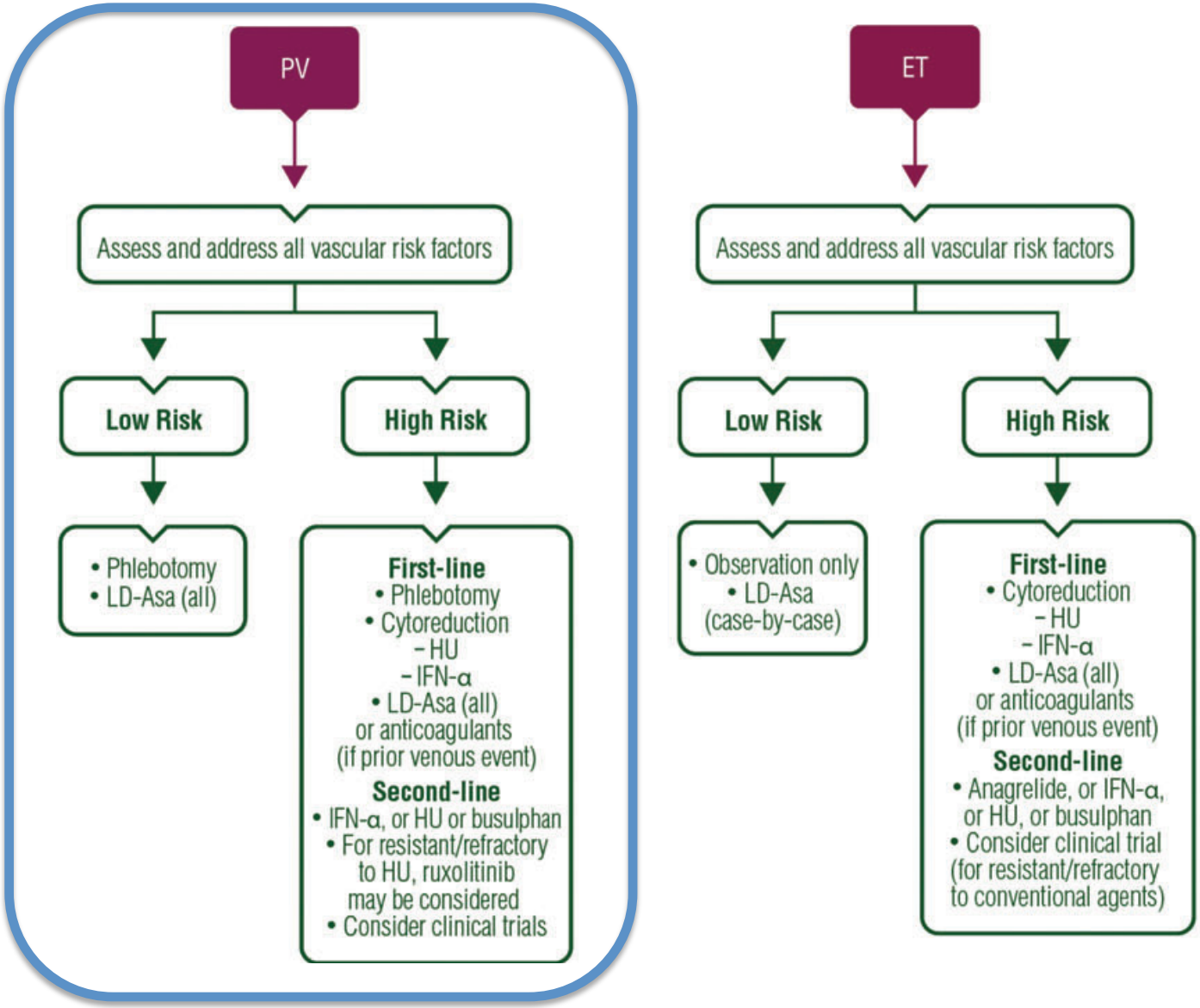
Novità terapeutiche nelle malattie mieloproliferative croniche Ph negative

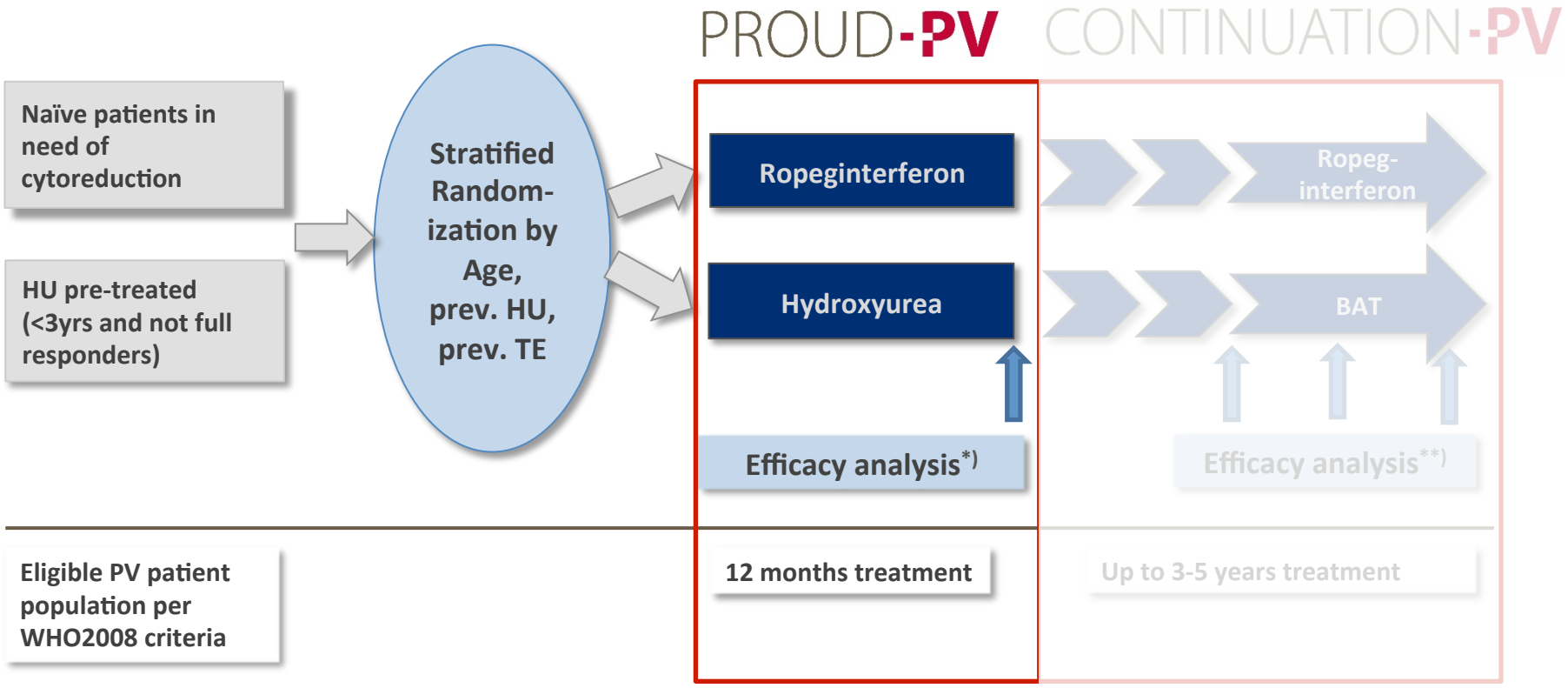
Francesco Passamonti
Università dell'Insubria
Varese - Italy

ESMO Guidelines for PV



Vannucchi et al, Ann Oncol. 2015 Sep;26 Suppl 5:v85-99

PROUD-PV, a randomized non-inferiority controlled phase 3 trial comparing ropeginterferon alfa-2b to hydroxyurea in PV (first line)



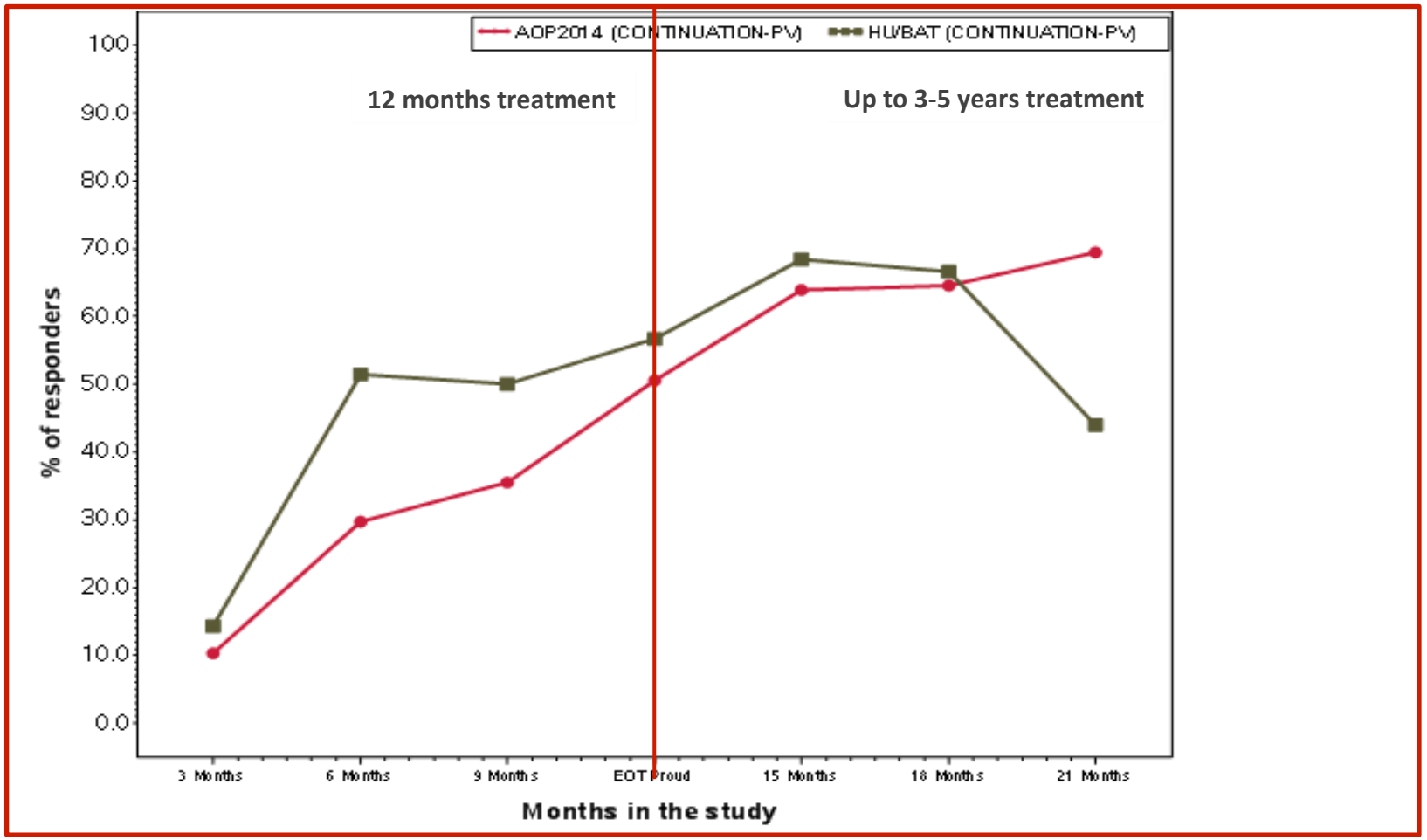
PRIMARY OBJECTIVE:
Complete Hematologic Response (with or without spleen response)

Gisslinger et al ASH 2016

PROUD-PV, a randomized controlled phase 3 trial comparing *ropeginterferon alfa-2b* to *hydroxyurea* in PV

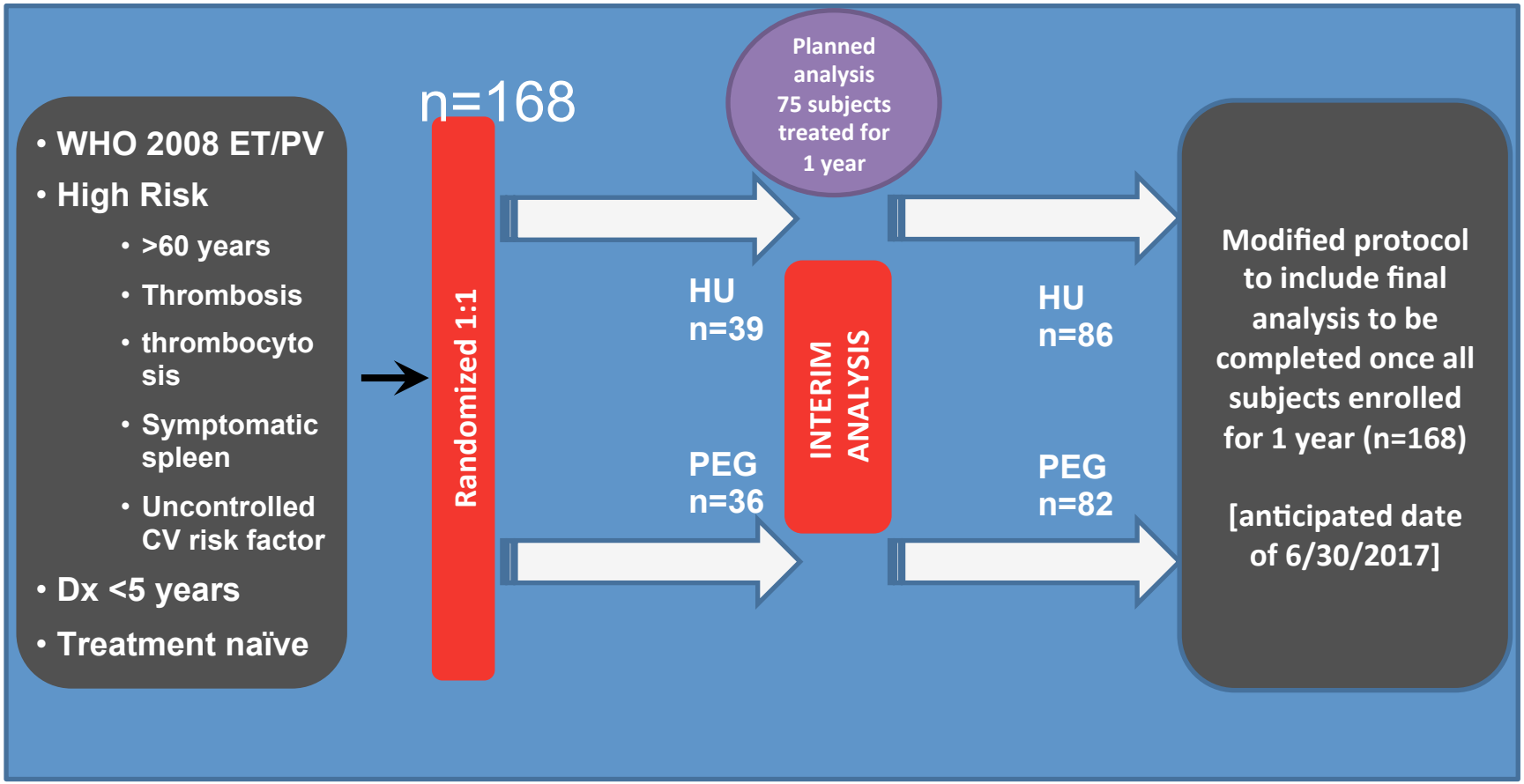
Complete hematologic response over time:

PROUD-PV CONTINUATION-PV



Gisslinger et al ASH 2016

MPD-RC 112 Study, a Phase III Trial of Front Line Pegylated Interferon Alpha-2a Vs. Hydroxyurea in High Risk PV and ET



Primary Objective: To compare the complete hematologic response (CR) rates (by ELN criteria - Barosi *et al* 2008) in patients randomized to treatment with PEG vs. HU by the end of 12 months of therapy

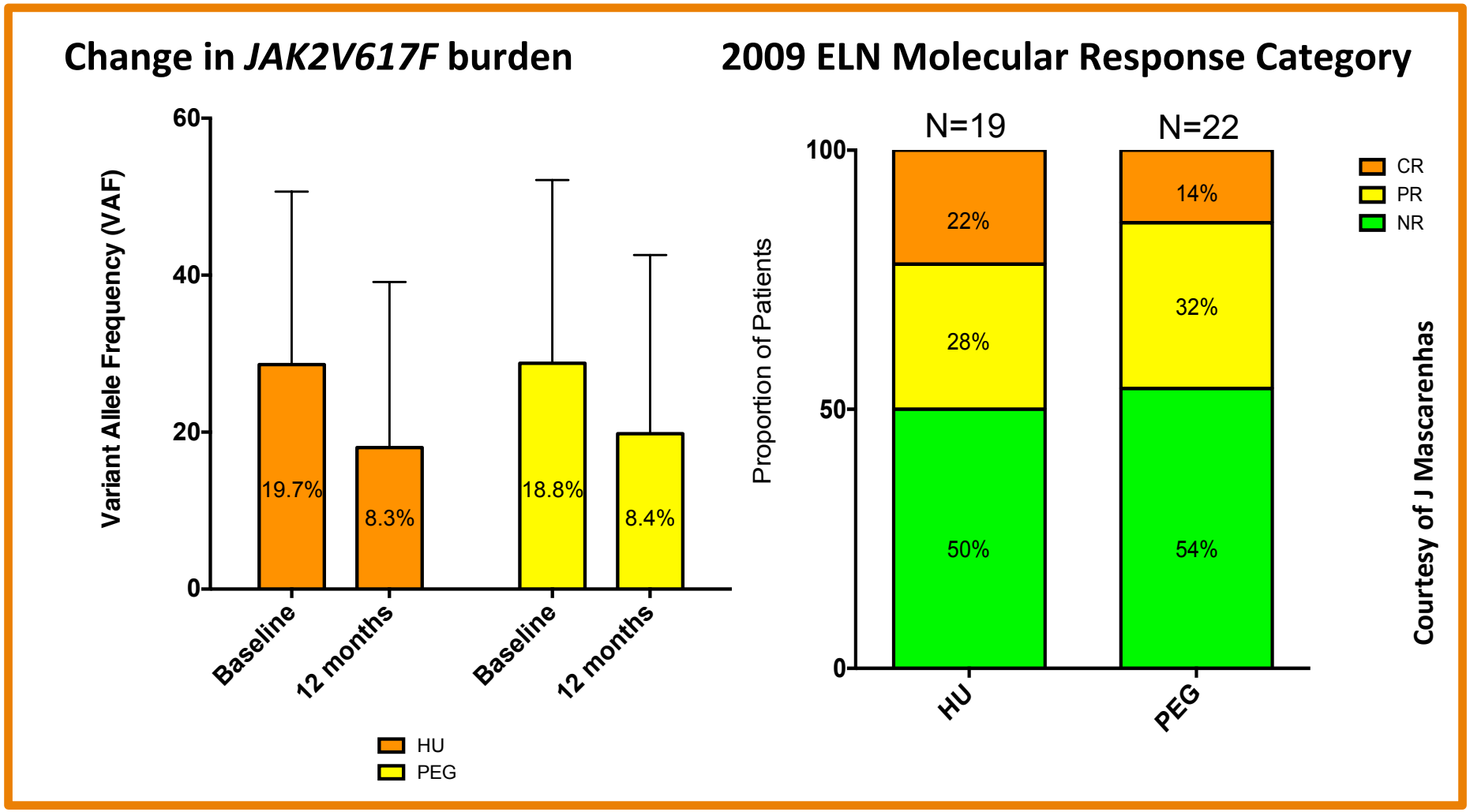
Mascarenas et al, ASH 2016. Oral 479

MPD-RC 112 Study: Overall Response Rates at 12 Months by Treatment Arm

	HU (n=39)			PEG (n=36)			P value
	PR n (%)	CR n (%)	ORR n (%)	PR n (%)	CR n (%)	ORR n (%)	
Entire cohort (n=75)	14 (36)	13 (33)	27 (69)	19 (53)	10 (28)	29 (81)	0.6*
ET (n=31)	4/16 (25)	7/16 (44)	11/16 (69)	6/15 (40)	6/15 (40)	12/15 (80)	0.8
PV (n=44)	**10/23 (44)**	**6/23 (26)**	**16/23 (70)**	**13/21 (62)**	**4/21 (19)**	**17/21 (81)**	**0.6**

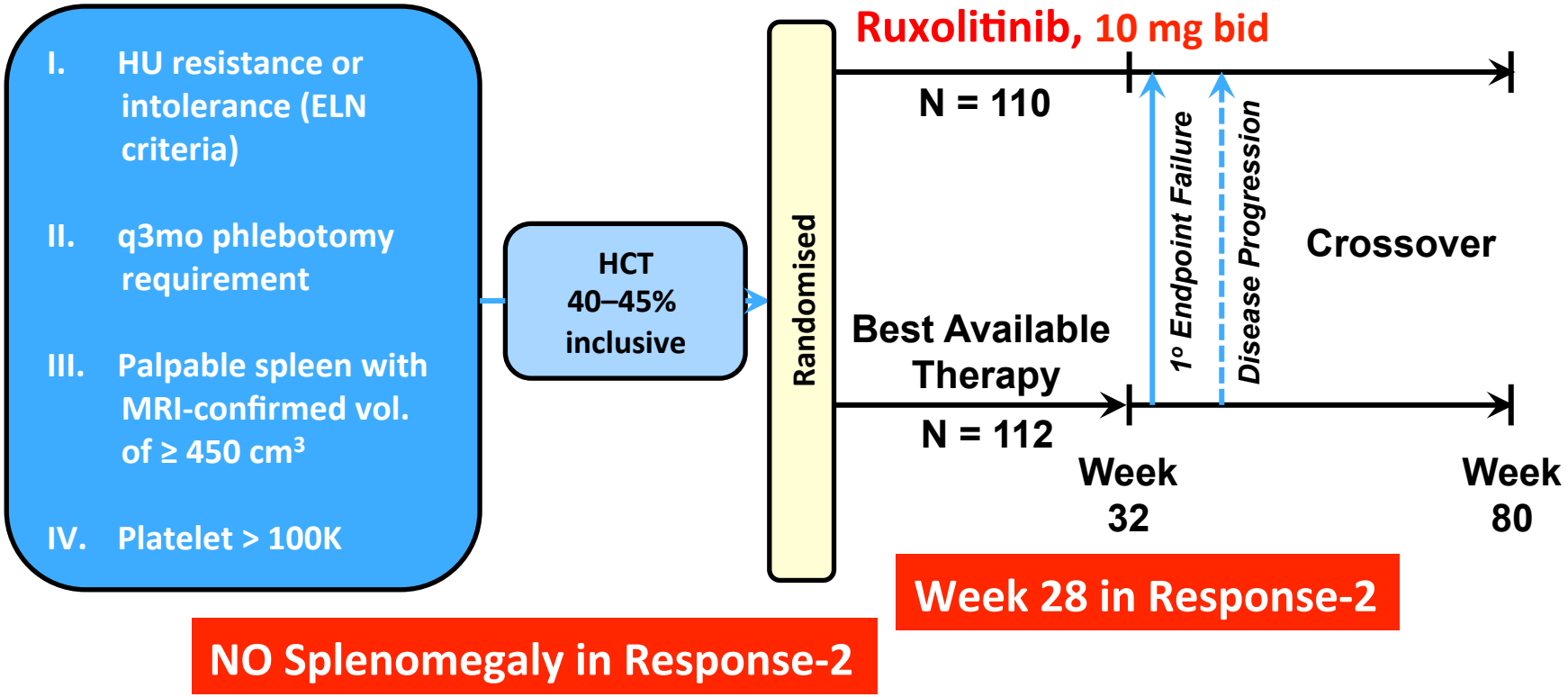
Mascarenas et al, ASH 2016. Oral 479

MPD-RC 112 Study, *JAK2* allele burden change from baseline



Mascarenas et al, ASH 2016. Oral 479

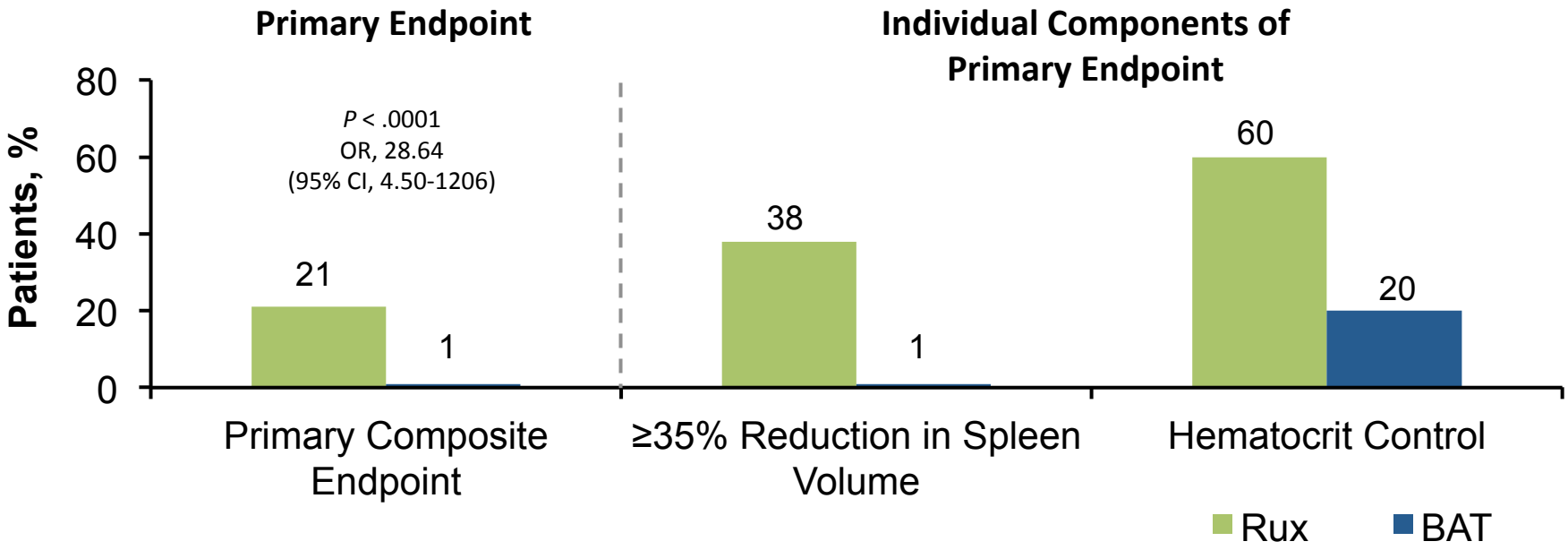
Ruxolitinib in PV: Phase 3 Trials *RESPONSE and RESPONSE 2*



- Primary composite endpoint: haematocrit control (phlebotomy independence from week 8 to 32, with ≤ 1 phlebotomy post randomization) in the absence of phlebotomy and 35% reduction in spleen volume at week 32 (this latter absent in Response 2)
- Secondary endpoints: complete haematological remission at week 32 (absence of phlebotomy requirement, PLT count ≤ 400 x 10^9/L, and WBC count ≤ 10 × 10^9/L); % of patients who maintain primary endpoint response for ≥ 48 weeks; Symptom improvement (MPN-SAF diary) and quality of life (EORTC QLQ-C30; PGIC).

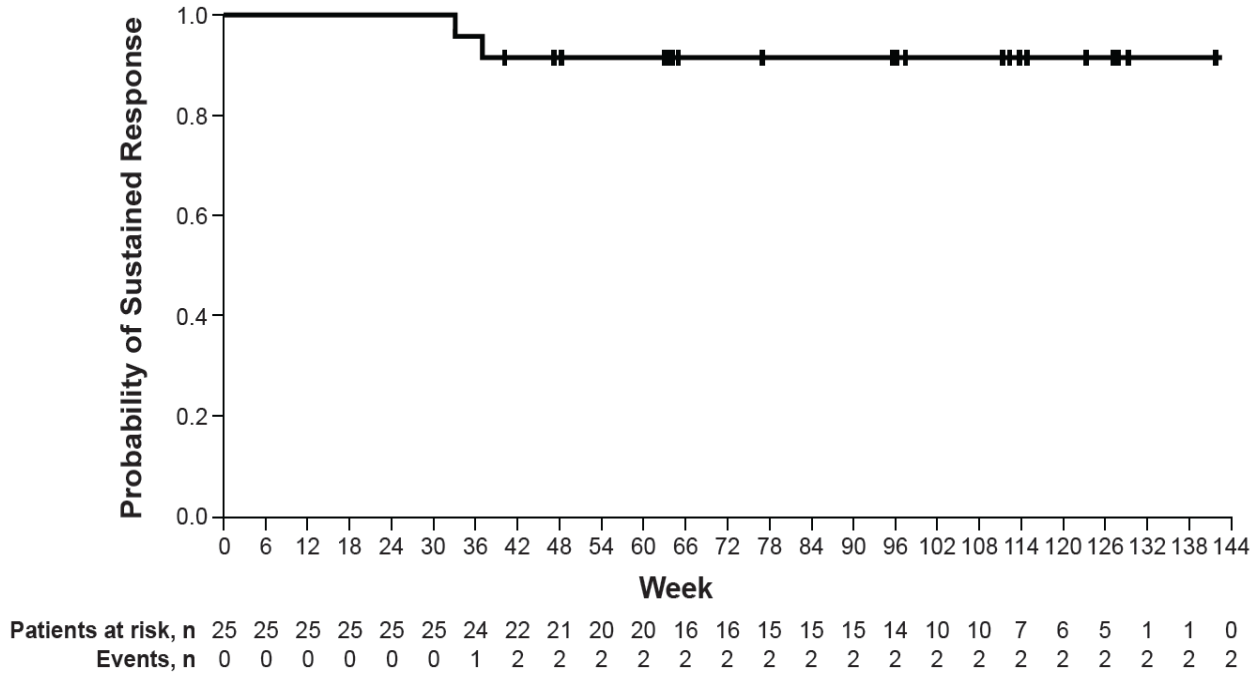
Vannucchi et al, N Engl J Med. 2015 Jan 29;372(5):426-35;
Passamonti et al, Lancet Oncol. 2016 Dec 1. pii: S1470-2045(16)30558-7.

RESPONSE study: haematocrit control and 35% reduction in spleen volume at Week 32



Vannucchi et al, N Engl J Med. 2015 Jan 29;372(5):426-35

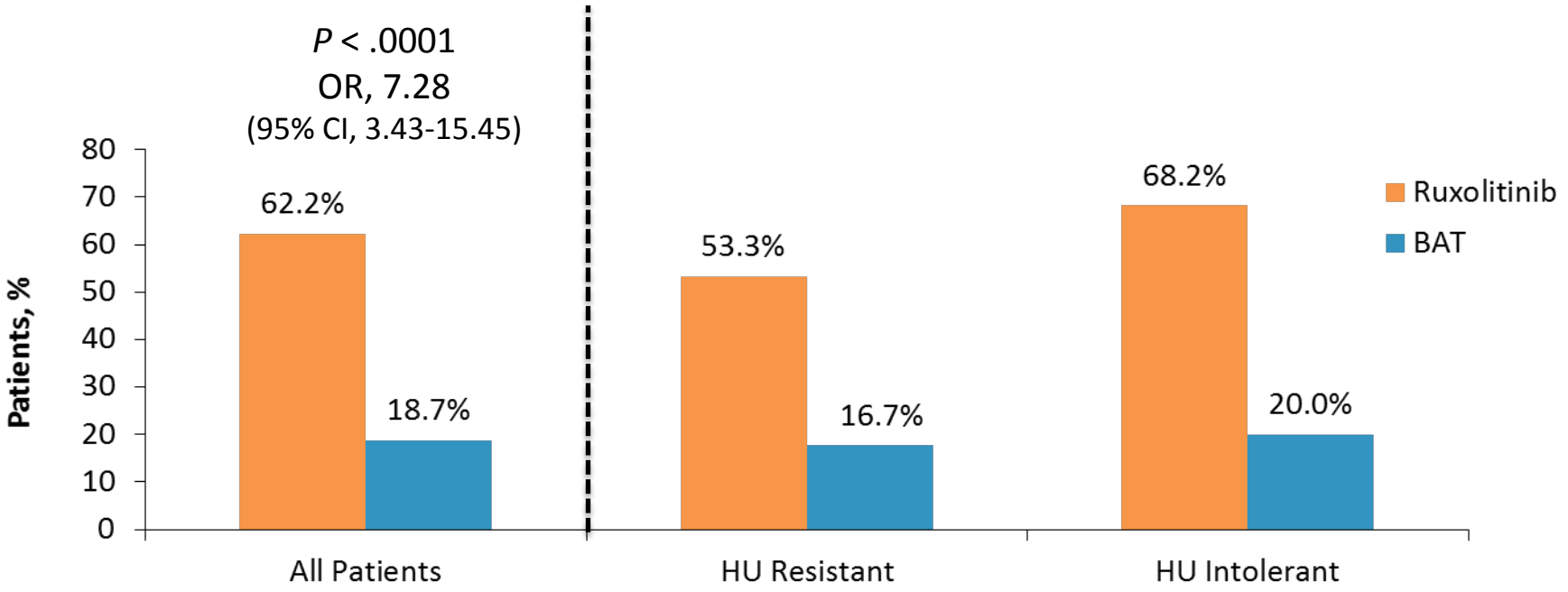
RESPONSE study: Durability of Primary Response With Ruxolitinib



- 20/25 (80%) ruxolitinib-treated patients had a durable primary response defined as maintenance for 48 weeks after initial response
  - 3 of the 5 without durable response were classified as nonresponders because of missing assessments
- The probability of maintaining the primary response in the ruxolitinib arm for at least 80 weeks from time of response was 92%

Verstovsek et al. Haematologica 2016

RESPONSE-2 study: haematocrit control at Week 28

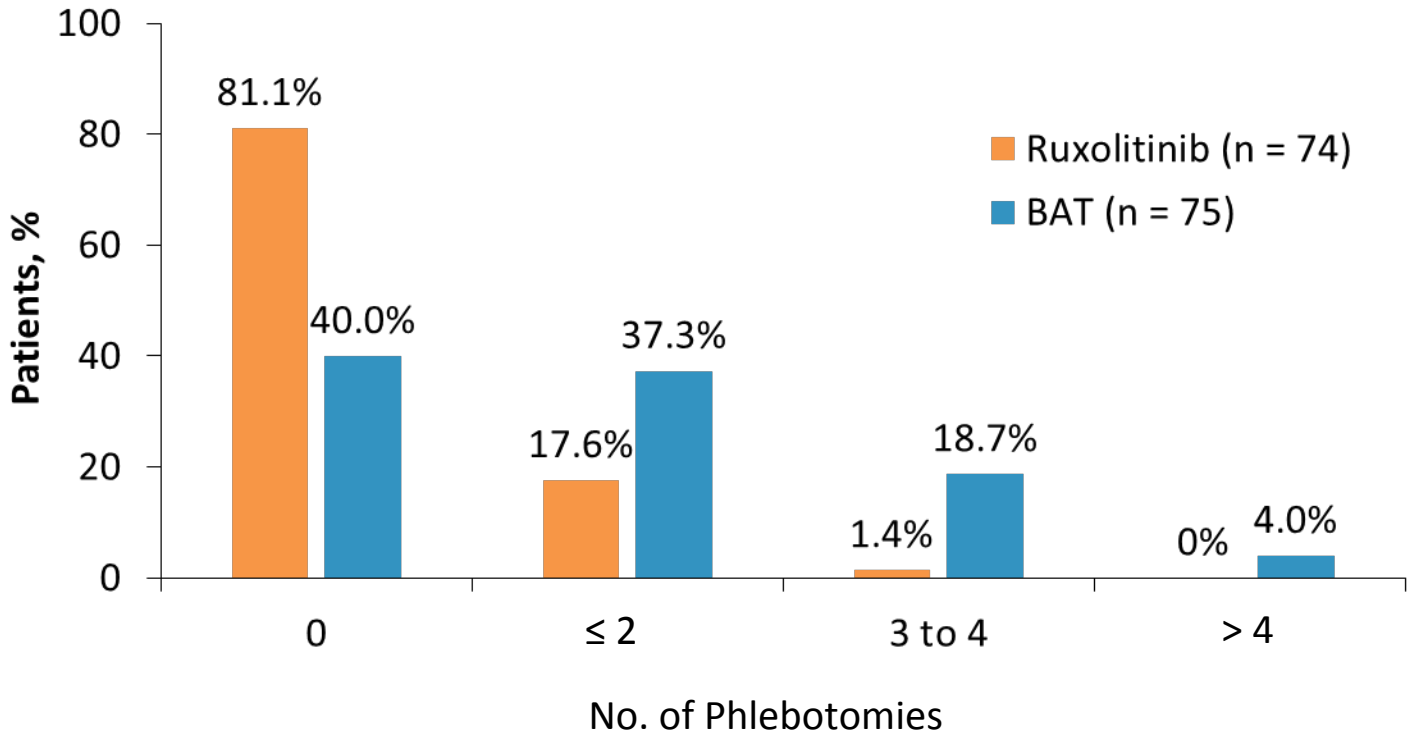


- Significantly more patients randomized to ruxolitinib achieved Hct control without phlebotomy (primary endpoint) compared with those randomized to BAT

OR, odds ratio.

Passamonti et al, Lancet Oncol. 2016 Dec 1. pii: S1470-2045(16)30558-7.

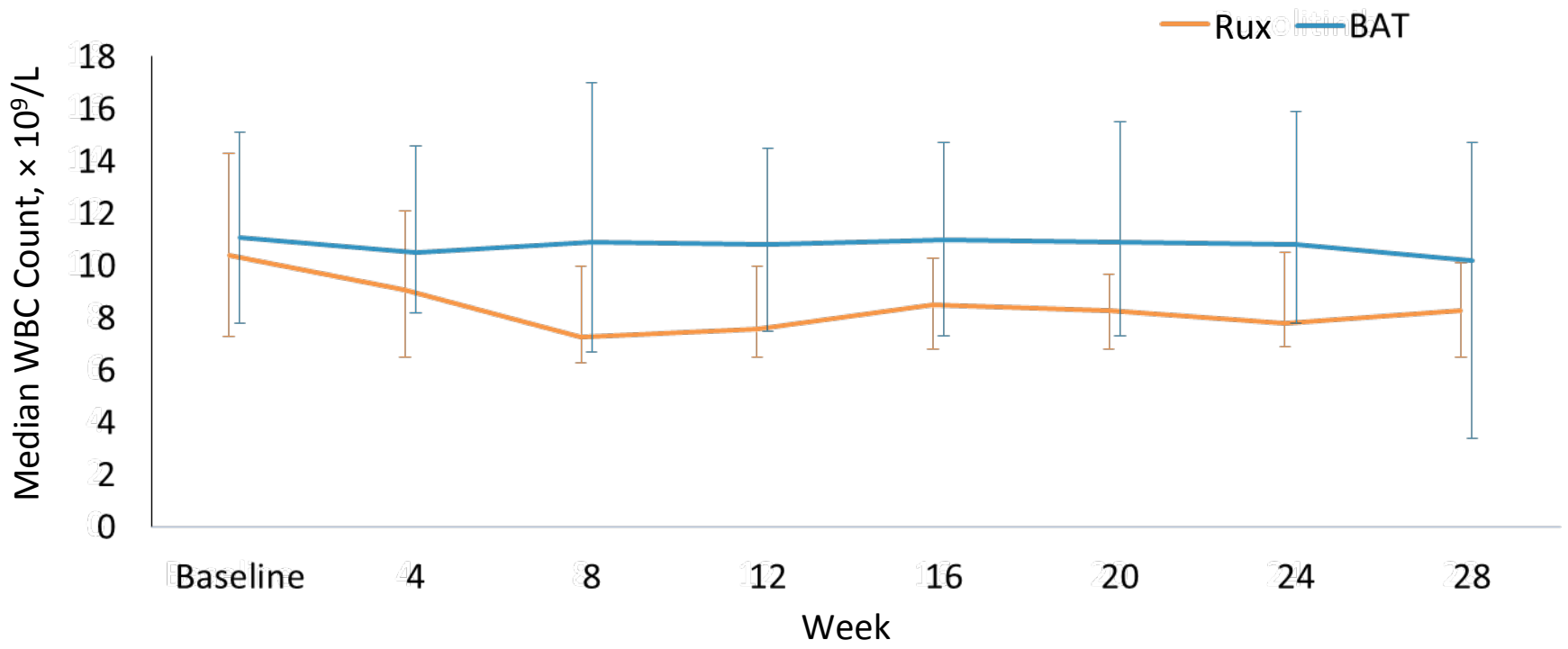
RESPONSE-2 study: Proportion of Patients NOT Receiving Phlebotomies Up to Week 28



- More than 80% of patients in the ruxolitinib arm did not have a phlebotomy, compared with 40% in the BAT arm
- The total number of phlebotomies was much higher in the BAT arm than in the ruxolitinib arm (98 vs 19)

Passamonti et al, Lancet Oncol. 2016 Dec 1. pii: S1470-2045(16)30558-7.

RESPONSE-2 study: WBC Count Over Time



Ruxolitinib, n =	74	68	65	66	69	69	67	68
BAT, n =	75	69	71	70	69	69	61	40

- WBC counts in the ruxolitinib arm were ≤ 10 × 10^9/L from week 8 onward, whereas they remained > 10 × 10^9/L in the BAT arm

Passamonti et al, Lancet Oncol. 2016 Dec 1. pii: S1470-2045(16)30558-7.

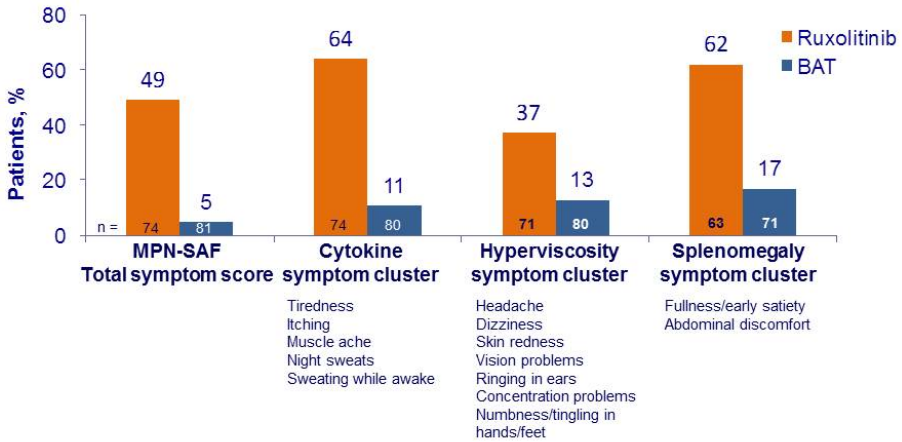
Thromboembolic complications with ruxolitinib in the Response studies

- **Response**: at the Week 80 analysis, the rates of thromboembolic events per 100 patient-years of exposure were 1.8 in the ruxolitinib arm vs. 8.2 in the BAT arm
- **Response-2**: there was 1 thromboembolic event in the ruxolitinib arm and 3 in the BAT arm

Vannucchi et al, N Engl J Med. 2015 Jan 29;372(5):426-35;
Passamonti et al, Lancet Oncol. 2016 Dec 1. pii: S1470-2045(16)30558-7.

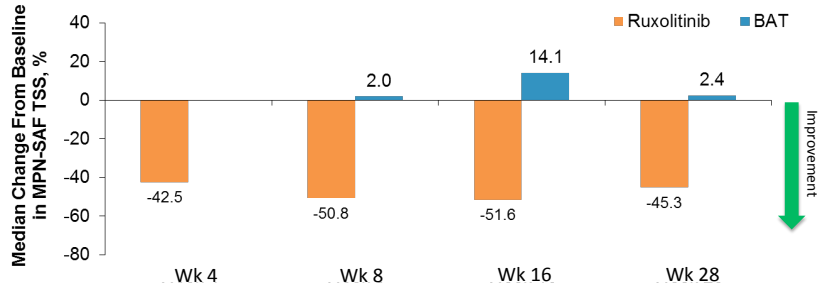
RESPONSE and RESPONSE -2 studies: improvement of symptomatology

- **Percentage of patients with a ≥50% improvement in MPN-SAF symptom score at week 32[a]**



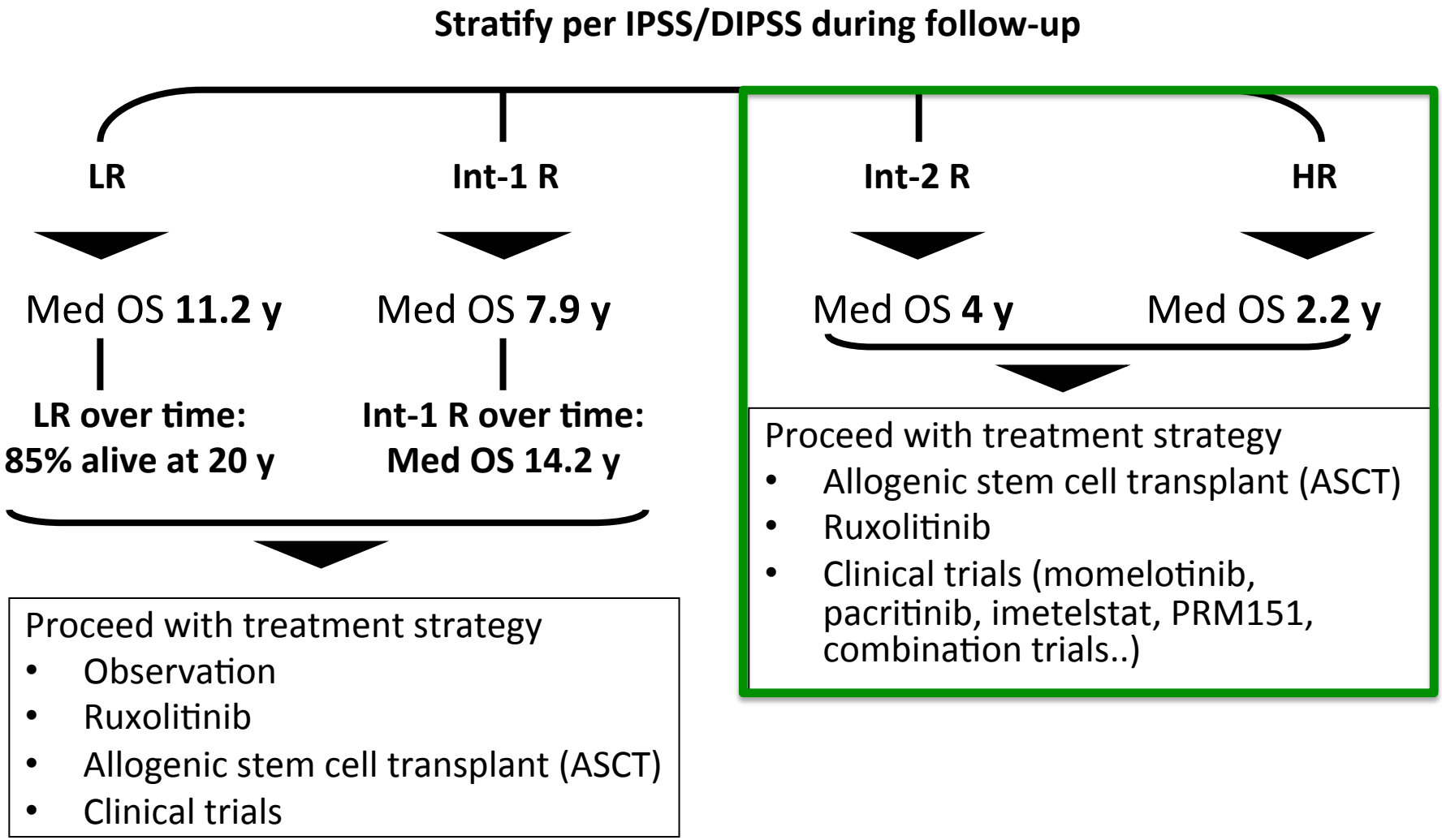
[a]In patients with scores at both baseline and week 32 MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form

- Median baseline total symptom score (TSS) was 18.0 for patients in the ruxolitinib arm and 14.5 for patients in the BAT arm



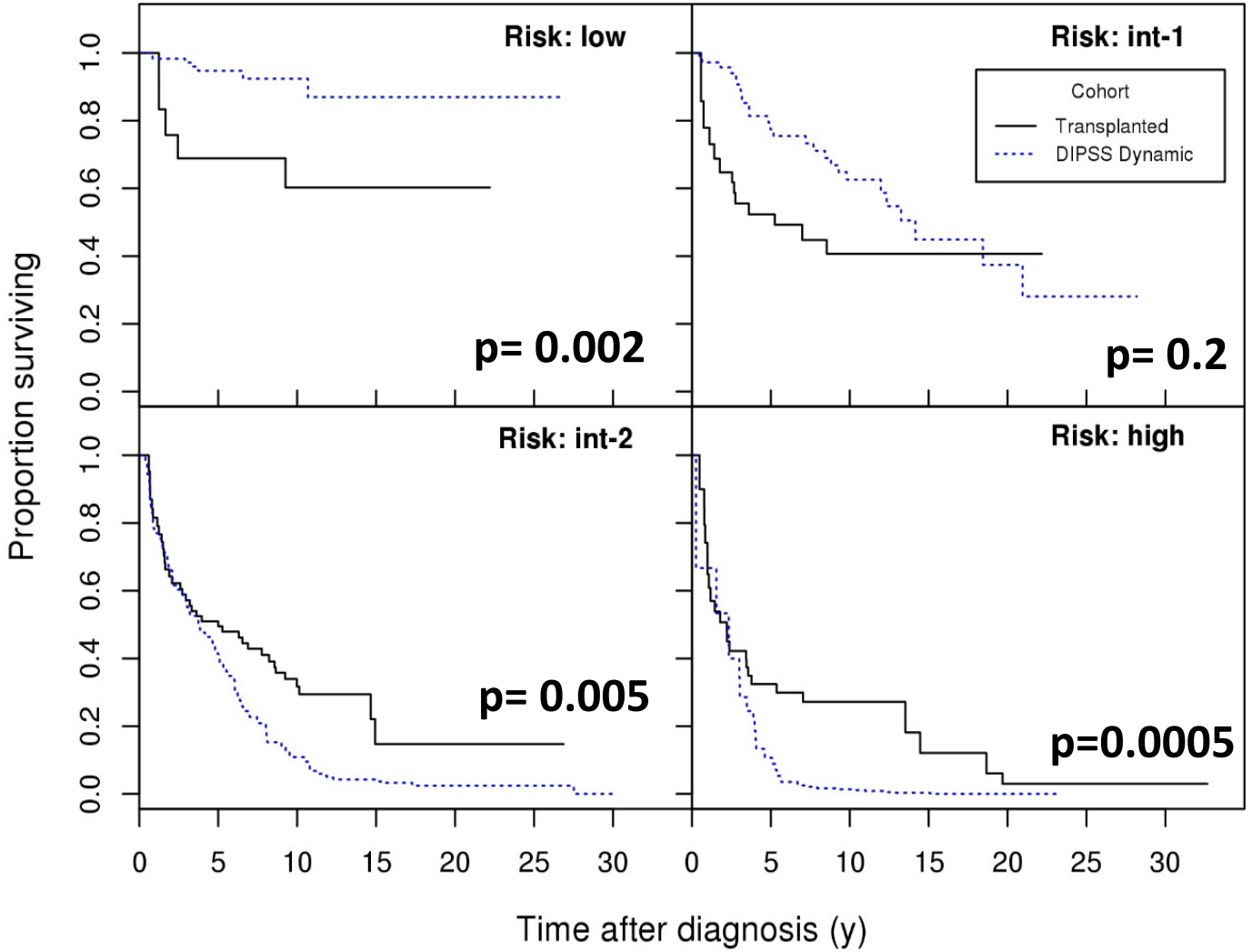
- A higher proportion of patients randomized to ruxolitinib achieved a ≥ 50% reduction in the MPN-SAF TSS at week 28 compared with those randomized to BAT (45.3% vs 22.7%)

Personalized approach to MF



Passamonti et al; Curr Opin Hematol. 2016 Mar;23(2):137-43

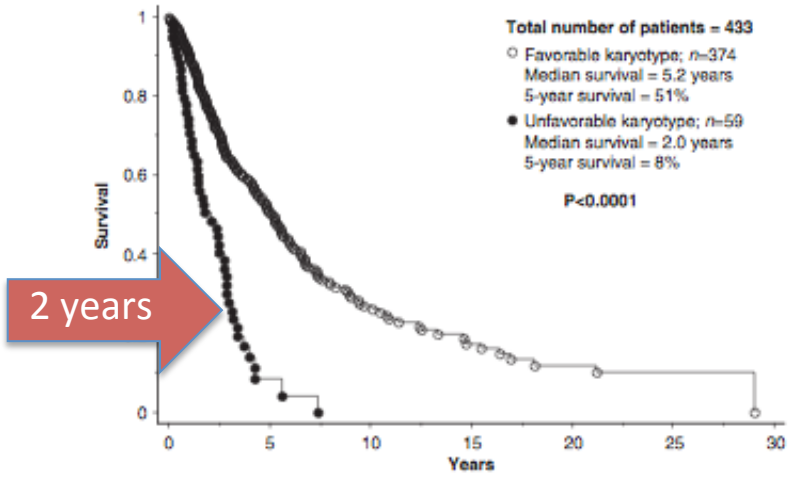
Toward a transplant indication from retrospective analysis
SCT (n=190) vs. non-JAKi standard therapy (N=248)

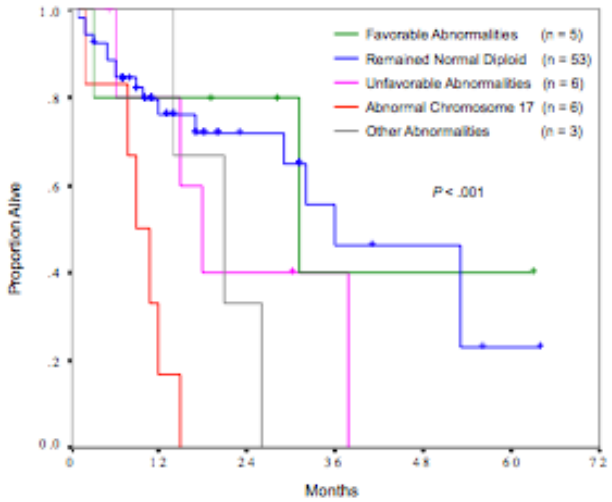


- SCT seems superior to standard therapy in Int-2/HR DIPSS patients

Kroger et al. Blood. 2015 ;125(21):3347-50

Cytogenetics identify high risk patients with PMF





Unfavourable

- Complex
- Sole or two including +8, -7/7q-, i(17q), inv (3), -5/5q-, 12p-, 11q23 rearrangements

Favourable

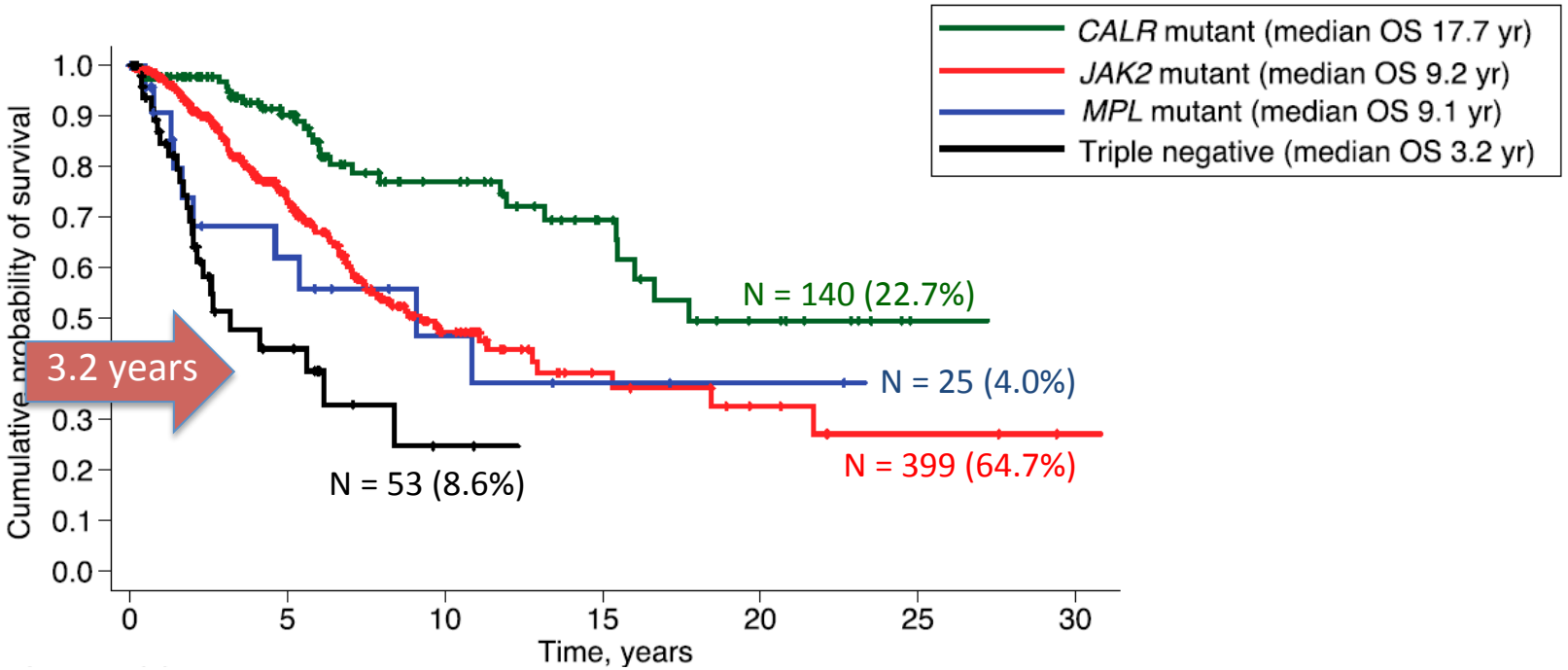
- Normal
- All others

Cytogenetic evolutions

- Patients who acquired over time an unfavourable or very unfavourable karyotype have an inferior survival than those who did not

Caramazza et al., Leukemia. 2011 Jan;25(1):82-8. Tam et al. Blood 2009 April; 113 (18) 4171-8.

Phenotype-driver mutations and survival in PMF

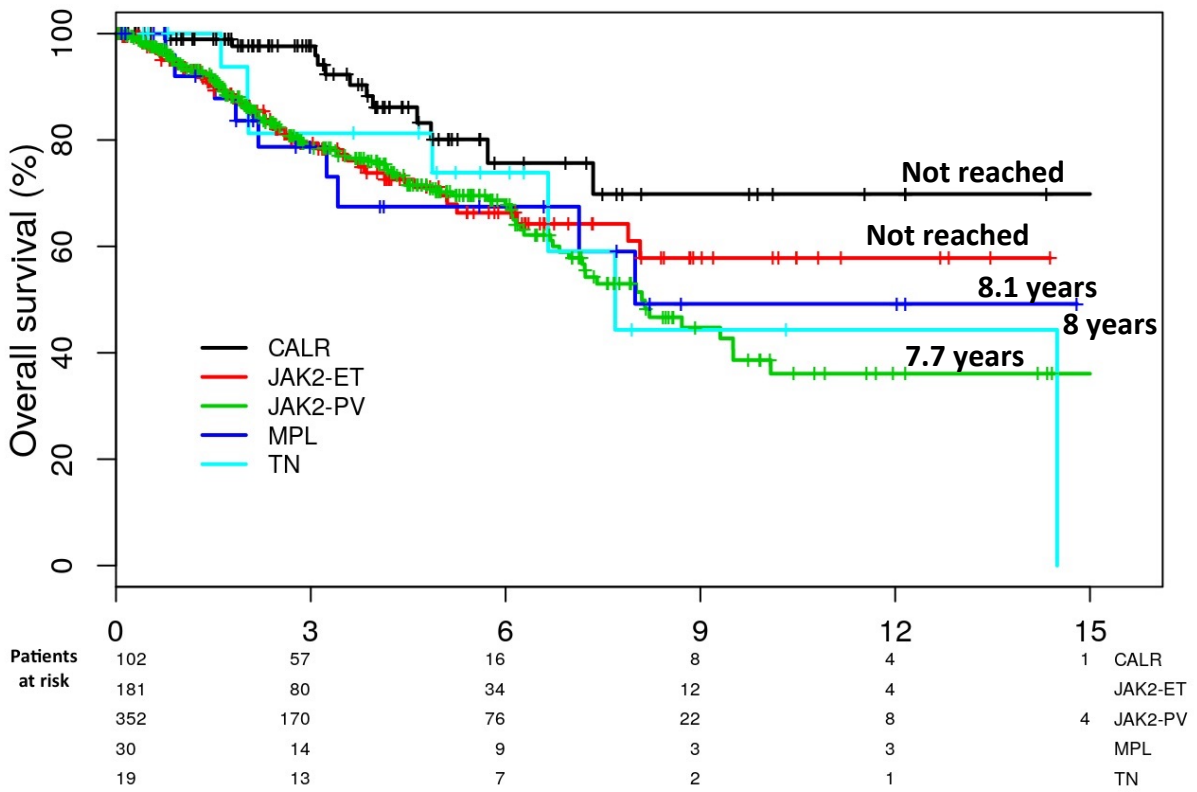


CALR-mutant pts have a better OS than:

- *JAK2* V617F-mutant pts (HR 2.3, P <0.001)
- *MPL*-mutant pts (HR 2.6, P <0.009)
- Triple-negative pts (HR 6.2, P <0.001)

Rumi E et al, Blood 2014;124(7):1062-9

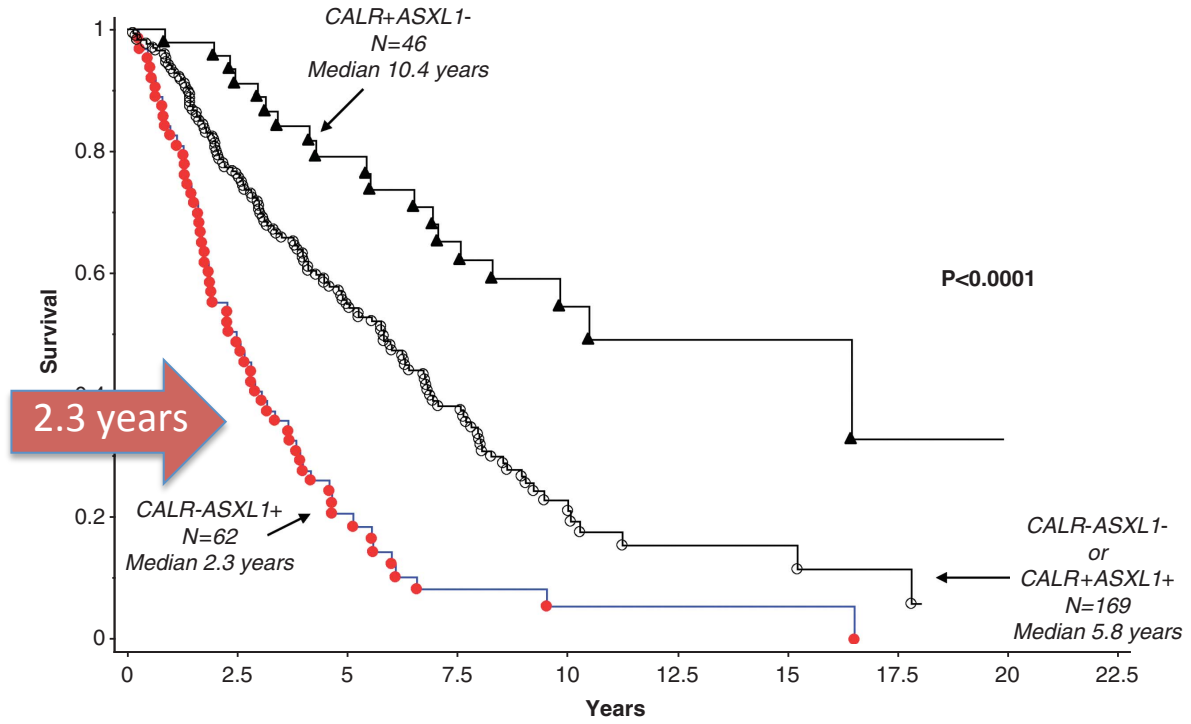
Phenotype-driver mutations and survival in post-PV MF and post-ET MF (n=685)



- *JAK2*-mutated PPV and PET MF had an inferior survival when compared to *CALR*-mutated
- A borderline difference in survival between *MPL*- and TN- cases versus *CALR*-mutated patients
- No difference in terms of survival between *CALR* type 1/type 1-like and type 2/type 2-like.

Passamonti et al. Leukemia. 2017 Jan 3. doi: 10.1038/leu.2016.351

ASXL1^{+}*CALR*$^{-}$ in PMF: the worse combination



Tefferi et al. Leukemia. 2014 Jul;28(7):1494-500

The MYSEC-PM predictors of survival

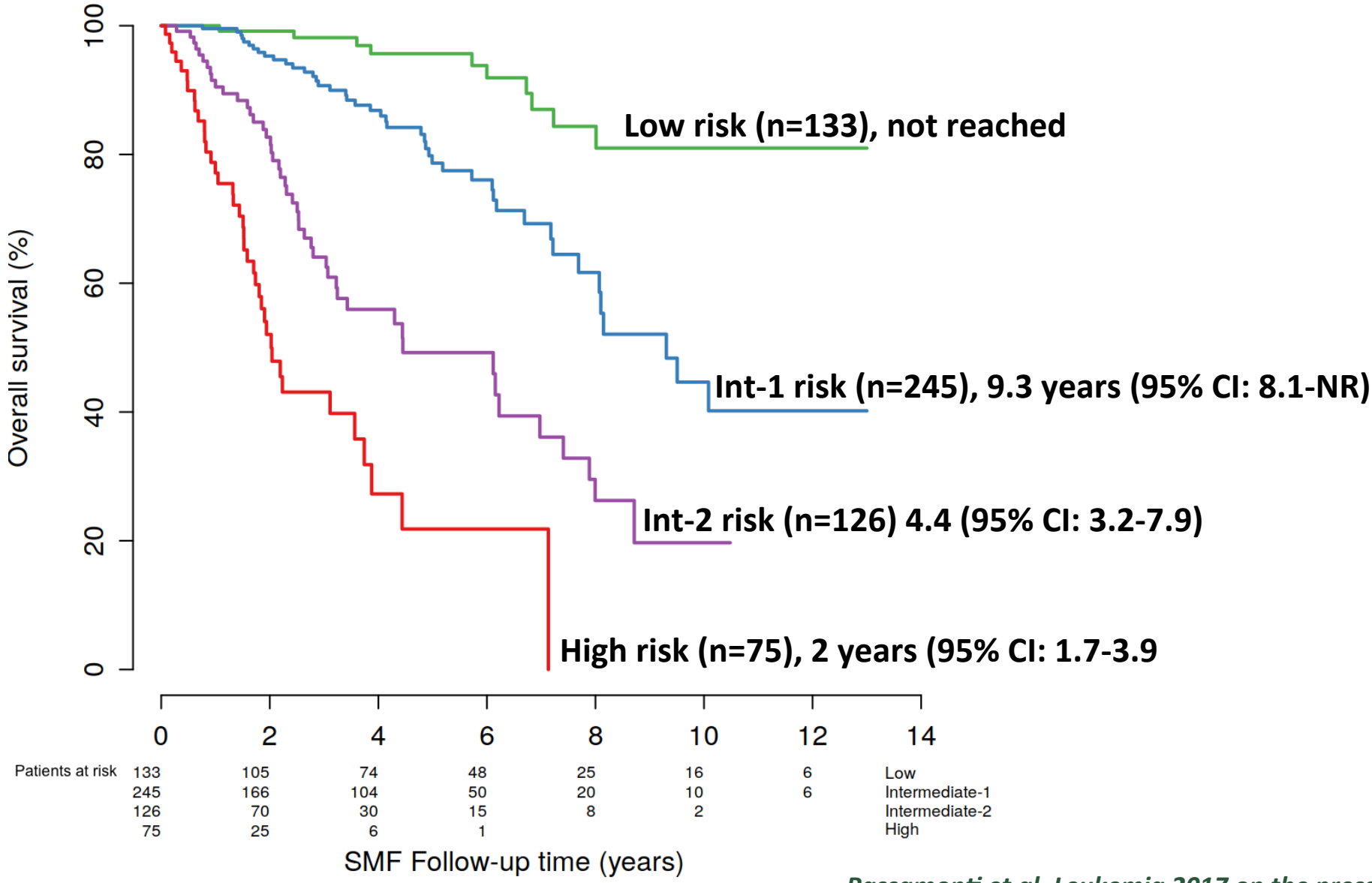
Covariates	HR	95% CI*	Points assigned in the MYSEC-PM °
Age, years	1.07	1.05-1.09	0.15
Hb <11 g/dL	2.3	1.6-3.3	2
Platelet < 150 x10^9/L	1.7	1.2-2.5	1
Circulating blast cells ≥ 3%	2.9	1.8-4.8	2
CALR-unmutated genotype	2.6	1.2-5.3	2
Constitutional symptoms	1.5	1.0-2.0	1

**P* values between .006 and < .0001

° Points assigned on the basis of the Risk coefficient Beta

Passamonti et al. Leukemia 2017 on the press

MYSEC-PM estimate of survival in post-PV/ET MF



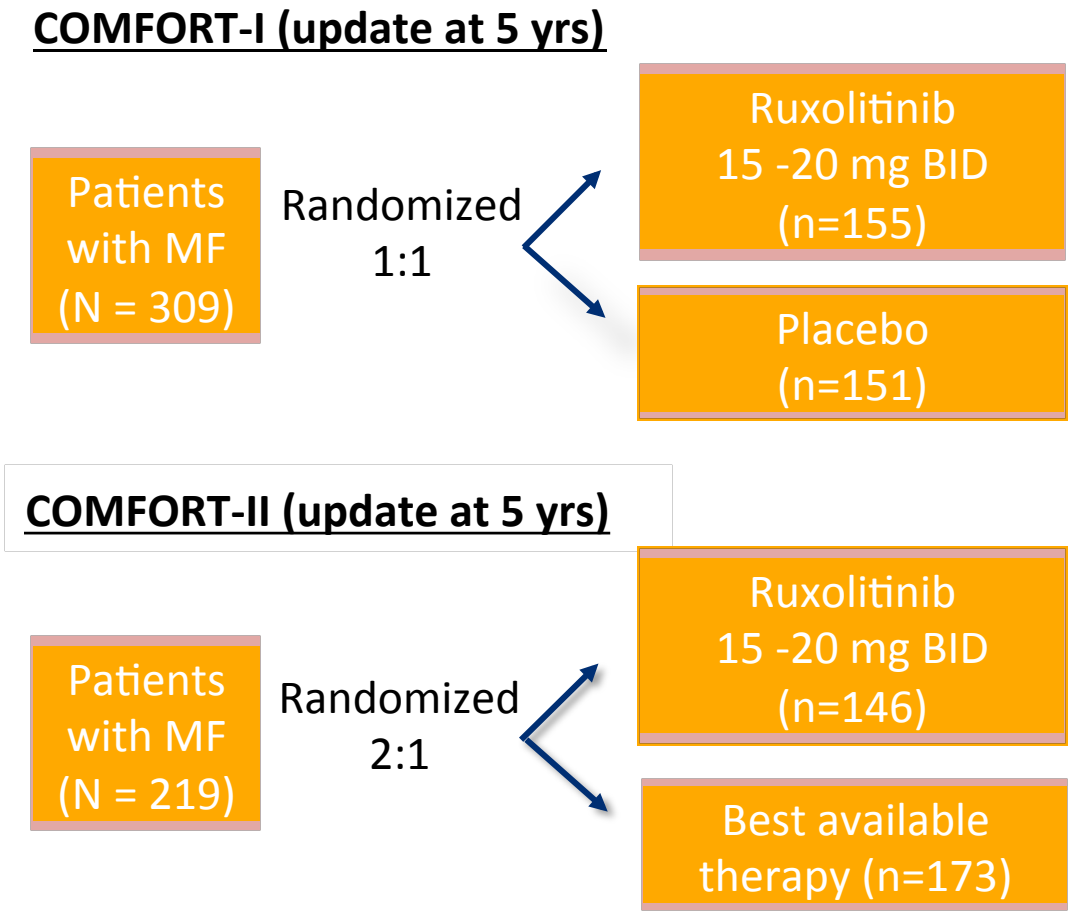
Passamonti et al. Leukemia 2017 on the press

Indication of ASCT: EBMT/ELN consensus

- Low risk disease should not undergo ASCT
- Intermediate-1 risk disease and age less than 65 years should be considered for ASCT if: refractory, transfusion-dependent anemia, circulating blasts greater than 2%, or adverse cytogenetics, triple negative, or *ASXL1+*
- All patients with intermediate-2 or high-risk disease according to IPSS, DIPSS, or DIPSS-plus, and age less than 70 years, should be considered potential candidates for allo-SCT.

Kroger et al. Leukemia 2015; 29: 2126

Ruxolitinib in the COMFORT 1 and 2 trials



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)

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

COMFORT-II: ruxolitinib hematologic adverse events

Hematologic toxicity

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hemoglobin			8-6.5	<6.5
Ruxolitinib (n = 146)	24 (16)	55 (38)	50 (34)	12 (8)
BAT (n = 70)	16 (23)	28 (40)	15 (21)	7 (10)
Platelet count			50-25	<25
Ruxolitinib (n = 146)	46 (32)	41 (28)	9 (6)	3 (2)
BAT (n = 69)	11 (16)	4 (6)	3 (4)	2 (3)

†Percentage is based on baseline total n.

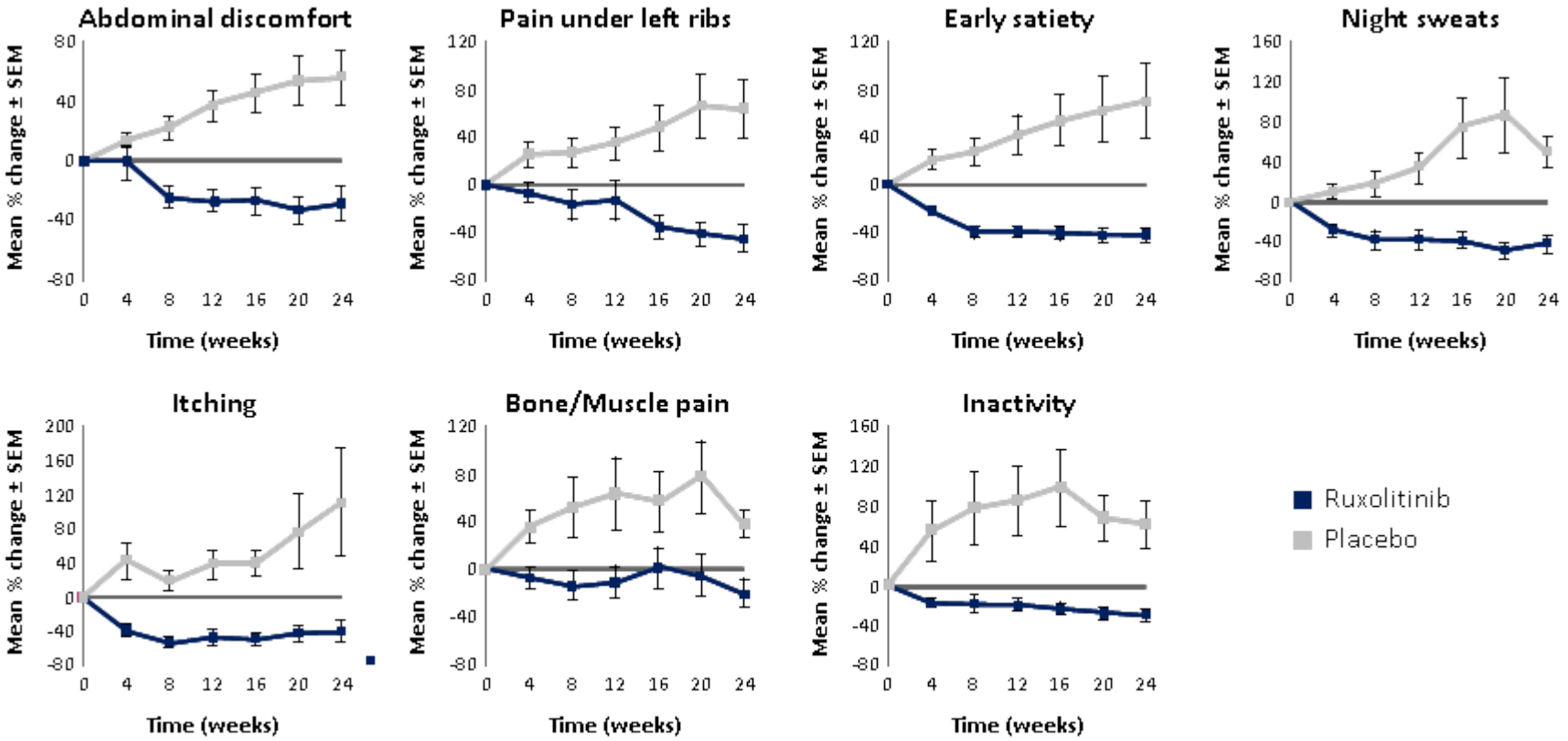
- Calibrate RUX dose on PLT value (as per label)
- Consider RUX dose reduction according to hemoglobin level at baseline (real life)
- Use RBC transfusions, if needed

Infections

	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

COMFORT-I: reduction of individual symptom burden* over time with Ruxolitinib



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 results at 5 years of follow-up (COMFORT-2)

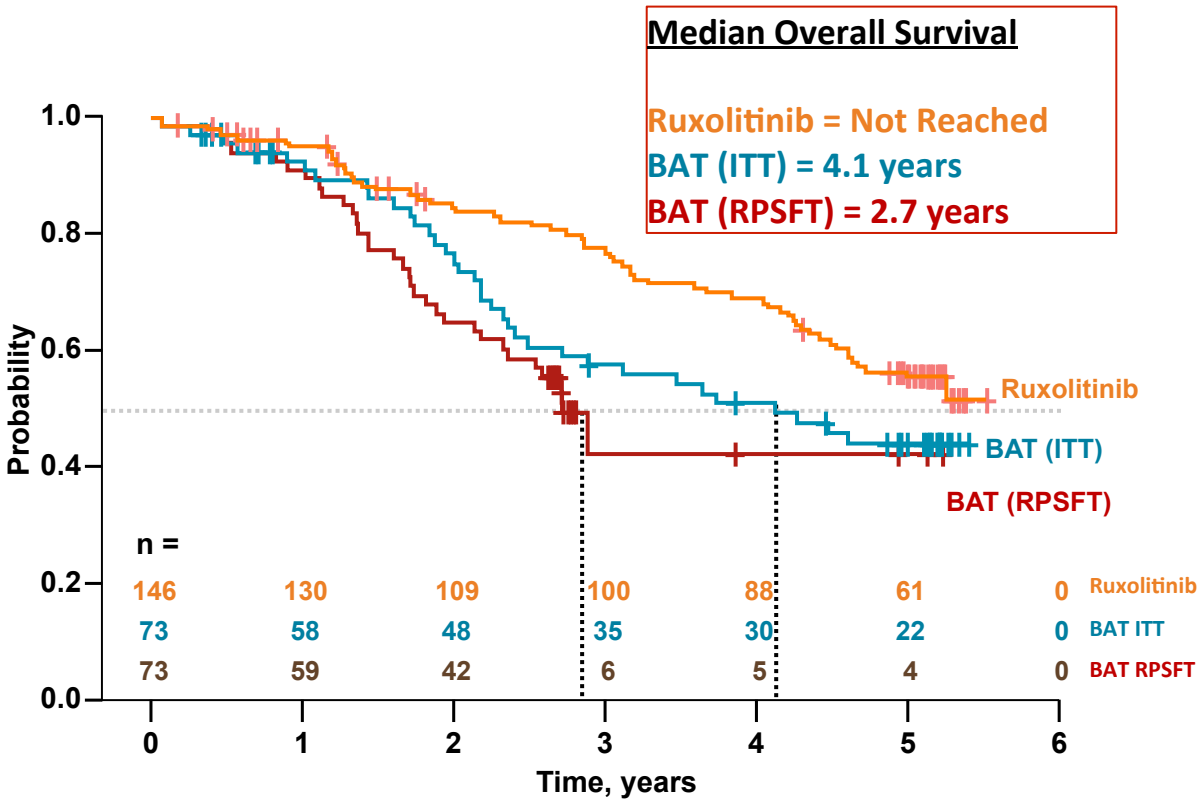
- 53% of patients receiving RUX achieved spleen response at any time
- The probability of maintaining a spleen response was 0.51 at 3 years and 0.48 at 5.0 years
- One-third of evaluable *JAK2* V617F-positive patients had a >20% reduction in allele burden
- 16% improved fibrosis; 32% had stable fibrosis, 18% had a worsening at their last assessment

- Adverse events grade 3-4: anemia (22%), thrombocytopenia (15%), pneumonia (6%)
- **Ruxolitinib-associated anemia, which occurs predominantly during early therapy, is not predictive of shortened survival**

Harrison et al; Leukemia. 2016 May 23

Ruxolitinib improves survival

results from the 5 years follow-up of the COMFORT-2

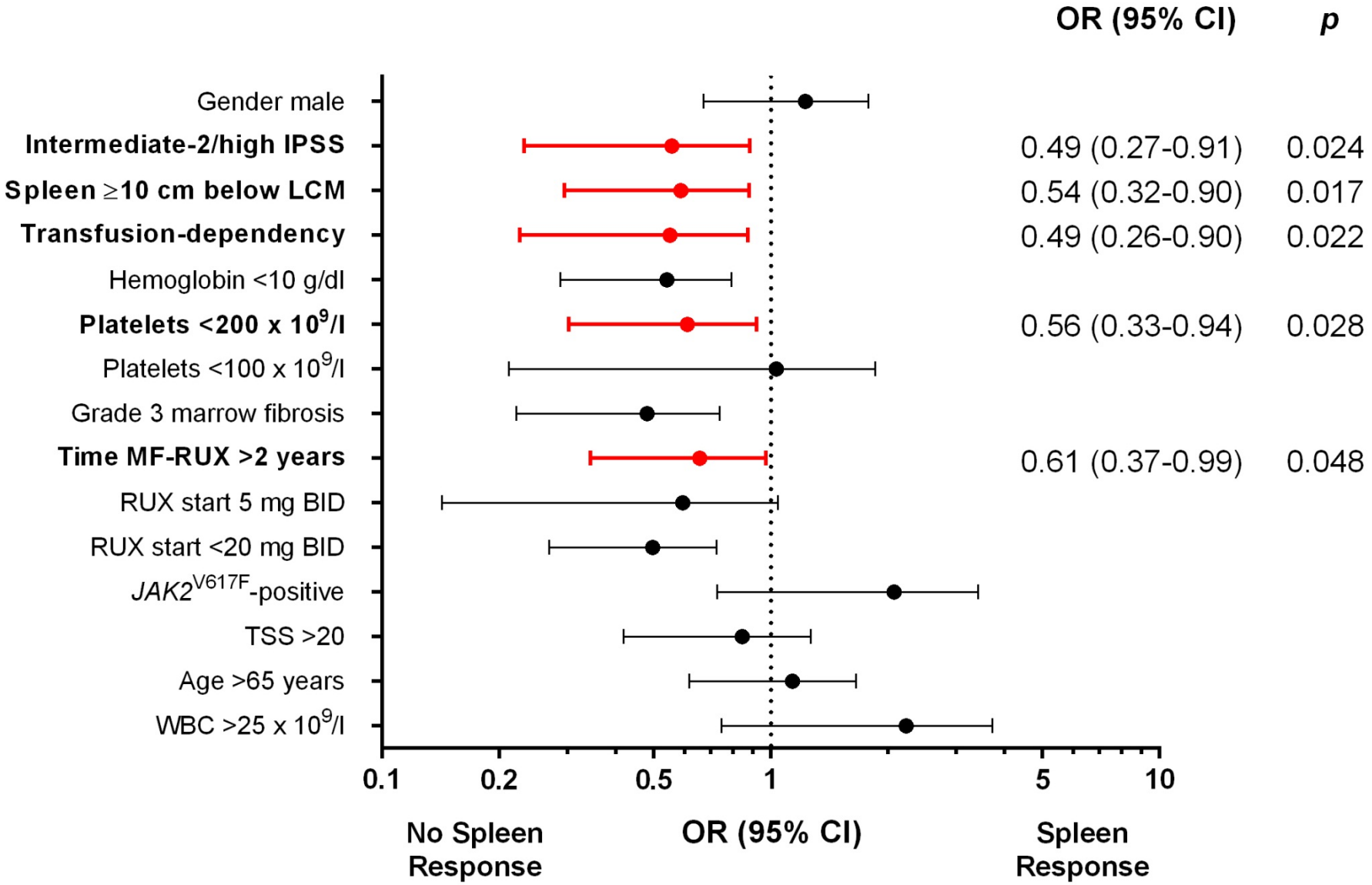


- Median OS was not reached with ruxolitinib
- ITT: HR, 0.67 (95% CI, 0.44-1.02); P = .06
- Ruxolitinib resulted in 33% reduction in risk of death compared with BAT
- RPSFT: HR, 0.44 (95% CI, 0.18-1.04) in favour of ruxolitinib vs BAT

Harrison et al; Leukemia. 2016 May 23

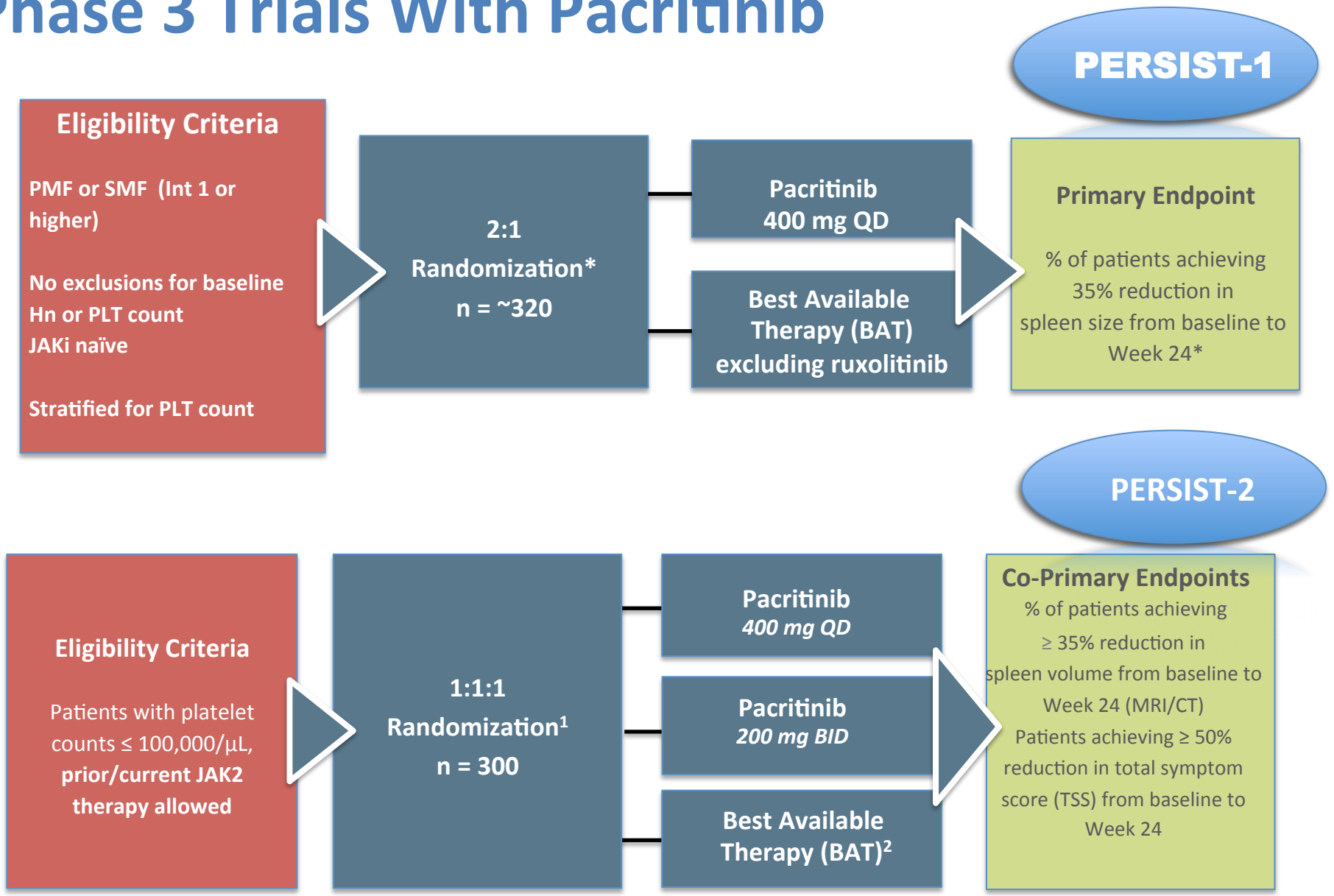
Predictors of spleen response with ruxolitinib

An observational, independent study on 408 MF



Palandri et al ASH 2016 (oral 1128)

Phase 3 Trials With Pacritinib



[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

PERSIST-1: results in 327 patients

- PAC: 220, BAT: 107), 62% PMF; 32% with PLT < 100 x10(9)/L; 16% with PLT < 50 x10(9)/L
- SVR rates at WK24: 19% vs. 5% (PAC vs. BAT) in ITT
- SVR improvement with PAC irrespective of baseline PLT
- TSS response rates: 25% vs 7% (PAC vs. BAT) in ITT
- 26% of RBC-TD PAC-treated pts (PAC: 35, BAT: 15), became RBC-TI vs 0% in BAT pts
- The most common adverse events (AEs) for PAC were gastrointestinal (GI): diarrhea, nausea, and vomiting.
- G3-4 anemia (17% vs 15% in PAC vs BAT) and thrombocytopenia (12% vs 9% in PAC vs BAT)

Mesa et al; Lancet Hematology 2017

Persist-2: Pacritinib - Efficacy Summary

Endpoint	Statistics	PAC QD+BID (n=149)	PAC QD (n=75)	PAC BID (n=74)	BAT (n=72)
Patients with ≥35% SVR from BL to Wk 24	n (%)	27 (18.1)	11 (14.7)	16 (21.6)	2 (2.8)
	95% CI*	12.3-25.3	7.6-24.7	12.9-32.7	0.3-9.7
	P value vs BAT	***0.001***	***0.017***	***0.001***	-
Patients with ≥50% reduction in TSS from BL to Wk 24	n (%)	37 (24.8)	13 (17.3)	24 (32.4)	10 (13.9)
	95% CI*	18.1-32.6	9.6-27.8	22.0-44.3	6.9-24.1
	P value vs BAT	***0.079***	***0.652***	***0.011***	-

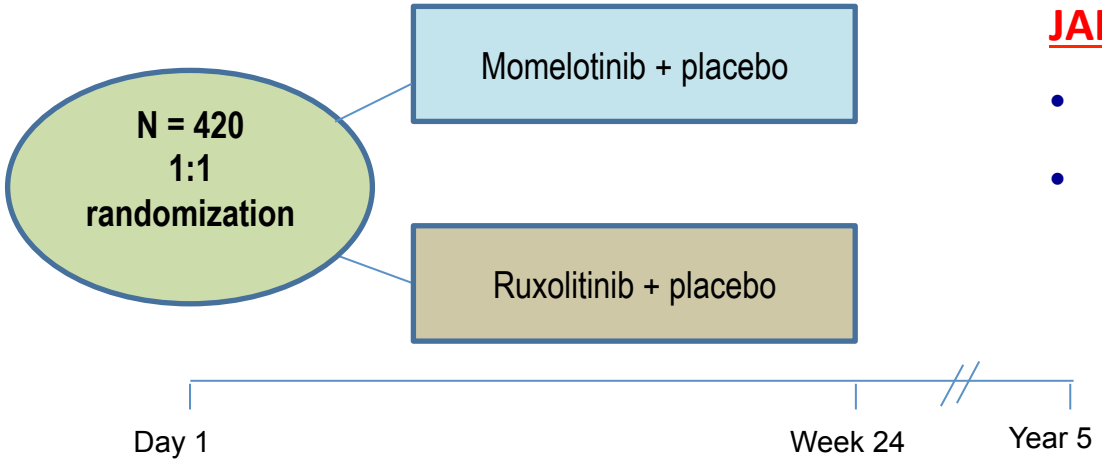
Mascarenas J et al. Blood 2016 128:LBA-5

Persist-2: Pacritinib - Most Common AEs (≥10%)

Characteristic	PAC QD n=104	PAC BID n=106	BAT n=98
Pts with ≥1 TEAE	104 (100)	100 (94)	87 (89)
Diarrhea	70 (67)	51 (48)	15 (15)
Nausea	39 (38)	34 (32)	11 (11)
Thrombocytopenia	34 (33)	36 (34)	23 (23)
Anemia	29 (28)	25 (24)	15 (15)
Vomiting	22 (21)	20 (19)	5 (5)
Peripheral edema	14 (13)	21 (20)	15 (15)
Dizziness	15 (14)	16 (15)	5 (5)
Abdominal pain	20 (19)	10 (9)	19 (19)
Pyrexia	11 (11)	16 (15)	3 (3)
Epistaxis	11 (11)	13 (12)	13 (13)
Constipation	15 (14)	8 (8)	6 (6)
Insomnia	12 (12)	10 (9)	4 (4)
Pruritus	10 (10)	11 (10)	6 (6)
Upper respiratory tract infection	8 (8)	11 (10)	6 (6)

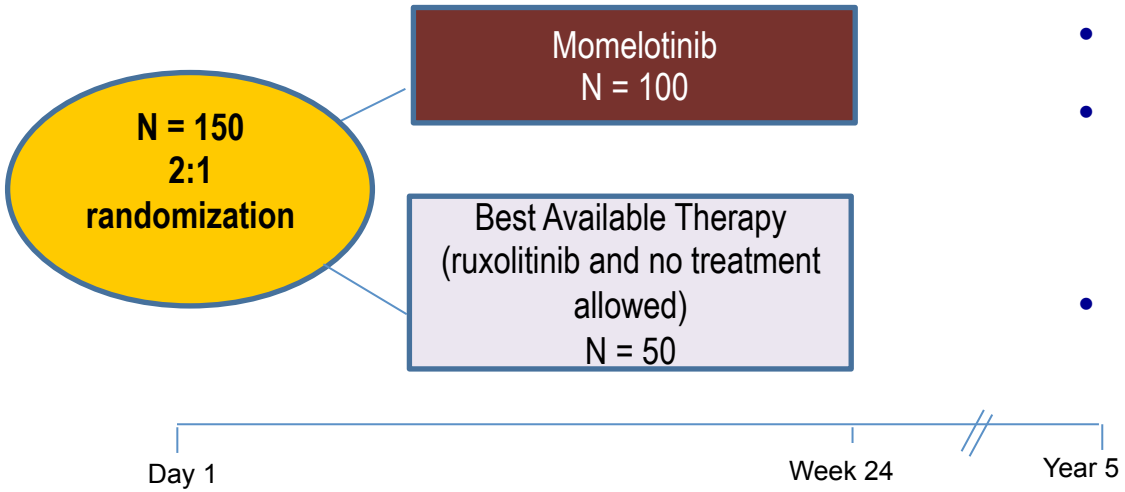
Mascarenas J et al. Blood 2016 128:LBA-5

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

- **SIMPLIFY-1:**
  - achieved non-inferiority to RUX for SR at Week 24
  - not achieved non-inferiority for TSS
  - greater improvements in all three pre-specified anemia-related secondary endpoints

- **SIMPLIFY-2:**
  - not achieved primary endpoint of superiority of momelotinib compared to BAT in patients previously treated with ruxolitinib in SR

Momelotinib - sponsor independet report

- 100 patients with MF enrolled in the phase-1/2 study (NCT00935987) (n. 166)
- two dose-escalation (100-400 mg OAD) and dose-confirmation (300 mg OAD) phases

	Patients
Primary MF	64
Palpable splenomegaly	87
Mutation status	
JAK2^{V617F}	73
CALR	16
MPL	7
triple negative	4
DIPSS-plus high	63
ASXL-1	44%
SRSF-2	18%

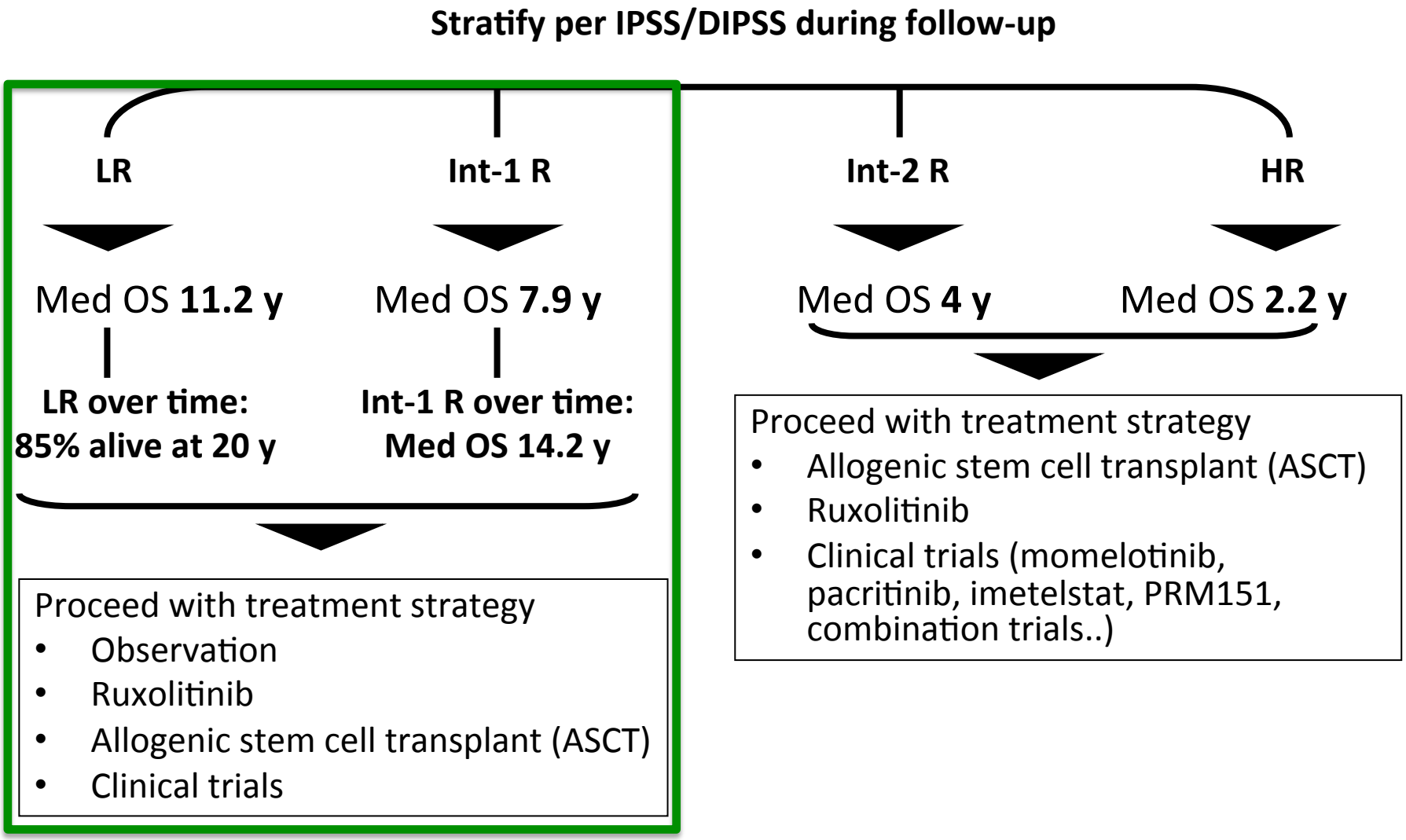
- 57% Clinical improvement
- 44% Anemia response
- 43% Spleen response
- 51% of transfusion-dependent patients became transfusion independent

- 34% G3-G4 thrombocytopenia
- 5% G3-G4 anemia
- 7% increased lipase
- 4% increased AST/ALT

- 47% G1-G2 peripheral neuropathy

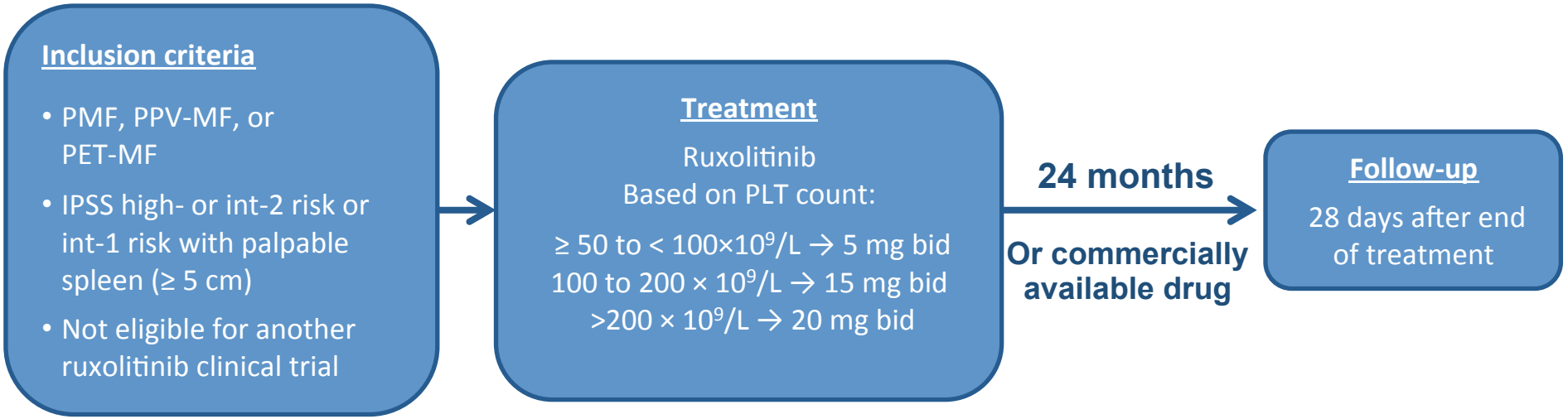
Tefferi A et al. Blood 2016 128:1123

Personalized approach to MF



Passamonti et al; Curr Opin Hematol. 2016 Mar;23(2):137-43

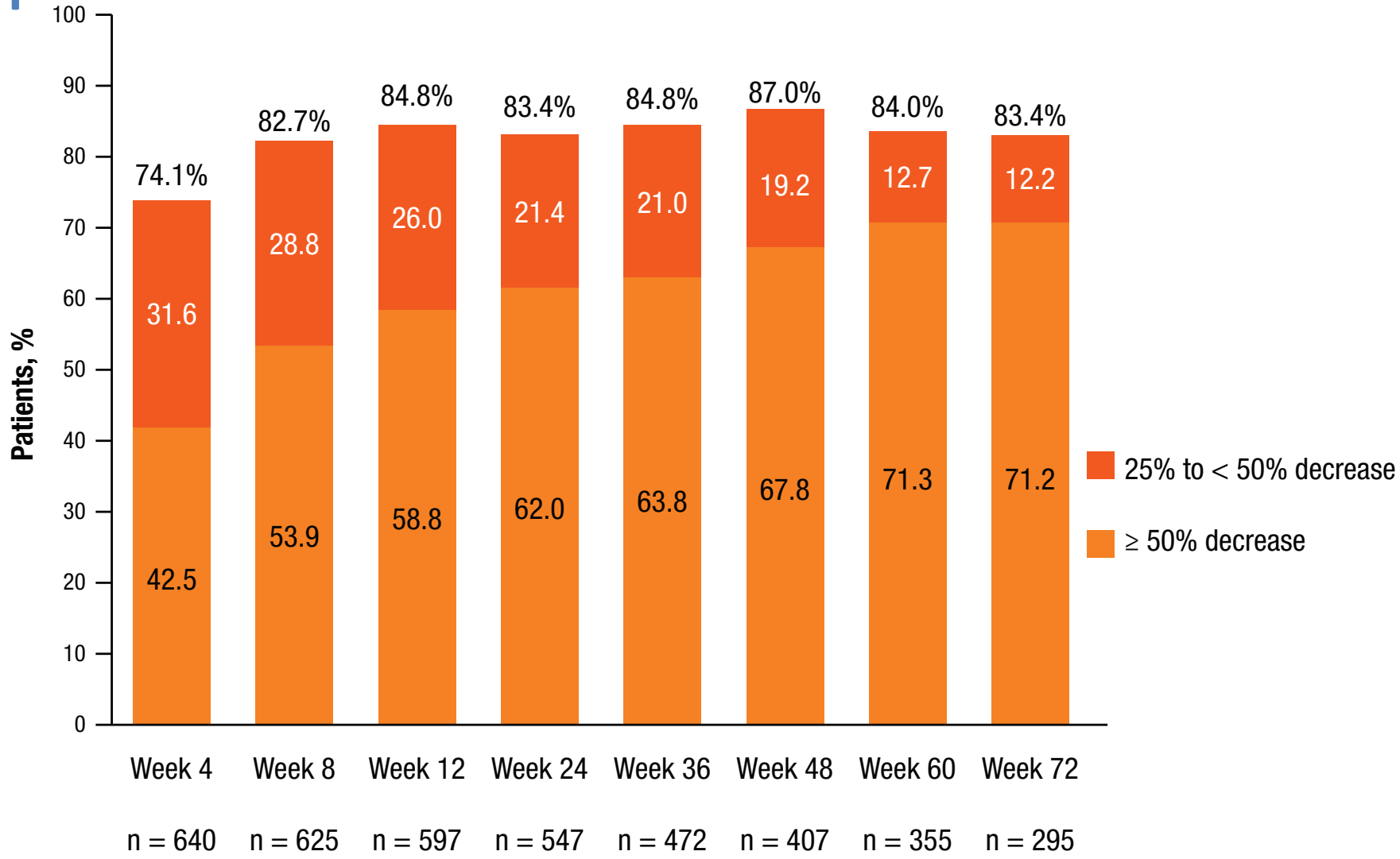
Ruxolitinib in the JUMP Trial
163 intermediate-1 patients



- The primary endpoint was assessment of safety and tolerability of ruxolitinib by the frequency, duration, and severity of adverse events (AEs)
  - Additional endpoints included the proportion of patients with a > 50% reduction in palpable spleen length, patient-reported outcomes (including the Functional Assessment of Cancer Therapy-Lymphoma [FACT-Lym] total score), and progression-free, leukemia-free, and overall survival

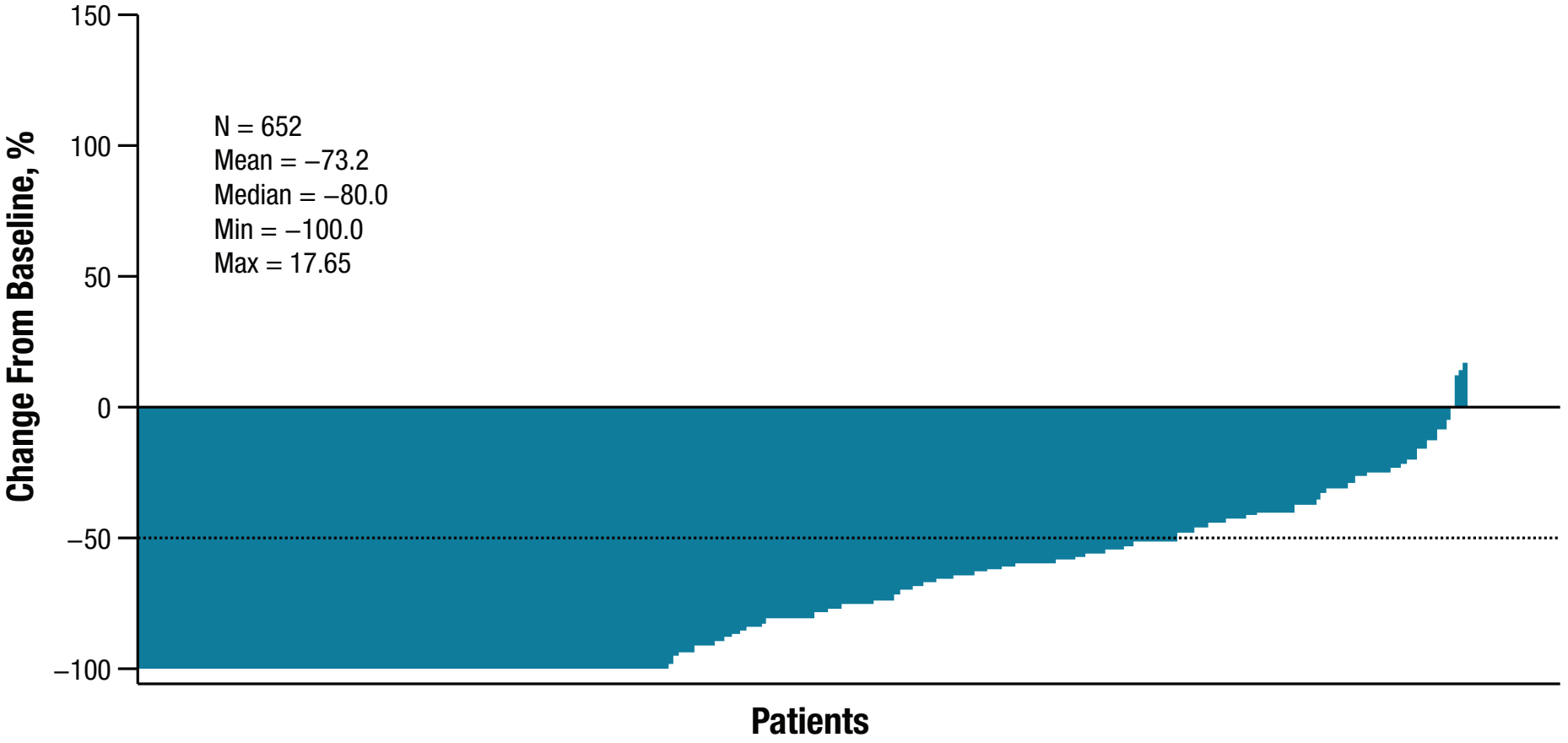
Giraldo P, et al. Haematologica 2016

JUMP study, analysis on 700 Int-1 DIPSS patients: Spleen Reduction



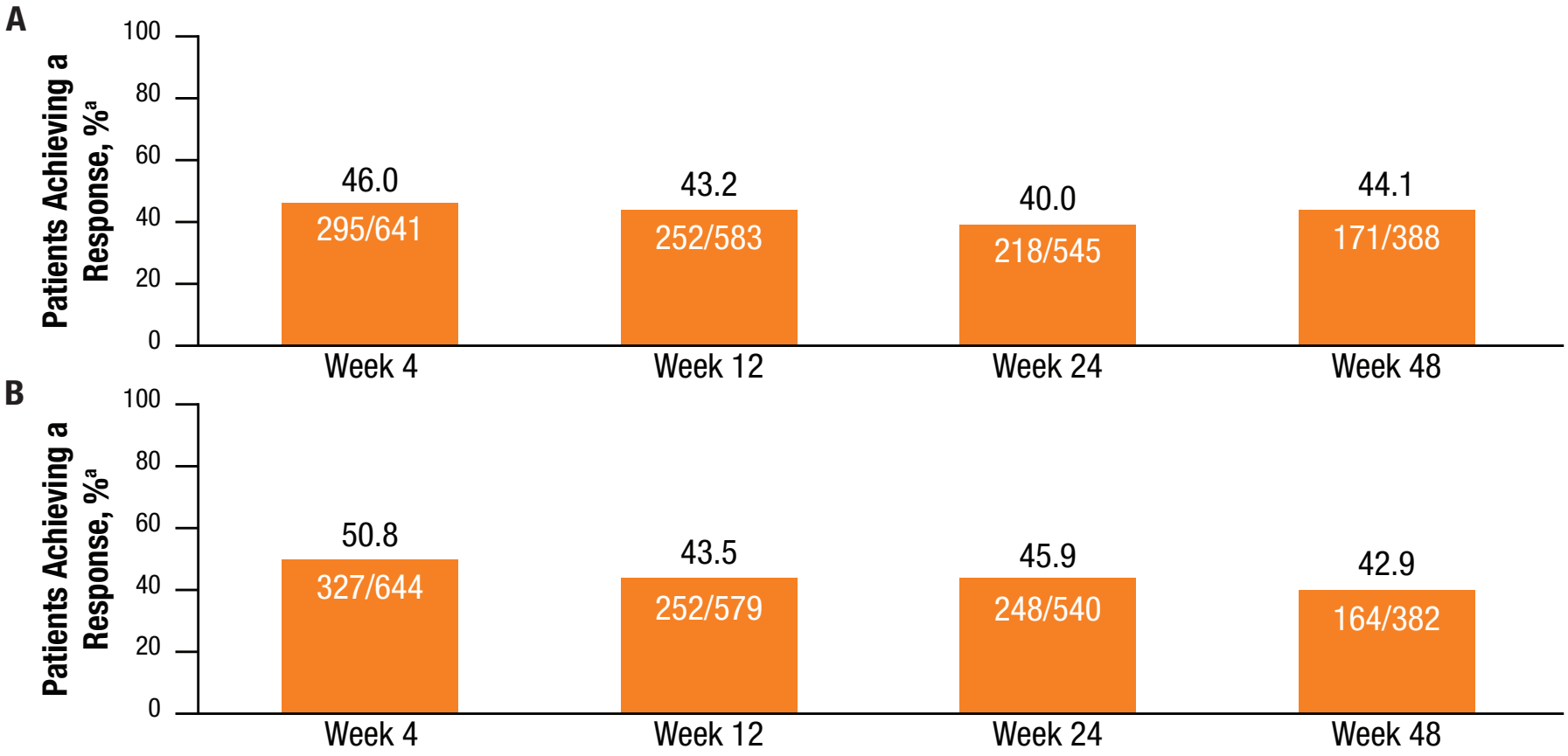
Passamonti et al, EHA 2016

JUMP study, analysis on 700 Int-1 DIPSS patients: 30% of the spleens became unpalpable



Passamonti et al, EHA 2016

JUMP study, analysis on 700 Int-1 DIPSS patients: FACT-Lym TS/FACIT Fatigue scale



Passamonti et al, EHA 2016

JUMP study, analysis on 700 Int-1 DIPSS patients: Safety

- The most common hematologic AEs were
  - anemia (all grade, 55.1%; grade 3/4, 22.0%)
  - thrombocytopenia (all grade, 39.7%; grade 3/4, 10.3%)
  - leukopenia (all grade, 5.4%; grade 3/4, 2.4%)
- Anemia and thrombocytopenia led to discontinuation in 1.4% and 2.2% of patients, respectively
- The most common nonhematologic AEs were:
  - Infections (≥ 5%) included urinary tract infection (all grade, 6.4% [grade 3/4, 0.7%]), herpes zoster (all grade, 6.0% [grade 3/4, 0.4%]), and nasopharyngitis (all grade, 5.4% [grade 3/4, 0%]); there was 1 report of hepatitis B reactivation (grade 3/4)

Passamonti et al, EHA 2016