Istituto di Ematologia "L. e A. Seragnoli"
Alma Mater Studiorum Università di Bologna
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Servizio Sanitario Regionale Emilia-Romagna
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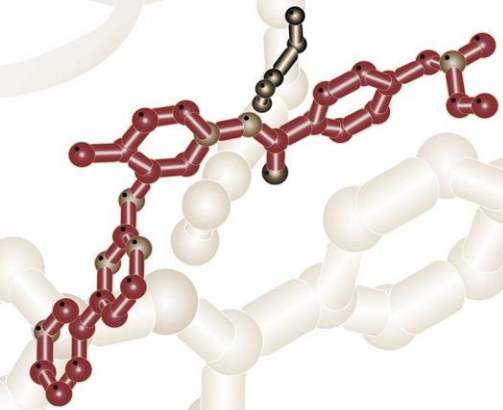
Policlinico S. Orsola-Malpighi



# New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo
Honorary President: Sante Tura

Bologna,
Royal Hotel Carlton
October 1-3, 2018

BOLOGNA, ROYAL HOTEL CARLTON

## Disclosures of John Mascarenhas

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Incyte | X | | | | | X | |
| Novartis | X | | | | | | |
| Promedior | X | | | | | | |
| CTI Biopharma | X | | | | | | |
| Roche | X | | | | | X | |
| Merck | X | | | | | | |
| Janssen | | | | | | | |

# New Drugs and Combination Therapy Approaches in Myeloproliferative Neoplasms

John Mascarenhas, MD
Associate Professor of Medicine
Icahn School of Medicine at Mount Sinai

Bologna 2018

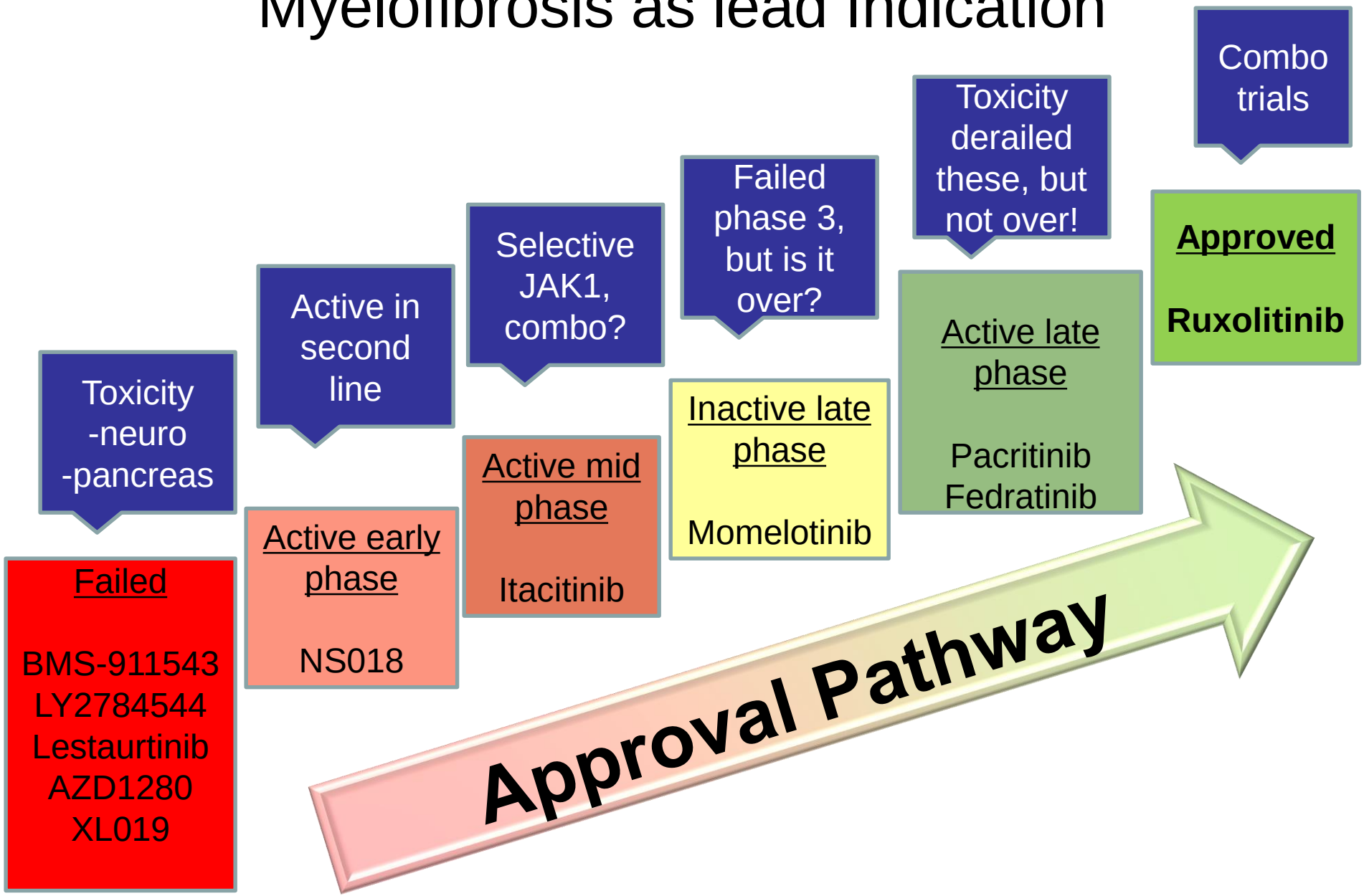
Icahn School of Medicine at Mount Sinai

MPD-RC Myeloproliferative Disorders Research Consortium

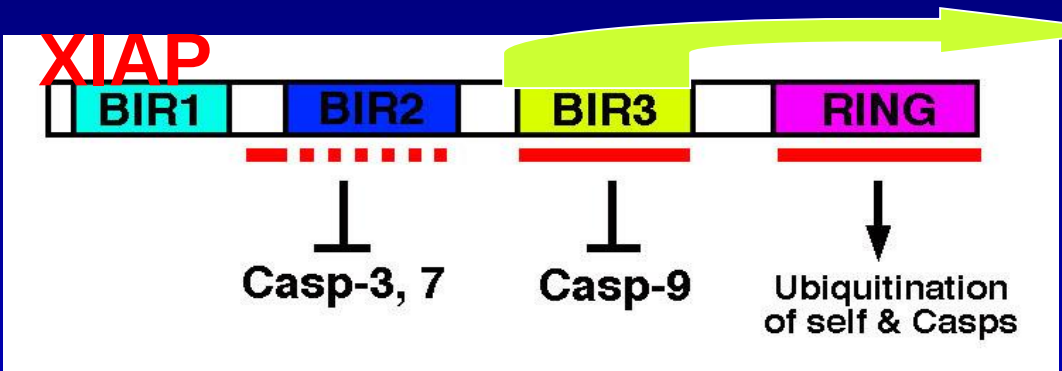
# (aggressivo) Agenda

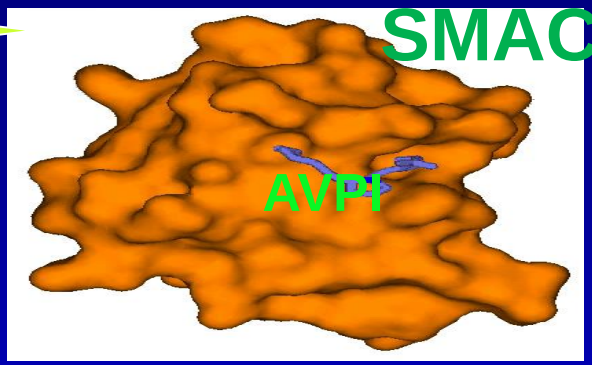
- SMAC Mimetic
- Activin Ligand Trap
- Telomerase Inhibitor
- Pentraxin-2 analogue
- TGF-β inhibitor
- MDM2 inhibitor
- Combination JAK inhibitor
  - PI3K inhibitor
  - BET inhibitor

# JAK Inhibitors and Status of Development in Myelofibrosis as lead Indication

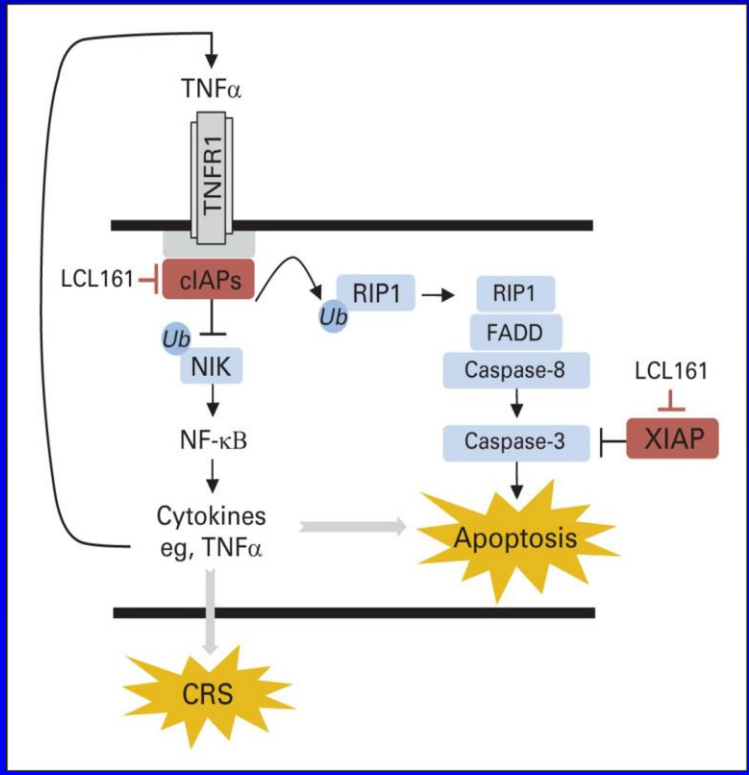


# SMAC Mimetics



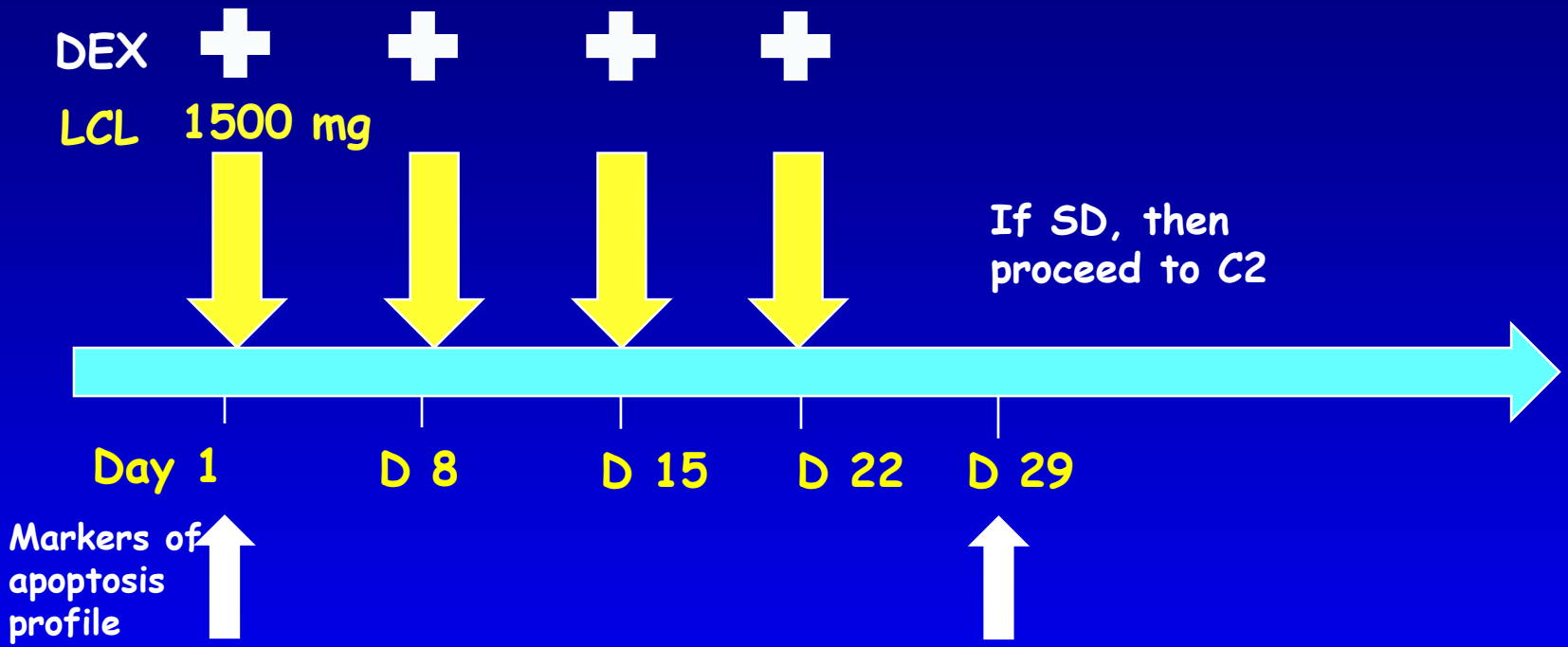

- Bind to cIAP1, cIAP2, and XIAP
- Cause rapid autoubiquitinylation and proteasomal degradation of cIAPs
- Relieve caspase repression by XIAP




Heaton et al. Leuekmia. 2018 Apr 18

Courtesy: Bing Carter, PhD

# Treatment Schema: LCL161 for MF




**1 cycle=28 days**

**BM bx=baseline and at 3 months**

Primary Objectives:

1. To determine efficacy of LCL161 as therapy for PMF, post-PV MF and post-ET MF
2. To determine objective response after 3 cycles of treatment

Pemmaraju et al ASH 2017

# LCL161 in MF: Overall Responses

| Objective Responses | No. of patients |
|---|---|
| -Clinical Improvement (CI): | |
| CI (Symptom) | 7 |
| CI (Anemia) | 5 |
| CI (Spleen) | 1 |
| Cytogenetic Remission (CR) | 1 |

- Response Criteria: IWG-MRT 2013 (Blood 2013;122(8):1395-1398)
- All responses must last for ≥ 12 weeks to qualify

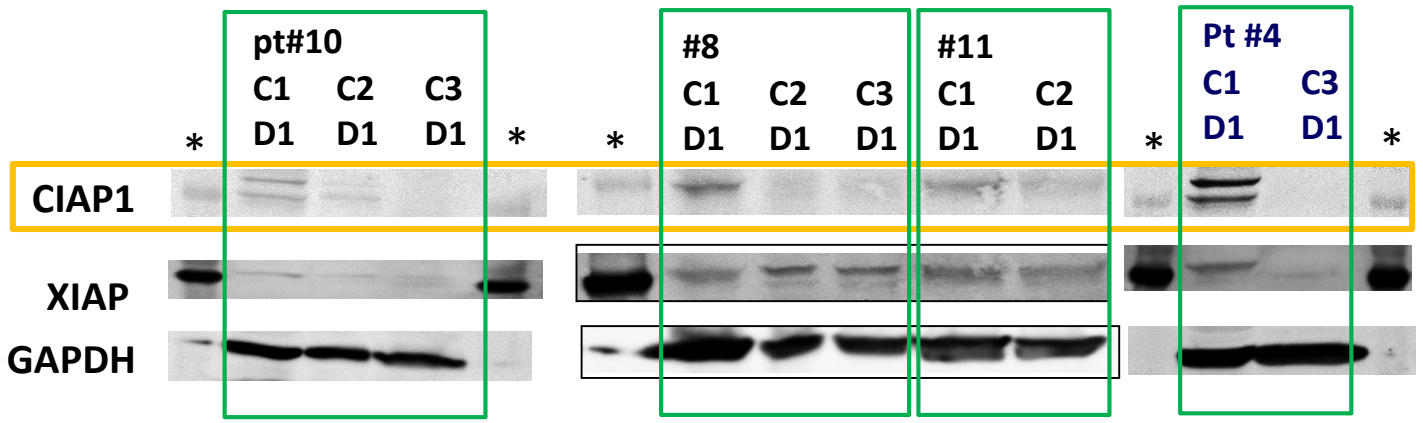
# LCL161 in MF: Toxicities

| Grade 1/2 AEs, ≥10%, Related | N (%) |
|---|---|
| **Non-Hematologic Grade 1/2** | |
| Fatigue | 21 (55) |
| Nausea/Vomiting | 19 (50) |
| Pain | 13 (34) |
| Dizziness/Vertigo | 12 (32) |
| Pruritis | 11 (29) |
| Diarrhea | 8 (21) |
| Fever/flu-like syndrome | 8 (21) |
| Skin eruption/rash | 6 (16) |

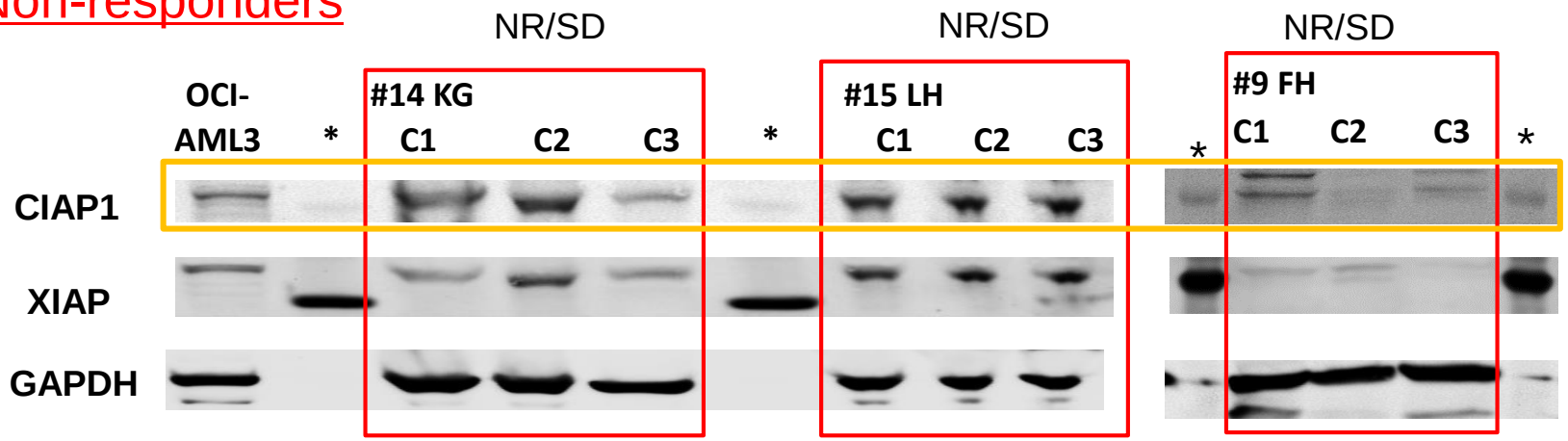
| All Grade 3/4 AEs, Related | N (%) |
|---|---|
| **Non-Hematologic Grade 3/4 AE** | |
| Syncope | 2 (5) |
| Nausea/Vomiting | 1 (3) |
| **Hematologic Grade 3/4 AEs, Related** | |
| Thrombocytopenia | 3 (8) |
| Anemia | 2 (5) |

# LCL161 in MF: On Target Reduction of CIAP1 in Responding Patients

Total: 10 responders (N=2 lack of adequate samples and N=4 still under the treatment)



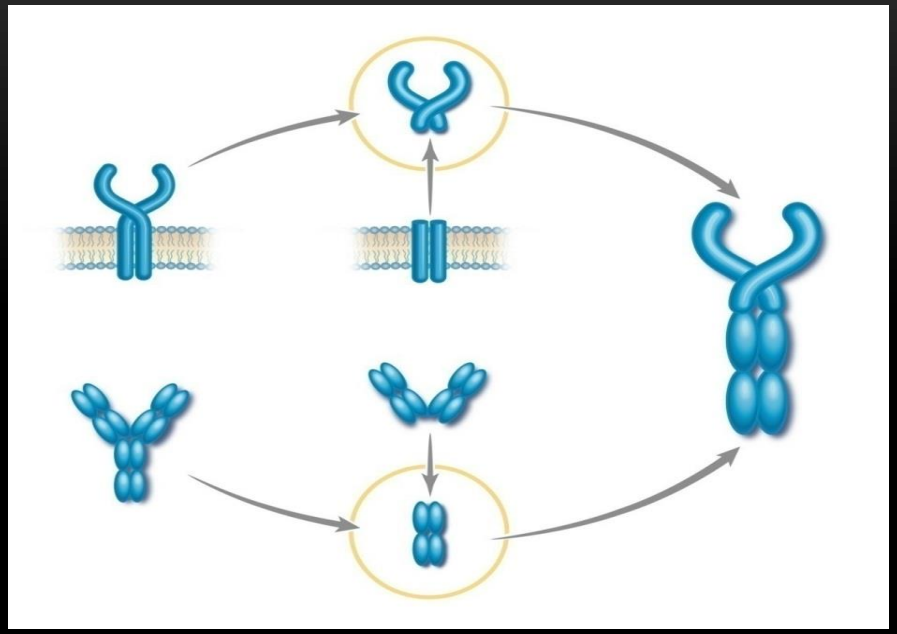

Non-responders

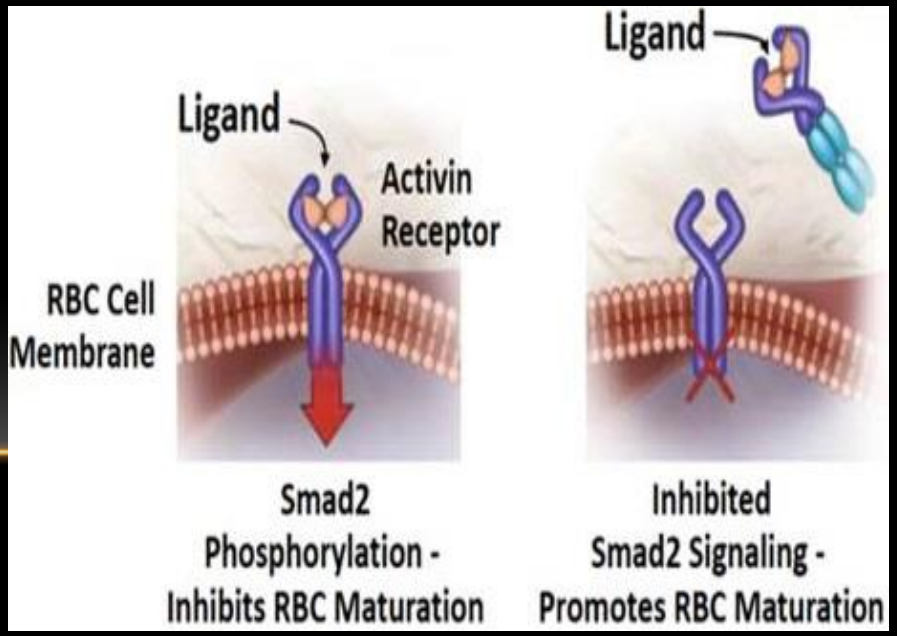



OCI-AML3, positive control . *, molecular weight markers

# SOTATERCEPT

- A first-in-class activin receptor IIA (ActRIIA) “ligand trap”
- Fusion protein consisting of the extracellular domain of ActRIIA conjugated to the Fc fragment of human IgG1





# SOTATERCEPT MECHANISM OF ACTION AND STUDY RATIONALE

- Sequesters ligands of TGF-ß superfamily secreted by bone marrow stromal cells, especially GDF11
- Removal of GDF11 relieves suppression of terminal erythropoiesis
- Improves erythropoiesis in preclinical models of ß-thalassemia, Diamond Blackfan anemia, and in hepcidin transgenic mice
- Effective against anemia of lower risk MDS

Iancu-Rubin C et al. Exp Hematol 2013. Carrancio S et al. BJH 2014. Dussiot M et al. Nat Med 2014. Ear J et al. Blood 2015. Langdon JM et al. AJH 2015. Komrokji R et al. ASH 2014.

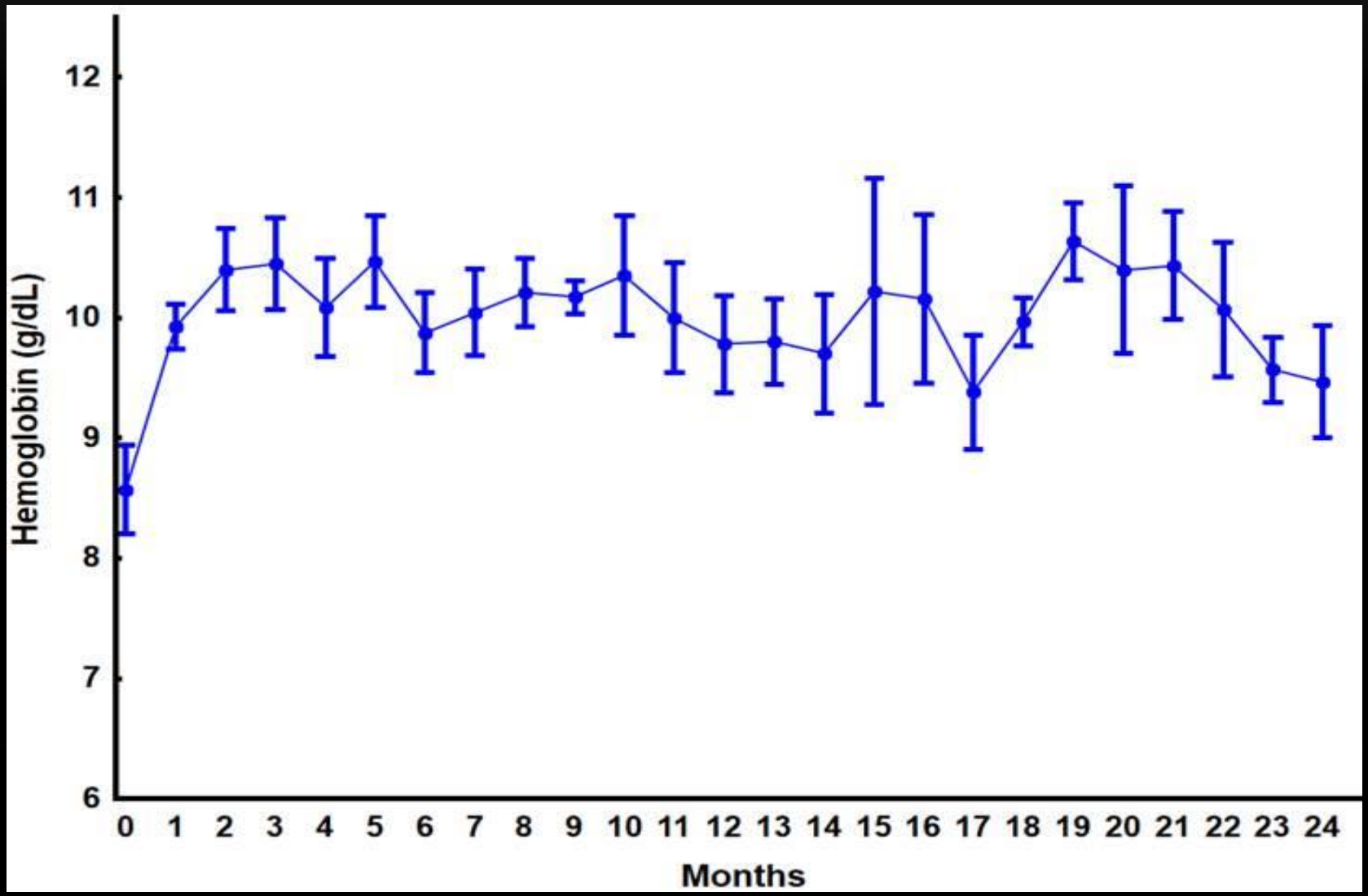
# PHASE II STUDY DESIGN

- PMF or post-PV/ET MF, Hgb <10 g/dL x ≥84 days
- **2 cohorts:**
  - Sotatercept alone, 0.75 or 1 mg/kg SC q3w
  - Sotatercept 0.75 mg/kg SC q3w in subjects on stable dose of ruxolitinib
- **Response (on study x ≥84 days):**
  - Anemic subjects: ≥1.5 g/dL ↑ from baseline x ≥84 d
  - Transfusion-dependent subjects: achievement of transfusion independence per IWG MRT 2013 criteria

# ADVERSE EVENTS POSSIBLY RELATED TO SOTATERCEPT (N = 35)

| Adverse event | Grade | No. of patients |
|---|---|---|
| Hypertension | 3 | 3 |
| | 2 | 2 |
| Pain (joints/muscle) | 3 | 1 |
| | 2 | 1 |
| | 1 | 1 |
| Elevated UMACR | 1 | 2 |
| Limb edema | 1 | 1 |
| Headache (in the context of HTN) | 2 | 1 |
| | 1 | 1 |
| Nausea | 1 | 1 |

# MEAN HEMOGLOBIN OVER TIME IN RESPONDERS (N=10)



# Sotatercept and Luspatercept: Novel Ligand Traps for TGF-β Superfamily Ligands

(ACE-011)
## Sotatercept

Extracellular Domain of **ActRIIA**

Fc Domain of human $IgG_1$ Antibody

(ACE-536)
## Luspatercept

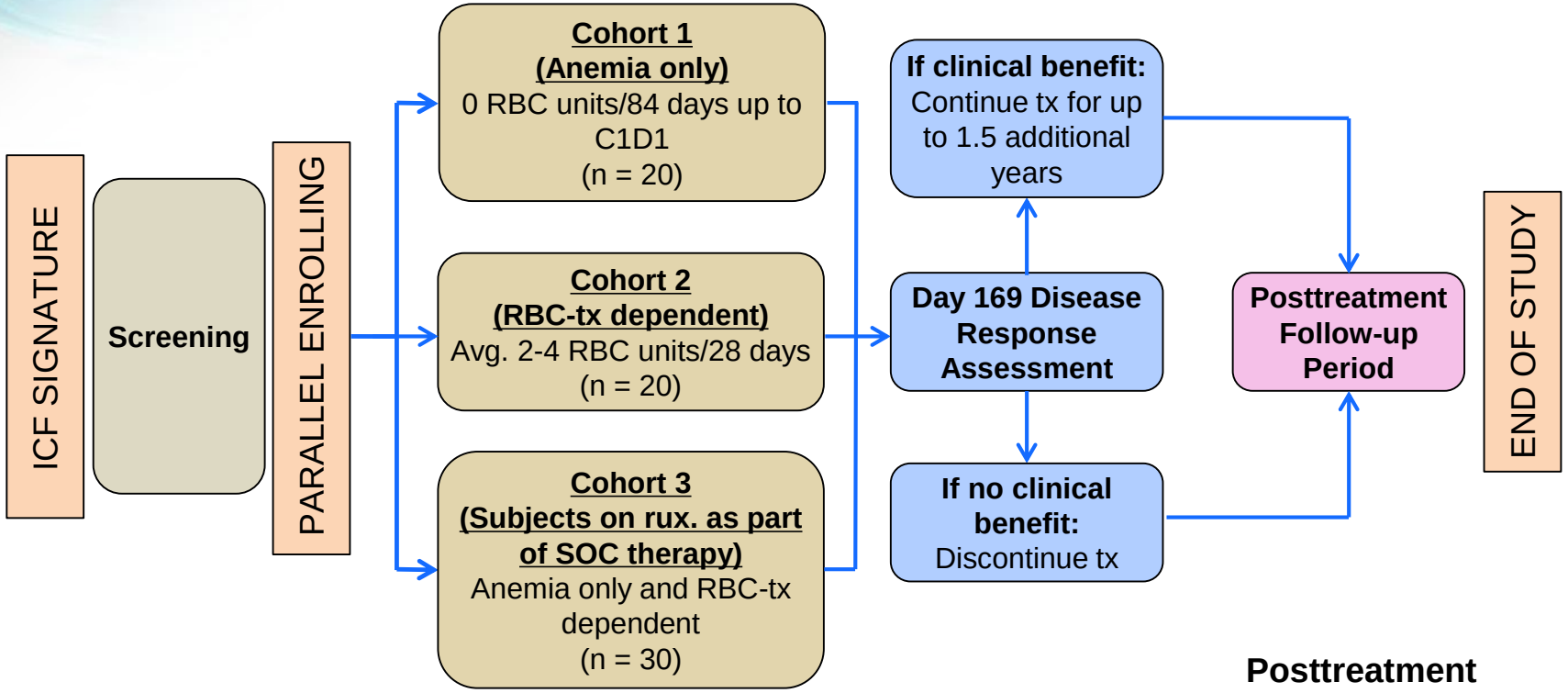
Modified Extracellular Domain of **ActRIIB**

Fc Domain of human $IgG_1$ Antibody

**Therapeutic Effects**

| | | |
|---|---|---|
| **RBC Increase** | + | + |
| **Bone Increase** | + | - |

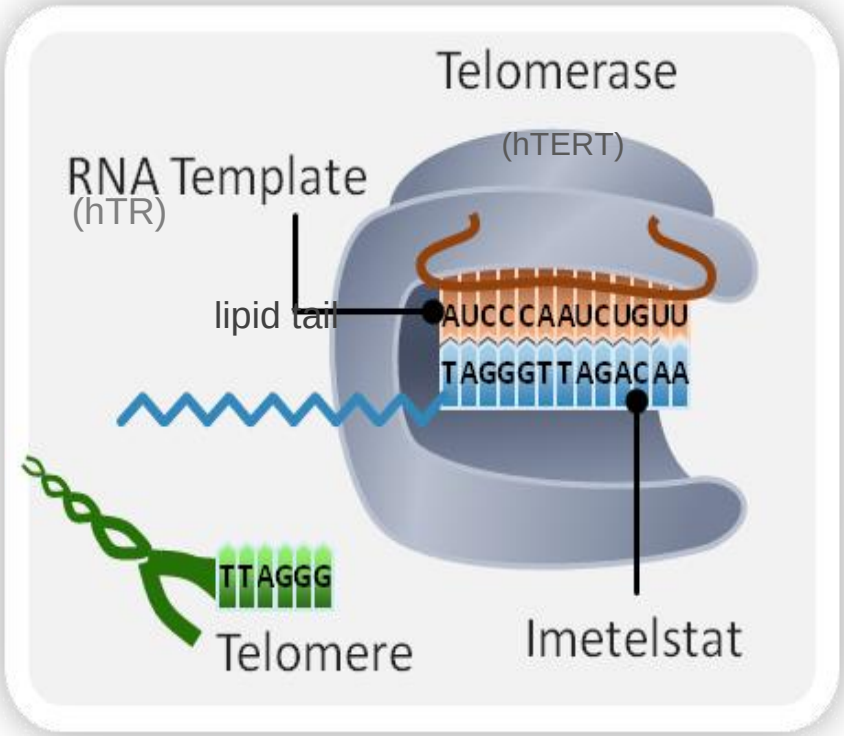
# Study Design: Luspatercept Phase 2 in MPN-Associated Myelofibrosis




The **Steering Committee** will review all available safety and efficacy data and will serve in an advisory capacity to the Sponsor.

# 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

# Primary Endpoint: Overall Response by IWG-MRT

| | N = 33 (%) |
|---|---|
| Overall Response (CR+PR+CI) | 12 (36.4%) |
| Complete Remission (CR) | 4 (12.1%) |
| Partial Remission (PR) | 3 (9.1%) |
| Clinical Improvement (CI) by Anemia | 1 (3.0%) |
| Clinical Improvement (CI) by Spleen | 4 (12.1%) |
| Stable Disease (SD) | 21 (63.6%) |
| | |
| Spleen Response (by palpation lasting ≥ 12 weeks ) | 8/23 (34.8%) |
| Transfusion dependent becoming transfusion independent | 4/13 (30.8%) |

**CR/PR/CI: 36.4%**

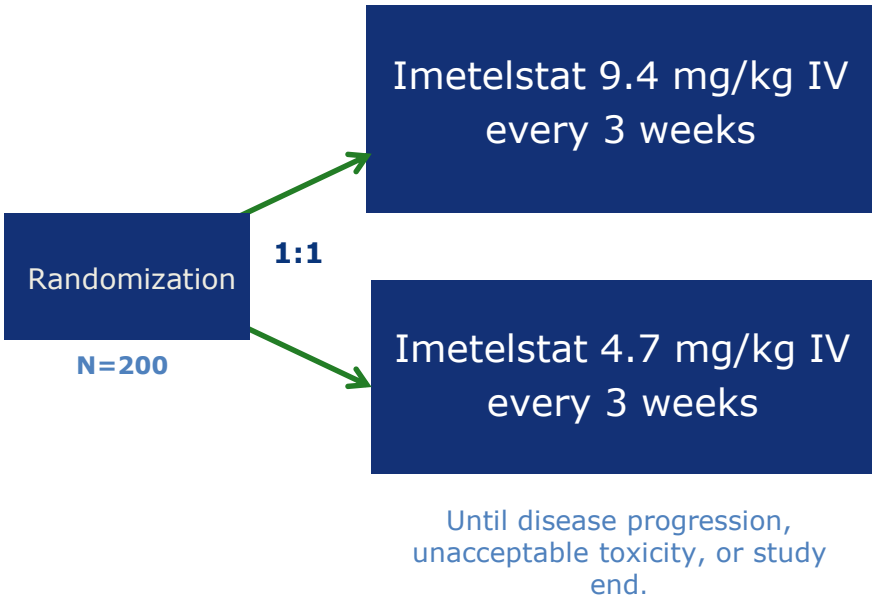
**CR/PR: 21.2%**

- All 4 CR patients achieved reversal of BM fibrosis and 3 complete molecular response.
- 3 CR/PR patients who were transfusion dependent at baseline became transfusion independent
- 3 CR/PR patients with splenomegaly at baseline achieved splenic response

Tefferi et al. N Engl J Med. 2015 Sep 3;373(10):908-19.

# A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects With Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor

IMbark™ (NCT02426086)




## Co - Primary Endpoints

- **To evaluate the spleen response rate at Week 24**
  - **The percentage of participants who achieve ≥ 35% reduction in spleen volume from baseline as measured by MRI**
- **To evaluate the symptom response rate at Week 24**
  - **The percentage of subjects who have ≥50% reduction in total symptom score as measured by modified MFSAF v2.0.**

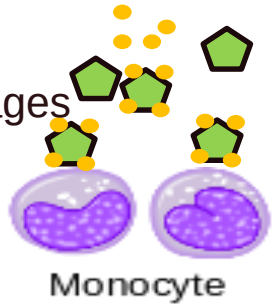
## Key Eligibility Criteria*

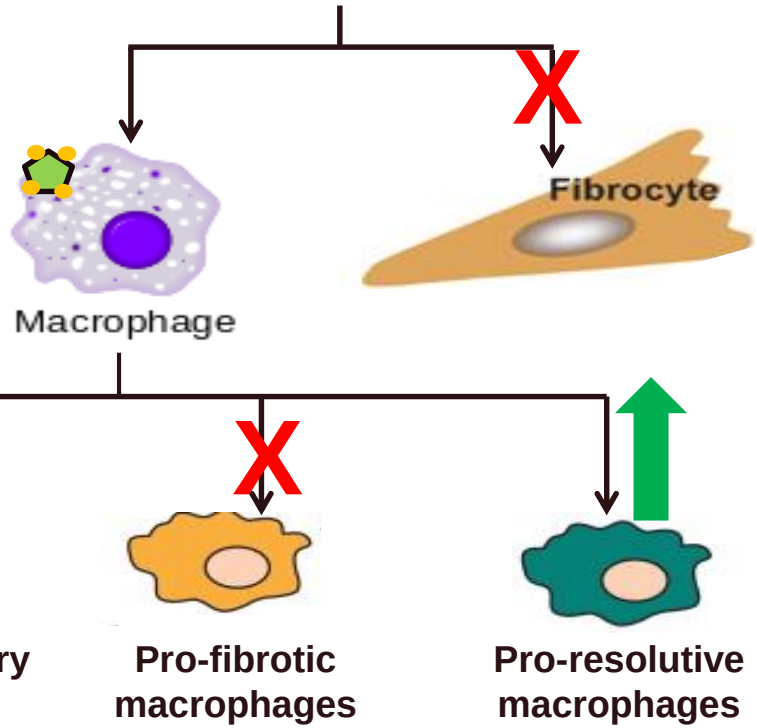
- **18 years of age and older**
- **Diagnosis of PMF; or PET-MF or PPV-MF**
- **DIPSS intermediate-2 or high risk MF**
- **Measurable splenomegaly**
- **Active symptoms of MF prior to study entry**
- **Documented progressive disease during or after JAK inhibitor**
- **ANC ≥ 1,500/ul**
- **Platelets ≥ 75,000/ $mm^3$**
- **Peripheral blood and bone marrow blast count of <10%**

*Not a complete list of inclusion and exclusion criteria

# PRM-151: Recombinant Human Pentraxin-2 (PTX-2)

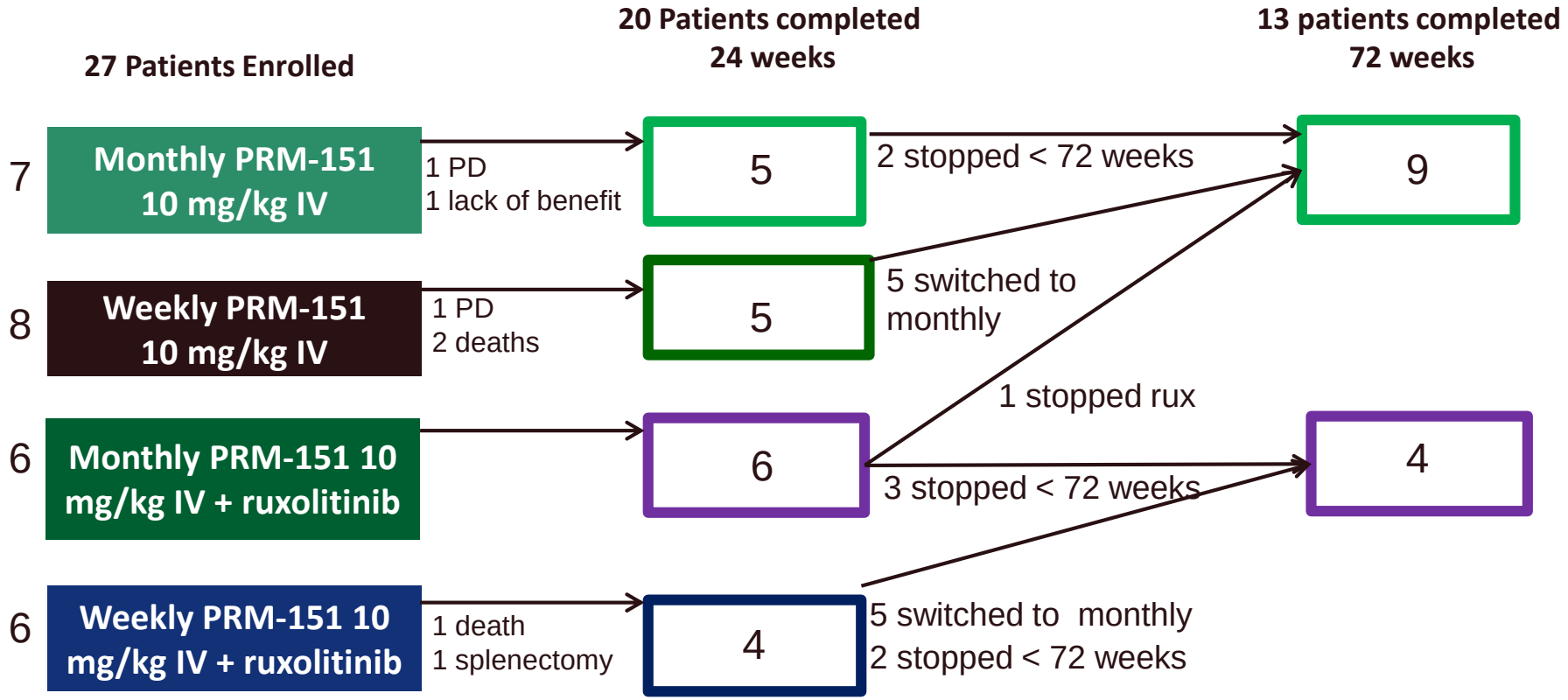
- PTX-2 ( ) is an endogenous regulator of tissue repair
- PTX-2 binds to damaged tissue ( ) and monocytes/macrophages
- PTX-2 prevents and reverses fibrosis in pre-clinical models
- PTX-2 levels are low in MF patients
  - Also low in patients with renal, pulmonary and liver fibrosis




**<u>Hypothesis</u>:**
**Reduction of bone marrow fibrosis will restore hematopoiesis and improve cytopenias**

# PRM-151G-101 Stage 1 and Extension



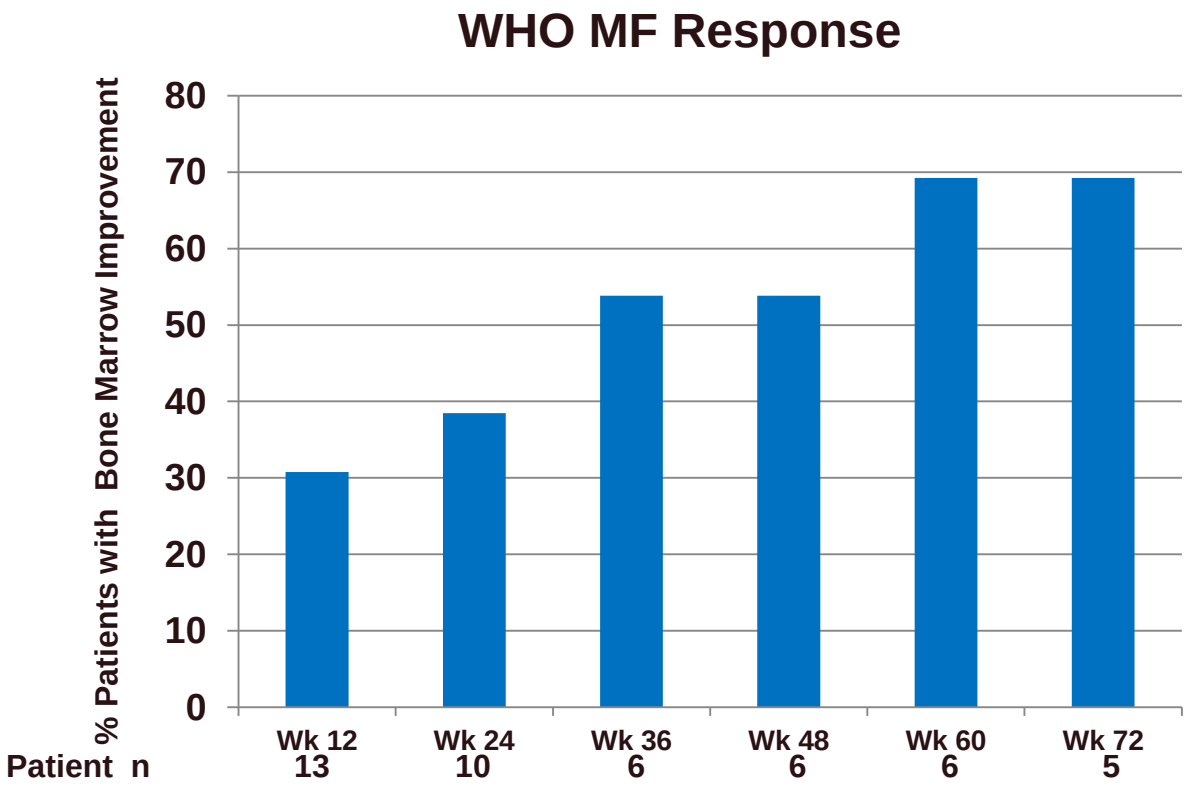

- 24 week treatment period
  - Patients with clinical benefit may continue beyond 24 weeks
- PRM-151 + RUX: stable RUX dose ≥3 months with no decrease in splenomegaly for ≥ 4 weeks
- No eligibility restrictions for anemia, thrombocytopenia, leukopenia, or spleen size

# All Possibly Related Adverse Events Through 72 Weeks (n=13)

| Adverse Event | Grade 1 | Grade 2 | Grade 3 | Total |
|---|---|---|---|---|
| ANKLE SWELLING | 1 | | | 1 |
| DIARRHEA | 1 | | | 1 |
| ANEMIA | | | 1 | 1 |
| COUGH NONPRODUCTIVE | 1 | | | 1 |
| HYPERURICEMIA | 1 | | | 1 |
| BLURRED VISION | 1 | | | 1 |
| FATIGUE | 2 | | | 2 |
| TOOTH INFECTION | 1 | | | 1 |
| SKIN INFECTION | 1 | | | 1 |
| HSV INFECTION | | 1 | | 1 |
| HOT FLASHES | 1 | | | 1 |
| SWEATING | 1 | | | 1 |

6 SAEs in 4 patients - none related: wound infection, multiple fractures, bladder rupture, bowel obstruction, focal pneumonia, and unspecified infection

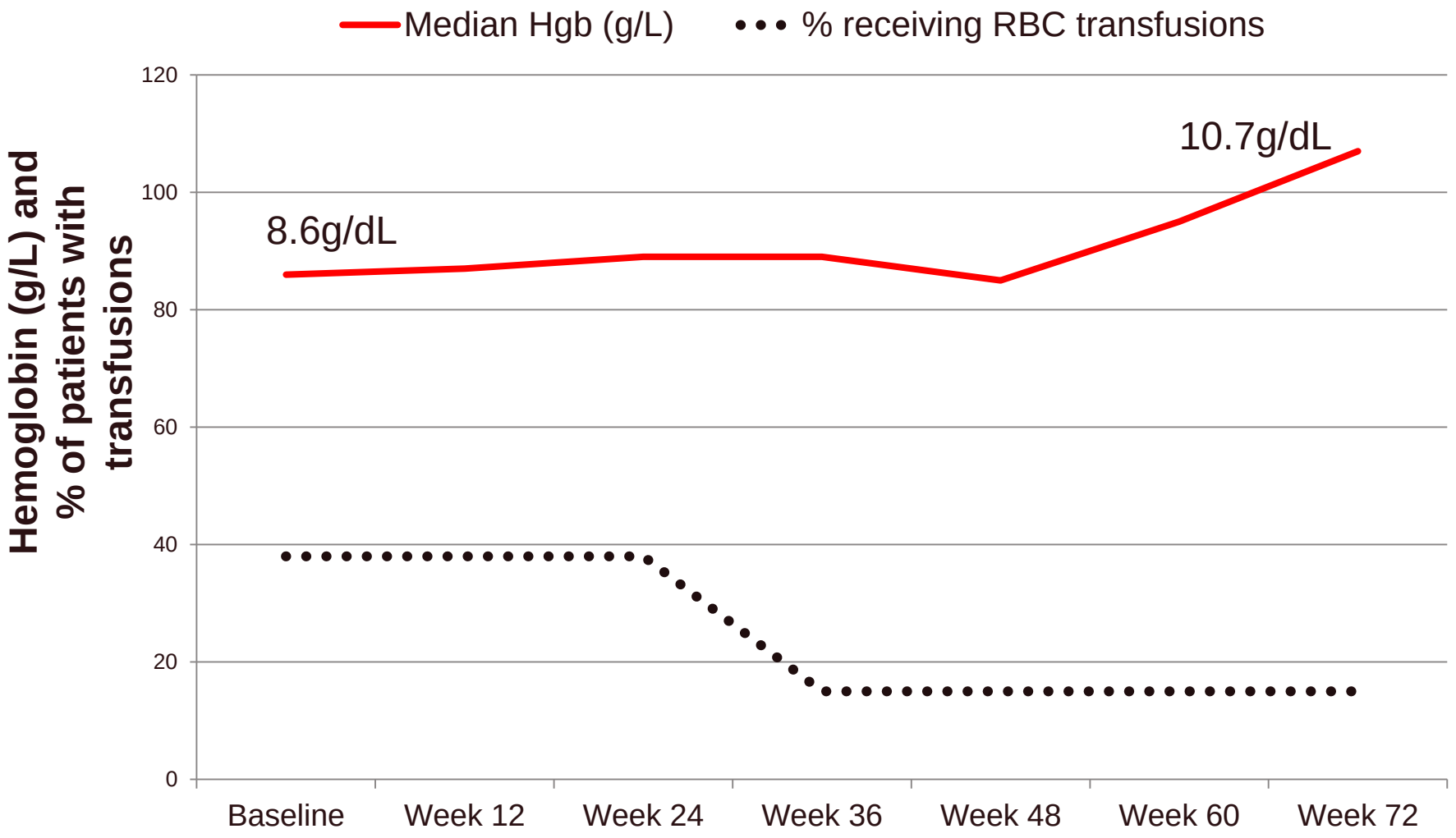
# Bone Marrow Fibrosis Improvement as Measured by WHO Criteria




- Response assessment by central hematopathologists blinded to patient, treatment and time point. WHO MF Response = % of patients with ≥1 grade reduction in MF score at any time point
- Reduction in BM fibrosis was associated with normalization of bone marrow architecture: Normal erythroid clustering, Normal or decreased myeloid:erythroid ratio, Fewer paratrabecular megakaryocytes

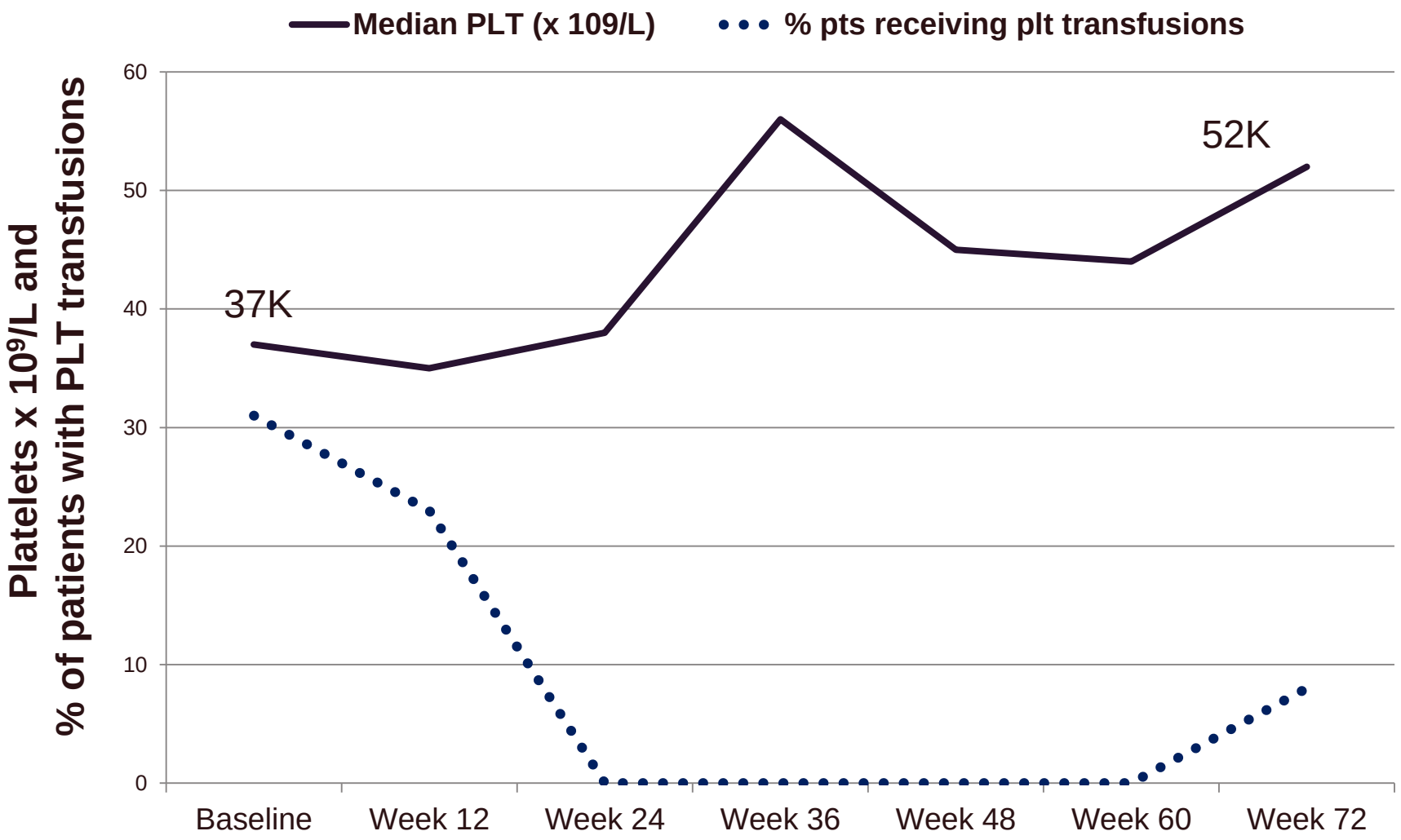
# Hemoglobin and RBC Transfusions

Patients with baseline Hgb < 100 g/L who completed ≥ 72 weeks (n=5)



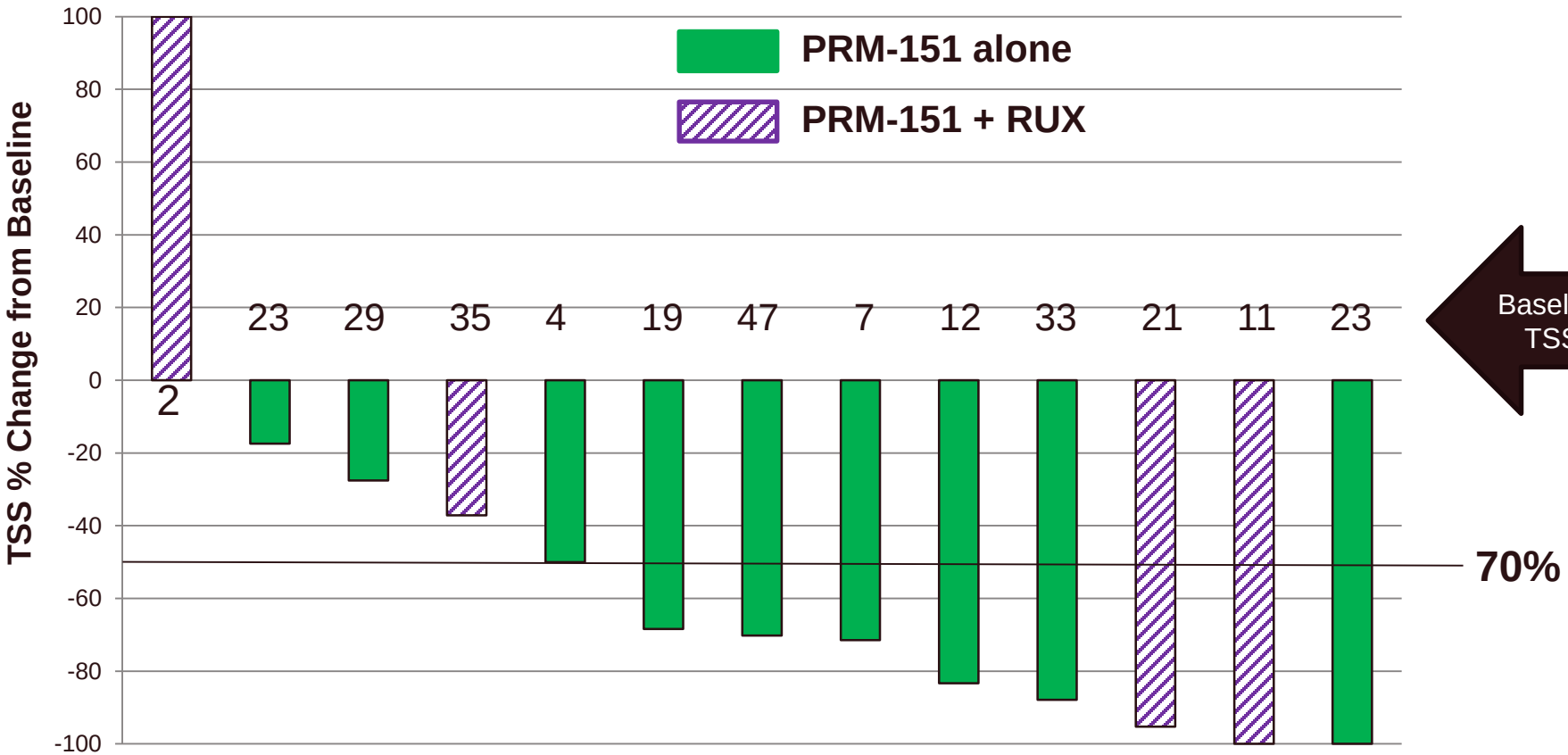
# Platelets and Platelet Transfusions

Patients with Baseline Platelets < 100 x $10^9$/L who completed ≥ 72 weeks (n=9)



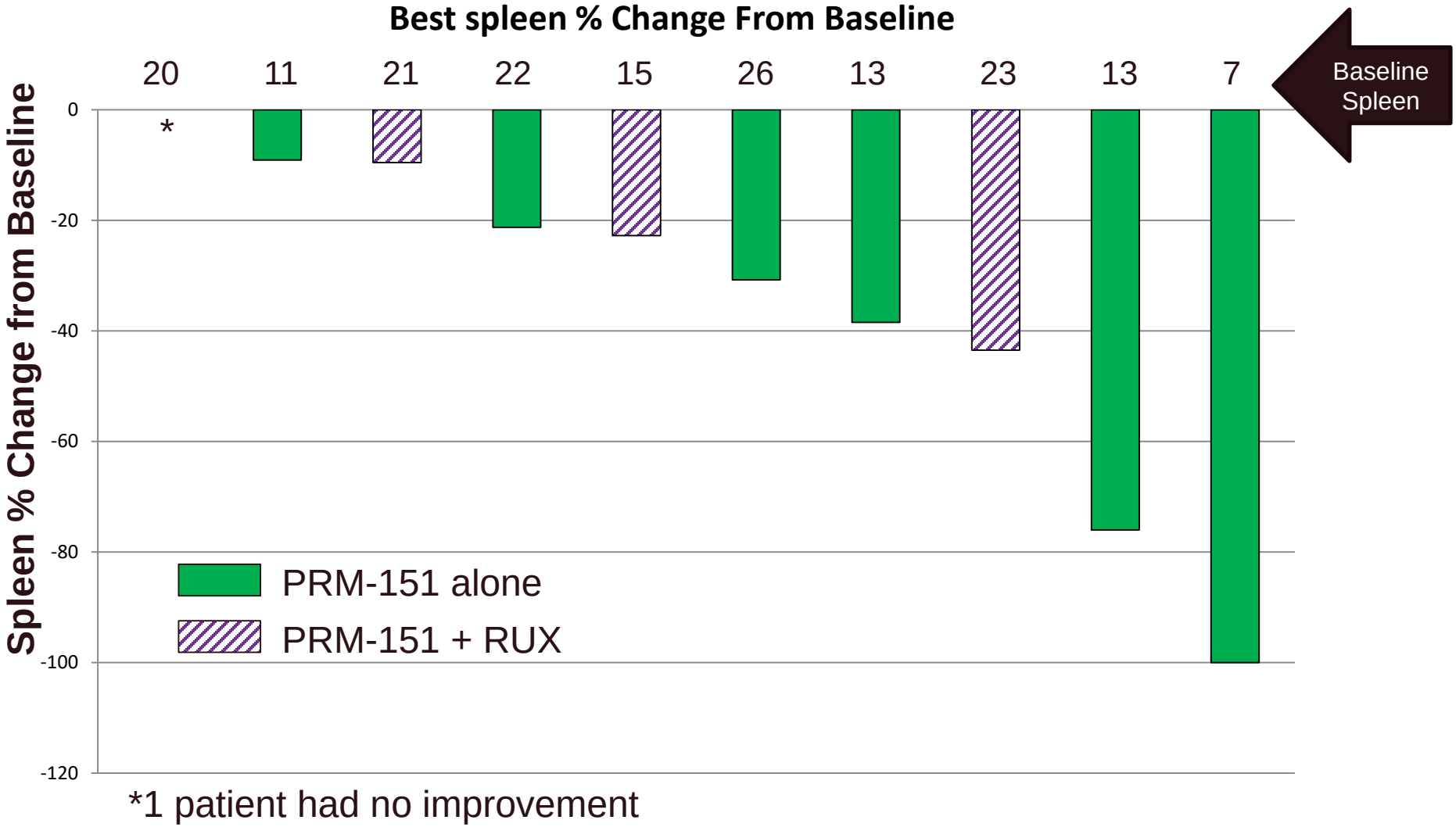
# Symptom Improvements

## MPN-SAF TSS Best % Change from Baseline (n=13)



# Spleen Reductions

Patients with palpable spleen at baseline (n = 10)



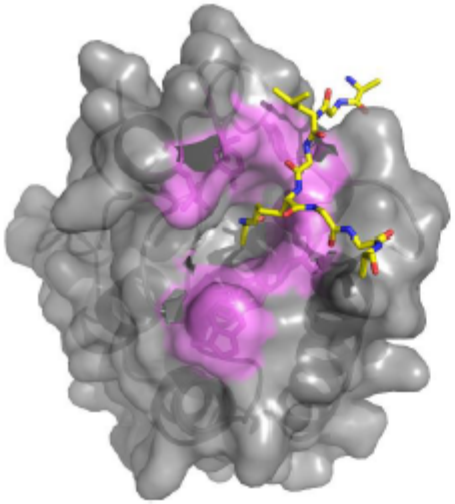

*1 patient had no improvement

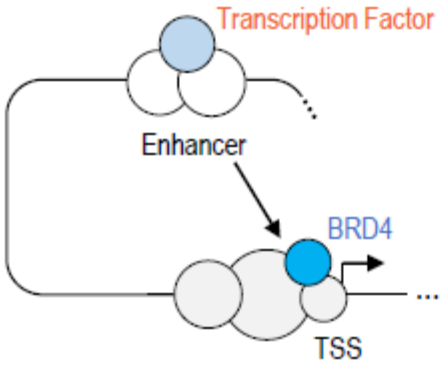
| JAK inhibitor | Combination partner/setting | MPN | Phase | Clinicaltrials.gov identifier |
|---|---|---|---|---|
| Ruxolitinib | TGR-1202 | PV, MF, MDS/MPN | 1 | NCT02493530 |
| Ruxoilitinib | Idelalisib | MF | 1 | NCT02436135 |
| Ruxolitinib | INCB050465 | MF | 2 | NCT02718300 |
| Ruxolitinib | Danazol | MF | 2 | NCT01732445 |
| Ruxolitinib | Thalidomide | MF | 2 | NCT03069326 |
| Ruxolitinib | Lenalidomide | MF | 2 | NCT01375140 |
| Ruxolitinib | Azacytidine | MF, MDS/MPN | 2 | NCT01787487 |
| Ruxolitinib | Panobinostat | MF | 1b<br>1/2 | NCT01433445<br>NCT01693601 |
| Ruxolitinib | Pracinostat | MF | 2 | NCT02267278 |
| Ruxolitinib | Decitabine | MPN-AML | 1/2<br>1/2 | NCT02257138<br>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

# BET – Epigenetic "Reader"

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






***Cancer Genetics***
- MYC, BCL2

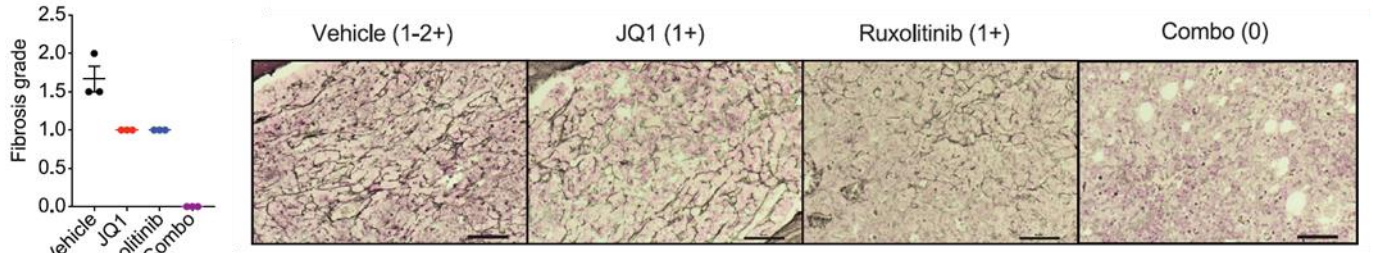
***Immune Signaling***
- NF-κB target genes

***Fibrosis***
- TGF-β target genes

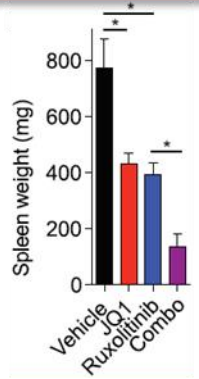
# Combination of BET and JAK Inhibitors is Efficacious in MF model

**Combination significantly improves spleen weight, fibrosis and tumor burden**

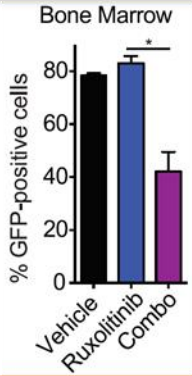
**Dramatic reduction in bone marrow fibrosis upon combination treatment**




**Decreased splenomegaly**



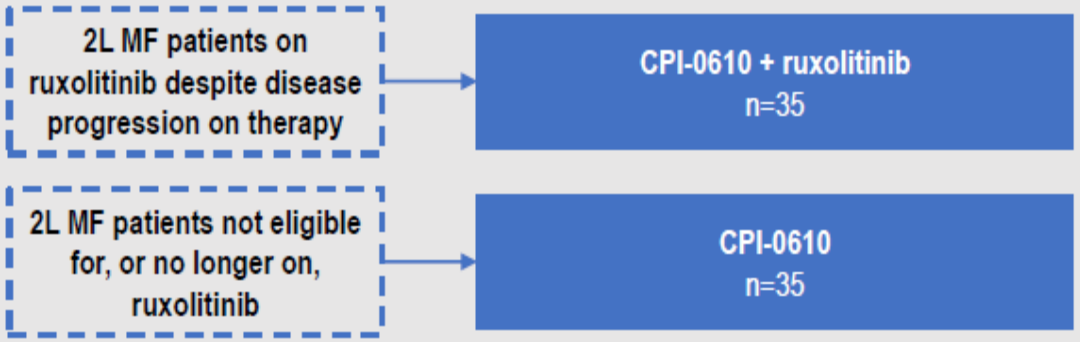

**Decreased mutant cell burden**




Kleppe *et al* 2018 *Cancer Cell*

***MPLW515L* bone marrow transplant model of MF**

# CPI-0610 Phase 2 Trial in Myelofibrosis



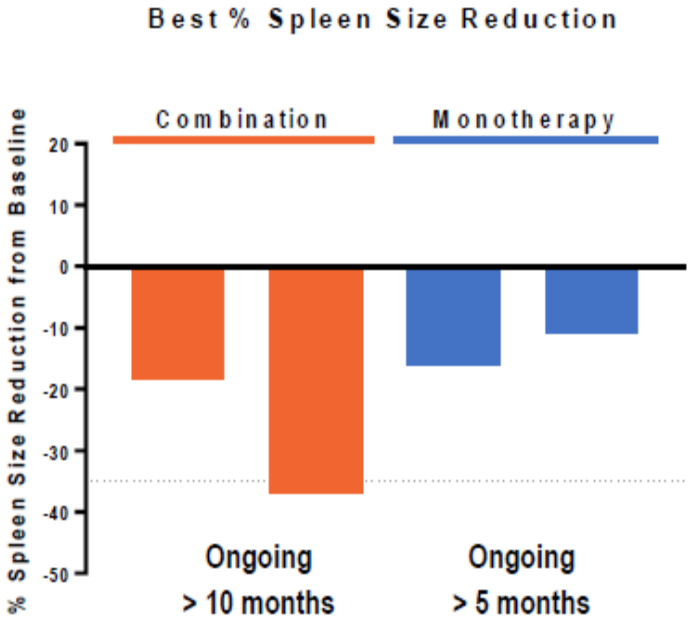

**Objectives:**

- 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*

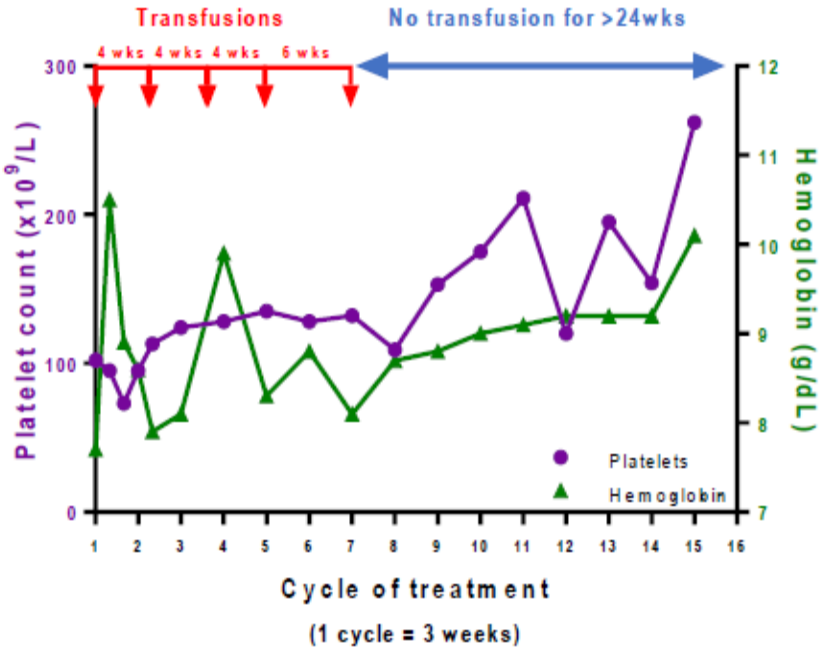



- *Reduced spleen size*
- *Symptom improvement*
- *1 patient with thrombocytosis and 1 patient transfusion dependent at baseline – both resolved*

# CPI-0160 Improving Hemoglobin Levels and Transfusion Dependence

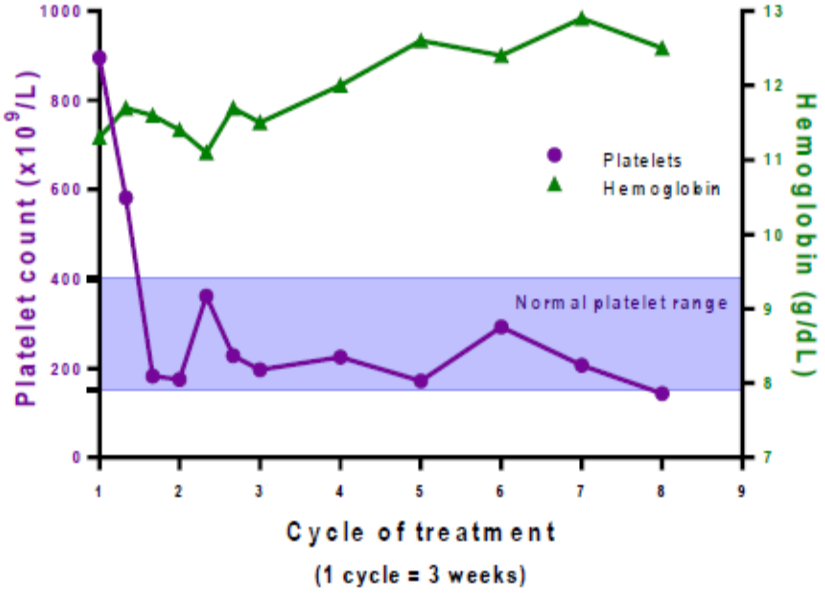
**Data as of May 25, 2018**

## *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

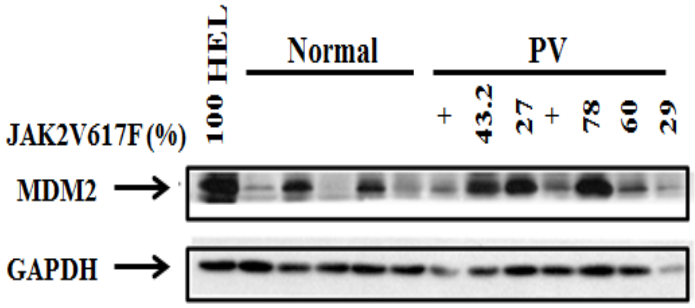
## *CPI-0610 Improved Hemoglobin Levels in Each Patient Treated*

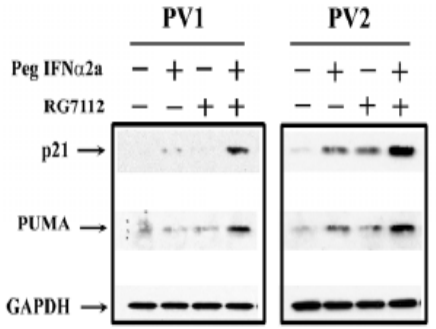


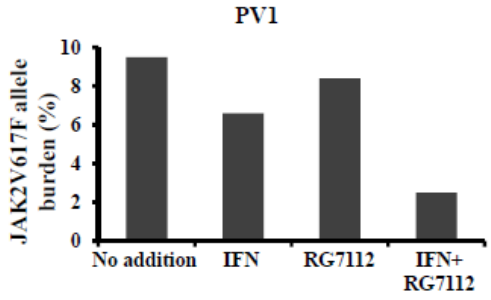

- Patient treated with CPI-0610 monotherapy
- Patient had thrombocytosis, at baseline and was refractory to prior treatment with ruxolitinib, a telomerase inhibitor, pembrolizumab and hydroxurea
- Patient's thrombocytosis was accompanied by severe headaches
- Platelet counts normalized after treatment 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

# 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

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

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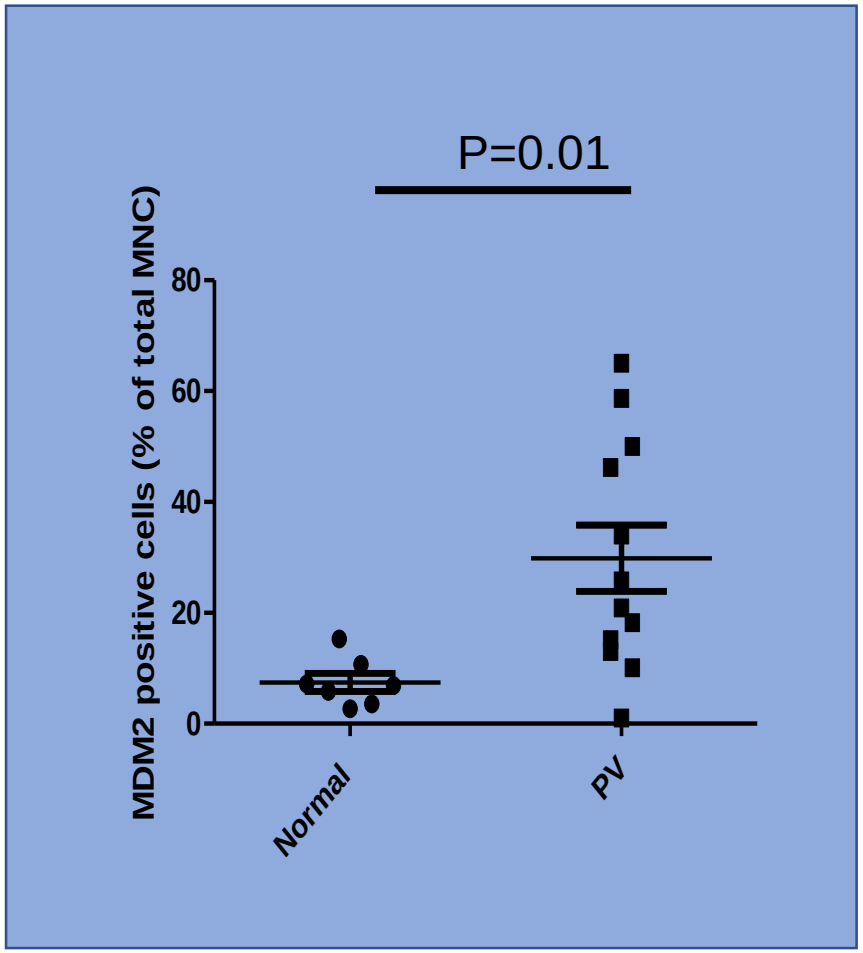
# Baseline MDM2 levels higher in study participants than normal controls

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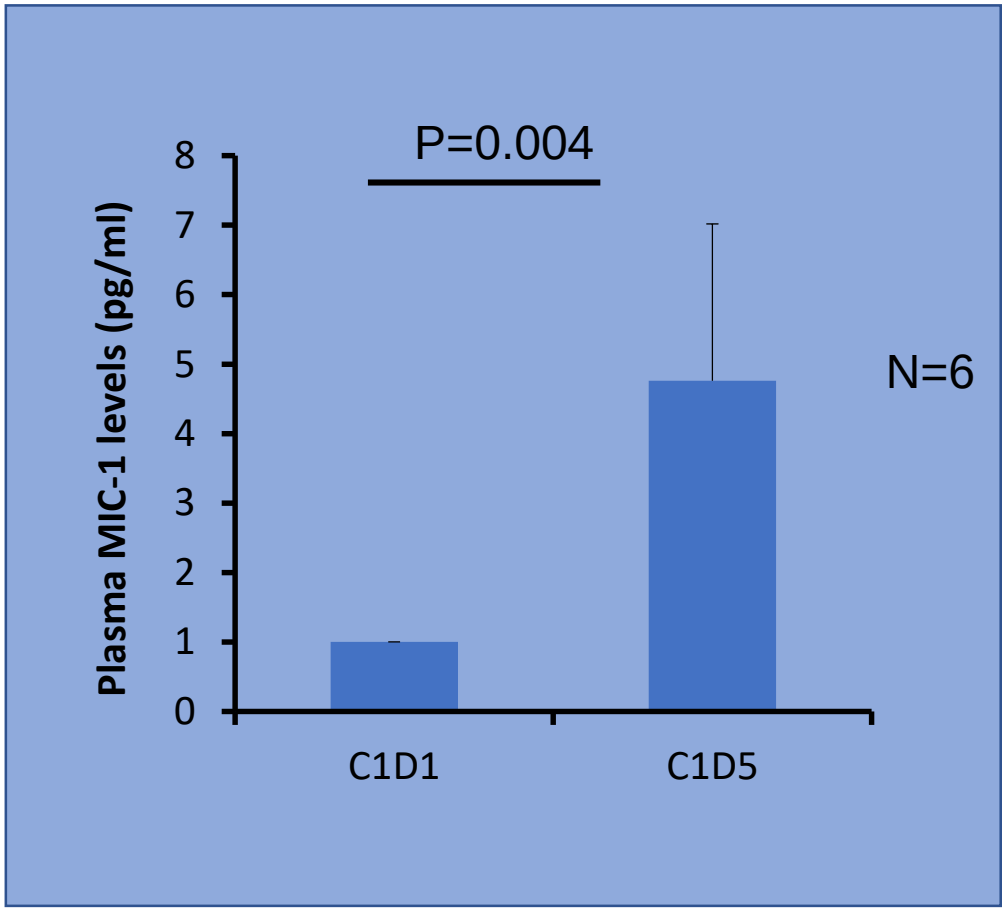
# Evidence of P53 pathway activation: Plasma MIC-1 levels are significantly increased in PV patients following treatment with idasanutlin

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# 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)^ | 1[+] | 1 | 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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[1]Barosi et al Blood 2013

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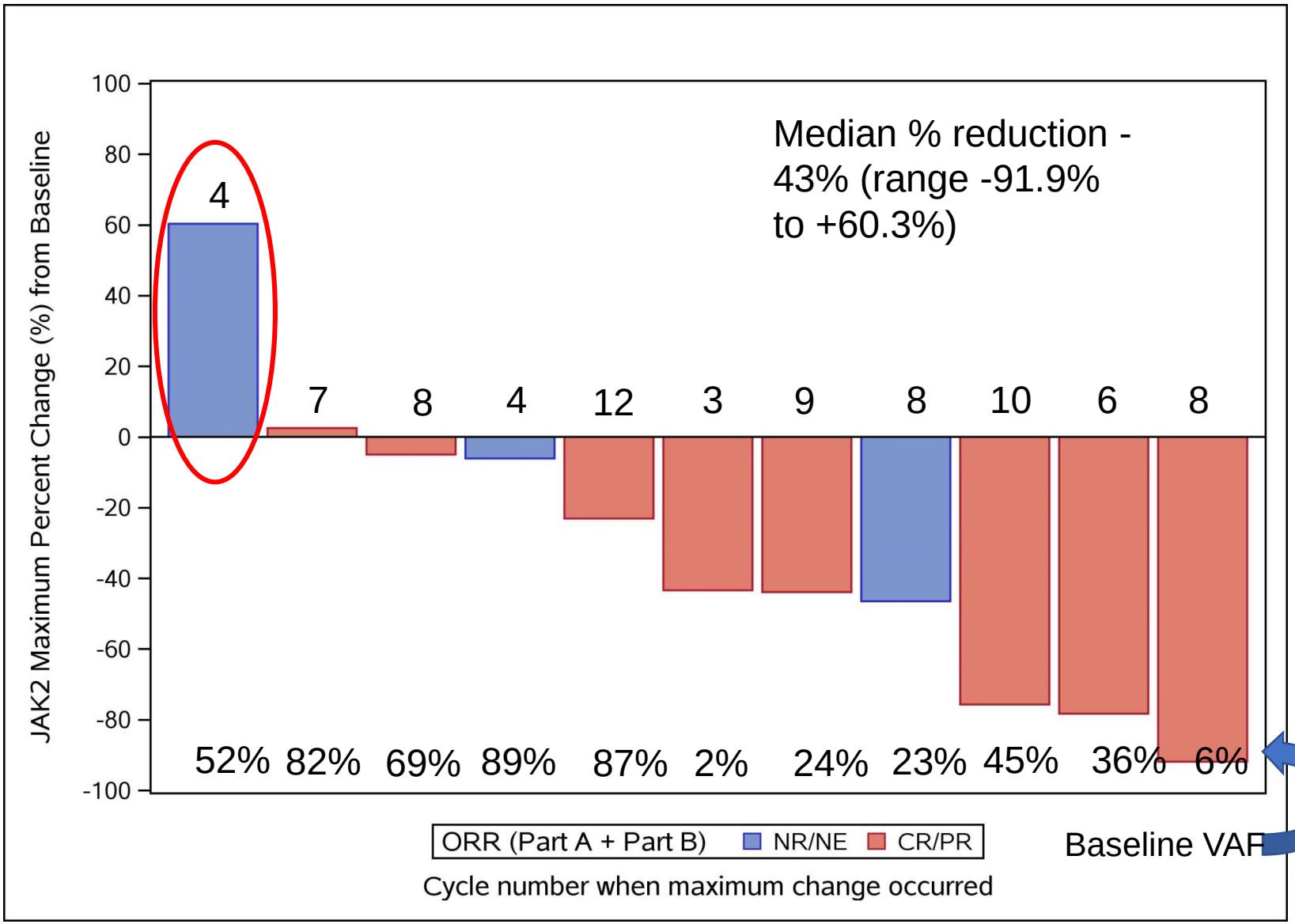
# Driver mutation responses with idasanutlin therapy

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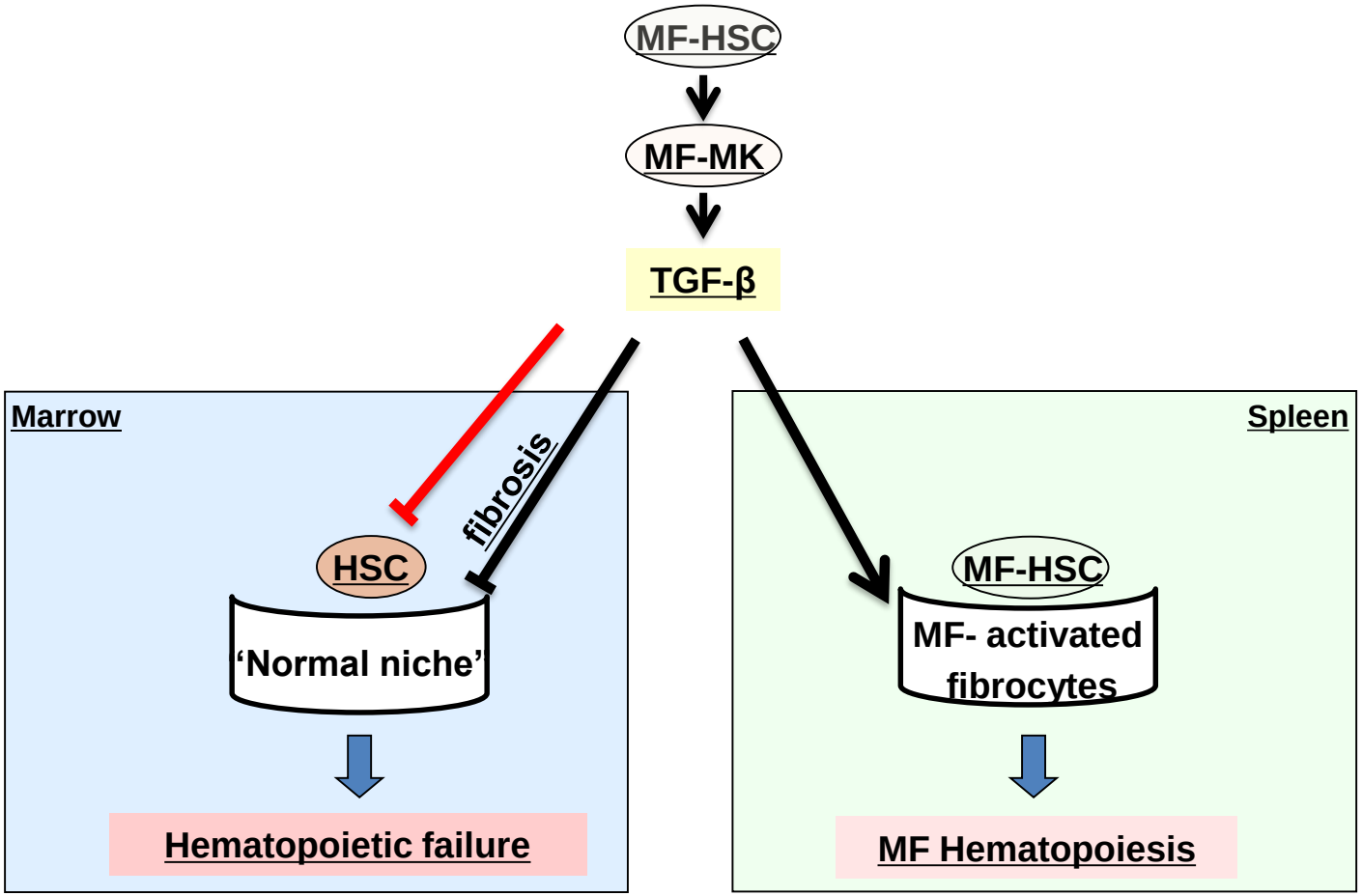
# BACK UP

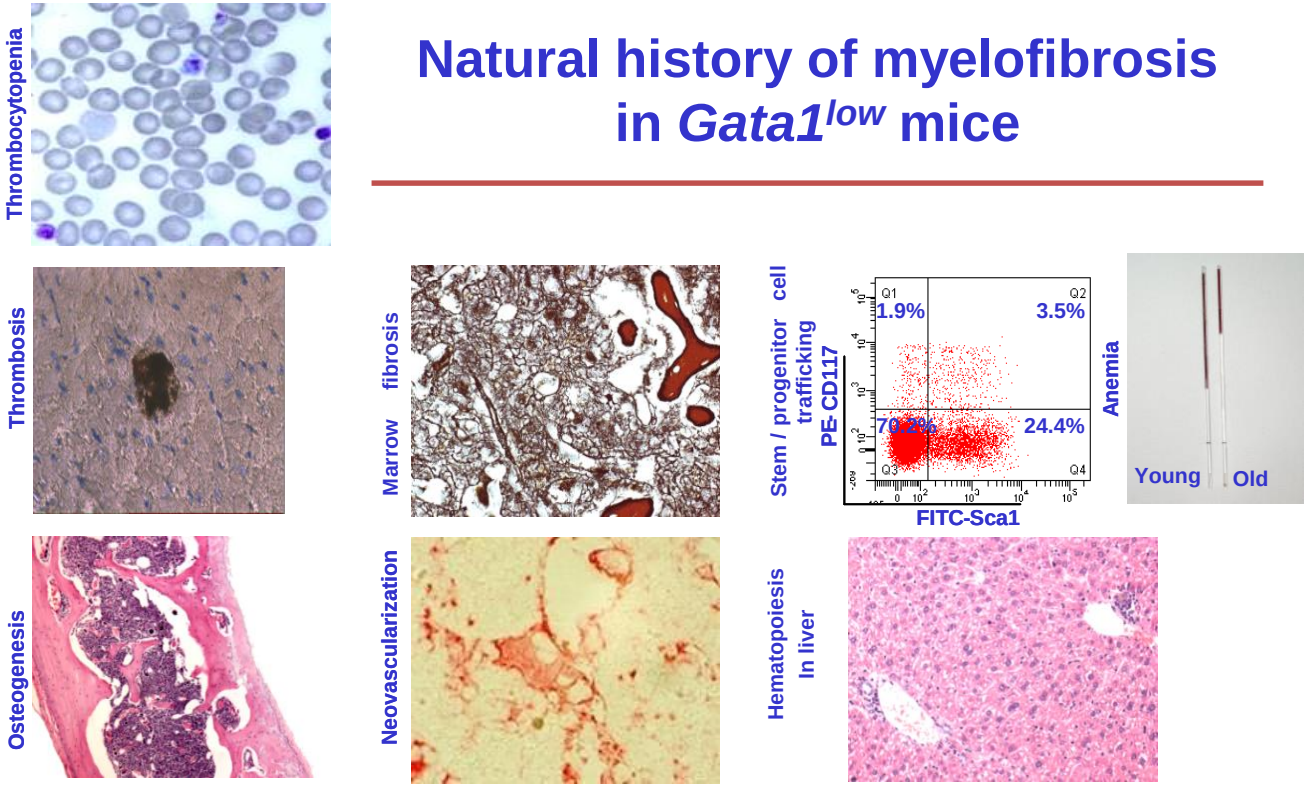
# Therapeutic Hypothesis

Treatment with a TGF-β inhibitor may treat PMF by providing proliferative advantage to healthy HSC in the marrow and preventing formation of myelofibrosis-HSC supporting niches in the spleen




Courtesy of Annarita Migliaccio

# Natural history of myelofibrosis in *Gata1$^{low}$* mice




Varricchio et al Expert Rev Hematol 2009;2:315

# Ruxolitinib based combination therapy: Setting a higher standard for success?

- Greater spleen reduction
- Greater symptom improvement
- Improvement in disease related cytopenias
- Deeper molecular responses
- Bone marrow morphologic responses
- IWG-MRT/ELN response criteria