Azienda Ospedaliero Universitaria Careggi

FONDAZIONE CAREGGI ONLUS

Settima
Giornata Fiorentina
dedicata ai pazienti con
malattie mieloproliferative
croniche

Sabato 13 Maggio 2017

CRIMM
Centro di Ricerca e Innovazione per le
Malattie Mieloproliferative
AOU Careggi

UNIVERSITÀ DEGLI STUDI FIRENZE

AIRC Programma Clinical Molecular Oncology AGIMM

Intro alla patologia

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La mielofibrosi

- ✓ Una malattia in evoluzione
- ✓ Una malattia (qualche volta) difficile da diagnosticare
- ✓ Una malattia molecolare
- ✓ Una malattia dalle scelte (terapeutiche) condivise

Italian diagnostic criteria for myelofibrosis (*Barosi et al, BJH 1998*)

Necessary criteria

1. *Diffuse bone marrow fibrosis*
2. *Absence of Philadelphia chromosome or BCR-ABL rearrangement*

Optional criteria

1. *Splenomegaly of any grade;*
2. *Anisopoikilocytosis with tear-drop erythrocytes*
3. *Presence of circulating immature myeloid cells*
4. *Presence of circulating erythroblasts*
5. *Presence of clusters of megakaryoblasts and anomalous megakaryocytes in bone marrow sections*
6. *Myeloid metaplasia.*

WHO diagnostic criteria for myelofibrosis (2016)

Prefibrotic/early stage

Major criteria

1. *Megakaryocyte proliferation and atypia, without reticulin fibrosis grade>1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and (often) decreased erythropoiesis*
2. *Not meeting WHO criteria for other myeloid neoplasms*
3. *JAK2, CALR, or MPL mutation, or presence of another clonal marker*

Minor criteria

1. *Presence of ≥1 of the following: anemia not attributed to comorbid condition; leukocytosis ≥11 x 10^9/L, palpable splenomegaly; lactate dehydrogenase level above the upper limit of the institutional reference range*

Fibrotic stage

Major criteria

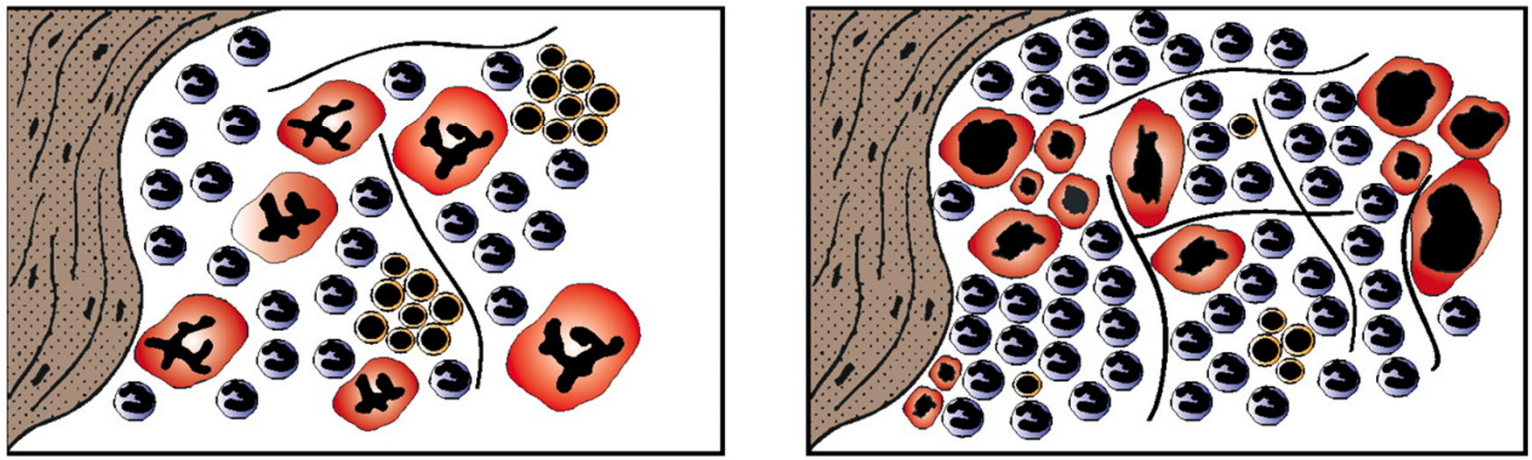
1. *Megakaryocyte proliferation and atypia, accompanied by reticulin and/or collagen fibrosis grade 2 or 3*
2. *Not meeting WHO criteria for other myeloid neoplasms*
3. *JAK2, CALR, or MPL mutation, or presence of another clonal marker*

Minor criteria

1. *Presence of ≥1 of the following: anemia not attributed to comorbid condition; leukocytosis ≥11 x 10^9/L, palpable splenomegaly; lactate dehydrogenase level above the upper limit of the institutional reference range*

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

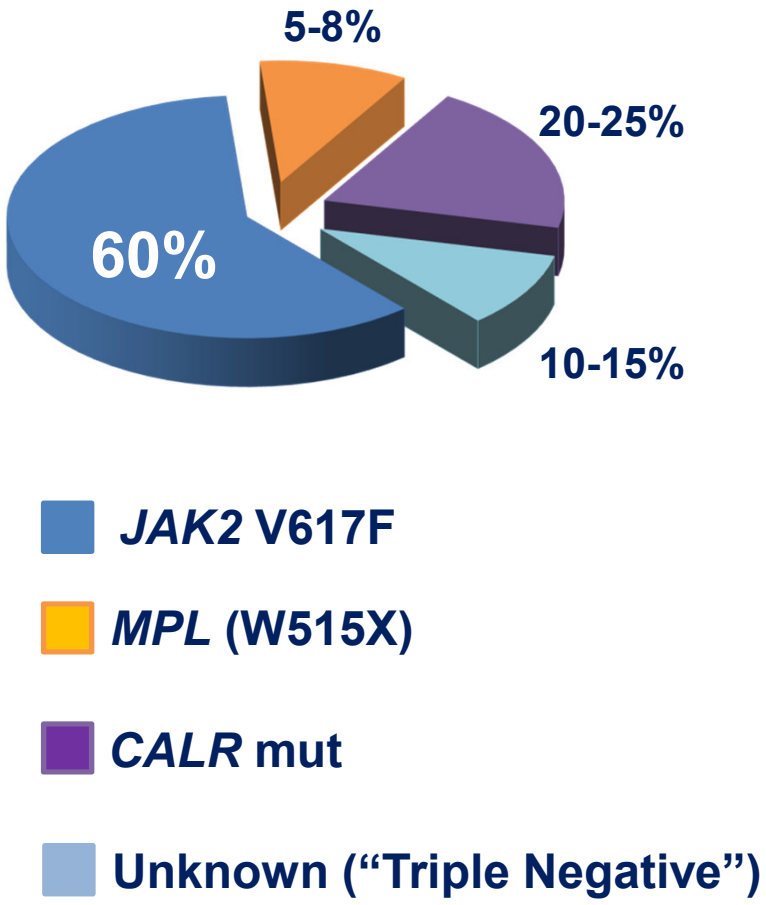
ET	PMF (early-prefibrotic stage)
• no or only slight increase in age-matched cellularity	• marked increase in age-matched cellularity
• no significant increase in granulo- and erythropoiesis	• pronounced proliferation of granulopoiesis and reduction of erythroid precursors
• prominent large to giant mature megakaryocytes with hyperlobulated or deeply folded nuclei, dispersed or loosely clustered in the marrow space	• dense or loose clustering and frequent endosteal translocation of medium sized to giant megakaryocytes showing hyperchromatic, hypolobulated, bulbous, or irregularly folded nuclei and an aberrant nuclear/cytoplasmic ratio
• no or very rarely minor increase in reticulin fibers	• no or no significant increase in reticulin fibers



Megakaryopoiesis; Granulopoiesis; Erythropoiesis; Reticulin fibers

Thiele J et al. Blood 2011;117:5710-5718

Phenotypic Driver Mutations in MPN



Klampfl T, et al. *NEJM* 2013;369(25):2379-90; Nangalia J, et al. *NEJM* 2013;369(25):2391-405.

Additional, Not-driver, Somatic Mutations

Gene	Chromosome location	PV (%)	ET (%)	MF (%)	Blast phase (%)
TET2	4q24	10-16	4-5	7-17	17-32
IDH1/2	2q33.3 / 15q26.1	2	1	4	9-22
DNMT3A	2p23	3-7	<1	2-15	14-17
EZH2	7q36.1	3	<1	7-13	---
ASXL1	20q11.1	2-7	0-3	13-32	18-33
SRSF2	17q25.1	---	---	≈15%	≈20%
SF3B1	2q33.1	---	---	7%	---
CBL	11q23.3	rare	rare	6%	---
TP53	17p13.1	---	---	4%	27%
U2AF1	21q22.3	---	---	16%	---

Vainchenker W et al, Blood. 2011; 18;118(7):1723-35;
Vannucchi AM et al, Leukemia 2013; 27:1861-9.

La medicina di precisione – un nuovo paradigma

Strategie di prevenzione e trattamento che considerano la individuale variabilità genetica e molecolare

Medicina di precisione nella mielofibrosi

1. Usare i marcatori molecolari (mutazioni) per migliorare la prognosi

2. Usare i marcatori molecolari (mutazioni) per scegliere la terapia

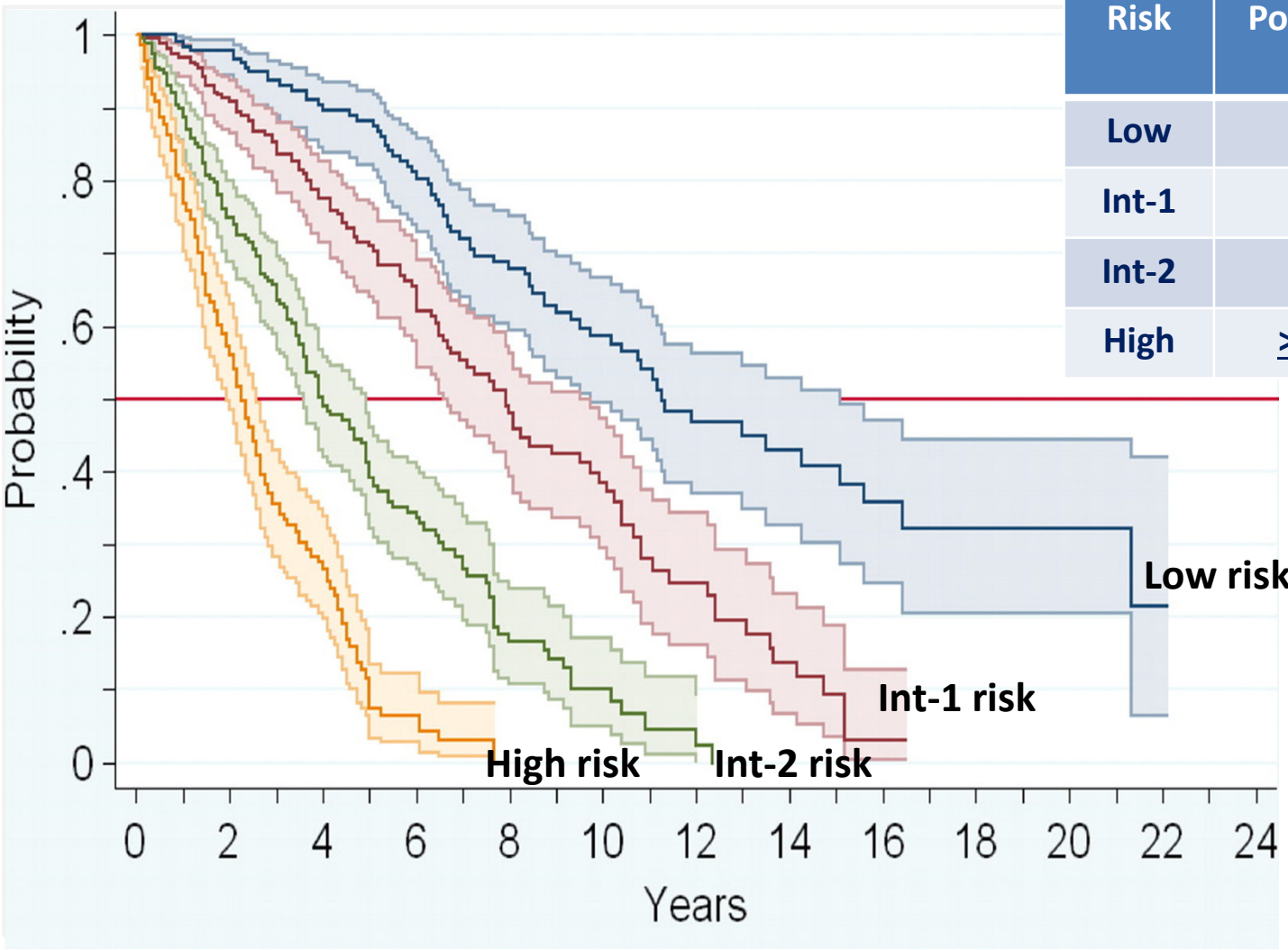
Clinical Scores for Risk Stratification in PMF

Variable	IPSS	DIPSS	DIPSS-plus
Age >65 y	√	√	**If DIPSS:** **Low= 0** **Int-1= 1** **Int-2=2** **High= 3**
Constitutional symptoms	√	√	
Hemoglobin <10 g/dL	√	√	
Leukocyte count >25x10^9/L	√	√	
Circulating blasts ≥ 1%	√	√	
Platelet count <100x10^9/L			√
RBC transfusion need			√
Unfavorable karyotype +8,-7/7q-,i(17q),inv(3), -5/5q-,12p-, 11q23 rearr.			√

Cervantes F, et al. *Blood.* 2009;113:2895-901
Passamonti F, et al. *Blood.* 2010; 115:1703-8
Gangat N, et al. *J Clin Oncol.* 2011; 29:392-7

International Prognostic Scoring System-IPSS

Risk	Points	Median survival (mo)
Low	0	135
Int-1	1	95
Int-2	2	48
High	≥3	27



Cervantes F, et al. *Blood*. 2009;113:2895-901

Genetically driven prognostic model in PMF

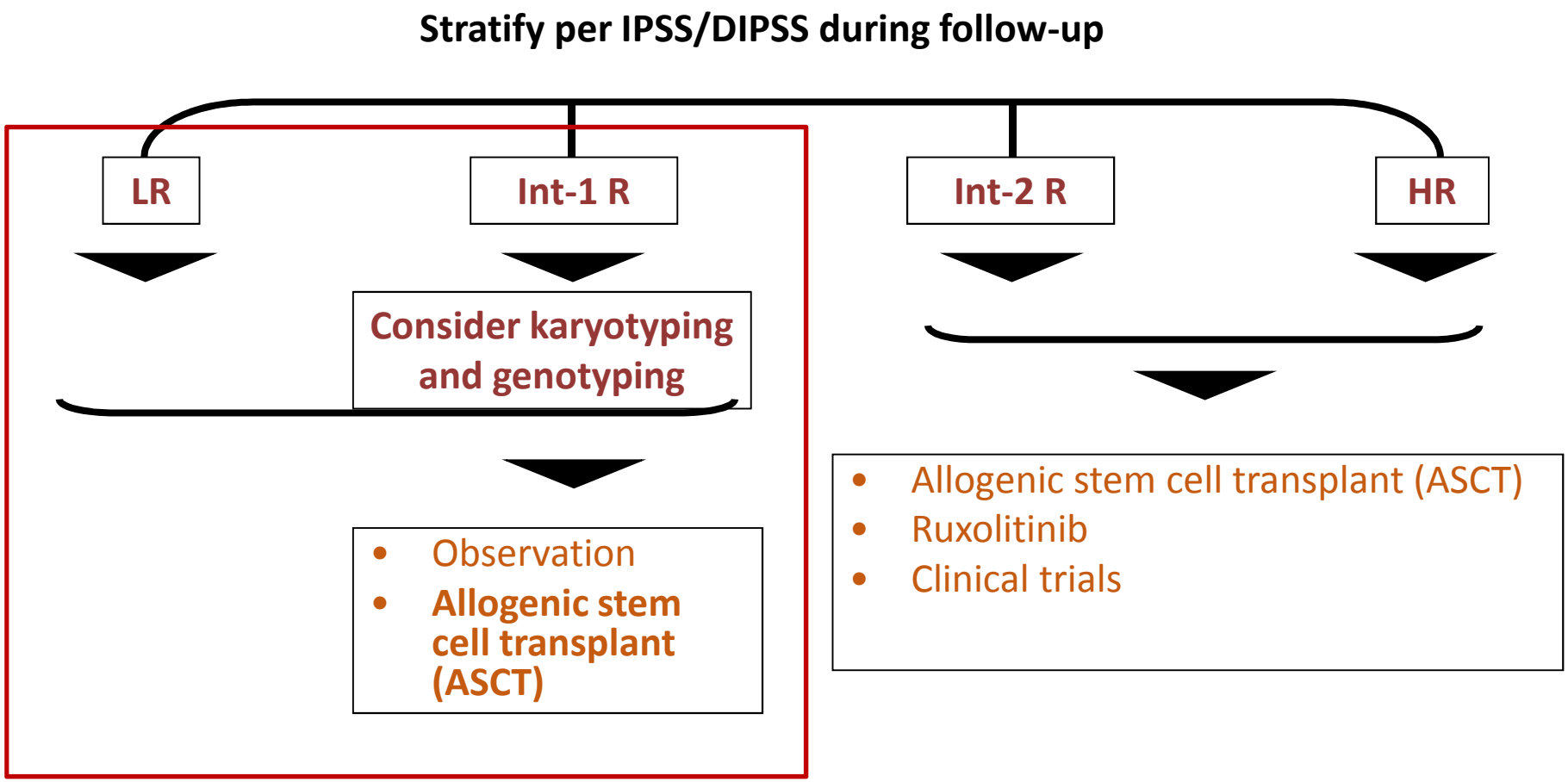
	MIPSS	GIPSS
Age >65	1.5	2
Constitutional symptoms	0.5	No
Hemoglobin <10 g/dL	0.5	No
Platelets < 200 x10^9/L	1	No
Triple negative	1.5	2
JAK2 or MPL mutation	0.5	2
ASXL1 mutation	0.5	1
SRSF2 mutation	0.5	1
CALR Type 2-Type 2 like	No	2
Unfavorable cytogenetics	No	3 for very high risk; 2 for high risk

MIPSS = Mutation-Enhanced International Prognostic Scoring System (Vannucci et al, Blood 2014;124:405)

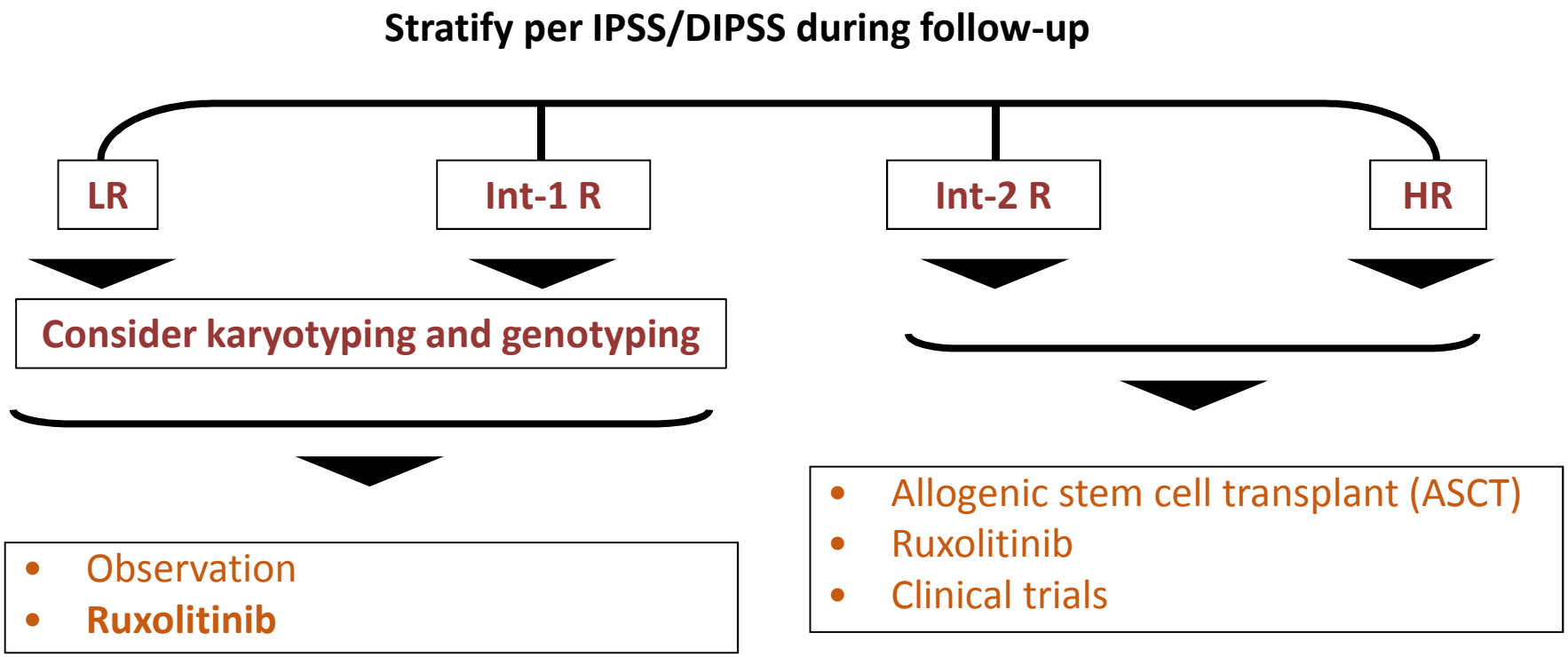
HMR: How Many Patients Would be Reclassified?

IPSS Risk Categories	*ASXL1* N. (%)	*EZH2* N. (%)	*SRSF2* N.(%)	*IDHs* N. (%)	N (%) Of HMR patients
LOW	24/162 (14.8%)	6/165 (3.6%)	7/151 (4.6%)	2/157 (1.3%)	**35/166 (21.1%)**
INT- 1	28/142 (19.7%)	6/143 (4.2%)	6/136 (4.4%)	6/142 (4.2%)	**34 /146 (23.4%)**
INT- 2	23/100 (23.0%)	4/99 (4.0%)	9/97 (9.3%)	2/96 (2.1%)	**31 /104 (29.8%)**
HIGH	27/65 (41.5%)	8/66 (12.1%)	16/63 (25.4%)	1/60 (1.7%)	**39/68 (57.3%)**

Personalized approach to MF: HSCT for DIPSS INT-1 disease

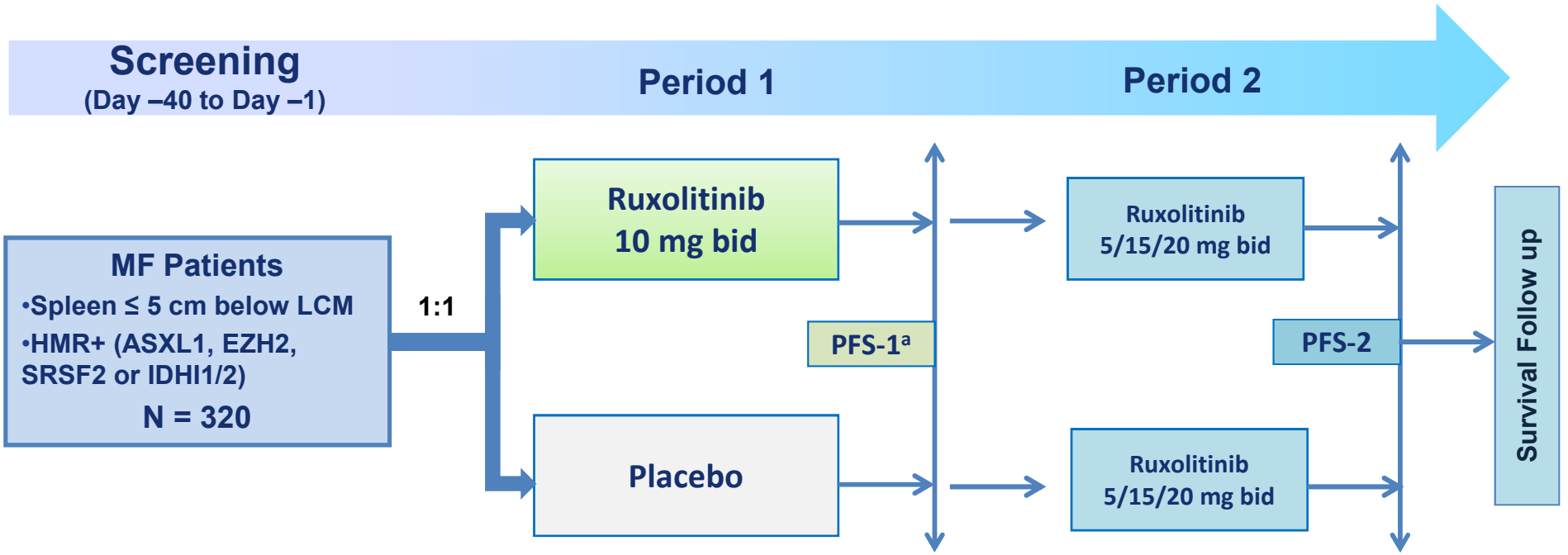


Personalized approach to MF: Ruxolitinib for early phase disease



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

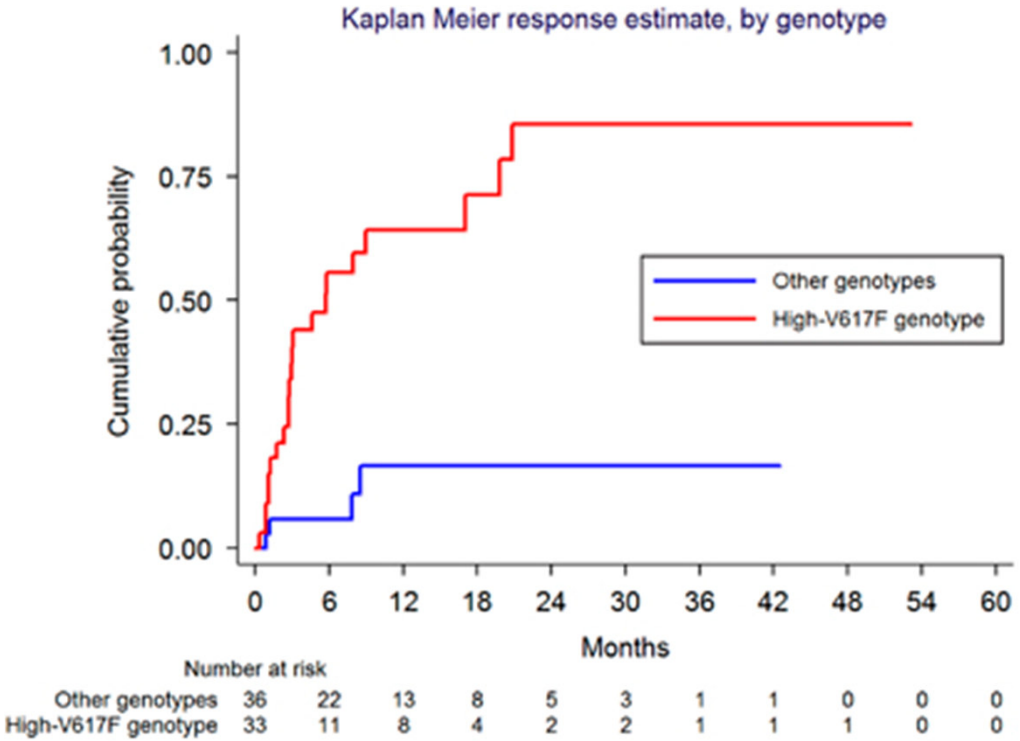


[a] If progression is achieved by spleen or symptoms.

Passamonti F, et al. J Clin Oncol 34, 2016 (suppl; abstr TPS7080).

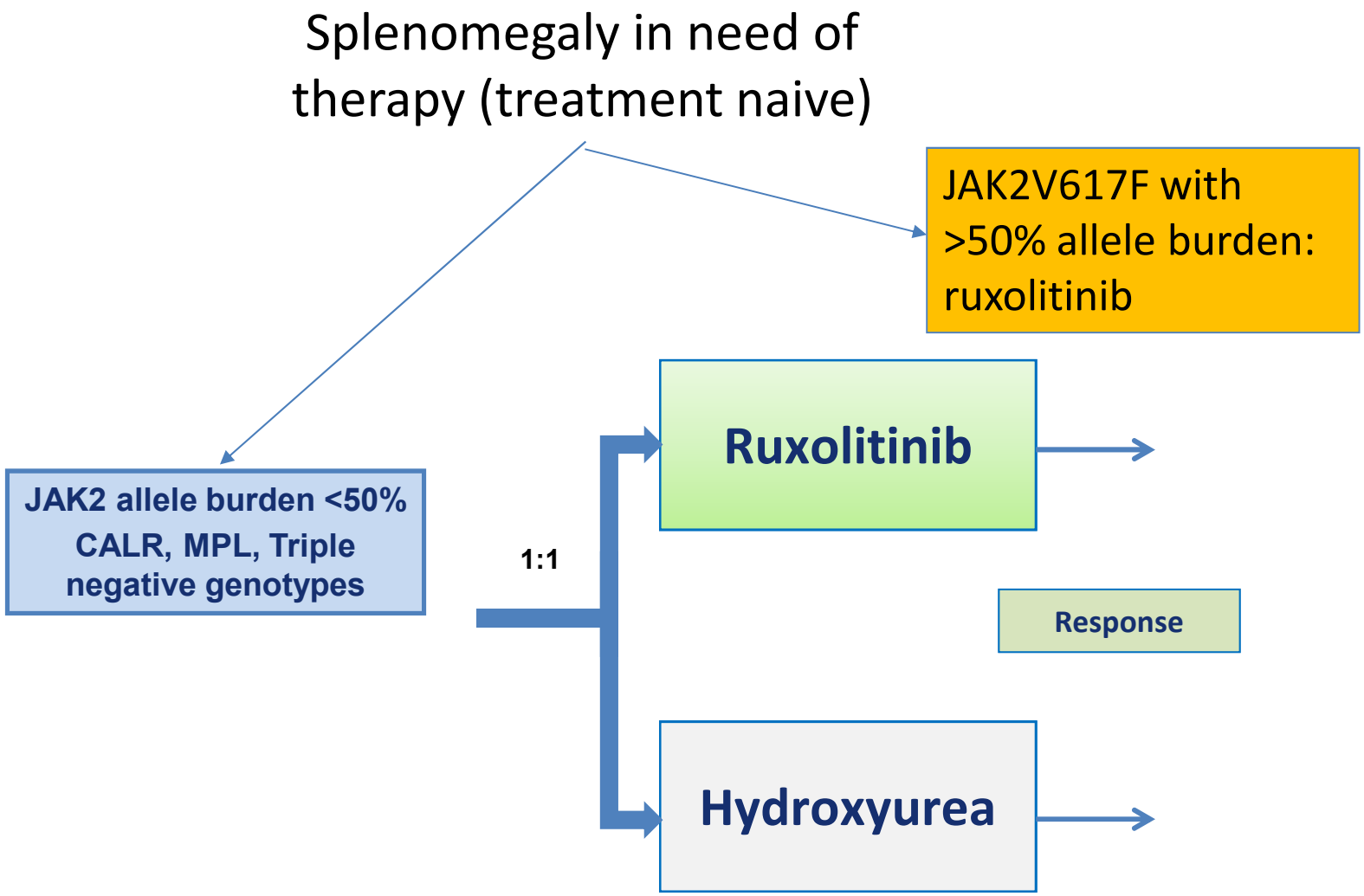
JAK2^{V617F} allele burden $\geqslant 50\%$ is associated with response to ruxolitinib in persons with MPN-associated myelofibrosis and splenomegaly requiring therapy

Leukemia (2016) **30,** 1772–1775; doi:10.1038/leu.2016.45

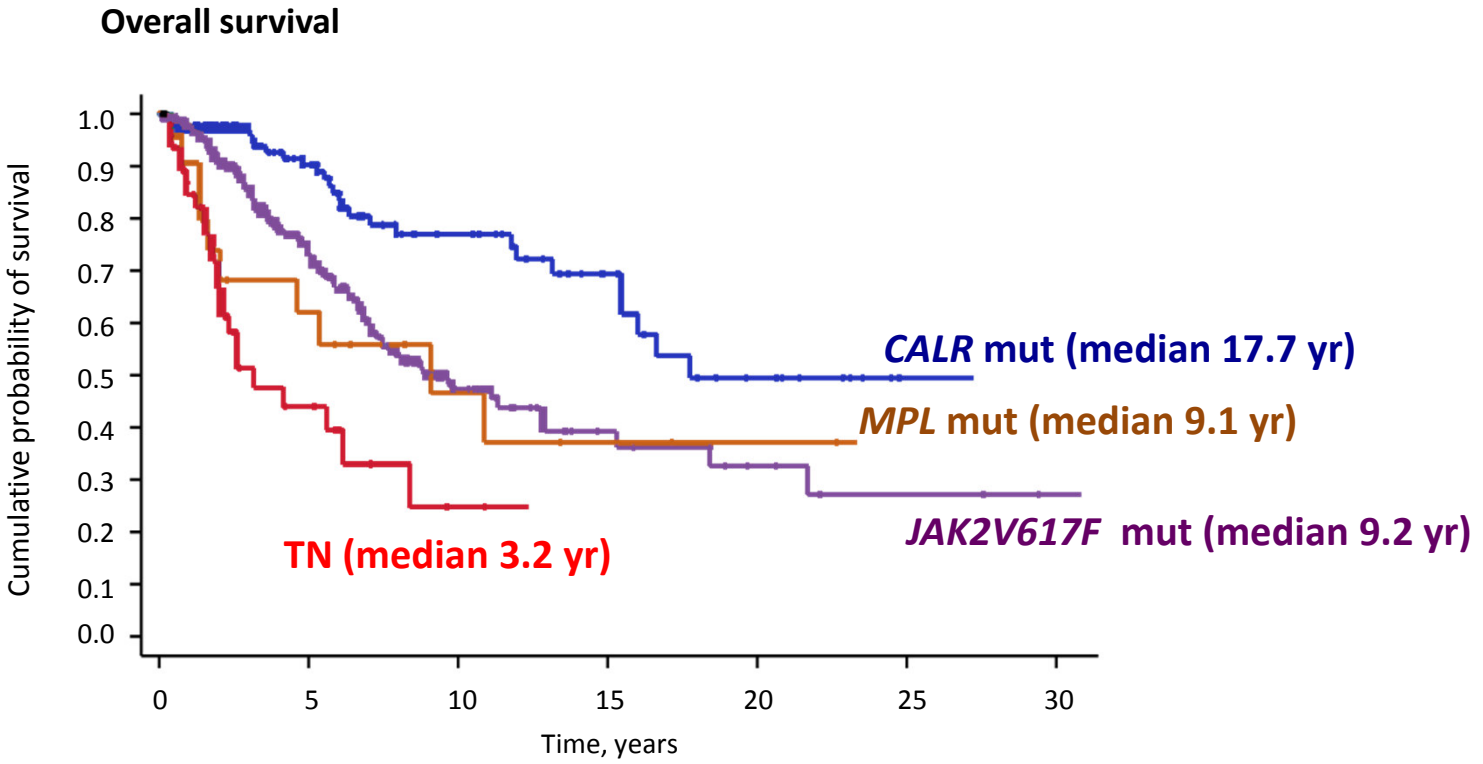


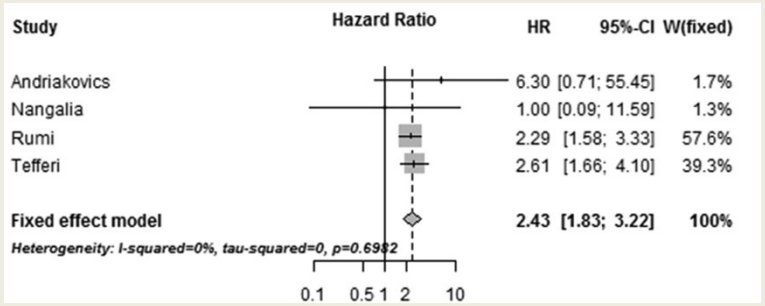
Barosi g, Leukemia 2016

Trial Design Hypothesis



Phenotype Driver Mutations Have a Strong Prognostic Impact in PMF





JAK2 mutated patients had shorter overall survival compared with those CALR⁺ (Meta-analysis combined hazard ratio, 2.43; 95% CI, 1.83-3.22; P= < .001).

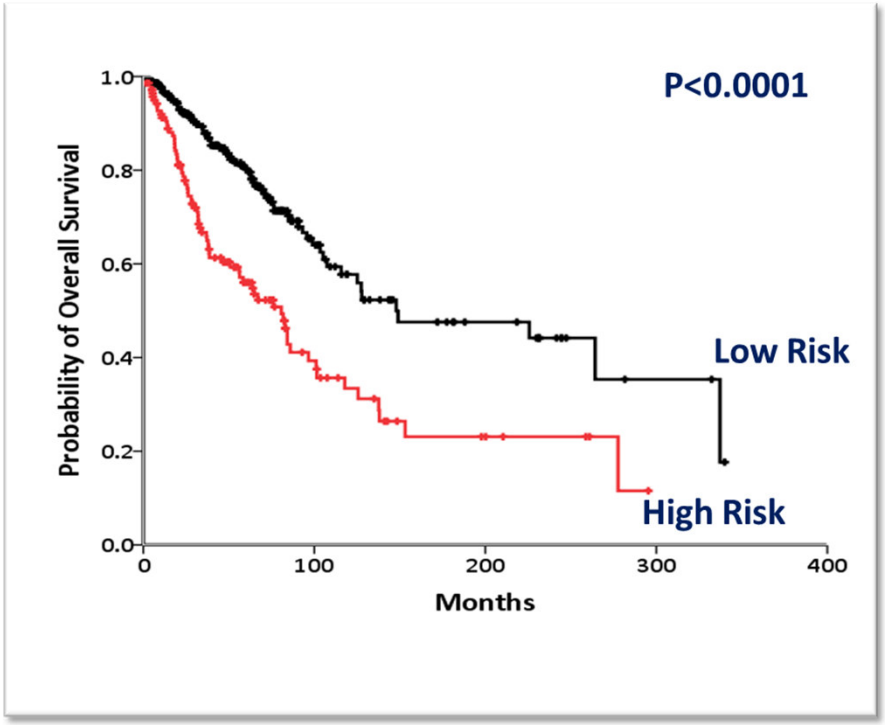
1919

Rumi E, et al. Blood. 2014 Aug 14;124(7):1062-9; Kourie HR et al, Clin Lymphoma Myeloma Leuk. 2016 Feb 6

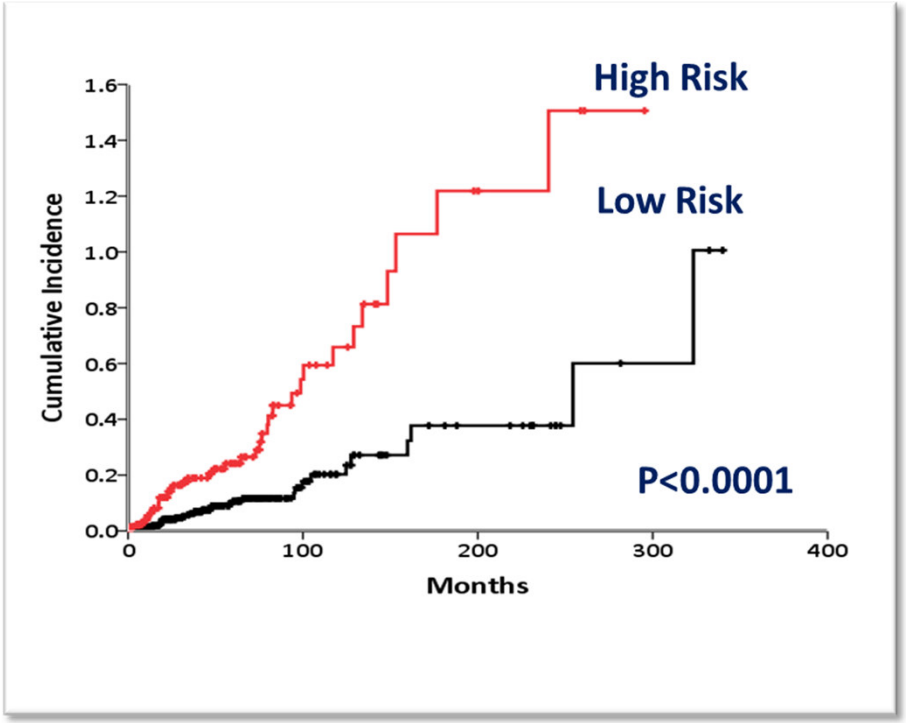
High Molecular Risk Prognostic Category

harboring ≥1 mutation in any one of ***ASXL1, EZH2, SRSF2, IDH1/2***

Overall Survival



Blast Transformation



- A HMR status is associated with reduced OS and increased risk of blast transformation in PMF patients independent of IPSS/DIPPS-plus

Vannucchi AM, et al. Leukemia. 2013;27:1861-9

2020

Trial Design Hypothesis