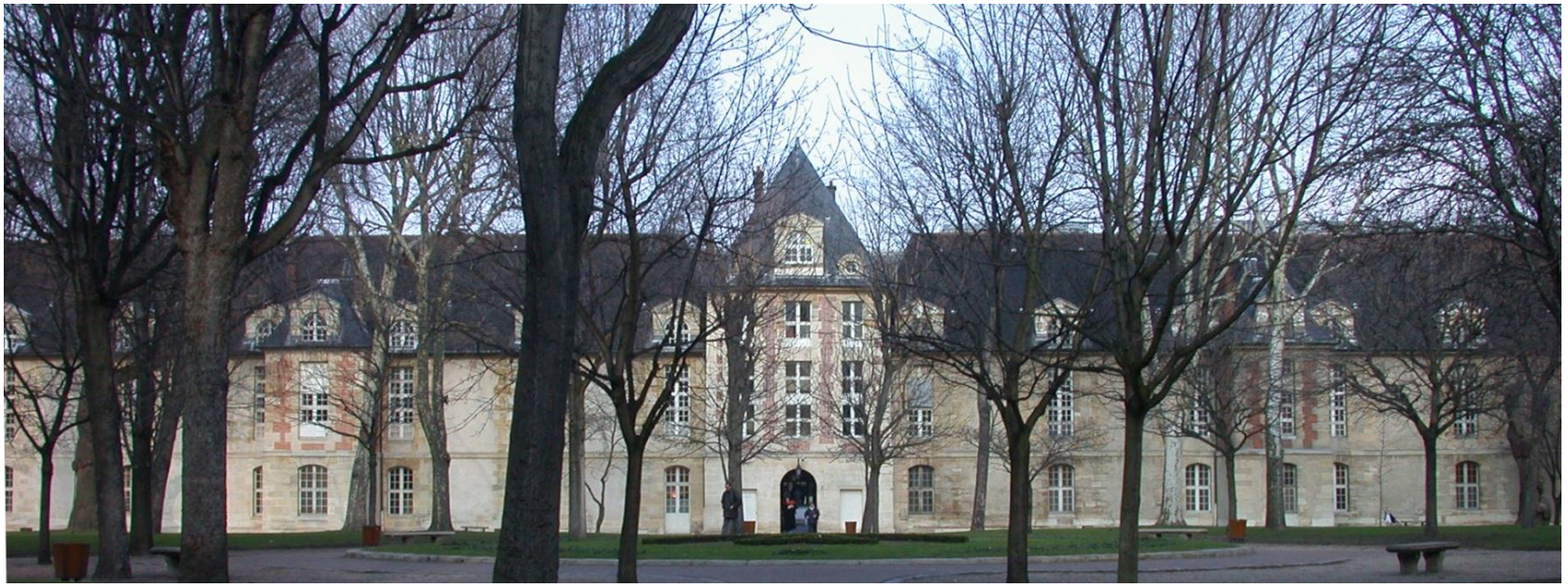
Chronic Myelomonocytic Leukemias



Raphaël Itzykson, Hôpital Saint-Louis, Paris

MDS, Chaos and Order, Meldola, Oct 26th 2018

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

université PARIS DIDEROT

Inserm

Conflicts of Interest

- Research Funding: Janssen, Novartis, Oncoethix (now Merck)
- Honoraria: Sanofi, BMS, Celgene
- Consulting: Novartis, Otsuka Pharma, Jazz Pharmaceuticals, Karyopharm

MDS/MPN in adults

Criterion	CMML-0	CMML-1	CMML-2	aCML	CNL	MDS/MPN-U	RARS-T
Monocytes (10^9/L)	> 1 *(>10%)*			<10%	< 1		
Neutrophils					≥ 80%		
IMC		<10%		>10%	<10%		
WBC (x 10^9/L)				> 13	≥ 25	> 13*	
Platelets (10^9/L)						> 450*	> 450
Basophils				<2%	<1%		
Peripheral Blasts	<2%	3-5%	5-19%	<20%	<1%		<1%
BM Blasts	<5%	5-10%	10-19%	<20%	< 5%		< 5%
RS >15%	No			No			Yes
Dysplasia	One or+			DysG	No	Yes	
t(9;22) / *BCR-ABL1*	No			No	No	No	No
PDGFRA/B	No			No	No	No	No

Incidence: 1/100 000

Arber, *Blood* 2016

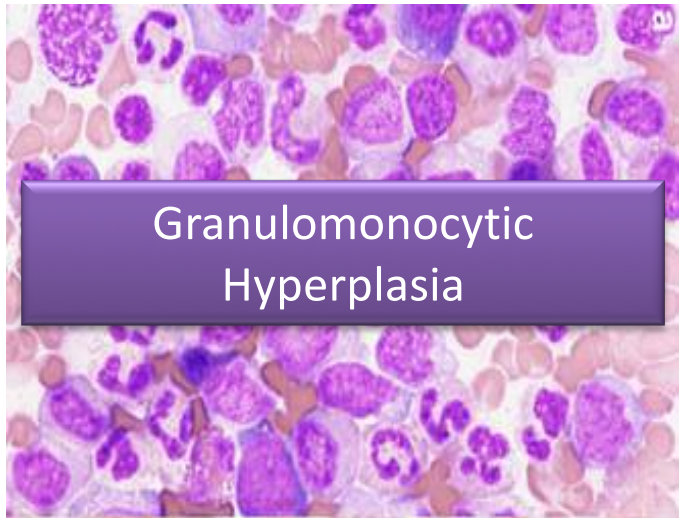
Clinical presentation of CMML

Myeloproliferation

Hyperleukocytosis

Monocytosis

Tumor symptoms



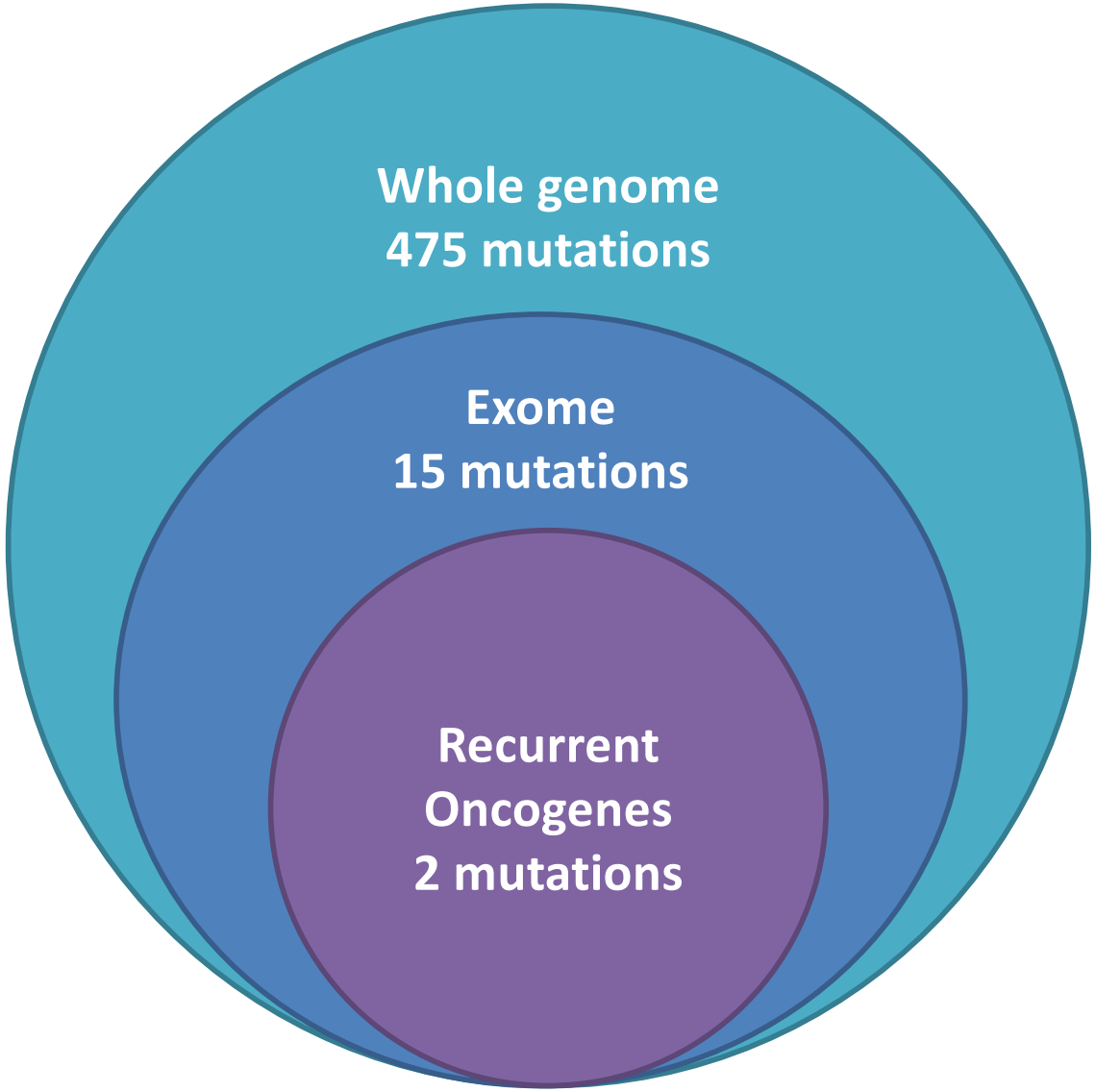
Dysplasia

Anemia

Thrombocytopenia

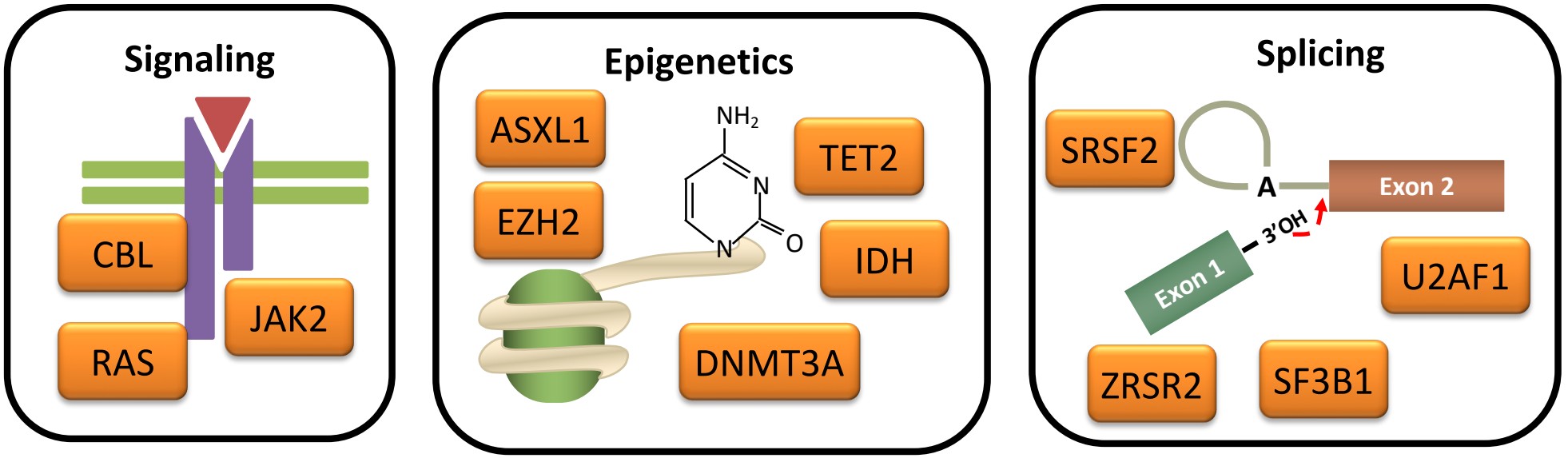
Myelodysplasia

Somatic mutations in CMML



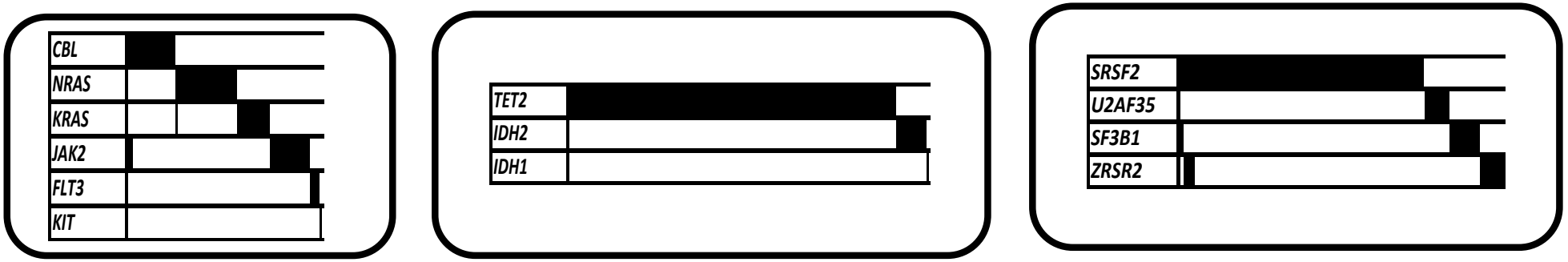
Nat Commun. 2016;7:10767. *J Clin Oncol*. 2013;31(19):2428-36.

Three families of recurrent mutations in CMML



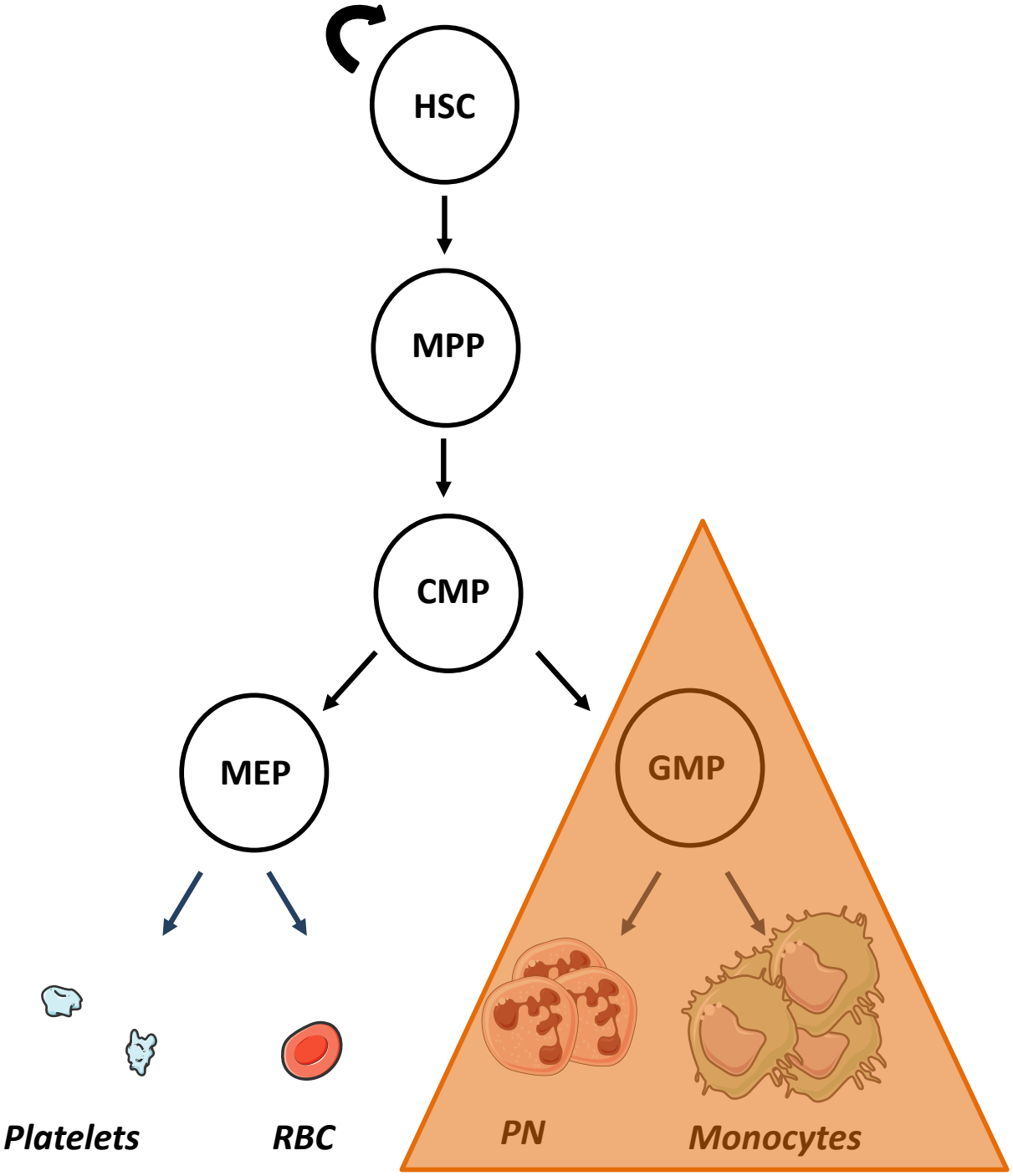
~60% ~90% ~75%

At least one of those in 95% of patients
None is specific of CMML



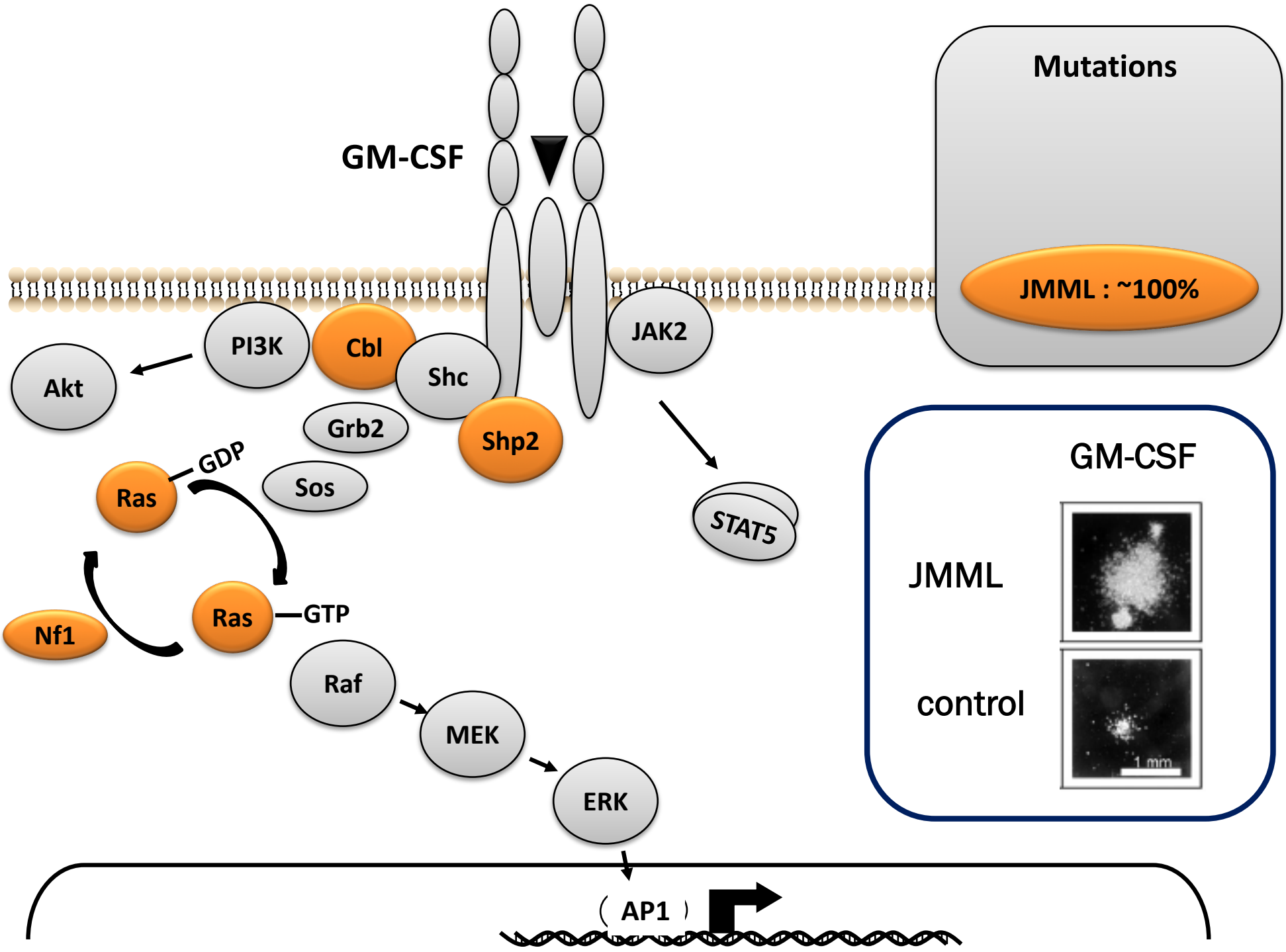
J Clin Oncol. 2013;31(19):2428-36.

Two mechanisms for the granulomonocytic hyperplasia in CMML

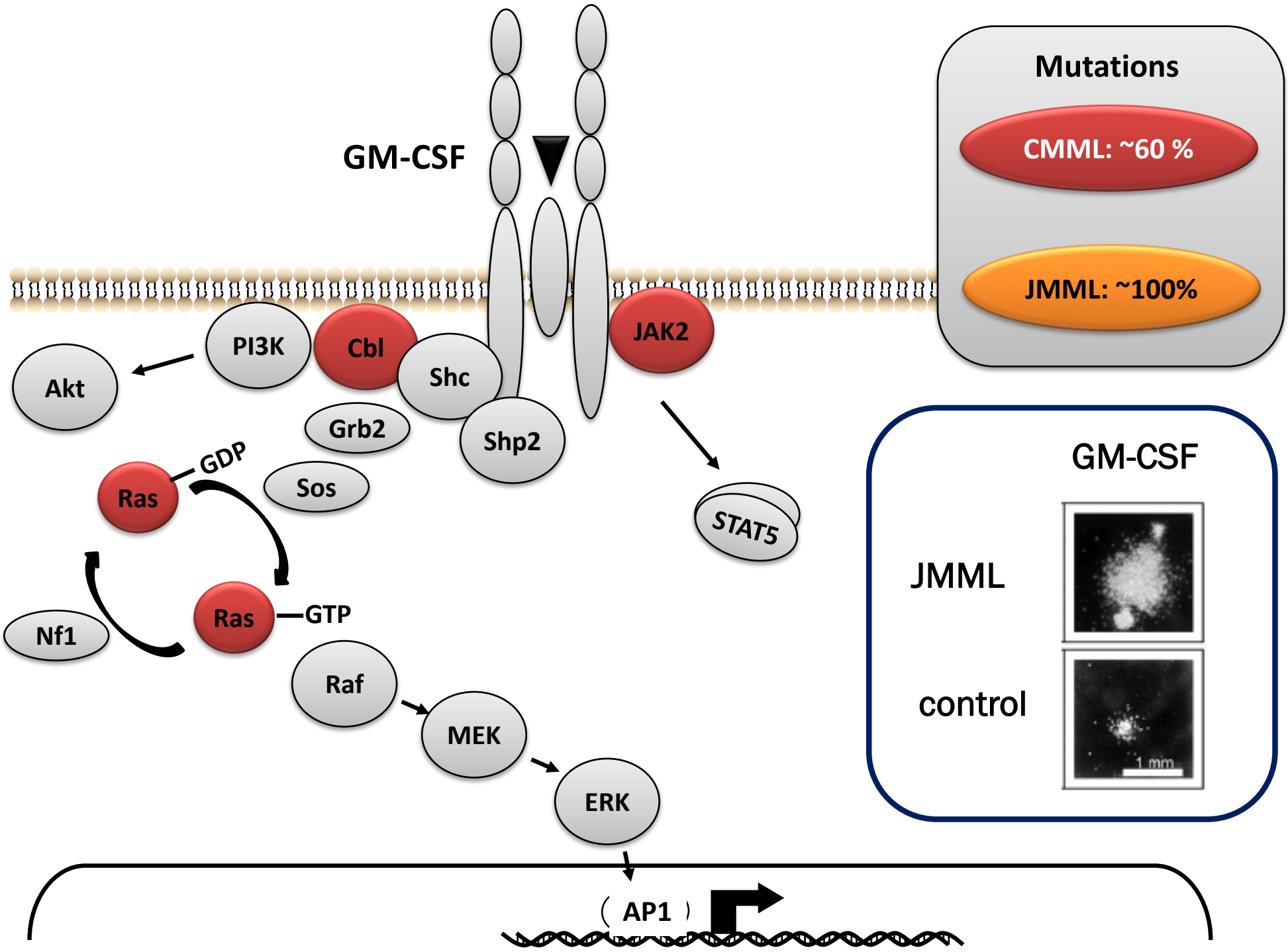


GM-CSF Hypersensitivity?

GM-CSF hypersensitivity in MDS/MPN

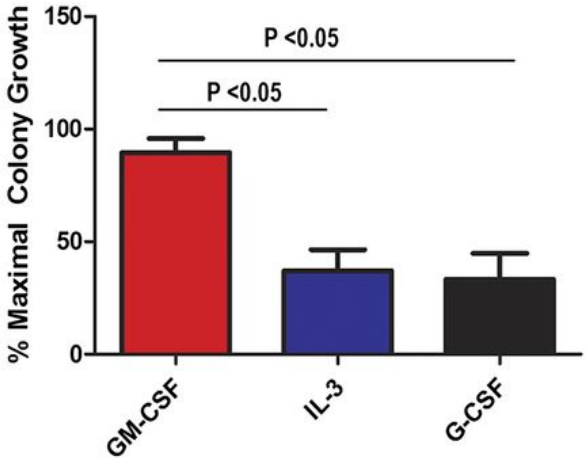


GM-CSF hypersensitivity in MDS/MPN

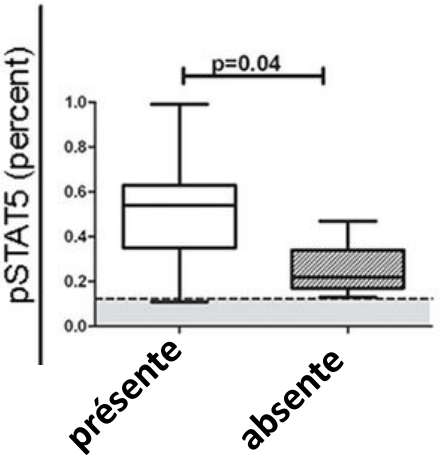


GM-CSF hypersensitivity in MDS/MPN

restricted to GM-CSF

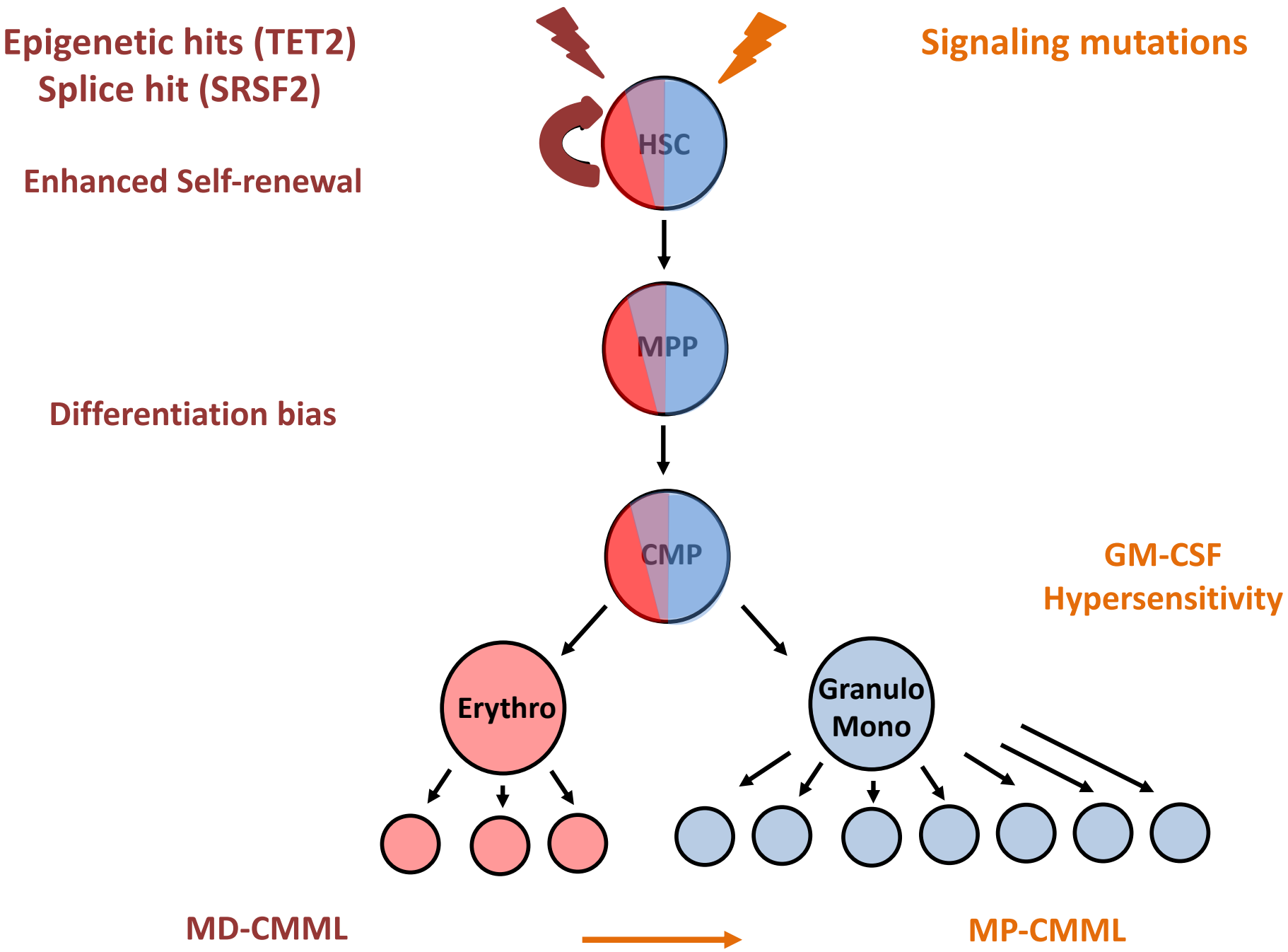


restricted to CMML with Signaling mutation (*RAS*, *CBL*, *JAK2*)



Blood. 2013;121(25):5068-77.

A model for the pathogenesis of CMML



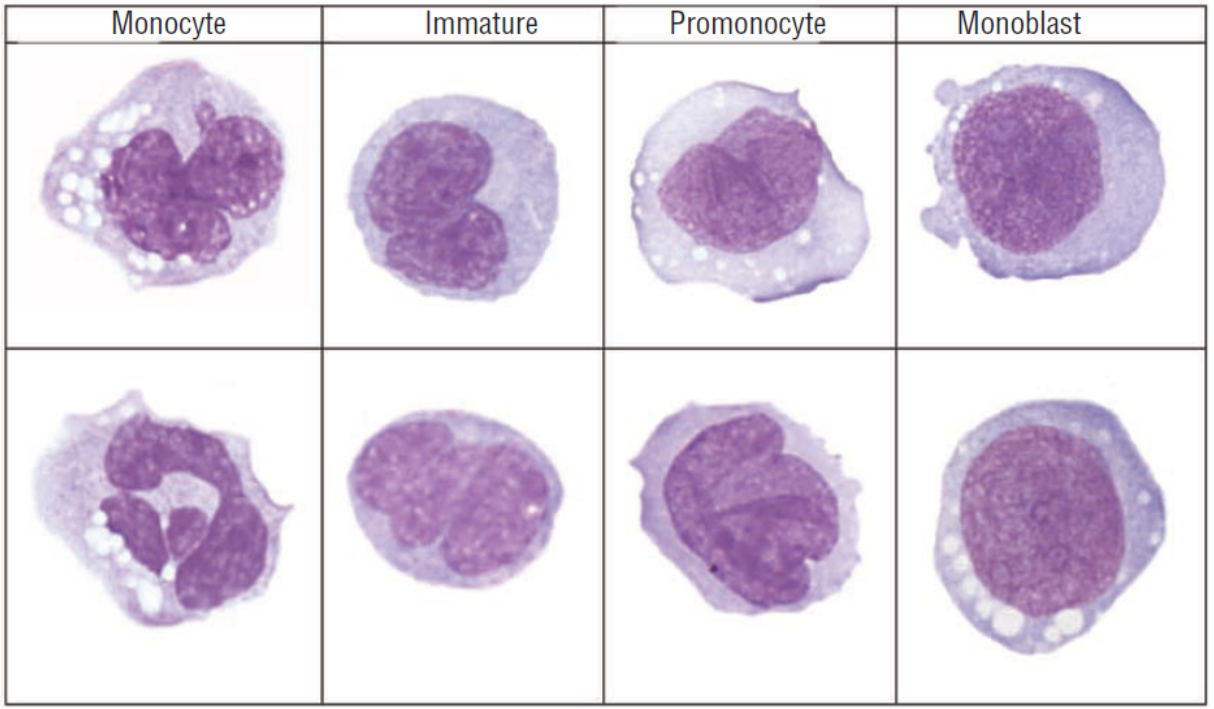
WHO-2016 criteria for CMML

1. Persistent PB monocytosis (≥1 x10^9/L and ≥ 10% of WBC)
   - No impact of BM monocyte %
2. Not meeting criteria for BCR-ABL11 CML, PMF, PV, or ET
3. If eosinophilia: No evidence of PDGFRA, PDGFRB, or FGFR1 rearrangement or PCM1-JAK2
4. <20% myeloblasts or monoblasts in PB or BM
   - Including promonocytes
5. Evidence of dysplasia in one or more lineages
   - If lacking: acquired, clonal cytogenetic **or genetic** abnormality
6. or persistent monocytosis > 3 months, with exclusion of all other causes

- CMML-0: <2% PB blasts and <5% BM blasts
- CMML-1: 2-4% PB blasts and 5-9% BM blasts
- CMML-2: 5–19% PB blasts and 10–19% BM blasts

Arber, *Blood* 2016

Promonocytes should be counted as blasts in CMML



	Nuclear shape	Chromatin	Cytoplasm	Comments
Monoblast	Round/oval	Delicate / lace-like Nucleolus prominent	Basophilic Rare azurophilic, Granules	Large: 20-30 µm
Promonocyte	Convoluted / indented	Delicate / lace-like Nucleolus prominent	Variably basophilic Variable azurophilic Granules	Except for nuclear shape, very similar to monoblast
Immature monocyte	Convoluted / indented	More condensed Rare nucleolus	Less basophilic than promonocyte or blast, but more basophilic than mature monocyte	Resemble monocytes but less mature and smaller
Monocyte	Lobulated/ indented	Condensed No visible nucleolus	Gray Occasional azurophilic granules. Occasional vacuole	Large : 20-25 µm

Goasguen *Haematologica* 2009

CMML Cytogenetics

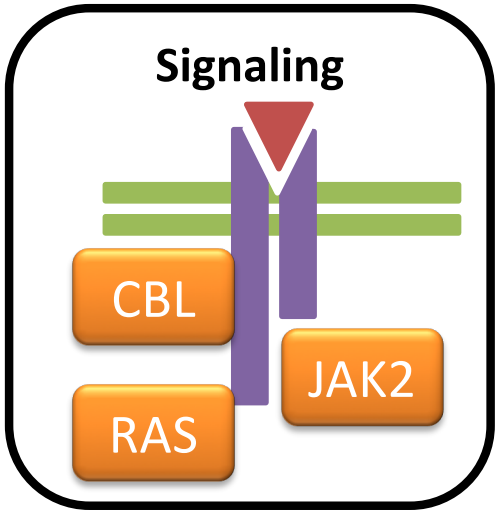
- Normal in 60-70% cases
- No specific alteration: +8, -Y, -7/7q-, 20q-, +21, der(3q)
- Prognosis of trisomy 8 debated
- Two CMML-specific classifications

CPSS	Definition	Freq	Median OS
high	+8, chr.7, cplex	12%	11 months
int	autre	9%	18 months
low	NK, -Y	79%	37 months

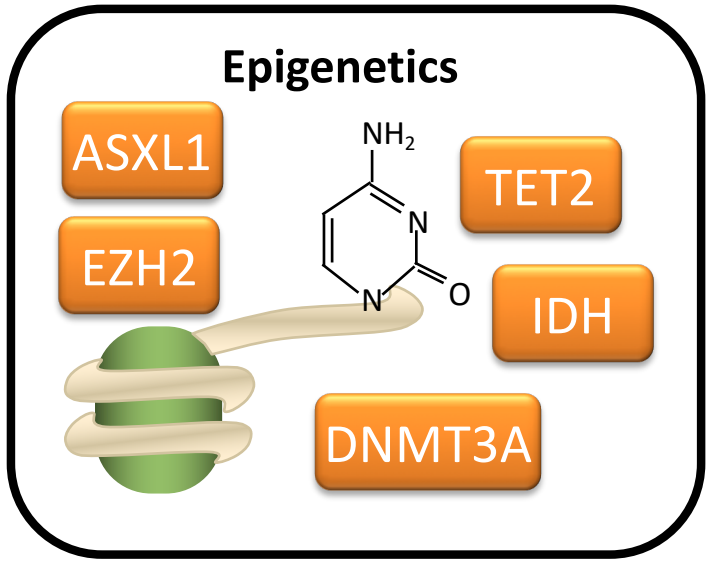
Mayo	Definition	Freq	Median OS
high	cplex, monoso.	3%	3 months
int	autre	19%	20 months
low	NK, -Y, der(3q)	78%	41 months

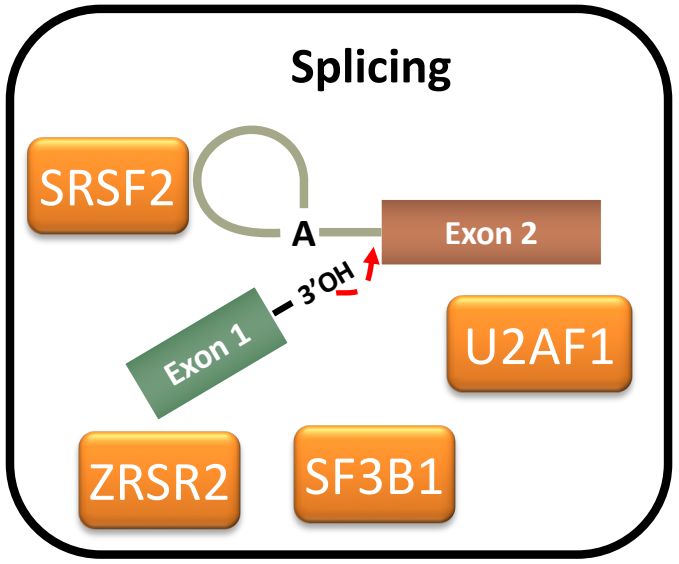
Such *Haematologica* 2011, Wassie *Am J Hematol* 2014, Tang *Am J Hematol* 2014

Molecular biology as diagnostic tool?



- No single specific mutation
- Preferential combo: *TET2/SRSF2*
- CHIP genes:
  - *TET2, DNMT3A, ASXL1*
  - *One mutation*
  - *Low VAF (<20%)*

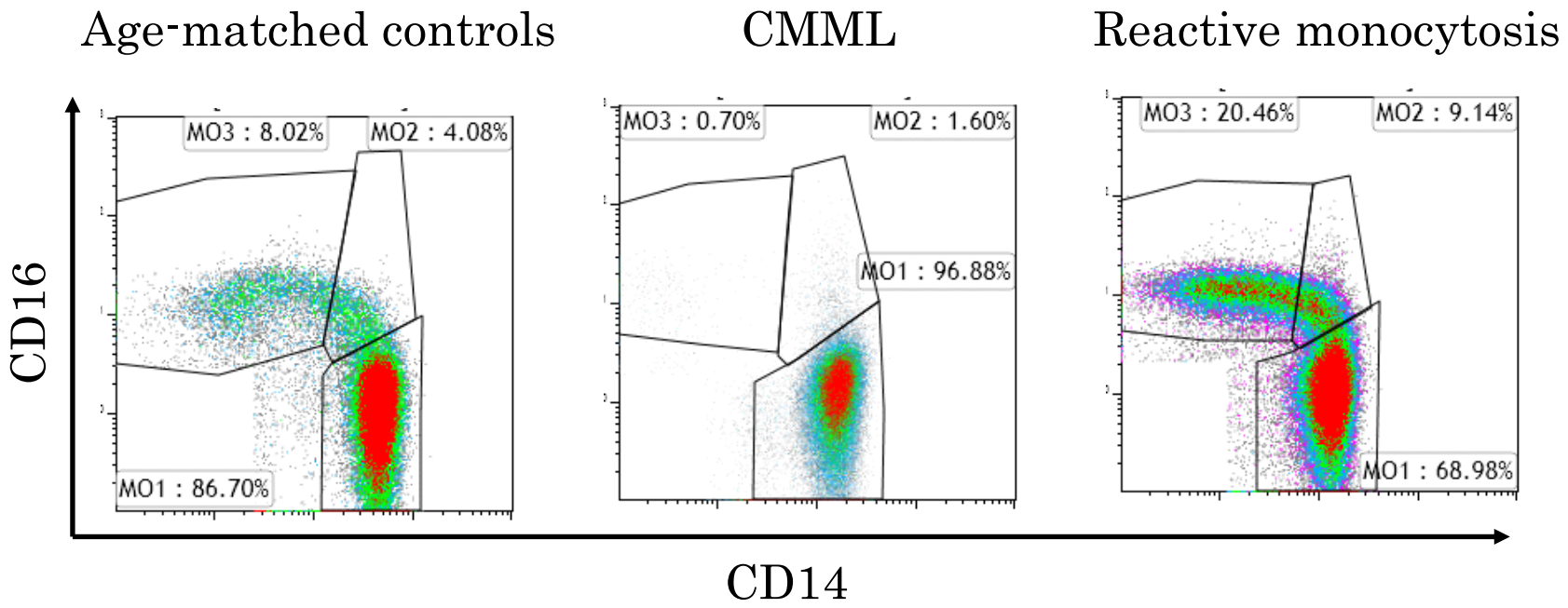




Itzykson *JCO* 2013, Busque *Nat Genet* 2011, Genovese *NEJM* 2014, Jaiswal *NEJM* 2014

Flow cytometry as diagnostic tool

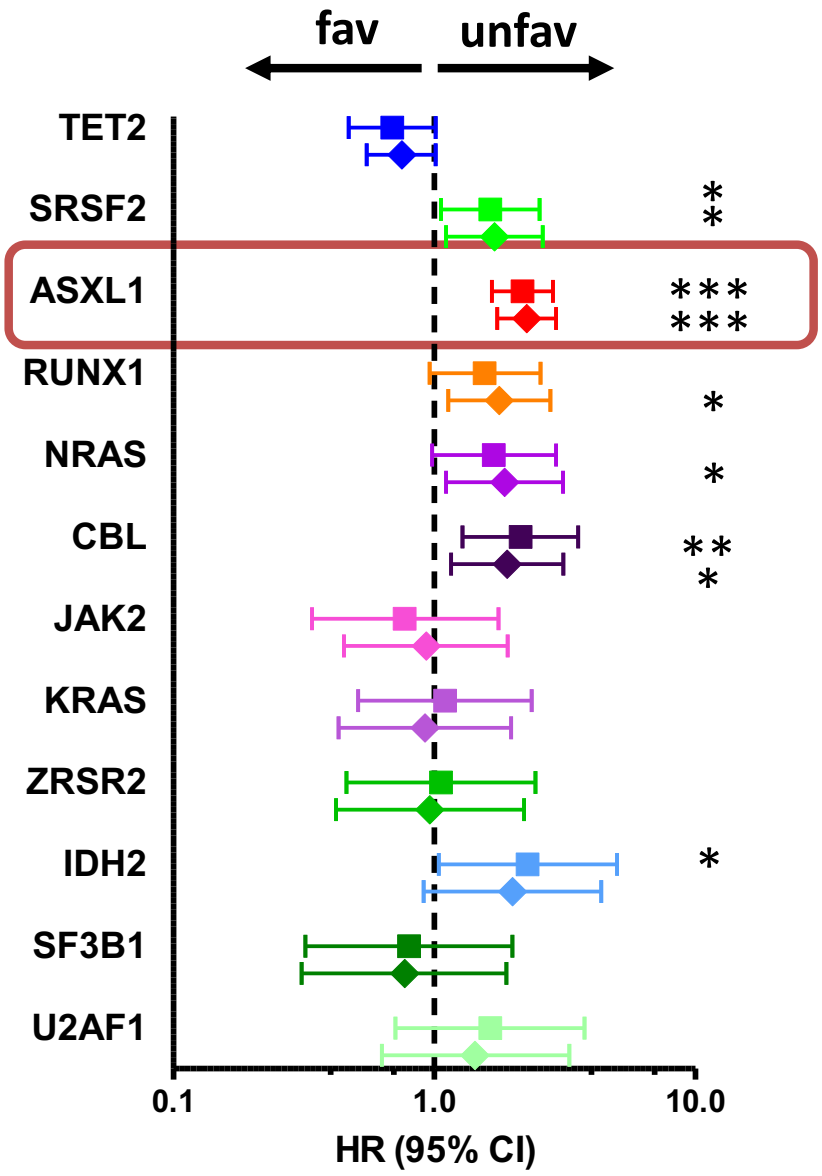
Accumulation of 'classical' monocytes (MO1) is a key feature of CMML

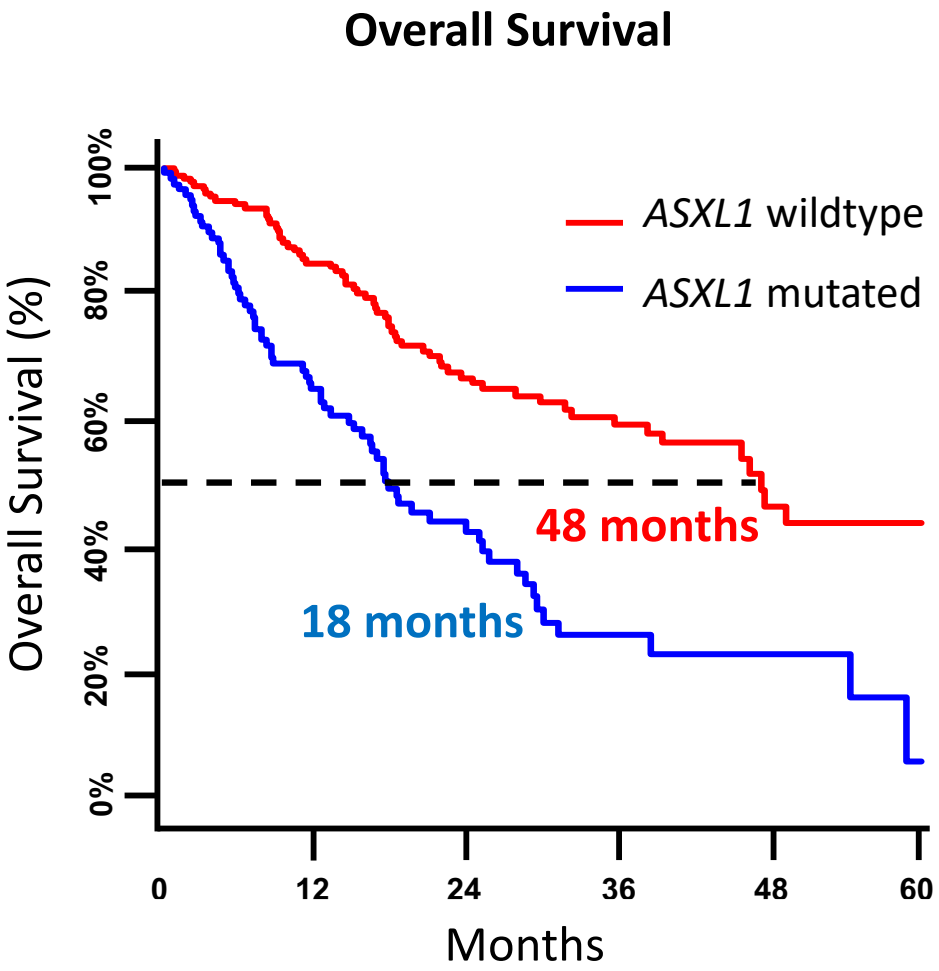


Groupe Francophone des Myélodysplasies

Selimoglu-Buet *et al.* Blood 2015

Prognostic Impact of Gene Mutations





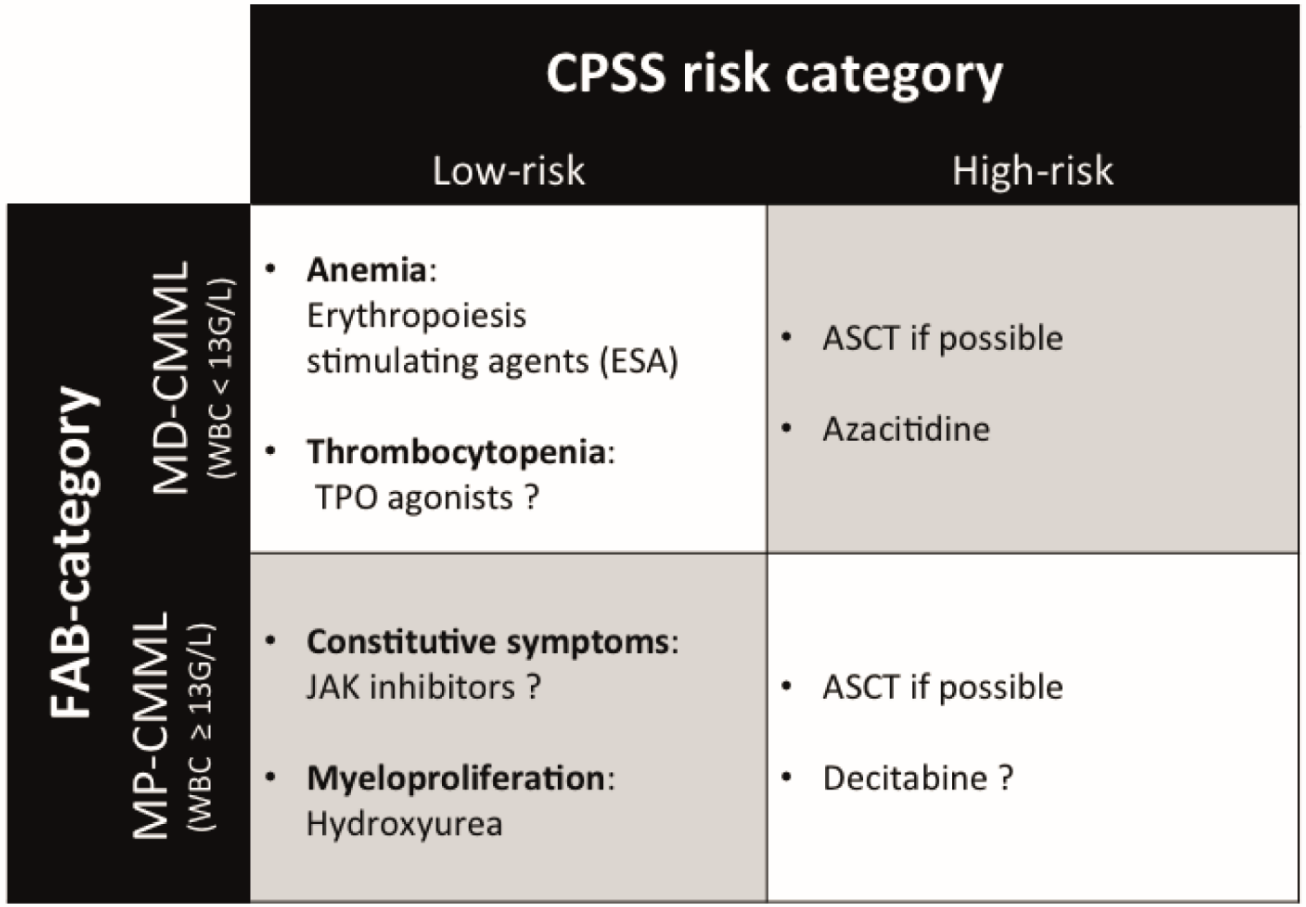
Groupe Francophone des Myélodysplasies

Itzykson, *JCO* 2013

‘Next-generation’ Prognostic scores in CMML

Score	CPSS	GFM	Mayo	CPPS-mol
Clinical Features	Blasts **WBC** **RBC-TD** Cytogenetics	Age **WBC** **Hb** Platelets	Monocytes IMC **Hb** Platelets	Blasts **WBC** **RBC-TD** Cytogenetics
Molecular Features	No	***ASXL1***	No	***ASXL1*** *NRAS* *RUNX1* *SETBP1*
Risk groups	4	3	3	4
mOS (mths)	5 - 72	14-60	10-32	17 - 70
Validation	**Yes**	**Yes**	**Yes**	**Yes**
Reference	Such *Blood* 2012	Itzykson *JCO* 2013	Patnaik *Leukemia* 2013	Elena *Blood* 2016

Management of CMML



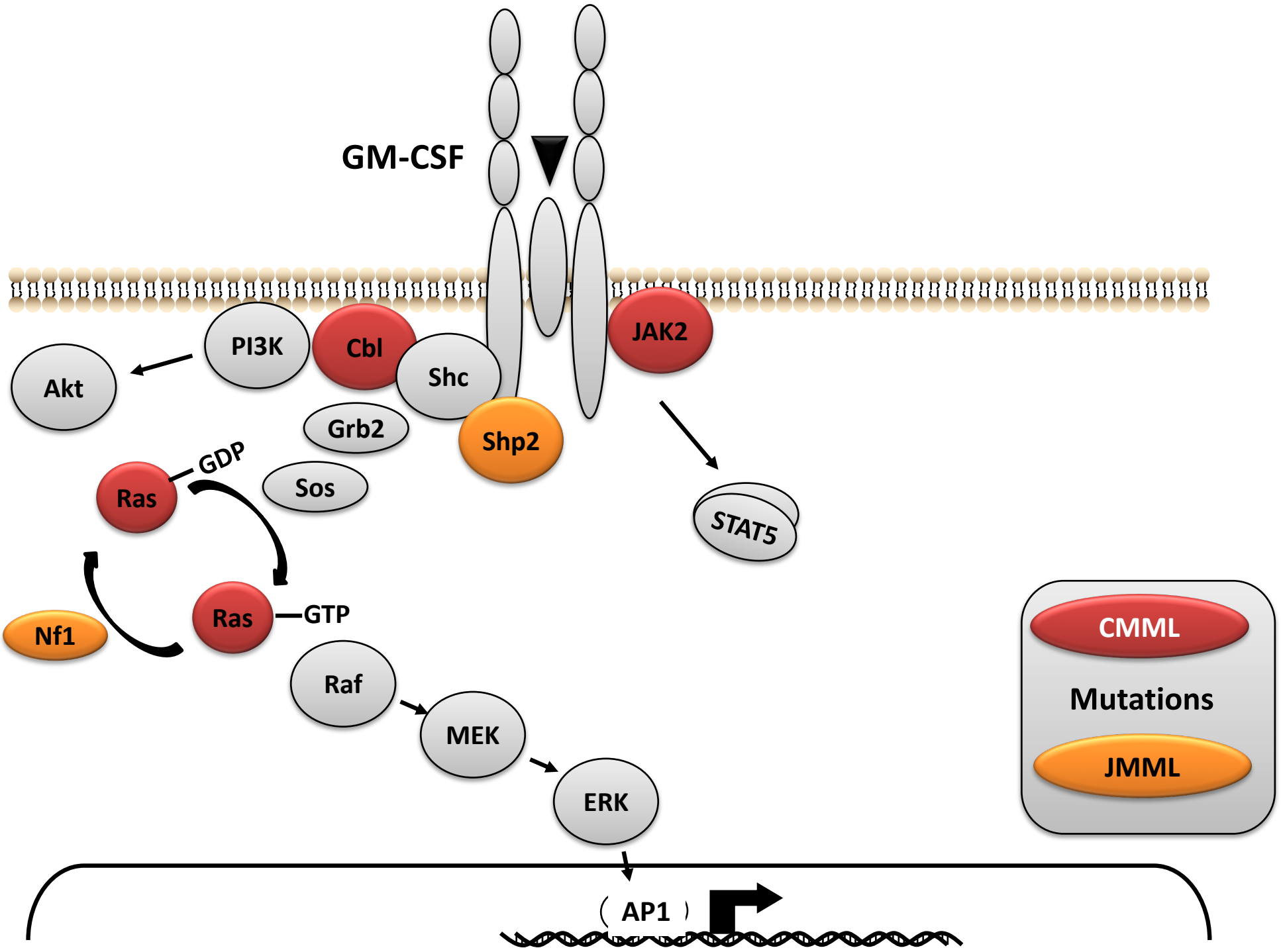
Eltrombopag in CMML with thrombocytopenia

- Prospective multicentric GFM Phase II trial
- Interim analysis n=19
- Lower-risk CMML-0 with platelets < 50 000/mm3
- **IWG 2006 Response rate: 63%**
- **Median response duration: 8 mois**
- **1-Year Cumulative Incidence of transformation to AML: 19%**
  - Historical control: 10%
- *RUNX1* mutations do not impair response achievement

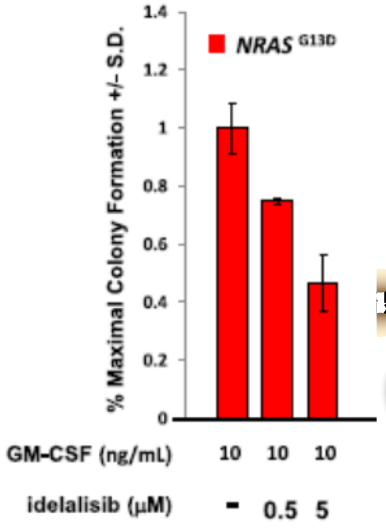
Itzykson et al ASH 2017

Groupe Francophone des Myélodysplasies

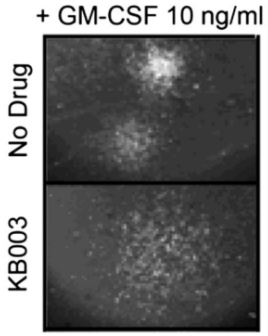
Targeting proliferative CMML



Targeting proliferative CMML



GM-CSF



PI3K

Cbl

Shc

Grb2

Shp2

JAK2

STAT5

Ras — GDP

Sos

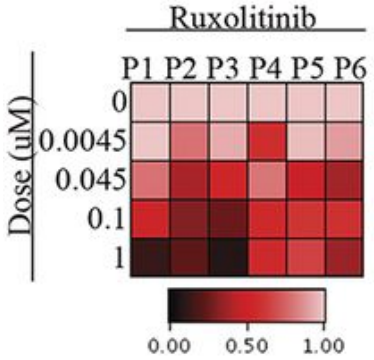
Ras — GTP

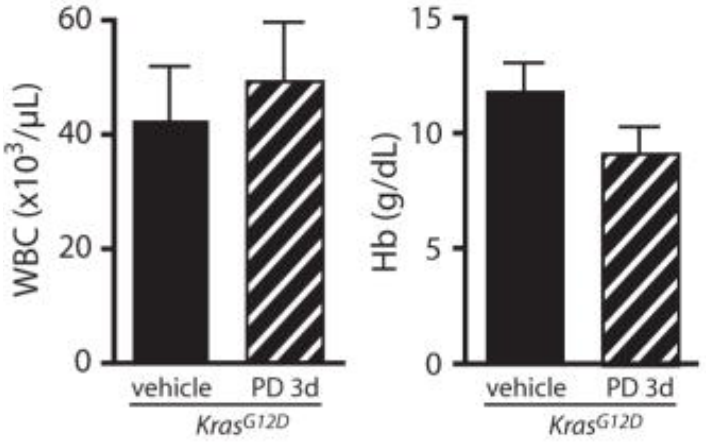
Nf1

Raf

MEK

ERK





Targets

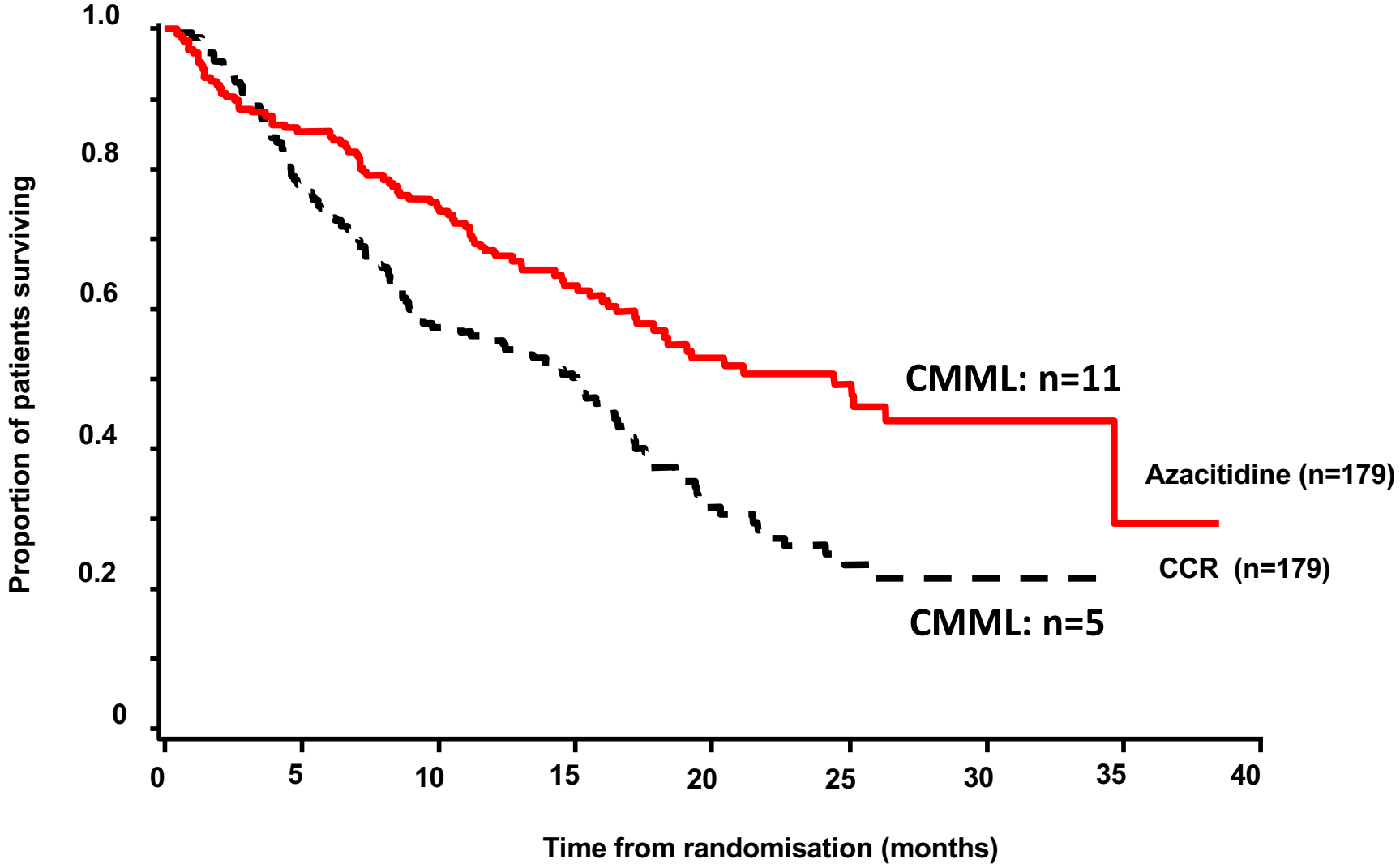
Lyubynska *Science Transl Med* 2012, Padron *Blood* 2013, Goodwin, *Blood* 2014, Kong, *J Clin Invest* 2014

Ruxolitinib in CMML

- US Phase 1/2 trial
- Few hematological responses captured by IWG 2006
- Spleen and general symptoms improvements
- Prolonged survival compared to historical control?

Padron et al ASH 2017

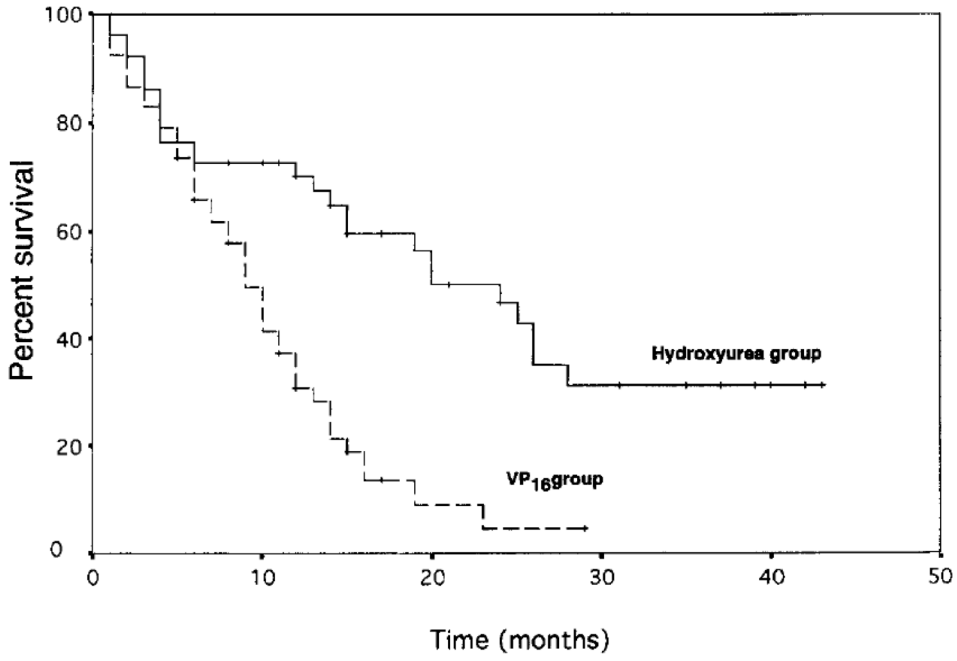
AZA is licensed in CMML-2 with WBC < 12 G/L



Lancet Oncol 2009;10:223–32

Hydroxyurea (HY) in CMML

- HY versus VP16 in ‘advanced’ MP-CMML (N=105)
- Overall Response Rate: 60% (CR: 20%)



Wattel *Blood* 1996

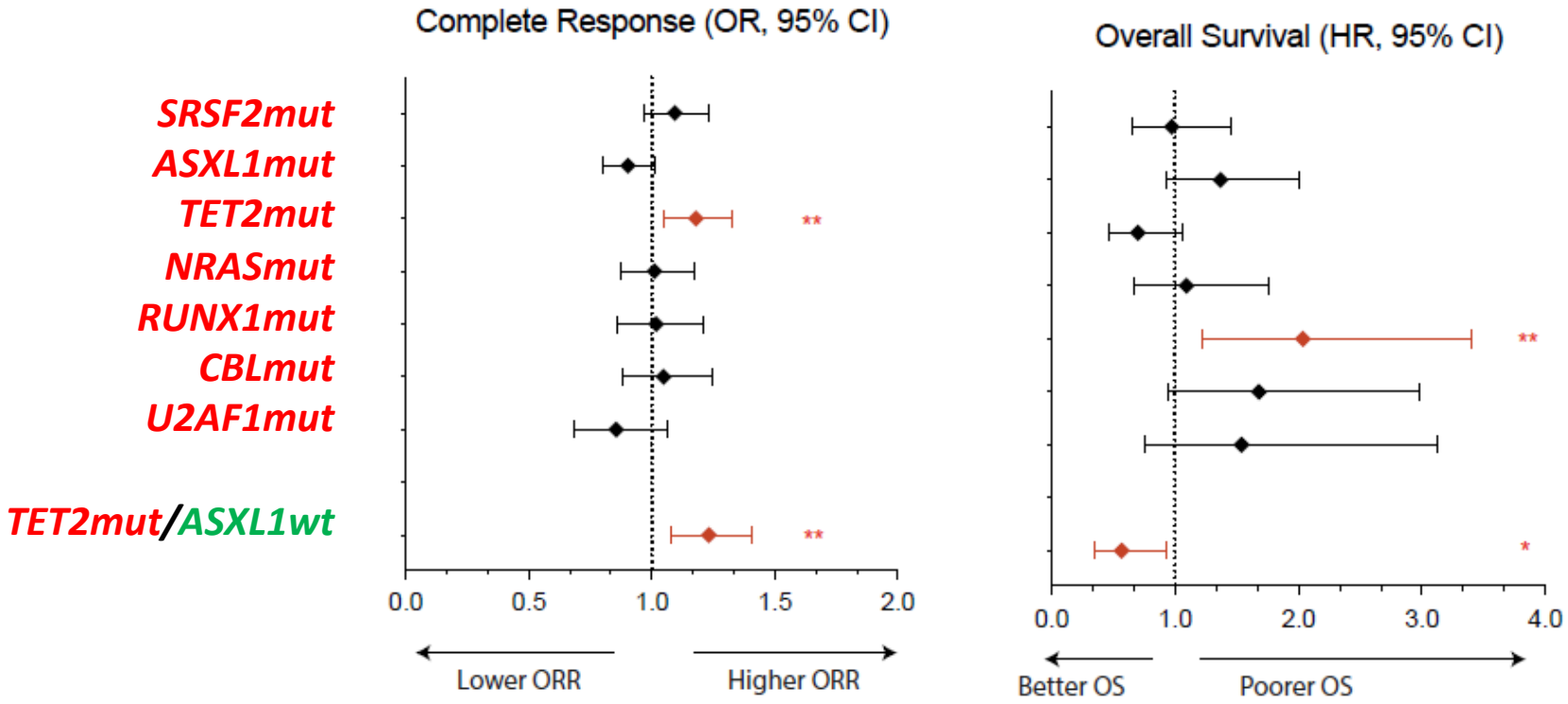
Hypomethylating agents in CMML

- « meta-analysis » of 17 studies
- **Overall Response Rate: 50%**
- **Complete Response Rate: 25%**
- **Regression of myeloproliferative features (poorly captured)**
- **MP-CMML retains adverse prognosis**
- **No difference between azacitidine and decitabine**
  - PSM models

Alfonso, *Am J Hematol* 2017 ; Duchmann, unpublished

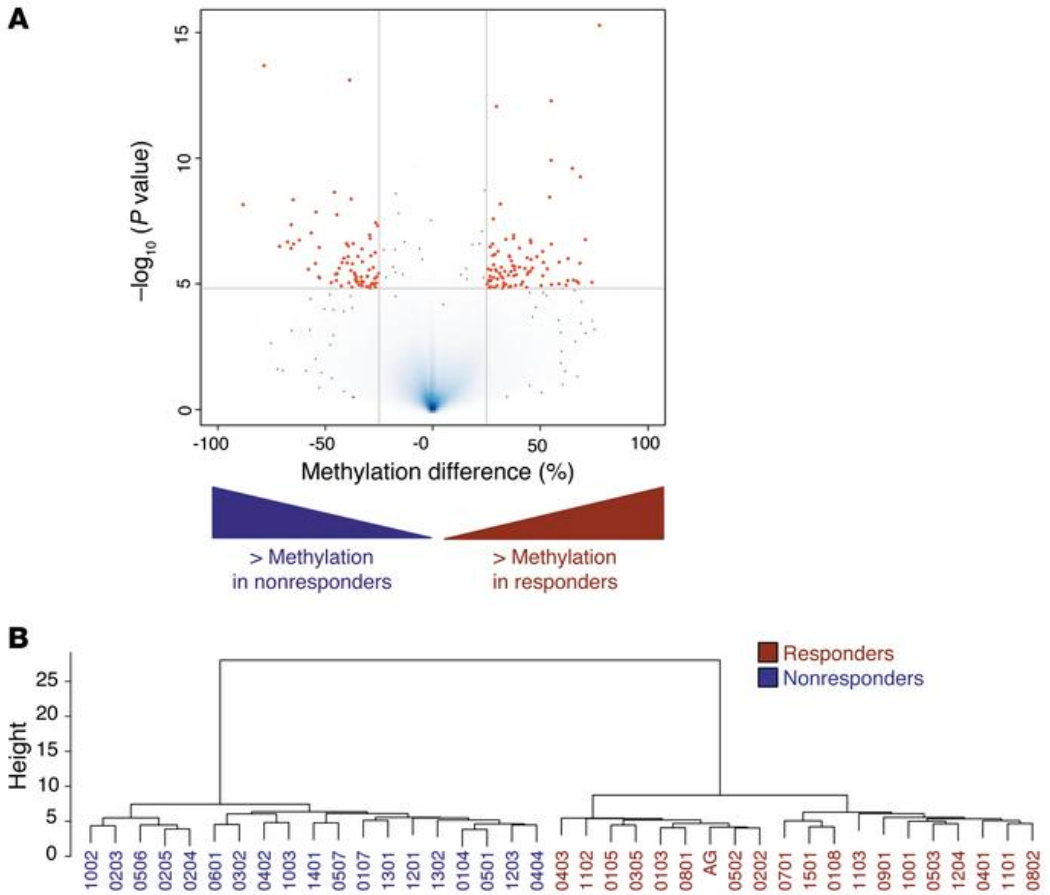
Molecular biomarkers for HMA - CMML

N=174, retrospective



Duchmann *Ebiomedicine* 2018

Specific molecular signatures predict decitabine response in chronic myelomonocytic leukemia



Meldi *J Clin Invest* 2015

CMML: DACOTA Trial

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

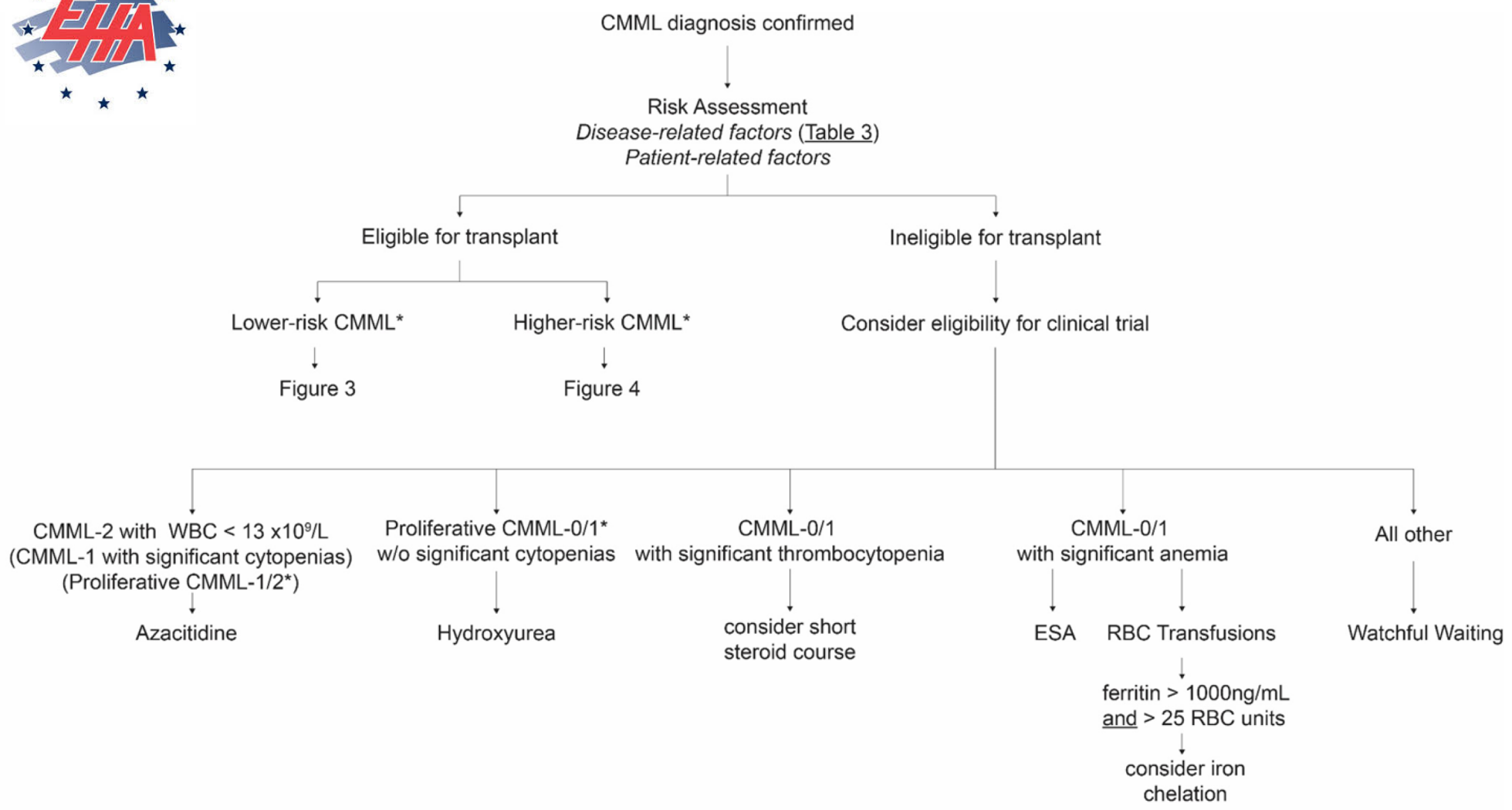
Decitabine 20mg/m^2/d x5d q.28d **N=84**
± HY during the first 3 cycles

HY **N=84**

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

V. Santini, U. Platzbecker, R. Itzykson

CMML: EHA/ELN guidelines



*including patients with extramedullary disease

Hemasphere 2018, in press

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