New JAK Inhibitors in MPNs and Combination Therapy

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JAK Inhibitors in Myelofibrosis

ATP-competitive inhibitors targeting both wild-type and JAK2^{V617F} *in vitro*

Agent	Other targets	Phase
Ruxolitinib	JAK1	Approved
Momelotinib	JAK1, JNK1, TYK2, CDK2	III
Pacritinib	FLT3	III (on hold)
CEP-701	FLT3, TrkA	II
Fedratinib	FLT3	III (filed)
AZD1480	JAK1, JAK3	II (filed)
LY2784544	NA	II (filed)
NS-018	Src	I
BMS-911543	-	I

Fedratinib (JAK2 Inhibitor): Effective in 1rst and 2nd Line in MF but Withdrawn Due to Encephalopathy

Results of a randomized, double-blind, placebo-controlled phase III study (JAKARTA) of the JAK2-selective inhibitor Fedratinib (SAR302503) in patients with MF

Pardanani et al, ASH 2013, abst. 393

	Placebo (n=96)		Fedratinib 400 mg (n=96)		Fedratinib 500 mg (n=97)	
Splenic volume response	Wk 24	Confirmed Wk 28	Wk 24	Confirmed Wk 28	Wk 24	Confirmed Wk 28
All patients, n (%)	1 (1)	1 (1)	45 (47)*	35 (36)*	48 (49)*	39 (40)*
Baseline platelets ≥100 ×10^9/L, n/N (%)	1/77 (1)	1/77 (1)	40/82 (49)	32/82 (39)	42/82 (51)	33/82 (40)
Baseline platelets <100 ×10^9/L, n/N (%)	0/18 (0)	0/18 (0)	5/14 (36)	3/14 (21)	6/15 (40)	5/15 (33)
Symptom response, n/N (%)	6/82 (7)		33/89 (37)*		31/90 (34)*	

*p<0.0001 vs placebo

Efficacy and safety of Fedratinib In patients with intermediate- or high-risk PMF, Post-PV MF, or Post-ET MF previously treated with ruxolitinib: Interim results from a phase II study (JAKARTA-2)

Harrison et al, ASH 2013, abst. 661

Pacritinib (JAK2 Inhibitor) Phase 2 Study: Response in Splenomegaly

Endpoint	Time Period	Baseline Platelets ≤100,000/μL (n=28)*	Baseline Platelets >100,000/μL (n=37)*	All (n=65)
≥ 50% Reduction in spleen size by PE	Up to 24 weeks	12 / 28 (43%)	14 / 34 (41%)	26 / 62 (42%)
	Up to last visit on treatment	13 / 28 (46%)	14 / 35 (40%)	27 / 63 (43%)
≥ 35% Reduction in spleen volume by MRI	Up to 24 weeks	7 / 23 (30%)	6 / 26 (23%)	13 / 49 (27%)
	Up to last visit on treatment	10 / 23 (44%)	8 / 26 (31%)	18 / 49 (37%)

* No significant differences were observed between the two groups

Komrojki *et al*., ASH 2013

PERSIST-1

Study Design

Key Eligibility Criteria

- PMF, PET-MF, or PPV-MF
- Intermediate- or high-risk disease
- Palpable spleen ≥5 cm
- No exclusion for baseline platelet levels; stratified for platelet counts <100,000/μL and <50,000/μL
- No exclusion for baseline Hgb levels
- No prior treatment with JAK2 inhibitors

[a] Cross-over from BAT allowed after progression or after Week 24 assessment.

- Stratification at randomization: platelet count, risk category, and region
- Study endpoints
  - **Primary**: proportion of patients achieving a ≥35% reduction in spleen volume (by MRI/CT) from baseline to Week 24
  - **Secondary**: proportion of patients with ≥50% reduction in TSS from baseline to Week 24 on the Myeloproliferative Neoplasm Symptom Assessment Form

CT, computed tomography; Hgb, hemoglobin JAK, Janus kinase; MRI, magnetic resonance imaging; PET-MF, post-essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythemia vera myelofibrosis; R, randomized; TSS, total symptom score.

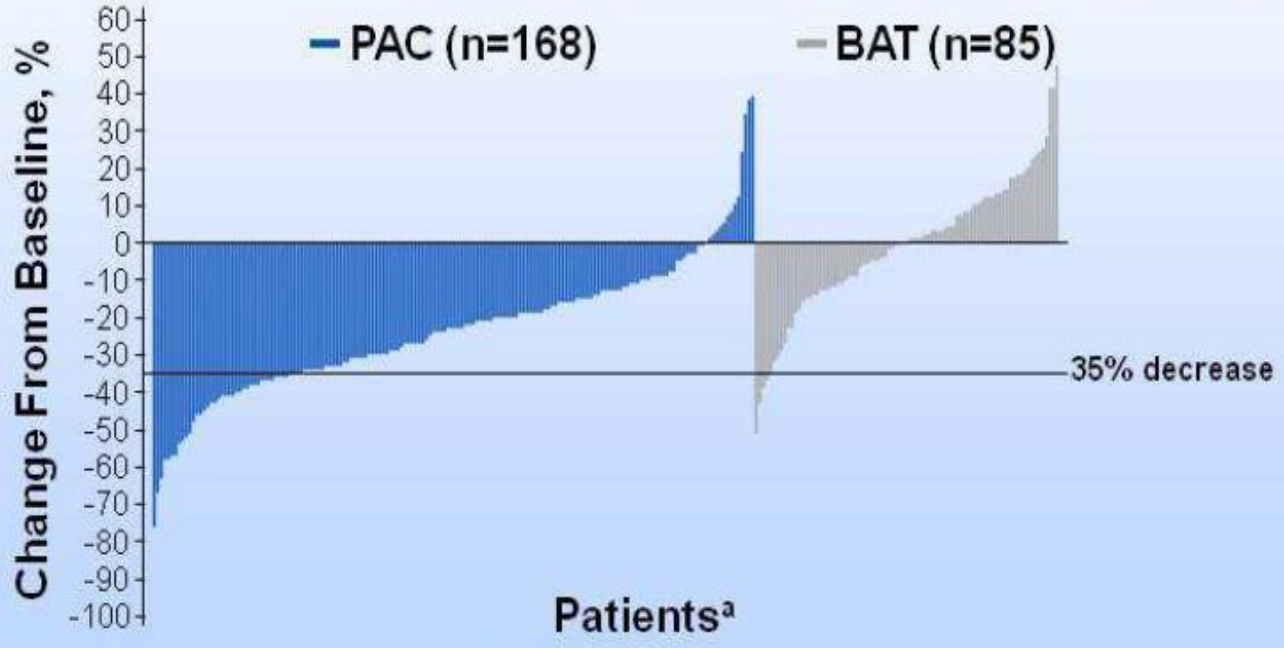
Mesa *et al*., ASCO 2015

PERSIST-1: Response in Splenomegaly

Spleen Volume Reduction ≥35%

At Week 24 as Assessed by MRI/CT

- **ITT population**: 19.1% vs 4.7%, PAC vs BAT (p=0.0003)
- **Evaluable[a] population**: 25.0% vs 5.9%, PAC vs BAT (p=0.0001)

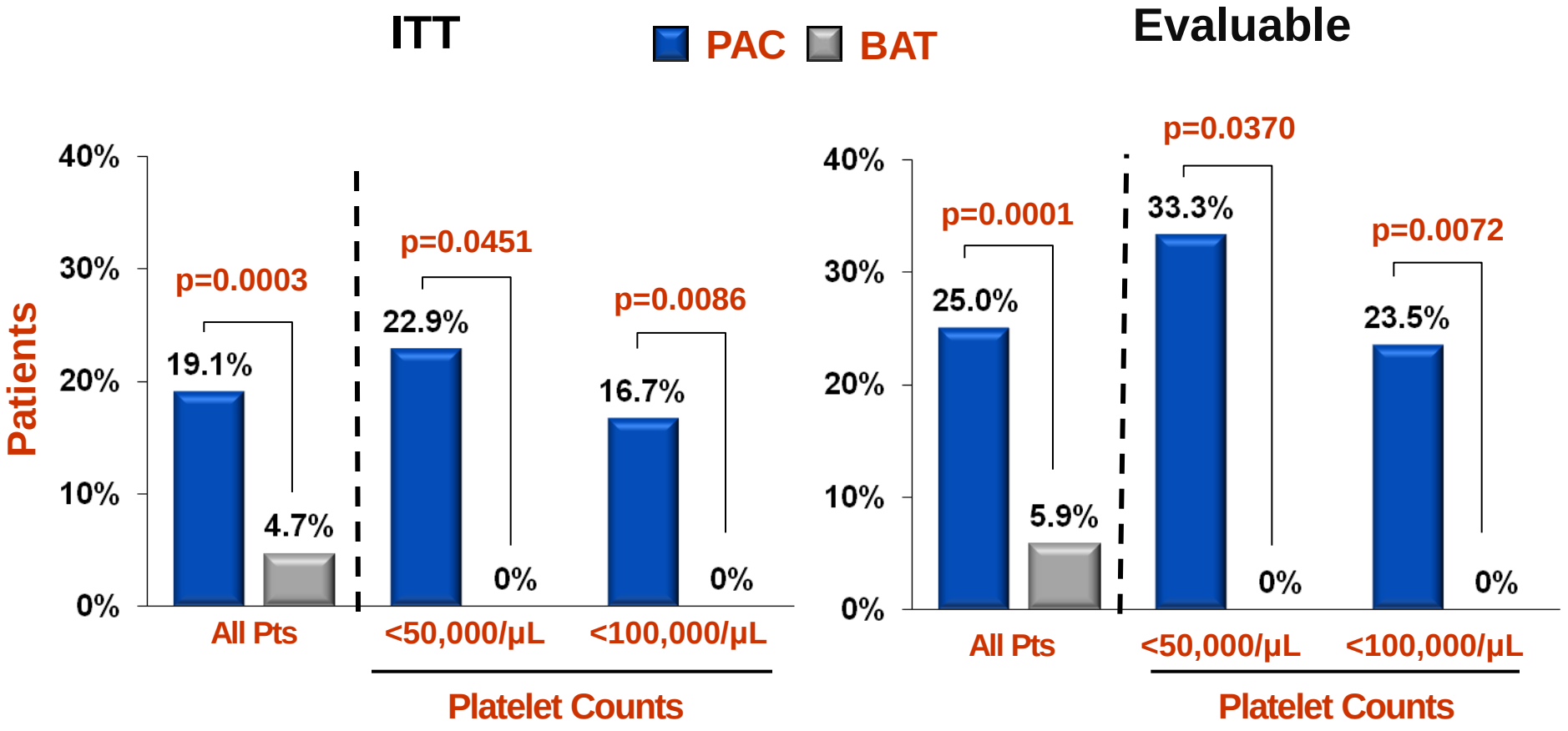


[a] Evaluable Population: patients had both baseline and Week 24 spleen assessment by MRI or CT; n=168 for PAC and n=85 for BAT.
BAT, best available therapy; CT, computed tomography; ITT, intent to treat; MRI, magnetic resonance imaging; PAC, pacritinib.

Mesa *et al*., ASCO 2015

PERSIST-1: Spleen Volume Reduction ≥35%

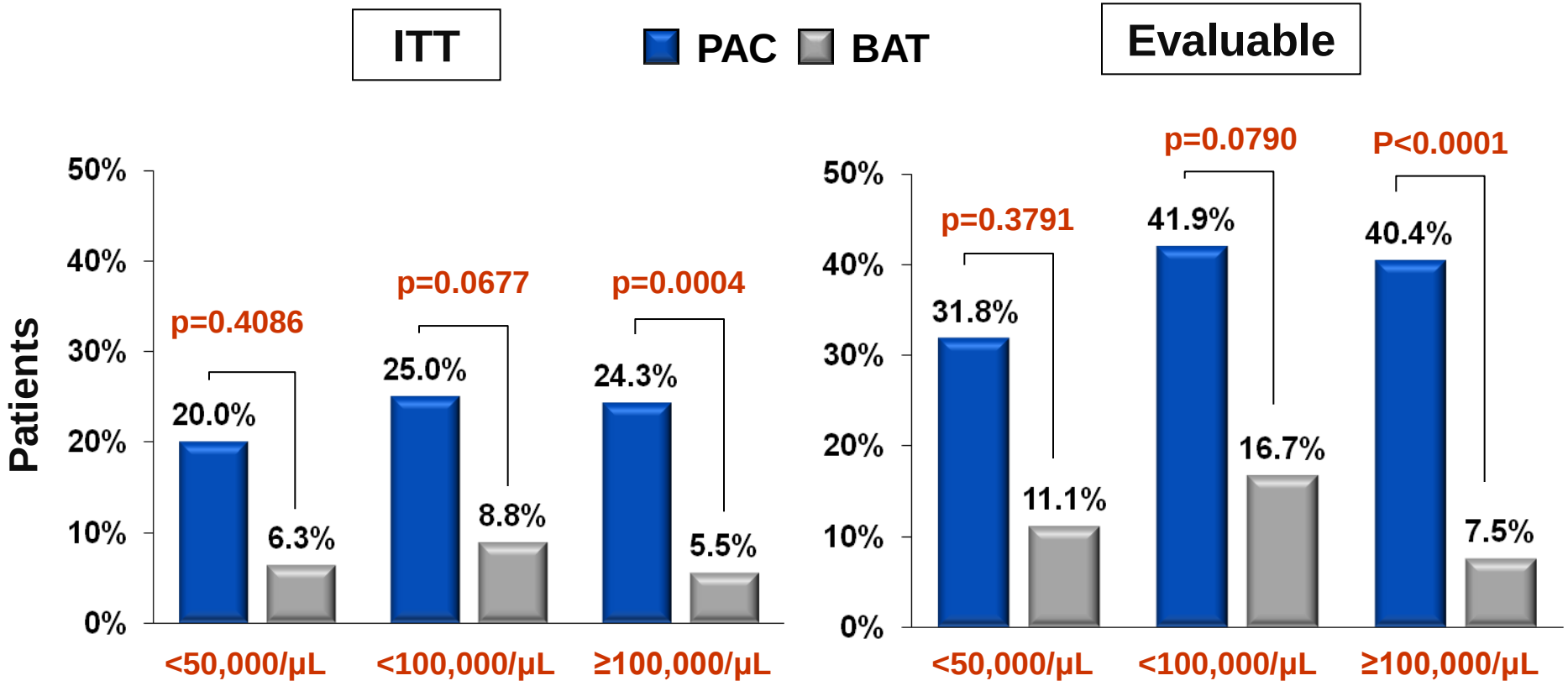
All Patients and Those with Baseline Thrombocytopenia



Mesa *et al*., EHA 2015

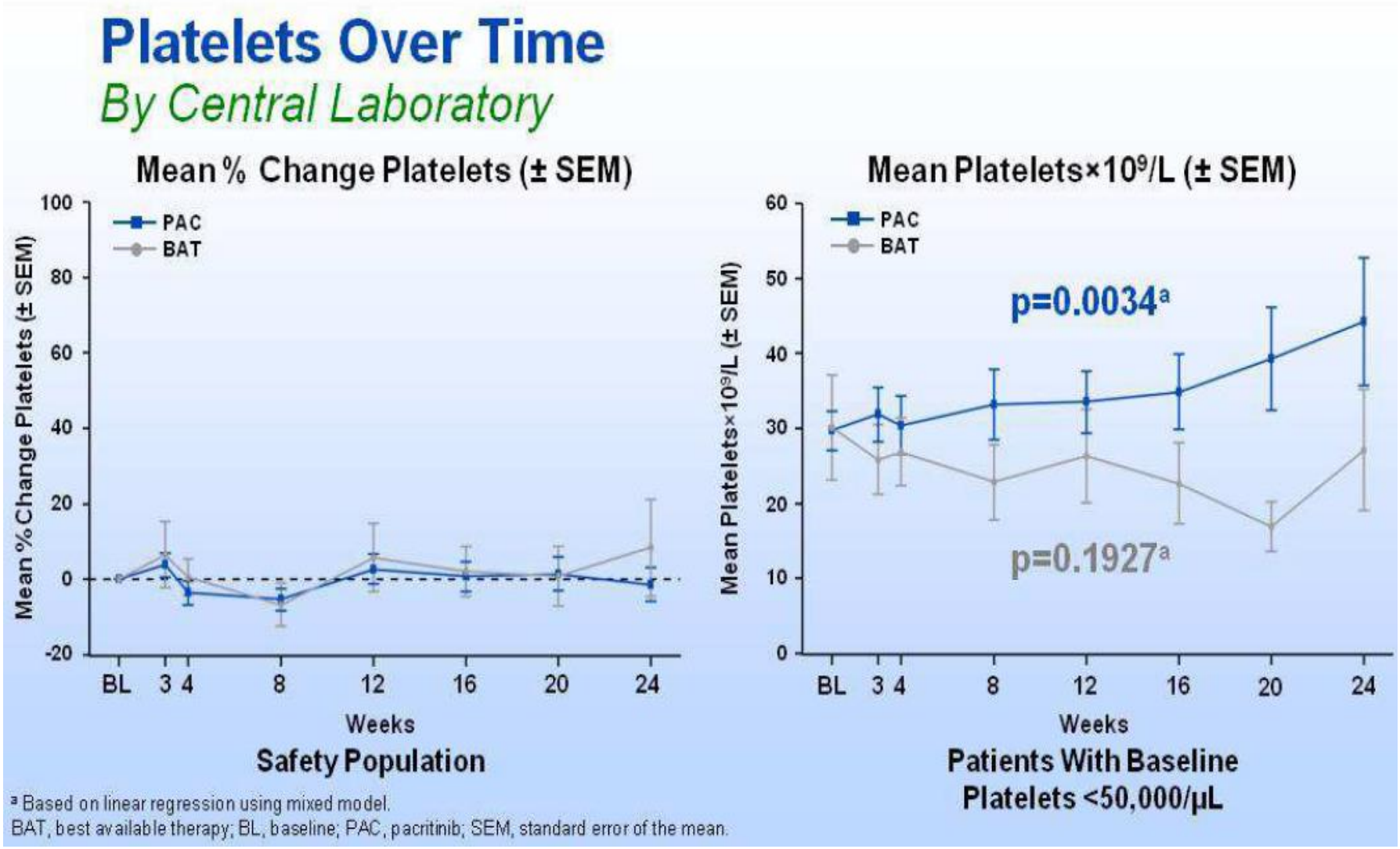
PERSIST-1: ≥50% Reduction in TSS[a]

At Week 24 by Baseline Platelet Counts



Mesa *et al*., EHA 2015

PERSIST-1: Platelets Over Time



Mesa *et al*., ASCO 2015

PERSIST-1: Adverse Events

Most Common Adverse Events
Within 24 Weeks (by Investigator)

Adverse Event, n (%)	All Grades		Grade 3		Grade 4	
	PAC (n=220)	BAT (n=106)	PAC (n=220)	BAT (n=106)	PAC (n=220)	BAT (n=106)
Non-hematologic (>10%)						
Diarrhea	117 (53.2)	13 (12.3)	11 (5.0)	0	0	0
Nausea	59 (26.8)	7 (6.6)	2 (0.9)	0	0	0
Vomiting	35 (15.9)	6 (5.7)	2 (0.9)	0	0	0
Peripheral edema	16 (7.3)	12 (11.3)	1 (0.5)	1 (0.9)	0	0
Pyrexia	11 (5.0)	11 (10.4)	4 (1.8)	1 (0.9)	0	0
Hematologic (>2%)						
Anemia	49 (22.3)	21 (19.8)	32 (14.5)	13 (12.3)	5 (2.3)	3 (2.8)
Thrombocytopenia	37 (16.8)	14 (13.2)	12 (5.5)	7 (6.6)	14 (6.4)	3 (2.8)
Neutropenia	8 (3.6)	2 (1.9)	1 (0.5)	1 (0.9)	4 (1.8)	1 (0.9)

- 10% of patients in the PAC arm had dose reductions due to AE (3% diarrhea; 2% anemia)

AE, adverse event; BAT, best available therapy; PAC, pacritinib.

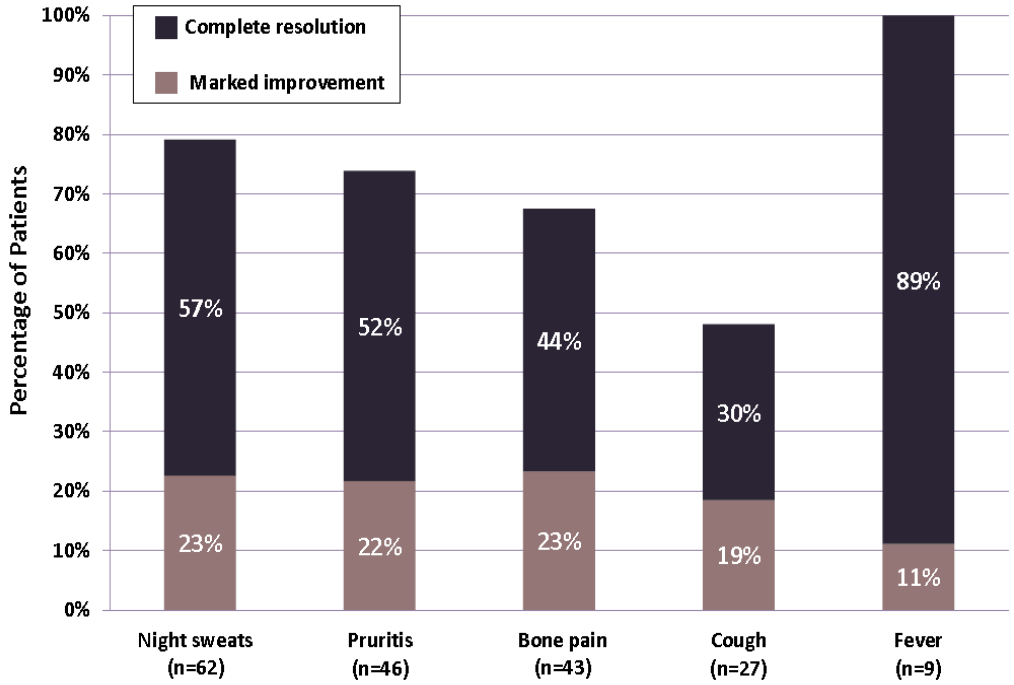
Mesa *et al*., ASCO 2015

However, …

All clinical studies with Pacritinib were recently put on total hold by the FDA because of an excess of deaths in the pacritinib arm due to brain bleeding, cardiac arrest, and cardiac failure.

Momelotinib (JAK1/JAK2 Inhibitor): Response in Splenomegaly and Symptoms at 6 months

Response by Dose (Core Study)	150 mg QD (n=52)	300 mg QD (n=60)	150 mg BID (n=42)	Total[1] (n=166)
Spleen evaluable (n)	47	51	37	145
Spleen response (IWG-MRT)	32%	39%	38%	37%
Median spleen decrease at six months[2]	-36%	-38%	-46%	-38%



Pardanani *et al*., Leukemia 2013

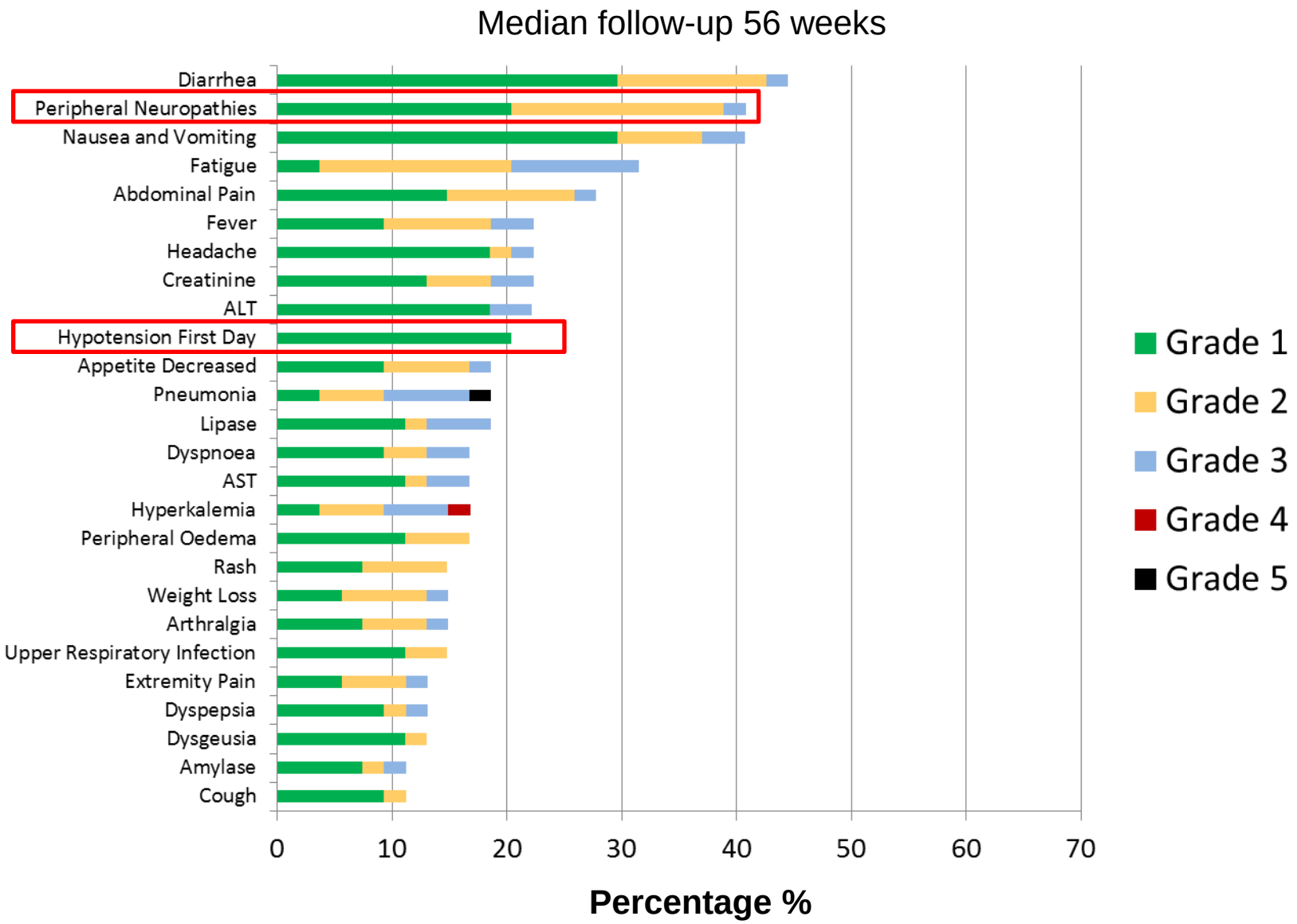
Momelotinib: Anemia Response

Anemia Response	Number of Subjects (%)
Transfusion dependent at baseline	72 (43%)
Achieved transfusion independence on study that lasts ≥ 12 weeks: C (C/72)	49 (68%)
Transfusion independent with Hgb < 10 g/dL at baseline	39 (24%)
Rise in Hgb ≥ 2 g/dL on study that lasts ≥ 12 weeks: D (D/39)	10 (26%)
Anemia Response: C + D	59 (53%)

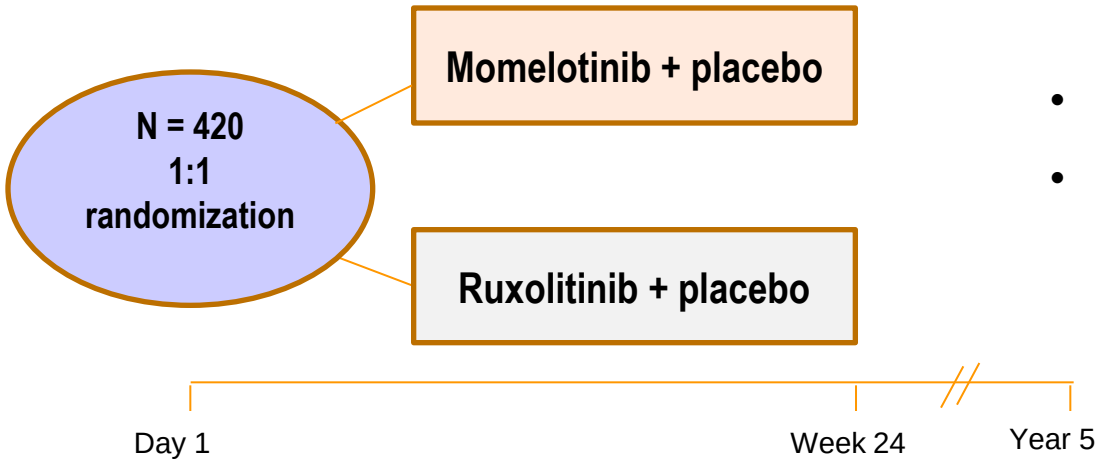
Transfusion dependence at baseline is defined as ≥ 2 units of RBC transfusions in the 30 days prior to C1/D1 and/or identified as transfusion dependent in medical history

Pardanani *et al*., ASH 2013

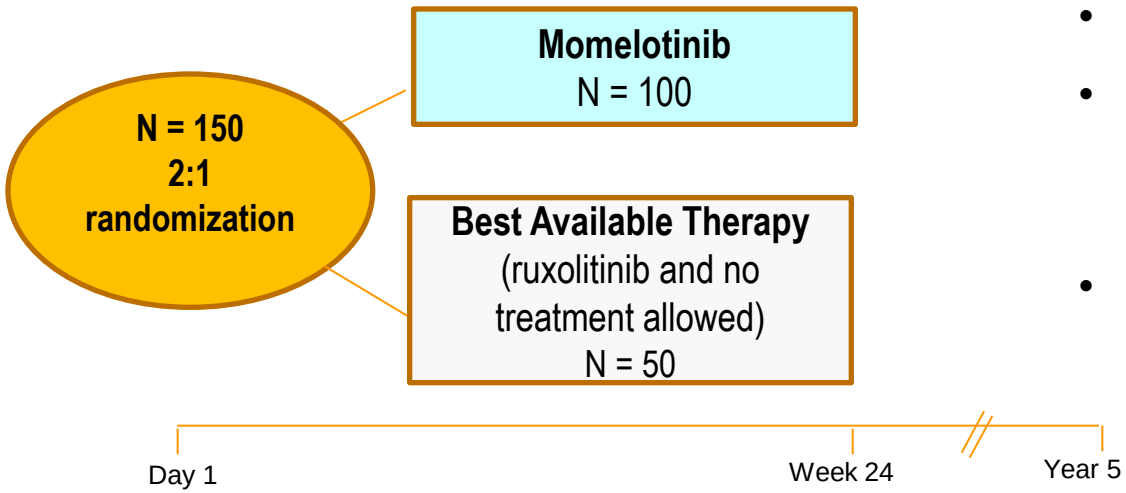
Momelotinib: Most Common (> 10%) Non-Hematologic Adverse Events, 200 mg BID Cohort (n= 54)



Momelotinib: Phase 3 Studies with 200 mg QD for Myelofibrosis



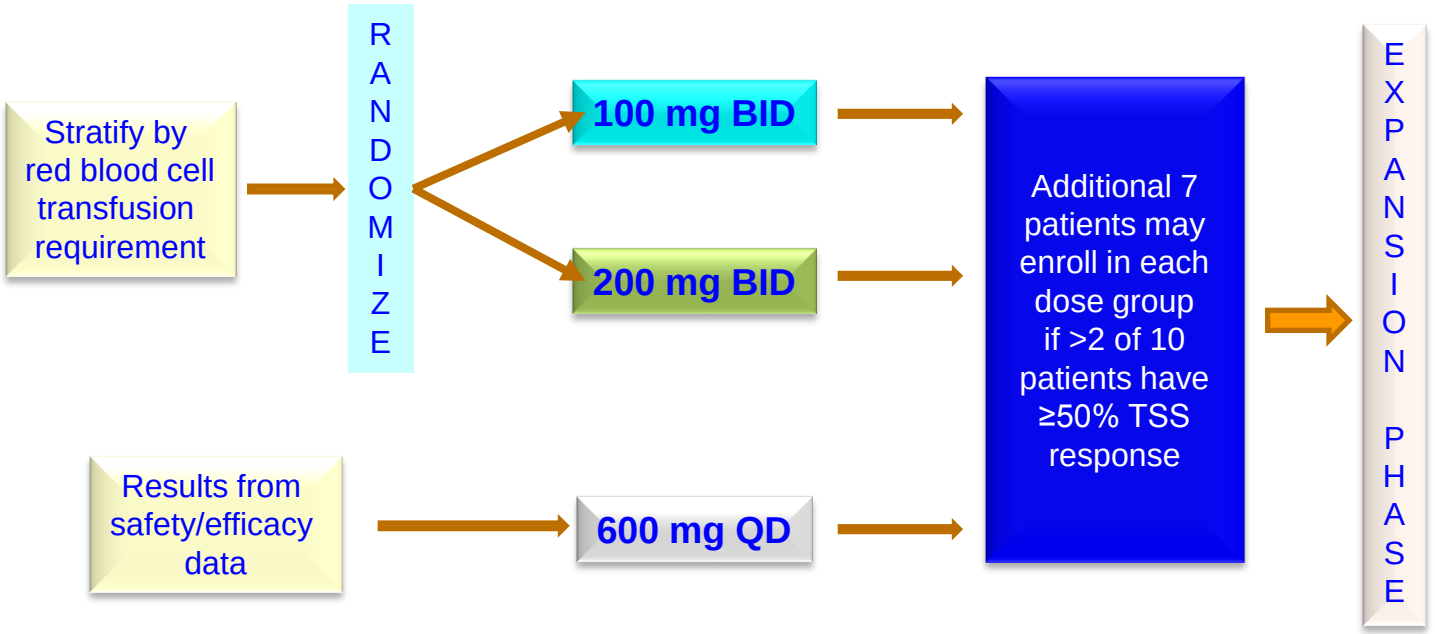
- **Randomized, Double Blind**
- **Primary endpoint: Spleen Response by MRI at week 24**



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

Phase II Study of INCB039110, a Selective JAK1 Inhibitor, in Myelofibrosis

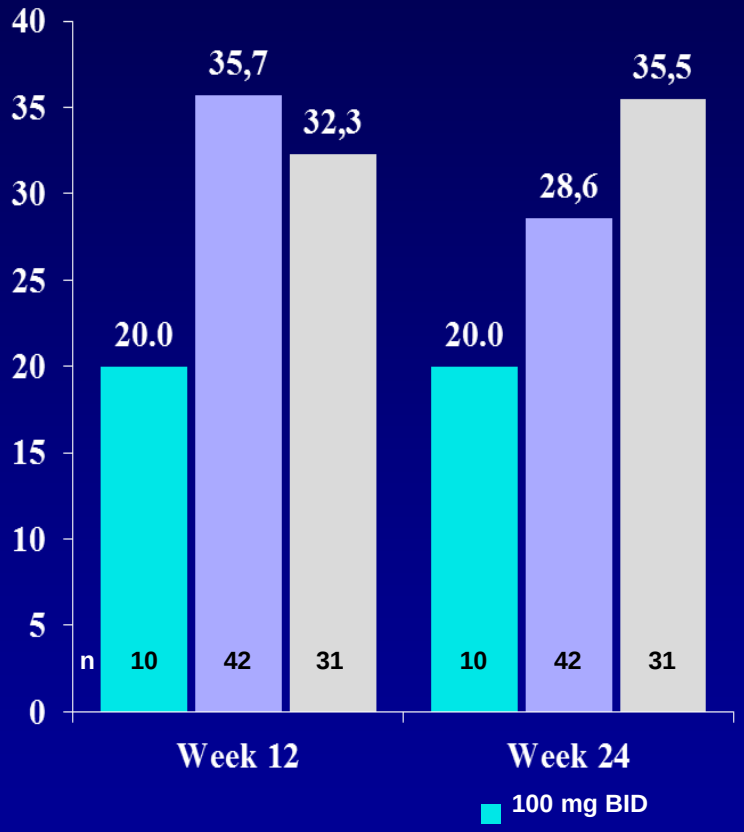
Primary endpoint:
Proportion of patients with ≥50% reduction from baseline in TSS in each dose group per the modified MFSAF v3.0 electronic diary at week 12



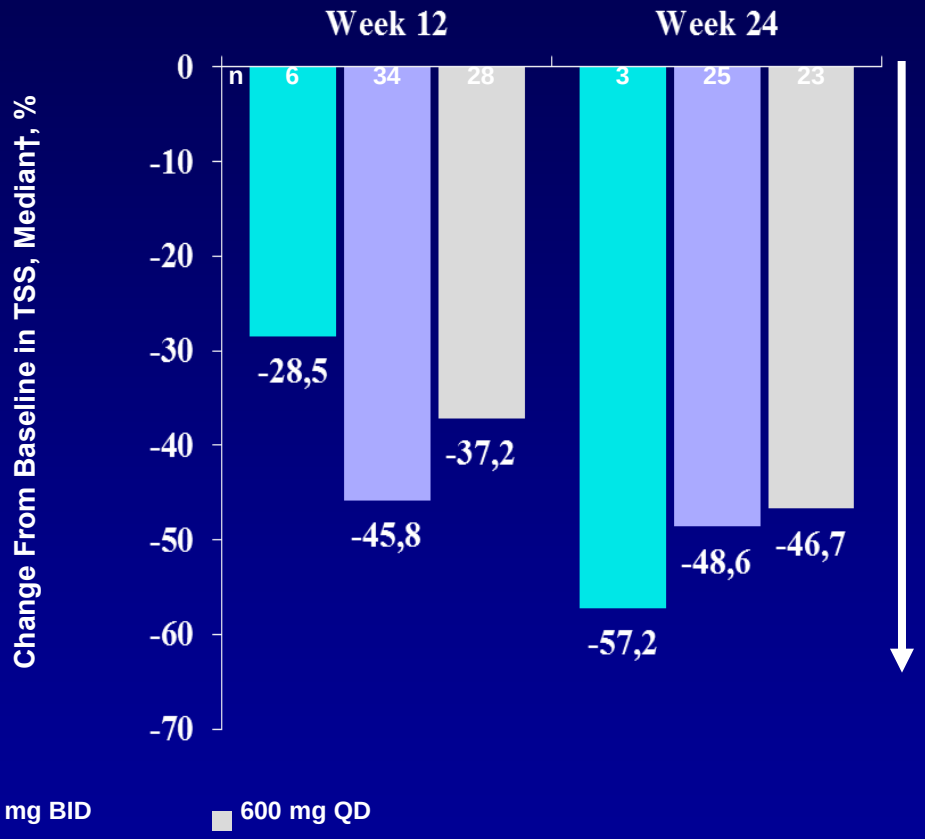
Mascarenhas J et al, ASH 2014, abst. 714

Improvement in TSS at Week 12 and 24 by Dose Cohort

≥50% Reduction in TSS*



Median % Change in TSS†



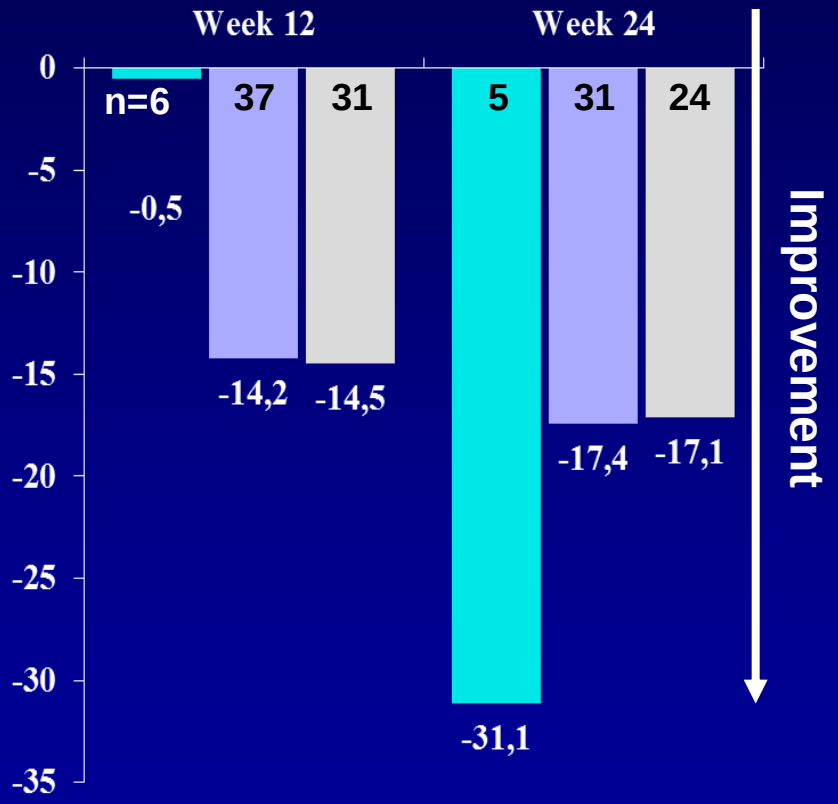
*Patients who discontinued prior to the week 12 or 24 visit were considered nonresponders. Patients without TSS at baseline were not included in the analysis.

†Patients who were not evaluable at baseline or week 12 or 24 due to missing data or discontinuation were not included in the analysis.

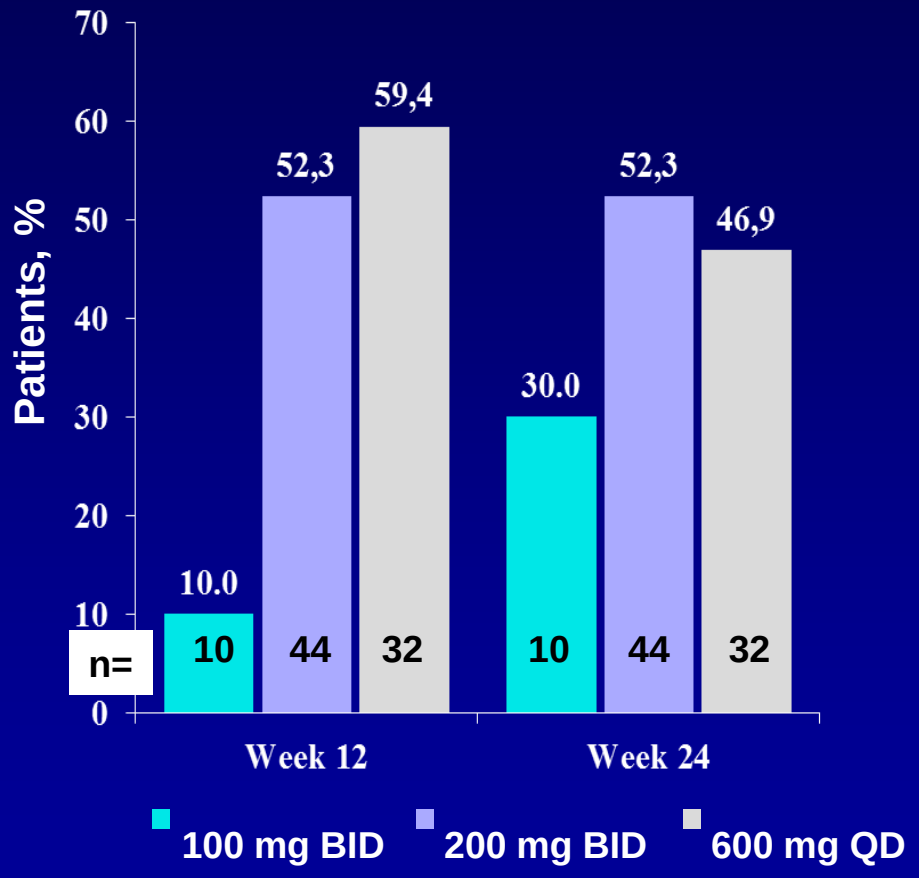
Mascarenhas J et al, ASH 2014, abst. 714

Changes in Spleen Volume at Weeks 12 and 24 by Dose Cohort

Median % Change in Spleen Volume*

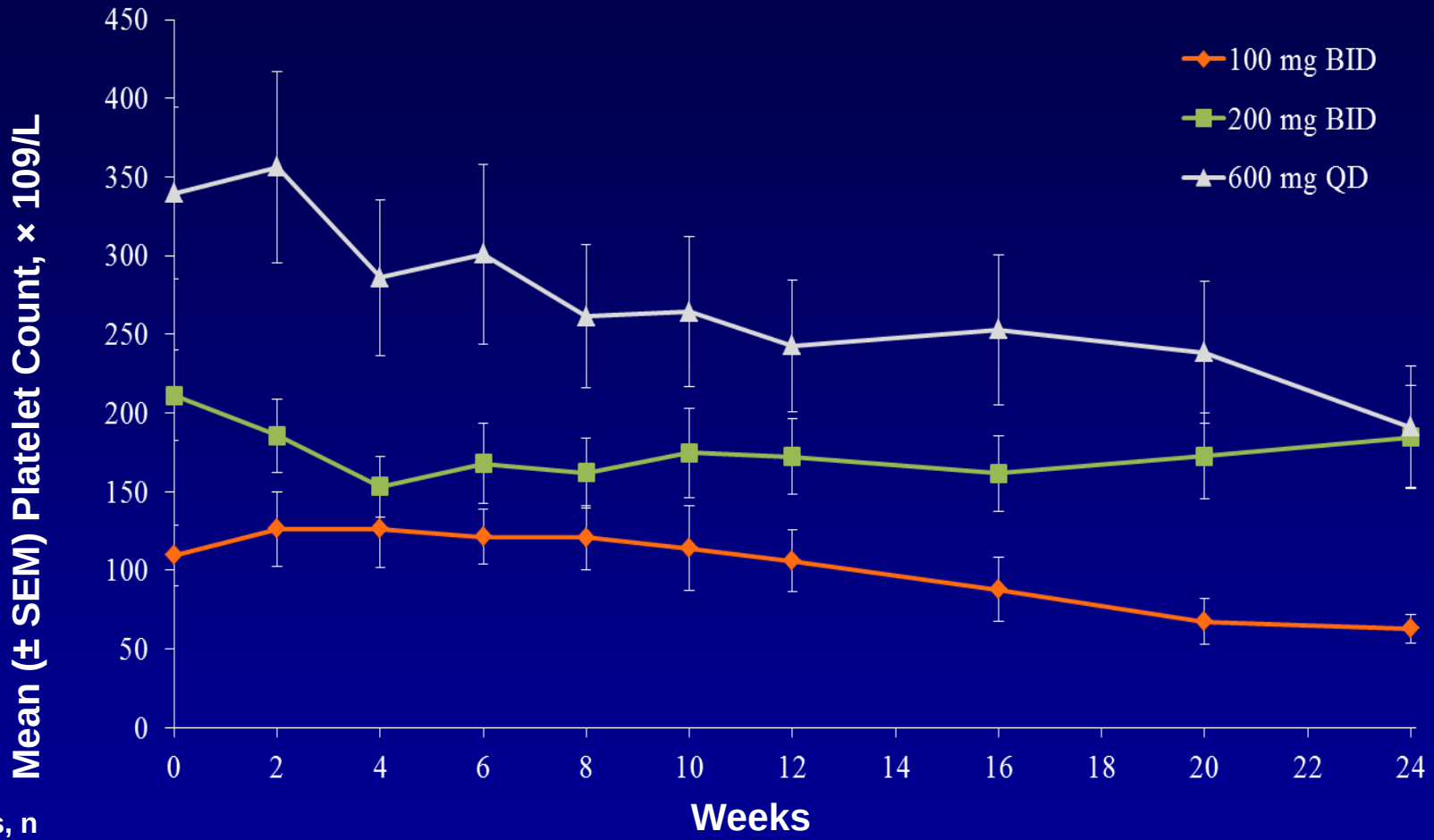


≥10% Reduction in Spleen Volume†



Mascarenhas J et al, ASH 2014, abst. 714

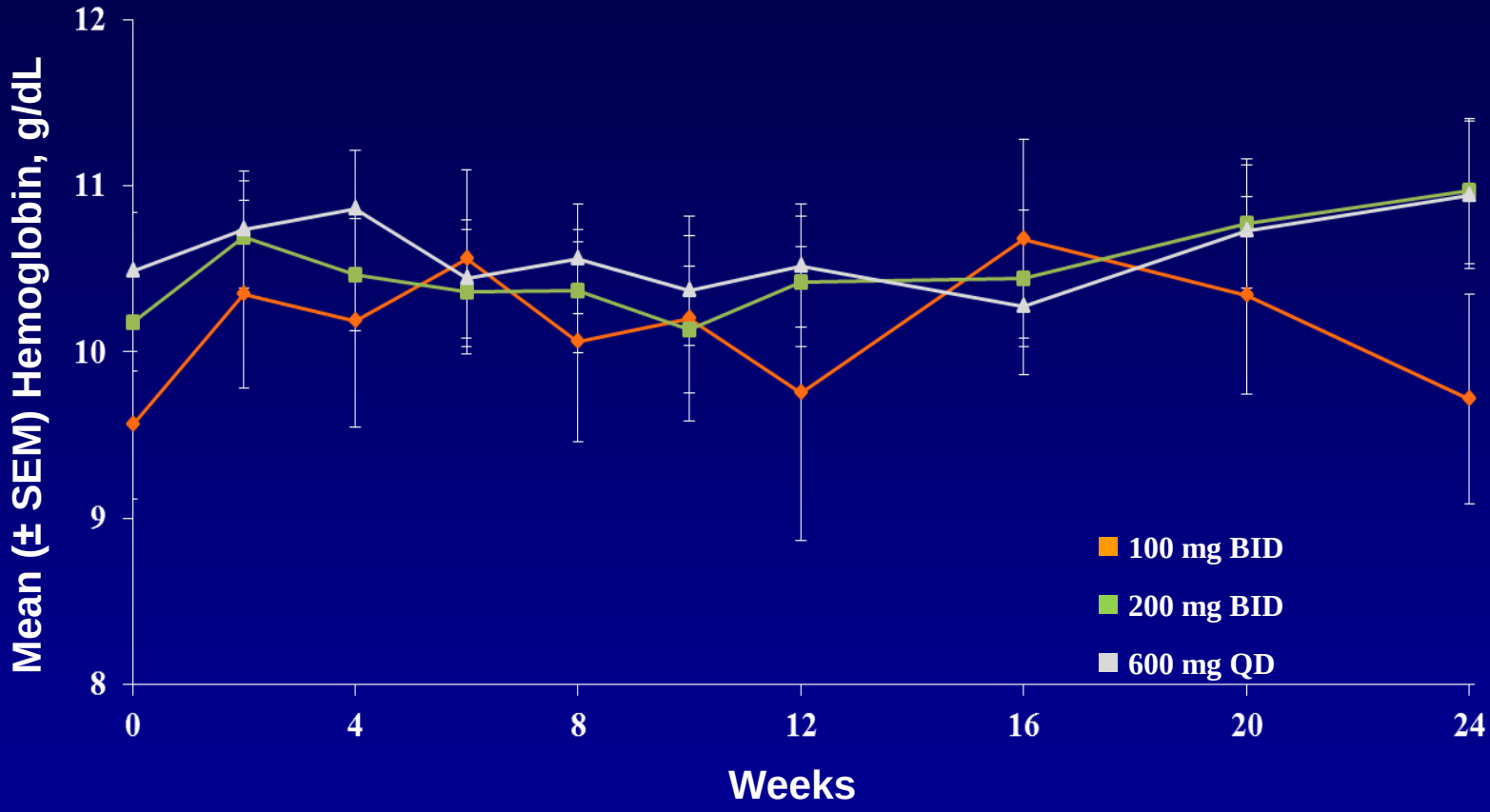
Mean Platelet Count Over Time: All Patients



Patients, n										
100 mg BID	10	10	9	8	8	6	6	5	5	5
200 mg BID	45	45	45	41	43	39	38	35	34	32
600 mg QD	32	31	32	31	32	31	31	27	27	24

Mascarenhas J et al, ASH 2014, abst. 714

Mean Hemoglobin Over Time: All Patients



100 mg BID	10	10	9	8	8	6	6	5	5	5
200 mg BID	45	45	45	41	43	39	37	35	34	32
600 mg QD	32	31	32	31	32	31	31	27	27	24

Mascarenhas J et al, ASH 2014, abst. 714

Combination Studies with Ruxolitinib*

Aimed at improving the anemia

- ESA
- Danazol
- Lenalidomide
- Pomalidomide
- Azacitidine
- Decitabine

Aimed at improving efficacy and modifying the disease

- Interferon
- Histone deacethylase inhib.
- Hedgehog inhibitors
- mTOR inhibitors
- PI3K inhibitors
- Hypomethylating agents
- Others …

* Not exhaustive

Combination of Ruxolitinib with Other Drugs: Clinical Trials in Myelofibrosis

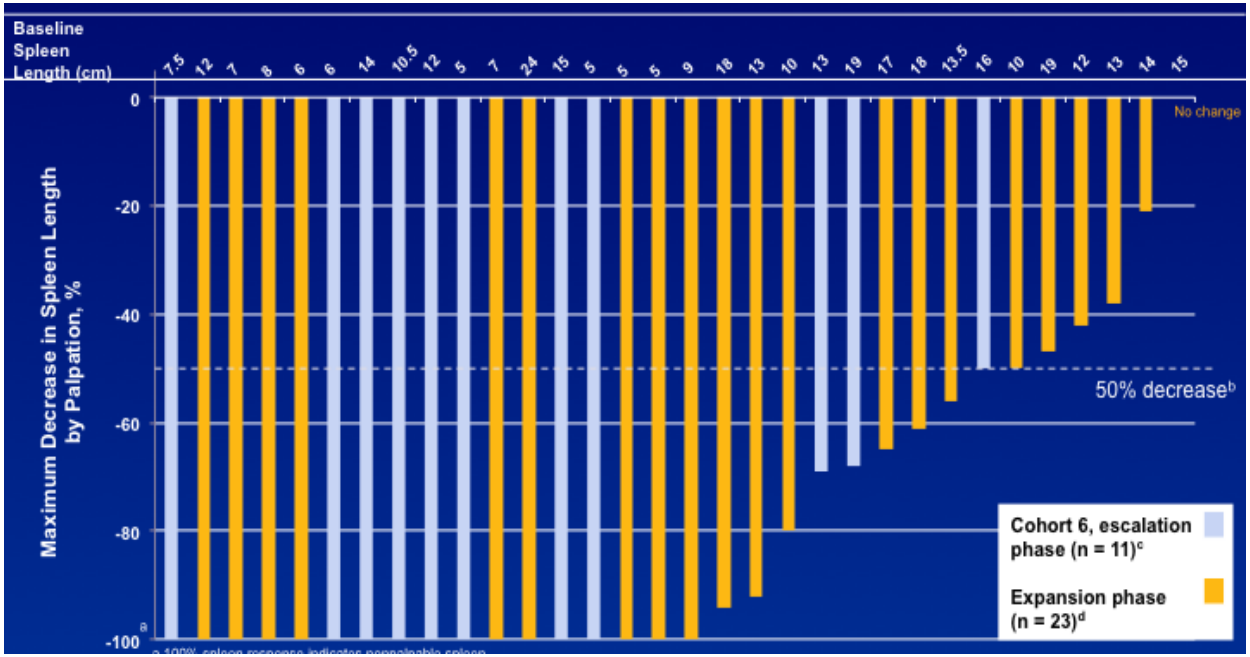
Ruxo + danazol	**(phase II)**
Ruxo + pomalidomide	**(phase I-II)**
Ruxo + lenalidomide	**(phase II)**
Ruxo + panobinostat	**(phase I-II)**
Ruxo + azacitidine	**(phase II)**
Ruxo + buparlisib	**(phase I)**
Ruxo + sonidegib	**(phase Ib-II)**
Ruxo + interferon α2	**(phase II)**

www.ClinicalTrials.gov

Combination of Ruxolitinib with Panobinostat (Histone Deacetylase Inhib.): Preliminary Results

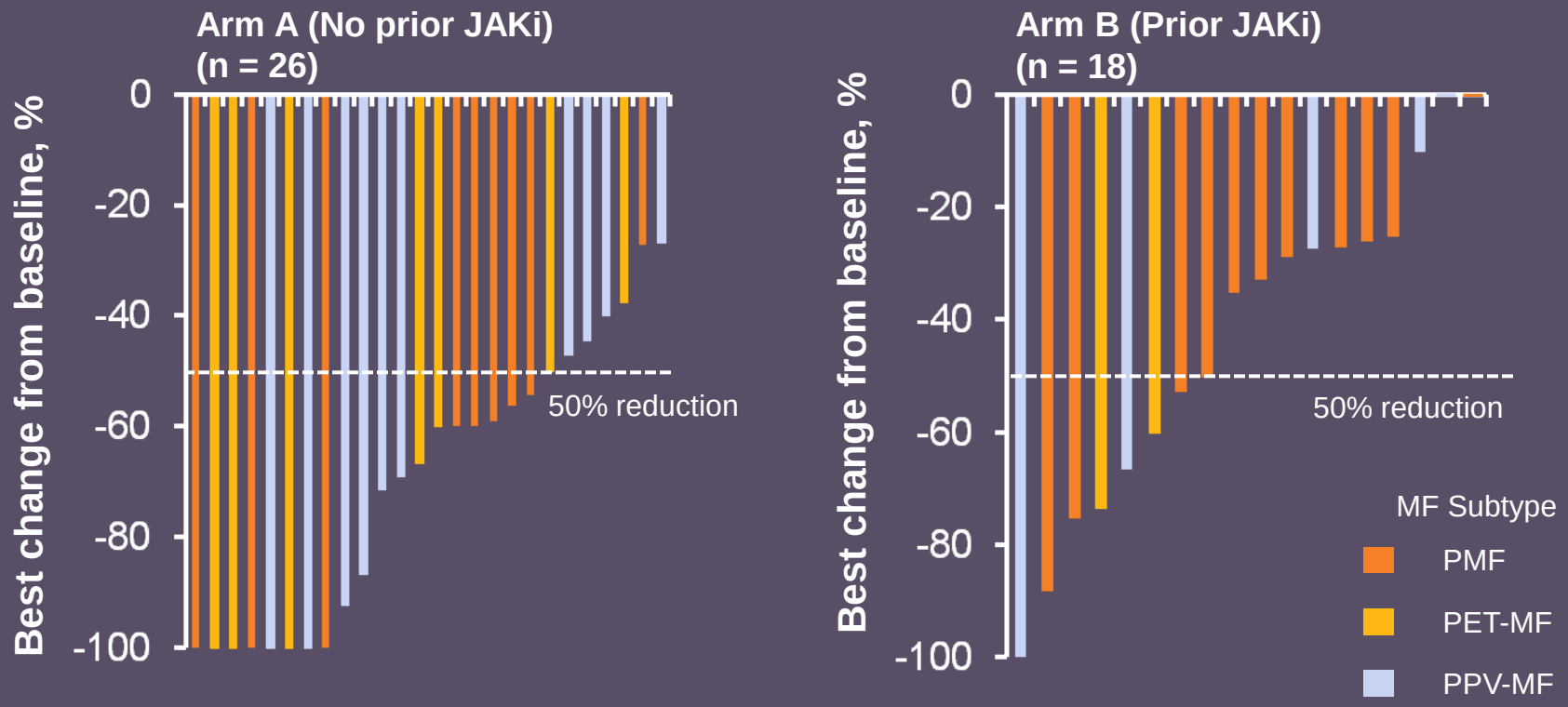
- The potential RP2D was determined to be panobinostat 25 mg TIW QOW in combination with ruxolitinib 15 mg BID
- The observed AE profile in this study was consistent with panobinostat treatment
  - Diarrhea was the most common nonhematologic AE, and anemia and thrombocytopenia were the most common hematologic AEs
- Most patients treated at the recommended dose of combination therapy achieved a spleen response

❖ **Combination therapy resulted in suggested improvements in allele burden reduction**



Vannucchi AM, *et al.,* EHA 2014, abstr.P410

Ruxolitinib plus Buparlisib (pan-PI3K Inhibitor) Best Response in Palpable Spleen Length



- 77% (20/26) and 44% (8/18) of patients in arms A and B achieved a ≥ 50% reduction from baseline in palpable spleen length
- 9 patients had a resolution of splenomegaly (ie, 100% reduction: 8 in arm A; 1 in arm B)
- 16 of 18 patients with prior JAK inhibitor treatment had spleen length reductions with the combination, including 6 who had no previous improvement

Durrant ST *et al.*, ASH 2014, abstr. 710

Preliminary Results of Ruxolitinib Combinations

	Target	Phase (N*)	Toxicity (DLT)	Conclusions
Buparlisib[1]	Pan-PI3K	1b (44)	Mucositis (thrombocytopenia)	**Effective for splenomegaly ruxo 15 bid/bupar 60 qd**
Panobinostat[2]	Deacetylase	2 (61)	Cytopenias,diarrhea (thrombocytopenia, nausea)	**Effective for splenomegaly ruxo 15 bid/pano 25 tiw qow**
Sonidegib[3]	Smoothened	1b/2 (30)	Cramps, alopecia (CPK increase)	**Effective for splenomegaly ruxo 20 bid/soni 400 qd**
Lenalidomide[4]	Immunomod.	2 (31)	Cytopenia	**Lenalidomide stop in most cases ruxo 15 bid + lena 5 qd (21/28)**
Pomalidomide[5]	Immunomod.	1b/2 (6)	Anemia, neuropathy	**Ruxo 10 bid + poma 0.5 qd**
Danazol[6]	Androgen	2 (10)	Electrolyte abnorm.	**Modest benefit (preliminary) Ruxo 5-10 bid + dana 200 tid**
Interferon α-2b[7]	Immunomod.	2 (10)	Neutropenia, infections	**Very preliminary**

[1]Durrant S, ASH 2014 abst. 710; [2]Kiladjian JJ, ASH 2014, abst 711; [3]Gupta V, ASH 2014, abst. 712; [4]Naval D, ASH 2014, abst. 1831; [5]Stegelmann F, ASH 2014, abst. 3161; [6]Gowin K, ASH 2014, abst. 3206; [7]Mikkelsen SU, ASH 2015 (abst. 824)

Thanks!

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