MDS/MPN overlap sd
Focus on CMML

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Learning objectives – Focus on CMML

- When should you think of CMML?
- How do you confirm the diagnosis?
- How do you estimate the risk?
- How do you decide on treatment, including transplantation?
- How do you manage non-transplant candidates?

MDS/MPN - Diagnostic requirements

- Ineffective hematopoiesis
  - Cytopenia
- Myeloproliferation
  - WBC, monocytes, platelets
- BCR-ABL negativity
  - Mandatory exclusion

MDS/MPN - WHO classification

WHO 2016	WHO 2022
CMML	CMML
Atypical CML	MDS/MPN with neutrophilia
MDS/MPN Ring Sideroblasts - Thrombocytosis	MDS/MPN with SF3B1 mutation and thrombocytosis
MDS/MPN-Unclassifiable	MDS/MPN NOS

How rare are MDS/MPN?

Cancer type	New cases/y (2022)*	
Breast	11302	Very frequent
MDS	950	Frequent in hematology
CMML	**130**	**Very rare**
Other MDS/MPN	< 5	Ultra rare

*Belgian Cancer Registry in 2022

Mister M, 72 yo

- No symptoms
- Fit patient
- Normal clinical exam
- Routine blood analysis

Parameter	Apr 2025	Ref Range
WBC × 10^9/L	12.0	4.5–11.0
Absolute Monocytes	1.2	0.2–0.8
Monocyte %	23%	2–8%
Neutrophils	10.8	1.8–7.7
Hb g/dL	11.2	13.5–17.5
MCV fL	101	80–100
Platelets × 10^9/L	142	150–400
Peripheral Blasts	0	0%
LDH U/L	270	140–280

Step 1: Confirm persistence and exclude reactive causes

- **repeat the CBC in 3 months**
- exclude common reactive causes
  - **Infections**
  - **Inflammatory/autoimmune diseases**

Mister M, 72 yo, 1 year later

- Fatigue
- Weight Los
- Splenomegaly

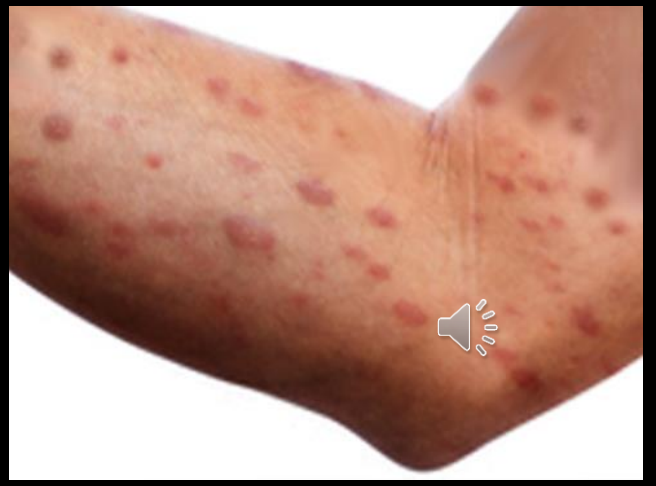
Parameter	Apr 2025	Apr 2026	Ref Range
WBC × 10^9/L	12.0	**28.5**	4.5–11.0
Absolute Monocytes	1.2	**4.6**	0.2–0.8
Monocyte %	23%	**26%**	2–8%
Neutrophils	10.8	**17.5**	1.8–7.7
Hb g/dL	11.2	**8.4**	13.5–17.5
MCV fL	101	**104**	80–100
Platelets × 10^9/L	142	**68**	150–400
Peripheral Blasts	0	**4%**	0%
LDH U/L	270	**420**	140–280

CMML symptoms and clinical features

Symptoms	No symptoms	**~20–30%**
	Fatigue	**~50–70%**
	Weight loss	**~10–20%**
	Night sweats	**~10–20%**
	Fever (non-infectious)	**~5–10%**
Organomegaly	Splenomegaly	**~25–50%**
	Hepatomegaly	**~10–20%**
	Lymphadenopathy	**~5–10%**

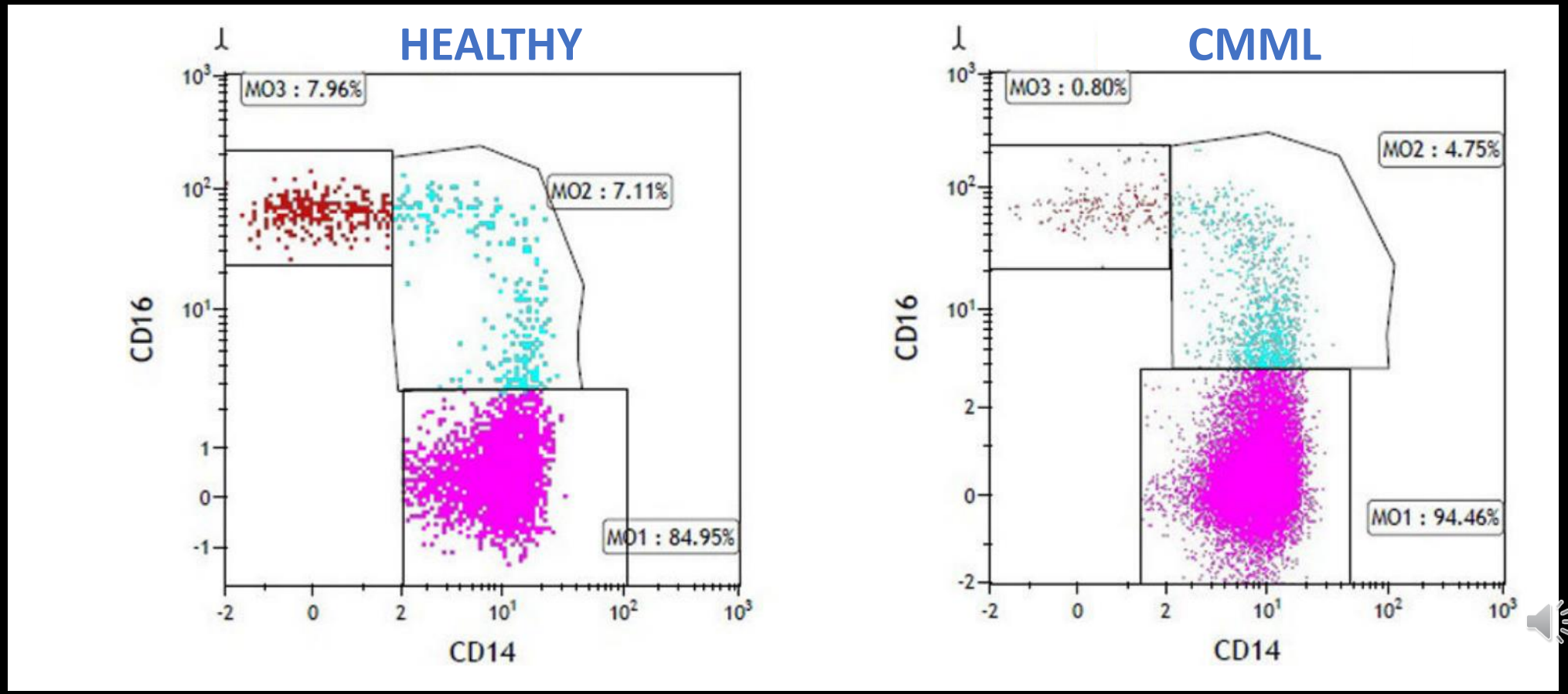
CMML-associated conditions

- **1. Immune dysregulation / inflammatory disorders** (20–30%)
  - Vasculitis (leukocytoclastic, large vessel…)
  - Inflammatory arthritis
  - Immune cytopenias (AIHA, ITP)
  - Serositis
  - Skin manifestations (Sweet syndrome…)
- **2. Clonal / associated hematologic conditions**
  - Systemic mastocytosis associated with CMML (SM-AHN)
- **3. Organ damage related to monocytosis**
  - **Lysozyme nephropathy**
  - Tissue infiltration (skin: leukemia cutis, lung, GI)



Step 2: Peripheral blood monocyte cytometry

Classical monocytes CD14+ CD16- ≥ 94%
CMML diagnosis: se 90–92% sp 94-95%



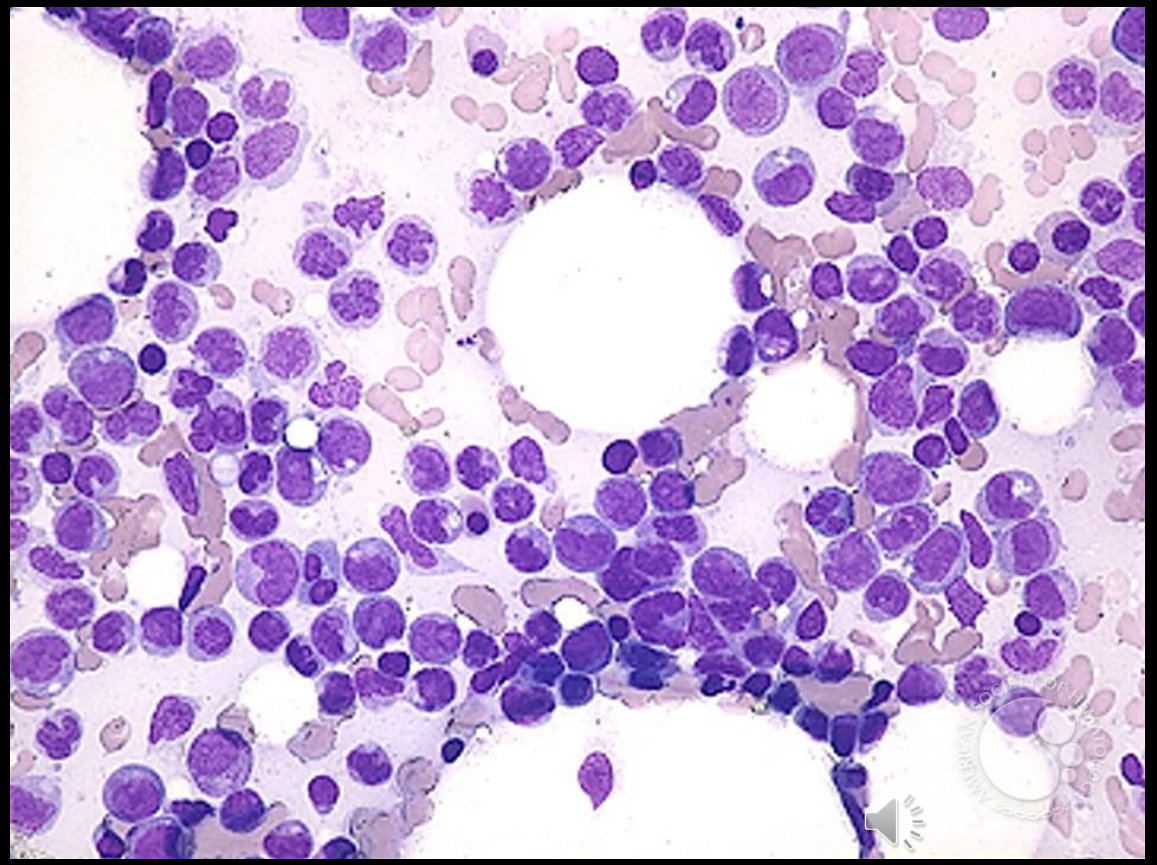
Patnaik M. et al. Am J Hematol. 2024 June ; 99(6): 1142–1165

Step 3: When to perform bone marrow and genetic testing

Indications

- Persistent unexplained monocytosis
- Cytopenias
- Circulating blasts
- Splenomegaly

  or constitutional symptoms
- >94% classical monocytes



Step 4: Classification - Diagnostic criteria (WHO 2022)

Prerequisite criteria

1. Persistent absolute ($\geq 0.5 \times 10^9$/L) and relative (≥10%) peripheral blood monocytosis.
2. Blasts constitute <20% of the cells in the peripheral blood and bone marrow.[a]
3. Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms[b]
4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions.[c]

Supporting criteria

1. Dysplasia involving ≥1 myeloid lineages.[d]
2. Acquired clonal cytogenetic or molecular abnormality.
3. Abnormal partitioning of peripheral blood monocyte subsets.[e]

Requirements for diagnosis

- Pre-requisite criteria must be present in all cases.
- If monocytosis is $\geq 1 \times 10^9$/L: one or more supporting criteria must be met.
- If monocytosis is ≥0.5 and $<1 \times 10^9$/L: supporting criteria 1 and 2 must be met.

Persistent ≥ 3 months

Blasts = myeloblasts, monoblasts and **promonocytes**

= No MPN BM and/nor high burden MPN-mutations (BCR-ABL, JAK2, CALR or MPL)

If eosinophilia, No PDGFRA and PDGRFB

≥10% Dysplasia in at least 1 lineage

CD14+CD16neg ≥ 94% without AI or infl°

Khoury, J.D. *et al. Leukemia* **36**, 1703–1719 (2022)

CMML diagnostic criteria (ICC 2022)

Same same but different

Monocytosis defined as monocytes ≥ 0.5 × 10^9/L and ≥ 10% of the WBC

Cytopenia (thresholds same as MDS)*

Blasts (including promonocytes) < 20% of the cells in blood and bone marrow

Presence of clonality: abnormal cytogenetics and/or presence of at least one myeloid neoplasm associated mutation of at least 10% allele frequency†

In cases without evidence of clonality,

monocytes ≥ 1.0 × 10^9/L and > 10% of the WBC, and

increased blasts (including promonocytes),‡ or morphologic dysplasia, or

an abnormal immunophenotype consistent with CMML would be required for its diagnosis.

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

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Bone marrow examination with morphologic findings consistent with CMML (hypercellularity due to a myeloid proliferation often with increased monocytes), and lacking diagnostic features of acute myeloid leukemia, MPN or other conditions associated with monocytosis§

No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

Features	WHO 2022	ICC 2022
Monocyte threshold **Duration of monocytosis**	AMC ≥0.5 × 10^9/L *and* monocytes ≥10% of WBC differential Persistent (≥3 months)	
Blast/promonocyte threshold	20% blasts (including promonocytes) in PB and BM	
Clonality requirement	Cytogenetic or molecular evidence of clonality (acquired mutation or cytogenetic)	
Monocyte immunophenotyping	Increase in classical monocytes (≥94%) supportive but not required	
Exclusions	Absence of *BCR::ABL1*, *PDGFRA/PDGFRB/FGFR1* rearrangements, *PCM1::JAK2*; absence of AML-defining genetic abnormalities	
Cytopenia requirement	Not an explicit separate criterion	≥ 1 cytopenia (ineffective hematopoiesis)
Morphologic criteria	BM morphology consistent with CMML; dysplasia in ≥1 lineage	More stringent morphologic criteria (myeloid proliferation and monocytes) → fewer cases qualifying as CMML compared to WHO
Practical impact	**More** oligomonocytosis cases as **CMML** than ICC.	**More** oligomonocytosis cases as **MDS, MDS/MPN-NOS** than WHO.
Prognostic impact	**NO DIFFERENCE**	

Step 5: Classify the CMML subtype
COMPLEMENTARY

WHO 2022° Blast-based		ICC 2022 WBC-based	
CMML-1	**CMML-2***	**CMML-MD**	**CMML-MP***
PB blasts <5%	5-19%	WBC <13 x10^9/L	WBC ≥13 x10^9/L
BM blasts <10%	10-19% Auer rods+		

*higher risk of AML transformation

°Khoury, J.D. *et al. Leukemia* **36**, 1703–1719 (2022)

Clonal monocytosis of undetermined significance (CMUS) – ICC 2022

= Clonal hematopoiesis *AND* monocytosis AND who **do not meet the diagnostic criteria for CMML or any other myeloid neoplasm**

Persistent monocytosis defined as monocytes ≥ 0.5 × 10^9/L and ≥ 10% of the WBC
Absence or presence of cytopenia (thresholds same as for MDS)*
Presence of at least one myeloid neoplasm associated mutation of appropriate allele frequency (ie, ≥2%)†
No significant dysplasia, increased blasts (including promonocytes) or morphologic findings of CMML on bone marrow examination‡
No criteria for a myeloid or other hematopoietic neoplasm are fulfilled
No reactive condition that would explain a monocytosis is detected

Clonal Cytopenia and Monocytosis of Undetermined Significance (CCMUS)

Dysplasia ≥ 1 lineage AND/OR
Hypercellularity, myeloid predominance +/- monocytes +/- monoblasts +/- blast equivalents

Mister M, 72 yo, 1 year later

Monocyte cytometry

Classical monocytes CD14+ $CD16^{neg}$: 97% (N 80-90)

Myelogram

- Hypercellular (80% cellularity)
- Monocytic proliferation
- Dysplasia in ≥1 lineages
- Blasts + promocytes : 6%

Diagnosis CMML-1, Proliferative subtype

Cytogenetics Normal karyotype (46, XY)

Molecular Studies TET2, SRSF2, ASXL1

Parameter	Apr 2025	Apr 2026	Ref Range
WBC × 10^9/L	12.0	**28.5**	4.5–11.0
Absolute Monocytes	1.2	**4.6**	0.2–0.8
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Peripheral Blasts	0	**4%**	0%
LDH U/L	270	**420**	140–280

Molecular landscape

Gene	Frequency mutation	Prognostic impact
TET2*	60%	Favorable (if no adverse mutation)
SRSF2**	50%	Neutral
ASXL1*	40%	Adverse
NRAS***	15%	Adverse
RUNX1****	15%	Adverse
DNMT3A*	15%	Adverse
SETBP1	10%	Adverse

Co-mutation TET2+ SRSF2
Highly specific of CMML

* Epigenetic regulators
** Spliceosome genes
*** Signaling pathway
**** Transcription factor

Step 6: Risk stratification

Variable	CPSS[1] (2013)	CPSS-Mol[2] (2016)
WBC ≥13	✓	✓
Hb / TD	RBC-TD	RBC-TD
PLT		
Blasts	✓ BM	✓ BM
Cytogenetics	✓	✓
Molecular		✓ ASXL1, RUNX1, NRAS, SETBP1
Risk groups	4	4
mOS (mo)	72/31/18/12	144/59/31/18
1ary purpose 2ary	OS AML transformat°	OS AML transformat°
Best value	Limited resources	HSCT if no BLAST-Mol or iCPSS

1. Such E. et al. Blood 2013 Apr 11;121(15):3005-15.
2. Elena C. et al. Blood 2016 Sep 8;128(10):1408-17.
3. Tefferi A. et al. Blood 2025 Aug 14;146(7):874-886.
4. Lanino L. et al. JCO 2026 Mar 27:JCO2502116.

Step 6: Risk stratification

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Variable	CPSS[1] (2013)	CPSS-Mol[2] (2016)	BLAST[3] (2025)	BLAST-Mol[3] (2025)
WBC ≥13	✓	✓	✓	✓
Hb / TD	RBC-TD	RBC-TD	Hb	Hb
PLT				
Blasts	✓ BM	✓ BM	✓ PB ≥2%	✓ PB ≥2%
Cytogenetics	✓	✓		✓
Molecular		✓ ASXL1, RUNX1, NRAS, SETBP1		✓ favorable: TET2, PHF6 Adverse: ASXL1, RUNX1, NRAS, SETBP1, DNMT3A, TP53, U2AF1, BCOR, PTPN11
Risk groups	4	4	3	3
mOS (mo)	72/31/18/12	144/59/31/18	63/28/13	N/A
1ary purpose 2ary	OS AML transformat°	OS AML transformat°	OS -	OS -
Best value	Limited resources	HSCT if no BLAST-Mol or iCPSS	Non transplant monitoring	HSCT

Step 6: Risk stratification

1. Such E. et al. Blood 2013 Apr 11;121(15):3005-15.
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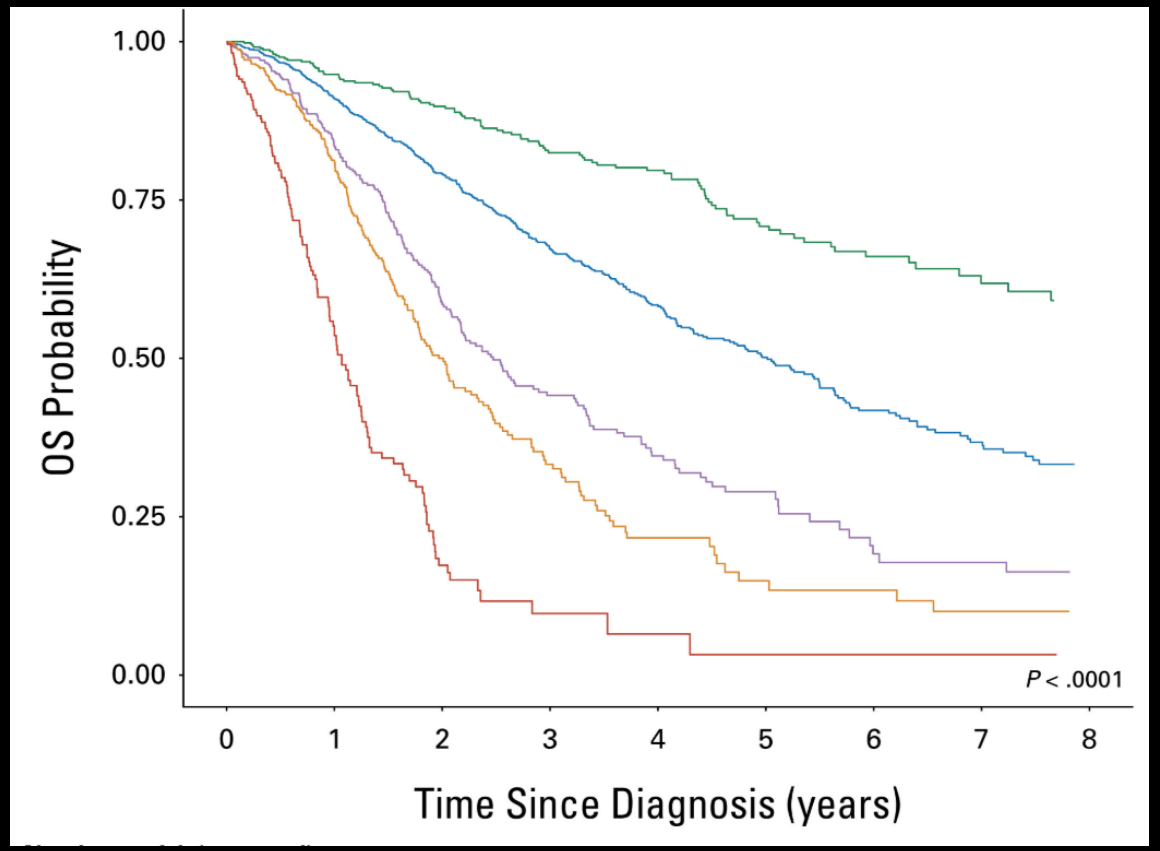
Variable	CPSS[1] (2013)	CPSS-Mol[2] (2016)	BLAST[3] (2025)	BLAST-Mol[3] (2025)	iCPSS[4] (2026)
WBC ≥13	✓	✓	✓	✓	✓
Hb / TD	RBC-TD	RBC-TD	Hb	Hb	Hb
PLT					✓
Blasts	✓ BM	✓ BM	✓ PB ≥2%	✓ PB ≥2%	✓ BM
Cytogenetics	✓	✓		✓	✓
Molecular		✓ ASXL1, RUNX1, NRAS, SETBP1		✓ favorable: TET2, PHF6 Adverse: ASXL1, RUNX1, NRAS, SETBP1, DNMT3A, TP53, U2AF1, BCOR, PTPN11	✓ ASXL1, RUNX1, TET2, SETBP1, DNMT3A, TP53, EZH2, STAG2, U2AF1
Risk groups	4	4	3	3	5
mOS (mo)	72/31/18/12	144/59/31/18	63/28/13	N/A	N/A
1ary purpose 2ary	OS AML transformat°	OS AML transformat°	OS -	OS -	OS HSCT timing
Best value	Baseline, no NGS	HSCT if no BLAST-Mol or iCPSS	Blood → routine monitoring	HSCT	Transplant timing decisions

iCPSS (2026)



Risk	OS	HSCT timing
Very Low	~10y	No upfront HSCT
Low	~5y	Deferred HSCT
Intermediate	~3y	Individualized decision
High	~2y	Early HSCT
Very high	~1y	Urgent HSCT

Lanino L. et al. JCO 2026 Mar 27:JCO2502116.

Mister M, 72 yo, CMML-1, MP

Parameter	Apr 2025	Apr 2026	Ref Range
WBC × 10^9/L	12.0	**28.5**	4.5–11.0
Hb g/dL	11.2	**8.4**	13.5–17.5
Platelets × 10^9/L	142	**68**	150–400
Peripheral Blasts	0	**4%**	0%
BM blasts		**6%**	<2%

CPSS Mol	Blast-Mol	iCPSS
Int-2 mOS 37 mo	High 12 mo	Intermediate ~ 30 mo

Cytogenetics Normal karyotype (46, XY)

Molecular Studies TET2, SRSF2, ASXL1

ONLINE CALCULATORS

CPSS-Mol

- https://qxmd.com/calculate/calculator_609/cmml-cpss-mol

BLAST and BLAST-MOL

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

iCPSS

- https://icpss-risk.com/

Step 7: Determine transplant eligibility

- Age and performance status
- Comorbidity index (HCT-CI)
- Donor availability → early HLA typing
- Risk score (CPSS-Mol, BLAST-mol, iCPSS)
- Patient preference and goals of care

Mister M, 72 yo, CMML-1, MP

Parameter	Apr 2025	Apr 2026	Ref Range
WBC × 10^9/L	12.0	**28.5**	4.5–11.0
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Platelets × 10^9/L	142	**68**	150–400
Peripheral Blasts	0	**4%**	0%
BM blasts		**6%**	<2%

CPSS Mol	Blast-Mol	iCPSS
Int-2	High	Intermediate
mOS 37 mo	12 mo	~ 30 mo

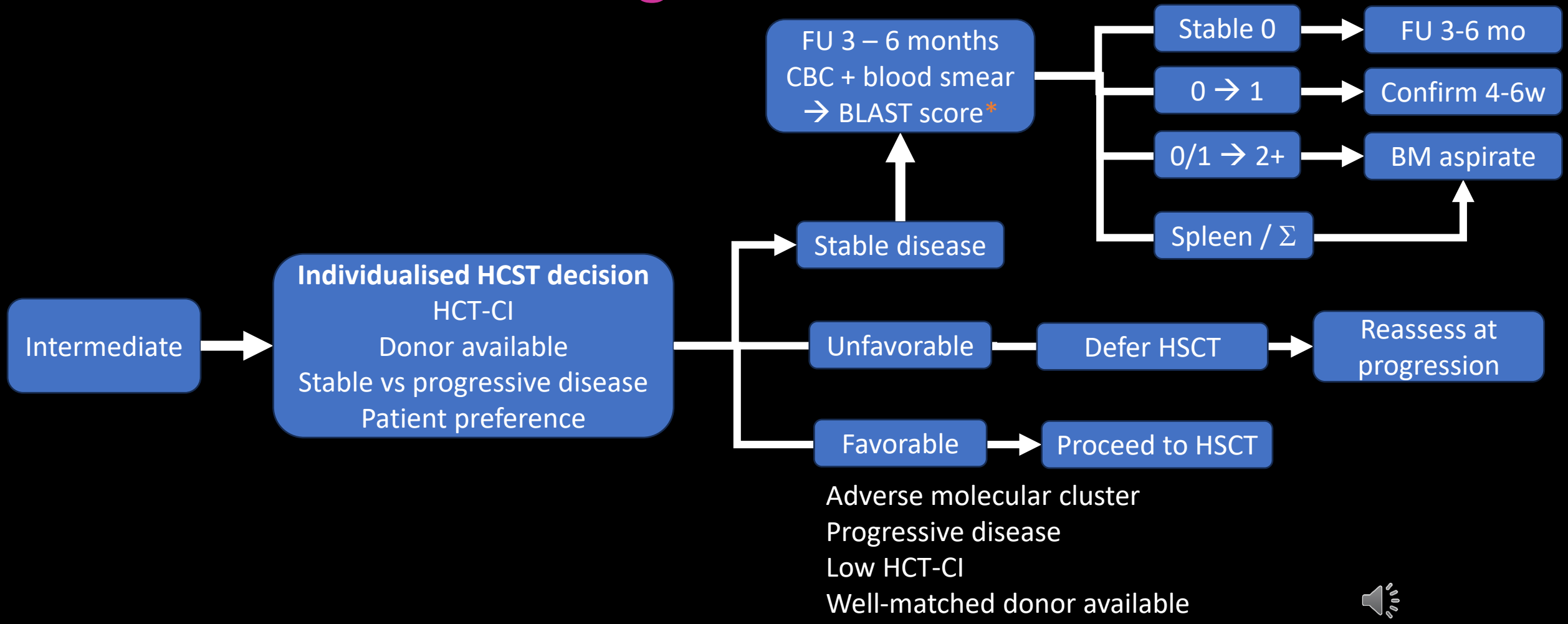
Cytogenetics Normal karyotype (46, XY)

Molecular Studies TET2, SRSF2, ASXL1

→ **Transplant should be discussed early**
but not performed immediately.

TRANSPLANT ELIGIBLE PATIENTS

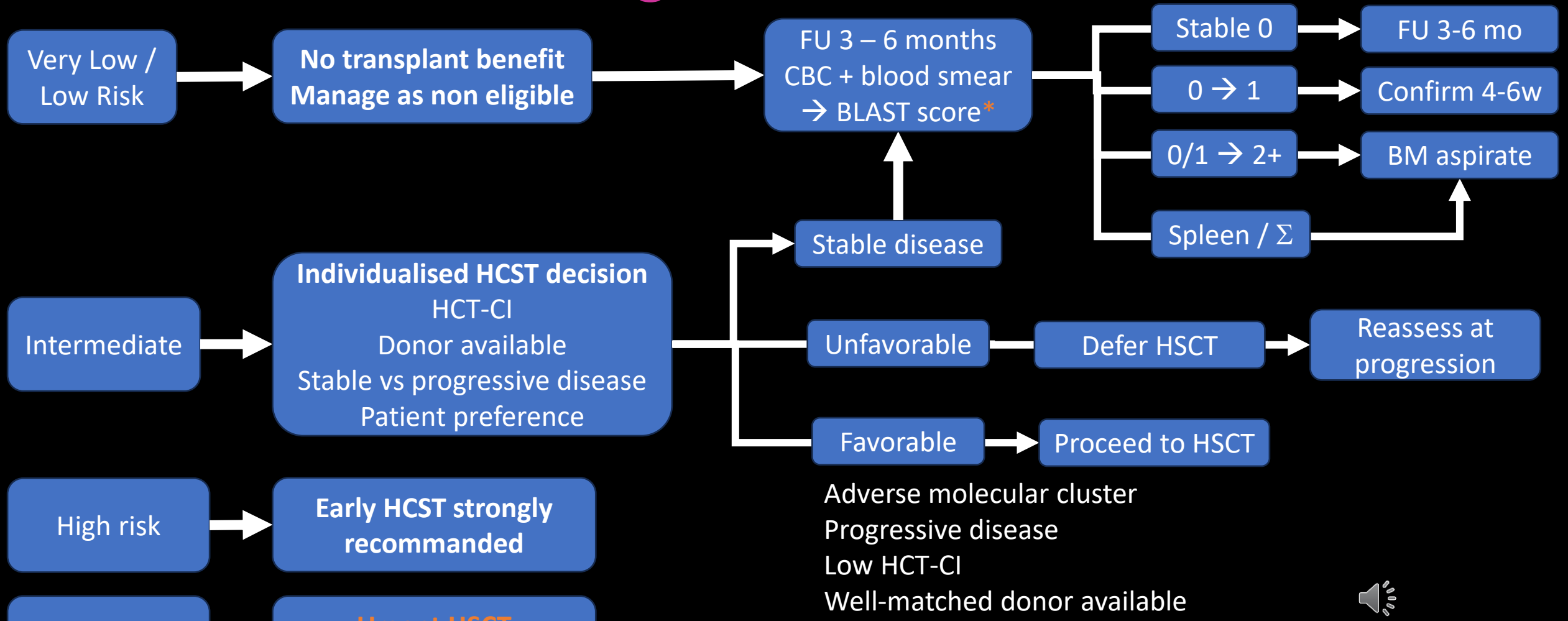
Treatment according to iCPSS risk assessment



*Tefferi A. et al. Blood 2025 Aug 14;146(7):874-886

TRANSPLANT ELIGIBLE PATIENTS

Treatment according to iCPSS risk assessment



*Tefferi A. et al. Blood 2025 Aug 14;146(7):874-886

Step 8: Treatment of non transplant eligible patients according to iCPSS risk assessment

… in an ideal setting …

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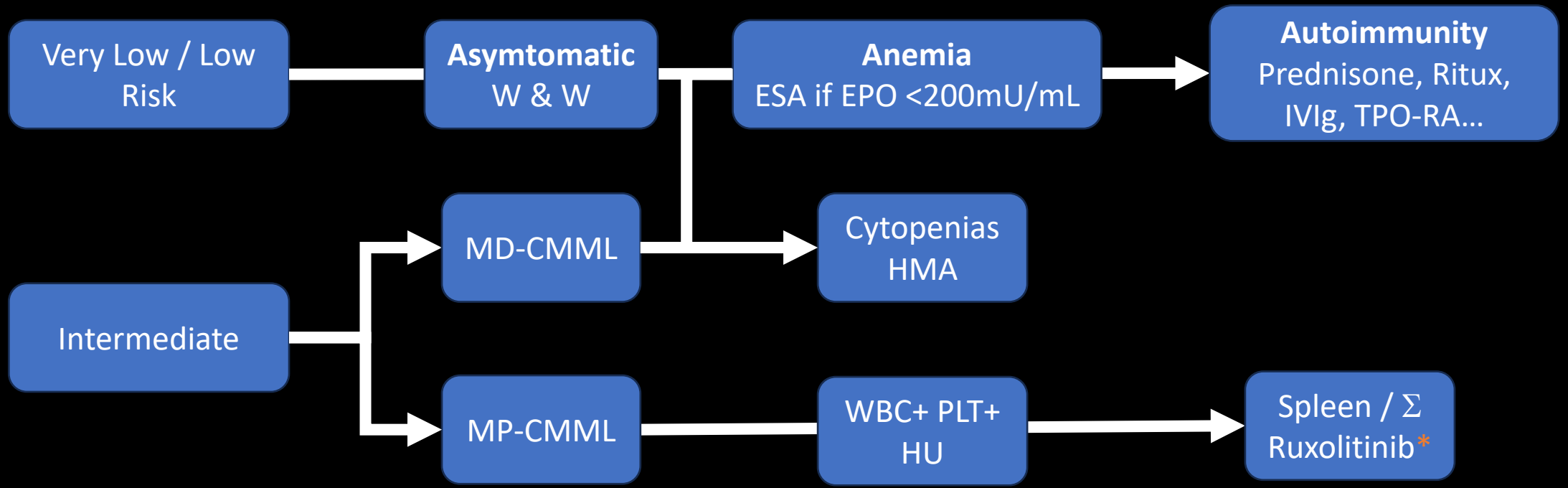
… in an ideal setting …

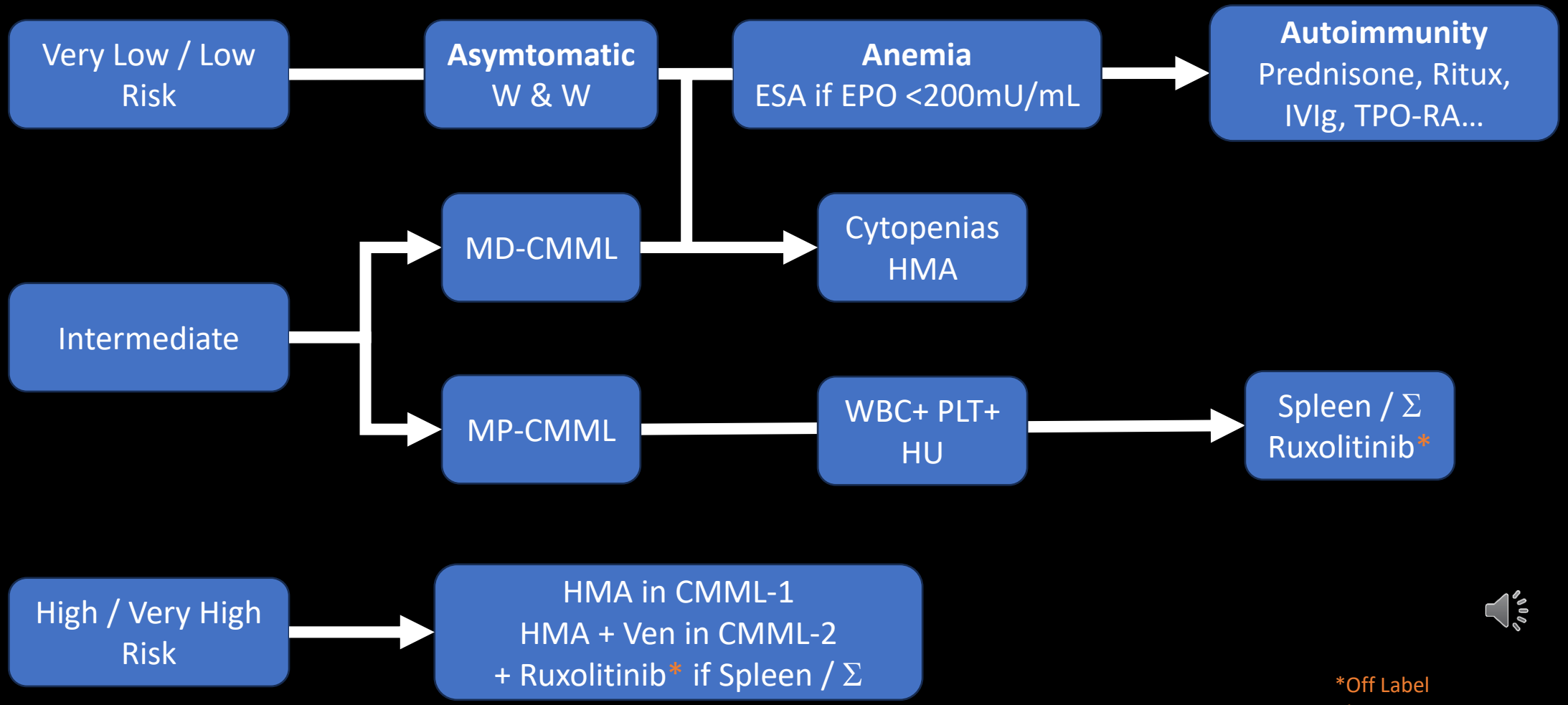


*Off Label

Clin Cancer Res 2021 Nov 15;27(22):6095

Step 8: Treatment of non transplant eligible patients according to iCPSS risk assessment

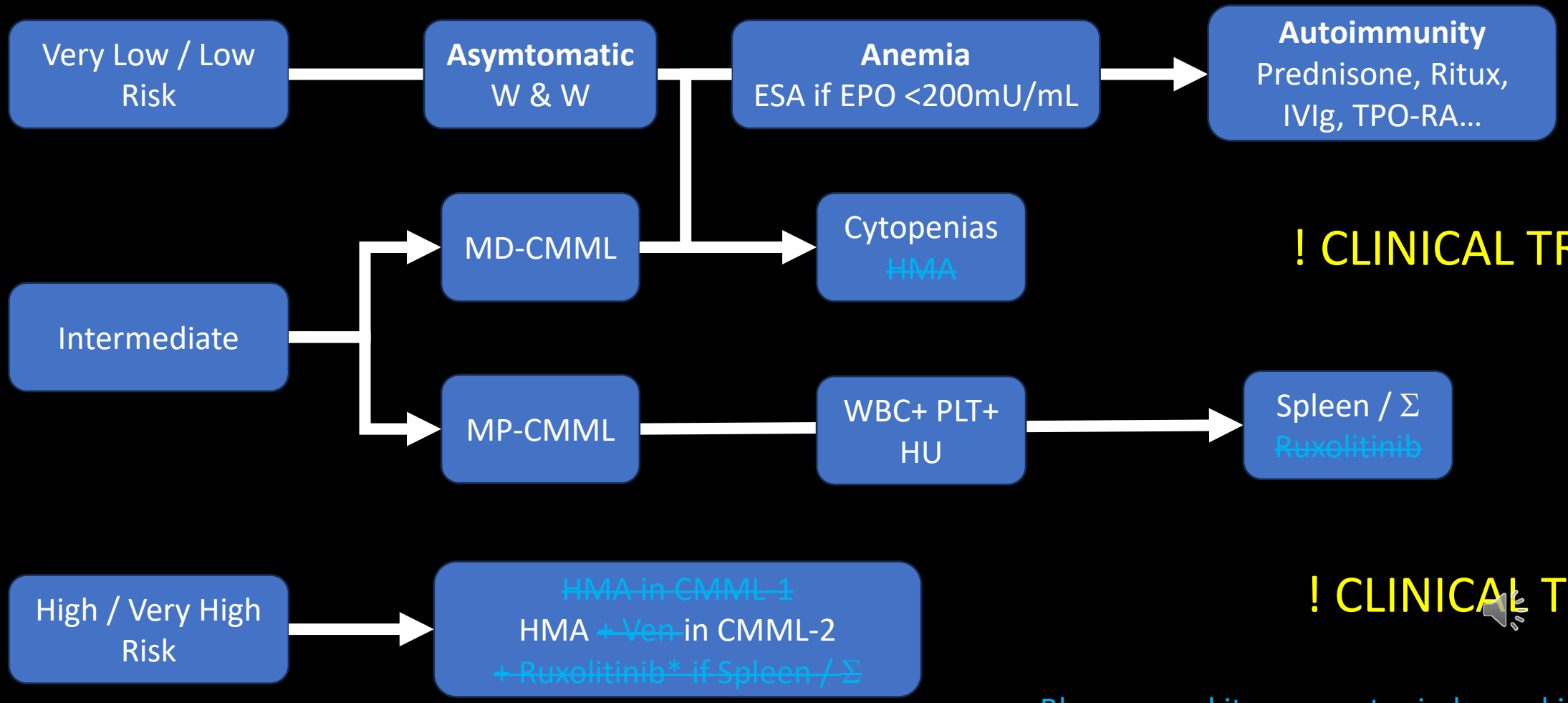
… in an ideal setting …



*Off Label

Clin Cancer Res 2021 Nov 15;27(22):6095

Treatment of non transplant eligible patients according to iCPSS risk assessment … in the Belgium setting …



Blue crossed items = not reimbursed in Belgium

Broader use of HMA across CMML subtypes

- **Multicenter retrospective**
- N 949 CMML
- First-line treatments
  - HMAs 43% (n=412)
  - Hydroxyurea 41% (n=391)
  - Intensive chemotherapy 9% (n=83)

Subgroup	N (%)	HMA OS Benefit?	mOS: HMA vs. non-HMA	p-value
MD-CMML, blasts 10%	182 (21%)	**No**	No significant difference	NS
MD-CMML, blasts ≥10%	111 (13%)	**Yes**	23.8 vs. 9.4 months	0.0014
MP-CMML, blasts 10%	345 (40%)	**Yes**	24.7 vs. 13.1 months	0.0002
MP-CMML, blasts ≥10%	219 (26%)	**Yes**	15.5 vs. 6.6 months	0.0002

- mOS HMA 20.7 vs mOS HU 15,6mo (p=0.0002)
- mOS HMA 20.7 and mOS intensive CT 14.0 mo (p=0.0027)

The Lancet. Haematology. 2021. Pleyer L, Leisch M, Kourakli A, et al.

Broader use of HMA across CMML subtypes?

- **Dacota trial: Randomized Phase 3**
- **1st line Decitabin vs HU**
- **Advanced MP-CMML:** WBC >13 + at least 2
  - BM blasts ≥5%,
  - Clonal cytogenetic abnormality,
  - Hemoglobin <10 g/dL,
  - Neutrophils >16 × 10^9/L,
  - Platelets <100 × 10^9/L,
  - Splenomegaly,
  - ECOG ≤2
- **Dissociation response rate / survival**
  - **Death without progression +++**
  - Treatment-related toxicity (infections…)

Endpoint	Decitabine (n=84)	Hydroxyurea (n=86)	p-value
Primary: Median EFS	12.1 months	10.3 months	0.27
Median OS	18.4 months	21.9 months	0.67
Overall Response Rate (ORR)	**63%** (53/84)	**35%** (30/86)	0.0004
Risk of AML transformation/progression	Reduced	Reference	0.005
Risk of death without progression	Increased	Reference	0.04
Median follow-up	17.5 months	17.5 months	—

JCO. ASCO 2023. Itzykson R, Santini V, Thepot S, et al.

Role of stringent cytoreduction?

- *Ancillary analysis of the DACOTA trial*
- **Monocytosis** >1 × 10^9/L or **Leucocytosis** >10 × 10^9/L after 6 cycles

→ Increased **death** **x5.38 (p = 0.0003)**.

- **Independent of**:
  - Treatment arm (decitabine vs. hydroxyurea)
  - Baseline CPSS risk category
  - Persistence of BM blast excess
- *Persistent myeloproliferation after treatment*

→ *Worsens prognosis*

→ *Irrespective of treatment arm or bone marrow response.*

- **To do: Prospective validation** in independent cohorts

Leukemia. 2026. Selimoglu-Buet D, Chevret S, Santini V, et al.

CMML: what really matters

- It’s not one disease → it’s **many diseases**
- Prognosis is not enough → we need **decision tools**
- Timing is everything → especially for **transplant**
- Treatment is not standardized → it must be **personalized**
- **Controlling proliferation** might matter more than response

Thank you

Good judgment comes from experience.
Experience comes from bad judgment.

Rita Mae Brown