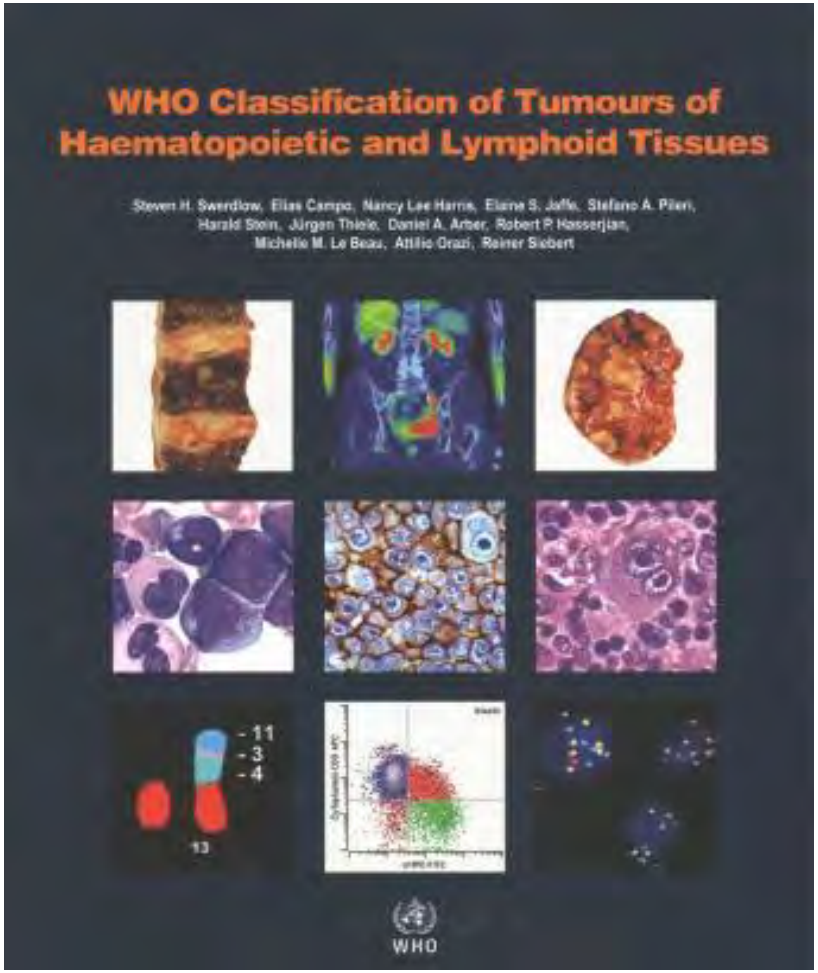
Hémopathies malignes

Quelques éclairages


WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues
Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri,
Harald Stein, Jürgen Thiele, Daniel A. Arber, Robert P. Hasserjian,
Michelle M. Le Beau, Attilio Orazi, Reiner Siebert
- 11
- 3
- 4
13
WHO

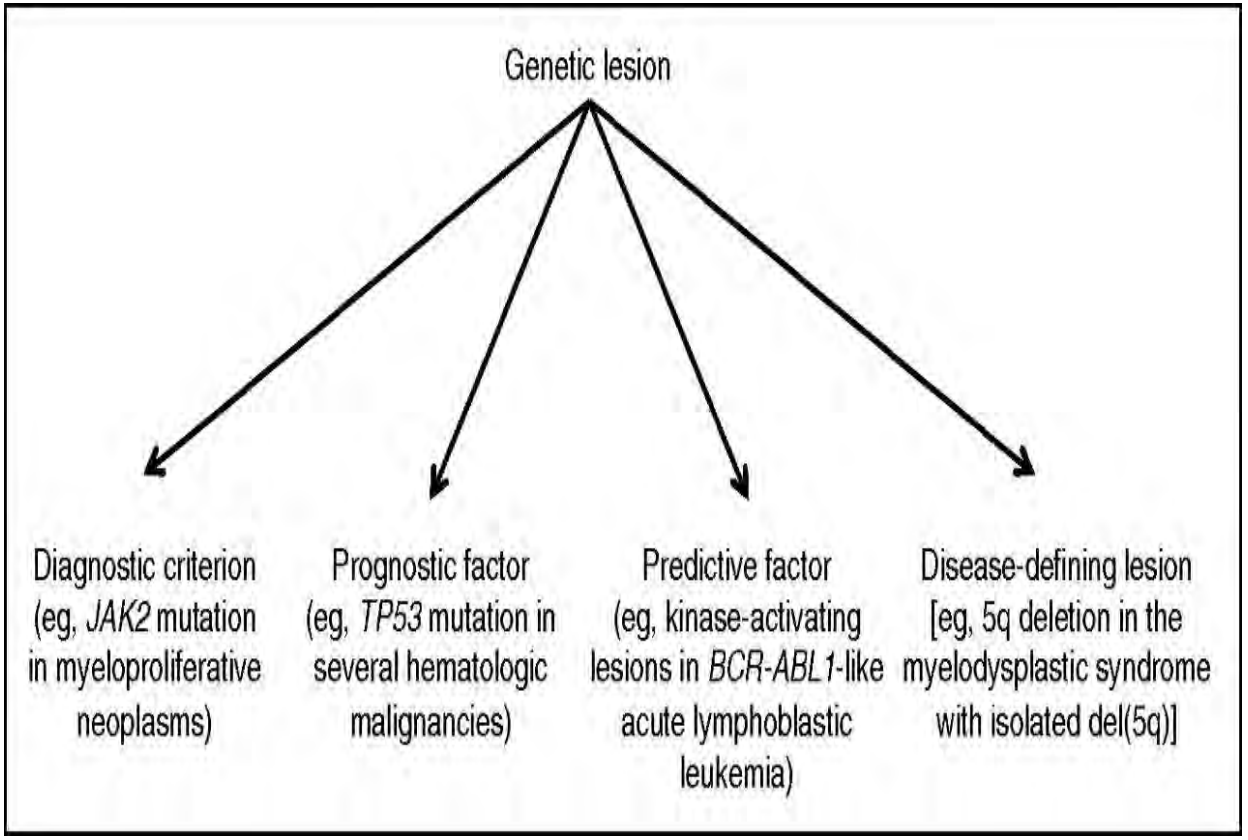
Analysis of patient cohorts for which clinical features, morphology, immunophenotype and genetic data are available

Class discovery

Identification of distinct disease entities through a consensus process aimed to provide terminology and diagnostic criteria

Class prediction

Use of previously defined diagnostic criteria to determine which entity or category an individual patient belongs to

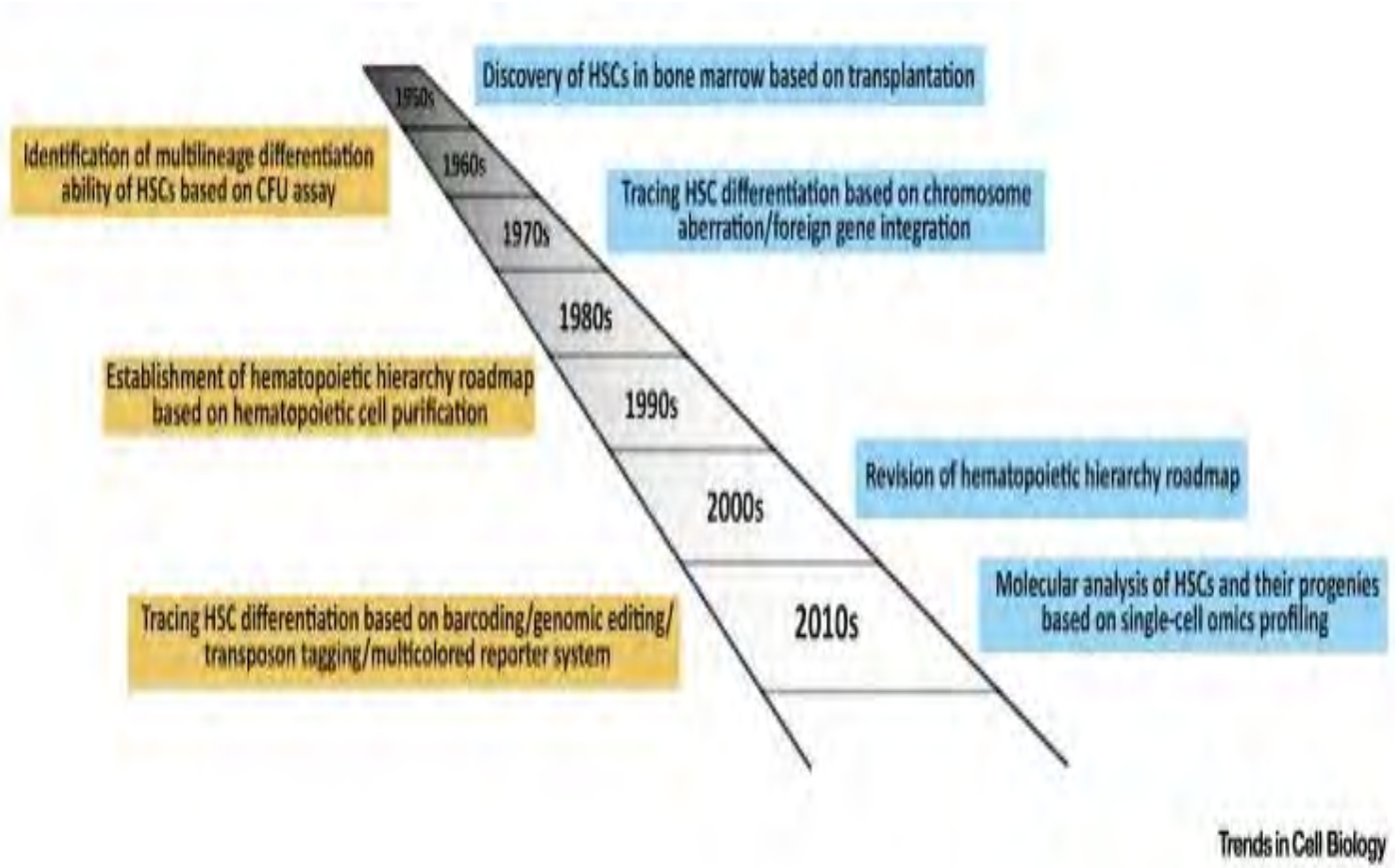

Genetic lesion
Diagnostic criterion (eg, *JAK2* mutation in myeloproliferative neoplasms)
Prognostic factor (eg, *TP53* mutation in several hematologic malignancies)
Predictive factor (eg, kinase-activating lesions in *BCR-ABL1*-like acute lymphoblastic leukemia)
Disease-defining lesion [eg, 5q deletion in the myelodysplastic syndrome with isolated del(5q)]

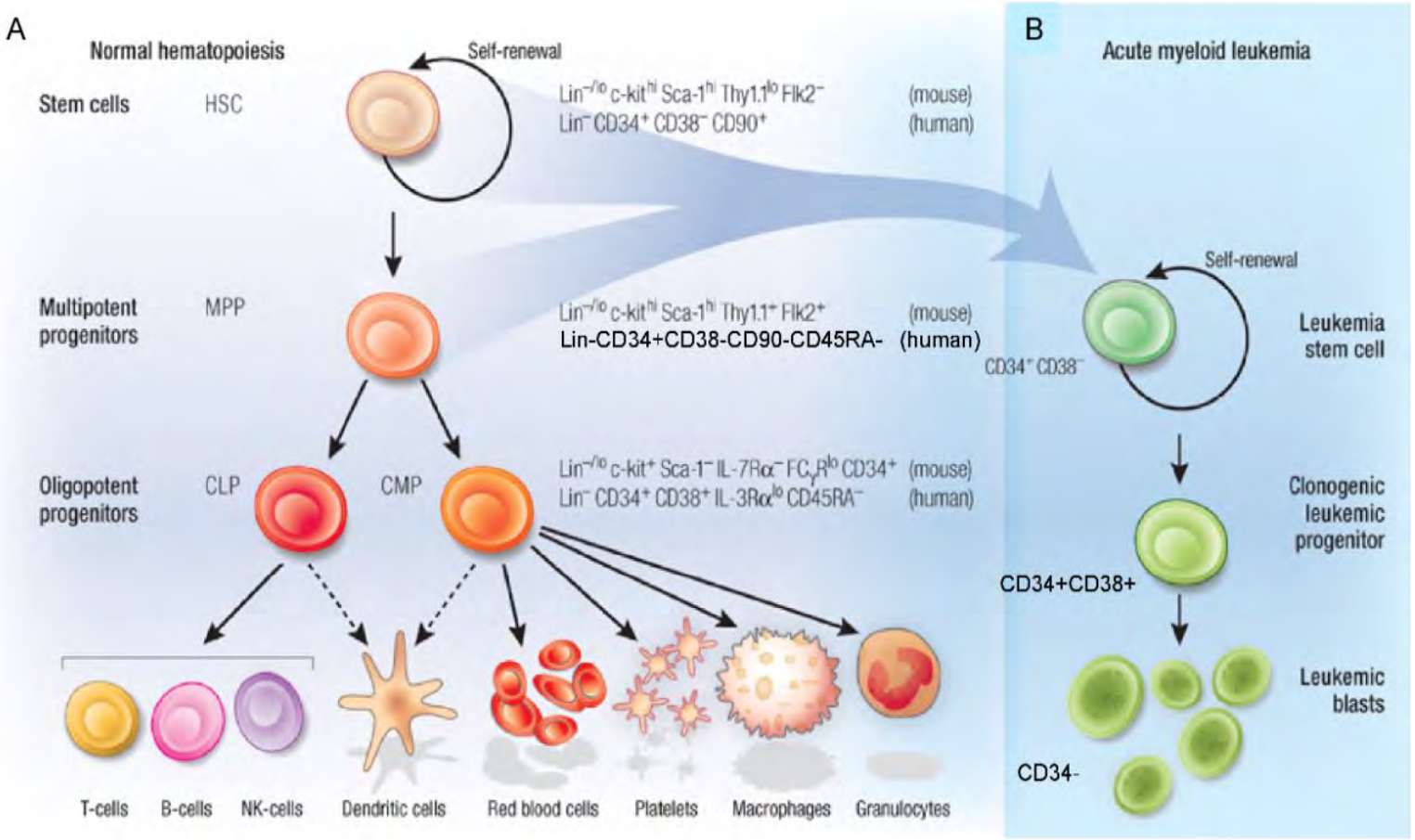
INTRODUCTION

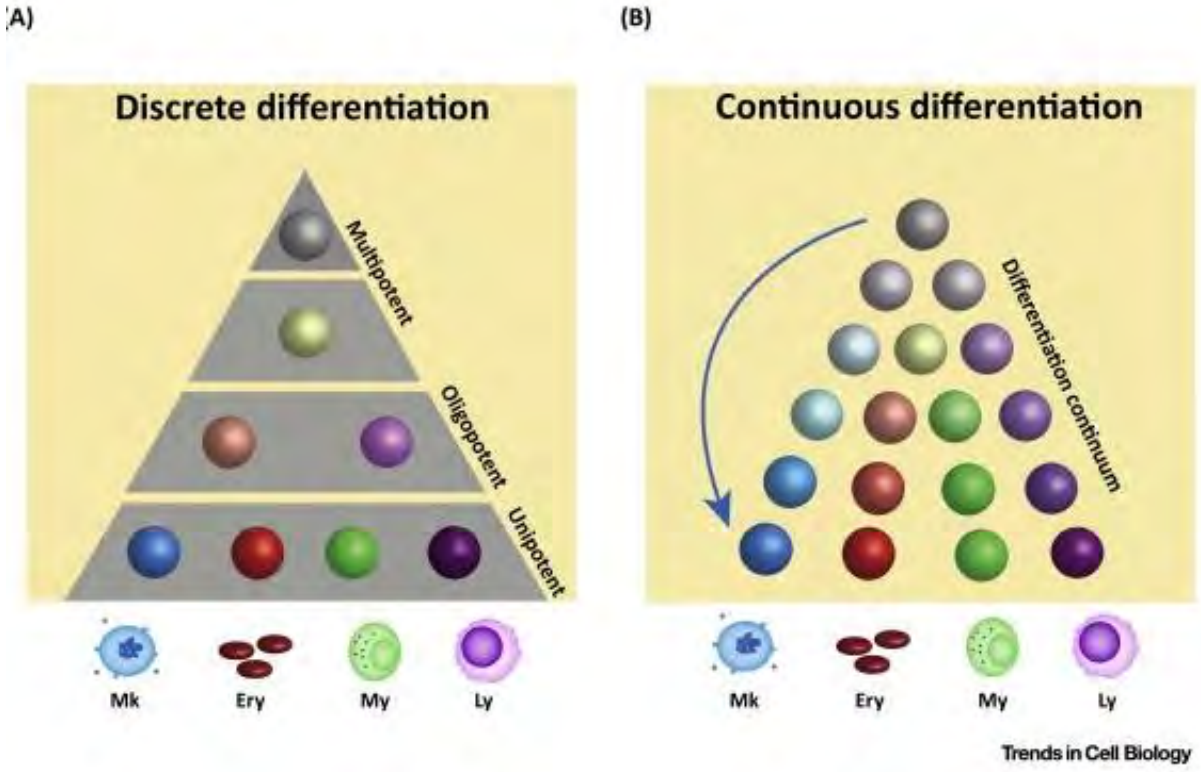
- **Hématopoïèse : renouvellement des 3 lignées à partir de la cellule souche**

- **2 micro-environnements à l'origine des hémopathies : la moelle osseuse et les organes lymphoïdes secondaires tels que la rate les ganglions, les muqueuses (MALT)**

- **Les pathologies sont détectées suite à un hémogramme, apparition de symptômes, organomégalie, adénopathies, thrombose, hémorragie, infections (neutropénie, hypogammaglobulinémie)**
- **Mutations somatiques conférant des caractéristiques de prolifération, modifications de l'apoptose**
- **Rôle de plus en plus important du microenvironnement des cellules souches (niche)**

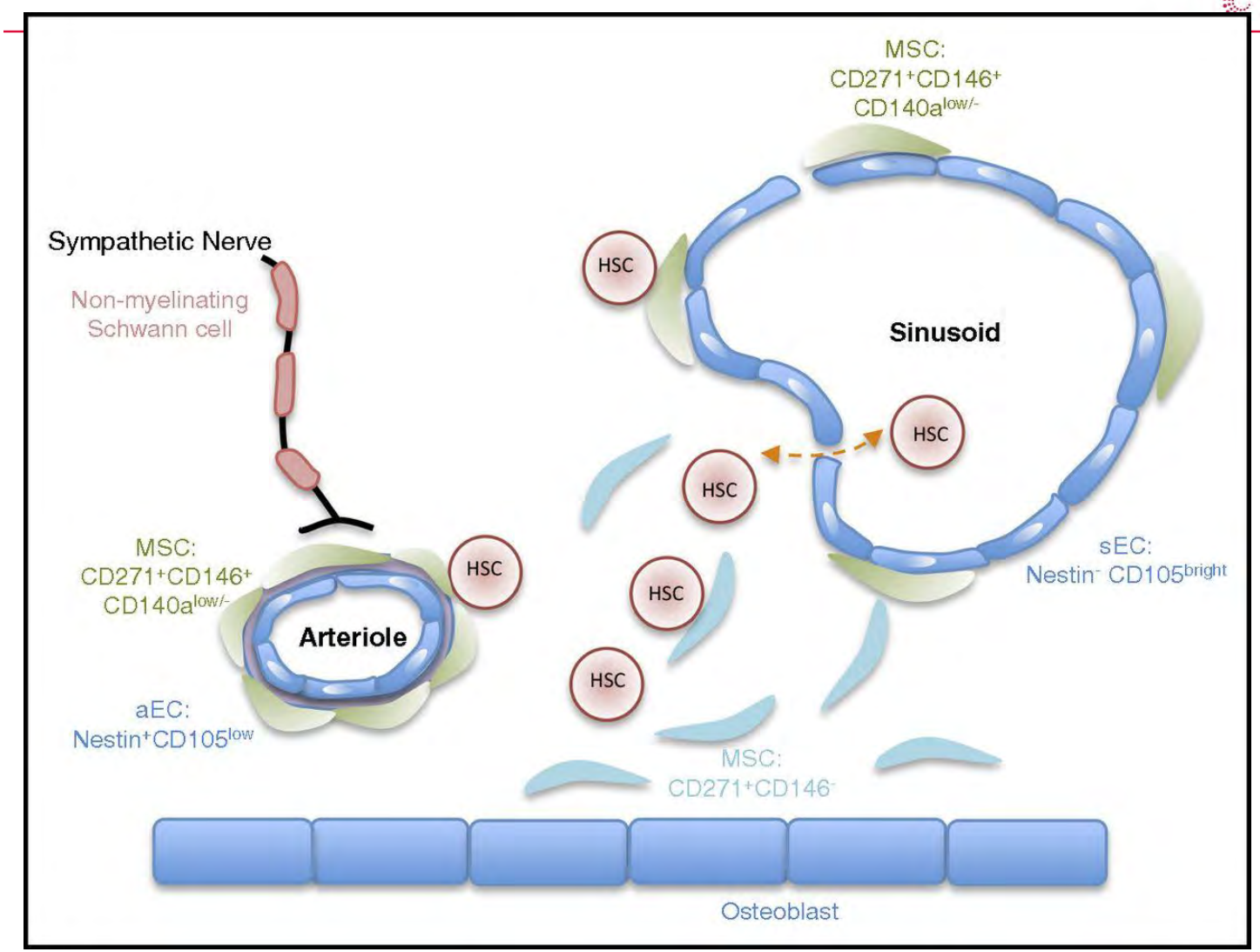

1950s
1960s
1970s
1980s
1990s
2000s
2010s
Discovery of HSCs in bone marrow based on transplantation
Identification of multilineage differentiation ability of HSCs based on CFU assay
Tracing HSC differentiation based on chromosome aberration/foreign gene integration
Establishment of hematopoietic hierarchy roadmap based on hematopoietic cell purification
Revision of hematopoietic hierarchy roadmap
Molecular analysis of HSCs and their progenies based on single-cell omics profiling
Tracing HSC differentiation based on barcoding/genomic editing/ transposon tagging/multicolored reporter system
Trends in Cell Biology


A
Normal hematopoiesis
Self-renewal
Stem cells
HSC
Lin−/lo c-kithi Sca-1hi Thy1.1lo Flk2−
Lin− CD34+ CD38− CD90+
(mouse)
(human)
Multipotent progenitors
MPP
Lin−/lo c-kithi Sca-1hi Thy1.1+ Flk2+
Lin-CD34+CD38-CD90-CD45RA-
(mouse)
(human)
Oligopotent progenitors
CLP
CMP
Lin−/lo c-kit+ Sca-1− IL-7Rα− FcγRlo CD34+
Lin− CD34+ CD38+ IL-3Rαlo CD45RA−
(mouse)
(human)
T-cells
B-cells
NK-cells
Dendritic cells
Red blood cells
Platelets
Macrophages
Granulocytes
B
Acute myeloid leukemia
Self-renewal
CD34+ CD38−
Leukemia stem cell
Clonogenic leukemic progenitor
CD34+CD38+
Leukemic blasts
CD34-



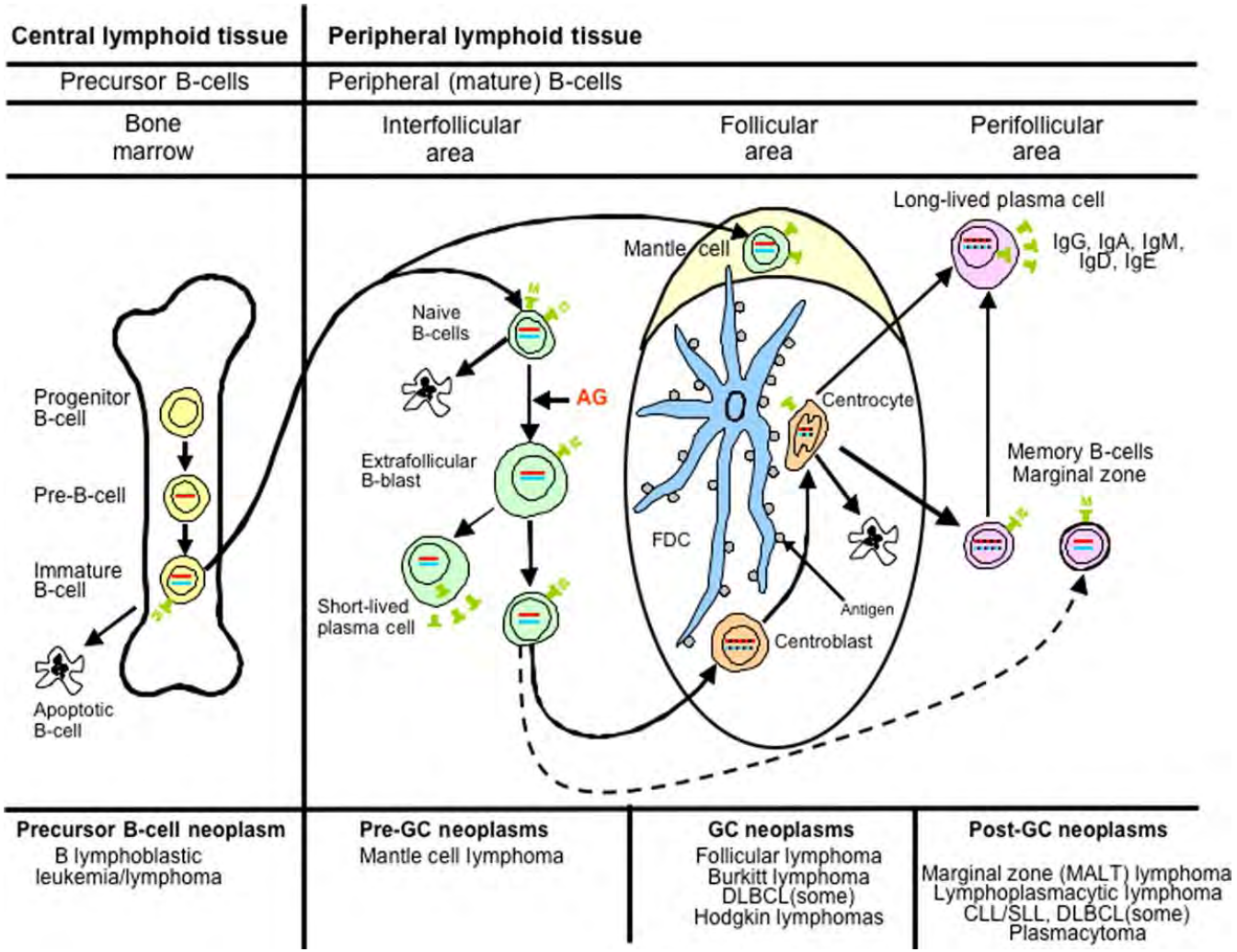
Protein and cell avril 2019

Pas forcément de lien entre les différents éléments



Blood journal 2017 129: 1617 1626

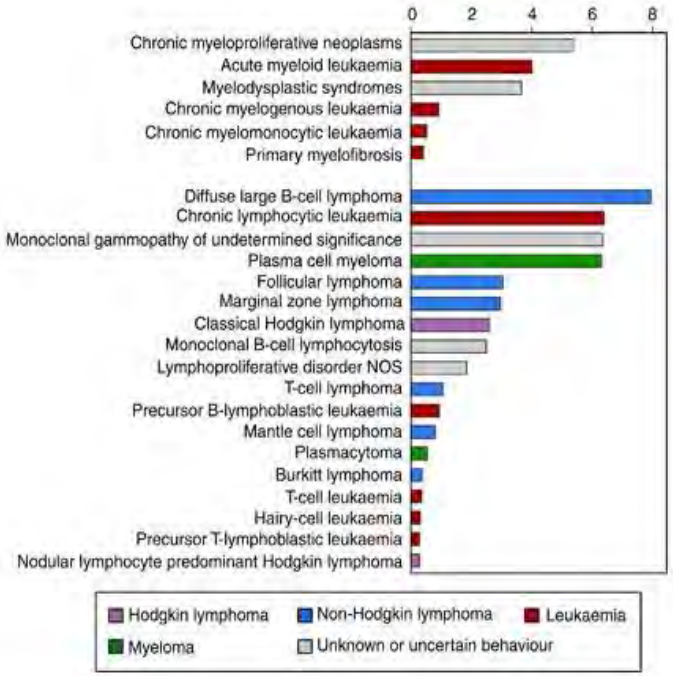
Diagrammatic representation of B-cell differentiation and relationship to major B-cell neoplasms.



Elaine S. Jaffe et al. Blood 2008;112:4384-4399

Figure 2

From: Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network

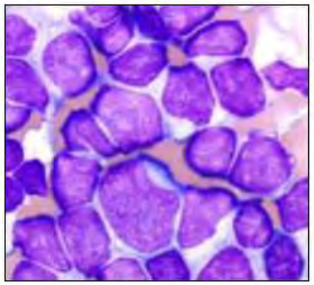


Annual crude rates per 100 000: Haematological Malignancy Research Network (HMRN), 2004–2009.

Table 1 Subtypes considered in this study, according to their incidence and survival categories[a]

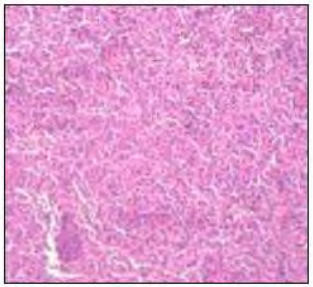
Incidence (per 100,000)	Survival		
	Poor (5-year survival <30 %)	Medium (5-year survival 30–70 %)	Good (5-year survival >70 %)
Low (<2)	Chronic myelomonocytic leukemia	Acute lymphoblastic leukemia	Chronic myelogenous leukemia
	Mantle cell lymphoma	T cell leukemia	Hairy cell leukemia
		Burkitt lymphoma	
		T cell lymphoma	
		Plasmacytoma	
		Lymphoproliferative disorder not otherwise specified	
Medium (2–5)	Acute myeloid leukemia	Marginal zone lymphoma	Follicular lymphoma
	Myelodysplastic syndromes		Hodgkin lymphoma
			Monoclonal B cell lymphocytosis
High (>5)		Chronic lymphocytic leukemia	Myeloproliferative neoplasms
		Diffuse large B cell lymphoma	Monoclonal gammopathy of undetermined significance
		Plasma cell myeloma	

[a] Incidence and 5-year survival rates in HMRN from 2004 to 2011. Categories were made for this analysis only and cannot be generalized to other diseases or other data

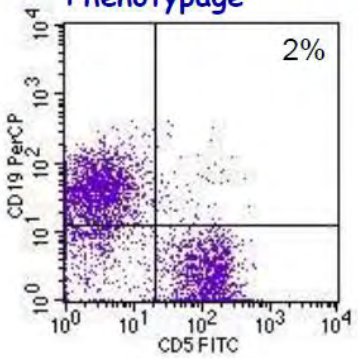


Cytologie

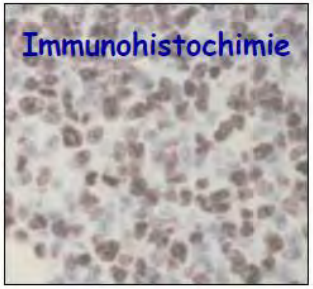
Histologie



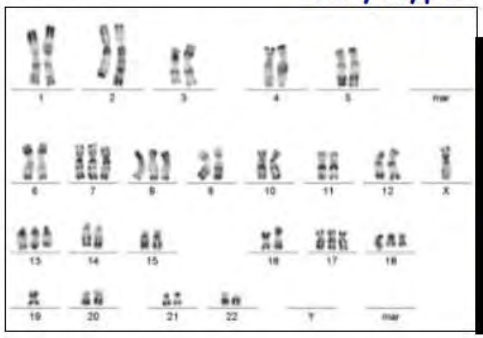
Phénotypage

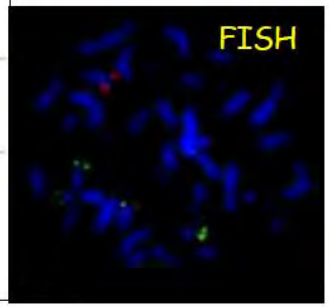


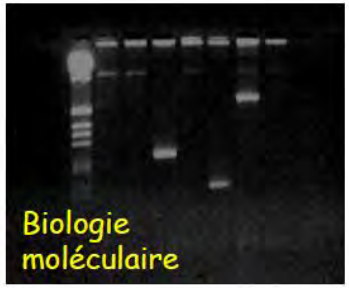
Diagnostic pluridisciplinaire d'une hémopathie



Caryotype







	Objectifs	Technique complémentaire	Intérêt dans les hémopathies
Cytologie	Aspect détaillés des cellules tumorales	Cytochimie : lignée (enzyme), fer	Diagnostic+++, Suivi++
Histologie	Aspect tissulaire, environnt, et cellulaires	Immunohistochimie : lignée, index de prolifération, classification	Diagnostic+++
Phénotypage (suspension)	Marqueurs de surface ou intracytopl.	Marquage multicouleur, IF sur lame,	Diagnostic+++, Suivi++ (maladie résiduelle ou MRD),
Cytogénétique Caryotype	Génome tumoral Anomalies Iaires et IIaires	FISH : précisions ou détection d'anomalies cryptiques	Diagnostic+++, Suivi+, pronostic+++
Biologie moléculaire	Recherche et quantification de transcrit pathologiques, clonalité T/B, mutations acquises oncogéniques	PCR nichée, Séquençage…	Diagnostic, Suivi+++ (MRD) Pronostic++,

Hôpital du Valais
Spital Wallis

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Zentralinstitut der Spitäler

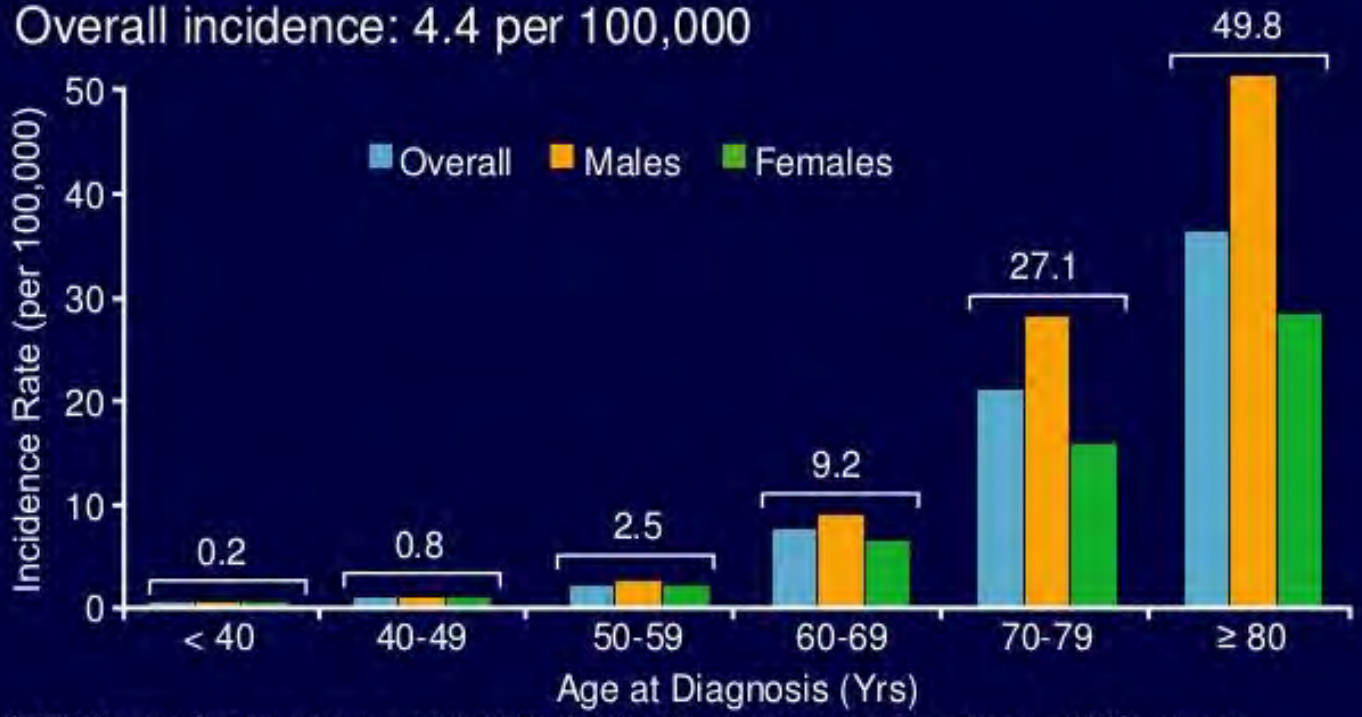
Hématopoïèse clonale n'est pas synonyme de syndrome myélodysplasque

Anomalies qualitatives et quantitatives syndromes myélodysplasiques

- En périphérie cytopénie(s) mais moelle riche (hématopoïèse inefficace)
- Anomalies morphologiques
- Apoptose pathologique, maturation pathologique
- Atteinte de la cellule souche
- Anomalies moléculaires, chromosomiques récurrentes ou non pour le diagnostic et le pronostic

MDS EPIDEMIOLOGY

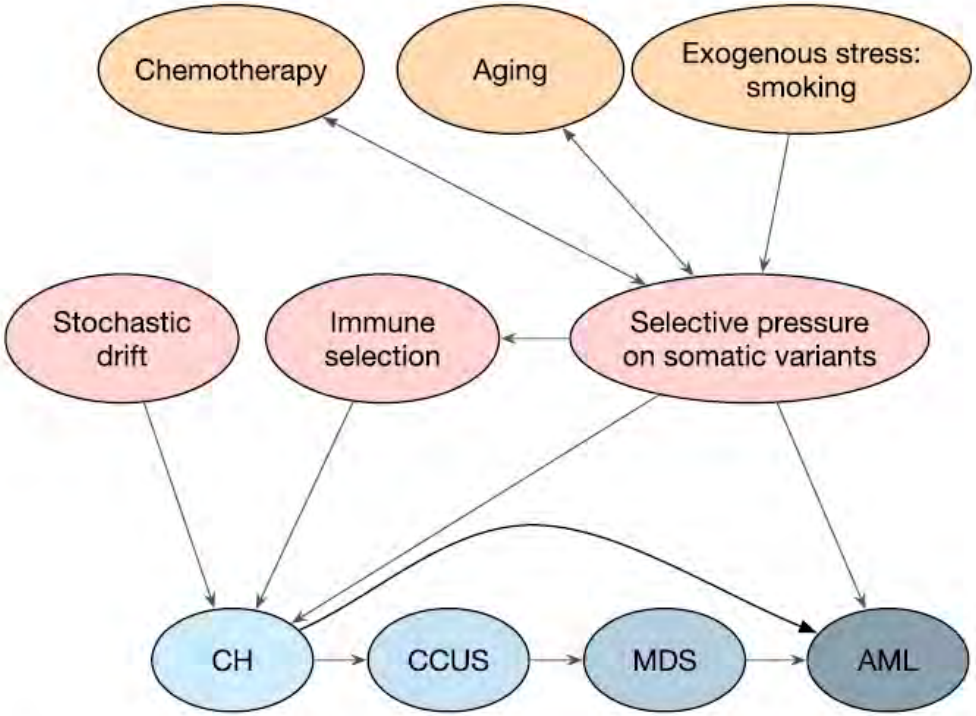
- Overall incidence: 4.4 per 100,000



SEER Cancer Statistics Review 1975-2008. Section 30, myelodysplastic syndromes (MDS), chronic myeloproliferative disorders (CMD), and chronic myelomonocytic leukemia (CMML).

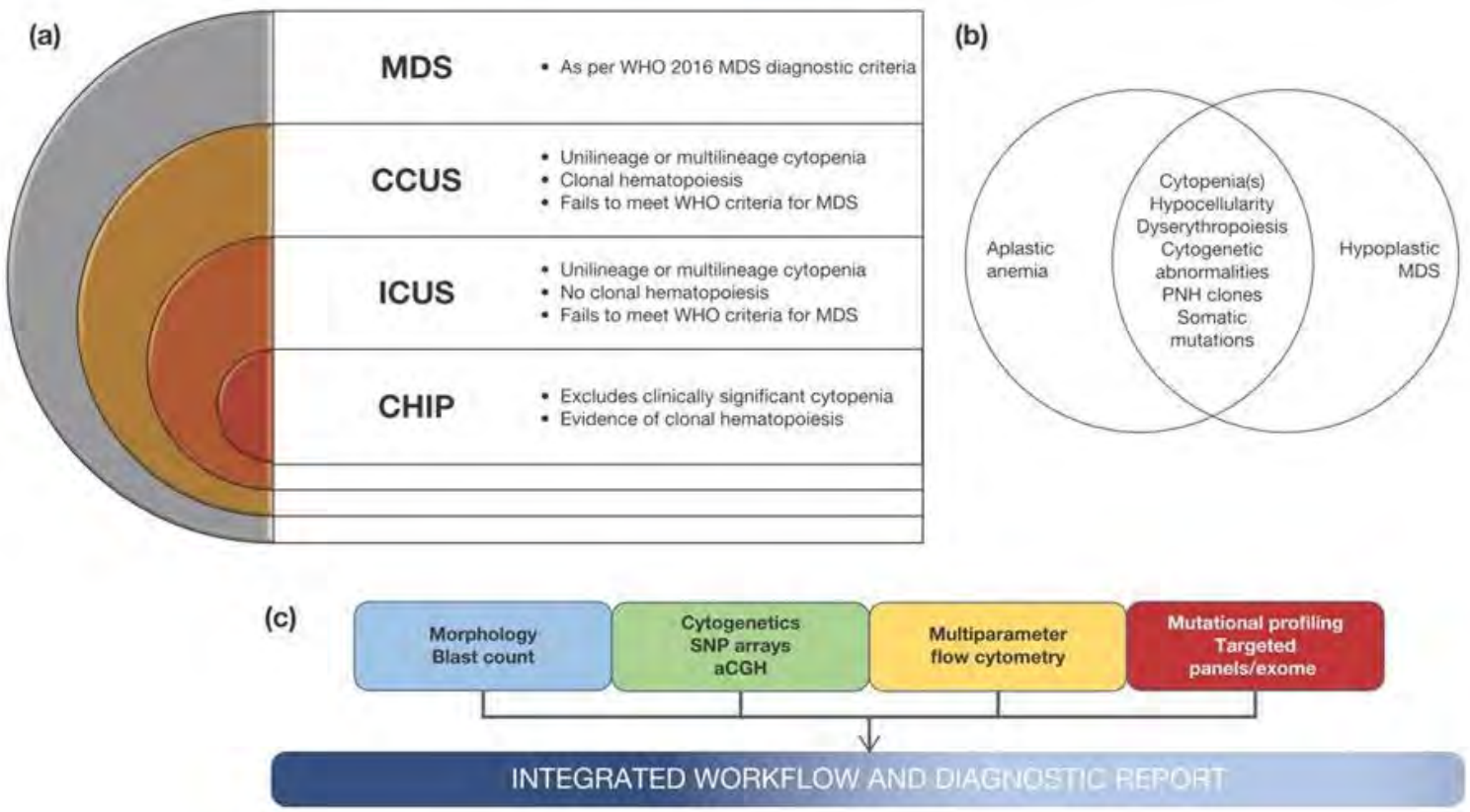
Cytopénies et SMD

- Toutes les cytopénies ne sont pas des SMD



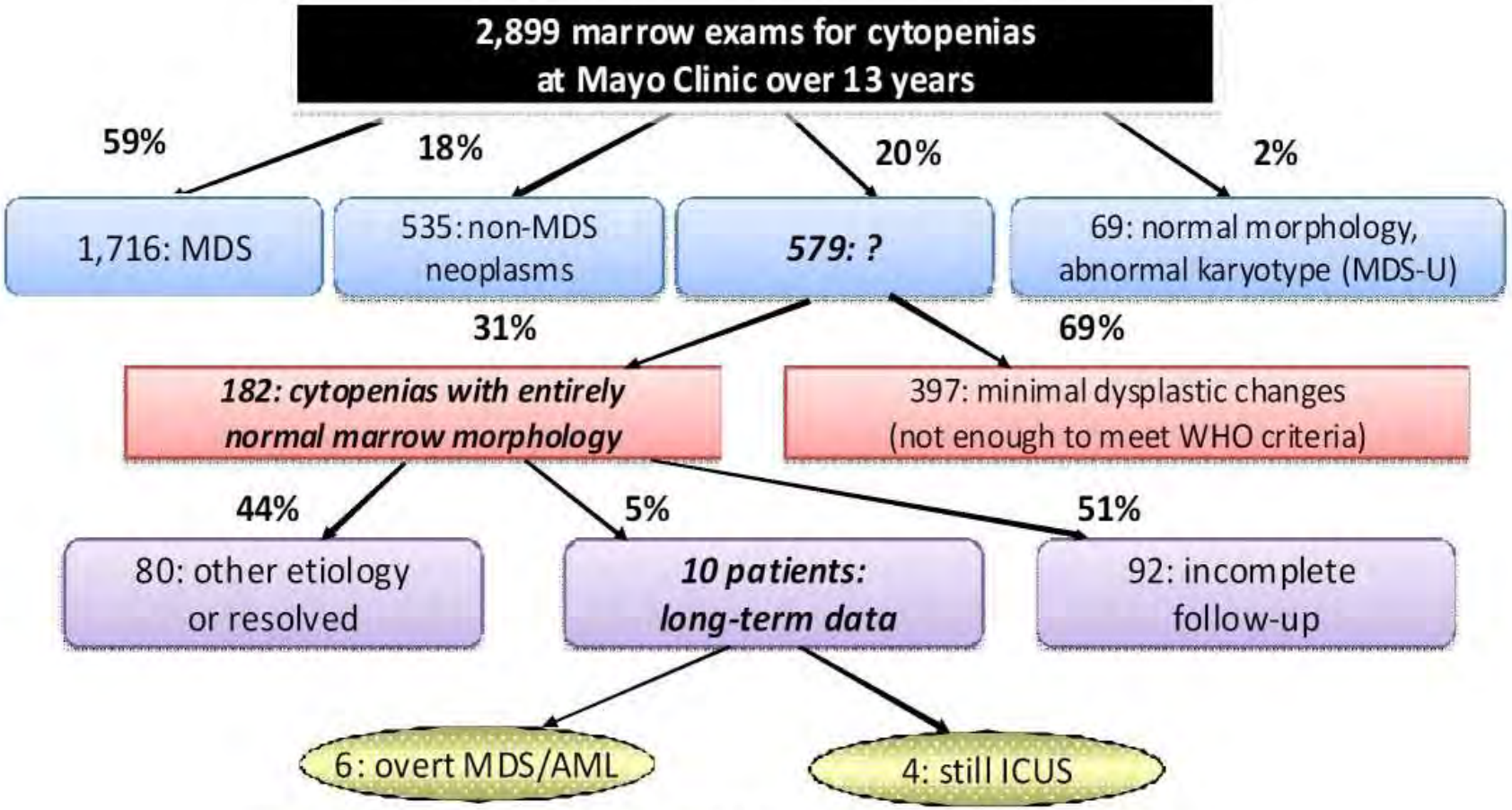
Somatic variation	+	+	+	+
Cytopenia	-	+	+	+
Dysplasia	-	-	+	+
Blast % in BM	<5%	<5%	<5-10%	>20%

From: Diagnostic algorithm for lower-risk myelodysplastic syndromes



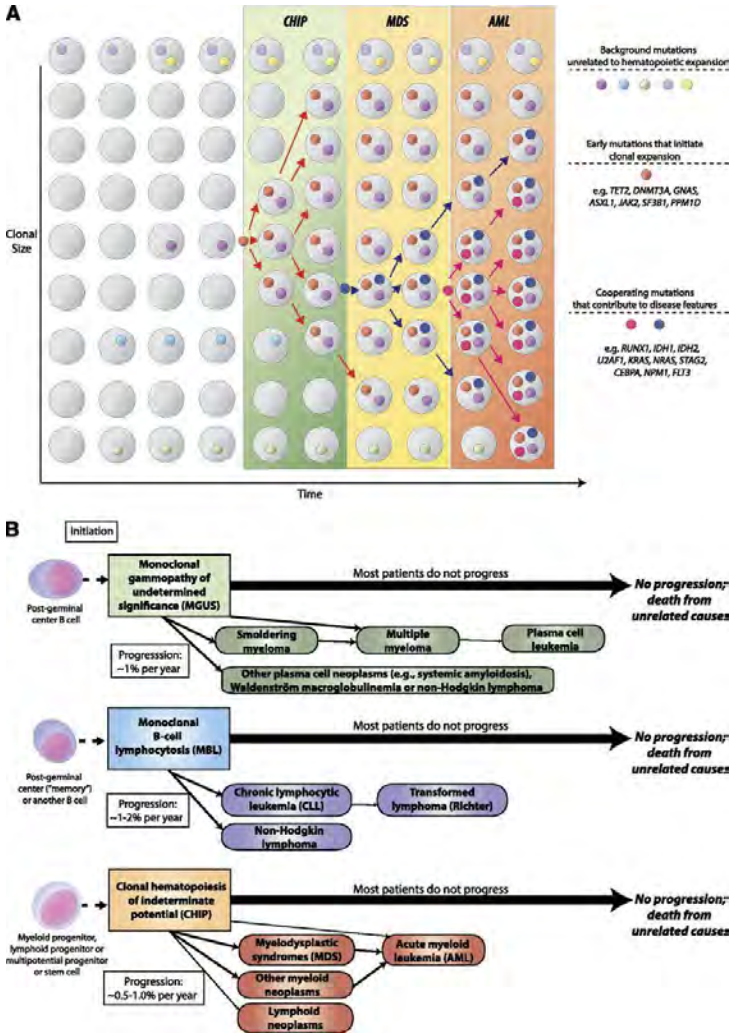
Leukemia, 32 1679-1690

ICUS Natural History

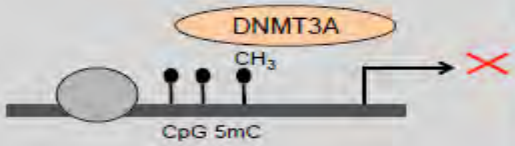
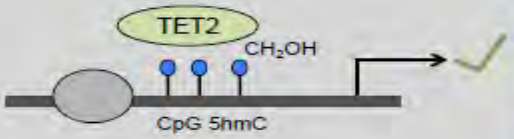
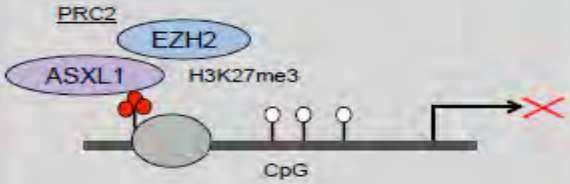


Hanson C and Steensma D. Abstract presented at: MDS Symposium; May 2009; Patras, Greece.

CHIP as a precursor state for hematological neoplasms.



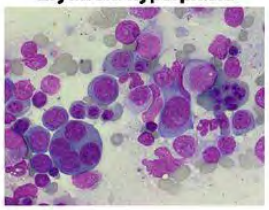
David P. Steensma et al. Blood 2015;126:9-16

Molecular Interactions	Mutation Phenotype	Hematological Disease
	Hypomethylation (h,m) Stem cell expansion (m) Anthtracycline resistance (h,m)	AML, MDS, MPN. T-ALL (h,m) Poor prognosis in AML (h) Point mutation and LOF (h,m)
	Hypermethylation (h,m) Stem cell expansion (h,m) Hypermutagenicity (m)	CMML, AML, MDS (h,m) Synergy with FLT3-ITD (m)
	H3K27 demethylation (m) Hox gene upregulation (h,m)	Poor prognosis in MDS (h) Truncation mutants and LOF (h)

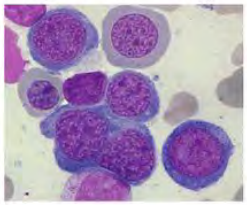
Cytopenia is a "sine qua non" for the diagnosis of MDS. Although the lowering of neutropenia prognostic threshold in IPSS-R to 0.8×10^9/L,[7] the WHO thresholds defining cytopenia still remain as in the original IPSS: hemoglobin < 10g/dL, platelets $<100\times 10^9$/L, absolute neutrophil count $<1.8\times 10^9$/L.[8] The classification considers blood and bone marrow blast proportion, which myeloid cell lineages exhibit dysplastic changes greater than 10% of cells morphologically, whether the ring sideroblast erythroid precursors or Auer rods are present or not and, to a limited extent, karyotype and molecular genetic findings. The degree and not the lineages of cytopenia impacts the MDS prognosis, and in MDS, the lineage(s) manifesting morphological dysplasia frequently do not correlate with the specific cytopenia(s).[9-11] So, the terms such as "refractory anemia" and "refractory cytopenia" are removed and replaced with "myelodysplastic syndrome", which means that the diagnosis of MDS needs be determined firstly, and then the classifications needs to be done.[6] The new terms for each subtypes of adult MDS are MDS followed by: single versus multilineage dysplasia, ring sideroblasts, excess blasts, or the del(5q) cytogenetic abnormality (Table 1 and Table 2). In childhood MDS, refractory cytopenia of childhood remains a provisional term in the category of MDS.

Erythroid lineage

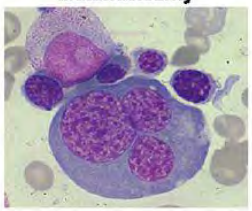
Erythroid hyperplasia



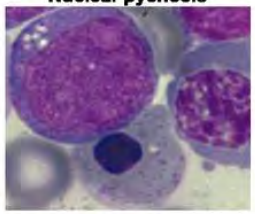
Megaloblastoid changes



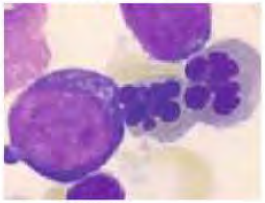
Multinuclearity



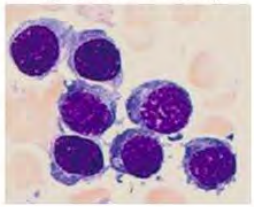
Nuclear pycnosis



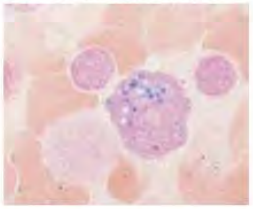
Nuclear lobulation



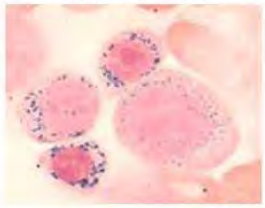
Cytoplasmic fraying



Ferritin sideroblast

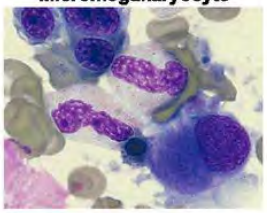


Ring sideroblasts

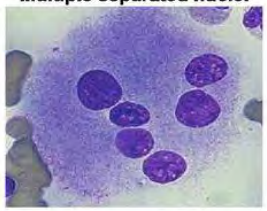


Megakaryocyte lineage

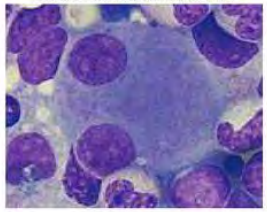
Micromegakaryocyte



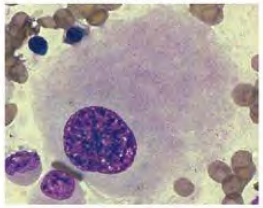
Multiple separated nuclei



Small binucleated cell

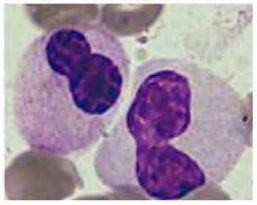


Monolobar cell

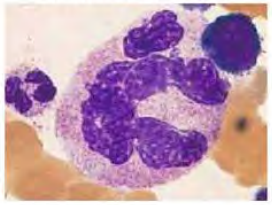


Granulocytic lineage

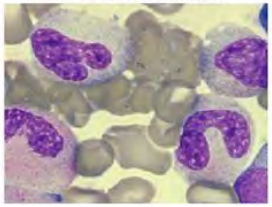
Pseudo-Pelger anomaly



Abnormal nuclear shape



Hypo-degranulation



Myeloblasts

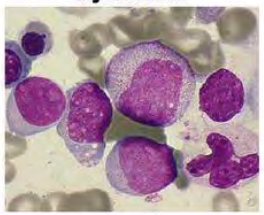


Table 2 WHO 2016 MDS and MDS/MPN disease subtypes

From: Diagnostic algorithm for lower-risk myelodysplastic syndromes

MDS	MDS/MPN
MDS with single lineage dysplasia	Chronic myelomonocytic leukemia (CMML)
MDS with ring sideroblasts (MDS-RS)	Atypical chronic myeloid leukemia (aCML), *BCR-ABL 1*$^-$
MDS-RS and single lineage dysplasia	Juvenile myelomonocytic leukemia (JMML)
MDS-RS and multilineage dysplasia	MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS with multilineage dysplasia	MDS/MPN, unclassifiable
MDS with excess blasts	
MDS with isolated del(5q)	
MDS, unclassifiable	
Provisional entity: refractory cytopenia of childhood	

MDS myelodysplastic syndromes, MDS-RS myelodysplastic syndromes-ring sideroblasts, MPN myeloproliferative neoplasm, WHO World Health Organization

Table 1 2012 revised international prognostic scoring system for MDS (IPSS-R)

From: Myelodysplastic syndromes current treatment algorithm 2018

Parameter	Categories and Associated Scores (Scores in italics)				
Cytogenetic risk group[a]	Very good	Good	Intermediate	Poor	Very Poor
	0	*1*	*2*	*3*	*4*
Marrow blast proportion	≤2.0%	>2.0–<5.0%	5.0–<10.0%	≥10.0%	
	0	*1*	*2*	*3*	
Hemoglobin	≥10 g/dL	8–<10 g/dL	<8 g/dL		
	0	*1*	*1.5*		
Absolute neutrophil count	≥0.8 × 10^9/L	<0.8 × 10^9/L			
	0	*0.5*			
Platelet count	≥100 × 10^9/L	50–100 × 10^9/L	<50 × 10^9/L		
	0	*0.5*	*1*		

[a] Cytogenetic risk group, very good: -Y, del(11q); good: normal; del(5q) ± 1 other abnormality del(20q), or del(12p); intermediate: + 8, i(17q), del(7q), + 19, any other abnormality not listed including the preceding with 1 other abnormality; poor: −7 ± del(7q), inv(3)/t(3q)/del(3q), any 3 separate abnormalities; very poor: more than 3 abnormalities, especially if 17p is deleted or rearranged

[b]Sum scores on a 0–10 point scale

Source: adapted from Greenberg P et al, *Blood* 120(12):2454–65

Risk group	Total score[b]	Proportion of patients in category (%)	Median survival (survival data based on *n* = 7012) (years)	Time until AML progression (AML data available based on *n* = 6485) (years)
Very low	0–1.0	19	8.8	Not reached
Low	1.5–3.0	38	5.3	10.8
Intermediate	3.5–4.5	20	3.0	3.2
High	5.0–6.0	13	1.5	1.4
Very high	>6.0	10	0.8	0.7

[a] Cytogenetic risk group, very good: -Y, del(11q); good: normal; del(5q) ± 1 other abnormality del(20q), or del(12p); intermediate: + 8, i(17q), del(7q), + 19, any other abnormality not listed including the preceding with 1 other abnormality; poor: −7 ± del(7q), inv(3)/t(3q)/del(3q), any 3 separate abnormalities; very poor: more than 3 abnormalities, especially if 17p is deleted or rearranged

[b]Sum scores on a 0–10 point scale

Source: adapted from Greenberg P et al, *Blood* 120(12):2454–65

From: Diagnostic algorithm for lower-risk myelodysplastic syndromes

Cytogenetic anomaly	Incidence among 1 202 MDS patients, % (Haase et al.) [68]	Median OS, months (Haase et al.) [68]	Prognostic significance according to IPSS-R (Greenberg et al.) [65]
−Y	2.8	39.4	Very good
del(11q)	0.9	26.1	
del(5q)	11.0	77.2	Good
del(12p)	0.6	NR	
del(20q)	2.0	71.0	
del(7q)	0.9	19.0	Intermediate
+8	5.3	23.0	
+19	0.4	19.8	
t(17q)	0.5	32.1	
−7	3.5	14.0	Poor
del(7q)	0.9	14.0	
inv(3q)/t(3;3)	1.3	19.9	
Complex (3 abnormalities)	2.7	17.0	
Complex (>3 abnormalities)	11.1	8.7	Very poor

[a]Includes isolated, +1, and complex karyotypes, unless otherwise specified

IPSS-R revised International Prognostic Scoring System, *MDS* myelodysplastic syndromes, *NR* not reached, *OS* overall survival

caculate risk score

cytogenetic risk group

very good	0	del(11q), -Y
good	1	normal, del(20), del(5q) alone or with other anomaly, del(12p)
intermediate	2	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones
poor	3	der(3q), -7, double with del(7q), complex with 3 abnormalities
very poor	4	complex with > 3 abnormalities

bone marrow blast %

≤ 2%	0
> 2% - < 5%	1
5% - 10%	2
> 10%	3

hemoglobin (g/dL)

≥ 10	0
8 - < 10	1
< 8	1.5

platelet count (x 10^9/L)

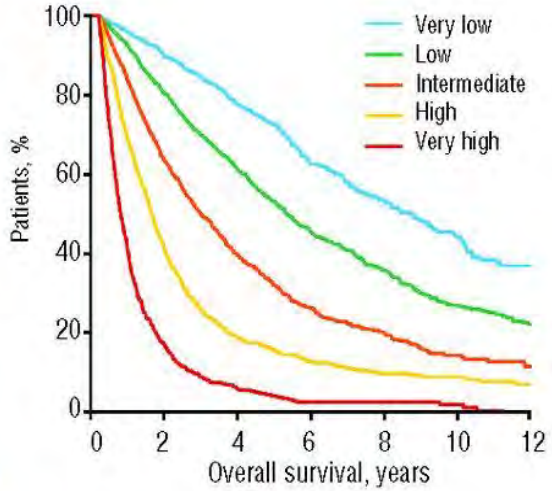
≥ 100	0
50 - < 100	0.5
< 50	1

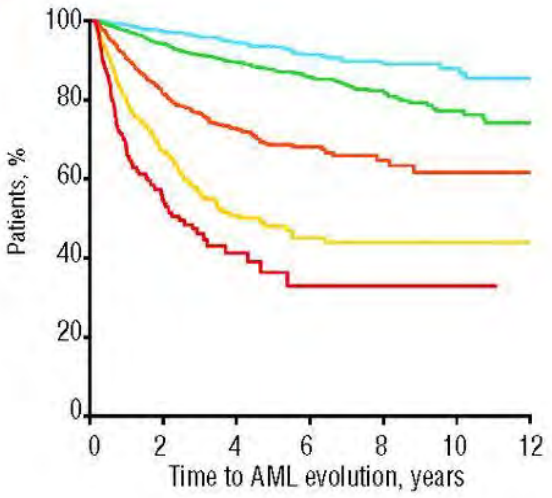
absolute neutrophil count (x 10^9/L)

≥ 0.8	0
< 0.8	0.5

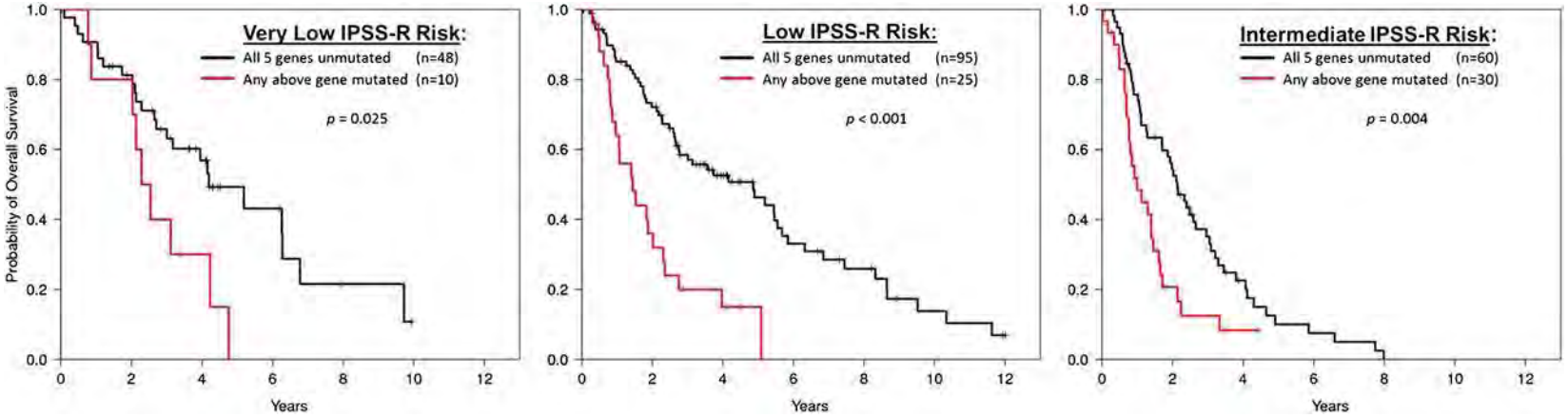
assign IPSS-R risk group

total score	% of patients	median survival, years	time to 25% with AML, years	IPSS-R risk group
≤ 1.5	19%	8.8	not reached	very low
> 1.5 - 3	38%	5.3	10.8	low
> 3 - 4.5	20%	3	3.2	intermediate
> 4.5 - 6	13%	1.6	1.4	high
> 6	10%	0.8	0.73	very high





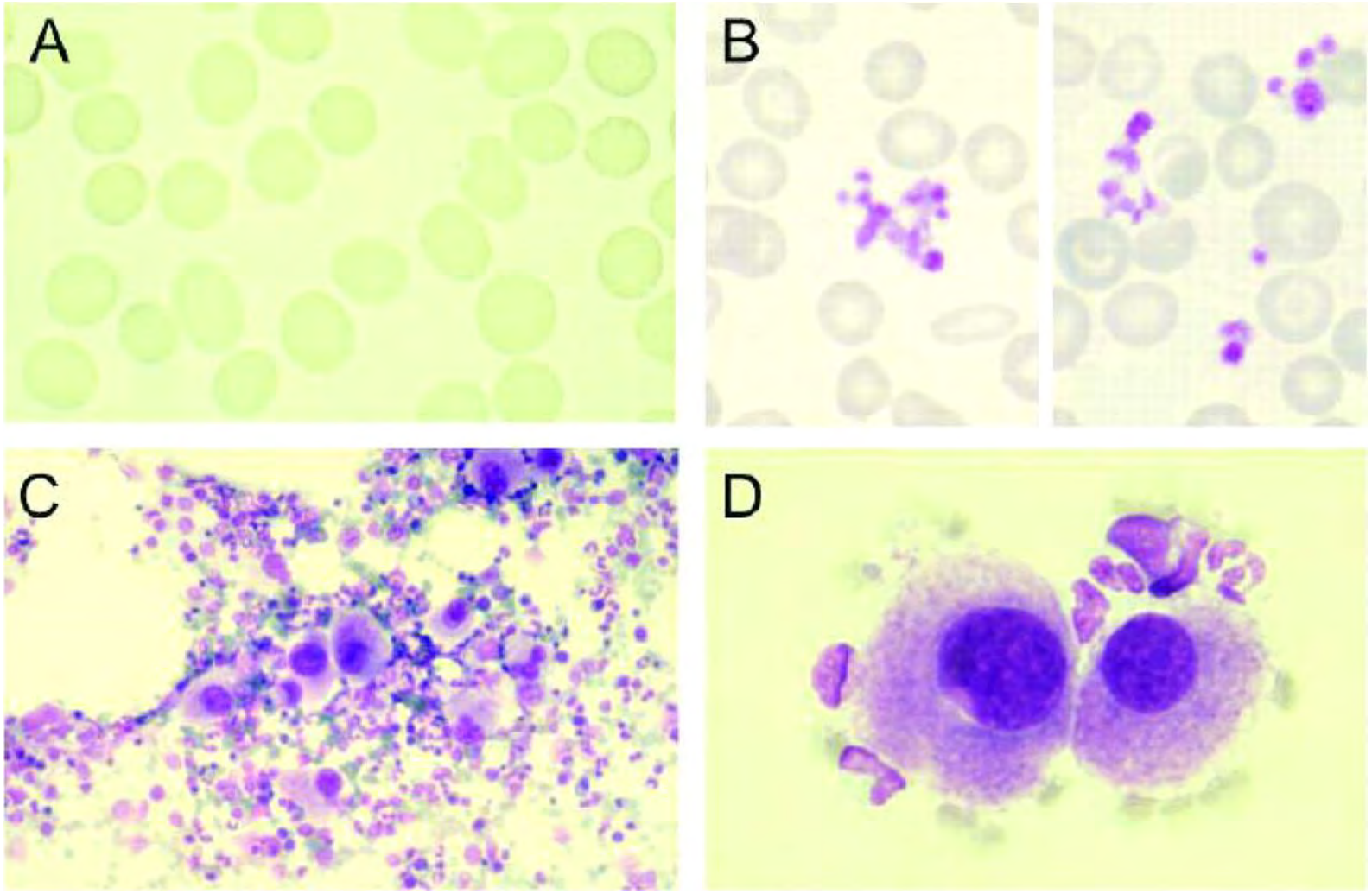
Somatic mutation in any of the 5 genes (TP53, EZH2, RUNX1, ASLX1, or ETV6) shown in Bejar et al48 to have prognostic significance independent of the International Prognostic Scoring System (IPSS) identifies patients from that same cohort with shorter overal...



Mutations influençant le pronostic de l'IPSS

Rafael Bejar, and David P. Steensma Blood 2014;124:2793-2803

Peripheral blood smear and bone marrow aspirate from a patient with 5q-syndrome.

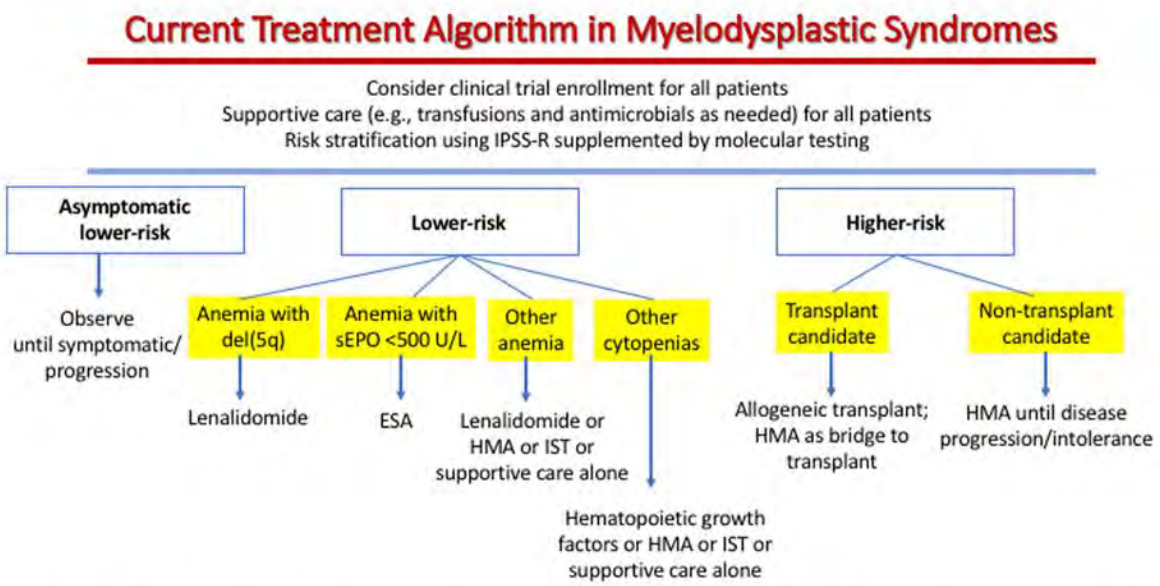


Mario Cazzola Haematologica 2008;93:967-972

haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

Fig. 1: MDS treatment algorithm as described in the text.

From: Myelodysplastic syndromes current treatment algorithm 2018



Clinical trials should be considered for all patients, but is recognized that many patients will not have access to trials or will not be eligible for available trials or will not want to go on trials, especially those requiring travel to a major center. In fact only a very small proportion of patients with MDS are currently enrolled on prospective interventional trials. However, increased trial enrollment is an important goal given the continued poor outcomes with MDS. EPO erythropoietin, ESA erythropoiesis-stimulating agent, HMA DNA hypomethylating agent, IST immunosuppressive therapy (anti-thymocyte globulin, cyclosporine, or tacrolimus)

Hôpital du Valais
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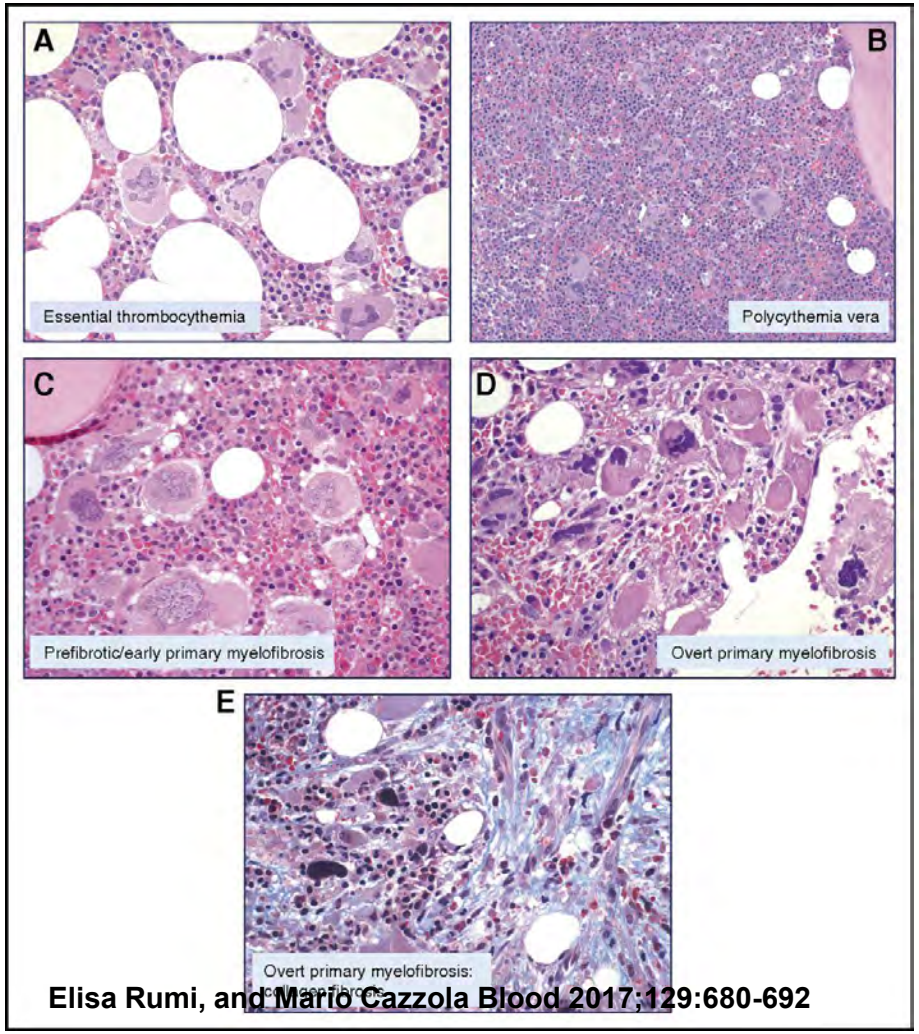
Zentralinstitut der Spitäler

Néoplasies myéloïdes chroniques

Representative bone marrow biopsies from patients with MPNs. (A) ET: Normocellular marrow, proliferation of giant megakaryocytes with hyperlobulated nuclei, scattered or in loose clusters (hematoxylin and eosin [H&E], original magnification ×40).



Elisa Rumi, and Mario Cazzola Blood 2017;129:680-692

WHO classification of myeloid neoplasms and acute leukemia

Myeloproliferative neoplasms (MPN)

- Chronic myeloid leukemia (CML), BCR-ABL1
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
  - prefibrotic/early stage
  - overt fibrotic stage
- Essential thrombocythemia (ET)
- Chronic eosinophilic leukemia, not otherwise specified (NOS)
- MPN, unclassifiable

- Mastocytosis

Excès de prolifération, néoplasie myéloprolifératives chroniques

- Hyperplasie d'une ou plusieurs lignées avec maturation complète sans bloc de maturation

- Mutation JAK2, CALR,MPL ,exon 12 (récepteurs des cytokines)

- Translocation : chromosome de Philadelphie

t(9;22) et transcrit de fusion

Se manifestent par des cytoses, organomégalie, thromboses, hémorragies

MPN symptoms by MPN subtype

	ET (n=874)		PV (n=729)		MF (n=486)		Total (n=2089)	
Symptom	Mean (SD)	Incidence (%)*	Mean (SD)	Incidence (%)*	Mean (SD)	Incidence (%)*	Mean (SD)	Incidence (%)*
Worst fatigue (one-item BFI)	3.9 (2.9)	84	4.2 (2.9)	85	4.9 (2.8)	94	4.3 (2.9)	87
Early satiety	2.1 (2.6)	56	2.4 (2.7)	60	3.2 (3.0)	74	2.4 (2.8)	61
Abdominal discomfort	1.6 (2.3)	48	1.6 (2.3)	48	2.6 (2.8)	65	1.8 (2.5)	52
Inactivity	1.9 (2.5)	54	2.4 (2.8)	60	3.3 (3.0)	76	2.4 (2.7)	61
Concentration	2.2 (2.7)	58	2.6 (2.8)	62	2.8 (2.9)	68	2.5 (2.8)	62
Night sweats	1.9 (2.7)	47	2.1 (2.8)	52	2.9 (3.2)	63	2.2 (2.9)	53
Itching	1.7 (2.6)	46	2.7 (3.1)	62	2.1 (2.9)	52	2.1 (2.9)	53
Bone pain	1.7 (2.6)	45	2.0 (2.8)	48	2.2 (2.9)	53	1.9 (2.7)	48
Fever	0.4 (1.2)	17	0.4 (1.2)	19	0.6 (1.6)	24	0.5 (1.3)	19
Weight loss	0.9 (2.0)	28	1.2 (2.2)	33	2.2 (3.1)	47	1.3 (2.4)	34
MPN - 10	**18.3 (15.4)**	---	**21.6 (16.7)**	---	**26.6 (18.0)**	---	**21.4 (16.8)**	---

ET, essential thrombocythemia; MF, myelofibrosis; PV, polycythemia vera

Geyer HL, et al. Hematology 2014:

Critères OMS 2016 Polyglobulie de Vaquez

Le diagnostic repose sur sur l'association des 3 critères majeurs ou des 2 premiers critères majeurs et du critère mineur en l'absence de mutation de JAK2

Critères majeurs	1. Hb > **16,5 g/dL** chez l'homme, > **16 g/dL** chez la femme, ou Ht > 49% chez l'homme, > 48% chez la femme ou augmentation de la masse sanguine totale (> 25% de la valeur théorique) 2. **Biopsie médullaire** : hypercellularité touchant les trois lignées (panmyélose) avec prolifération mégacaryocytaire pléomorphe 3. Présence de la mutation JAK2V617F ou de JAK2 exon 12
Critère mineur	Taux sanguin d'EPO subnormal

Critères OMS 2016 Thrombocytémie essentielle

Le diagnostic de TE requiert les 4 critères majeurs
ou les 3 premiers critères majeurs et le critère mineur

Critères majeurs	1. Plaquettes > 450 G/L 2. Biopsie médullaire avec prolifération surtout de la lignée mégacaryocytaire avec une augmentation du nombre de formes matures de grande taille avec un noyau hyperlobé. Pas d'augmentation significative ou de shift gauche des lignées granuleuse et érythroblastique et très rarement augmentation minime de la réticulinique (grade 1) 3. Absence des critères diagnostiques de LMC, PV, MFP, SMD ou autre néoplasie myéloïde 4. Mutation de JAK2, **CALR ou MPL**
Critères mineurs	Présence d'un marqueur de clonalité ou absence d'étiologie de thrombocytose réactionnelle *

(IPSET) and IPSET-thrombosis

Risk factor	IPSET	IPSET-thrombosis
Age > 60 years	2	1
Previous thrombosis	1	2
WBC count ≥ 11×10^9/L	1	
Cardiovascular risk factors		1
$JAK2^{V617F}$-positive		2
Prognostic score (median survival or rate of thrombosis)		
Low	0 points (not reached)	< 2 points (1.03% patients/year)
Intermediate	1–2 points (24.5 years)	2 points (2.35% patients/year)
High	3–4 points (14.7 years)	> 2 points (3.56% patients/year)

WBC = white blood cell

Critères OMS 2016 Pré-Myélofibrose Primitive

Le diagnostic requiert les 3 critères majeurs et au moins 1 critère mineur

Critères majeurs	1-Prolifération mégacaryocytaire **avec** atypies, **sans fibrose réticulinique** > grade 1, avec augmentation de la richesse médullaire, prolifération granuleuse et souvent diminution de l'érythropoïèse 2-Absence des critères diagnostiques de LMC, de PV, de TE, de SMD ou autre néoplasie myéloïde 3-Présence de mutation de **JAK2, CALR ou MPL** ou, en l'absence de ces mutations, présence d'un autre marqueur de clonalité (**ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1**), ou absence de fibrose réticulinique mineure réactionnelle
Critères mineurs	Présence d'au moins un des trois critères suivants, confirmé par 2 déterminations : a. Anémie non liée à une comorbidité b. Hyperleucocytose > 11 x G/L c. Splénomégalie palpable d. Augmentation des LDH au-delà de la norme supérieure ou du seuil de référence local

Critères OMS 2016 Myélofibrose primitive

Le diagnostic requiert les 3 critères majeurs et au moins 1 critère mineur

Critères majeurs	1. Présence d'une prolifération mégacaryocytaire avec atypies cellulaires, **accompagnée d'une fibrose réticulinique et/ou collagène de grade 2 ou 3** 2. Pas de critères OMS de PV, TE, LMC, SMD ou autre hémopathie myéloïde 3. Présence d'une mutation de JAK2, CALR or MPL ou si absence, présence d'un autre marqueur clonal*, ou absence de cause de fibrose médullaire secondaire**
Critères mineurs	Présence d'au moins un des trois critères suivants, confirmé par 2 déterminations : a. Anémie sans autre étiologie **b. Leucocytose > 11 G/L** c. Splénomégalie palpable d. LDH > normale e. Erythro-myélémie

TABLE 3: International Working Group for Myelofibrosis Research and Treatment recommended criteria for diagnosis of post–polycythemia vera and post–essential thrombocythemia myelofibrosis

	Post-PV MF	Post-ET MF
Required criteria	• Previous diagnosis of PV by WHO criteria	• Previous diagnosis of ET by WHO criteria
	• Bone marrow fibrosis grade 2–3 (on 0–3 scale)[a] or 3–4 (on 0–4 scale)[b]	• Bone marrow fibrosis grade 2–3 (on 0–3 scale)[a] or 3–4 (on 0–4 scale)[b]
Additional criteria[c]	• Anemia or loss of requirement for phlebotomy	• Anemia and ≥ 2 mg/mL decrease in Hg from baseline
	• Leukoerythroblastosis	• Leukoerythroblastosis
	• Increase in palpable splenomegaly ≥ 5 cm or appearance of newly palpable splenomegaly	• Increase in palpable splenomegaly ≥ 5 cm or appearance of newly palpable splenomegaly
	• Development of one or more of the following: > 10% weight loss in 6 mo; night sweats; unexplained fever	• Increased LDH level
		• Development of one or more of the following: > 10% weight loss in 6 mo; night sweats; unexplained fever

[a]European classification of bone marrow fibrosis.
[b]Standard classification of bone marrow fibrosis.
[c]Two additional criteria are required for diagnosis of post-PV MF.
ET = essential thrombocythemia; LDH = lactate dehydrogenase; MF = myelofibrosis; PV = polycythemia vera; WHO = World Health Organization

TABLE 2: Treatment approaches for patients with polycythemia vera (PV) or essential thrombocythemia (ET)

Risk category	Treatment approach for PV	Treatment approach for ET
Low	Phlebotomy + low-dose aspirin	Low-dose aspirin for microvascular symptoms
High	Phlebotomy + low-dose aspirin + cytoreductive agent First-line options: • Hydroxyurea • (Pegylated) IFN-α Second-line options: • Ruxolitinib in hydroxyurea-resistant patients • Experimental agents as part of clinical trial	Low-dose aspirin + cytoreductive agent First-line options: • Hydroxyurea Second-line options: • Anagrelide • (Pegylated) IFN-α • Experimental agents as part of clinical trial (eg, JAK inhibitors)

IFN-α = interferon alpha; JAK = janus kinase

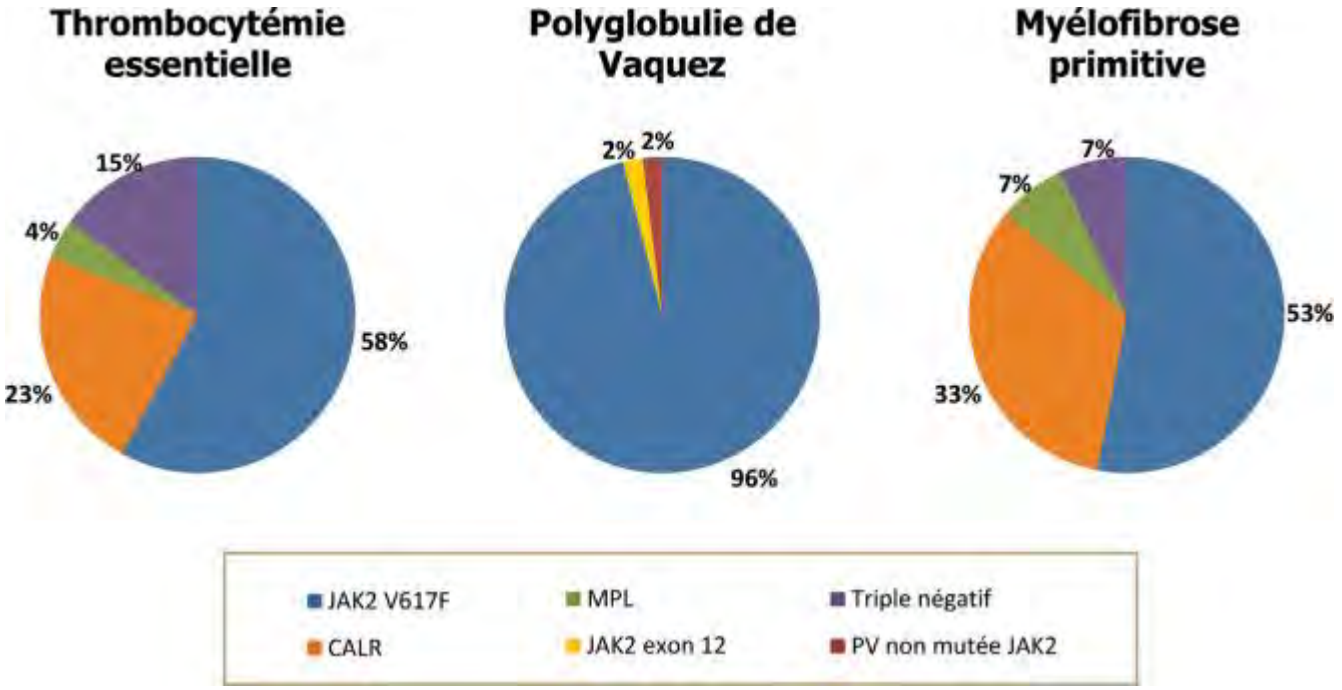
Mutations clé des SMP récepteur des cytokines

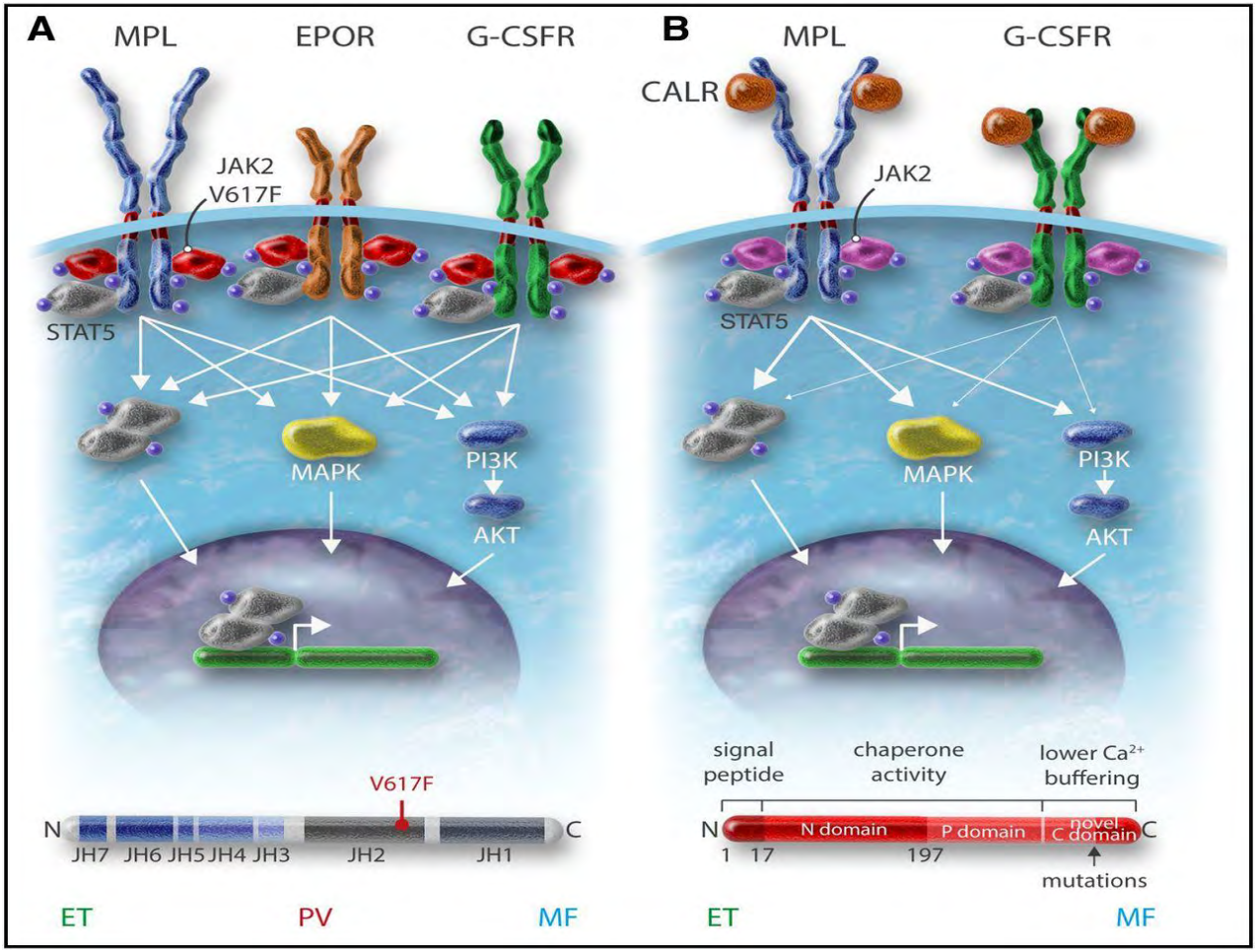
JAK 2, CALR, MPL

- La mutation la plus fréquente JAK2V61F active les 3 récepteurs principaux des cytokines myéloïdes soit le récepteur à l'EPO, granulocyte-colony-stimulating factor et MPL (myeloproliferative leukemia virus)

- Les mutants CALR et MPL sont restreint à l'activation de MPL

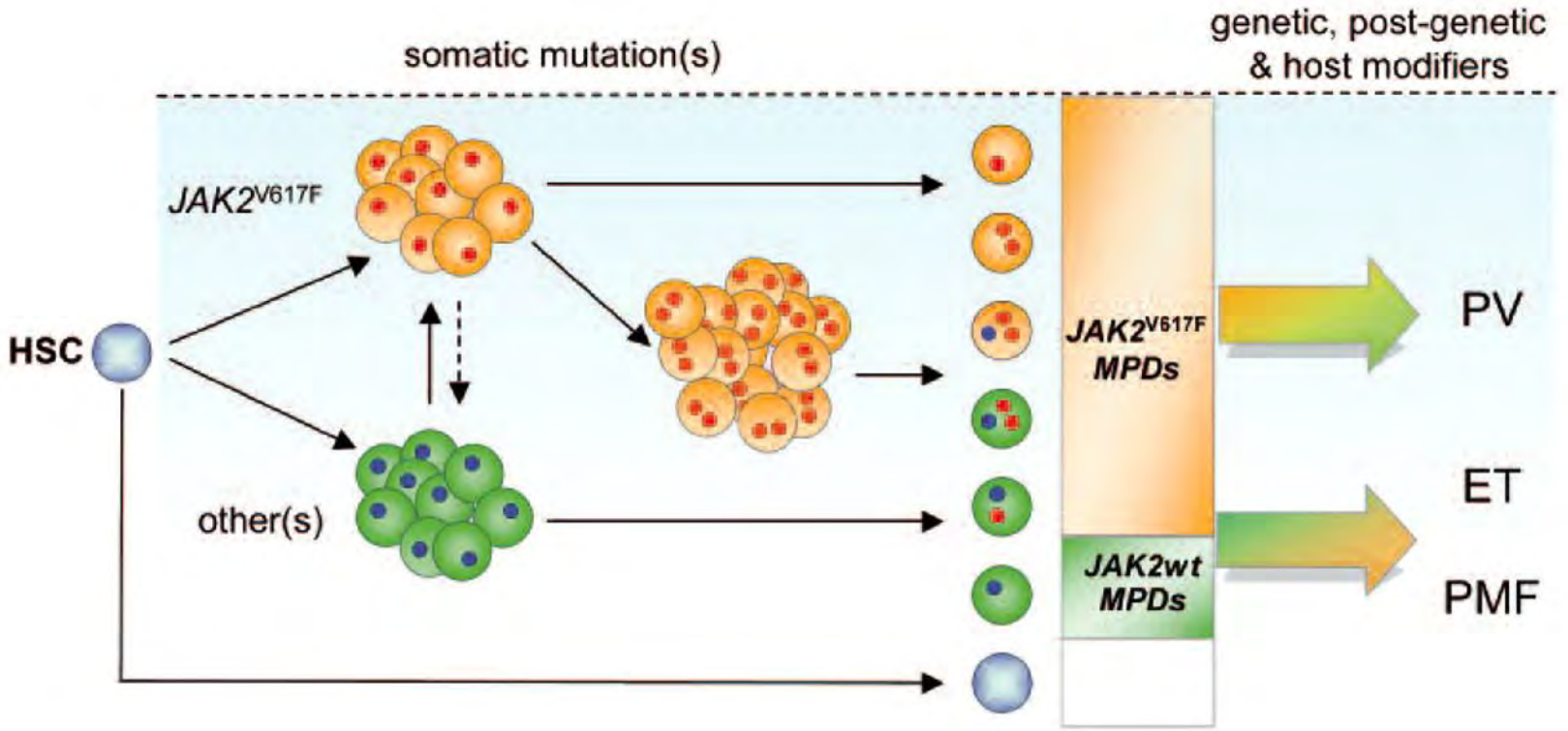
- Ceci explique pourquoi la mutation de JAK 2 est associée au phénotype des 3 SMP alors que les autres mutants sont associés à et MF


Thrombocytémie essentielle
15%
4%
58%
23%
Polyglobulie de Vaquez
2%
2%
96%
Myélofibrose primitive
7%
7%
53%
33%
JAK2 V617F
MPL
Triple négatif
CALR
JAK2 exon 12
PV non mutée JAK2



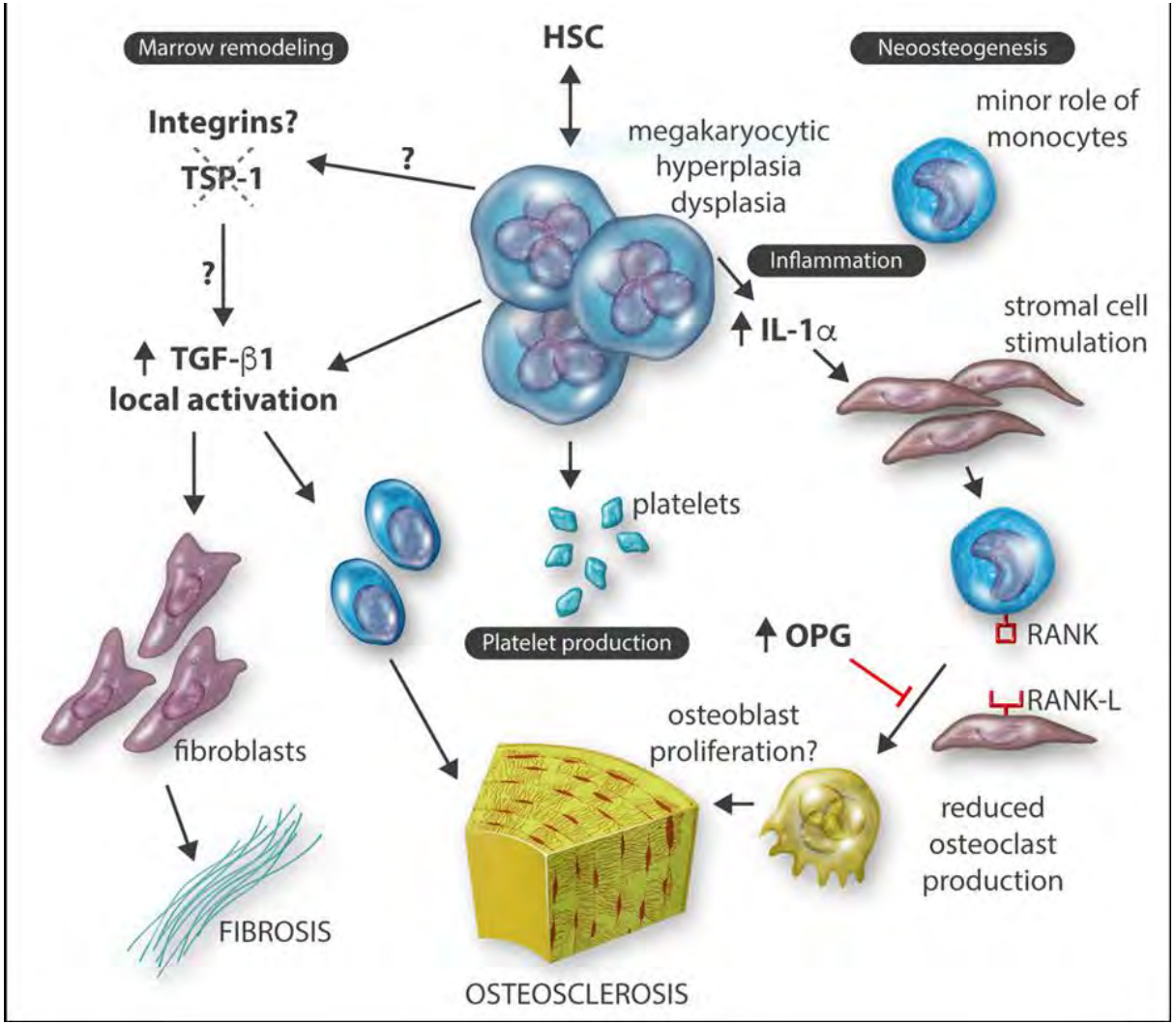
Blood feb 2017 vol 129

The figure describes a working model of genetic events and other mechanisms possibly involved in the pathophysiology of myeloproliferative disorders.

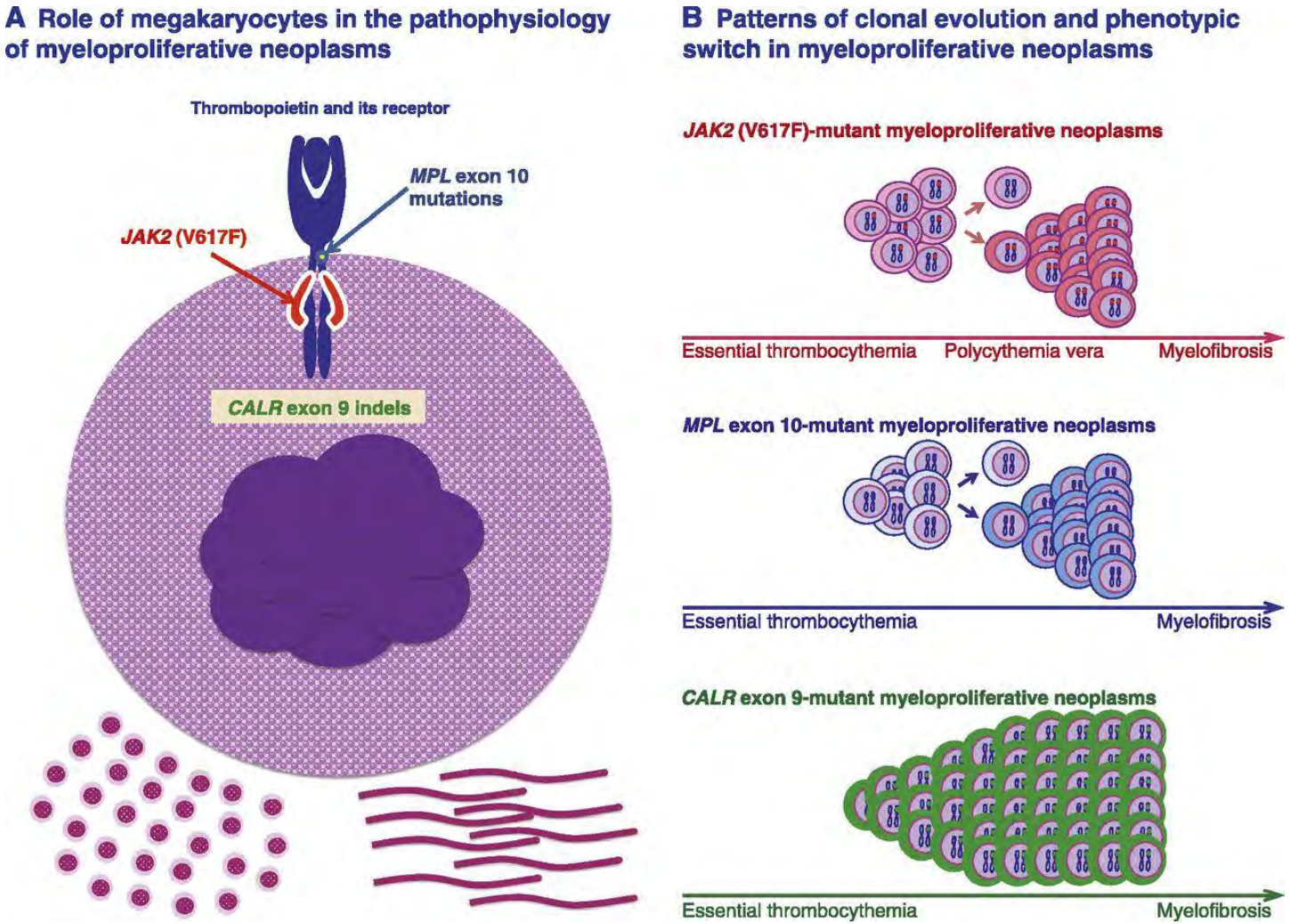


Alessandro M. Vannucchi, and Paola Guglielmelli
Haematologica 2008;93:972-976

haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

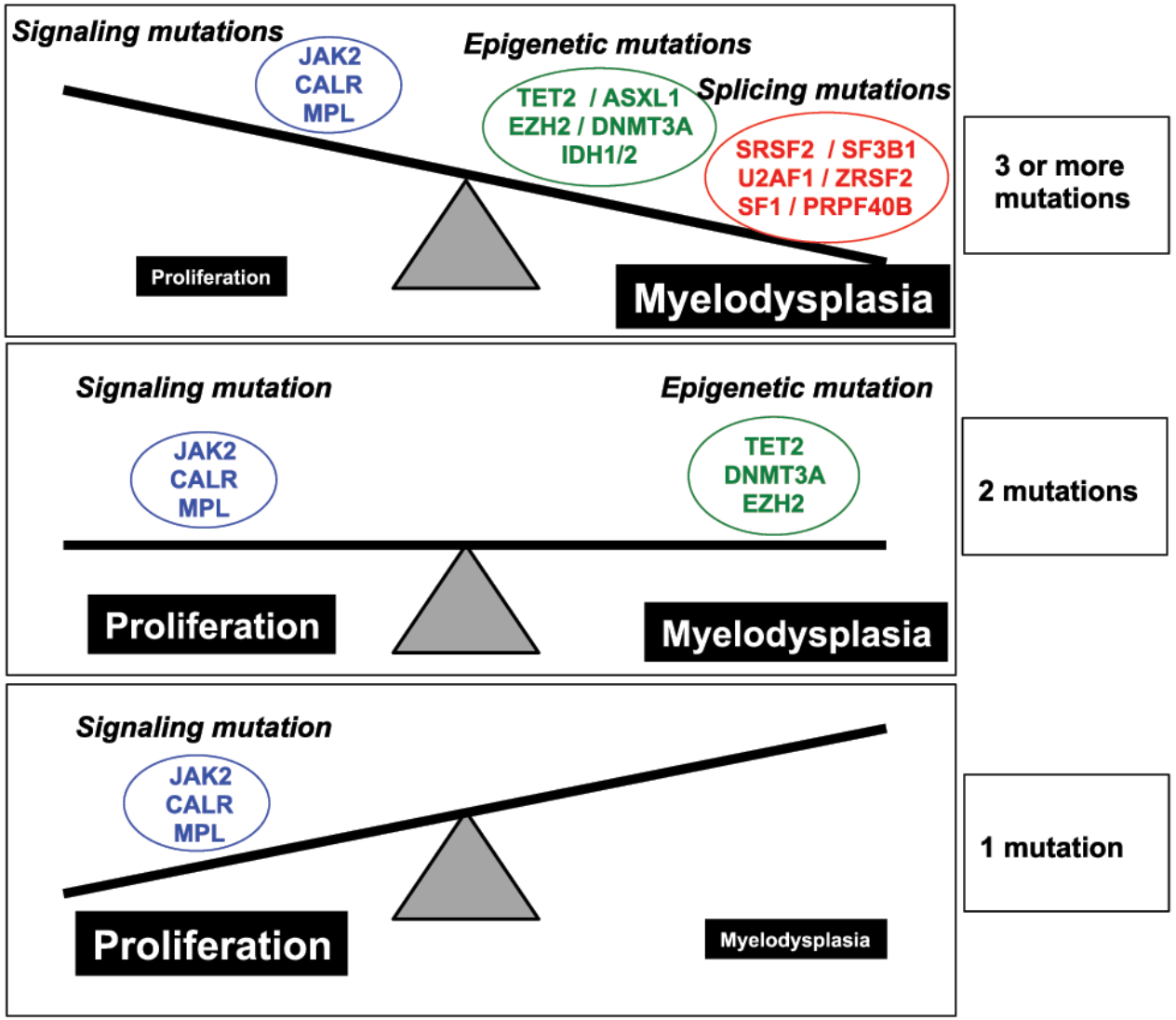

Marrow remodeling
HSC
Neoosteogenesis
Integrins?
TSP-1
?
megakaryocytic
hyperplasia
dysplasia
minor role of
monocytes
?
Inflammation
↑ TGF-β1
local activation
↑ IL-1α
stromal cell
stimulation
platelets
Platelet production
↑ OPG
RANK
RANK-L
fibroblasts
osteoblast
proliferation?
reduced
osteoclast
production
FIBROSIS
OSTEOSCLEROSIS

Role of megakaryocytes in the pathophysiology of myeloproliferative neoplasms, and patterns of clonal evolution and phenotypic switch in these disorders.

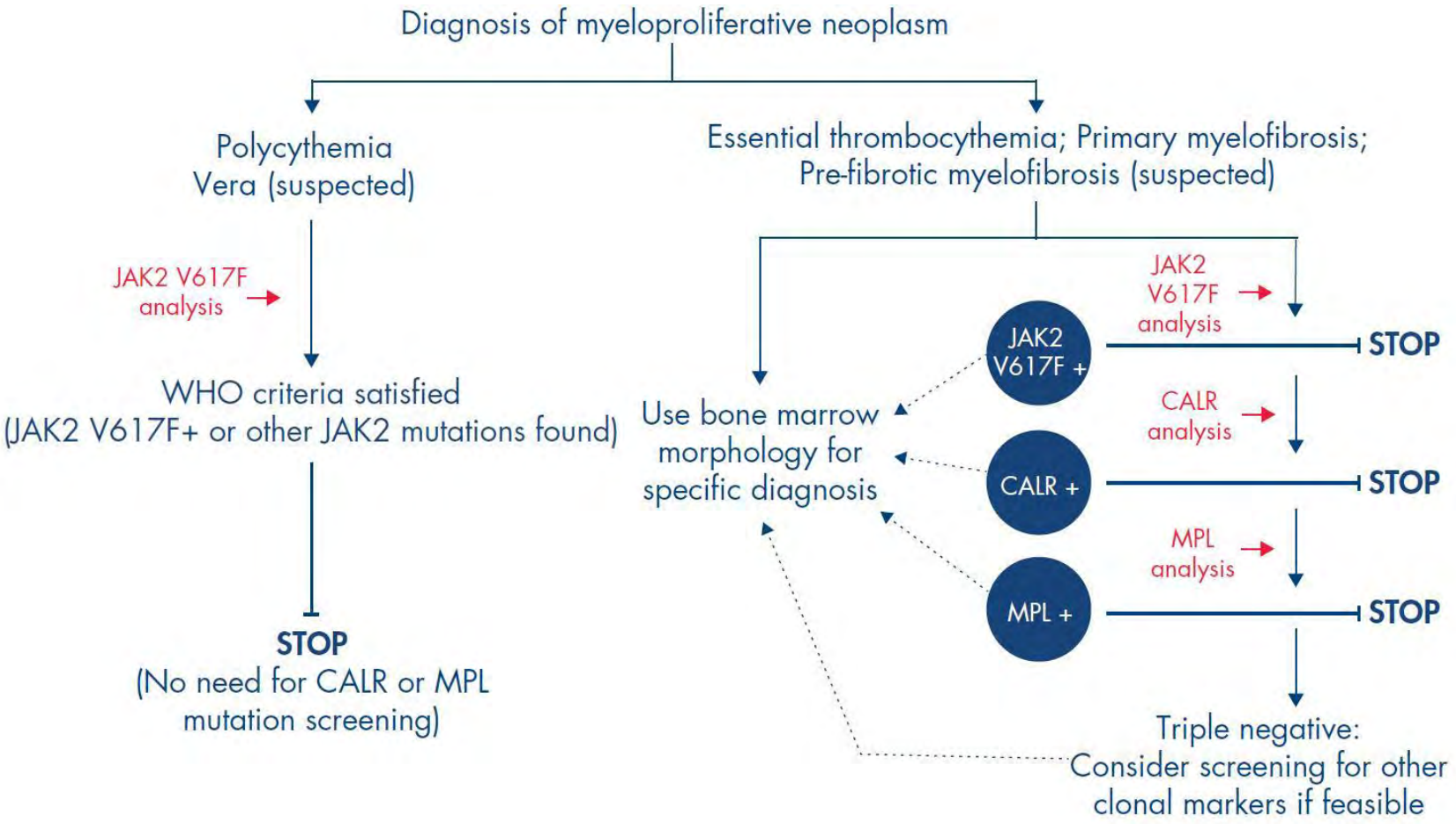


Mario Cazzola, and Robert Kralovics Blood 2014;123:3714-3719

Figure 3. The type and the number of mutations determine the phenotype of the disease



Vainchenker W, Constantinescu SN and Plo I. Recent advances in understanding myelofibrosis and essential thrombocythemia [version 1]. F1000Research 2016, 5:700 (doi: 10.12688/f1000research.8081.1)

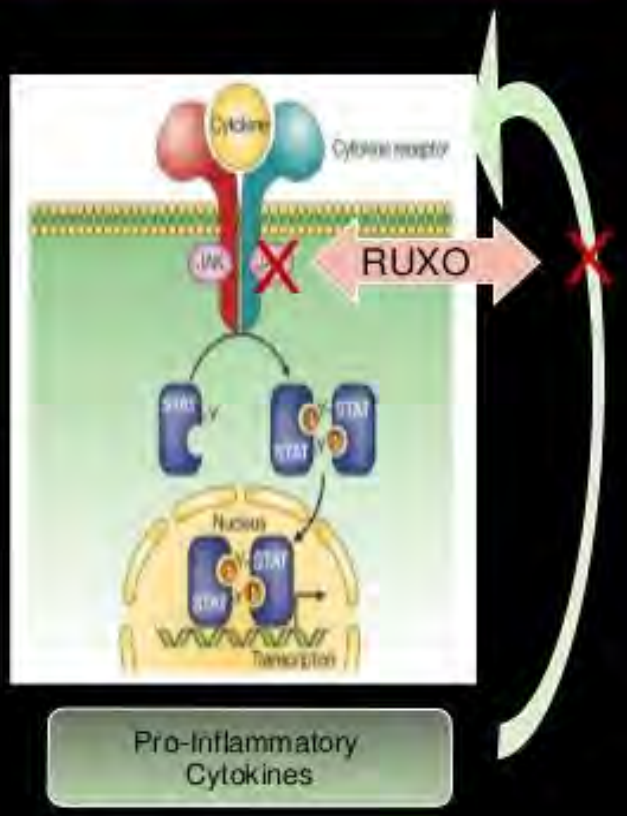

Diagnosis of myeloproliferative neoplasm
Polycythemia Vera (suspected)
JAK2 V617F analysis
WHO criteria satisfied (JAK2 V617F+ or other JAK2 mutations found)
STOP (No need for CALR or MPL mutation screening)
Essential thrombocythemia; Primary myelofibrosis; Pre-fibrotic myelofibrosis (suspected)
JAK2 V617F analysis
JAK2 V617F +
STOP
CALR analysis
CALR +
STOP
MPL analysis
MPL +
STOP
Use bone marrow morphology for specific diagnosis
Triple negative: Consider screening for other clonal markers if feasible

Essential thrombocythemia	Polycythemia vera	Primary myelofibrosis
Thrombosis: • previous thrombosis • age ≥ 60 years • *JAK2* (V617F) ***Bleeding:*** • previous major bleeding • high PLT count (≥1500 x 10^9/L) ***Polycythemic transformation:*** • *JAK2* (V617F) ***Myelofibrotic transformation:*** • *CALR* mutation • co-operating mutations in myeloid genes ***Leukemic transformation:*** • co-operating mutations in myeloid genes ***Survival:*** • previous thrombosis • leukocytosis • co-operating mutations in myeloid genes	***Thrombosis:*** • previous thrombosis • age ≥ 60 years ***Myelofibrotic transformation:*** • *JAK2* (V617F)-mutant allele burden>50% • co-operating mutations in myeloid genes ***Leukemic transformation:*** • co-operating mutations in myeloid genes ***Survival:*** • previous thrombosis • leukocytosis • co-operating mutations in myeloid genes	***Survival & leukemic transformation:*** • age >65 years • presence of constitutional symptoms • anemia (Hb <10 g/dL) • leukocytosis (WBC count >25 x 10^9/L) • thrombocytopenia (<100 x 10^9/L) • circulating blasts (≥1%) • degree of bone marrow fibrosis • unfavorable karyotype • driver mutation (triple negative vs *JAK2/MPL* vs *CALR* mutation) • co-operating mutations in myeloid genes

Ruxolitinib is JAK1 and JAK2 Inhibitor

Potential mechanism of action:

- Inhibits signaling of cytokine and growth factor receptors that use JAK1 and JAK2 for signaling
- Suppresses the growth (JAK2 inhibition) of malignant cells
- Down-regulates the cytokines (JAK1 and JAK2 inhibition) that contribute to hypermetabolic state



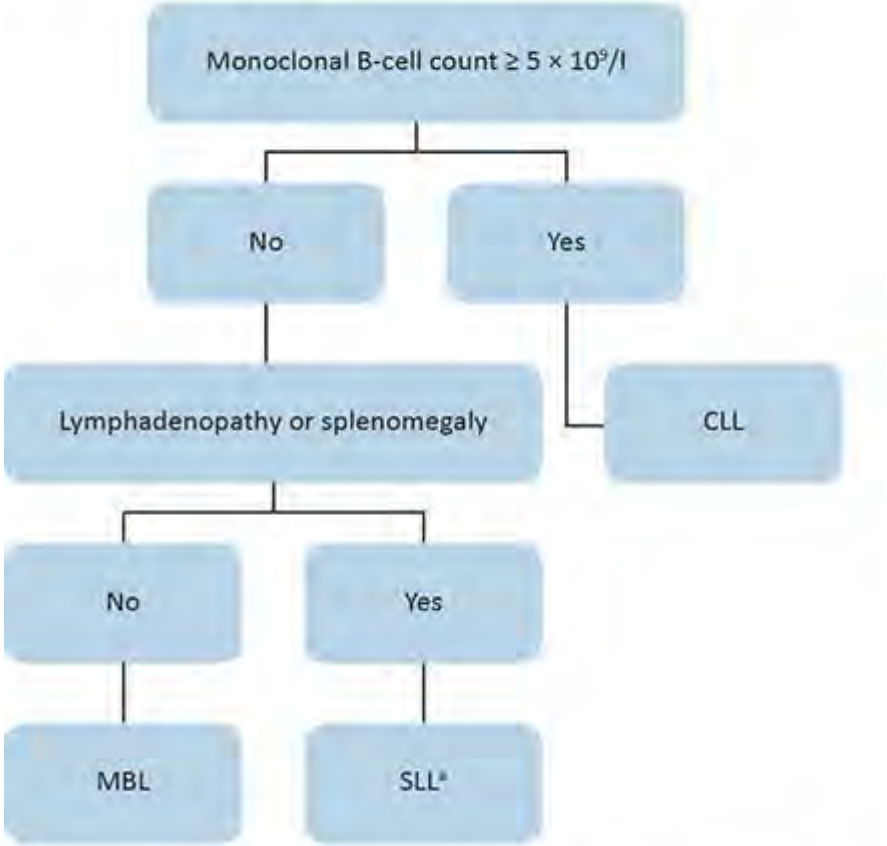
- **CLL**
- L’hémopathie lymphoïde chronique B la plus fréquente
- 5/100000 avant 60 ans et beaucoup plus après
- Souvent découverte fortuite
- CAVE phénomènes auto-immuns

Tableau 1. Stades selon Rai et Binet

Stades selon Rai	Stades selon Rai modifiés		Survie médiane
0	Bas risque	Lymphocytose (sang ou moelle) seule	150 mois
1	Risque intermédiaire	Lymphocytose et adénopathie	101 mois
2		Lymphocytose et splénomégalie et/ou hépatomégalie	71 mois
3	Haut risque	Lymphocytose et anémie (hémoglobine < 110 g/l)	19 mois
4		Lymphocytose et thrombopénie (plaquettes < 100 G/l)	19 mois
Stades selon Binet			
A	Bas risque	Adénopathies (< 3 aires ganglionnaires)	Comme population générale
B	Risque intermédiaire	Adénopathies (≥ 3 aires ganglionnaires)	84 mois
C	Haut risque	Hémoglobine < 100 g/l ou plaquettes < 100 G/l	24 mois

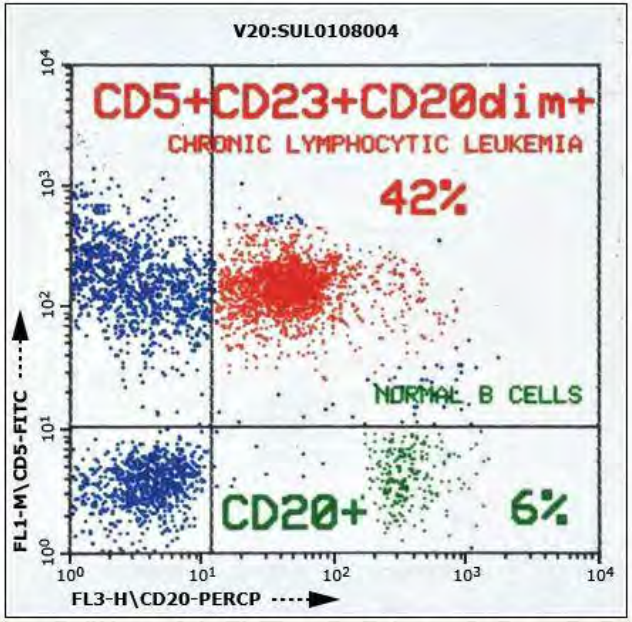
FIGURE 3

Flow chart of the diagnosis of B-cell chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and monoclonal B-cell lymphocytosis (MBL) based on the 2016 World Health Organization criteria.



a) Diagnosis requires histopathological evaluation of lymph node.

Flow cytometry of chronic lymphocytic leukemia



Typically, the cells express dim CD20, dim CD5, and CD23. This figure displays flow cytometry results for CD5 and CD20 expression. The CLL cells are shown in red and demonstrate weak expression of both CD5 and CD20

Table 1 The CLL-International Prognostic Index[30]

Prognostic factor	Points
Del17p on FISH or *TP53* mutation	4
Unmutated *IGHV* genes	2
Serum β2 microglobulin >3.5 mg/L	2
Rai stage I–IV	1
Age >65 years	1

Cumulative CLL-IPI score	Risk category	5-year TFS[a]
0–1	Low risk	78%
2–3	Intermediate risk	54%
4–6	High risk	32%
7–10	Very high risk	0%

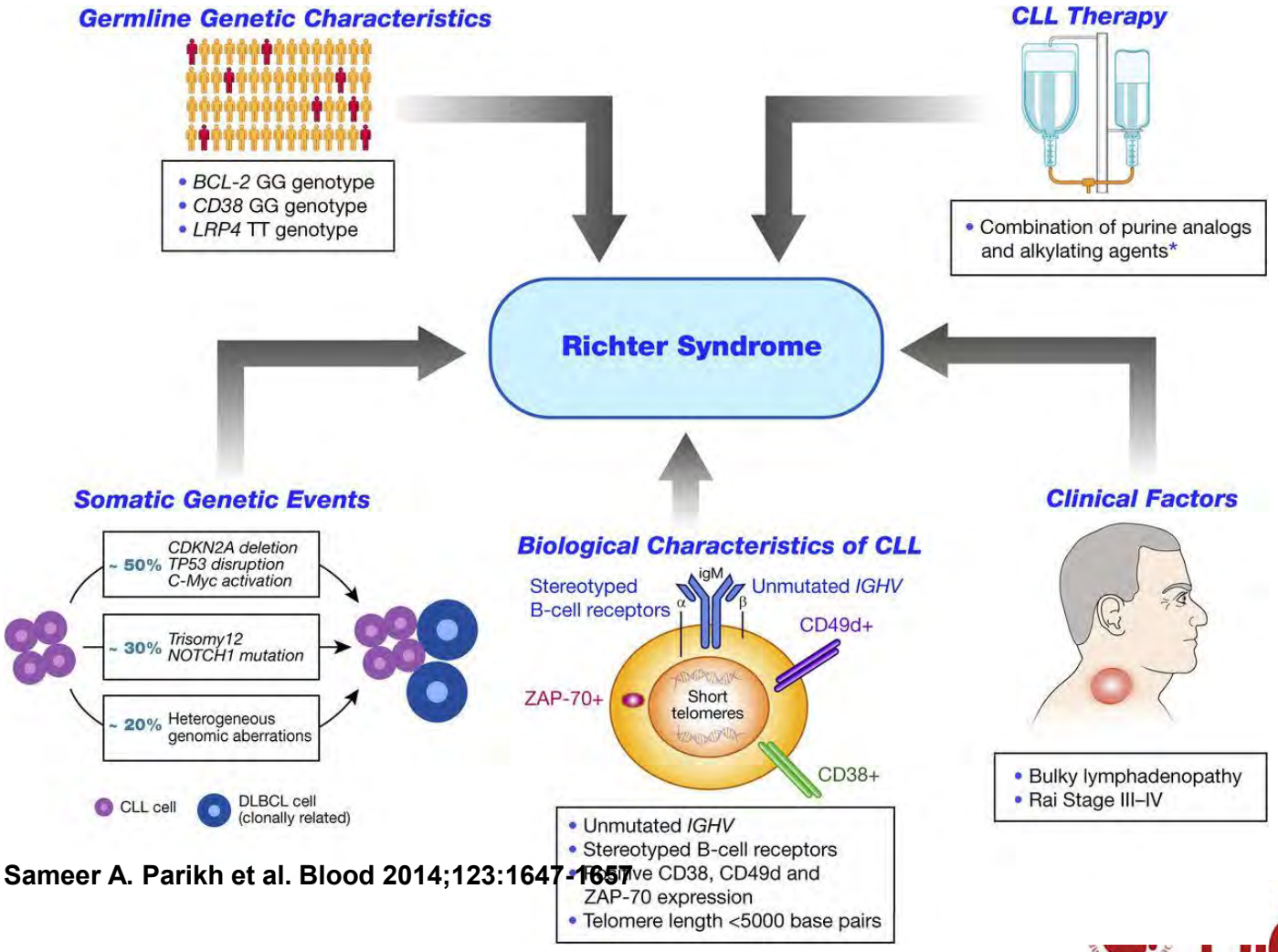
FISH fluorescence in situ hybridization, *IGHV* immunoglobulin heavy chain gene, *TFS* treatment-free survival
[a]For the Mayo validation cohort

Table 2 Updated 2018 International Workshop on CLL (IWCLL) guidelines to initiate CLL therapy[5]

Any **one** of the following criteria should be met to initiate CLL therapy:

- Progressive marrow failure, hemoglobin <10 gm/dL or platelet count of $<100 \times 10^9$/L
- Massive (≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly
- Massive (≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of ≥50% over a 2-month period or lymphocyte doubling time of <6 months
- Autoimmune complications of CLL, that are poorly responsive to corticosteroids
- Symptomatic extranodal involvement (e.g., skin, kidney, lung, spine)
- Disease-related symptoms, including:
  - Unintentional weight loss of ≥10% within the previous 6 months
  - Significant fatigue
  - Fever ≥38 ℃ for 2 or more weeks without evidence of infection
  - Night sweats for ≥1 month without evidence of infection

Risk factors associated with development of Richter syndrome in patients with CLL. *Data on the role of CLL therapy are controversial, with some studies suggesting they are contributory to the development of RS in CLL patients, and other studies suggesting ...



Sameer A. Parikh et al. Blood 2014;123:1647-1657

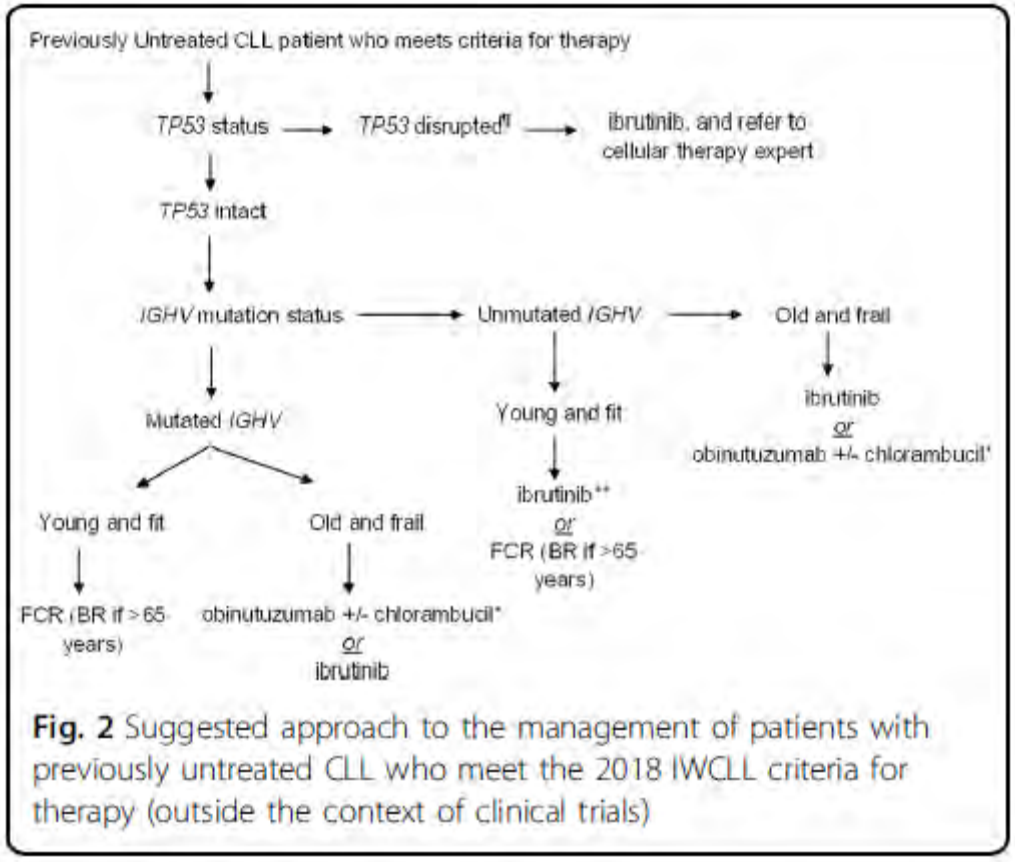
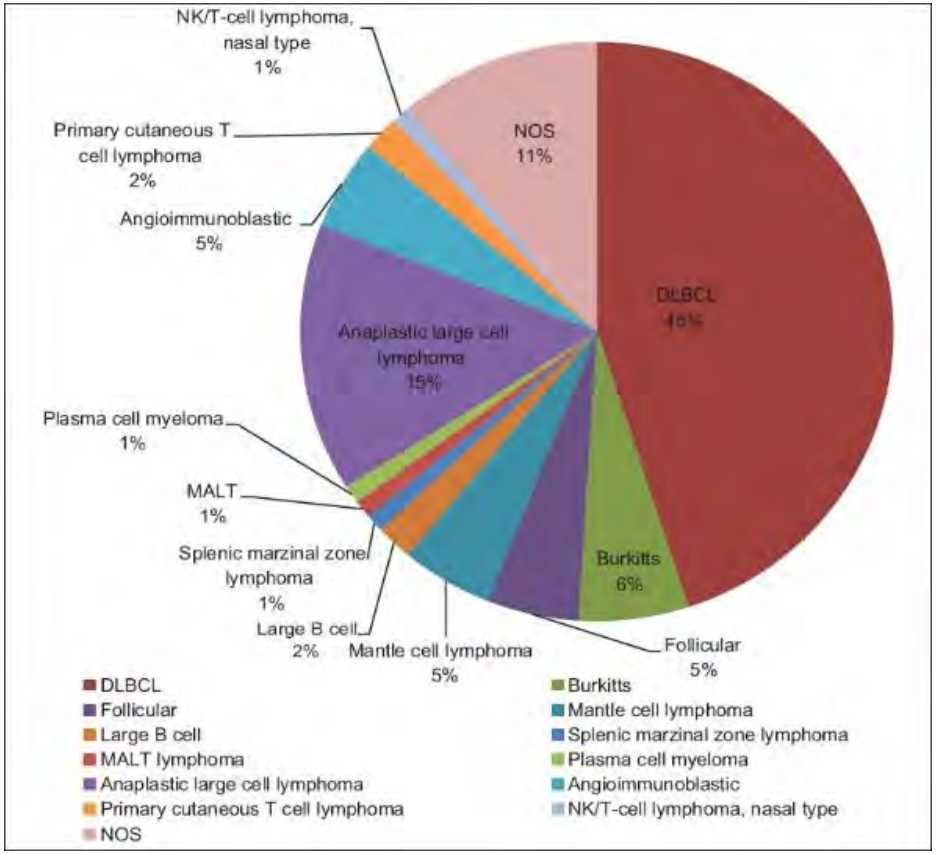
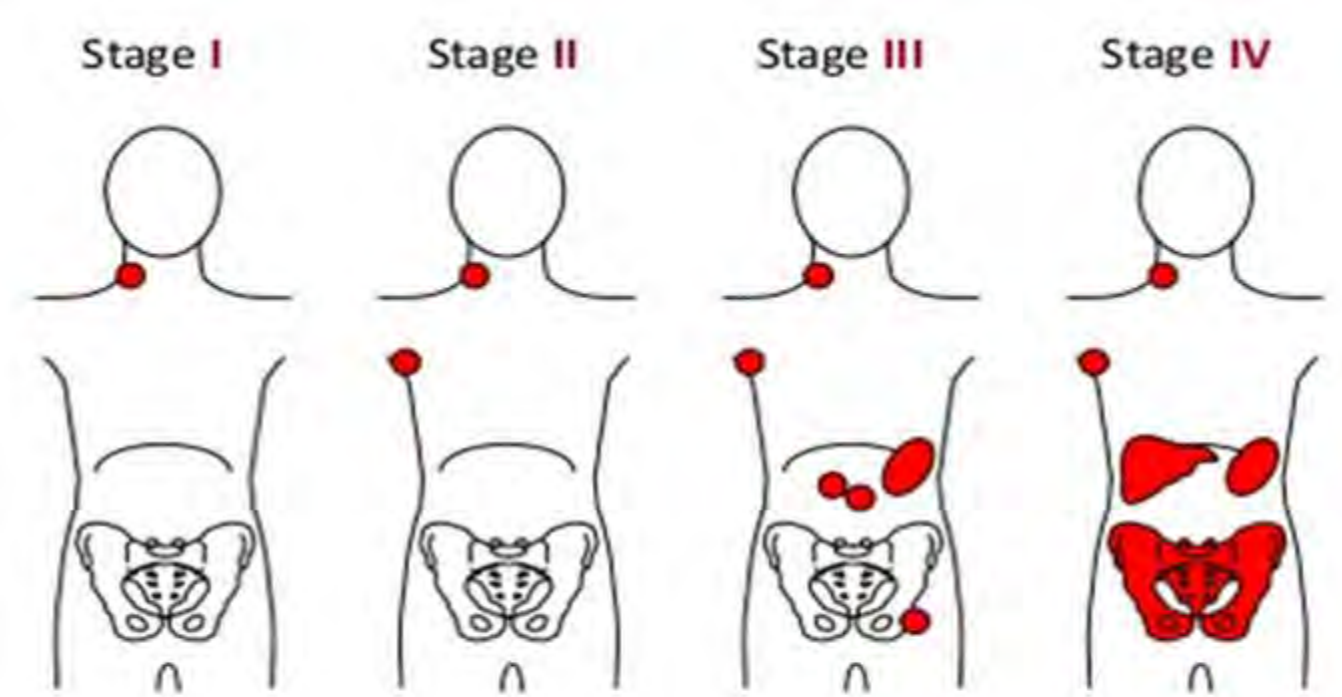


Fig. 2 Suggested approach to the management of patients with previously untreated CLL who meet the 2018 IWCLL criteria for therapy (outside the context of clinical trials)

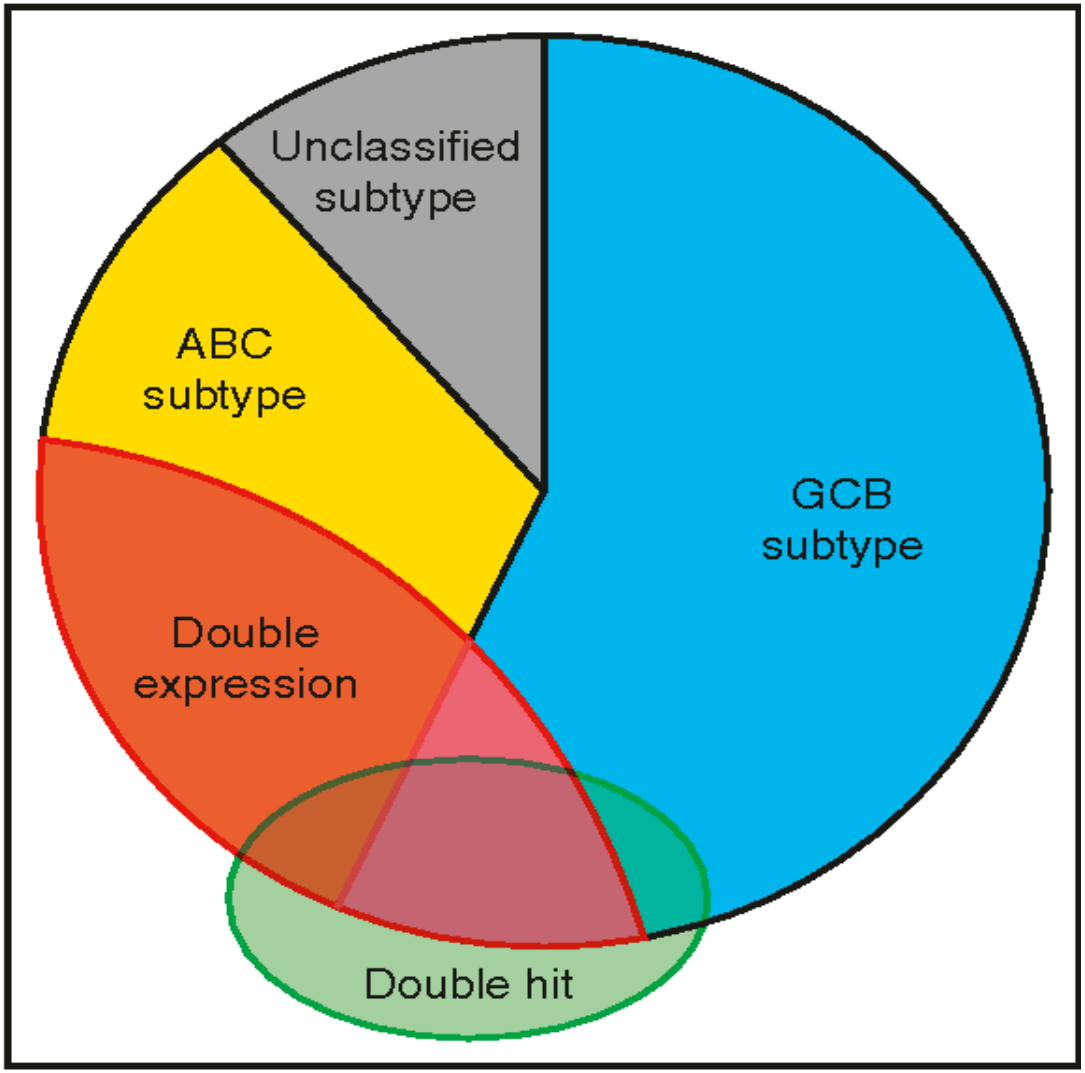
Lymphome B diffus à grandes cellules

- Une des hémopathies les plus fréquentes
- Modifications du pronostic depuis l'introduction du Mabthera
- Nouveaux facteurs de risques biologique pour stratifier le pronostic
- Nouveaux développements dans la compréhension de la biologie pour aboutir à une thérapie adaptée au profil

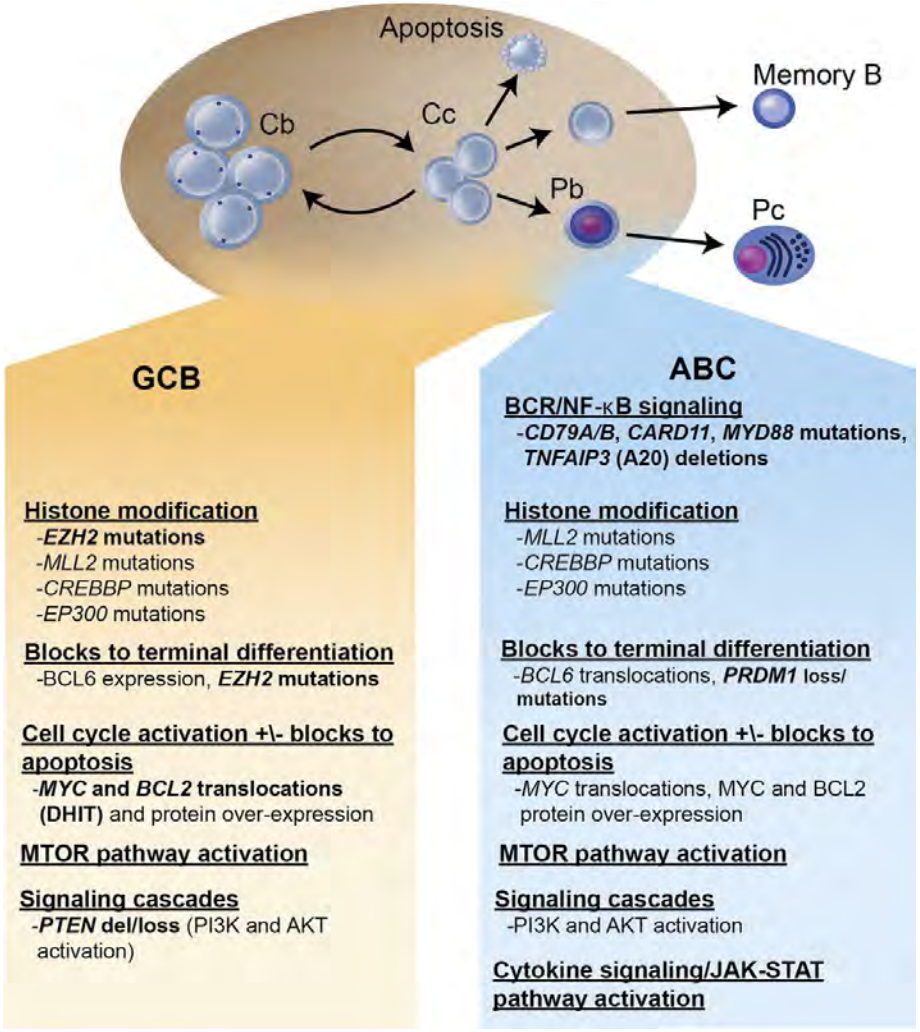

NK/T-cell lymphoma, nasal type 1%
Primary cutaneous T cell lymphoma 2%
Angioimmunoblastic 5%
NOS 11%
DLBCL 46%
Anaplastic large cell lymphoma 15%
Plasma cell myeloma 1%
MALT 1%
Splenic marzinal zone lymphoma 1%
Large B cell 2%
Mantle cell lymphoma 5%
Burkitts 6%
Follicular 5%
DLBCL
Follicular
Large B cell
MALT lymphoma
Anaplastic large cell lymphoma
Primary cutaneous T cell lymphoma
NOS
Burkitts
Mantle cell lymphoma
Splenic marzinal zone lymphoma
Plasma cell myeloma
Angioimmunoblastic
NK/T-cell lymphoma, nasal type



A: absence of B symptoms
B: fever, night sweats, weight loss


Unclassified subtype
ABC subtype
GCB subtype
Double expression
Double hit

Key oncogenic pathways in DLBCL. The 2 major molecular subtypes of DLBCL are shown: the GCB and the ABC type.

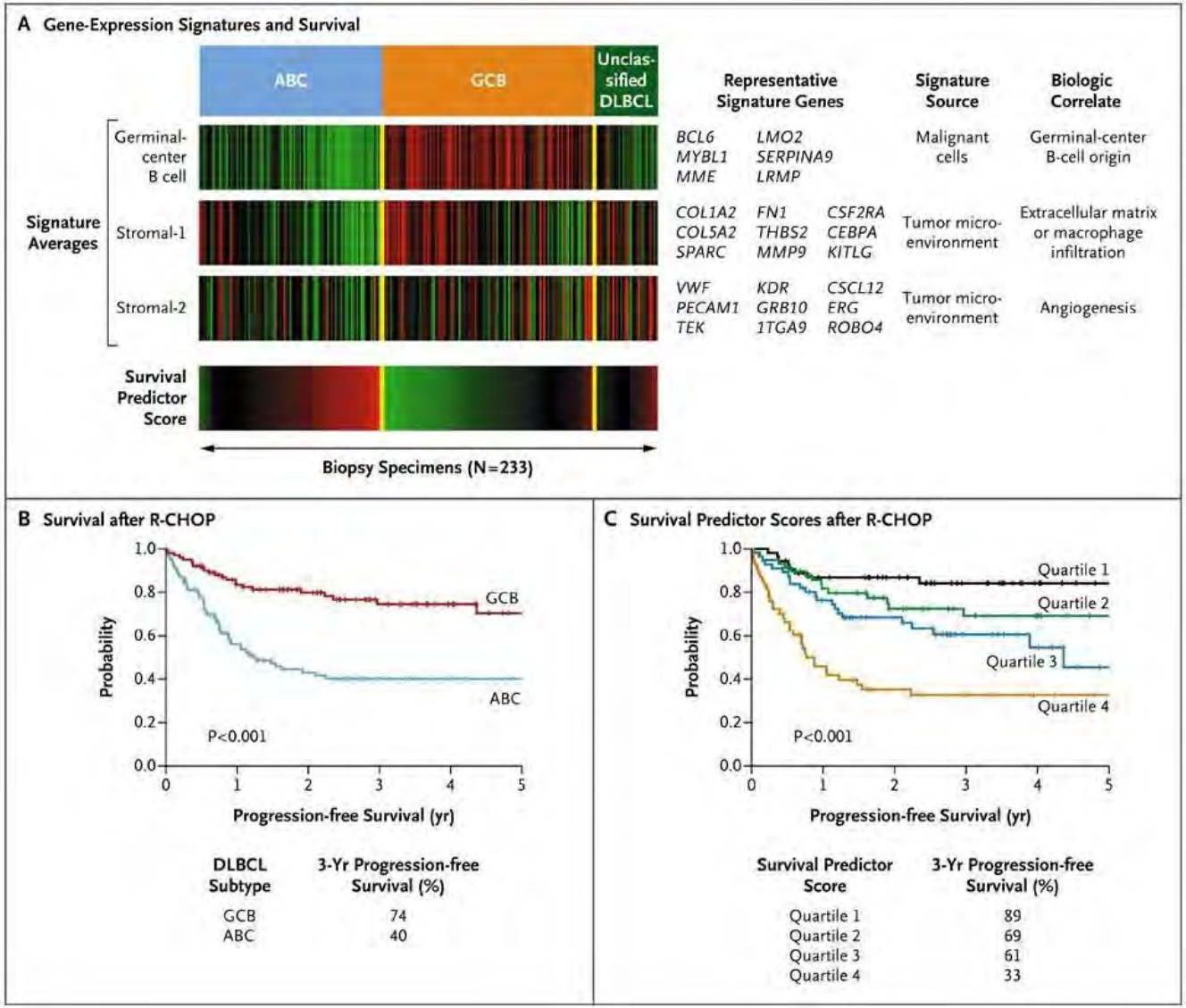


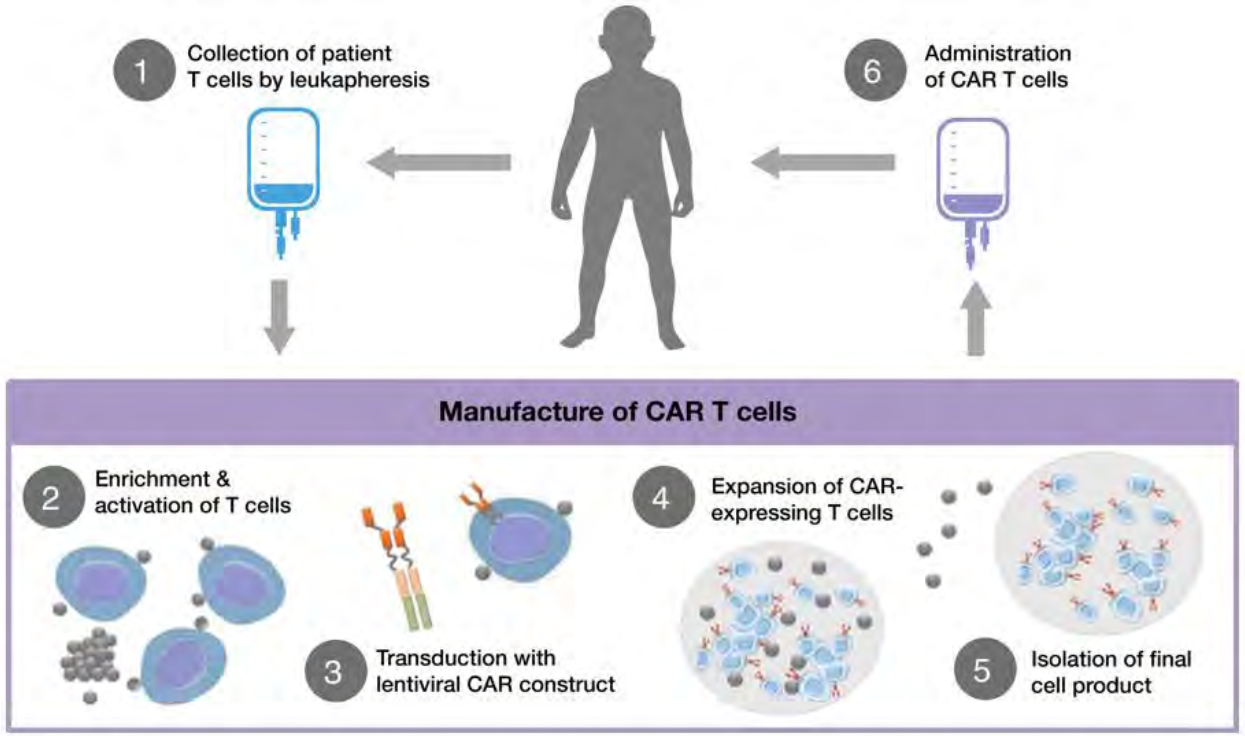
Laurie H. Sehn, and Randy D. Gascoyne Blood 2015;125:22-32

FLIPI (Follicular Lymphoma)		IPI (Large Cell Lymphoma)	
Age >60 yr Ann Arbor stage (III or IV) Hemoglobin level <12 g/dL (120 g/L) Number of nodal* areas >4 Serum LDH level above normal		Age >60 yr Stage I or II Performance status 0 or 1 Extranodal involvement >1 site Serum LDH level >1x normal	
Risk Categories (Factors)	5-/10-yr Overall Survival (%)	Risk Categories (Factors)	5-yr Overall Survival
Low (0-1)	90/70	Low (0-1)	73
Intermediate (2)	77/50	Low Intermediate (2)	51
High (>3)	52/35	High Intermediate (3)	43
		High (4-5)	26

FLIPI = Follicular Lymphoma International Prognostic Index; IPI = International Prognostic Index; LDH = lactate dehydrogenase

*The nodal categories are cervical, mediastinal, axillary, mesenteric, para-aortic, inguinal, epitrochlear, and poplit


A Gene-Expression Signatures and Survival
ABC
GCB
Unclas-sified DLBCL
Representative Signature Genes
Signature Source
Biologic Correlate
Signature Averages
Germinal-center B cell
BCL6 LMO2 MYBL1 SERPINA9 MME LRMP
Malignant cells
Germinal-center B-cell origin
Stromal-1
COL1A2 FN1 CSF2RA COL5A2 THBS2 CEBPA SPARC MMP9 KITLG
Tumor micro-environment
Extracellular matrix or macrophage infiltration
Stromal-2
VWF KDR CSCL12 PECAM1 GRB10 ERG TEK ITGA9 ROBO4
Tumor micro-environment
Angiogenesis
Survival Predictor Score
Biopsy Specimens (N=233)
B Survival after R-CHOP
Probability
GCB
ABC
P<0.001
Progression-free Survival (yr)
DLBCL Subtype
3-Yr Progression-free Survival (%)
GCB 74
ABC 40
C Survival Predictor Scores after R-CHOP
Quartile 1
Quartile 2
Quartile 3
Quartile 4
P<0.001
Survival Predictor Score
3-Yr Progression-free Survival (%)
Quartile 1 89
Quartile 2 69
Quartile 3 61
Quartile 4 33



The treatment process for patients receiving CAR T cell therapy begins with leukapheresis of the patient's T cells. Once isolated, autologous T cells are sent for manufacturing to produce genetically modified CAR T cells, which are reprogrammed to facilitate targeted killing of CD19+ B cells. The treatment process is completed with intravenous infusion of CAR T cells back to the patient. CAR chimeric antigen receptor

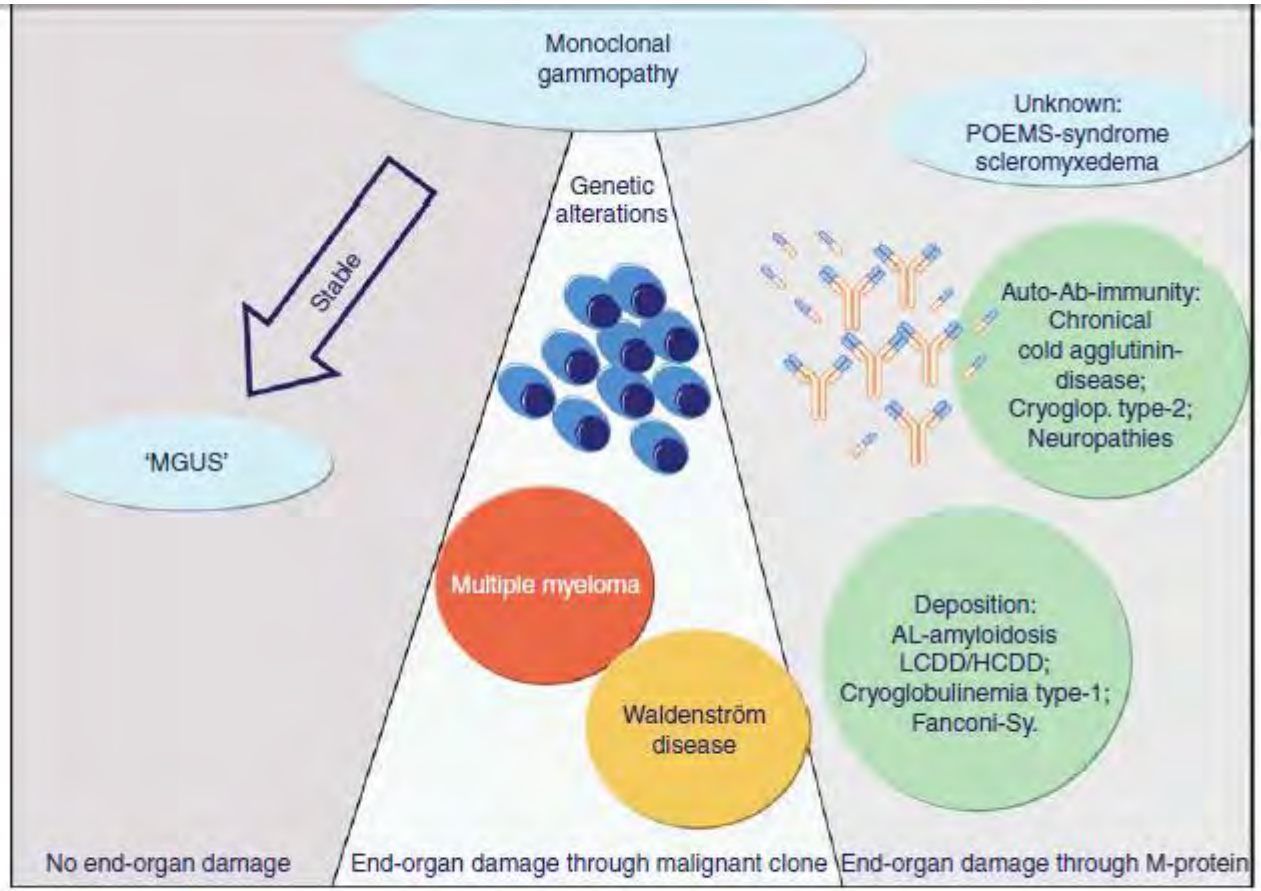
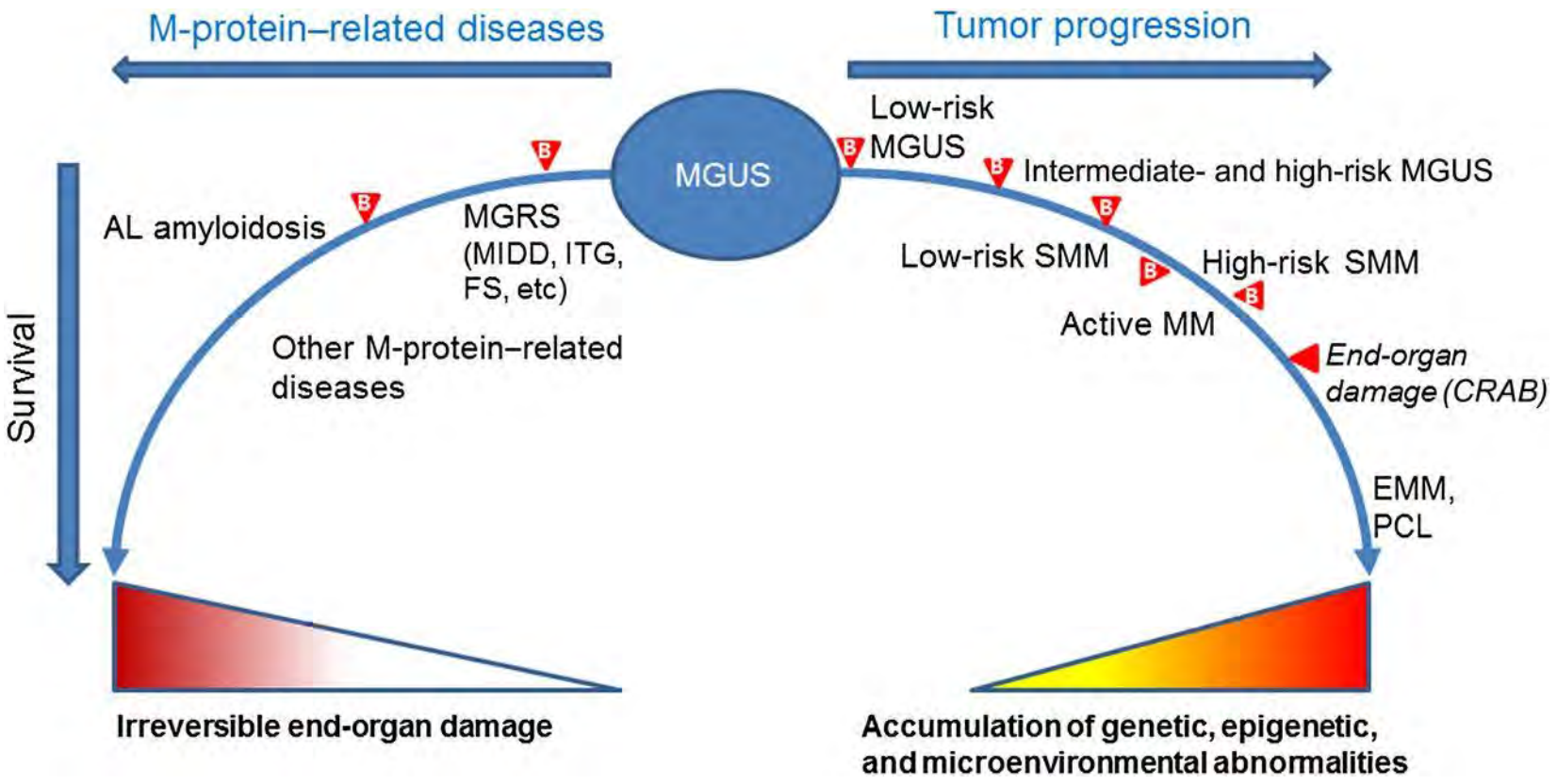


Figure 1. Monoclonal gammopathy and related diseases.
Adapted from Merlini, Palladini, Hematology 2012 [84].

Spectrum of the possible progression of MGUS. Acquisition of somatic genetic and epigenetic abnormalities in the tumor cells and changes in the bone marrow microenvironment lead to the transformation of non-IgM MGUS into SMM, to MM, extramedullary myeloma (...



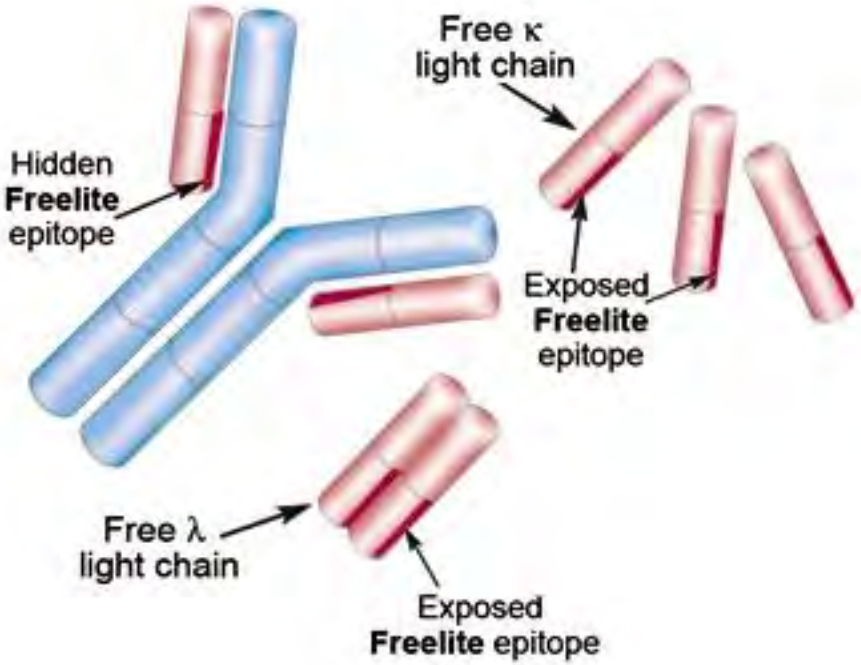
Giampaolo Merlini Blood 2014;123:305-307

Gammapathie monoclonale de signification indéterminée

- Produite par une clone anormal de cellules plasmocytaires ou lymphoïdes
- La gammapathie la plus fréquente
- Critères diagnostic précis
- Comporte un risque d'évolution en pathologie plus grave, dysfonction d'organe
- Immunoglobuline intacte 2 chaînes lourdes et 2 chaînes légères :IgG, IgA,IgM ou que chaîne légère
- 1% / an de risque de progression

Clinique

- Le plus souvent découverte lors d'un bilan fait pour autre chose
- Screening le plus souvent réalisé par l'interniste : anémie, insuffisance rénale, VS élevée, neuropathie
- Pas d'indication à réaliser un screening chez le patient asymptomatique


Free κ
light chain
Hidden
Freelite
epitope
Exposed
Freelite
epitope
Free λ
light chain
Exposed
Freelite epitope

Comment mettre en évidence une gammapathie

- Électrphorèse des protéines : permet de la quantifier, apparaît sous forme d'un pic
- Ne permet pas de détecter les gammapathies de faible concentration
- L'immunofixation doit toujours être réalisée. Permet d'identifier le type de chaîne lourde et légère.
- Dosage des chaînes légère libres, rapport K/L
- Combinaison des tests : sensibilité de l'électrophorèse 82 % et 93 % si ajout de l'immunofixation, 98 % si chaînes lég ajoutées.
- On ajoute toujours les dosages pondéraux des immunoglobules.

MGUS diagnostic différentiel et diagnostic

- MM
- Smodering MM
- Waldenström
- Amyloïdose AL
- Lymphome B low grade
- MGRS
- …..
- M protéine de moins de 30 g/l
- Moins de 10 % de plasmocytose clonale dans la moelle
- Facteurs de risques pour progression
- Suivi à long terme

Stratification

- Taux de la protéine monoclonale : ≥15 g/l
- Type de la protéine : non IgG
- Rapport K/L :anormal
- Faible risque : 0
- Low/ intermédiate : 1 facteur
- High/ intermediate 2 facteurs
- High 3 facteurs

Référer à l'hématologue

- Pour les MGUS risque intermédiaire à haut
- Rapport K/L anormal
- Signes clairs d'évolution
- En fonction de la stratification : examen médullaire
- Suspicion de Waldenström our d'amyloïdose AL
- MGRS

Risk factors for progression per Mayo criteria[3]
M-protein > 1.5 g/dL (15 g/L)
Non-IgG isotype (IgA or IgM)
FLC Ratio < 0.26 or > 1.65

Classification of MGUS and Recommendations for Monitoring and Evaluation

Recommendations for monitoring and evaluation of a confirmed diagnoses of MGUS vary based on risk stratification. Table 4 lists the criteria that determine the likelihood of a patient with MGUS progressing to smoldering multiple myeloma or multiple myeloma.

Table 4

Associated Lab Values (from table 3)	Classification	Monitoring and Evaluation
No risk factors present	Low-risk MGUS *(5% absolute risk of progression at 20 years)*[3]	Repeat serum protein electrophoresis in 6 months and every 2–3 years thereafter if stable No need for bone marrow biopsy or skeletal survey
1 risk factor present	Low intermediate-risk MGUS *(21% absolute risk of progression at 20 years)*[3]	BM biopsy with FISH Consider CT abdomen if IgM monoclonal protein to exclude Waldenström Macroglobulinemia LDH, β_2 microglobulin, CRP If all above are unremarkable, follow CBC serum protein electrophoresis, creatinine in 6 months, and then annually for life
2 risk factors present	High intermediate-risk MGUS *(37% absolute risk of progression at 20 years)*[3]	
3 risk factors present	High-risk MGUS *(58% absolute risk of progression at 20 years)*[3]	

MGUS Risk/ Recommended Tests	UK Myeloma Forum/ Nordic Study Group (2009)[14]	International Expert Consensus (2010)[16]	International Myeloma Working Group (2010)[15]	European Myeloma Network (2014)[17]
Low-Risk MGUS (IgG, <1.5 gm/dL, and normal FLC ratio)	First year, every 3-4 months; then every 6-12 months if stable	First 2 years, every 4-6 months; then every 6-24 months	At 6 months; then every 2-3 years if stable	At 6 months; then every 1-2 years if stable or no follow-up
All other MGUS	At least every 3-4 months	First 2 years, every 4-6 months; then every 6-24 months	At 6 months; then every year if stable	At 6 months; then every year thereafter
Life Expectancy <5 years	Can consider discontinuing follow-up	Not mentioned	Not mentioned	No follow-up
Recommended tests	Quantification of M-protein Serum urea nitrogen CBC Calcium Creatinine Electrolytes Immunoglobulin levels	Quantification of M-protein	Quantification of M-protein CBC	Quantification of M-protein CBC Calcium Creatinine

Myélome multiple

- **Dyscrasie plasmocytaire maligne**
- **Infiltration médullaire par des plasmocytes malins monoclonaux**
- **Plasmocytomes : isolé/multiples, extra-médullaire ou même extra-osseux**
- **Le plasmocytes malins produisent une protéine monoclonale, M protein ou paraprotéine**
- **IgG, IgA ou chaîne légère**
- **Soit asymptomatique ou symptômes parfois non spécifiques**
- **Douleurs**
- **Anémie, infections, hypercalcémie, insuffisance rénale**

Multiple myeloma	Both criteria must be met:
	• Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma
	• Any one or more of the following myeloma defining events:
	  • Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
	  • Hypercalcemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
	  • Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 µmol/L (>2 mg/dL)
	  • Anemia: hemoglobin value of >2 g/dL below the lower limit of normal, or a hemoglobin value <10 g/dL
	  • Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT)
	  • Clonal bone marrow plasma cell percentage ≥60%
	  • Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved free light chain level must be ≥100 mg/L)
	  • >1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5 mm in size)

Table 1. International staging system for multiple myeloma.

Stage	Criteria	Median survival (months)
I	S. β2 microglobulin < 3.5 mg/L, s. Albumin $\geqslant 35$ g/L	62
II	Two categories: • S. β2 microglobulin < 3.5 mg/L, s. Albumin < 35 g/L • S. β2 microglobulin 3.5 to < 5.5 mg/L	44
III	S. β2 microglobulin $\geqslant 5.5$ mg/L	29

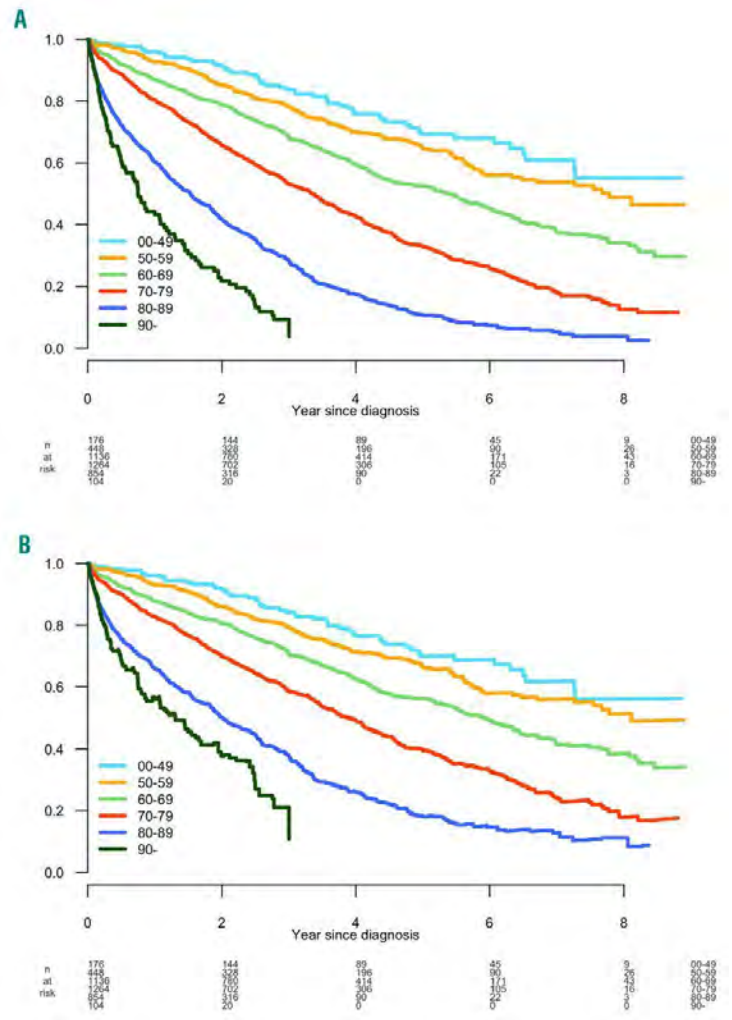
Adapted from Greipp et al.[38]

Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin $<$ 3.5 mg/L, serum albumin $\geq$ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin $\geq$ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH $<$ the upper limit of normal
High	Serum LDH $>$ the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

Survival in active myeloma (MM) in the Swedish Myeloma Registry: observed (A) and relative (B) survival, by 10-year age cohorts. n: number.



Cecilie Hveding Blimark et al. Haematologica 2018;103:506-513

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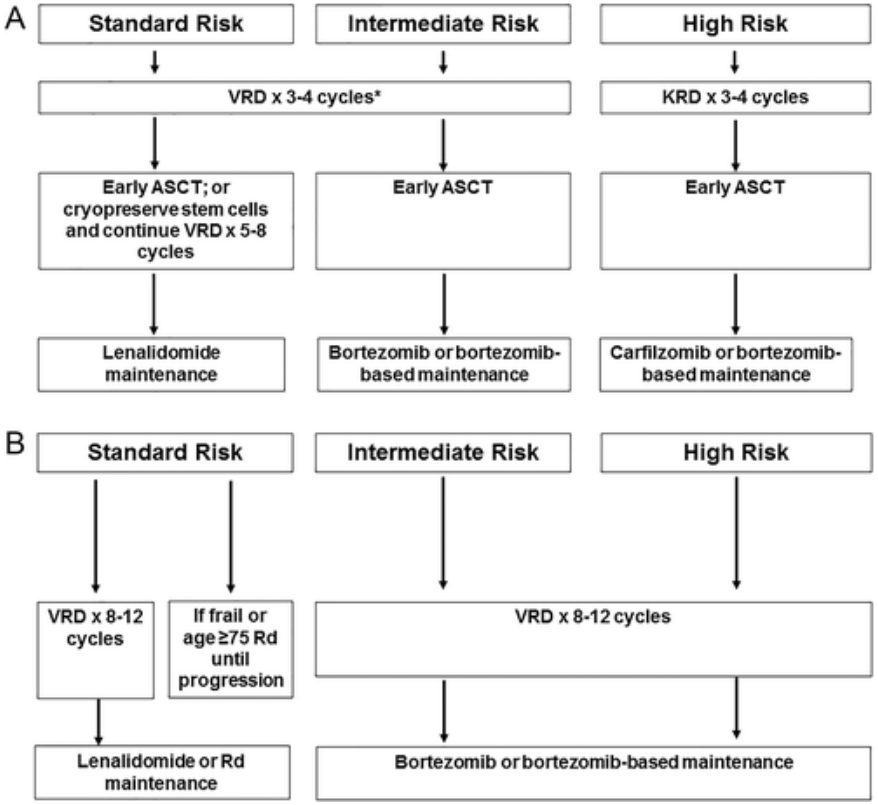
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

Multiple myeloma: 2018 update on diagnosis, risk-stratification, and management



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