A Phase 2 Study of the LSD1 Inhibitor IMG-7289 (Bomedemstat) in Patients with Advanced Myelofibrosis

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ASH Abstract 556

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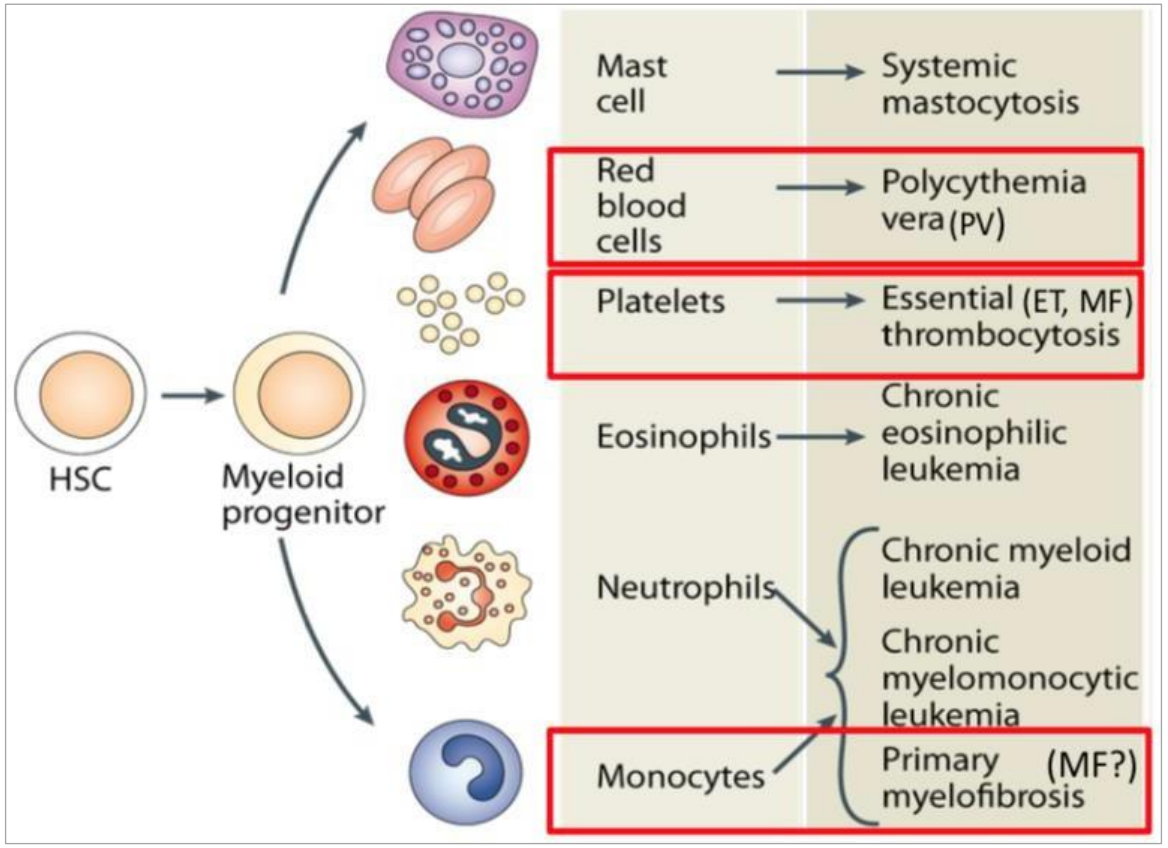
LSD1 is a key regulator of hematopoietic differentiation

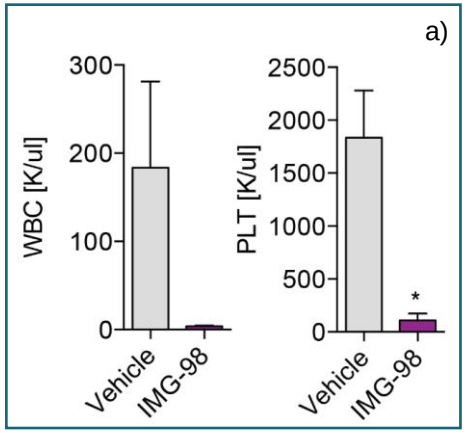
- LSD1 (Lysine-specific demethylase 1) demethylates H3K4 and other chromatin-associated proteins, *e.g.*, p53
- Loss of LSD1 activity associated with loss of clonogenic potential in malignant HSCs[1]
- Is required for the differentiation of megakaryocyte-erythroid progenitors to mature megakaryocytes[2]
- Overexpressed in MPNs[3]

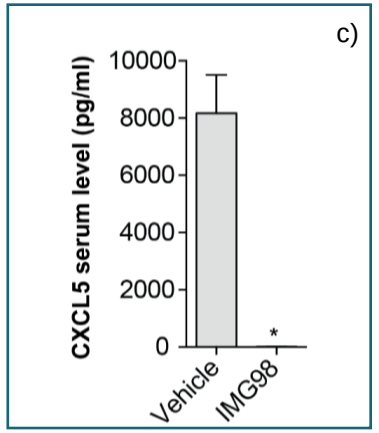


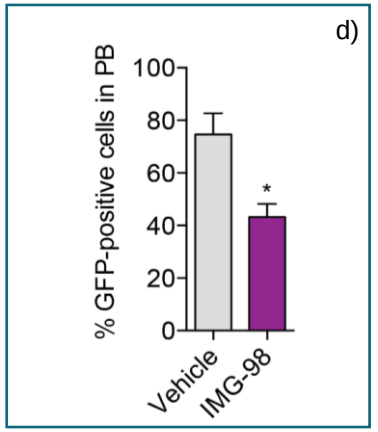
[1]Harris *et al*. Cancer Cell 2012; 21:473-487; [2]Sprussel *et al. Leukemia* 2012; 26(9):2039-51
[3]Niebel *et al. Blood* 2014; 124 (1): 151-152
Image courtesy of Maria Kleppe

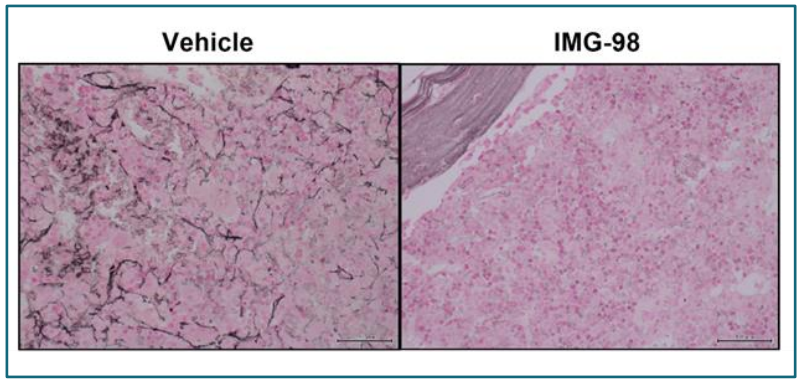
Preclinical evidence of activity in MPN (*Mpl*^{W515L} and *JAK2*^{V617F} murine models)

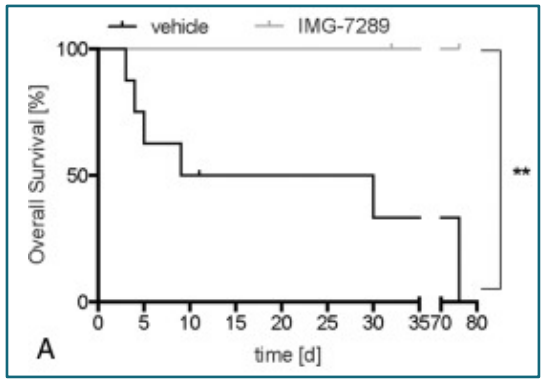
- Reduced WBC and platelets[1,2]
- Favorably altered cytokine profiles[1,2]
- Depleted malignant stem cell population[3]
- Decreased reticulin fibrosis in BM, spleen, and liver[1,2]
- Reduced mutant allele burden[1]
- Improved survival[1]







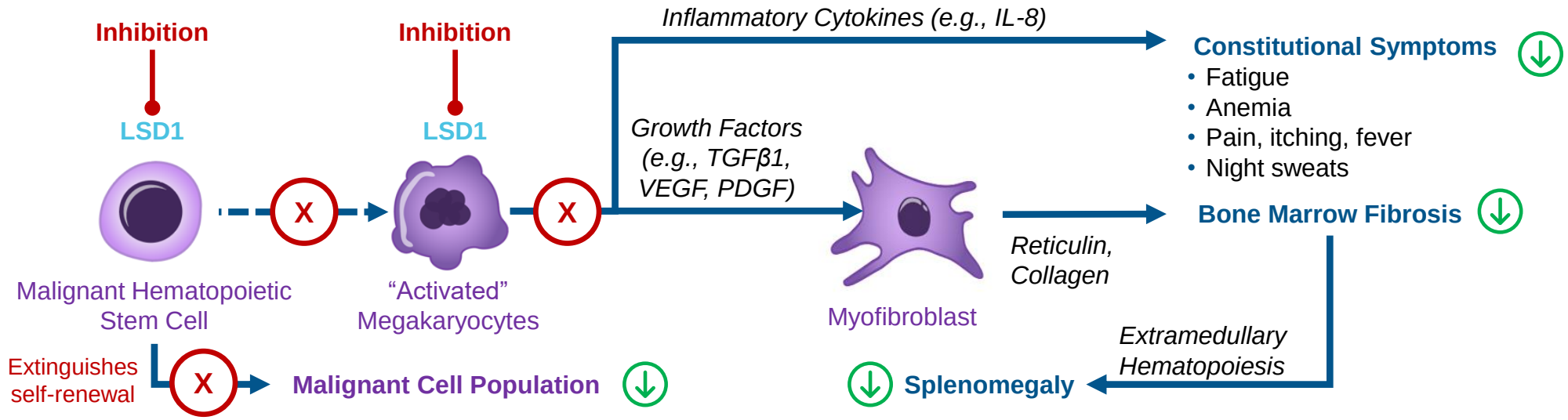




[1]Jutzi et al. LSD1 Inhibition Prolongs Survival in Mouse Models of MPN by Selectively Targeting the Disease Clone. *HemaSphere* 2018; 2(3):e54; [2]Kleppe et al. Lysine-Specific Histone Demethylase, LSD1, (KDM1A) As a Novel Therapeutic Target in Myeloproliferative Neoplasms. *Blood* 2015; 126(23): 601; [3]Harris et al. The histone demethylase KDM1A sustains the oncogenic potential of MLL-AF9 leukemia stem cells. *Cancer Cell* 2012; 21(4):473-87

LSD1 Inhibition has Strong Therapeutic Rationale in MPNs

- LSD1 inhibition impairs function of both “activated” megakaryocytes and malignant stem cells
- Megakaryocytes produce cytokines and growth factors that drive bone marrow remodeling (myelofibrosis)



LSD1 inhibition reduces production of megakaryocytes, growth factors and cytokines = symptom improvement
Potential to extinguish self-renewal of malignant stem cells = potential to improve overall survival

Study Design

↳ **Phase 2 Study of IMG-7289 in Patients with Myelofibrosis *(Multicenter, International Study)***

Primary Endpoints:

- Safety and tolerability
- Pharmacokinetics in first 15 patients
- Spleen volume reduction

Exploratory Endpoints:

- Symptom reduction (MPN-SAF TSS)
- Changes in cytokine profiles
- Changes in VAF
- Changes in BM fibrosis

Key Eligibility Criteria:

- Dx of PMF, PET MF, or PPV MF
- IPSS Intermediate-2 or High-risk disease
- Refractory or resistant to, intolerant of, or ineligible for ruxolitinib or fedratinib
- **Platelets ≥100 x10^9/L**
- Peripheral blasts ≤10%
- Spleen of *any size*
- ECOG PS ≤2

Treatment Plan

- IMG-7289 self-administered PO once daily
- Each patient dose-titrated to platelet count

Phase 1/2a

- Starting dose: 0.25 mg/kg once daily
- Dose titrated weekly to target platelet range **50-100 x10^9/L**
- 1 Cycle = 84 days (12 weeks)
- Washout period (2-4 weeks) after Cycle 1

Phase 2b

- Starting dose: 0.5 mg/kg once daily (Protocol Amendments 4/5)
- Dose up-titrated tri-weekly to target platelet range **50-75 x10^9/L**
- 1 Cycle = 168 days (24 weeks)
- No washout

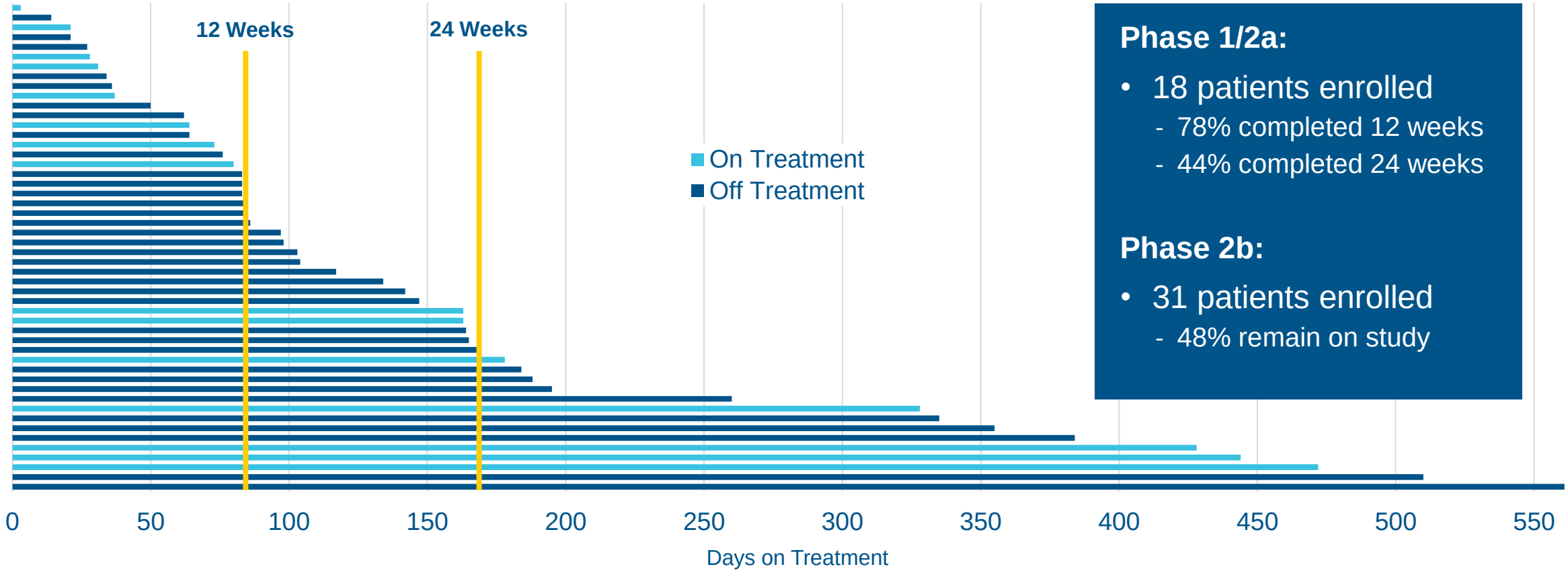
Platelet Count (x10^9/L)	%Platelet Reduction (from prev week)	Dose Titration
≥100	<50%	Add 0.125 mg/kg/day
≥100	>50%	Add 0.0625 mg/kg/day
75-99	<30%	Add 0.0625 mg/kg/day
75-99	>30%	Maintain current dose
50-74	N/A	Maintain current dose
25-49	N/A	Decrease dose by 50%
<25	N/A	Hold dose

Platelet Count (x10^9/L)	%Platelet Reduction (from prior week)	Dose Titration
≥90	<50%	Add 0.2 mg/kg/day
≥90	≥50%	Add 0.1 mg/kg/day
40-89	N/A	Maintain Dose
25-39	N/A	Decrease dose by 25%
<25	N/A	Hold dose

Baseline Demographics and Disease Characteristics

Characteristic (N=49 unless otherwise specified)	
Median Age	68 (range 34-88)
Male	55%
Disease subtype (n=47) PMF Post-ET MF Post-PV MF	 49% n=23 36% n=17 15% n=7
IPSS Risk classification (n=47) High risk Intermediate-2 risk	 55% 45%
Multiple mutations/HMR	68%/51%
Spleen length (for those with palpable spleen, n=36)	Median: 15 cm BLCM (range: 3-27)
Spleen volume (n=41)	Median: 1451.91 cm^3 (range: 193-6819 cm^3)
Symptom score (MPN-10)(n=43)	Median: 33 (range: 1-82)
Blood counts (Mean) (N=48) WBC Hemoglobin Platelets	 24.9 x 10^9/L (range: 1-96) 10.2 g/dL (range: 7.1-15.1) 324.6 x 10^9/L (range: 100-1585)

Enrollment and Treatment Duration



Phase 1/2a:

- 18 patients enrolled
  - 78% completed 12 weeks
  - 44% completed 24 weeks

Phase 2b:

- 31 patients enrolled
  - 48% remain on study

Safety and Tolerability Profile

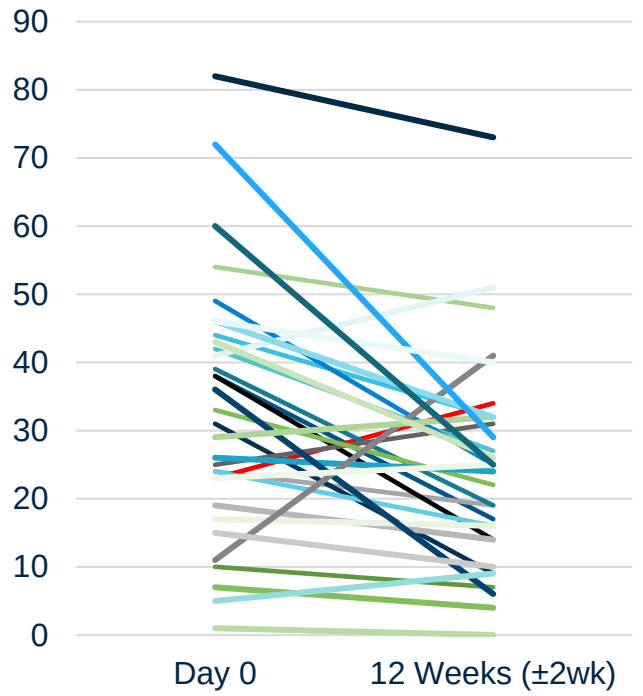
- No dose limiting toxicities (at 6mg/kg)
- No safety signals in >4 years
- No genotoxicity
- No deaths related to study drug
- Out of 917 AEs reported, 307 attributed to IMG-7289
- The most common non-hematologic AE related to IMG-7289 was dysgeusia (35% of patients)

- 6 SAEs attributed by Investigators as possibly related to IMG-7289
  (1 Grade 2, 5 Grade 3)
  - Vertigo
  - Painful splenomegaly
  - Headache
  - Heart failure
  - Rectal bleeding
  - Upper GI bleeding

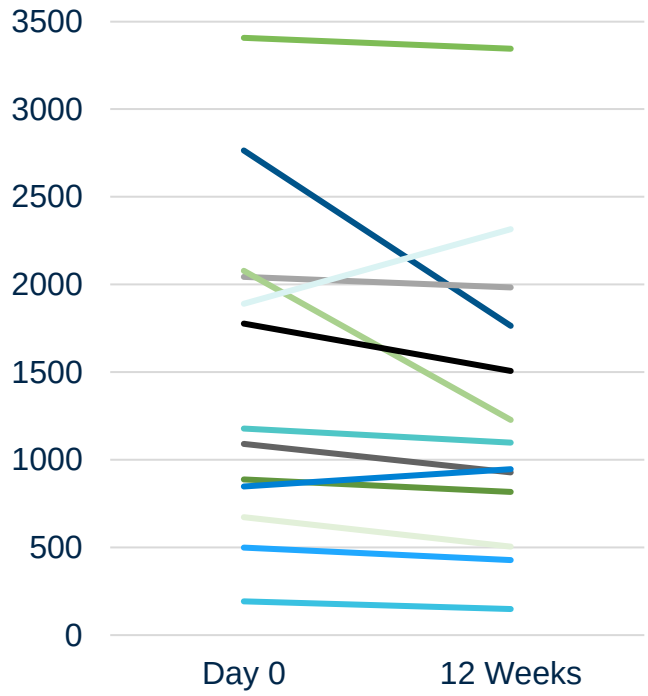
Efficacy of IMG-7289 in Advanced MF

- All Patients at Week 12*
  - ***Total Symptoms (n=32)***
    - 78% (25) had a decrease in symptom score
    - 25% (8) had a reduction of ≥50%
- Phase 2b Patients at Week 12
  - ***Spleen Volume (n=14)***
    - 86% (12) had a decrease in spleen volume
    - 14% (2) had a reduction of ≥35%
    - 29% (4) had a reduction of ≥20%
    - Median change to Wk 12 = -15%

Absolute change in MPN SAF TSS



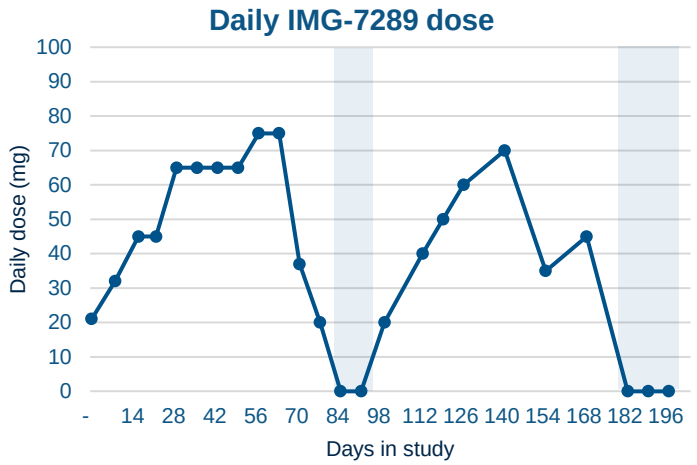
Absolute change in spleen volume by MRI/CT

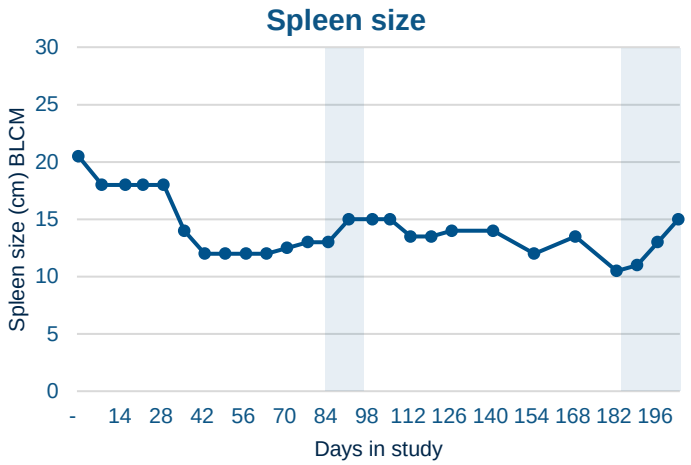


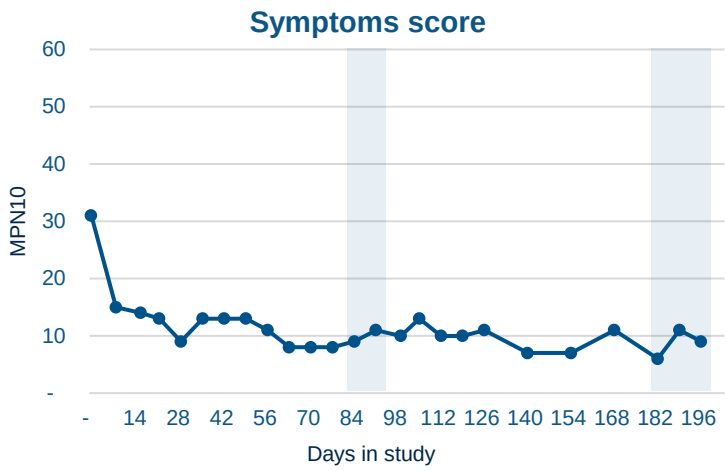
*If Wk12 data were unavailable, data within 2 weeks was used

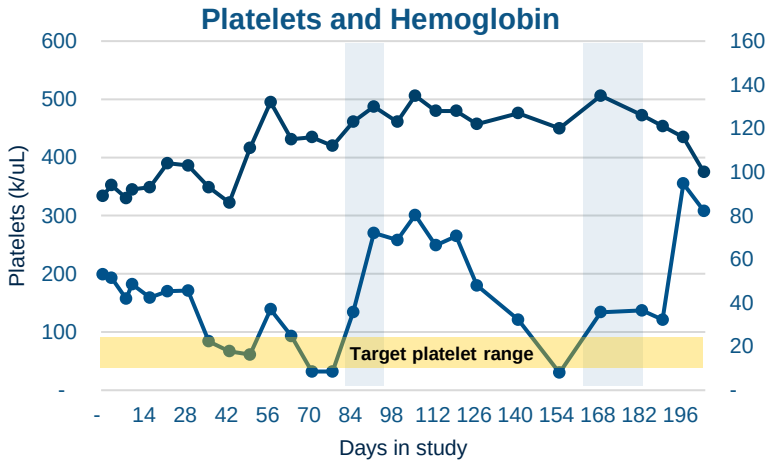
008-103

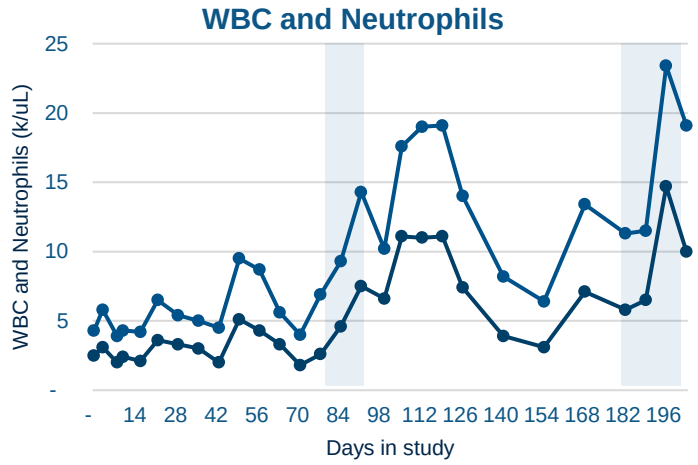
Diagnosis	Post ET MF	Status	On study	Spleen size (cm BLCM)	21 to 11 (-48%)
Risk group	High	Days in study	550+	Symptom score	31 to 6 (-81%)
Genotype	*CALR, ASXL1*	Days at Rx in target range	14/43	Fibrosis score	MF3 to MF3 to MF2
Prior Rx	HU, Anagrelide, Rux	Transfusion dependent	Yes		

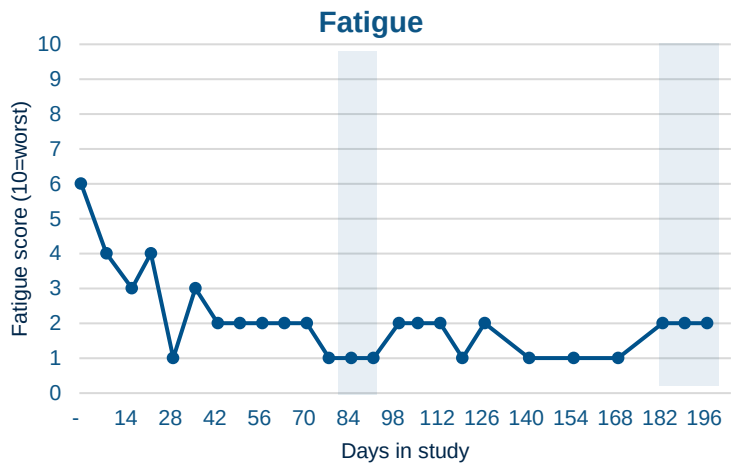












Sequencing Protocol and Pipeline

- Samples: **Germline** (buccal or hair) and **"Tumor"** (bone marrow, peripheral blood, granulocytes)
- Target enrichment: 11,736 hybridization probes in IDT AML panel targeting 261 genes (~6300 exons) recurrently mutated in myeloid neoplasms
- Illumina sequencing: 2x150bp paired-end sequencing; ~ 10 million pairs sequenced per sample
  - Aiming for sequencing depth >500; Actual: >1000 for >90% of samples
- Analysis: Burrows-Wheeler alignment (BWA) => VARSCAN2 genotyper => IGV for CALR, etc.
- Cutoffs for somatic calls: Sequencing Depth: >20 Mutant (or Variant) Allele Frequency (VAF): >15%
- Annotation: All calls submitted to CADD (Combined Annotation Dependent Depletion) at University of Washington
  - CADD score cutoff >20 identifies the top 1% of the most deleterious mutations

VAFs at follow-up time points

- 7/22 (32%) show a *decrease* in some or all somatic mutations
- 12/22 (55%) have *stable* VAFs
- 3/22 (14%) patient have an *increased* VAFs

- No new mutations identified in patients followed up to 550+ days
- No progression to AML

Patient ID	MPN somatics	Others somatics			Column3	VAF @ follow up
003-101	JAK2_V617F	U2AF1_Q157R				Stable
006-101	JAK2_V617F	ZBTB33_Y56S				Partial Improvement
006-102	JAK2_V617F					Stable
007-104	CALR_52b_del	ASXL1_-642X				Stable
008-101	MPL_W515K	ASXL1_Q780*				Partial Improvement
008-102	JAK2_V617F	TET2_NRN1890-				Stable
008-103	CALR_K385NCX	ASXL1_R693*				Partial Improvement
008-105	JAK2_V617F	ASXL1_-884X	PRPF8_R1832C			Stable
010-102	CALR_52b_del	CBL_C396S	ASXL1_-642X	EZH2_-262X		Partial Increase
010-103	JAK2_V617F	CBL_R420Q	EZH2_F145L	CNTN5_P220L	ASXL1_QLL695HX	Stable
010-104	JAK2_V617F	SF3B1_K700E	DNMT3A_V687G	TET2_S1284F		Improvement
010-105	JAK2_V617F	DNMT3A_V687G				Stable
011-101	MPL_W515K					Increase
011-102	JAK2_V617F	ASXL1_Q768*	PRPF8_D1598V	FREM2_S204R		Stable
011-104	JAK2_V617F	MAP1B_D1587N	ASXL1_-642X			Stable
011-105	JAK2_V617F	ASXL1_HHCHREAA630X				Improvement
012-101	JAK2_V617F					Stable
020-102	CALR_52b_del					Increase
021-101	CALR_KKRK374X					Stable
022-101	JAK2_V617F					Improvement
030-101	JAK2_V617F	EZH2_F120X	GPR183_T81I			Stable
032-101	JAK2_V617F	ASXL1_-642X				Improvement

Examples of changing VAFs

patient	mutation	Diagnosis	Day91
010-104	SF3B1_K700E	26.37	14.92
	DNMT3A_V687G	94.96	90.47
	JAK2_V617F	27.02	13.53
	TET2_S1284F	45.72	42.09
			Day182
011-105	ASXL1_HHCHREAA630X	21.48	17.02
	JAK2_V617F	41.45	12.71
			Day112
008-101	MPL_W515*	94.64	91.46
	ASXL1_Q780*	18.58	12.16
			Day570
008-103	ASXL1_R693*	22.42	15.3
	CALR_K385NCX	29.22	61.29

010-104 Probable *DNMT3A* CHIP followed by *TET2* followed by *JAK2/SF3B1* – only *JAK2/SF3B1*-bearing clone is reduced; treatment associated with dramatic improvement of Hb and normalized platelet count.

011-105 Disproportionate reduction of *JAK2* clone compared to *ASXL1;* significant improvement in Hb, spleen volume, and WBC count.

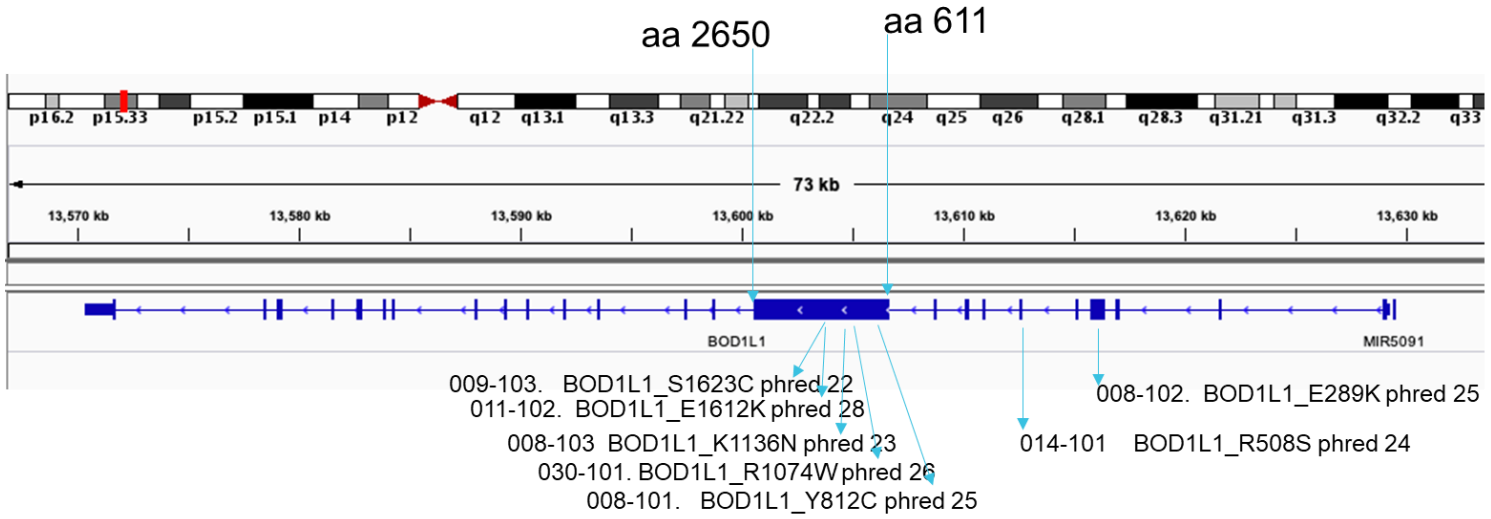
008-101 *ASXL1* clone is reduced while homozygous *MPL* virtually unaffected; good clinical response but Day 84 washout rebound was discouraging – withdrew consent. *(Washout later eliminated.)*

008-103 *ASXL1* clone reduced while the *CALR* clone has homozygosed – excellent clinical improvement for first year but spleen volume improvement waned. Went to transplant.

Germline mutations unique to MF population

↳ Top gene: ***BOD1L1***

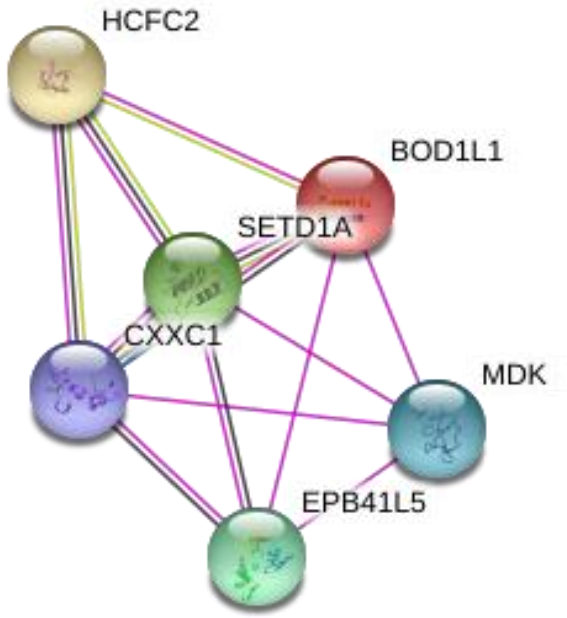
- Filtered:
  - deleterious alleles (CADD >20)
- Results:
  - 0/66 patients with AML
  - 7/42 patients with MF
- All 7 alleles are very rare:
  - present at <0.1 to 0.001% dbVar and 1000 Genome Project
- Preponderance of substitutions of acid amino acids



BOD1L1

- BOD1L1 protein
  - Highest expression in myeloid lineage of BM cells
  - Component of SETD complex that methylates H3K4 and…
  - Stabilizes RAD51 at paused replication forks preventing DNA2 resection
  - Loss of function leads to genome instability

- *BOD1L1*$^{+/-}$ MF patients
  - High proportion of structural genomic rearrangements
  - Links pathological epigenetic changes and genome instability



Conclusions and Development Plans for Bomedemstat

- Bomedemstat (IMG-7289) is safe and well tolerated in patients with advanced MF
- IMG-7289 monotherapy has clinical activity in patients with advanced MF
  - Improvements in symptoms, spleen volumes, anemia, bone marrow fibrosis have been demonstrated
- Bomedemstat decreases mutant allele frequencies in 1/3 of patients, especially ***ASXL1***
- No new mutations or progression to AML during treatment
- Similar studies of bomedemstat for the treatment of ET and PV are currently enrolling
- A combination of bomedemstat and ruxolitinib will begin next year

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