THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Evolving Management of Myelofibrosis

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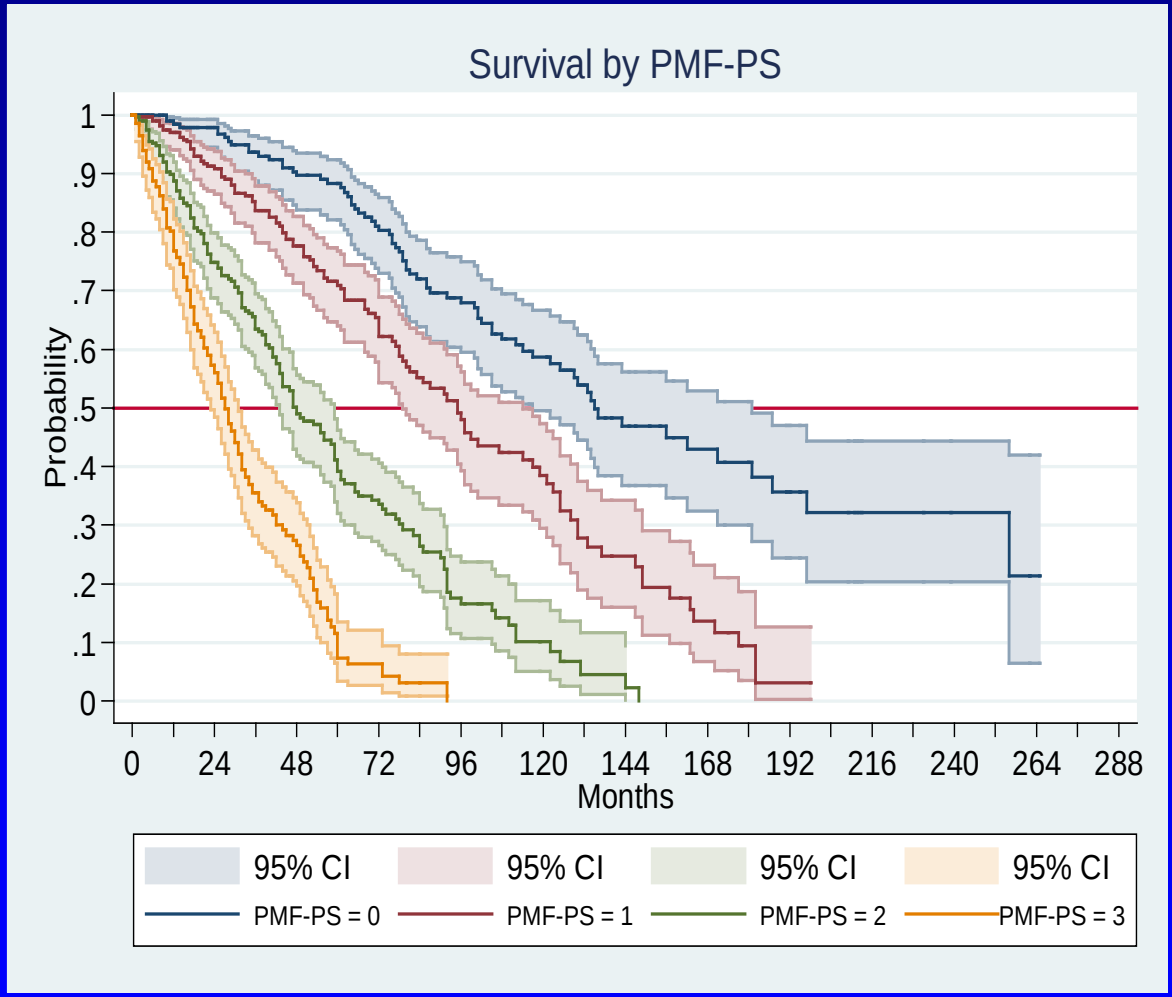
Why do we prognosticate? International Prognostic Scoring System (IPSS) in Primary Myelofibrosis

Prognostic factors

- Age > 65 years
- Constitutional symptoms
- Hb < 10 g/dL
- Leukocytes > 25 x 10^9/L
- Blood blasts ≥ 1%

Risk groups #factors

• Low	0
• Intermediate-1	1
• Intermediate-2	2
• High	≥ 3



Allogeneic SCT in Myelofibrosis

- Consider in younger, higher risk patients whose survival is expected to be <5 years

IPSS high risk	Median survival: ~27 mo
IPSS intermediate-2 risk	Median survival: ~48 mo

- Traditionally limited to patients aged <60 years and those with HLA-identical sibling match
- High transplant related mortality due to acute and chronic GVHD
- Estimated 1-year treatment-related mortality: approximately 20-30%
  - Overall survival with alloSCT: approximately 50-70%

BOTTOM LINE: less than 10% of patients undergo SCT

Patients are treated for specific problems, not based on prognosis

Medicines for Anemia

- *Prednisone*
- *Androgens*
- *EPO*
- *Thalidomide or Lenalidomide +/- prednisone*

Medicines for Spleen

- *Ruxolitinib*
- *Hydroxyurea*
- *Busulfan*
- *2-CDA*

- *Splenectomy*
- *Splenic Radiation*

Medicines for Symptoms

- *Ruxolitinib*
- *Prednisone*

Dynamic IPSS in Primary MF

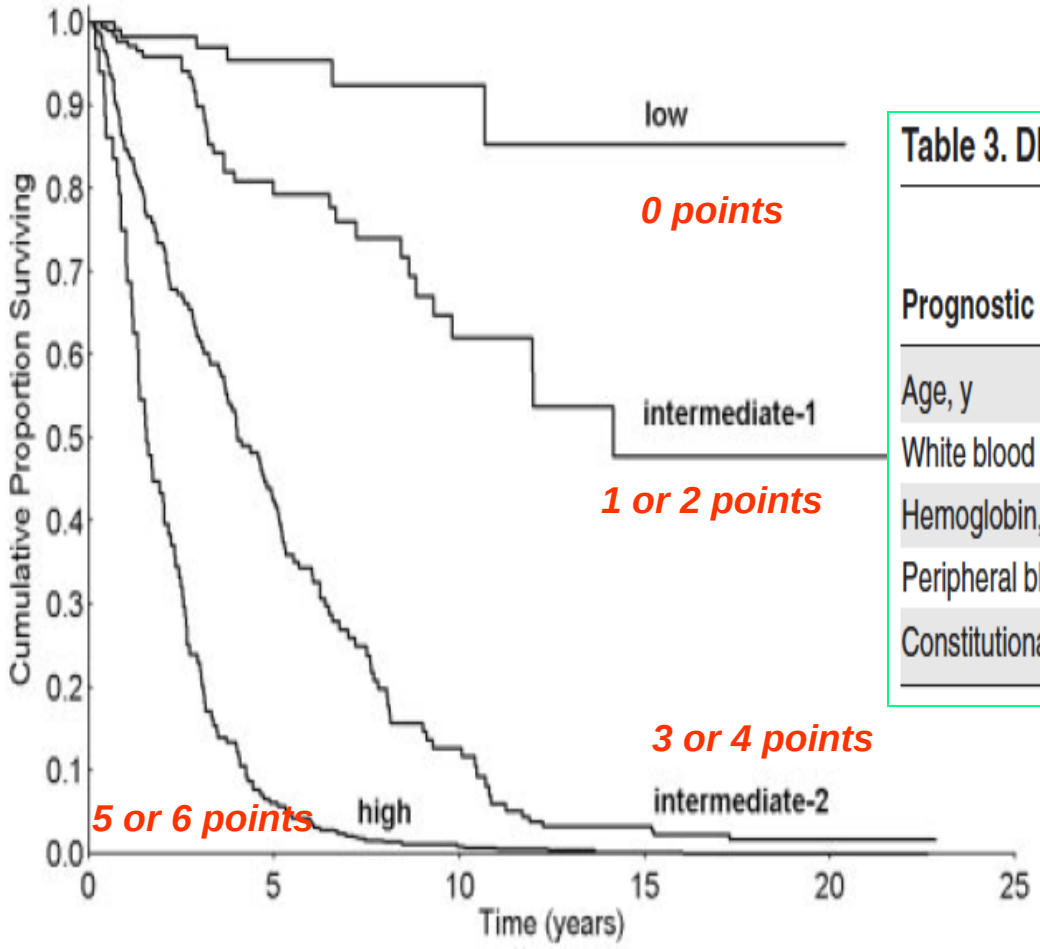


Table 3. DIPSS for survival in primary myelofibrosis

Prognostic variable	Value 0	1	2
Age, y	≤ 65	> 65	
White blood cell count, $\times 10^9$/L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional symptoms, Y/N	N	Y	

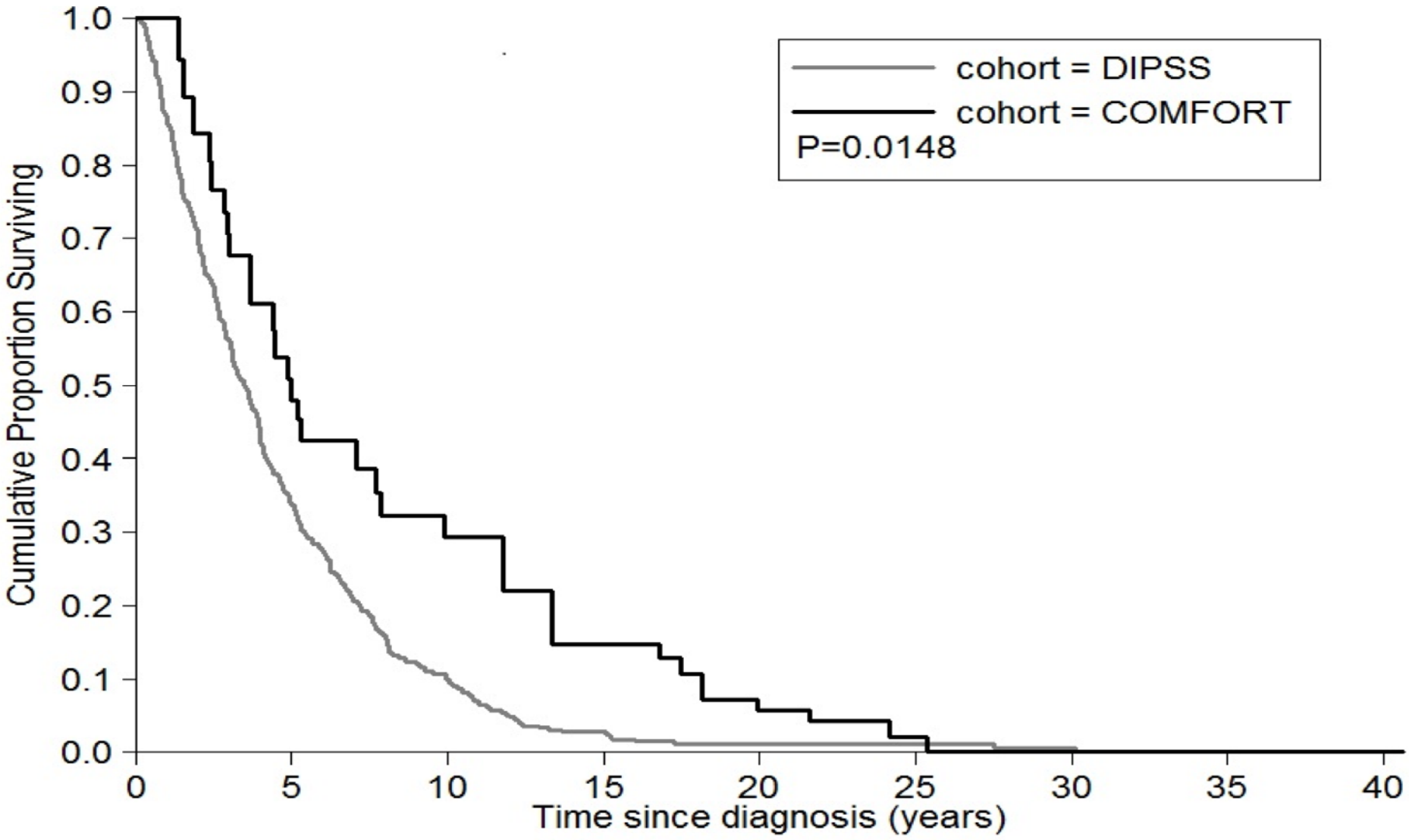
How accurate is prognostication during the disease course?

Impact Of Ruxolitinib On The Natural History Of Patients With Primary Myelofibrosis

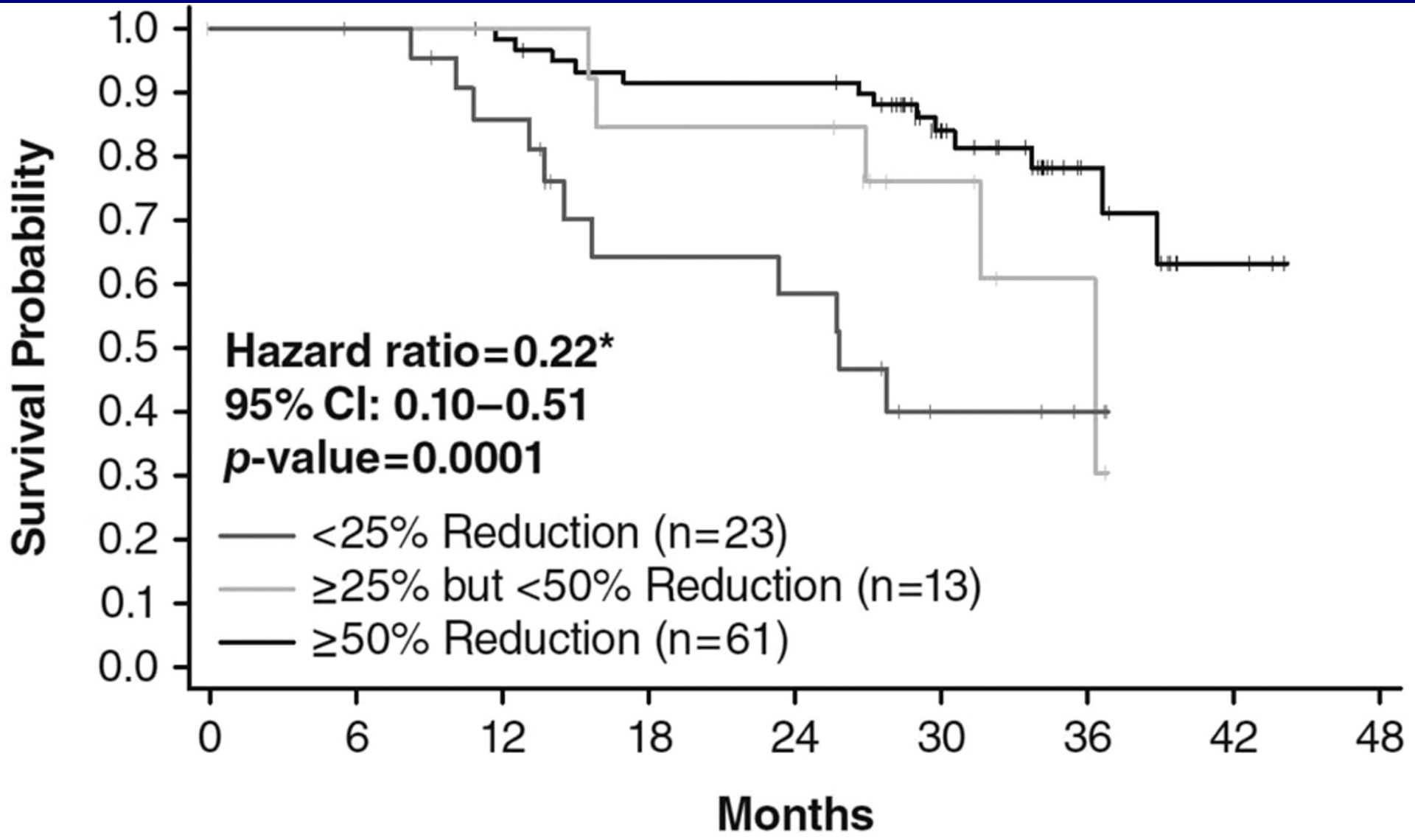
	COMFORT-2 cohort	DIPSS cohort
Patients	100	350
Deaths (%)	30 (30%)	258 (86%)
10- year survival probability (95% CI)	29.3% (14.4-45.9)	9.8% (6.5-14)
Logrank test	P=0.0148	
Hazard ratio (95% CI)	0.61 (0.4-0.91)	

Patients who introduced ruxolitinib at some point during their disease history (COMFORT-2) had a better survival when compared to those who continued standard treatments for the whole follow-up (DIPSS)

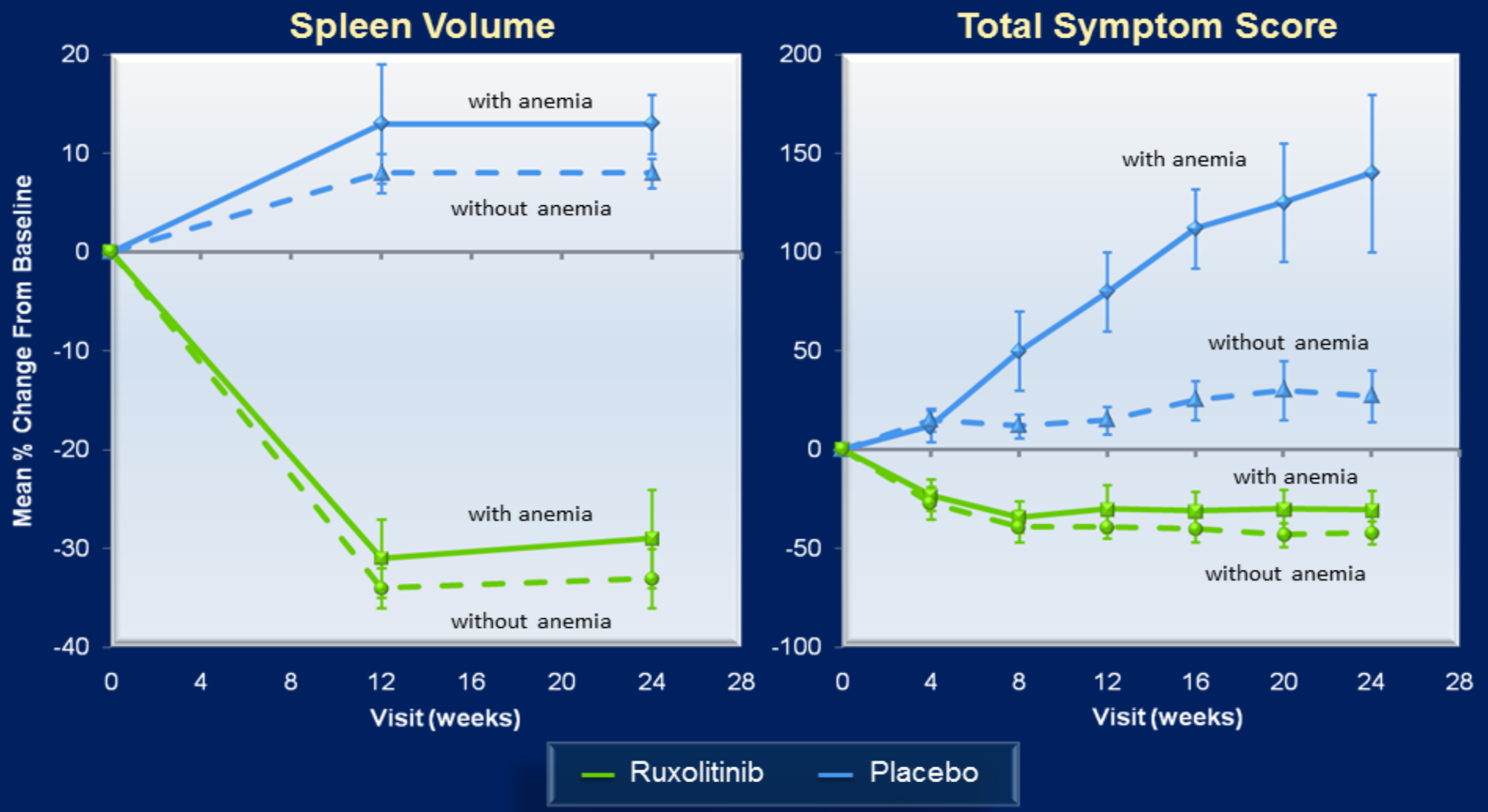
Impact Of Ruxolitinib On The Natural History Of Patients With Primary Myelofibrosis



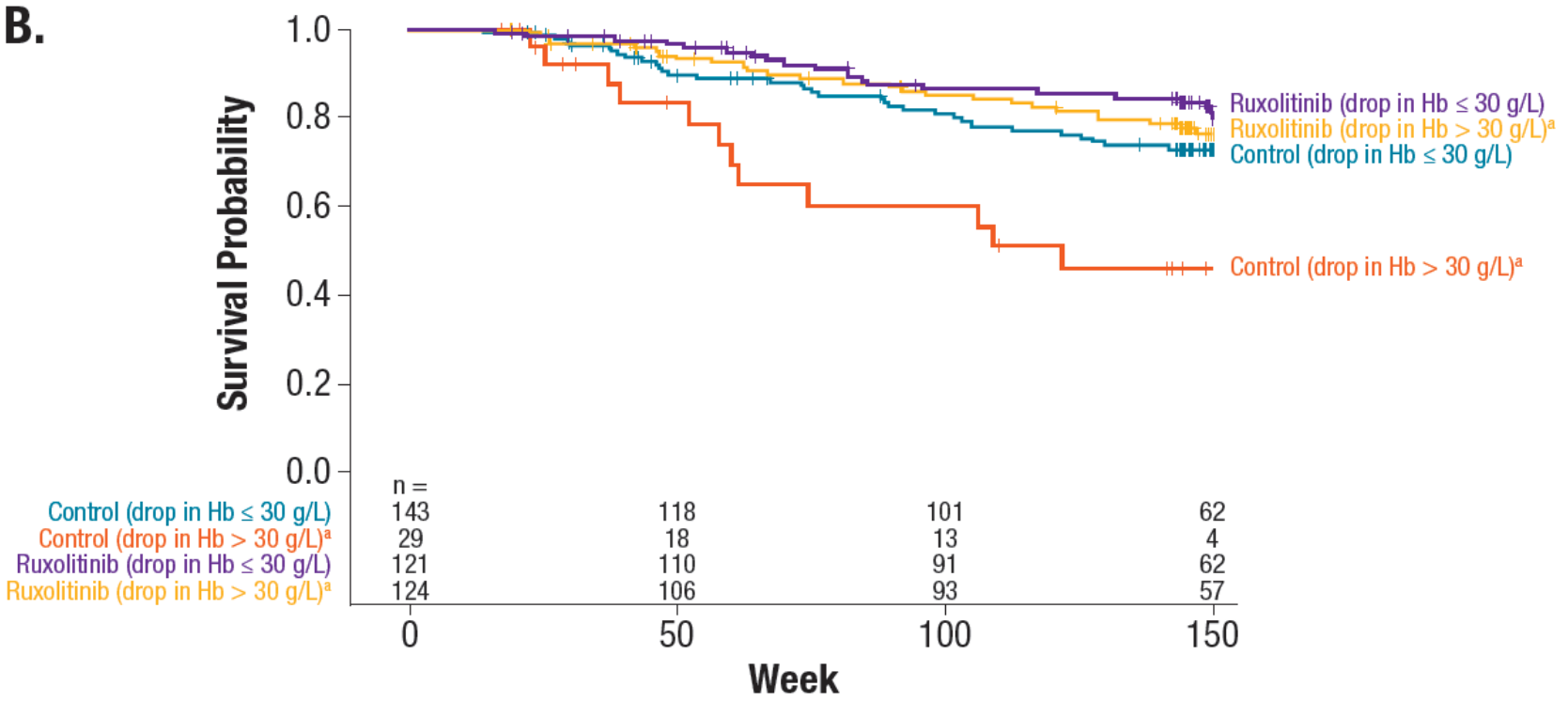
Overall survival of patients by degree of splenomegaly reduction



Development of Anemia Does not Affect Response to Ruxolitinib Treatment



Ruxolitinib Overcomes the Adverse Prognostic Effect of Anemia in Patients With Myelofibrosis



Hemoglobin changes on ruxolitinib treatment do not bear the same prognostic implications as hemoglobin changes that occur as a consequence of MF pathology

Transient hemoglobin changes during ruxolitinib therapy initiation should not lead to premature interruption or discontinuation; dose adjustment may be needed

We need more than one JAK2 inhibitor

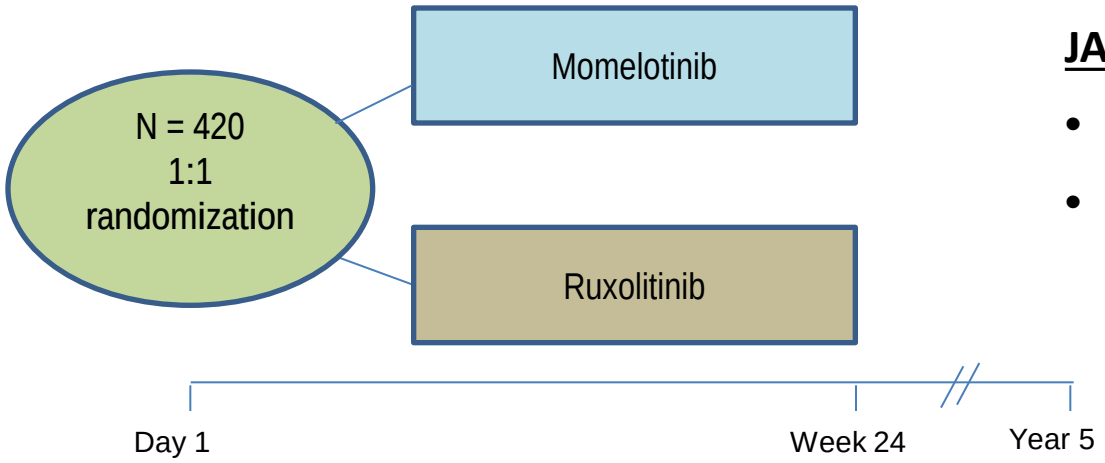
PACRITINIB (JAK2 Inh.) Phase 3 MF Trial

PERSIST-2

Sites: USA and EU

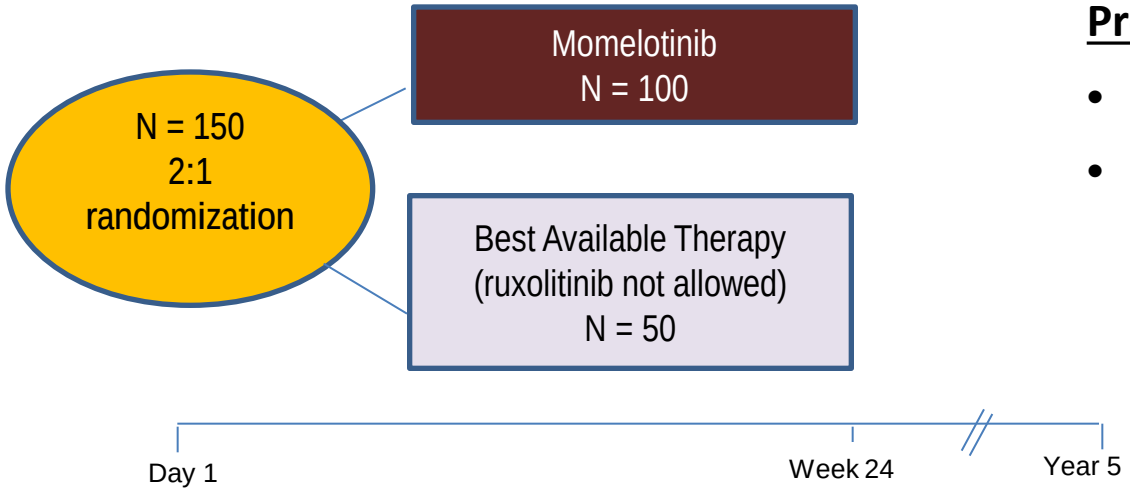
*Cross-over from BAT allowed after progression or assessment of the primary endpoint.

Phase 3 Studies with Momelotinib (JAK inh.) for Myelofibrosis



JAK inhibitor naïve

- Randomized, Double Blind
- Primary endpoint: Spleen Response by MRI at week 24



Previous JAK inhibitor exposure

- Randomized, Open Label
- Primary endpoint: Spleen Response by MRI at week 24

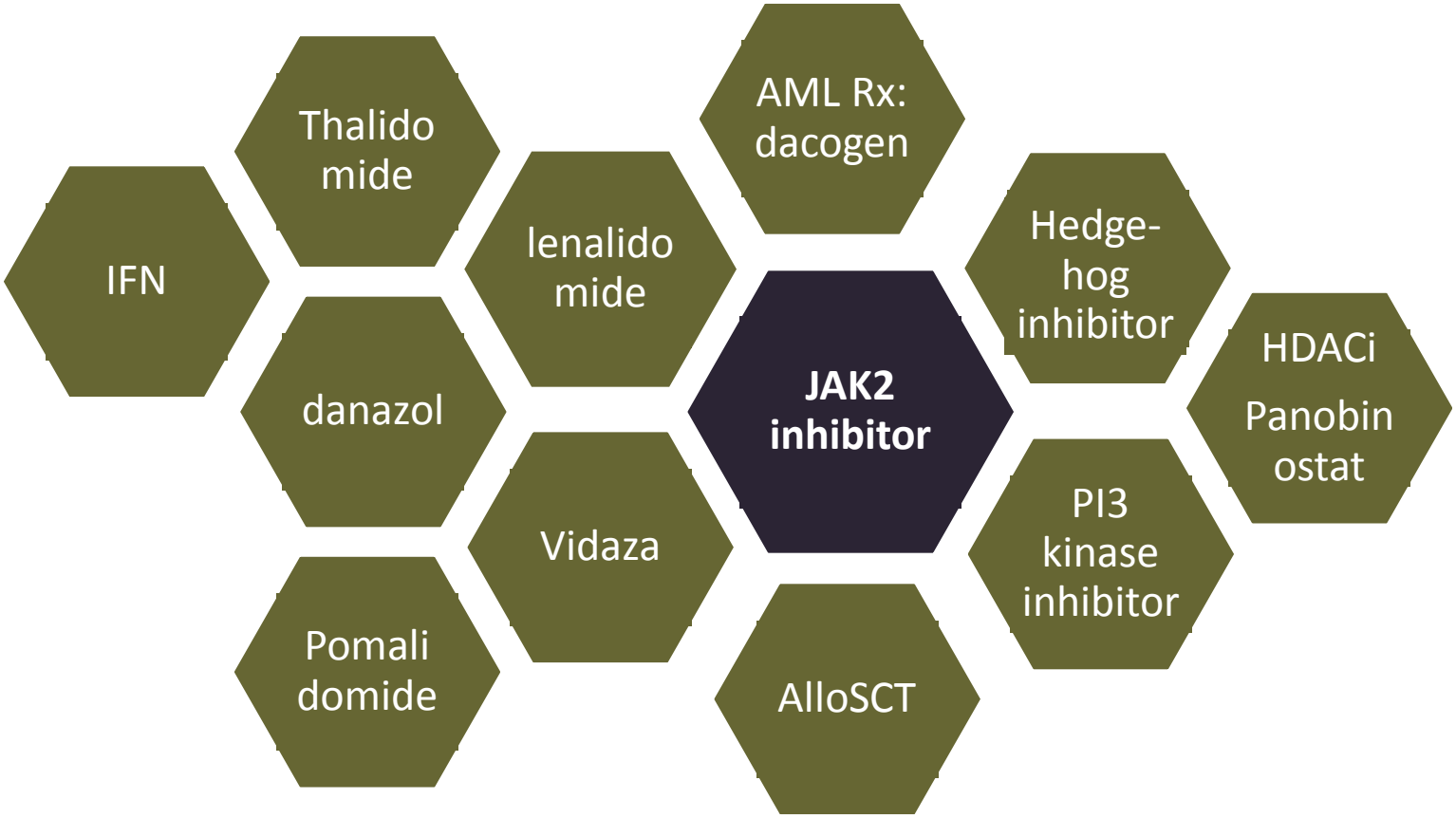
NS018 JAK2 Inh. Results of Phase 1

- Of evaluable patients, 53% (19/36) achieved a ≥50% reduction in spleen size.
- Among evaluable patients who had received prior JAK2 inhibitor treatment, 47% (9/19) achieved a ≥50% splenic size reduction.
- Clinical improvement in hemoglobin was recorded in four patients, and clinical improvement in platelets in one patient.
- Reductions in MF-SAF symptom score were observed for all symptoms by Week 4.

- The Phase 2 portion of the study is ongoing and only includes patients who have received prior JAK2 inhibitor treatment

Optimizing MF Therapy

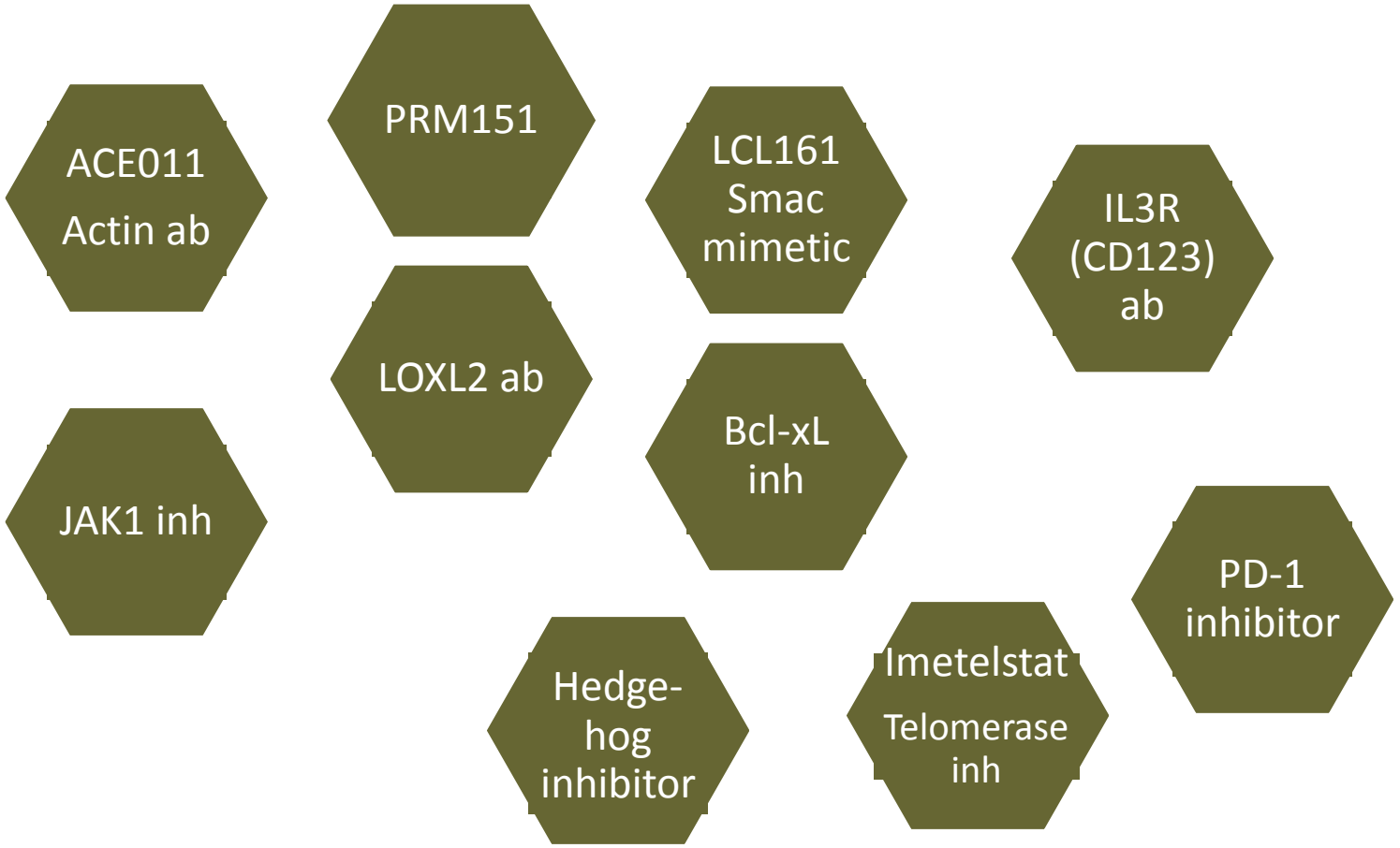
Potential combination partners
with JAK2 inhibitor



Goal is to improve response with JAK2 inh, or bring additional benefits (anemia or bone marrow improvement), if safe (!)

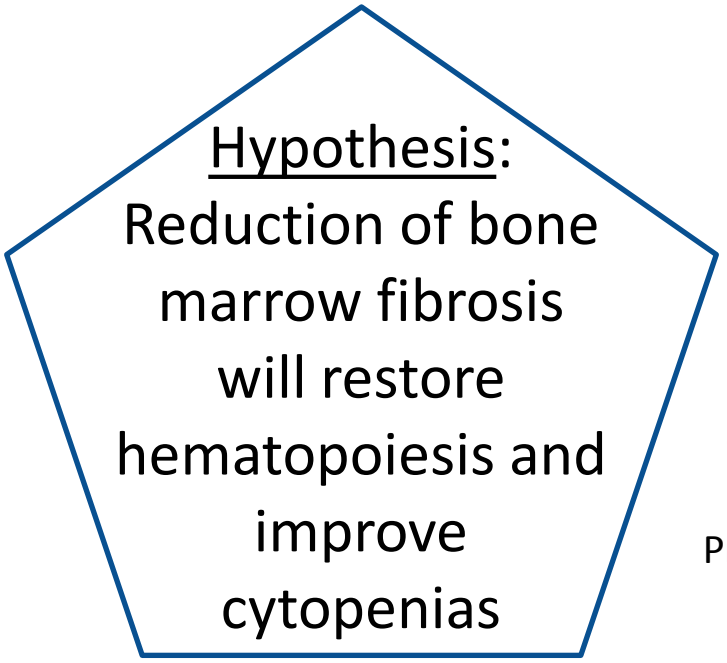
Optimizing MF Therapy

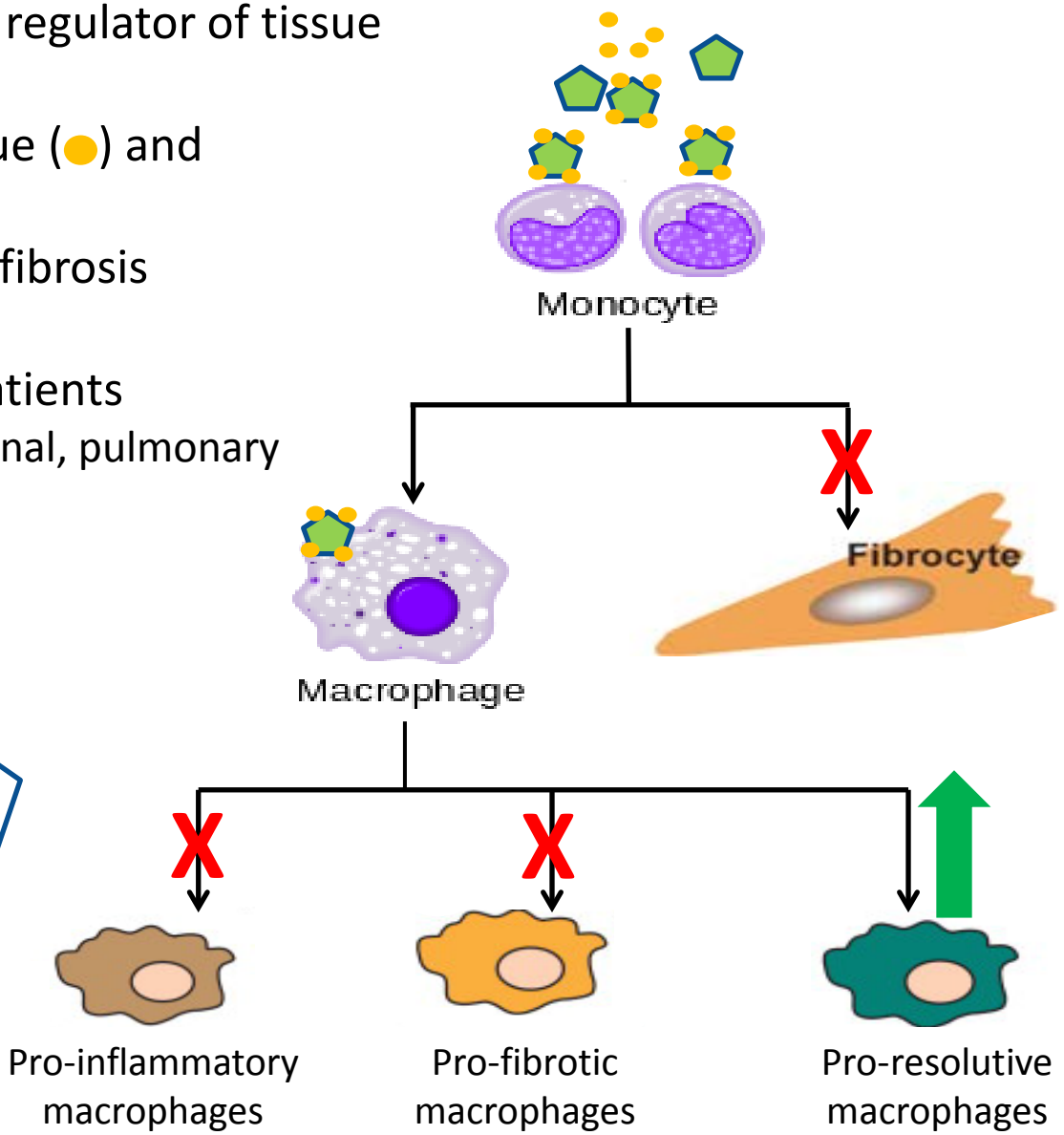
New targets



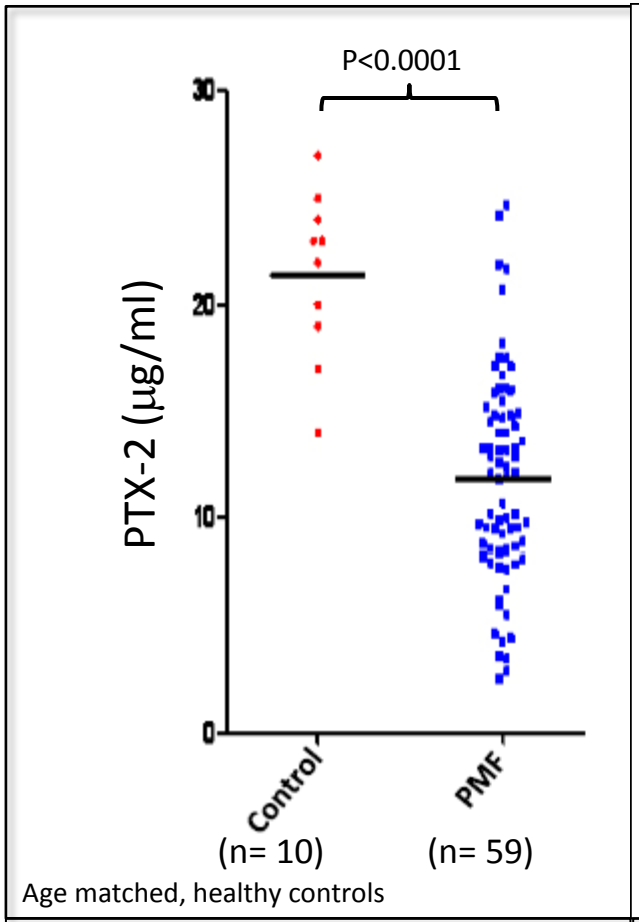
PRM-151: Recombinant Human Pentraxin-2 (PTX-2)

- 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



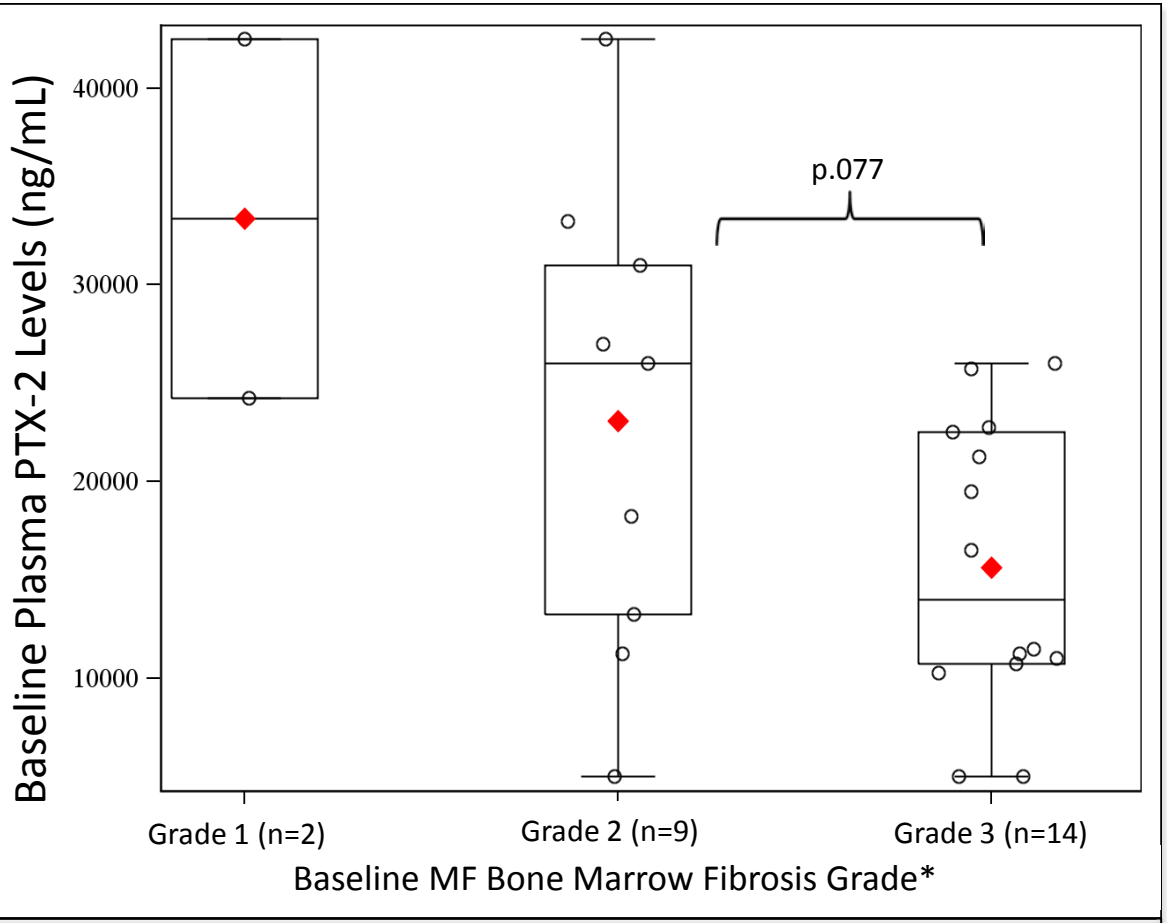


Baseline PTX-2 Plasma Levels are Lower in Patients with MF: Levels Decline with Increasing Bone Marrow Fibrosis Grade



Age matched, healthy controls

Independent study, Verstovsek et al



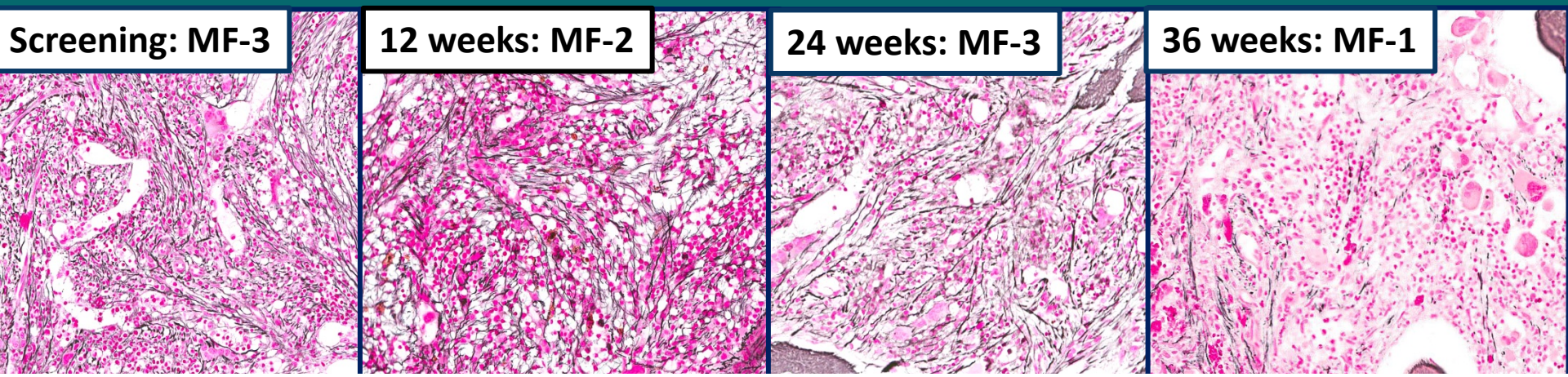
*central, blinded review; 2 patients reclassified as Grade 1

Reduction in Bone Marrow Fibrosis in 11/25 Patients by central, blinded, adjudicated review

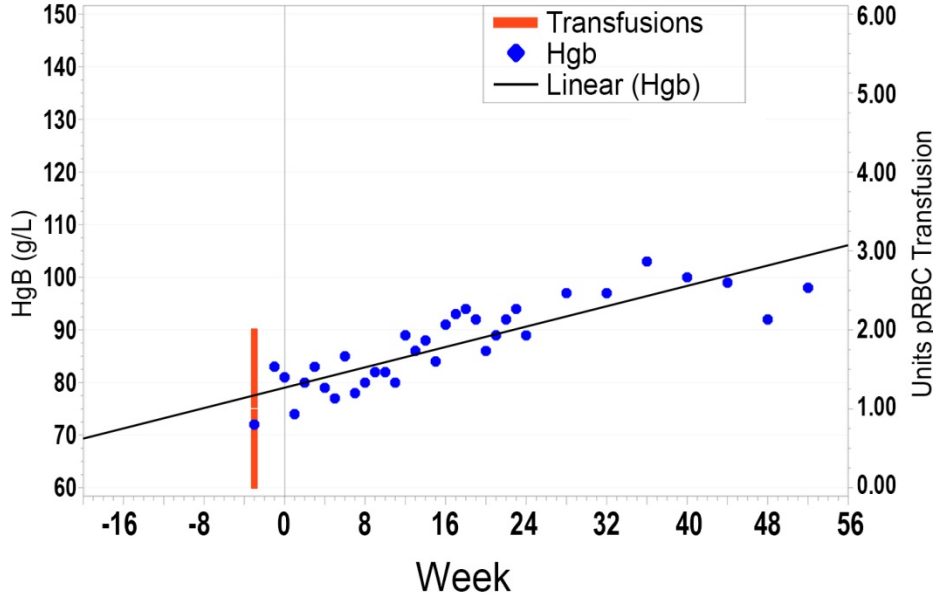
- **Reduction** in BM fibrosis was associated with normalization of bone marrow architecture
  - Normal erythroid clustering (p=.07)
  - Normal or decreased myeloid:erythroid ratio (p= .02)
  - Fewer paratrabecular megakaryocytes (p=.07)

Number of Patients		Best BM Fibrosis Grade After Baseline			
		Grade 3	Grade 2	Grade 1	Grade 0
BM Fibrosis Grade at Baseline	Grade 3 (N= 15)	7	4	3	1
	Grade 2 (N=8)	0	5	3	0
	Grade 1 (N=2)	0	1	1	0

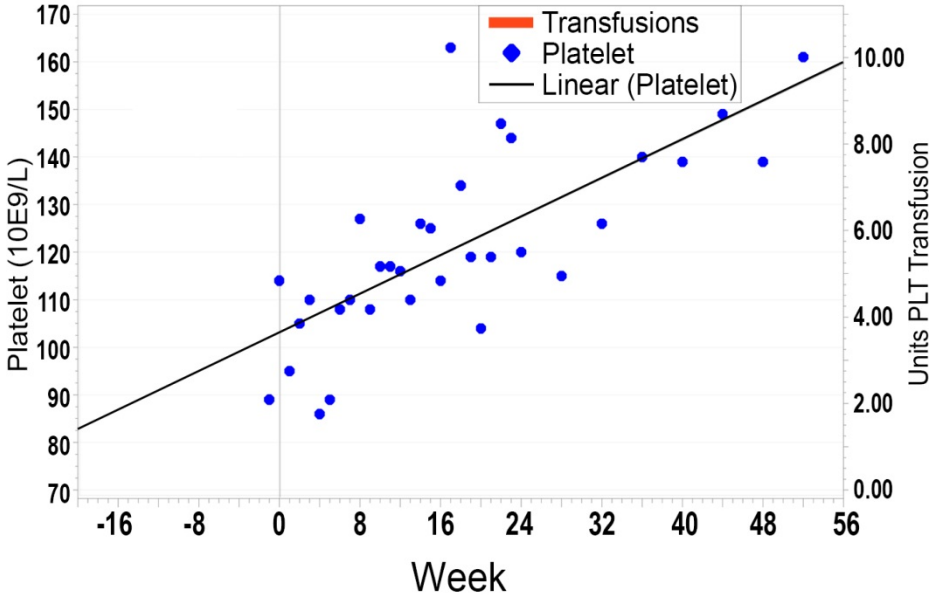
Patient 101-004: PRM-151 QW



Hemoglobin

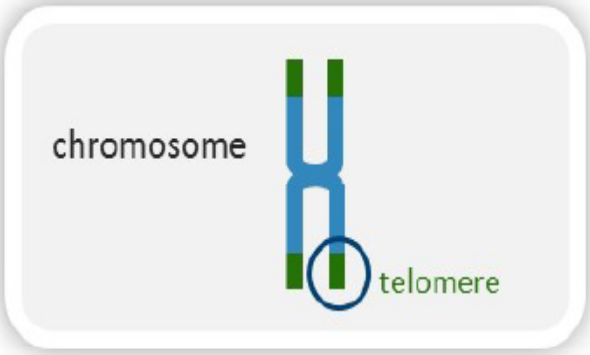


Platelets

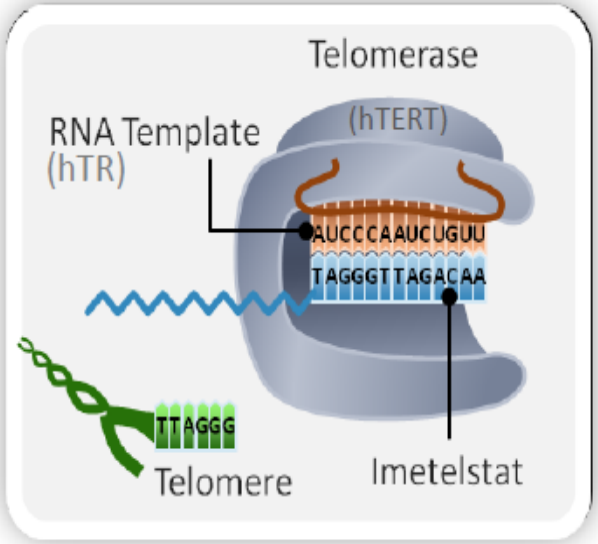


Toxicity profile: no safety issues in the study so far

Imetelstat: A Telomerase Inhibitor



imetelstat binds to RNA template preventing maintenance of telomeres



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:

- **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

geron

Efficacy Results: Primary Endpoint (Overall Response by IWG-MRT)

	Total (n=33)
Best Response by IWG-MRT	N (%)
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%)

CR/PR/CI: 36.4%

CR/PR: 21.2%

- All 4 CR patients achieved reversal of bone marrow fibrosis including 3 with 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

*CR (3 Arm A, 1 Arm B); PR (1 Arm A, 2 Arm B)

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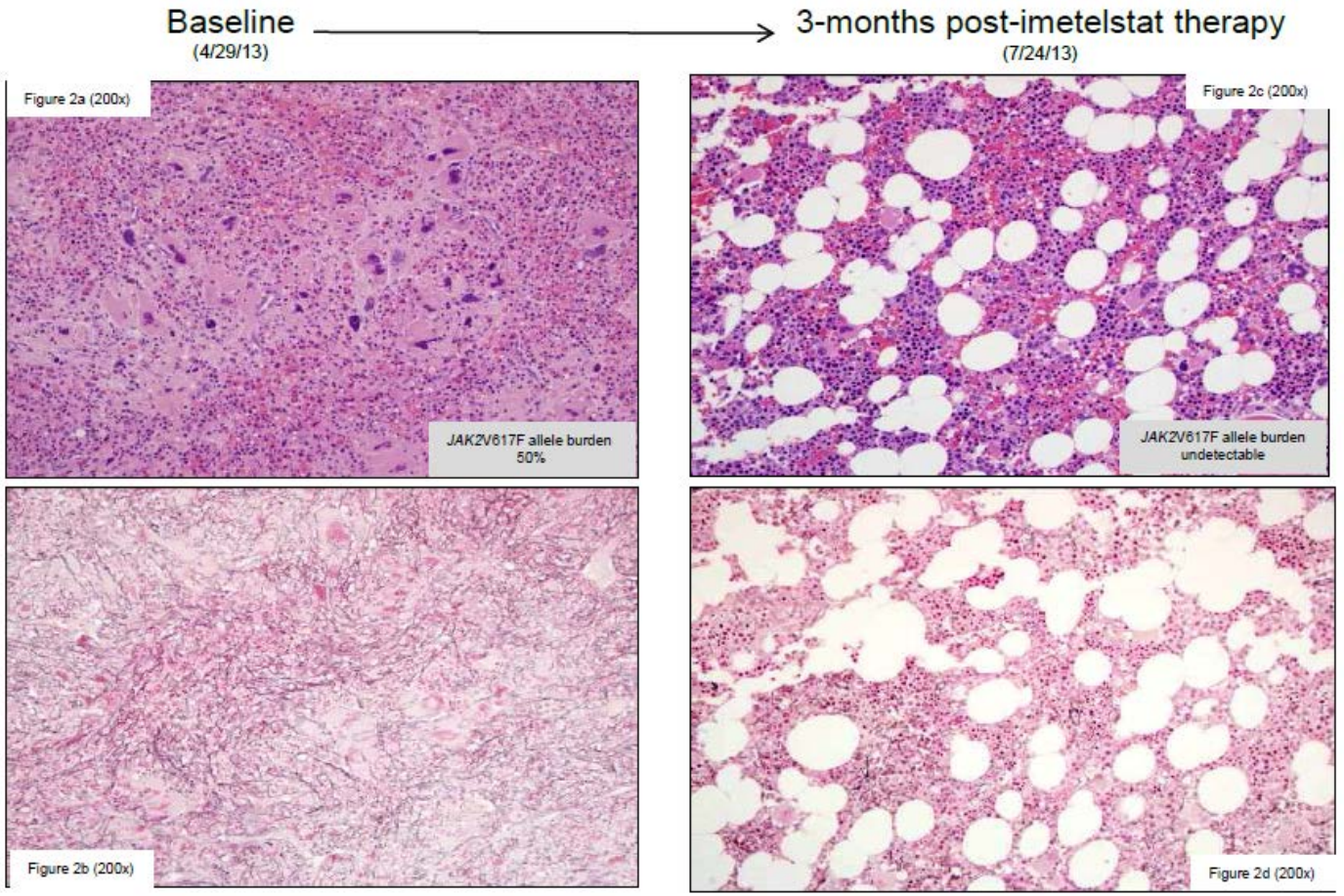
Imetelstat for Myelofibrosis



Median duration of response was 9 months.

Toxicity profile: Agent was on FDA clinical hold for liver toxicity; lowering of blood count significant in 50% of patients

THANK YOU

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