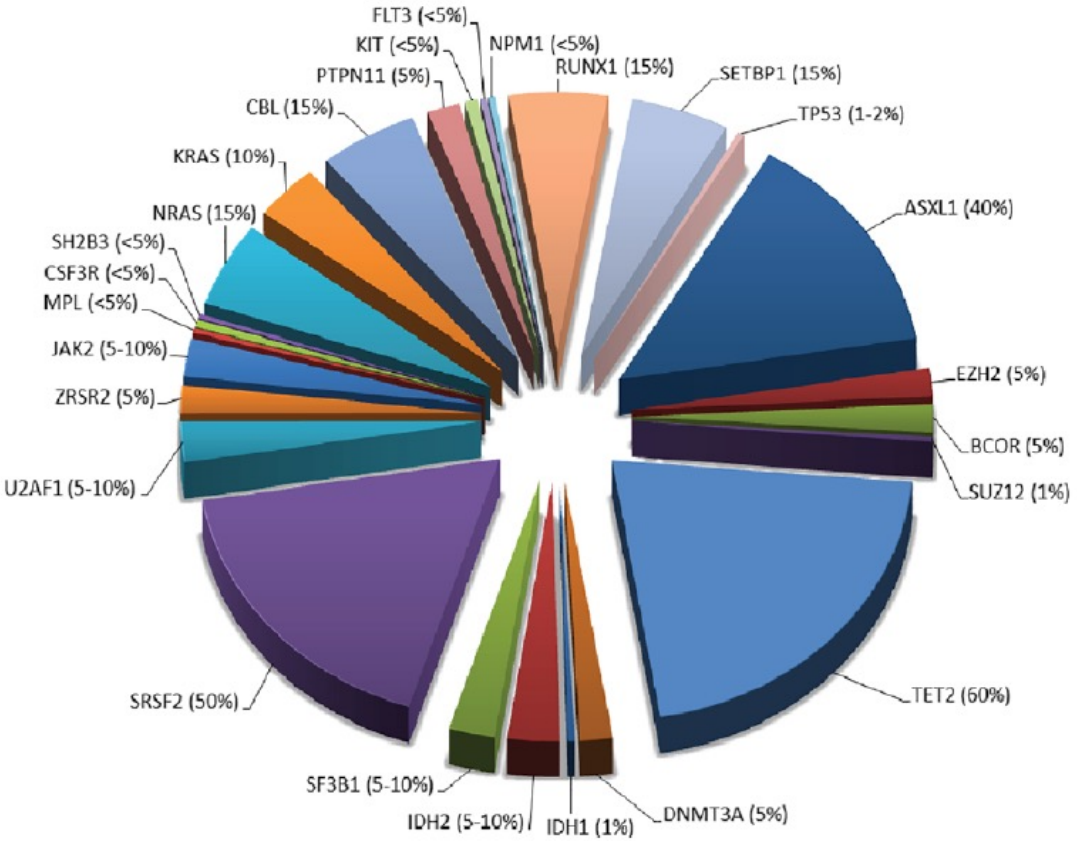
Figure 1. Unadjusted probability of overall survival according to (A) the new CMML-specific and (B) the IPSS cytogenetic risk classifications.

Risk Groups	*P* value
Low *vs.* Intermediate	0.017
Low *vs.* High	< 0.001
Intermediate *vs.* High	0.007

Risk Groups	*P* value
Low *vs.* Intermediate	< 0.001
Low *vs.* High	< 0.001
Intermediate *vs.* High	0.51

Such et al. Haematologica 2011; 96(3): 375

CMML: Genomic Landscape

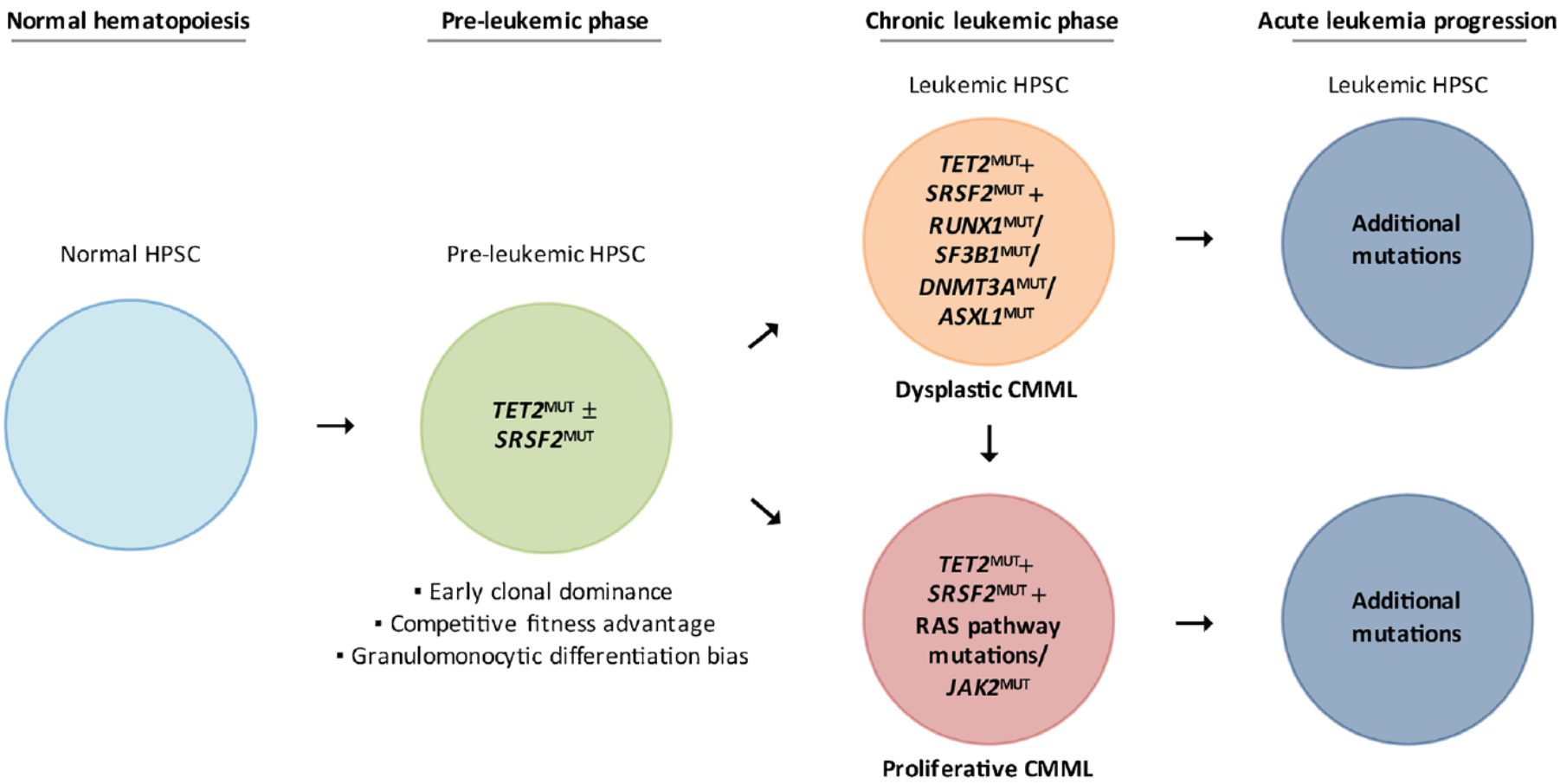


Major class of genetic mutation		Gene	Frequency of mutation (%)
Epigenetic control	Histone modification	*ASXL1*[a]	40
		EZH2	5
	DNA methylation	*TET2*	60
		DNMT3A[a]	5
	Dual effect	*IDH1*	1
		IDH2	5
Cell signaling		*JAK2V617F*	10
		CBL	15
		NRAS[a]	15
		KRAS	10
		PTPN11	5
		NF1	<5
		FLT3	<5
Pre-mRNA splicing		*SRSF2*	50
		SF3B1	5–10
		U2AF1	5–10
		ZRSR2	5
Transcription and nucleosome assembly		*RUNX1*[a]	15
		SETBP1[a]	15
		GATA2	5
DNA damage		*TP53*[b]	<1
		PHF6	5

~ 90% of CMML patients harbour at least one mutation

Coltro G & Patnaik M. Curr Oncol Rep 2019
Patnaik MM & Tefferi A. AJH 2022

Clonal onset and evolution in CMML



Coltro G & Patnaik M. Curr Oncol Rep 2019

CPSS-molecular

Table 2. Variables and prognostic score values of the CMML genetic score

	CPSS cytogenetic risk group*	*ASXL1*	*NRAS*	*RUNX1*	*SETBP1*
Variable score					
0	Low	Unmutated	Unmutated	Unmutated	Unmutated
1	Intermediate	Mutated	Mutated	—	Mutated
2	High	—	—	Mutated	—
Genetic risk group	**Score**				
Low	0				
Intermediate-1	1				
Intermediate-2	2				
High	≥3				

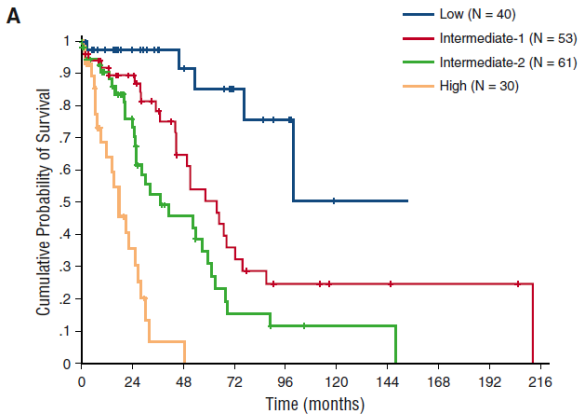
Table 3. Variables and prognostic score values of the CPSS-Mol

	Genetic risk group*	BM blasts	WBC count	RBC transfusion dependency†
Variable score				
0	Low	<5%	$<13 \times 10^9$/L	No
1	Intermediate-1	≥5%	$\geq 13 \times 10^9$/L	Yes
2	Intermediate-2	—	—	—
3	High	—	—	—
CPSS-Mol risk group	**Score**			
Low	0			
Intermediate-1	1			
Intermediate-2	2-3			
High	≥4			

Elena C et al Blood. 2016 Sep 8;128(10):1408-17

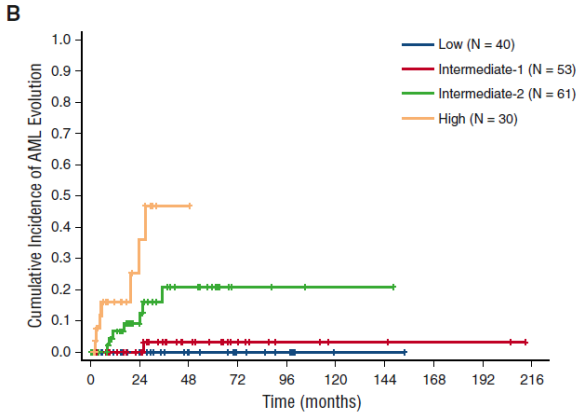
CPSS-molecular

Learning cohort (n=214)

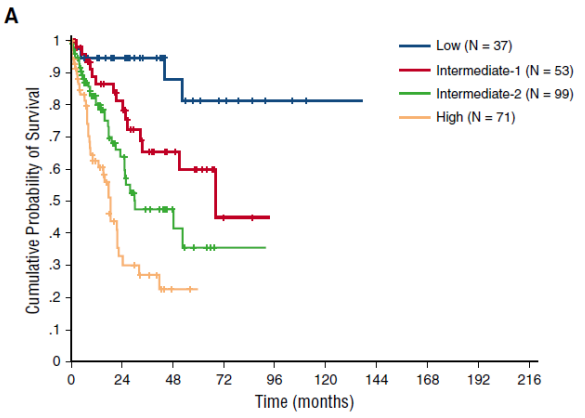


Median OS

>144 months
64 months
37 months
18 months

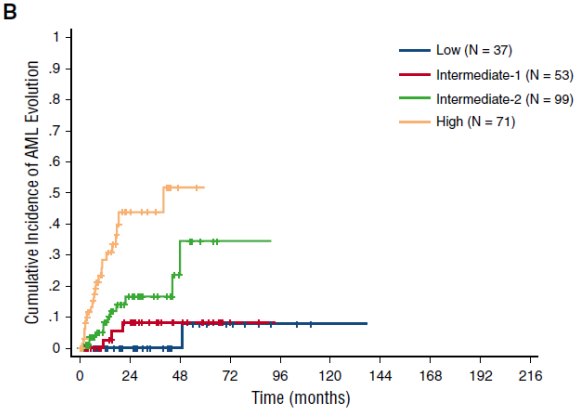


Validation cohort (n=260)



Median OS

NR
68 months
30 months
17 months



Elena C et al Blood. 2016 Sep 8;128(10):1408-17

EHA/ELN 2018 Recommendations: molecular genetics

HemaSphere
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EHA EUROPEAN HEMATOLOGY ASSOCIATION

Guideline Article

OPEN ACCESS

Diagnosis and Treatment of Chronic Myelomonocytic Leukemias in Adults

Recommendations From the European Hematology Association and the European LeukemiaNet

Raphael Itzykson[1], Pierre Fenaux[1], David Bowen[2], Nicholas C.P. Cross[3], Jorge Cortes[4], Theo De Witte[5], Ulrich Germing[6], Francesco Onida[7], Eric Padron[8], Uwe Platzbecker[9], Valeria Santini[10], Guillermo F. Sanz[11,12], Eric Solary[13,14], Arjan Van de Loosdrecht[15], Luca Malcovati[16], on behalf of the European Hematology Association, the European LeukemiaNet

- **Analysis of 4 genes (ASXL1, NRAS, RUNX1, SETBP1) is mandatory for risk assessment** according to accepted risk scoring systems in patients eligible for transplant.

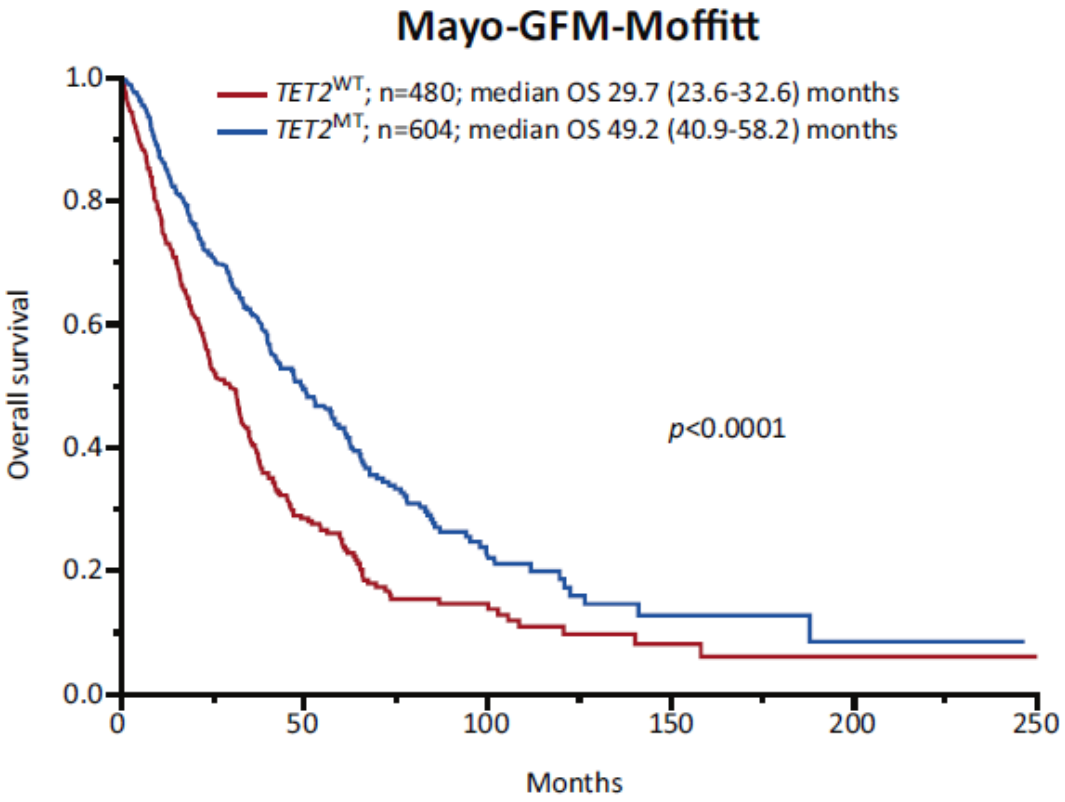
- **Analysis of a minimum of 20 genes is recommended** for patients being considered **for active treatment, including transplantation**.

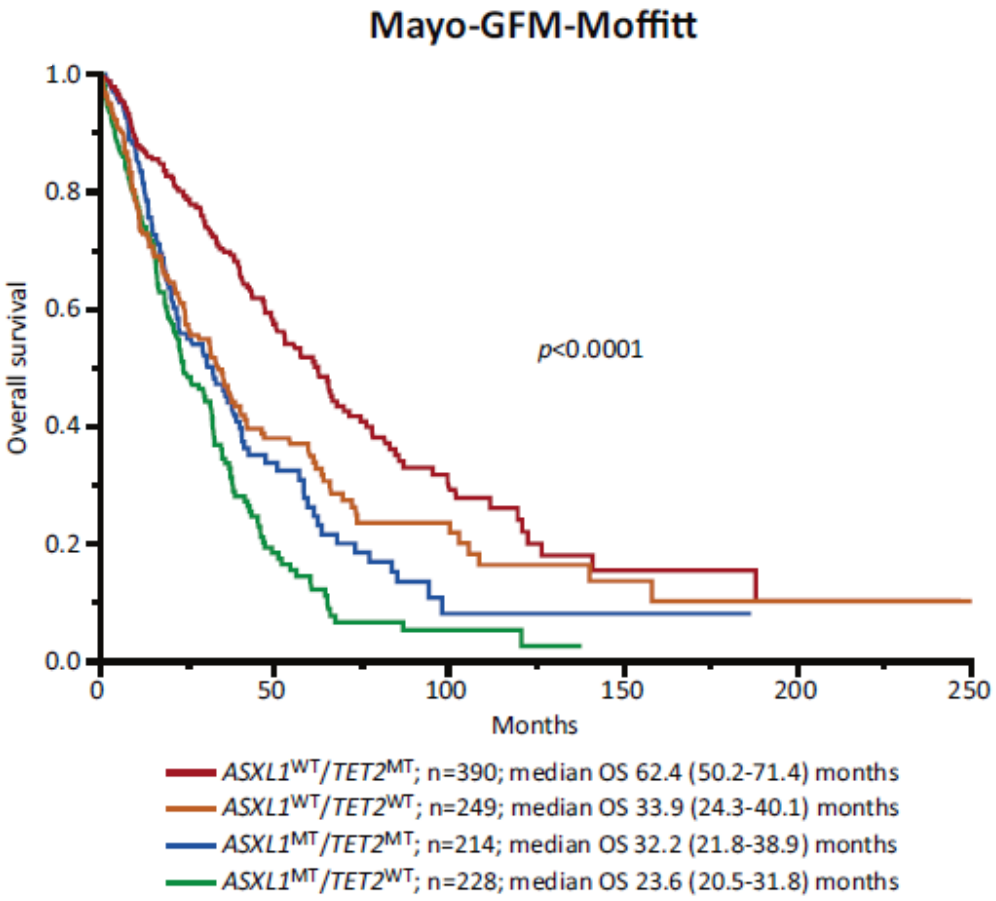
Recommended minimal Next Generation Sequencing panel in CMML

Gene	Frequency, %	Pathway
TET2	29–61	Epigenetic modifiers
ASXL1	32–44	
DNMT3A	2–12	
EZH2	5–13	
IDH1[a]	1–2	
IDH2[a]	6–7	
BCOR	6–7	
SRSF2	29–52	Spliceosome
U2AF1	4–10	
SF3B1	6–10	
ZRSR2	4–8	
CBL	8–22	Signaling
KRAS	7–16	
NRAS	4–22	
NF1	6–7	
JAK2	1–10	
RUNX1	8–23	Other
SETBP1	4–18	
NPM1[b]	1–3	
FLT3[a,b]	1–3	

Itzykson E et al. HemaSphere 2018

Prognostic impact of TET2 mutations in CMML





Coltro G et al. Leukemia 2020

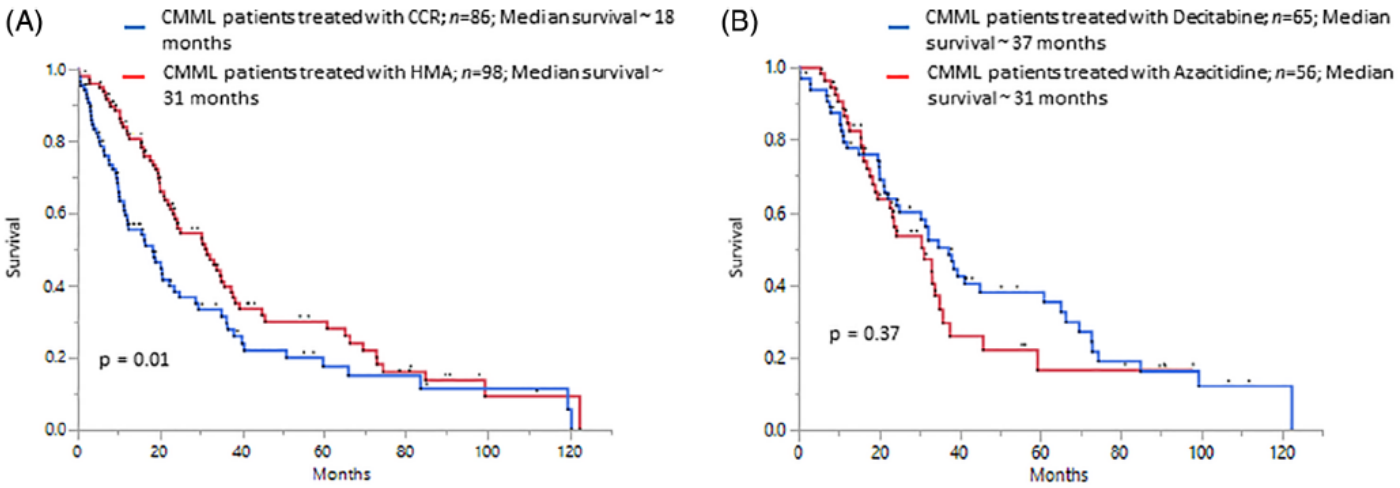
CMML: TREATMENT OPTIONS

- Watch & Wait
- Supportive care (EPO, activin type II receptor ligand traps? TPO-RA?)
- HMAs (5-aza, DAC, guadecitabine?, oral HMAs?)
- Cytoreductive (Hydroxyurea, VP16, 6-MP)
- Intensive chemotherapy (AML-like)
- New drugs in clinical trial
- Allogeneic-HSCT

Suboptimal response rate to HMAs in CMML

121 CMML patients: AZA = 56 / DAC = 65

- ORR 56% by the IWG MDS/MPN (AZA 56% / DAC 58%)
- CR <20% for both HMAs
- MD- vs MP-CMML: No difference
- 29% of pts in CR progressed to AML
- PD after response = Median OS 8 months
- Primary failure = Median OS 4 months
- Low LDH (<250 U/L) associated to ORR
- No impact of ASXL1 or TET2 mut
- **HMAs vs CCR: 31 vs 18 months with no difference between AZA and DAC**



Coston T. et al AJH 2019

An Italian phase II multicentre trial of Decitabine in HR-CMML

- Age > 18 years (no upper limit)
- *If WBC <12000/mm^3*: IPSS high or Int-2
- *If WBC ≥ 12000/mm^3*: at least two of the following criteria

  Blast cells > 5% in the bone marrow

  Cytogenetic abnormality other than t(5;12) (q33;p13)

  Anemia (Hb < 10 g/dl)

  Thrombocytopenia (Plt < 100.000/mm^3)

  Splenomegaly (> 5 cm below costal margin)

  Extramedullary localization

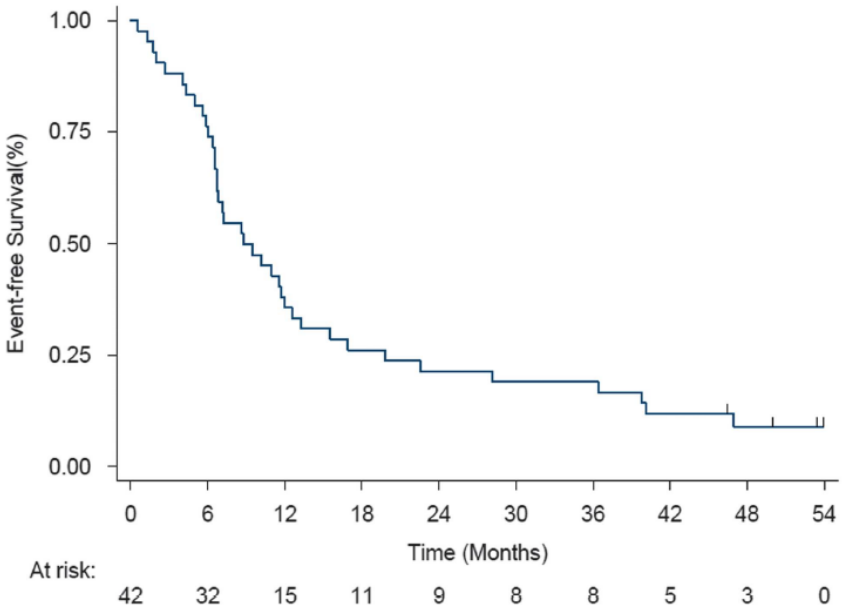
Patients untreated or previously treated with Hydroxyurea or Etoposide given orally or non intensive chemotherapy or intensive chemotherapy given more than 3 months before inclusion

PS 0-2 , Expected survival > 6 months

Santini et al. Leukemia 2017

An Italian phase II multicentre trial of Decitabine in HR-CMML

Overall clinical response (end of cycle 6 or at early withdrawal)



	Number (%) of patients				
	ITT (n = 42)	*CMML-1[a] (n = 26)*	*CMML-2[a] (n = 16)*	*dCMML (n = 14)*	*pCMML (n = 28)*
ORR	20 (47.6)	15 (57.6)	5 (31.25)	9 (64.3)	11 (39.3)
CR	7 (16.6)	5 (19.2)	2 (12.5)	3 (21.4)	4 (14.3)
mCR	8 (19.0)	6 (23.1)	2 (12.5)	4 (28.6)	4 (14.3)
PR	1 (2.4)	0 (0.0)	1 (6.2)	0 (0.0)	1 (3.5)
HI	4 (9.5)	4 (15.3)	0 (0.0)	2 (14.2)	2 (7.2)
SD	9 (21.4)	4 (15.3)	5 (31.3)	0 (0.0)	9 (32.1)
PD	13 (31.0)	7 (26.9)	6 (37.5)	5 (35.7)	8 (28.6)

Santini et al. Leukemia 2017

EMSCO
MYELODYSPLASTIC SYNDROMES

A Randomized Phase III study of Decitabine with or without Hydroxyurea versus Hydroxyurea in patients with advanced proliferative Chronic Myelomonocytic Leukemia

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

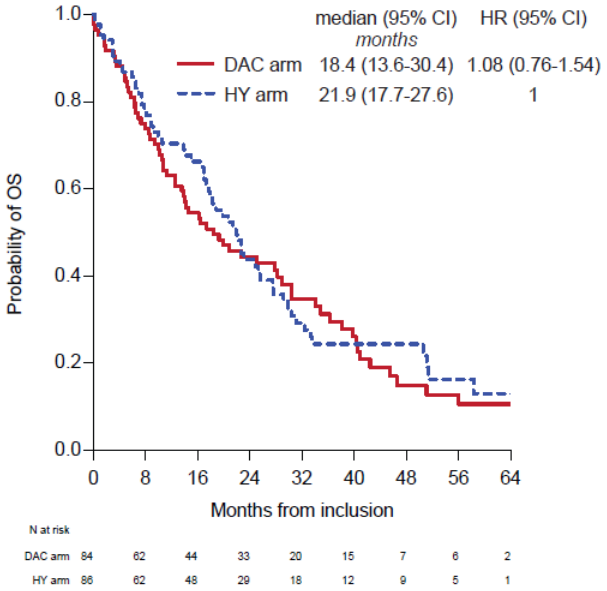
Decitabine 20mg/m²/d x5d q.28d **N=84**
± HY during the first 3 cycles

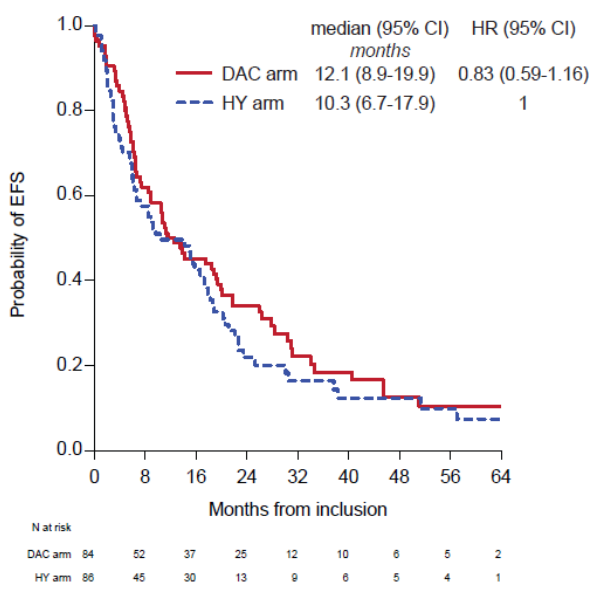
HY **N=84**

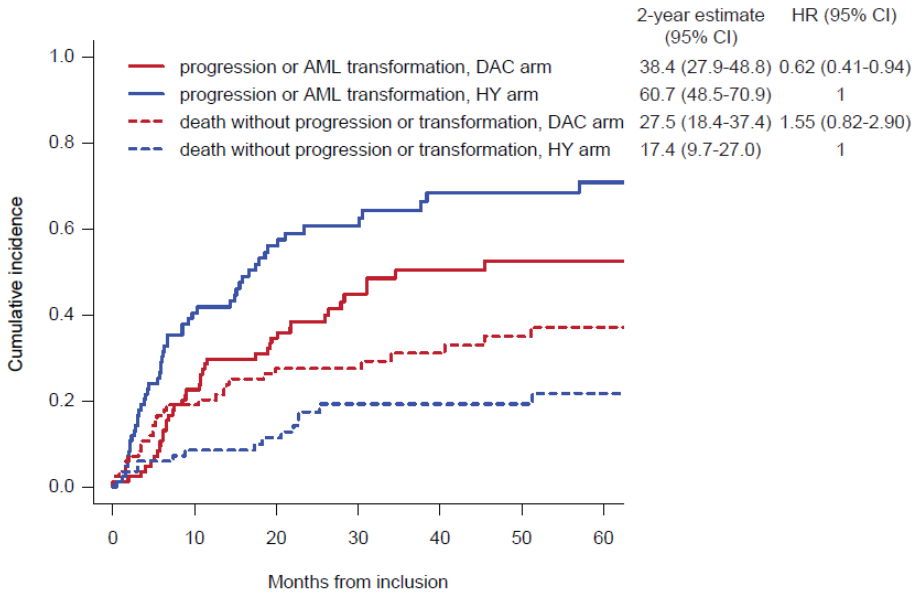
Primary Endpoint: Event-free Survival
- Disease Progression
- Transformation to AML
- Death

V. Santini, U. Platzbecker, R. Itzykson

DAC vs HY (DACOTA Trial)







Itzikson R et al. ASH 2020

CIBMTR retrospective study

Pts number = 209 (2001-2012)

Median age 57 yrs (range 23-74)

Median F-UP 51 months (2-122)

- OS for CPSS low/int-1 3-yr: 48% - 5-yr: 44%
- OS for CPSS int-2/high 3-yr: 32% - 5-yr: 19%
- REL for CPSS low/int-1 3-yr: **50%** - 5-yr: **52%**
- REL for CPSS int-2/high 3-yr: **56%** - 5-yr: **60%**
- NRM 3-yr: **23%** - 5-yr: **28%**

Multivariate analysis:

- CPSS score
- Karnosky PS
- Graft SC source (PB better that BM)

- High CPSS score and KPS did not associate with TRM
- No difference between untreated vs treated (HMA or CT)

Liu HD et al. BBMT 2017

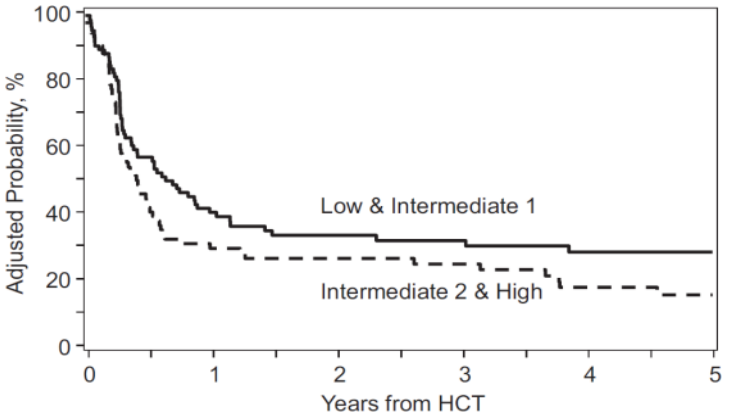


Figure 1. Adjusted disease-free survival, starting at the time of transplantation, by HCT-specific CPSS.

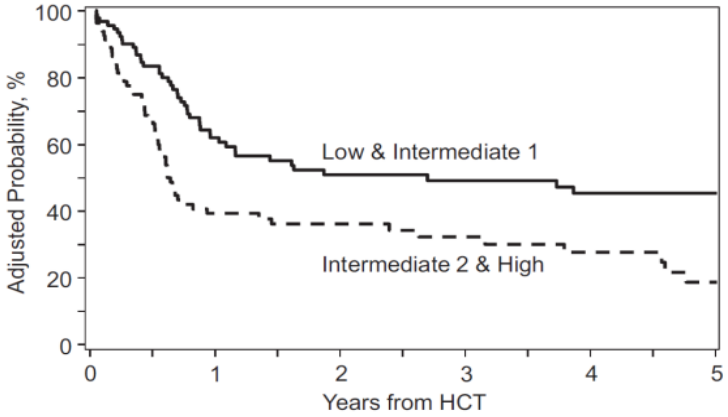


Figure 2. Adjusted overall survival, starting at the time of transplantation, by HCT-specific CPSS.

Impact of molecular profiles on post-transplant long term survival in CMML

Ferrata Storti Foundation

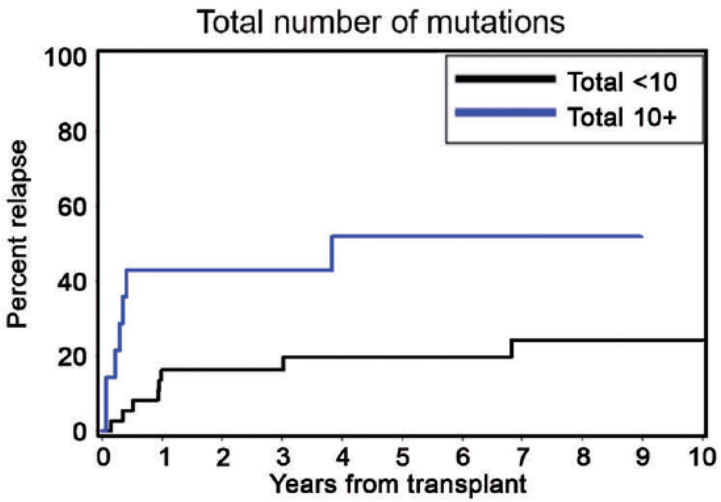
Haematologica 2020
Volume 105(3):652-660

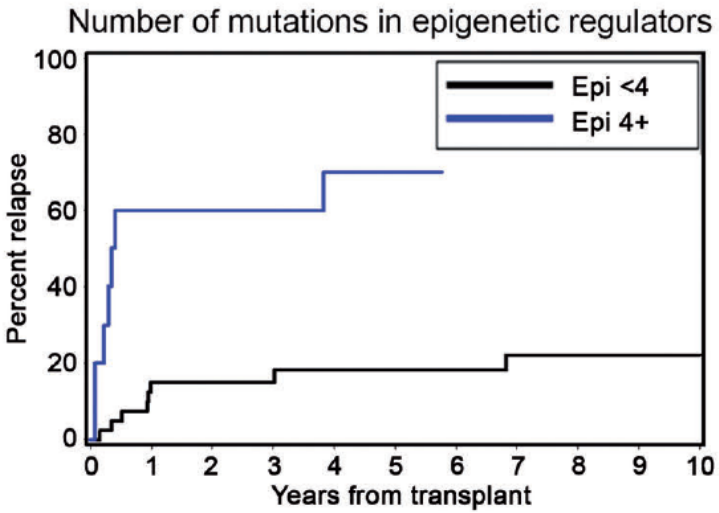
Impact of clinical, cytogenetic, and molecular profiles on long-term survival after transplantation in patients with chronic myelomonocytic leukemia

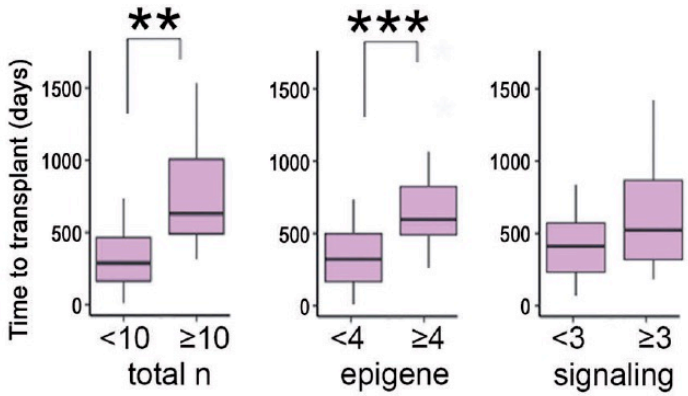
Janghee Woo,[1,2] Dae Ro Choi,[1] Barry E. Storer,[1] Cecilia Yeung,[1,2] Anna B. Halpern,[1,2] Rachel B. Salit,[1,2] Mohamed L. Sorror,[1,2] David W. Woolston,[1] Tim Monahan,[1] Bart L. Scott[1,2] and H. Joachim Deeg[1,2]

[1]Fred Hutchinson Cancer Research Center and [2]University of Washington School of Medicine, Seattle, WA, USA

129 pts allo-TX 1986-2017
NGS BM pre TX = 52 pts
Total mut ≥10 = 15 pts
Epigenetic mut ≥ 4 = 10 pts







Woo J et al. Haematologica 2020

Transplantation and Cellular Therapy 27 (2021) 991.e1–991.e9

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

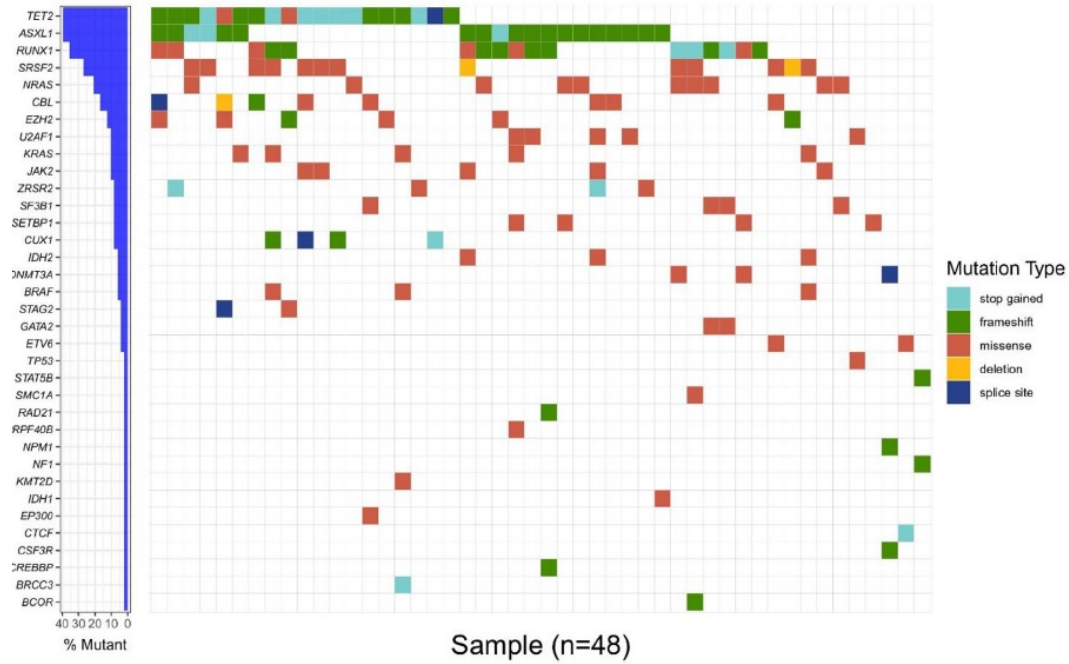
ASTCT American Society for Transplantation and Cellular Therapy

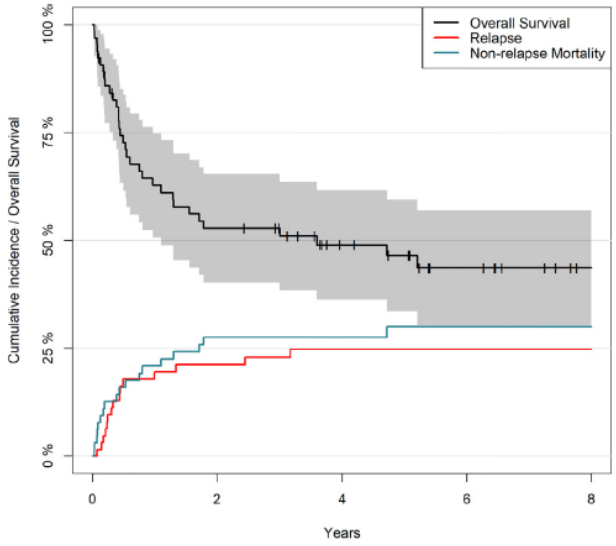
Full Length Article

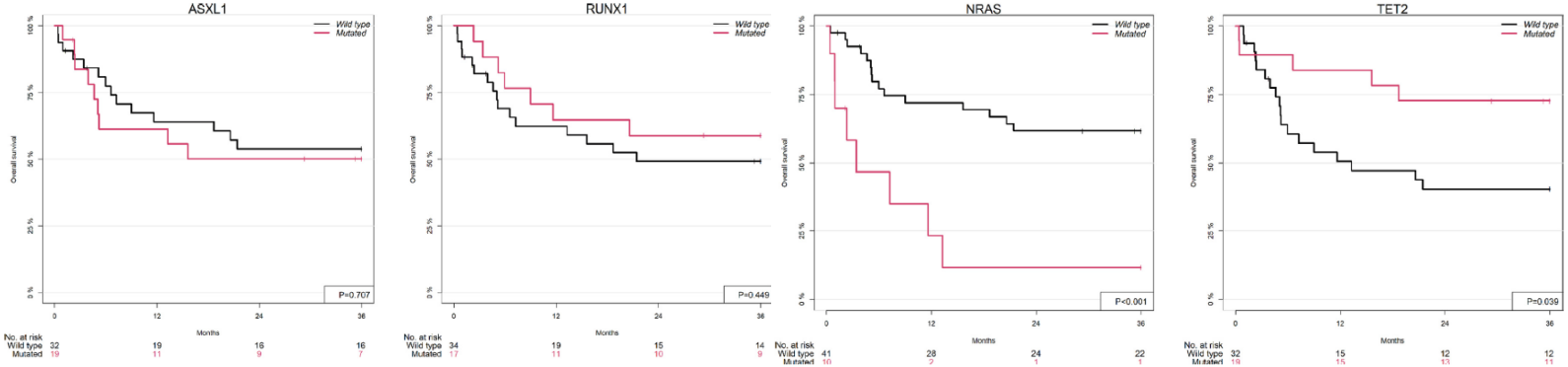
Allogeneic – Adult

Allogeneic Hematopoietic Stem Cell Transplantation for Chronic Myelomonocytic Leukemia: Clinical and Molecular Genetic Prognostic Factors in a Nordic Population

Eileen Wedge[1,2,3], Jakob Werner Hansen[1,2,3], Ingunn Dybedal[4], Maria Creignou[5,6], Elisabeth Ejerblad[7], Fryderyk Lorenz[8], Olle Werlenius[9], Johanna Ungerstedt[5,6], Mette Skov Holm[10], Lars Nilsson[11], Astrid Olsnes Kittang[12], Peter Antunovic[13], Peter Rohon[14], Mette Klarskov Andersen[15], Elli Papaemmanuil[16,17], Elsa Bernard[16,17], Martin Jädersten[5,6], Eva Hellström-Lindberg[5,6], Kirsten Grønbæk[1,2,3], Per Ljungman[5,6], Lone Smidstrup Friis[1,*]





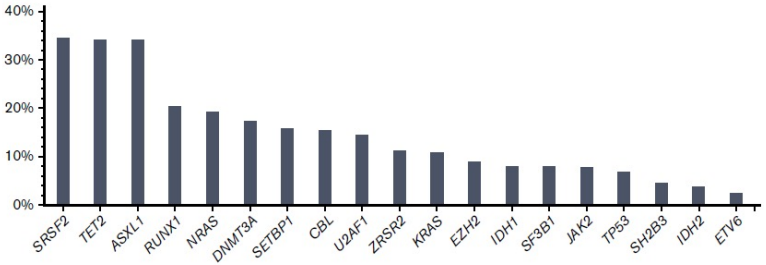


CMML Transplant Score

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

Nico Gagelmann,[1] Anita Badbaran,[1] Dietrich W. Beelen,[2] Rachel B. Salit,[3] Friedrich Stölzel,[4] Christina Rautenberg,[5] Heiko Becker,[6] Aleksandar Radujkovic,[7] Victoria Panagiota,[8] Rashit Bogdanov,[2] Maximilian Christopeit,[1] Yong Park,[3] Olivier Nibourel,[9] Thomas Luft,[7] Michael Koldehoff,[2] Maarten Corsten,[10] Michael Heuser,[8] Jürgen Finke,[6] Guido Kobbe,[5] Uwe Platzbecker,[11] Marie Robin,[12] Bart L. Scott,[3] and Nicolaus Kröger[1]

Total cohort = 240 pts
Median age = 59 (19-74)
WHO 0/1/2 = 10%/50%/40%



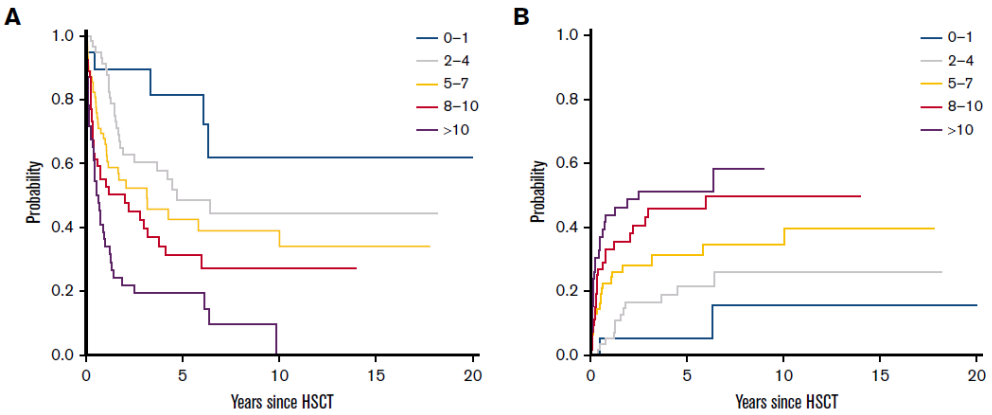


Table 4. Multivariate analysis

Factor	Beta	HR	95% CI	*P*	Points
Continuous comorbidity index	0.15	1.16	1.07-1.25	<.001	1
>2 BM blasts, %	0.53	1.70	1.11-2.61	.02	4
Genotype					
ASXL1- and/or *NRAS*-mutated	0.49	1.63	1.15-2.31	.006	4

Concordance index: 0.68; corrected: 0.67.

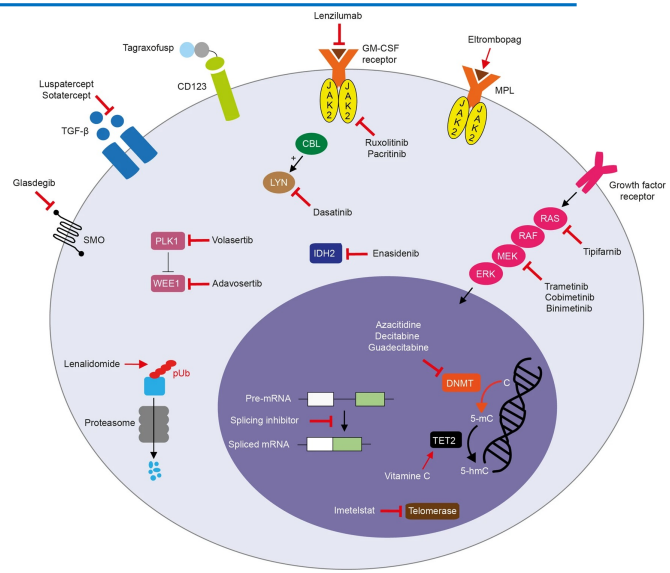
5-year OS:
Score 0-1 = 81% (95% CI 64-100%)
Score 2-4 = 49% (95% CI 36-66%)
Score 5-7 = 43% (95% CI 30-60%)
Score 8-10 = 31% (95% CI 20-49%)
Score >10 = 19% (95% CI 11-36%)

Gagelmann et al. Blood Advances 2021

Possible new treatments in CMML (experimental phase)

- Modulating late stages of erythropoiesis (Luspatercept, Sotatercept)
- Inhibiting the GM-CSF axis (Lenzilumab, Mavrilumab)
- Stimulating thrombopoietin (Eltrombopag, Romiplostin)
- Novel epigenetic therapies (Guadecitabine, oral Azacytidine, oral DAC/cedazuridine)
- Non-epigenetic therapies:

JAKi, SF3B-inhibitor, Tagraxofusp, Tipifarnib, BH3 mimetic, IDH1/2i, IDOi, PLKi, WEE1i



Mc Cullough KB, Patnaik M. Best Pract Res Clin Hematol 2020 / Lasho T, Patnaik M. Best Pract Res Clin Hematol 2021

Conclusions and future directions

- CMML is an **aggressive hematopoietic stem cell malignancy** of older adults, with a **median survival of <36 months**
- The **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**
- **Allo-HSCT** may provide **durable remission for selected patients with CMML,** but it is still associated to **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 be possibly investigated** (e.g. HMA+Tagraxofusp)

Acknowledgements

- CTMO – Osp Maggiore Policlinico, Milano
- EBMT-CMWP
- MDACC Leukemia Dept
- International CMML Consortium
- MDS/MPN-IWG
- EHA-ELN
- International CMML Working conference
- FISiM

Thanks!

Any questions?

francesco.onida@unimi.it

"I would rather make mistakes in kindness and compassion than work miracles in unkindness and hardness"