Terapia della mielofibrosi

Francesco Passamonti
Università degli Studi dell'Insubria, Varese

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

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

Test additional mutations (*ASXL1* first) and assess karyotype only for post transplant monitoring

Passamonti *et al*, COH 2016

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

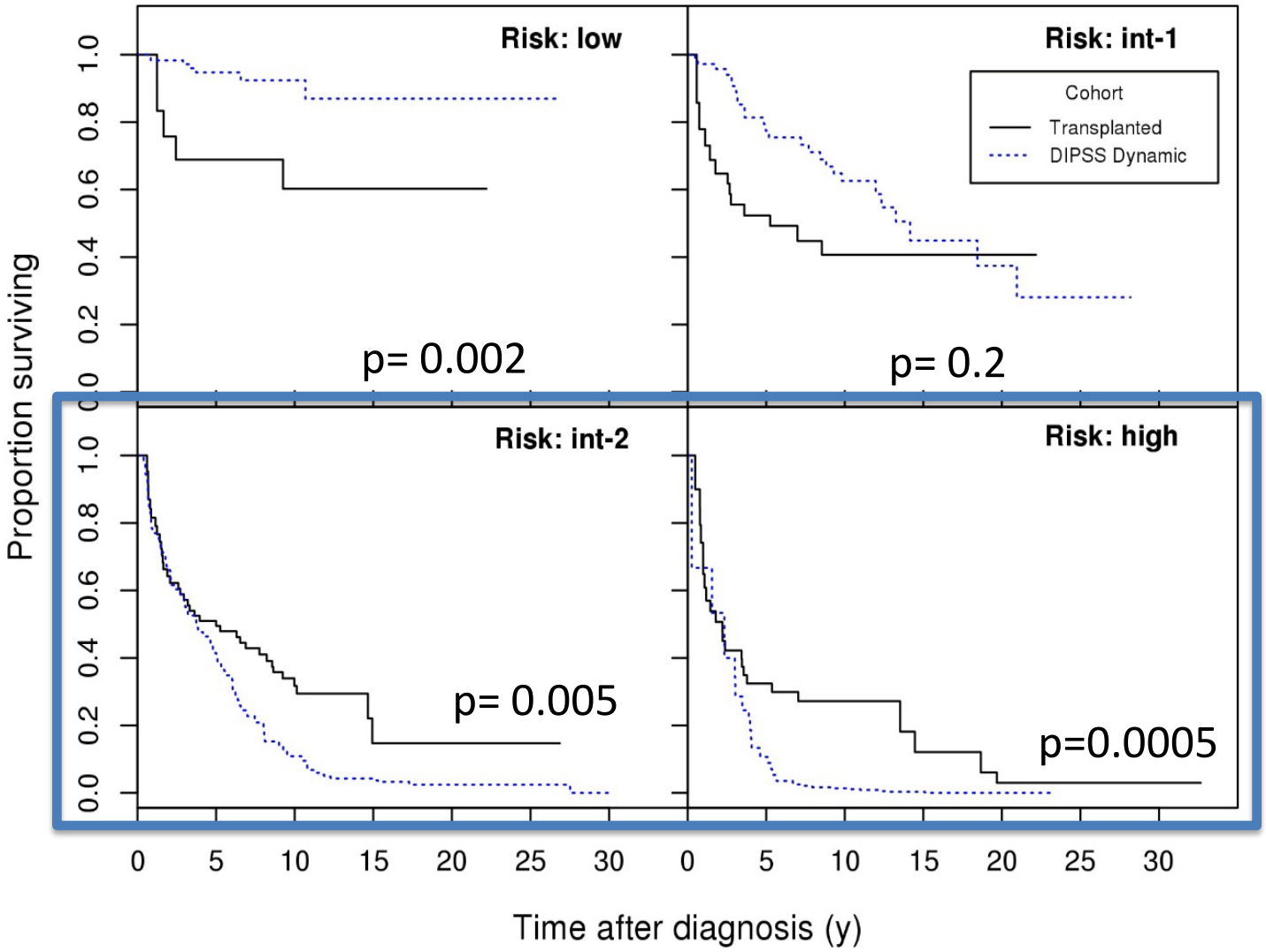
Proceed with treatment strategy
- Observation
- Ruxolitinib
- Clinical trials
- Stem cell transplant

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

Test additional mutations (*ASXL1* first) and assess karyotype only for post transplant monitoring

Passamonti *et al*, COH 2016

ASCT-based approach improves OS in higher risk DIPSS vs. conventional approaches



Kröger N, Giorgino T, Scott BL, Ditschkowski M, Alchalby H, Cervantes F, Vannucchi A, Cazzola M, Morra E, Zabelina T, Maffioli M, Pereira A, Beelen D, Deeg HJ, Passamonti F. Blood. 2015 Mar 17. pii: blood-2014-10-608315

What are the risk factors for NRM?

- Advanced age
- Thrombocytopenia
- Anemia
- RBC transfusion need
- Higher Dupriez/DIPSS score
- Grade III fibrosis
- Disease duration
- Transplantation time
- CMV status
- Unrelated/mismatched donor
- GVHD occurrence

Patient-related

MF-related

Transplant-related

Lissandre et al., BMT 2011; Guardiola et al., Blood 1999; Steward et al., BMT 2010; Deeg et al., Blood 2003; Patriarca et al., Haematologica 2008; Scott et al., Blood 2012

Ruxolitinib reduces splenomegaly and the greater the reduction of the spleen the longer the survival

COMFORT-I (update at 3 yrs)

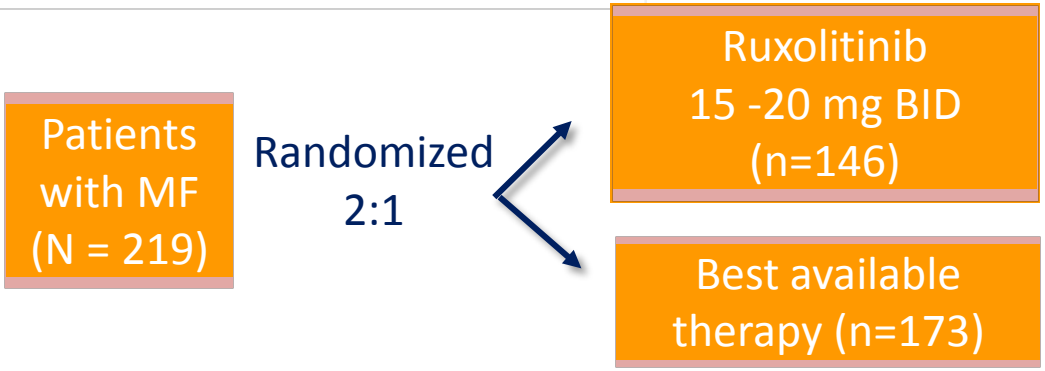
Primary Endpoint

- 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

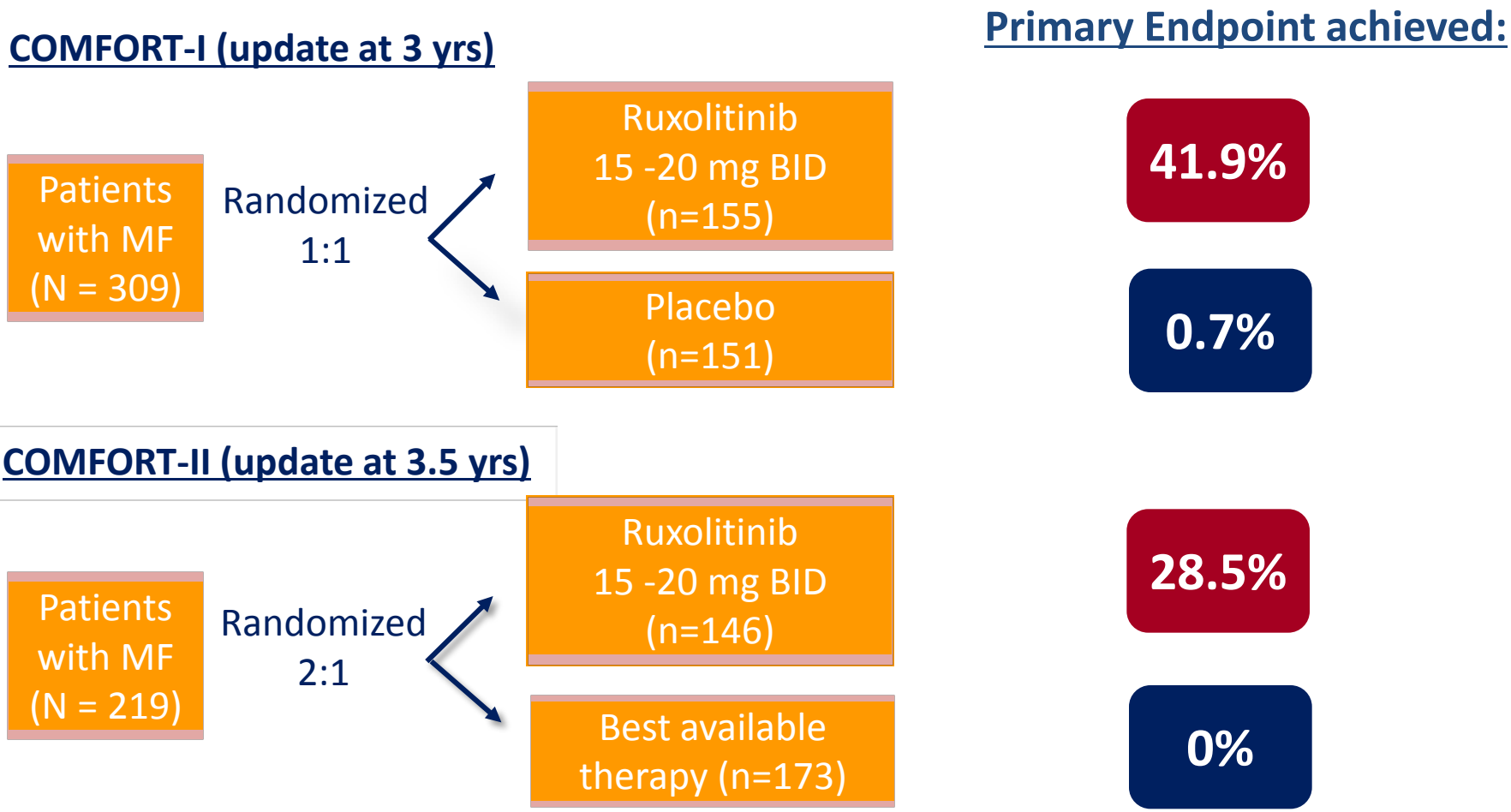
- Number of subjects achieving ≥35% reduction in spleen volume from baseline to week 48

Secondar/Exploratory endpoints

- Changes in functioning and symptoms

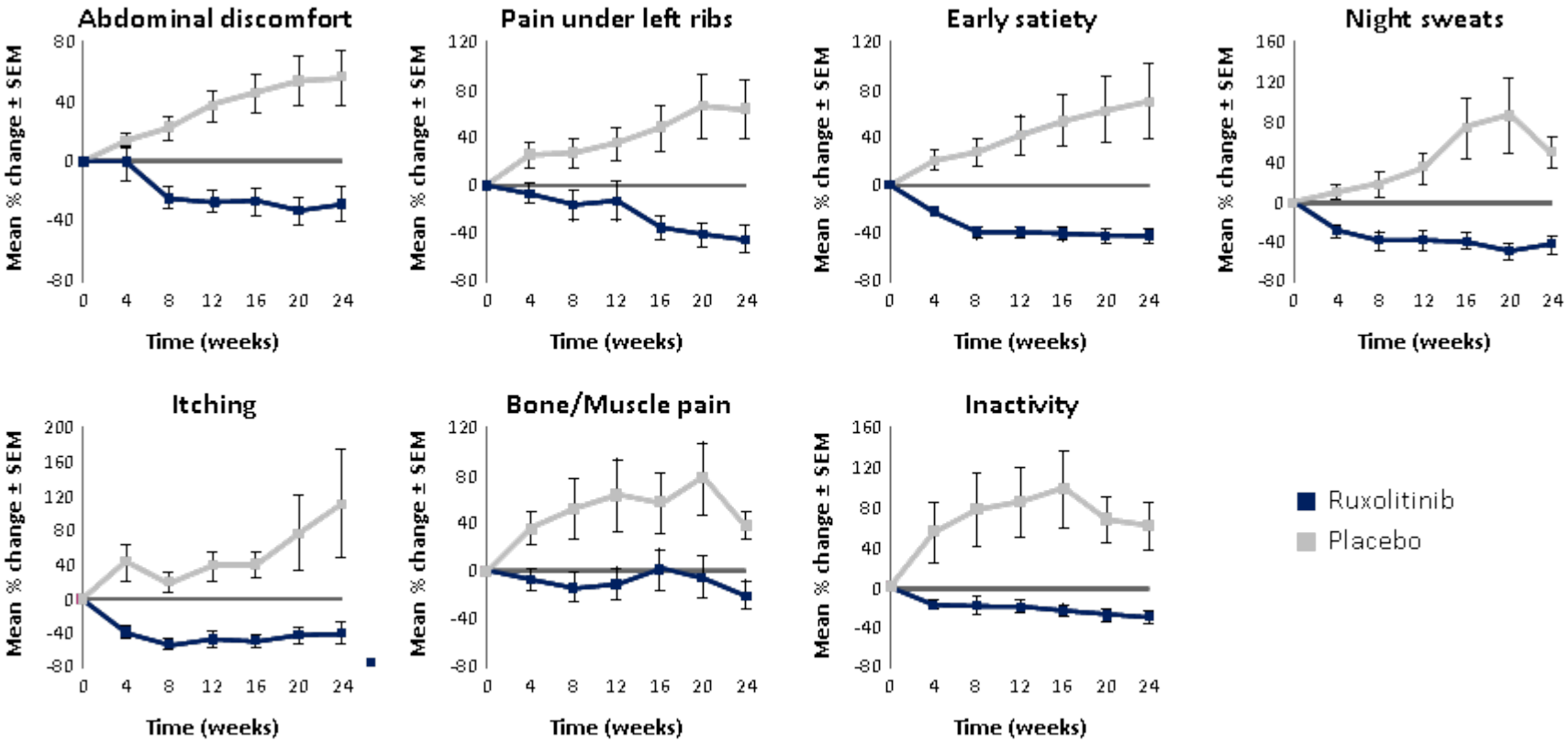
Verstovsek *et al*, N Engl J Med 2012;366(9):799-807; Harrison C *et al*, N Engl J Med 2012;366(9):787-98

Ruxolitinib reduces splenomegaly and the greater the reduction of the spleen the longer the survival



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



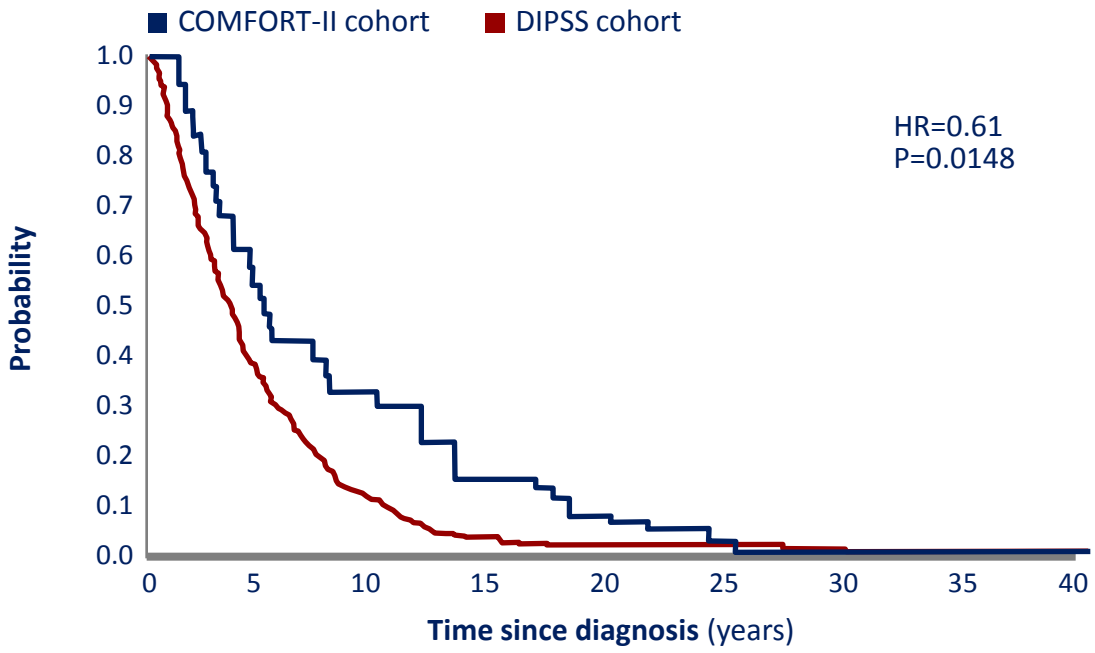
TSS: Total Symptoms Score; PGIC: Patient Global Impression of Change.

* As assessed by the Modified MFSAF v2.0

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

Ruxolitinib modifies the natural history of MF

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



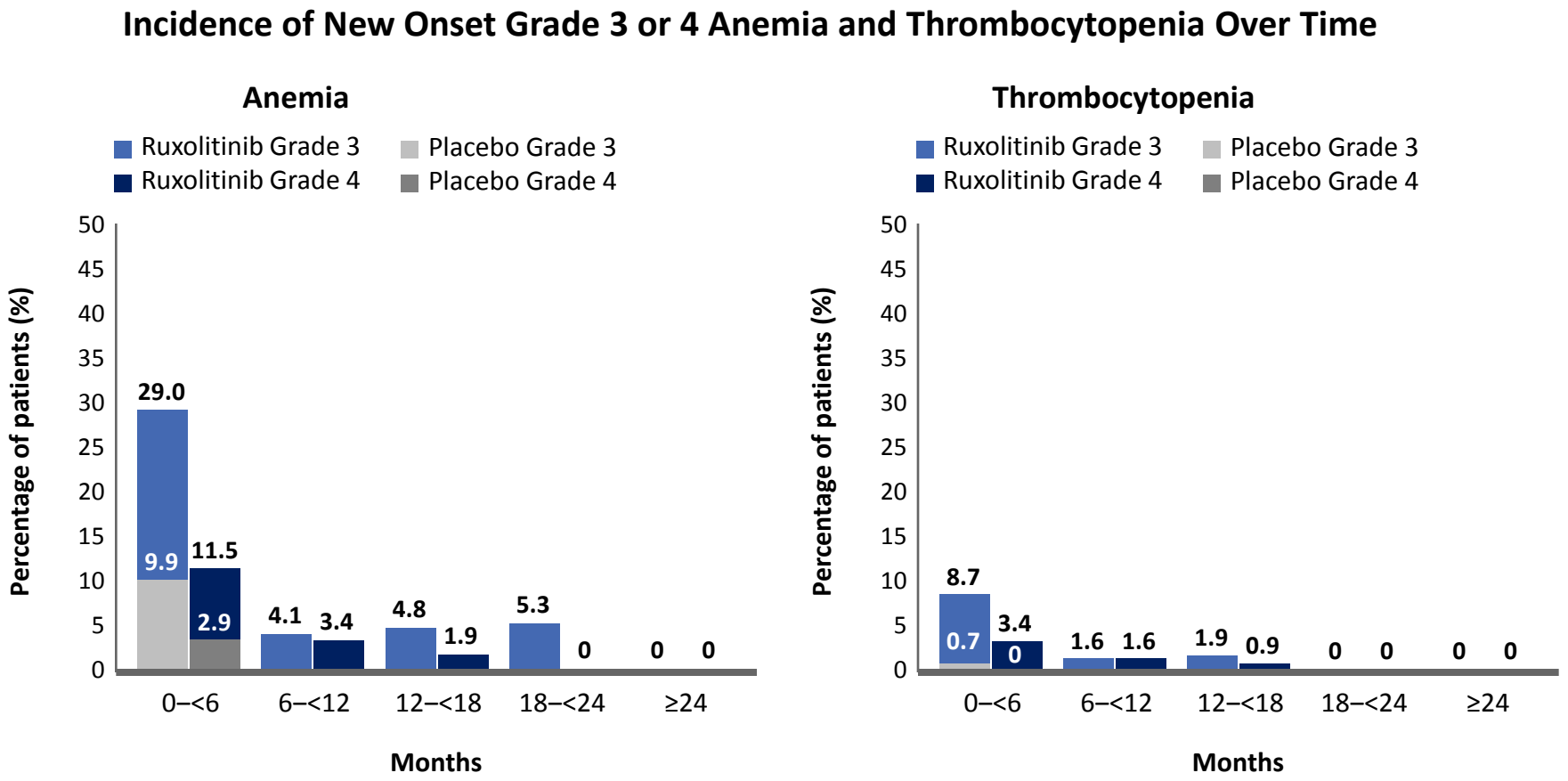
The risk of death might be reduced by ~40% by introducing ruxolitinib in the treatment of PMF patients

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.

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): 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.

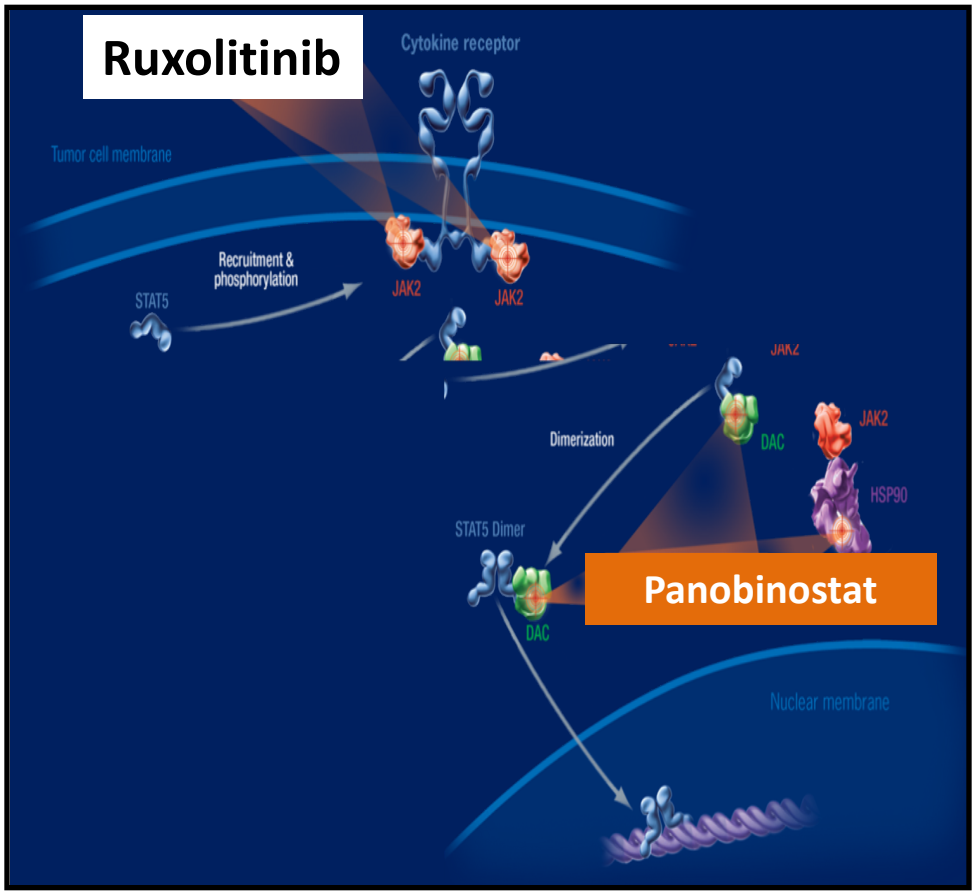
Harrison et al; Blood 2015 126:59; published ahead of print December 4, 2015

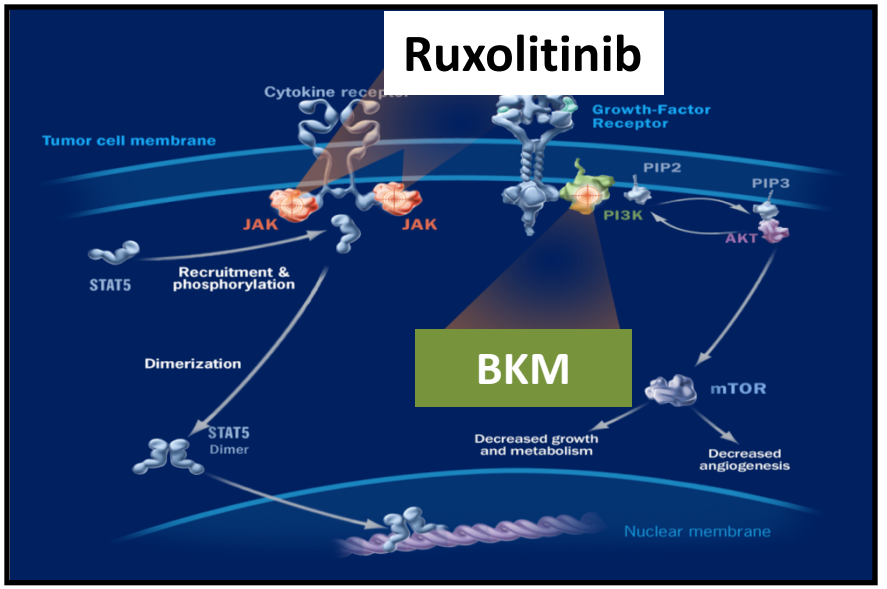
Ruxolitinib at 5 years follow-up: How many patients continue treatment?

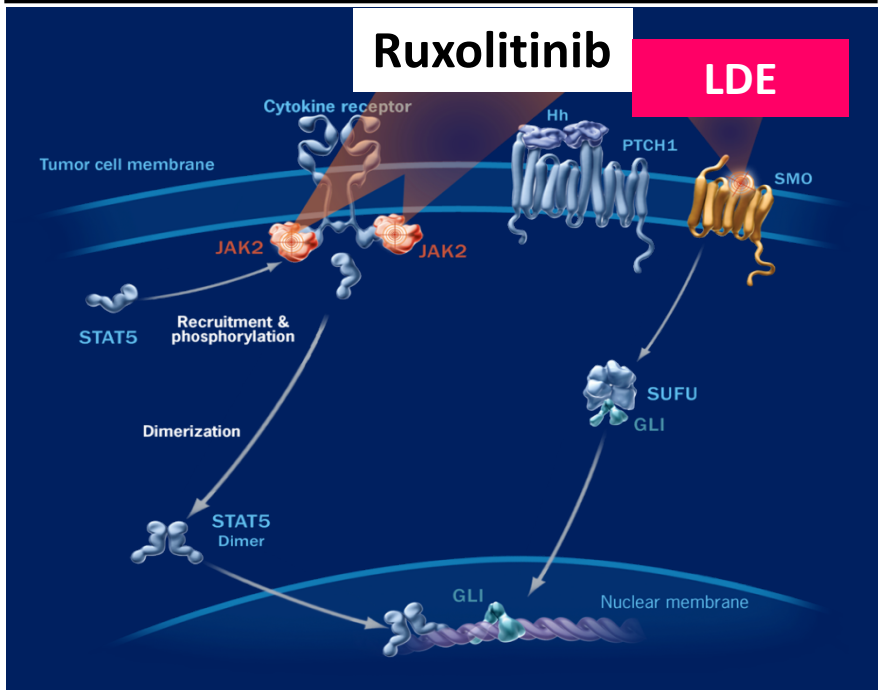
- 27% in the RUX arm and 24% who crossed over from BAT completed 5 years of on-study treatment
- Primary reasons for premature discontinuation before 5 years were adverse events (AEs; 24.0%) and disease progression (21.9%) in the RUX arm

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

Combination trials in MF







Efficacy and Safety of Combo trials

Spleen responses	RUX-PAN	RUX-LDE	RUX-BKM naive	RUX-BKM pretreat
W 24	56.5%	44.4%	45.5%	22.2%
Mean SVR at w 24	41.7	30.8	38.8%	26.5%

- Diarrhea: 68%, 18% Grade 3+
- Asthenia: 50%, 12% Grade 3+
- Fatigue: 29%, 6% Grade 3+

- CK increase: 37%, 18.5% Grade 3+
- Myalgia: 29.6%, 7.4% Grade 3+
- Diarrhea: 25.9%, 3.7% Grade 3+
- Fatique: 25.9%, 0 Grade 3+

- Anxiety: 15.9%, 4.8% Grade 3+
- Depression: 14,3%, 3.2% Grade 3+
- Hyperglycemia: 12,7%, 3.2% Grade 3+

Kiladjian; et al, ASH 2014, updated at ASH 2015
Durrant; et al, ASH 2014, updated at ASH 2015
Gupta et al, ASH 2014, updated at ASH 2015

Phase 3 Trials With Pacritinib

PERSIST-1

Eligibility Criteria

Primary or Secondary MF (Int 1 or higher)

No prior treatment with JAK2 inhibitors

Stratified for platelet counts of 100,000/µL

2:1 Randomization*
n = ~320

- **Pacritinib**
- **Best Available Therapy (BAT) excluding ruxolitinib**

Primary Endpoint

% of patients achieving 35% reduction in spleen size from baseline to Week 24*

PERSIST-2

Eligibility Criteria

Patients with platelet counts ≤ 100,000/µL, **prior/current JAK2 therapy allowed**

1:1:1 Randomization[1]
n = 300

- **Pacritinib** *400 mg QD*
- **Pacritinib** *200 mg BID*
- **Best Available Therapy (BAT)[2]**

Co-Primary Endpoints

% of patients achieving ≥ 35% reduction in spleen volume from baseline to Week 24 (MRI/CT)

Patients achieving ≥ 50% reduction in total symptom score (TSS) from baseline to Week 24

[1] Cross-over from BAT allowed after progression or assessment of the primary endpoint

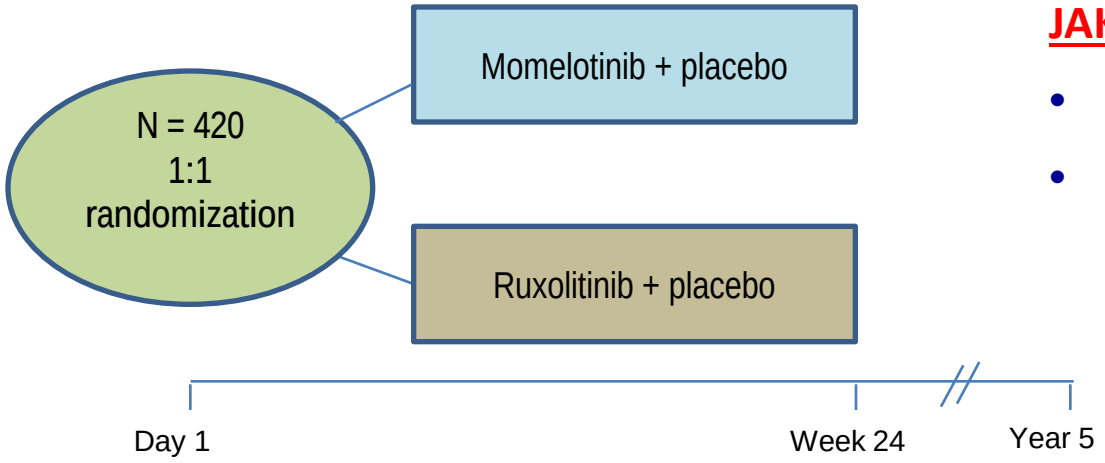
[2] BAT may include ruxolitinib at the approved dose for platelet count

Pacritinib sum

- Treatment with pacritinib resulted in consistent rates of SVR ≥35% and TSS reduction ≥50%, irrespective of baseline characteristics, including baseline platelet count
- Significant treatment effect ($p<0.05$) in highest-risk subset (baseline platelets <50,000/μL)
- Significantly higher proportion of patients became RBC transfusion independent ($p<0.05$)
- Comparisons of pacritinib vs BAT were favorable for all patient subgroups examined for both endpoints

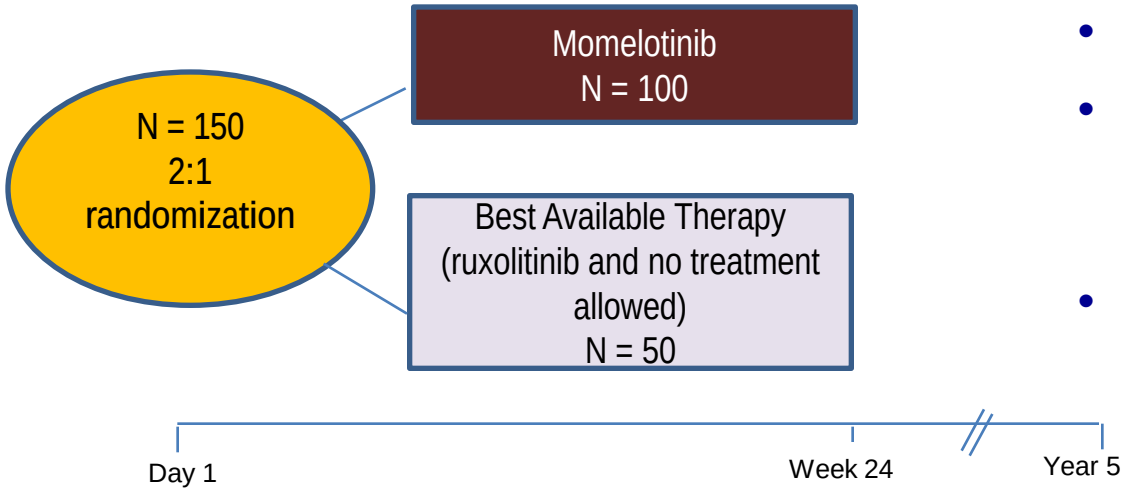
February 2015: "full hold" by the FDA due to concerns regarding excess mortality, cardiovascular events that included QTc prolongation and heart failure, as well as increased bleeding.

Phase 3 Studies With Momelotinib



JAK inhibitor naïve

- Randomized, Double Blind
- Primary endpoint: Spleen Response by MRI at week 24

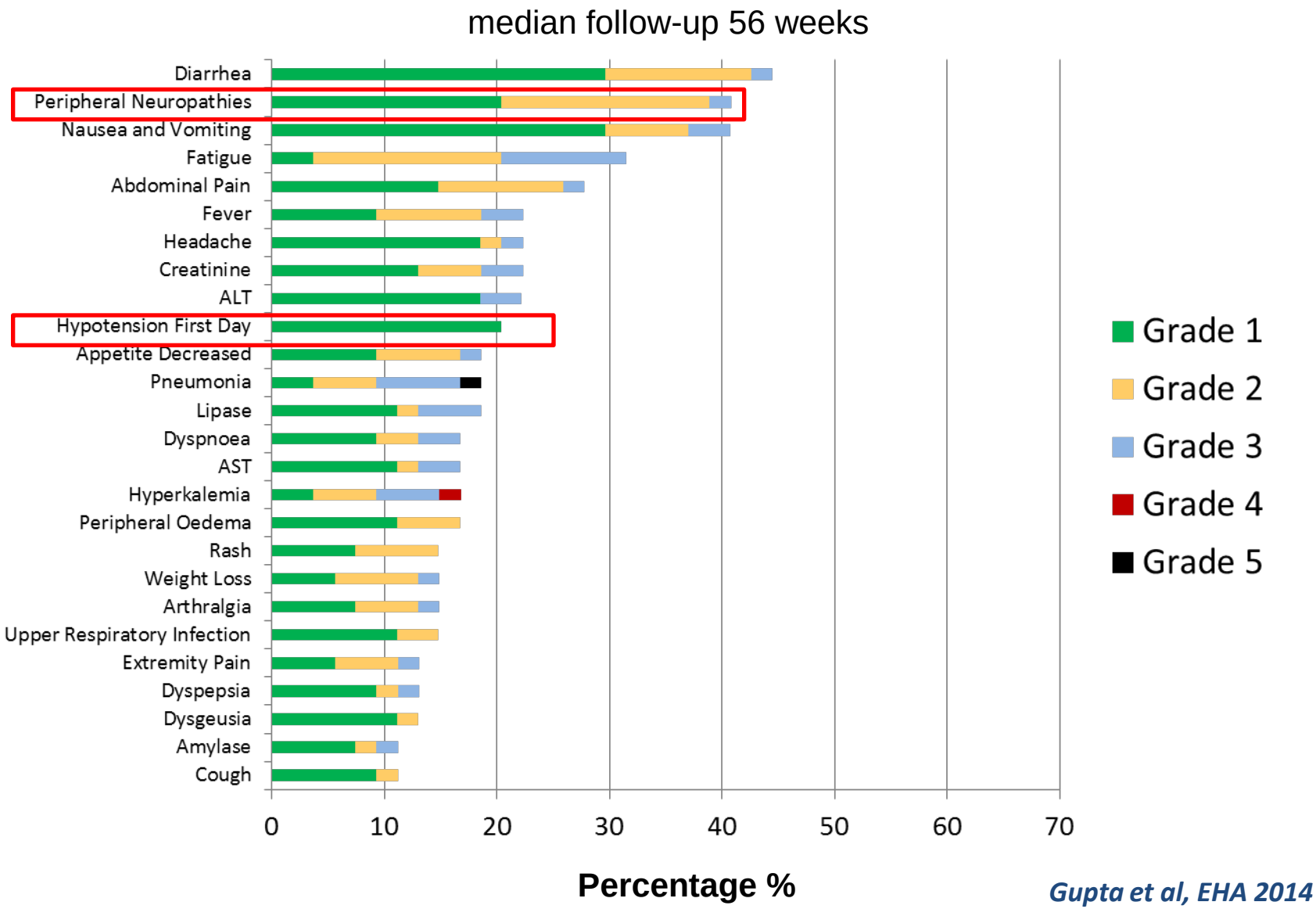


Previous JAK inhibitor exposure

- Randomized, Open Label
- Required ruxolitinib dose adjustment to < 20mg BID and concurrent hematologic toxicity
- Primary endpoint: Spleen Response by MRI at week 24

200 mg Tablet QD

Momelotinib: Most Common (> 10%) Non-Hematologic Adverse Events Regardless of Causality 200 mg BID Cohort (n= 54)



Gupta et al, EHA 2014

Momelotinib, Phase 2 trial

- 100 patients, DIPSS-plus int-2, high risk
- CI spleen in 57%: 43% for spleen, 44% anemia
- Median treatment duration: 30 months

- Peripheral Neuropathy (PN)
  - 44% (42, no PN at baseline), all G1
  - Not reversible, not related to dose
  - Feet 28, hands 1, feet & hands 15
  - Median time of onset: 32 weeks
  - Median duration. 11 months

Abdelrahman et al Br J Haematol. 2015 Apr;169(1):77-80

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

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

Test additional mutations (*ASXL1* first) and assess karyotype only for post transplant monitoring

Passamonti *et al*, COH 2016

Diagnose MF and genotype *JAK2, CALR, MPL*

IPSS at diagnosis

LR → Med OS **11.2 y** → **LR over time: 85% alive at 20 y**

Int-1 R → Med OS **7.9 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
- Clinical trials
- Stem cell transplant (few selected)

Int-2 R → Med OS **4 y**

HR → Med OS **2.2 y**

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

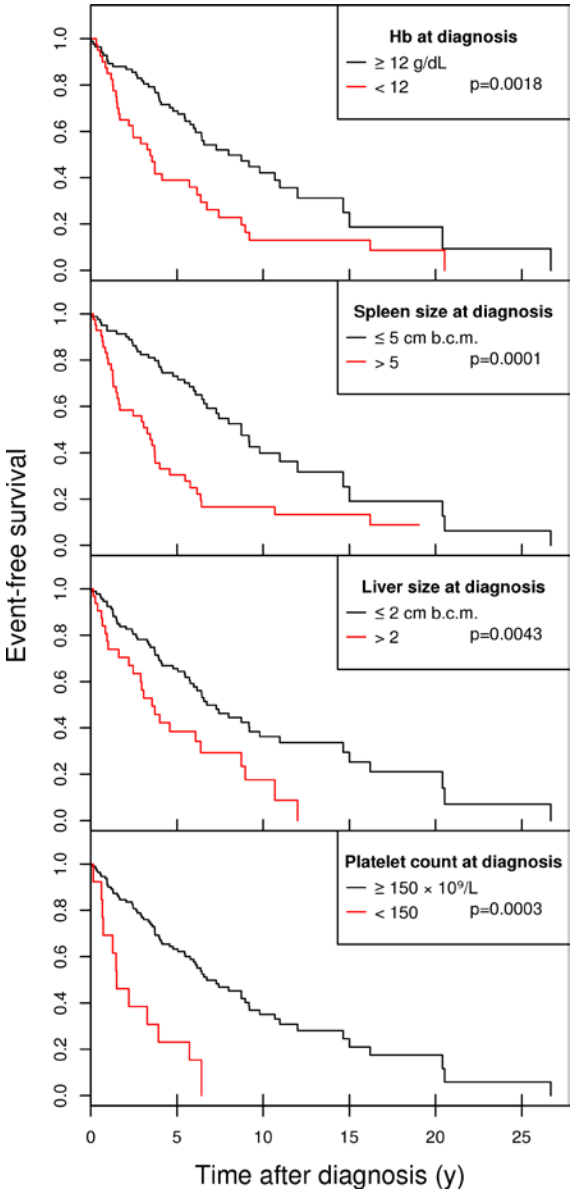
Test additional mutations (*ASXL1* first) and assess karyotype only for post transplant monitoring

Passamonti *et al*, COH 2016

Some clinical parameters predict worse event-free survival in low risk MF patients

- Events were defined as death, leukemic transformation, and shift to a higher risk DIPSS category

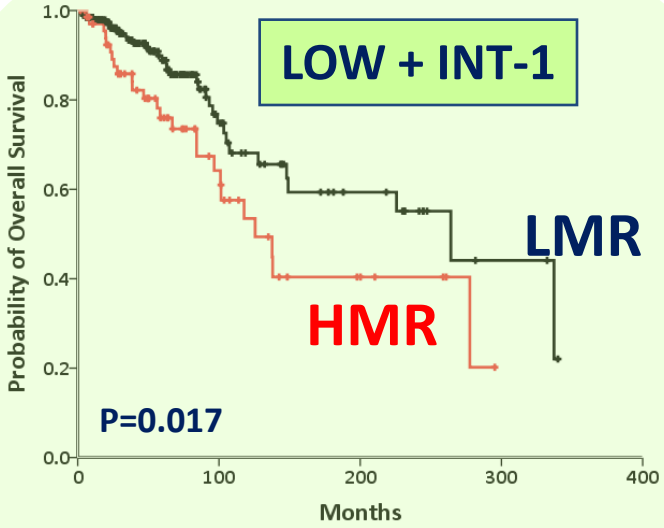
Covariates	Risk ratio (95 %CI)	P
Hb <12 g/dL	1.67 (1.02 - 2.72)	0.040
Plt <150 x 10^9/L	2.38 (1.22 - 4.65)	0.011
Spleen >5 cm BCM	1.84 (1.13 - 2.99)	0.014
Liver >2 cm BCM	2.04 (1.19 - 3.51)	0.0097



Maffioli M et al. ASH 2014, abstract 3187

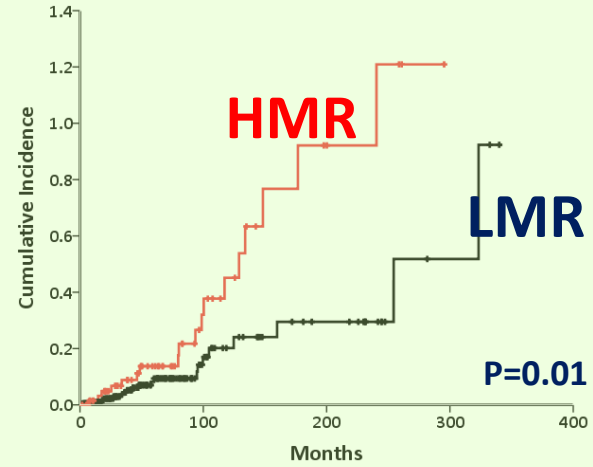
Mutation profile recognizes LR+Int-1 IPSS patients with worsening survival and leukemia

OS



HR= 1.87 (95%CI: 1.11 - 3.14)

LFS



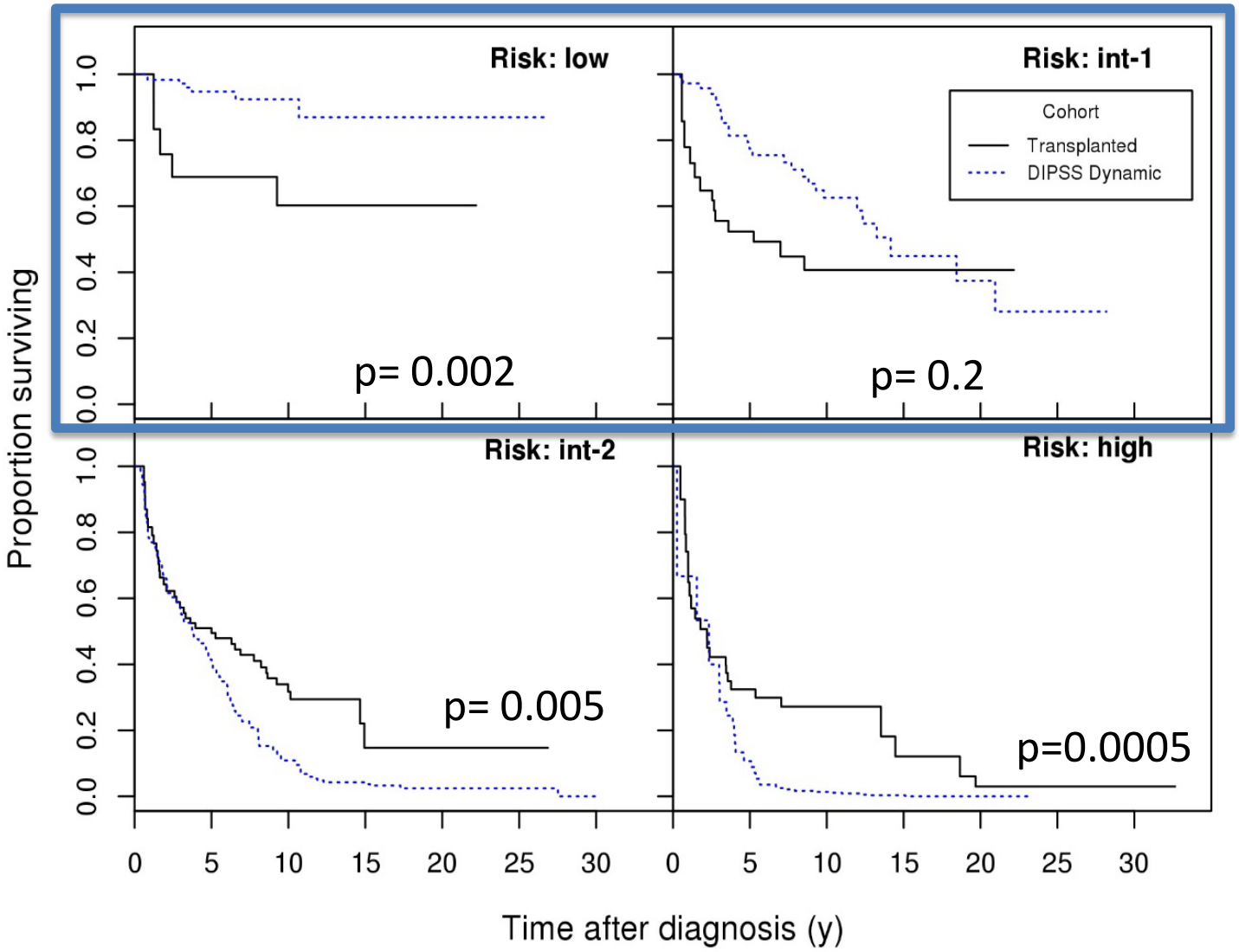
HR= 2.28 (95%CI:1.20 - 4.36)

21% of LR patients are reclassified according to the mutational profile

OS, overall survival; LFS, leukemia-free survival

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

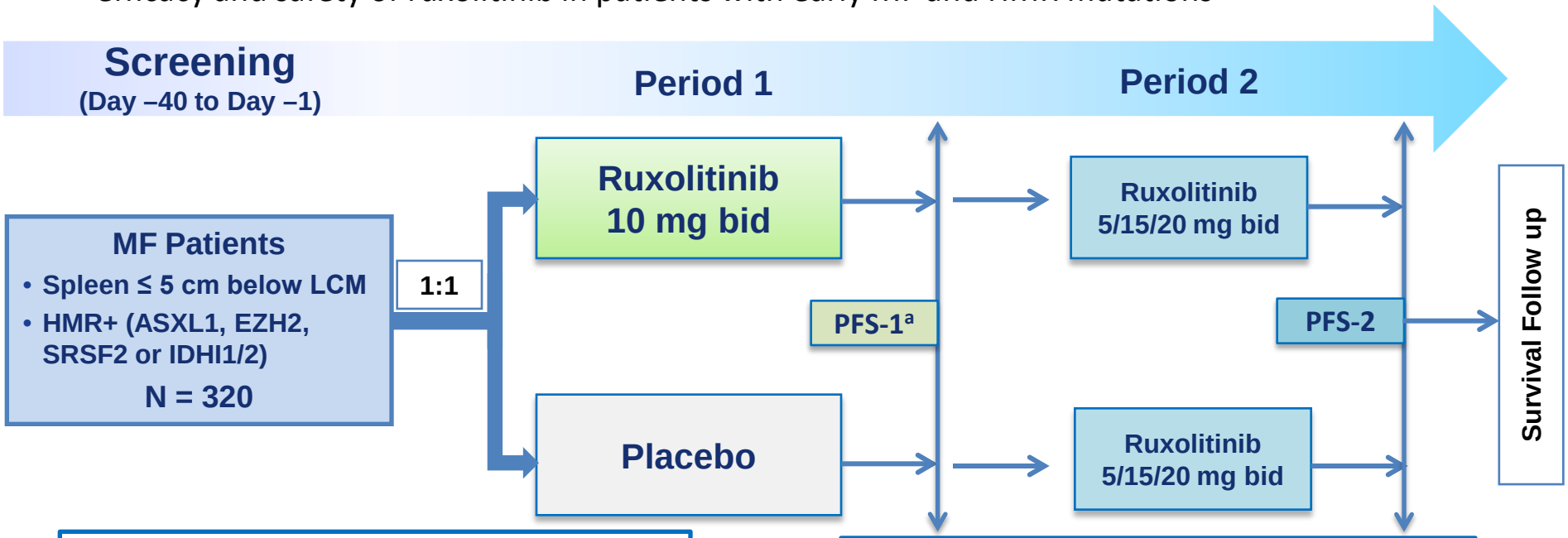
ASCT for lower risk patients balancing efficacy and mortality



Kröger N, Giorgino T, Scott BL, Ditschkowski M, Alchalby H, Cervantes F, Vannucchi A, Cazzola M, Morra E, Zabelina T, Maffioli M, Pereira A, Beelen D, Deeg HJ, Passamonti F. Blood. 2015 Mar 17. pii: blood-2014-10-608315

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