Classical Ph-1neg myeloproliferative neoplasms: Ruxolitinib in myelofibrosis

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Diagnose MF and genotype *JAK2, CALR, MPL*

IPSS at diagnosis

LR | **Int-1 R** | **Int-2 R** | **HR**

Med OS **11.2 y** | Med OS **7.9 y** | Med OS **4 y** | Med OS **2.2 y**

LR over time: 85% alive at 20 y

Int-1 R over time: Med OS 14.2 y

DIPSS during f-up

Test additional mutations (*ASXL1* first) and assess karyotype to identify patients at higher risk, if younger and fit for stem cell transplant

Proceed with treatment strategy
- Observation
- Ruxolitinib
- Clinical trials
- Stem cell transplant

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Passamonti *et al*, COH 2016

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Passamonti *et al*, COH 2016

Ruxolitinib reduces splenomegaly

COMFORT-I (update at 3 yrs)

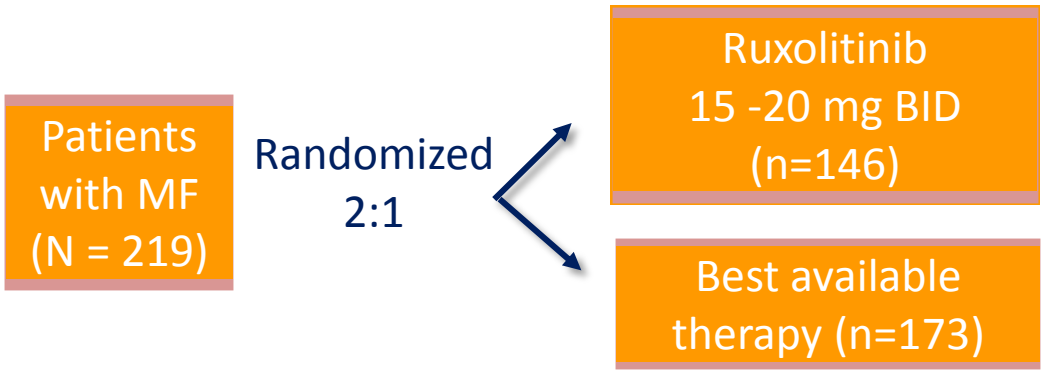
Primary Endpoint

- Number of subjects achieving ≥35% reduction in spleen volume from baseline to week 24

Secondary Endpoint

- Proportion of patients with ≥50% reduction in Total Symptom Score (mod. MFSAF v2.0)

COMFORT-II (update at 3.5 yrs)



Primary Endpoint

- Number of subjects achieving ≥35% reduction in spleen volume from baseline to week 48

Secondar/Exploratory endpoints

- Changes in functioning and symptoms

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

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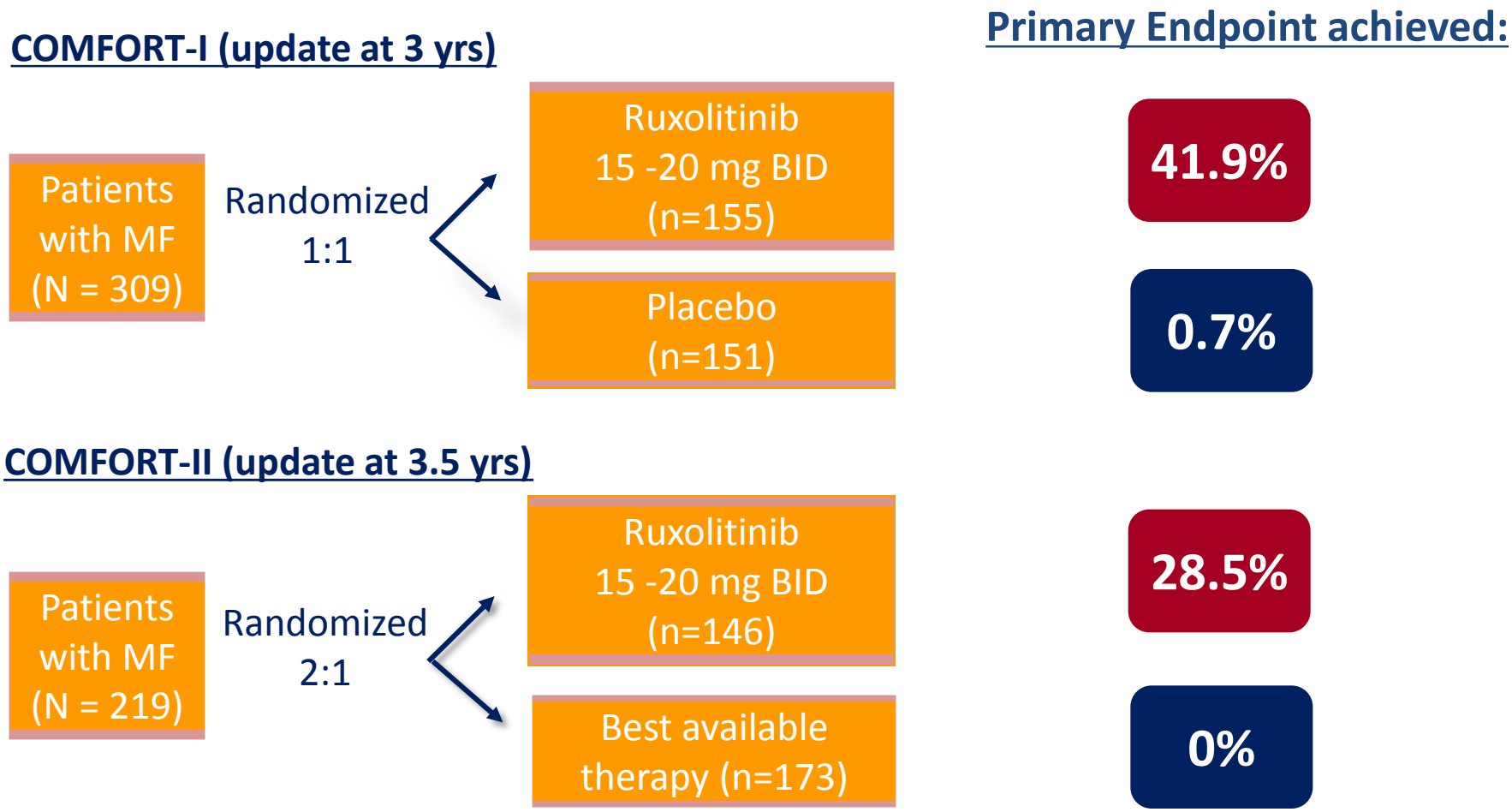
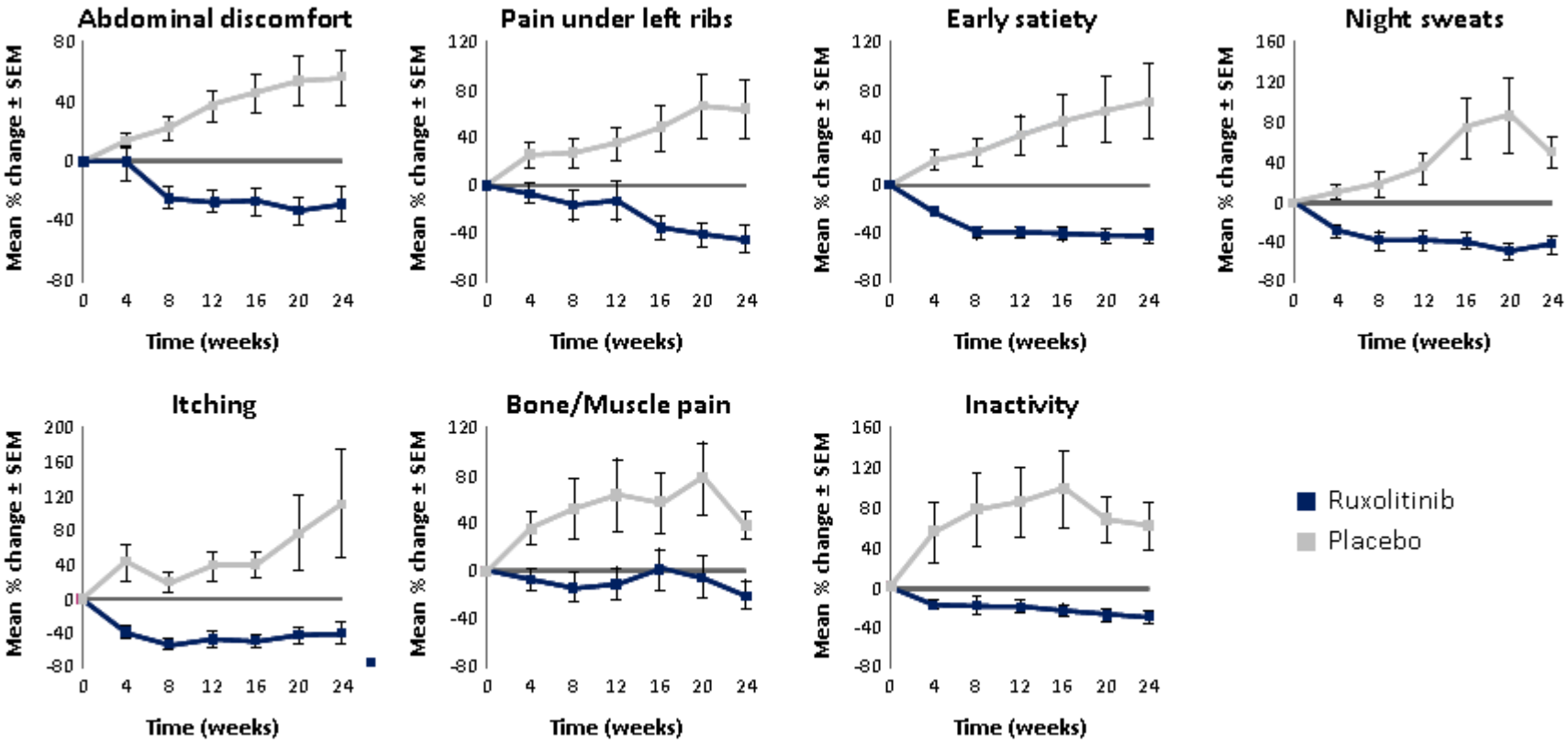


Verstovsek *et al*, N Engl J Med 2012;366(9):799-807; Harrison C *et al*, N Engl J Med 2012;366(9):787-98

Ruxolitinib controls symptomatology impacting on quality of life



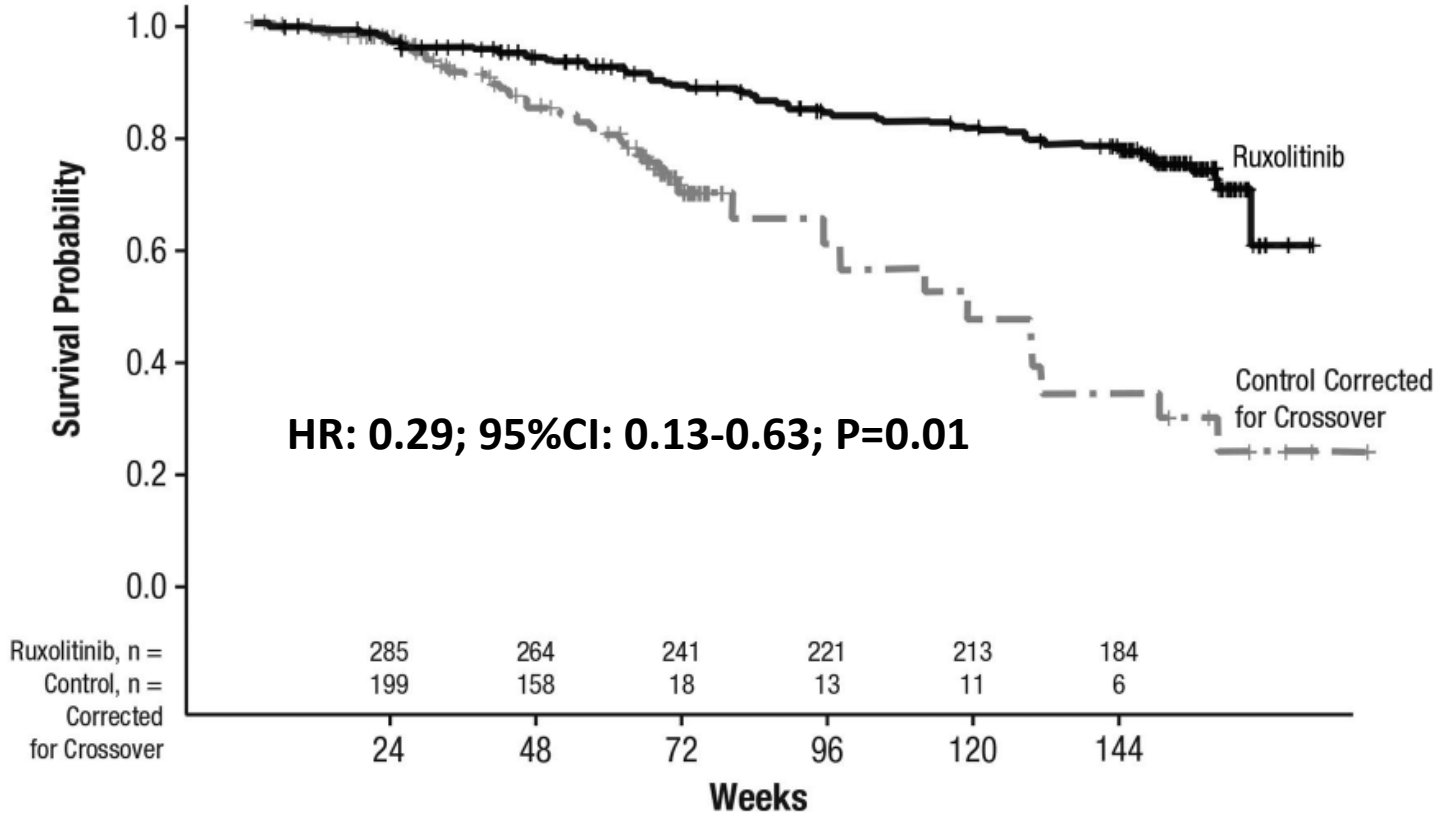
TSS: Total Symptoms Score; PGIC: Patient Global Impression of Change.

* As assessed by the Modified MFSAF v2.0

Mesa RA *et al*, J Clin Oncol. 2013; 31(10):1285-92

Ruxolitinib improves survival

(results from the pooled analysis with 301 RUX-treated and 227 PBO/BAT-treated)

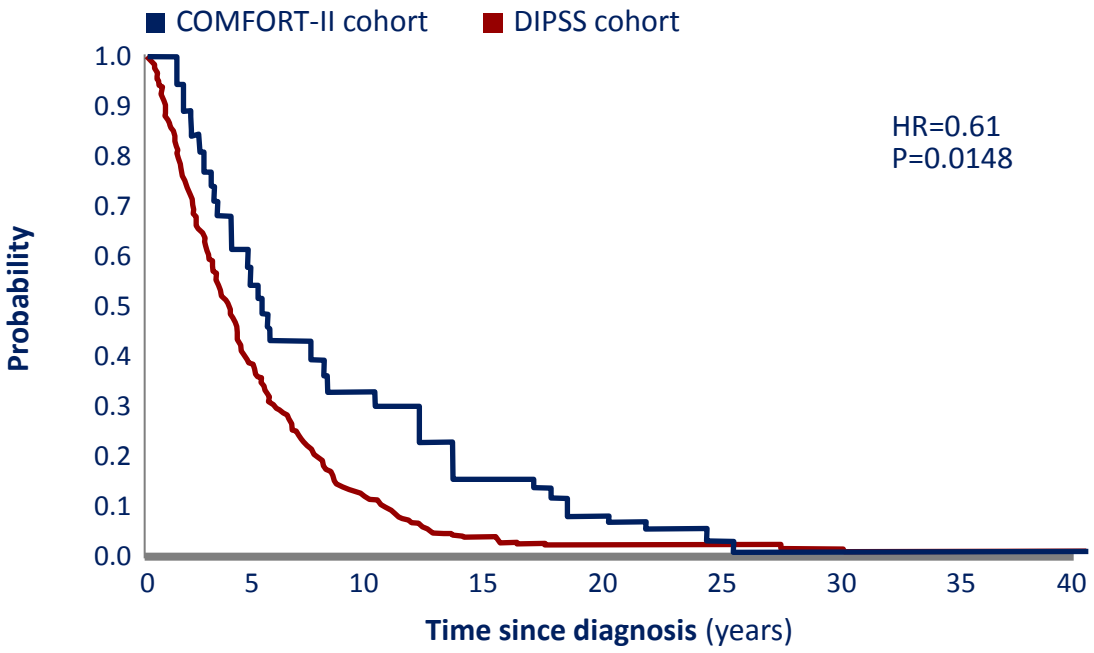


Curves were obtained after correcting for crossover from the control arms (rank-preserving structural failure time analysis)

Vannucchi et al.; Haematologica. 2015 Sep;100(9):1139-45.

Ruxolitinib modifies the natural history of MF

Survival estimate from diagnosis of PMF patients treated with ruxolitinib or BAT



The risk of death might be reduced by ~40% by introducing ruxolitinib in the treatment of PMF patients

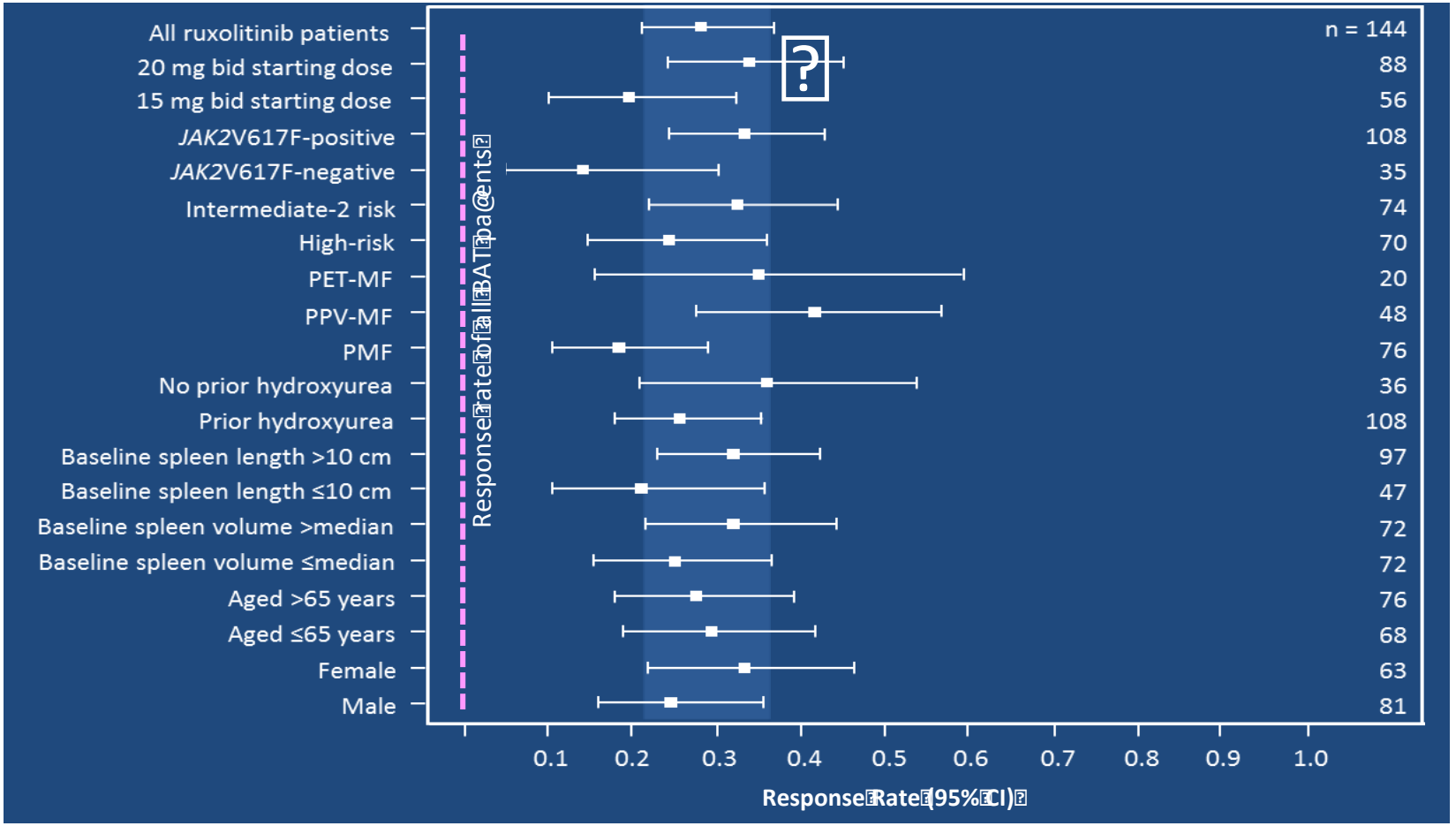
Survival estimate from diagnosis of PMF patients who become intermediate-2 and high-risk IPSS with a blast cell count below 10% at any time of their follow-up according to the COMFORT-II (n=100) and DIPSS (N=350) cohorts.

- The 8-year survival probability from initial diagnosis was 32.2% for COMFORT-II and 15.9% for DIPSS

Passamonti F, et al. Blood. 2014;123(12):1833-5.

Predictors of response:

COMFORT-II: proportion of Patients in Each Subgroup With ≥ 35% Reduction in Spleen Volume From Baseline at Week 48



Response rates were observed for ruxolitinib-treated patients in all subgroups and were higher than patients receiving BAT

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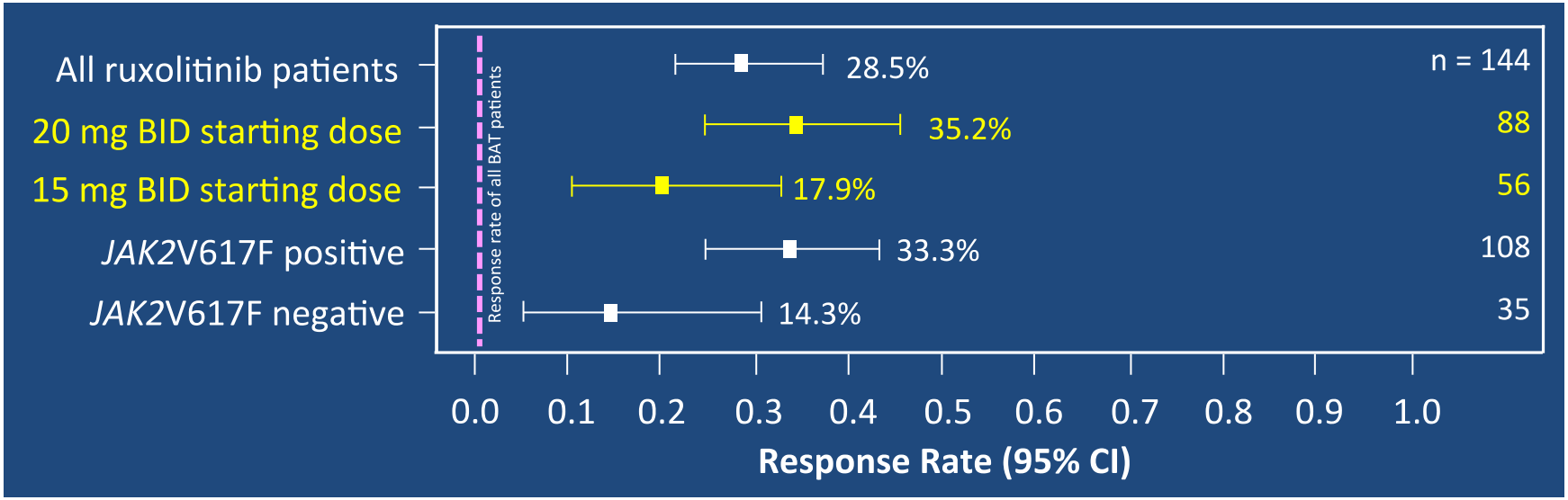


Positive trend (not stat. significant) in favor of :

- 20 mg BID vs. 15 mg BID,
- JAK2mut vs JAK2WT

Predictors of response:

Multivariable analysis of the COMFORT-II: proportion of Patients in Each Subgroup With ≥ 35% Reduction in Spleen Volume From Baseline at Week 48

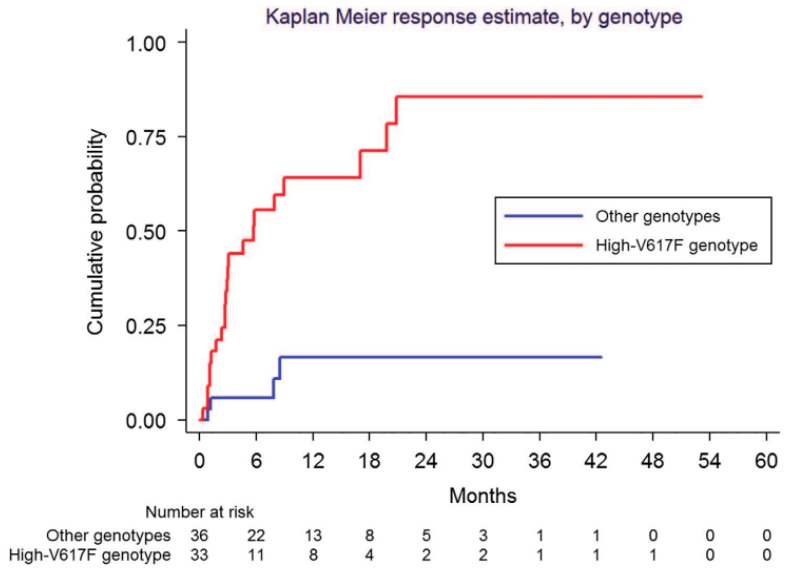
	Odds Ratio[a]	95% CI
Starting dose (15 vs 20 mg BID)	0.441	(0.184; 1.055)
Gender (female vs male)	1.646	(0.726; 3.732)
Age (≤ 65 vs > 65 years)	0.911	(0.389; 2.135)
Baseline MF type		
PMF vs PET-MF	0.237	(0.063; 0.891)
Previous hydroxyurea use (no vs yes)	2.521	(0.964; 6.595)
Baseline palpable spleen length (≤ 10 vs > 10 cm)	0.419	(0.166; 1.058)
JAK2 V617F mutation (negative vs positive)	0.383	(0.112; 1.310)
IWG risk category (high vs intermediate-2 risk)	0.640	(0.268; 1.531)

Multivariate analysis suggests:

- a higher response rate among patients with PET-MF compared with PMF

Predictors of response: potential role of *JAK2* allele burden

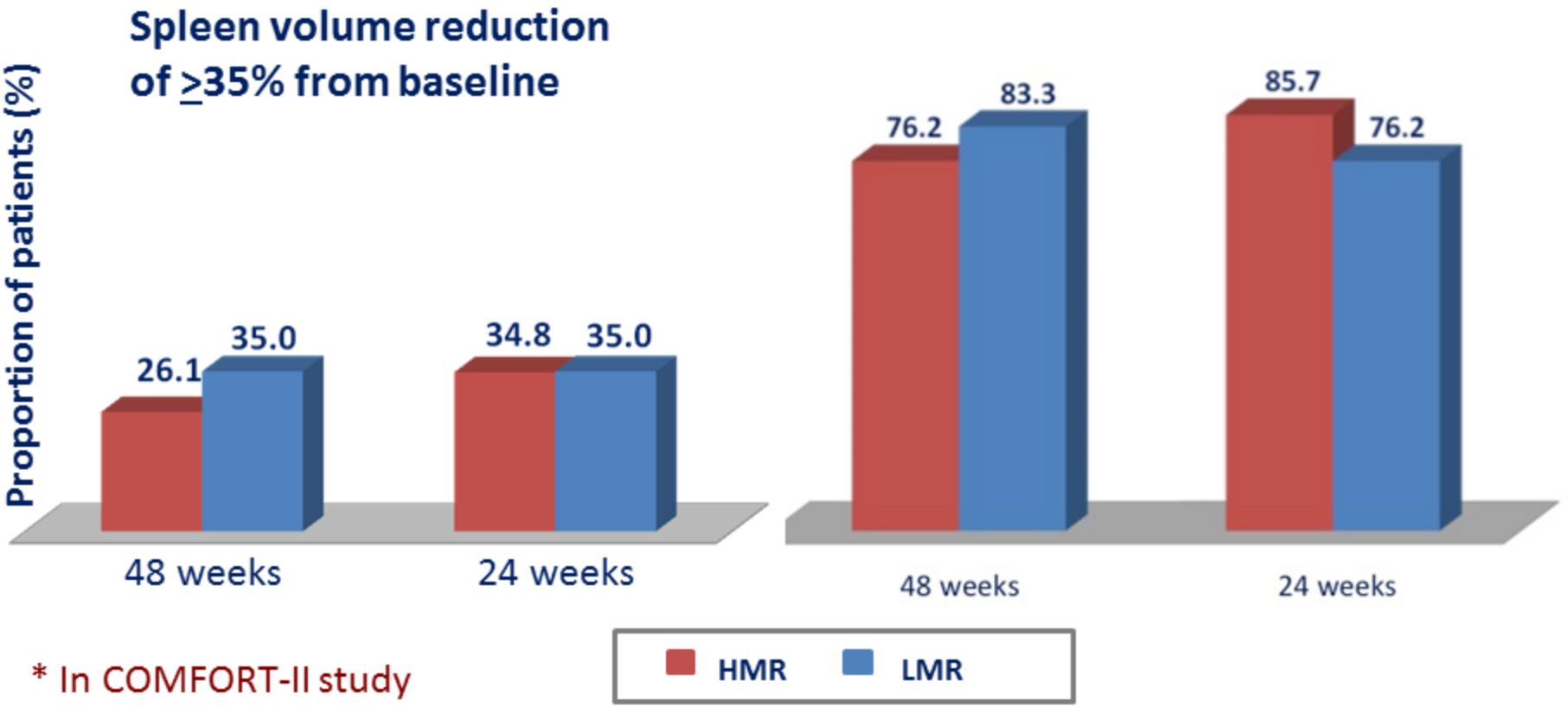
- 69 MF treated for progressive splenomegaly
- 83% with PMF
- 70% with >50% mutant alleles
- 71% were low-Int-1 MF by DIPSS prognostic score



- The probability of spleen response in patients with a JAK2V617F allele burden ⩾ 50% was 5.5-fold higher than subjects with JAK2V617F allele burden <50% or any other mutation

Barosi et al; Leukemia. 2016 Feb 29. doi: 10.1038/leu.2016.45.

Additional mutation-based risk does not predict response on spleen and symptoms

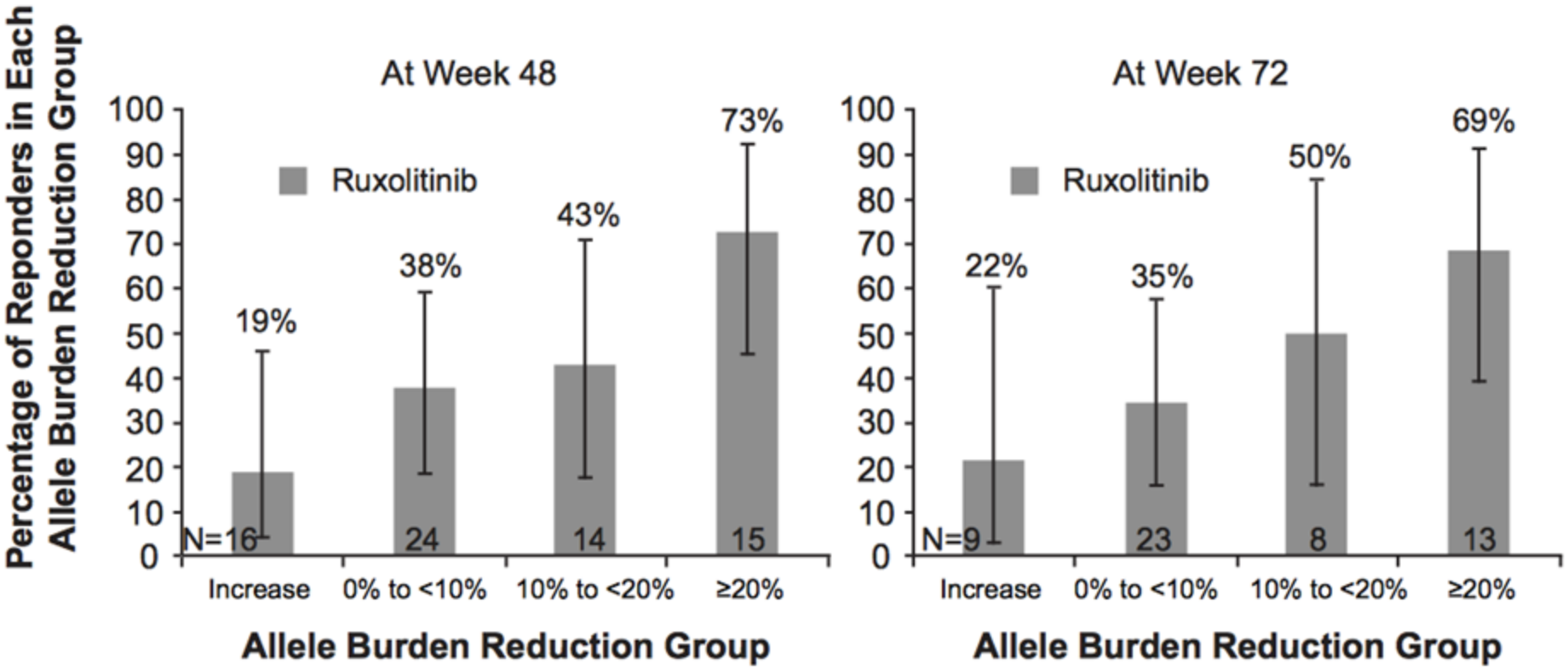


* In COMFORT-II study

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

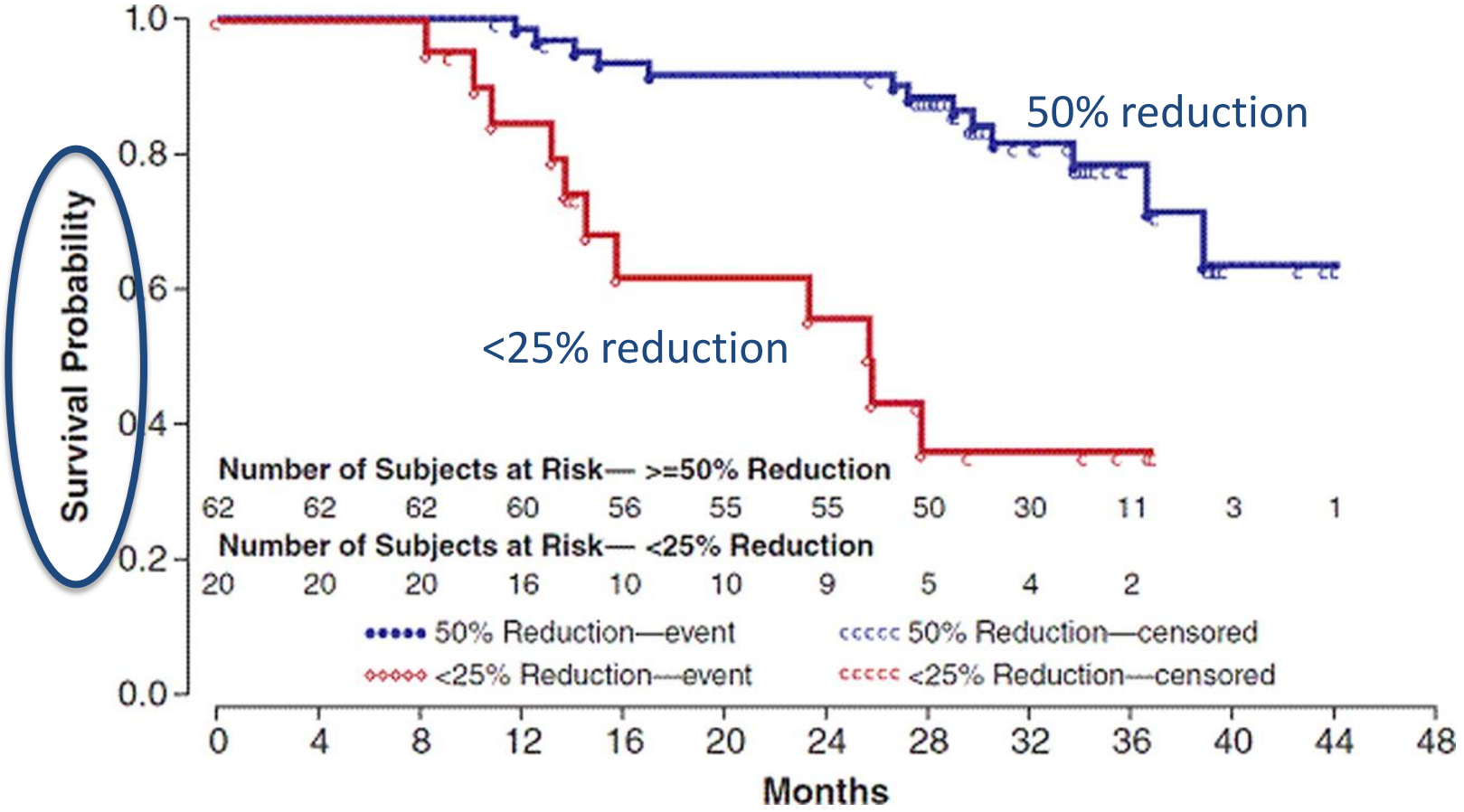
Guglielmelli P, et al. *Blood.* 2014; 123:2157-60

The more the reduction of JAK2 allele burden, the more the reduction of the splenomegaly



Cervantes F, et al. *Blood* 2013;122(25):4047-53

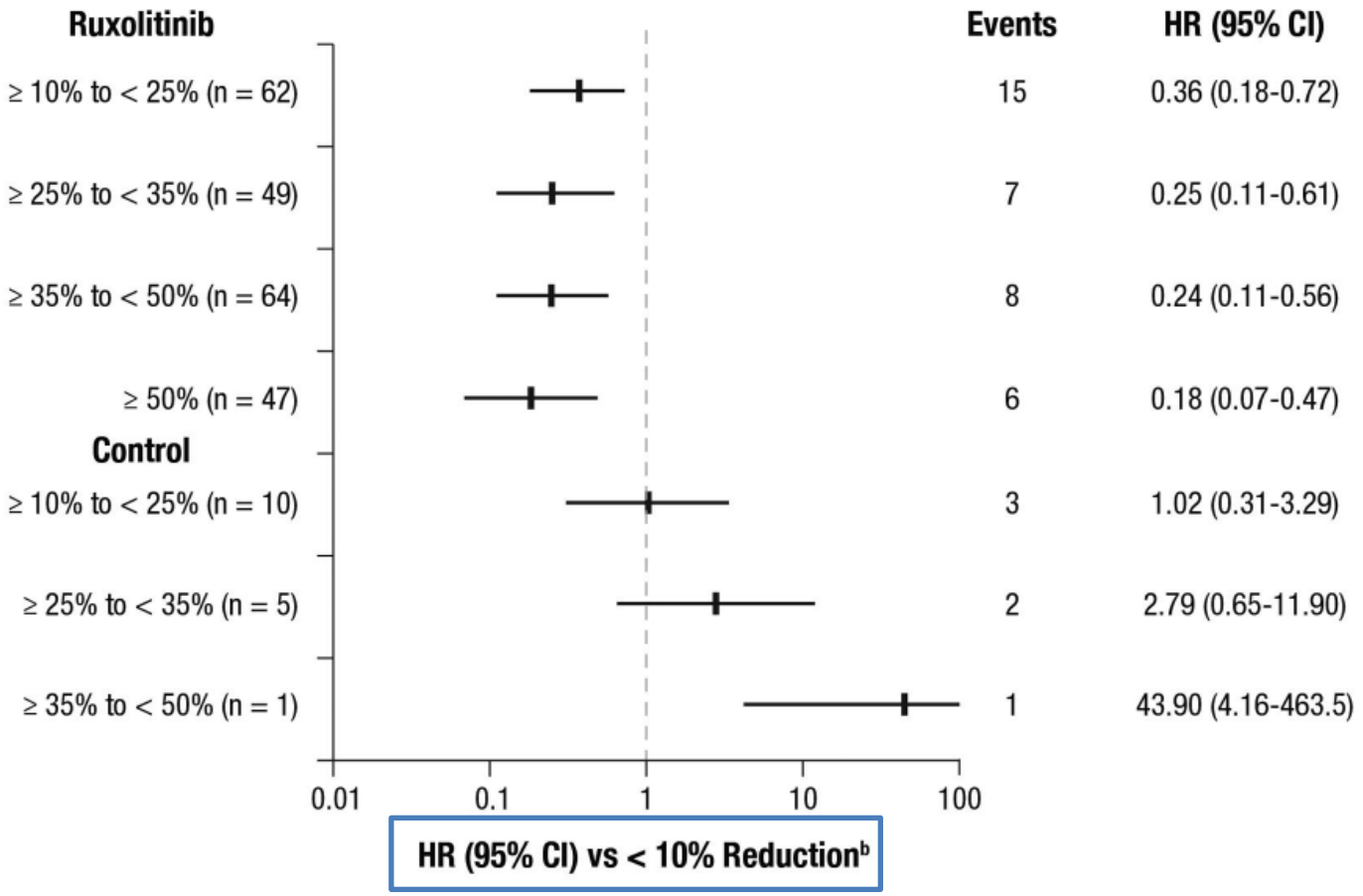
Spleen Reduction by Palpation on Ruxolitinib Implies Survival Advantage



Patients with a reduction >50% of spleen size had better survival than those with <25%

Verstovsek S et al. Blood 2012;120:1202-1209

Spleen volume reductions at week 24 impact on overall survival (pooled analysis)



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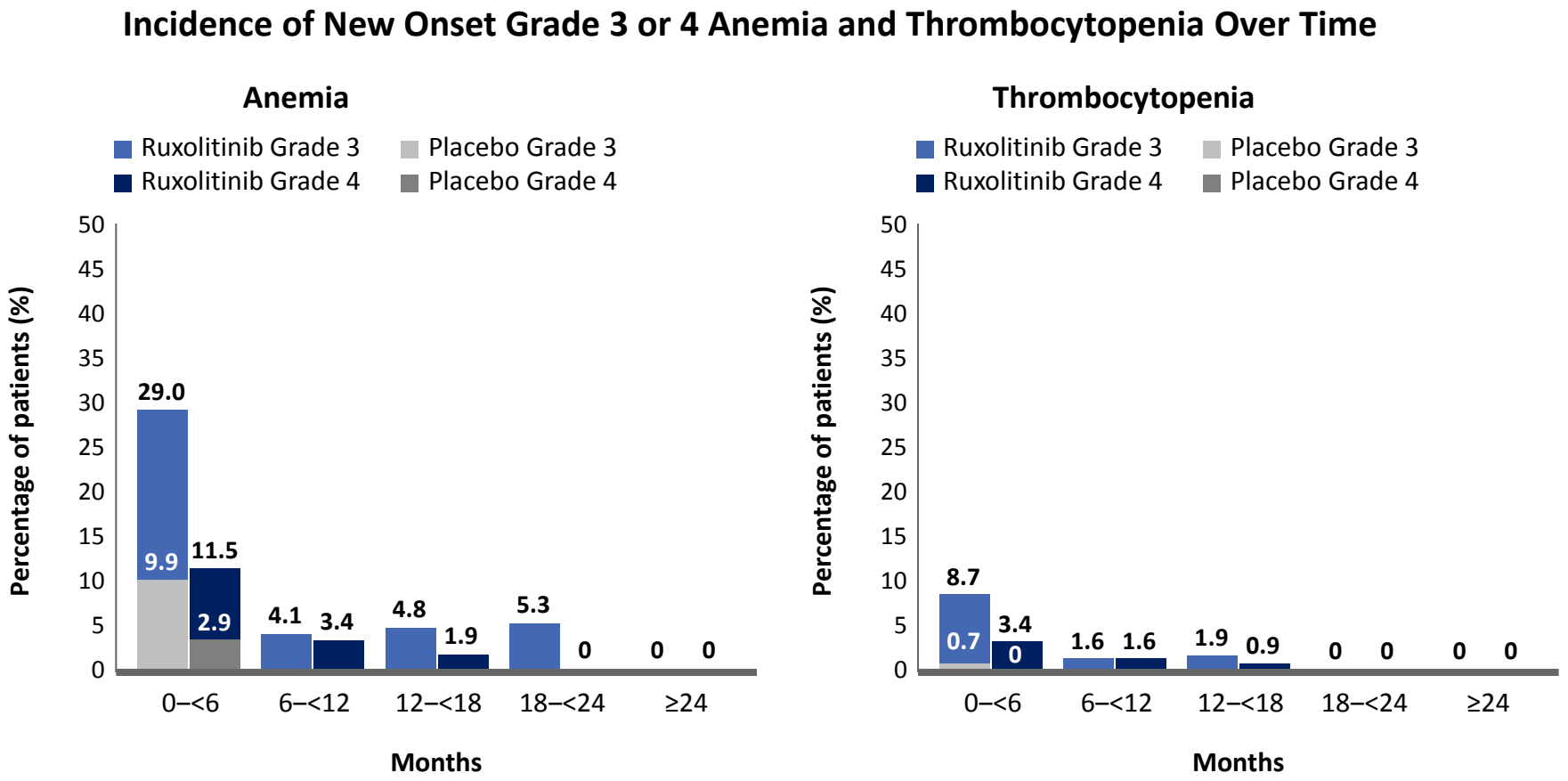
Anemia and thyrombocytopenia on ruxolitinib



All patients receiving placebo at the primary analysis crossed over or discontinued within 3 months of the primary analysis; therefore, data for patients receiving placebo is shown for 0–<6 months only.

The incidence of new-onset Grade 3 or 4 anemia and thrombocytopenia decreased over time to levels observed with placebo treatment (prior to crossover)

Verstovsek S, et al. Haematologica. 2013;98(12):1865-71.

Infections on ruxolitinib therapy

Ruxolitinib randomized 1 extension, %	Week						
	0-24 (n=146)	24-48 (n=134)	48-72 (n=116)	72-96 (n=101)	96-120 (n=93)	120-144 (n=81)	144-168 (n=72)
Infections	50.0	35.1	37.9	25.7	43.0	33.3	25.0
Bronchitis	3.4	6.7	8.6	3.0	10.8	4.9	4.2
Gastroenteritis	5.5	3.0	0.9	1.0	2.2	1.2	0
Nasopharyngitis	13.7	5.2	7.8	4.0	10.8	3.7	4.2
Urinary tract infection	4.8	2.2	5.2	4.0	5.4	3.7	2.8

Cervantes F, et al. Blood. 2013 122: 4047-4053

Ruxolitinib at 5 years follow-up (COMFORT-2): efficacy

- 53% of RUX achieved a ≥ 35% reduction in spleen volume from baseline at any time with a median duration of response of 3.2 years.
- One-third of evaluable *JAK2* V617F-positive pts had a >20% reduction in allele burden at 3.2 years.
- 16% improved fibrosis; 32% had stable fibrosis, 18% had a worsening at their last assessment.

Harrison et al; Blood 2015 126:59; published ahead of print December 4, 2015

Ruxolitinib at 5 years follow-up (COMFORT-2): safety

- AEs: thrombocytopenia (52%), anemia (49%), diarrhea (35%), and peripheral edema (33%);
- AEs grade 3-4: anemia (22%), thrombocytopenia (15%), pneumonia (6%), general physical health deterioration (4%), and dyspnea (4%).
- 8 pts (5.5%) and 5 pts (6.8%) developed leukemia in the RUX and BAT arms, respectively.

Harrison et al; Blood 2015 126:59; published ahead of print December 4, 2015

Ruxolitinib at 5 years follow-up (COMFORT-2): survival

- Overall, 59 (40.4%) and 35 (47.9%) deaths were reported in the RUX and BAT arms, respectively.
- Median OS was not reached in the RUX arm and was 4.1 years in the BAT arm.
- There was a 33% reduction in risk of death with RUX compared with BAT (HR, 0.67; 95% CI, 0.44-1.02; *P* = .06).

Harrison et al; Blood 2015 126:59; published ahead of print December 4, 2015

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IPSS at diagnosis

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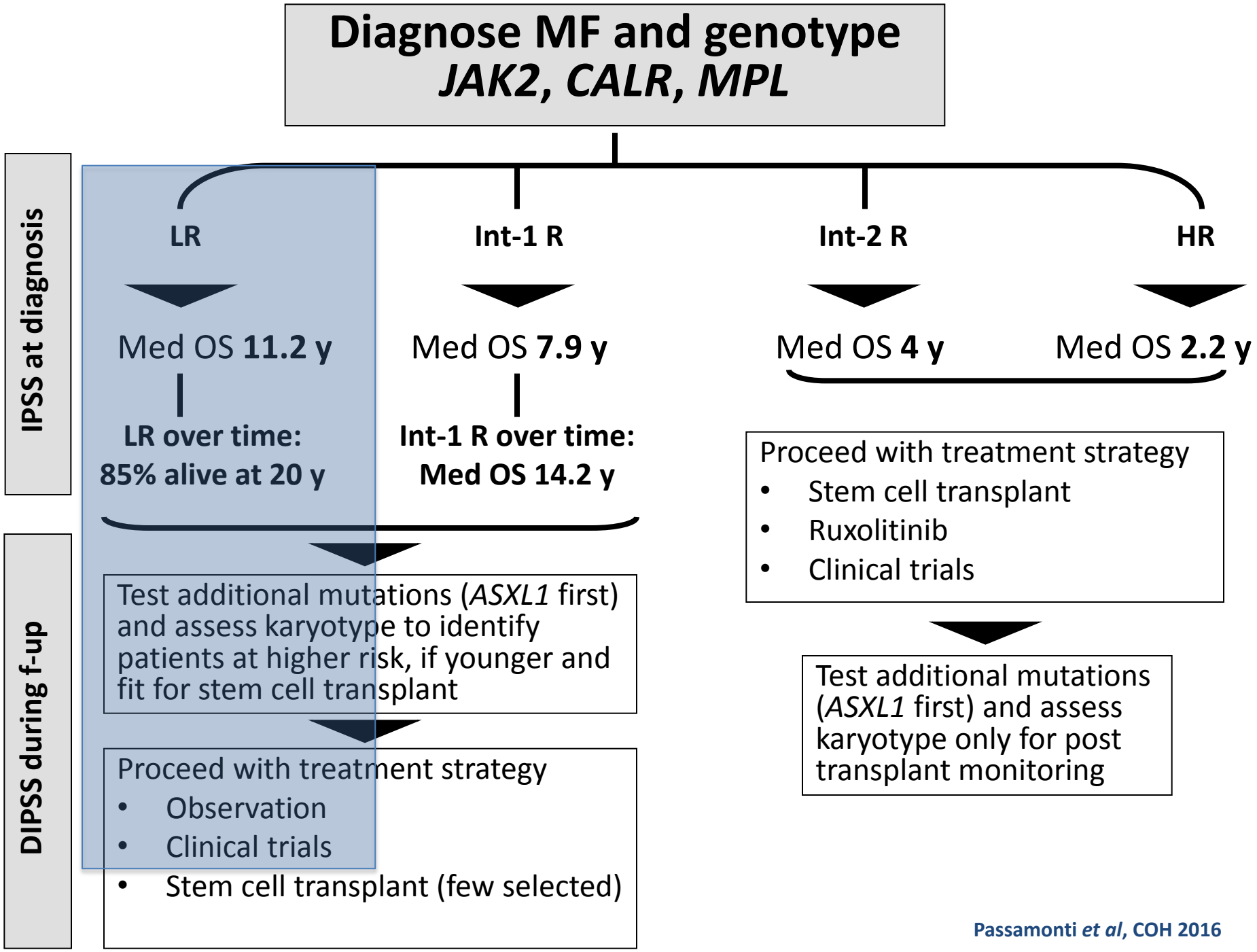
Passamonti *et al*, COH 2016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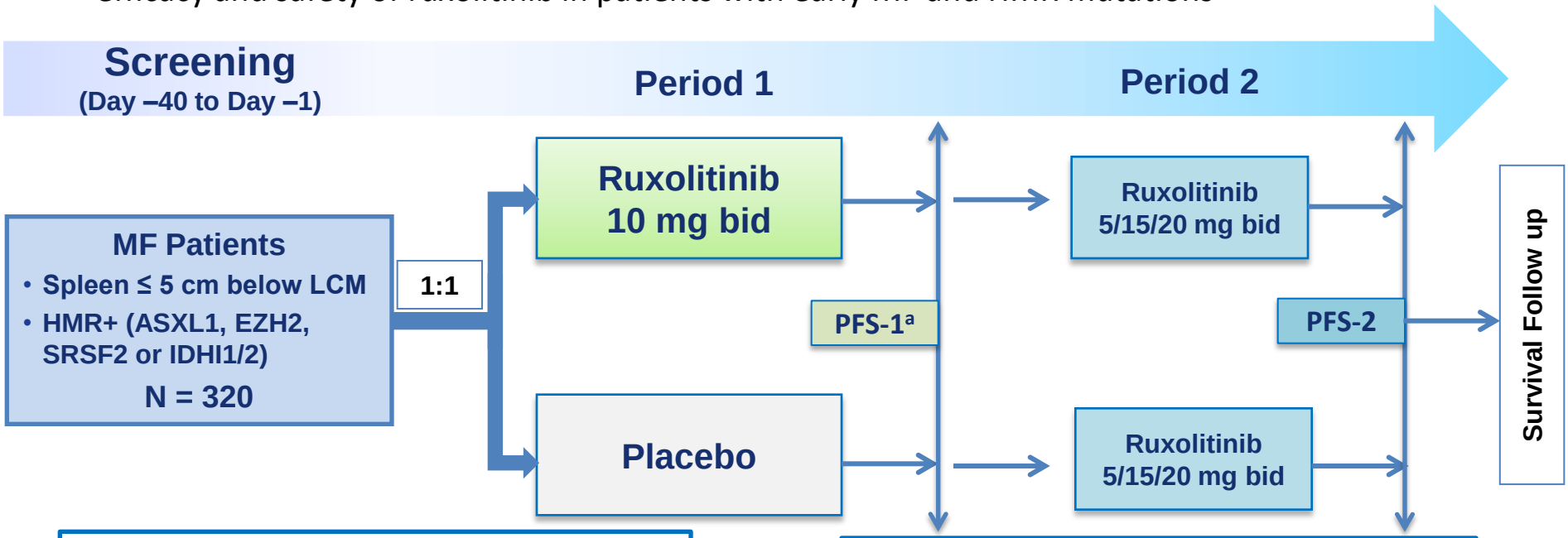
• Observation
• Clinical trials
• Stem cell transplant (few selected)
Passamonti et al, COH 2016

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

Conclusions

- Ruxolitinib is the treatment of choice in patients with PMF/SMF at intermediate-2 and high risk (IPSS/DIPSS) with spleen and symptoms
- Patients who obtain a significant spleen reduction improve survival
- For patients with low-risk disease but carrying a HMR profile, there is a new possibility of treatment: **The RE-Think trial**