Syndrome myéloprolifératifs

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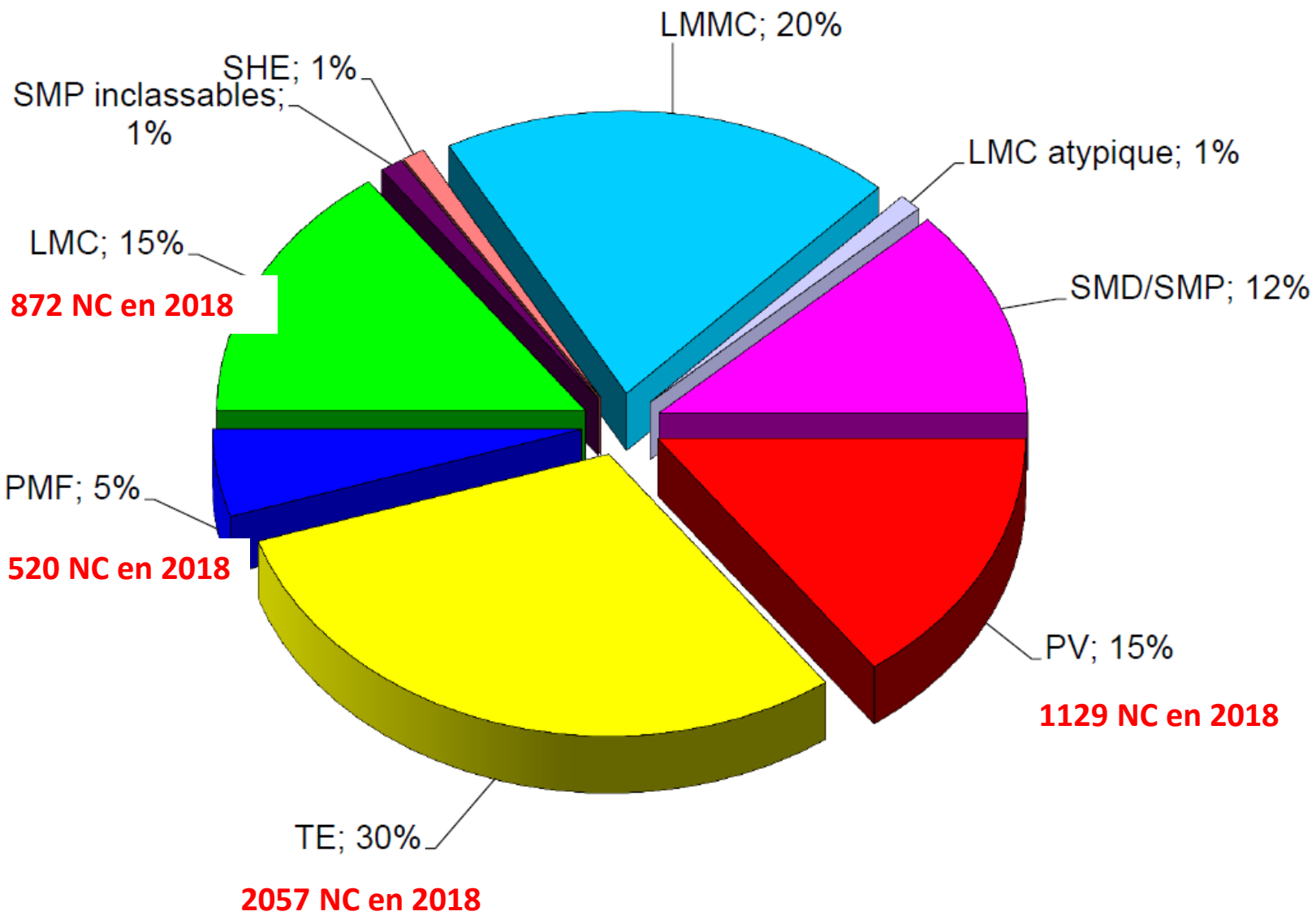
WHO 2016

Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable

Arber Blood 2016

Répartition des SMP



Leucémie myéloïde chronique

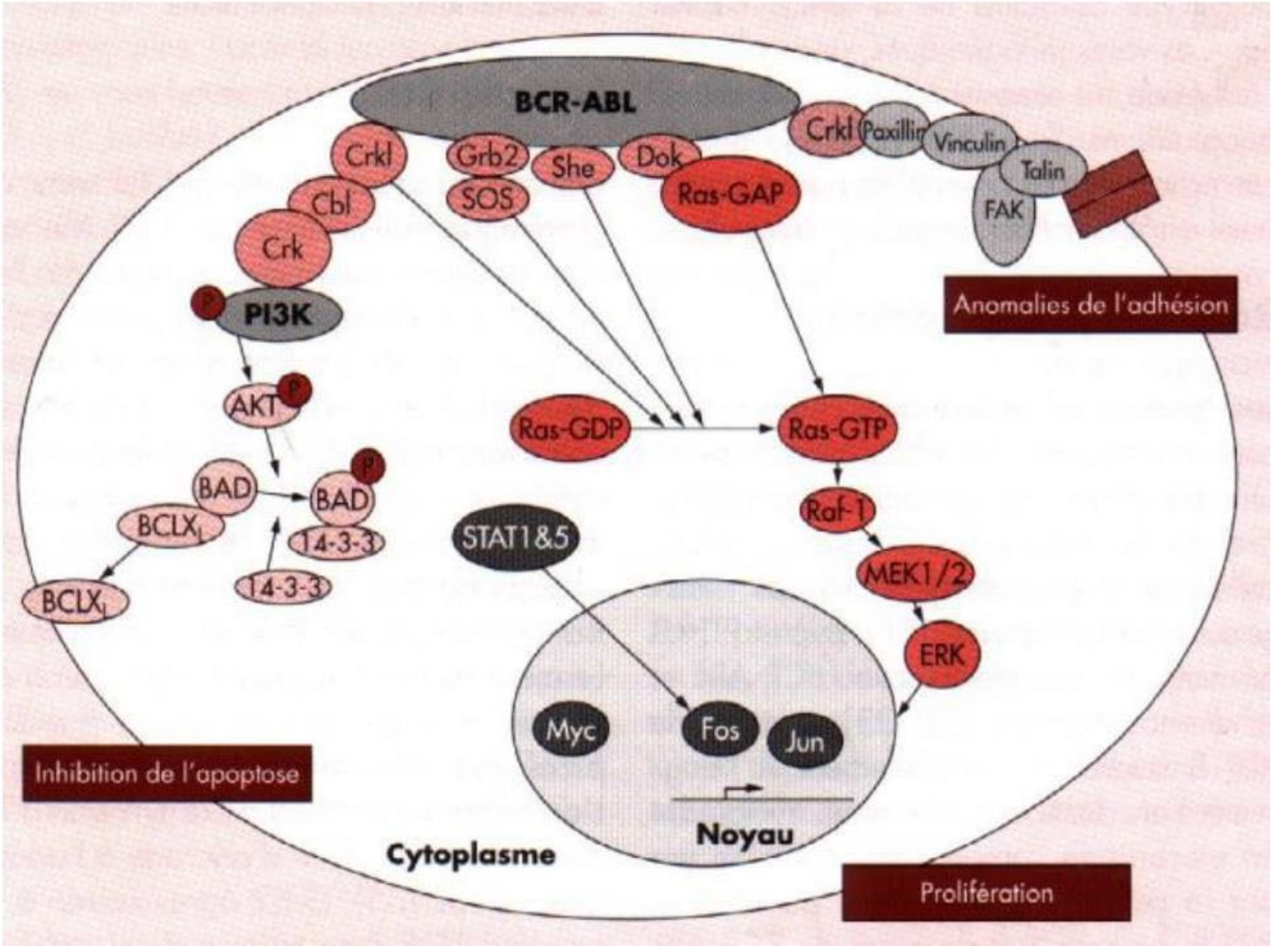
Épidémiologie

- Maladie rare
  - Incidence : environ 10 cas /an/million d'habitants
- Légère prédominance **masculine**
  - Sexe ratio 1,1-1,2
- Plus fréquente **au-delà de 60 ans**
  - Âge médian 61-62 ans
  - Exceptionnelle dans l'enfance
- Quelques facteurs étiologiques identifiés (<5% des cas)
  - Hydrocarbures, chimiothérapies cytotoxiques, rayonnements ionisants

Généralités

- Maladie de la cellule souche hématopoïétique
- Phase chronique, phase accélérée, phase blastique (LAM 2/3 ou LAL 1/3)
- t(9;22)(q34.1;q11.2)= chromosome Philadelphie
- Transcrit de fusion BCR-ABL1
- Protéine de fusion à forte activité tyrosine kinase

Effets oncogénique de *BCR-ABL1* dans les cellules hématopoïétiques



NFS

- **Hyperleucocytose franche**
  - > 100 G/L dans 50% des cas, pouvant atteindre 500 G/L
  - médiane au diagnostic = 105 G/L

- **Polynucléose neutrophile avec myélémie importante**
  - Polynucléaires neutrophiles 40 -60 %
  - Myélémie 30 - 60 %, ++ métamyélocytes et myélocytes, et quelques promyélocytes (< 5 %).
- **Blastes non différenciés et myéloblastes < 5 %**
  - si Nb élevé : envisager une phase accélérée
- Absence de dysgranulopoïèse
- **Excès quasi constant de granulocytes basophiles**
  - jusqu'à 10 - 15% du total leucocytaire
- **Petit excès d'éosinophiles**
  - pouvant parfois dépasser 10 G/L (= 5 - 20% du total leucocytaire)
- Lymphocytes : nombre normal mais parfois augmenté en valeur absolue (augmentation du Nb de lymphocytes T)
- Monocytes : nombre normal (sauf très rares cas d'hypermonocytose associée à un transcrit particulier)

- Hb normale ou anémie
- **Plaquettes augmentées** dans 50% des cas

Myélogramme

- Indispensable pour
  - Définir phase (chronique/accélérée/blastique)
    - Chronique <10/% blastes
    - Accélérée 10-19% blastes
    - Blastique ≥20% blastes
  - Caryotype
  - Biologie moléculaire

Phase accélérée, WHO 2016

Table 2. Criteria for CML, accelerated phase

CML, accelerated phase criteria	
Any 1 or more of the following hematologic/cytogenetic criteria or response-to-TKI criteria:	
• Persistent or increasing WBC (>10 × 10^9/L), unresponsive to therapy	**"Provisional" response-to-TKI criteria**
• Persistent or increasing splenomegaly, unresponsive to therapy	• Hematologic resistance to the first TKI (or failure to achieve a complete hematologic response* to the first TKI) or
• Persistent thrombocytosis (>1000 × 10^9/L), unresponsive to therapy	• Any hematological, cytogenetic, or molecular indications of resistance to 2 sequential TKIs or
• Persistent thrombocytopenia (<100 × 10^9/L) unrelated to therapy	• Occurrence of 2 or more mutations in *BCR-ABL1* during TKI therapy
• 20% or more basophils in the PB	
• 10%-19% blasts† in the PB and/or BM	
• Additional clonal chromosomal abnormalities in Ph^+ cells at diagnosis that include "major route" abnormalities (second Ph, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, or abnormalities of 3q26.2	
• Any new clonal chromosomal abnormality in Ph^+ cells that occurs during therapy	

Large clusters or sheets of small, abnormal megakaryocytes, associated with marked reticulin or collagen fibrosis in biopsy specimens may be considered as presumptive evidence of AP, although these findings are usually associated with 1 or more of the criteria listed above.

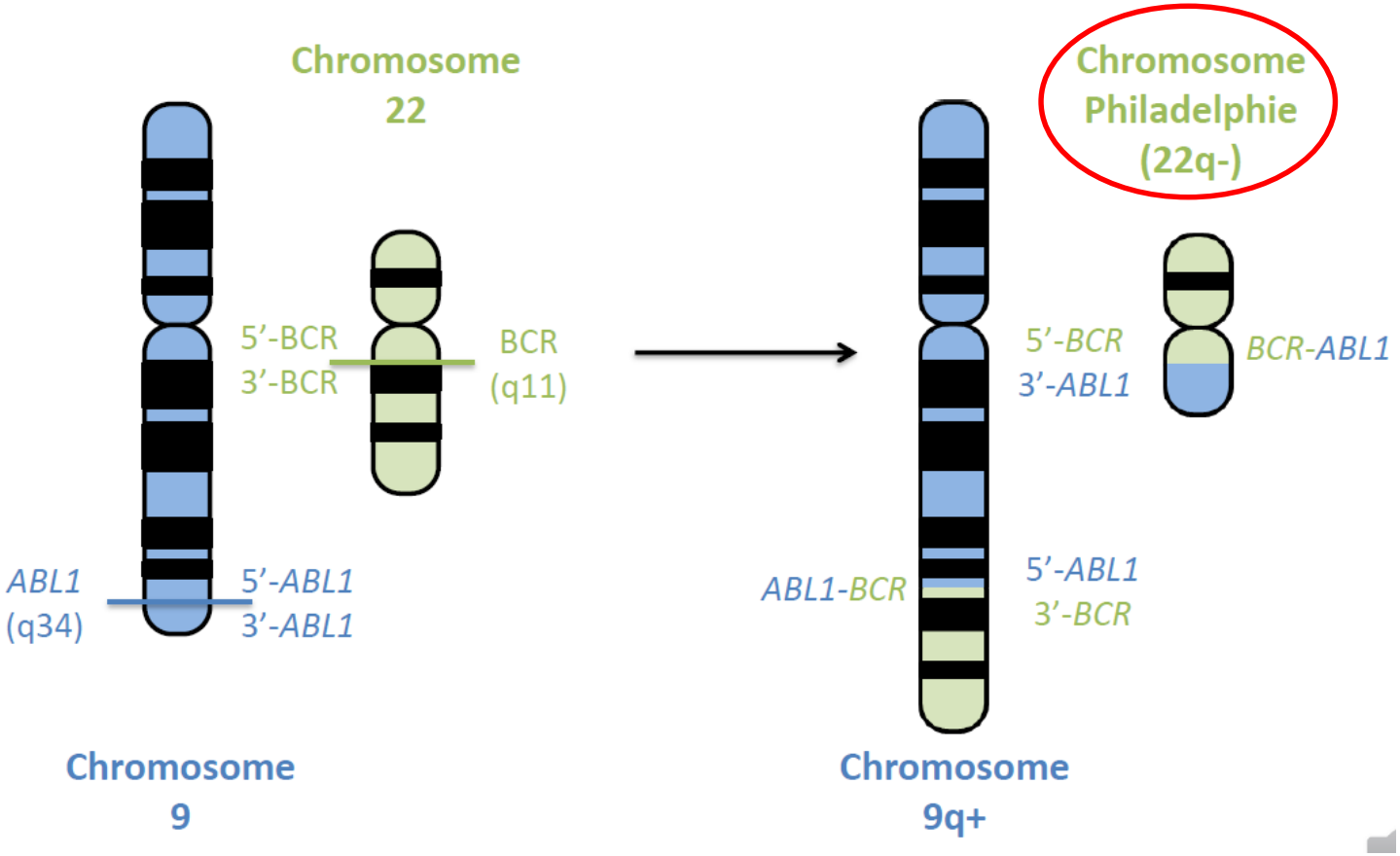
*Complete hematologic response: WBC, <10 × 10^9/L; platelet count, <450 × 10^9/L, no immature granulocytes in the differential, and spleen nonpalpable.

†The finding of bona fide lymphoblasts in the blood or marrow, even if <10%, should prompt concern that lymphoblastic transformation may be imminent and warrants further clinical and genetic investigation; 20% or more blasts in blood or BM, or an infiltrative proliferation of blasts in an extramedullary site is CML, blast phase.

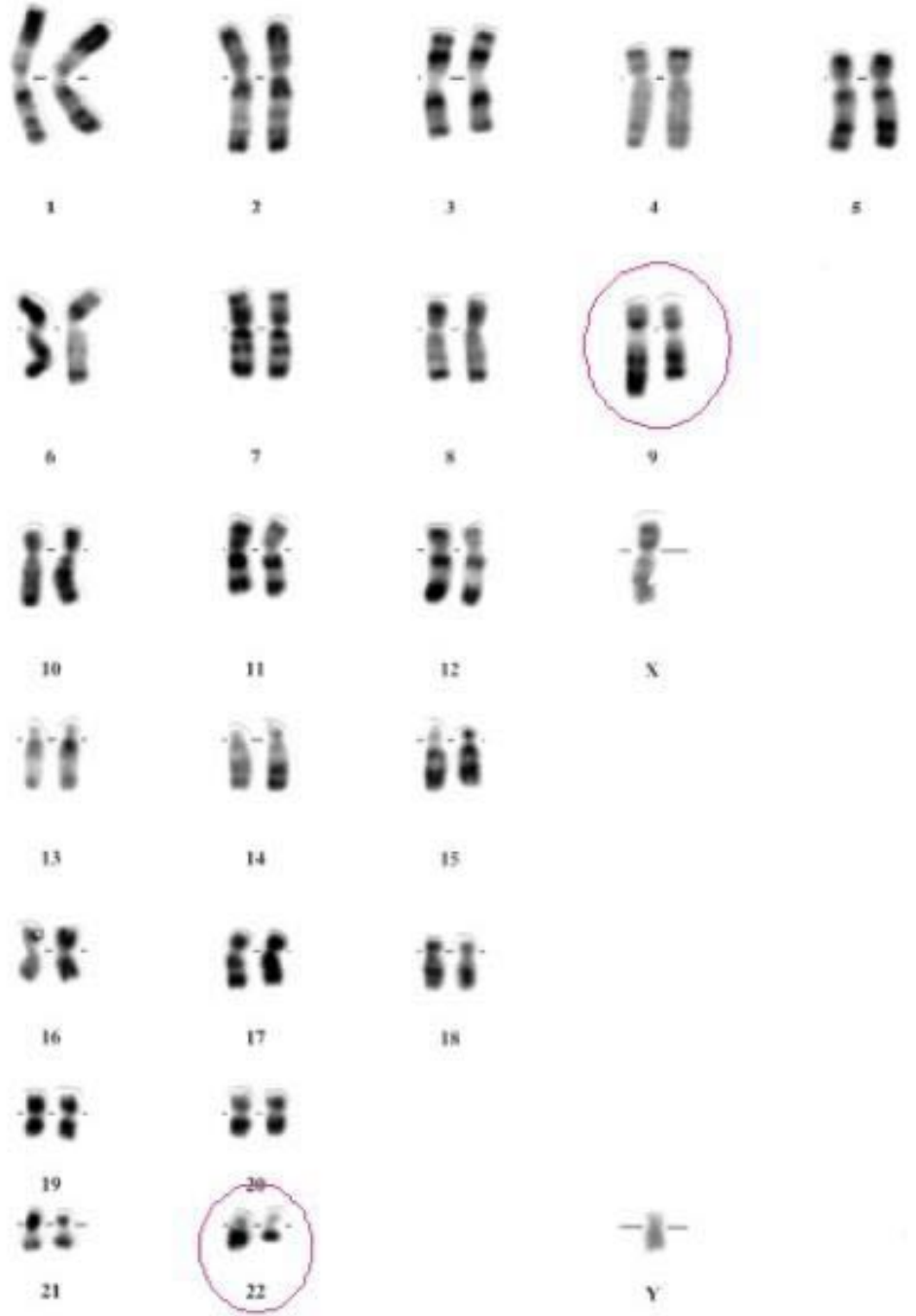
Blood 2016 Arber

Caryotype

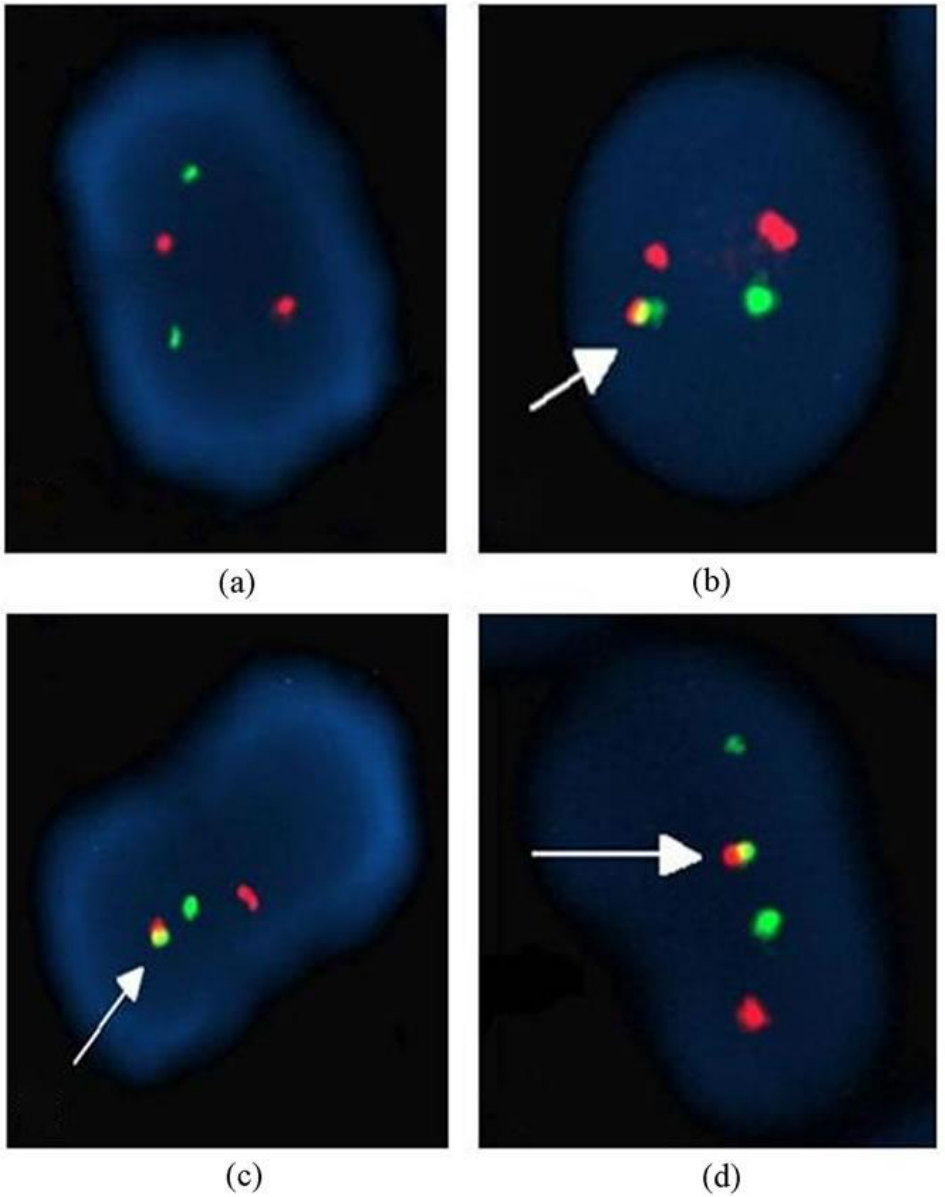
Translocation t(9;22)(q34;q11)



Caryotype



FISH



BCR

ABL1

Biologie moléculaire

- *Points de cassure plutôt regroupés sur abl, alors qu'il existe plusieurs régions de cassure sur bcr*

- **M bcr (Major bcr)**
  - b3a2 (= e14a2) = 60% des cas
  - b2a2 (= e13a2) = 35% des cas
    - protéine de fusion p210

- **m bcr (minor bcr)**
  - 0.4 % des LMC
  - Transcrit e1a2 (=>protéine p190)
  - Fréquemment associé à : monocytose, absence de basophilie, et absence de splénomégalie
  - (m bcr retrouvé dans environ 2/3 des LAL Ph+)

- **µ bcr (micro bcr)**
  - < 0.1 % des LMC
  - Transcrit e19a2 (=>protéine p230)
  - **LMC à polynucléaires neutrophiles** : expansion essentiellement de polynucléaires neutrophiles, thrombocytose parfois > 1000 G/L, évolution plus indolente que la LMC classique, une tendance moindre à transformer

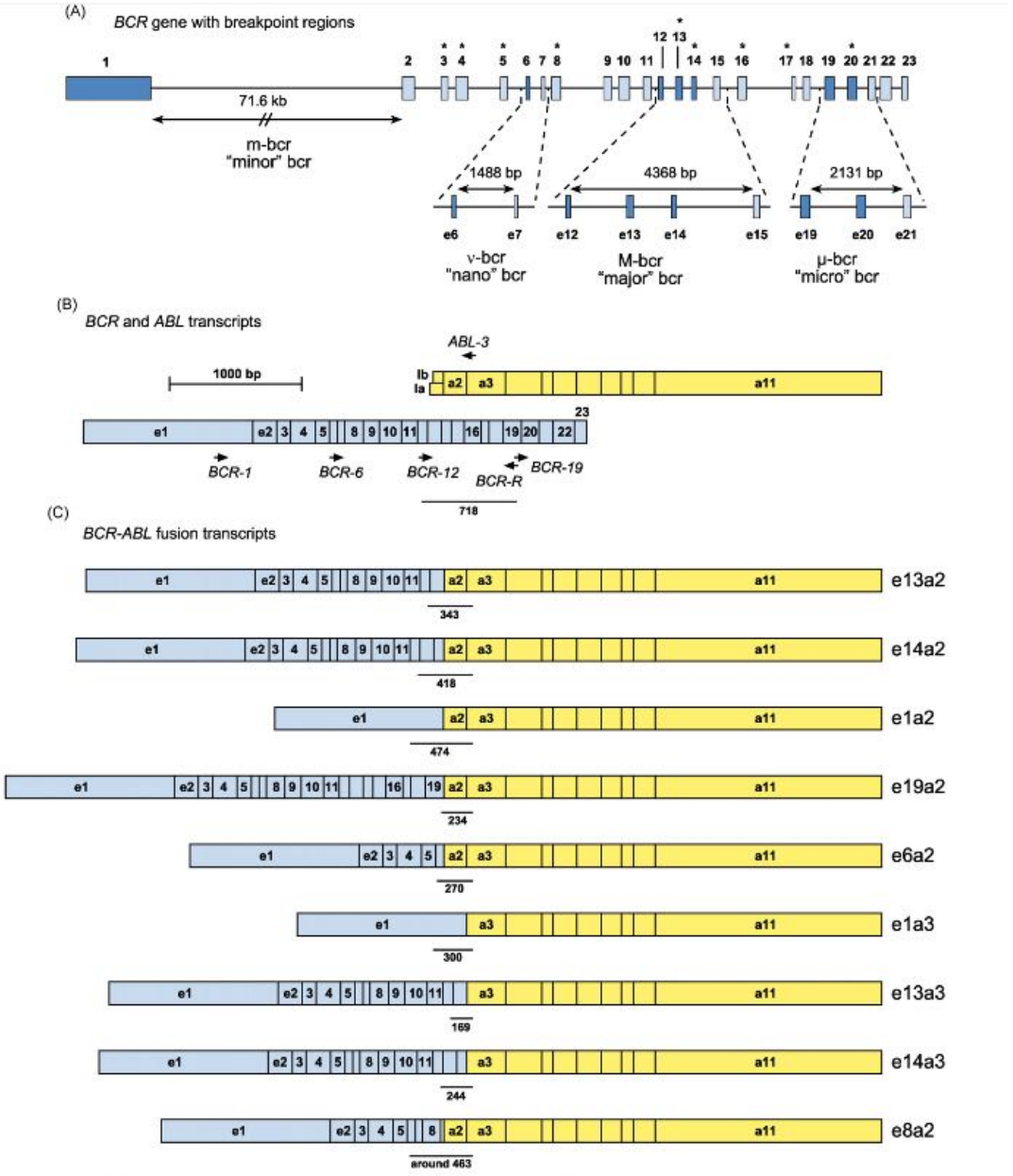


Fig. 1. *BCR* and *ABL* breakpoint regions and resulting fusion transcripts. (A) *BCR* gene with breakpoint regions. The *BCR* exons that can be fused *in-frame* with *ABL* exons 2 or 3 are e1, e6, e12, e13, e14, e19, and e20. Thus four breakpoint cluster regions (bcr) can be distinguished in the *BCR* gene: *minor (m-) bcr* between e1 and e2, *major (M-) bcr* between e12 and e15, *micro* (*µ-*) *bcr* between e19 and e21, and the region between e6 and e7, here analogously denoted "*nano*" (*ν-*) *bcr*. *BCR* exons that could theoretically be spliced without a reading frame shift, i.e. with a nucleotide number divisible by three, are marked with an asterisk (*). The size of the introns is not to scale. (B) *ABL* and *BCR* mRNAs with location of primers and the 718 bp control band. (C) *BCR–ABL* mRNA fusion transcripts with PCR products (see Table 2).

Scores pronostiques

- **Score de Sokal** (Sokal, Blood 1984)
  - Age (ans)
  - Taille rate (cm débord)
  - Nb de plaquettes (G/L)
  - % de blastes circulants

Groupe de risque	Score	% de patients
Faible risque	< 0,8	39%
Risque intermédiaire	0,8-1,2	38%
Haut risque	>1,2	23%

- **Score de Hasford** (Hasford, JNTL Cancer Inst 1998)
  - % éosinophiles
  - % basophiles

Groupe de risque	Score	% de patients
Faible risque	≤ 780	40,6%
Risque intermédiaire	781-1480	44,7%
Haut risque	≥ 1481	14,6%

Scores pronostiques

- **ELTS (EUTOS long-term survival)-score**, (Pfirrmann, Leukemia 2016)
  - *Celui à utiliser d'après les reco de l'ELN 2020, en particulier pour les patients âgés*

    Hochhaus, Leukemia 2020
  - $0{,}0025 \times (age/1)^3$

    $+ 0{,}0615 \times$ taille rate

    $+ 0{,}1052 \times$ % blastes sanguins

    $+ 0{,}4104 \times (Plq/1000)^{-0{,}5}$

Groupe de risque	Score	% de patients	OS à 10 ans
Faible risque	<1,5680	55%	88%
Risque intermédiaire	1,5680-2,2185	28%	79%
Haut risque	>2,2185	13%	68%

Objectifs du suivi moléculaire

- Monitoring initial (24 premiers mois)
  - Définir la qualité de la réponse de chaque patient au traitement de 1ère ligne pour évaluer le risque de progression AP/BC
- Monitoring sur le long terme
  - Identifier les patients en perte de réponse
    - Rapide : crise blastique ou arrêt du traitement
    - Intermédiaire : mauvaise observance
    - Lente : mutation avec persistance de la phase chronique
  - Définir la qualité de la réponse au traitement > L1
  - Identifier les patients éligibles pour un arrêt de traitement

Surveillance et prise en charge des patients

- Le caryotype médullaire (et non la FISH) le suivi n'est plus obligatoire en dehors des transcrits rares, non mesurables
  - Au diagnostic
  - A 3 mois
  - A 6 mois
  - Puis tous les 6 mois jusqu'à l'obtention d'une rémission cytogénétique complète confirmée
  - Ensuite 1 fois par an, si un monitoring moléculaire sanguin n'est pas possible
  - Toujours en cas d'échec (résistance primaire ou secondaire) et en cas d'anémie, leucopénie ou thrombopénie inexpliquée

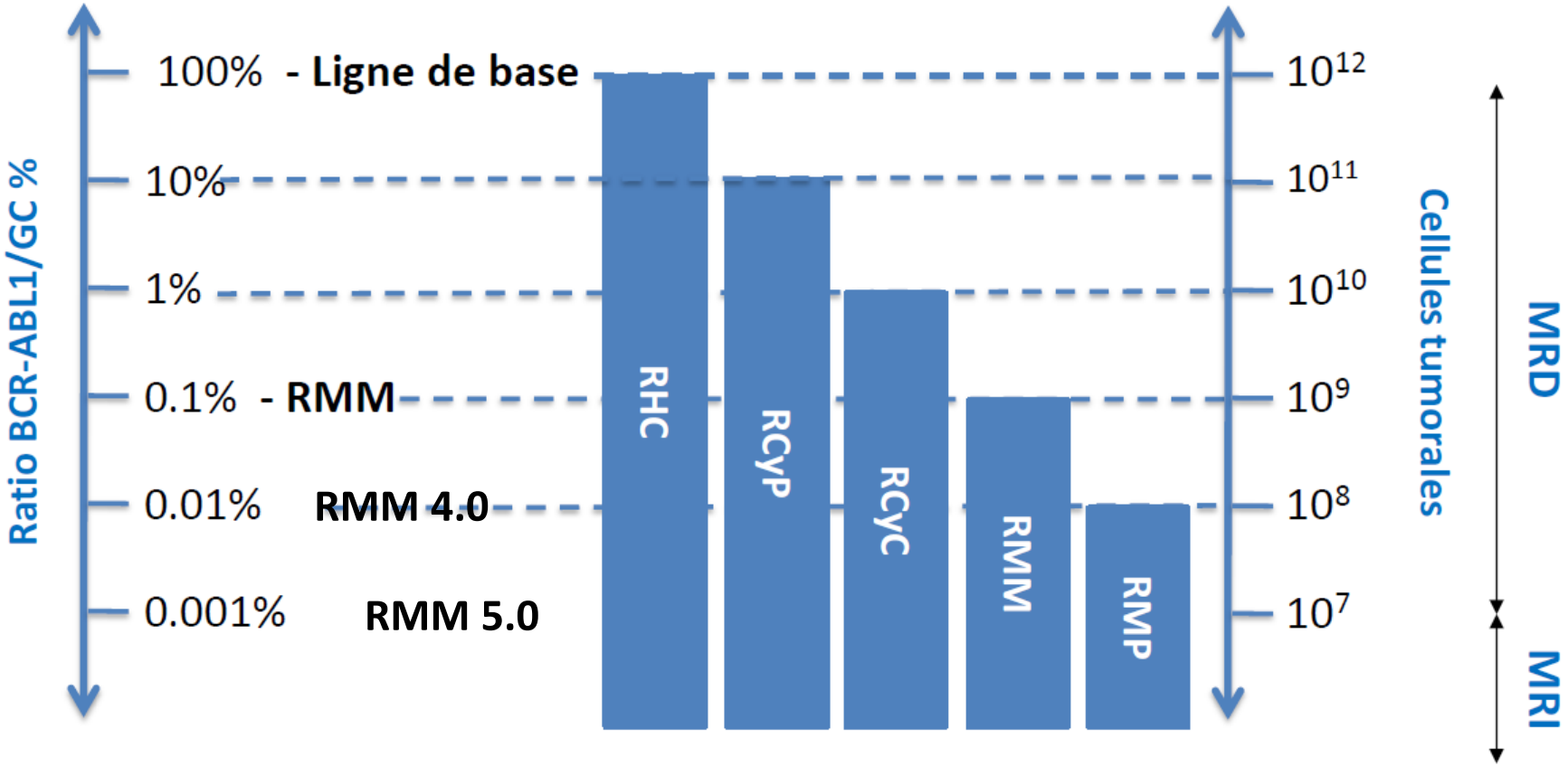
- Analyse moléculaire (RT-PCR puis RT-QPCR)
  - Au diagnostic avant traitement
  - Tous les 3 mois jusqu'à l'obtention d'une réponse moléculaire majeure (RMM, *i.e.* rapport BCR-ABL/ABL ≤ 0,1%), confirmée à 3 mois.
  - Maintenir tous les 3 mois dans l'idée d'une perspective d'arrêt de traitement pour vérifier l'éligibilité

- Recherche moléculaire d'une mutation
  - En cas de réponse sub-optimale ou d'échec. Cette recherche est nécessaire avant la décision de proposer un traitement par ITK de 2nde génération

ELN 2020 : réponse au traitement de 1ère ligne

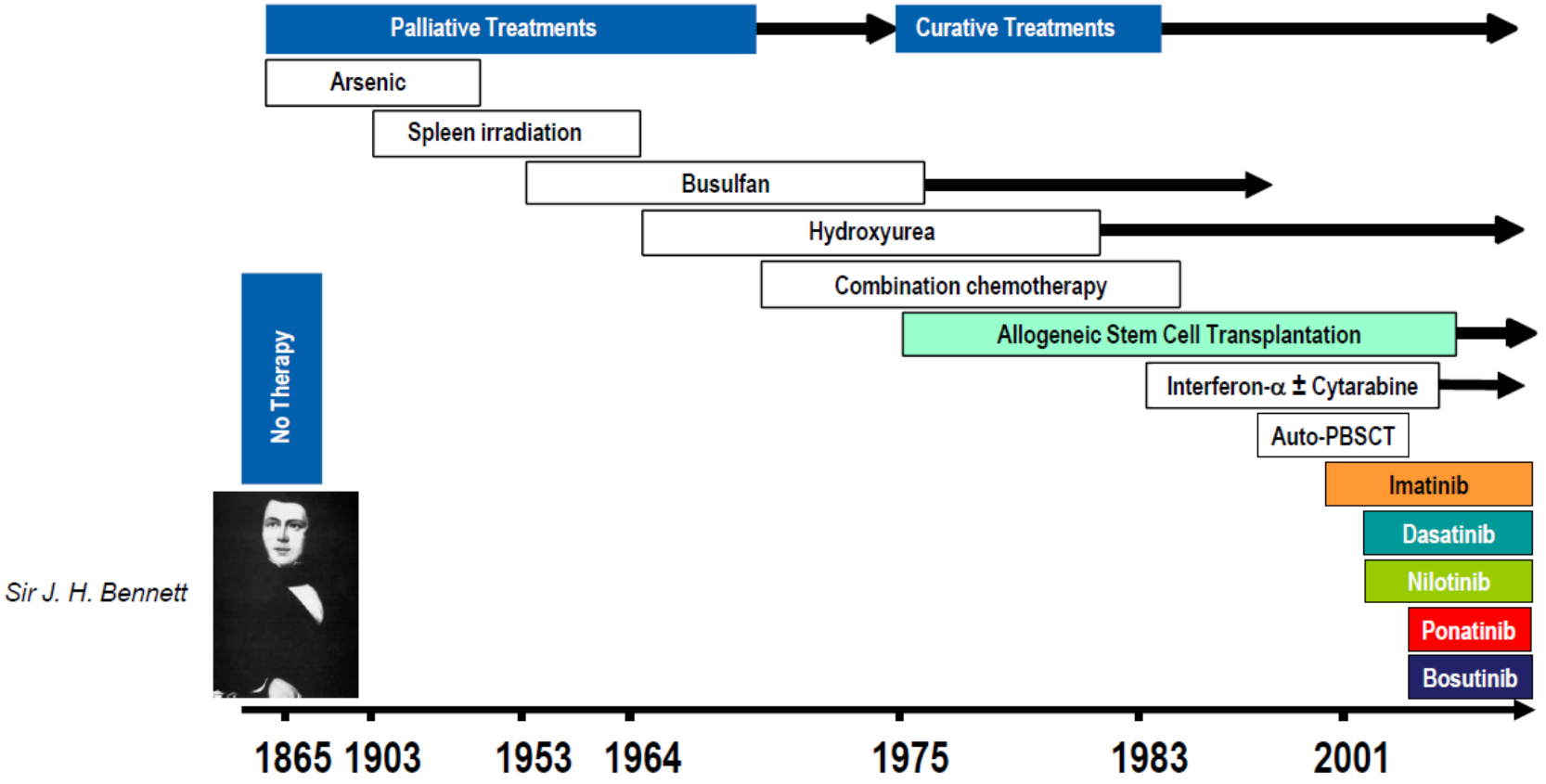
	Optimale	« warning »	Échec
Diagnostic	N.A.	Haut risque ACA/Ph+ majeures : *+8, i(17)(q10), +19, +der(22)*	N.A.
3 mois	RHC et (RCyP (Ph+≤ 35%) ou) BCR-ABL≤10%	RHC et (35<Ph+≤95% ou) BCR-ABL>10%	Absence de RHC ou Ph+>95%
6 mois	(RCyC (Ph+=0) ou) BCR-ABL≤1%	(0<Ph+≤35% ou) 1%<BCR-ABL≤10%	(Ph+>35% ou) BCR-ABL>10%
12 mois	RMM (BCR-ABL≤0,1%)	0,1%<BCR-ABL≤1%	(Ph+>0% ou) BCR-ABL>1%
Puis	RMM (BCR-ABL≤ 0,1%)	0,1%<BCR-ABL≤1%	BCR-ABL>1% Perte réponse ACA/Ph+

L'échelle internationale IRIS



Hughes Blood 2006

Therapeutic history of CML



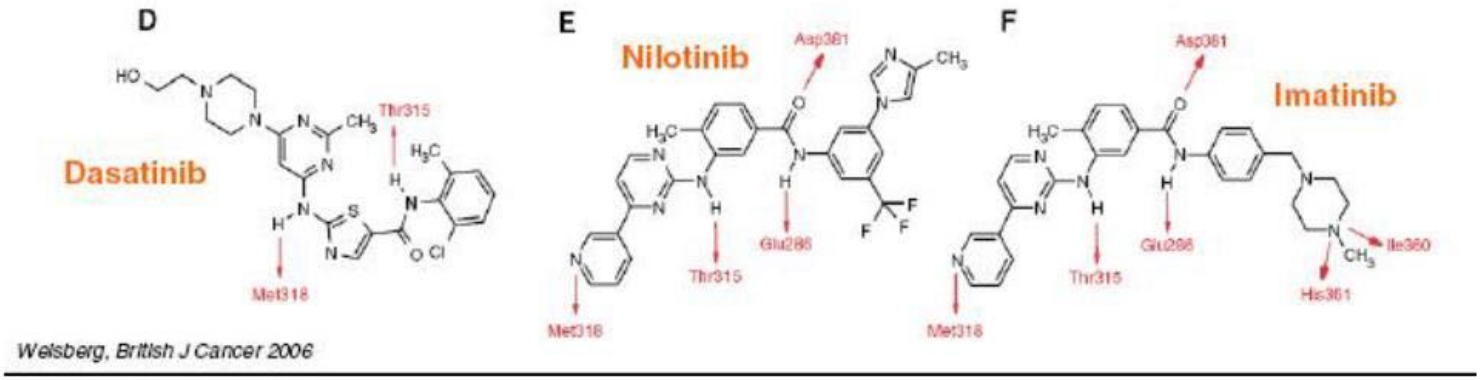
Adapted from Pavlu Blood 2011 et Nicolini EBMT 2012

Le traitement de première ligne

- Imatinib 400 mg/j
- Nilotinib 600 mg/j
- (Dasatinib)

SaglioG et al. N Engl J Med 2010;362:2551-2559.

Kantarjian H et al. N Engl J Med 2010; 362:2260-2270.



Weisberg, British J Cancer 2006

Le traitement de 1ère ligne

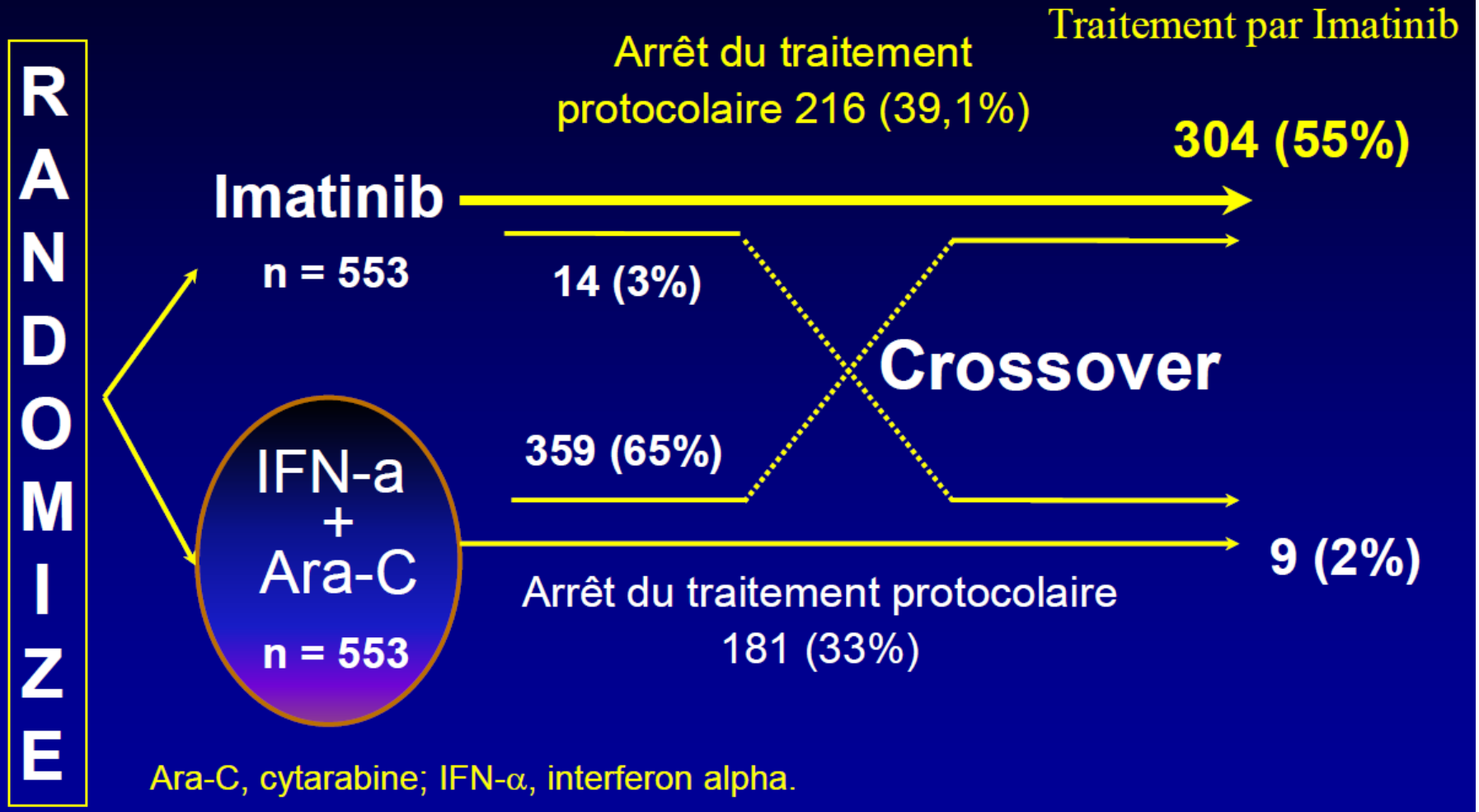
- Imatinib 400 mg/j

- Nilotinib 300 mg x2/j
- Dasatinib 100 mg/j

- Bosutinib 400 mg/j

Etude IRIS: comparaison imatinib versus interferon + cytarabine

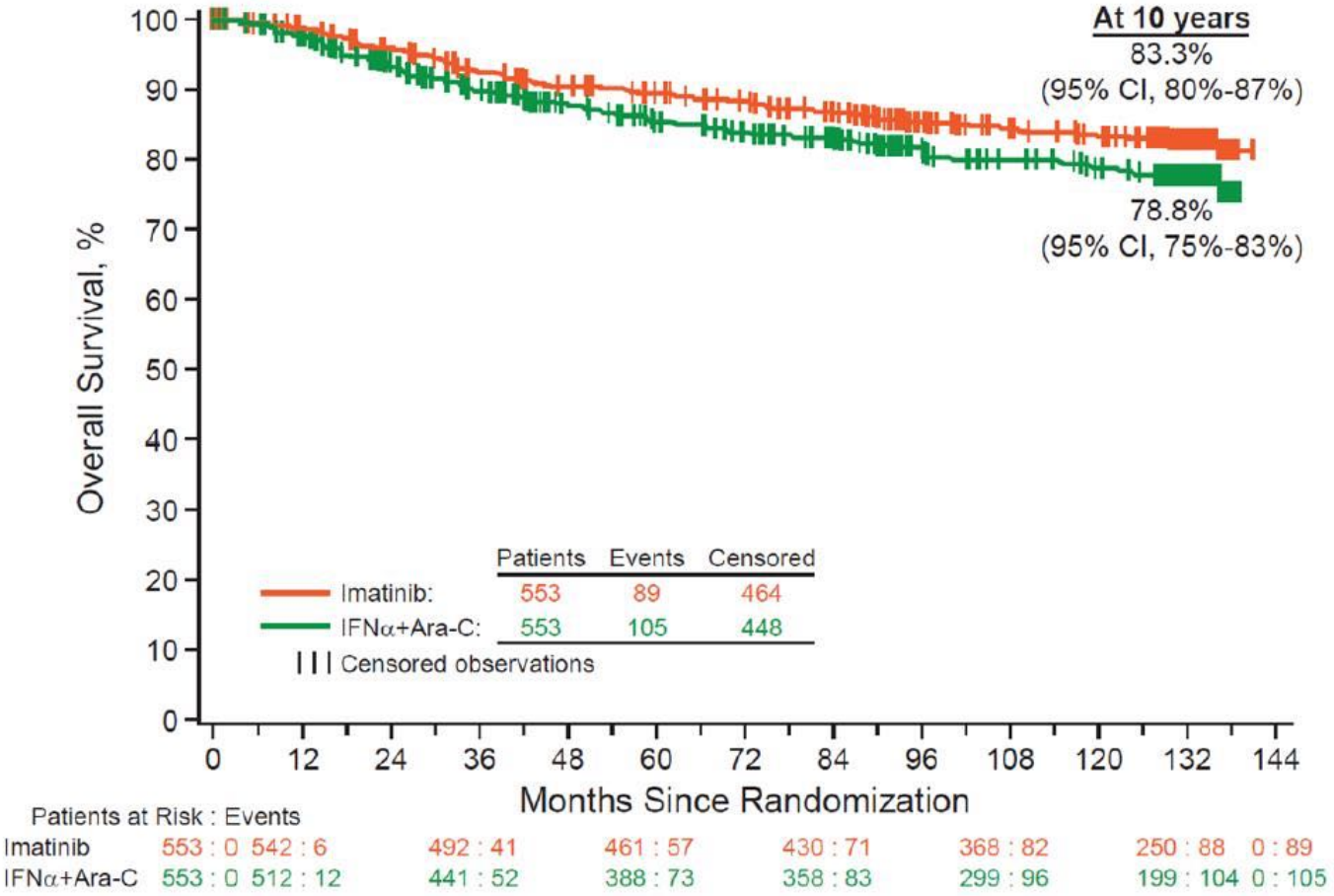
Phase III



Ara-C, cytarabine; IFN-α, interferon alpha.

Guilhot et al, Blood 2009; ASH; NEJMED 2003; 2006

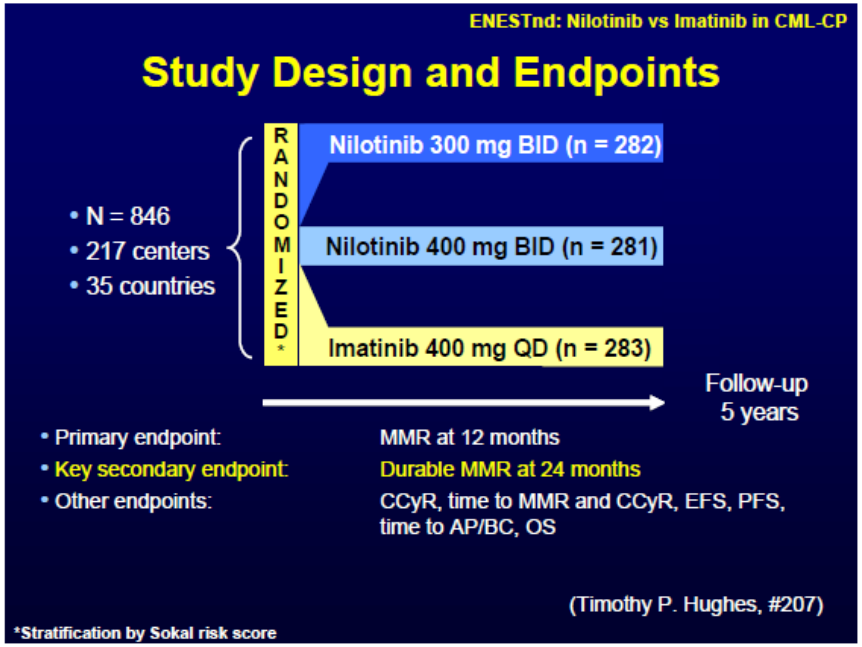
IRIS Study : Résultats long terme



Hochhaus NEJM 2017

Les ITK2 en première ligne

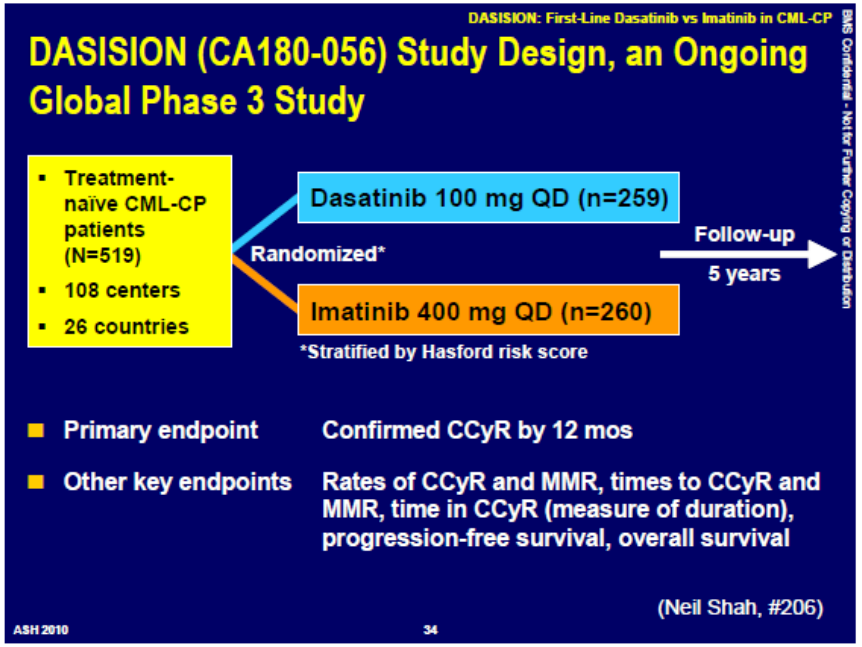
ENESTnd



Nilotinib

T Hughes, ASH 2010

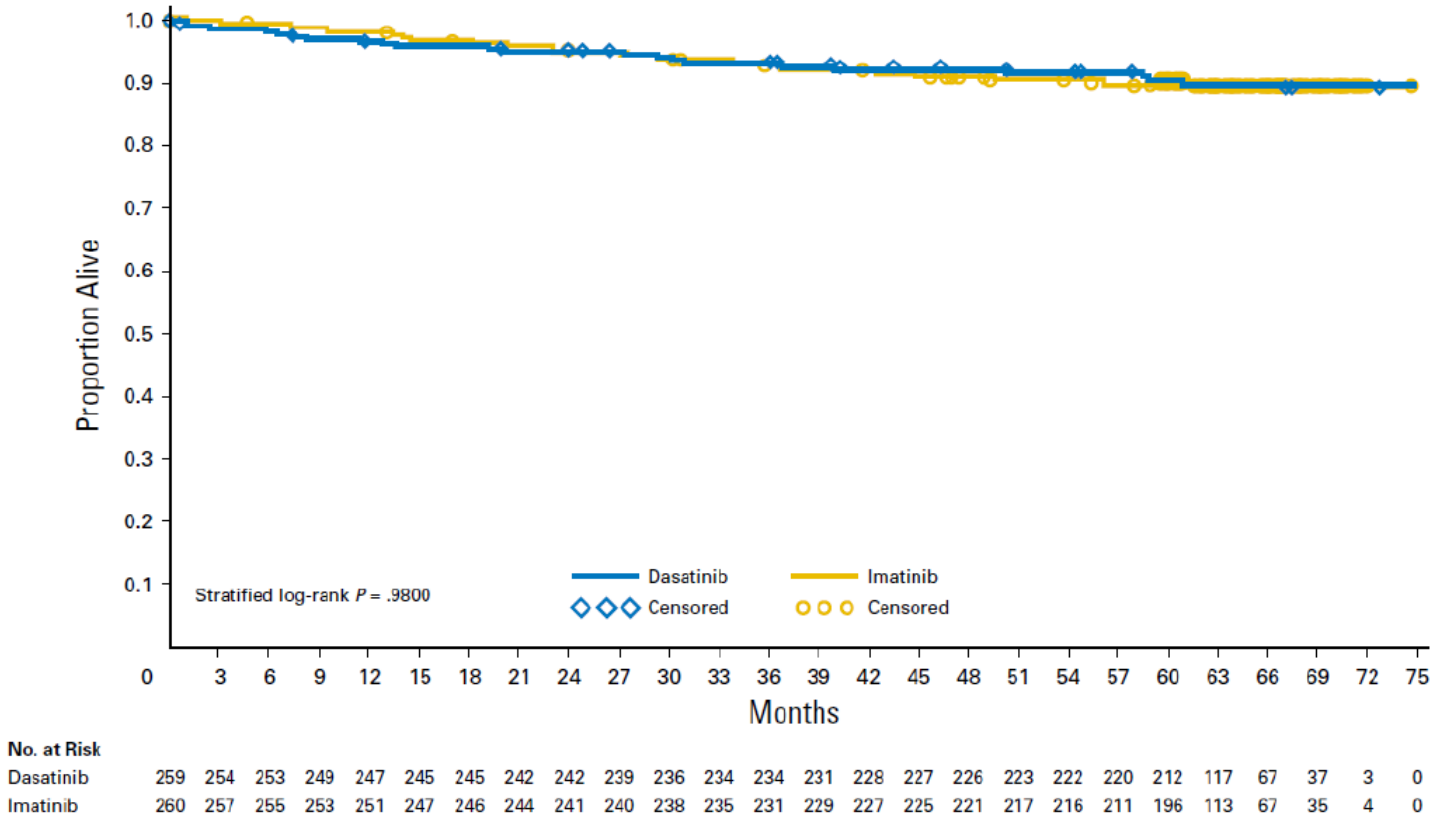
DASISION



Dasatinib

N Shah, ASH 2010

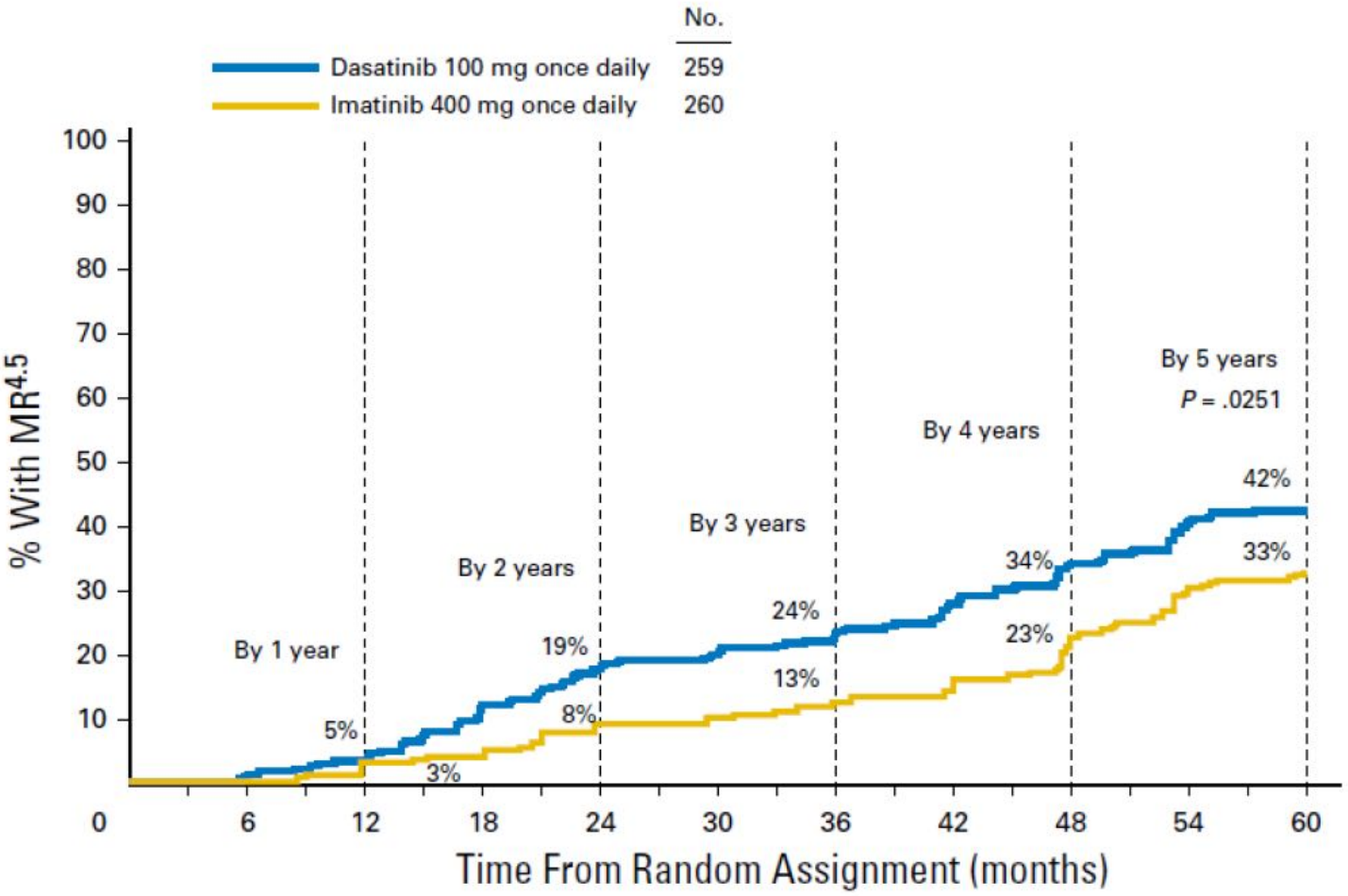
Long terme survival and dasatinib DASISION 5 years



No. at Risk																									
Dasatinib	259	254	253	249	247	245	245	242	242	239	236	234	234	231	228	227	226	223	222	220	212	117	67	37	3	0
Imatinib	260	257	255	253	251	247	246	244	241	240	238	235	231	229	227	225	221	217	216	211	196	113	67	35	4	0

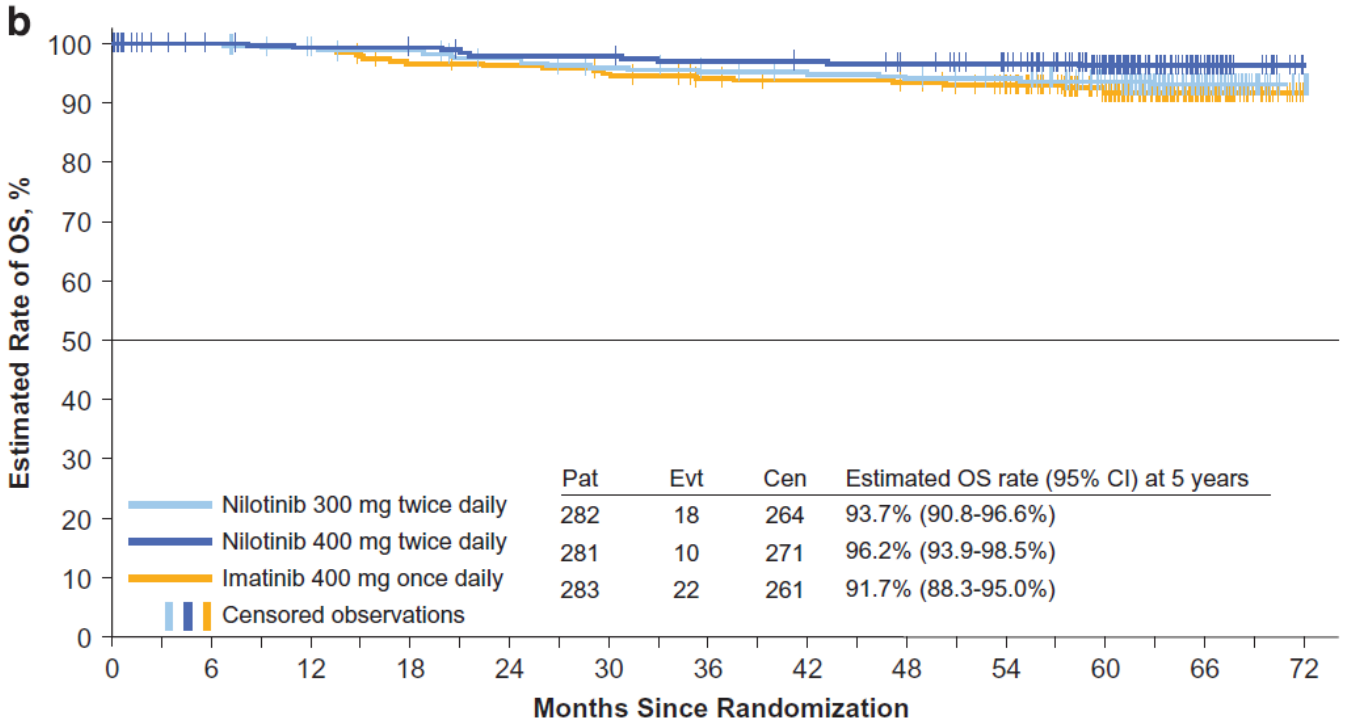
Cortes JCO 2016

Dasatinib first line
Deep molecular responses



Cortes JE, et al. J Clin Oncol. 2016 Jul 10;34(20):2333-40.

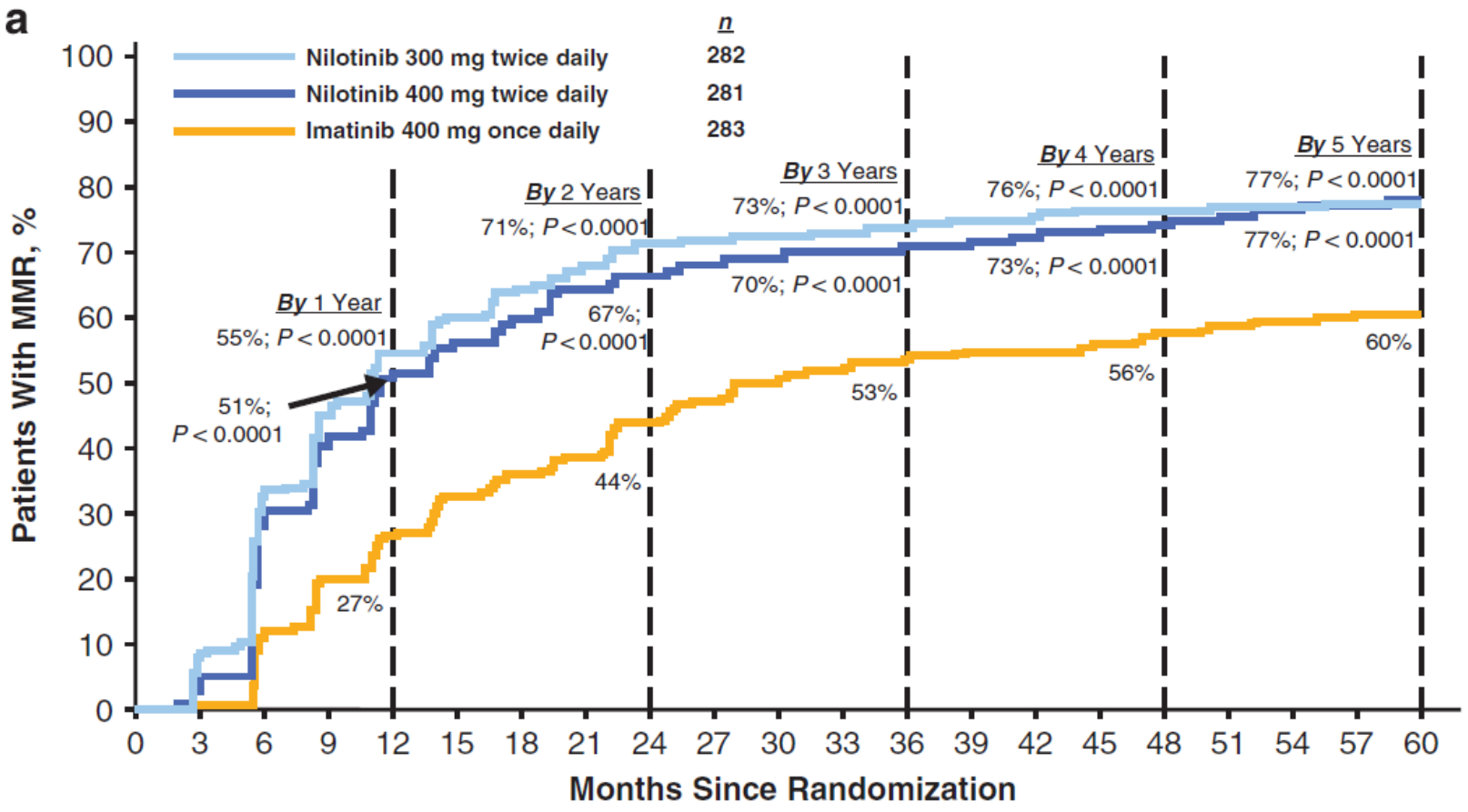
Long term survival and nilotinib ENESTnd 5 years



At-risk : Events							
Nilotinib 300 mg twice daily	282 : 0	271 : 2	263 : 7	254 : 13	249 : 16	207 : 17	1 : 18
Nilotinib 400 mg twice daily	281 : 0	270 : 2	264 : 6	261 : 8	256 : 9	206 : 10	0 : 10
Imatinib 400 mg once daily	283 : 0	274 : 2	262 : 10	250 : 16	245 : 18	197 : 22	0 : 22

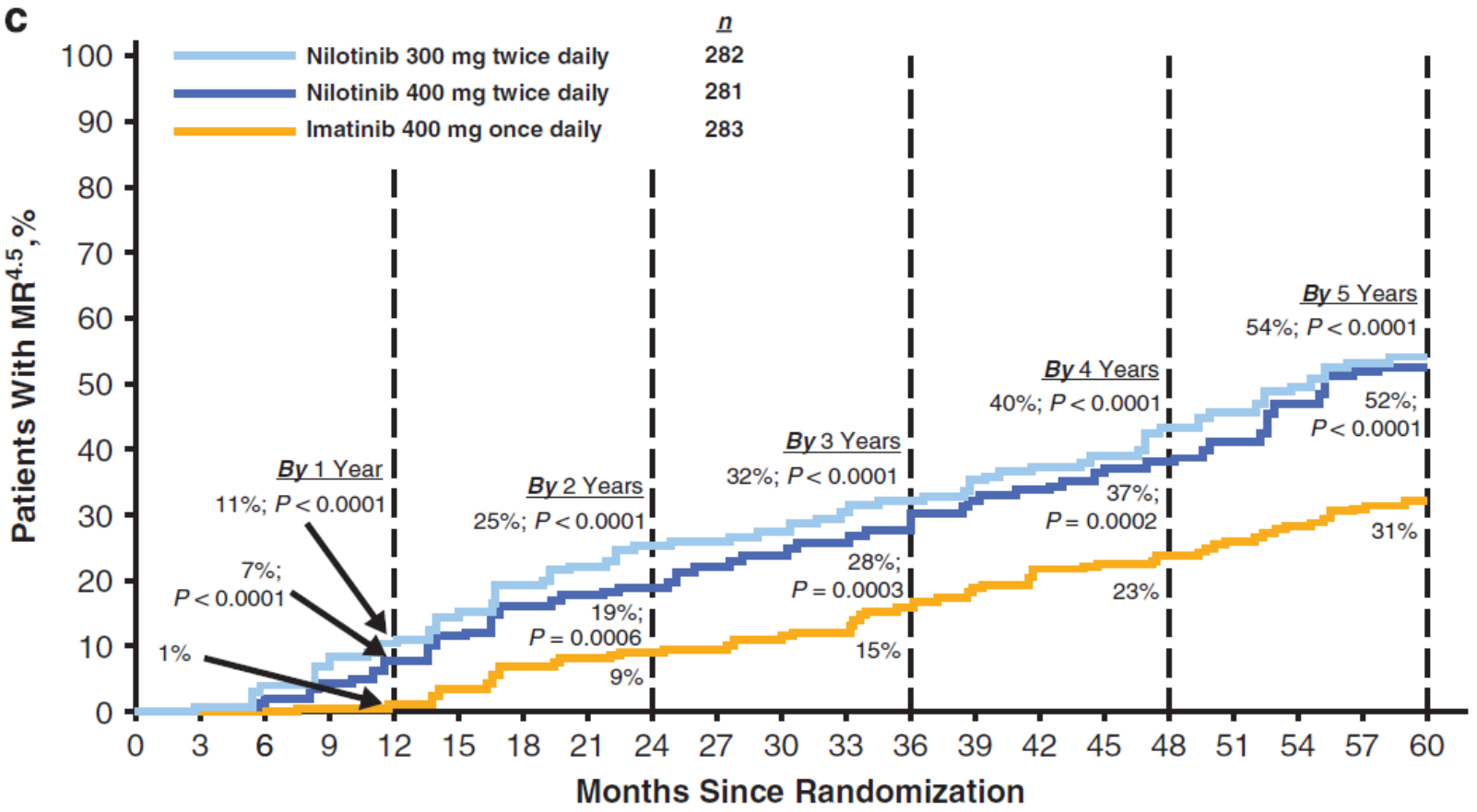
Hochhaus Leukemia 2016

Nilotinib First Line
Deep molecular response



Hochhaus Leukemia 2016

Nilotinib First Line
Deep molecular response



Hochhaus Leukemia 2016

	Nilotinib 300 mg twice daily group (n=282)	Nilotinib 400 mg twice daily group (n=281)	Imatinib group (n=283)
Progression to accelerated phase or blast phase			
Number of events	2	3	12
Estimated 24-month rate of patients free from progression	99·3%	98·1%	95·2%
Hazard ratio (95% CI)	0·16 (0·04–0·71)	0·25 (0·07–0·88)	..
p value	0·0059	0·0196	..
Progression to accelerated phase or blast phase including clonal evolution			
Number of events	2	5	17
Estimated 24-month rate of patients free from progression	99·3%	97·3%	93·2%
Hazard ratio (95% CI)	0·11 (0·03–0·48)	0·29 (0·11–0·78)	..
p value	0·0003	0·0089	..
EFS*			
Number of events	9	5	16
Estimated 24-month EFS	96·4%	97·8%	93·6%
Hazard ratio (95% CI)	0·53 (0·24–1·21)	0·30 (0·11–0·83)	..
p value	0·1244	0·0141	..
PFS*			
Number of events	5	4	12
Estimated 24-month PFS	98·0%	97·7%	95·2%
Hazard ratio (95% CI)	0·40 (0·14–1·13)	0·33 (0·11–1·02)	..
p value	0·0736	0·0437	..
Overall survival including follow-up after discontinuation of treatment			
Number of deaths	9	6	11
Estimated 24-month overall survival	97·4%	97·8%	96·3%
Hazard ratio (95% CI)	0·82 (0·34–1·97)	0·54 (0·20–1·45)	..
p value	0·6485	0·2125	..
Deaths related to CML	5	3	10
Estimated 24-month overall survival (CML-related deaths only)	98·9%	98·9%	96·7%
Hazard ratio for CML-related deaths only (95% CI)	0·50 (0·17–1·45)	0·29 (0·08–1·07)	..
p value (CML-related deaths only)	0·1930	0·0485	..

p values calculated with log-rank test stratified by Sokal score vs imatinib group. EFS=event free survival. PFS=progression free survival. CML=chronic myeloid leukaemia. *Among events for EFS and PFS, three deaths that occurred on treatment in the nilotinib 300 mg twice daily group were considered to be unrelated to disease and study treatment by the investigators (suicide, pre-existing comorbid conditions leading to small bowel obstruction, and perioperative myocardial infarction following planned coronary artery bypass).

Table 4: **Long-term endpoints on treatment**

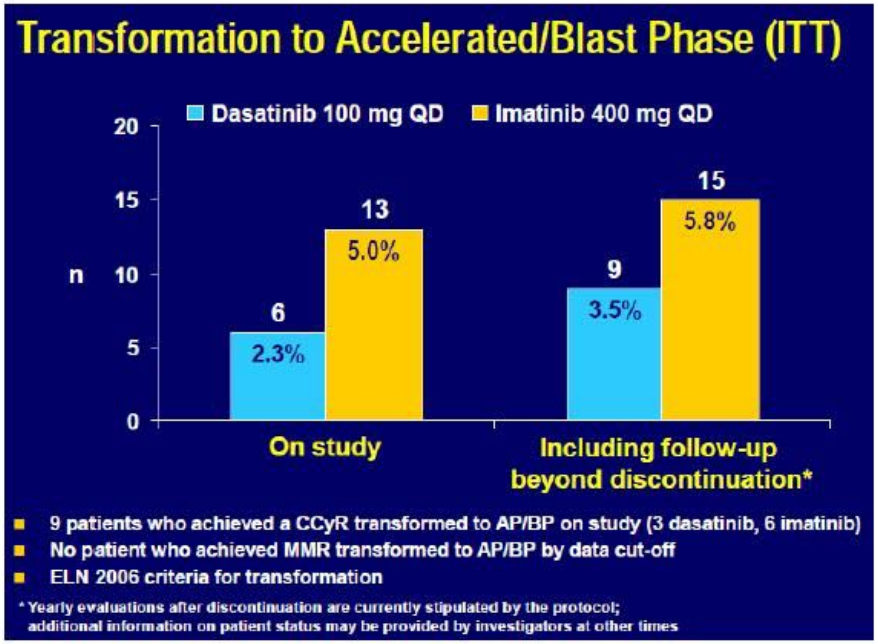
Nilotinib et Risque de progression Résultats 24 mois

Kantarjian Lancet Oncol 2011

Gain potential sur la reduction du risque de progressions précoces

DASISION trial at 24 months

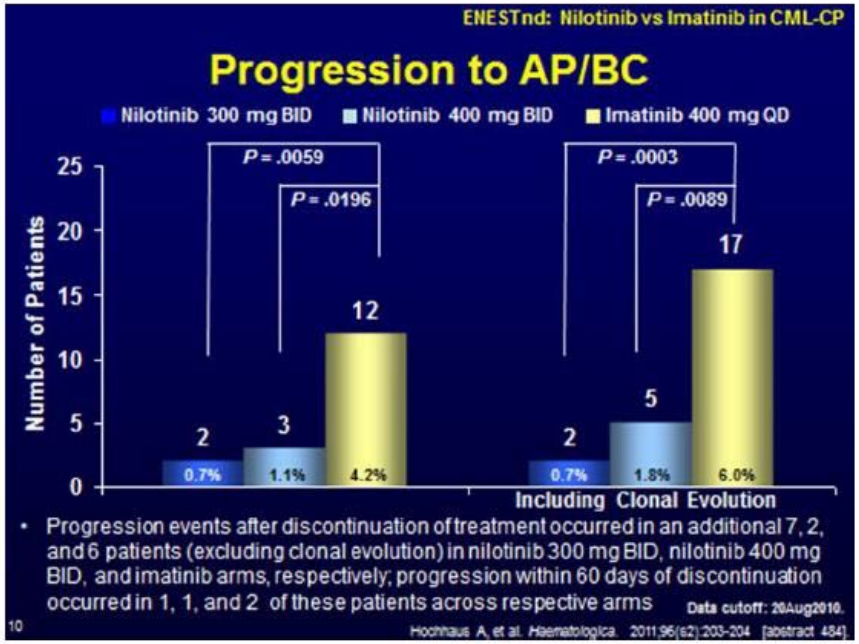
Risk reduction : 2.3%



Hochhaus EHA 2011 Abstract 1011

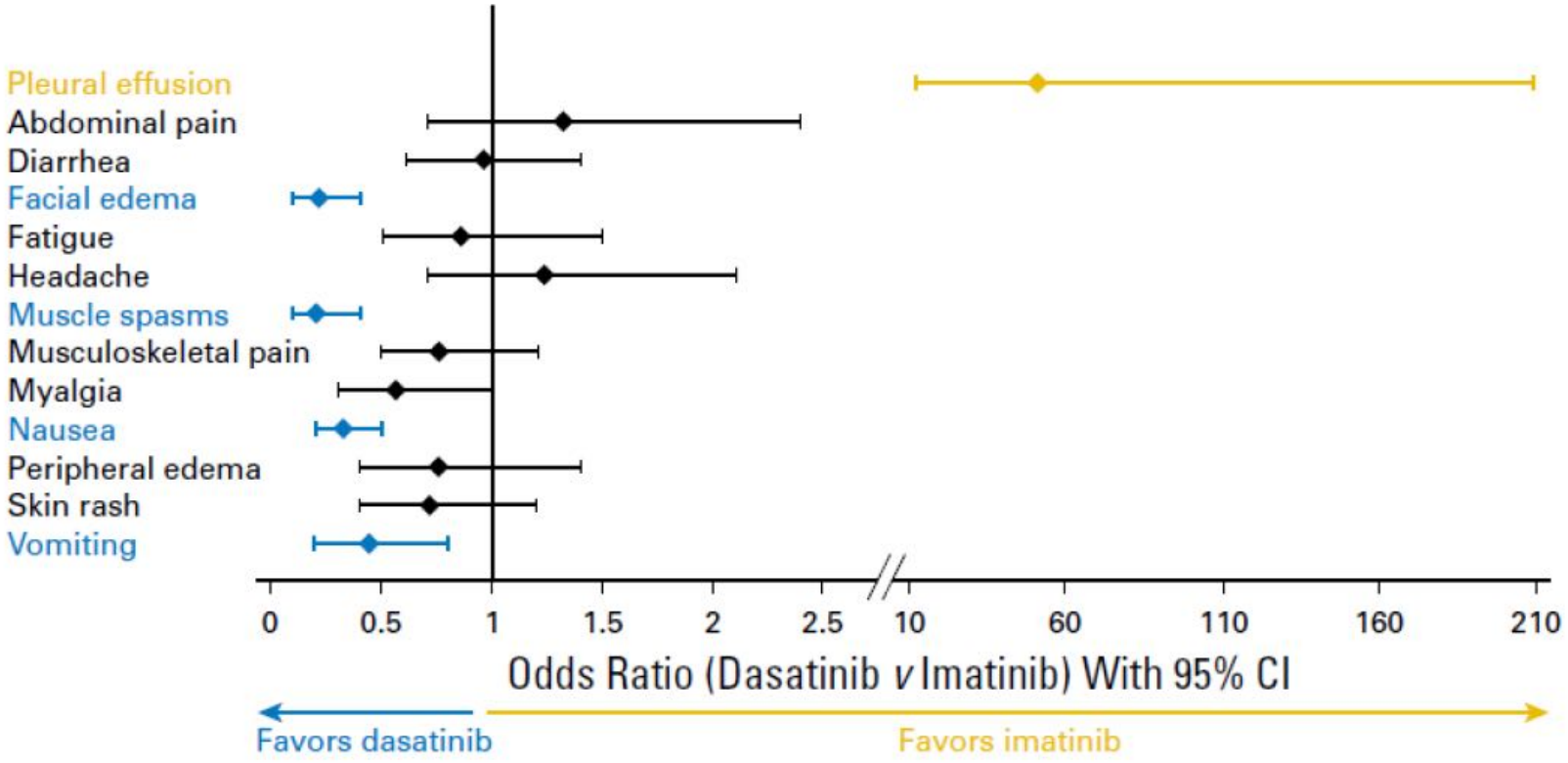
ENESTnd trial at 24 months

Risk reduction : 3.1%



Hochhaus EHA 2011 Abstract 0484

Dasatinib et Epanchements pleuraux

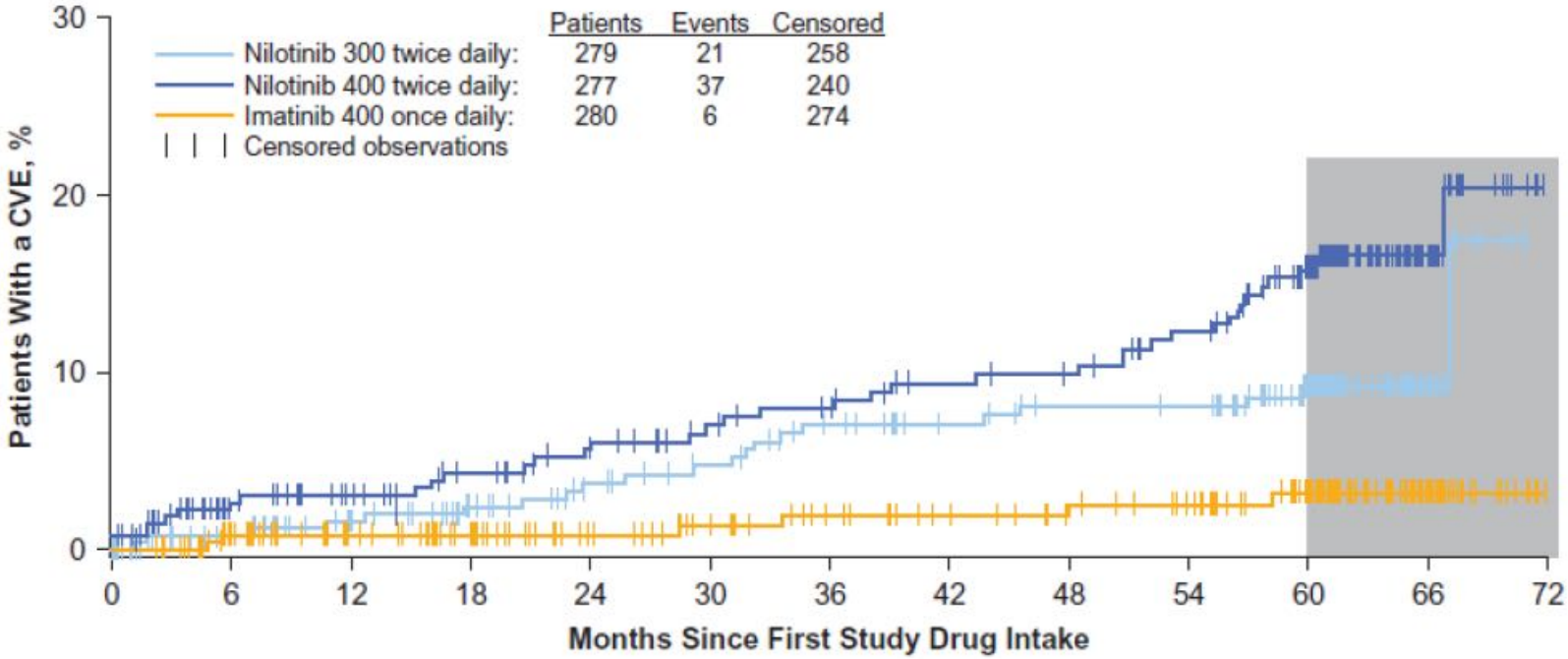


Cortes JCO 2016

Dasatinib et HTAP

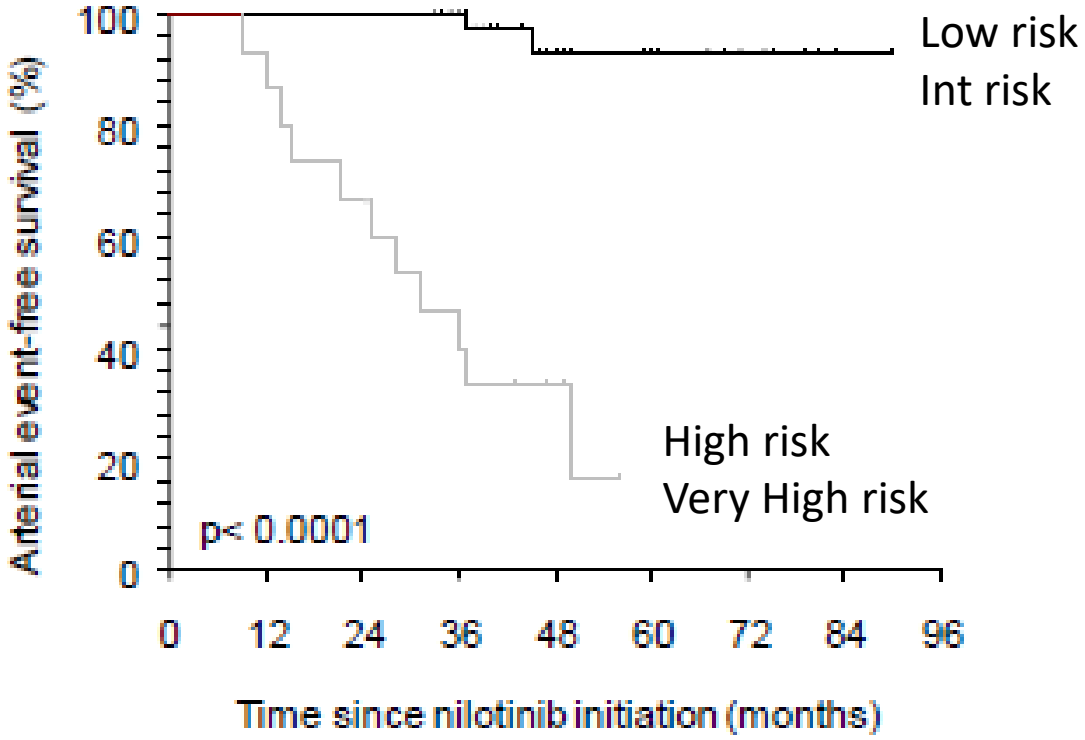
Montani Circulation 2012

Evénements cardiovasculaires sous Nilotinib



Hochhaus Leukemia 2016

Evénements cardiovasculaires sous Nilotinib



Réa Leukemia 2015

Recommandations françaises 2015 LMC-Risque Cardiovasculaire-Nilotinib

TABLEAU II

Classification ESC 2012 du risque de mortalité cardiovasculaire globale à 10 ans

Groupe de risque	Au moins 1 des items suivants
Très élevé	Maladie cardiovasculaire documentée Infarctus du myocarde Syndrome coronarien Accident vasculaire cérébral ischémique Artériopathie périphérique Revascularisation artérielle Diabète avec au moins 1 autre facteur de risque cardiovasculaire majeur ou atteinte microvasculaire Insuffisance rénale chronique sévère SCORE[a] $\geq$ 10 %
Élevé	Un facteur de risque majeur très élevé (HTA sévère, dyslipidémie familiale) Diabète sans autre facteur de risque cardiovasculaire majeur et sans atteinte microvasculaire Insuffisance rénale chronique modérée SCORE[a] $\geq$ 5 % et $\leq$ 10 %
Moyen	SCORE[a] $\geq$1 % et $\leq$ 5 %
Faible	SCORE[a] $\leq$ 1 %

[a]SCORE: Systematic Coronary Risk Evaluation (http://www.escardio.org/Guidelines-&-Education/Practice-tools/CVD-prevention-toolbox/SCORE-Risk-Charts).

Réa Bull Cancer 2016

Recommandations françaises 2015 LMC-Risque Cardiovasculaire-Nilotinib

Bilan initial avant traitement par nilotinib

Paramètres	Modalités
Antécédents	Personnels : événements cardiovasculaires, maladies métaboliques, tabagisme, traitements médicamenteux Familiaux : dyslipidémie familiale, morbidité cardiovasculaire précoce dans la parentèle au 1er degré (< 55 ans chez l'homme et < 65 ans chez la femme)
Examen clinique	Interrogatoire : douleur thoracique ou des membres inférieurs à l'effort, amaurose ou déficit transitoire d'un membre Examen clinique : palpation des pouls, auscultation, tension artérielle, indice de masse corporelle
Examens biologiques	Créatininémie Glycémie, HbA1C Cholestérol total, HDL, LDL. Triglycéridémie Microalbuminurie chez le diabétique
Imagerie ou bilan de médecine cardiovasculaire	Risque faible : inutile Risque moyen : ECG (recherche d'une onde Q de nécrose, trouble du rythme) et échographie cardiaque (mesure de la FEVG et recherche de troubles de la cinétique). Écho-doppler des troncs supra-aortiques et des membres inférieurs à la recherche de plaques d'athérome asymptomatiques Risque élevé ou très élevé : bilan spécialisé en médecine cardiovasculaire systématique

Bilan de suivi des patients traités par nilotinib

Paramètres	Fréquence	Modalités
Examen clinique	Tous les 3 à 6 mois	Interrogatoire : douleur thoracique ou des membres inférieurs à l'effort, amaurose ou déficit transitoire d'un membre Examen clinique : palpation des pouls, auscultation, tension artérielle, indice de masse corporelle
Examens biologiques	Tous les 3 mois pendant 12 mois, puis tous les 6 à 12 mois (sauf chez le diabétique)	Créatininémie Glycémie, HbA1C Cholestérol total, HDL, LDL. Triglycéridémie Microalbuminurie chez le diabétique
Imagerie ou bilan de médecine cardiovasculaire	Tous les ans en cas de risque moyen Tous les 6 mois en cas de risque élevé ou très élevé (à déterminer en médecine cardiovasculaire)	Risque faible : inutile Risque moyen : écho-doppler des troncs supra-aortiques et des membres inférieurs à la recherche de plaques d'athérome Risque élevé ou très élevé : suivi spécialisé en médecine cardiovasculaire

Réa Bull Cancer 2016

Bosutinib, TKI de 2ème génération

Table 3. Response Rates, Modified Intent-to-Treat Population

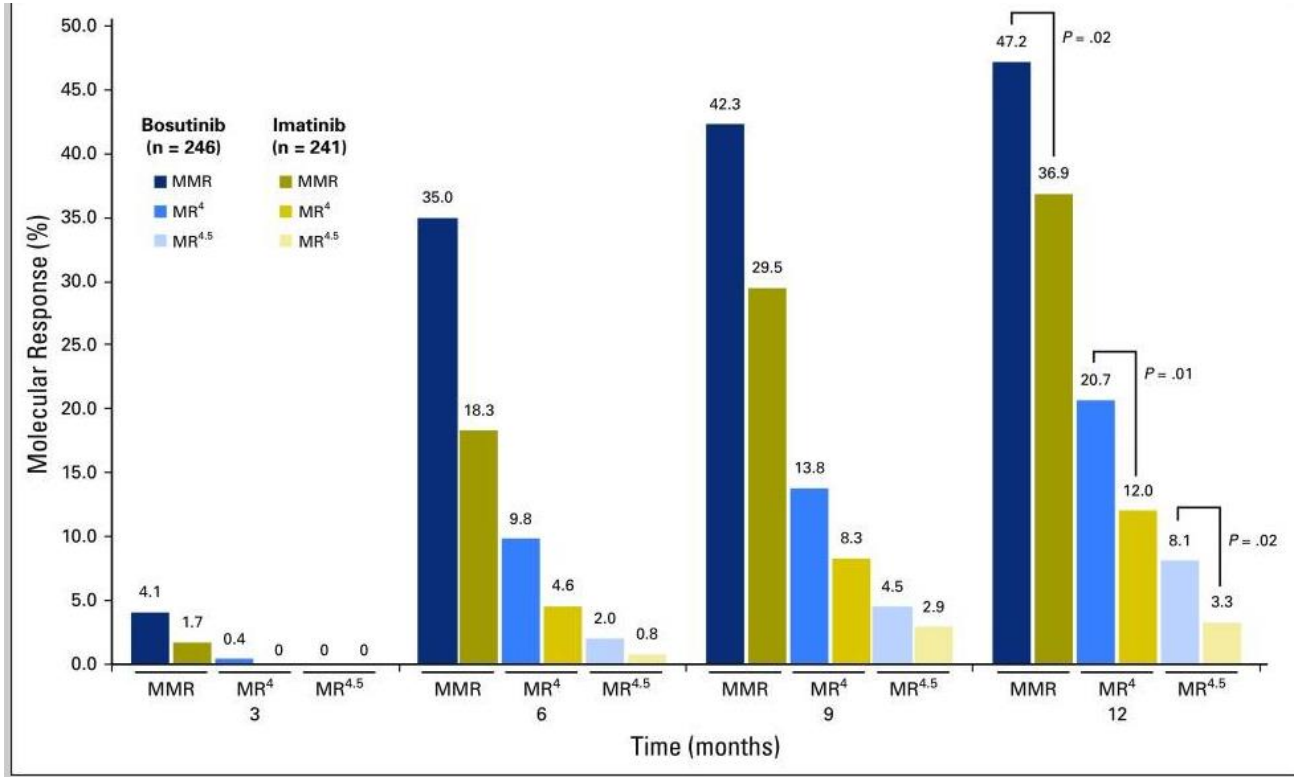
Response	% (95% CI)*			
	Bosutinib, (n = 246)	Imatinib (n = 241)	Odds Ratio (95% CI)†	P‡
Major molecular response at 12 months	47.2 (40.9 to 53.4)	36.9 (30.8 to 43.0)	1.55 (1.07 to 2.23)	.0200
Complete cytogenetic response by 12 months	77.2 (72.0 to 82.5)	66.4 (60.4 to 72.4)	1.74 (1.16 to 2.61)	.0075

NOTE. Modified intent-to-treat population includes patients with Philadelphia chromosome–positive status with typical (e13a2 and/or e14a2) *BCR-ABL1* transcript types.

*Asymptotic 95% CIs are presented for response rates.

†Adjusted for Sokal risk group (low, intermediate, high) and geographic region at time of random assignment. 95% CIs for odds ratios based on asymptotic Wald confidence limits.

‡*P* value was based on a Cochran-Mantel-Haenszel test for general association between treatment and response with stratification by Sokal risk group (low, intermediate, high) and region as determined at time of random assignment.



Cortes JCO 2018

EI transitoires en général :
-diarrhée
-élévation des transa

Echecs

Echecs primaires

- à 3 mois : absence de la RCH ou Ph+>95%
- à 6 mois : Ph+>35% ou BCR-ABL>10%
- à 12 mois : Ph+>0% ou BCR-ABL>1%

Echecs secondaires

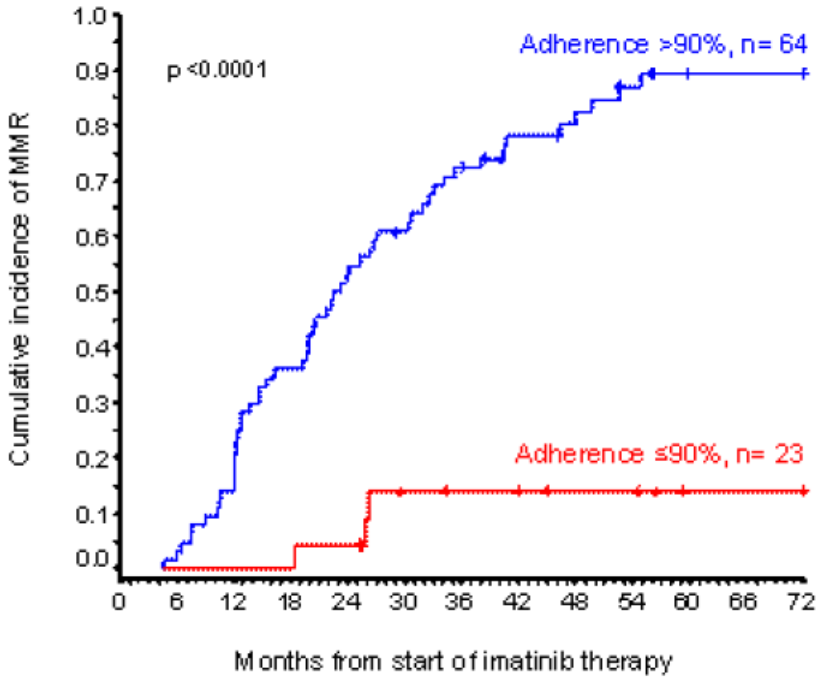
- Perte de la RCH
- Perte de la RCyC
- Mutations de résistance[1]
- ACA/Ph+[2]
- Perte de la RMM confirmée[3]

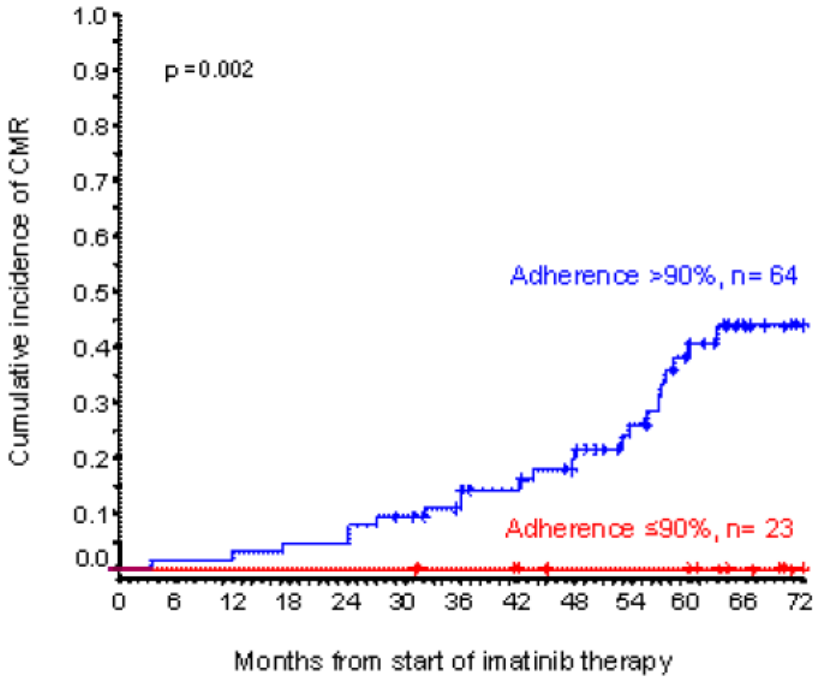
[1]Toutes les mutations de résistance
[2]Phase accélérée
[3]2 analyses consécutives > 0,1% dont un devant être >1%

Baccarani JCO 2009
Baccarani Blood 2013

Lack of compliance to imatinib puts patients at risk

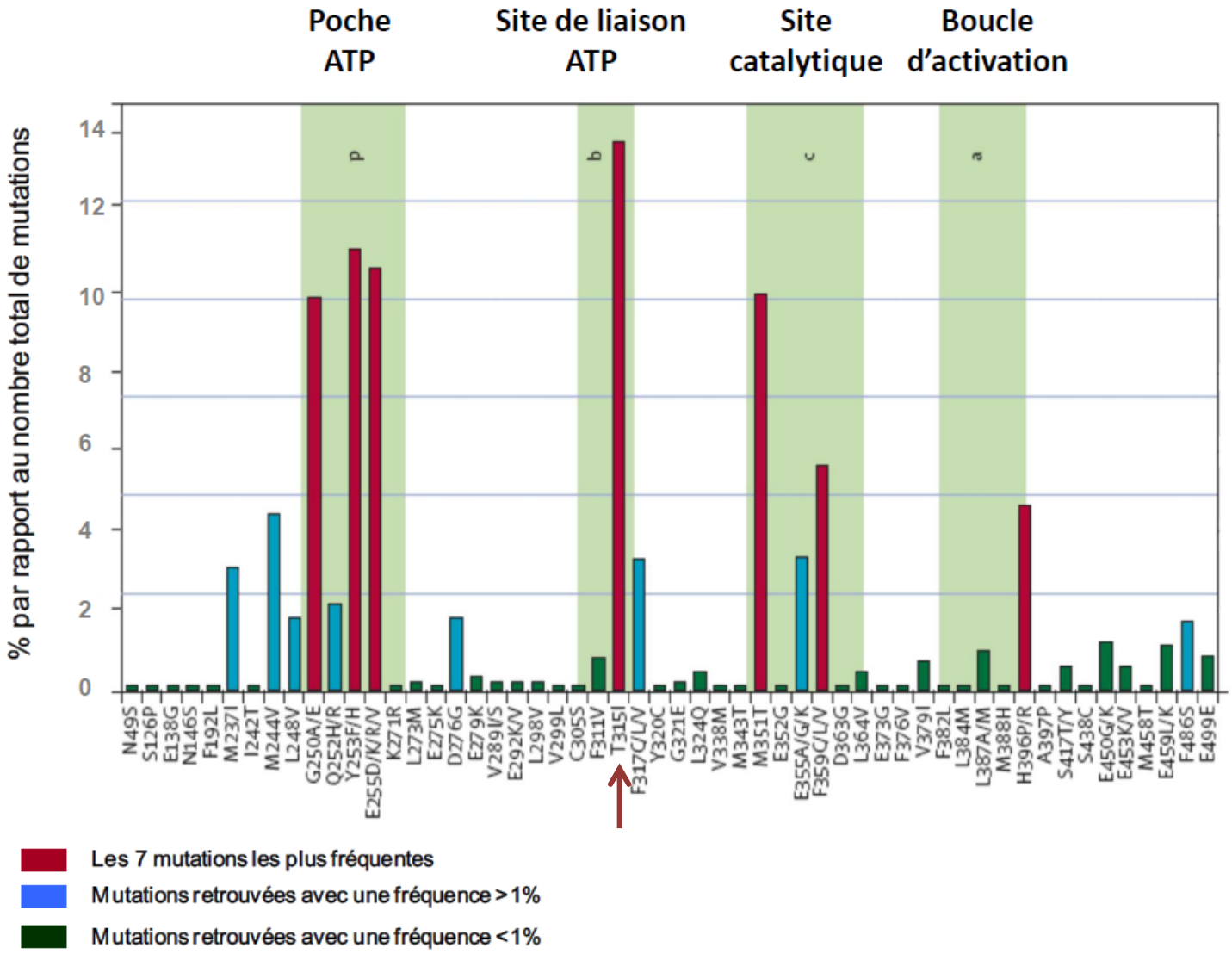
- In a study of 87 patients with CML-CP in CCyR, adherence to imatinib treatment (≤90% or >90%) was a significant predictor of response on imatinib





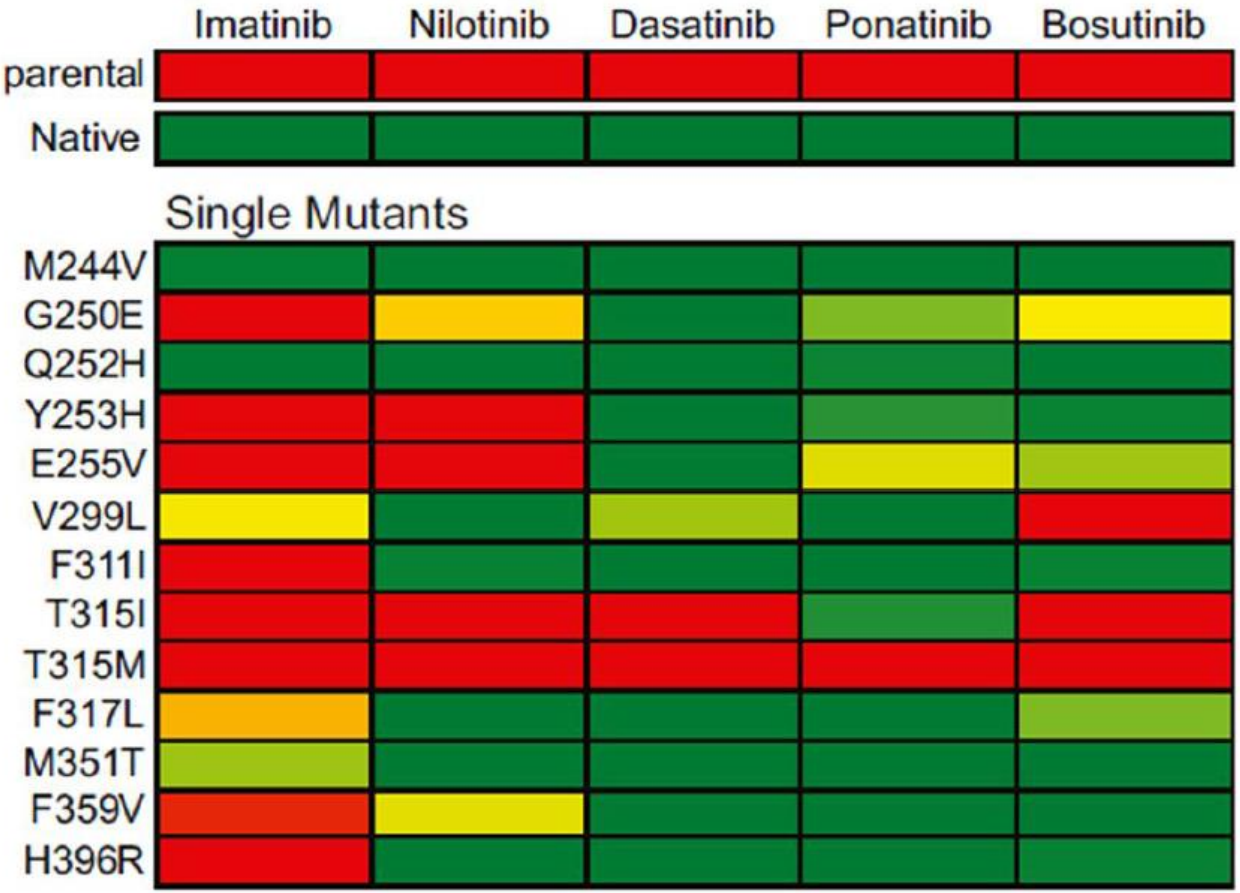
Bazeos ASH 2009

Mutations de résistance



D'après Apperley JF, Lancet Oncol 2007, nov 8(11) :1018-1029

Mutations de *BCR-ABL1* et sensibilité aux inihibiteurs de tyrosine kinase (*in vitro*)



Zabriskie Cancer Cell 2014

Options thérapeutiques et mutations

Mutation	Option thérapeutique
T315I	Ponatinib
F317L/V/I/C, T315A	Nilotinib, Bosutinib*, ou Ponatinib
V299L	Nilotinib ou Ponatinib
Y253H, E255V/K, F359V/I/C	Dasatinib, Bosutinib*, ou Ponatinib

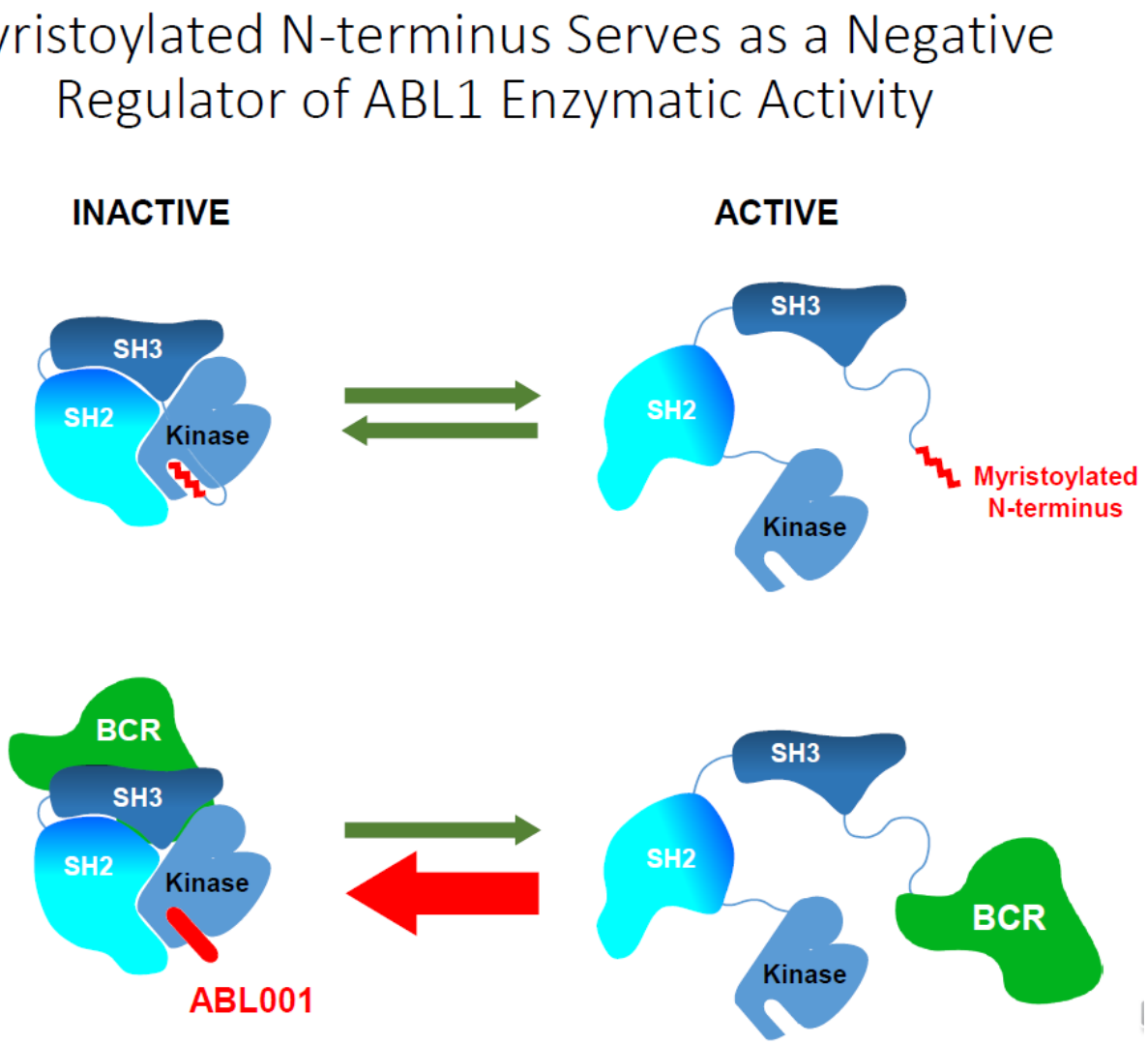
**Data limitées concernant les mutation associées avec une résistance clinique au Bosu in vivo. Des données in vitro suggèrent une possible sensibilité diminuée au Bosu pour les mutation E255K et eventuellement E255V*

En dehors de la situation de mutations, n'importe quel ITK2 ; à choisir en fonction du profil de tolérance.

Ponatinib

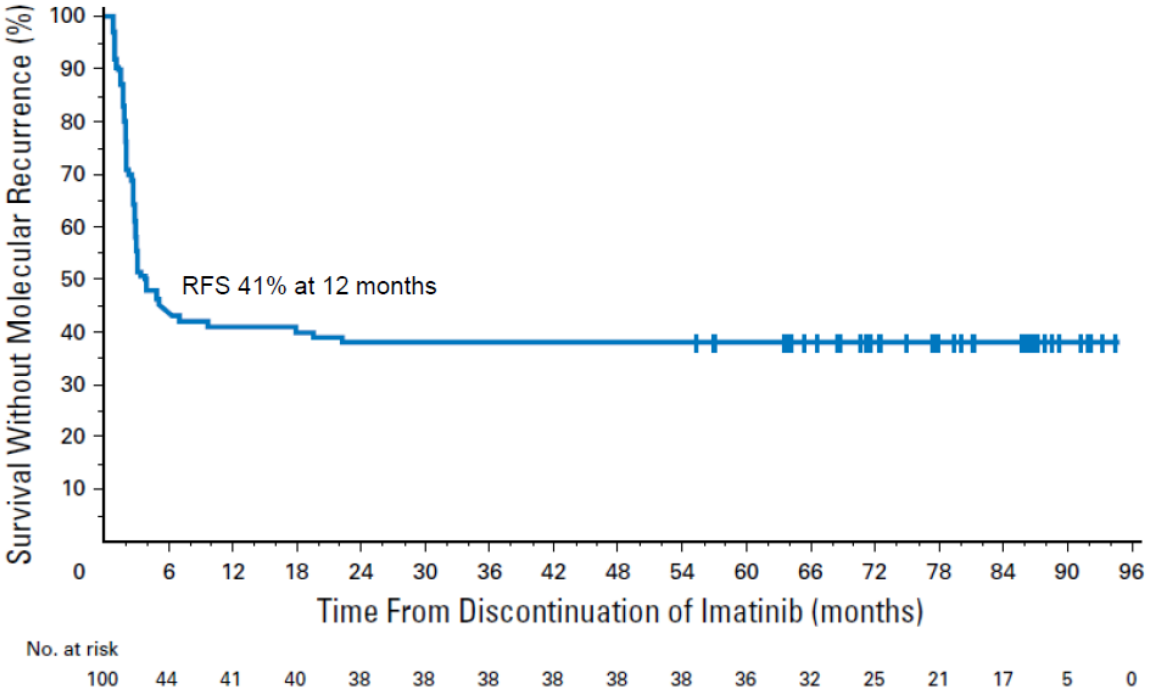
- Indication :
  - Mutation T315I
  - Echec d'au moins 2 ITK
- 45 mg x1/j
- 30% de toxicité cardio-vasculaire
  - Possiblement dose dépendant
  - Discuter dose initiale moindre selon situation de résistance en fonction du profil CV du patient
  - Discuter réduction de dose quand CCyR ou MMR
- Toujours rediscuter indication d'allogreffe

ABL 001 : Inhibiteur Allostérique



Arrêt de traitement

- **STIM Study**
  - Stop Imatinib
  - 100 patients avec MDR indétectable depuis au moins 2 ans
  - Définition de la rechute
    - 2 PCR consécutives positives



Other imatinib discontinuation studies

Study	Main inclusion criteria	Definition of relapse
TWISTER	Imatinib ≥ 3 years Undetectable MR4.5 ≥ 2 years	Detectable *BCR-ABL1* on 2 consecutive tests or MMR loss
STIM2 (Fi-LMC)	Imatinib ≥ 3 years Undetectable MR4.5 ≥ 2 years	At least 1 log increase in *BCR-ABL1* or MMR loss
KID	Imatinib ≥ 3 years Undetectable MR4.5 ≥ 2 years	MMR loss
ISAV	Imatinib ≥ 2 years Undetectable MR4 ≥ 18 months	Detectable *BCR-ABL1* on 2 consecutive tests and MMR loss
STIM123	Imatinib ≥ 3 years RM4.5 ≥ 2 years	MMR loss
EUROSKI	TKI ≥ 2 years MR4 ≥ 1 year	MMR loss

Ross et al. Blood. 2013;122(4):515-22.
Mahon et al. Blood (ASH 2013): abstract 654.
Lee et al. Haematologica. 2016;101(6):717-23.
Mori et al. Am J Hematol. 2015;90(10):910-4.
Takahashi et al. Blood (ASH 2015): abstract 4035.
Mahon et al. Blood (2016): abstract 787.

Factors associated with successful imatinib discontinuation

	Mahon et al	Ross et al	Yim, Lee et al	Takahashi et al
Age	Not significant	Not significant	Not reported	Not significant
Sex	Not significant	Not significant	Not reported	Not significant
Sokal score	Significant	Significant	Not reported	Not significant
Imatinib duration	Significant	Not significant	Not reported	Significant
IFN-a	Not significant	Significant	Not reported	Significant
Time to CMR	Not significant	Not significant	Significant	Not significant
Duration of CMR	Not significant	Not significant	Significant	Significant

Mahon FX, et al, Lancet Oncol. 2010; 11:1029-35.
Ross D, et al. *Blood*. 2013;122:515-522.
Yhim HY, et al. Leuk Res. 2012;36(6):689-693.
Takahashi N, et al. *Haematologica*. 2012;97:903-906.

Reco de l'ELN 2020 pour les Arrêts de traitement

Table 8 Requirements for tyrosine kinase inhibitor discontinuation.

Mandatory:

- CML in first CP only (data are lacking outside this setting)
- Motivated patient with structured communication
- Access to high quality quantitative PCR using the International Scale (IS) with rapid turn-around of PCR test results
- Patient's agreement to more frequent monitoring after stopping treatment. This means monthly for the first 6 months, every 2 months for months 6–12, and every 3 months thereafter.

Minimal (stop allowed):

- First-line therapy or second-line if intolerance was the only reason for changing TKI
- Typical e13a2 or e14a2 BCR–ABL1 transcripts
- Duration of TKI therapy >5 years (>4 years for 2GTKI)
- Duration of DMR (MR^4 or better) >2 years
- No prior treatment failure

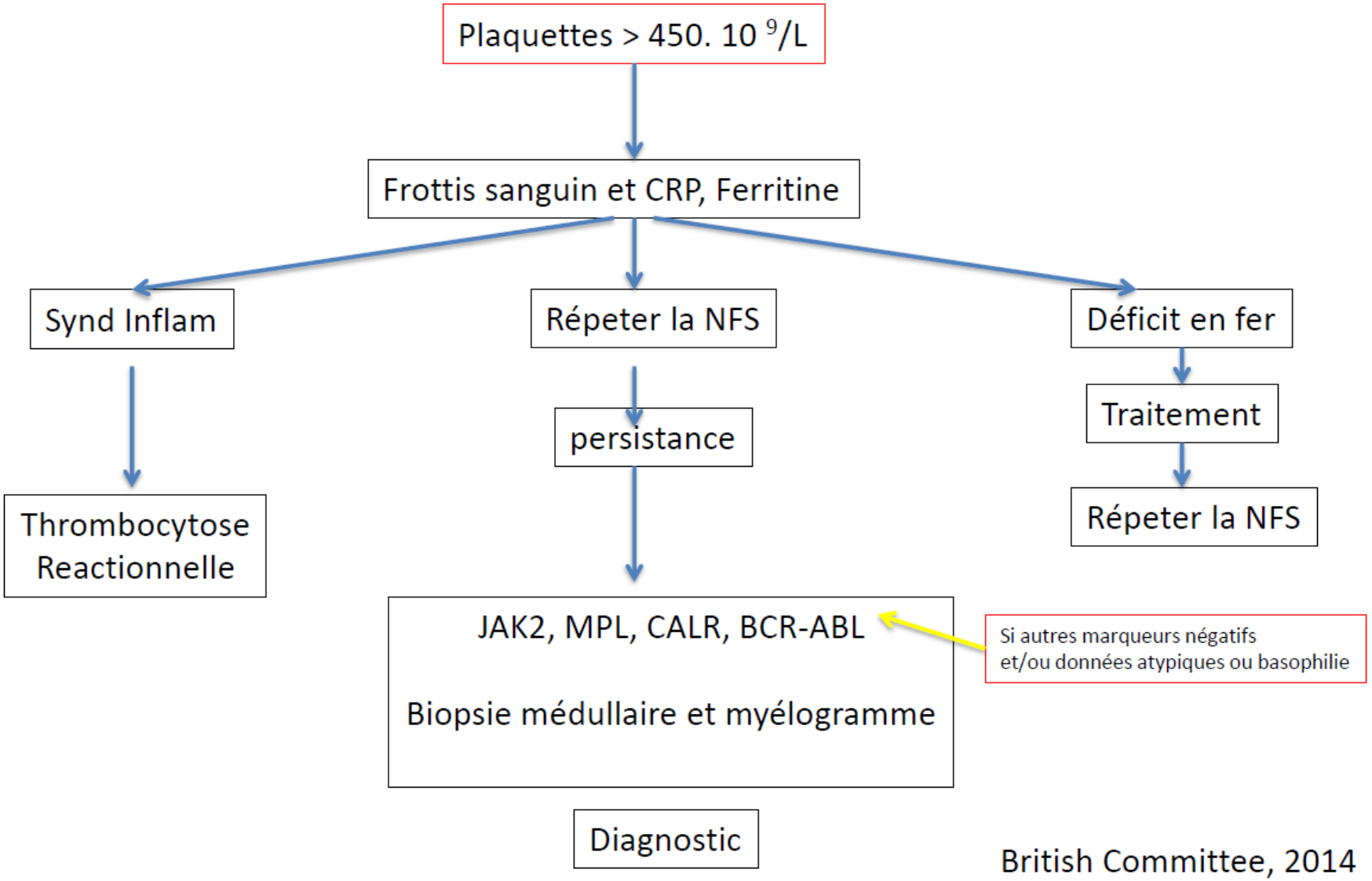
Optimal (stop recommended for consideration):

- Duration of TKI therapy >5 years
- Duration of DMR > 3 years if MR^4
- Duration of DMR > 2 years if $MR^{4.5}$

Hochhaus Leukemia 2020

Thrombocytémie essentielle

Algorithme



British Committee, 2014

Table 5. WHO criteria for ET

WHO ET criteria
Major criteria
1. Platelet count ≥450 × 10^9/L
2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
3. Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
4. Presence of *JAK2*, *CALR*, or *MPL* mutation
Minor criterion
Presence of a clonal marker or absence of evidence for reactive thrombocytosis
Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion

Arber Blood 2016

Table 13. Diagnostic criteria for MDS/MPN with ring sideroblasts and thrombocytosis

MDS/MPN diagnostic criteria
• Anemia associated with erythroid lineage dysplasia with or without multilineage dysplasia, ≥15% ring sideroblasts,* <1% blasts in PB and <5% blasts in the BM
• Persistent thrombocytosis with platelet count ≥450 × 10^9/L
• Presence of a *SF3B1* mutation or, in the absence of *SF3B1* mutation, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features†
• No *BCR-ABL1* fusion gene, no rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*; or *PCM1-JAK2*; no (3;3)(q21;q26), inv(3)(q21q26) or del(5q)‡
• No preceding history of MPN, MDS (except MDS-RS), or other type of MDS/MPN

*At least 15% ring sideroblasts required even if *SF3B1* mutation is detected.

†A diagnosis of MDS/MPN-RS-T is strongly supported by the presence of *SF3B1* mutation together with a mutation in *JAK2* V617F, *CALR*, or *MPL* genes.

‡In a case which otherwise fulfills the diagnostic criteria for MDS with isolated del (5q)-no or minimal absolute basophilia; basophils usually <2% of leukocytes.

Arber Blood 2016

Généralités

- Âge moyen 50 ans
  - Sous groupe de moins de 30 ans, prédominance féminine
- Espérance de vie quasi-comparable à la population générale
- Risque de thrombose VEINEUSE et ARTERIELLE
  - 7.5% par an
  - Incidence cumulée 65% à 10 ans
  - 1ère cause de mortalité dans les SMP
- Risque de transformation (MF > SMD/LAM)
  - 10% à 10 ans, 20% à 20 ans

Facteurs influençant la Survie

Table 3. International Prognostic Scoring in essential thrombocythemia for survival in WHO-ET

	Scores		
Risk factors	**0**	**1**	**2**
Age, y	< 60		≥ 60
WBC count, × 10^9/L	< 11	≥ 11	
History of thrombosis	No	Yes	

Low risk implies a sum of scores equal to 0; intermediate risk, a sum of scores equal to 1-2; and high risk, a sum of scores equal to 3-4.

ET indicates essential thrombocythemia; and WBC, white blood cell count.

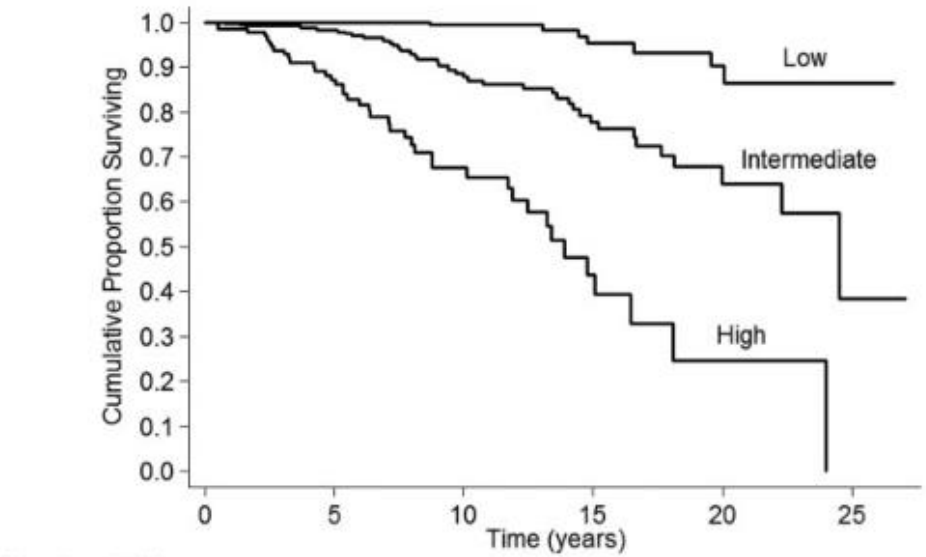
IPSET Score

Barbui Blood 2012

Cohorte de 867 patients

Passamonti Blood 2012

Figure 1. Estimate of survival of 867 patients with essential thrombocythemia, by IPSET score. Three risk factors were taken into account: age ≥ 60 years (2 points), leukocyte count ≥ 11 × 10^9/L (1 point) and prior thrombosis (1 point). The resulting risk categories were low (sum of scores = 0), intermediate (sum of scores = 1 or 2), and high (sum of scores = 3 or 4) with significantly different survivals: not reached in low-risk patients, 24.5 years (95% CI: 22.3-NR) in intermediate risk, and 14.7 years (95% CI: 11.9-18) in high-risk patients.



Number at risk						
Low	342	211	123	63	25	3
Intermediate	374	223	109	51	15	2
High	151	84	32	10	2	0

Facteurs influençant la Survie

Mutations

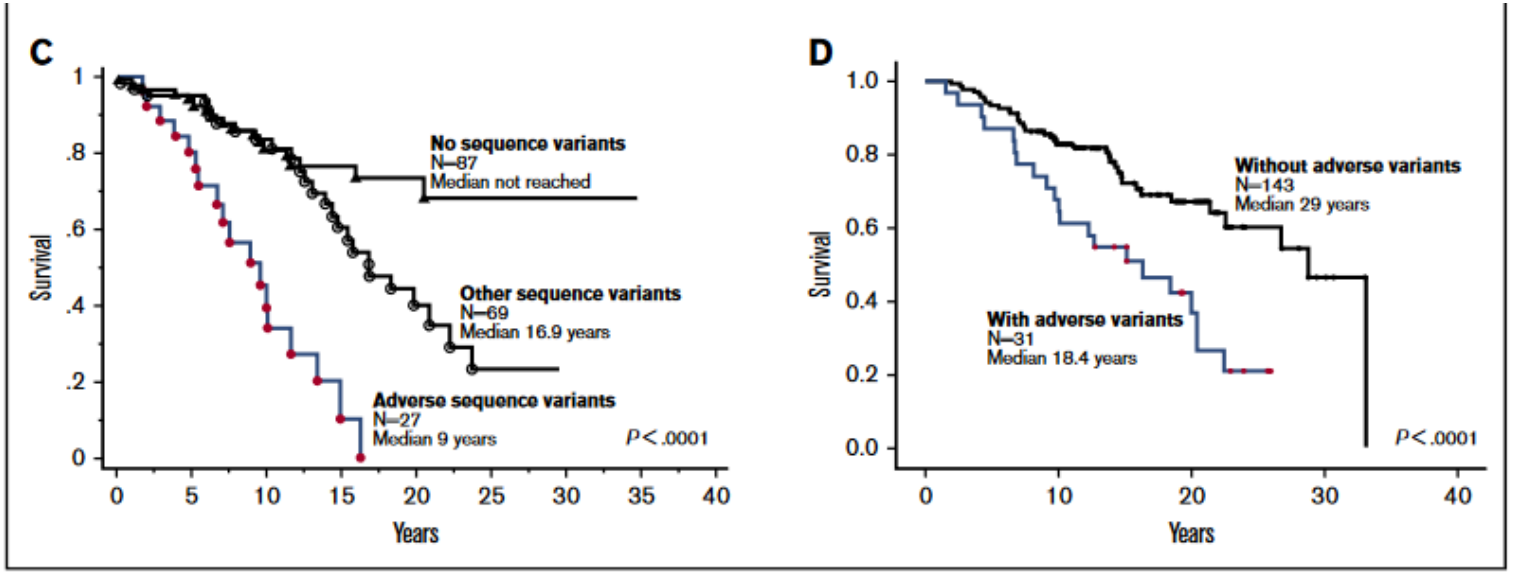


Figure 2. Overall survival curves.

(C) Survival in 183 Mayo Clinic patients with ET stratified by the presence or absence of "adverse" (*SH2B3*, *IDH2*, *SF3B1*, *U2AF1*, *EZH2*, *TP53*) or "other" (*TET2*, *ASXL1*, *PTP11*, *SUZ12*, *ZRSR2*, *CBL*, *CEBPA*, *CSF3R*, *DNMT3A*, *SRSF2*, *FLT3*, *KIT*, *NRAS*, *RUNX1*, *SETBP1*) sequence variants/mutations. (D) Survival in 174 Italian patients with ET stratified by the presence or absence of adverse (*SH2B3*, *IDH2*, *SF3B1*, *U2AF1*, *EZH2*, *TP53*) variants/mutations.

Tefferi Blood 2016

Taux de LDH

Mudireddy Am J Hematol 2017

Traitements de la TE

- **Aucun traitement** n'a encore fait preuve d'une efficacité à **modifier l'histoire naturelle** de la maladie, ou à **prévenir le risque** d'évolution vers la MF ou de transformation vers SMD/LAM, ou à **améliorer la survie**
- **L'indication de traitement** est de **prévenir les complications thrombotiques**

Risque thrombotique

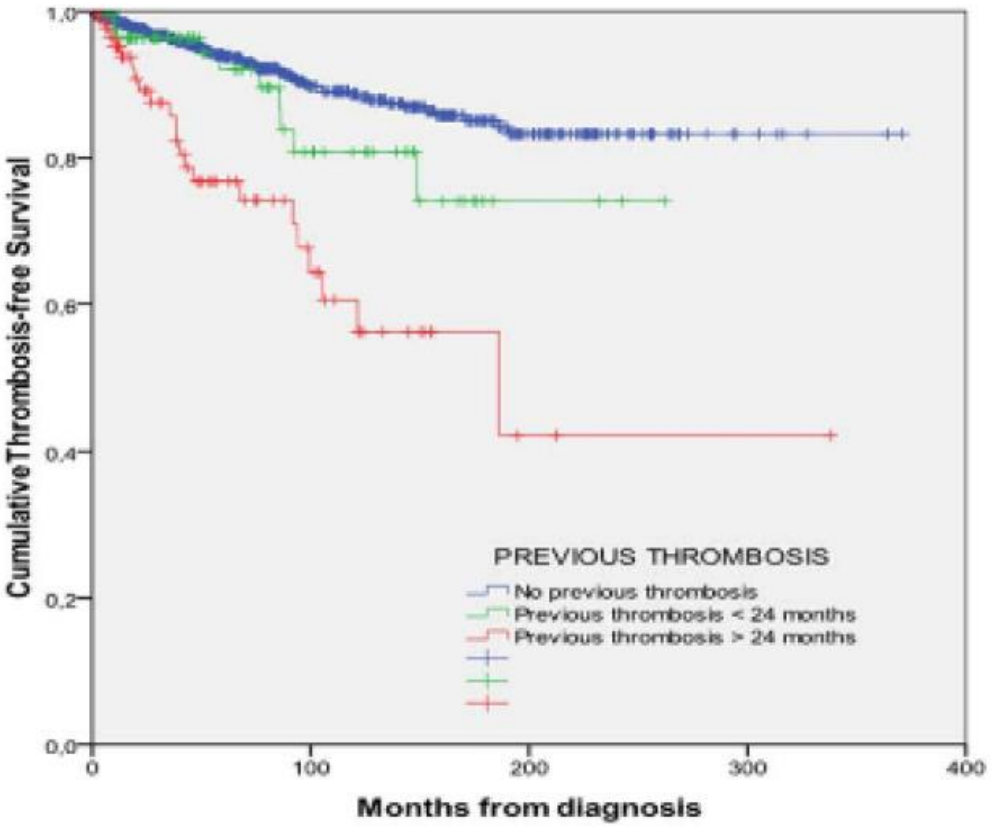
Table 2. Multivariate analysis for risk factors predicting fatal and nonfatal thrombotic events in the follow-up of 891 WHO-ET patients

	Major thrombosis (n = 109)		Arterial thrombosis (n = 79)		Venous thrombosis (n = 37)	
Parameters at diagnosis	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age > 60 y	1.50 (1.00-2.25)	0.049	1.69 (1.05-2.73)	0.031	1.26 (0.63-2.52)	.506
Previous thrombosis	1.93 (1.27-2.91)	0.002	2.07 (1.28-3.34)	0.003	1.78 (0.86-3.66)	.119
Male sex	1.34 (0.91-1.95)	0.135	0.98 (0.62-1.54)	0.919	1.99 (1.03-3.83)	.039
CV risk factors*	1.56 (1.03-2.36)	0.038	1.91 (1.19-3.07)	0.007	0.77 (0.33-1.83)	.556
WBC > 11 × 10^9/L	1.14 (0.72-1.79)	0.583	1.66 (1.01-2.72)	0.044	0.52 (0.19-1.38)	.516
Hemoglobin < 12 g/dL	1.36 (0.58-3.18)	0.479	1.53 (0.60-3.93)	0.376	0.48 (0.06-3.72)	.479
Platelet count > 1000 × 10^9/L	0.50 (0.30-0.84)	0.009	0.42 (0.22-0.78)	0.007	0.97 (0.44-2.15)	.943
$JAK2^{V617F}$	2.04 (1.19-3.48)	0.009	2.57 (1.27-5.19)	0.009	1.43 (0.65-3.11)	.372

Analysis adjusted also for chemotherapy and antiplatelet needs during follow-up.
CV indicates cardiovascular; and WBC, white blood cell count.
*Smoking, arterial hypertension, and diabetes (at least one).

Carobbio Blood 2011

Risque thrombotique



ATCD de thrombose

Montanaro Am Journal Hematol 2014

Risque thrombotique

TABLE VII. Comparison of Prognostic Factors for TFS at Multivariate Analysis in Different Studies

Author (years)	Tefferi (2007)	Passamonti (2008)	Carobbio (2008)	Girodon (2010)	Palandri (2011)	Carobbio (2011)	Barbui (2012)	Present study
No. patients	605	605	657	311	532	891	1220	1144
Median follow-up (yrs)	13.6	5.6	4.5	9.5	7.6	6.2	NR	5.4
Age > 60 yrs	YES	YES	YES	YES	YES	YES	YES	NO
Previous thromboses	YES (A)	YES	YES	YES	YES	YES (A)	YES	YES
Cardiovascular risk factors	NR	NR	NR	NR	NR	YES (A)	YES	YES (A)
WBC $>11.10^9$/L	YES	NR	YES	NO	YES	YES (A)	NO	NO
JAK2 ^{V617F} mutation	NR	NR	NO	NO	NO	YES (A)	YES	NO
JAK2 ^{V617F} allele burden	NR	NR	NO	NR	NO	NR	NR	NO
Gender	NR	NR	NO	YES	NO	YES	NO	NO

- FDR CV
  - Surtout à partir de $\geq$2, p=0.0072 vs p=0.014
- Taux de leucocytes ?
- Mutation JAK2

Montanaro Am Journal Hematol 2014

Risque thrombotique

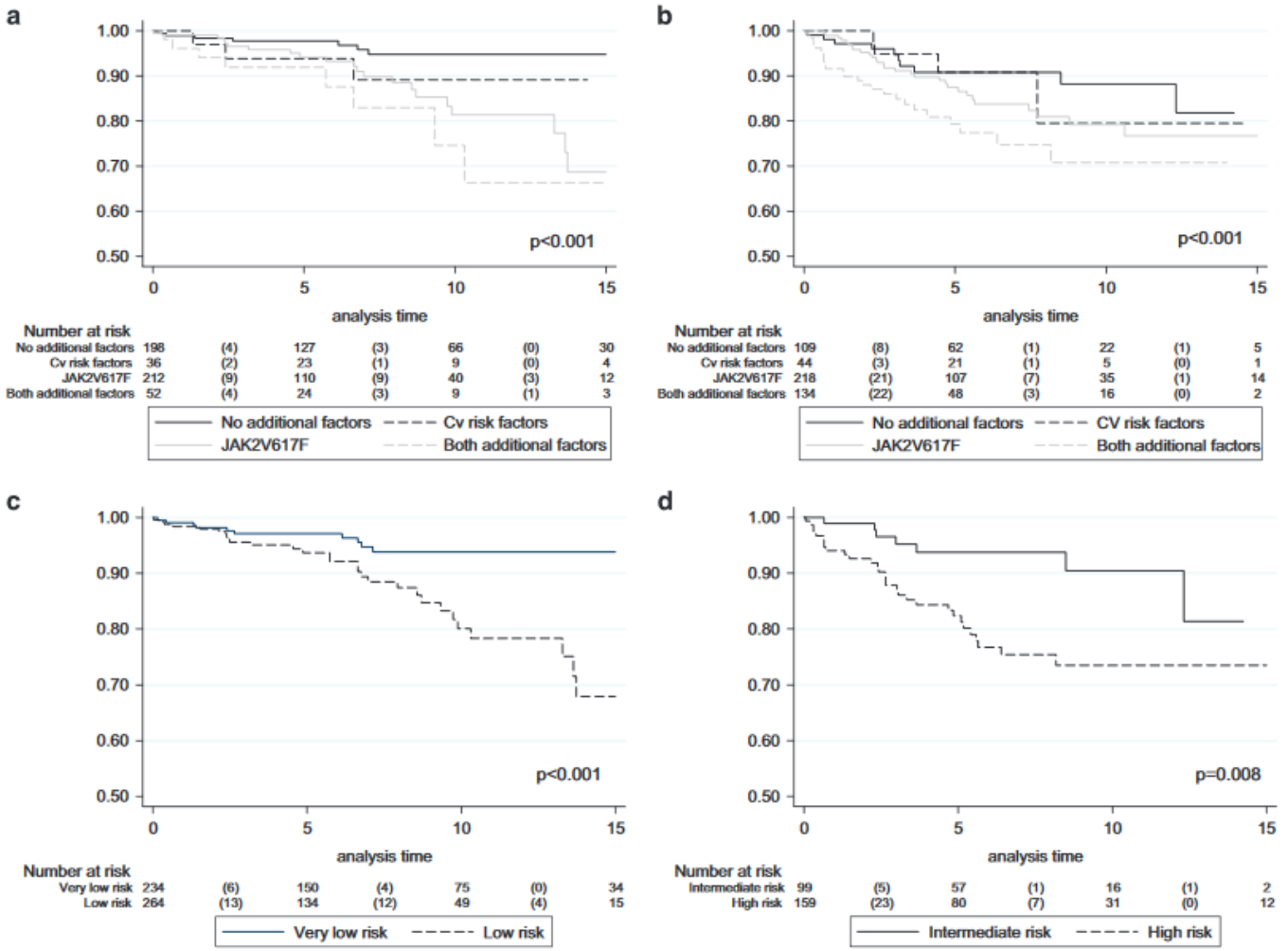


Figure 1. Thrombosis-free survival in conventionally defined low- and high-risk (**a** and **b**) and in the revised risk classification (**c** and **d**). (**a**) Low-risk patients with or without additional risk factors (CV risk factors and JAK2 mutation); (**b**) High-risk patients with or without additional risk factors (CV risk factors and JAK2 mutation); (**c**) 'Very low risk' (no thrombosis history, age ⩽60 years and JAK2-unmutated); 'Low risk' (no thrombosis history, age ⩽60 years and JAK2-mutated); (**d**) 'Intermediate risk' (no thrombosis history, age >60 years and JAK2-unmutated); 'High risk' (thrombosis history or age >60 years with JAK2 mutation).

- **JAK2 V617F**
- **FDRCV**

Barbui Blood Cancer J 2015

Risque thrombotique et **Cytoréduction**

Table 3. Multivariate Analysis of Prognostic Factors for Thrombosis in 114 Patients with Essential Thrombocythemia.

Variable	Relative Risk (95% Confidence Interval)	P Value
Hydroxyurea treatment	0.13 (0.03–0.58)	0.0072
Age	1.01 (0.95–1.07)	0.7625
Sex	1.10 (0.30–3.40)	0.8624
Platelet count at enrollment	0.999 (0.997–1.001)	0.4277
Newly diagnosed disease	0.82 (0.28–2.37)	0.7143
Cigarette smoker	4.57 (1.44–14.55)	0.0100
Diabetes*	—	—
Hypertension	1.87 (0.69–5.06)	0.2167
Hyperlipidemia	3.28 (0.42–25.83)	0.2583
Previous thrombosis	1.39 (0.51–3.73)	0.5175
Previous chemotherapy	2.15 (0.78–5.90)	0.1368
Current use of antiplatelet drugs	0.53 (0.19–1.49)	0.2311

*Only three patients had diabetes, and all had thrombosis.

Cortelazzo NEJM 1995

Risque thrombotique et **Cytoréduction**

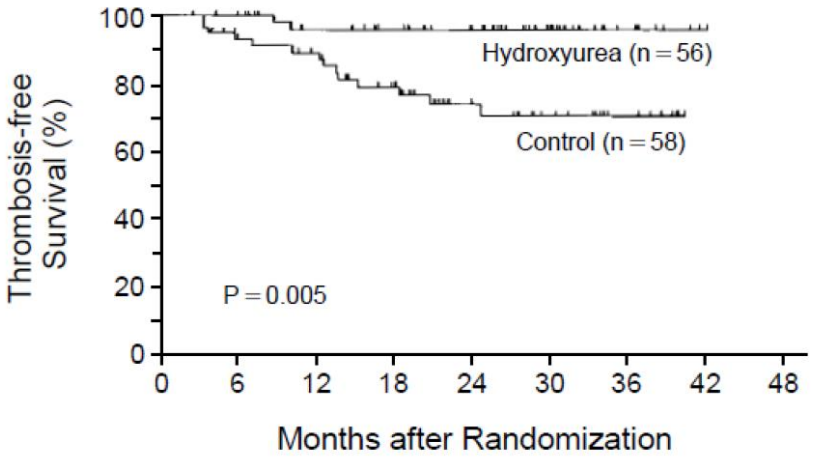


Figure 2. Probability of Thrombosis-free Survival in 114 Patients with Essential Thrombocythemia Treated with Hydroxyurea or Left Untreated.

The P value is for the difference between the two groups (by the log-rank test). The median follow-up was 27 months. Tick marks indicate surviving patients who were continuously free of thrombosis.

Cortelazzo NEJM 1995

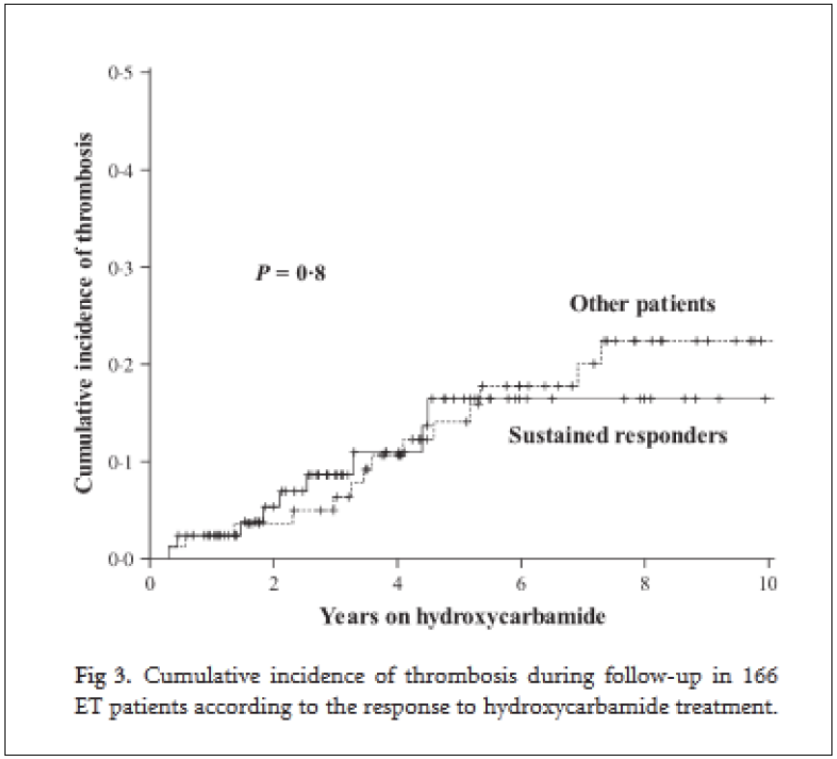


Fig 3. Cumulative incidence of thrombosis during follow-up in 166 ET patients according to the response to hydroxycarbamide treatment.

Hernandez-Boluda BJH 2010

Risque thrombotique et **ASA**

Table 3. Multivariate Analysis of Prognostic Factors for Thrombosis in 114 Patients with Essential Thrombocythemia.

Variable	Relative Risk (95% Confidence Interval)	P Value
Hydroxyurea treatment	0.13 (0.03–0.58)	0.0072
Age	1.01 (0.95–1.07)	0.7625
Sex	1.10 (0.30–3.40)	0.8624
Platelet count at enrollment	0.999 (0.997–1.001)	0.4277
Newly diagnosed disease	0.82 (0.28–2.37)	0.7143
Cigarette smoker	4.57 (1.44–14.55)	0.0100
Diabetes*	—	—
Hypertension	1.87 (0.69–5.06)	0.2167
Hyperlipidemia	3.28 (0.42–25.83)	0.2583
Previous thrombosis	1.39 (0.51–3.73)	0.5175
Previous chemotherapy	2.15 (0.78–5.90)	0.1368
Current use of antiplatelet drugs	0.53 (0.19–1.49)	0.2311

*Only three patients had diabetes, and all had thrombosis.

Cortelazzo NEJM 1995

Risque thrombotique et **ASA**

- ASA diminue le risque de thrombose artérielle chez patients de faible risque avec FDRCV
- ASA diminue le risque de thrombose veineuse chez patients de faible risque JAK2 V617F

Alvarez-Larran Blood 2010

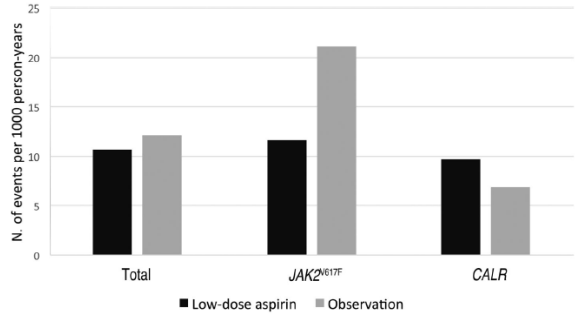


Figure 2. Incidence rate of thrombosis (arterial or venous) in ET patients treated with low-dose aspirin or careful observation. Rates according to therapy are provided for the whole cohort of patients (*P*=0.7), *JAK2*^{V617F}-mutated patients (*P*=0.2) and *CALR*-mutated patients (*P*=0.6).

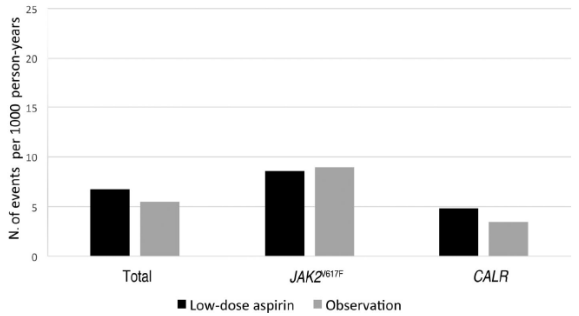
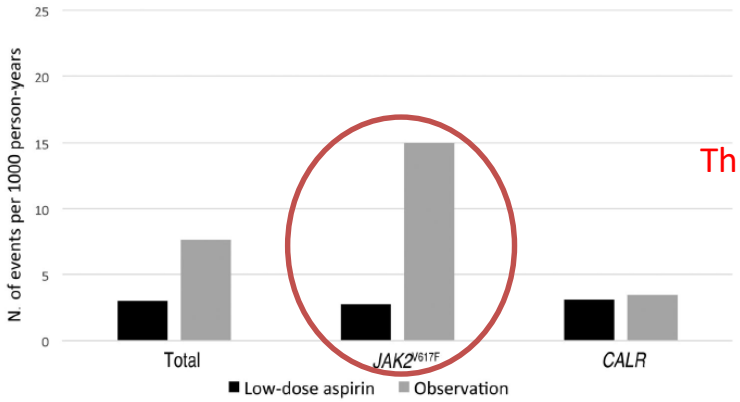


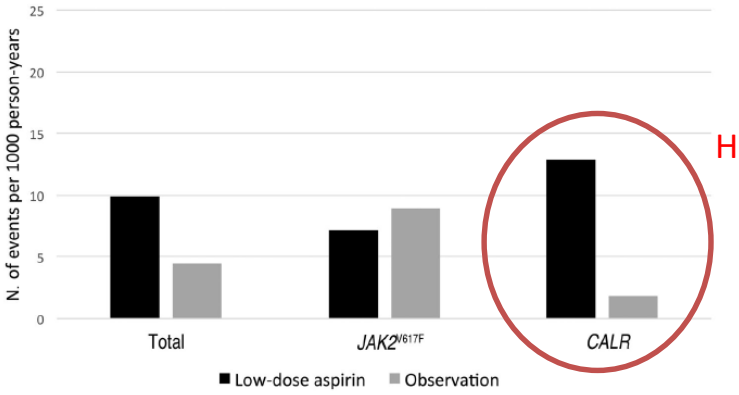
Figure 3. Incidence rate of arterial thrombosis in ET patients treated with low-dose aspirin or careful observation. Rates according to therapy are provided for the whole cohort of patients (*P*=0.7), *JAK2*^{V617F}-mutated patients (*P*=0.9) and *CALR*-mutated patients (*P*=0.7).

Alvarez-Larran Haematol 2016



Thrombose Veineuse

Figure 4. Incidence rate of venous thrombosis in ET patients treated with low-dose aspirin or careful observation. Rates according to therapy are provided for the whole cohort of patients (*P*=0.1), *JAK2*^{V617F}-mutated patients (*P*=0.045) and *CALR*-mutated patients (*P*=0.9).



Hémorragie Majeure

Figure 5. Incidence rate of major bleeding in ET patients treated with low-dose aspirin or careful observation. Rates according to therapy are provided for the whole cohort of patients (*P*=0.17), *JAK2*^{V617F}-mutated patients (*P*=0.8) and *CALR*-mutated patients (*P*=0.03).

Stratification des FdR et Traitement

- **Faible risque**
  - <40 ans, pas d'ATCD thrombotique, GB<11 G/L
  - *15% des patients*
    - **OBSERVATION SEULE**
- **Risque intermédiaire**
  - 40-60 ans sans ATCD
  - *20% des patients*
    - **ASA ?**
- **Risque élevé**
  - *65% des patients*
    - **CYTOREDUCTION (+ASA?)**

Current Treatment Algorithm in Essential Thrombocythemia

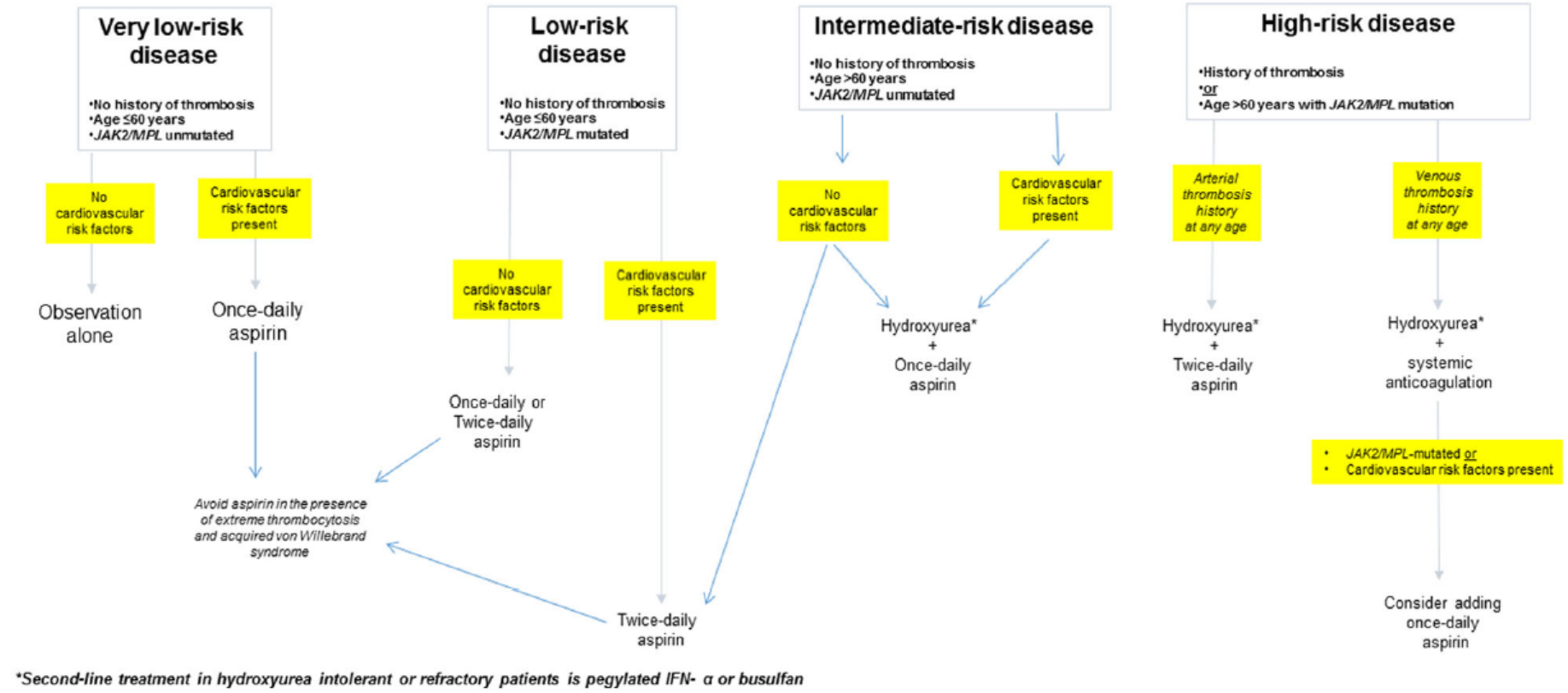
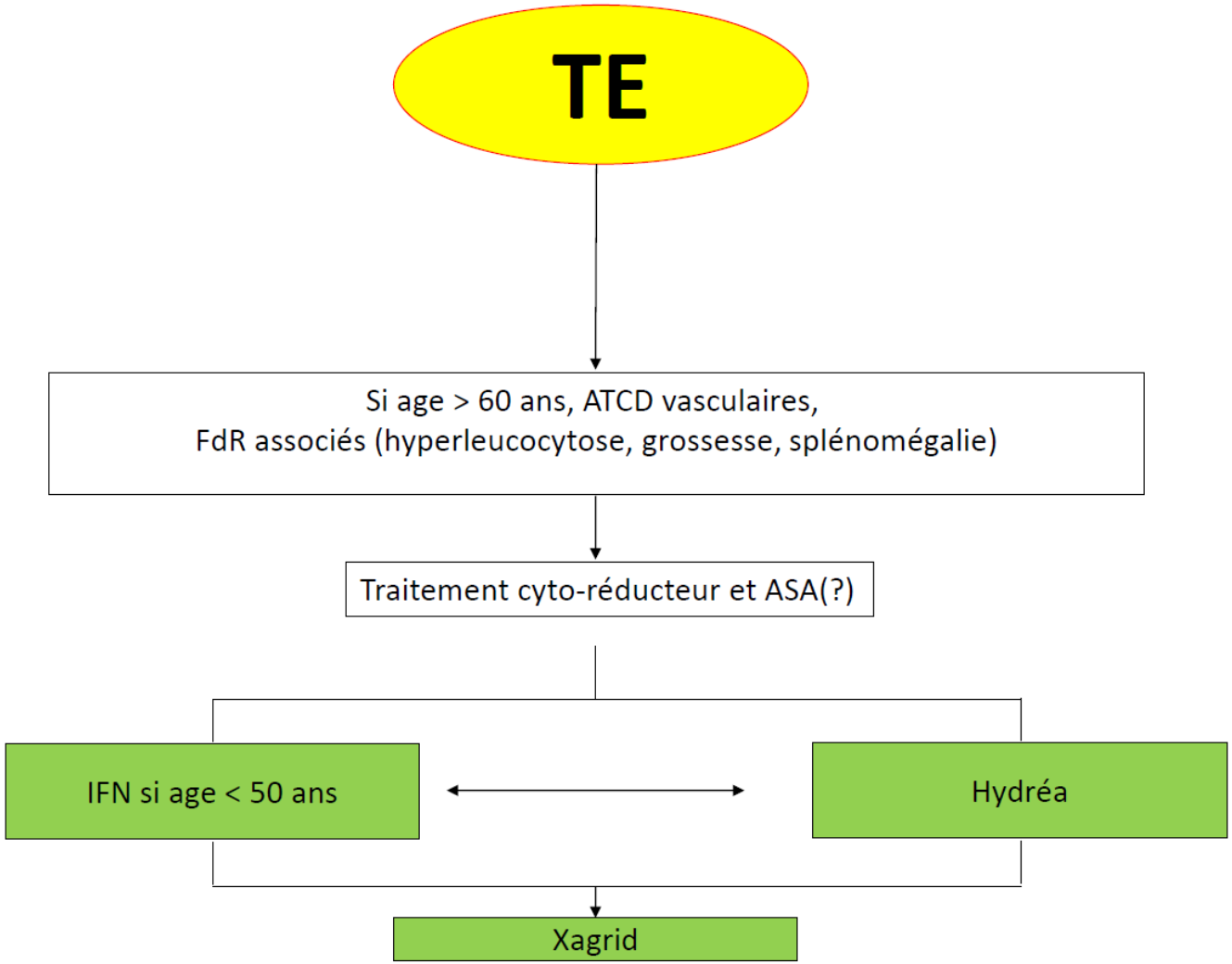


Fig. 1 Current treatment algorithm in essential thrombocythemia Second-line treatment in hydroxyurea intolerant or refractory patients in pegylated IFN-α or busulfan

Pas d'accord sur le choix du ttt cytoréducteur !!!!

Tefferi Blood Cancer J 2018

Traitement cytoréducteur



Interféron et TE

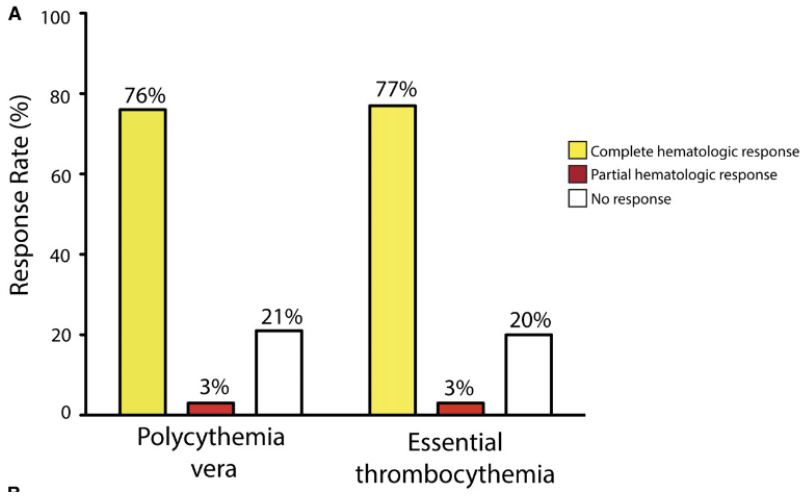
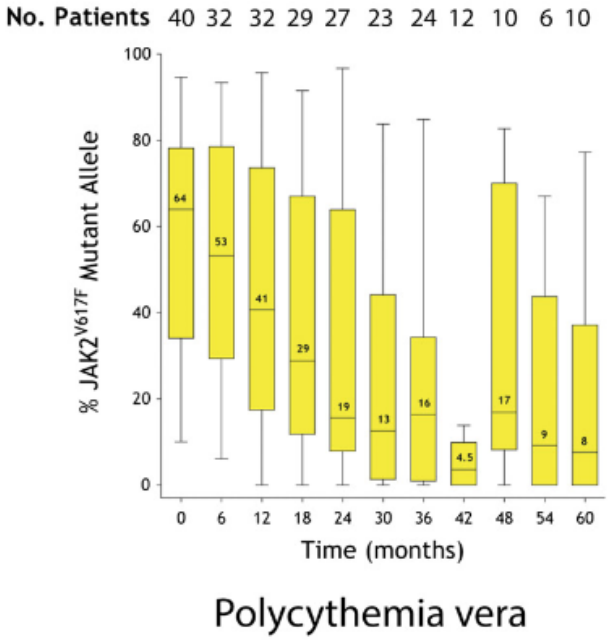


Table 2. Molecular response rates to PEG-IFN-α-2a therapy

*JAK2*V617F allele burden	PV (n = 40) number (%)	ET (n = 18) number (%)
CMR (undetectable)	7 (18)	3 (17)
PMR (>50% decrease)	14 (35)	6 (33)
mMR (20%-49% decrease)	3 (8)	3 (17)
No response	16 (40)	6 (33)



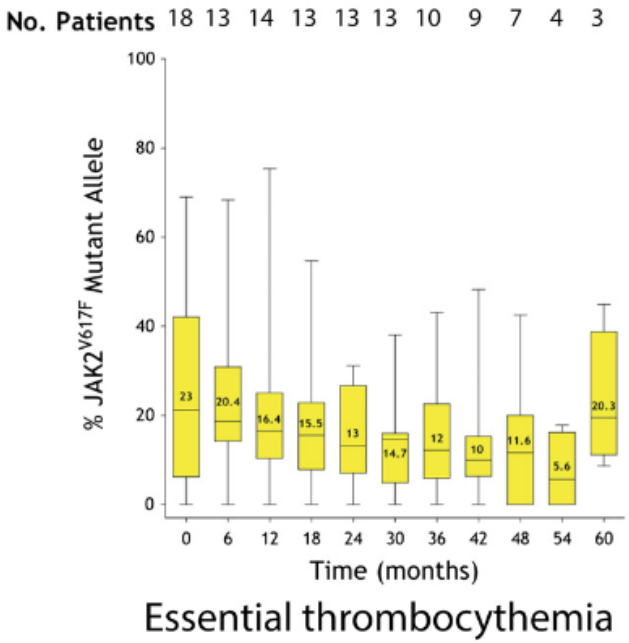


Figure 1. Long-term follow-up of response to PEG-IFN-α-2a. (A) Hematologic response in patients with PV or ET. (B) Dynamics of *JAK2*V617F mutant allele burden in patients with PV or ET over time. Black horizontal lines indicate median values; black bars represent minimum and maximum values; yellow rectangular boxes represent values included between the 25% and the 75% percentiles.

Essai de Phase 2
-43 PV
- 40 TE

Quintas-Cardama
Blood 2013

Interféron et TE CALR

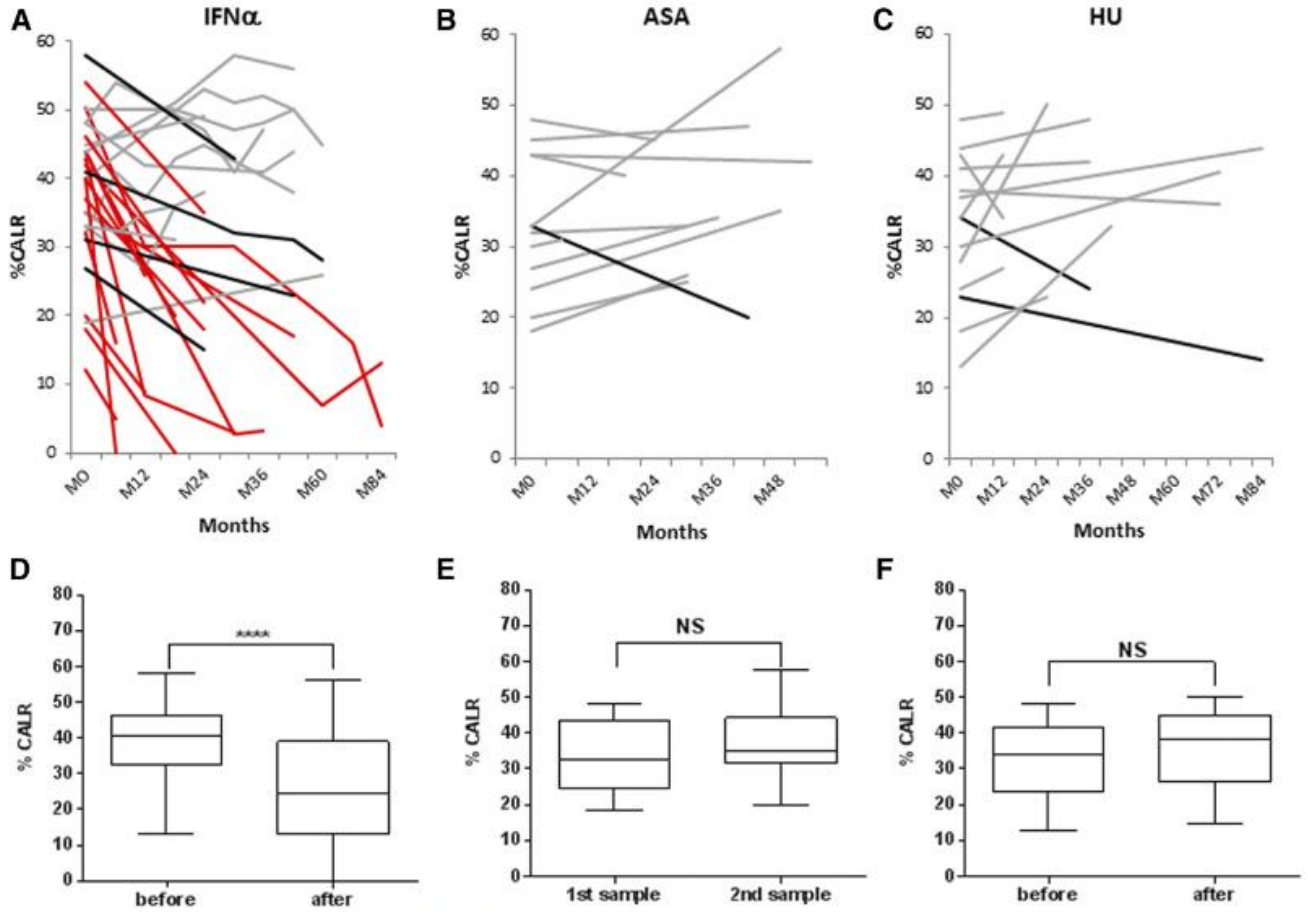
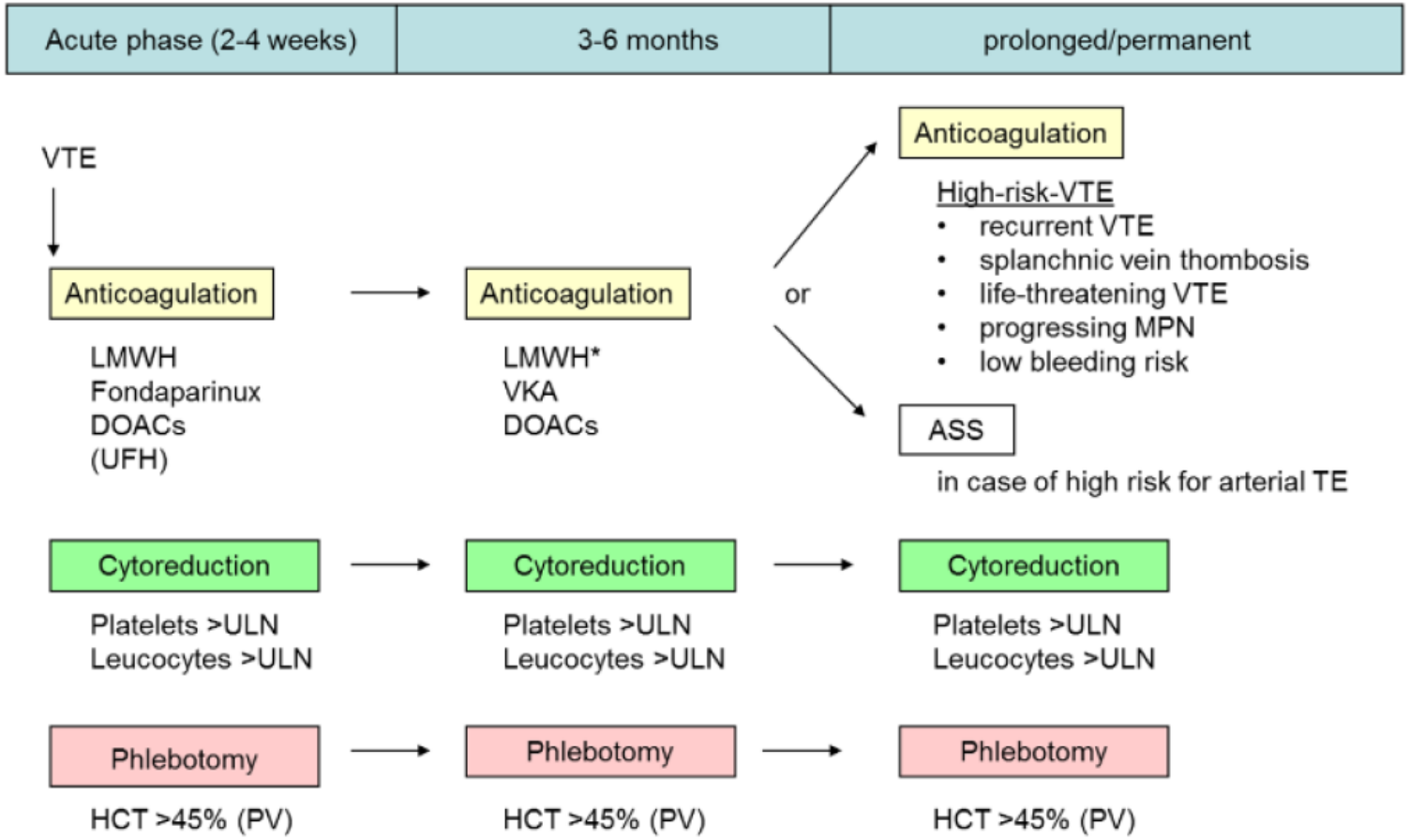


Figure 1. Evolution of *CALR* mutant allele burden (%CALR) with time. Evolution of %CALR in each patient at different time points during treatment with peg-IFNα (A), aspirin only (B), or HU (C). Patients with CMR or PMR are depicted in red, and patients with no response or mMR are depicted in gray and black, respectively. Median %CALR before treatment and at the last time point during follow-up for patients treated with peg-IFNα (D), aspirin only (E), or HU (F). ASA, aspirin.

Verger Blood 2015

TE et Thrombose veineuse



•e.g. Dalteparin 150 IE/kg QD or Tinzaparin 175 IE/kg QD, in case of high bleeding risk reduced-dose

Kreher S., Am Hematol. 2014, DGHO and OGHO and GTHeV

TE et Grossesse

Preconception planning:
Hematologist/obstetrician consultation
Assessment of the risk / screening for thrombophilia
Cessation of teratogenic drugs (Hydroxyurea, Anagrelide…)

⇩

Management of pregnancy in ET
•Ultrasound scan
•Uterine artery Doppler scanning between 20 and 26 weeks
•Careful monitoring of blood count and blood pressure

Low risk patient
•Observation alone
•Observation associated with low dose aspirin (75-100 mg/d)

High risk patient
•Low dose aspirin (75-100 mg/d)
•Interferon α
•LMWH (Enoxaparin 4000 unit, once daily)

Delivery
Stop aspirin > 1 weeks prior to delivery
Stop LMWH according to local protocol

⇩

Post-partum
Aspirin +/- LMWH at least 6 weeks
Breastfeeding : decision on an individual basis.

LMWH: low molecular weight heparin.

- Valera MC, Eur J of Obst & Gynecol., 2011

SMP non Phi et grossesse

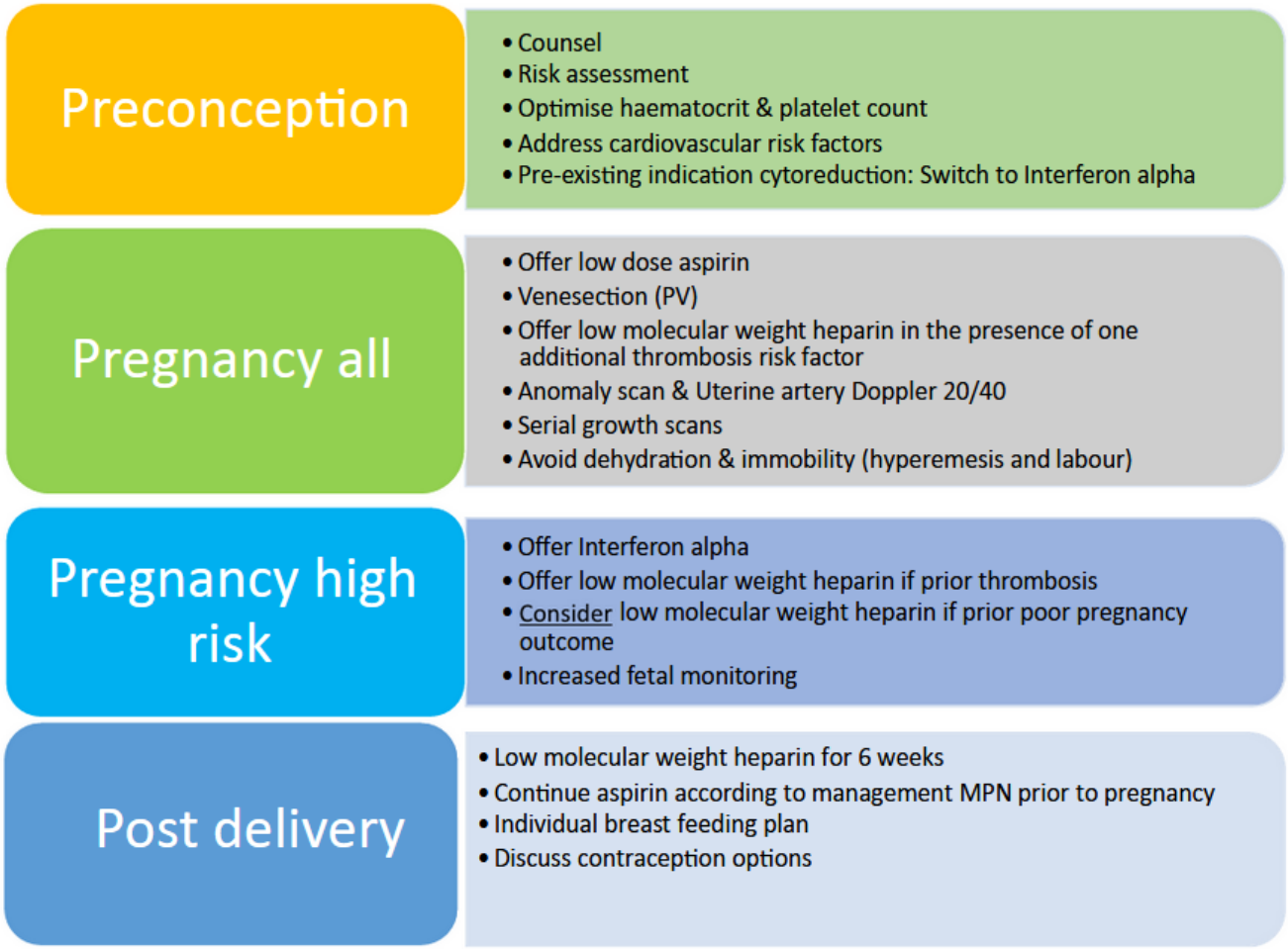


Figure 1. Management approach Philadelphia-negative myeloproliferative neoplasms in pregnancy.

Robinson BHJ 2020

Polyglobulie de Vaquez

CLASSIFICATION DES POLYGLOBULIES

- **PRIMITIVES (érythropoïèse anormale)**
  - Acquises : **Polyglobulie primitive ou Polyglobulie de Vaquez**
  - Congénitales : Mutations Epo-R

- **SECONDAIRES (érythropoïèse normale)**
  - **Acquises (Epo):**
    - Hypoxie centrale: maladie respi. chronique, SAS, shunts D-G, tabac, altitude
    - Hypoxie locale: Maladie rénale (sténose, PKR, hydronéphrose, post-transplant)
    - Production d'Epo anormale: hépatoK, RCC, léiomyome, phéo, hémangioblastome cérébelleux
    - Médicamenteuses: Epo, androgènes
  - **Congénitales:**
    - Voie de détection de l'oxygénation: mutations VHL, PHD2, HIF-2α
    - Autres: Hb hyper-affine, Déficit 2-3 DPG

- **ERYTHROCYTOSE IDIOPATHIQUE**

Table 4. WHO criteria for PV

WHO PV criteria
Major criteria
1. Hemoglobin >16.5 g/dL in men
Hemoglobin >16.0 g/dL in women
or,
Hematocrit >49% in men
Hematocrit >48% in women
or,
increased red cell mass (RCM)*
2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of *JAK2*V617F or *JAK2* exon 12 mutation
Minor criterion
Subnormal serum erythropoietin level
Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion†

*More than 25% above mean normal predicted value.

†Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

Arber Blood 2016

PV - Evolution au long cours

- Causes de décès :

- **Etude ECLAP**
- Suivi médian F-U: 2.8 ans

Causes of Deaths (n= 164)	
Cardio-vascular	45%
Cancer	19%
Hematological transformation	13%

Table 2. Main Outcome Events During Follow-Up in 1,638 Patients With Polycythemia Vera

	Patients	
	No.	%
All causes of mortality	164	10.0
Cardiovascular death	74	4.5
Cardiac death	43	2.6
Coronary heart disease	25	1.5
Congestive heart failure	13	0.8
Other cardiac disease	5	0.3
Vascular death	31	1.9
Nonhemorrhagic stroke	13	0.8
Pulmonary embolism	6	0.4
Intracranial hemorrhage	2	0.1
Other hemorrhage	5	0.3
Other vascular death	5	0.3
Noncardiovascular death	79	4.8
Cancer	54	3.3
Hematologic transformation*	22	1.3
Solid tumors†	32	2.0
Other noncardiovascular causes	25	1.5
Unknown cause of death	11	0.7

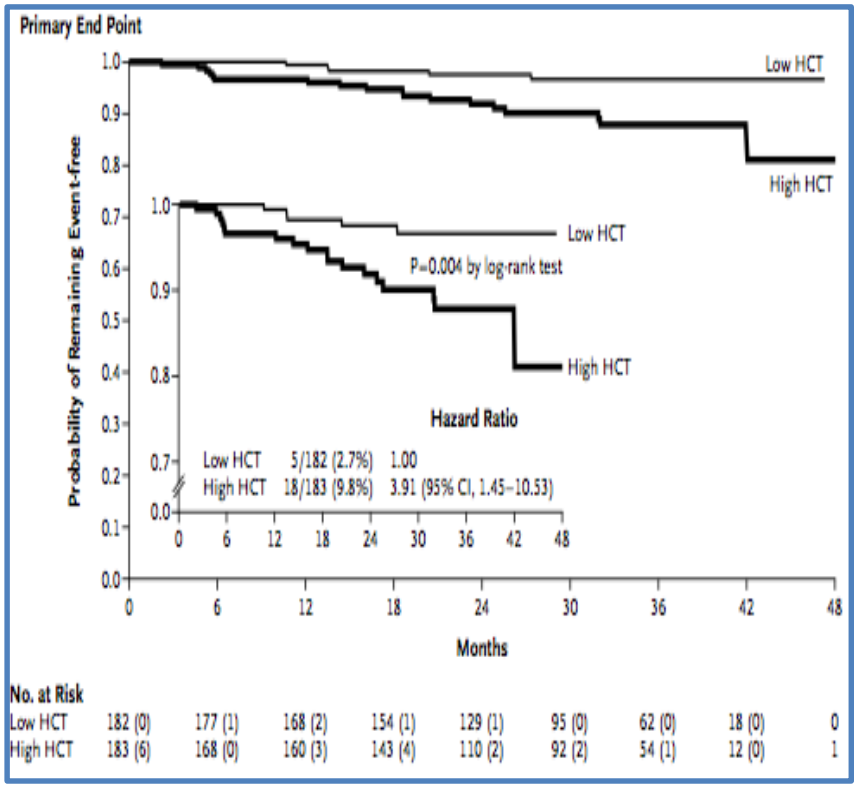
Marchioli et al, J Clin Oncol, 2005

Prise en charge de la Polyglobulie de Vaquez

Age, ATCD Vasculaire	Faible risque	Haut risque
	Contrôle des facteurs de risque CV	
	Aspirine faible dose	
Age < 60 ET *pas d'ATCD vasculaire*	**Saignées**	
Age > 60 ET / OU *ATCD vasculaire*		**Cytoréduction** ***1ère ligne: HU ou IFNα***

Barbui T, J Clin Oncol. 2011;29(6):761-70

Prise en charge de la Polyglobulie de Vaquez



365 patients
Traités par HU, Saignées ou les deux
-bras intensif = obj Ht<45%
-bras moins intensif = obj Ht 45-50%

Critère de jugement principal = temps jusqu'à décès par cause CV ou évènement thrombotique majeur

Hematocrite cible < 45 %

Marchioli et al. N Engl J Med. 2013;368(1):22-33

Polyglobulie de Vaquez

Prise en charge

Première ligne : hydroxyurée ou interferon alpha ?

Hydroxyurée

- Traitement le plus utilisé dans la PV suite aux essais du PVSG
- Bon contrôle de la NFS, diminue le risque de thrombose

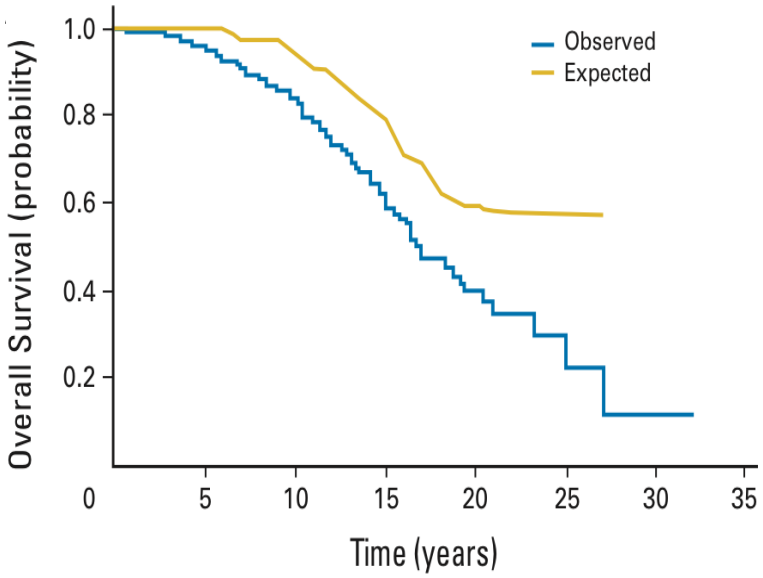
- Traitement palliatif
- 15 à 20% des patients développent une résistance et/ou une intolérance
- Risque leucémogène ?

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Treatment of Polycythemia Vera With Hydroxyurea and Pipobroman: Final Results of a Randomized Trial Initiated in 1980

Jean-Jacques Kiladjian, Sylvie Chevret, Christine Dosquet, Christine Chomienne, and Jean-Didier Rain

- 285 patients de moins de 65 ans
- Survie médiane : 17 ans (95% CI: 15.4 - 19.4)
  - Racourcie rapport à la population générale
- Causes de décès (n=95):
  - **Leucémie aigue : 54%**
  - Vasculaire : 19%
  - Second cancer : 12%



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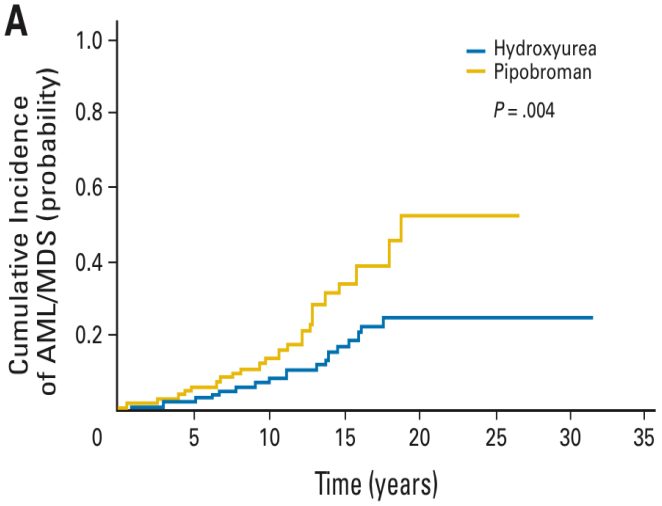
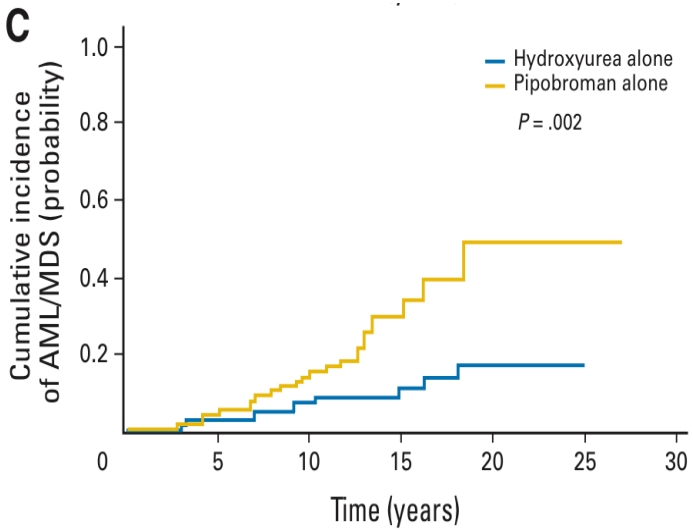
Jean-Jacques Kiladjian, Sylvie Chevret, Christine Dosquet, Christine Chomienne, and Jean-Didier Rain

- Evolution to AML/MDS

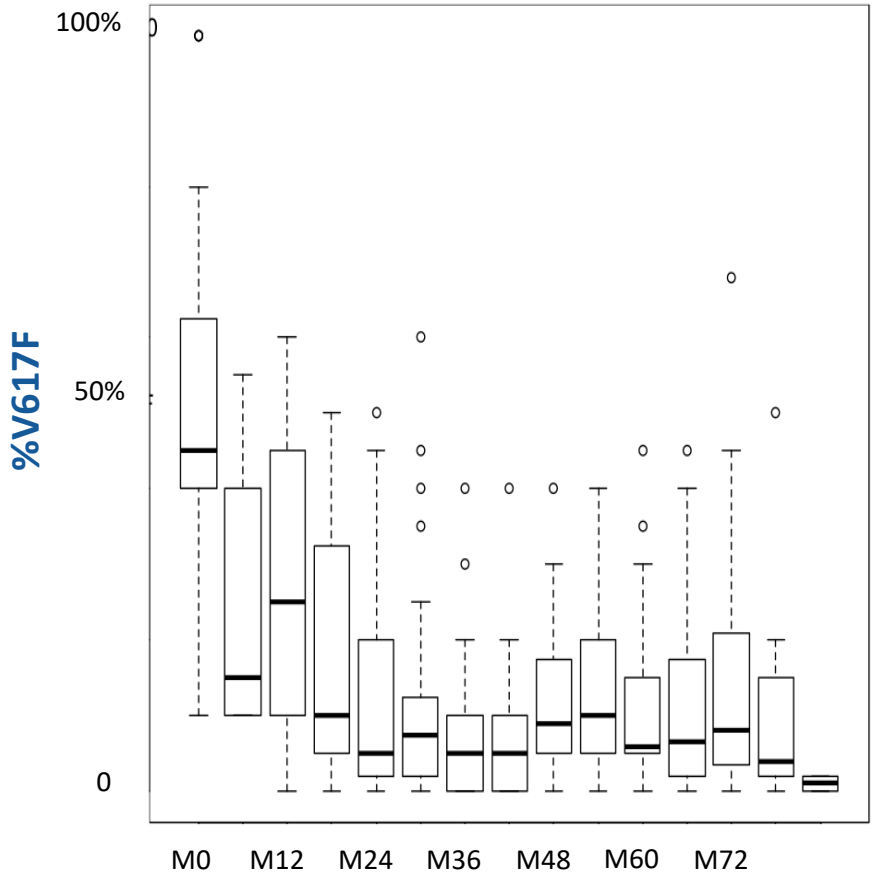
	10 years	**15 years**	20 years
Total cohort	9.8%	24%	34%
HU (ITT)	6.6%	**16.5%**	24%
Pipo (ITT)	13%	34%	52%
HU (PP)	7.5%	**14%**	22%
Pipo (PP)	12%	37%	56%
HU (alone, n=94)	7.3%	**11%**	17%
Pipo (alone, n=130)	14.6%	34%	49.4%





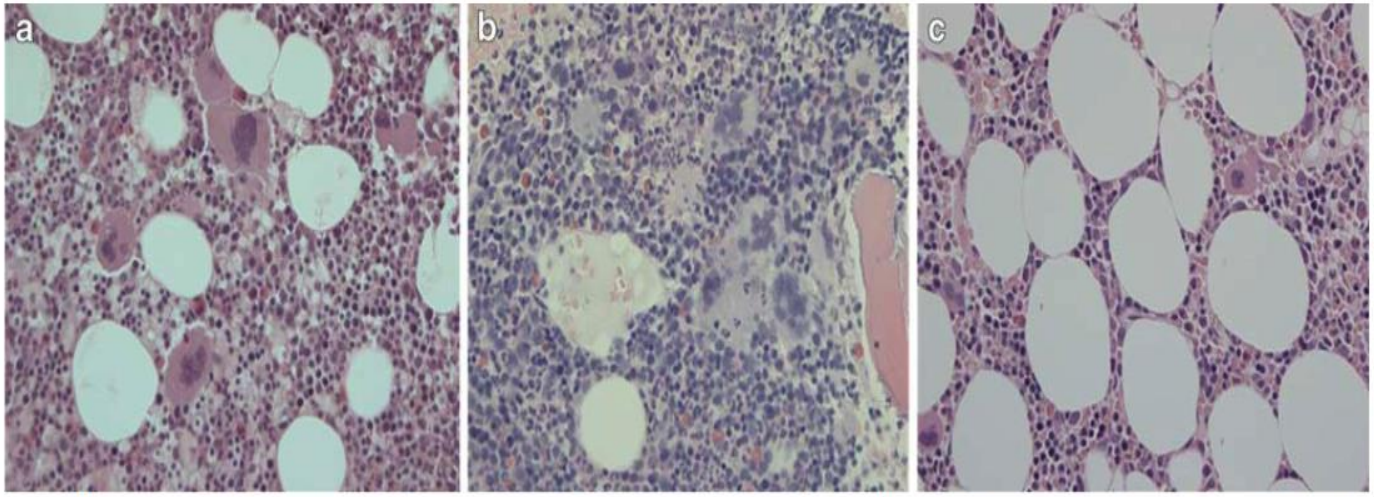
Advantages de l'IFNα *(hors AMM)*

- ✓ **Réduction du clone myéloprolifératif**



Kiladjian, Hematology Am Soc Hematol Educ Program. 2012;2012:561-6

Advantages de l'IFNα *(hors AMM)*



Diagnostic | Avant IFN | Après 8 ans d'IFN

Larsen et al., Ann Hematol. 2008 Oct;87(10):847-50

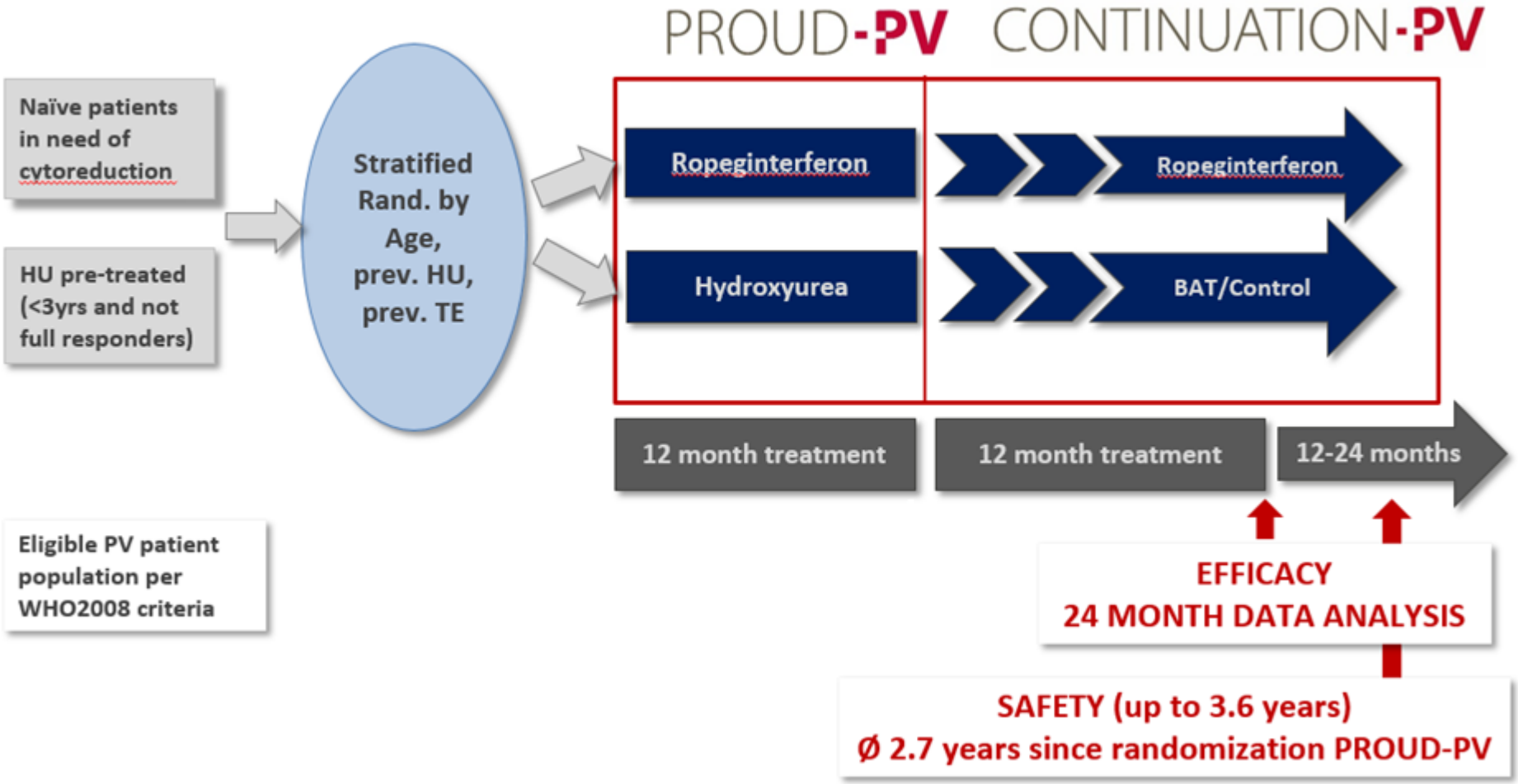
- ✓ **Altère l'histoire naturelle ?**
  - ✓ RC cliniques et hématologiques
  - ✓ RC moléculaires
  - ✓ RC morphologiques

Ropeginterferon Alfa-2b Induces High Rates of Clinical, Hematological and Molecular Responses in Polycythemia Vera: Two-Year Results from the First Prospective Randomized Controlled Trial

Heinz Gisslinger, Christoph Klade, Pencho Georgiev, Dorota Krochmalczyk, Liana Gercheva-Kyuchukova, Miklos Egyed, Viktor Rossiev, Petr Dulicek, Arpad Illes, Halyna Pylypenko, Lylia Sivcheva, Jiri Mayer, Vera Yablokova, Kurt Krejcy, Barbara Grohmann-Izay, Hans C. Hasselbalch, Robert Kralovics and Jean-Jacques Kiladjian

ASH 2017

Design PROUD- & CONTINUATION-PV



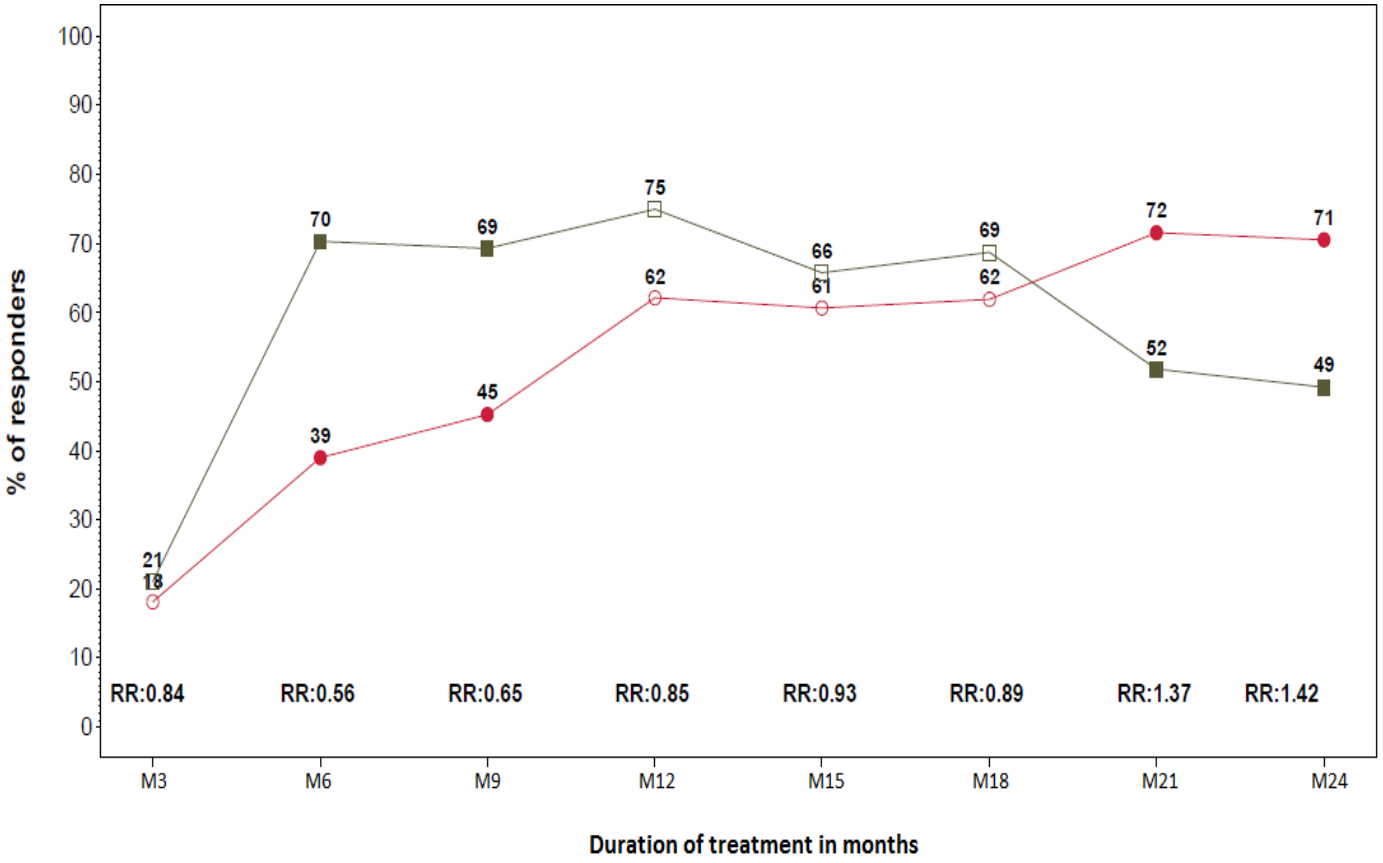
Efficacy Results (24 month analysis)

	AOP2014	Control	RR [95% CI] (AOP2014/Control)	P-value
Complete Hematologic Response at M24	**70.5%** (67/95)	**49.3%** (33/67)	1.42 [1.09-1.87]	0.0101
CHR & Improvement in Disease Burden at M24	**49.5%** (47/95)	**36.6%** (26/71)	1.34 [0.93-1.92]	0.1183
Partial Molecular Response at M24 (LOCF)	**68.1%** (64/94)	**34.7%** (26/75)	1.85 [1.33-2.56]	0.0002

Ropeginterferon alfa-2b induces high rates of hematological, clinical and molecular responses after 24 months of treatment

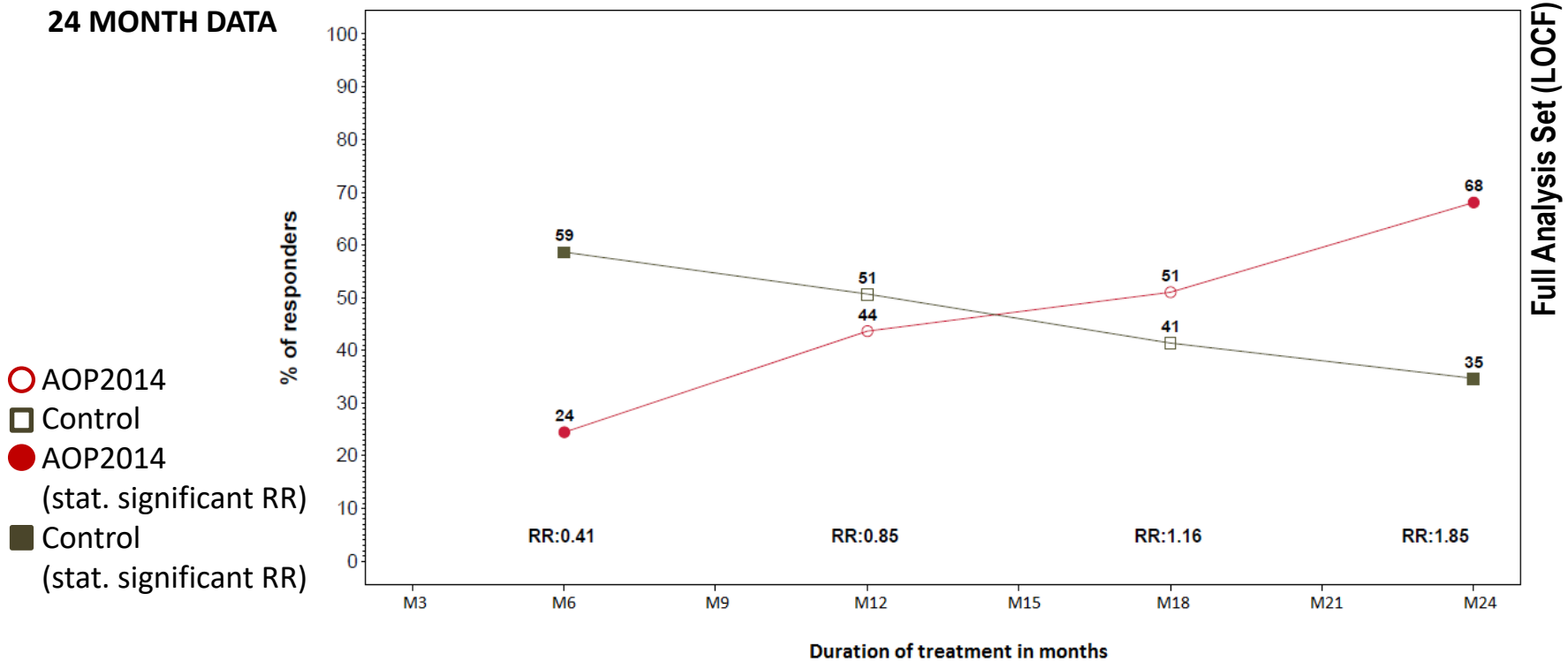
Complete Hematological Response

24 MONTH DATA



AOP2014
Control
AOP2014
(stat. significant RR)
Control
(stat. significant RR)

Molecular Response



Safety Profile – Overview

Long-term Safety (up to 3.6 years of treatment; mean 2.7 years)		
	AOP2014 (n=127)	**Control** (n=127)
Patients with AE	114 (89.8%)	113 (89.0%)
Patients with treatment-related AE	89 (70.1%)	98 (77.2%)
Patients with ≥ Grade 3 AE	35 (27.6%)	33 (26.0%)

Malignancies

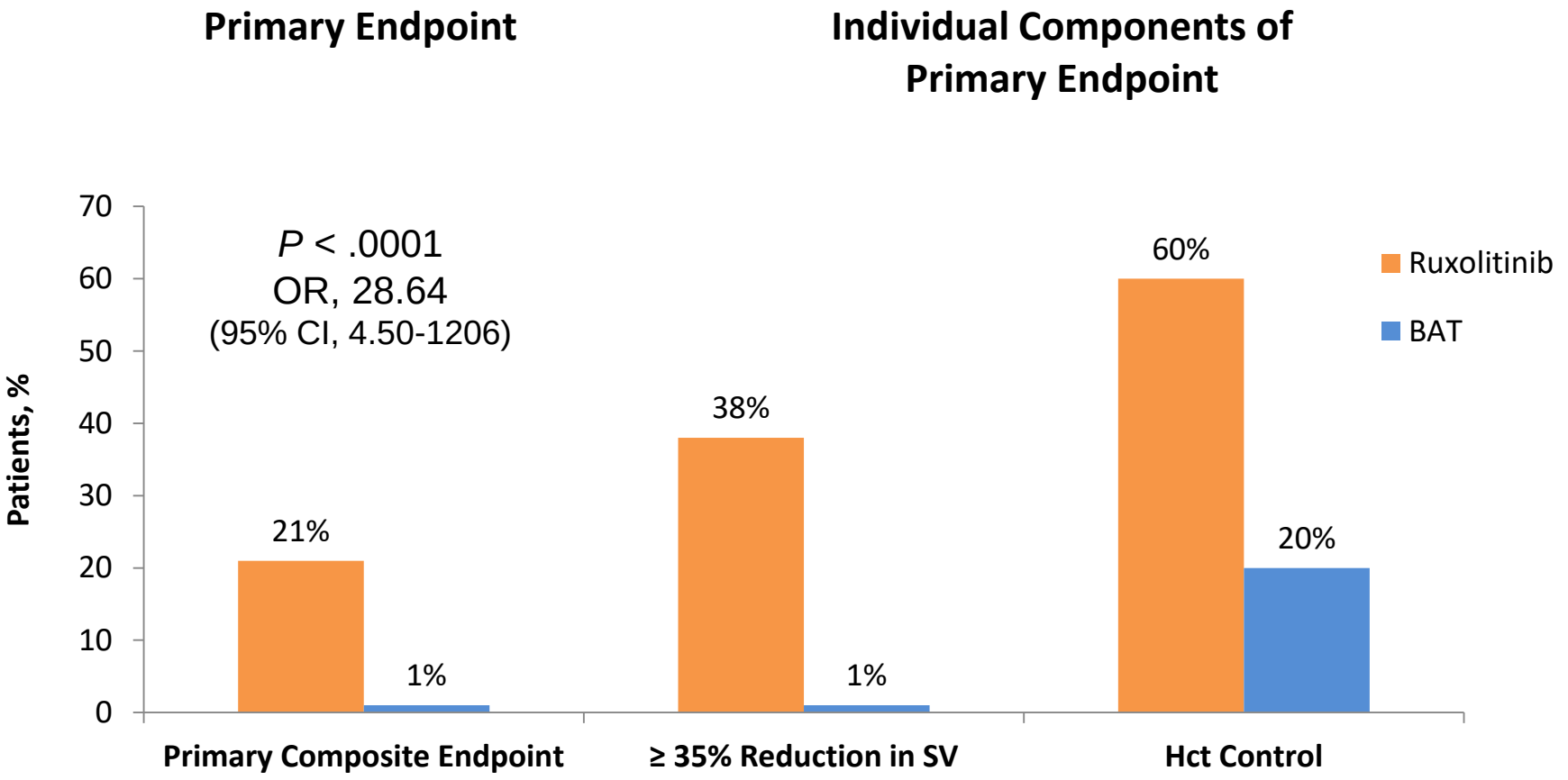
Long-term Safety (up to 3.6 years of treatment; mean 2.7 years)		
	AOP 2014 (n=127)	**Control** (n=127)
Acute leukemia		2
Basal cell carcinoma		2
Malignant melanoma		1
Adrenal neoplasm*	1	
Glioblastoma	1	
Spermatocytic seminoma	1	

* No additional information on type of neoplasm available

Deuxième ligne

- **Ruxolitinib** a obtenu l'AMM pour le traitement des PV résistantes / intolérantes à l'HU
- Inhibiteur JAK1/JAK2
- Résultats de l'étude "RESPONSE"
  - Phase 3, ruxolitinib vs. meilleur traitement disponible
  - 222 patients randomisés
  - Objectif principal : Hématocrite < 45 % et diminution du volume de la rate de plus de 35 %

Réponse à 32 semaines

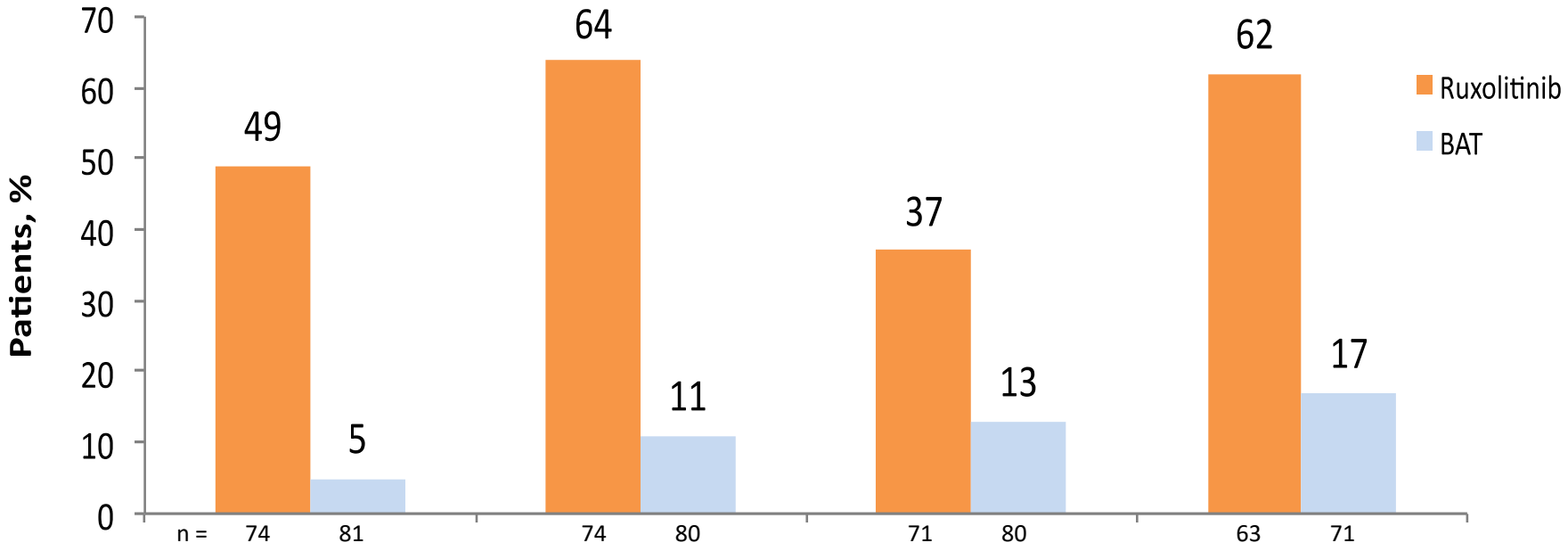


77% of patients randomized to ruxolitinib met at least 1 component of the primary endpoint

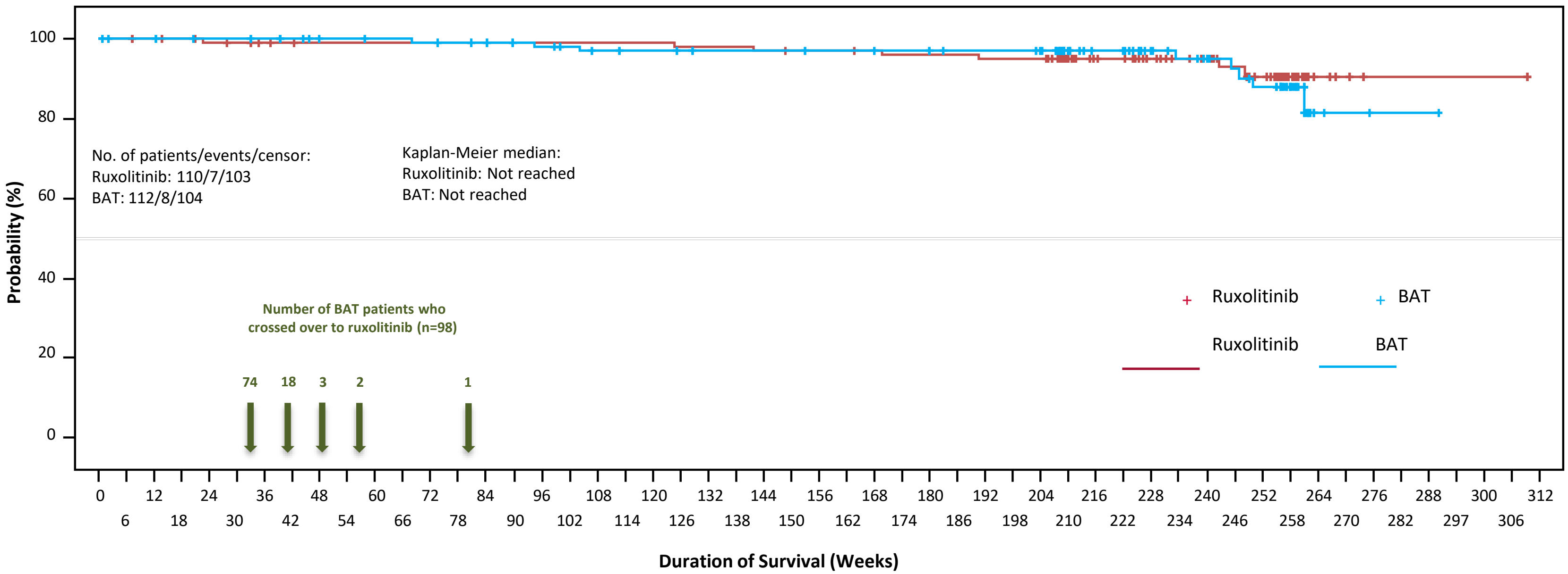
Vannucchi et al. N Engl J Med. 2015 ;372:426-35

Amélioration des Symptômes

Percentage of Patients with a ≥ 50% Improvement in MPN-SAF Symptom Score at W32



Overall Survival Analysis in the Intent-to-Treat Population



At Risk – Ruxolitinib	110	109	107	106	104	103	101	100	99	99	99	99	99	99	99	99	99	99	99	99	99	98	98	98	97	96	96	96	95	94	94	94	93	93	93	76	69	68	57	53	49	42	38	21	5	3	1	1	1	1	1	1	0
Events – Ruxolitinib	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	3	3	3	3	3	3	4	4	4	5	5	5	5	5	5	5	5	5	6	7	7	7	7	7	7	7	7	7	7	7
At Risk – BAT	112	110	110	109	108	108	107	105	102	102	101	101	100	99	98	96	95	93	91	90	90	89	88	88	88	88	88	87	87	86	86	84	84	84	83	66	61	61	51	47	45	39	36	24	3	2	1	1	1	0			
Events – BAT	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	5	7	7	8	8	8	8	8	8			

- In the ITT analysis not accounting for crossover, the K-M estimates for **overall survival at 5 years was 90.6%** (95% CI: 80.1, 95.7) in the ruxolitinib arm and 87.7% (95% CI: 74.8, 94.3) in the BAT arm.
- Patients were allowed to cross over from BAT to ruxoltinib at or after week 32, no patient remained on randomized BAT treatment after week 80.

BAT, best available therapy; CI, confidence interval; CO, crossover; K-M, Kaplan-Meier; ITT, intent- to- treat.

Adverse Events

(Adjusted for Patient-Year Exposure, Regardless of Study Drug Relationship [All Grades, Rate ≥ 5 in Either Arm])

	208-Week (4-Year) Analysis				80-Week Analysis			
	Ruxolitinib n = 110 Exposure, Patient-Years = 409		Crossover n = 98 Exposure, Patient-Years = 310		Ruxolitinib n = 110 Exposure, Patient-Years = 227.7		Crossover n = 98 Exposure, Patient-Years = 147.6	
Rate per 100 Patient-Years of Exposure	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Hematologic adverse events								
Anemia	9.3	1.0	9.4	0.6	13.2	0.9	14.9	1.4
Thrombocytopenia	4.6	1.0	1.3	0.3	6.1	1.8	2.7	0.7
Non-hematologic adverse events								
All infections	19.6	3.7	19.7	6.5	29.4	4.0	27.8	5.4
Herpes zoster infection	4.9	0.5	4.2	0.6	5.3	0.9	5.4	0.7
Pruritus	7.3	0.5	5.8	0	9.7	0.4	8.8	0
Diarrhea	7.1	0.2	3.2	0	9.7	0	5.4	0
Headache	6.1	0.5	5.5	0	10.5	0.9	8.8	0
Fatigue	5.1	0.2	4.2	0	8.3	0.4	6.8	0
Increased weight	5.6	0.7	4.2	0.3	7.5	0.4	6.8	0
Arthralgia	5.9	0.2	3.2	0.3	6.1	0	4.7	0
Muscle spasms	5.4	0.2	3.2	0	7.9	0.4	3.4	0
Dizziness	4.2	0.0	6.1	0	7.5	0	7.5	0

Thromboembolic Adverse Events (SMQ)

(Adjusted for Patient-Year Exposure, Regardless of Study Drug Relationship [All Grades, Rate ≥ 0.2 in Either Arm])

	208-Week (4-Year) Analysis				80-Week Analysis			
	Ruxolitinib n = 110 Exposure, Patient-Years = 409		Crossover n = 98 Exposure, Patient-Years = 310		Ruxolitinib n = 110 Exposure, Patient-Years = 227.7		Crossover n = 98 Exposure, Patient-Years = 147.6	
n (Rate per 100 Patient-Years of Exposure)	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
All thromoboembolic events[a]	**5 (1.2)**	**3 (0.7)**	**9 (2.9)**	**5 (1.6)**	**4 (1.8)**	**2 (0.9)**	**6 (4.1)**	**4 (2.7)**
Cerebral infarction	1 (0.2)	1 (0.2)	0	0	1 (0.4)	1 (0.4)	0	0
Ischemic stroke	1 (0.2)	0	1 (0.3)	1 (0.3)	1 (0.4)	0	0	0
Transient ischemic attack	0	0	2 (0.6)	2 (0.6)	0	0	2 (1.4)	2 (1.4)
Portal vein thrombosis	1 (0.2)	1 (0.2)	0	0	1 (0.4)	1 (0.4)	0	0
Pulmonary embolism	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Retinal vascular thrombosis	1 (0.2)	0	0	0	1 (0.4)	0	0	0
Myocardial infarction	0	0	2 (0.6)	1 (0.3)	0	0	2 (1.4)	1 (0.7)
Deep vein thrombosis	0	0	1 (0.3)	0	0	0	0	0
Thrombophlebitis	0	0	1 (0.3)	0	0	0	0	0
Thrombosis	0	0	1 (0.3)	0	0	0	1 (0.7)	0
Bone infarction	0	0	1 (0.3)	0	0	0	1 (0.7)	0
Coronary artery occlusion	0	0	1 (0.3)	0	0	0	1 (0.7)	0
Disseminated intravascular coagulation	0	0	1 (0.3)	1 (0.3)	0	0	1 (0.7)	1 (0.7)

Other Adverse Events of Interest

(Adjusted for Patient-Year Exposure, Regardless of Study Drug Relationship [All Grades, Rate ≥ 0.5 in Either Arm])

	208-Week (4-Year) Analysis		80-Week Analysis	
	Ruxolitinib n = 110 Exposure, Patient-Years = 409	Crossover n = 98 Exposure, Patient-Years = 310	Ruxolitinib n = 110 Exposure, Patient-Years = 227.7	Crossover n = 98 Exposure, Patient-Years = 147.6
	n (Rates)	n (Rates)	n (Rates)	n (Rates)
Disease Progression				
Acute myeloid leukemia	1 (0.2)	1 (0.3)	1 (0.4)	1 (0.7)
Myelofibrosis	9 (2.2)	6 (1.9)	3 (1.3)	3 (2.0)
Other Malignancies				
Prostate cancer	1 (0.2)	2 (0.6)	0	2 (1.4)
Breast cancer	2 (0.5)	0	2 (0.9)	0
Chronic myelomonocytic leukemia	1 (0.2)	1 (0.3)	0	1 (0.7)
Malignant fibrous histiocytoma	0	0	0	1 (0.7)

- While on BAT, no patient progressed to acute myeloid leukemia or myelofibrosis.

Other Adverse Events of Interest

(Nonmelanoma Skin Cancer Adjusted for Patient-Year Exposure)

n (Rate per 100 Patient-Years of Exposure)	208-Week (4-Year) Analysis				80-Week Analysis			
	Ruxolitinib n = 110 Exposure, Patient-Years = 409		Crossover n = 98 Exposure, Patient-Years = 310		Ruxolitinib n = 110 Exposure, Patient-Years = 227.7		Crossover n = 98 Exposure, Patient-Years = 147.6	
Prior history of Nonmelanoma Skin Cancer	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Total events	**13 (3.6)**	**8 (18.6)**	**6 (2.1)**	**2 (9.5)**	**4 (2.0)**	**6 (24.2)**	**2 (1.4)**	**1 (10.6)**
Basal cell carcinoma	10 (2.7)	7 (16.3)	4 (1.4)	1 (4.7)	3 (1.5)	5 (20.2)	1 (0.7)	1 (10.6)
Squamous cell carcinoma of skin	4 (1.1)	4 (9.3)	3 (1.0)	0	1 (0.5)	2 (8.1)	0	0
Bowen's disease	1 (0.3)	1 (2.3)	0	0	0	1 (4.0)	0	0
Carcinoma in situ of skin	0	2 (4.7)	0	0	0	1 (4.0)	0	0
Metastatic squamous cell carcinoma	0	2 (4.7)	0	0	0	1 (4.0)	0	0
Keratoacanthoma	1 (0.3)	0	0	0	0	0	0	0
Squamous cell carcinoma*	2 (0.5)	3 (7.0)	2 (0.7)	2 (9.5)	1 (0.5)	4 (16.1)	1 (0.7)	0

*Categorized as non-skin squamous cell carcinoma cases.

Polyglobulie de Vaquez - Conclusion

- Aspirine et hématocrite < 45 %
- HU ou IFN alpha (hors AMM) sont les traitements cytoréducteurs recommandés en première ligne pour les PV de haut risque
- Le ruxolitinib est une nouvelle option pour les patients résistants ou intolérants à l'HU

Myélofibrose Primitive

Table 6. WHO criteria for prePMF

WHO prePMF criteria
Major criteria
1. Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1*, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis
2. Not meeting the WHO criteria for *BCR-ABL1*$^{+}$ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,† or absence of minor reactive BM reticulin fibrosis‡
Minor criteria
Presence of at least 1 of the following, confirmed in 2 consecutive determinations:
a. Anemia not attributed to a comorbid condition
b. Leukocytosis $\geq 11 \times 10^9$/L
c. Palpable splenomegaly
d. LDH increased to above upper normal limit of institutional reference range
Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion

*See Table 8.

†In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*) are of help in determining the clonal nature of the disease.

‡Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Table 8. Grading of myelofibrosis

Myelofibrosis grading	
MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal BM
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis*
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis*

Semiquantitative grading of BM fibrosis (MF) with minor modifications concerning collagen and osteosclerosis. Fiber density should be assessed only in hematopoietic areas.

*In grades MF-2 or MF-3 an additional trichrome stain is recommended.

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Table 7. WHO criteria for overt PMF

WHO overt PMF criteria
Major criteria
1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3*
2. Not meeting WHO criteria for ET, PV, *BCR-ABL1*$^{+}$ CML, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,† or absence of reactive myelofibrosis‡
Minor criteria
Presence of at least 1 of the following, confirmed in 2 consecutive determinations:
a. Anemia not attributed to a comorbid condition
b. Leukocytosis $\geq 11 \times 10^9$/L
c. Palpable splenomegaly
d. LDH increased to above upper normal limit of institutional reference range
e. Leukoerythroblastosis
Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion

*See Table 8.

†In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*) are of help in determining the clonal nature of the disease.

‡BM fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

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MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis*

Semiquantitative grading of BM fibrosis (MF) with minor modifications concerning collagen and osteosclerosis. Fiber density should be assessed only in hematopoietic areas.

*In grades MF-2 or MF-3 an additional trichrome stain is recommended.

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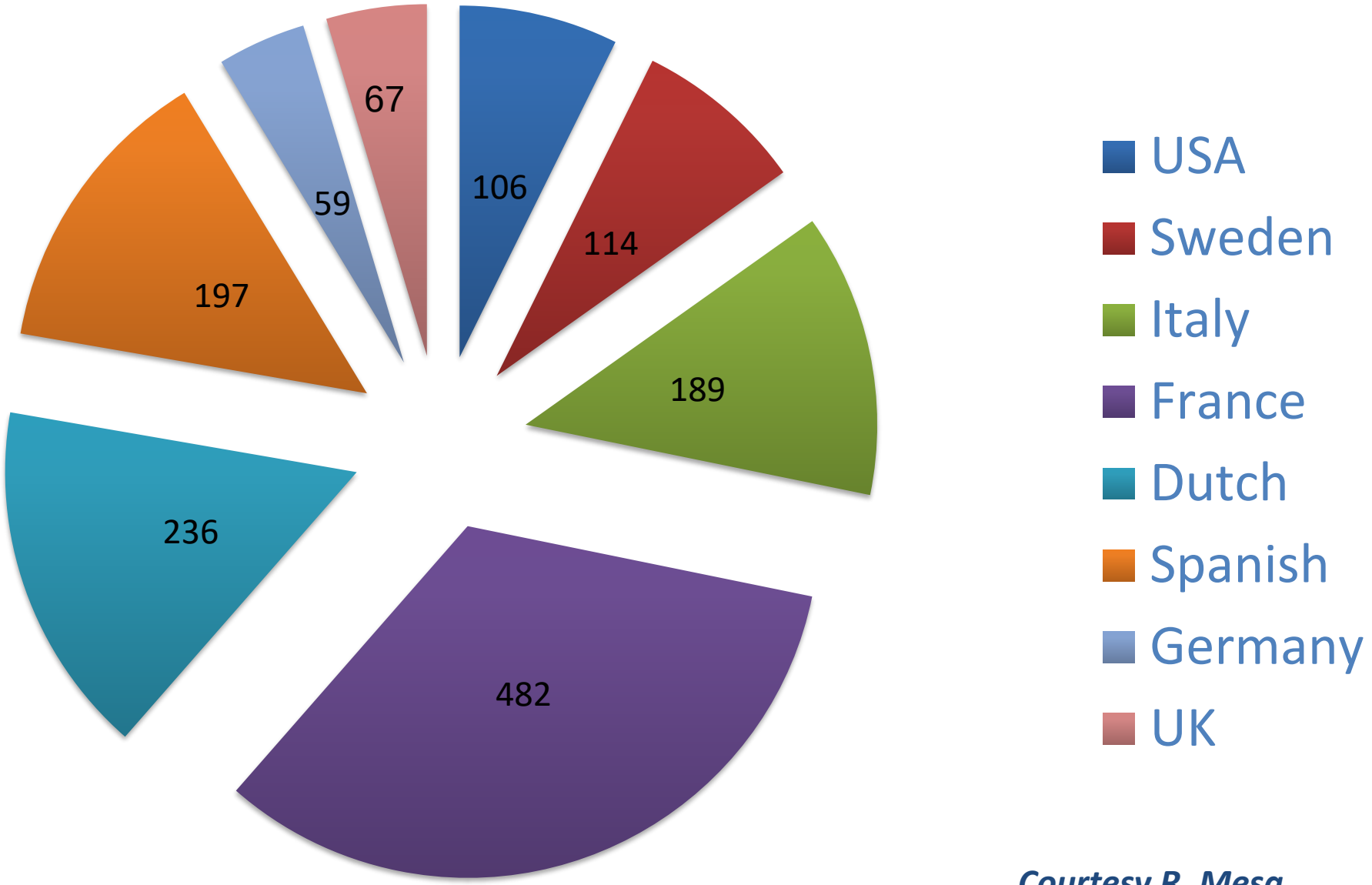
Clinique au diagnostic

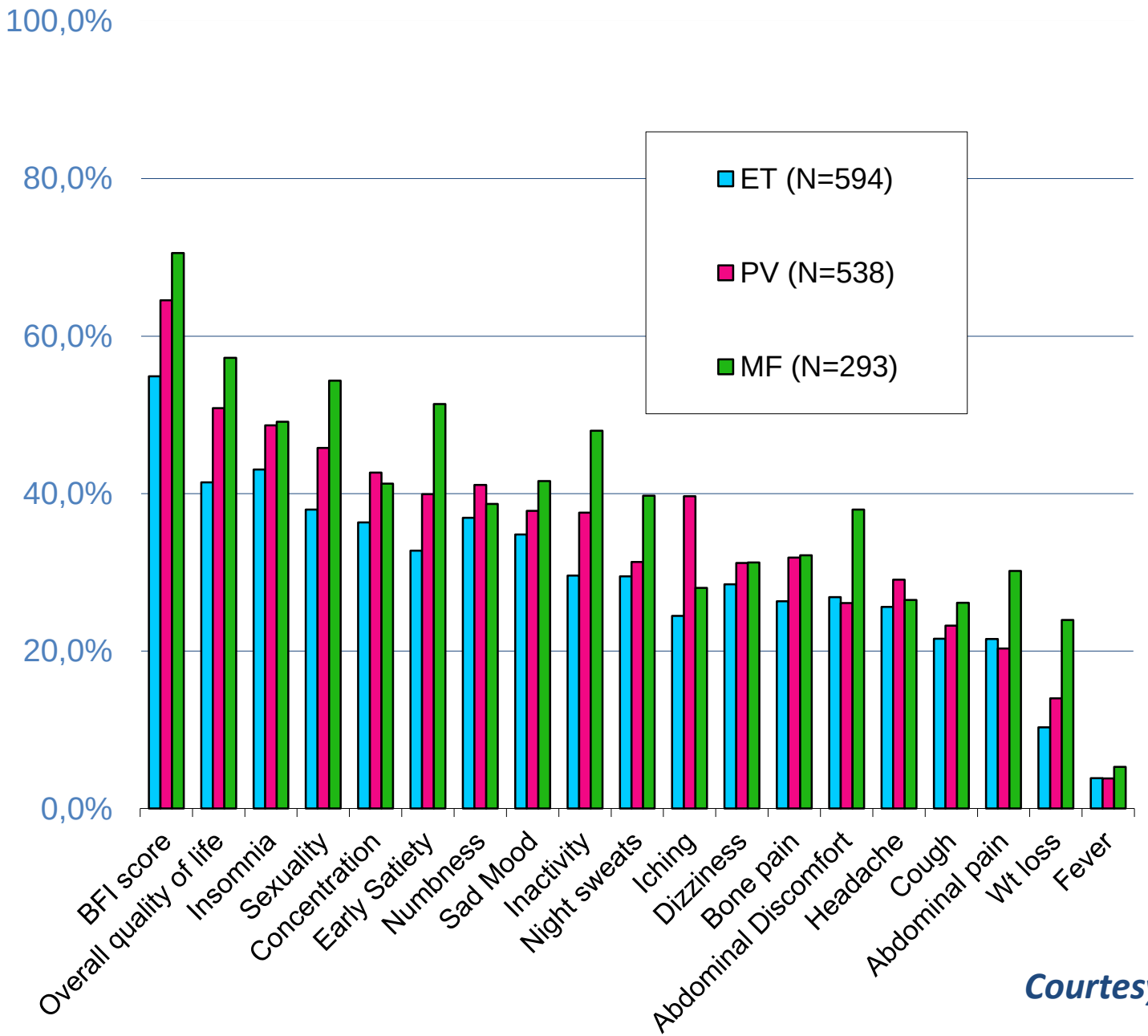
- Splénomégalie
- Anémie
- Symptômes
  - Fièvre
  - Sueurs nocturnes
  - Perte de poids
  - Douleur
  - SF digestifs
  - Prurit …

Signes généraux

Symptoms - 1427 MPN Patients 2010-2011



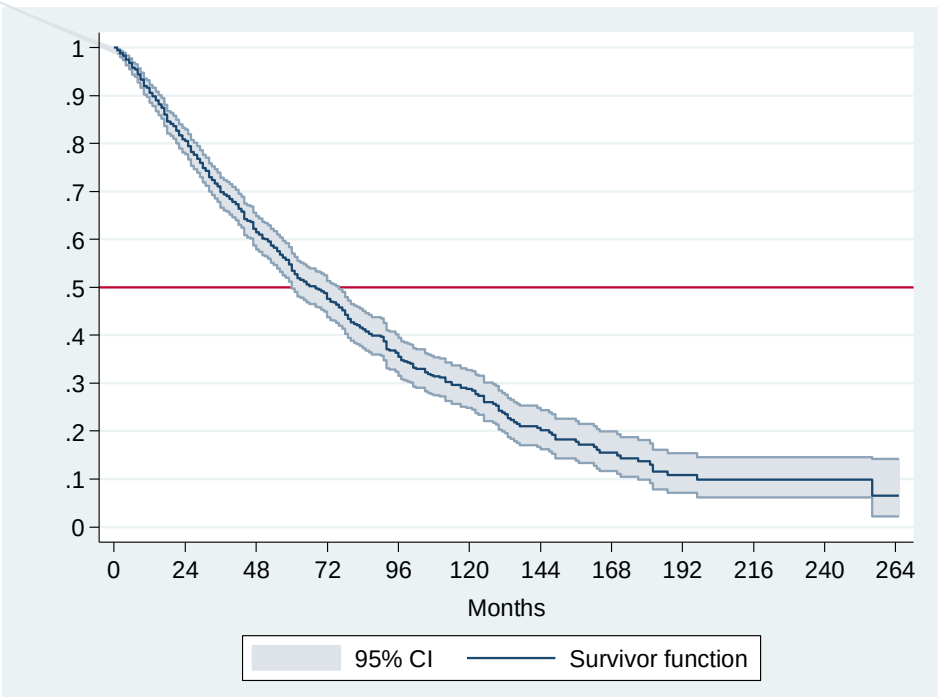
Courtesy R. Mesa



Courtesy R. Mesa

Myelofibrosis management

- Myelofibrosis is an heterogeneous disease
  - symptoms
  - phenotype
  - molecular lesions
  - prognosis
- Affects life expectancy
  - Median survival: 69 month

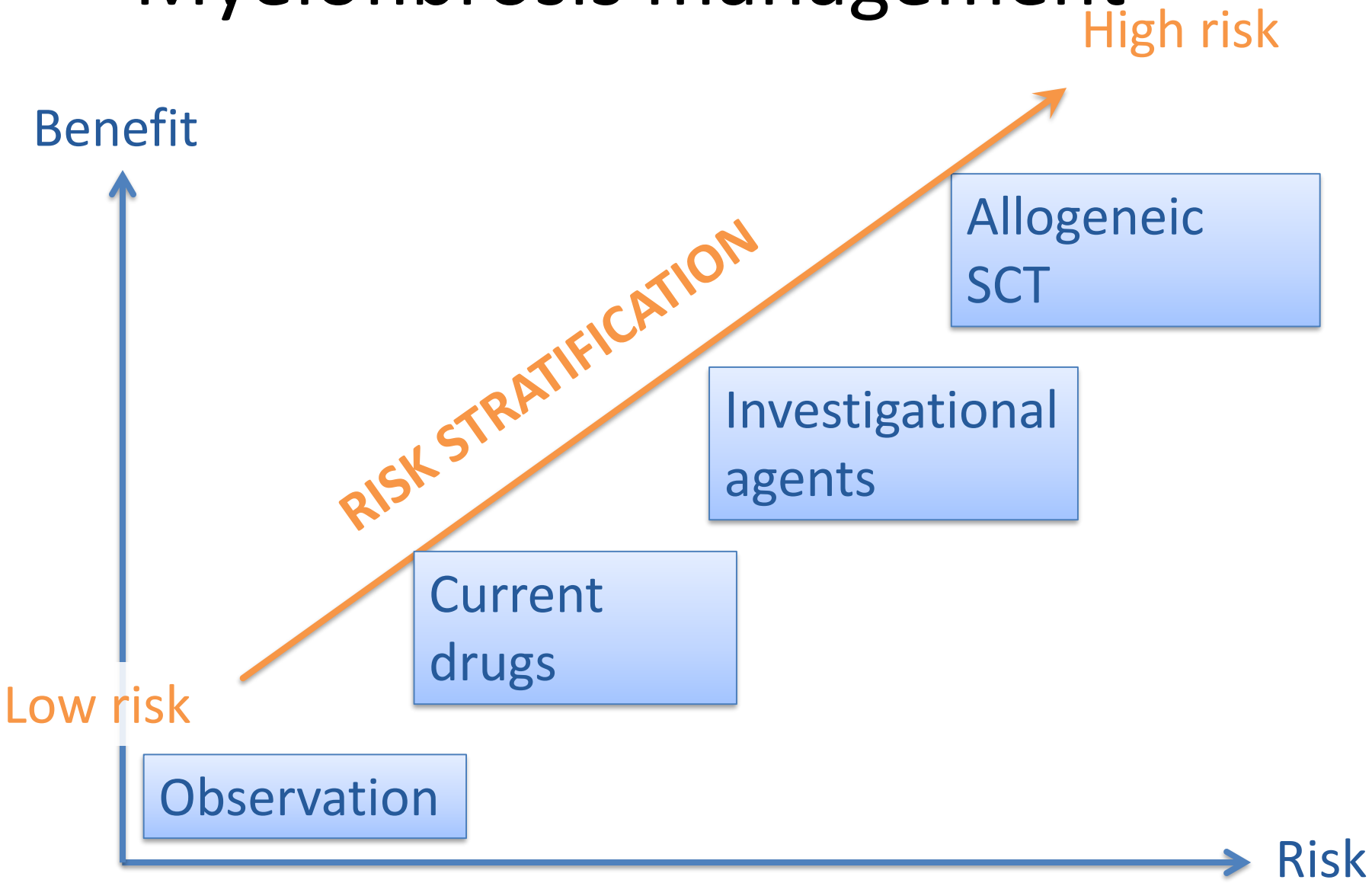


Cervantes et al. Blood 2009;113:2895-2901

Myelofibrosis management

- Myelofibrosis therapy is challenging
  - no curative medicine
  - allo-BMT may cure eligible patients
  - no approved drug until recently
  - each drug is effective only for some symptoms

Myelofibrosis management

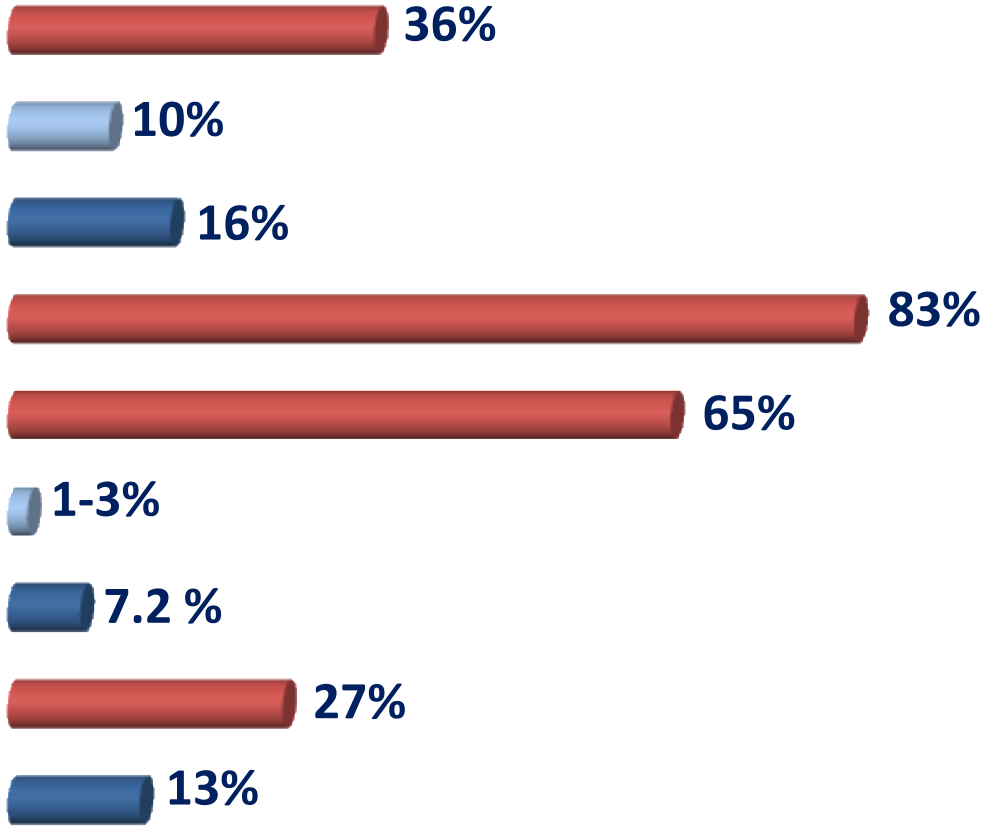


	Lille	IPSS	DIPSS	aaDIPSS	DIPSS-plus
Anemia	X	X	X	X	X
Leukocytes	X	X	X	X	X
Blasts		X	X	X	X
Constitutional Symptoms		X	X	X	X
Age >65		X	X		X
Karyotype (-8,-7,-5, i17q,12p-,inv3, 11q23 or Complex)					X
PLT <100					X
RBC Transfusion Dep					X
	Dupriez 1996	*Cervantes 2009*		*Passamonti 2010*	*Gangat 2011*

Therapy of myelofibrosis

Main Clinical Problems in MF

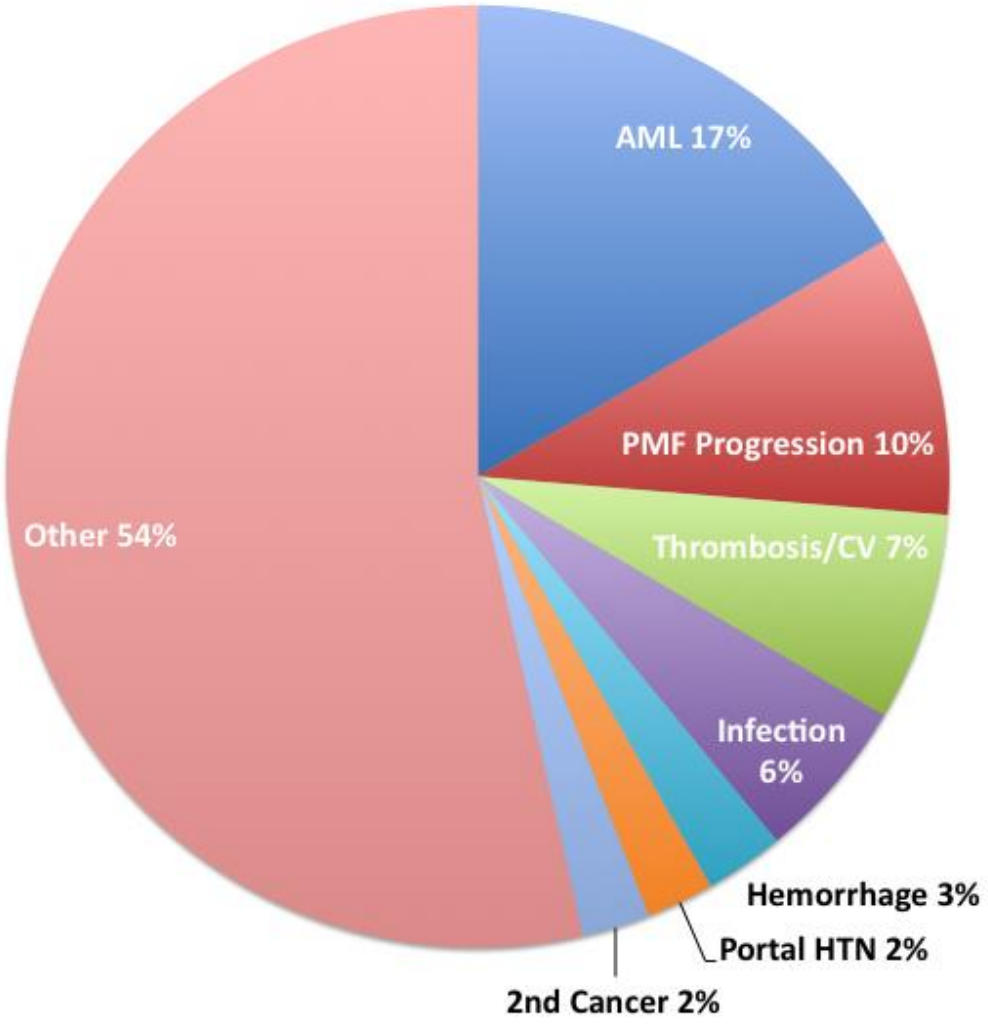
Clinical need	
Anemia (Hb <10 g/dL)	36%
Leukocytosis (>25x10^9/L)	10%
Thrombocytopenia (<100x10^9/L)	16%
Splenomegaly	83%
Hepatomegaly	65%
Extramedullary hematopoiesis	1-3%
Thrombosis	7.2 %
Constitutional symptoms	27%
Leukemia transformation	13%



Passamonti F. et al. *Blood.* 2010;115:1703-8, Barbui T, et al. *Blood.* 2010;115;778-82, Passamonti F, et al. *Blood* 2010;116:2857-8.

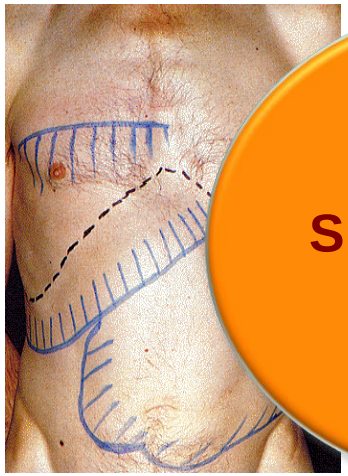
Mortality in PMF

Median Survival 69 Months (517/1001 Expired)



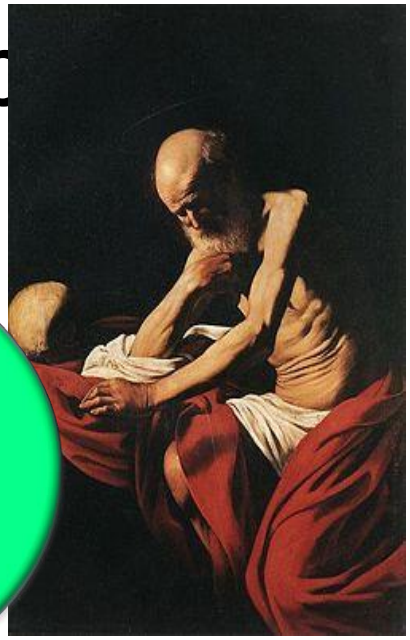
Cervantes et al. Blood 2009;113:2895-2901

Goals of therapy in myelofib



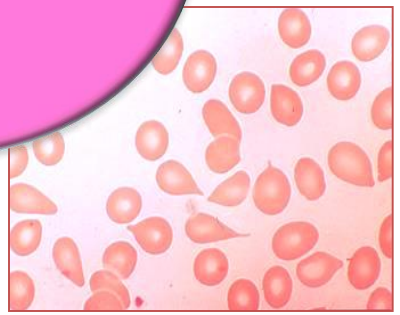
Splenomegaly

Symptoms



Premature death

Anemia / cytopenias



Since 2005: the molecular era

Driver mutations	JAK2 CALR MPL
Signaling	LNK SOCSs CBL1
Epigenetic regulators	TET2 IDH 1-2 ASXL1 EZH2 DNMT3A
Leukemic transformation	IDH1 - 2 IKZF1 RUNX1 RB TP53

New perspective for "targeted" therapy

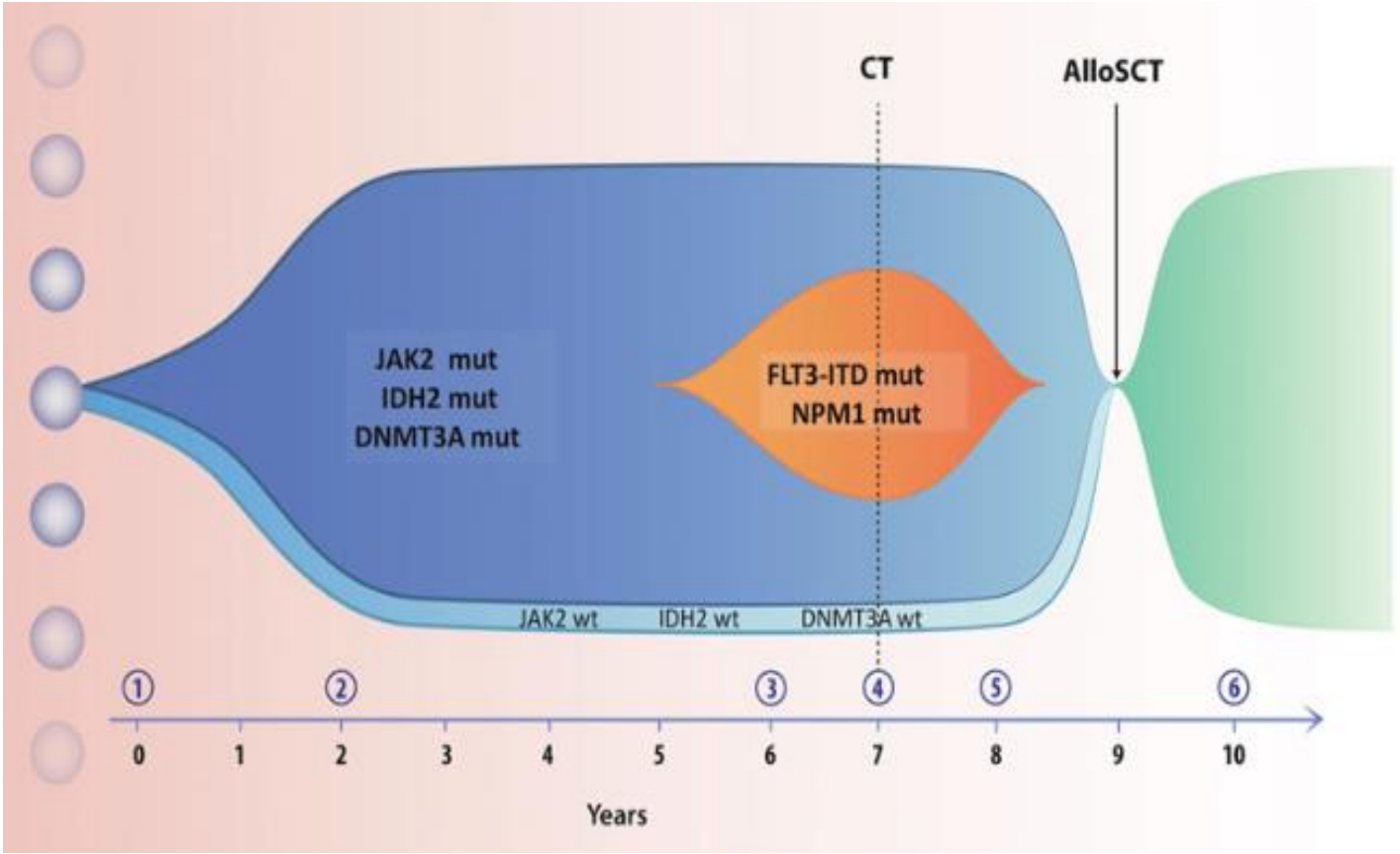
LEUKEMIA & LYMPHOMA, 2016
http://dx.doi.org/10.1080/10428194.2016.1213833

Taylor & Francis
Taylor & Francis Group

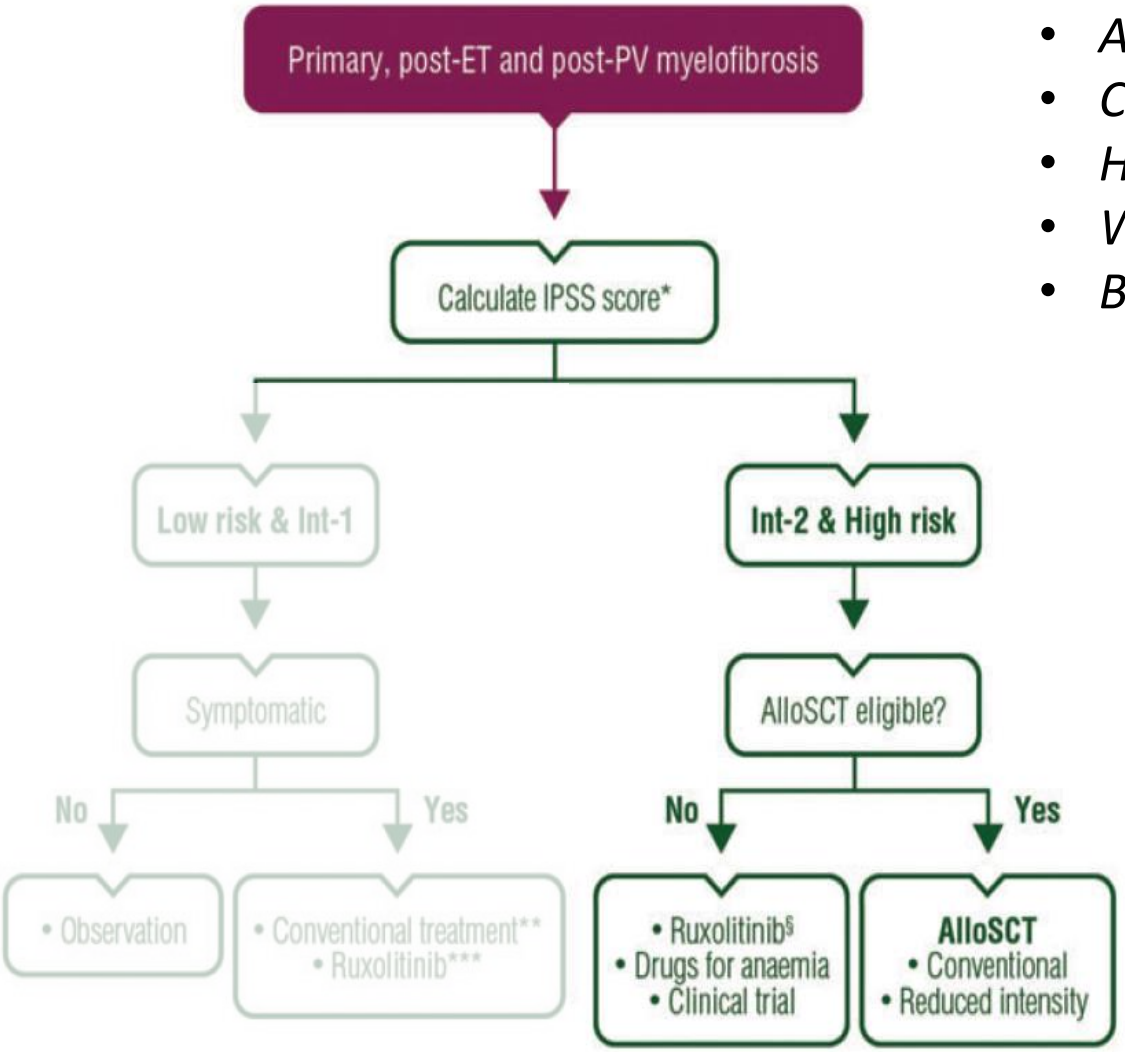
LETTER TO THE EDITOR

Chemotherapy for post-myelofibrosis acute myeloid leukemia: eradication of the leukemic clone but not the MPN clone

Emmanuelle Verger[a,b], Ekarat Rattarittamrong[c], Gil Letort[b], Emmanuel Raffoux[d], Bruno Cassinat[a,b] and Jean-Jacques Kiladjian[e]



Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†



- *Age (65)*
- *Constit. symptoms*
- *Hgb (10 g)*
- *WBC (25 000)*
- *Blasts (yes or no)*

Vannucchi et al. *Annals of Oncology* September 2015

When to transplant if patient median survival ranges from a few months to > 10 years ?

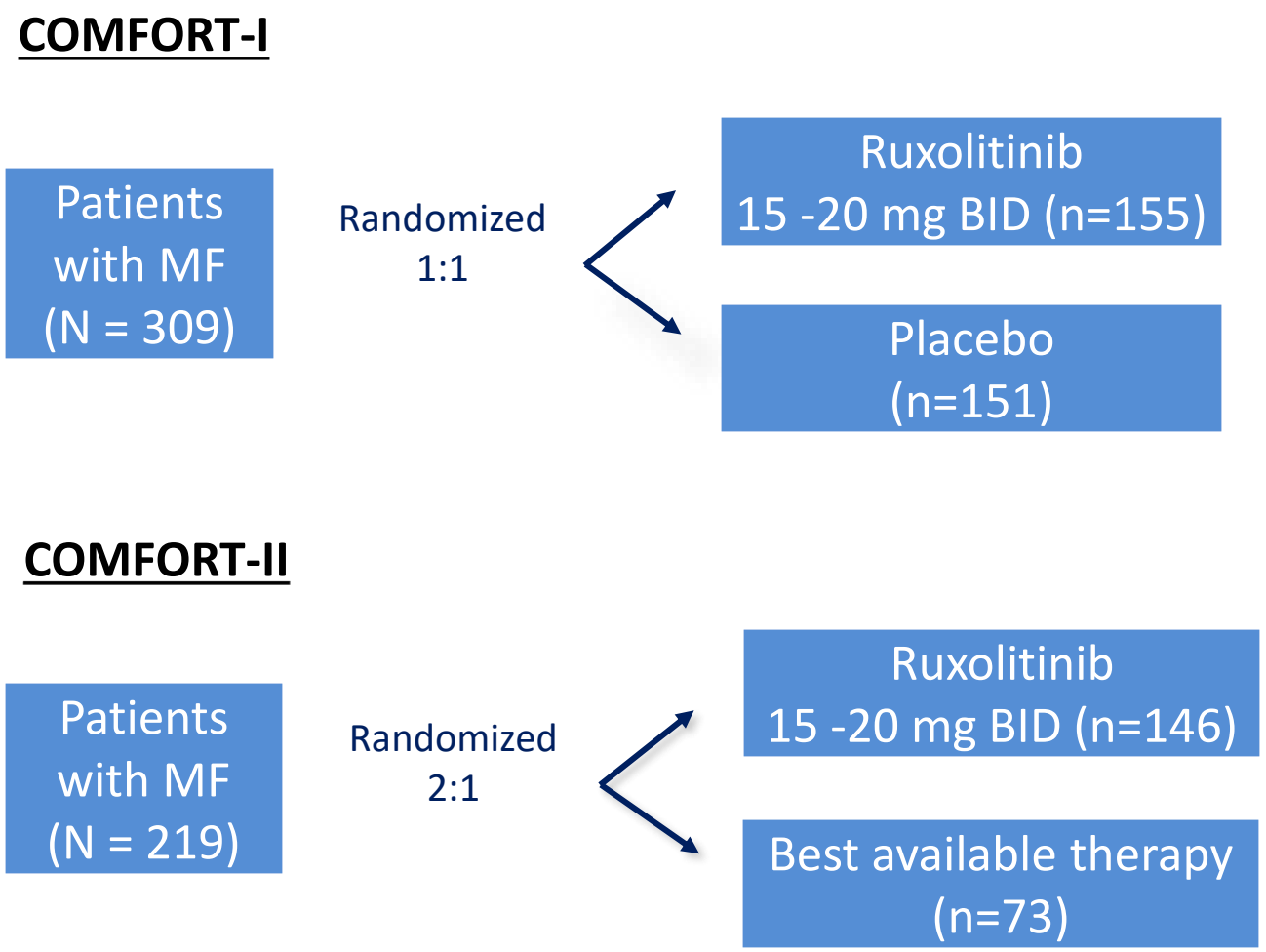
- **In MF**, different prognostic scoring systems help to the decision to transplant (LILLE, CERVANTES, *D*IPSS-*plus*…)
- Patients with survival > 4 years (in median) can be postponed to transplantation because median survival after HSCT ranges from 4 to 6 years
- No study prospectively compares outcome of patients with or without transplantation

Allo SCT for MF

	Median Ages	TRM (1y)	OS (5y)
Full MA (N=504)	40-49	20-42%	31-61%
RIC (N=263)	50-56	0-37%	50-67%

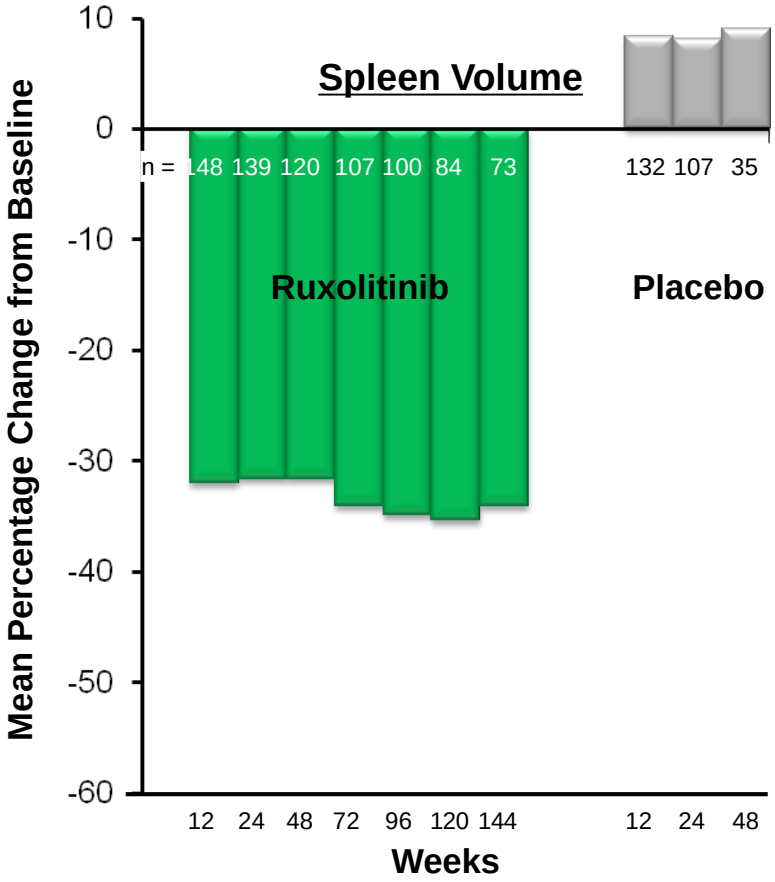
Adapted from Alchalby et. al. CHMR 2010;5:53-61

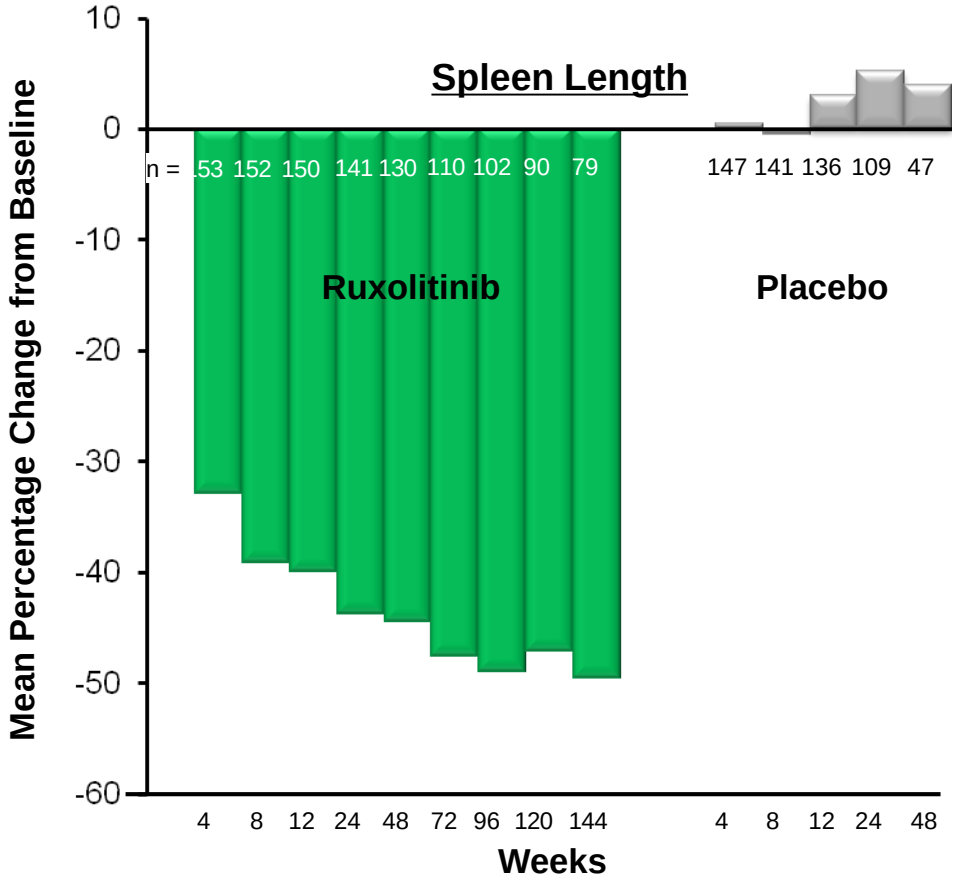
Ruxolitinib in Myelofibrosis: COMFORT Trials



Verstovsek et al. N Engl J Med. 2012;366(9):799-807, Harrison C, et al. N Engl J Med. 2012;366(9):787-98

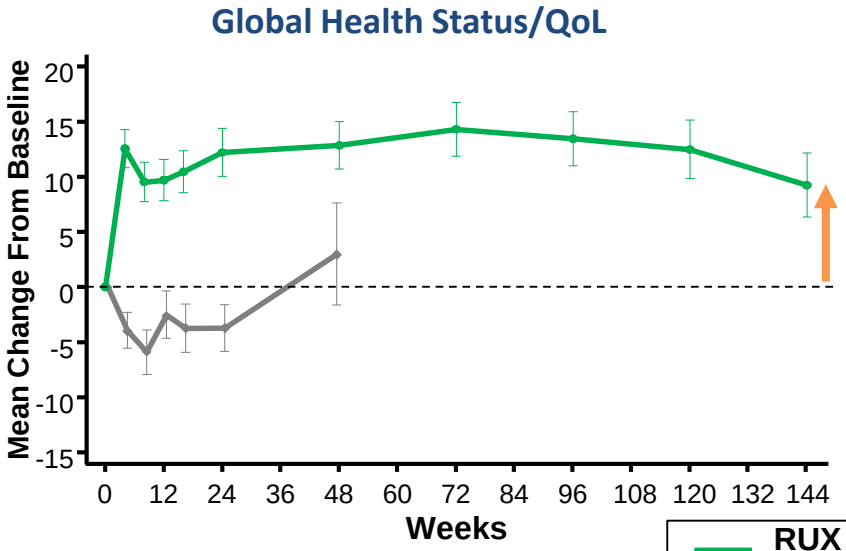
Spleen Response

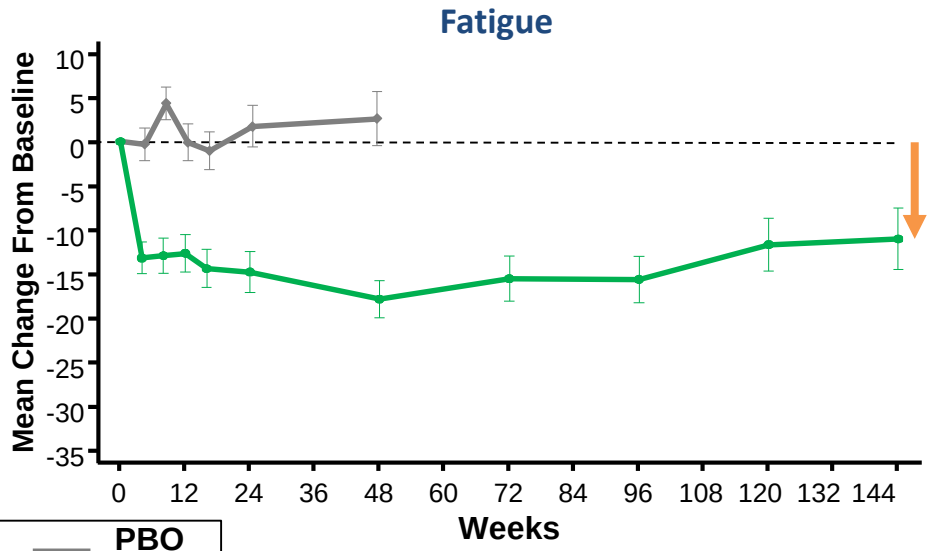




Verstovsek S, et al. ASH 2013, Abstr. 396

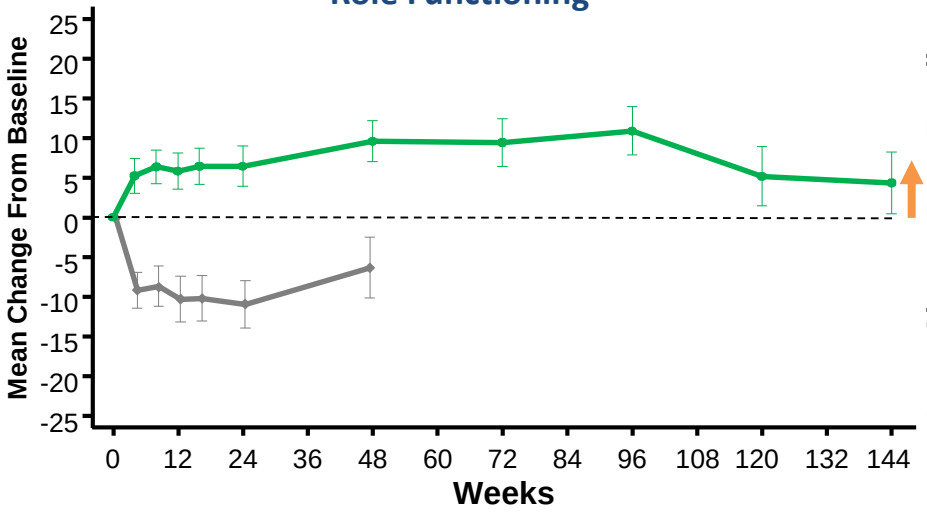
Improvements in EORTC QLQ-C30 Over Time

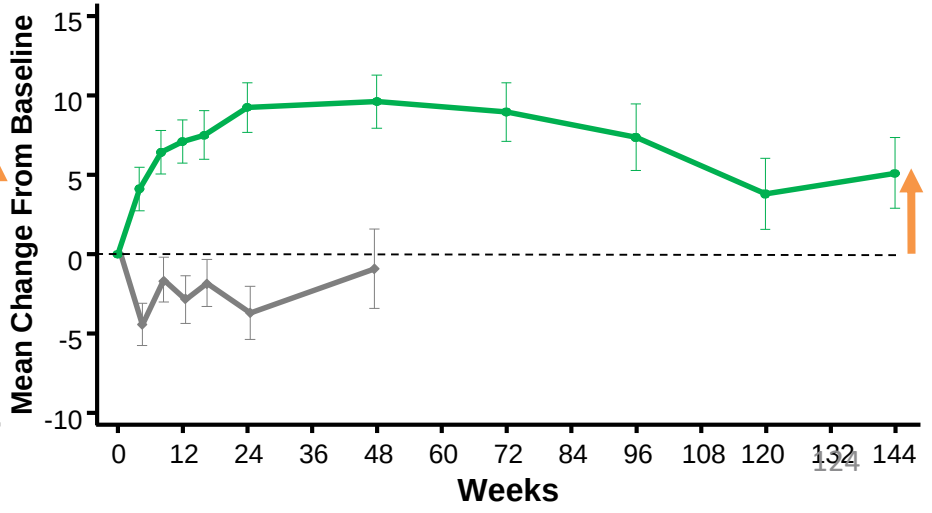




RUX PBO

Arrows indicate improvement

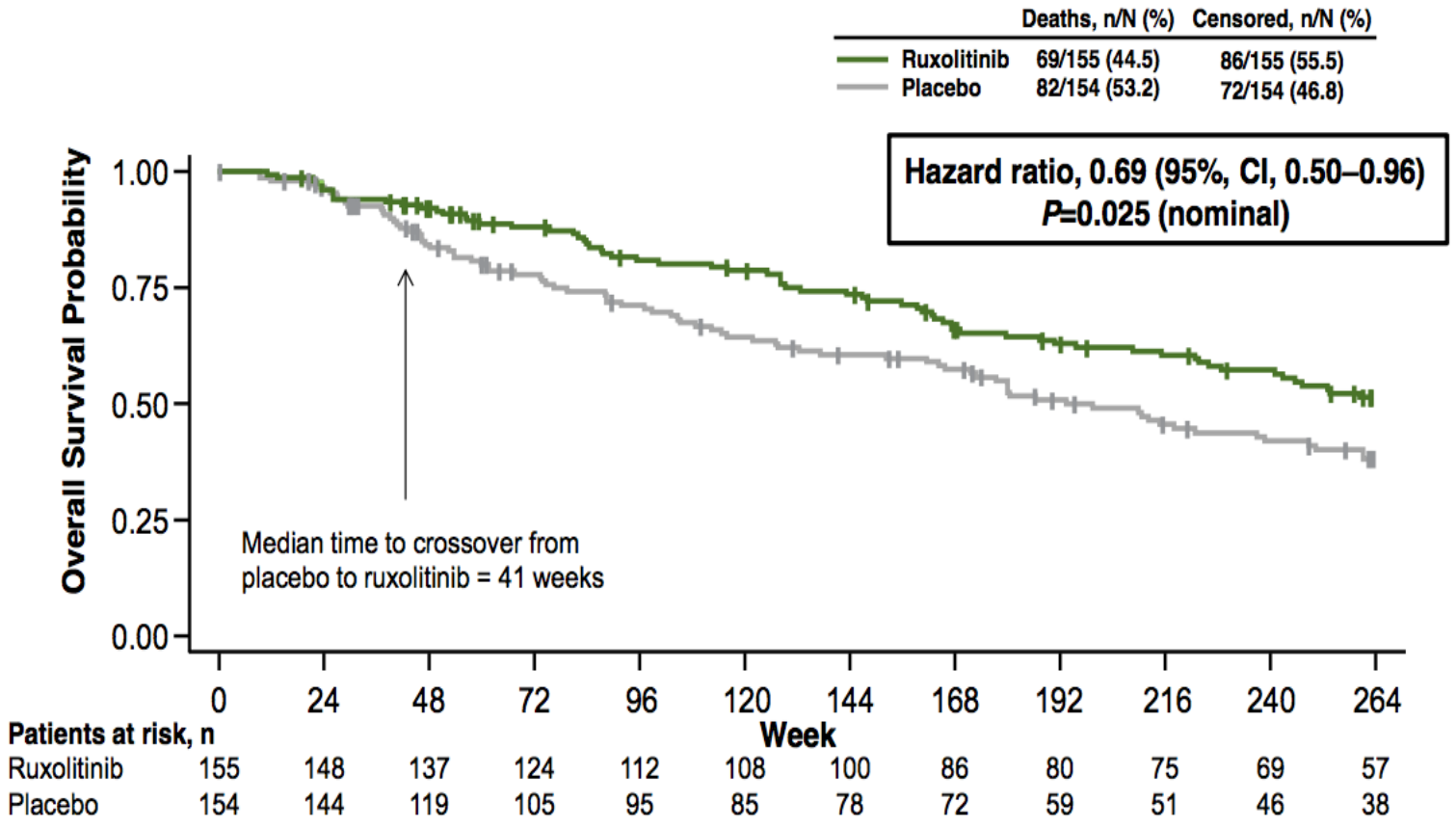




Verstovsek S, et al. ASH 2013, Abstr. 396

Overall Survival (ruxolitinib vs placebo, 5 years analysis, ITT)

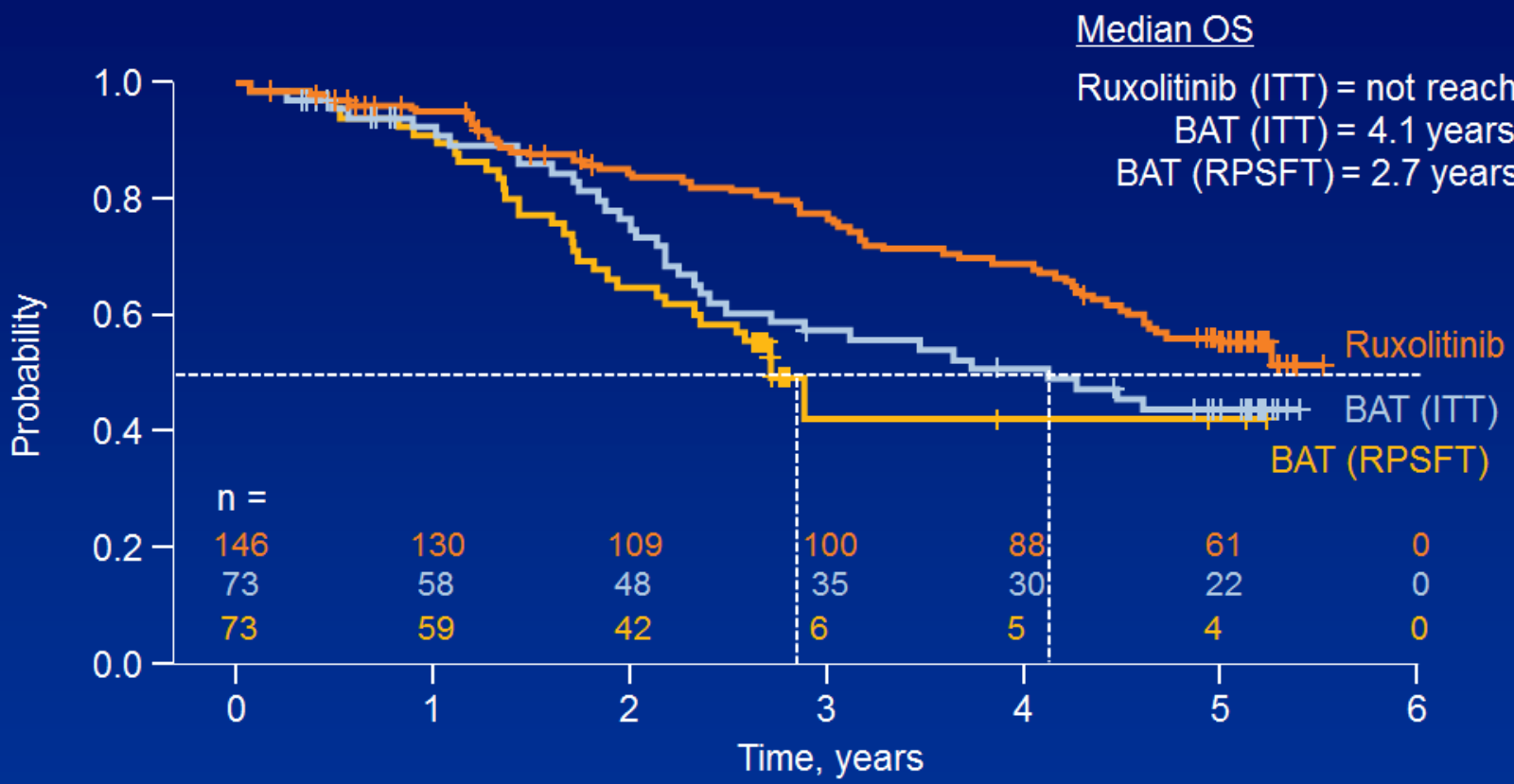
- Median OS was not reached for patients randomized to ruxolitinib (median follow-up 268 weeks) and was 200 weeks for patients in the placebo arm (median follow-up 269 weeks)



OS, overall survival

Verstovsek S, et al. EHA 2016, Abstr. S452

K-M Analysis of OS by ITT Analysis and RPSFT Corrected for Crossover From the BAT Arm

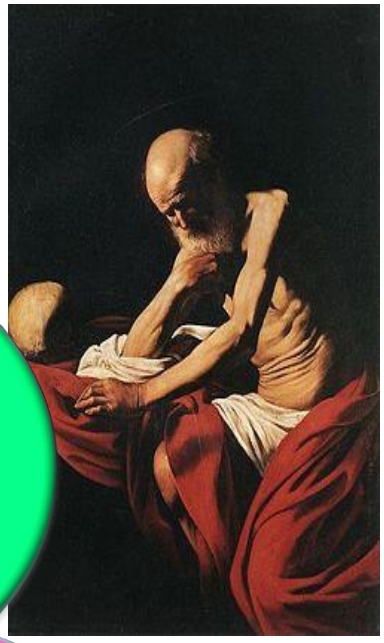


- Median OS was not yet reached in the ruxolitinib arm (ie, > 5 years)
  - ITT: HR, 0.67 (95% CI, 0.44-1.02); P = .06
  - RPSFT: HR, 0.44 (95% CI, 0.18-1.04) in favor of ruxolitinib vs BAT

BAT, best available therapy; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; K-M, Kaplan-Meier; OS, overall survival; RPSFT, rank-preserving structural failure time

Harrison CN, et al. *Leukemia*.2016;30(8):1701-1707.

Goals of therapy



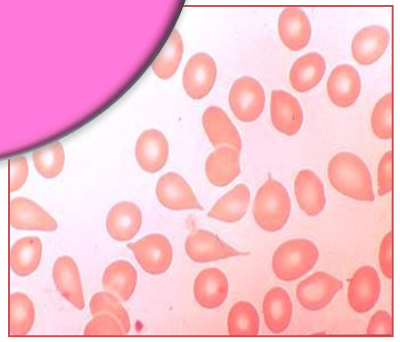
Splenomegaly

Symptoms

ruxolitinib

Premature death

Anemia / cytopenias



Pacritinib

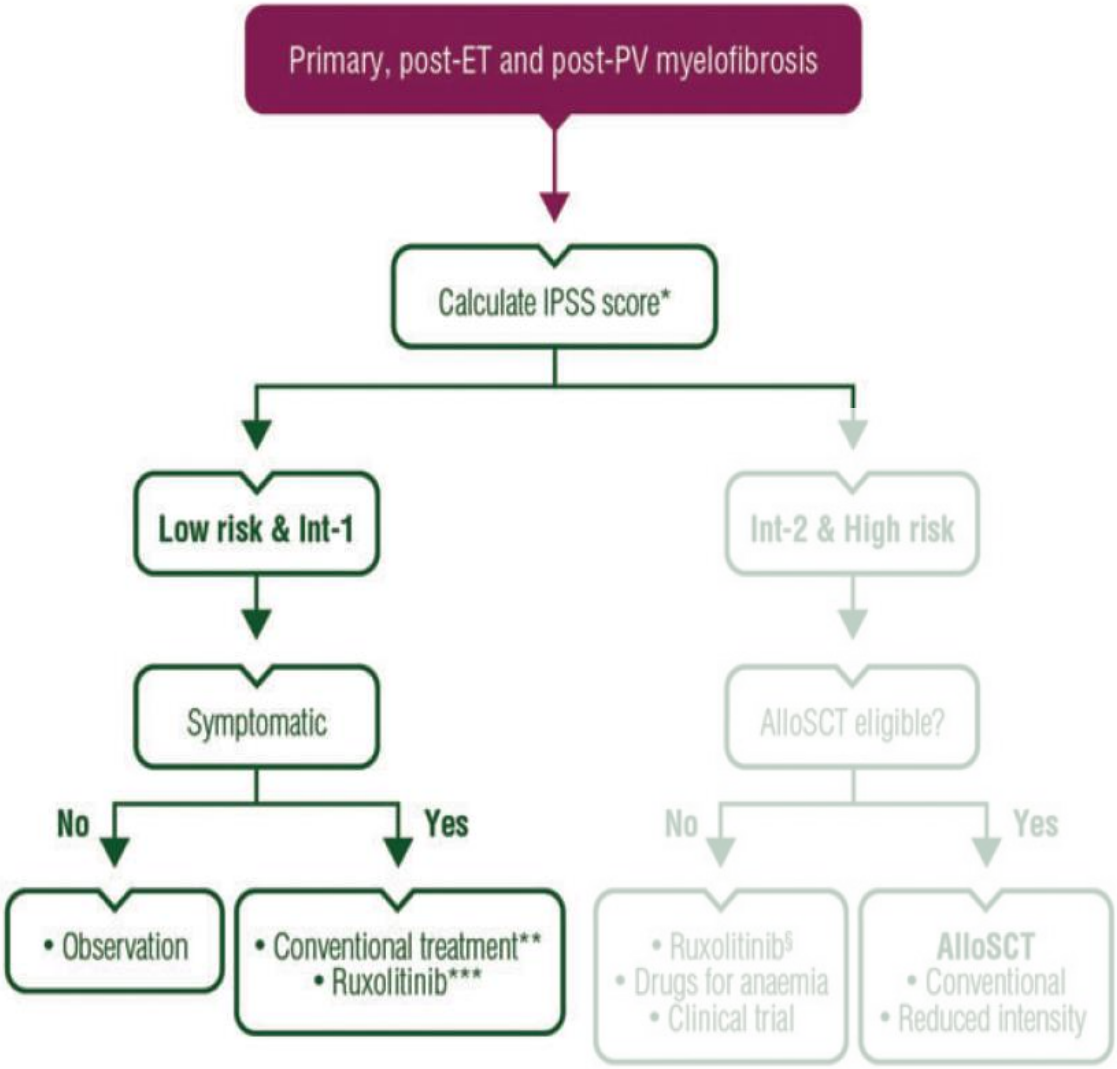
- JAK2/FLT3 inhibitor
- PERSIST-1 study:
  - Spleen volume reduction
  - Without significant changes in Hgb or plt counts
  - RBC Transfusion independence

FDA full clinical hold (2/8/16):
excess mortality in pacritinib-treated patients
compared to the control arm in the PERSIST-1 trial
after cross over to the pacritinib arm

New dose finding phase 2 study started

R. Mesa et al., ASCO 2015, abstr. 7006

Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†



- *Age (65)*
- *Constit. symptoms*
- *Hgb (10 g)*
- *WBC (25 000)*
- *Blasts (yes or no)*

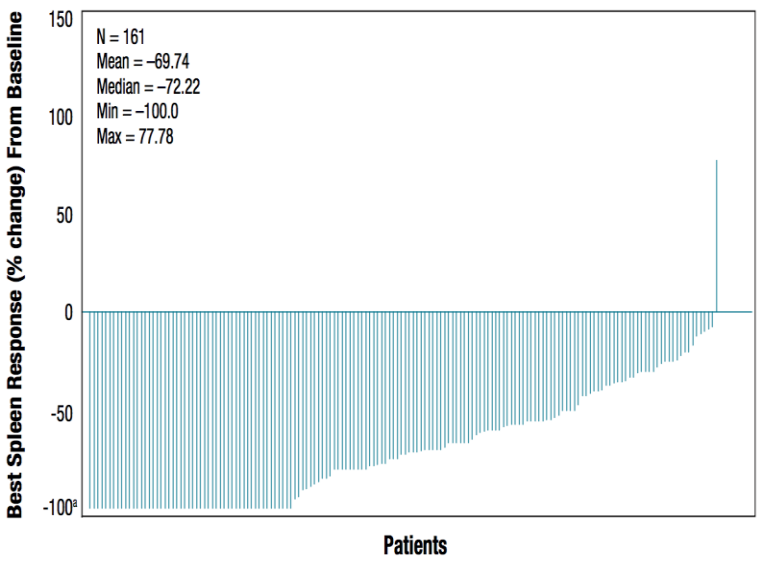
Vannucchi et al. *Annals of Oncology* September 2015

Ruxolitinib for patients at lower IPSS risk

Safety And Efficacy Of Ruxolitinib In Patients With Intermediate-1–Risk Myelofibrosis From an Open-Label, Multicenter, Single-Arm Expanded-Access Study

Pilar Giraldo,[1] Francesca Palandri,[2] Giuseppe A. Palumbo,[3] Andrey Zaritskey,[4] Elisabetta Calistri,[5] Aleksander Skotnicki,[6] Timothy Devos,[7] Domingo Saavedra,[8] Martin Griesshammer,[9] Haifa Kathrin Al-Ali,[10] Renato Tavares,[11] Alessandro M. Vannucchi,[12] Vikas Gupta,[13] Pia Raanani,[14] Bayane Tannir,[15] Jagannath Ghosh,[16] Julian Perez Ronco,[15] Lynda Foltz[17]

Figure 5. Best Percent Change From Baseline in Palpable Spleen Length at Any Time by Week 72



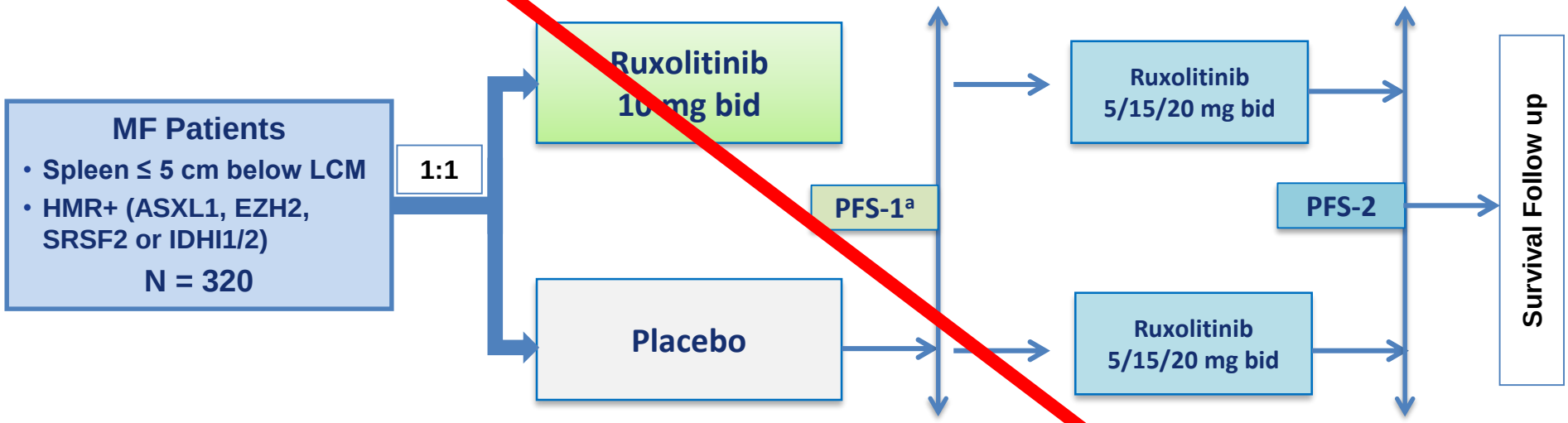
Full report in: Al-Ali et al. Haematologica. 2016 Sep;101(9):1065-73.

CONCLUSIONS

- The JUMP study includes the largest cohort of patients with MF treated with ruxolitinib reported to date and the largest cohort of patients with IPSS intermediate-1–risk MF, a risk group not included in the COMFORT studies
- In this cohort of patients, ruxolitinib demonstrated an AE profile consistent with that previously reported in intermediate-2– and high-risk patients treated in the COMFORT studies
  - The most common AEs were anemia and thrombocytopenia; however, these AEs led to discontinuation in only 0.6% and 1.8% of patients, respectively
  - Nonhematologic AEs were mainly grade 1/2 and led to few discontinuations
  - The rates of infections were low, and infections were primarily grade 1/2
- Patients with intermediate-1–risk MF achieved clinically meaningful reductions in spleen size and symptom improvement consistent with those seen in the overall JUMP population[10]
- Overall, the safety and efficacy profile of ruxolitinib in patients with intermediate-1–risk MF in JUMP is consistent with that seen in the phase 3 COMFORT studies
- These findings indicate that ruxolitinib is an effective treatment for patients with intermediate-1–risk disease

Re-THINK: Trial Design

- ReTHINK is a randomized, double-blind, placebo-controlled, multi-center, phase 3 study of the efficacy and safety of ruxolitinib in patients with early MF and HMR mutations



Inclusion Population:

- Hb > 10 g/dl; transfusion Independent
- ANC > 1, WBC < 15000
- Blast < 1%
- Platelets > 75000
- MF-7 ≤15 (individual items ≤ 3)

Primary Endpoint:

- PFS-1 (90 events)

Secondary Endpoints

- PFS-2, Safety &Tolerability, QOL, OS

“Clinical needs”- oriented conventional RX

Clinical need	Dugs / Intervention	
Anemia	• Corticosteroids • Danazol • ESA	• Thalidomide • Lenalidomide • *Pomalidomide*
Symptomatic splenomegaly	• Hydroxyurea • Cladribine, others	• Splenectomy • Radiation
Extramedulary hematopoiesis	• Radiation	• Hydroxyurea
Risk of thrombosis or recurrence	• Low-dose ASA	• Hydroxyurea
Constitutional symptoms/ QoL	• None specifically directed	
Risk of leukemia transformation	• None specifically directed	
Improved survival	• Allo SCT (?)	

Barbui T et al., J Clin Oncol. 2011; 29:761-70

“Newer” Drugs for MPN (Excluding JAKi)

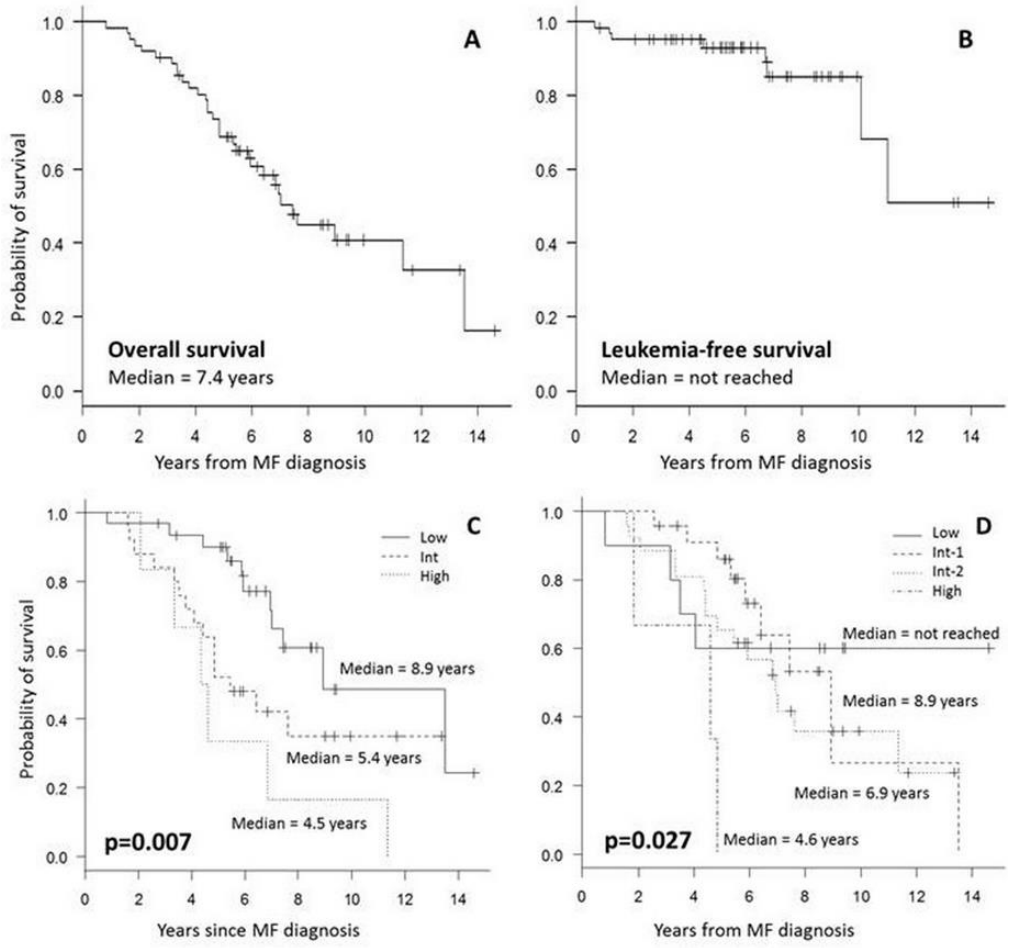
Class	Agent*	Target
PI3K pathway inhibitors	• BKM120/Buparlisib • RAD001/Everolimus	PI3K/Akt/ mTOR
Histone deacetylase (HDAC) inhibitors	• Panobinostat • Vorinostat • Givinostat • Pacrinostat	HDACs (different classes) HSP90
DNA methyltransferase inhibitors	• Azacitidine • Decitabine	DNA methyltransferase
Hedgehog inhibitors	• LDE225	Smo
Telomerase inhibitors	• Imetelstat	Telomerase
Bone marrow fibrosis inhibitors	• Pentraxin	DAMPs and monocytes / macrophages

* list not exhaustive

Long Term Outcome of Patients With MPN-Associated Myelofibrosis Treated With Peg-Interferon-α2a, a French Intergroup of Myeloproliferative Neoplasms (FIM) study

62 MF patients treated with IFN
Survival data
Correlations with mutational patterns

- OS meilleure que cohortes historiques
- Diminution de la charge allélique



Ianotto ASH 2017

Conclusion

- “myelofibrosis” is comprised of very heterogeneous clinical situations and needs, and stratification of patients using new prognostic systems is useful to develop individualized management
- Except allo-SCT, no medicine has been shown to cure patients or to significantly alter the natural history of the disease
- JAK inhibitors have a significant impact on splenomegaly and symptoms and clearly improved our therapeutic arsenal against myelofibrosis
- Combination or sequential strategies will hopefully further improve outcomes for MF patients