Neoplasie Mieloproliferative:

I Nuovi Agenti Terapeutici

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Programma Clinical Molecular Oncology AGIMM

AIRC

I Nuovi Agenti Terapeutici

- **Nuovi JAK2 inibitori**
- **Nuove idee per Ruxolitinib**
- **Nuovi target**
- **Cocktails**

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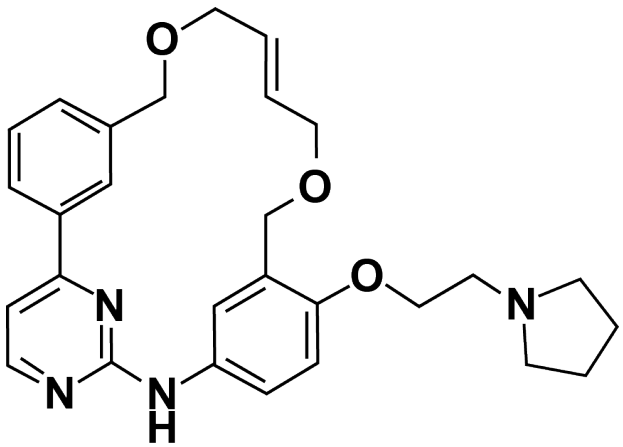
JAK2 Inhibitors: Molecules and Clinical Trials

JAK inhibitor (Company)	MF	PV/ET	Note
CEP701 (Cephalon)			STOPPED
AZD1480 (AstraZeneca)			STOPPED
XL019 (Exelixis)			STOPPED
NS-018 (NS Pharma)	I, ongoing		STOPPED
BMS-911543 (BMS)	I/II, ongoing		STOPPED
LY2784544 (Lilly)	II, ongoing	I finished	STOPPED
Momelotinib (Gilead)	**III,** ongoing		**ONGOING**
Pacritinib (CTI)	III, ongoing		**COMPLETED, on Hold**
Fedratinib (Sanofi)	III, completed	I/II completed	STOPPED
Ruxolitinib (Incyte/Novartis)	III, completed (2) II, ongoing (low plt)	II, completed (ET,PV) III, completed (PV)	**MF, APPROVED**

Pacritinib

- Pacritinib is a kinase inhibitor with specificity for JAK2, FLT3, IRAK1, and CSF1R that has demonstrated minimal myelosuppression in clinical trials[1-4]

Structure of Pacritinib



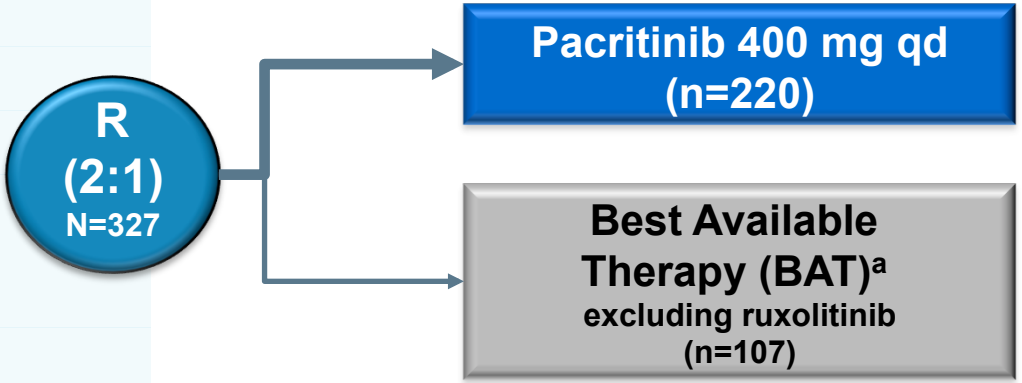
In Vitro Activity of Pacritinib	
Kinase	**IC_{50} (nM)**
JAK1	*1280*
$JAK2^{wt}$	6.0
$JAK2^{V617F}$	9.4
JAK3	18.3
TYK2	27.0
FLT3-ITD	13.4
$FLT3^{D835Y}$	4.7
CSF1R	39.5
IRAK1	13.6

CSF1R, colony stimulating factor 1 receptor; FLT, FMS-like tyrosine kinase; IC_{50}, half-maximal inhibitory concentration; IRAK1, interleukin-1 receptor–associated kinase; ITD, internal tandem duplication; JAK, Janus kinase; TYK, tyrosine kinase.

1. Hart S, et al. *Leukemia*. 2011;25:1751-1759. 2. Komrokji RS, et al. *Blood*. 2015;125:2649-2655. 3. Mesa RA, et al. ASCO 2015. Abstract LBA7006. 4. Singer JW, et al. ASH 2014. Abstract 1874.

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 by platelet counts ≥100,000/μL, ≥50,000-<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

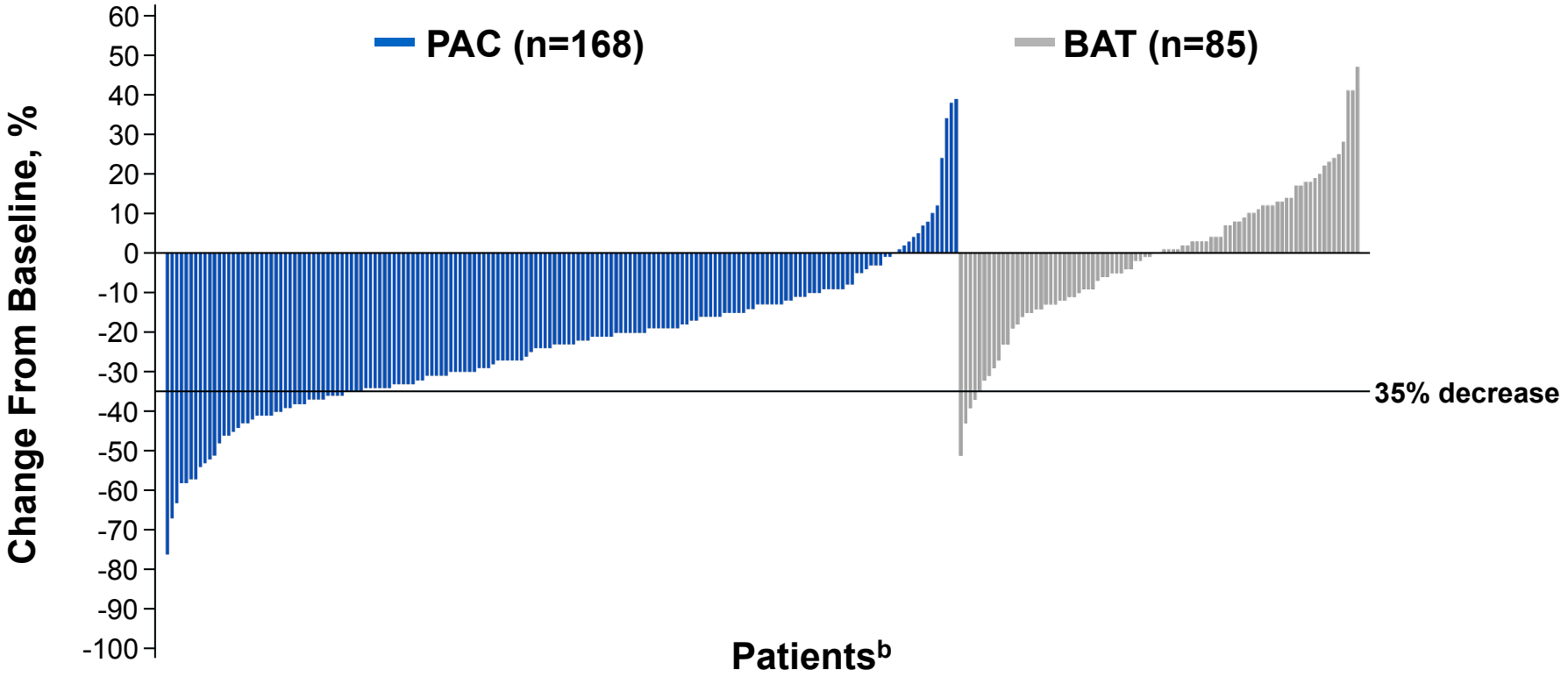
- Stratification at randomization: platelet count category, risk category, and region
- Study endpoints
  - **Primary**: proportion of patients achieving a ≥35% reduction in spleen volume (by MRI/CT) from baseline to Week 24
  - **Secondary**: proportion of patients with a ≥50% reduction in Total Symptom Score (TSS) from baseline to Week 24 on the Myeloproliferative Neoplasm Symptom Assessment Form v 2.0
- Trial conducted in US, Europe, Russia, and Oceania

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.

Mesa RA, et al. ASCO 2015. Abstract LBA7006.

Primary Objective: Spleen Volume Reduction

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

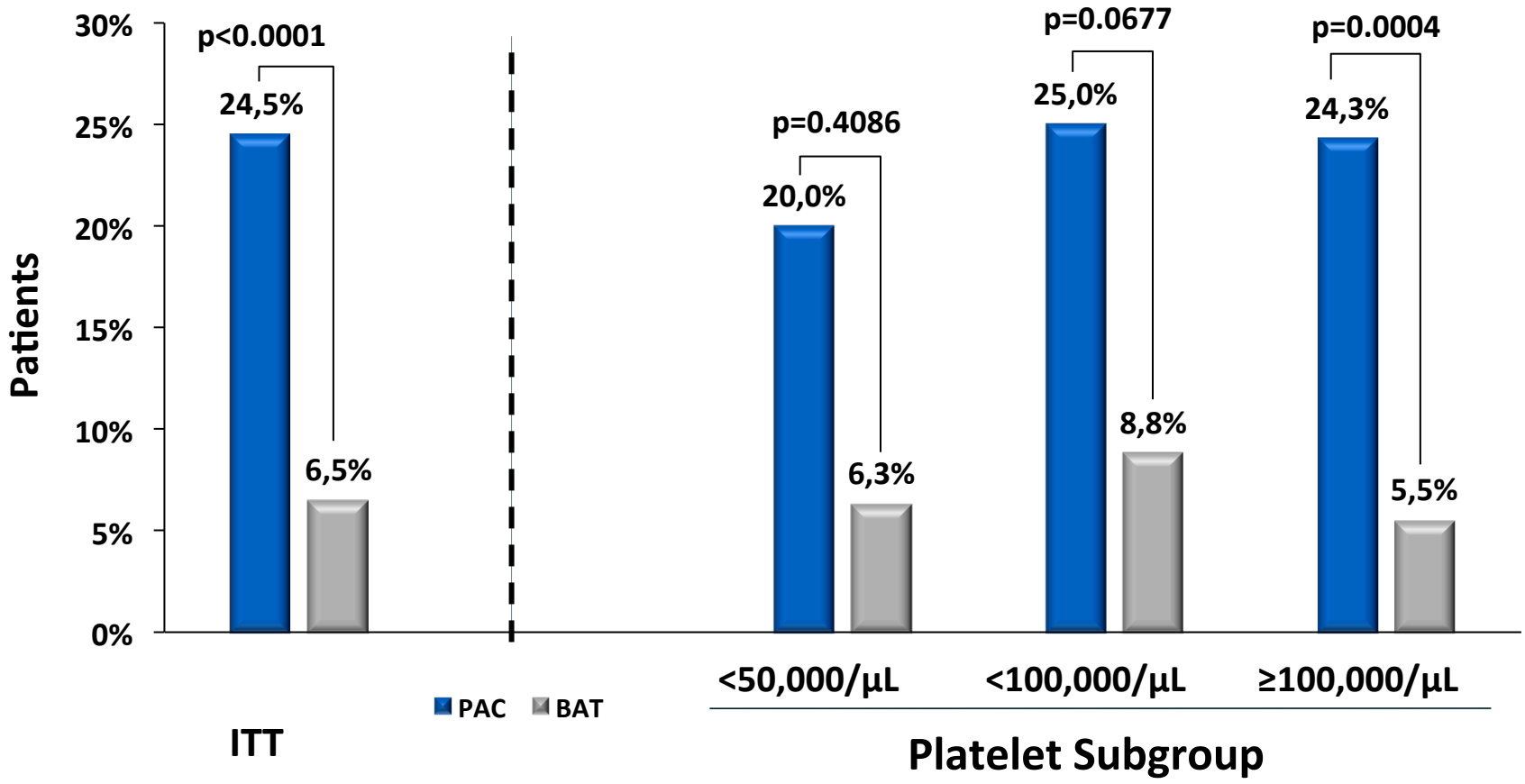


[a]Evaluable population: patients had both baseline and Week 24 spleen assessment by MRI or CT; n=168 for PAC and n=85 for BAT. [b]As of last patient's 24 week visit.

BAT, best available therapy; CT, computed tomography; ITT, intent to treat; MRI, magnetic resonance imaging; PAC, pacritinib.
Mesa RA, et al. ASCO 2015. Abstract LBA7006.

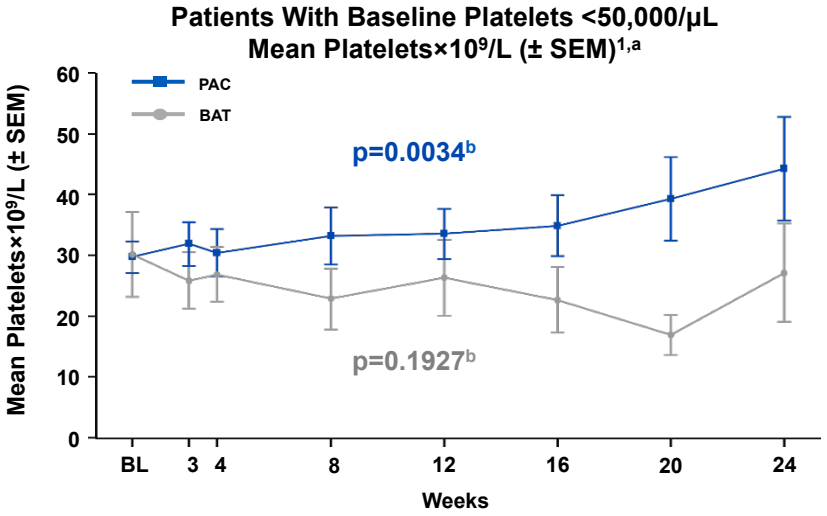
Secondary Objective: Symptom Improvement

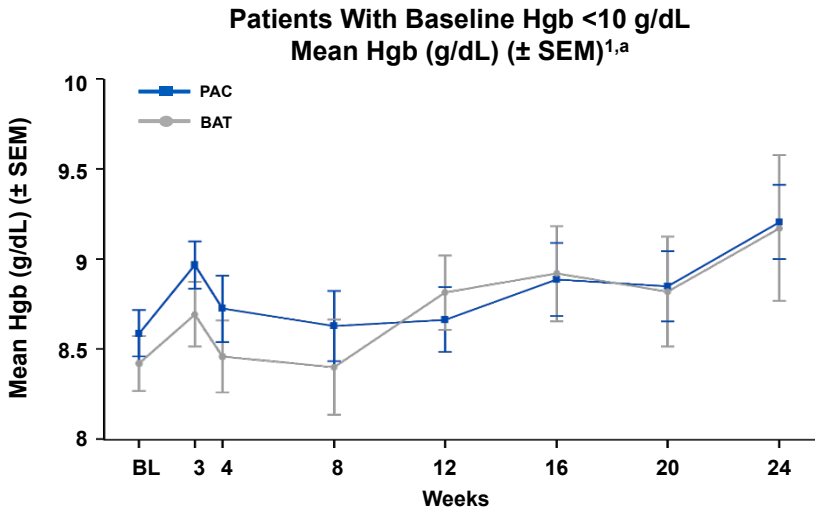
Patients Achieving ≥50% Reduction in TSS
At Week 24 (ITT Population)



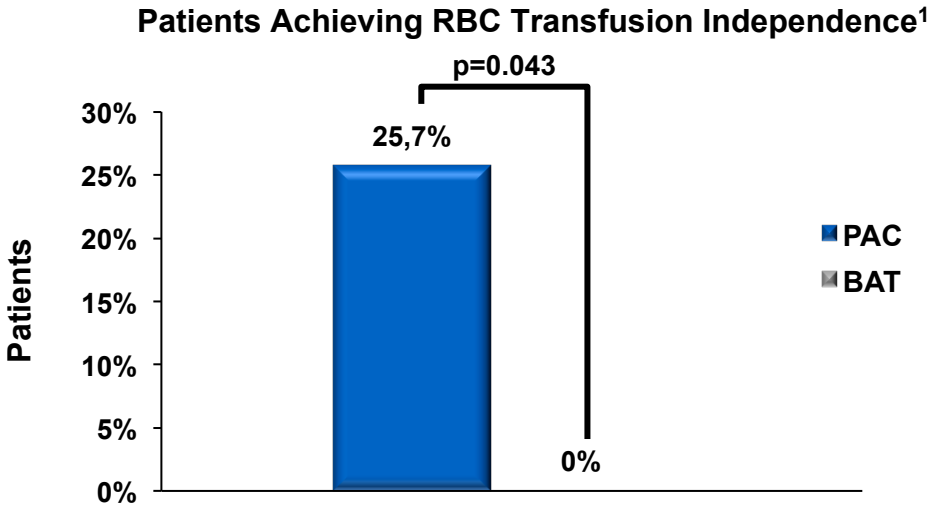
BAT, best available therapy; ITT, intent to treat; PAC, pacritinib; TSS, total symptom score.

Hematological Toxicity





- At baseline, 15.9% of PAC and 14.0% of BAT patients were RBC transfusion dependent, per Gale criteria (≥6 units/90 days[2])



[a]By central laboratory. [b]Based on linear regression using mixed model.
BAT, best available therapy; BL, baseline; Hgb, hemoglobin; PAC, pacritinib; RBC, red blood cell.

1. Mesa RA, et al. ASCO 2015. Abstract LBA7006. 2. Gale RP, et al. *Leuk Res*. 2011;35:8-11.

Most Common (>10%) Adverse Events

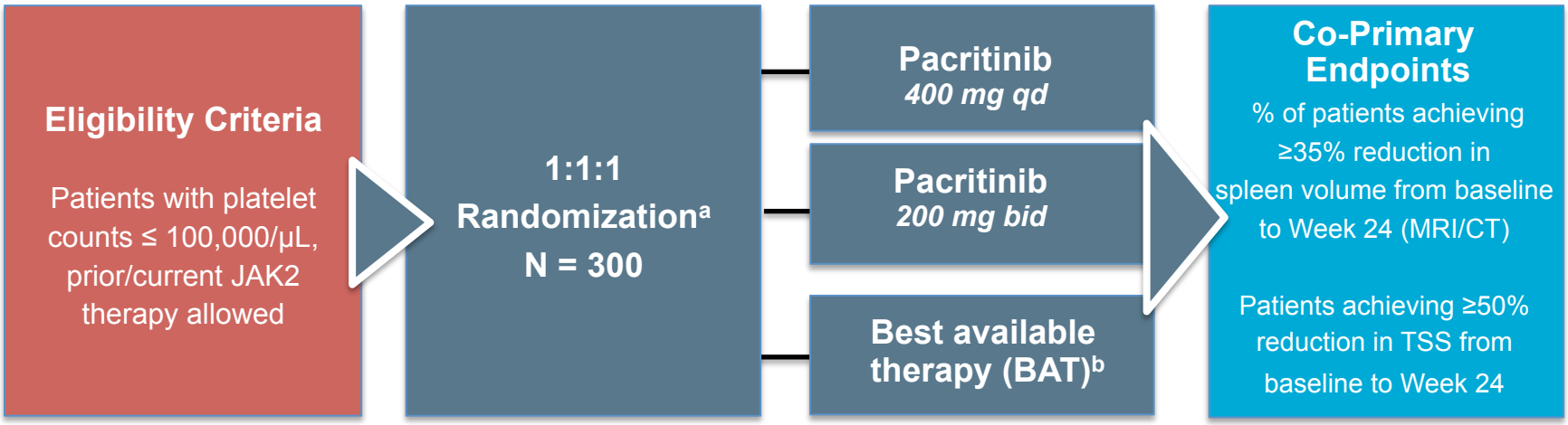
Within 24 Weeks

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)
Gastrointestinal disorders						
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
Blood and lymphatic system disorders						
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)

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

PERSIST-2

Study Design



Sites: North America, Europe, Russia, and Australia

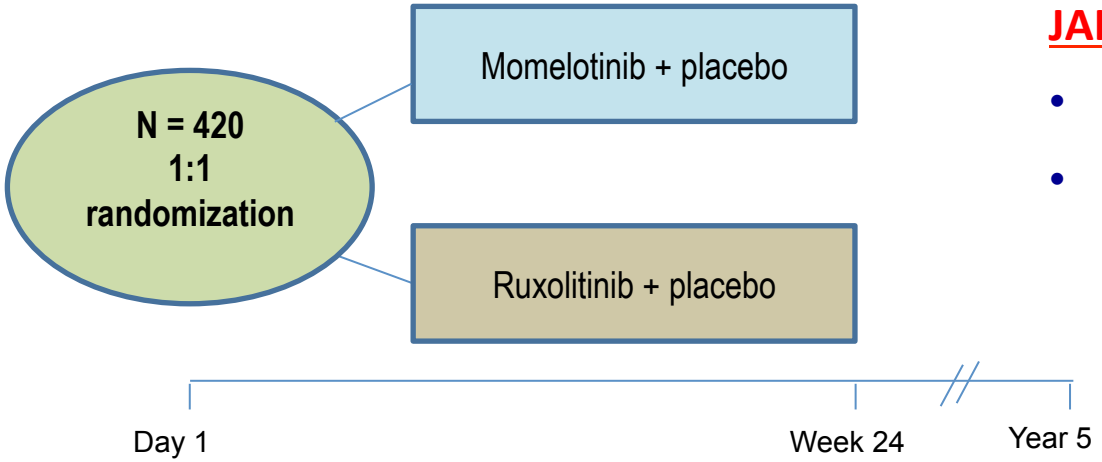
Anticipated patient accrual: ~ 300

[a]Crossover from BAT allowed after progression or assessment of the primary endpoint.

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

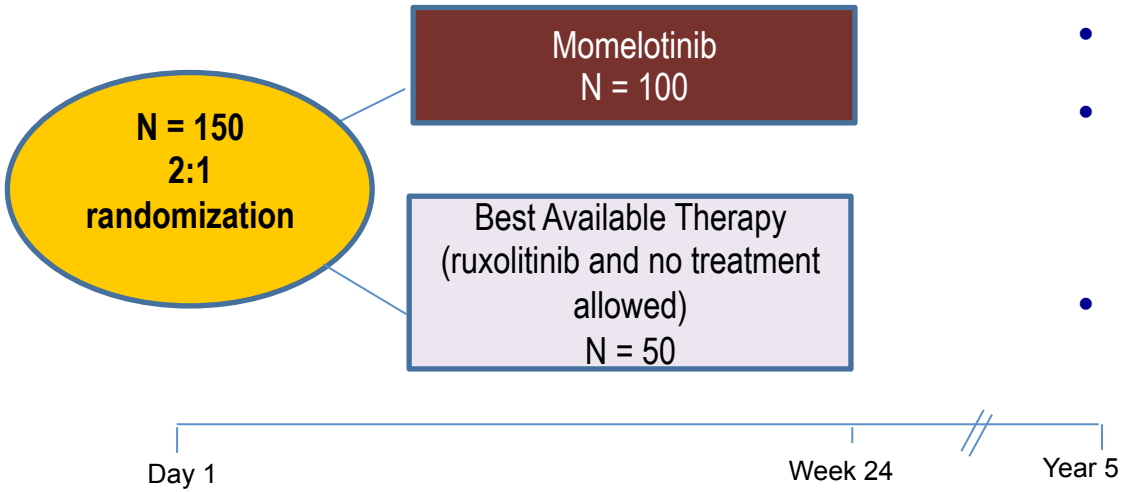
BAT, best available therapy; CT, computed tomography; JAK, Janus kinase; MRI, magnetic resonance imaging; TSS, total symptom score.

Momelotinib: Phase 3 Studies



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

Characteristics of Type II JAKi CHZ868

CHZ868

A novel Type II JAKi under development that inhibits proliferation and JAK2 signaling of naive MPN cells

- Is an alternative mode to target hyperactive JAK2
- Is effective in naive *JAK2*V617F^{mut} and *MPL*W515L^{mut} cells
- Abrogates persistent JAK signaling, inhibits proliferation and induces apoptosis in persistent JAK2V617F^{mut} and MPLW515L^{mut} cells
- Is active in different preclinical MPN models
- Reduces mutant allele burden and reticulin fibrosis in *Jak2*V617F and *MPL*W5151L MPN models

There is no planned clinical study at this time

Sara Meyer et al. – ASH 2015 Abst 160, OC

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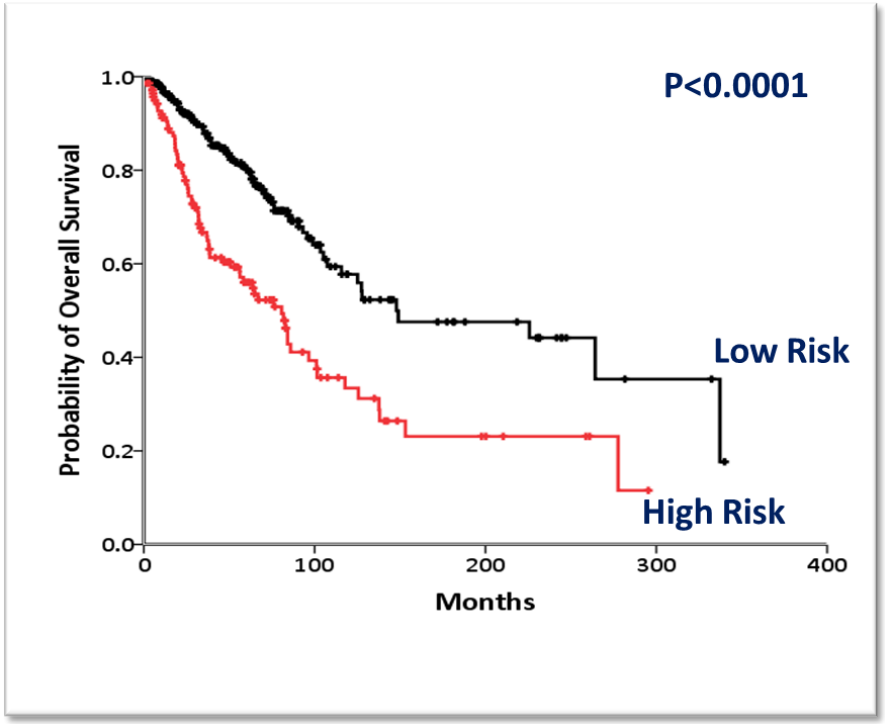
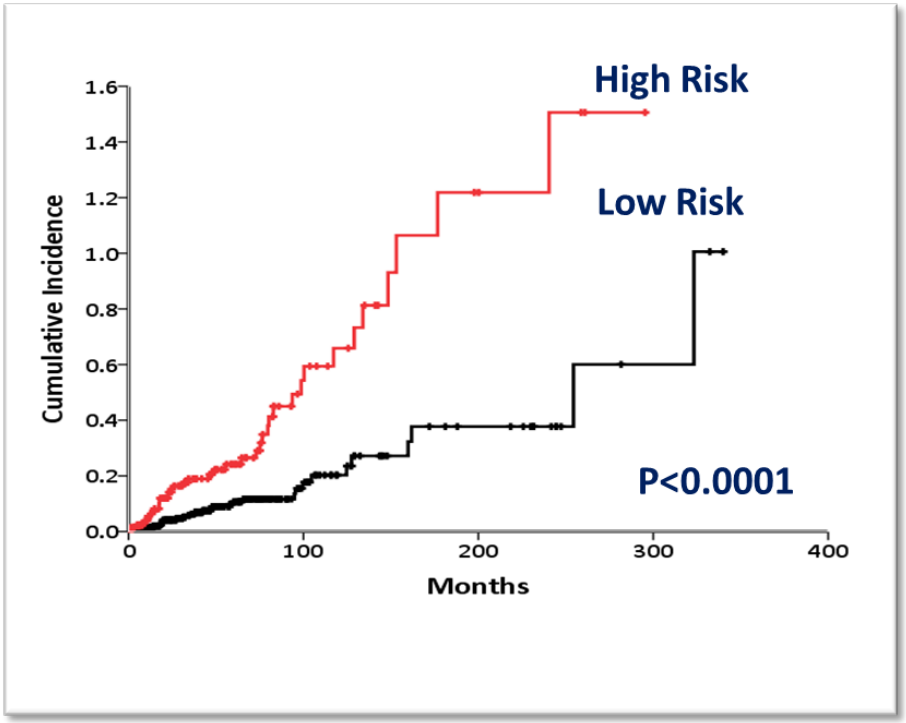
High Molecular Risk Prognostic Category

harboring ≥1 mutation in any one of ***ASXL1, EZH2, SRSF2, IDH1/2***

Overall Survival



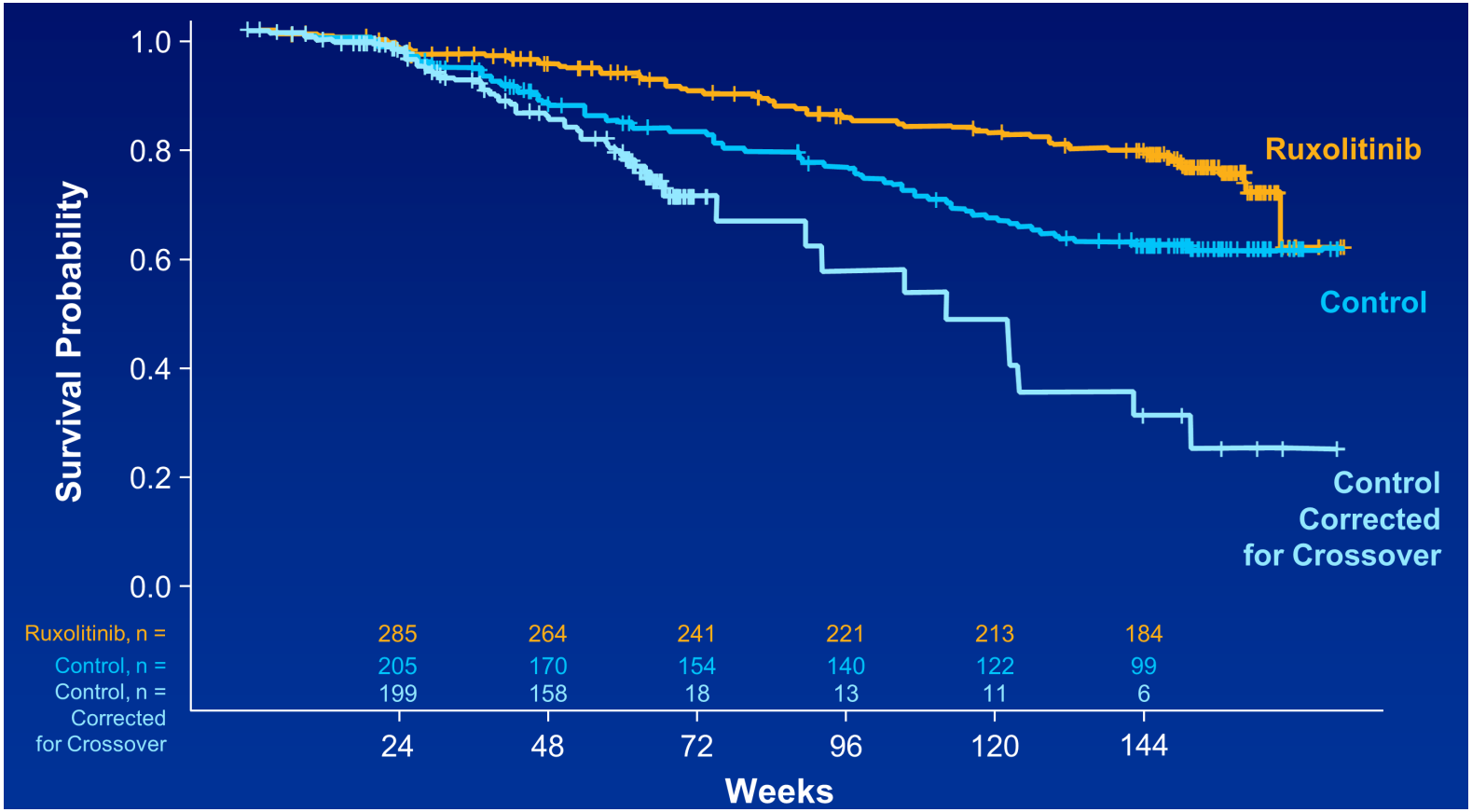
Blast Transformation



- A HMR status is associated with reduced OS and increased risk of blast transformation in PMF patients independent of IPSS/DIPPS-plus

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

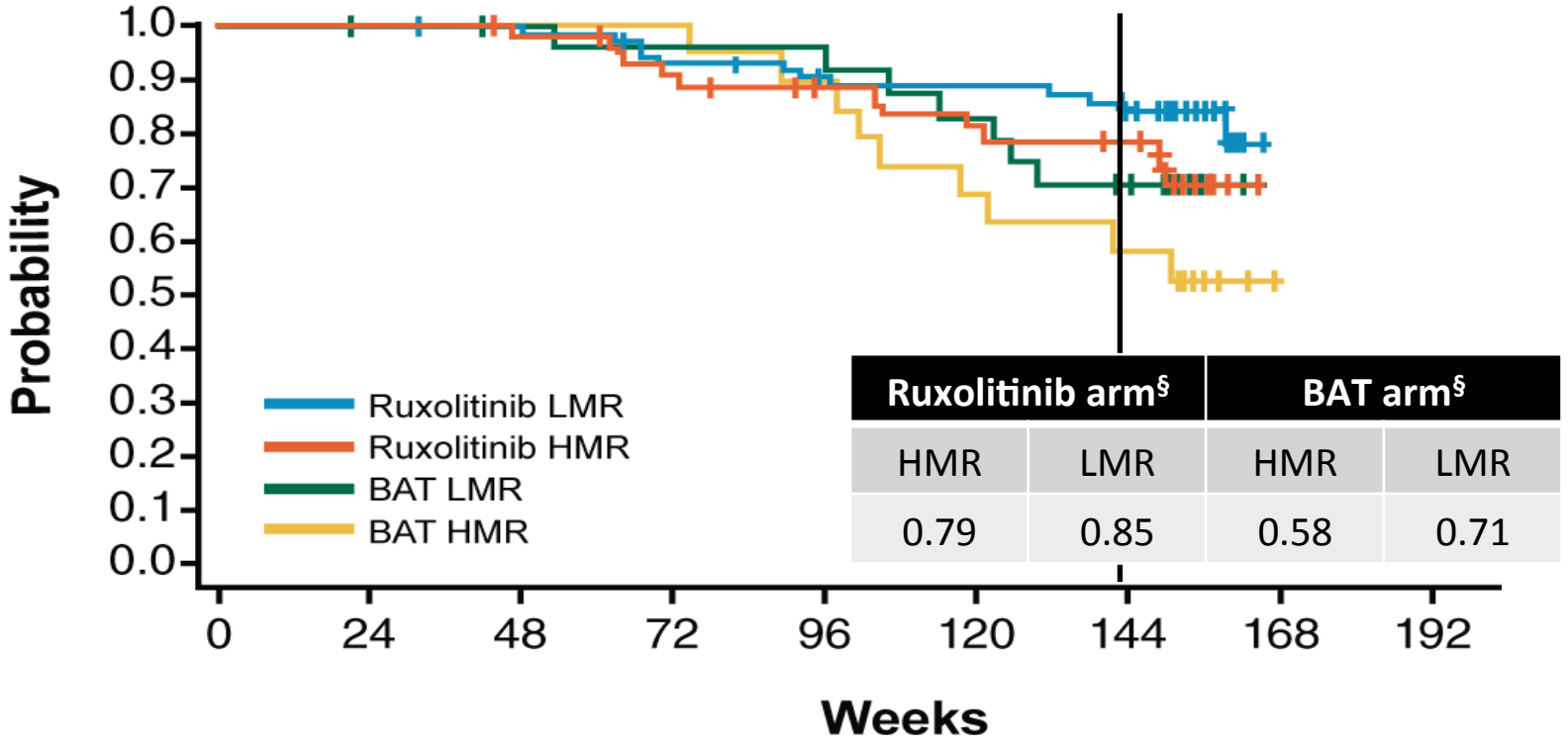
Rank Preserving Structural Failure Time (RPSFT) Analysis of Survival in COMFORTs



- Ruxolitinib vs control (ITT): HR = 0.65; 95% CI, 0.46-0.90; *P* = .01.
- Ruxolitinib vs control (RPSFT-corrected for crossover) HR = 0.29; 95% CI, 0.13-0.63; *P* = .01.

Vannucchi AM, et al. Haematologica 2015; 100: 1139-1145.

Survival Estimates in Patients in COMFORT-II Stratified by Treatment and Molecular Score



Ruxolitinib arm§		BAT arm§	
HMR	LMR	HMR	LMR
0.79	0.85	0.58	0.71

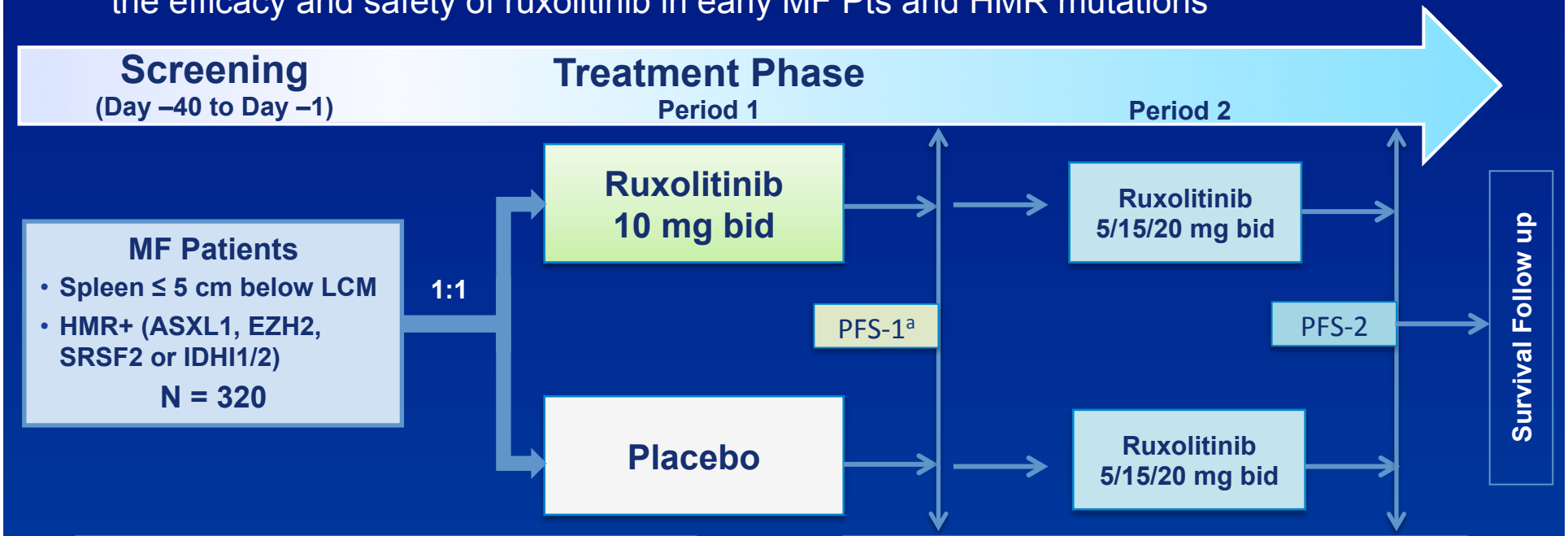
- In multivariate analysis of overall survival by treatment and molecular risk, the HR for treatment (ruxolitinib vs BAT) was 0.57 (95%CI= 0.30-1.08) and for LMR vs HMR the HR was 0.62 (95%CI=0.33-1.16)

§Median follow up= 151 weeks; Kaplan Meier estimates at 144 weeks

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

ReTHINK
Trial Design

- ReTHINK is a phase III randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of ruxolitinib in early MF Pts 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

[a] If progression is achieved by spleen or symptoms

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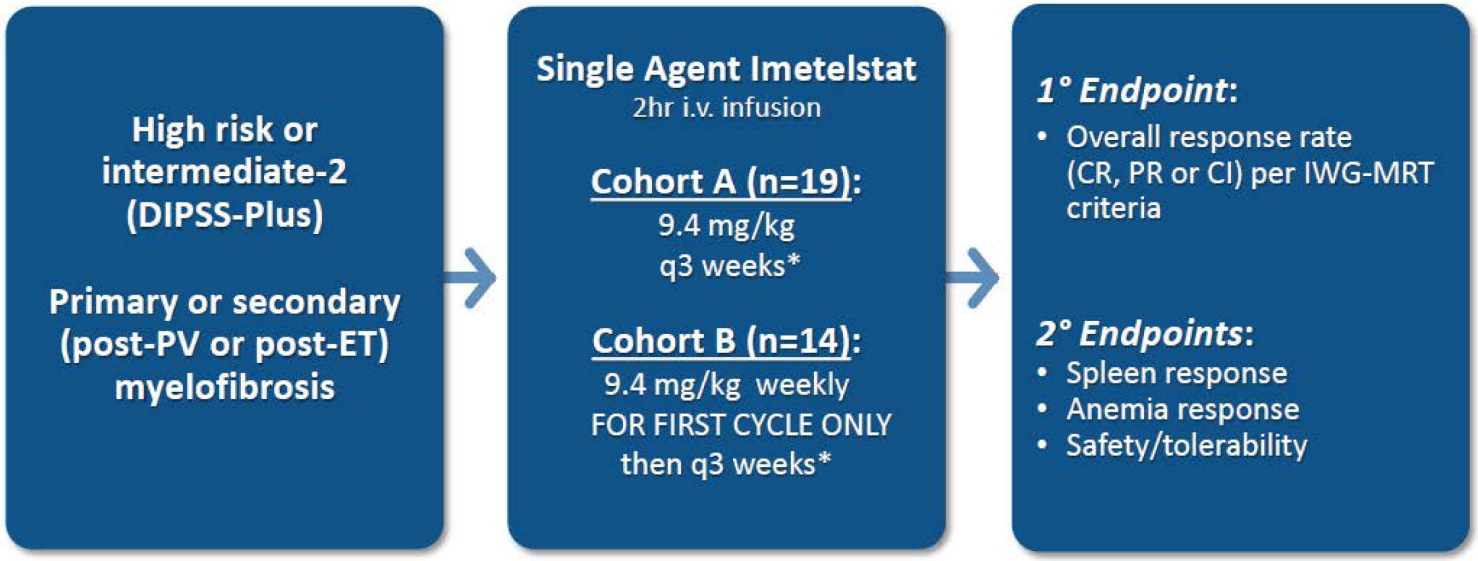
New Targets for MPN

Class	Agent*	Target
PI3K pathway inhibitors	• BKM120/Buparlisib • RAD001/Everolimus	PI3K/Akt/ mTOR
Histone deacetylase (HDAC) inhibitors	• Panobinostat • Vorinostat • Givinostat • Pacrinostat	HDACs (different classes) HSP90
DNA methyltransferase inhibitors	• Azacitidine • Decitabine	DNA methyltransferase
Hedgehog inhibitors	• LDE225	Smo
Telomerase inhibitors	• Imetelstat	Telomerase
Bone marrow fibrosis inhibitors	• Pentraxin • LXO inhibitors	Various

* list not exhaustive

Inhibition of Telomerase Activity in MPN

- Upregulated telomerase activity favours proliferation and replication immortality of neoplastic progenitor cells
- MPN cells have evidence of dysregulated telomerase activity
- **IMETELSTAT** is the first telomerase inhibitor in clinical development
- Competitively binds to RNA template of telomerase and inhibits is activity
- **IMETELSTAT** inhibited growth of spontaneous CFU-MK from ET pts

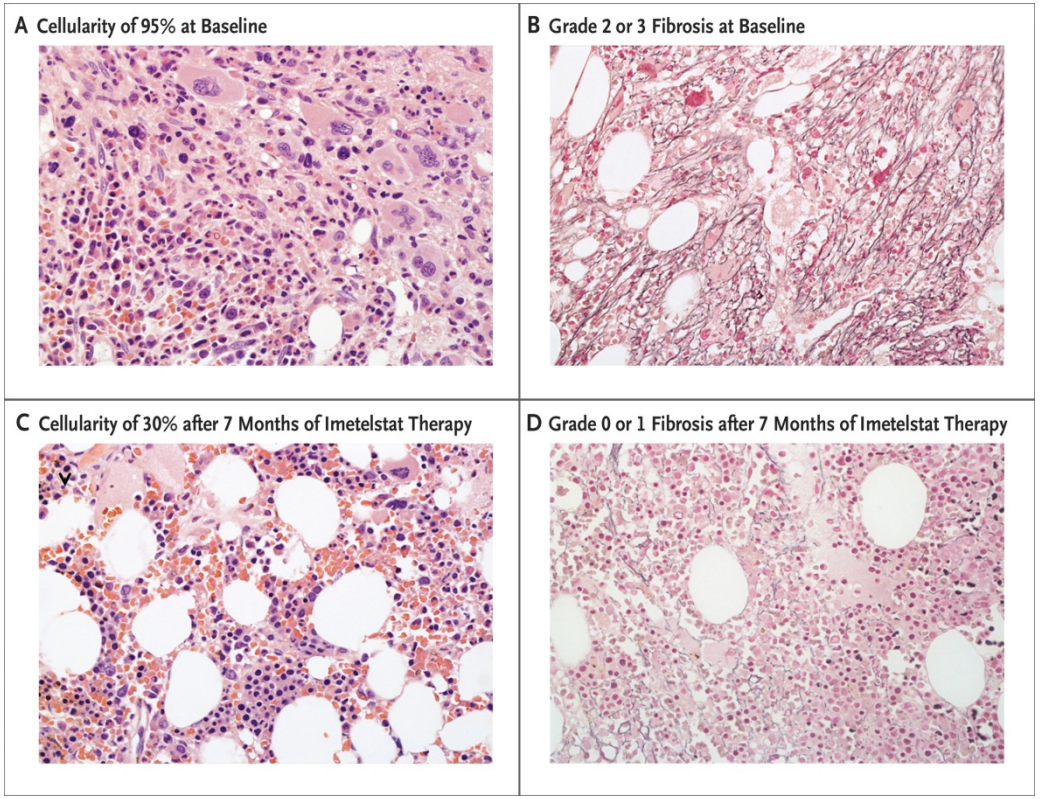


Tefferi A et al, NEJM 2015; 373:908-919

Ruella M et al, *Exp Hematol*. 2013 Jul;41(7):627-34; Baerlocher GM, et al. *Blood* Nov 2012; 120: 179.

Complete/Partial Responses Induced by Imetelstat

- Imetelstat induced **complete or partial responses in 21% of patients with refractory myelofibrosis**.



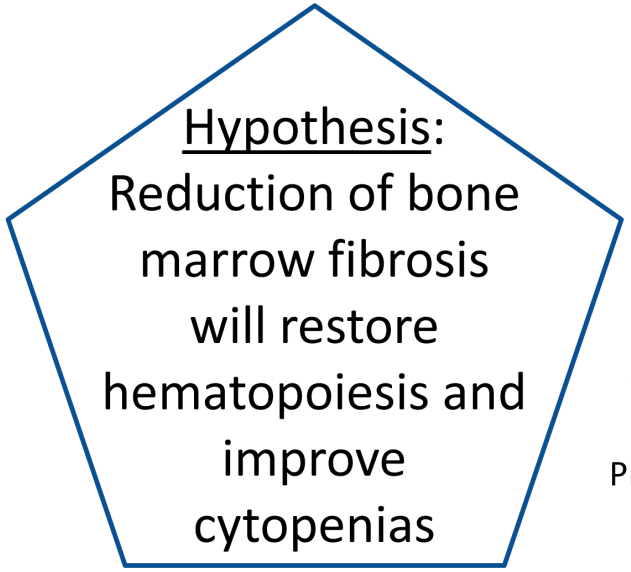
- In some patients, reversal of marrow fibrosis was documented and the burden of mutant clones decreased.
- Myelosuppression was the key toxic effect.

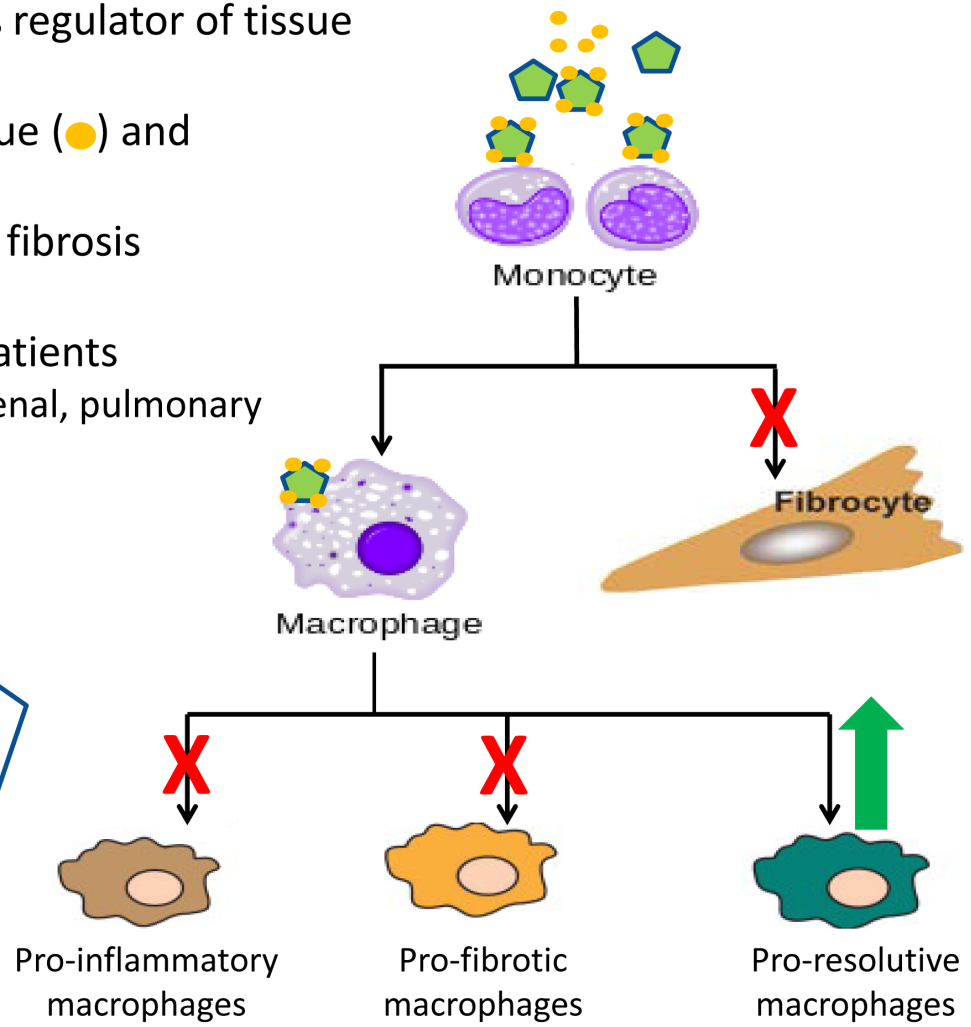
A phase-2 study in Ruxo-resistant patients with 2 dose levels is ongoing

Tefferi A et al, NEJM 2015; 373:908-919

PRM-151: Recombinant Analog of PTX-2

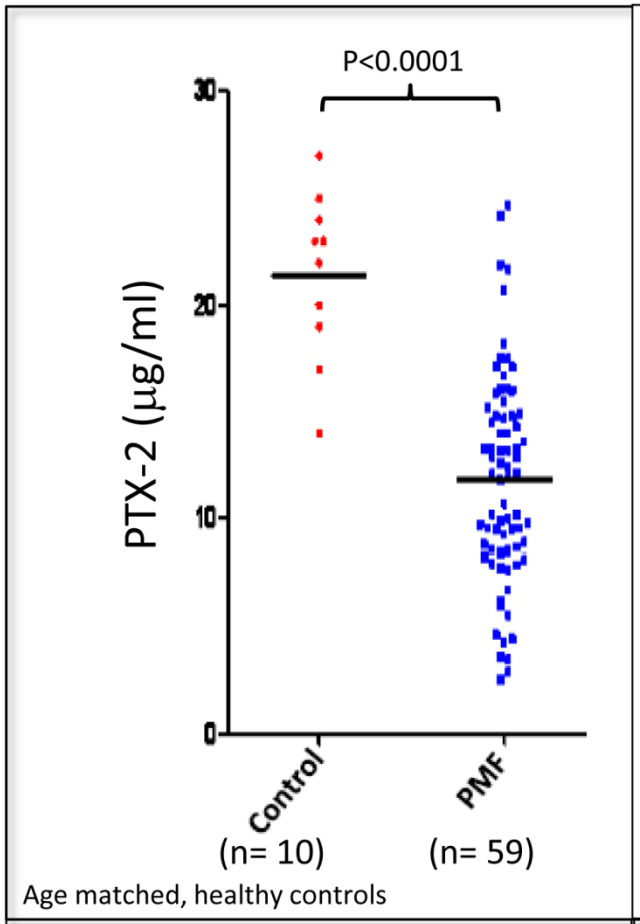
- PTX-2 ( ) is an endogenous regulator of tissue repair
- PTX-2 binds to damaged tissue ( ) and monocytes/macrophages
- PTX-2 prevents and reverses fibrosis in pre-clinical models
- PTX-2 levels are low in MF patients
  - Also low in patients with renal, pulmonary and liver fibrosis



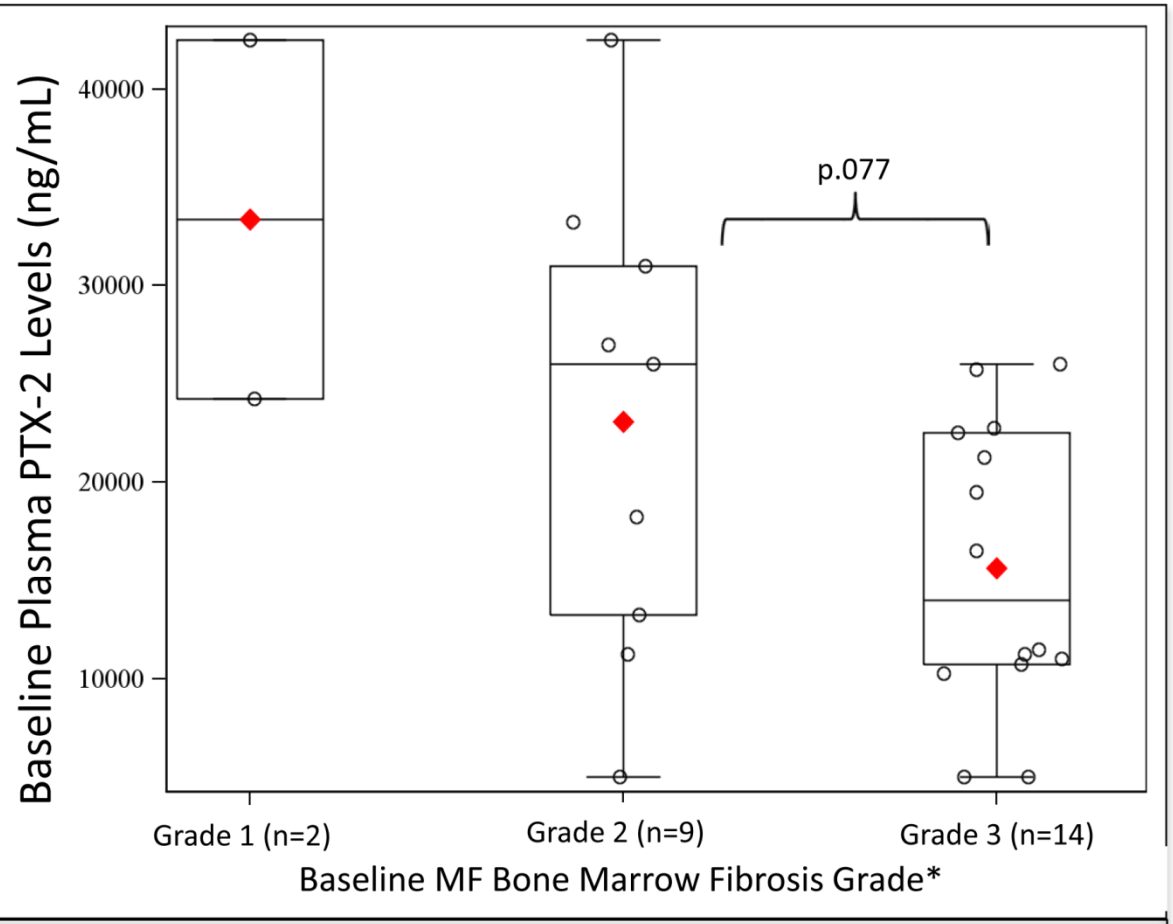


Verstrovsek S, courtesy

Reduced PTX-2 Levels in Patients with MF



Independent study, Verstovsek et al



*central, blinded review; 2 patients reclassified as Grade 1

Verstrovsek S, courtesy

PRM-151: Results of a Phase 2 Study in MF

- PRM-151 treatment resulted in:
  - Decreases in bone marrow fibrosis
  - Improvements in hemoglobin and platelets, including transfusion independence
  - Modest reductions in symptoms
  - Modest reductions in splenomegaly
- Benefits increase with longer treatment duration
  - Increased number of patients benefit
  - Increased magnitude and duration of benefit
  - Monthly Rx equal to weekly Rx
- PRM-151 was safe and well-tolerated alone and in combination with a stable dose of ruxolitinib

A phase-2 study in Ruxo-resistant patients is ongoing

Verstrovsek S, courtesy

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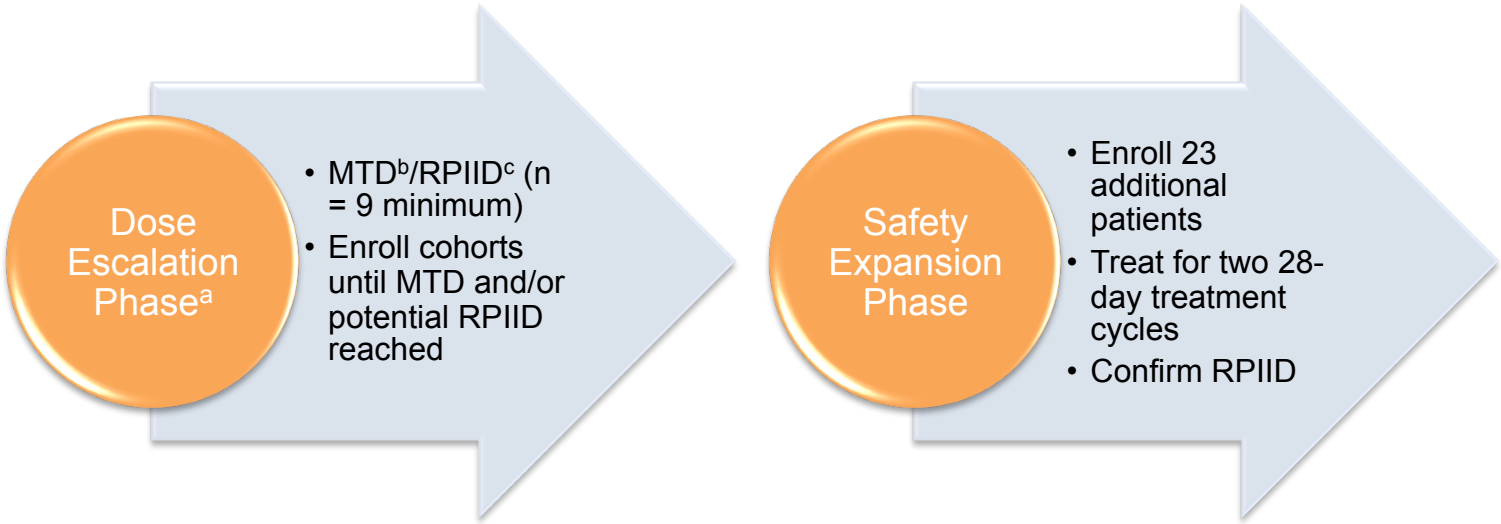
Rationale for New Drugs and Drug Combinations

- Activation of JAK/STAT pathway does not explain the full spectrum of MPN-associated abnormalities: targeting other pathways might be rewarding
- JAK2 inhibitors have remarkable clinical efficacy but they do not induce molecular remission, and changes in allele burden are modest at all
- Dose maximization is limited by hemato toxicity due to inhibition of wild-type JAK2

Phase Ib, Dose-Finding Study of Ruxolitinib Plus Panobinostat in MF Patient



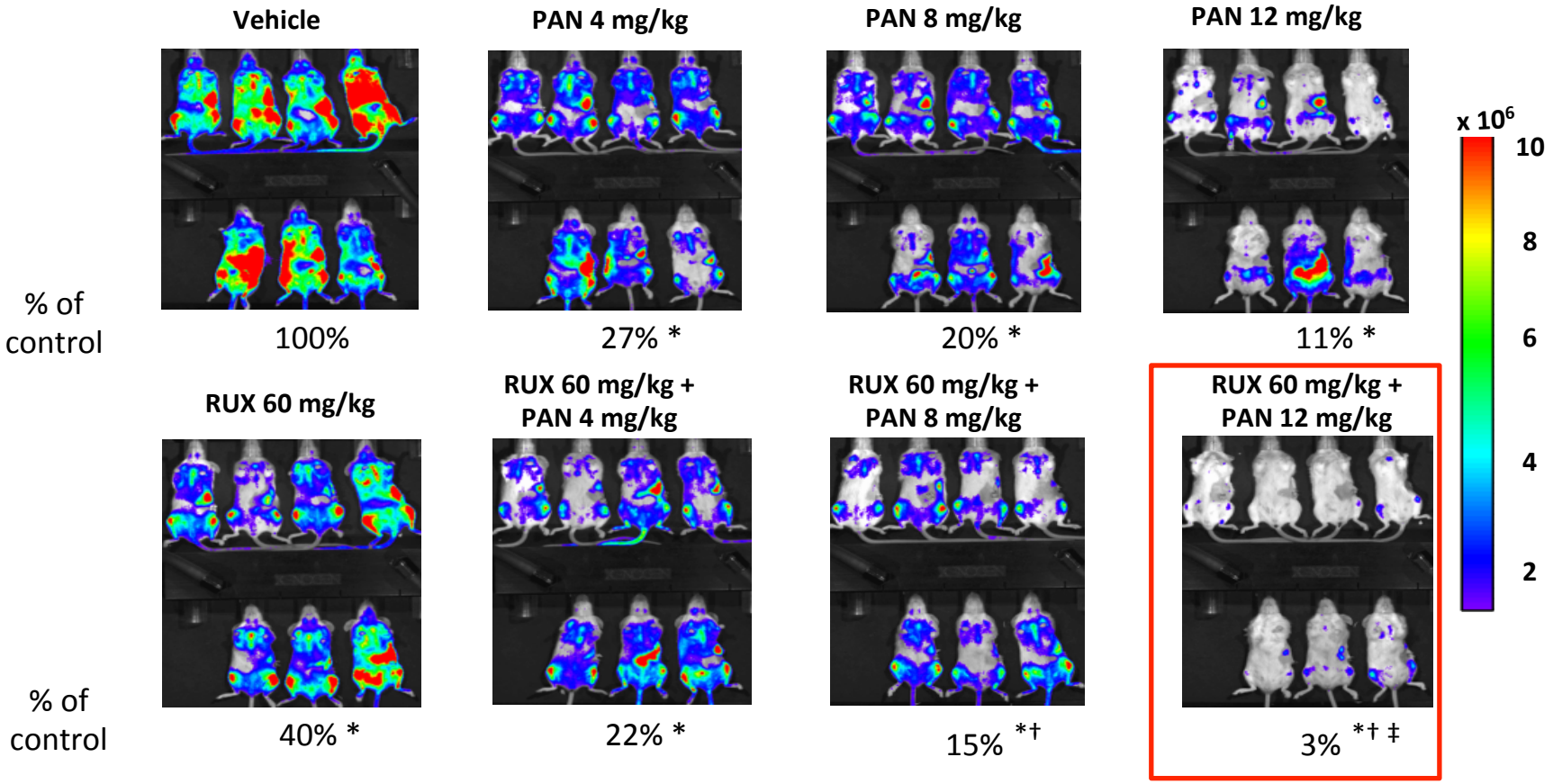
Proposed Dose Level	Proposed Combination Treatment Dose
Cohort 1	RUX 5 mg BID, PAN 10 mg TIW/QOW
Cohort 2	RUX 10 mg BID, PAN 10 mg TIW/QOW
Cohort 3	RUX 15 mg BID, PAN 10 mg TIW/QOW
Cohort 4	RUX 15 mg BID, PAN 15 mg TIW/QOW
Cohort 5	RUX 15 mg BID, PAN 20 mg TIW/QOW
Cohort 6 (potential RPIID)	RUX 15 mg BID, PAN 25 mg TIW/QOW

[a] A total of 38 patients were enrolled across 6 cohorts in the dose-escalation phase.
[b] The MTD is defined as the highest drug dose not causing medically unacceptable, dose-limiting toxicity in more than 33% of the patients treated in the first cycle of treatment.
[c] The RPIID is defined as a dose less than or equal to the MTD/last dose level evaluated after at least 22 patients have been treated at this dose.

BID, twice daily; MTD, maximum tolerated dose; PAN, panobinostat; RPIID, recommended phase II dose; RUX, ruxolitinib; TIW/QOW, 3 times a week, every other week.

Harrison CN, et al. EHA 2012 abst. 0364.

Combined Effects of Ruxolitinib and Panobinostat in an In Vivo Model of JAK2V617F Mutated MPN

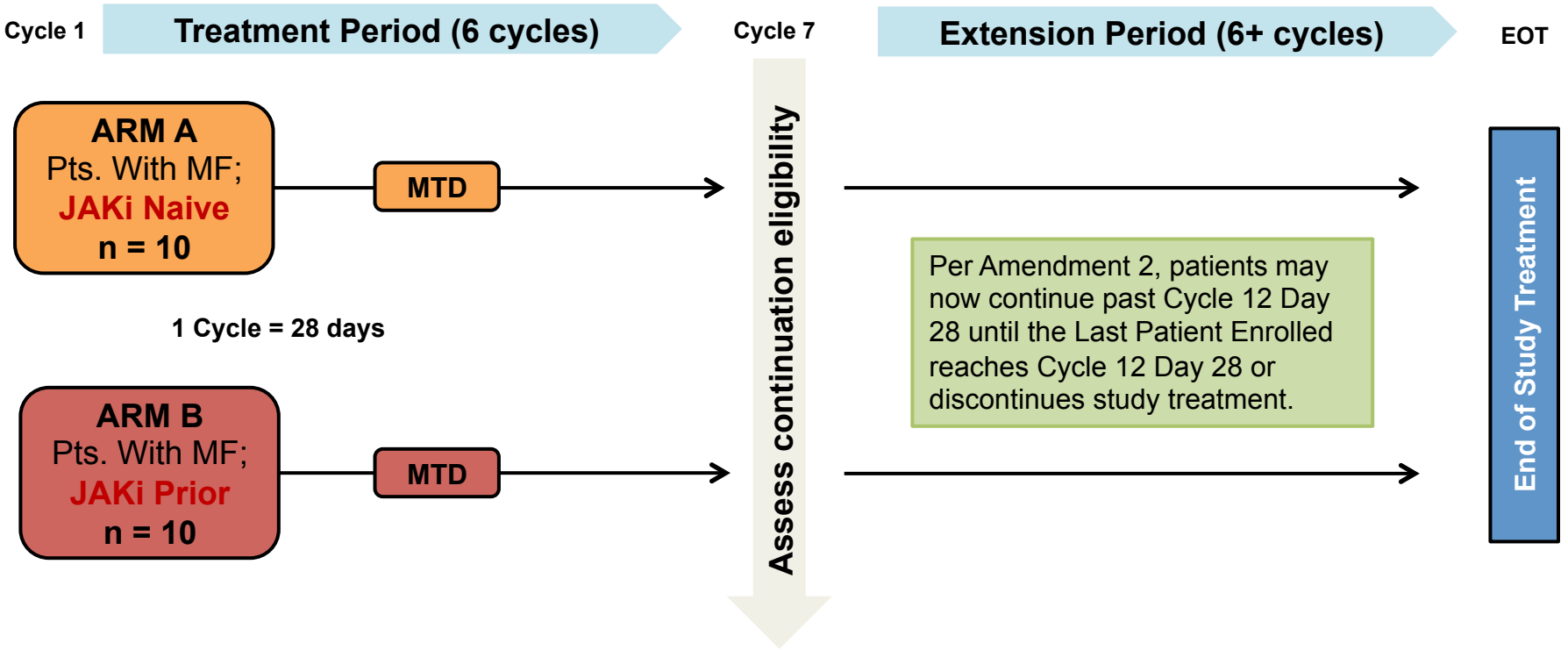


- Enhanced efficacy was observed with a combination of RUX and PAN
- There was no major change in tolerability, as assessed by body weight, between panobinostat alone or in combination with ruxolitinib

- $P < 0.05$ vs. vehicle control; † $P < 0.05$ vs. ruxolitinib;
- ‡ $P < 0.05$ vs .panobinostat at same dose

Evrot E, et al. *Clin Canc Res* 2013; 19:6230-41

A Phase Ib Dose Finding Evaluation of Oral Combination of Ruxolitinib and BKM120 in MF

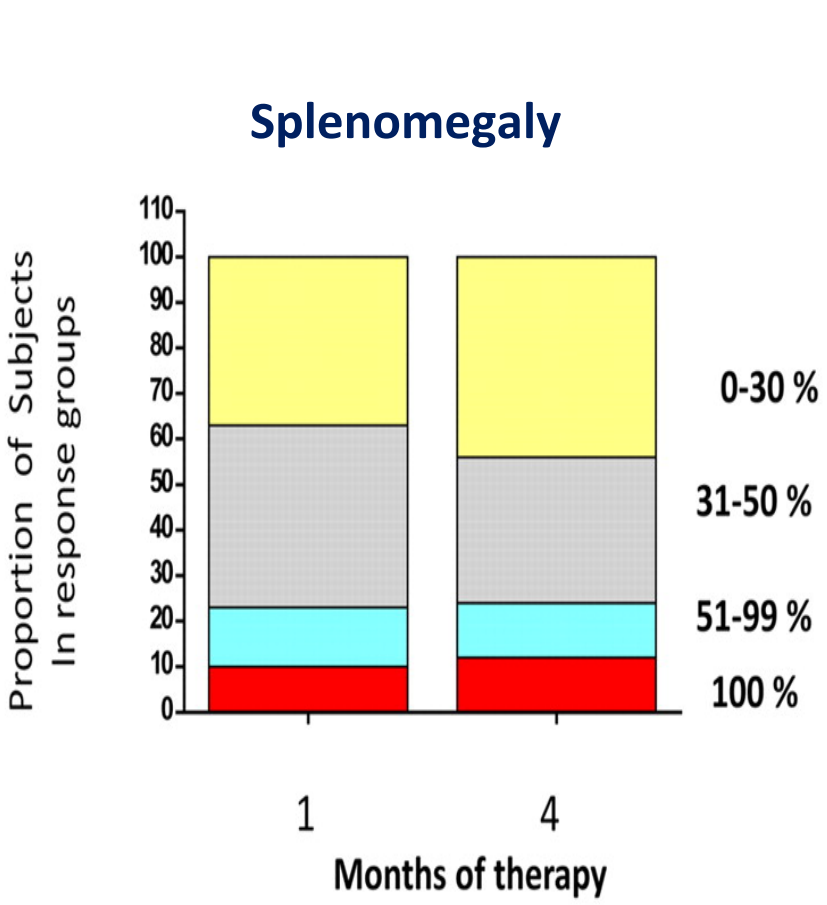


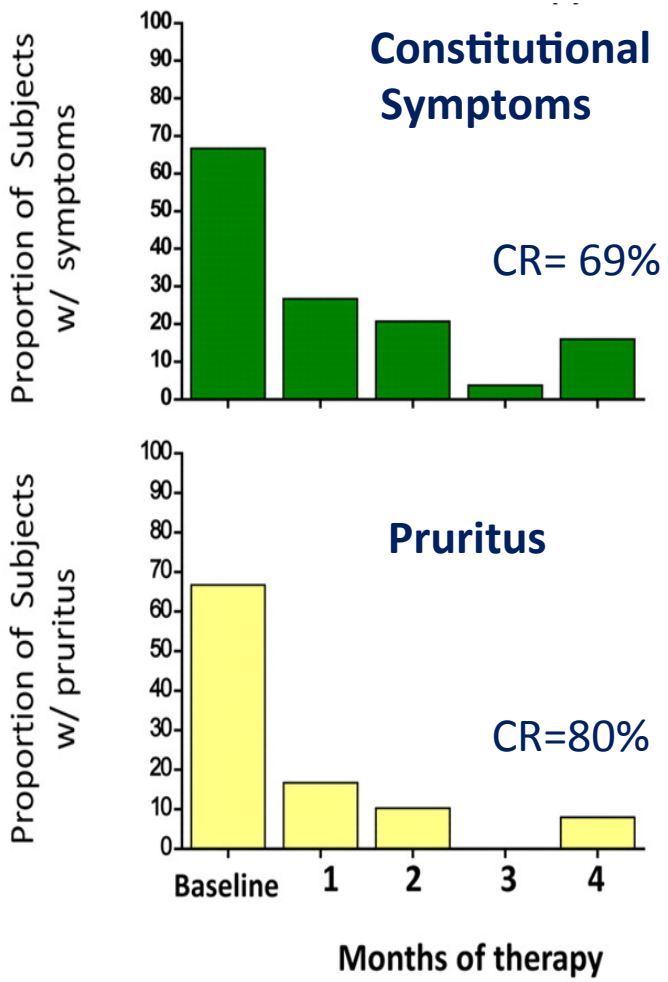
On **Cycle 7 Day 1**, patient must meet below two criteria to continue on study treatment:

- Patient is benefitting from treatment per PI
- No evidence of disease progression defined as spleen length increase of > 40% from baseline as assessed by palpation

HARMONY
A PHase Ib Dose finding evAluation of oRal coMbination Of INC424 and BKM120 in mYelofibrosis patients

Phase I/II Trials of Everolimus in Myelofibrosis: Clinical Activity



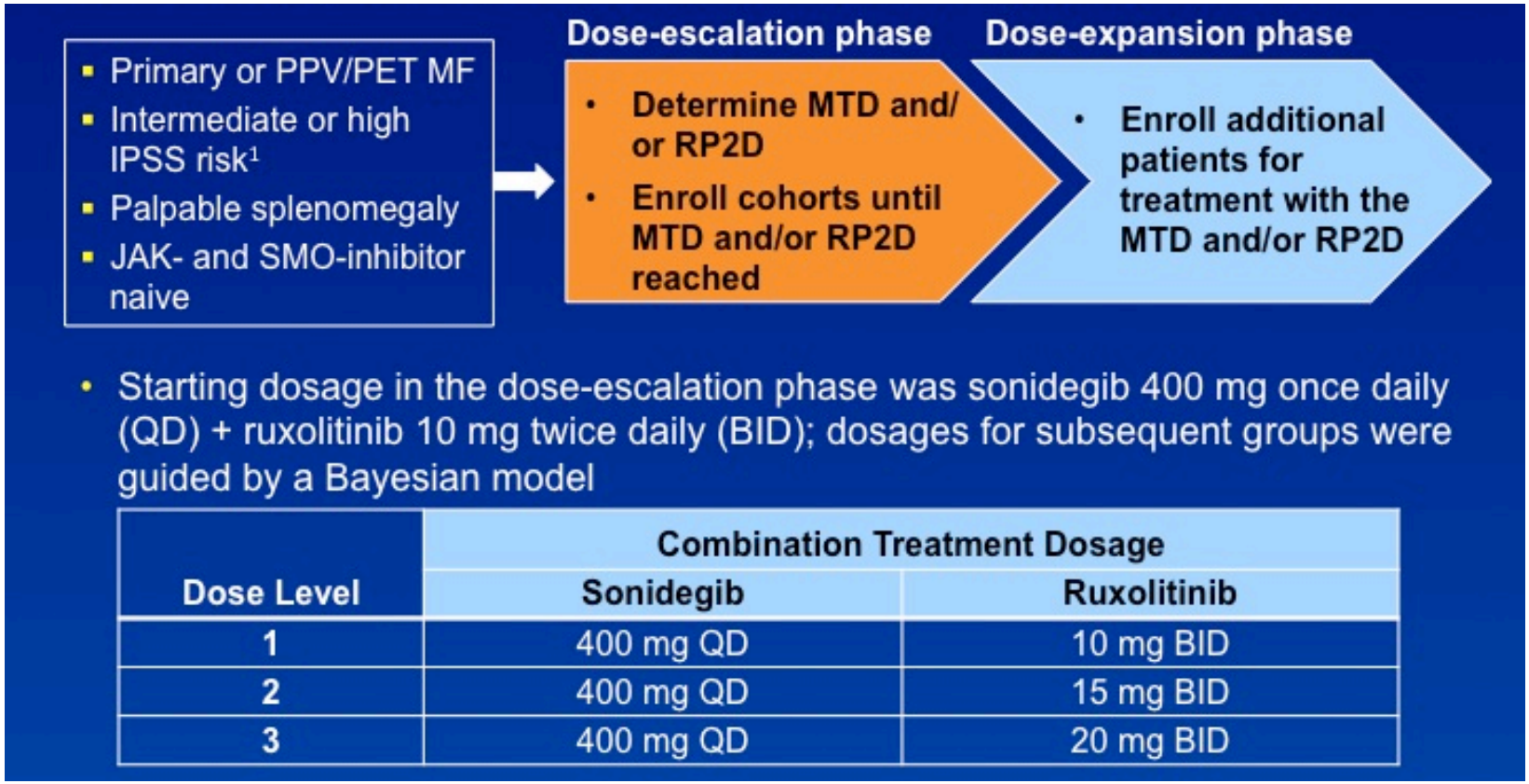


IWG-MRT Responses (ITT):

Overall 23%, PR 3%, CI 20%, SD 77%

Guglielmelli P, et al. *Blood* 2011;118:2069-2076

Phase 172 Study of Sonidegib (LDE225) in Combination with Ruxolitinib in MF



- Starting dosage in the dose-escalation phase was sonidegib 400 mg once daily (QD) + ruxolitinib 10 mg twice daily (BID); dosages for subsequent groups were guided by a Bayesian model

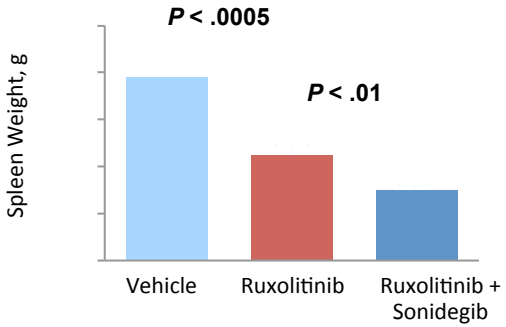
Dose Level	Combination Treatment Dosage	
	Sonidegib	Ruxolitinib
1	400 mg QD	10 mg BID
2	400 mg QD	15 mg BID
3	400 mg QD	20 mg BID

Tibes R, Mesa RA. *J Hematol Oncol.* 2014;7:18. Pan S, et al. *ACS Med Chem Lett*. 2010;1:130-134. Bhagwat N, et al. *Blood*. 2013;122(21) [abstract 666]. Gupta V et al. ASH 2014.

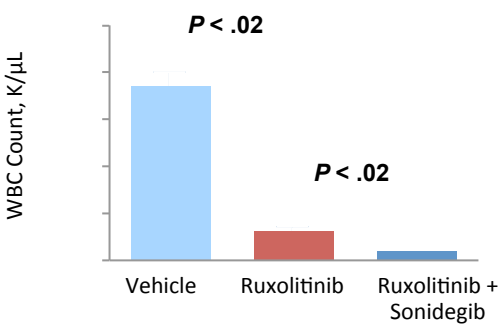
Study Rationale

- The Hh pathway is involved in hematopoietic stem cell proliferation and is active in hematologic malignancies[1]
  - In a murine model of MF, ruxolitinib in combination with the Hh pathway inhibitor sonidegib (selectively inhibits SMO[2]) improved splenomegaly and bone marrow fibrosis better than ruxolitinib alone[3]

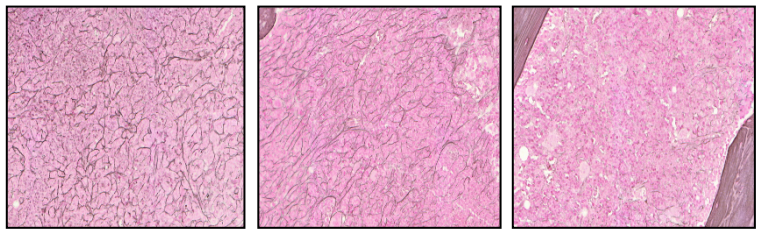
Spleen Weight



WBC Count



Bone Marrow Fibrosis



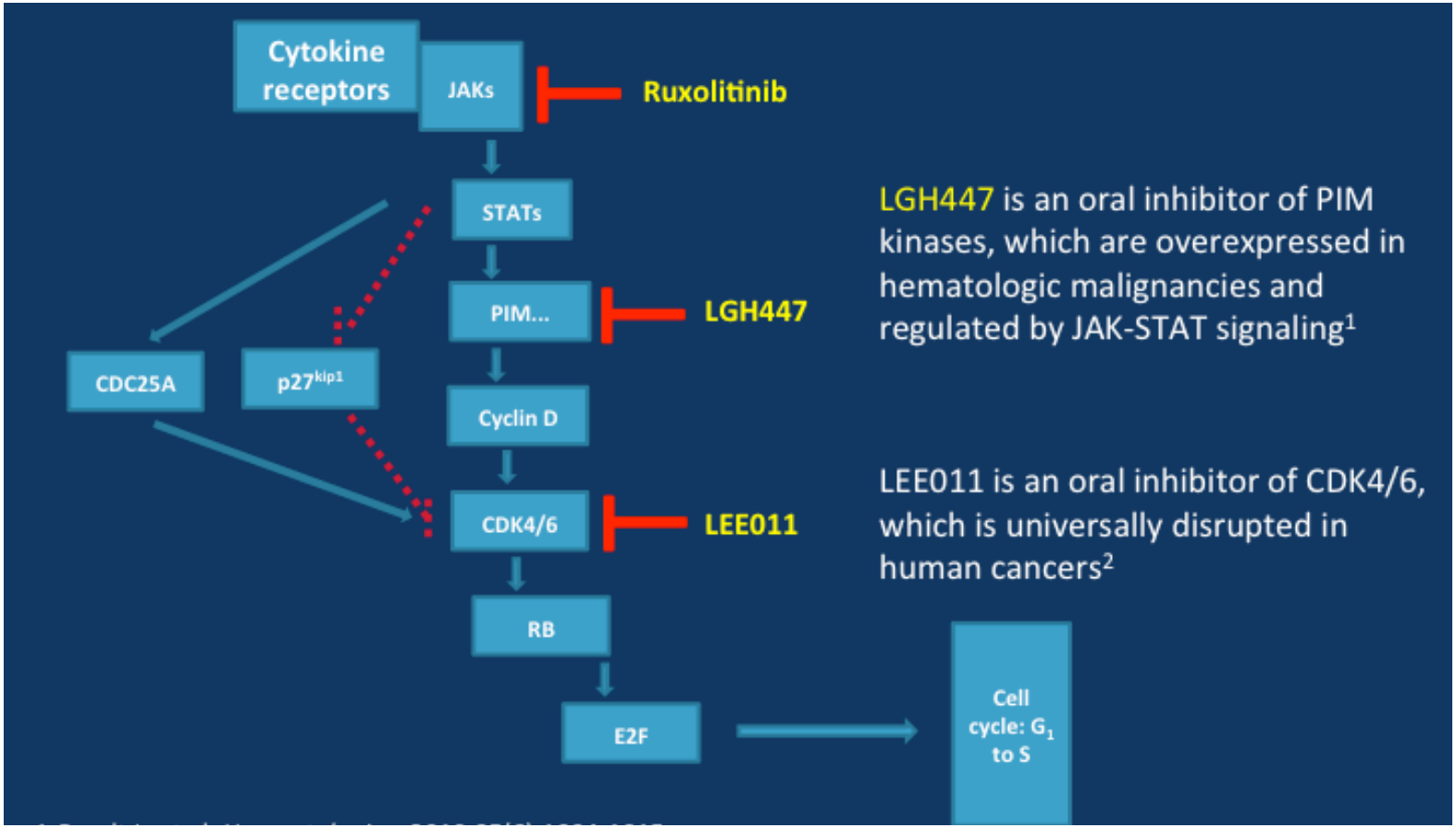
1. Tibes R, Mesa RA. *J Hematol Oncol.* 2014;7:18.
2. Pan S, et al. *ACS Med Chem Lett*. 2010;1:130-134.
3. Bhagwat N, et al. *Blood*. 2013;122(21) [abstract 666].

Safety and Efficacy of Ruxolitinib Combinations

	RUX-PAN	RUX-LDE	RUX-BKM naive	RUX-BKM pretreat
Spleen Response (at 24w)	56.5%	44.4%	45.5%	22.2%
Mean spleen reduction at 24w	41.7%	30.8%	38.8%	26.5%
Adverse events	• Diarrhea: 68%, 18% gradoe3/4 • Astenia :50%, 12% grade 3/4 • Fatigue: 29%, 6% grade 3/4	• Raised CK 37%, 18,5% grade 3/4 • Myalgia:29,6%, 7,4% grade 3/4 • Diarrhea: 25,9%, 3,7% grade 3/4 • Fatigue: 25,9%; 0 grade 3/4	• Anxiety 15,9%, 4,8% grade 3-4 • Depression: 14,3%, 3,2% grade 3/4 • Iperglycemia: 12,7%; 3,2% grade 3/4	

Kiladjian; et al, ASH 2014
Durrant; et al, ASH 2014
Gupta et al, ASH 2014

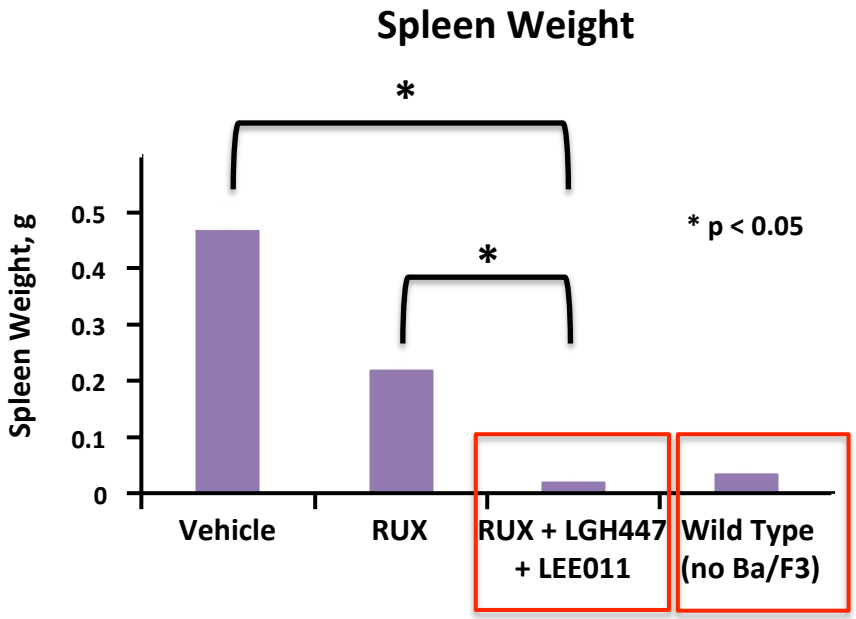
If 2 is good, 3 may be even better???

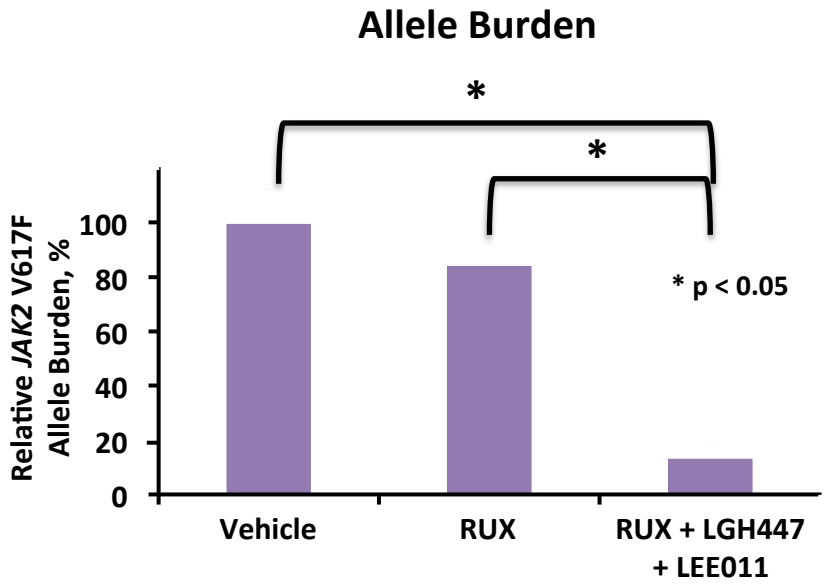


Brault L, et al. *Haematologica*. 2010;95(6):1004-1015.
Shapiro GI. *J Clin Oncol*. 2006;24(11):1770-1783.

Pinzon-Ortiz M, et al. EHA 2014 abst. S710

Ruxolitinib + LGH447 + LEE011 Reduced Spleen Size and Allele Burden to a Greater Degree than Ruxolitinib Alone





- The triple combination resulted in greater reductions in spleen size compared with ruxolitinib alone, reducing spleen weight to levels at or below those in wt animals
- The triple combination solely resulted in a substantial reduction in *JAK2* V617F allele burden in Ba/F3-JAK2^{V617F} mice compared with ruxolitinib monotherapy

A phase-1b study in Ruxo-resistant patients is ongoing

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