Myeloproliferative Neoplasms: What about JAK? PV, ET, MF

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Conflict of Interest

Clinical research funding paid to the institution	Incyte, CTI, Promedior, Janssen, Merck, Roche
Employee	None
Consultant	None
Major stockholder	None
Speakers Bureau	None
Scientific Advisory Board	CTI
Will discuss off label use of	Ruxolitinib

Learner Objectives

- Identify appropriate patients with PV for JAK2 inhibitor therapy
- Understand the role (if any) of JAK2 inhibitor therapy in ET
- Recognize ruxolitinib failure and second line JAK inhibitor monotherapy and combination therapy options in MF

Thrombotic Risk Stratification in ET/PV

Risk Category	Age >60 Years or Prior Thrombosis	CV* Risk Factors
Low	No	No
Intermediate	No	Yes
High	Yes	

*Diabetes, hypertension, dyslipidemia, tobacco use.

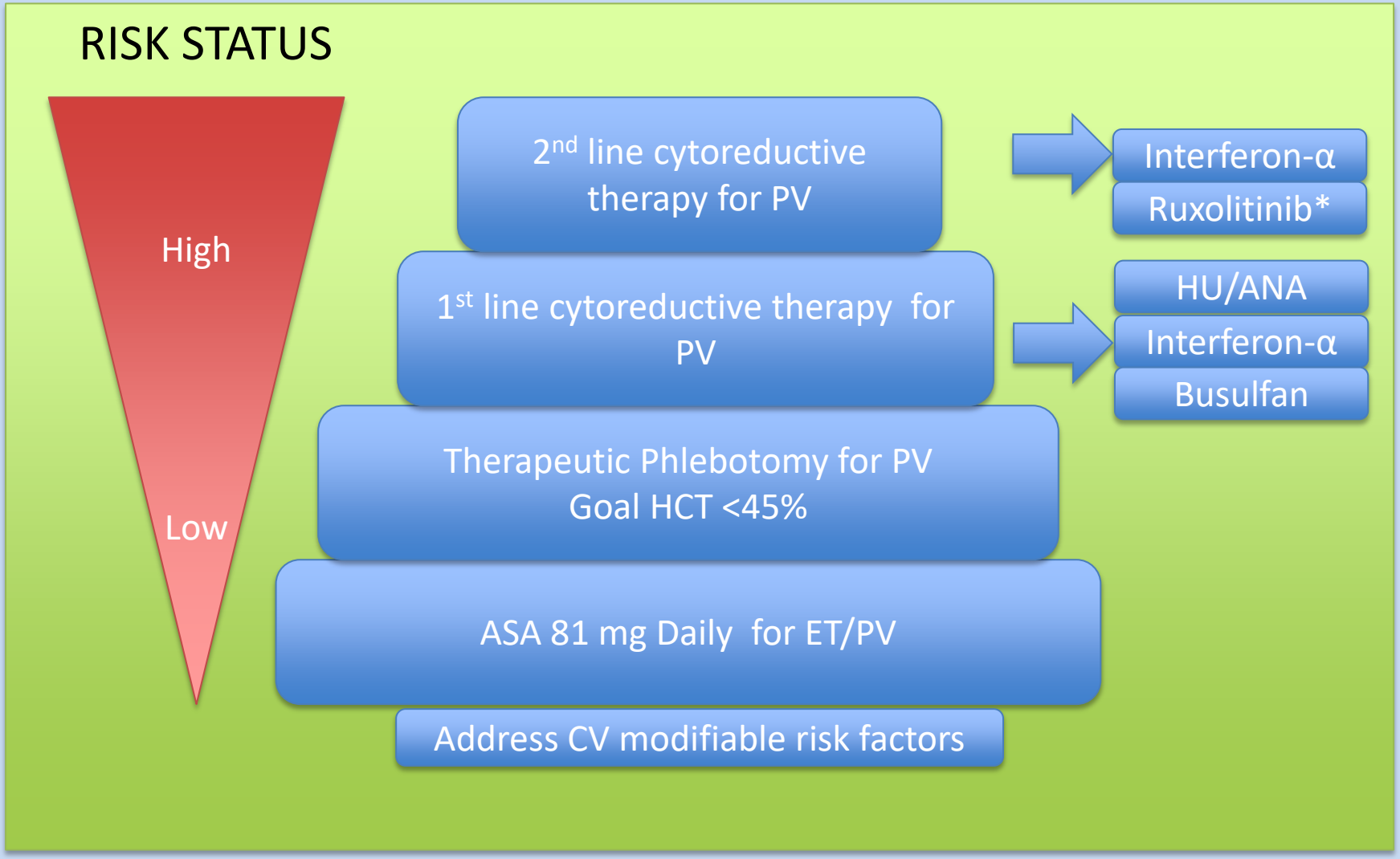
Goals of treatment: reduce thrombosis rate and delay disease transformation

Short term
- Thrombosis
- Hemorrhage

Long term
- Post-ET/PV MF
- MPN blast phase

Marchioli R, et al. *J Clin Oncol*. 2005;23:2224-2232; Barbui T, et al. J Clin Oncol. 2011;29:761-770.

Risk Adapted Management of ET/PV



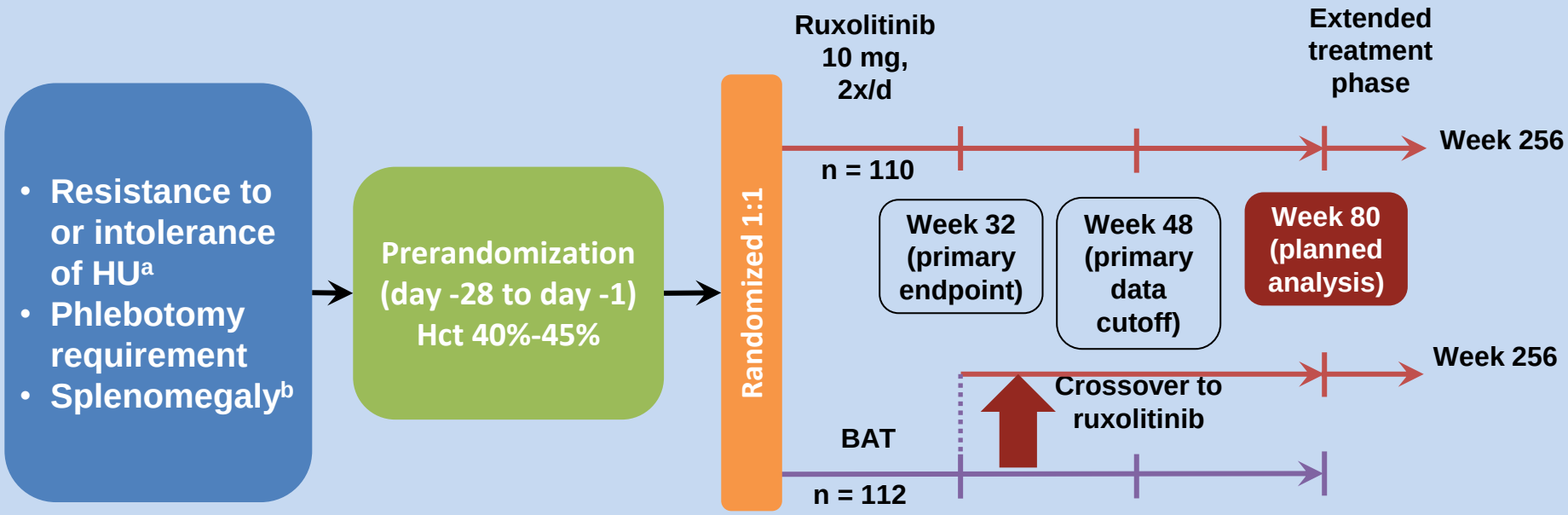
Hypotheses Behind the Rationale for JAK1/2 Inhibition in Polycythemia Vera*

- The need for repeated therapeutic phlebotomy is a negative prognostic indicator of outcome (PVSG-01)[1]
- Hydroxyurea (HU) resistance/intolerance is associated with increased risk of death[2]
- PV patients carry a symptom burden (underappreciated) in need of palliation[3]
- Control of hematocrit (Hct), white blood cell (WBC) count, and platelets (PLTs) will reduce the risk of thrombosis and progression to myelofibrosis (MF)/acute myeloid leukemia (AML)[2]

*Whether these are ALL actually reasonable or not is a different talk.

1. Berk PD, et al. Semin Hematol. 1986;23:132-143; 2.. Alvarez-Larran A, et al. Blood. 2012;119:1363-1369; 3. Geyer HL, et al. ASH 2014: a1848

Ruxolitinib in PV: RESPONSE Study[1]



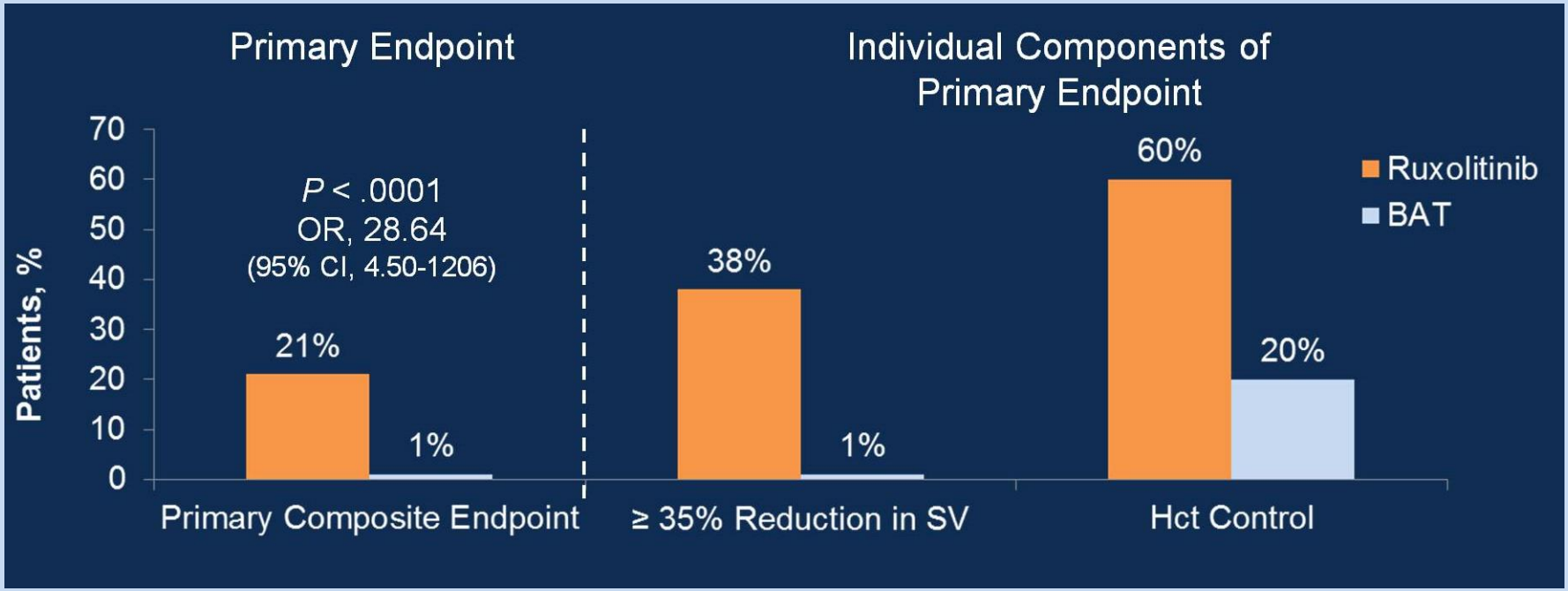
Compared with BAT, results showed ruxolitinib led to:

1. Superior control of hematocrit
2. Superior control of CBC (including WBC and platelets)
3. Superior reduction in splenomegaly
4. Superior reduction in PV-related symptoms
5. Trend for fewer thrombotic events

[a] Modified ELN criteria. [b] Spleen volume ≥450 cm^3.

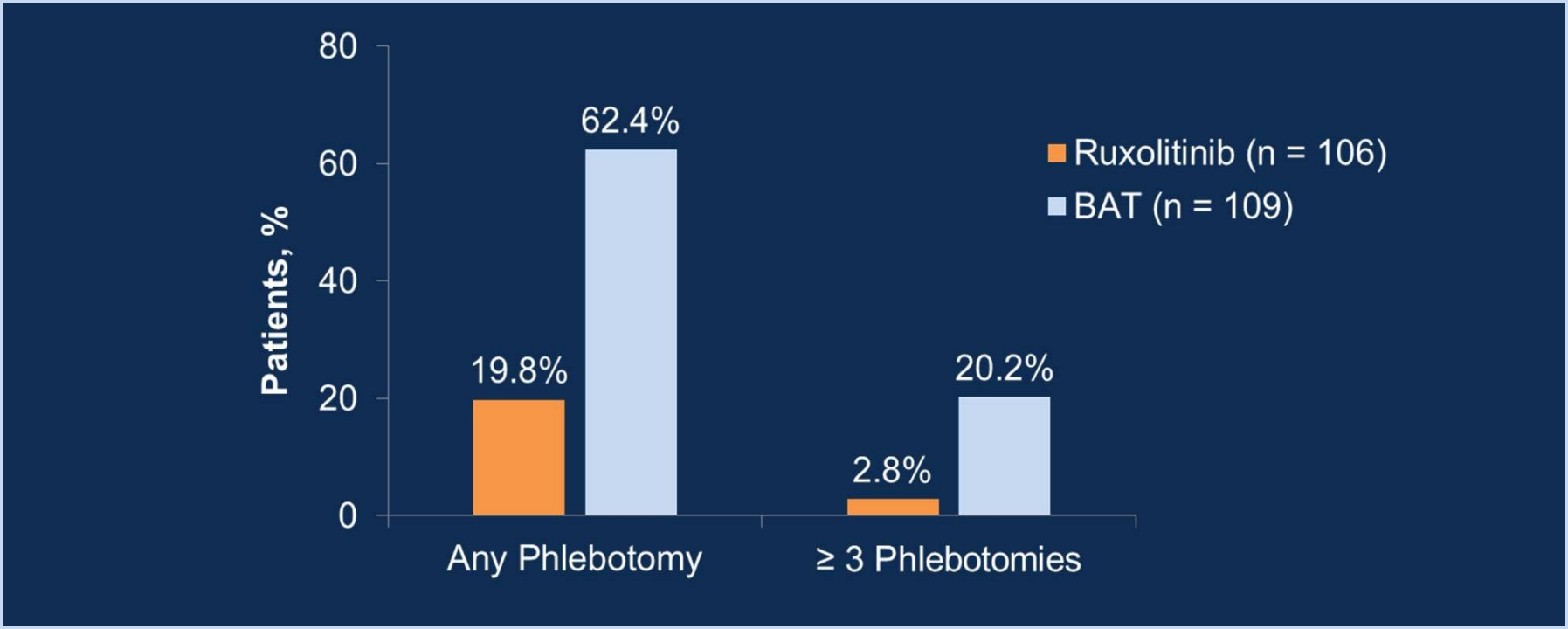
1. Vannucchi AM et al. *N Engl J Med.* 2015;372:426-435.

Primary Response at Week 32



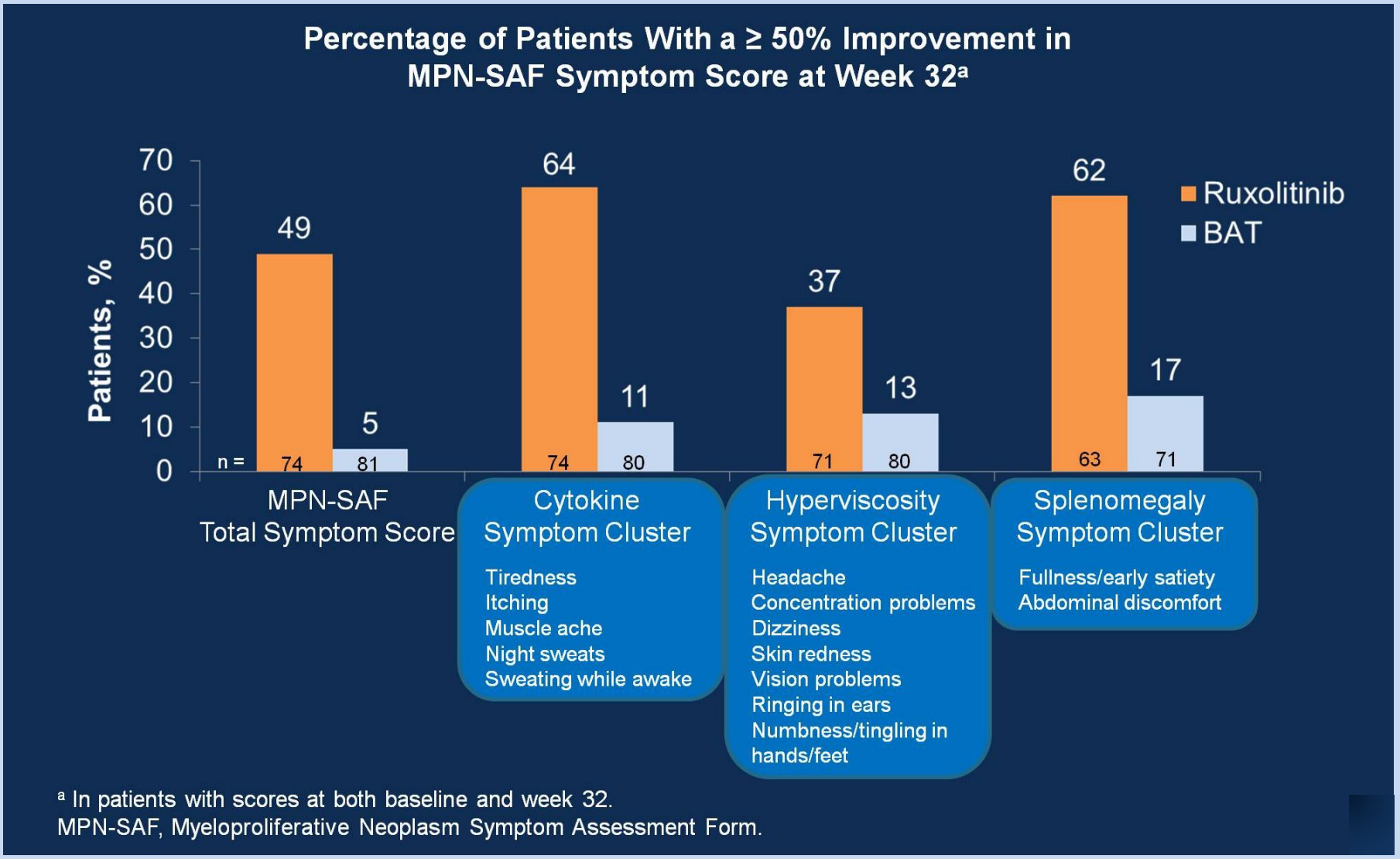
Vannucchi et al. N Engl J Med 2015; 372:426-435

Rate of Therapeutic Phlebotomy Between Week 8 and 32



Vannucchi et al. N Engl J Med 2015; 372:426-435

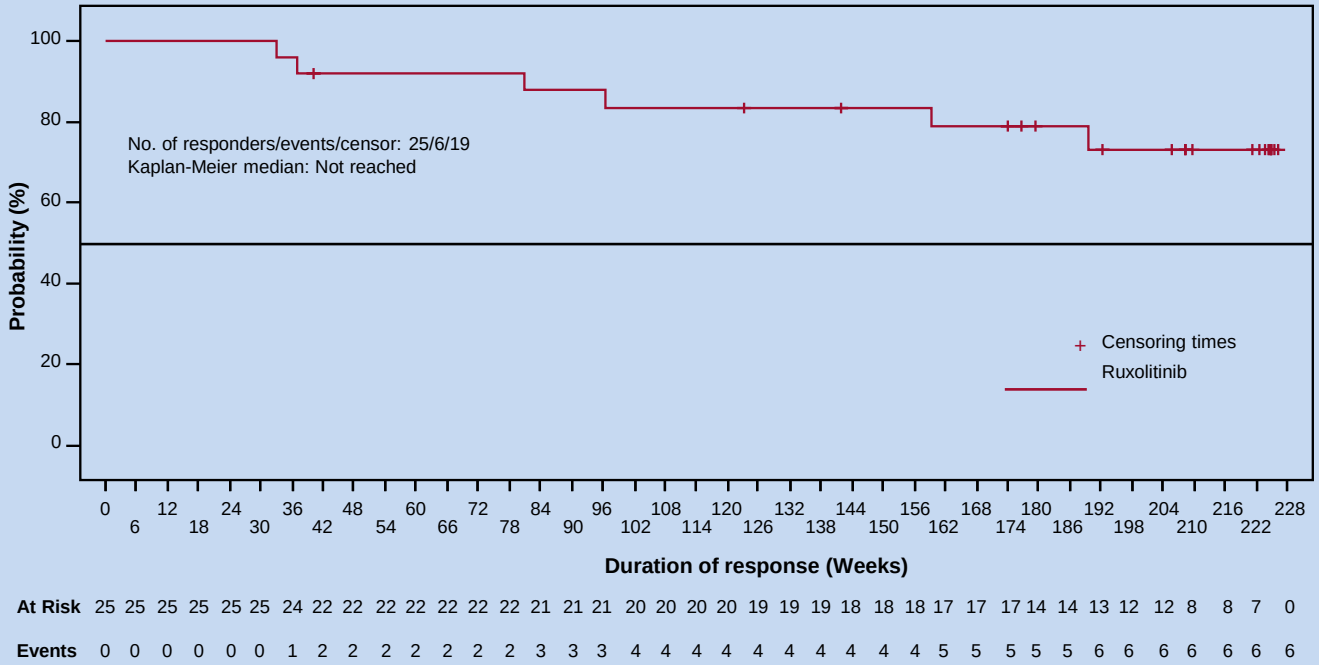
Improvement in Symptoms



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

Vannucchi et al. N Engl J Med 2015; 372:426-435

Durability of Primary Response With Ruxolitinib



- At the time of analysis in the ruxolitinib arm, 6 of 25 primary responders have progressed.
- The K-M estimate of duration of maintaining primary response for 208 weeks (4 years) was 0.73 (95% CI: 0.49, 0.87).
  - The K-M estimates of duration of hematocrit control for 208 weeks was 0.73 (95% CI: 0.60, 0.83).
  - The K-M estimates of duration of at least 35% reduction in the spleen volume was 0.86 (95% CI: 0.61, 0.95).
- Median duration of primary response has not been reached.

CI, confidence interval; K-M, Kaplan–Meier.

Adverse Events

(Adjusted for Patient-Year Exposure, Regardless of Study Drug Relationship [All Grades, Rate ≥ 5 in Either Arm])

	208-Week (4-Year) Analysis				80-Week Analysis			
	Ruxolitinib n = 110 Exposure, Patient-Years = 409		Crossover n = 98 Exposure, Patient-Years = 310		Ruxolitinib n = 110 Exposure, Patient-Years = 227.7		Crossover n = 98 Exposure, Patient-Years = 147.6	
Rate per 100 Patient-Years of Exposure	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Hematologic adverse events								
Anemia	9.3	1.0	9.4	0.6	13.2	0.9	14.9	1.4
Thrombocytopenia	4.6	1.0	1.3	0.3	6.1	1.8	2.7	0.7
Non-hematologic adverse events								
All infections	19.6	3.7	19.7	6.5	29.4	4.0	27.8	5.4
Herpes zoster infection	4.9	0.5	4.2	0.6	5.3	0.9	5.4	0.7
Pruritus	7.3	0.5	5.8	0	9.7	0.4	8.8	0
Diarrhea	7.1	0.2	3.2	0	9.7	0	5.4	0
Headache	6.1	0.5	5.5	0	10.5	0.9	8.8	0
Fatigue	5.1	0.2	4.2	0	8.3	0.4	6.8	0
Increased weight	5.6	0.7	4.2	0.3	7.5	0.4	6.8	0
Arthralgia	5.9	0.2	3.2	0.3	6.1	0	4.7	0
Muscle spasms	5.4	0.2	3.2	0	7.9	0.4	3.4	0
Dizziness	4.2	0.0	6.1	0	7.5	0	7.5	0

Thromboembolic Adverse Events (SMQ)

(Adjusted for Patient-Year Exposure, Regardless of Study Drug Relationship [All Grades, Rate ≥ 0.2 in Either Arm])

	208-Week (4-Year) Analysis				80-Week Analysis			
	Ruxolitinib n = 110 Exposure, Patient-Years = 409		Crossover n = 98 Exposure, Patient-Years = 310		Ruxolitinib n = 110 Exposure, Patient-Years = 227.7		Crossover n = 98 Exposure, Patient-Years = 147.6	
n (Rate per 100 Patient-Years of Exposure)	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
All thromoboembolic events[a]	**5 (1.2)**	**3 (0.7)**	**9 (2.9)**	**5 (1.6)**	**4 (1.8)**	**2 (0.9)**	**6 (4.1)**	**4 (2.7)**
Cerebral infarction	1 (0.2)	1 (0.2)	0	0	1 (0.4)	1 (0.4)	0	0
Ischemic stroke	1 (0.2)	0	1 (0.3)	1 (0.3)	1 (0.4)	0	0	0
Transient ischemic attack	0	0	2 (0.6)	2 (0.6)	0	0	2 (1.4)	2 (1.4)
Portal vein thrombosis	1 (0.2)	1 (0.2)	0	0	1 (0.4)	1 (0.4)	0	0
Pulmonary embolism	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Retinal vascular thrombosis	1 (0.2)	0	0	0	1 (0.4)	0	0	0
Myocardial infarction	0	0	2 (0.6)	1 (0.3)	0	0	2 (1.4)	1 (0.7)
Deep vein thrombosis	0	0	1 (0.3)	0	0	0	0	0
Thrombophlebitis	0	0	1 (0.3)	0	0	0	0	0
Thrombosis	0	0	1 (0.3)	0	0	0	1 (0.7)	0
Bone infarction	0	0	1 (0.3)	0	0	0	1 (0.7)	0
Coronary artery occlusion	0	0	1 (0.3)	0	0	0	1 (0.7)	0
Disseminated intravascular coagulation	0	0	1 (0.3)	1 (0.3)	0	0	1 (0.7)	1 (0.7)

- While on BAT, the rates of all grade and grade 3/4 thromboembolic events per 100 patient-years of exposure were 8.2 (n = 6) and 2.7 (n = 2), respectively.

Other Adverse Events of Interest

(Adjusted for Patient-Year Exposure, Regardless of Study Drug Relationship [All Grades, Rate ≥ 0.5 in Either Arm])

	208-Week (4-Year) Analysis		80-Week Analysis	
	Ruxolitinib n = 110 Exposure, Patient-Years = 409	Crossover n = 98 Exposure, Patient-Years = 310	Ruxolitinib n = 110 Exposure, Patient-Years = 227.7	Crossover n = 98 Exposure, Patient-Years = 147.6
	n (Rates)	n (Rates)	n (Rates)	n (Rates)
Disease Progression				
Acute myeloid leukemia	1 (0.2)	1 (0.3)	1 (0.4)	1 (0.7)
Myelofibrosis	9 (2.2)	6 (1.9)	3 (1.3)	3 (2.0)
Other Malignancies				
Prostate cancer	1 (0.2)	2 (0.6)	0	2 (1.4)
Breast cancer	2 (0.5)	0	2 (0.9)	0
Chronic myelomonocytic leukemia	1 (0.2)	1 (0.3)	0	1 (0.7)
Malignant fibrous histiocytoma	0	0	0	1 (0.7)

- While on BAT, no patient progressed to acute myeloid leukemia or myelofibrosis.

BAT; best available therapy.

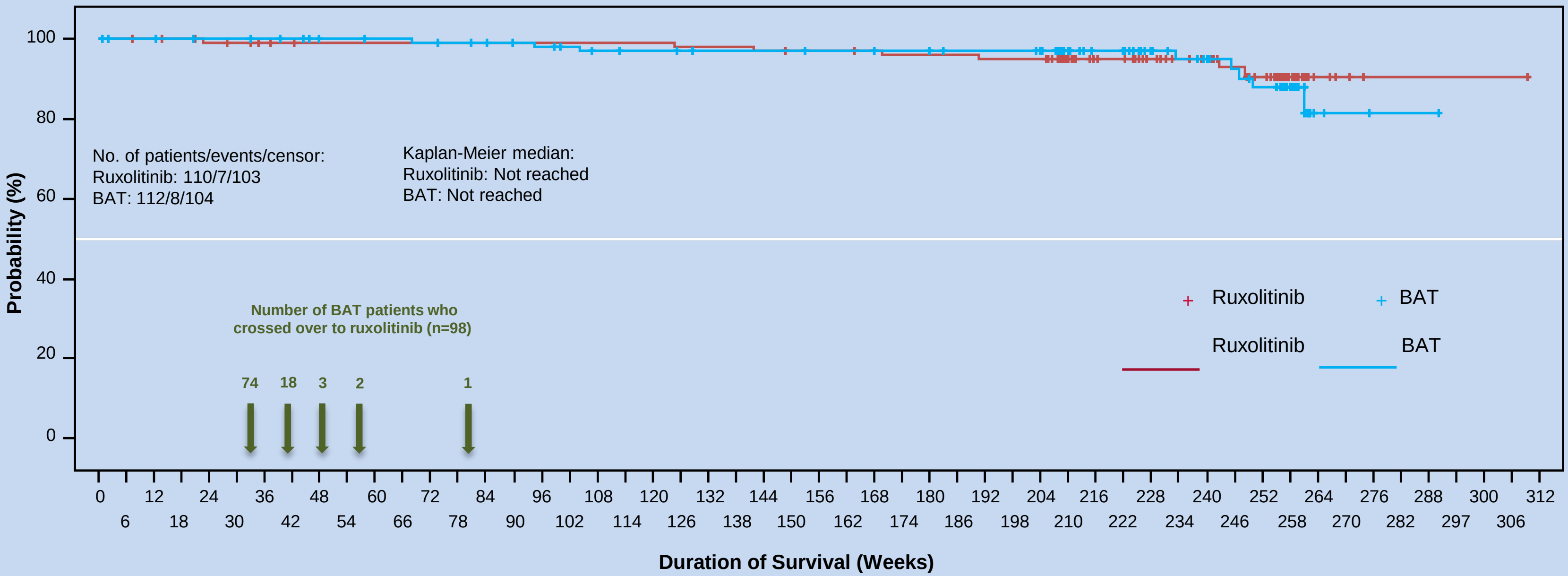
Other Adverse Events of Interest

(Nonmelanoma Skin Cancer Adjusted for Patient-Year Exposure)

n (Rate per 100 Patient-Years of Exposure)	208-Week (4-Year) Analysis				80-Week Analysis			
	Ruxolitinib n = 110 Exposure, Patient-Years = 409		Crossover n = 98 Exposure, Patient-Years = 310		Ruxolitinib n = 110 Exposure, Patient-Years = 227.7		Crossover n = 98 Exposure, Patient-Years = 147.6	
Prior history of Nonmelanoma Skin Cancer	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Total events	**13 (3.6)**	**8 (18.6)**	**6 (2.1)**	**2 (9.5)**	**4 (2.0)**	**6 (24.2)**	**2 (1.4)**	**1 (10.6)**
Basal cell carcinoma	10 (2.7)	7 (16.3)	4 (1.4)	1 (4.7)	3 (1.5)	5 (20.2)	1 (0.7)	1 (10.6)
Squamous cell carcinoma of skin	4 (1.1)	4 (9.3)	3 (1.0)	0	1 (0.5)	2 (8.1)	0	0
Bowen's disease	1 (0.3)	1 (2.3)	0	0	0	1 (4.0)	0	0
Carcinoma in situ of skin	0	2 (4.7)	0	0	0	1 (4.0)	0	0
Metastatic squamous cell carcinoma	0	2 (4.7)	0	0	0	1 (4.0)	0	0
Keratoacanthoma	1 (0.3)	0	0	0	0	0	0	0
Squamous cell carcinoma*	2 (0.5)	3 (7.0)	2 (0.7)	2 (9.5)	1 (0.5)	4 (16.1)	1 (0.7)	0

*Categorized as non-skin squamous cell carcinoma cases.

Overall Survival Analysis in the Intent-to-Treat Population



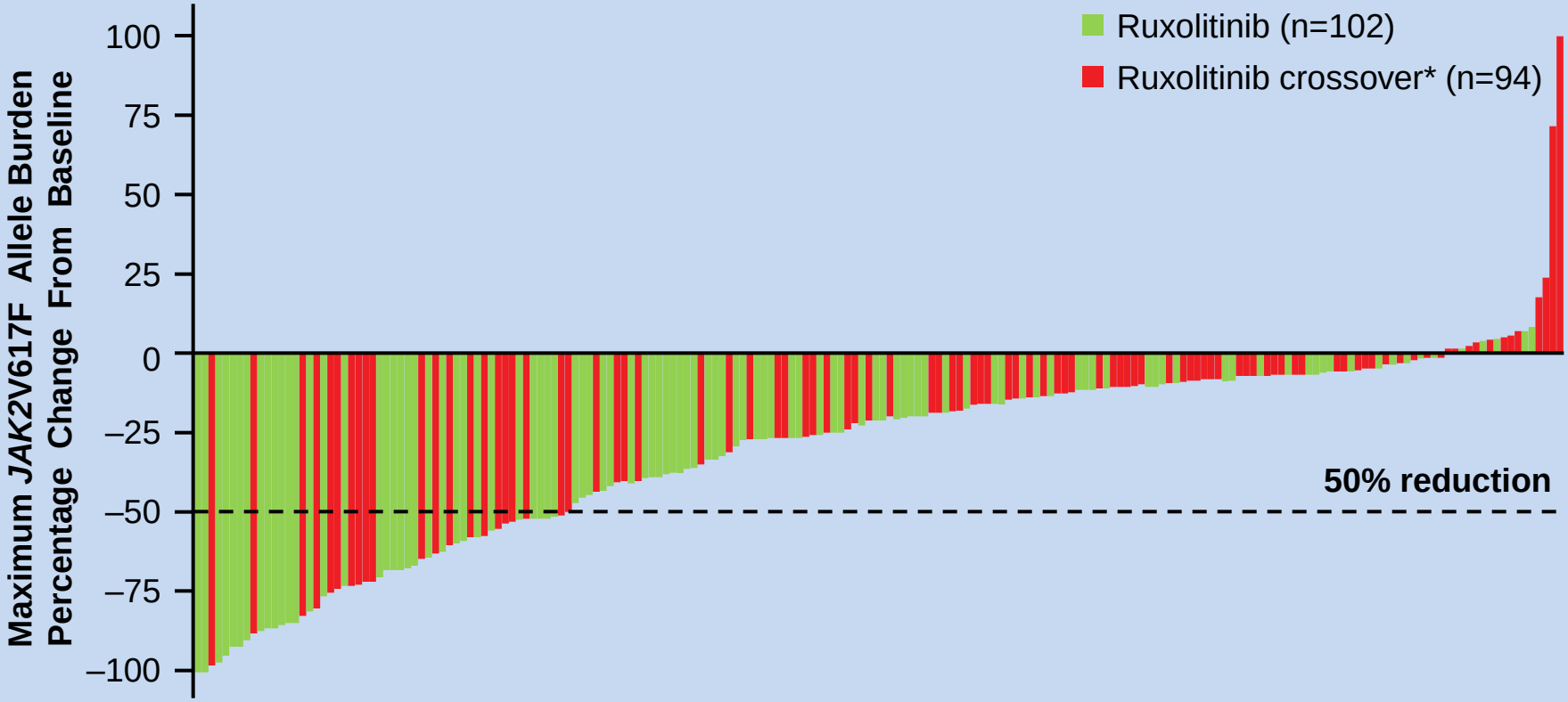
At Risk – Ruxolitinib	110	109	107	106	104	103	101	100	99	99	99	99	99	99	99	99	99	99	99	99	99	98	98	98	97	96	96	96	95	94	94	94	93	93	93	76	69	68	57	53	49	42	38	21	5	3	1	1	1	1	1	1	0
Events – Ruxolitinib	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	3	3	3	3	3	3	4	4	4	5	5	5	5	5	5	5	5	5	6	7	7	7	7	7	7	7	7	7	7	7
At Risk – BAT	112	110	110	109	108	108	107	105	102	102	101	101	100	99	98	96	95	93	91	90	90	89	88	88	88	88	88	87	87	86	86	84	84	84	83	66	61	61	51	47	45	39	36	24	3	2	1	1	1	0			
Events – BAT	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	5	7	7	8	8	8	8	8	8			

- In the ITT analysis not accounting for crossover, the K-M estimates for overall survival at 5 years was 90.6% (95% CI: 80.1, 95.7) in the ruxolitinib arm and 87.7% (95% CI: 74.8, 94.3) in the BAT arm.
- Patients were allowed to cross over from BAT to ruxoltinib at or after week 32, no patient remained on randomized BAT treatment after week 80.

BAT, best available therapy; CI, confidence interval; CO, crossover; K-M, Kaplan-Meier; ITT, intent- to- treat.

RESPONSE: Maximum Percentage Change From Baseline in *JAK2*V617F Allele Burden

- The average maximal percentage reductions in allele burden (median time to maximal reduction) in ruxolitinib randomized and ruxolitinib crossover arms were –35.9% (25.9 mo) and –21.2% (18.2 mo), respectively



BAT, best available therapy

* Baseline in the ruxolitinib crossover arm was the final assessment before crossing over from BAT to ruxolitinib

RESPONSE-2: Ruxolitinib in HU-Resistant or Intolerant PV Without Splenomegaly

Safety and efficacy results are consistent with RESPONSE-1

Endpoint	Ruxolitinib	BAT
HCT control	62% ($P < .0001$)	19%
CHR	23% ($P = .0019$)	5%
≥50% improvement in MPN-SAF TSS	45%	23%
Complete resolution of symptoms	50%	7.7%

Passamonti F et al. EHA 2016. Abstract S112.

JAK2 inhibition in PV

Agent	Phase	Status	Clinicaltrials.gov identifier
XL019	1	Terminated	NCT00595829
Ruxolitinib (RELIEF)	3	Completed	NCT01632904
Ruxolitinib (RESPONSE-2)	3	Ongoing	NCT02038036
Ruxoltinib (RESPONSE)	3	Resulted	NCT01243944
Fedratinib	2	Completed	NCT01420783
Lestaurtinib	2	Resulted	NCT00668421
Momelotinib	2	Terminated	NCT01998828
Gandotinib	1	Completed	NCT01520220

Future Directions

Novel Agents in Clinical Trial of Polycythemia Vera and Essential Thrombocythemia			
Agent	**Mechanism of action**	**Disease type**	**NCT number**
Ropeginterferon	Immune modulation	PV	NCT01949805
Givinostat	Histone deacetylase inhibitor	PV; MPN	NCT01901432, NCT01761968
TGR-1202	PI3K delta inhibitor	PV	NCT02493530
RG7388	MDM2 inhibitor	ET/PV	NCT02407080
Mirabegron (Betmiga®)	beta-3-sympathicomimetic	JAK2V16F+ MPN	NCT02311569

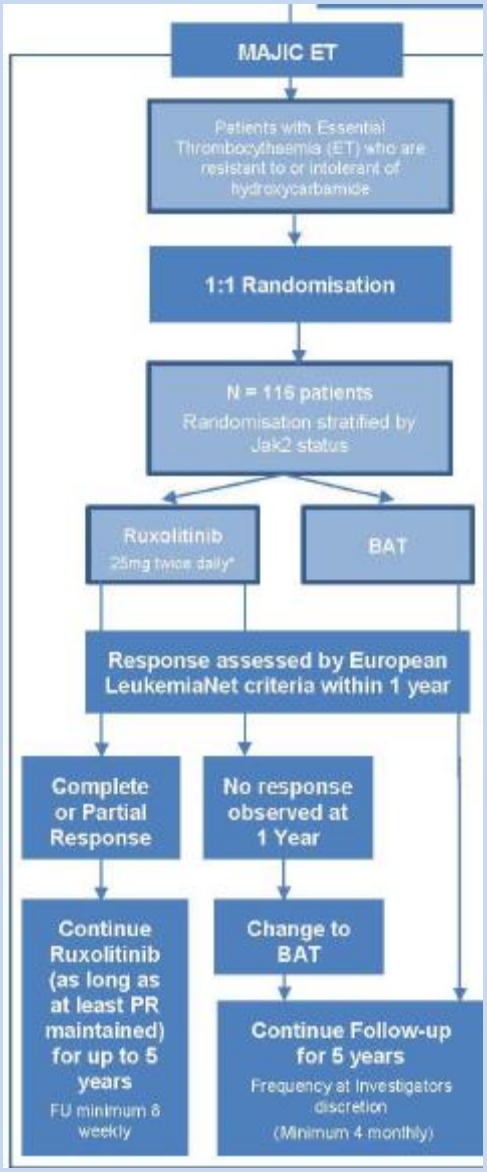
ASH 2017
Abstract 254: Open Label Phase I Study of Single Agent Oral RG7388 (idasanutlin) in Patients with Polycythemia Vera and Essential Thrombocythemia
December 9th 4-5:30pm
Georgia World Congress Center, Bldg C, Lvl 2, C208-C210

Aruch and Mascarenhas. Curr Opin Hematol. 2016 Mar;23(2):150-60

Key Ruxolitinib Trials for Essential Thrombocythemia

Name	identifier	Phase	Design/key feature
MAJIC	ISRCTN61925716	2	HU resistant/intolerant vs BAT
RUXO-BEAT	NCT02577926	2	Treatment naïve and previously treated
RUXBETA	NCT02962388	2/3	Ruxolitinib vs anagrelide or IFN
	NCT03123588	3	Ruxolitinib vs anagrelide

MAJIC-ET Trial Schema



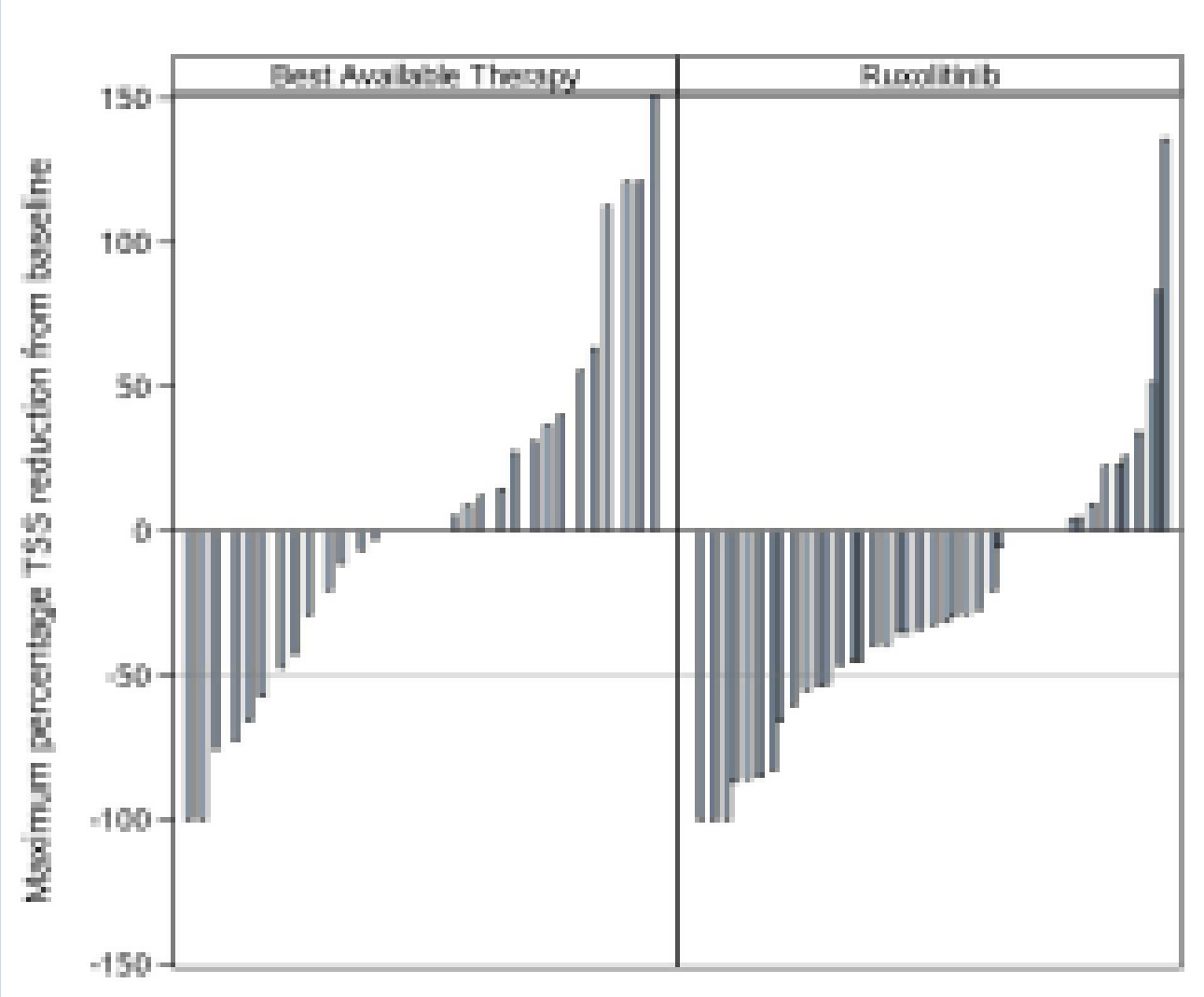
Harrison et al. Blood. 2017 Oct 26;130(17):1889-1897.

MAJIC: Thrombotic and Hemorrhagic events

		BAT			Ruxolitinib			Total
		Grade 1&2	Grade 3&4	Grade 5	Grade 1&2	Grade 3&4	Grade 5	
Hemorrhagic events								
Hematuria		1	0	0	0	0	0	1
Intracranial hemorrhage		0	0	1	0	0	0	1
Oral hemorrhage		1	0	0	1	0	0	2
Rectal hemorrhage		1	1	0	0	0	0	2
Total		*3*	*1*	*1*	*1*	*0*	*0*	*6*
Thrombotic events								
Chest pain - cardiac		0	1	0	0	0	0	1
Myocardial infarction		0	0	0	0	2	0	2
Cerebrovascular ischemia		1	0	0	0	0	0	1
Retinal vascular disorder		1	0	0	1	0	0	2
Thromboembolic events	PE	0	0	0	0	3*	0	3
	DVT	0	0	0	1	1	0	2
	Calf vein DVT	0	0	0	0	1	0	1
Transient ischemic attacks		2	0	0	2	0	0	4
Total		*4*	*1*	*0*	*4*	*7*	*0*	*16*

Harrison et al. Blood. 2017 Oct 26;130(17):1889-1897.

MAJIC- Symptom Improvement with Ruxolitinib



Harrison et al. Blood. 2017 Oct 26;130(17):1889-1897.

Defining Ruxolitinib Failure in Clinical Practice

PRIMARY RESISTANCE*	SECONDARY RESISTANCE†	INTOLERANCE‡	PROGRESSION‡
▪ No change in spleen length by palpation ▪ No reduction in spleen-related symptoms ▪ < 50% reduction in MPN-SAF score OR considered to remain unacceptable to pt	▪ Loss of initial spleen response and return to baseline ▪ Loss of initial symptom response and return to baseline	▪ Any unacceptable treatment-emergent toxicity ▪ Platelet count < 35 x 10^9/L ▪ Doubling of RBC transfusion rate after 3 mos and requiring 2 units at least every 8 wks	▪ Increase in blast % in bone marrow or peripheral blood to ≥ 10% ▪ Increase in spleen length by 25% from baseline at initiation of therapy

← Any single criterion is sufficient →

*Requires a minimum of 12 wks on therapy at maximally tolerated dose or ≥ 20 mg/day. †Preferably captured by MPN-SAF; alternatively, responses no longer considered acceptable by pt. ‡After any duration of therapy.

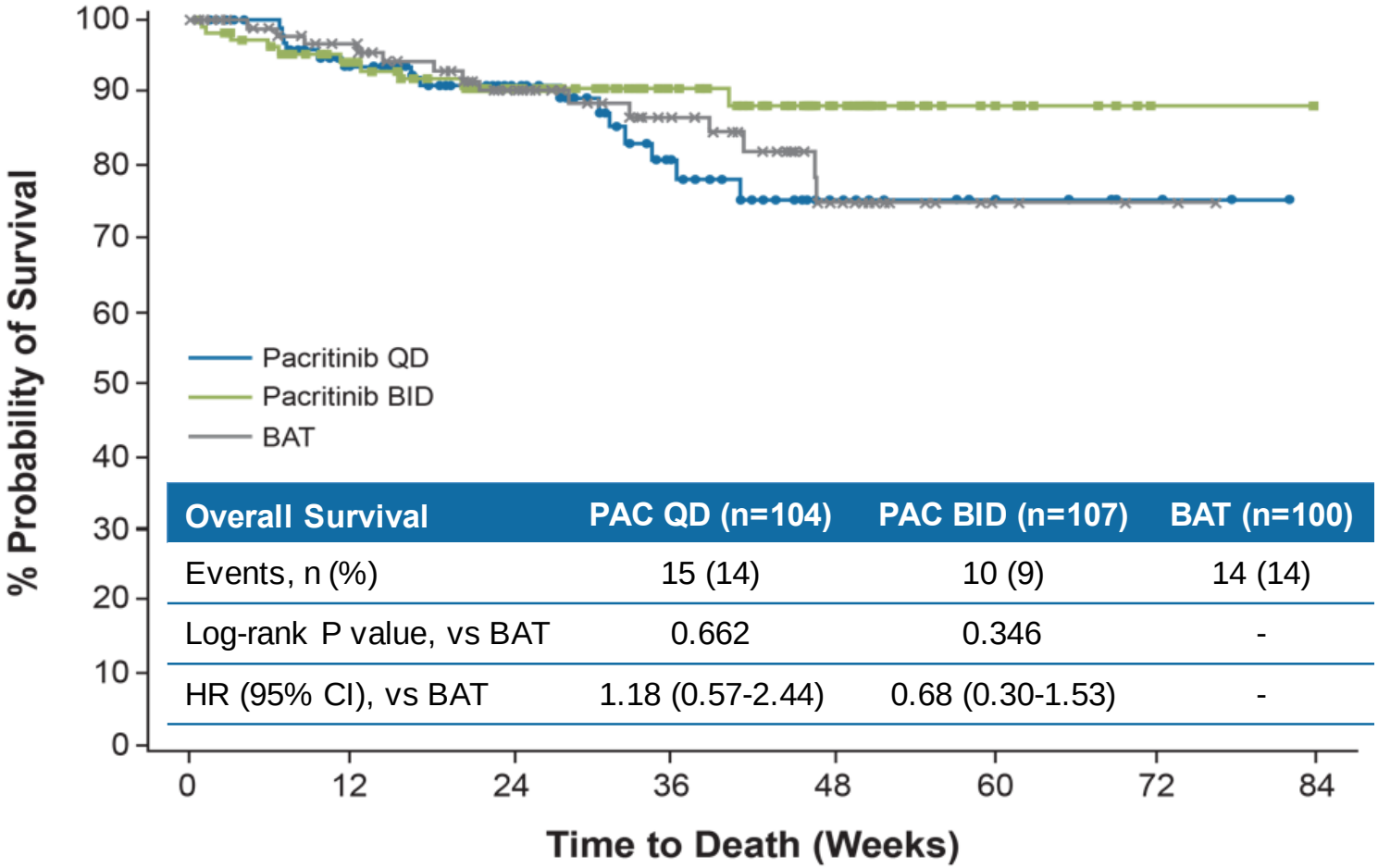
Additional JAK Inhibitors Under Investigation for MF

Agent	Study	Key Findings
Pacritinib[1-4] ▪ JAK2 and FLT3 kinase inhibitor	▪ Phase III PERSIST-1: vs BAT (no JAKi) for higher-risk pts (N = 327)	▪ Spleen volume reduction ≥ 35%, Wk 24: **19%** vs BAT 5% **(*P* = .0003)**
	▪ Phase III PERSIST-2: vs BAT (JAKi ok) for pts with platelets < 100 x 10^9/L (N = 311)	▪ Spleen volume reduction ≥ 35%, Wk 24: **18%** vs BAT 3% **(*P* = .0001)** ▪ ≥ 50% reduction in MF-SAF TSS, Wk 24: **25%** vs BAT 14% **(*P* = .079)** ▪ No significant differences in OS between groups
	▪ Phase II study: higher-risk pts with platelets ≤ 100 x 109/L who failed ruxolitinib	▪ Ongoing
Fedratinib[5,6] ▪ JAK2 inhibitor	▪ Phase III JAKARTA: vs PBO for higher-risk pts (N = 286)	▪ Spleen volume reduction ≥ 35%, Wk 24: 36%-40% vs PBO 1% (P < .001) ▪ ≥ 50% reduction in MF-SAF TSS, Wk 24: 34%-36% vs PBO 7% (P < .001) ▪ Wernicke encephalopathy, n = 3
	▪ Phase II JAKARTA-2: higher-risk pts with ruxolitinib intolerance/resistance (N = 97)	▪ Spleen volume reduction ≥ 35%, Wk 24: 55% ▪ ≥ 50% reduction in MF-SAF TSS, Wk 24: 26%
NS-018[7] ▪ JAK2 inhibitor	▪ Phase I/II study for pts previously treated with other JAK2 inhibitors	▪ 20/48 (56%) had >50% spleen length reduction ▪ Ongoing phase 2

1. Mesa RA, et al. Lancet Haematol. 2017;4:e225-e236. 2. Mesa RA, et al. ASCO 2016. Abstract 7065.
3. Mascarenhas J, et al. ASH 2016. Abstract LBA-5. 4. ClinicalTrials.gov. NCT03165734.
5. Pardanani A, et al. JAMA Oncol. 2015;1:643-651. 6. Harrison CN, et al. Lancet Haematol. 2017;4:e317-e324.
7. ClinicalTrials.gov. NCT01423851.

PERSIST-2: Overall Survival

(Censored at Date of Clinical Hold)



Overall Survival	PAC QD (n=104)	PAC BID (n=107)	BAT (n=100)
Events, n (%)	15 (14)	10 (9)	14 (14)
Log-rank P value, vs BAT	0.662	0.346	-
HR (95% CI), vs BAT	1.18 (0.57-2.44)	0.68 (0.30-1.53)	-

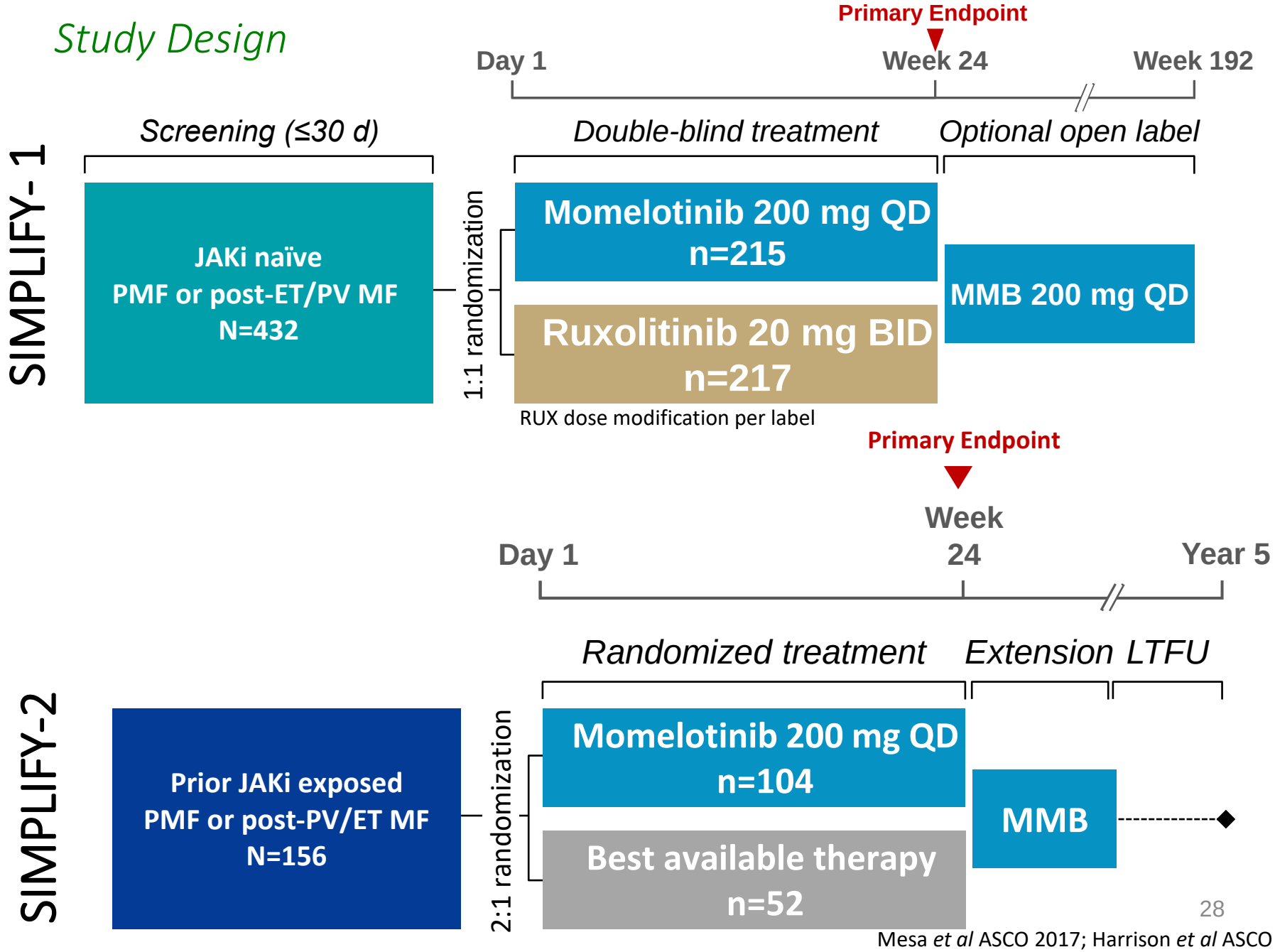
Paitents at Risk

Pacritinib QD	104	80	55	31	13	7	3	0
Pacritinib BID	107	85	62	41	22	9	1	0
BAT	100	83	60	41	18	4	2	0

Mascarenhas et al. ASH Annual Meeting, LBA 2016

SIMPLIFY Randomized Phase III Trials

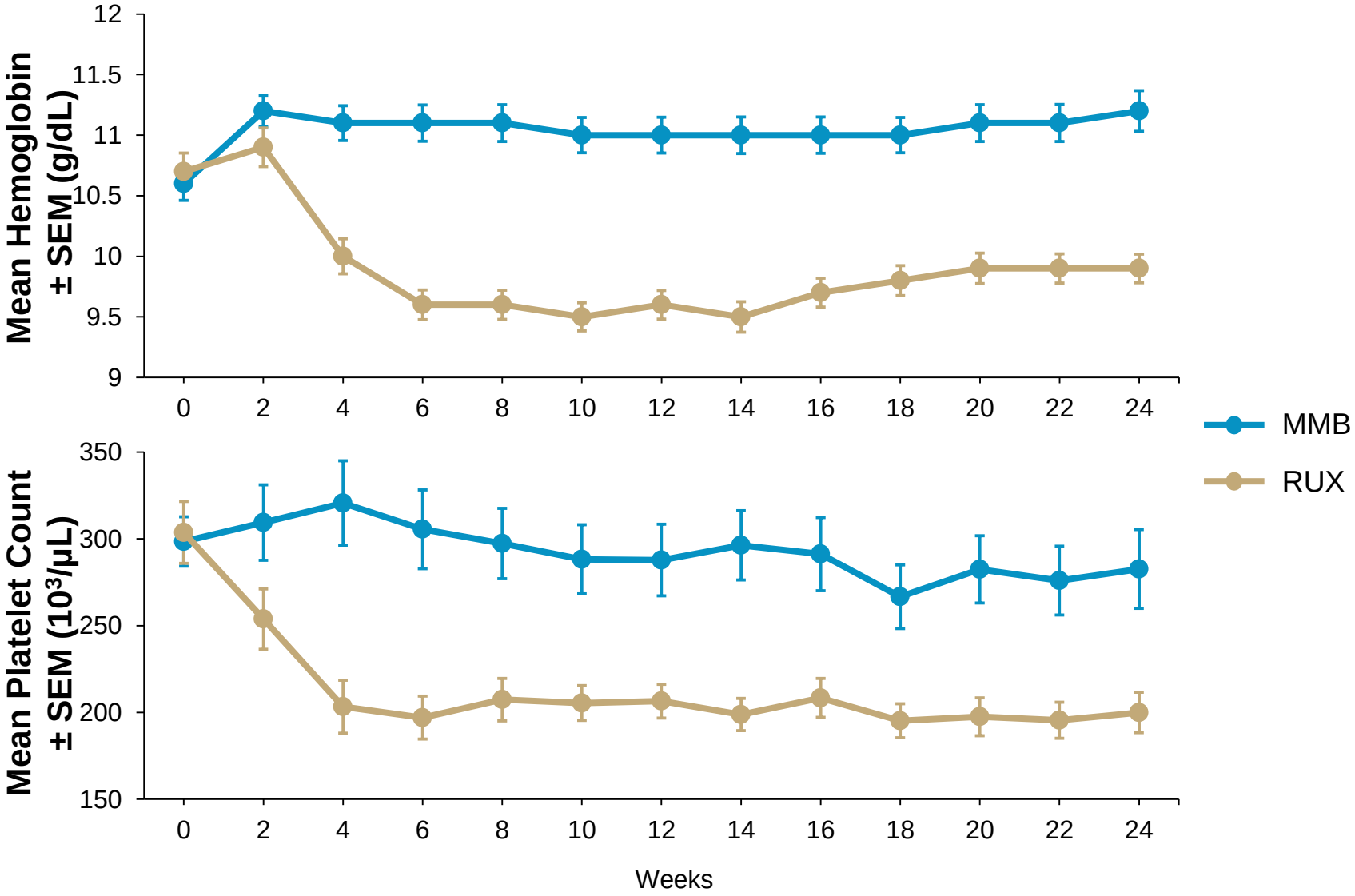
Study Design



Mesa *et al* ASCO 2017; Harrison *et al* ASCO 2017

SIMPLIFY-1 Hemoglobin and Platelet Count

Double-blind Treatment Phase



Ruxolitinib-Based Combination Therapy: Setting a Higher Standard for Success

- Goals of ruxolitinib-based combination therapy
  - Improved spleen reduction
  - Improved symptom improvement
  - Improvement in disease-related cytopenias
  - Deeper molecular responses
  - Bone marrow morphologic responses
- IWG-ELN response?

Ruxolitinib-Based Combination Therapy for MPNs: Ongoing Early-Phase Clinical Trials

Partner	Phase	ClinicalTrials.gov
Azacytidine	II	NCT01787487
Danazol	II	NCT01732445
Decitabine	I/II I/II	NCT02257138 NCT02076191
INCB050465	II	NCT02718300
Idelalisib	I	NCT02436135
Itacitinib	II	NCT03144687
Lenalidomide	II	NCT01375140
Navitoclax	II	NCT03222609
Panobinostat	Ib I/II	NCT01433445 NCT01693601
PegIFN α-2a	I/II	NCT02742324
PIM447 + ribociclib	I	NCT02370706
Pomalidomide	I/II	NCT01644110

Partner	Phase	ClinicalTrials.gov
Pracinostat	II	NCT02267278
Sonidegib	I/II	NCT01787552
Sotatercept	II	NCT01712308
Thalidomide	II	NCT03069326
Umbralisib	I	NCT02493530

Summary

- Ruxolitinib is optimal therapy for second line after HU to address spleen and symptom burden and to control HCT in patients with PV
- Ruxolitinib has not proven to reduce thrombotic risk and does not induce molecular remissions in PV
- Ruxolitinib has not been shown to be optimal therapy in second line patients with ET
- Novel JAK inhibitors pacritinib, momelotinib, and perhaps fedratinib may still have a place in MF treatment paradigm, perhaps after ruxolitinib
- JAK inhibitor based combination therapy trials have not yet confirmed a clear benefit over monotherapy
- Novel agents targeting the MPN hematopoietic stem cell and effecting disease course are still needed in ET/PVMF

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