Fattori prognostici e fattori predittivi come guida per un trattamento individualizzato

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Precision medicine – a new paradigm

Prevention and treatment strategies that take individual variabilty (genetic) into account

Technological facilities

- ✓ Development of large scale biological data (human genome sequence)
- ✓ Powerful methods for characterizing patients (proteomics, metabolomics, genomics..)
- ✓ Computational tools for analyzing large sets of data

Successful hypothesis-testing cancer trials

ABL kinase

The study of ABL kinase inhibitors for BCR-ABL driven chronic myeloid leukemias is arguably the most important development in the treatment of hematological malignancy transforming disease epidemiology, biological understanding and treatment

KIT an PDGFR kinases

Small-molecule inhibitros in kit and PDGFR for gastrointestinal stromal tumors (GIST) with mutations of these tyrosine kinases.

PERSPECTIVE

The precision–oncology illusion

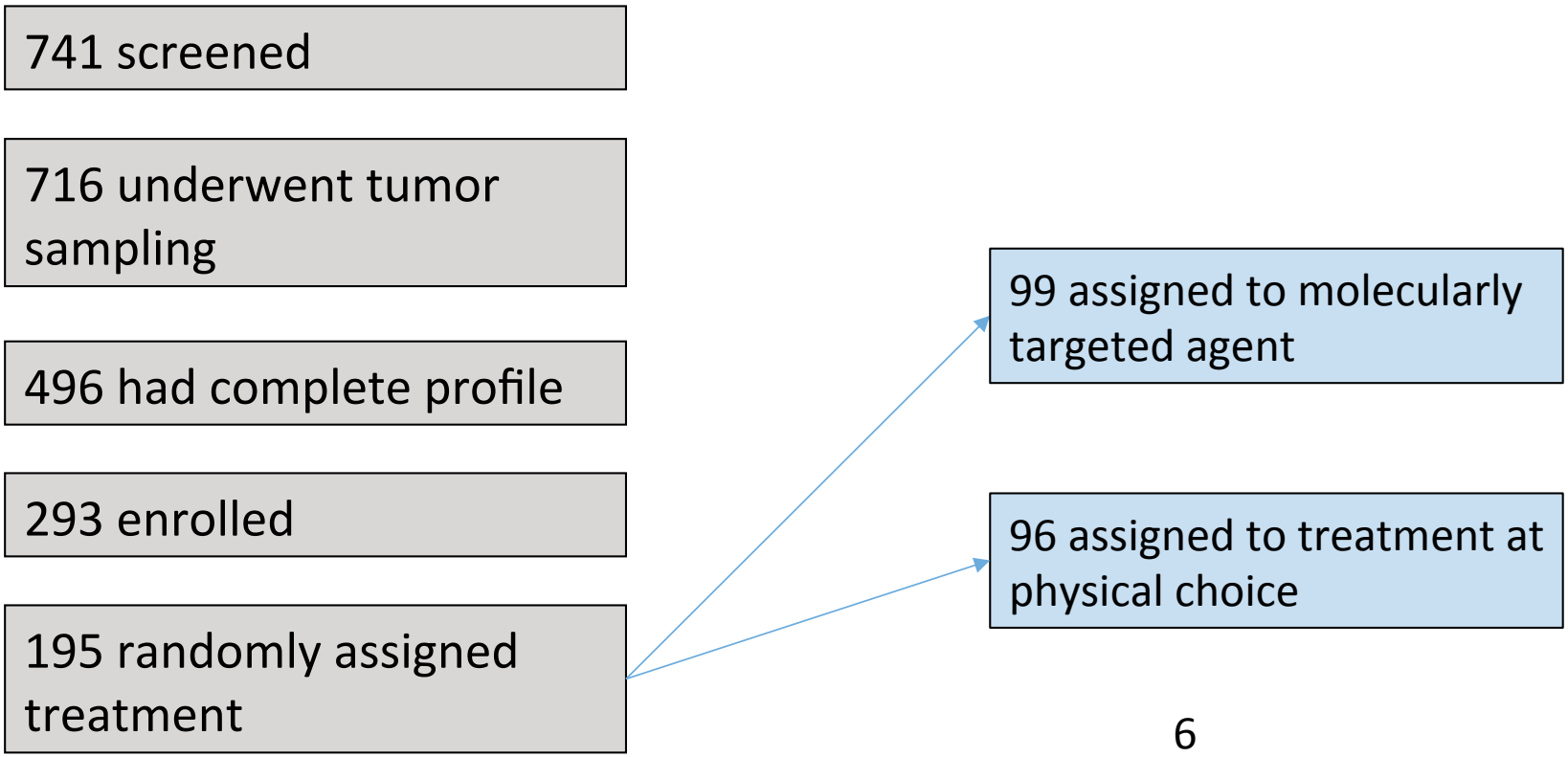
Precision oncology has not been shown to work, and perhaps it never will, says **Vinay Prasad**.

«As of 2016, the proposal is neither feasible, cost-effecticve nor assured of future success»

Prasad V. Nature, 8 September 2016

Unsuccessfull hypothesis testing – The SHIVA trial *(Le Tourneau C, Lancet Oncol 2015;16:1324)*

Study design: a proof-of concept, multicentre, open label, randomized, controlled phase 2 trial of moleculary targeted agents based on tumor molecular profiling versus treatment at physician's choice in patients with refractory cancer



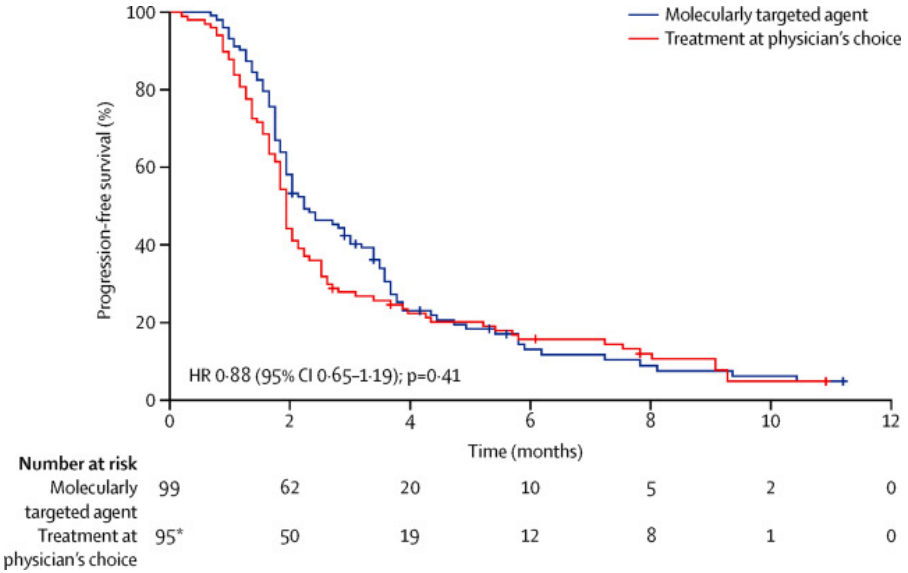
The Shiva trial

Randomization was stratified by three pathways:

- A hormone receptor pathway
- A PI3K/AKT/mTOR pathway
- RAF/MEK pathway

The molecularly targeted agents used were: Erlotinib, Sorafenib, Dasatinib, Imatinib, Vemurafenib, Everolimus, Abiraterone, Letrozole, Tamoxifen

The Shiva trial



Patents in the experimental group did not outperform those of the control group in any of the three prespecified pathway strata.

Not only did precision oncology have little efficacy, but it appeard to cause more toxic effect that chemotherapy did.

Precision oncology – a new methodological paradigm

Achieving the benefit of personalized oncology for patients and health care costs will require a change of the methodological paradigm for clinical and statistical investigators, industry and regulatory agencies

Precision medicine in myelofibrosis

1. Clinical utility of the molecular **prognostic biomarkers** (scores) in myelofibrosis

2. Predictive value of the **mutational genotype** for ruxolitinib therapy in myelofibrosis

Prognostic biomarkers

- ✓ Baseline (pretreatment) measures that provide information on the outcome of the patients both untreated and with a standard treatment

- ✓ To be used to determine if the patient needs a therapy that is different from the standard treatment

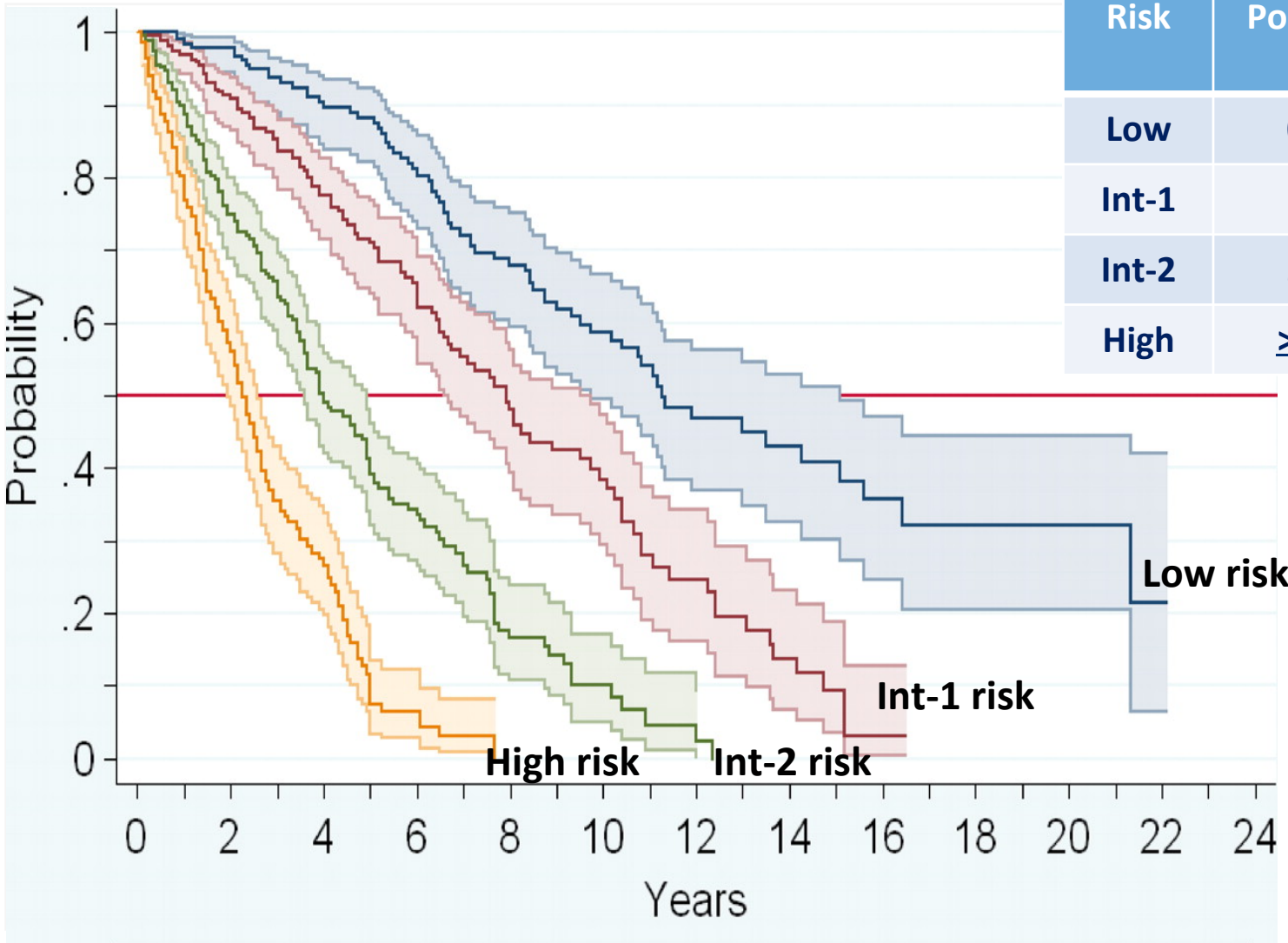
Clinical Scores for Risk Stratification in PMF

Variable	IPSS	DIPSS	DIPSS-plus
Age >65 y	√	√	**If DIPSS:**
Constitutional symptoms	√	√	**Low= 0**
Hemoglobin <10 g/dL	√	√	**Int-1= 1**
Leukocyte count >25x10^9/L	√	√	**Int-2=2**
Circulating blasts ≥ 1%	√	√	**High= 3**
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

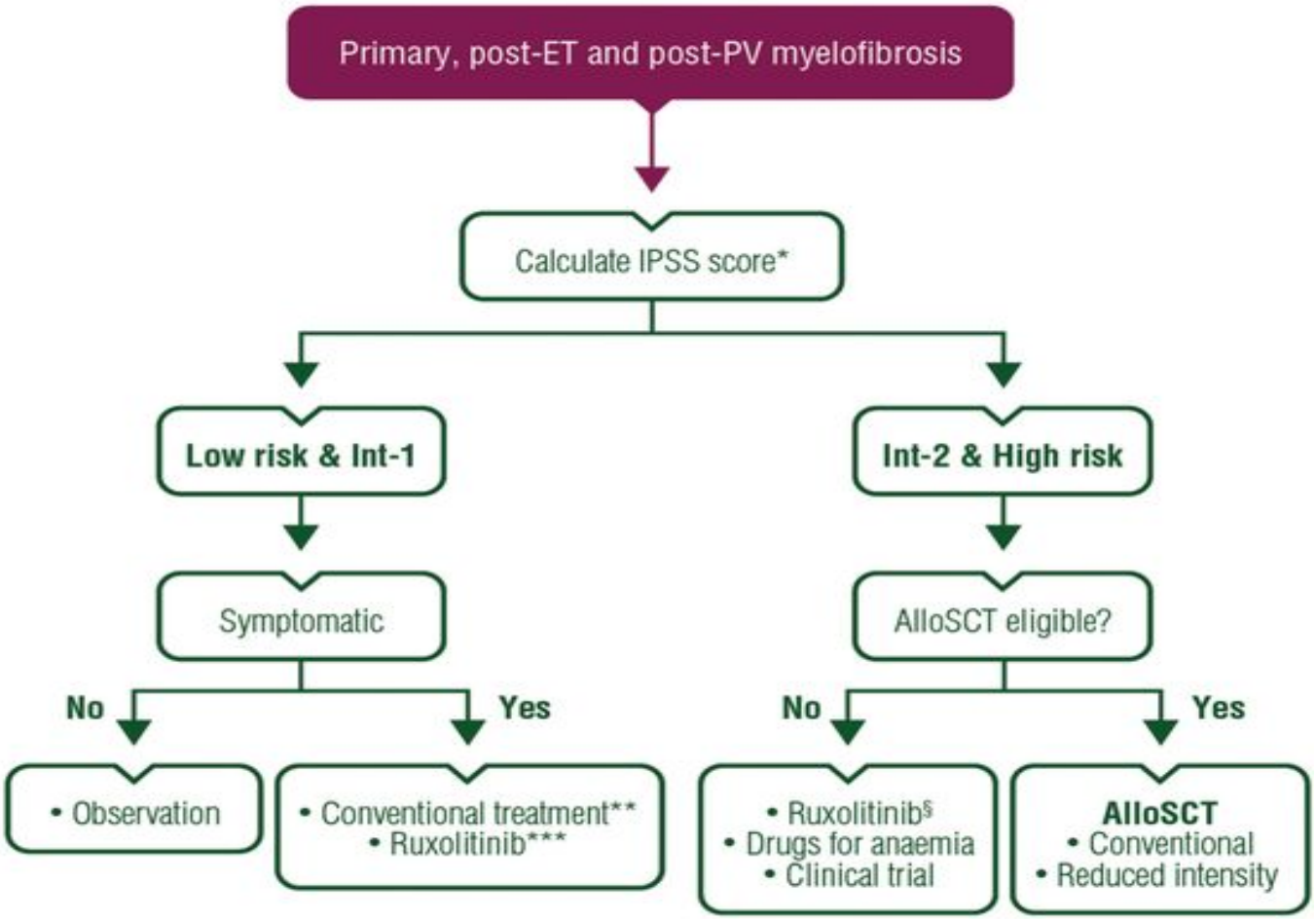
International Prognostic Scoring System-IPSS

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



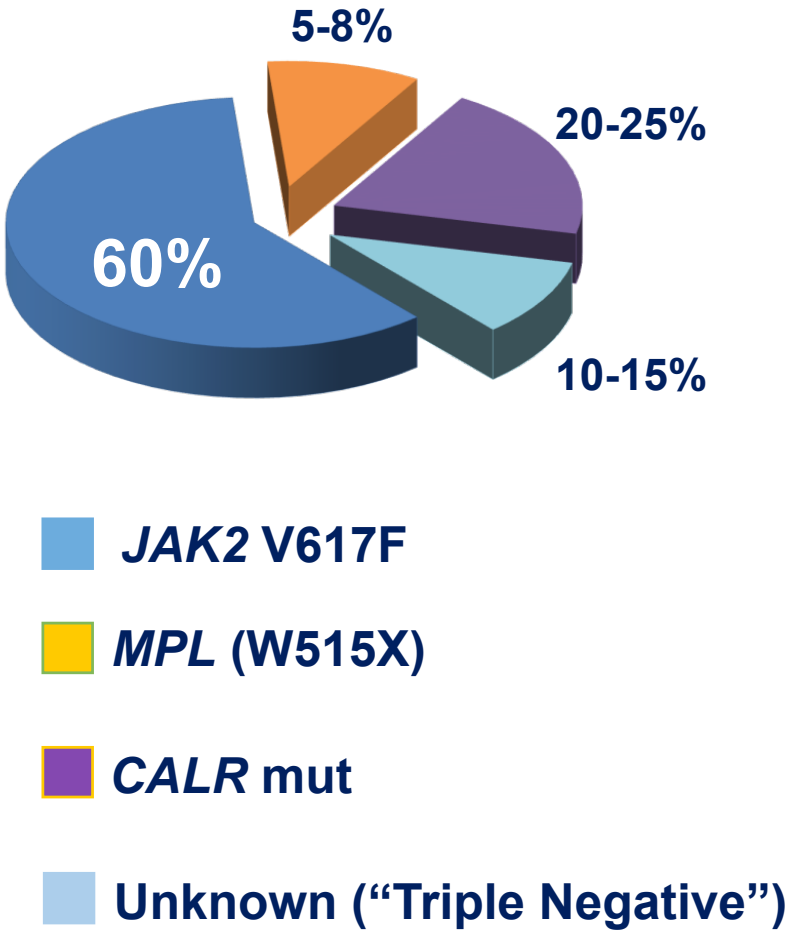
Cervantes F, et al. *Blood.* 2009;113:2895-901

ESMO- Therapeutic algorithms for myelofibrosis



A. M. Vannucchi et al. Ann Oncol 2015;26:v85-v99

Phenotypic Driver Mutations in MPN



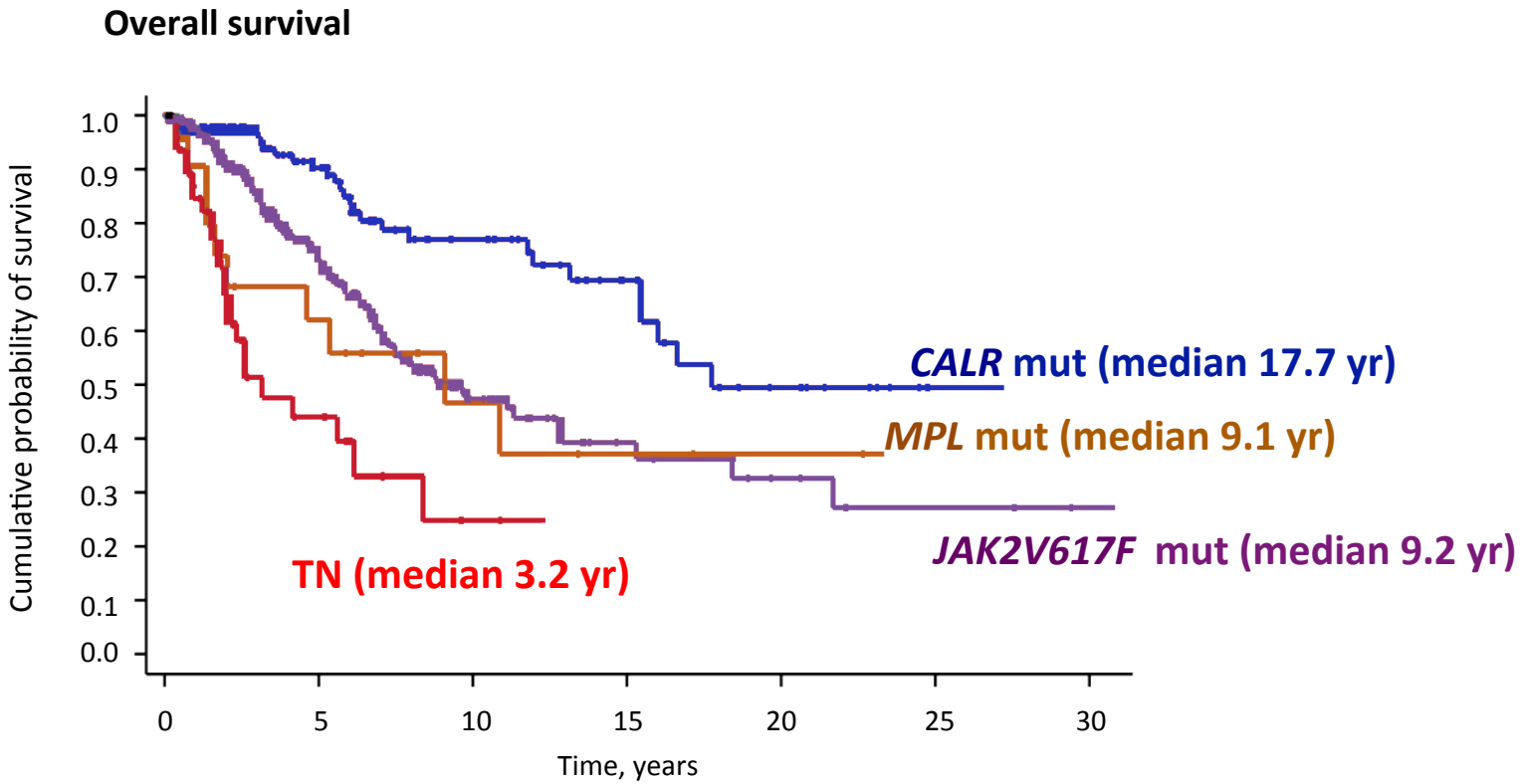
Klampfl T, et al. *NEJM* 2013;369(25):2379-90; Nangalia J, et al. *NEJM* 2013;369(25):2391-405.

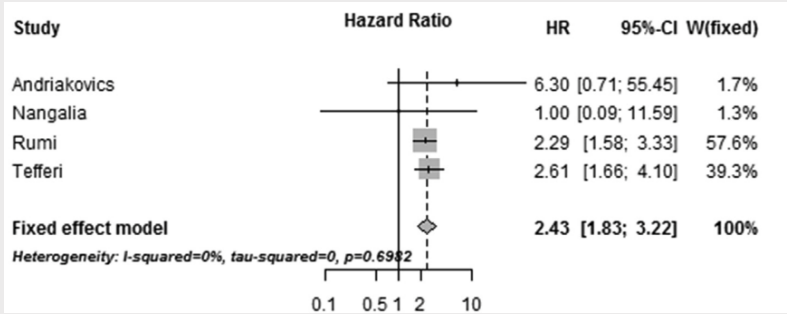
Additional, Not-driver, Somatic Mutations

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.

Phenotype Driver Mutations Have a Strong Prognostic Impact in PMF

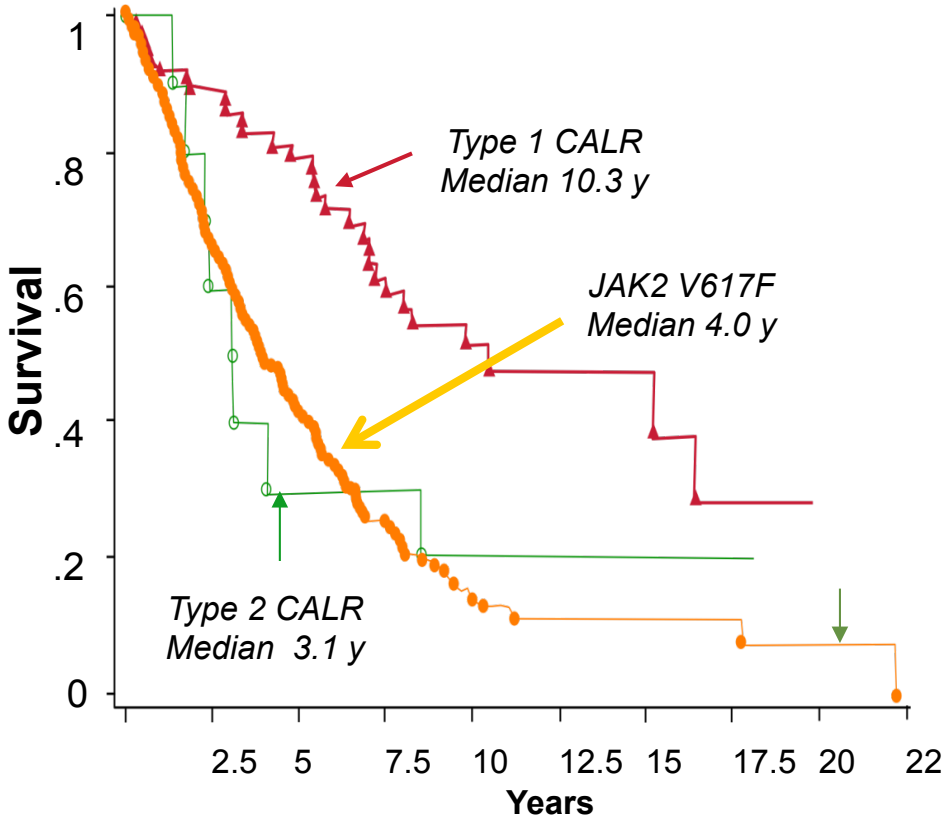


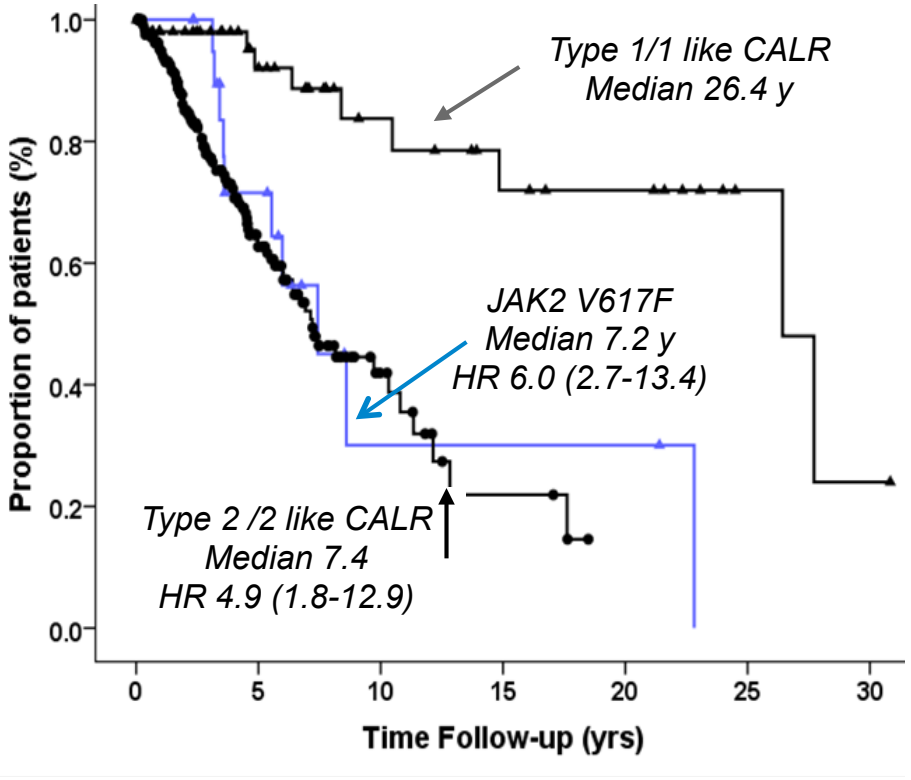


JAK2 mutated patients had shorter overall survival compared with those CALR^{+} (Meta-analysis combined hazard ratio, 2.43; 95% CI, 1.83-3.22; P= < .001).

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

CALR Type 1/1-like *vs* Type 2/2-like Mutations in PMF Make a Difference



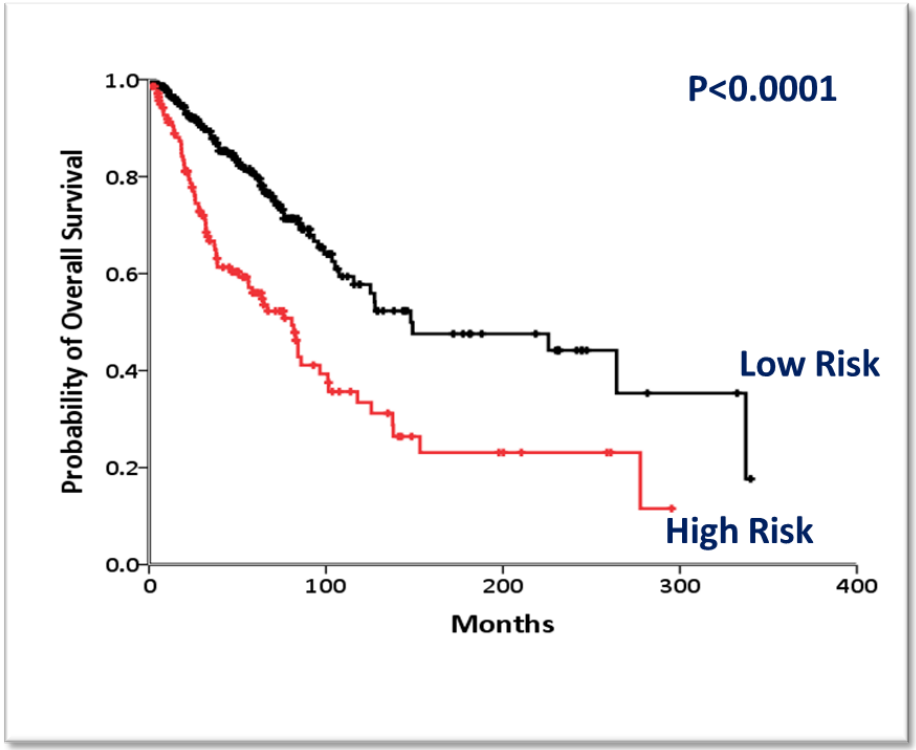


Tefferi A, et al. Leukemia. 2014; 28:1568-70;
Guglielmelli P et al, BCJ, 2015, Online

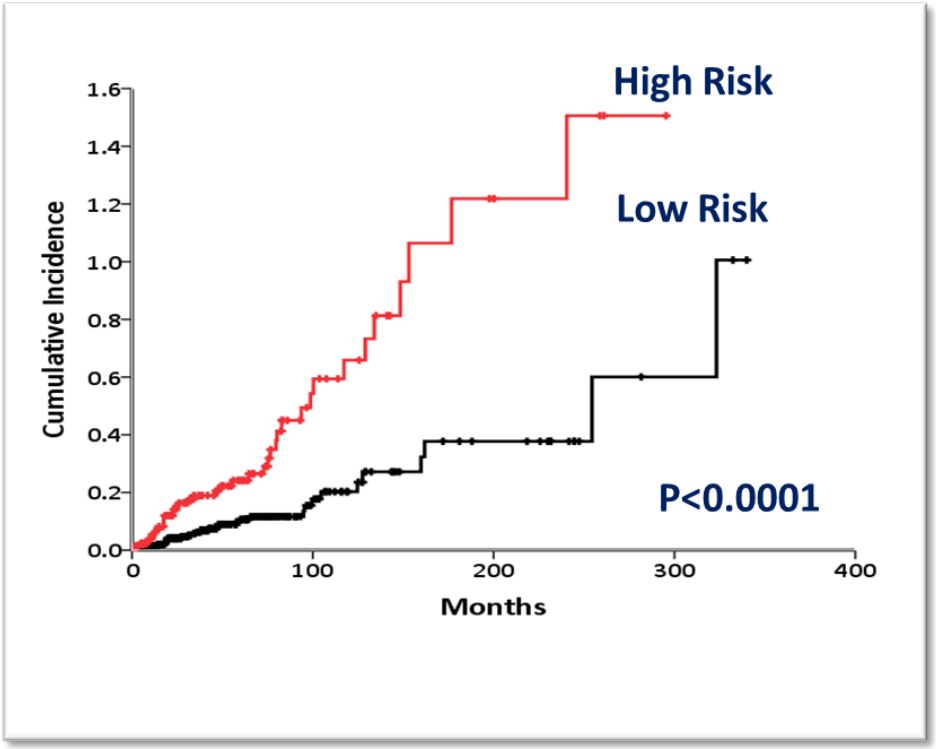
High Molecular Risk Prognostic Category

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

Overall Survival



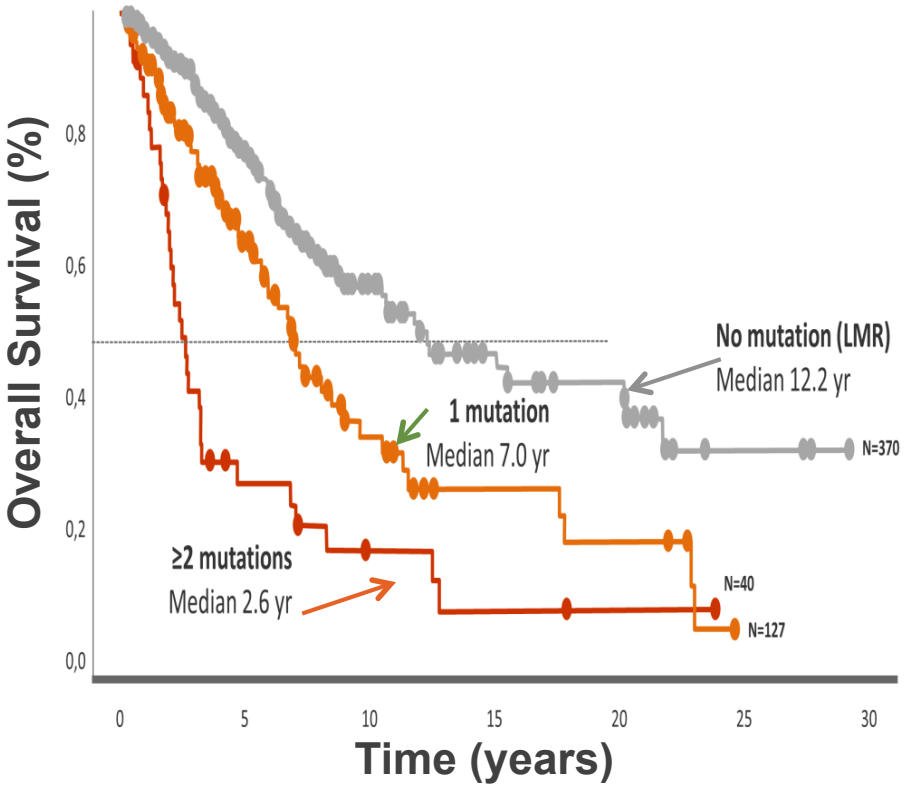
Blast Transformation

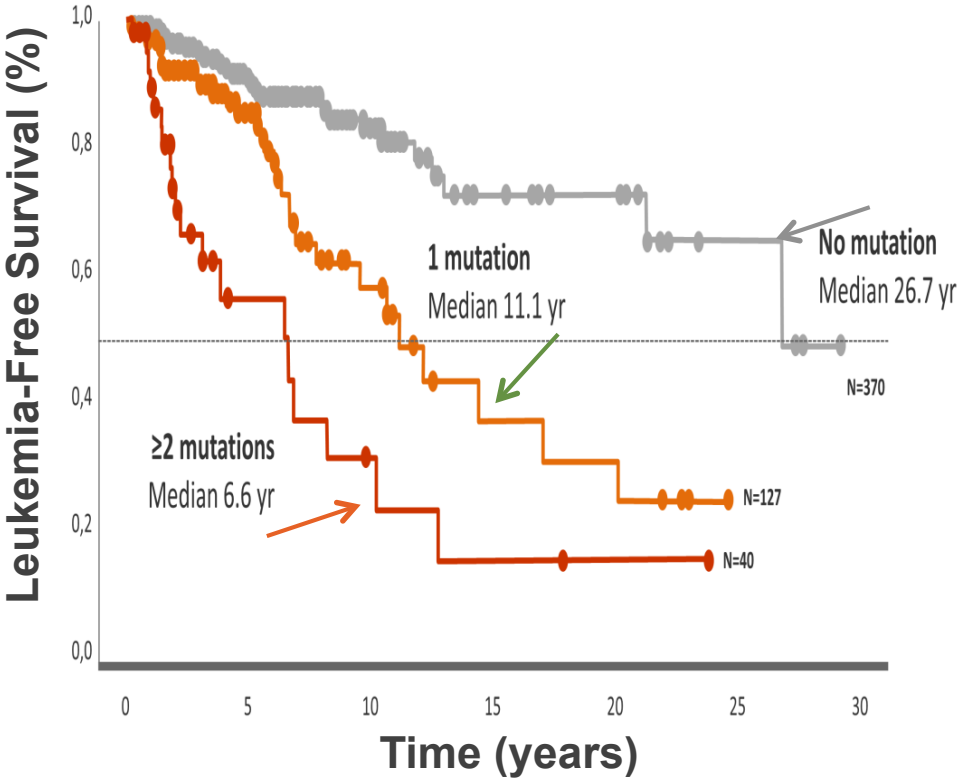


- A HMR status is associated with reduced OS and increased risk of blast transformation in PMF patients independent of IPSS/DIPPS-plus

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

Influence of the Number of HMR Mutations on Overall Survival and Leukemia-FS in PMF





Guglielmelli P, et al. Leukemia. 2014; 28: 1804-1810

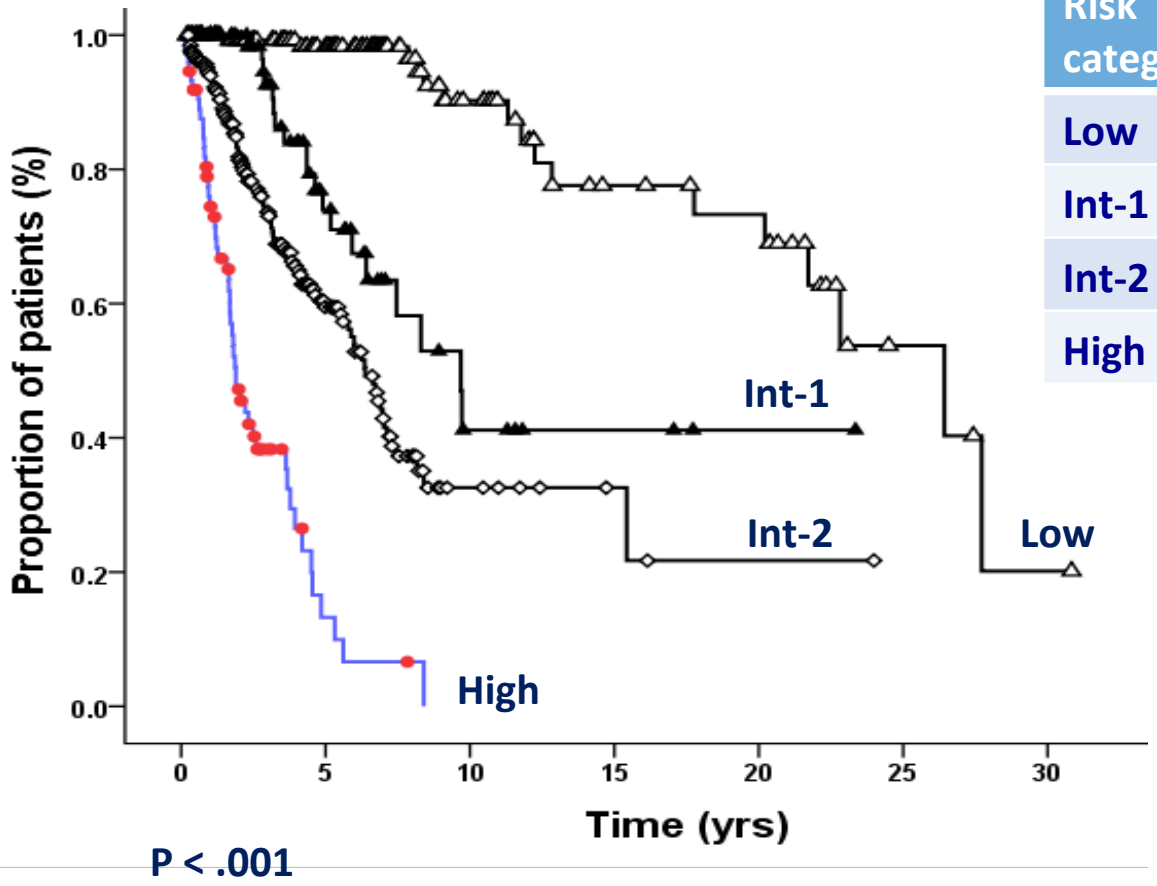
2020

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)

Mutation-Enhanced International Prognostic Scoring System (MIPSS) for PMF



P < .001

Risk category	Score	% of pts	OS (y)	HR
Low	0-0.5	27	26.4	1
Int-1	1-1.5	14	9.7	4.7
Int-2	2-3.5	46	6.4	9.9
High	≥4	13	1.9	36.5

Akaike information criterion indicated that MIPSS performed better than IPSS in predicting survival (1611.6 *vs* 1649.0).

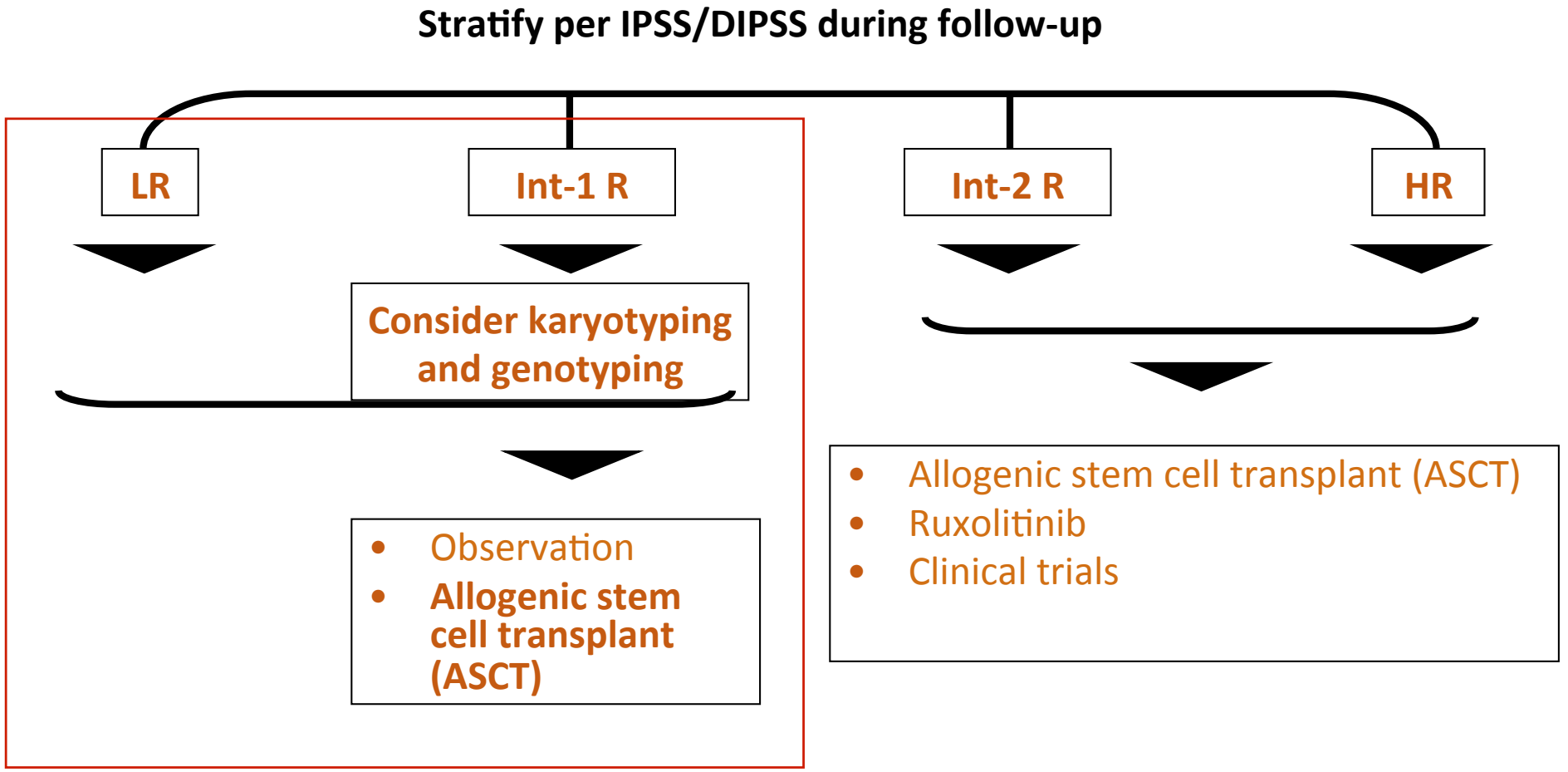
Vannucchi AM, et al. ASH2014. Abstract 405

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%)**

2323

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



Allo SCT in PMF: A Consensus Process by an EBMT/ELN International Working Group

3. *Patients with low-risk disease should not undergo allo-SCT. They should be monitored and evaluated for transplantation when disease progression occurs.*

4. *Although the use of molecular risk classification for the identification of candidates for allo-SCT among intermediate-1 risk patients deserves further clinical validation, patients in this risk category who are Triple Negative or ASXL1 positive, or both, should be considered for allo-SCT*

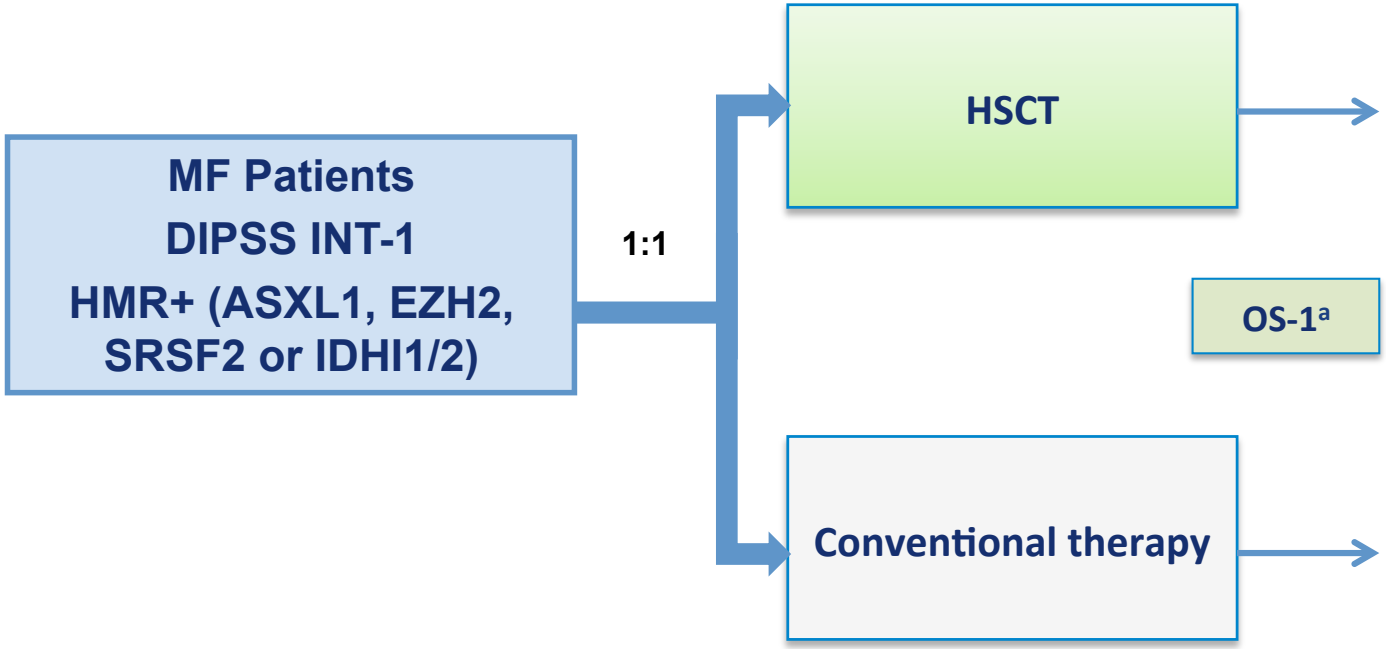
Prognostic markers validation

Analytical validity: test accuracy (reproducibility)

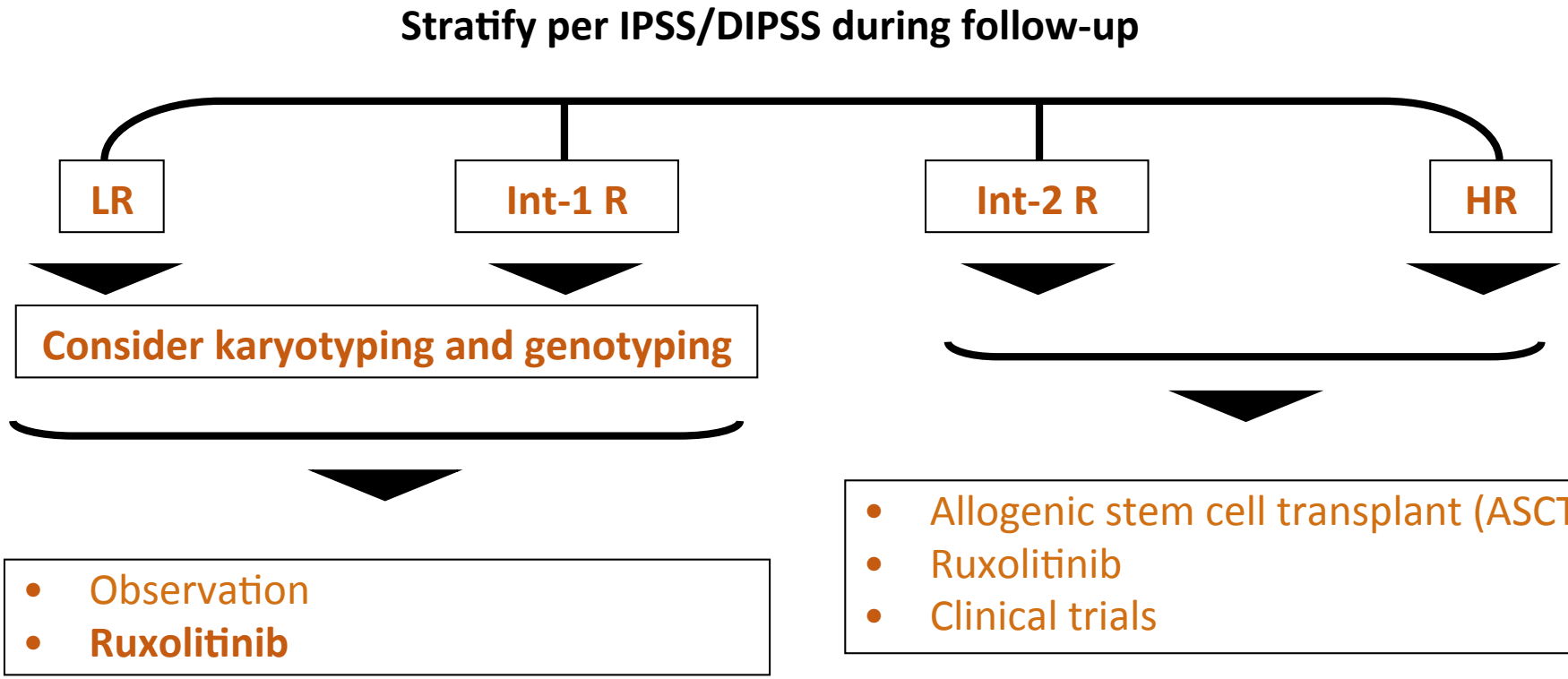
Clinical validity: test result correlates with a clinical endpoint (response to therapy, survival) – Usually established in a retrospective study.

Clinical utility: the use of the prognostic marker results in improved outcome for patients - Usually requires conduction of a prospective clinical trial.

Trial Design Hypothesis

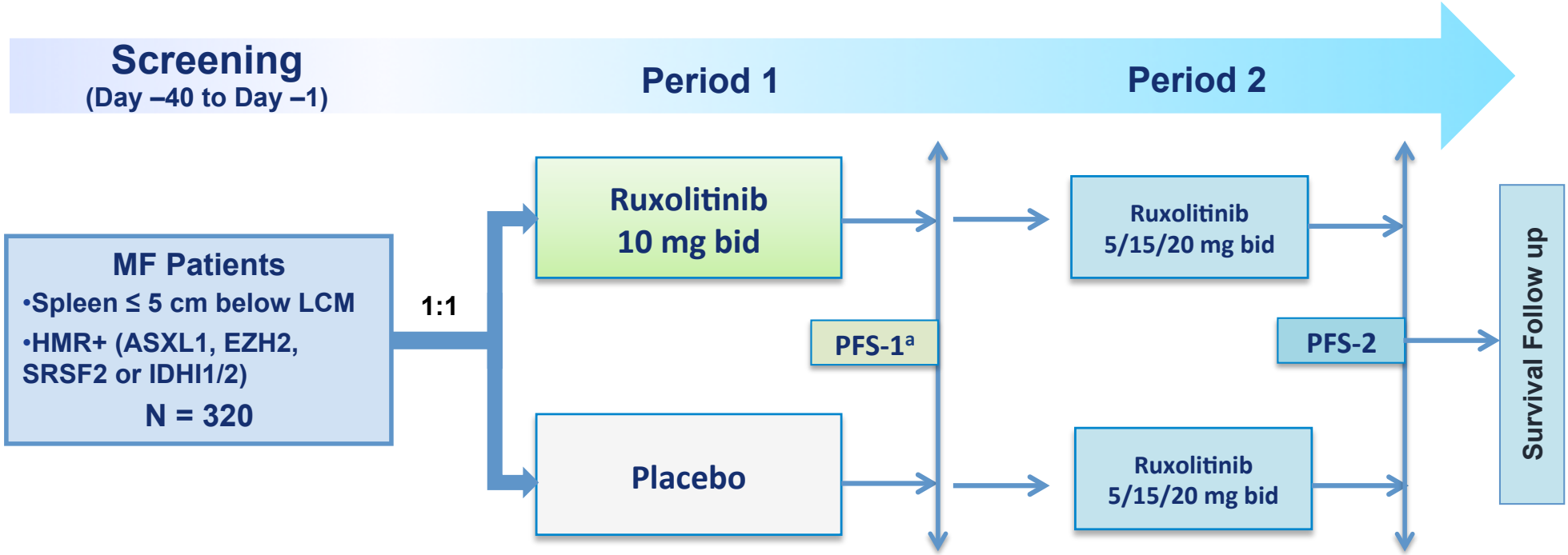


Personalized approach to MF: Ruxolitinib for early phase disease



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).

Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Confirmed MF diagnosis with a bone marrow fibrosis grade ≥ 1
- Patients with ≥ 1 mutation in 1 of the 5 HMR genes (*ASXL1*, *EZH2*, *SRSF2*, or *IDH1/2*), irrespective of JAK2 mutational status
- Patients with nonpalpable spleen or spleen palpable ≤ 5 cm from the left costal margin to the point of greatest splenic protrusion
- Myelofibrosis 7-item symptom scale (MF-7) score of ≤ 15, with each individual symptom score of ≤ 3
- Hb > 10 g/dL; PLT ≥ 75 × 10^9/L; ANC ≥ 1000/µL; WBC ≤ 15 × 10^9/L; peripheral blasts < 1%

Key Exclusion Criteria

- Prior treatment with ruxolitinib or other JAK inhibitor therapy
- Eligible for HSCT

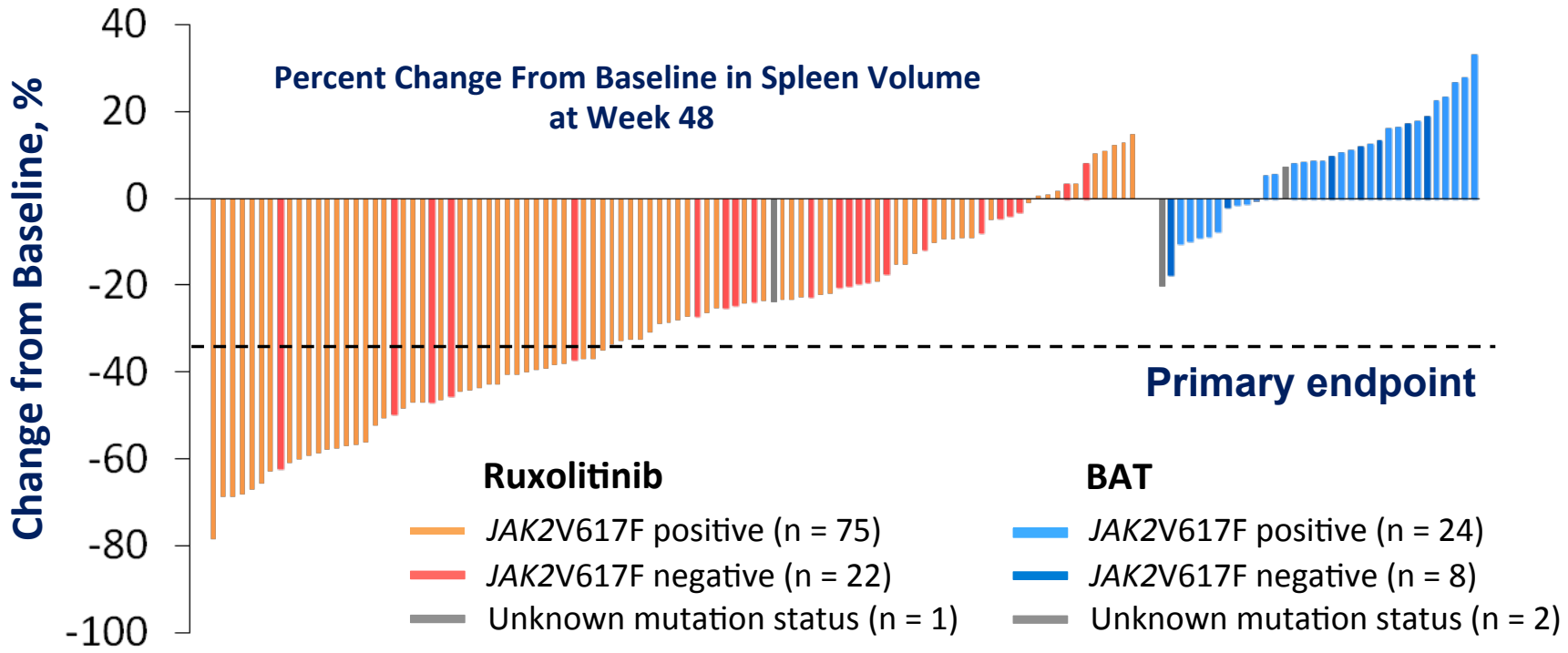
Passamonti F, et al. J Clin Oncol 34, 2016 (suppl; abstr TPS7080).

Predictive biomarkers

Predictive biomarkers identify patients who are likely or unlikely to benefit from a specific treatment

Example: Gene mutations for the selection of patients woth PMF who are likely to benefit from ruxolitinib

Efficacy of Ruxolitinib on Spleen Volume Reduction Is Regardless of *JAK2* V617F Mutation Status

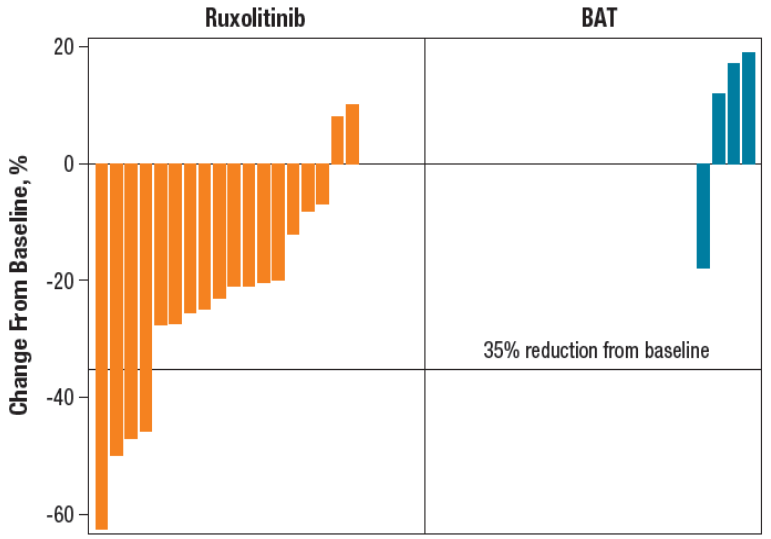


- At week 48, most patients receiving ruxolitinib experienced spleen volume reductions, including *JAK2*V617F-positive (88% [66/75]) and *JAK2*V617F-negative (91% [20/22]) patients

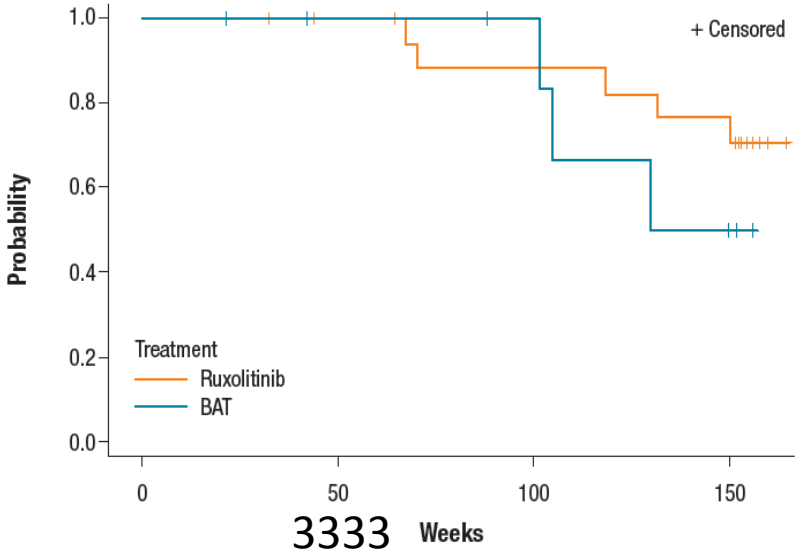
Harrison CN, et al. ASH 2011. Abstract 279.

Efficacy of Ruxolitinib in *CALR* Mutated Patients in COMFORT-II

- In *CALR*+ patients, a ≥35% reduction from baseline in spleen volume at week 48 was achieved by 20% in the ruxolitinib arm *vs* 0% in the BAT arm



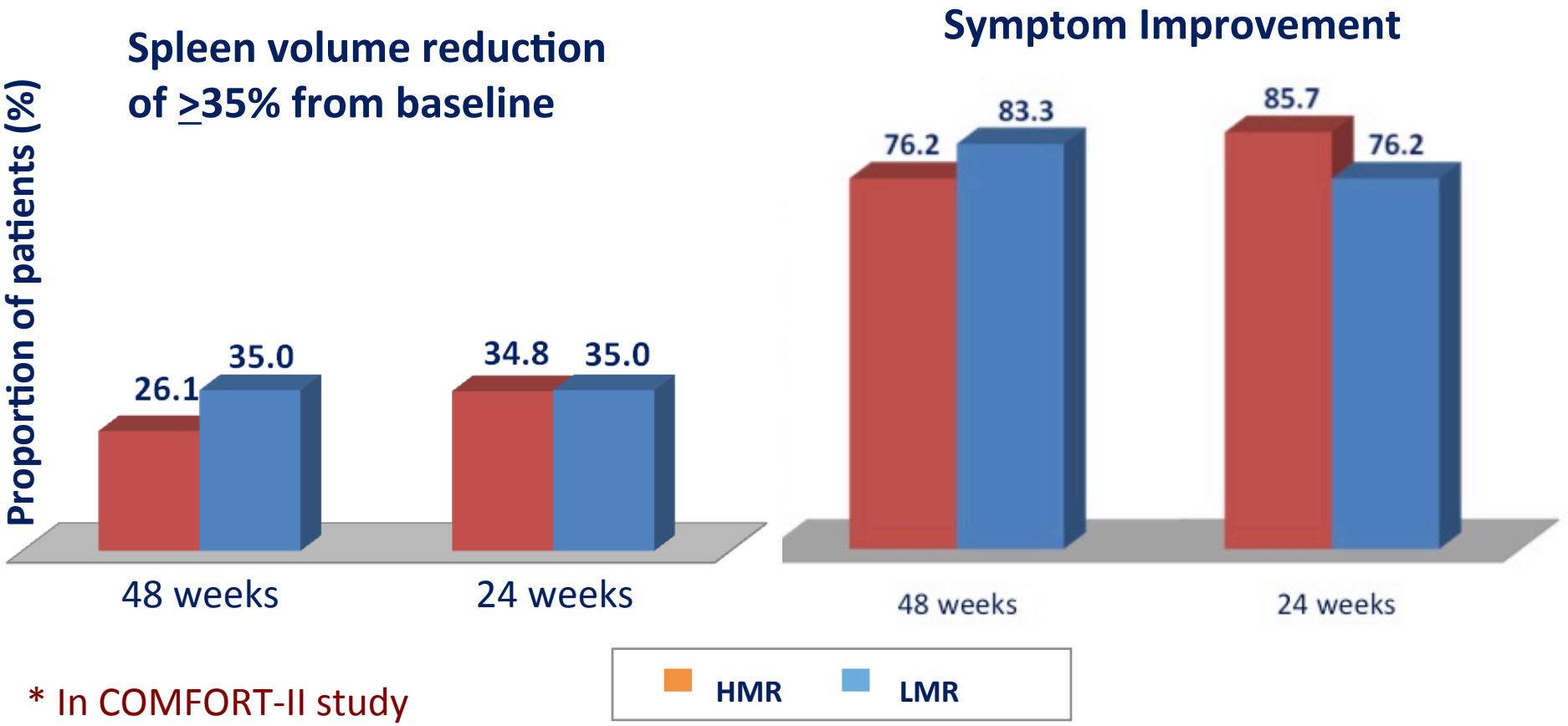
- The Kaplan-Meier–estimated probability of survival at 144 weeks was 0.76 in the ruxolitinib arm *vs* 0.50 in the BAT arm



Analysis conducted on 29/166 (17.5%) patients, with baseline mutation status assessments, who were *CALR* +

Guglielmelli P et al. ASH 2014. Abstract 1853

Spleen Response and Symptomatic Improvement by Molecular Status in Patients Receiving Ruxolitinib*



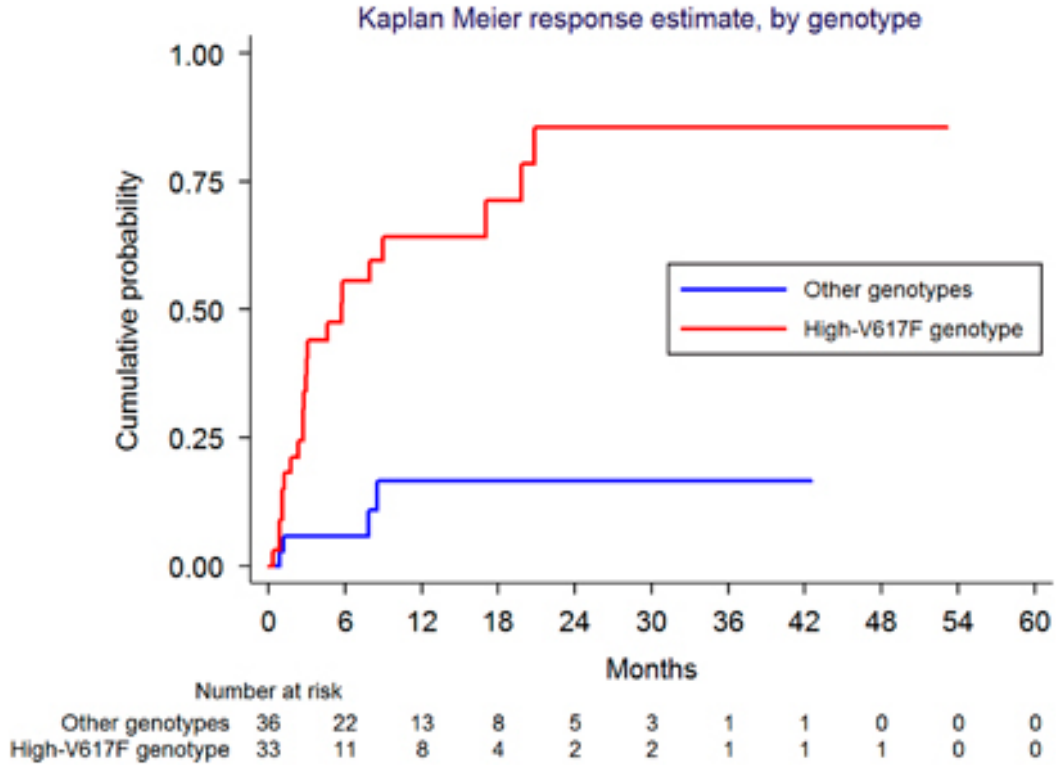
* In COMFORT-II study

HMR status did not increase the risk of developing anemia or thrombocytopenia under ruxolitinib treatment

Guglielmelli P, et al. Blood. 2014; 123:2157-60

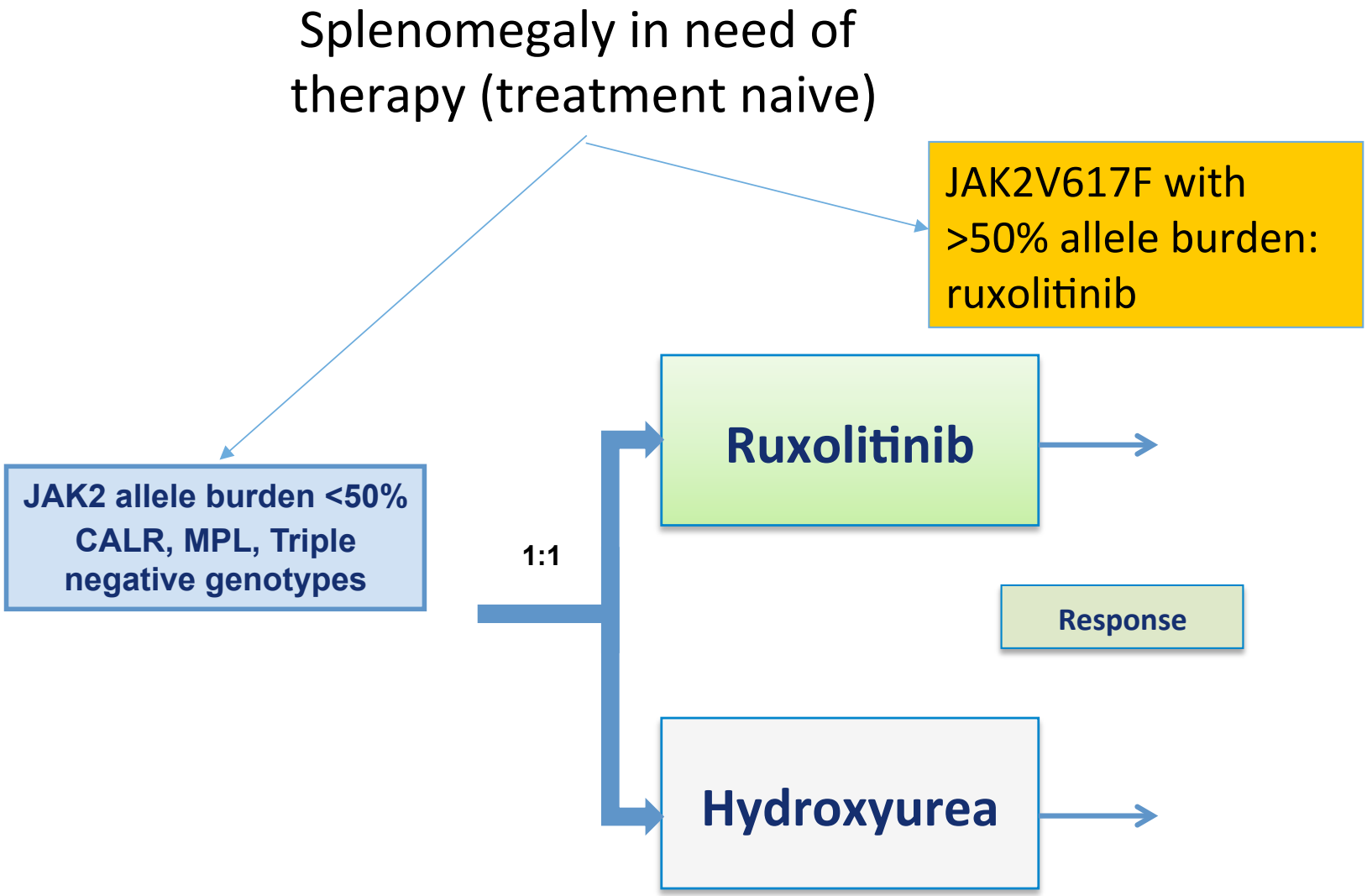
JAK2^{V617F} allele burden $\geqslant 50\%$ is associated with response to ruxolitinib in persons with MPN-associated myelofibrosis and splenomegaly requiring therapy

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



Barosi g, Leukemia 2016

Trial Design Hypothesis



Take home messages

Achieving the benefits of personalized hematology for patients and healthcare costs will require strong evaluation of the clinical utility and robustness of prognostic and predicitive biomarkers