Disclosures for Ayalew Tefferi

Principal investigator role	Janssen, Geron, Celgene, Sanofi-Aventis, Gilead Sciences, Incyte
Employee	None
Consultant	None
Major Stockholder	None
Speakers' Bureau	None
Scientific Advisory Board	None

Presentation includes discussion of the following off-label use of a drug or medical device: Hydroxyurea, Interferon-alpha, Busulfan, Thalidomide, Lenalidomide, Pomalidomide, Ruxolitinib, Androgen preparations, Erythropoiesis stimulating agents

MAYO CLINIC

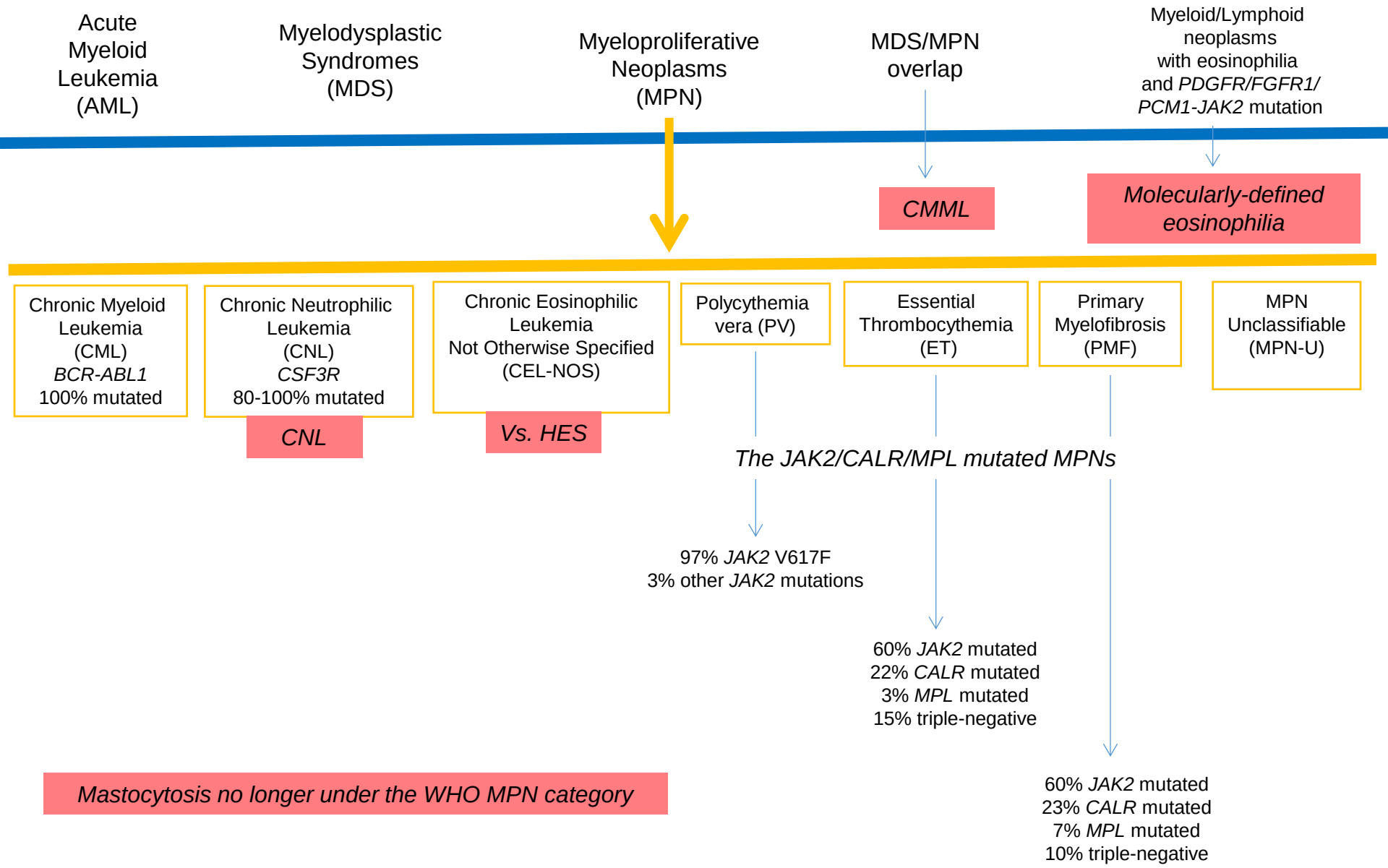
Myeloproliferative neoplasms other than PV, ET and PMF:
CMML: chronic myelomonocytic leukemia
Mastocytosis
Eosinophilic disorders
CNL: chronic neutrophilic leukemia

Ayalew Tefferi, MD
Professor of Medicine and Hematology
Mayo Clinic College of Medicine

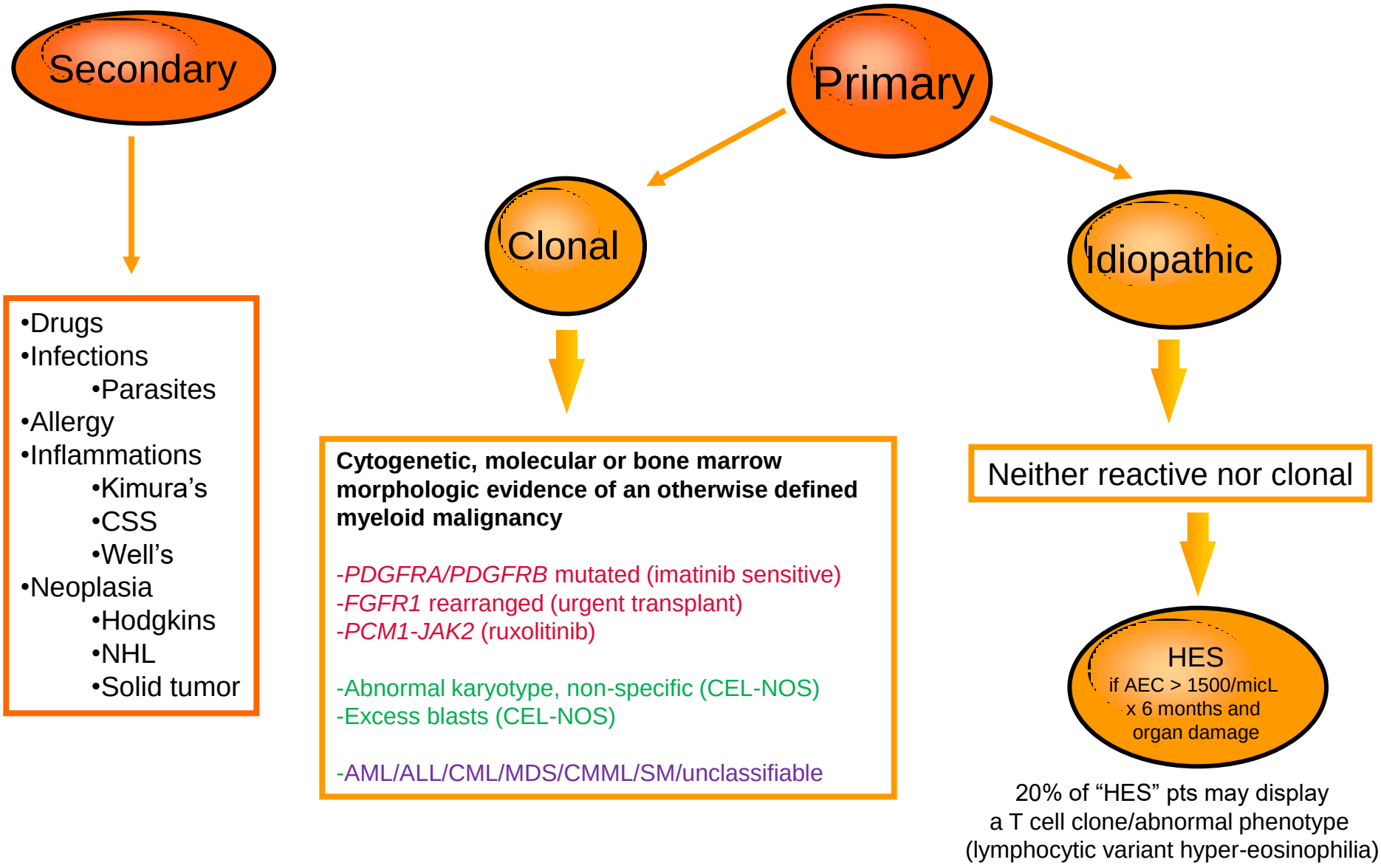
Objectives

- Disease definitions
- Diagnosis
- Current prognostication
- Treatment

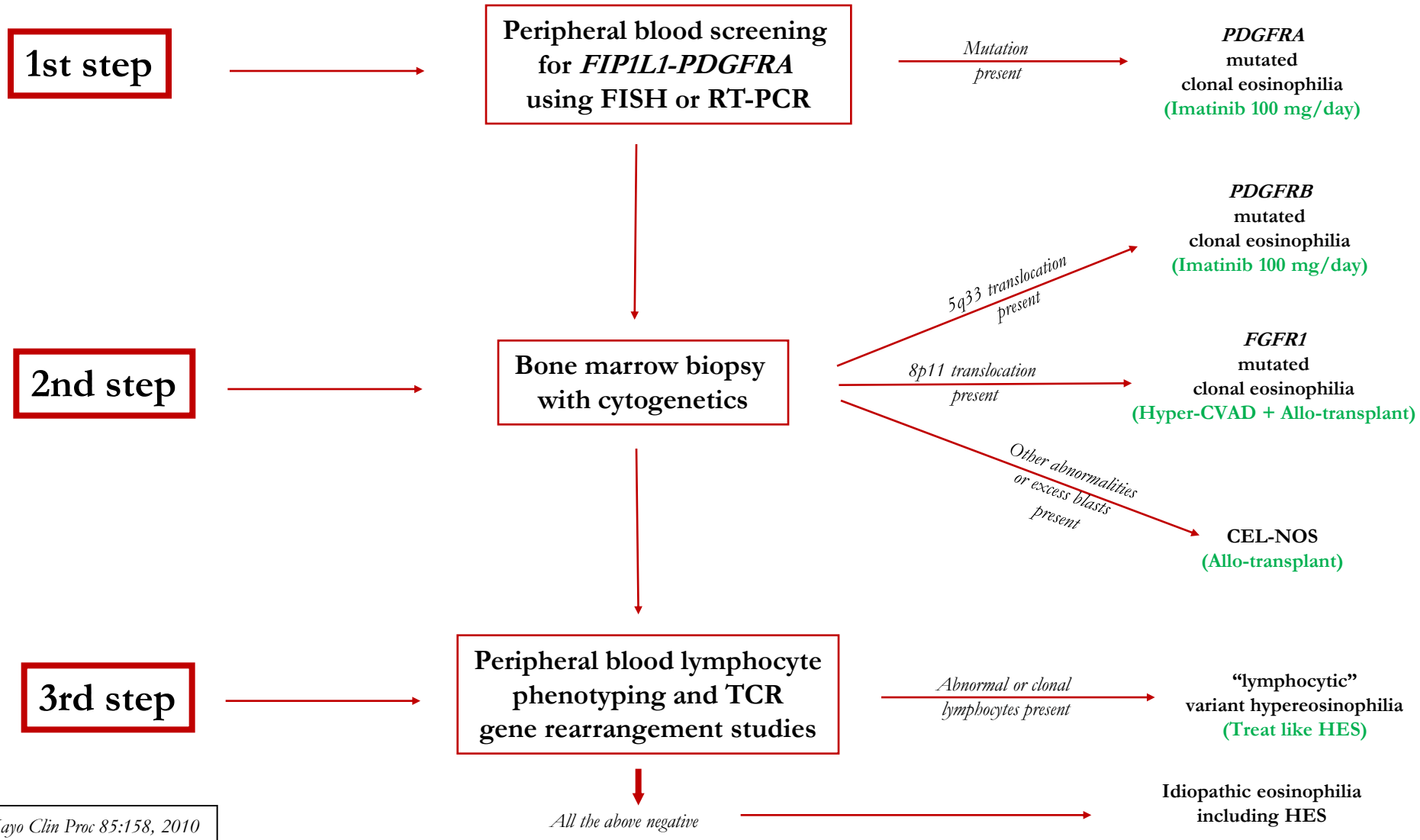
2016 WHO Classification of Myeloid Malignancies



Acquired eosinophilia



Primary eosinophilia diagnostic algorithm



Mayo Clin Proc 85:158, 2010

Hyper-eosinophilic syndrome/idiopathic eosinophilia

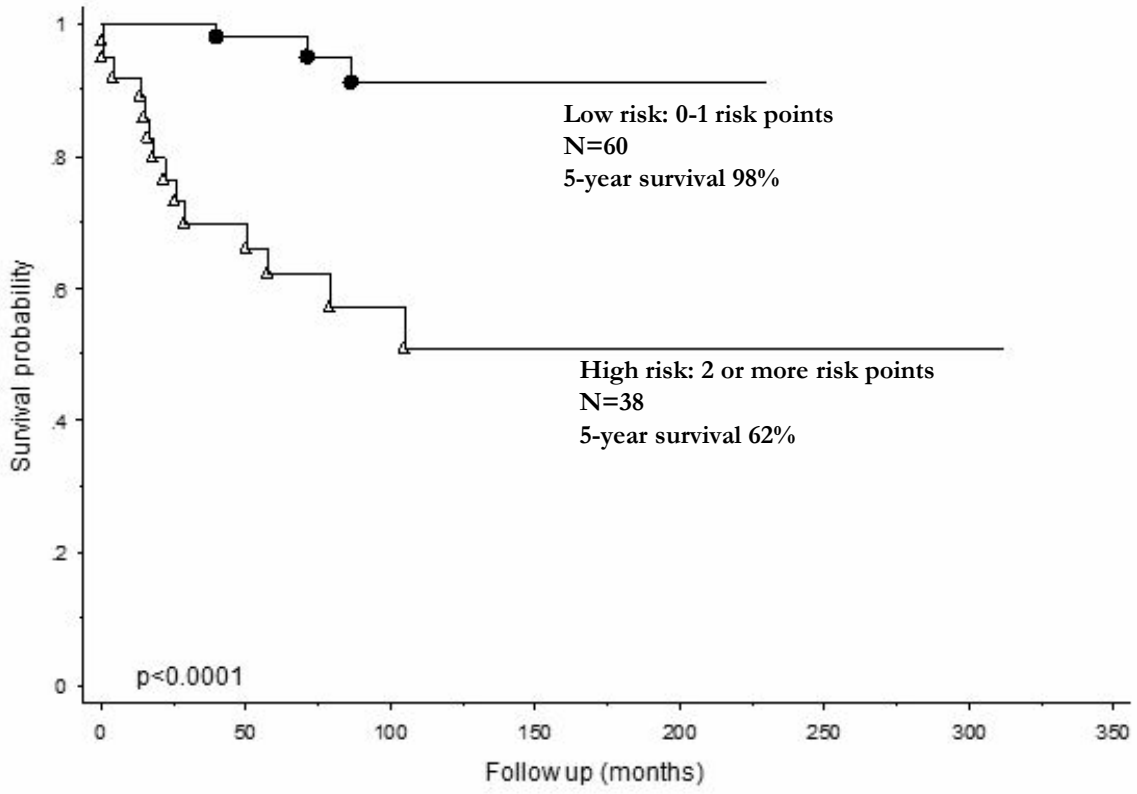
98 Mayo Clinic patients with WHO-defined HES/IH (*Leukemia 2016;30:1924*)

NGS revealed 11% harbored pathogenic mutation;
TET2=3, *ASXL1* =2, *KIT*=2, and *IDH2*, *JAK2*, *SF3B1 and TP53*=1 each.
15% harbored a variant of unknown significance (VUS);
TET2=8, *ASXL1*=2, *SETBP1*=2, and *CALR*, *CEBPA* and *CSF3R*=1 each.

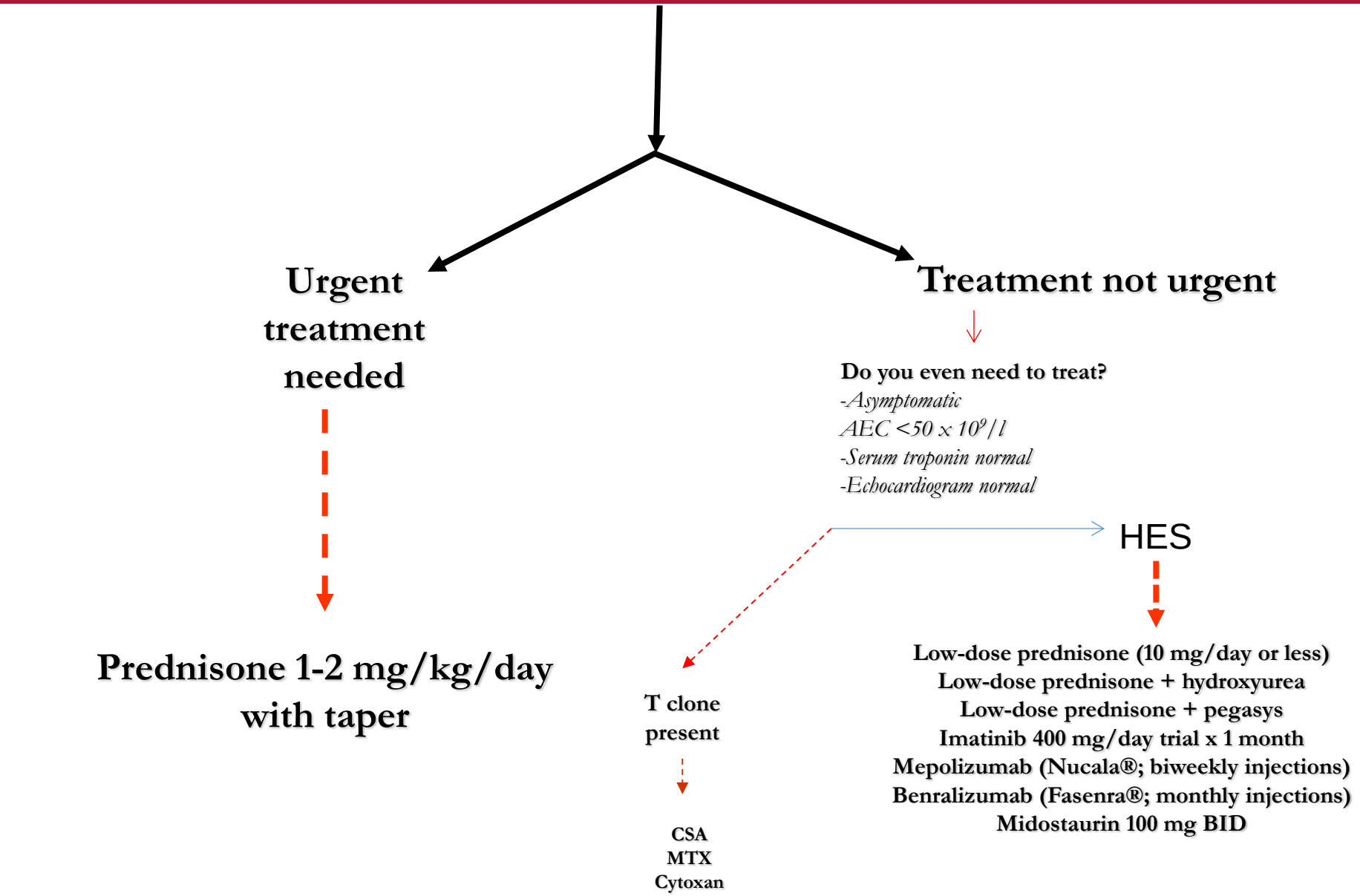
NO DIFFERENCE IN MUTATED VS NON-MUTATED IN PHENOTYPE
MUTATED PATIENTS HAD INFERIOR SURVIVAL IN UNIVARIATE ANALYSIS

Risk factors for survival:

Hepatosplenomegaly (3 points)
Advanced age (2 points)
Hgb <10 g/dl (one point)
Cardiac involvement (one point)



HES treatment algorithm



Novel targeted therapies for eosinophilic disorders

Anti-IL-5
- Mepolizumab
- Reslizumab

Anti-IL-5Rα
- Benralizumab

Eotaxin receptor
- LMW CCR3 inhibitors

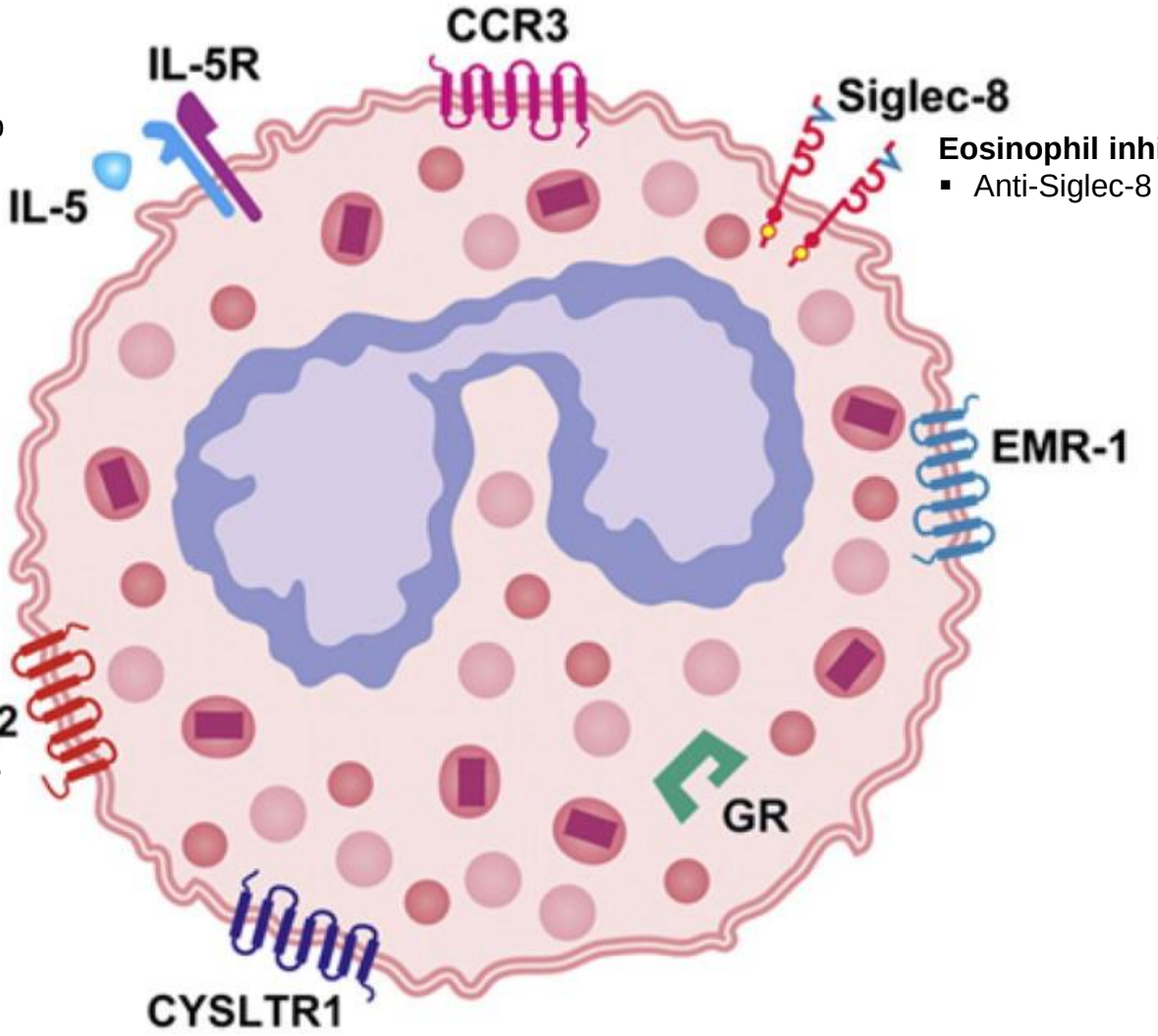
Eosinophil inhibitory receptor
- Anti-Siglec-8 Ab

Anti-CD52
- Alemtuzumab

Anti-IgE
- Omalizumab

Multi-targeted TKI
- Midostaurin

Prostaglandin D_2 receptor
- LMW CRTH2 inhibitors

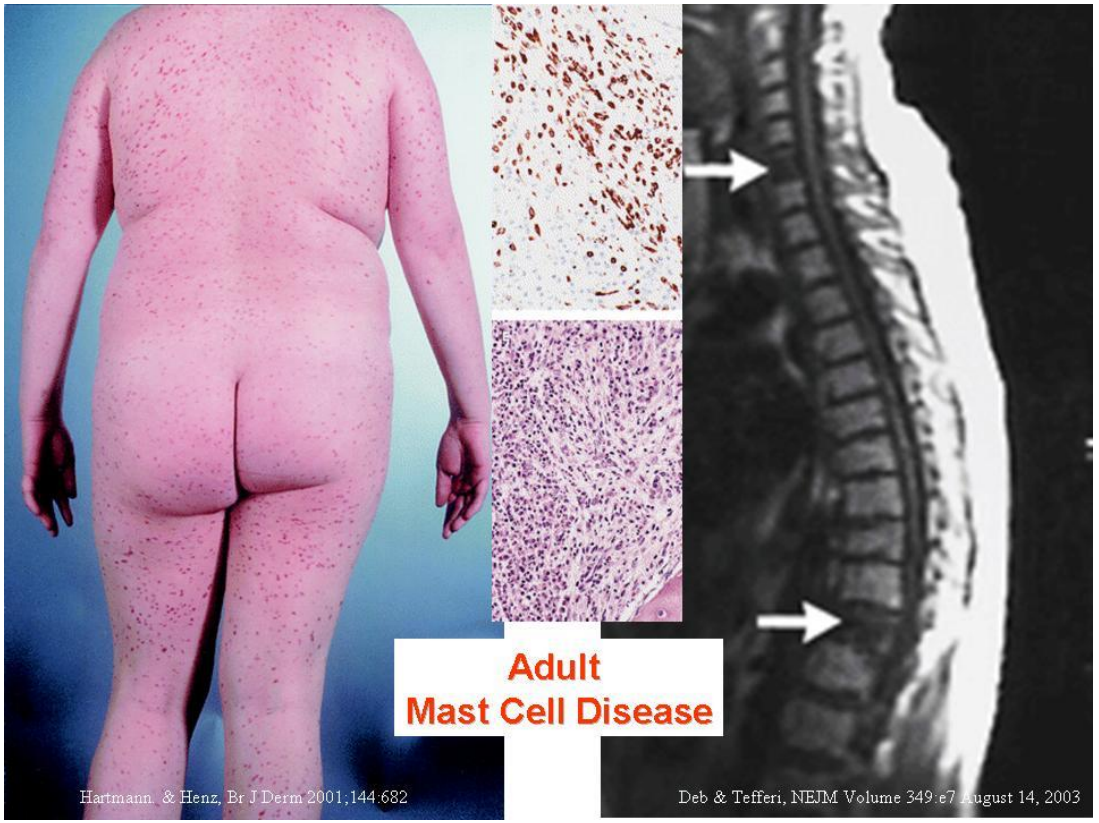


Wechsler et al. J Allergy Clin Immunol. 2012 Sep;130(3):563-71.

When should you suspect mastocytosis?

- Urticaria pigmentosa
- Mast cell mediator symptoms

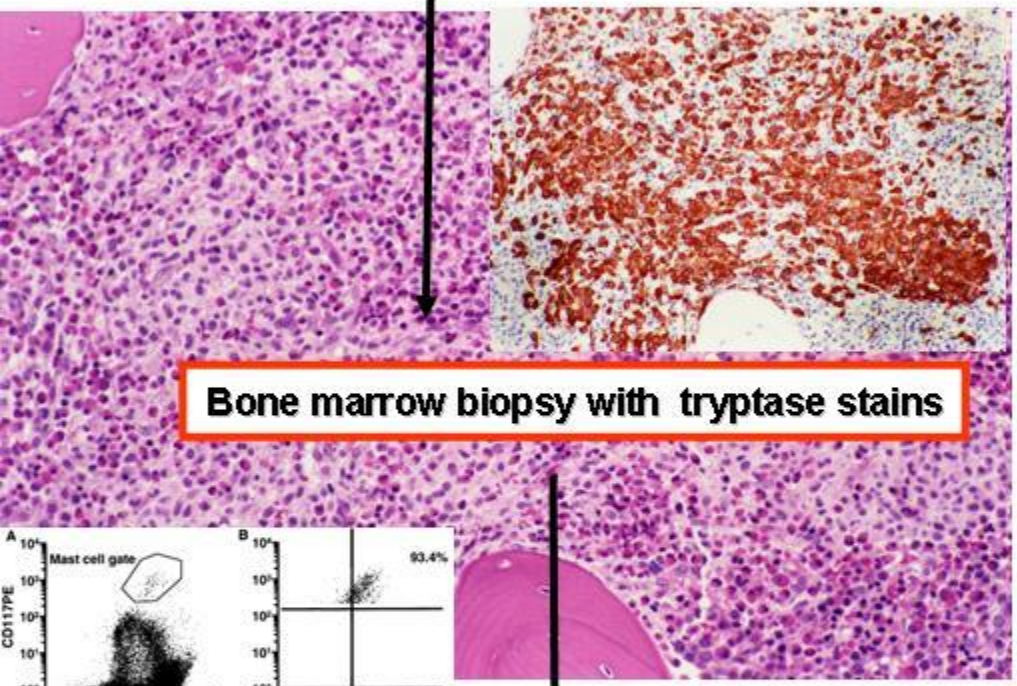
  -Anaphylactoid
  -Diarrhea
  -Flushing/urticaria



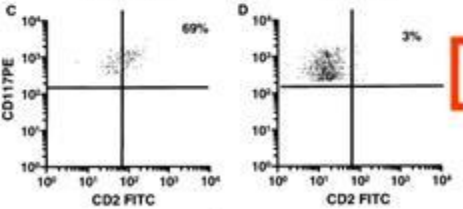
- Osteopenia/unexplained fractures

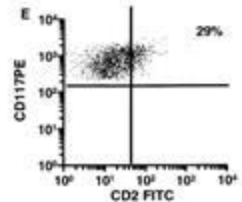
Diagnostic Evaluation in Systemic Mastocytosis

serum tryptase



Bone marrow biopsy with tryptase stains



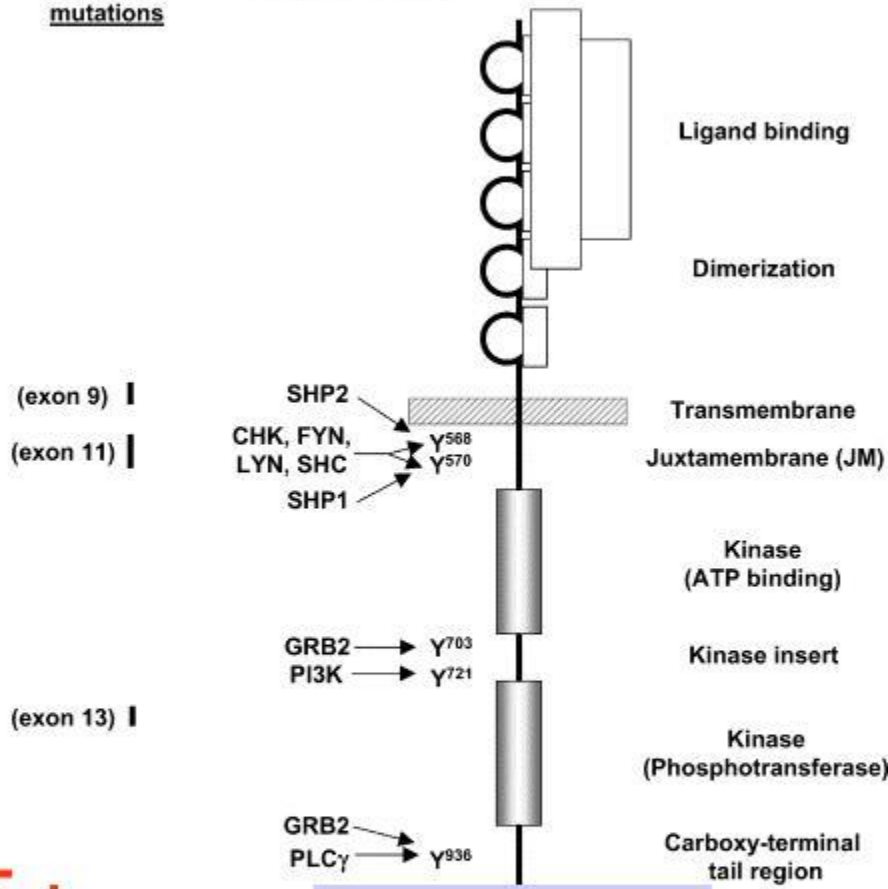


Bone marrow mast cell flow cytometry

Normal mast cells —
CD117+, CD25-, CD2-

Abnormal mast cells —
CD117+, CD25+, CD2 ±

Pardanani et al. BJH 2003;120:691



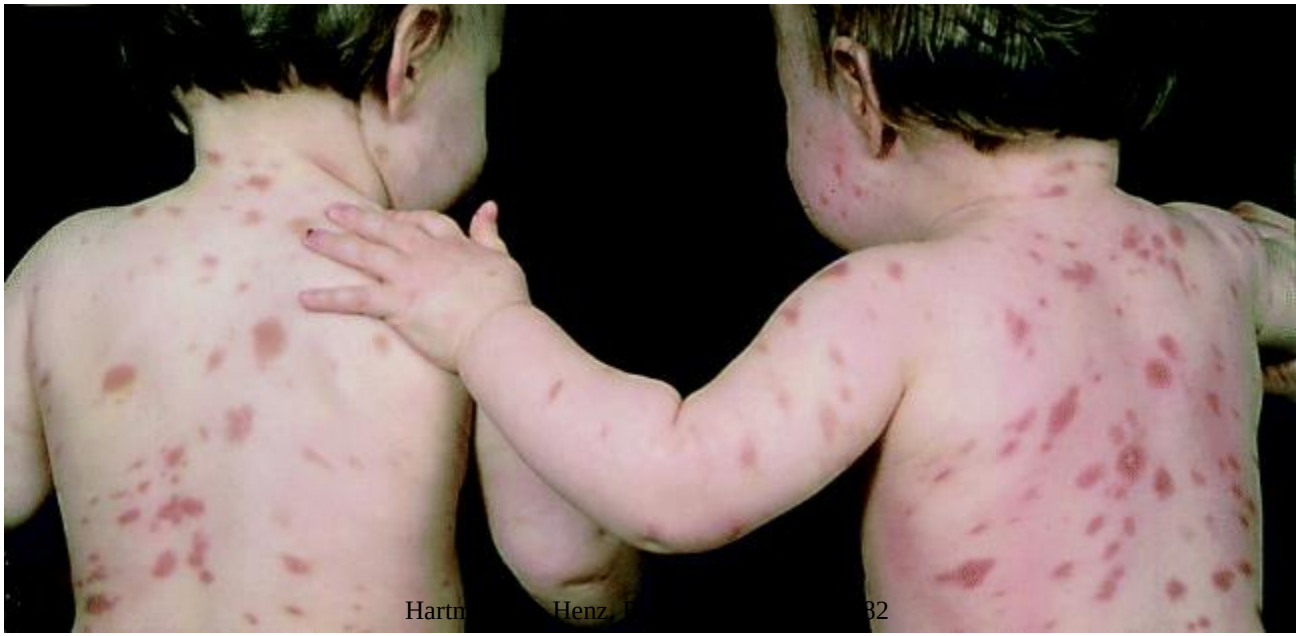
±C-kit mutations
Asp816Val (kinase domain)
Val560Gly (JM domain)

Sattler & Salgia, Leukemia Research, 2004

Practical classification of mast cell disease

1

Cutaneous mastocytosis (skin-only disease)



Both can manifest mast cell mediator release symptoms

2

Systemic mastocytosis (SM)

i

Indolent SM

ii

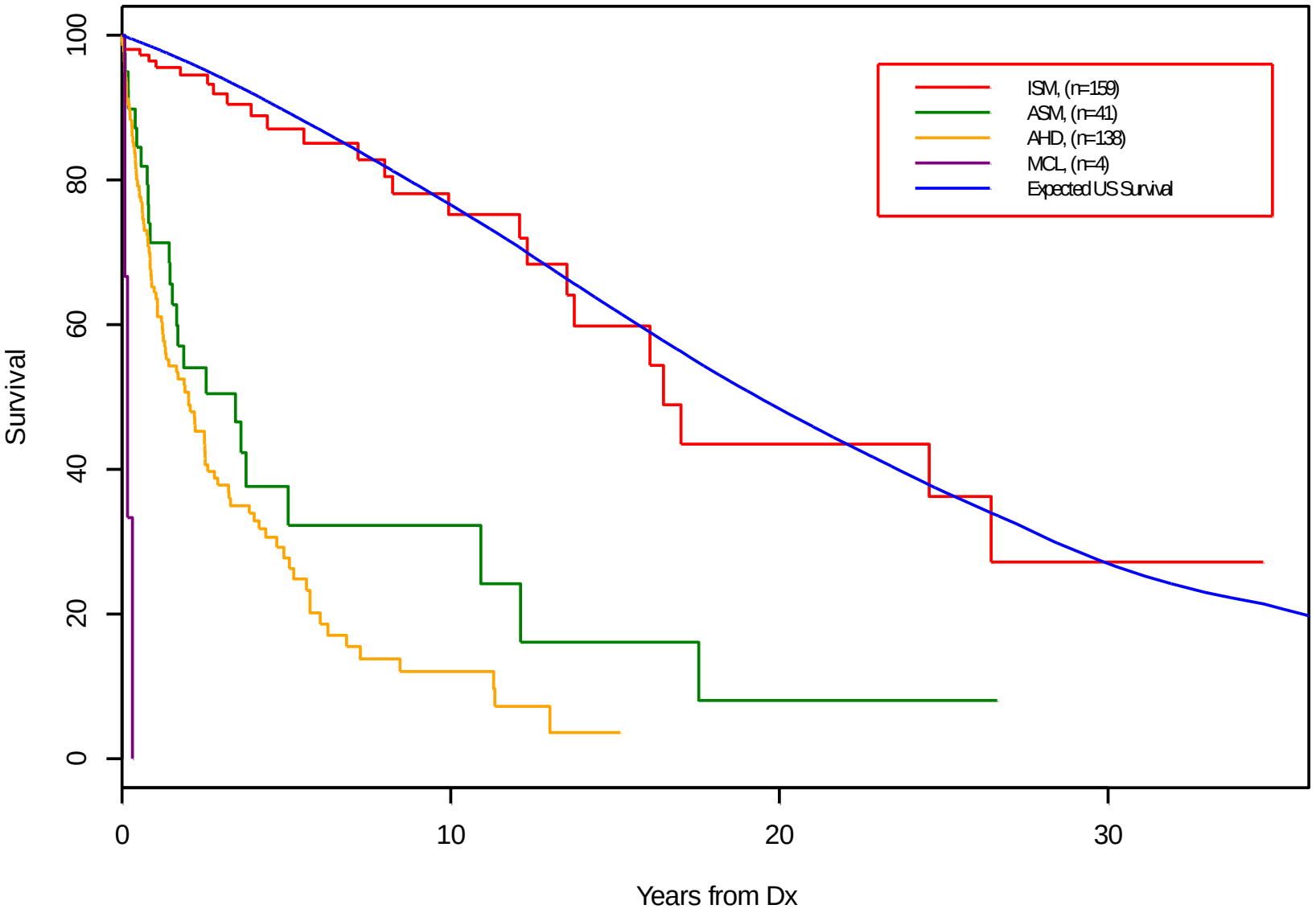
Aggressive SM (cytopenia, bone disease, organomegaly, etc.)

1. SM without associated 2nd myeloid neoplasm
2. SM with associated 2nd myeloid neoplasm
3. Mast cell leukemia

Medicine 1988;67:345

Leukemia Research 2001;25:603

Survival for 342 systemic mastocytosis patients classified by disease type compared with the expected age and gender matched US Population's survival



Blood 2009;113:5727.

Mutation-augmented prognostic scoring system (MAPSS) in 94 patients with advanced mastocytosis

ISM (n=44)
KIT 73%
TET2 7%
No other mutations

ASM (n=25)
KIT 84%
TET2 20%
ASXL1 16%

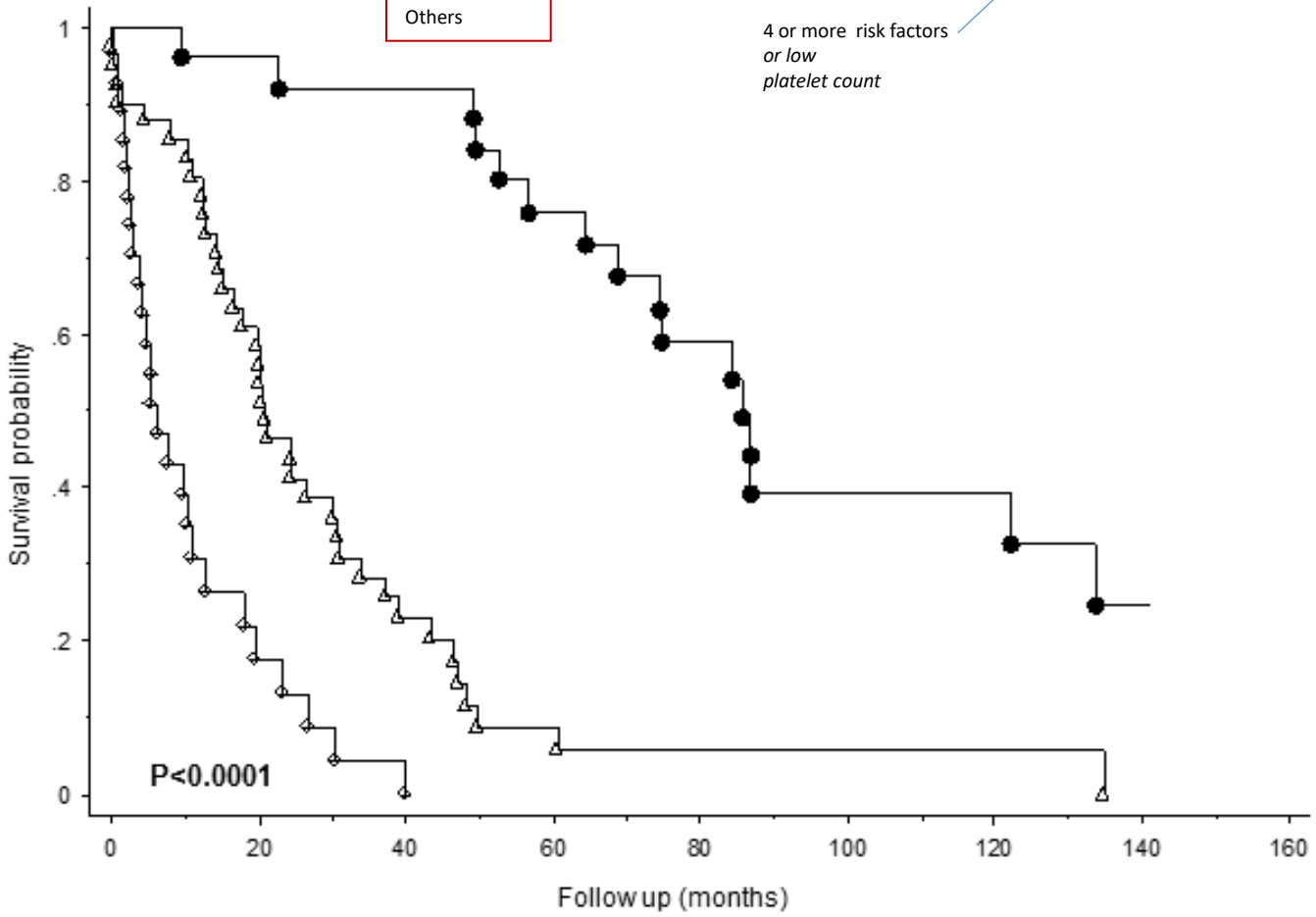
AHN (n=80)
KIT 75%
TET2 45%
ASXL1 26%
CBL 19%
JAK2
DNMT3A
U2AF1
RUNX1
SF3B1
Others

One risk factor *other than platelet count* → ● Low-risk: n=26 (16 events), median OS=86 months

2-3 risk factors *or low platelet count* → △ Intermediate-risk: n=41 (38 events), median OS=21 months

◇ High-risk: n=27 (25 events), median OS=5 months

4 or more risk factors *or low platelet count*



Risk factors:

Platelet count <150
albumin <3.5
age >60
ASXL1/CBL mutated
Hgb <10

AJH 2016;91:888
BJH 2016;175:531

Treatment for Systemic mastocytosis

Indolent

H1 and H2 blockers
Cromolyn
Phototherapy
Topical steroids

If this fails, OK to try IFN-a or cladribine

Aggressive

Cladribine
5 mg/m2 x 5 days;
monthly x 4
(first choice)

Midostaurine
100 mg BID
(second choice)

Avapritinib (BLU-285)
300 mg once-daily
32 treated
OR 72% at 9 months
56% CR/PR
Edema, fatigue, GI toxicity
50% grade ≥3 AEs

Associated with MDS or CMML

Treat as MDS or CMML

Mast cell leukemia

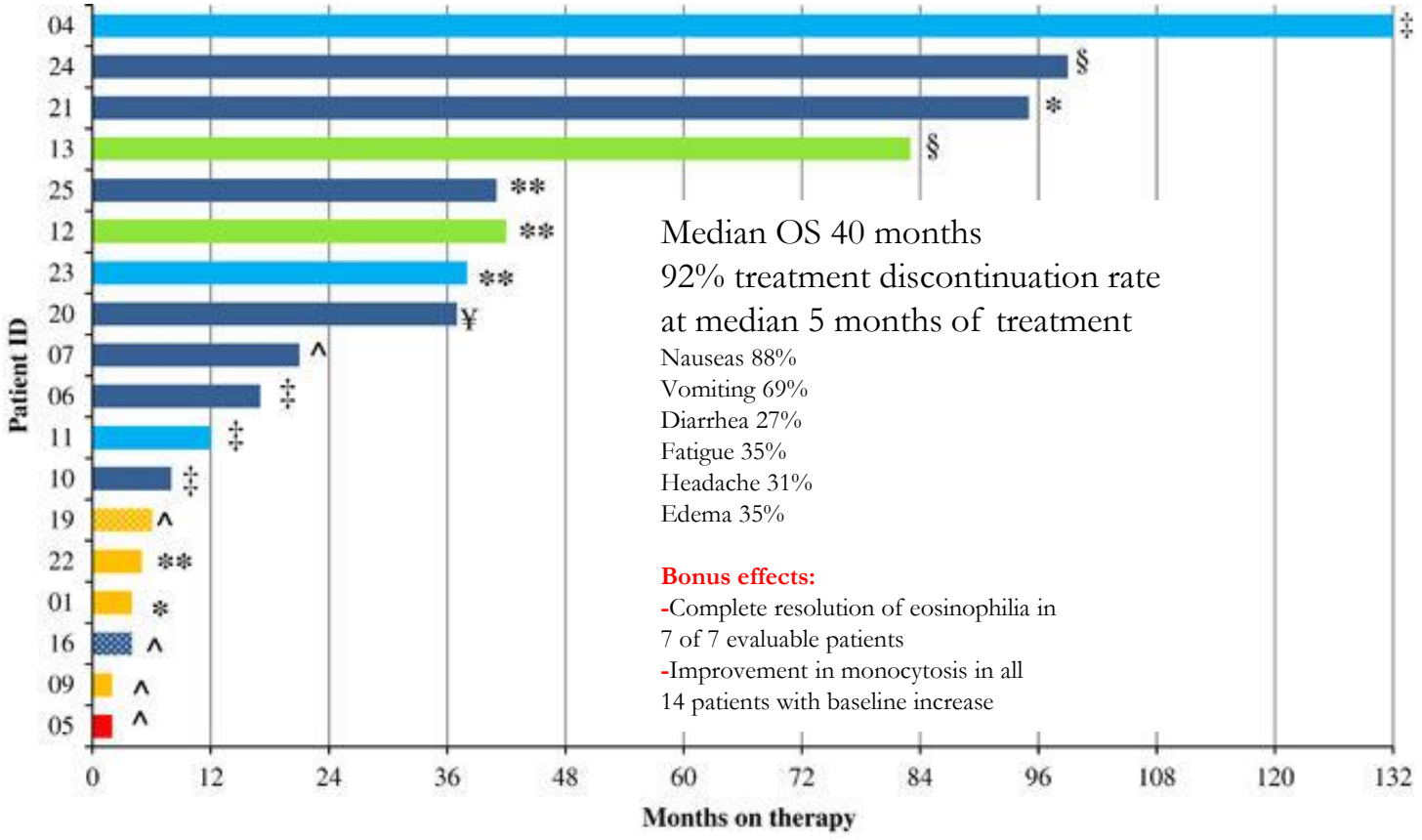
Midostaurine
or
Avapritinib
or
Cladribine
or
AML-like therapy

<u>followed by</u>

Transplant?

J Clin Oncol. 2014 ;32:3264

Phase-2 study of midostaurin 10-year follow-up (N=26; responders = 18 (69%; major response 50%)
SM-AHN = 17 (13 responders); ASM = 3 (1 responder), MCL = 6 (4 responders)



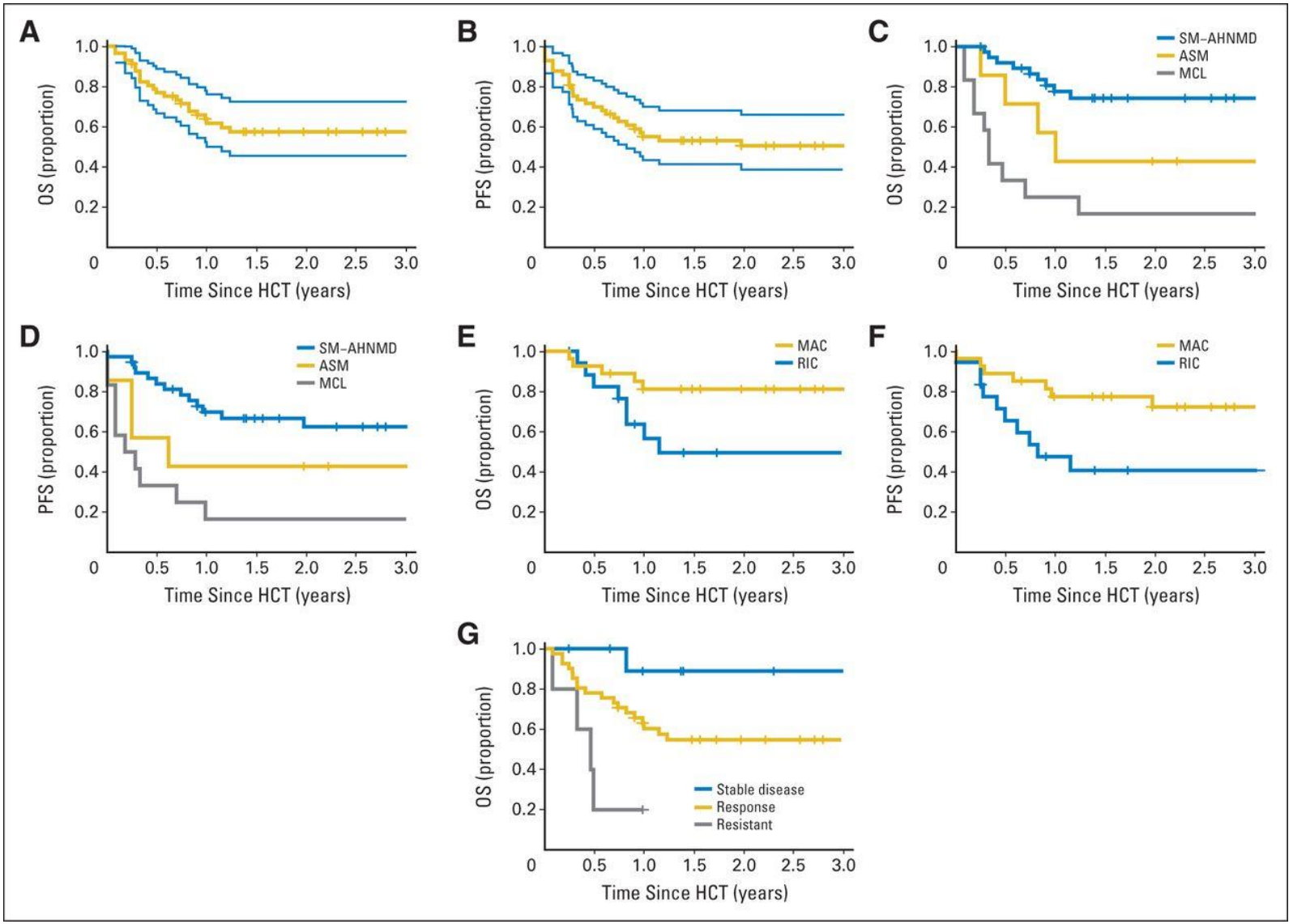
Study status/reason for discontinuation (# of patients)[¶]
§ Continuing treatment (n=2)
* Adverse event: Grade 3 or 4 thrombocytopenia (n=2)
** Serious adverse event: sepsis (n=3), inflammatory mixed neuropathy/myopathy and altered mental status (n=1)
¥ Withdrew consent (n=1)
^ Unsatisfactory therapeutic effect; discontinued per investigator discretion (n=5)
‡ Disease progression (n=4)

Median duration of treatment (months)	
median	19
range	2-132

[¶] Data through 3/1/2017; best response at any time on therapy
Solid bars are *KIT* D816 mutation-positive, two patterned bars are *KIT* D816 mutation-negative

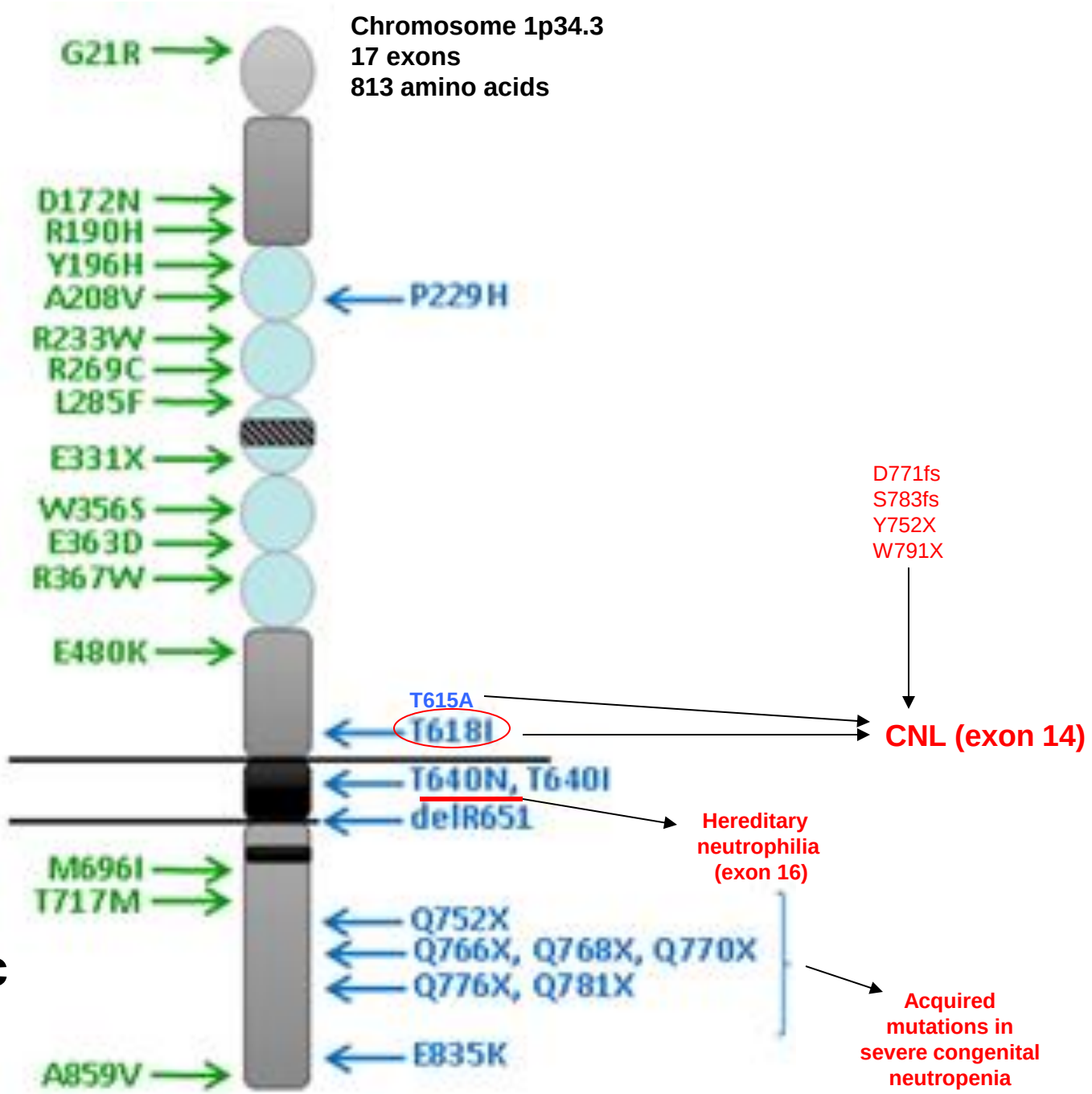
Leukemia 2018

Allogeneic hematopoietic stem-cell transplantation (alloHCT or HCT) outcomes in 57 patients with advanced systemic mastocytosis (SM): 38 SM-AHNMD; 12 MCL and 7 aggressive SM.



JCO 2014;32:3264

CSF3R mutations



Kosmider et al. Leukemia

WHO diagnostic criteria for CNL

1. Leukocytosis ≥ 25 x 10^9/L
- **Neutrophils plus bands ≥80%**
- **Neutrophil precursors < 10%**
- **Myeloblasts rarely observed**
- **No dysgranulopoiesis**

2. Hypercellular bone marrow
- **Neutrophil granulocytes increased**
- **Neutrophil maturation normal**
- **Myeloblasts < 5%**

3. Not meeting WHO criteria for BCR-ABL1+ CML, PMF, PV or ET

4. No PDGFRA/PDGFRB/FGFR1/PCM1-JAK2

5. CSF3RT618I or other activating CSF3R mutation

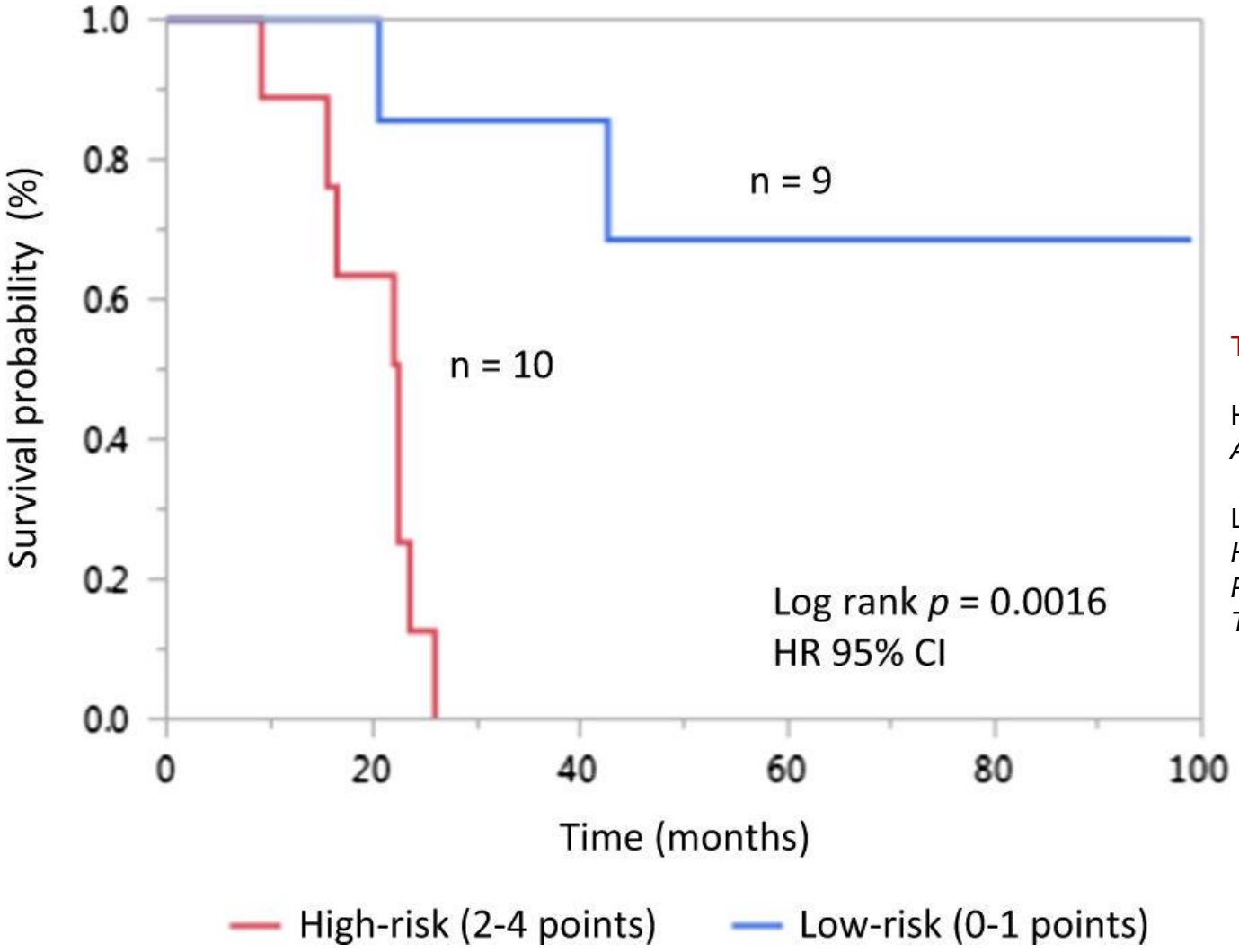
or

no identifiable cause of reactive neutrophilia

WHO diagnostic criteria for aCML

- Leukocytosis with ≥10% precursors
- Dysgranulopoiesis
- Basophils <2%
- Monocytes <10%
- Hypercellular bone marrow with dysgranulopoiesis
- <20% blasts in the blood and bone marrow
- No PDGFRA/PDGFRB/FGFR1/PCM1-JAK2
- Not meeting WHO criteria for
- BCR-ABL1+ CML, PMF, PV or ET

Risk-stratified Kaplan–Meier survival curves for 19 *CSF3R*-mutated CNL patients.



Treatment:

High-risk:
ASCT

Low risk:
Hydroxyurea (first)
Ruxolitinib (second)
Transient response

Risk points: platelet count <160 × 10^9/L (2 points); leukocyte count >60 × 10^9/L (1 point); *ASXL1* mutation (1 point)

CMML

2016 WHO Diagnostic Criteria

- AMC >1 x 10(9) /L and monocytes >10%
- Dysplasia in one or more myeloid lineages

- Not meeting WHO criteria for CML, PV, ET or MF
- No *PDGFRA*/*PDGFRB*/*FGFR1*/*PCM1-JAK2*
- <20% blasts in the blood and BM

In the absence of dysplasia, a diagnosis of CMML can still be made if:
-An acquired clonal cytogenetic or molecular genetic abnormality can be documented. these include *ASXL1, TET2, SRSF2* and *SETBP1* mutations
-Monocytosis has persisted for >3 months
-Other causes of reactive monocytosis have been ruled out

Blood 2016

Differential diagnosis of Monocytosis

Reactive

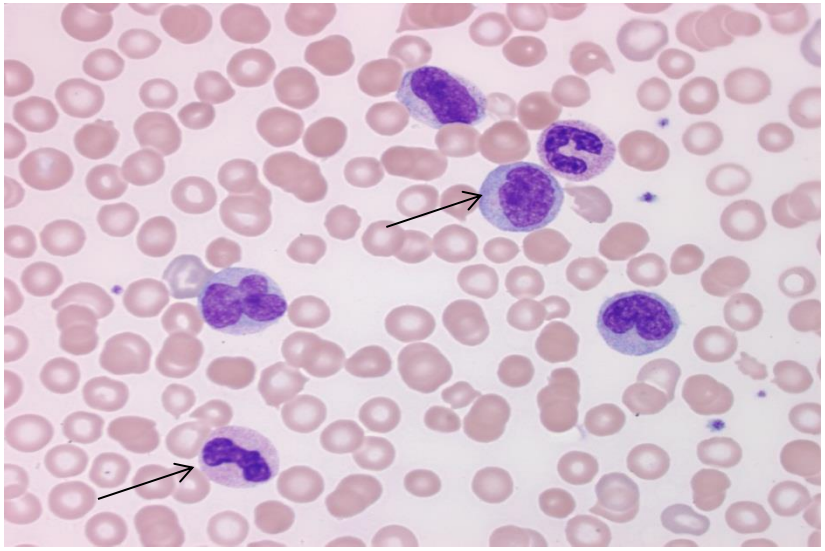
1. Viral infections.
2. Recovering bone marrow.
3. Connective tissue disorders.
4. Sarcoidosis
5. Tuberculosis, Brucellosis, Leishmaniasis.
6. SABE.

Clonal

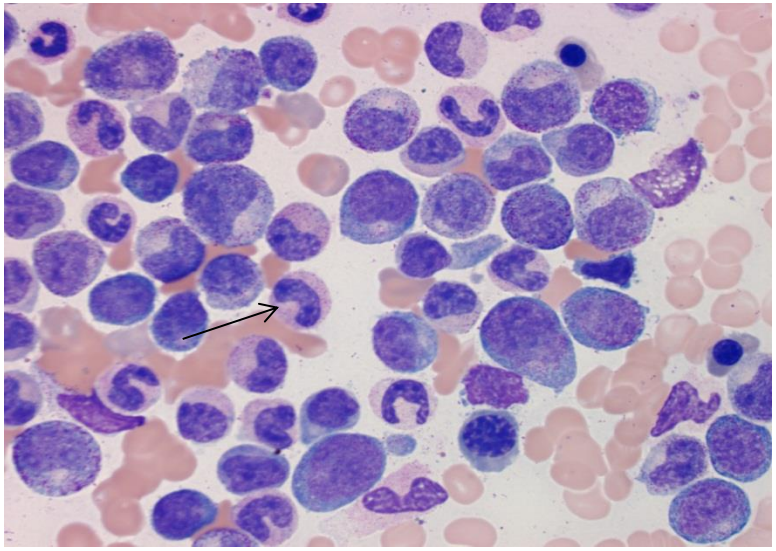
1. CMML
2. JMML
3. AML with monocytic differentiation.
4. MDS/MPN overlap syndromes-unclassifiable.

BJH 2014

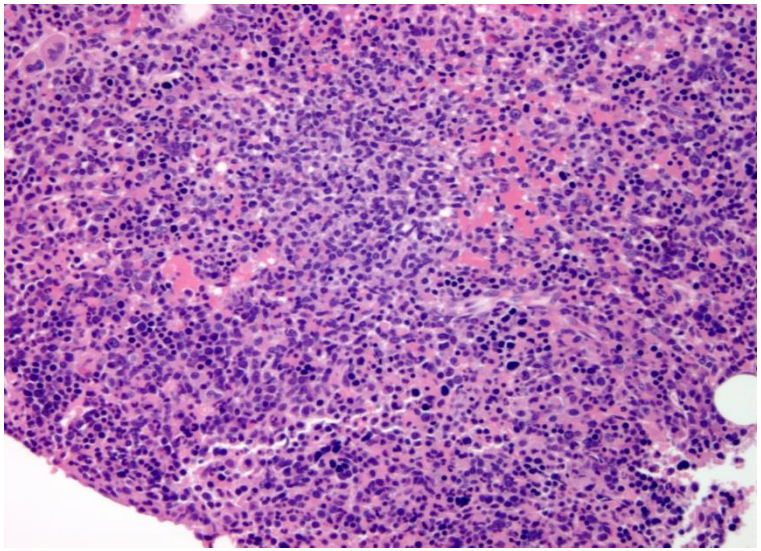
CMML- Peripheral Blood and Bone Marrow Findings



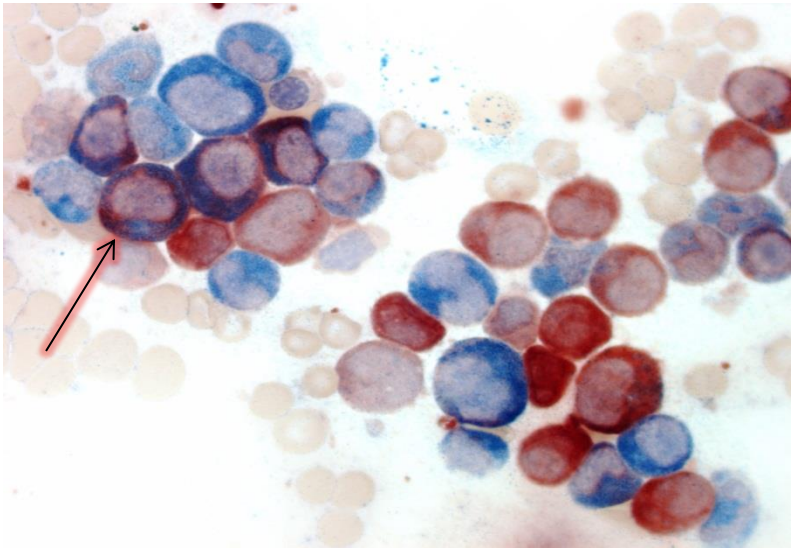
Peripheral Blood Smear



Bone Marrow Aspirate



Core Biopsy



Dual Esterase Stain

WHO CMML Subcategories

CMML-0

- Blasts + promonocytes <2% in PB.
- Blasts + promonocytes <5% in BM.

CMML-1

- Blasts + promonocytes 2-4% in PB.
- Blasts + promonocytes 5-9% in BM

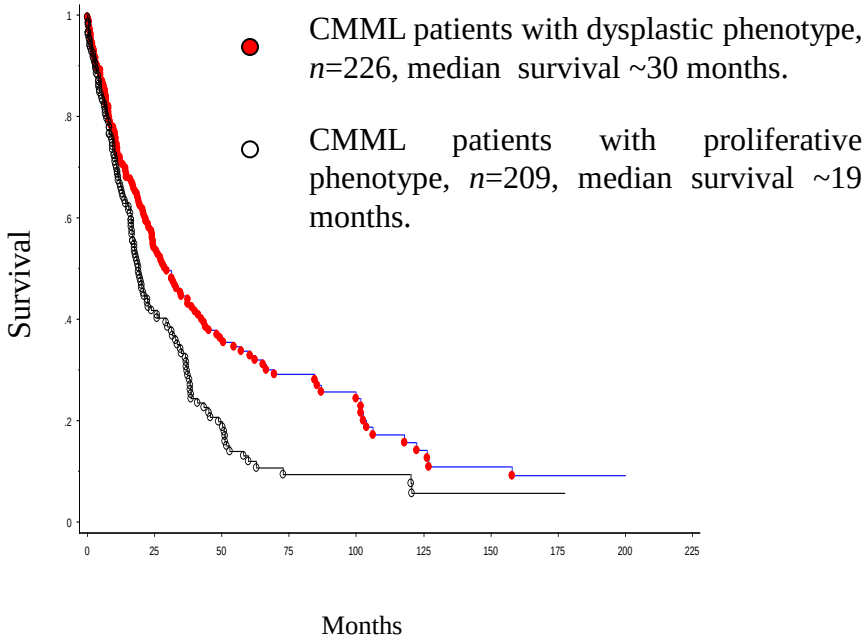
CMML-2

- Blasts + promonocytes 5-19% in PB.
- Blasts + promonocytes 10-19% in BM.
- Presence of Auer rods, irrespective of blast count.

Blood 2016

Proliferative vs Dysplastic CMML

Survival data for 435 patients with WHO defined chronic myelomonocytic leukemia stratified by "Proliferative" versus "Dysplastic" sub-types.



CMML patients with dysplastic phenotype, *n*=226, median survival ~30 months.

CMML patients with proliferative phenotype, *n*=209, median survival ~19 months.

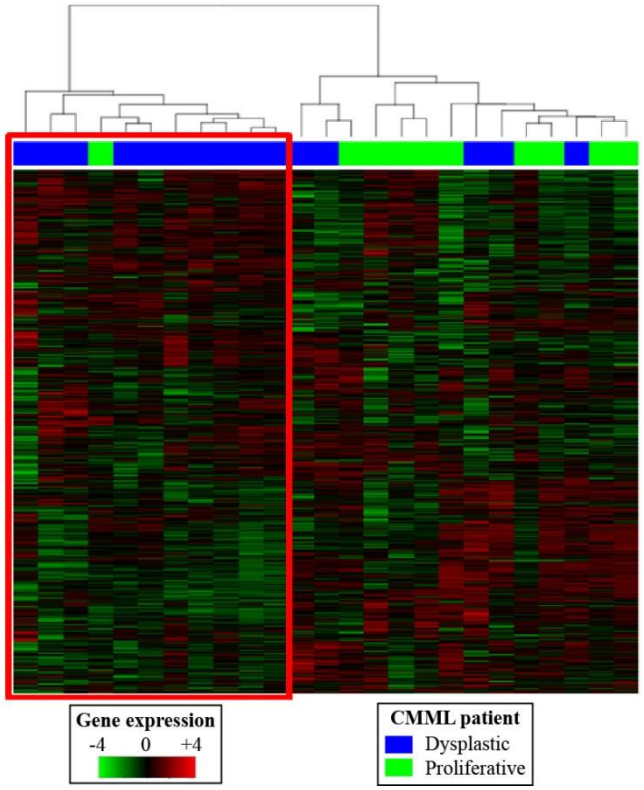


Figure 2: Heat map of an unsupervised differential gene expression profile in peripheral blood CMML samples , demonstrating two predominantly unique clusters, segregating dysplastic (cluster 1) from proliferative (cluster 2) CMML subtypes.

CMML – Genomics

- Epigenetic regulators – *TET2* (~60%), *IDH1, IDH2, DNMT3A*
- Chromatin modeling – *ASXL1* (~40%), *EZH2*
- Spliceosome components – *SRSF2* (~45%), *SF3B1, U2AF1, ZRSR2*
- Transcription factors – *RUNX1* (~15%)
- Signal pathways – *JAK2, KRAS, NRAS, CBL, PTPN11* (*RAS* pathway ~30%)
- Others – *SETBP1* (~15%), *PHF6*, *BCOR*, *Tp53*

> 90% CMML patients have ≥ 1 somatic mutations

Leukemia 2014
B Cancer Journal 2015

Cytogenetic abnormalities in CMML

- Cytogenetic abnormalities seen in 20-40% of cases
- Most common are +8, chromosome 7 abnormalities and 12p deletions

Spanish Cytogenetic Risk Stratification.

- Low: Normal, -Y
- Intermediate: all others
- High: +8, chromosome 7 abnormalities and complex changes

5 year OS- 35%, 26% and 4%.

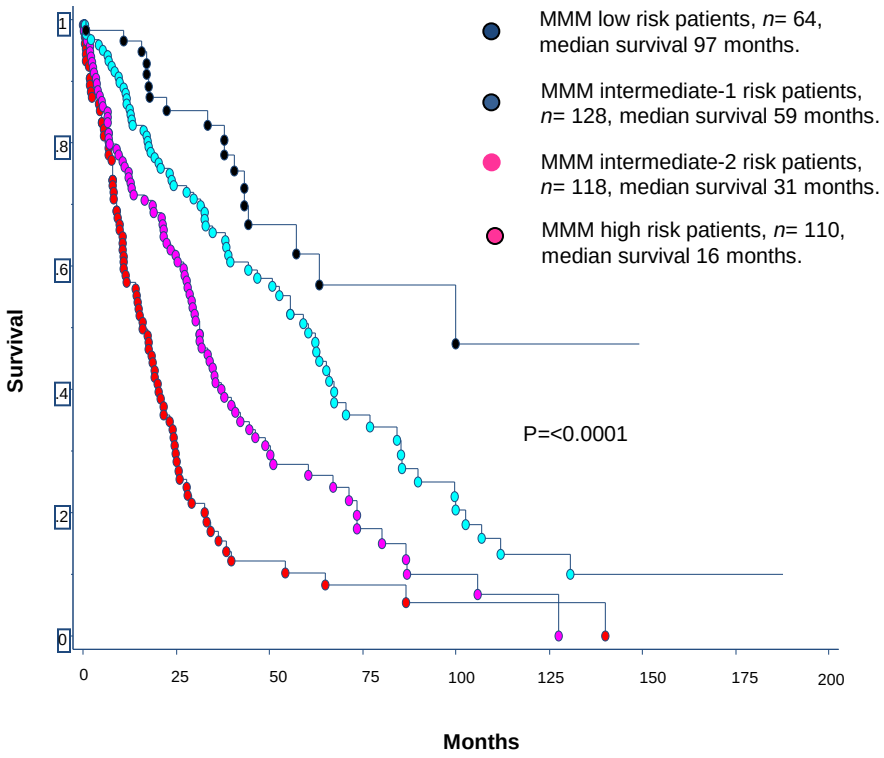
Haematologica 2011
AJH 2013

CMML Prognostic Models

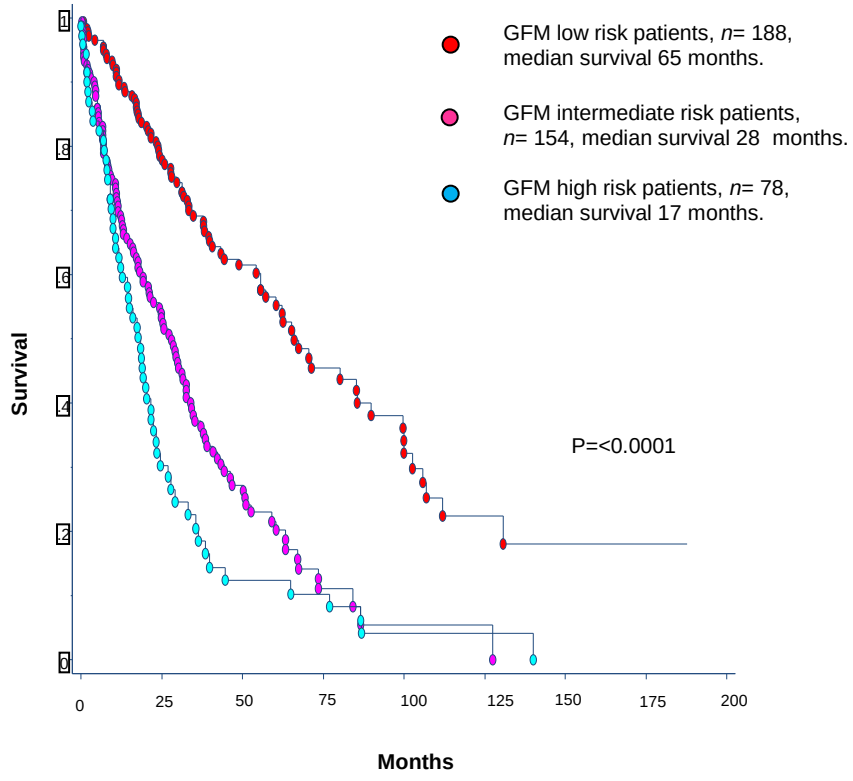
Variables	Mayo Model	Molecular Mayo Model	GFM Model	CPSS-Molecular
HB < 10 gm/dl	+	+	+	Red blood cell transfusion dependance
High WBC			+ (>15)	+ (>13)
AMC >10	+	+		
Platelets < 100	+	+	+	
Circulating IMC	+	+		
BM blasts				+ (>5%)
Age >65			+	
Cytogenetic risk groups				+
Molecular genetics		*ASXL1*	*ASXL1*	*ASXL1/ NRAS/ RUNX1 and SETBP1*

***Blood* 2002; *Blood* 2012; *JCO* 2013; *Leukemia* 2013; *Leukemia* 2014; *Blood* 2016**

Survival data for 420 patients with CMML stratified by the Molecular Mayo Model.



Survival data for 420 patients with CMML stratified by the GFM Model.



Leukemia 2014

CMML Therapeutics

Supportive care

- Transfusions
- Hydroxyurea
- ESA
- Iron chelation therapy

Directed Therapies

- Hypomethylating agents
- Allogeneic SCT
- Clinical trials

Hypomethylating (HMA) Agents in CMML

Study	N	Median Age (years)	Phase	Drug used	Response rates (%).	Median survival (months)
Wijermans 2008	31	71	II	Decitabine	CR-10 PR-16 HI-19	15
Costa 2011	38	70	II	Azacitidine	CR-11 PR- 3 HI- 25	12
Braun 2011	39	71	II	Decitabine	CR-10 PR-20 HI-8	18
Thorpe 2012	10	66	II	Azacitidine	CR-20 HI-40	NR
Ades 2013	76	70	II	Azacitidine	CR-17 PR-1 HI-17	29
Wong 2013	11	65	II	Azacitidine	CR-9 PR-9 HI-9	17
Fianchi 2013	31	69	II	Azacitidine	CR-45 PR-3 HI-6	37

BJH 2014

Role for Allogeneic SCT in CMML

Study	N	Age median (range)	Donor Source	Conditioning regimen	Relapse rate and TRM	Outcome OS & DFS
Kroger 2002	50	44 (19-61)	MRD-43 MUD-7	MAC- 50	RR-28% TRM-52%	5 yr DFS-18% 5 yr OS-21%
Symeonidis 2010	283	50	MRD-160 MUD-85	MAC-152 RIC-87	RR-25% TRM-37%	5 yr DFS-38% 5 yr OS-42%
Eissa 2011	85	51 (21-66)	MRD-38 MUD-47	MAC- 58 RIC- 27	RR-27% TRM-35%	10 yr DFS-40% 10 yr OS-40%
Park 2013	73	53 (27-66)	MRD-41 MUD-32	MAC- 30 RIC- 43	RR-35%	3 yr DFS-29% 3 yr OS-32%

BJH 2014

Novel Agents- Clinical Trials.

- MEK inhibitors.
- Hedgehog pathway inhibitors.
- GM-CSF monoclonal antibody (KB003).
- Neddylation inhibitors.
- MAP kinase inhibitor.
- P38/Tie-2 inhibitor.
- Aminopeptidase inhibitors.