Myeloproliferative Neoplasms: Drugs in Clinical Trial

Joyce Niblack Memorial Patient-Physician MPN Conference
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Mount Sinai

New York, New York

Disclosures for John Mascarenhas, MD

In compliance with ACCME policy:

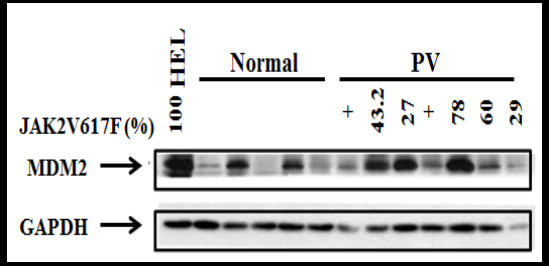
- **Consultancy:** Celgene; Incyte; Roche
- **Research Funding:** Celgene; CTI Biopharma; Incyte; Janssen; Merck; Novartis; Promedior; Roche

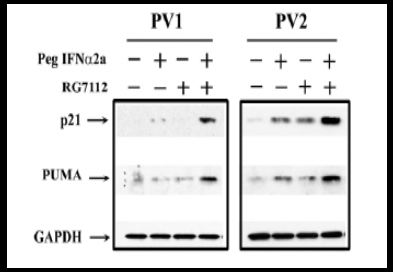
Objectives

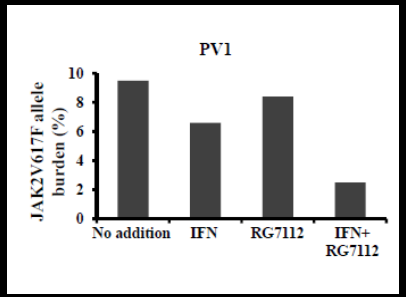
- ET/PV
  - Encouraging MPN cells to commit suicide
- *MF*
  - *Final stretch for second generation JAK inhibitors*
  - *Addressing anemia and avoiding RBC transfusions*
  - *An option to improve/salvage ruxolitinib response*
  - *An option for post-ruxolitinib failure*
  - *Reducing/eliminating bone marrow fibrosis*
  - *“targeted therapy” in the truest sense*

Background: MDM2 and PV

- PV CD34+ cells contain higher levels of MDM2 compared to normal CD34+ cells
- Low doses of a Nutlin and Peg-IFNα 2a increase p21 and PUMA protein levels in PV CD34+ cells and promote apoptosis
- Treatment with low doses of a Nutlin and Peg-IFNα 2a reduce the numbers of JAK2V617F-positive cells transplanted in NOD/SCID mice

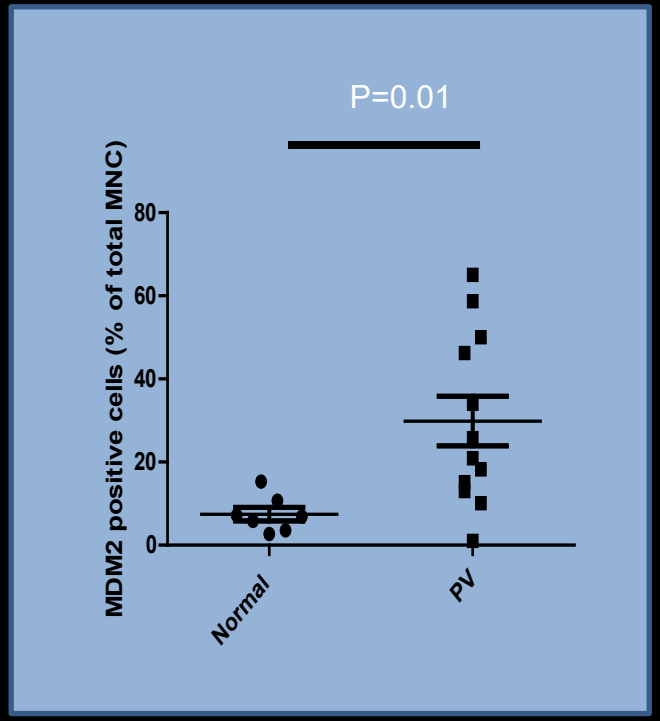






Lu M et al. Blood. 2012 Oct 11;120(15):3098-105;Lu et al. Blood. 2014 Jul 31;124(5):771-9

Baseline MDM2 levels higher in study participants than normal controls



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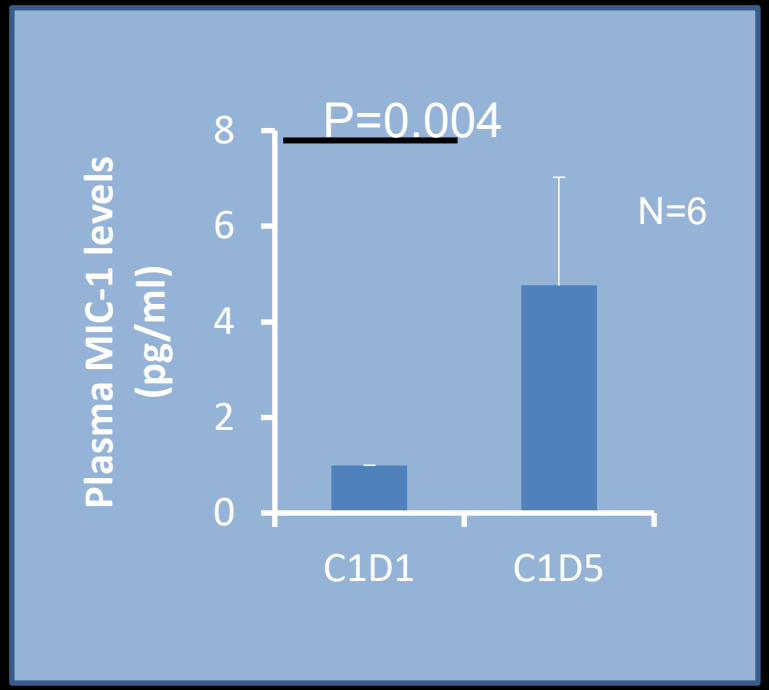
Myeloproliferative Disorders Research Consortium MPD-RC

Mascarenhas ASH 2017

Evidence of P53 pathway activation: Plasma MIC-1 levels are significantly increased in PV patients following treatment with idasanutlin



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Myeloproliferative Disorders Research Consortium MPD-RC

Responses by 2013 ELN-IWG[1] criteria

By 6 cycles of therapy with idasanutlin monotherapy in PART A and combination pegylated interferon-α in PART B

	Not evaluable (NE)	No response (NR)	Partial Response (PR)	Complete Response (CR)	Overall Response (PR+CR)
PART A (n=12)	1[#]	4	3*	4	7 (58%)
PART B (n=4)^		2	1	1	2 (50%)
				PART A + PART B ORR	9 (75%)

- # not evaluable due to patient decision to withdraw from study after 4 cycles due to GI toxicity
- *Residual splenomegaly likely due to known portal vein thrombosis, likely a CR (n=1)
- ^4 subjects from PART A that had NR continued on to PART B combination idasanutlin + interferon-α
- [+] not yet completed cycle 7

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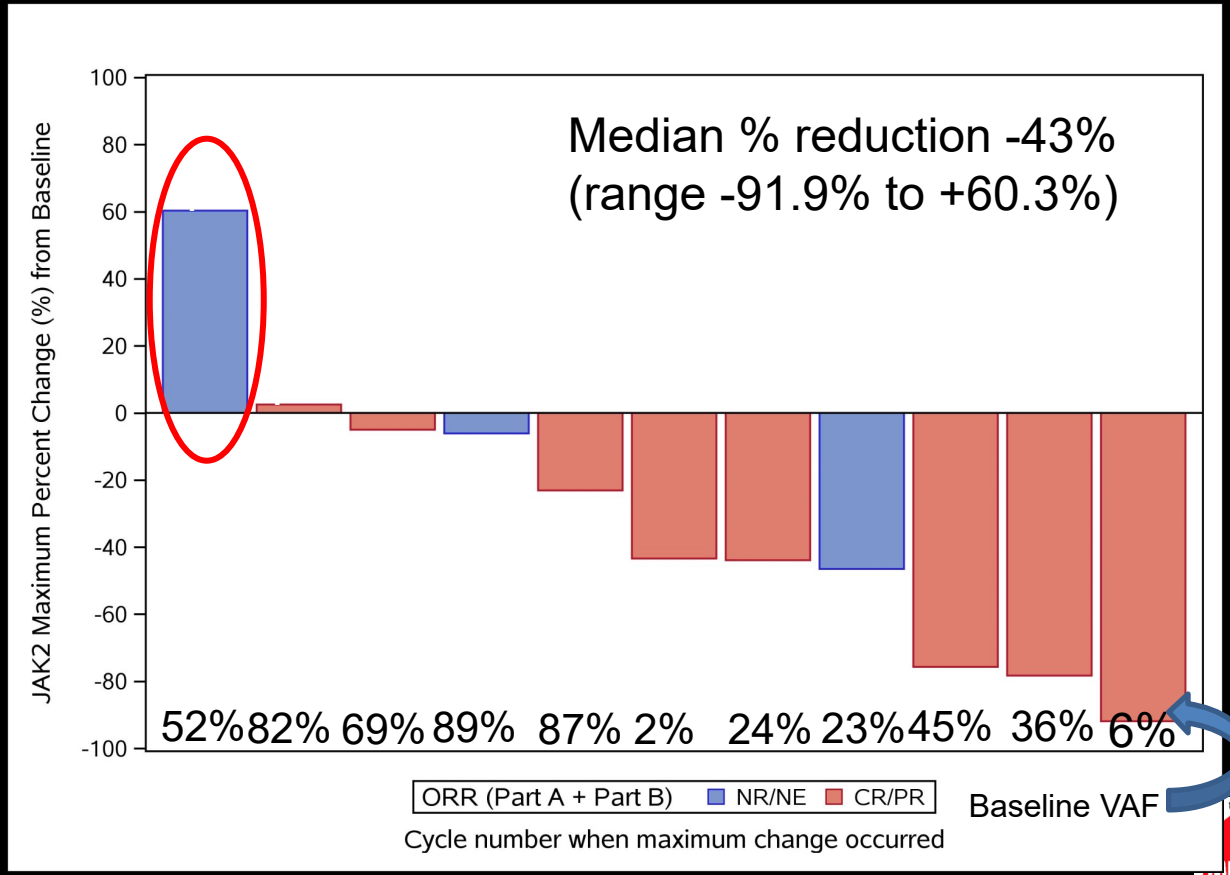
Driver mutation responses with idasanutlin therapy



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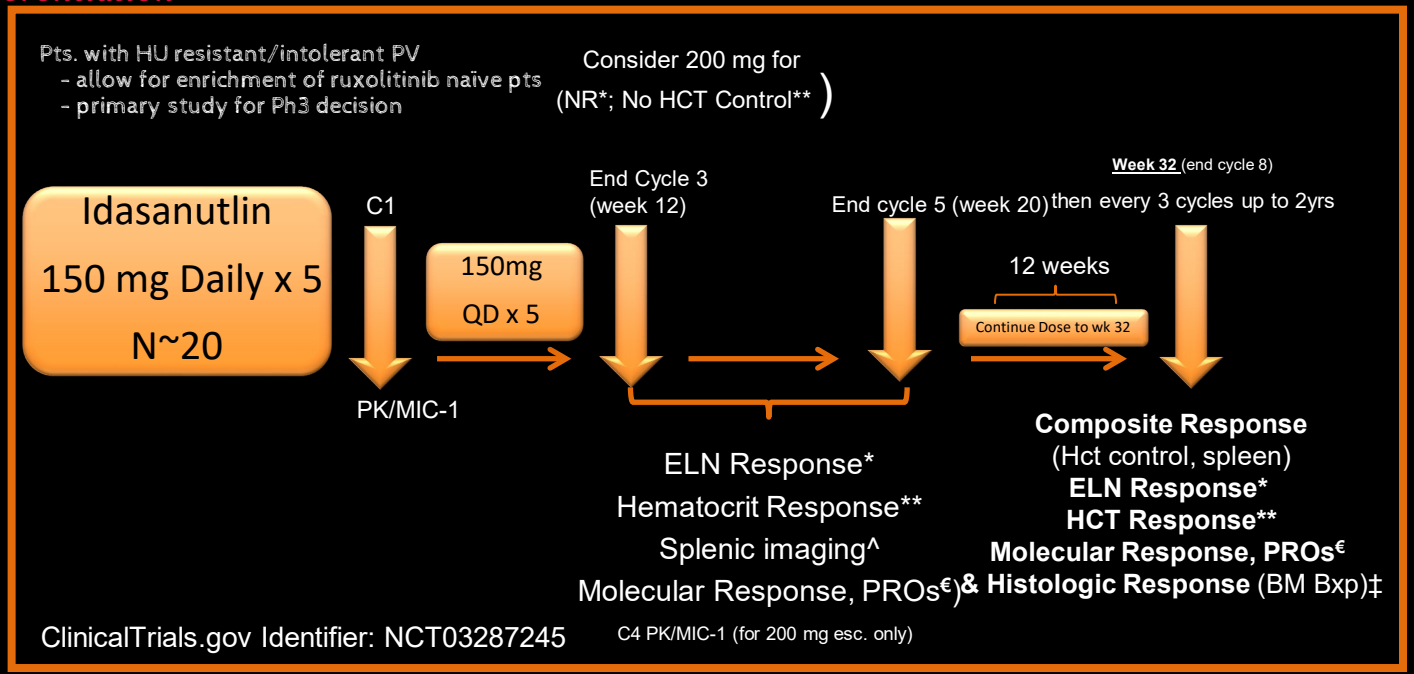
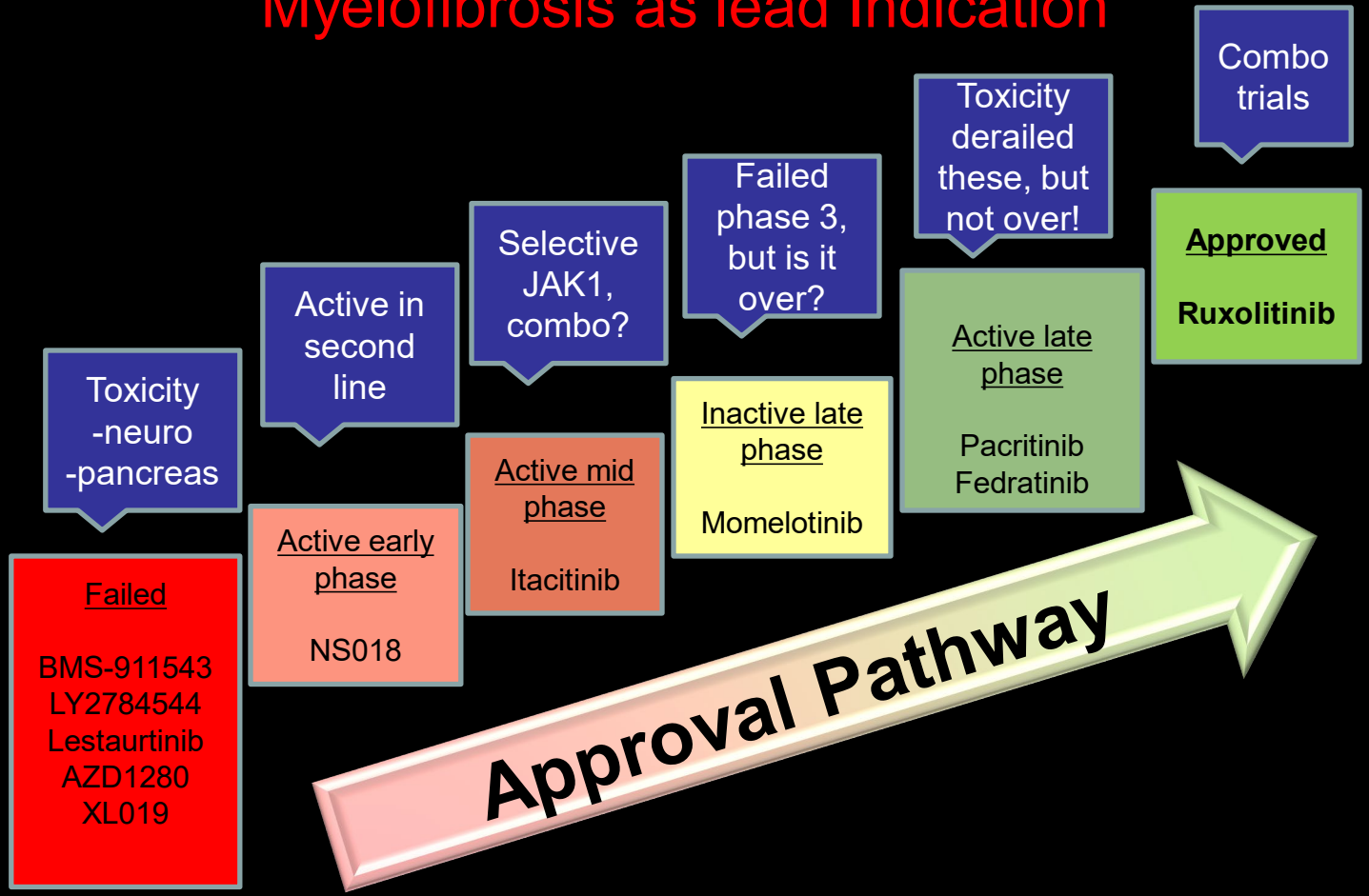
Single arm Phase 2 study

Population and endpoint to match Ruxolitinib, explore ELN , molecular criteria for differentiation

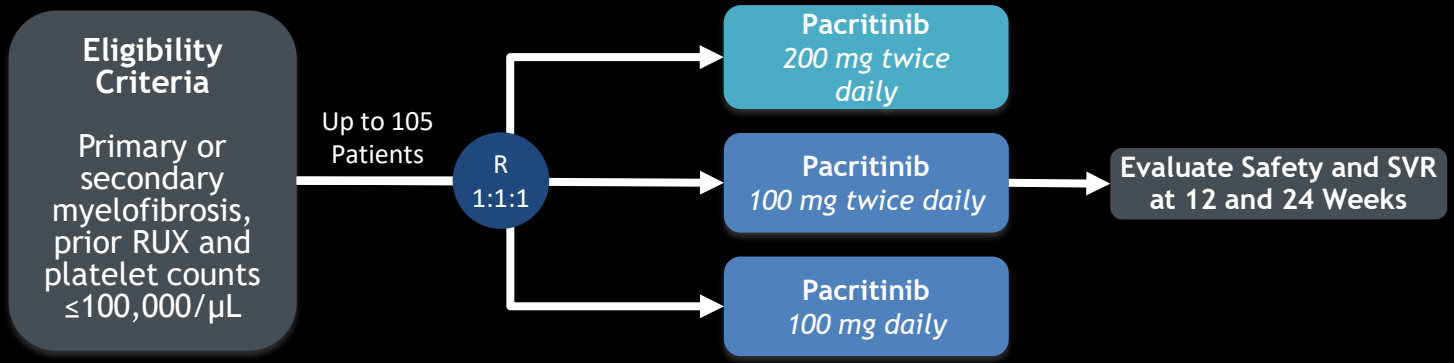


*NR per 2009 ELN Criteria **Patients without measurable splenomegaly at baseline ^spleen imaging at end C5 only if <35% reduction at end C3 €MPN-SAF-TSS, EORTC QLQ-C30 , PGIC ‡Bone Marrow biopsy every 6 cycles post week 32 per PI discretion in context of ELN CHR response

JAK Inhibitors and Status of Development in Myelofibrosis as lead Indication



PAC203: Dose Ranging Clinical Trial



- PAC203 is dose finding study in patients with PMF, post-PV MF, and post-ET MF:
  - Who have failed or were intolerant to therapy with RUX
  - With platelet count <100,000/μL
  - Who are highly symptomatic (DIPSS risk score of intermediate-1 to high risk)
  - With splenomegaly (assessed by physical examination).
- ClinicalTrials.gov. NCT03165734.

FED-MF-001: A Multicenter, Single-arm, Open-label efficacy and safety study of Fedratinib in subjects previously treated with Ruxolitinib and with Intermediate or High-Risk PMF, Post-PV MF, or Post-ET MF

FEDR-MF-002: A Phase 3, Randomized, Open-label study of Fedratinib in subjects with Intermediate or High-Risk PMF, Post-PV MF, or Post-ET MF who have been previously exposed to Ruxolitinib

Key eligibility criteria
PMF, pET-MF, pPV-MF
DIPSS: Int/High risk disease
Spleen ≥450ml or ≥5cm
Previous exposure with Ruxolitinib
Platelets ≥50K
Normal thiamine level

N=110 → Fedratinib 400mg

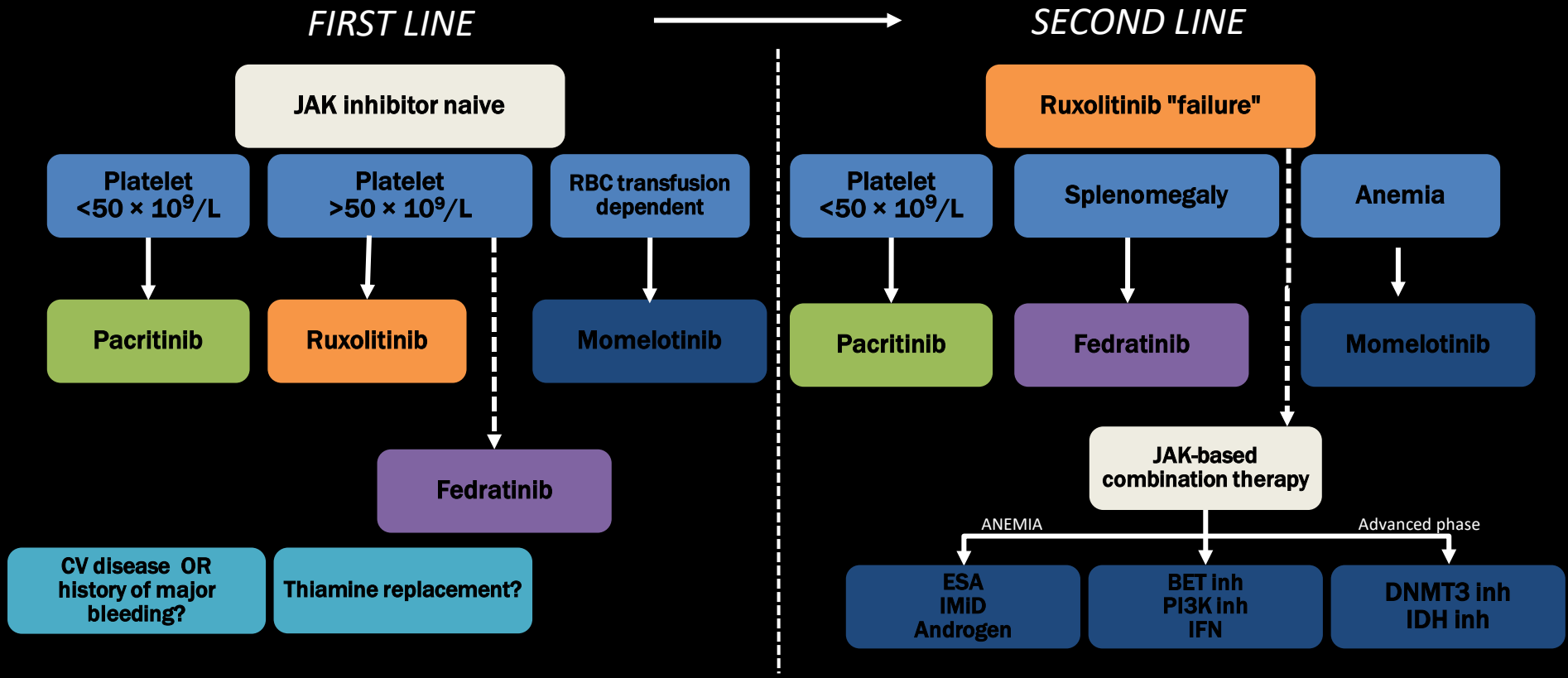
- **Primary**: Spleen volume response by MRI/CT scan at the End of Cycle 6
- **Secondary**: Safety, Spleen response by palpation, duration of spleen response, symptom response, assess mitigation strategies for WE and GI AEs, QoL

Key eligibility criteria
PMF, pET-MF, pPV-MF
DIPSS: Int-2/High risk disease
R/R/intolerant to Rux treatment
Spleen ≥450ml and ≥5cm
Platelets ≥50K
Normal thiamine level

R (2:1) N=~192 → Fedratinib 400mg

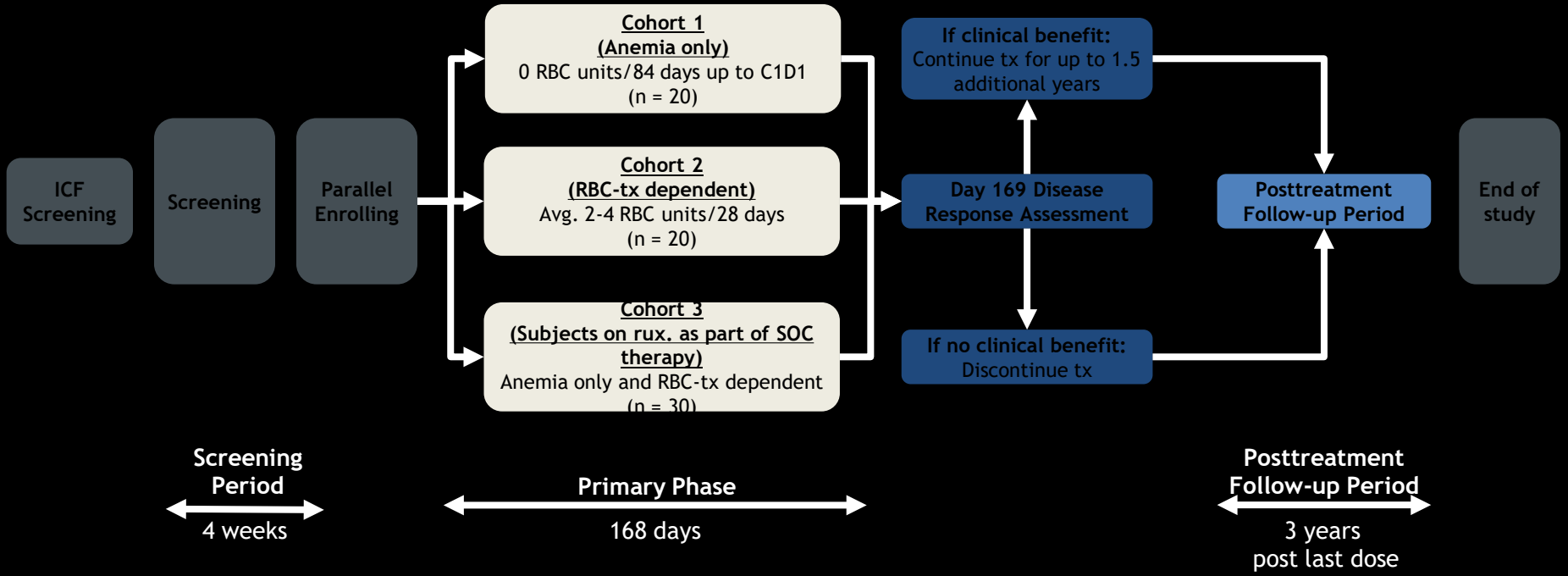
R (2:1) N=~192 → Best Available Therapy (BAT)

- Stratification at randomization: platelets, spleen size, R/R vs intolerant
- **Primary Endpoint**: ≥35% reduction in spleen volume at end of cycle 6


FIRST LINE
SECOND LINE
JAK inhibitor naive
Platelet <50 × 10⁹/L
Platelet >50 × 10⁹/L
RBC transfusion dependent
Pacritinib
Ruxolitinib
Momelotinib
Fedratinib
CV disease OR history of major bleeding?
Thiamine replacement?
Ruxolitinib "failure"
Platelet <50 × 10⁹/L
Splenomegaly
Anemia
Pacritinib
Fedratinib
Momelotinib
JAK-based combination therapy
ANEMIA
Advanced phase
ESA
IMiD
Androgen
BET inh
PI3K inh
IFN
DNMT3 inh
IDH inh

JAK inhibitor	Combination partner/setting	MPN	Phase	Clinicaltrials.gov identifier
Ruxolitinib	TGR-1202	PV, MF, MDS/MPN	1	NCT02493530
Ruxoilitinib	Idelalisib	MF	1	NCT02436135
Ruxolitinib	INCB050465	MF	2	NCT02718300
Ruxolitinib	Danazol	MF	2	NCT01732445
Ruxolitinib	Thalidomide	MF	2	NCT03069326
Ruxolitinib	Lenalidomide	MF	2	NCT01375140
Ruxolitinib	Azacytidine	MF, MDS/MPN	2	NCT01787487
Ruxolitinib	Panobinostat	MF	1b 1/2	NCT01433445 NCT01693601
Ruxolitinib	Pracinostat	MF	2	NCT02267278
Ruxolitinib	Decitabine	MPN-AML	1/2 1/2	NCT02257138 NCT02076191
Ruxolitinib	PIM447 + LEE011	MF	1	NCT02370706
Ruxolitinib	Vismodegib	MF	1/2	NCT02593760
Ruxolitinib	Navitoclax	MF	2	NCT03222609
Ruxolitinib	Pegasys	MF	1/2	NCT02742324
Ruxolitinib	HSCT	MF	2	NCT01790295
Ruxolitinib	HSCT	MF	Pilot	NCT02917096
Ruxolitinib	AutoSCT	MF	Pilot	NCT02469974

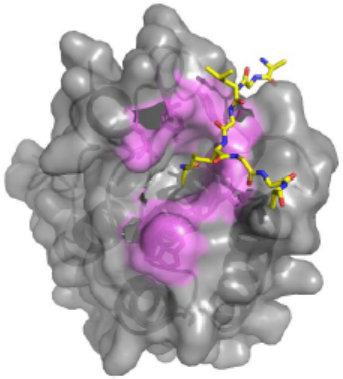
Modified from Mascarenhas et al. Hematology Am Soc Hematol Educ Program. 2015;2015:329-39

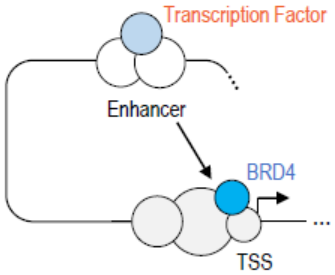


ClinicalTrials.gov. NCT03194542 .

BET – Epigenetic "Reader"

Control of Key Oncogenic, Immune, Fibrotic Pathways Leads to Opportunity in Myelofibrosis





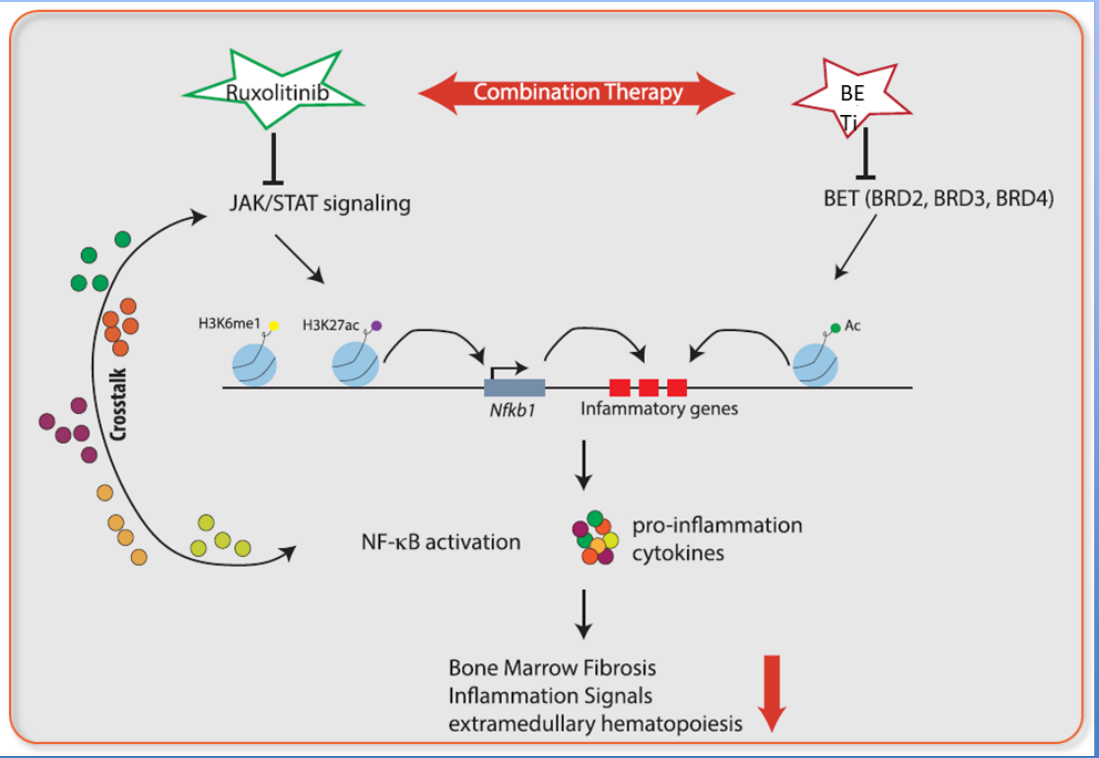
Cancer Genetics
- MYC, BCL2

Immune Signaling
- NF-κB target genes

Fibrosis
- TGF-β target genes

Rationale for Combination of BET and JAK Inhibitors in Myelofibrosis

Cooperative reduction of disease associated inflammation

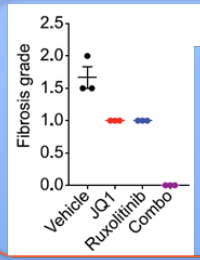


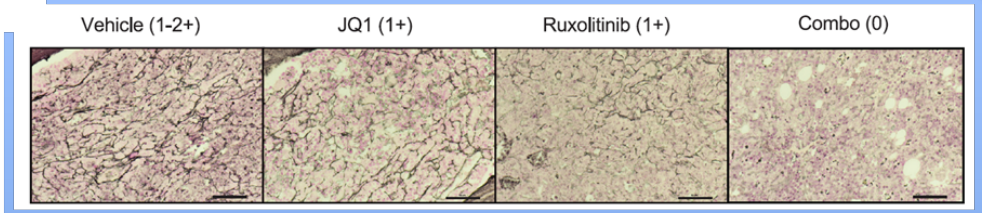
Adapted from Jiang and Jamieson 2018 *Cancer Cell*

Combination of BET and JAK Inhibitors is Efficacious in MF model

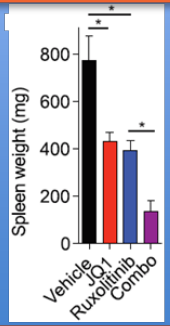
Combination significantly improves spleen weight, fibrosis and tumor burden

Dramatic reduction in bone marrow fibrosis upon combination treatment

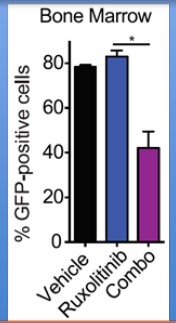




Decreased splenomegaly



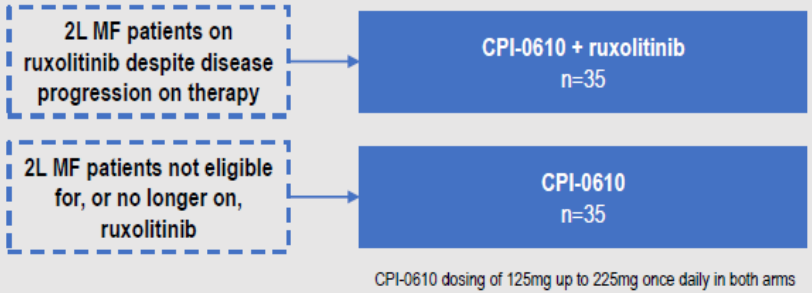
Decreased mutant cell burden



Kleppe *et al* 2018 *Cancer Cell*

MPLW515L **bone marrow transplant model of MF**

CPI-0610 Phase 2 Trial in Myelofibrosis



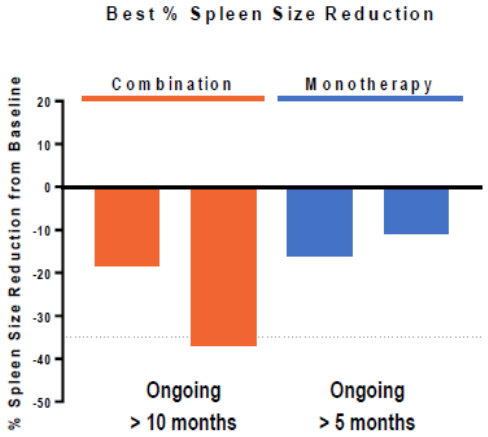
Objectives:

- Evaluate spleen size reduction after 24 weeks of treatment
- Evaluate patient-reported symptom improvement
- Evaluate transfusion independence rate, if applicable

CPI-0610 Myelofibrosis Phase 2 Trial Status Update

Data as of May 25, 2018

Significantly reduced spleen size in all four evaluable patients by MRI



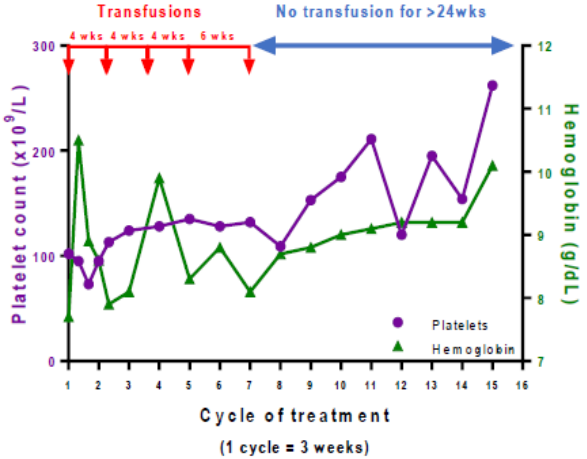
- *Reduced spleen size*
- *Symptom improvement*
- *1 patient with thrombocytosis and 1 patient transfusion dependent at baseline – both resolved*

Constellation PHARMACEUTICALS

CPI-0160 Improving Hemoglobin Levels and Transfusion Dependence

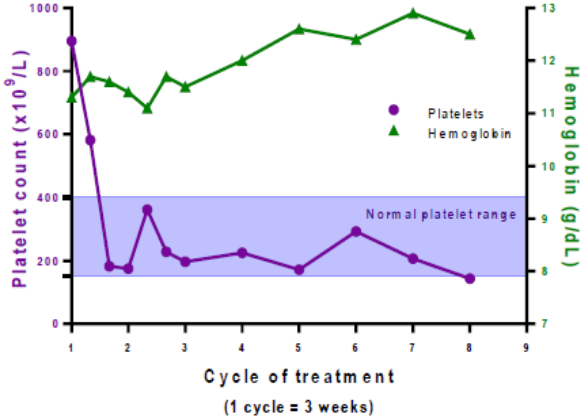
Data as of May 25, 2018

Example: Transfusion independence and improved hemoglobin levels



- Patient treated with CPI-0610 + ruxolitinib combination therapy
- Patient required regular red blood cell transfusions prior to treatment
- Transfusion independent for more than 24 weeks as of May 25, 2018
- Additionally, hemoglobin increased by 2 g/dL and platelet counts improved despite not receiving red blood cell transfusions

CPI-0610 Improved Hemoglobin Levels in Each Patient Treated



- Patient treated with CPI-0610 monotherapy
- Patient had thrombocytosis, at baseline and was refractory to prior treatment with ruxolitinib, a telomerase inhibitor, pembrolizumab and hydroxurea
- Patient's thrombocytosis was accompanied by severe headaches
- Platelet counts normalized after treatment with CPI-0610, and have remained normal for more than 20 weeks as of May 25, 2018
- Patient's severe headaches were resolved after platelets normalized

Constellation PHARMACEUTICALS

Imetelstat Is Effective Treatment for Patients with Intermediate-2 or High-Risk Myelofibrosis Who Have Relapsed on or Are Refractory to Janus Kinase Inhibitor Therapy: Results of a Phase 2 Randomized Study of Two Dose Levels

John Mascarenhas, MD[1], Rami S. Komrokji[2], Michele Cavo, MD[3], Bruno Martino, MD[4], Dietger Niederwieser, MD[5], Andreas Reiter, MD[6], Bart L Scott, MD[7], Maria R. Baer, MD[8], Ronald Hoffman, MD[9], Olatoyosi Odenike, MD[10], Jacqueline Bussolari, PhD[11], Eugene Zhu, PhD[11], Fei Huang, PhD[11], Esther Rose, MD[11], Laurie Sherman, BSN[11], Souria Dougherty, BS, MBA[11], Faye M. Feller, MD[11] and Jean-Jacques Kiladjian, MD, PhD[12]

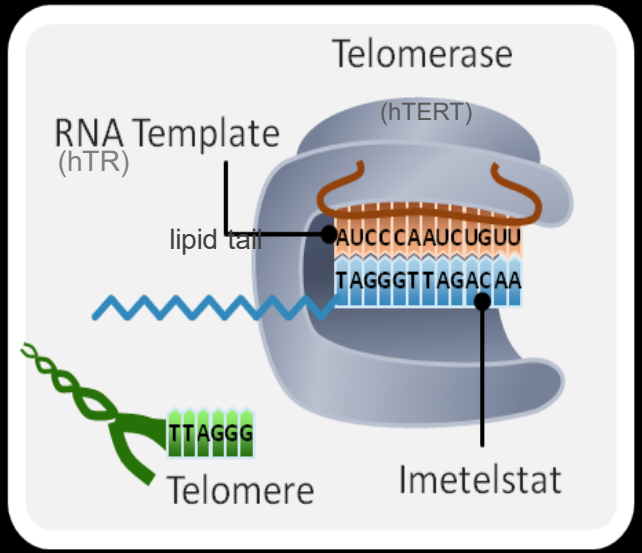
[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai; MPN-RC (US), [2]H Lee Moffitt Cancer Center (US), [3]"Seràgnoli" Institute of Hematology, University of Bologna (IT), [4]Grande Ospedale Metropolitano-G.O.M. Bianchi-Melacrino-Morelli (IT), [5]University Hospital Leipzig (DE), [6]University Hospital Mannheim (DE), [7]Fred Hutchinson Cancer Research Center (US), [8]University of Maryland Greenebaum Comprehensive Cancer Center (US), [9]Tisch Cancer Institute, Mount Sinai School of Medicine (US), [10]University of Chicago (US), [11]Janssen Research & Development, LLC (US), [12]Hôpital Saint-Louis, Université Paris (FR)

Funded by Janssen Research & Development and Geron Corporation

Abstract #685

Imetelstat: First in Class Telomerase Inhibitor

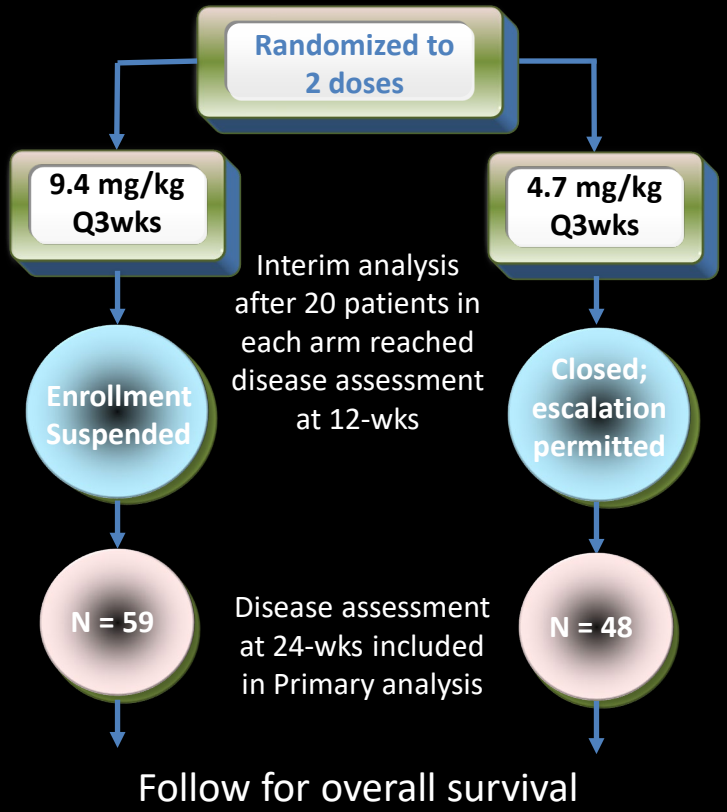
imetelstat binds to RNA template preventing maintenance of telomeres



- **Proprietary:** 13-mer thio-phosphoramidate oligonucleotide complementary to hTR, with covalently-bound lipid tail to increase cell permeability/tissue distribution
- **Long half-life** in bone marrow, spleen, liver (estimated human t½ = 41 hr with doses 7.5 – 11.7 mg/kg);
- **Potent competitive inhibitor of telomerase**: IC50 = 0.5-10 nM (cell-free)
- **Target:** malignant progenitor cell proliferation

Study Design

- Co-primary endpoints at Week 24
  - **Spleen response rate**: proportion of patients achieving ≥ 35% reduction in spleen volume by MRI at 24 weeks
  - **Symptom response rate**: proportion of patients achieving ≥ 50% reduction in total symptom score per modified MFSAF v2.0 at 24 weeks
- Key secondary endpoints: safety, overall survival (OS), treatment response, and pharmacokinetic and pharmacodynamic relationships
- Stratification
  - Spleen size ≥ 15 cm (yes/no)
  - Platelets 75K – 150K vs ≥ 150K



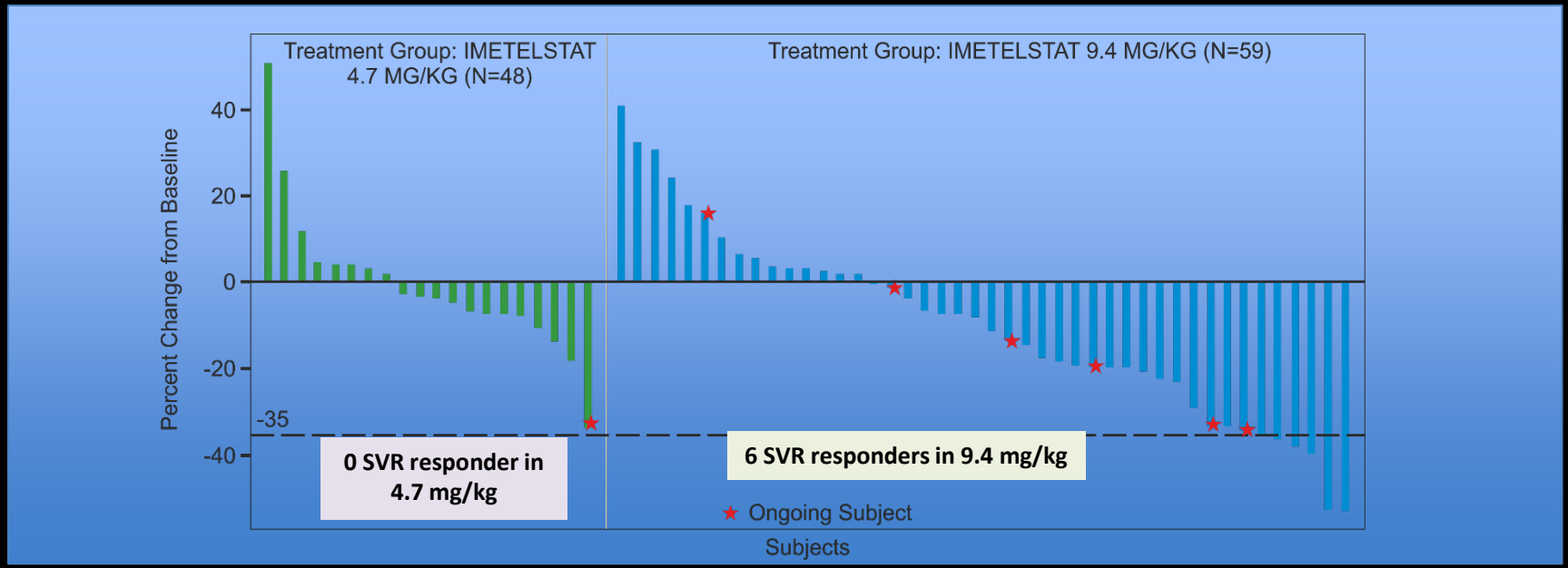
Baseline Mutation Summary on Selected Genes

n (%)	4.7 mg/kg	9.4 mg/kg	Total
Biomarker population, n	48	57	105
With ≥ 1 mutation	48 (100)	55 (96.5)	103 (98)
≥ 3 mutations	40 (83)	38 (67)	78 (74)
Triple Negative	10 (21)	16 (28)	26 (25)
JAK2 V617F	32 (67)	32 (56)	64 (61)
CALR	2 (4)	7 (12)	9 (9)
MPL	4 (8)	2 (4)	6 (6)
HMR[a]	36 (75)	35 (61)	71 (68)
ASXL1	24 (50)	25 (44)	49 (47)
EZH2	10 (21)	18 (32)	28 (27)
SRSF2	5 (10)	2 (4)	7 (7)
IDH1	2 (4)	2 (4)	4 (4)
IDH2	4 (8)	5 (9)	9 (9)

[a]HMR, high molecular risk; ie, 1 or more mutations in ASXL1, EZH2, SRSF2, IDH1, or IDH2.

SVR Per IRC at Week 24

- 6 (10%) patients in the 9.4 mg/kg arm had ≥ 35% SVR at Week 24
- 23 (37%) patients in the 9.4 mg/kg arm had ≥ 10% SVR at Week 24

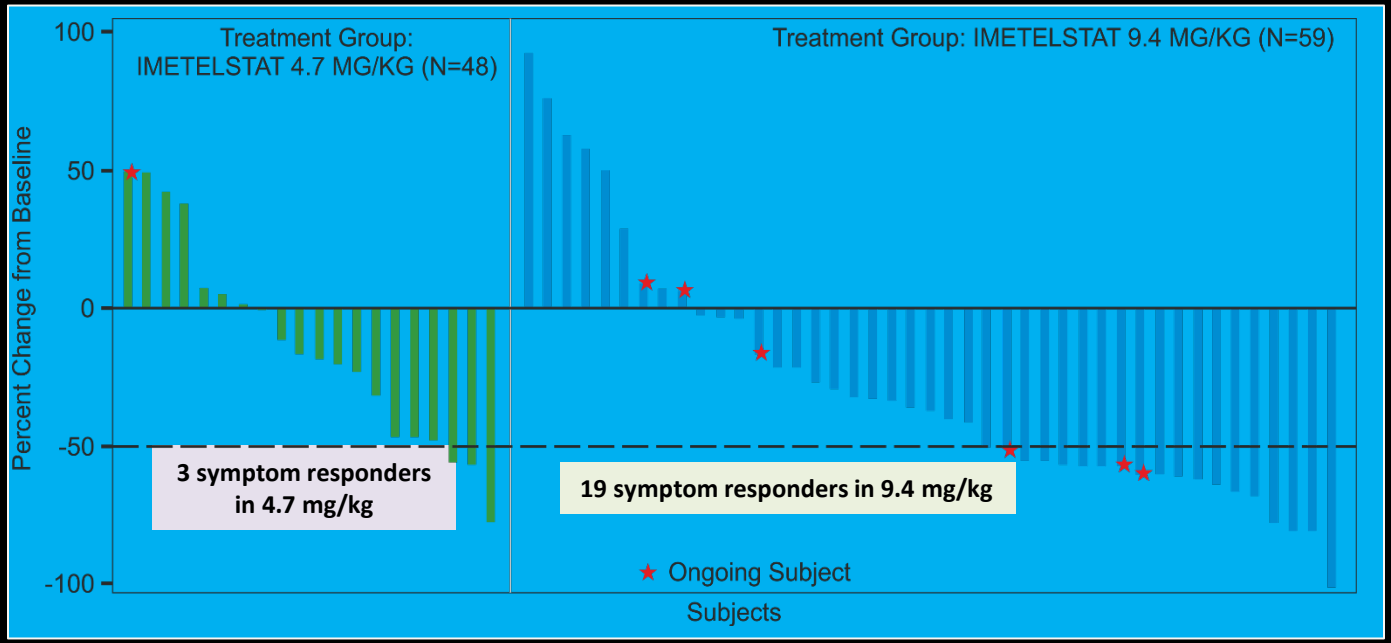


At time of cut-off, 20 patients in the 4.7 mg/kg and 44 patients in the 9.4 mg/kg had Week 24 MRI, however, ITT is used as denominator for percentages.

IRC, Independent Review Committee; SVR, spleen volume reduction.

Symptom Response based on TSS at Week 24

- **19 (32%) patients in the 9.4 mg/kg arm had ≥ 50% symptom response at Week 24**

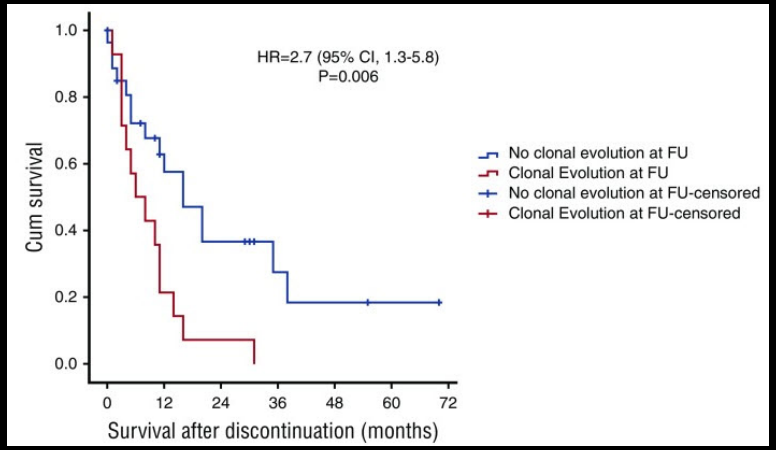


At time of cut-off, 20 patients in the 4.7 mg/kg and 43 patients in the 9.4 mg/kg had Week 24 TSS e-diary entries, however, ITT is used as denominator for percentages.

TSS, total symptom score.

Outcomes After Ruxolitinib Discontinuation

- Retrospective analysis of clonal evolution and outcomes after ruxolitinib discontinuation in an open-label phase 1/2 study (N = 56)

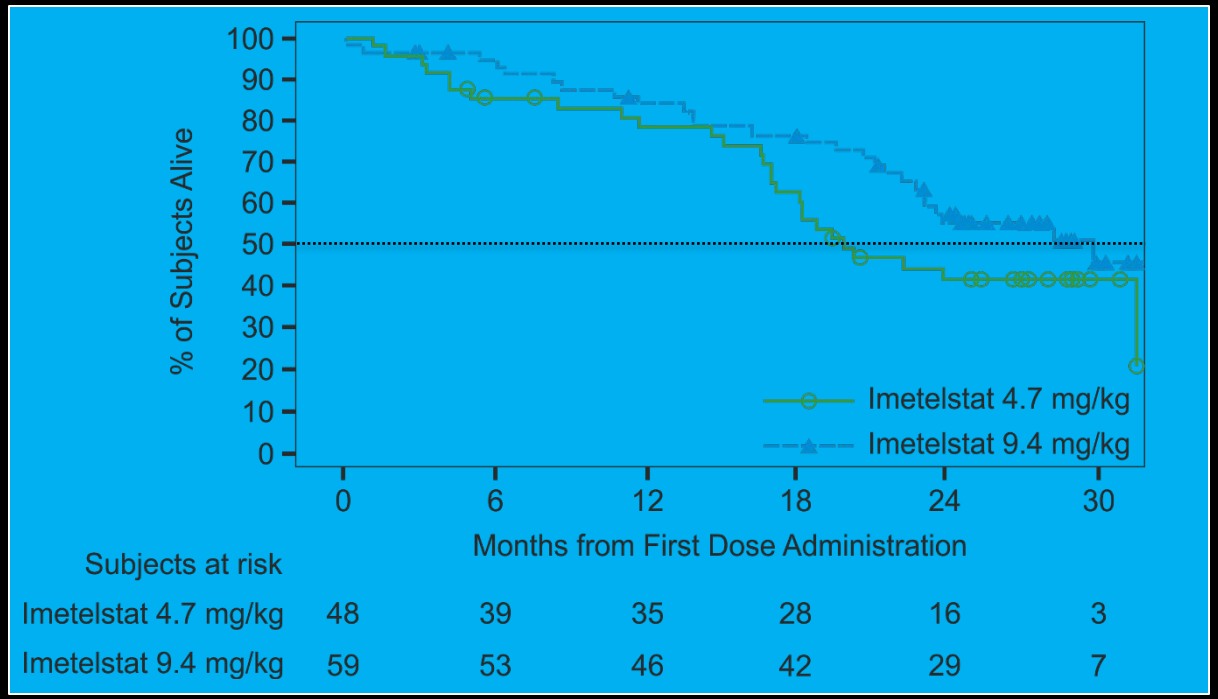


Hashed lines = censored.

Newberry KJ, et al. *Blood*. 2017;130:1125-1131.

- Median OS: 14 mo
- Survival improved if baseline platelets ≥ 260 vs < 260 × 10^9/L (HR = 2.7; *P* =.006)
- Survival improved if follow-up platelets ≥ 100 vs < 100 × 10^9/L (HR = 4.1; *P* =.001)
- 35% of patients acquired a new mutation while on ruxolitinib, most commonly *ASXL1*

Overall Survival (ITT) for Imetelstat at Different Dose Levels



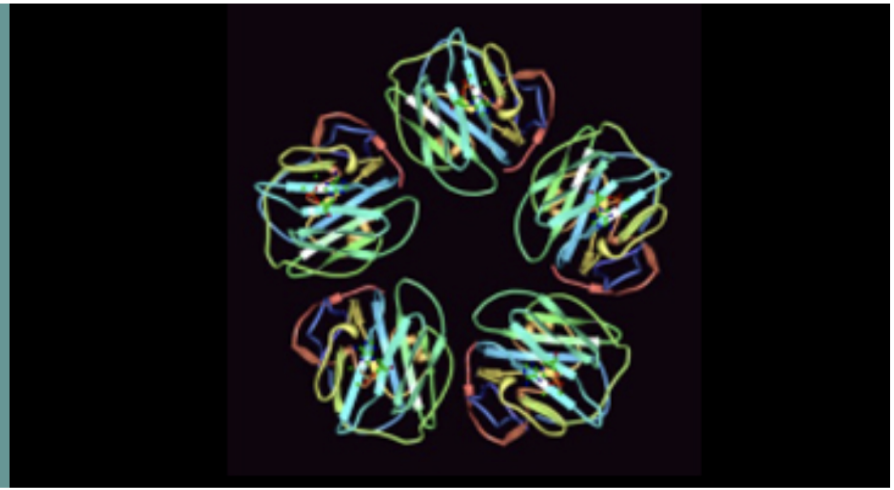
- **Median follow-up: 27.4 months**
- **Median survival:**
  - **19.9 months (95% CI, 17.1, NE) in 4.7 mg/kg**
  - **29.9 months (95% CI, 22.8, NE) in 9.4 mg/kg**

Multiple sensitivity analyses were performed (including data censoring at time of dose escalation, censoring at subsequent JAK inhibitor or stem cell transplant and excluding patients who were dose escalated or randomized after closure of the 4.7 mg/kg arm), all generating similar results

PRM-151 in Myelofibrosis: Efficacy and Safety in an Open-Label Extension Study

December 3, 2018

Dr. Srdan Verstovsek, MD, PhD



NOVEL THERAPEUTICS FOR FIBROSIS

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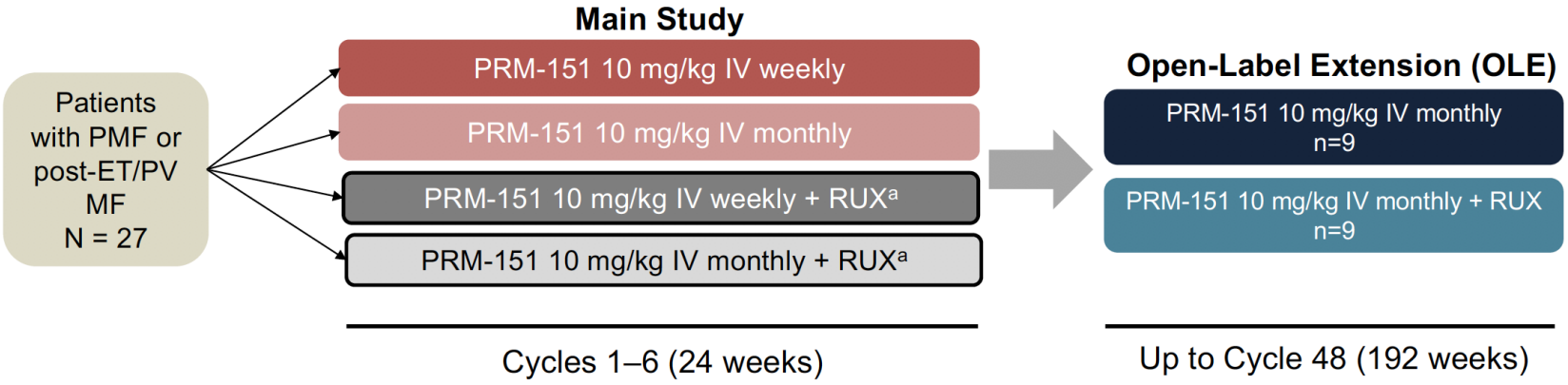
PRM-151G-101 Stage 1 Study Design



Main Study

- **Key Eligibility Criteria**:
  - PMF or post-ET/PV MF with grade ≥ 2 BM fibrosis
  - Int-1, Int-2, or high risk disease (IWG-MRT DIPSS)
  - No restrictions for anemia, thrombocytopenia, leukopenia, or spleen size
- **Primary Endpoint:** ORR according to IWG criteria or stable disease with ≥1 grade reduction in BM fibrosis

OLE

- Safety and hematology parameters assessed monthly
- MPN-SAF TSS and spleen size assessed every 3 months
- BM biopsies obtained at physician's discretion

- **Primary Endpoints:** safety and efficacy of long-term administration of PRM-151

[a] Patients on RUX were required to be on a stable dose for ≥ 3 months with no decrease in splenomegaly for ≥ 4 weeks.
BM, bone marrow; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Int, intermediate; IV, intravenously; IWG-MRT, International Working Group – Myeloproliferative Neoplasms Research and Treatment; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; ORR, overall response rate; PMF, primary myelofibrosis; PV, polycythemia vera; RUX, ruxolitinib.

Baseline Characteristics of Patients Enrolled in OLE

Characteristic	All Patients N=18
Median age (range), years	66 (51–78)
Median months since diagnosis (range)	44.7 (6.0–126.3)
DIPSS stage, n (%) Int-1/Int-2/High	8/9/1 (44/50/6)
Fibrosis grade[a], n (%) MF 3/2/1	9/7/2 (50/39/11)
Median no. of prior therapies (range)	1 (0–3)
Prior or current JAK inhibitor[b], n (%)	14 (78)
Mean duration of ongoing RUX (range), years	1.5 (0.6–2.2)
Median daily RUX dose[c] (range), mg	30 (10–50)
Hemoglobin level < 100 g/L, n (%)	6 (33)
Patients receiving RBC transfusions[d], n (%)	6 (33)
Platelet count < 50 x 10^9/L, n (%)	7 (39)
Platelet count < 100 x 10^9/L, n (%)	12 (67)
Patients receiving platelet transfusions[d], n (%)	2 (11)
Patients with palpable spleen, n (%)	13 (72)
Mean MPN-SAF TSS (SD)	19.2 (15.0)

[a] Measured by central pathologists; [b] 5 patients in the PRM-151 monotherapy arm had previously received a JAK inhibitor; [c] One patient in the PRM-151 + RUX arm for the main study discontinued RUX before entering the OLE; all other patients on RUX were on a stable dose throughout the OLE; [d] Within 30 days prior to first PRM-151 dose.

DIPSS, Dynamic International Prognostic Scoring System; Int, intermediate; JAK, Janus kinase; MF, myelofibrosis; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; OLE, open-label extension; RBC, red blood cell; RUX, ruxolitinib.

Shifts in Bone Marrow Reticulin and Collagen Fibrosis Grades from Main Study BL to Best OLE Result

Reticulin grade

Best OLE Result, n (%)	Main Study BL			
	n=2	n=7	n=9	n=0
	Grade 1	Grade 2	Grade 3	Missing
Grade 0	0	0	0	0
Grade 1	0	5 (71)	2 (22)	0
Grade 2	0	0	2 (22)	0
Grade 3	0	0	2 (22)	0
Missing	2 (100)	2 (29)	3 (33)	0

Collagen grade

Best OLE Result, n (%)	Main Study BL				
	n=2	n=2	n=6	n=7	n=1
	Grade 0	Grade 1	Grade 2	Grade 3	Missing
	1 (50)	1 (50)	2 (33)	1 (14)	0
Grade 1	0	0	3 (50)	1 (14)	0
Grade 2	0	0	0	0	0
Grade 3	0	0	0	2 (29)	0
Missing	1 (50)	1 (50)	1 (17)	3 (43)	1 (100)

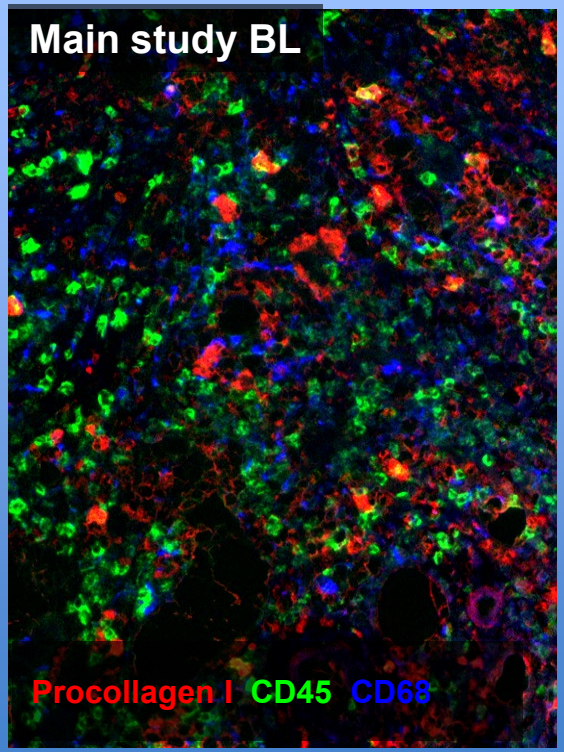
No improvement | 1-grade improvement | 2-grade improvement | 3-grade improvement

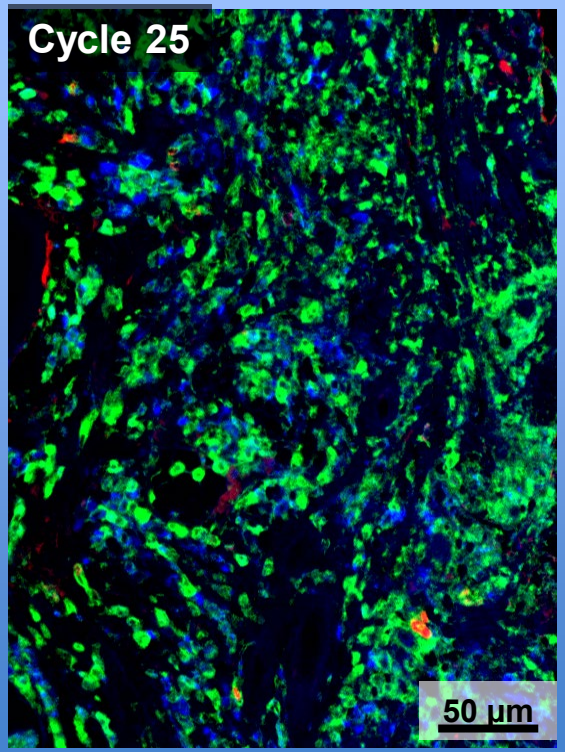
- Reticulin grade improvements were observed in 50% (9/18) of patients
- Collagen grade improvements were observed in 44% (8/18) of patients

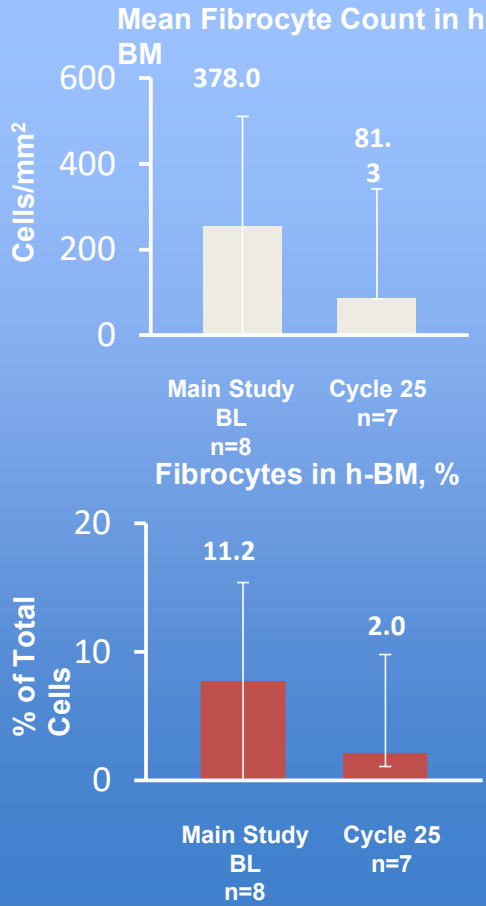
BL, baseline; OLE, open-label extension.

Thiel J, et al. Primary myelofibrosis. In: Swerdlow SH, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Revised 4th ed. Lyon, France: IARC Press; 2017.

Bone Marrow Fibrocyte Immunostaining

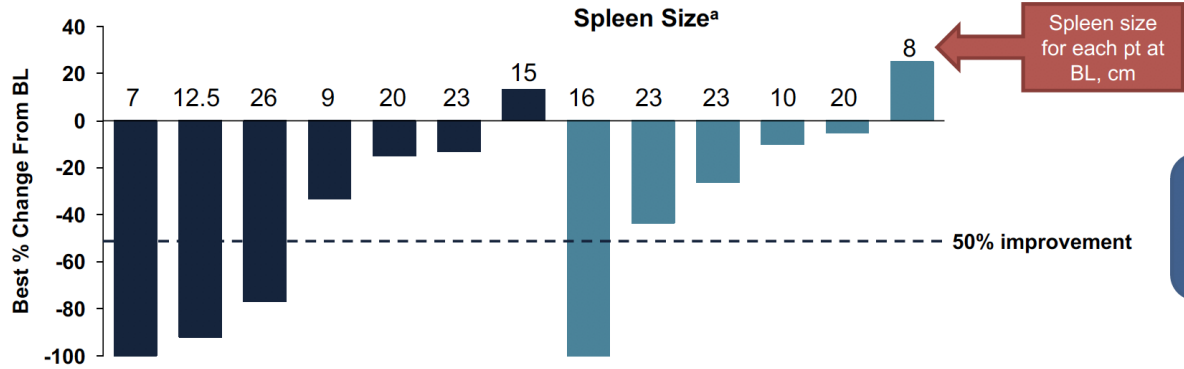




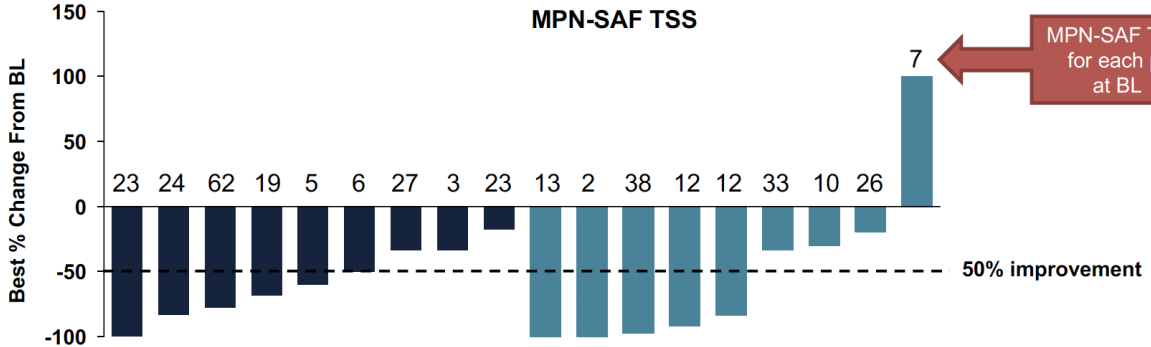


BL, baseline; h-BM, hematopoietic bone marrow.

Best Percentage Change in Palpable Spleen Size and MPN-SAF TSS from Main Study BL to OLE



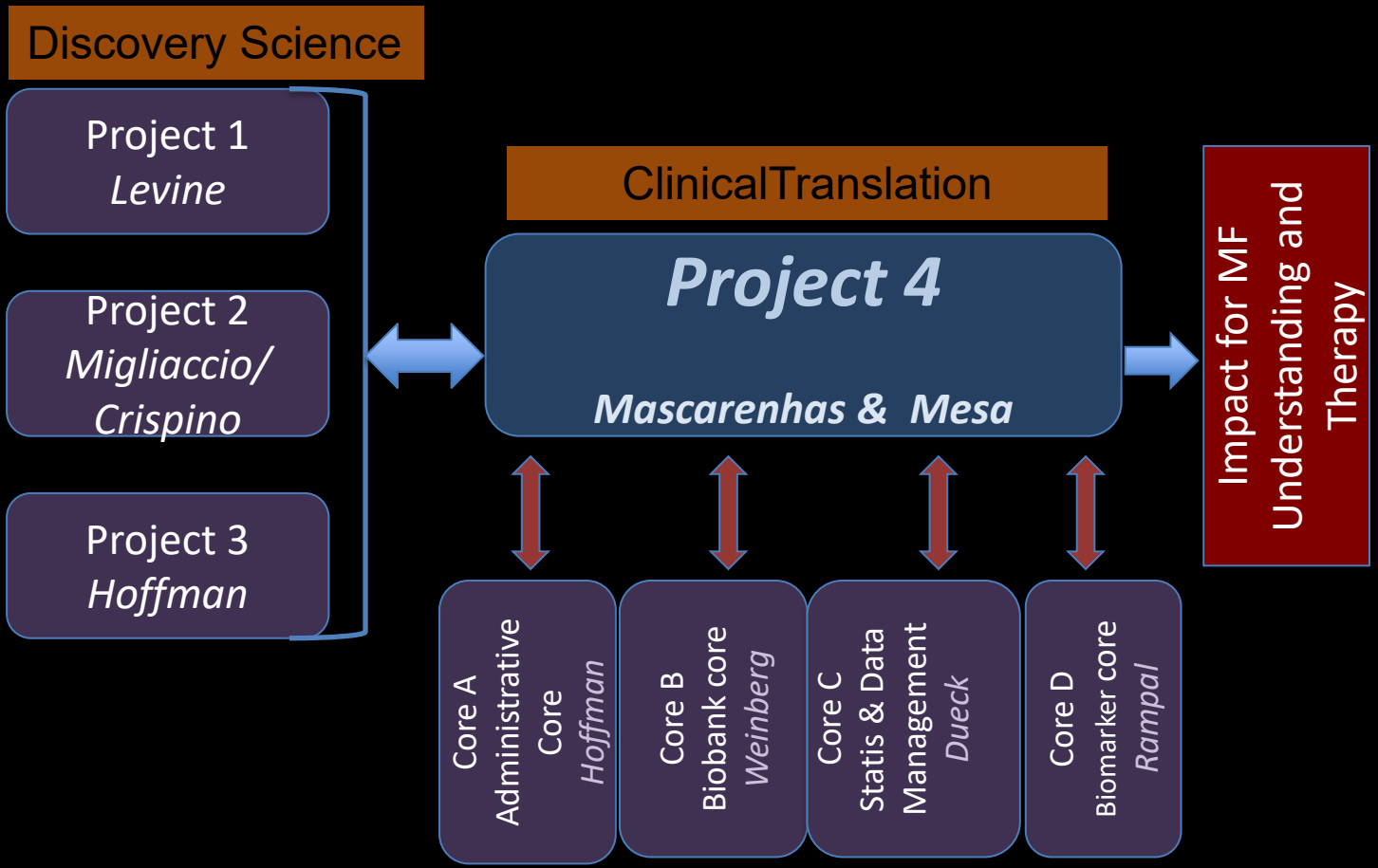
Best % change, spleen size:
Mean: −37%
Median: −26%



Best % change, MPN-SAF TSS:
Mean: −54%
Median: −64%

[a] 5/18 OLE patients did not have a palpable spleen at BL.
BL, baseline; MPN-SAF TSS, Myeloprolferative Neoplasm Symptom Assessment Form Total Symptom Score; OLE, open-label extension; pt, patient; RUX, ruxolitinib.

MPN-RC *Project Interactions*



CLINICAL SITES OF THE MPN RESEARCH CONSORTIUM (January 2019)

U.S.

Icahn School of Medicine at Mount Sinai, NY John Mascarenhas

Memorial Sloan-Kettering Cancer Center, NY Raajit Rampal

Mays Cancer Center at UT Health San Antonio, TX Ruben Mesa

Mayo Clinic, AZ Jeanne Palmer

Wake Forest School of Medicine, NC Rupali Bhave

University of Kansas Cancer Center, KS Abdulraheem Yacoub

University of Michigan Rogel Cancer Center, MI Moshe Talpaz

Cleveland Clinic Taussig Cancer Center, OH Aaron Gerds

Moffitt Cancer Center, FL Rami Komrokji

Cedars-Sinai Medical Center, CA Ronald Paquette

Ex-U.S.

Princess Margaret Cancer Center, Toronto CA Vikas Gupta

Myeloproliferative Neoplasms Research Consortium

MPN – RC

Phase I study of AVID200 in patients with myelofibrosis (Myeloproliferative Neoplasms Research Consortium [MPN-RC] 118)

Study Chairs

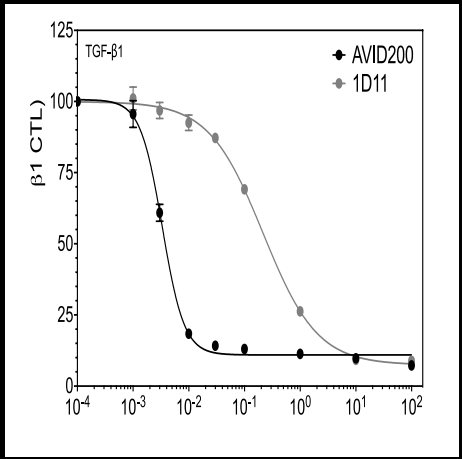
Mascarenhas and Mesa

Trial Rationale

- Transforming growth factor-beta (TGF-β) is a pleiotropic cytokine implicated in the promotion of angiogenesis, tumor growth, collagen fibrosis, metastatic spread and down-regulation of anti-tumor immunity.
- TGF-β1 has also been shown to be the fibrogenic cytokine involved in the pathogenesis of BMF (Shehata 2004).
- Increased levels of TGF-β1 were detected in serum, plasma and BM and positively correlated with both grade of BMF and extent of leukemic cell infiltration in the marrow.
- TGF-β plays a key role in the negative regulation of granulocytes, erythroid, megakaryocyte, and macrophage progenitor cell proliferation (Hino 1988, Hooper 1991, Fortunel 2000).
- TGF-β is expressed in early CD34+ hematopoietic stem cells (HSC) and exerts a negative regulatory function on cell cycle progression in an autocrine fashion (Le Bousse-Keridiles 1999).
- Paradoxically, TGF-β has normal expression levels in CD34+ HSC and increased expression in megakaryocytes in patients with MF

AVID200

Avidity-enhanced decoy trap with very high and selective potency



100 fold more potent than 1D11 benchmark neutralizing antibody against TGFb

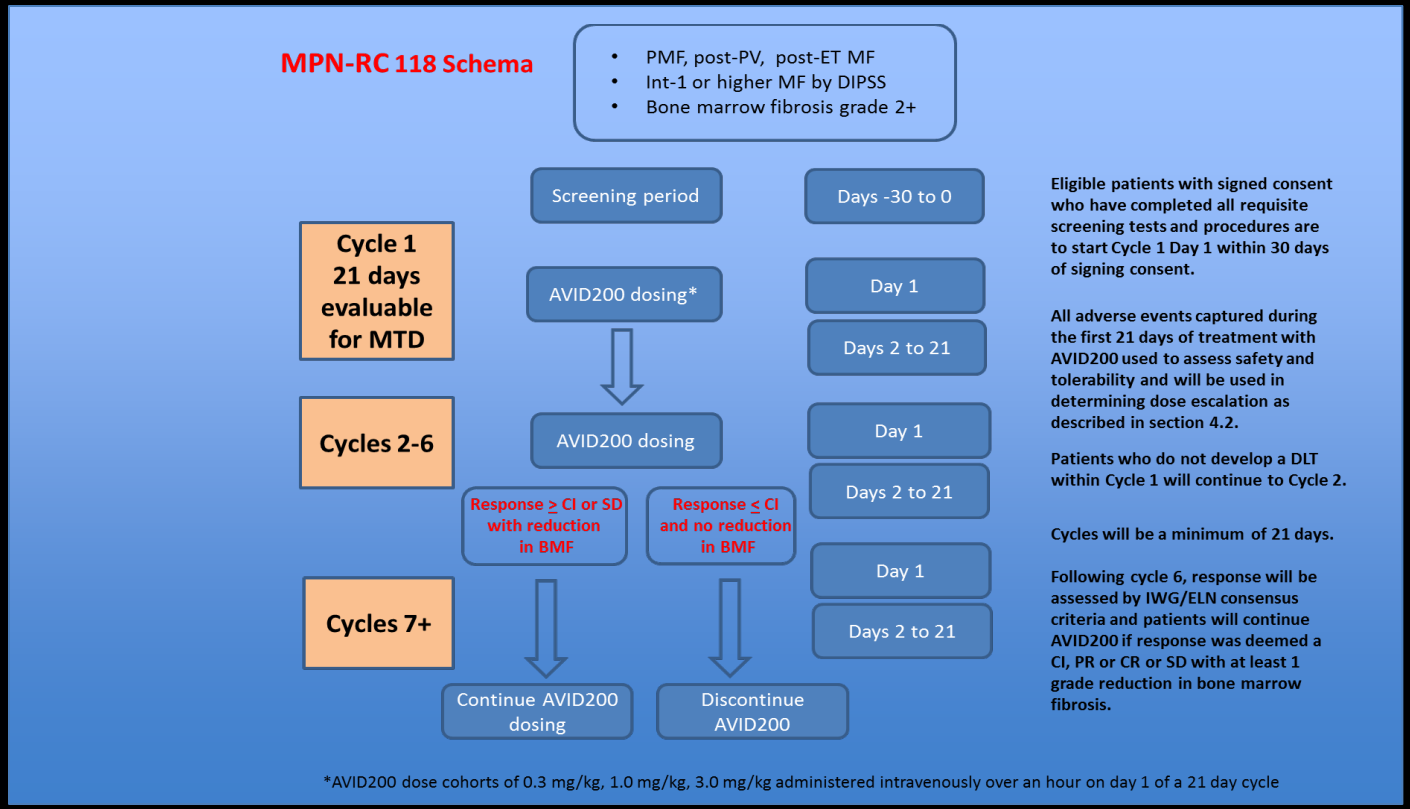
- Targets TGFb1&3 and not 2 (murine and human)
- Minimizes cardiotoxicity since not pan-TGFb inhibitor
- Ligand trap linked to IgG Fc region
- Reduced immunogenicity
- The ligand sequestration approach using decoy ectodomain-based traps has been previously validated with approvals of etanercept (targeting tumor necrosis factor [TNF]) and aflibercept (targeting vascular endothelial growth factor [VEGF]) both of which are traps that utilized a similar design.

MPN - RC

Study Summary

- This is a first in human, open-label, multicenter, Phase I/Ib trial of AVID200.
- Patients must have intermediate-2 or higher primary myelofibrosis (PMF), post-essential thrombocythemia or polycythemia-vera related MF (Post ET/PV MF).
- This study will enroll up to 24 patients.
- AVID200 follows the Modified toxicity probability interval (mTPI) dose escalation design
  - Dose levels— 180 mg/m^2, 550 mg/m*2*, or 1100 mg/m^2
- AVID200 is delivered by IV infusion on day 1 of each 3 week cycle

Study Schema



Eligible patients with signed consent who have completed all requisite screening tests and procedures are to start Cycle 1 Day 1 within 30 days of signing consent.

All adverse events captured during the first 21 days of treatment with AVID200 used to assess safety and tolerability and will be used in determining dose escalation as described in section 4.2.

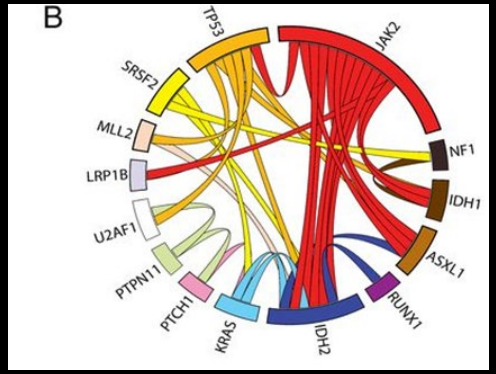
Patients who do not develop a DLT within Cycle 1 will continue to Cycle 2.

Cycles will be a minimum of 21 days.

Following cycle 6, response will be assessed by IWG/ELN consensus criteria and patients will continue AVID200 if response was deemed a CI, PR or CR or SD with at least 1 grade reduction in bone marrow fibrosis.

IDH2 mutations in MPNs

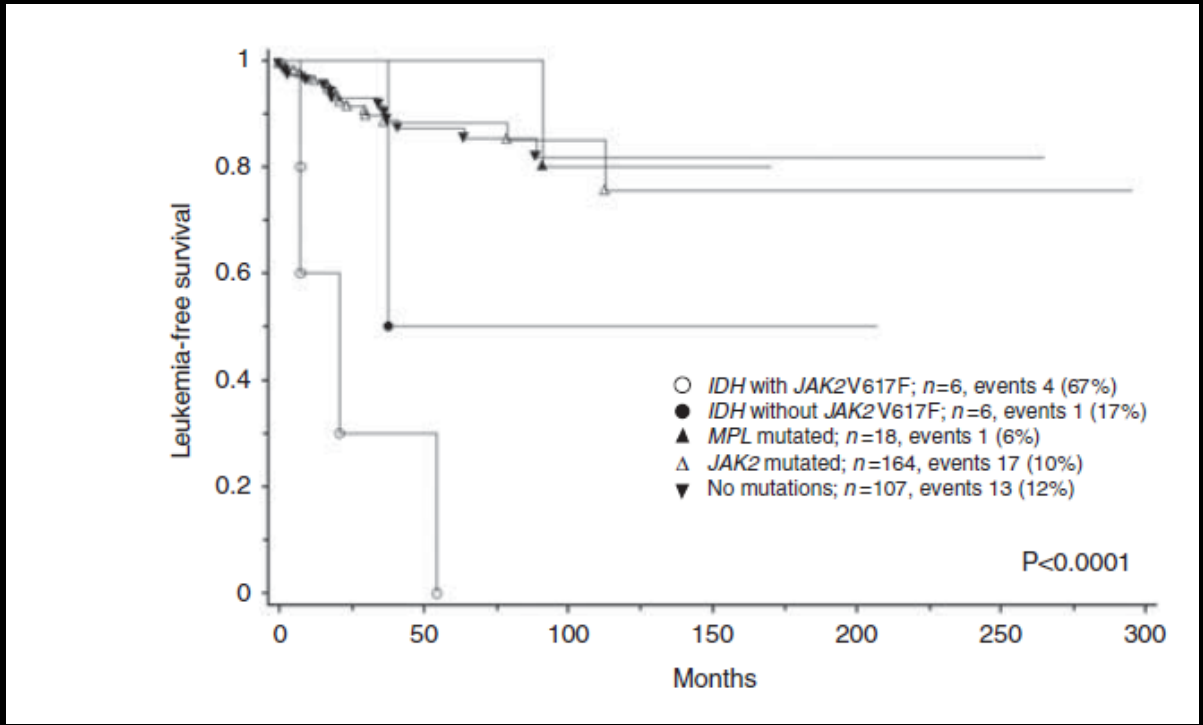
- GAIN OF FUNCTION
- 15q26.1
- Cluster in normal or trisomy 8 karyotype
- Associated with increase risk of LT (Tefferi Leukemia. 2012 Mar;26(3):475-80)
- *IDH2* mutations in 21% of MPN-BP (Pardanani *Leukemia* volume 24, pages 1146–1151 (2010))
- *IDH1/2* and *JAK2V617F* are poor prognostic combo
- 50% of IDH2 mutants co-express JAk2V617F
  - (Vannucchi Leukemia. 2013 Sep;27(9):1861-9 and Tefferi Leukemia. 2012 Mar; 26(3): 475–480.)



Raajit Rampal et al. PNAS 2014;111:50:E5401-E5410

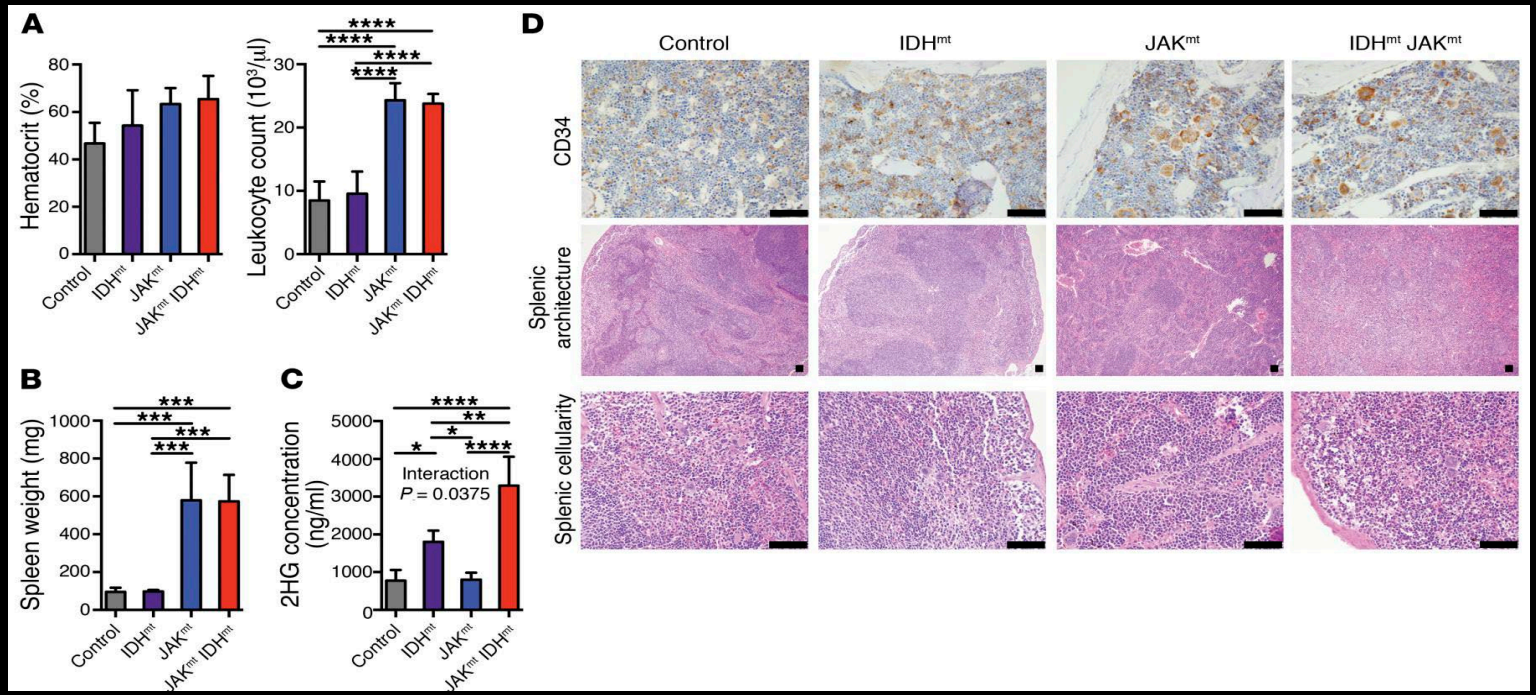
Myeloproliferative Neoplasms Research Consortium
MPN – RC

Leukemia Free Survival for PMF patients (301) stratified by mutation status



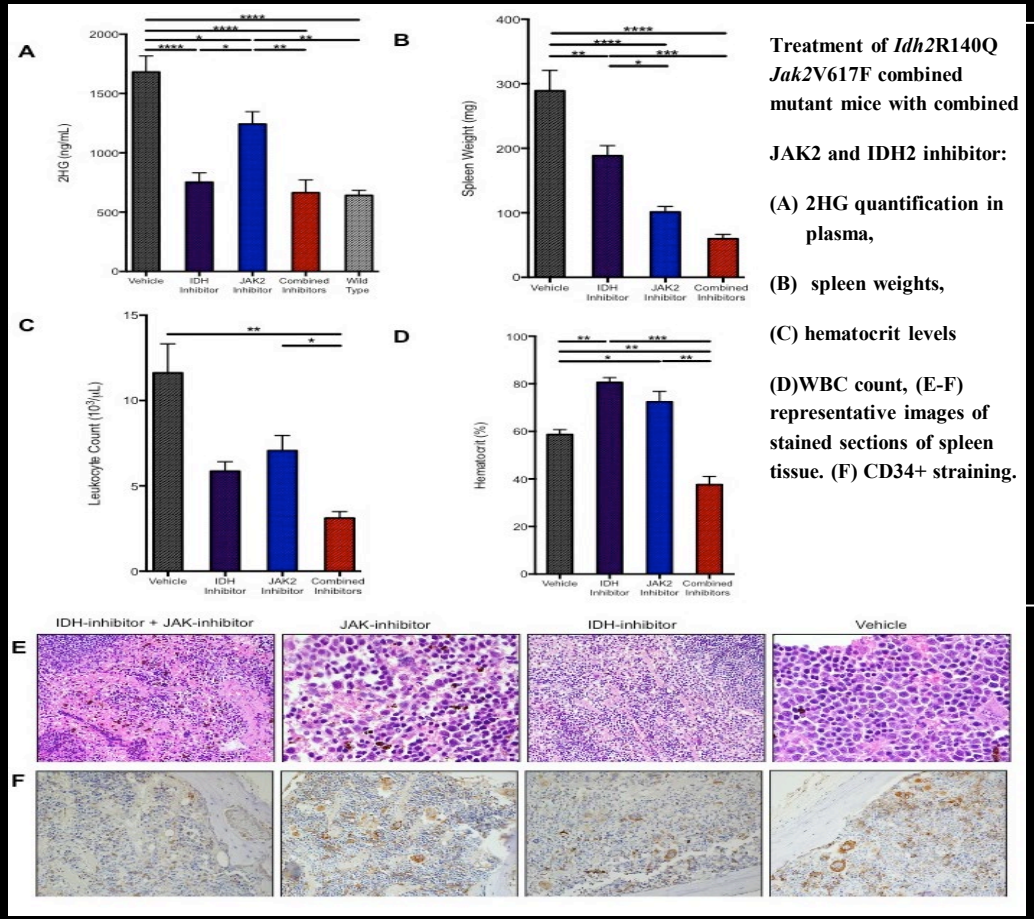
Tefferi et al Leukemia. 2012 Mar; 26(3): 475–480.

JAK2/IDH2 mutant murine model mimics a pre-leukemic MPN phenotype



McKenney J Clin Invest. 2018;128(2):789-804

Treatment of *Idh2*R140Q *Jak2*V617F combined mutant mice with combined JAK2 and IDH2 inhibitor:



Treatment of *Idh2*R140Q *Jak2*V617F combined mutant mice with combined JAK2 and IDH2 inhibitor:

(A) 2HG quantification in plasma,

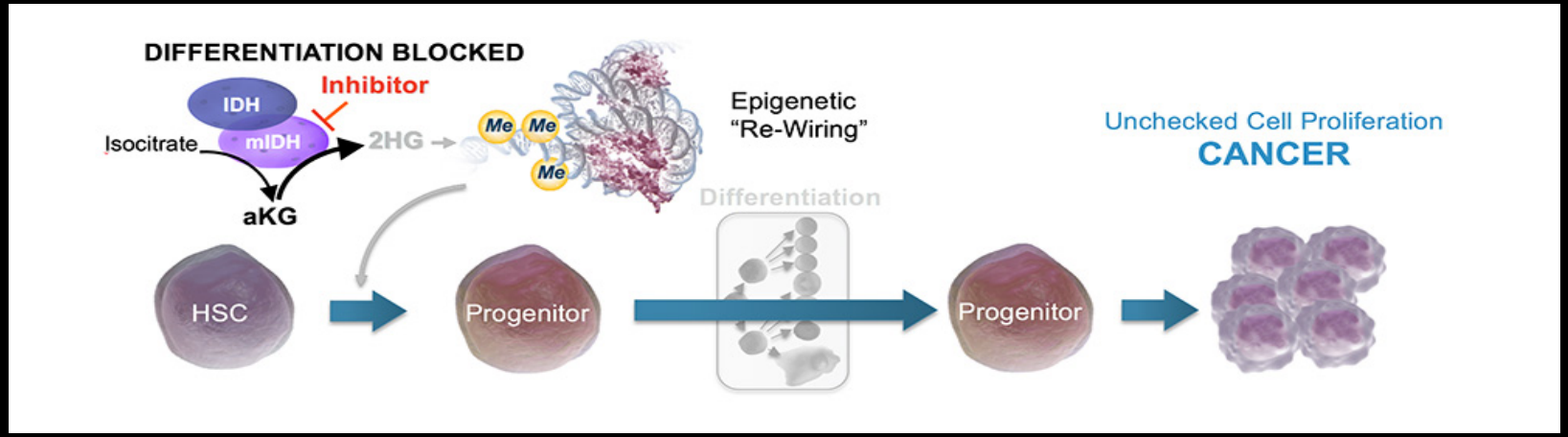
(B) spleen weights,

(C) hematocrit levels

(D)WBC count, (E-F) representative images of stained sections of spleen tissue. (F) CD34+ straining.

McKenney J Clin Invest. 2018;128(2):789-804

Enasidenib (Idhifa) selective IDH2 inhibitor



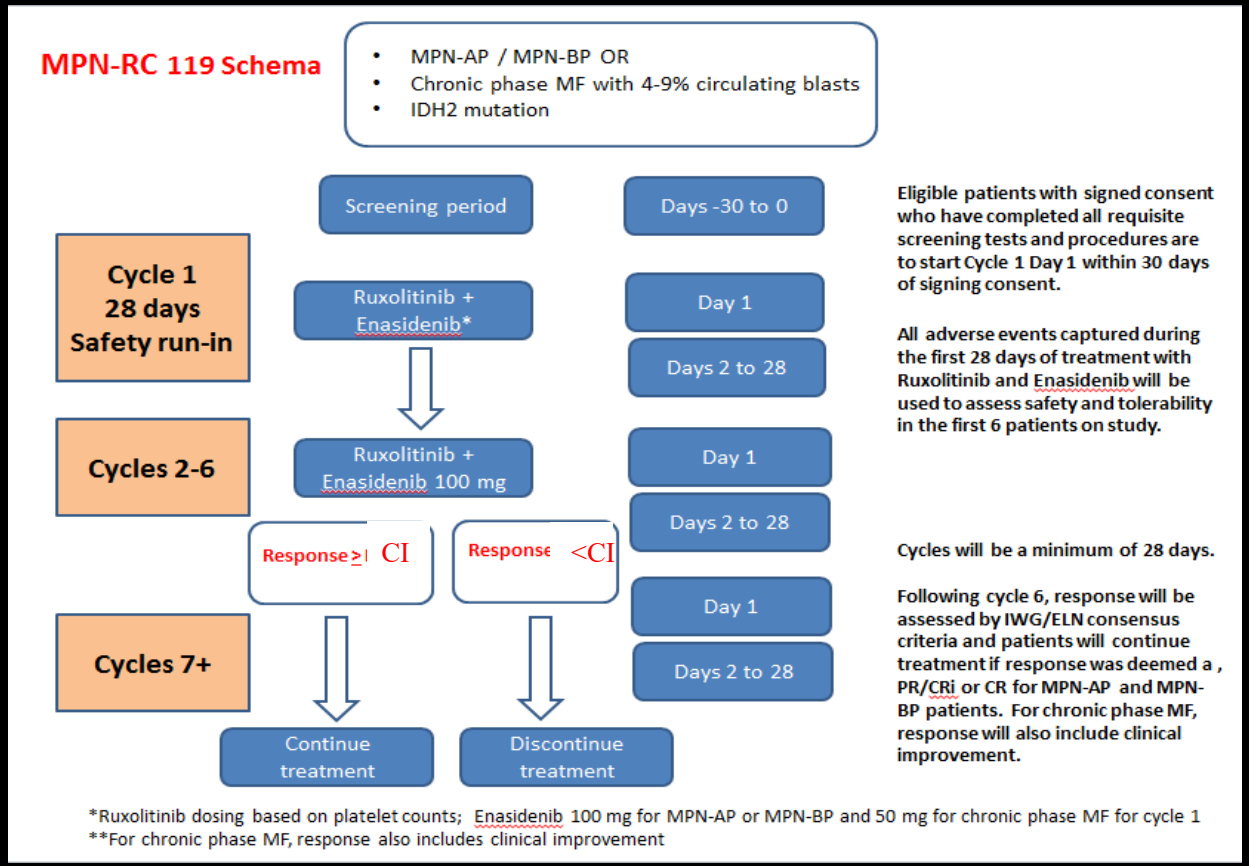
A Phase II Open-label Study of Combined Ruxolitinib and Enasidenib in Patients with Accelerated/Blast-phase Myeloproliferative Neoplasm or Chronic-phase Myelofibrosis with an IDH2 Mutation

(Myeloproliferative Neoplasms Research Consortium [MPN-RC] 119)

Study Chairs

Rampal and Bar-Natan

Study Schema



Summary

- Novel therapy for ET and PV
  - Idasanutlin shows early clinical activity and ongoing phase 2 results pending
- Addressing anemia
  - Keep an eye on luspatercept
- Improving upon JAK inhibition for myelofibrosis
  - Many different combination trials ongoing with different goals
  - BET inhibitor (CPI-0610) is a rational combination partner with early signal of activity
- Improving outcomes after ruxolitinib failure
  - Imetelstat may offer opportunity for survival benefit
- Targeting bone marrow fibrosis
  - PRM-151 is safe and can be combined with ruxolitinib
  - AVID200 is aiming at TGF-β and now the trial is activating across North America
- Mutational-targeted therapy
  - Combination ruxolitinib + IDH2 inhibitor (enasidenib) in IDH2 mutated MF patients

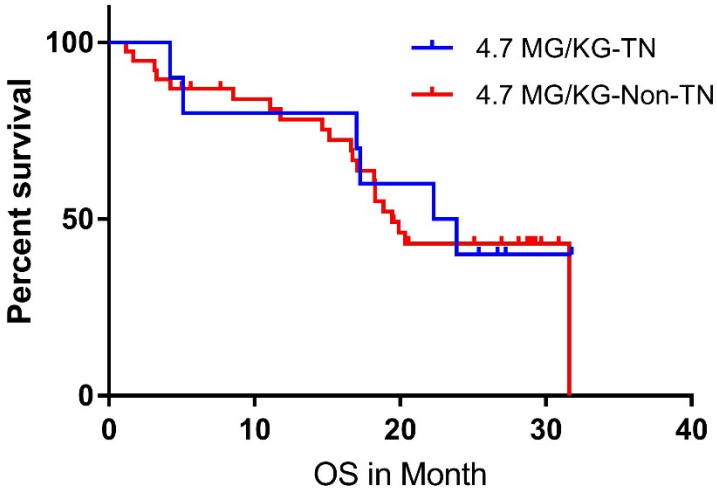
BACK UP ADDITIONAL SLIDES

Treatment Exposure

- 107 patients were enrolled at 55 institutions
- Clinical cutoffs for analyses:
  - April 26, 2018 – Primary analysis of efficacy and safety, with a median follow-up of 22.6 (0.2-27.4) months
  - October 22, 2018 – Overall survival, with a median follow-up of 27.4 (0.2-33.0) months
- Median treatment duration: 26.9 (0.1-118.1) weeks
  - Median duration on treatment was 33.3 weeks on the 9.4 mg/kg arm
    and 23.9 weeks on the 4.7 mg/kg arm
  - The 4.7 mg/kg arm had been closed early, influencing duration of treatment

OS in Triple Negative Disease

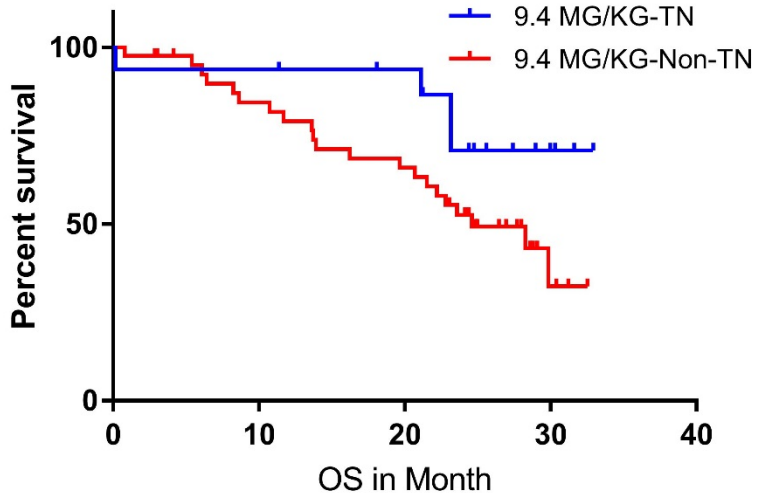
4.7 mg/kg	Death Rate	Median Survival (months)
TN	60%	23.1 (17.0, NE)
Non-TN	55%	19.4 (17.1, NE)



Patients at risk

TN	10	9	7	1
Non-TN	38	30	16	2

9.4 mg/kg	Death Rate	Median Survival (months)
TN	25%	NE (NE, NE)
Non-TN	51%	24.6 (20.7, NE)



Patients at risk

TN	16	16	14	3
Non-TN	41	33	20	4