A look into the Future: innovative approaches in MPN (why I believe there is hope)

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What do MPN patients want?

- Highly effective therapy
- Low toxicity
- “Disease course modifying”
- Convenient administration
- Cure

What do MPN clinical Investigators want?

- Highly effective therapy
- Low toxicity
- “Disease course modifying”
- Convenient administration
- Cure
- Mechanism based therapy with preclinical rationale and biomarker evidence of on target effect and remission

Emerging Treatments

- JAK2 inhibitor based combination trials in MF
- Telomerase Inhibition in MF (not covering ET)
- Anti-Fibrotic therapy in MF
- JAK2i + DNMTi combination in MPN-AP/BP
- MDM2 antagonist therapy in PV

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

Double and triple combination therapy trials in chronic and advanced phases of myelofibrosis

Agent 1 Class	Agent 1	Agent 2 class	Agent 2	Agent 3 class	Agent 3	Phase of study	NCT identifier
JAK 1/2 inhibitor	Ruxolitinib	Epigenetic	Panobinostat			I/II Ib	NCT01693601 NCT01433445
			Pracinostat			II	NCT02267278
			Azacytidine			II	NCT01787487
			Decitabine			I/II	NCT02076191
		IMiD	Lenalidomide			II	NCT01375140
			Pomalidomide			Ib/II	NCT01644110
		Androgen	Danazol			II	NCT01732445
		Anti-fibrosing agent	PRM-151*			II	NCT01981850
			GS-6624			II	NCT01369498
		HH Pathway inhibitor	Sonidegib			I/II	NCT01787552
		PI3K inhibitor	Buparlisib			Ib	NCT01730248
		Chaperone inhibitor	PU-H71			I	NCT01393509
		PIM kinase inhibitor	PIM447	CDK4/6 inhibitor	LEE011	I	NCT02370706

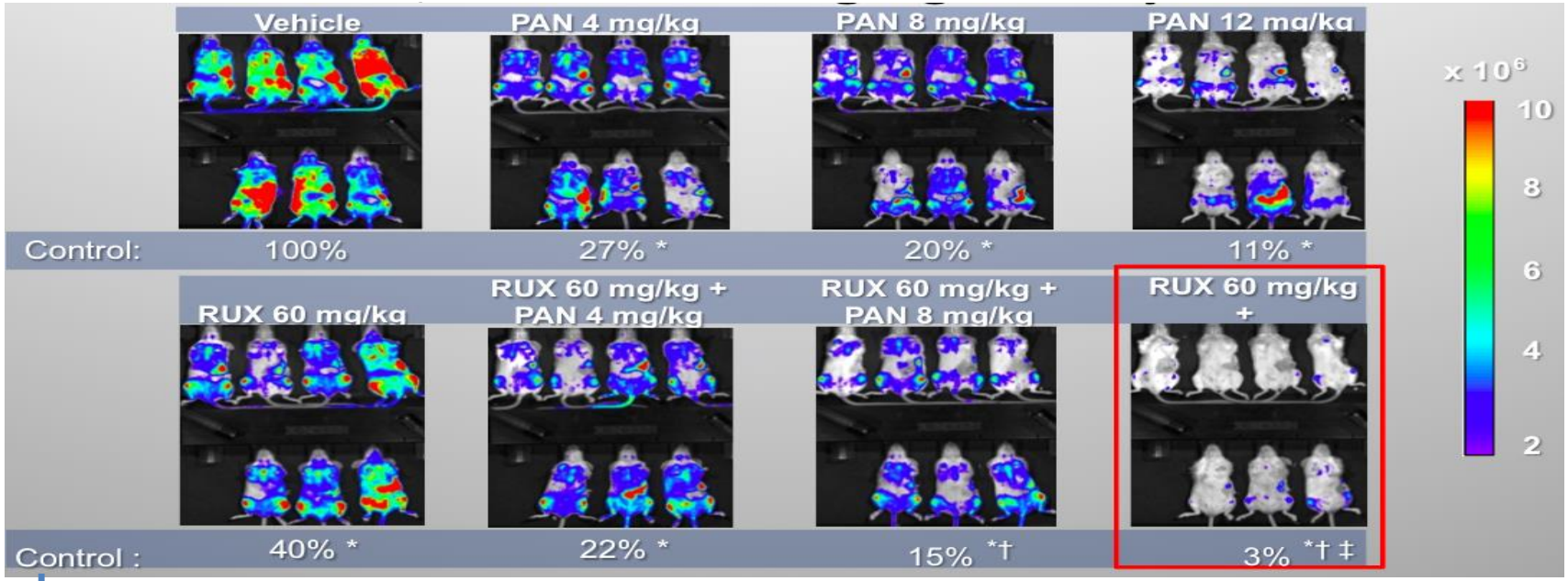
Mascarenhas J. Hematology Am Soc Hematol Educ Program. 2015

Efficacy, Safety, and Confirmation of the Recommended Phase 2 Starting Dose of the Combination of Ruxolitinib and Panobinostat in Patients With Myelofibrosis

Claire N. Harrison,[1] Jean-Jacques Kiladjian,[2] Florian H. Heidel,[3] Alessandro M. Vannucchi,[4] Francesco Passamonti,[5] Amjad Hayat,[6] Eibhlin Conneally,[7] Bruno Martino,[8] Thomas Kindler,[9] Daniel B. Lipka,[3,10] Suddhasatta Acharyya,[11] Prashanth Gopalakrishna,[12] Susan Ide,[11] Tracy Liu,[11] Song Mu,[11] Vincent Ribrag[13]

[1]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [2]Hôpital Saint-Louis et Université Paris Diderot, Paris, France; [3]Otto-von-Guericke-University Medical Center, Magdeburg, Germany; [4]University of Florence, Florence, Italy; [5]Ospedale di Circolo e Fondazione Macchi, Varese, Italy; [6]National University of Ireland Galway, Galway, Ireland; [7]St James's Hospital, Dublin, Ireland; [8]Divisione di Ematologia, Azienda Ospedaliera Bianchi Melacrino Morelli, Reggio Calabria, Italy; [9]University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; [10]German Cancer Research Center, Heidelberg, Germany; [11]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [12]Novartis Pharma AG, Basel, Switzerland; [13]Institut de Cancérologie Gustave Roussy, Villejuif, France.

Ba/F3 model:
Effects of Ruxolitinib and Panobinostat Treatment on



‡ 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 rux** **‡ P < 0.05 vs pan at same dose**

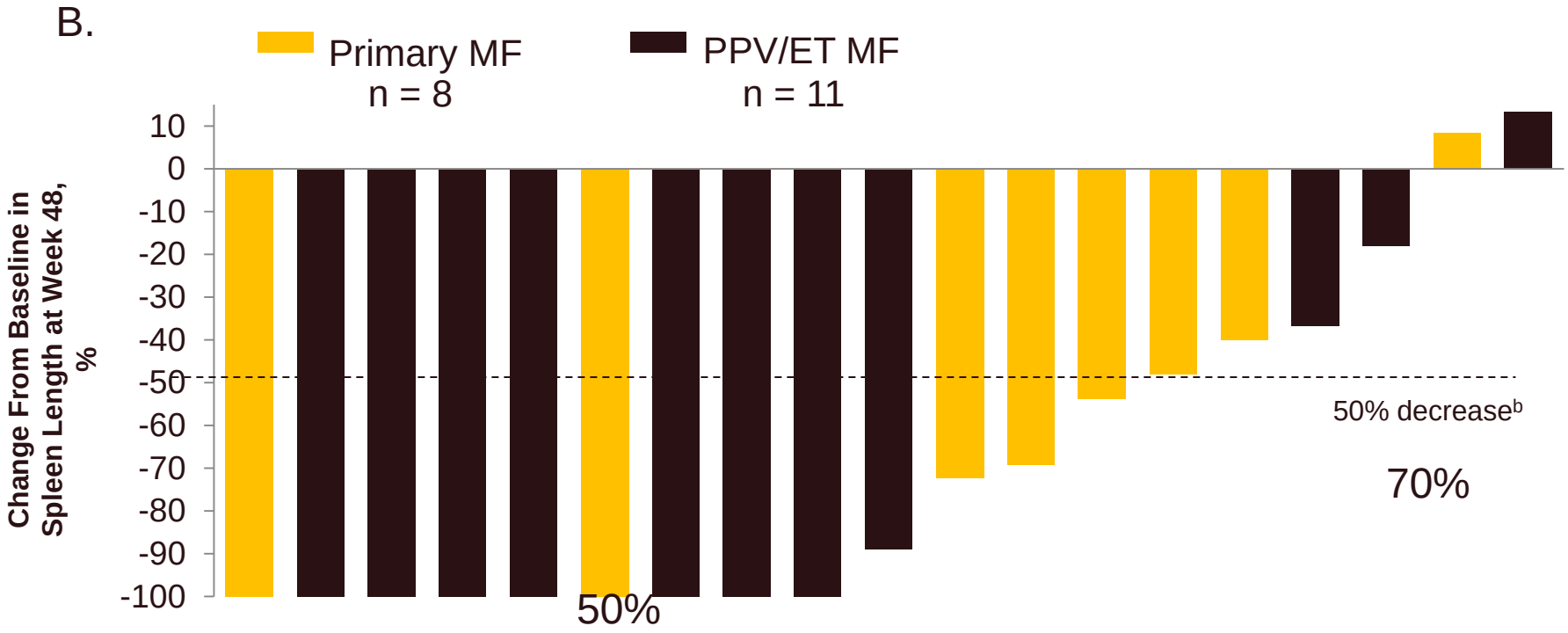
Baffert F, et al. ASH 2011. Abstract 798.

Common Hematologic Adverse Events (in ≥ 5% of Patients)

n (%)[a]	Escalation Phase n = 38		Expansion Phase n = 23		Patients Treated at the RP2D n = 34	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Anemia	24 (63.2)	16 (42.1)	18 (78.3)	8 (34.8)	26 (76.5)	11 (32.4)
Thrombocytopenia	21 (55.3)	9 (23.7)	11 (47.8)	7 (30.4)	17 (50.0)	10 (29.4)
Neutropenia	3 (7.9)	2 (5.3)	1 (4.3)	1 (4.3)	3 (8.8)	2 (5.9)
Leukopenia	1 (2.6)	0	1 (4.3)	1 (4.3)	2 (5.9)	1 (2.9)

[a] Includes AEs in ≥ 5% of patients regardless of relationship to study treatment at any time during or up to 30 days after last dose.

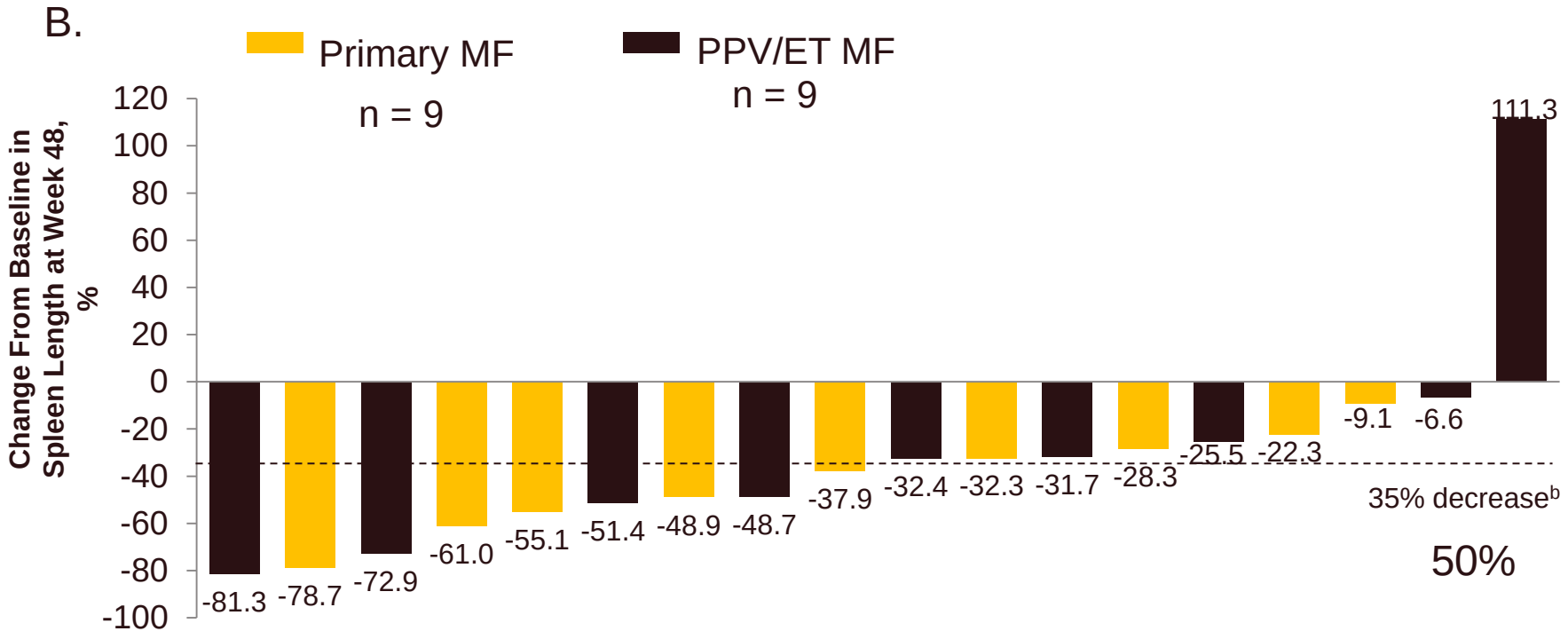
Change in Spleen Length at Week 48 in the Expansion Phase[a]



[a] Only patients with assessments at baseline and at week 24 (20/23) or at week 48 (19/23) are included.

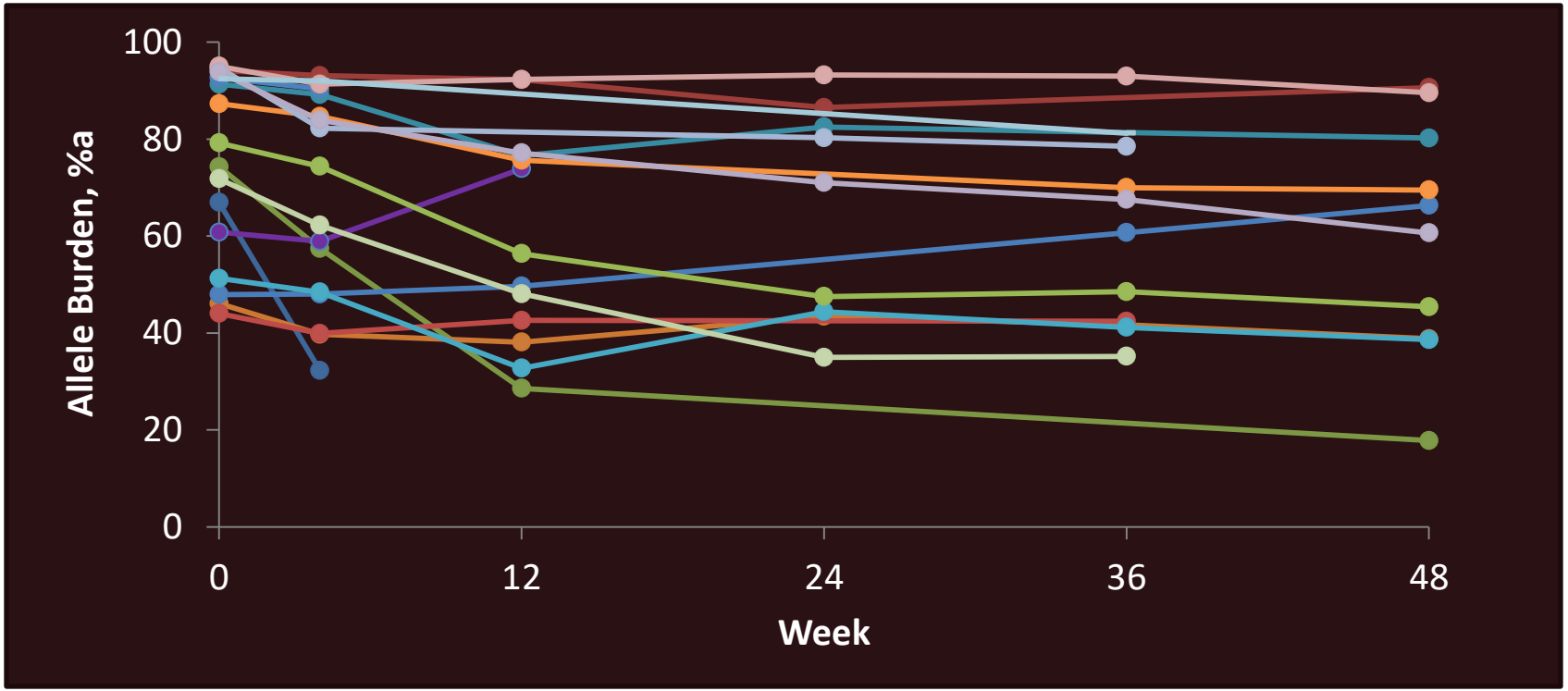
[b] Patients with a ≥ 50% reduction in spleen length were considered responders.

Change in Spleen Volume at Week 48 in the Expansion Phase[a]



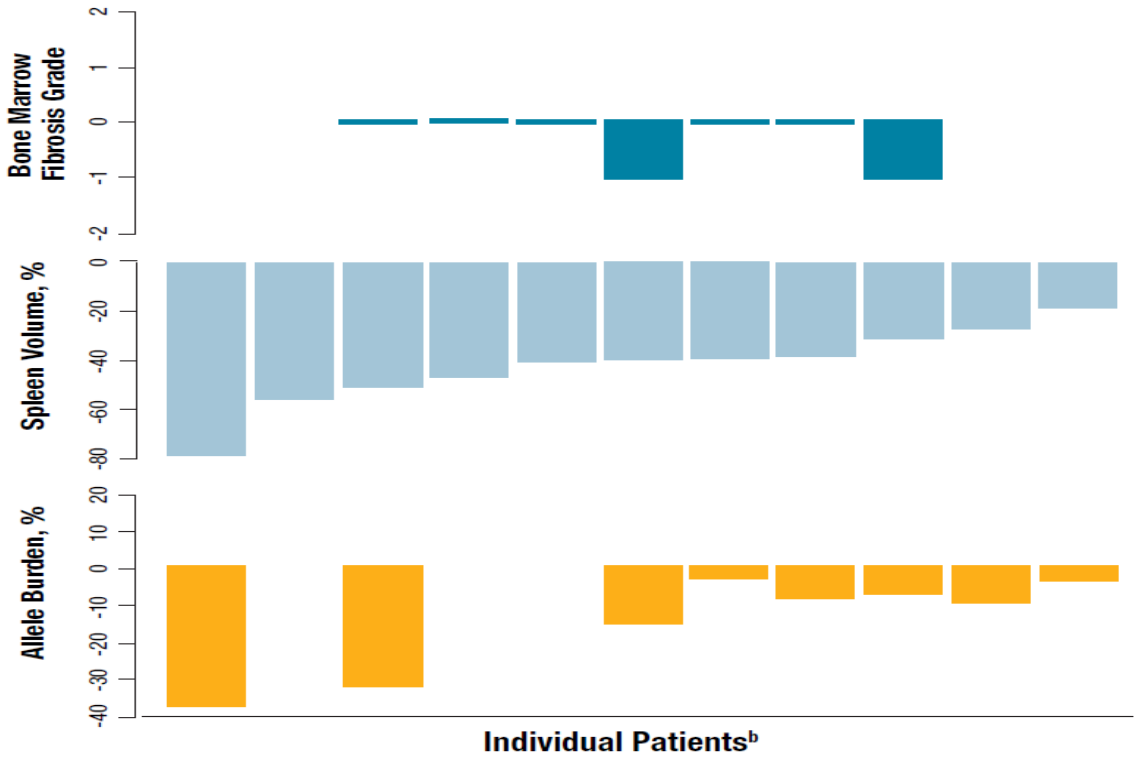
[a] Only patients with assessments at baseline and at week 24 (20/23) or at week 48 (18/23) are included.
[b] Patients with a ≥ 35% reduction in spleen volume were considered responders.

JAK2 V617F Allele Burden Over Time on Treatment



[a] Expansion phase; only patients with ≥ 2 on treatment assessments were included (n =17).

Change From Baseline at Week 24 in Bone Marrow Fibrosis Grade, Spleen Volume, and *JAK2* V617F Allele Burden for Individual Patients[a]

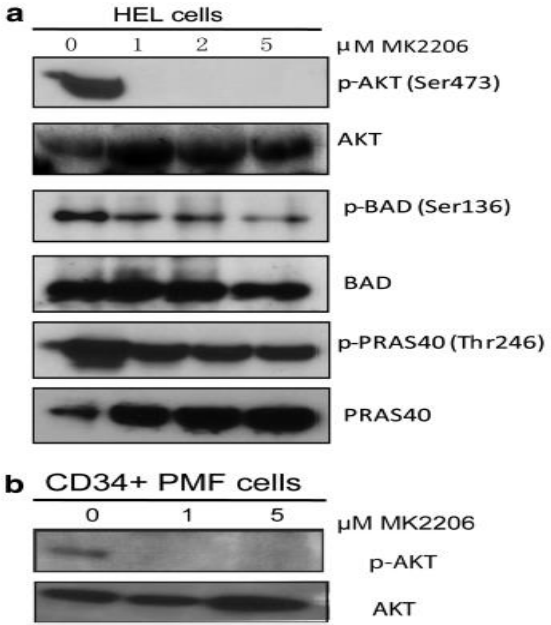


[a] For patients with data at baseline and week 24 for any of the following: bone marrow fibrosis grade, spleen volume, or allele burden.
[b] Each column is for an individual patient. A horizontal line represents no change, and a blank represents missing data.

PI3K/AKT pathway and MF

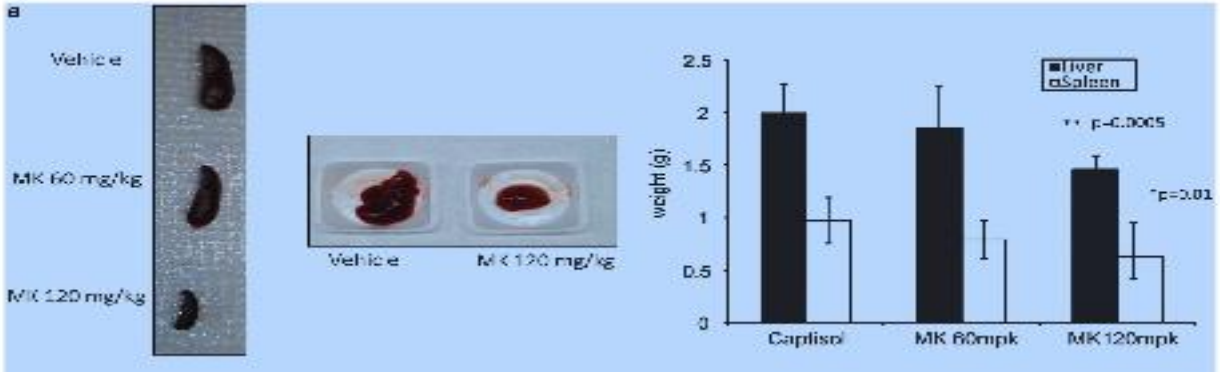
- The PI3Kδ/AKT pathway is constituitively upregulated in MF
- Inhibition of AKT (using a specific AKT inhibitor) reduces signaling in MPN cell lines and MF patient samples

  Khan et al, 2013



Blockade of PI3K/AKT Pathway Reduces Disease Burden in Mouse MF models

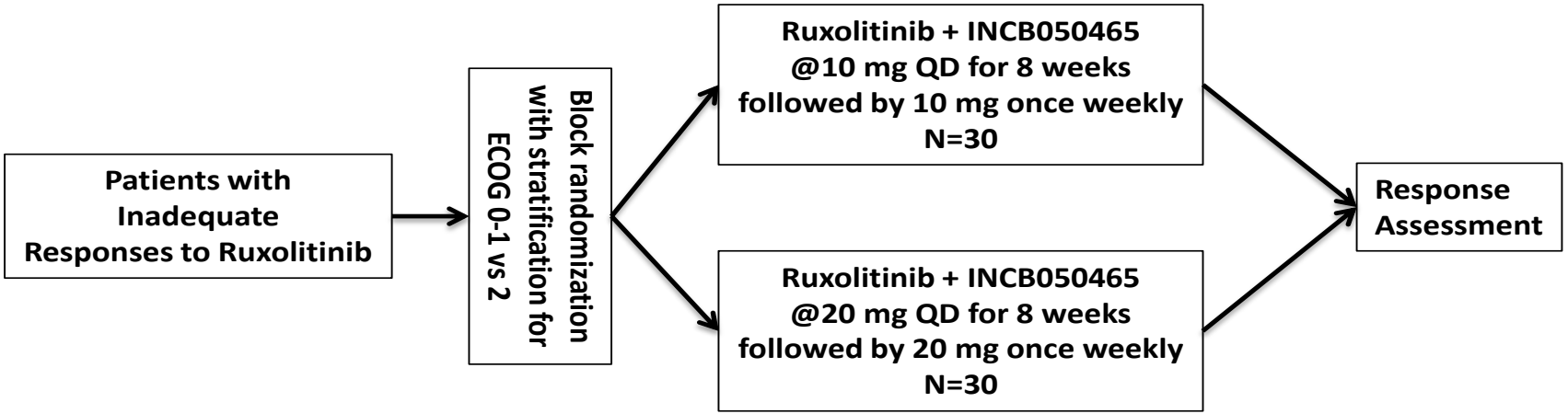
Inhibition of AKT decreases spleen and liver size in mice expressing MPL mutations.



Khan et al, 2013

A Study of INCB050465 in Combination With Ruxolitinib in Subjects With Myelofibrosis

Part 2 will be enrolled and conducted provided that a tolerable dose can be established for INCB050465 in combination with ruxolitinib in Part 1 of the study.



NCT02718300

Novel Non-JAK2 inhibitors in clinical trials for patients with myelofibrosis

	Target	Agent	Trial phase	NCT #
Epigenetic	HDAC	Panobinostat	I/II	NCT01298934
			II	NCT00931762
		Givinostat	II	NCT00606307
		Vorinostat	I	NCT00357305
	DNMT	Azacytidine	II	NCT00569660
		Decitabine	II	NCT00630994
			II	NCT00095784
Signaling pathway	JAK1	INCB39110	II	NCT01633372
	mTOR	Everolimus	I/II	NCT00081874
	SMO	PF-04449913	II	NCT02226172
	Wnt	PRI-724	I/II	NCT01606579
	Aurora-B	TAK-901	I	NCT00807677
	TGF-B/Activin	Sotatercept	II	NCT01712308
Anti-fibrotic	PTX-2	PRM-151	II	NCT01981850
	TGF-β	Fresolimumab	I	NCT01291784
	LOXL2	Simtuzumab	II	NCT01369498
Leukemic stem cell	Epha3	KB004	I/II	NCT01211691
Chaperone	HSP90	AUY922	II	NCT01668173
Checkpoint inhibitor and immunomodulator	PD-1	Nivolumab	II	NCT02421354
	Immune functions	IFN-α2a	II	NCT00452023
		IFN-α2b	II	NCT01758588
			II	NCT02370329
		Pomalidomide	III	NCT01178281
Pro-Apoptosis	Telomerase	Imetelstat	I	NCT01731951
			II	NCT02426086
	IAP	LCL161	II	NCT02098161
	Peptide toxin	SL-401	I/II	NCT02268253

Mascarenhas J. Hematology Am Soc Hematol Educ Program. 2015

Emerging Treatments

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- Telomerase Inhibition in MF (not covering ET)
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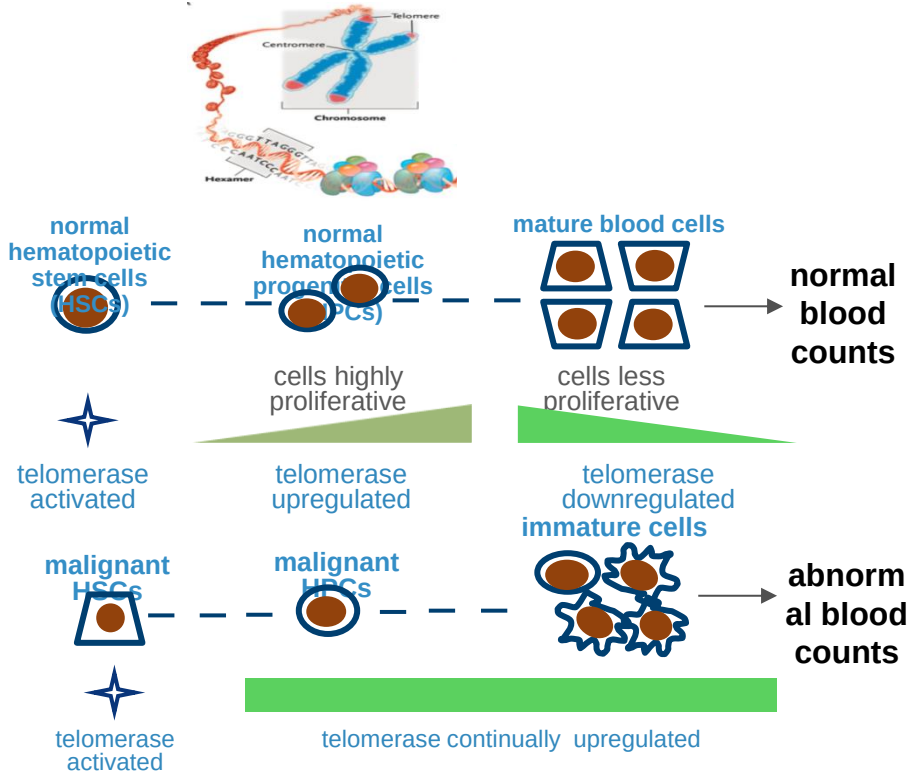
Telomerase as a novel target

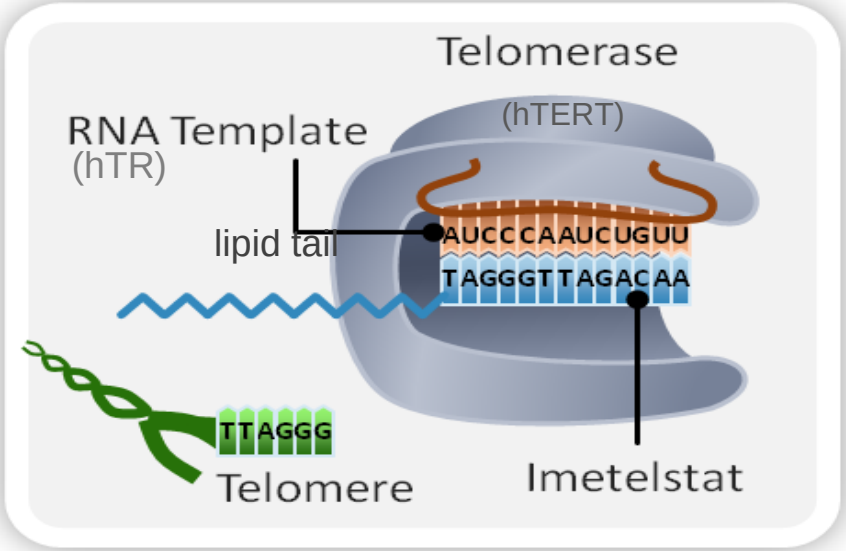


Telomerase enzyme:

- Reverse transcriptase comprised of an RNA component (hTR) and a reverse transcriptase catalytic protein subunit (hTERT)
- Binds to the 3’ strand of DNA and adds TTAGGG nucleotide repeats to offset the loss of telomeric DNA occurring with each replication cycle
- Not active in somatic cells; transiently upregulated in normal hematopoietic progenitor cells to support controlled proliferation
- Highly upregulated in malignant progenitor cells, enabling continued and uncontrolled proliferation

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

Imetelstat, a telomerase inhibitor, induces morphologic and molecular remissions in myelofibrosis and reversal of bone marrow fibrosis

Tefferi A,[1] Begna KH,[1] Laborde RR,[1] Patnaik MM,[1] Lasho TL,[1] Zblewski DL,[1] Finke CM,[1] Schimek L,[1] LaPlant B,[1] Hanson CA,[1] Stuart M,[2] Pardanani A.[1]

[1]Mayo Clinic, Rochester, MN, USA
[2]Geron Corporation, Menlo Park, CA, USA

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

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%)

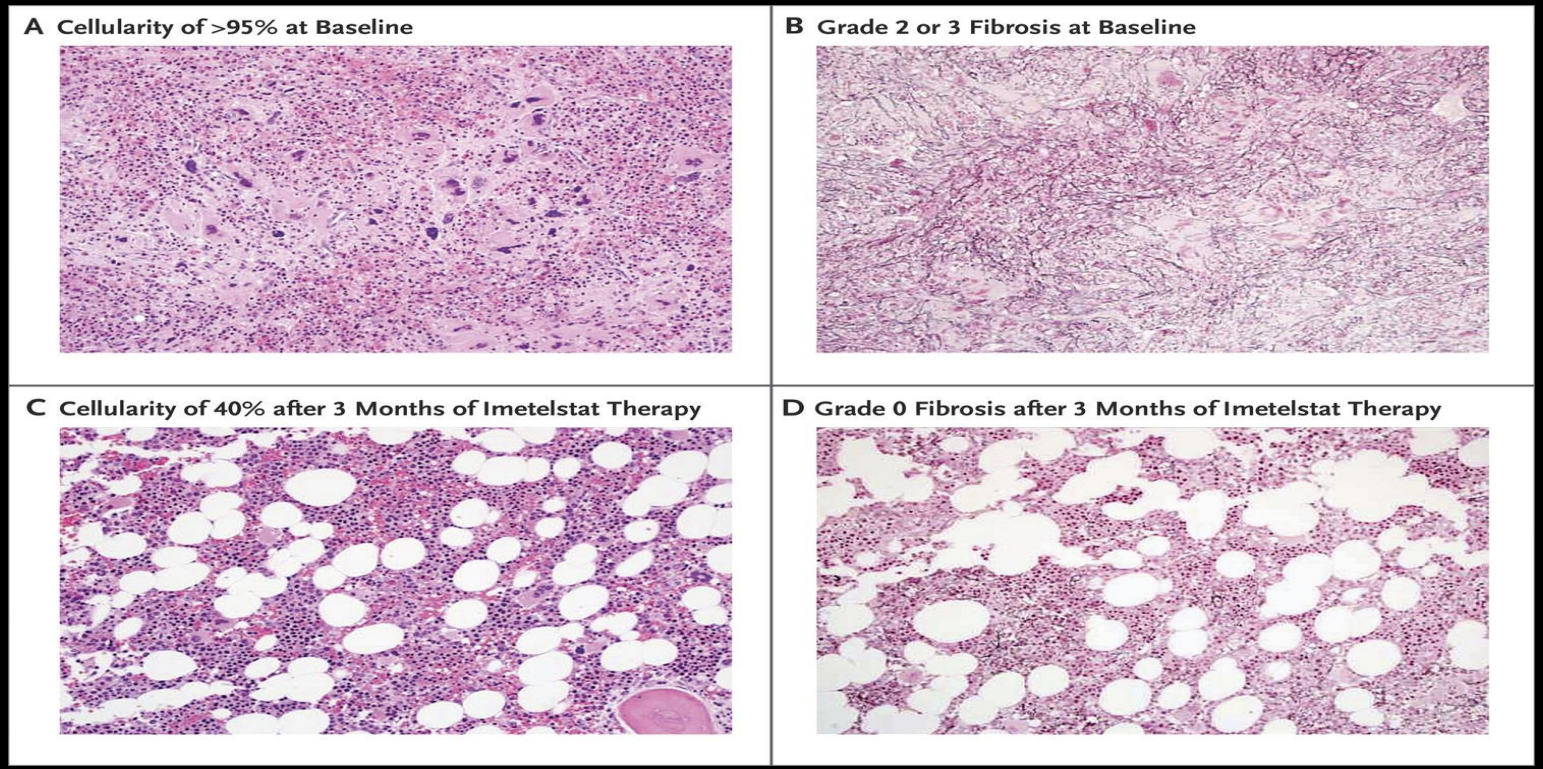
CR/PR/CI: 36.4%

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.

Reversal of Bone Marrow Fibrosis in Patient 4.

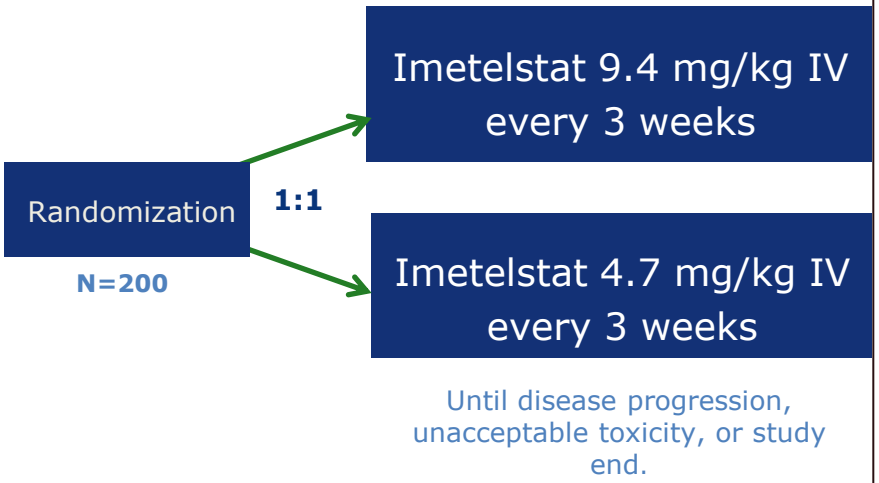


Tefferi A et al. N Engl J Med 2015;373:908-919.

The NEW ENGLAND JOURNAL of MEDICINE

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.

Secondary Endpoints

- To measure complete remission (CR) or partial remission (PR) per modified 2013 IWG-MRT criteria
- To measure clinical improvement (CI) per modified 2013 IWG-MRT criteria
- PK profile
- Safety profile
- Overall Survival

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

Interim Analysis 9/12/2016

- No new safety signal
- 4.7 mg/kg dosing arm did not meet pre-specified response criteria and is closed
- 9.4 mg/kg did not meet criteria but “encouraging trend” and further enrollment suspended
- Protocol amendment
- Second analysis 2ndQ 2017

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PRM-151 in Myelofibrosis: Durable Efficacy and Safety at 72 Weeks

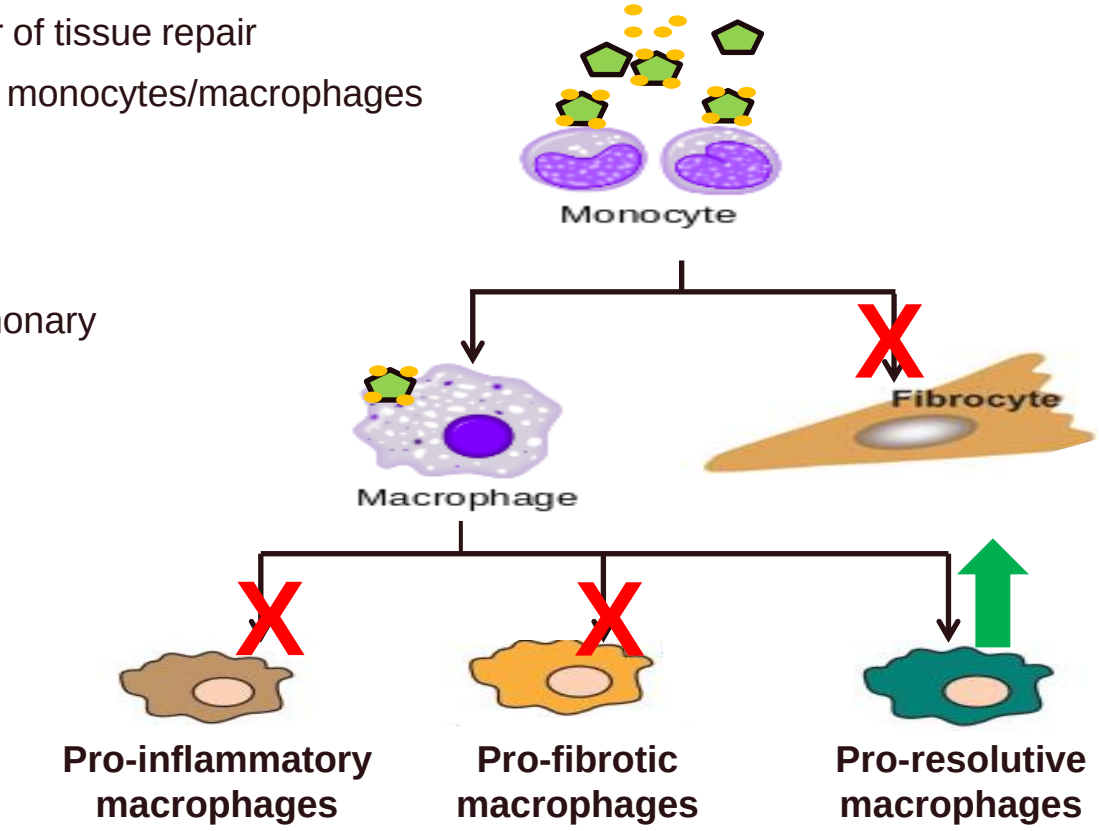
Srdan Verstovsek[1], Olga Pozdnyakova[2],Robert Hasserjian[3], Mohamed Salama[4], Ruben Mesa[5], Lynda Foltz[6], Vikas Gupta[7], John Mascarenhas[8], Ellen Ritchie[9], Ronald Hoffman[8], Richard Silver[9], Marina Kremyanskaya[8], Zeev Estrov[1], Elizabeth Trehu[10], Hagop Kantarjian[1], Jason Gotlib[11]

[1]MD Anderson Cancer Center, Houston, TX, [2]Brigham and Women's Hospital, Boston, MA, [3]Massachusetts General Hospital, Boston, MA, [4]University of Utah, Salt Lake City, UT, [5]Mayo Clinic, Scottsdale, AZ, [6]St. Paul's Hospital, University of British Columbia, BC, CA, [7]Princess Margaret Hospital, Toronto, ON, CA, [8]Mt Sinai Medical Center, New York, NY, [9]Weill Cornell Medical Center, New York, NY, , [10]Promedior, Inc., Lexington, MA, [11]Stanford Cancer Institute, Stanford, CA

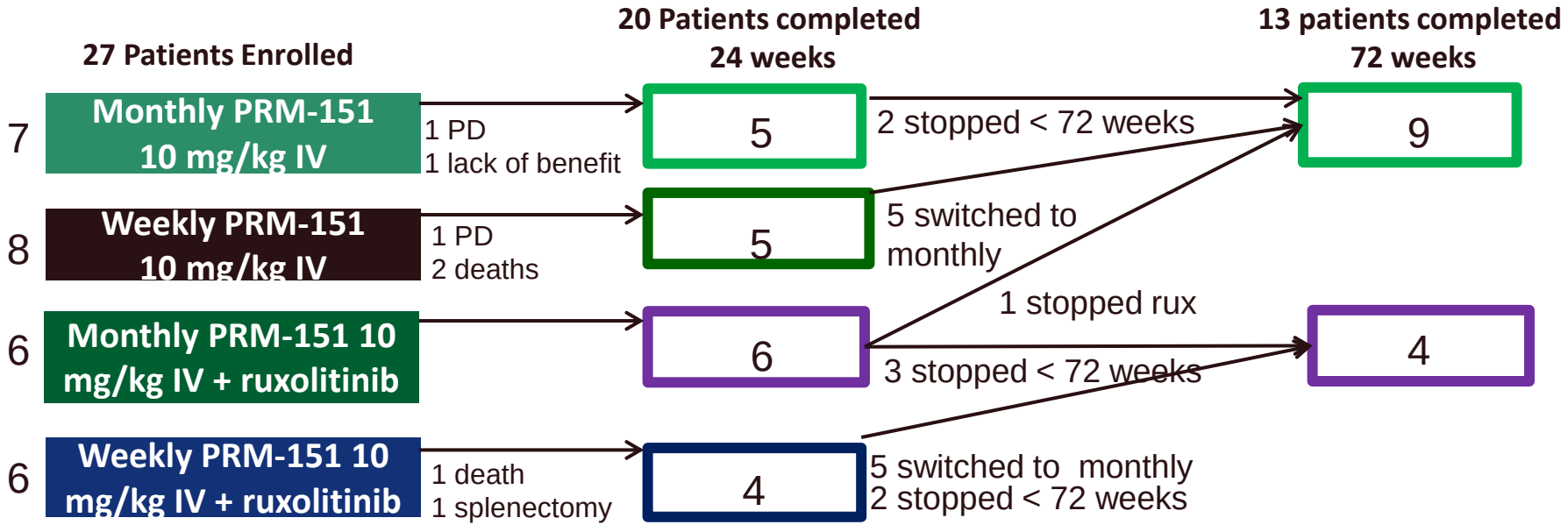
PRM-151: Recombinant Human Pentraxin-2 (PTX-2)

- 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



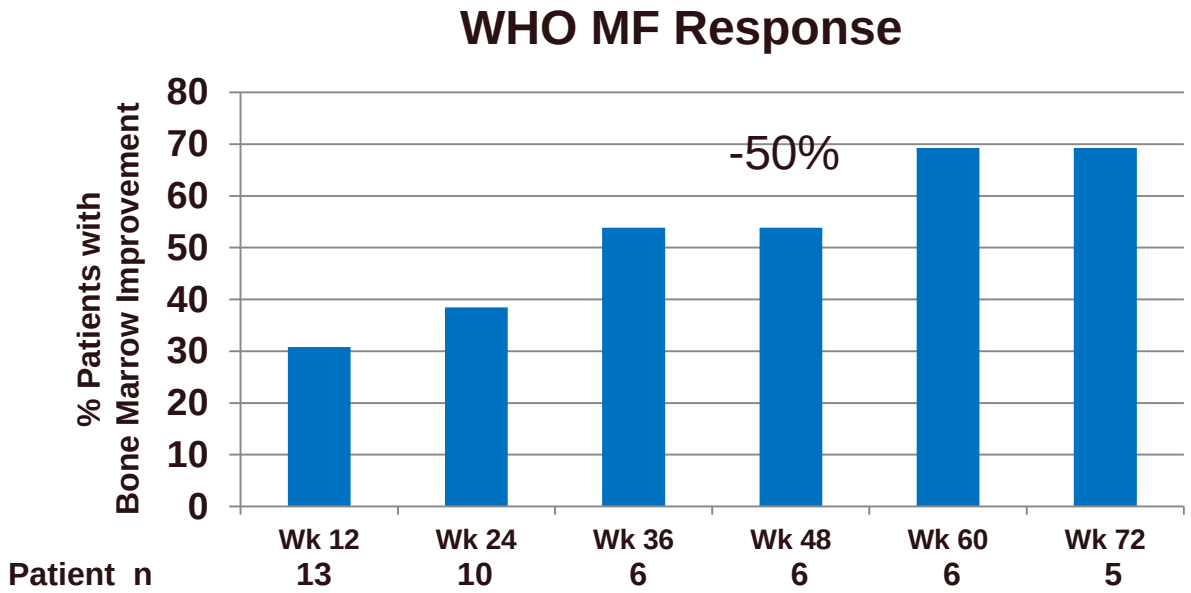
- 24 week treatment period
  - Patients with clinical benefit may continue beyond 24 weeks
- PRM-151 + RUX: stable RUX dose ≥3 months with no decrease in splenomegaly for ≥ 4 weeks
- No eligibility restrictions for anemia, thrombocytopenia, leukopenia, or spleen size

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

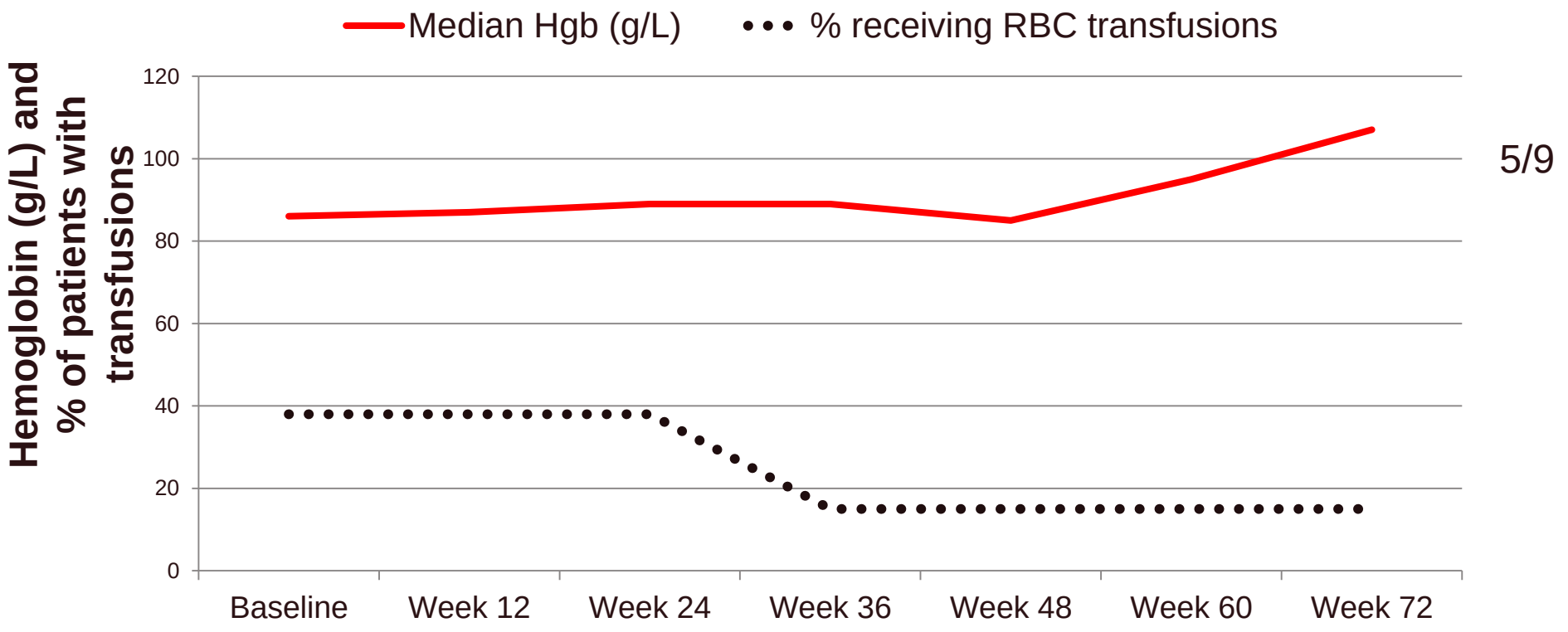
Bone Marrow Fibrosis Improvement as Measured by WHO Criteria



- 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

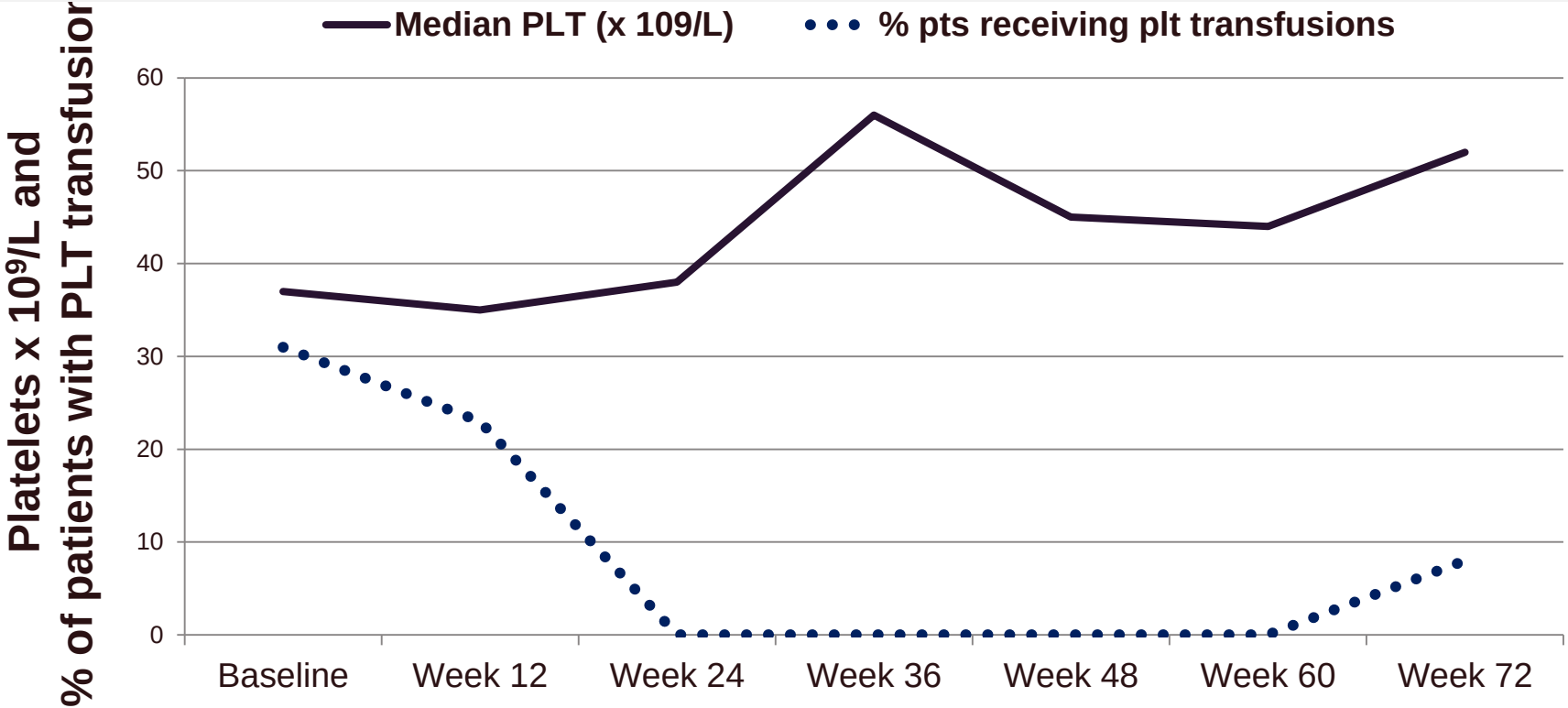
Hemoglobin and RBC Transfusions

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



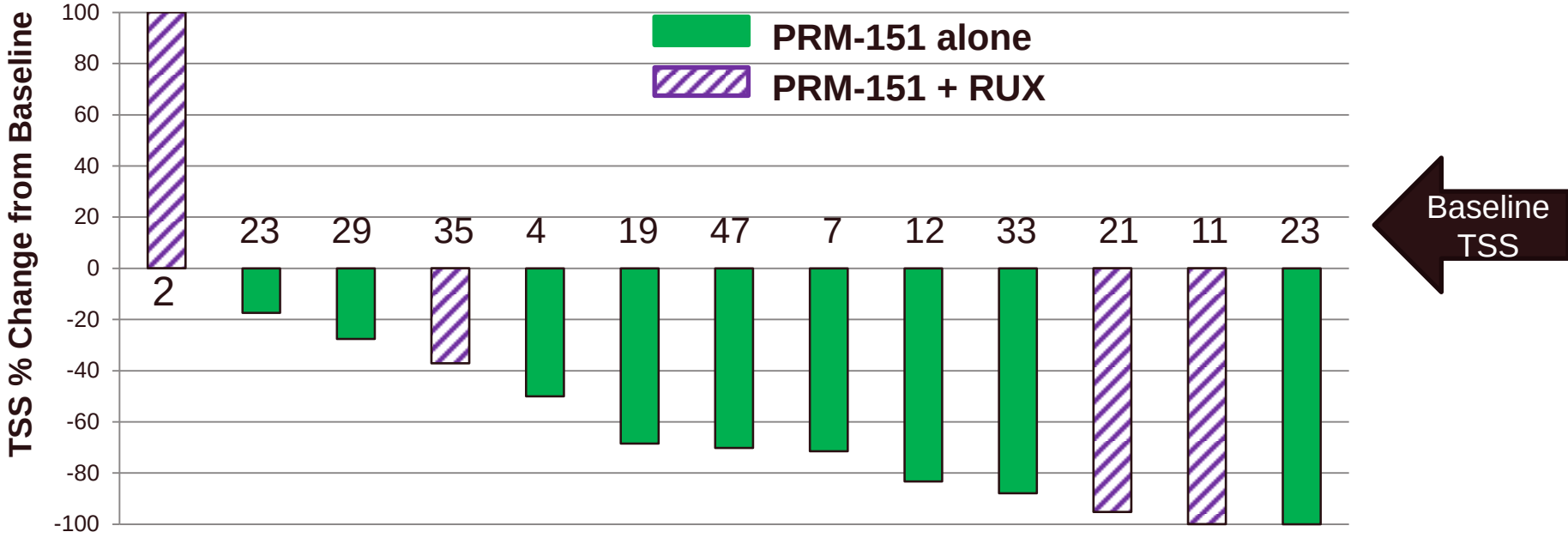
Platelets and Platelet Transfusions

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



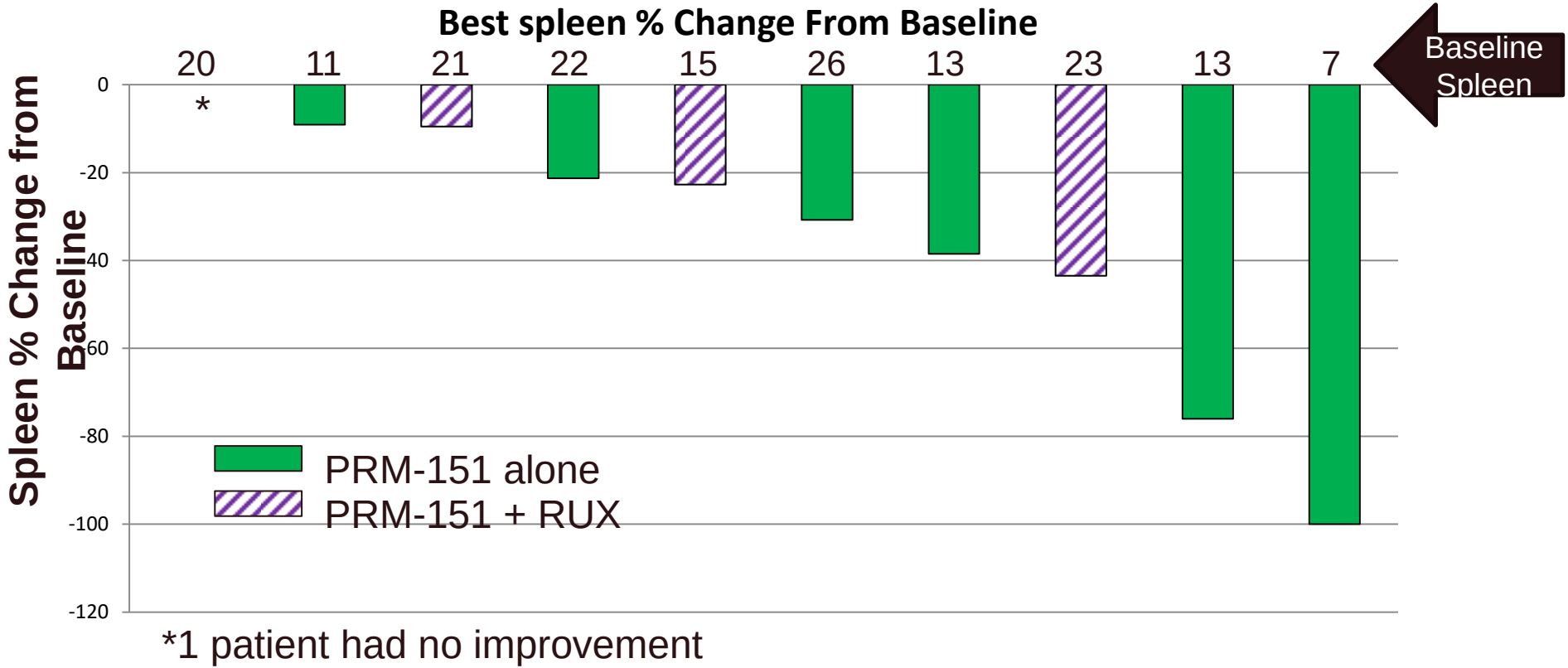
Symptom Improvements

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



Spleen Reductions

Patients with palpable spleen at baseline (n = 10)

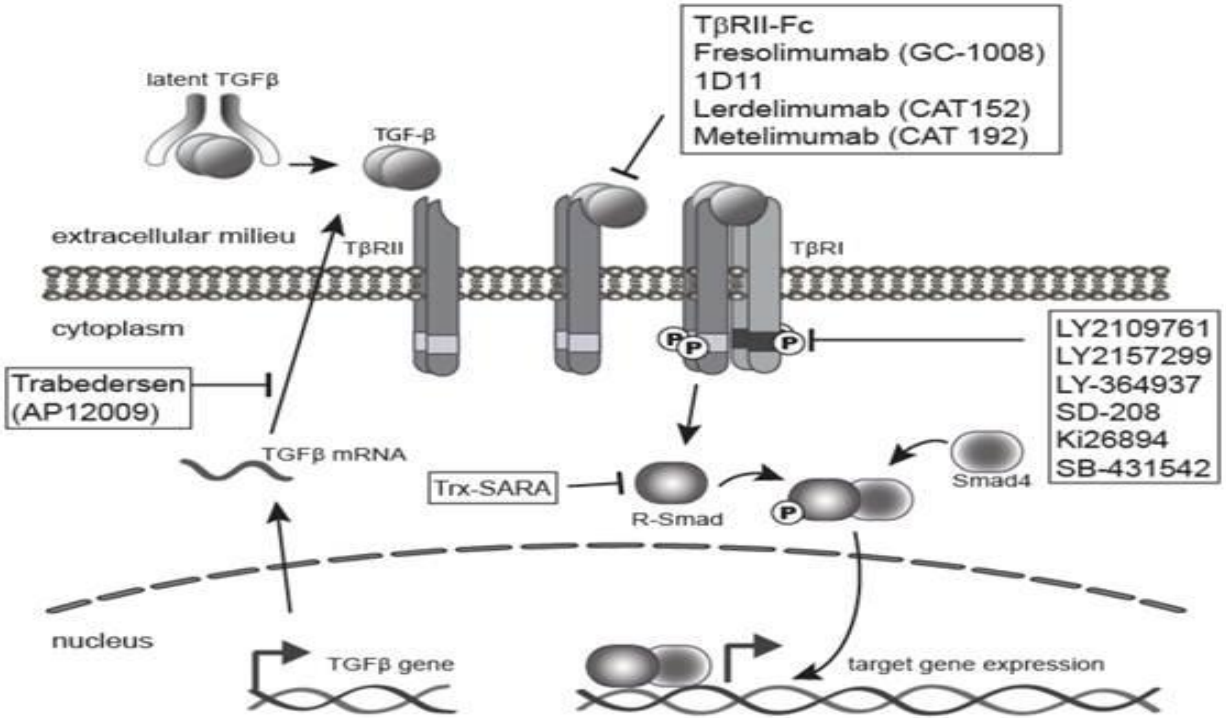


*1 patient had no improvement

Next Steps

- **Stage 2 of this adaptive study has now completed enrollment:**
  - Single agent PRM-151 Q4W x 36 weeks: blinded randomization to 1 of 3 doses
  - Patients may continue beyond 36 weeks in open label extension
  - Eligibility
    - DIPSS Intermediate -1, Intermediate-2, or High Risk
    - WHO Grade 2 or 3 myelofibrosis
  - Patients not candidates for ruxolitinib based on:
    - **EITHER** Hgb < 100 g/L, requiring ≥ 2 units RBC in prior 12 weeks, and intolerance of or inadequate response to ruxolitinib
    - **AND/OR** Platelet count < 50 x 10^9/L

Targeting TGF-β



Connolly et al. Int J Biol Sci 2012; 8(7):964-978

Anti-transforming growth factor beta (TGF-β) therapy in patients with myelofibrosis (NCT01291784)

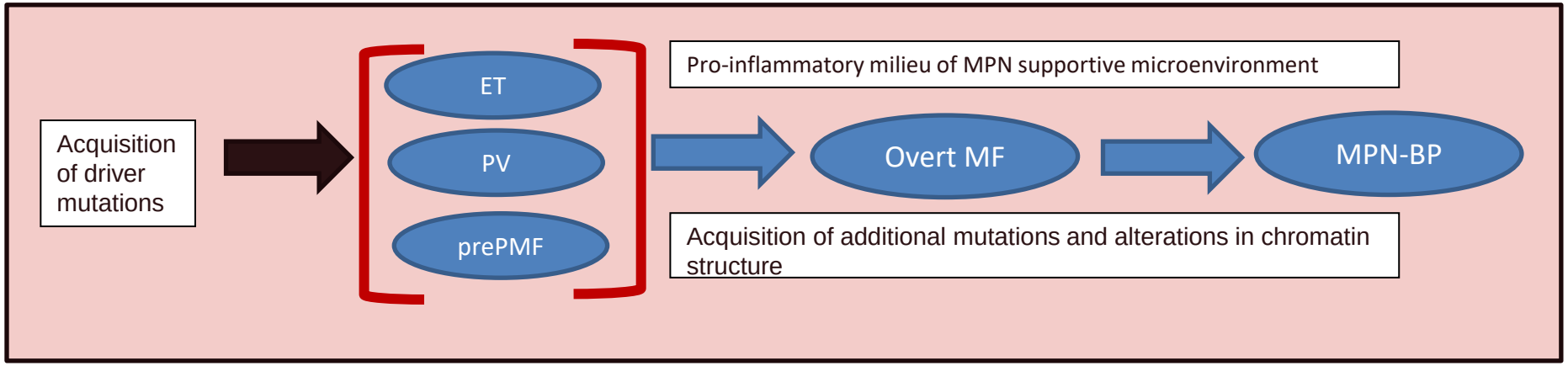
John Mascarenhas[1], Timmy Li[1], Lonette Sandy[1], Carrie Newsom[1], Bruce Petersen[2], James Godbold[3], and Ronald Hoffman[1]

[1]Tisch Cancer Institute, Mount School of Medicine, New York, New York, USA
[2]Department of Pathology, Mount School of Medicine, New York, New York, USA
[3]Department of Preventative Medicine, Mount School of Medicine, New York, New York, USA

Icahn School of Medicine at Mount Sinai

MPN-RC APPROACH TO TRANSLATIONAL RESEARCH

Model for MPN Disease Progression



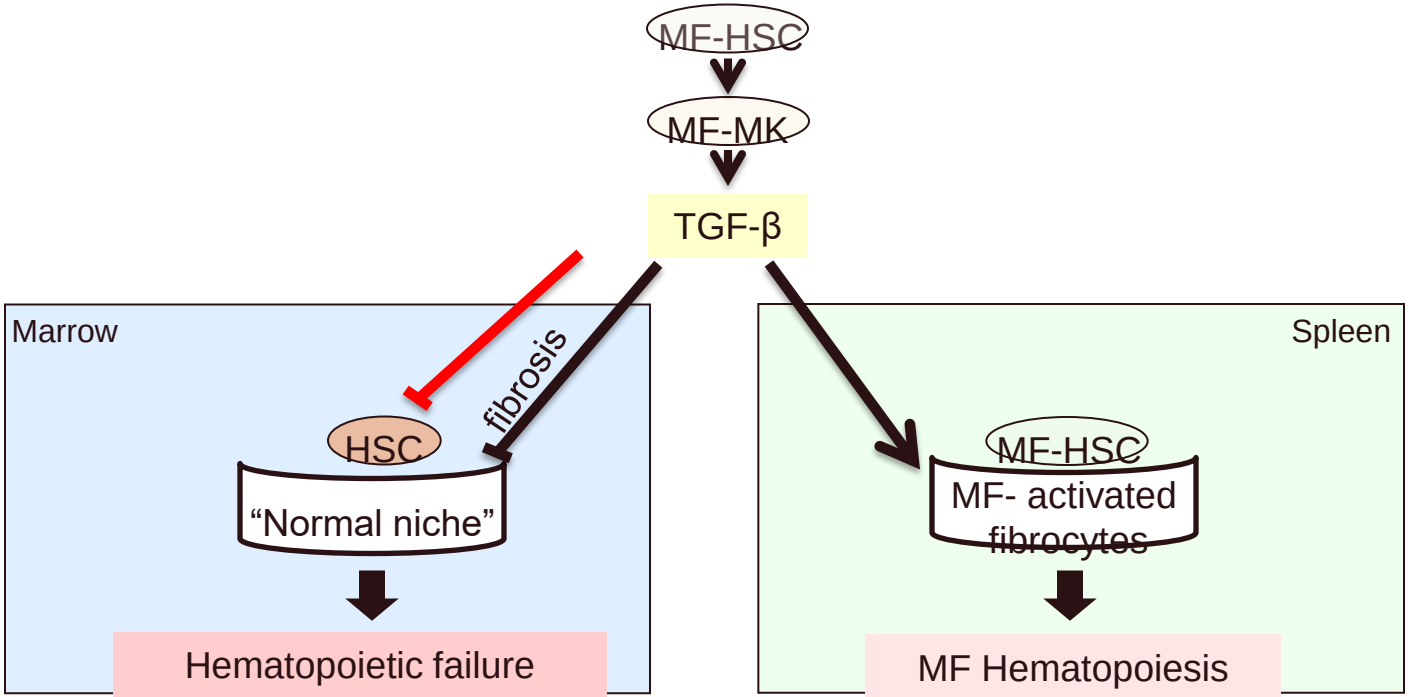
In solid tumors, disease progression is favored by a TGF-β circuit that promotes proliferation of cancer stem cells

- Cancer stem cells activate a TGF-β-dependent process(s) that leads to formation of activated fibroblasts (CAF).
- CAF provide the “niche” that support proliferation of cancer stem cells.

Orimo & Weinberg, Cell Cycle. *5*:1597, 2006

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



Myeloproliferative Disorders-Research Consortium (MPD-RC)
MPD-RC Protocol # 118
Phase II study of Galunisertib in patients with myelofibrosis

Mandatory Companion Protocol MPD-RC 107

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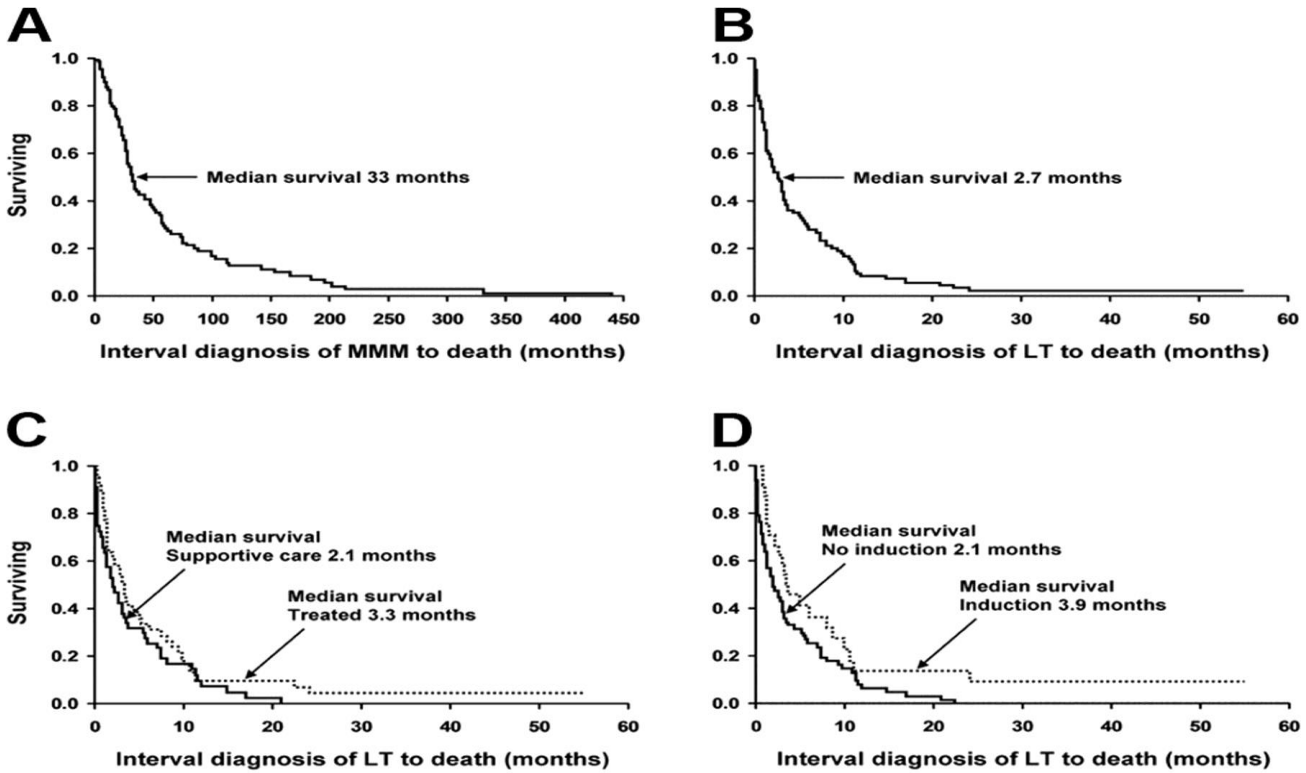
Emerging Treatments

- JAK2 inhibitor based combination trials in MF
- Telomerase Inhibition in MF (not covering ET)
- Anti-Fibrotic therapy in MF
- JAK2i + DNMTi combination in MPN-AP/BP
- MDM2 antagonist therapy in PV

Kaplan-Meier survival curves of 91 patients with MF



Mesa R A et al. Blood 2005;105:973-977

blood

11 patients with MPN-BP
Mount Sinai Experience

	DECITABINE (6 pts)	HSCT (5pts)
Median age (years)	72	58
PMF, Post ET/PV MF, MDS/MPN	0,3,1,2	1,3,0,1
JAK2V617F	50%	0%
Unfavorable karyotype	50%	80%
Median # Cycles of DEC (range)	5.5 (2,14)	4*
Median Overall Survival from MF in months (range)	33 (12, 152+)	25 (12,165+)
Survival from BP (median, range)	Not yet reached at 9 months (5,45+)	Not yet reached at 20 months (9,23)

*One patient received 4 cycles of DEC and then received HSCT

Mascarenhas et al. Leuk Res. 2010 Sep;34(9):1246-9.

Icahn School of Medicine at Mount Sinai

Phase II ruxolitinib in patients with refractory leukemia (NCT00674479)

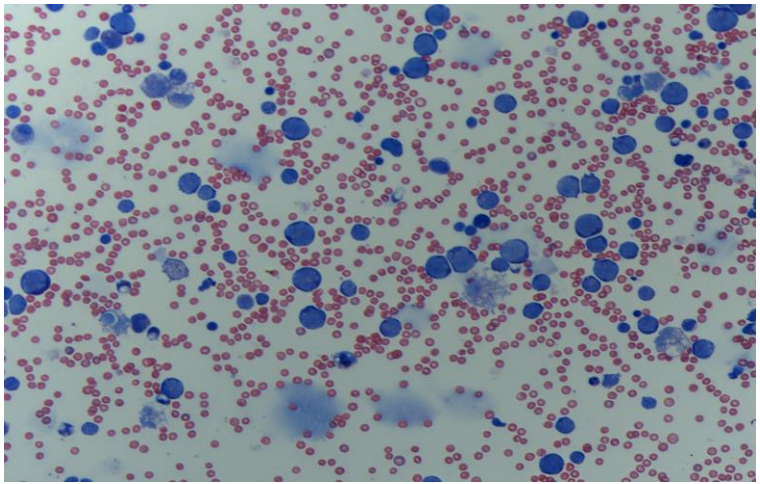
- Single center Phase II
- 38 patients
- Median age 69 years
- Median (range) cycles: 2 (1,22)
- 18 MPN-BP patients
- 12 (31%) JAK2V617F-positive
- Well tolerated, grade 3/4 in 4 patients
- 3 CR/CRi

Eghtedar et al. Blood. 2012 May 17;119(20):4614-8.

*Jak2*V617F/*Tp53* null mice develop Acute Myeloid Leukemia

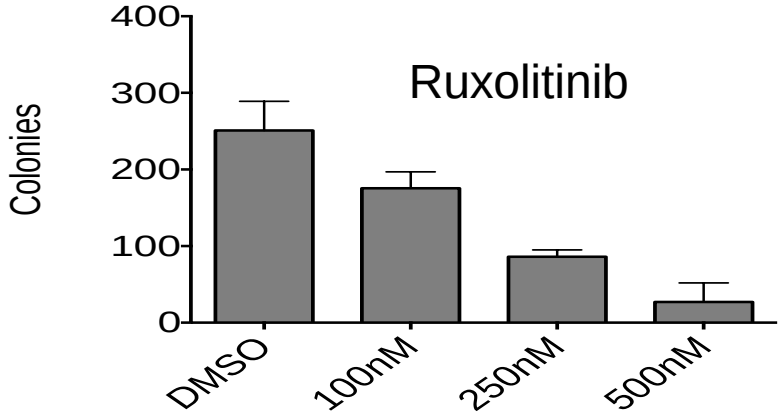
Tp53 wildtype mice (control)

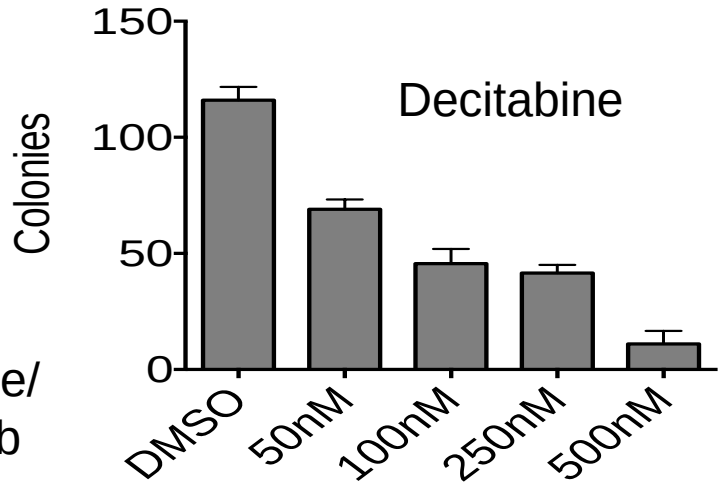
Tp53 null mice

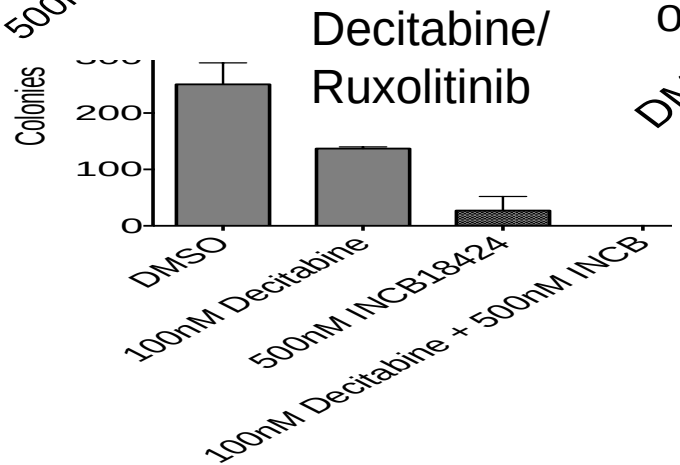


Rampal et al. Proc Natl Acad Sci U S A. 2014 Dec 16;111(50):E5401-10

Spectrum of anti-leukemic agents demonstrate efficacy in murine post-MPN AML







Rampal et al. Proc Natl Acad Sci U S A. 2014 Dec 16;111(50):E5401-10

Myeloproliferative Disorders-Research Consortium (MPD-RC)
MPD-RC 109
Combination Therapy of Ruxolitinib and Decitabine in patients with Myeloproliferative Neoplasms in Accelerated and Blast Phase Disease

NCT02076191

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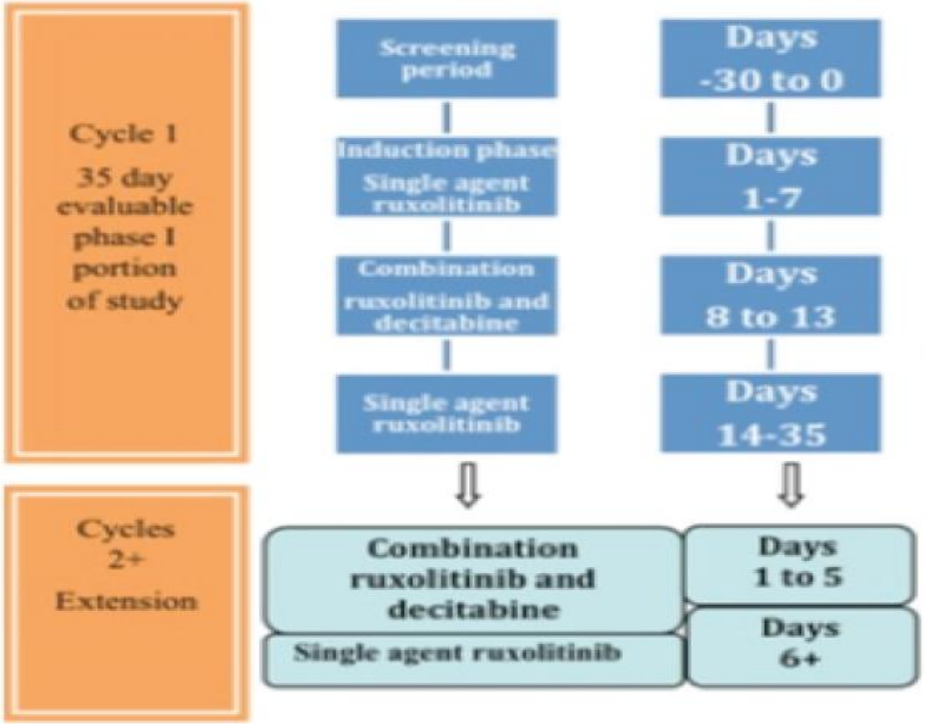
Study Schema

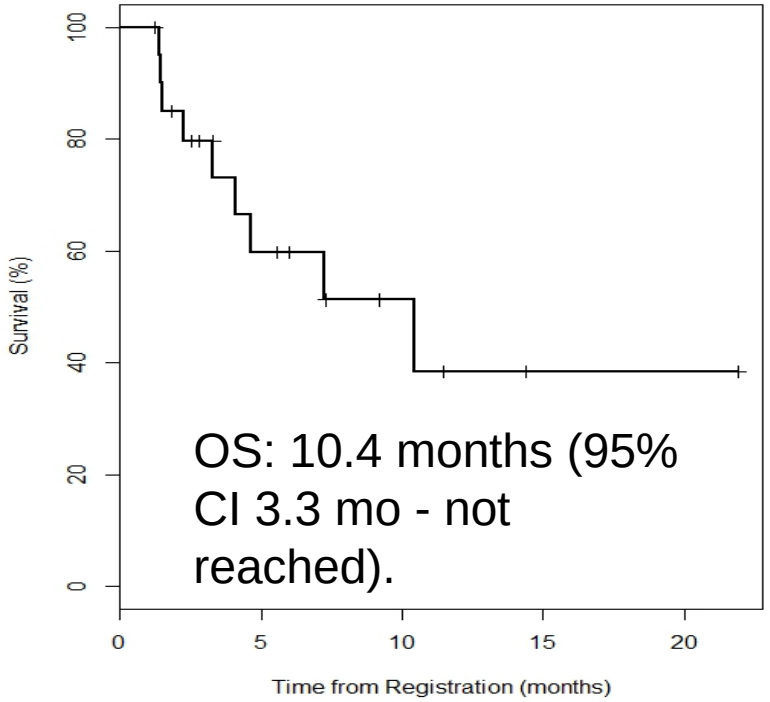


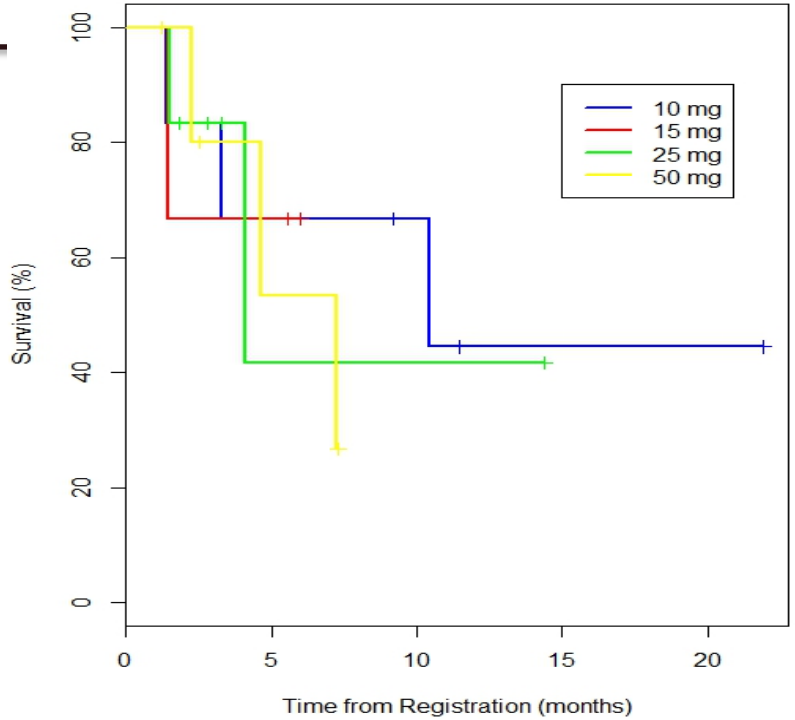
Dose level	Ruxolitinib dose
-1	5mg PO BID
1	10mg PO BID
2	15mg PO BID
3	25mg PO BID
4	50mg PO BID

Response

	10mg BID	15mg BID	25mg BID	50 mg BID	Total
CR	-	-	1 (17%)	1 (17%)	2 (10%)
CRi	1 (17%)	-	1 (17%)	3 (50%)	5 (24%)
PR	2 (33%)	2 (67%)	1 (17%)	-	5 (24%)
NR	3 (50%)	1 (33%)	3 (50%)	2 (33%)	9 (43%)
CR/CRi	**1 (17%)**	**-**	**2 (33%)**	**4 (67%)**	**7 (33%, 95% CI 15-57%)**
Overall response rate (CR/CRi/PR)	**3 (50%)**	**2 (67%)**	**3 (50%)**	**4 (67%)**	**12 (57%, 95% CI 34-78%)**

Survival





	10mg	15mg	25mg	50mg	Total
Median cycles received (range)	10.5 (1-22)	4.0 (1-6)	2.0 (1-16)	2.5 (1-7)	3.0 (1-22)

Emerging Treatments

- JAK2 inhibitor based combination trials in MF
- Telomerase Inhibition in MF (not covering ET)
- Anti-Fibrotic therapy in MF
- JAK2i + DNMTi combination in MPN-AP/BP
- MDM2 antagonist therapy in PV

P53/MDM2 in MPNs

- P53 regulates cell cycle, apoptosis, DNA repair, and senescence
- Wild type p53 seen in chronic phase MPN
- Inactivating p53 mutations frequency in MPN-BP
- Down regulation of p53 by MDM2 overexpression
  - Promotes proteosomal degradation
  - Inhibits p53 transcription
  - Inhibits transactivation
  - Facilitates export from nucleus

Nakatake M et al. Oncogene,. (2012) 31 (10) 1323-33.
Shangary and Wang. Clin Cancer Res. (2008) 14 (17) 5318-24

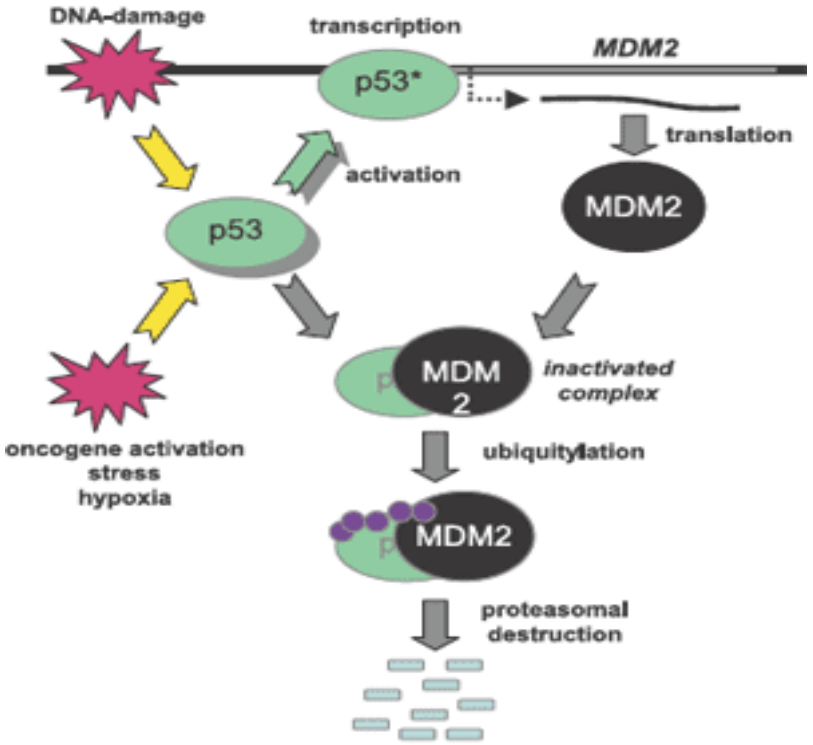
JAK2V617F, MDM2, La autoantigen, P53

Nakatake et al. Oncogene (2012) 31, 1323–1333

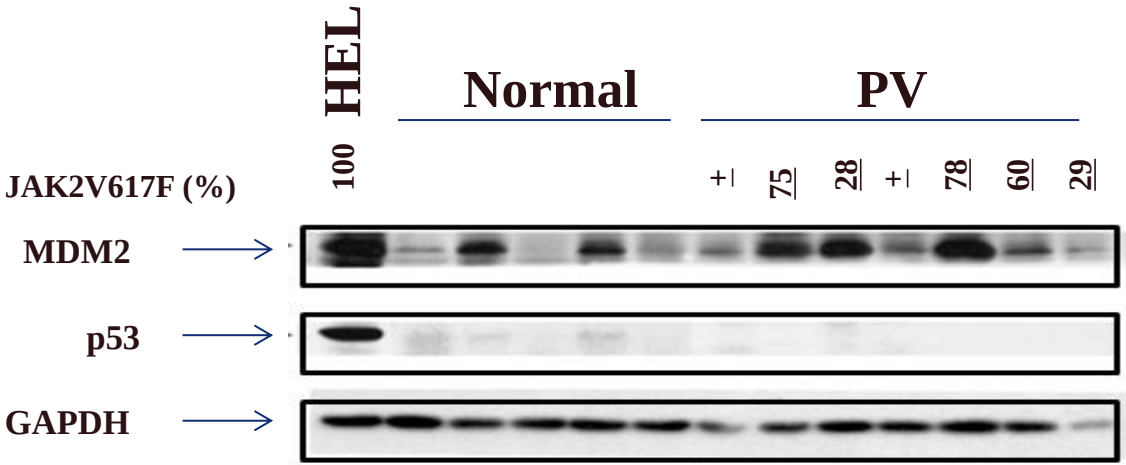
Lu M et al. Blood (2012)11; 120(15):3098-105

Cassinat and Kiladjian (2012) Blood. 11;120(15):2933-4.

Lu and Hoffman Oncotarget (2012) 3 (10) 1052-1053.



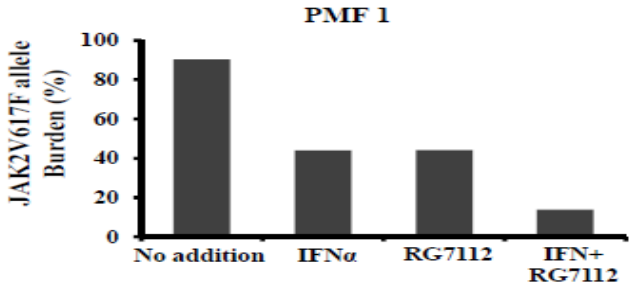
PV CD34+ cells contain higher levels of MDM2



Lu M et al. Blood. 2012 Oct 11;120(15):3098-105

Treatment with low doses of RG7112 and Peg-IFNα 2a reduced the numbers of JAK2V617F-positive cells in NOD/SCID mice

A.



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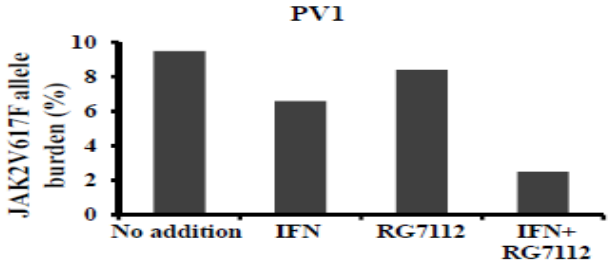
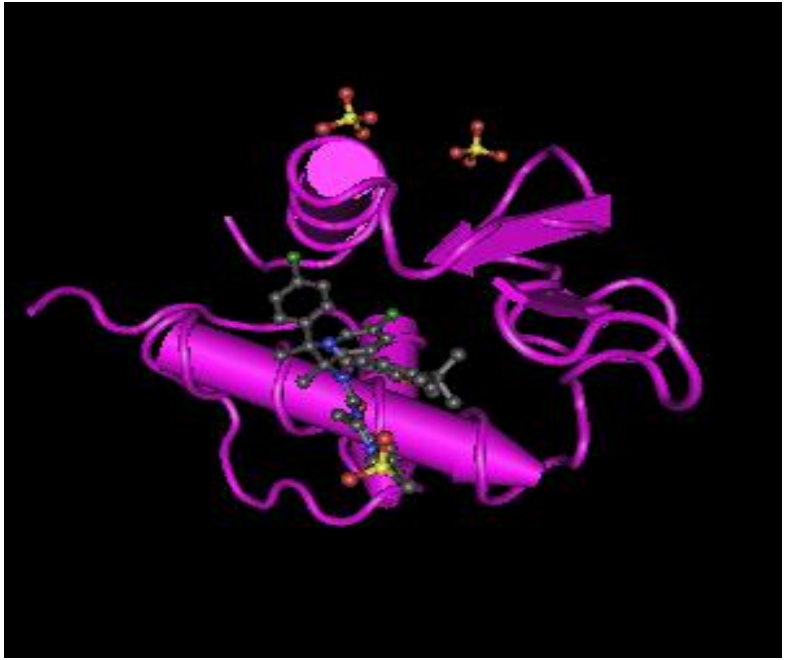


Lu et al. Blood May 28 2014.

RG7388 (Idasanutlin)

- Roche compound 2nd generation nutlin family member
- Oral selective small molecule inhibitor of MDM2
- Improved pharmacological properties over RG7112



Open Label Phase I Study of Single Agent Oral RG7388 in Patients with Polycythemia Vera and Essential Thrombocythemia
(With pilot feasibility study in combination with pegylated interferon alfa 2a for patients who do not respond to the single agent at each dose level)

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Future Direction- 5 year view summary

- Combination studies
- Molecularly personalized approaches
  - IDH inhibitor
- Immunomodulation
  - PD-1 pathway
  - Dendritic vaccine
- Gene editing CRISPR?
- CAR-T?
- Optimizing Hematopoietic stem cell transplantation

Conclusions

- The portfolio of trials available indicate continued and sincere interest in developing better therapies for MPN
- Combination therapy is the mainstay of treatment for most malignancies and the future of MPN therapy
- Genetic and epigenetic insights gained today inform the therapies of tomorrow
- Clinical trial participation drives us closer to cure
- It will happen

Thank You

Mount Sinai MPD Program

Icahn School of Medicine at Mount Sinai

Myeloproliferative Disorders Research Consortium
MPD-RC