New Treatments in Myelofibrosis: Novel Agents and Early Phase Trials

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Conflicts

- Research: Jazz Pharmaceuticals and Pfizer
- Advisory: Incyte, BMS, Agios
- Speaker Bureau: Incyte, Celgene

Perfect drug for MF

Criteria needed	
Normalize blood counts	
Improve QOL and symptoms	
Decrease spleen size	
Manageable side effects/no additional meds needed	
Decrease allele burden of driver genes JAK2, CALR, MPL	
Decrease allele burden of other mutated genes	
Decrease bone marrow fibrosis	
Increase PFS and OS	

Ruxolitinib: How does it stack up?

Criteria needed	
Normalize blood counts	No, anemia and possible low plts and wbc
Improve QOL and Symptoms	Yes
Decrease Spleen Size	Yes
Manageable side effects w/out addition of meds/transfusion	No
Decrease allele burden of driver genes JAK2, CALR, MPL	No
Decrease allele burden of other genes	No
Decrease bone marrow fibrosis	No
Increase PFS and OS	No

What new drugs are in the pipeline with promise for MF?

- Bomedemstat (LSD1 inhibitor)
- Tagraxofusp (CD123-targeted therapy)
- Pelabresib (CPI-0610, bromodomain BET inhibitor)
- Selinexor (blocks the karyopherin protein exportin 1 XPO1/CRM1)

Bomedemstat—LSD1 inhibitor

Study Design

IMG-7289-CTP-102 is an ***ongoing*** Phase 1/2 global study of IMG-7289 (bomedemstat) in patients with MF

Primary Endpoints

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

Secondary Endpoints

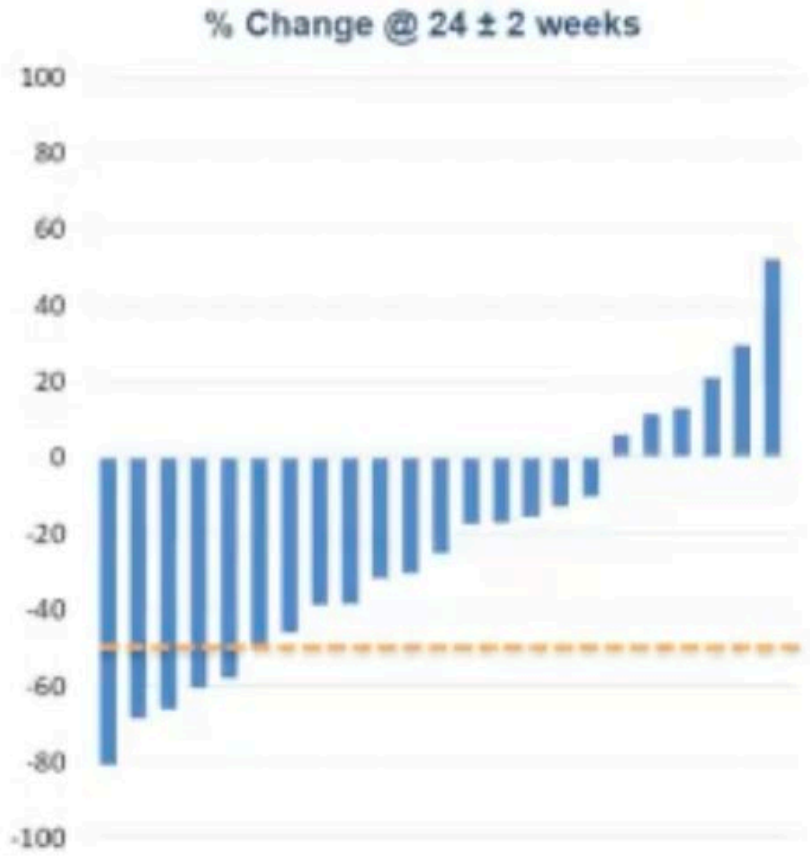
- Symptom reduction (MPN-SAF TSS)
- Changes in cytokine profiles
- Changes in mutant allele frequencies (MAF)
- Changes in bone marrow (BM) fibrosis

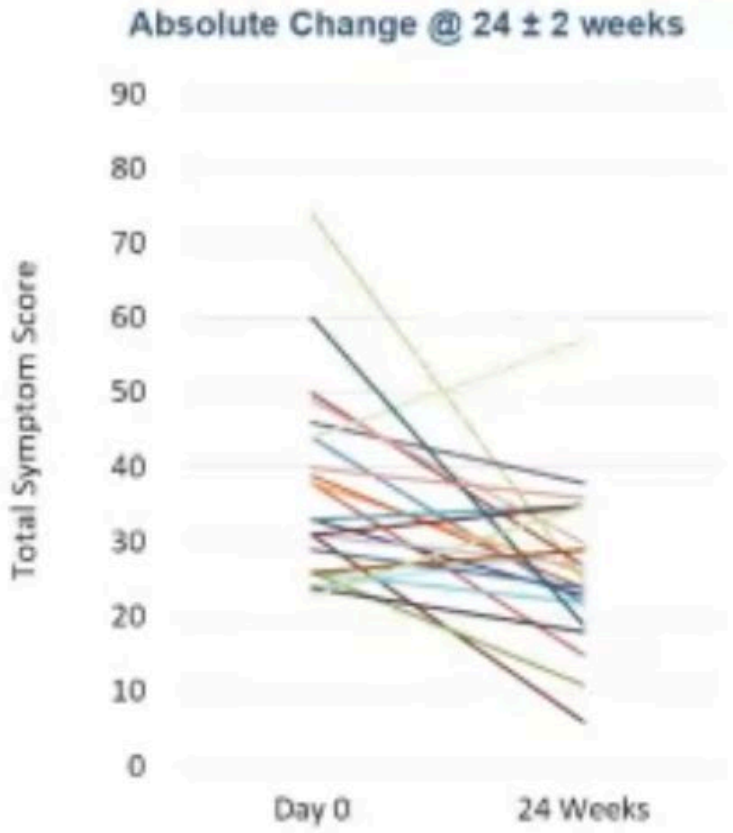
Key Eligibility Criteria

- Dx of PMF, PET-MF, or PPV-MF
- Refractory or resistant to, intolerant of, inadequate control by, or ineligible for, available approved therapies
- IPSS Intermediate-1, -2 or High-risk disease
- **Platelets ≥100 x10^9/L**
- Peripheral blasts ≤10%
- Spleen of ***any size***
- ECOG PS ≤2

Total Symptom Score (TSS) at 24 weeks

Changes in MPN-SAF TSS – Patients with significant symptom burden (≥20)



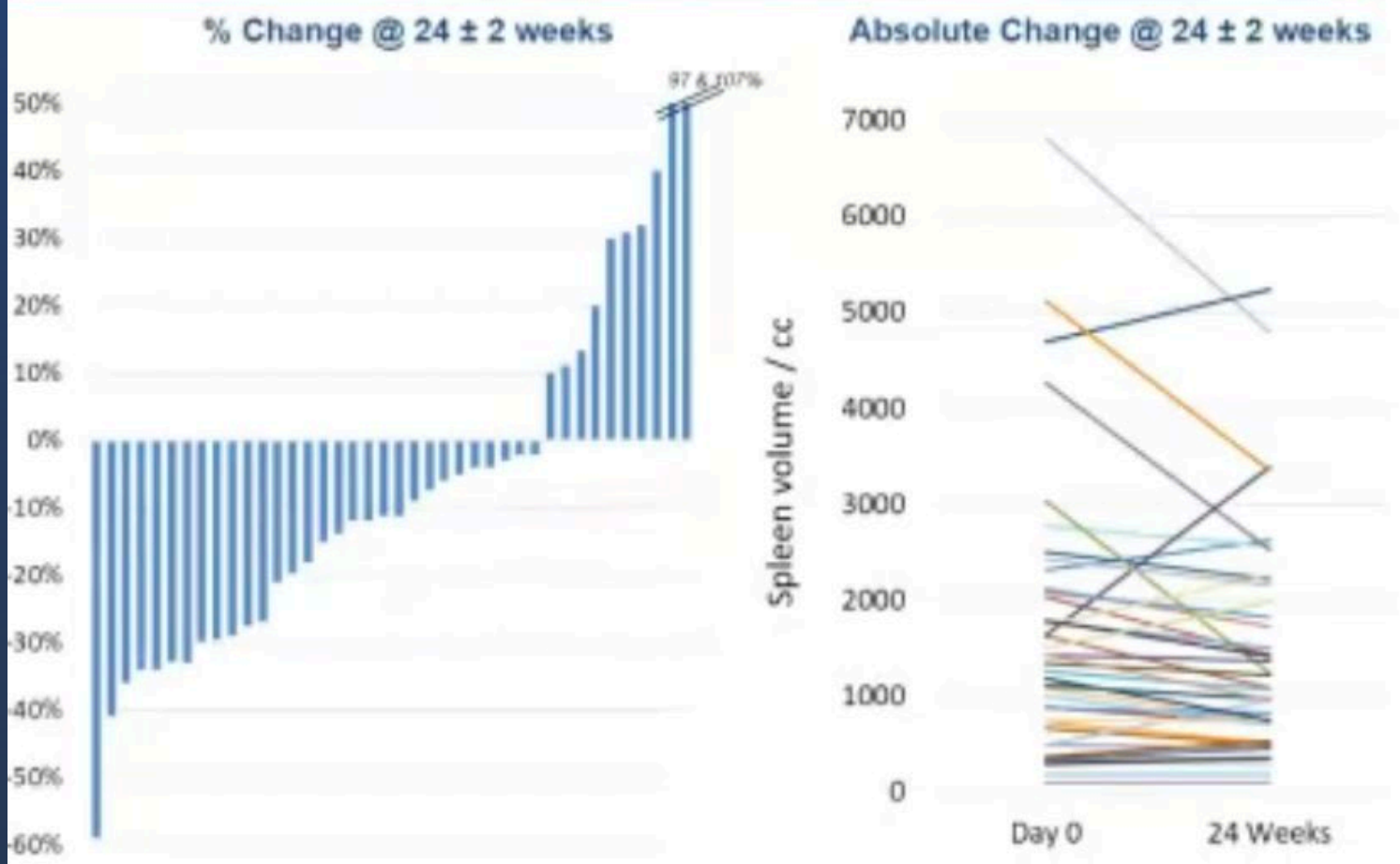


- 17/23 **(74%)** had a decrease in TSS
- 6/23 **(26%)** had a decrease of ≥50%

Data cut-off date: 31Oct 2021

Spleen Volume Reduction at 24 Weeks

Change in Spleen Volume



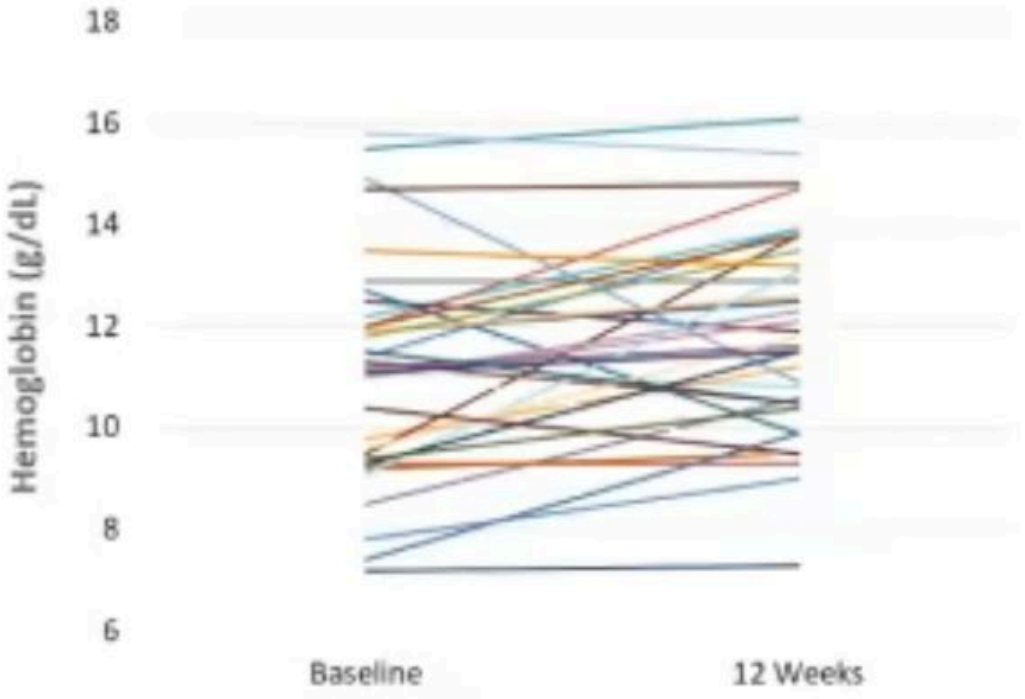
All spleen sizes allowed at study entry

- 30/40 **(75%)** had any decrease
- 14/40 **(35%)** had ≥20% decrease
- 3/40 **(8%)** had ≥35% decrease

Data cut-off date: 31Oct 2021

Changes in Hemoglobin

Changes in Hb in Tx-Independent Patients



In patients (N=36*) who were **transfusion-independent** at baseline, at 12 weeks:

- 89% (32/36) had stable or improved Hb
  - 44% (16/36) had an increase ≥1.0 g/dL
  - 44% (16/36) had stable Hb Δ <± 1.0

In patients (N=17*) who were **transfusion-dependent** at baseline, to last time on study:

- 59% (10/17) had stable or reduced transfusion burden
- 1 patient became transfusion-independent

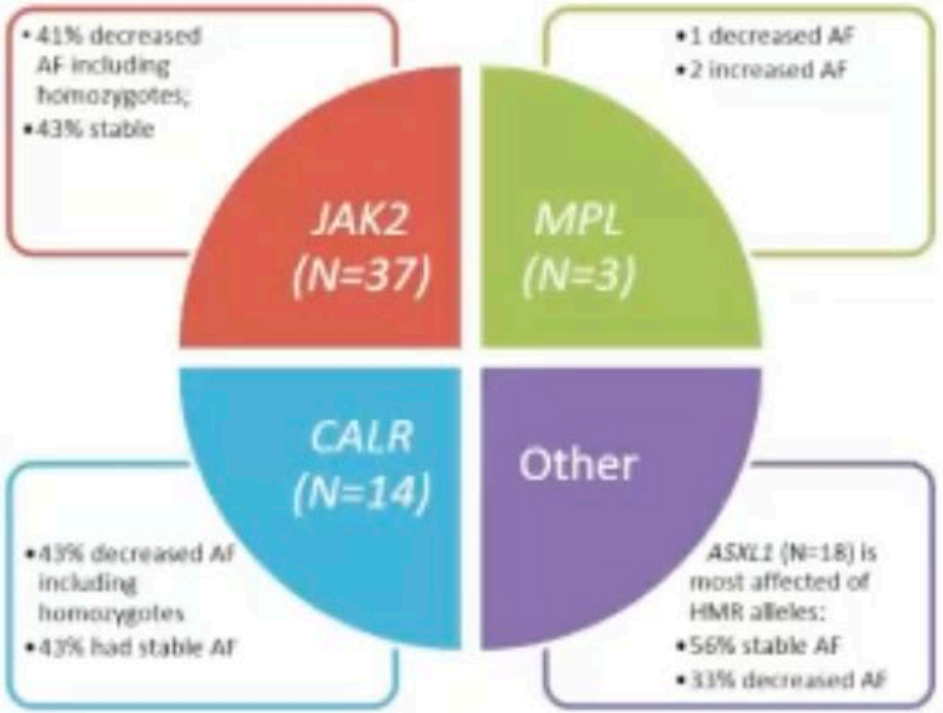
Data cut-off date: 31Oct 2021

* Exclusions due to: ET prior to Wk12

Impact on Mutant Alleles

261 genes serially sequenced by NGS to an average depth of 1015 bp

Changes in Specific Mutant Alleles



AF = Allele frequency

Overall Changes in Allele Frequency

- 45% showed stable AFs (N=127)
- 36% showed a reduction in AF
- 19% showed an increase in AF

- There were 4 complete molecular responses (AF → 0)

- No new mutations or transformation to AML in treatment for up to >600 days

Standard deviation in this study at a read depth of 1000 is ~5%

Change defined as ≥5% for heterozygotes, ≥10% for increase/ ≥2.5% decrease for homozygous clones for up to >600 days

Change from pre-dose to last timepoint *on drug* = 2days

Tagraxofusp

Fusion protein consisting of IL-3 (CD123) fused to diphtheria toxin

Tagraxofusp

- Targeting CD123
- Phase 1/2 single-arm study
- Lead in cohort—4 patients
- Single arm expansion—35 patients
- Pts had relapsed/refractory disease Inter-1 or higher risk
- Evidence of acceleration
- Endpoints: Reduction of TSS and spleen size reduction as documented on CT or MRI

Spleen Responses* (N=24)

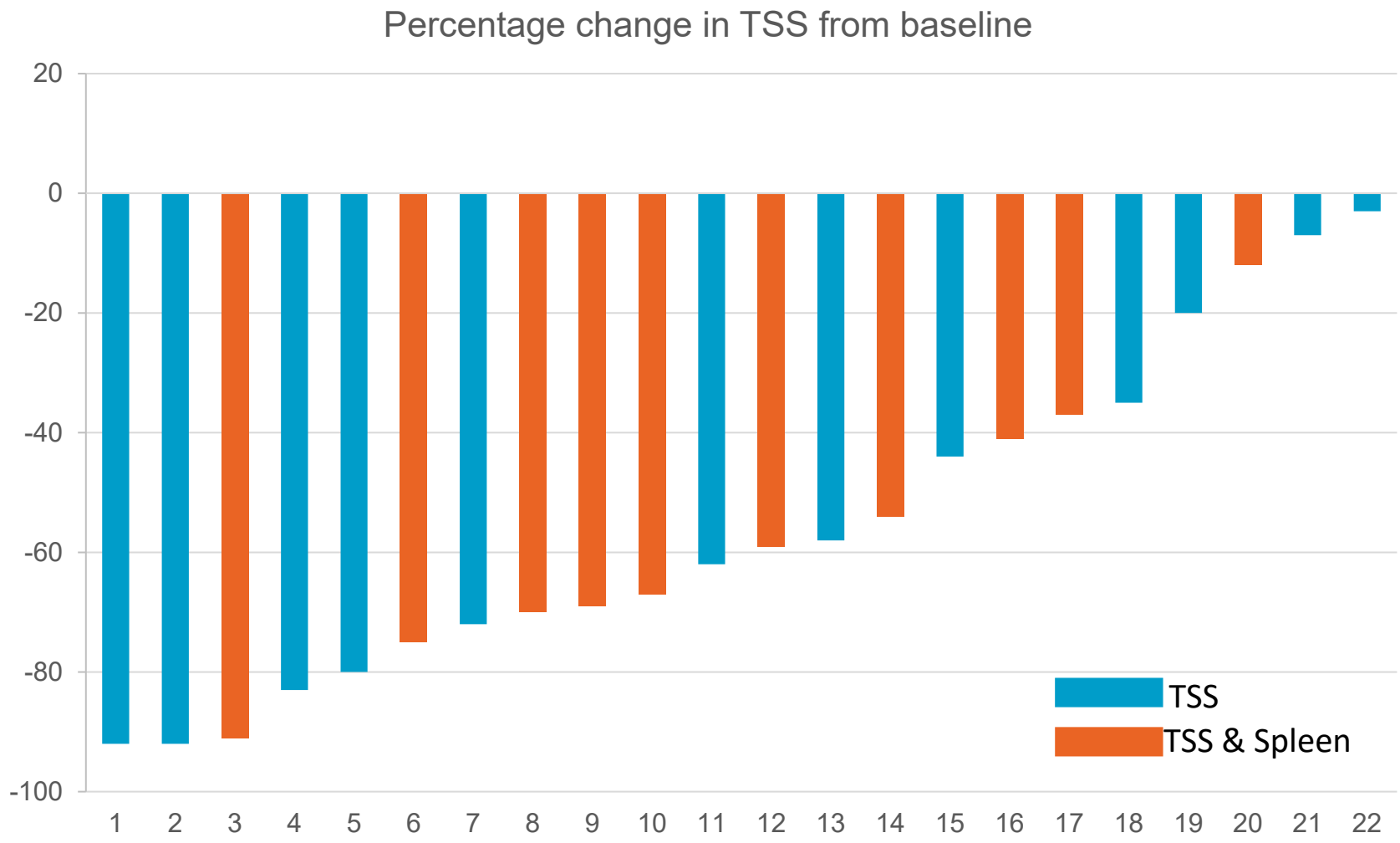
- 24/39 patients (62%) had baseline splenomegaly (≥5 cm palpable BCM)

	n (%)	Baseline Thrombocytopenia		Baseline Monocytosis
		Platelets <100× 10^9/L	Platelets <50× 10^9/L	Monocytes ≥1%
Any reduction	13 (54%)	5 (21%)	5 (21%)	3 (13%)
≥50% reduction	7 (29%)	2 (12%)	2 (12%)	0

- 3/24 (13%) with concomitant monocytosis
- 10/24 (42%) with concomitant thrombocytopenia

* Patients with palpable spleen at baseline
BCM, below costal margin

TSS & Spleen Responses

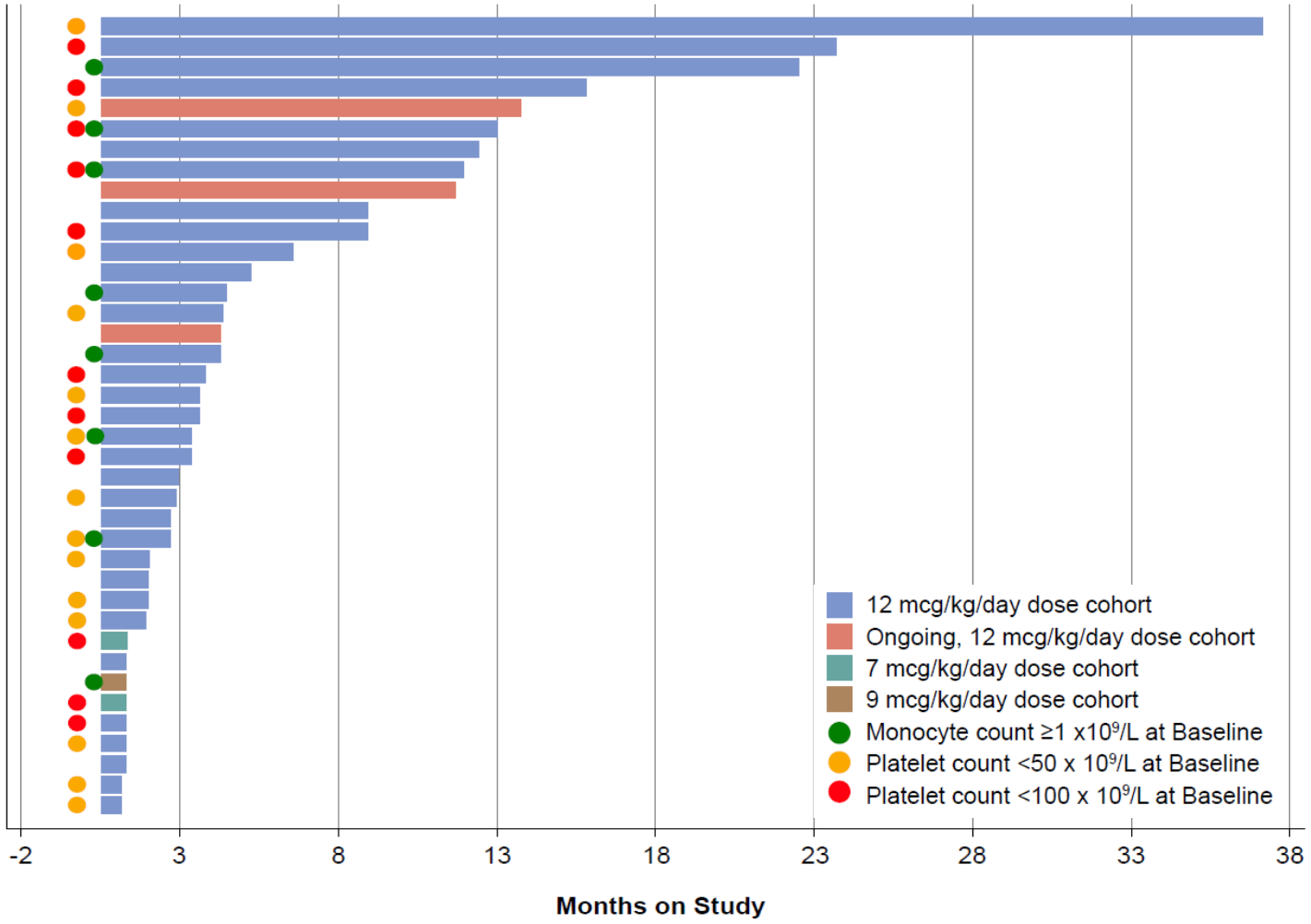


- Total Symptom Score (TSS)[1] was reduced in 22/39 patients (56%)
- 14/39 patients had a ≥50% improvement in clinical symptom score
- 10/39 (26%) had reductions from baseline in both TSS and spleen size

1. Mesa et al., *Cancer* 2011: 117(21); 4869-4877.

Treatment Duration

- Median duration of follow-up was 26.1 months (95% CI 16.0, 46.6)

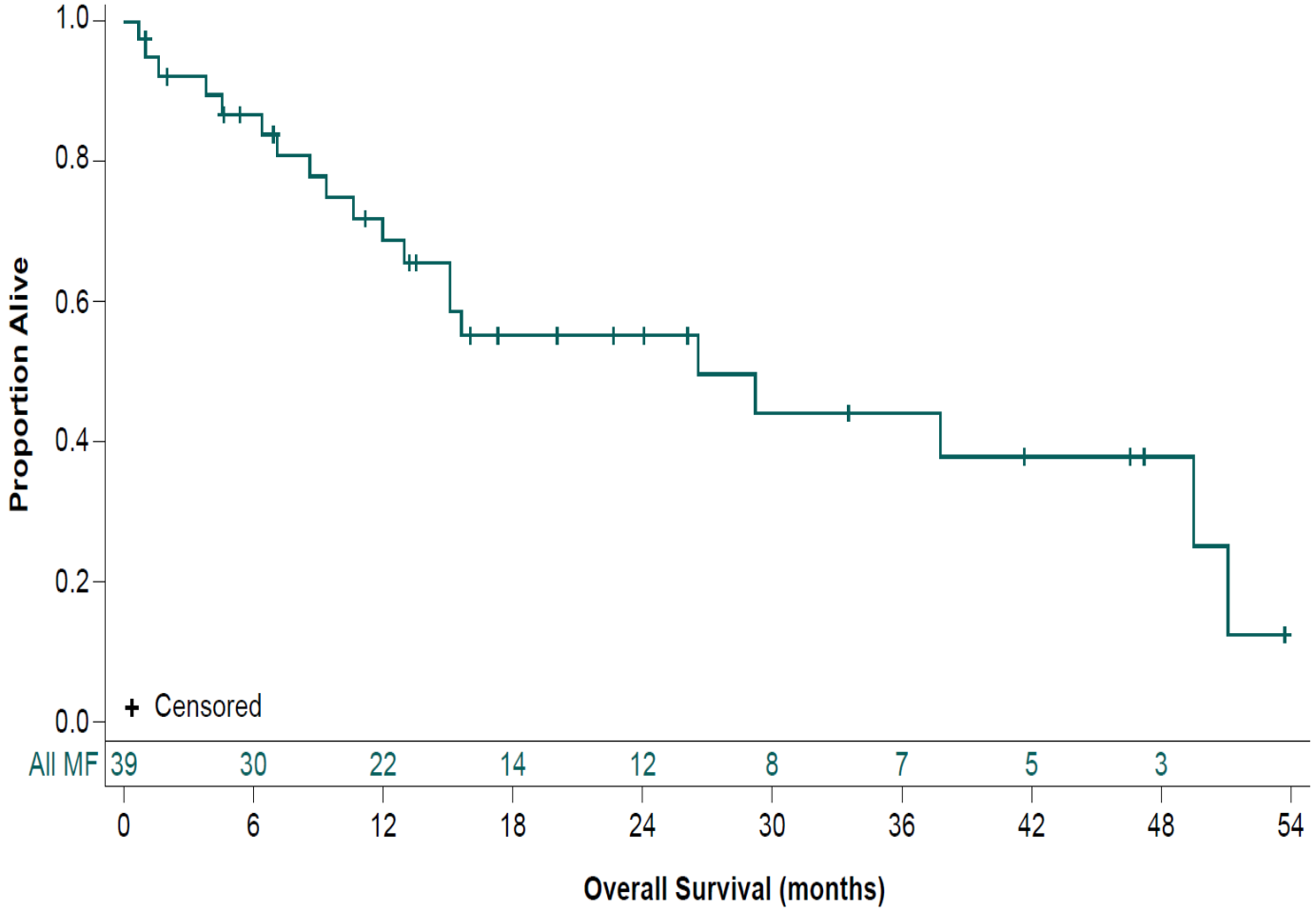


Patient Disposition

- 36/39 patients (92%) have discontinued treatment

Reason, n (%)	
Disease progression	10 (26)
Adverse event	9 (23)
Other	6 (15)
Physician decision	5 (13)
Patient withdrawal of consent	3 (8)
Death from any cause	2 (5)
Patient received allogenic stem cell transplant	1 (3)

Overall Survival



- 19/39 patients (49%) remain alive at data cutoff date of September 30, 2021
- Median overall survival:
  - 26.6 months (95%: CI 12.9, 51.1)
  - Range, months [0.66, 53.72]

Pelabresib

Bet Inhibitor (bromodomain inhibitor preventing protein-protein interaction between BET proteins and acetylated histones and transcription factors)

Pelabresib monotherapy in myelofibrosis patients with unmet medical need

MANIFEST Arm 1: Refractory/resistant, intolerant, or ineligible for JAKi treatment

Study Population

- No longer on ruxolitinib
- DIPSS Int-2 or higher[1]
- Platelet count ≥ 75 x 10^9/L
- TD cohort: ≥2 units of RBC transfusions/mo for 12 wks
- Non-TD cohort must have baseline spleen size of >450 cm^3

Arm/Cohort

Transfusion Dependent (TD) (Cohort 1A)
N=36/60, **Ongoing**

Non-transfusion Dependent (Non-TD) (Cohort 1B)
N=50, **Completed**

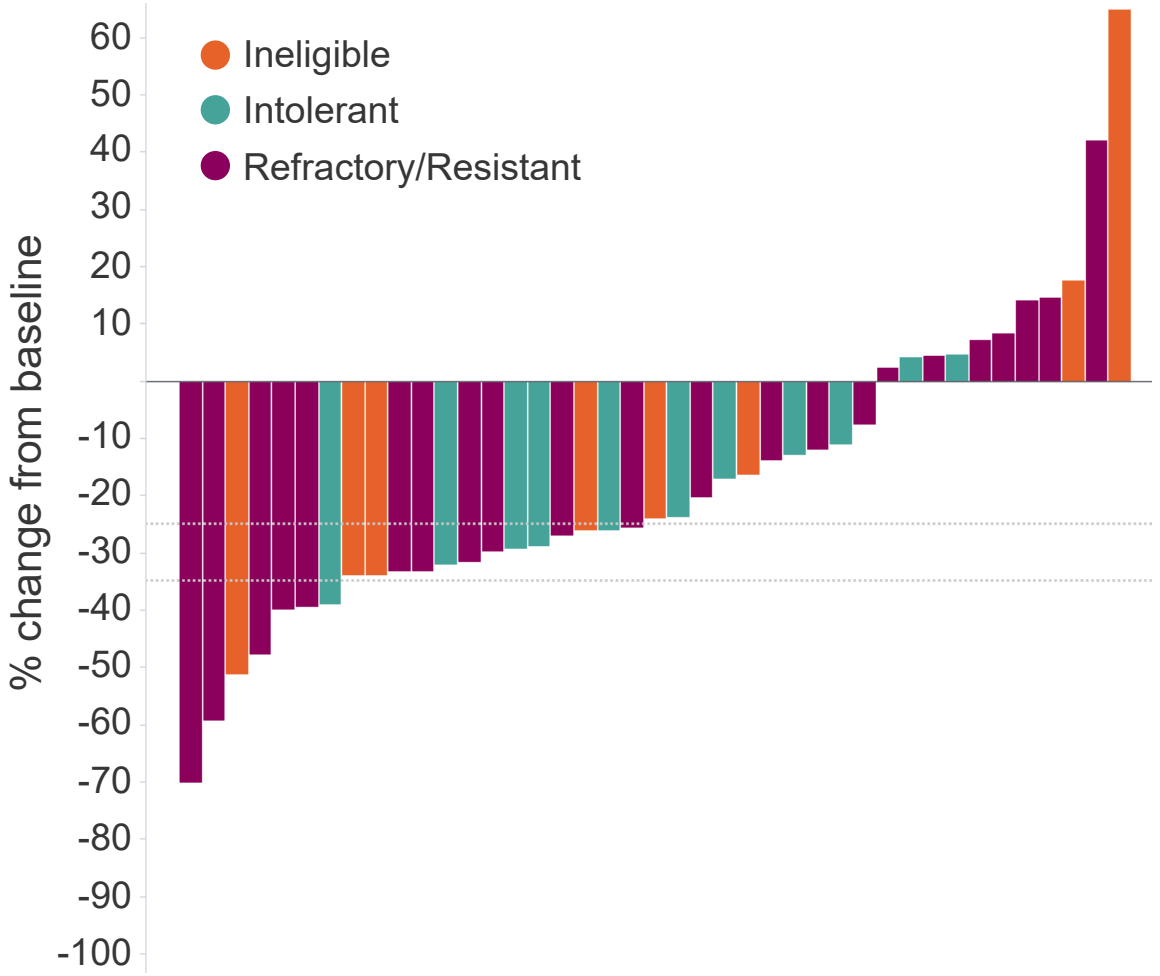
Endpoints

TD cohort (1A)	
Primary Endpoint	**Key Secondary**
TD to TI	SVR35, TSS50

Non-TD cohort (1B)	
Primary Endpoint	**Key Secondary**
SVR35	TSS50

- DIPSS: Dynamic International Prognostic Scoring System
- [1]Patients with DIPSS Int-1 were allowed to enroll prior to the protocol amendment
- SVR35: Spleen volume response defined as ≥35% reduction from baseline (MRI or CT) after 24wk
- TSS50: Total symptom score response defined as ≥50% total symptom score reduction from baseline after 24-wk
- TD to TI: Conversion from Transfusion Dependent (TD) to Transfusion Independent (TI), defined as absence of RBC transfusions over any consecutive 12-wk period

Pelabresib in myelofibrosis, MANIFEST Arm 1: Spleen volume percent change at week 24



Arm 1B Non-TD cohort primary endpoint:
SVR35 at week 24
18% (7/38)

	Arm 1 (TD and Non-TD) N=64
SVR35	11% (7/64)
SVR25	31% (20/64)
Median spleen volume % change	-24%
Mean spleen volume % change	-17%

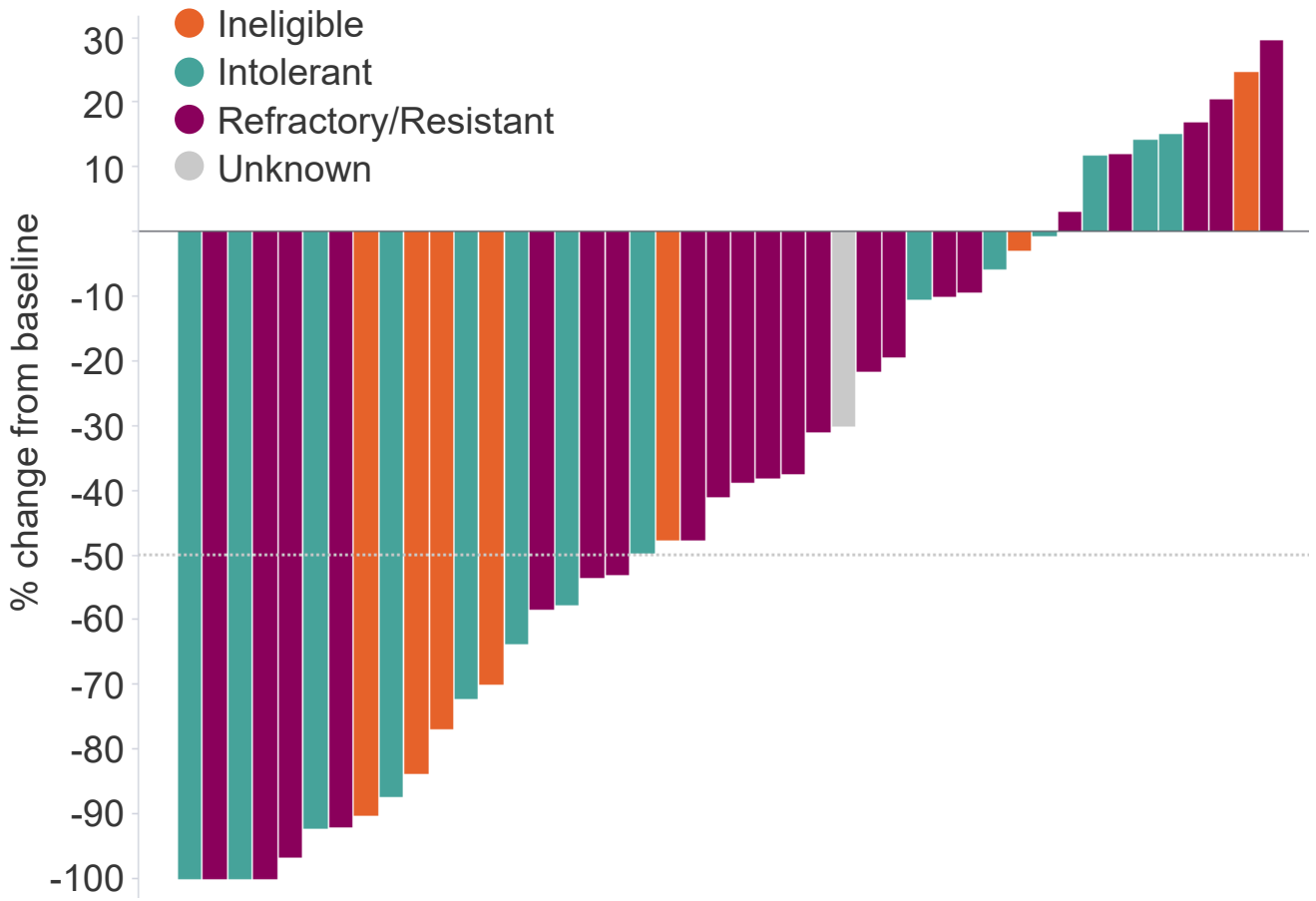
SVR: Spleen volume reduction per local radiology review; SVR25: ≥25% reduction in spleen volume from baseline; SVR35: ≥35% reduction in spleen volume from baseline

- Patients evaluable if non-missing baseline and week 24 spleen assessment or discontinued at any time without wk 24 spleen assessment

22 patients non-evaluable: 4 pts due to missing baseline and 18 ongoing pts without wk 24 assessment. 23 pts discontinued without having wk 24 assessment included as non-responders

Patients evaluable for SVR at wk 24: JAKi ineligible (n=10); JAKi intolerant (n=15); JAKi refractory/resistant (n=38); 1 patient with unknown subgroup

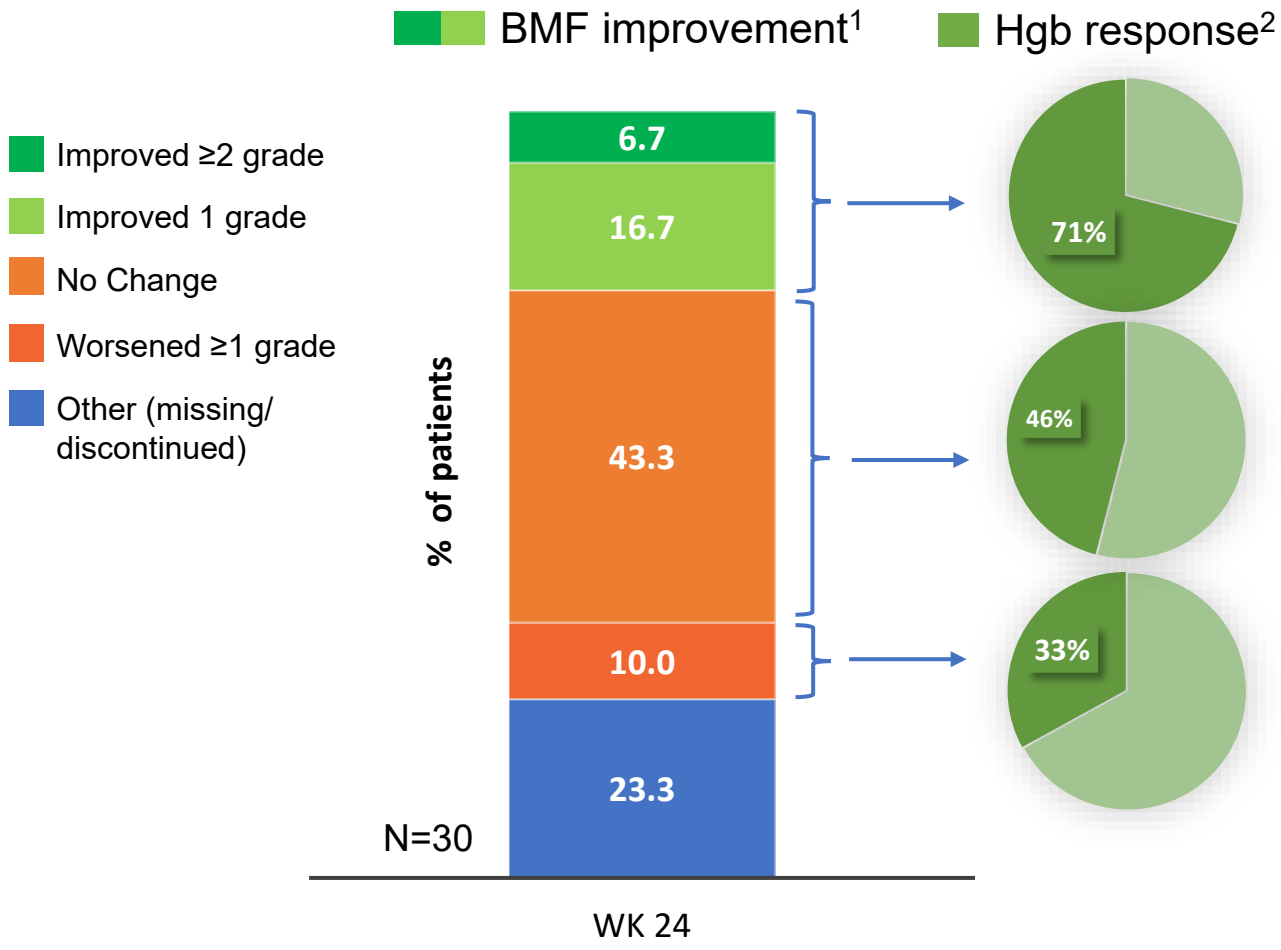
Pelabresib in myelofibrosis, MANIFEST Arm 1
TSS percent change at week 24



	Arm 1 (TD and Non-TD) N=64
TSS50	28% (18/64)
Median TSS % change	-40%
Mean TSS % change	-40%

- TSS: Total Symptom Score; TSS50: ≥50% reduction in total symptom score from baseline
- Patients evaluable if non-missing baseline and week 24 TSS assessment or discontinued at any time without wk 24 TSS assessment
- 22 patients non-evaluable: 7 pts due to missing baseline and 15 ongoing pts did not reach wk 24 as of data cut-off. 20 patients discontinued without wk 24 assessment are included as non-responders
- Patients evaluable for TSS at wk 24: JAKi ineligible (n=8); JAKi intolerant (n=18); JAKi refractory/resistant (n=37); UNK: 1 patient with unknown subgroup

Pelabresib in myelofibrosis, MANIFEST Arm 1: Bone marrow fibrosis improvement[1] per central read and hemoglobin response[2]

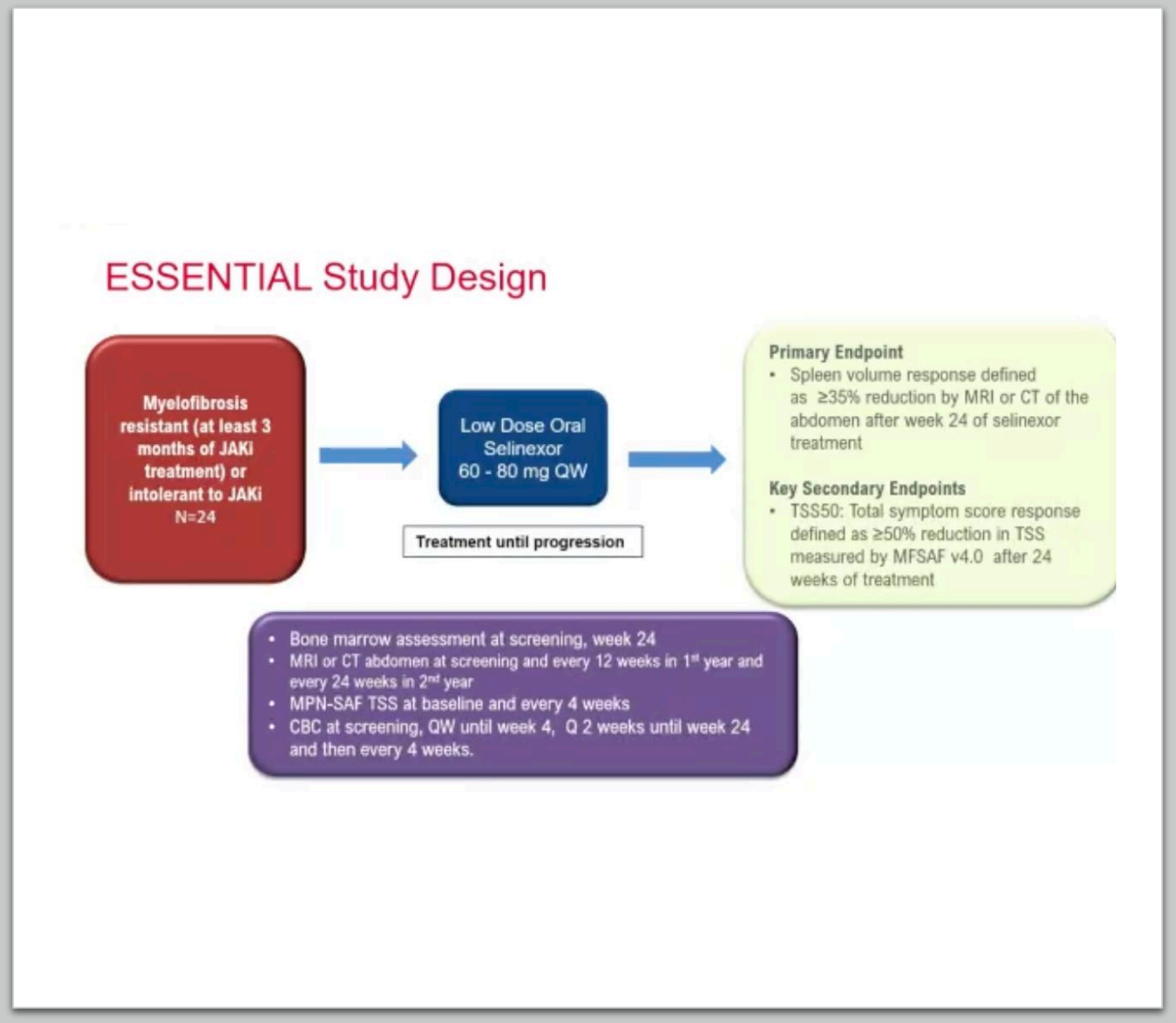


- 71% (5/7) of the patients with BMF improvement were also hemoglobin responders[2]
- 47% (14/30) of patients had grade 3 BMF at baseline, 3/16 (19%) patients with grade 1/2 BMF at baseline had BMF worsening

- [1]Exploratory endpoint: Patients evaluable if non-missing baseline bone marrow assessment
- [2]Secondary endpoint: Post-baseline mean Hgb increase of at least 1.5g/dL for any 12 wks RBC transfusion free period
- BMF: bone marrow fibrosis grade by central pathology review; maturing data with central review ongoing

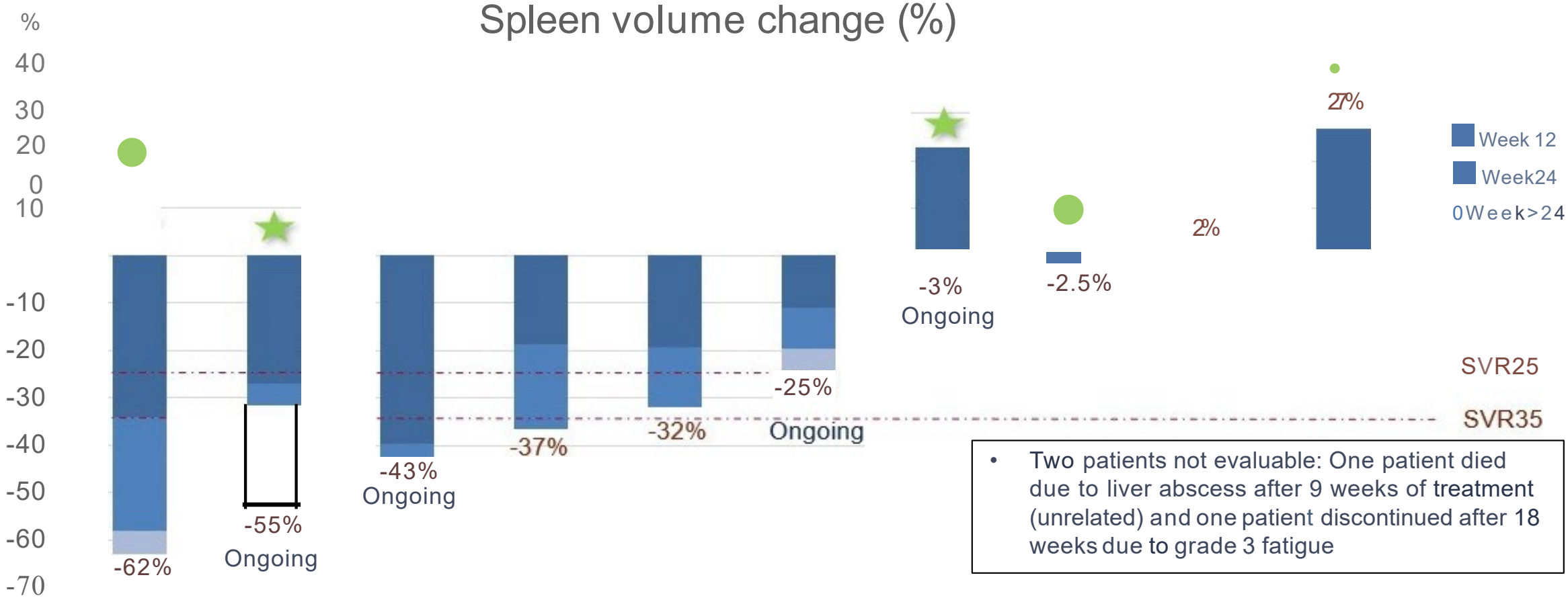
Selinexor

Selective inhibitor of nuclear export



- Selinexor: Oral, selective inhibitor of nuclear export (SINE) compound that blocks the karyopherin protein exportin 1 (XPO1, CRM1).
- Open-label single center study in adults with R/R MF or are intolerant of JAK2 inhibitors

Single agent Selinexor resulted in robust SVR35 rate of 40% at 24 weeks in MF resistant or intolerant to *JAKi*



- Two patients not evaluable: One patient died due to liver abscess after 9 weeks of treatment (unrelated) and one patient discontinued after 18 weeks due to grade 3 fatigue

SVR35 at week 24 = 30%; SVR35 at ≥ week 24 = 40% (4/10 pts)
SVR25 at week 24 = 50%; SVR25 at ≥ week 24 = 60% (6/10 pts)

Presence of high-risk mutation
(ASXL1, EZH2, IDH1/2, SRSF2 or U2AF1)

Hemoglobin improvement is observed in 4 out of 8 pts with hemoglobin < 10 g/dL at screening

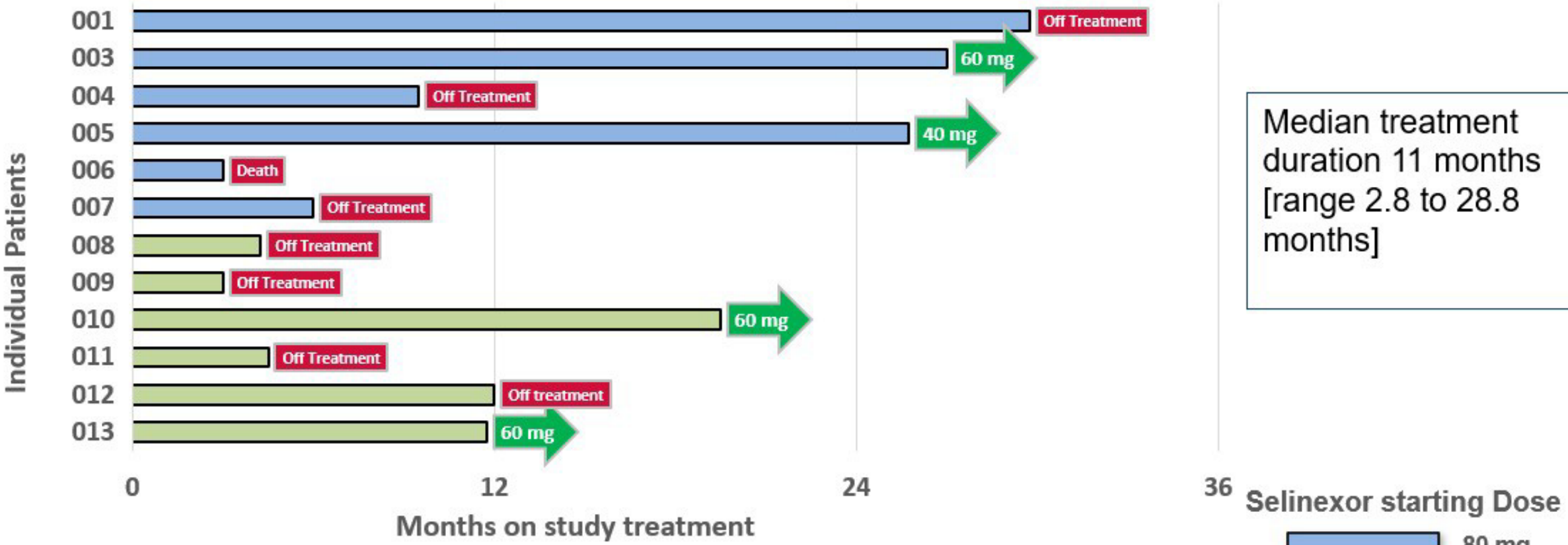
Patient	Baseline	Best response	Transfusion requirements
01-001	TD	Became TI	
01-003	TD (<6u/ 12 weeks)	Became TI	
01-004	TD	Unchanged	
01-010	TD	Unchanged	
01-011	TD	Unchanged	(chart not available)

TD to TI occurred in 40%
(2 out of 5)

Patient	At screening	Best response	Anemia response
01-005	Hgb 8.7	Hgb 13.7	2.0 g/dl increase
01-008	Hgb 9.3	Hgb 10.5	1.2 g/dl increase
01-012	Hgb 9.7	Hgb 11.8	2.1 g/dl increase

Hemoglobin increased by 2g/dl in 67%
(2 out of 3)

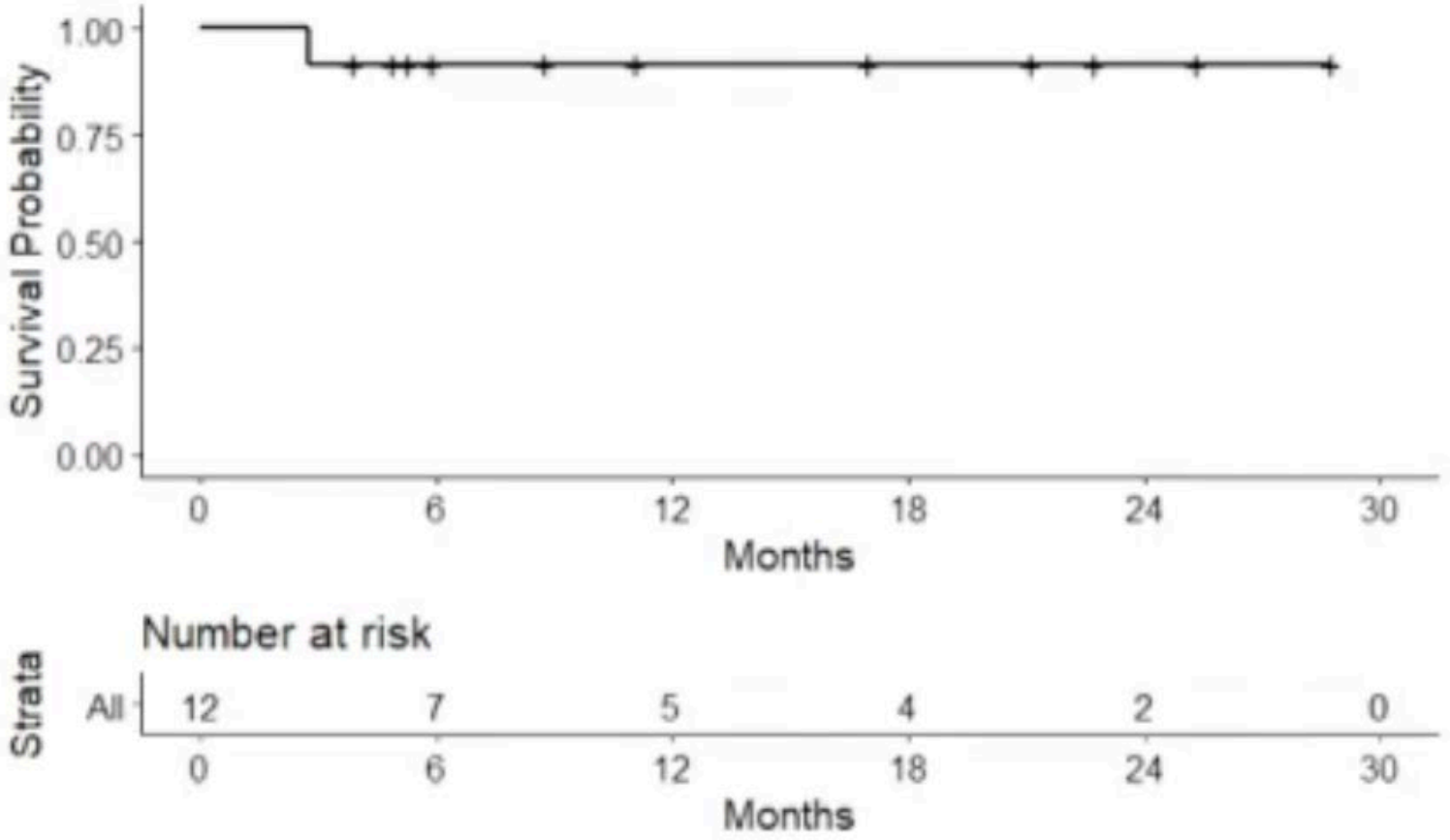
Swimmers Plot: Durable responses with long term therapy beyond 2 years



Median treatment duration 11 months [range 2.8 to 28.8 months]

Eight pts (70%) discontinued selinexor due to death (n=1), progression (n=2; 1 spleen size progression and 1 AML), changed to another clinical trial (n=2), and toxicity (n=3; 1 fatigue and 2 weight loss)

Overall Survival Status: current 2-year survival probability is 91.7%



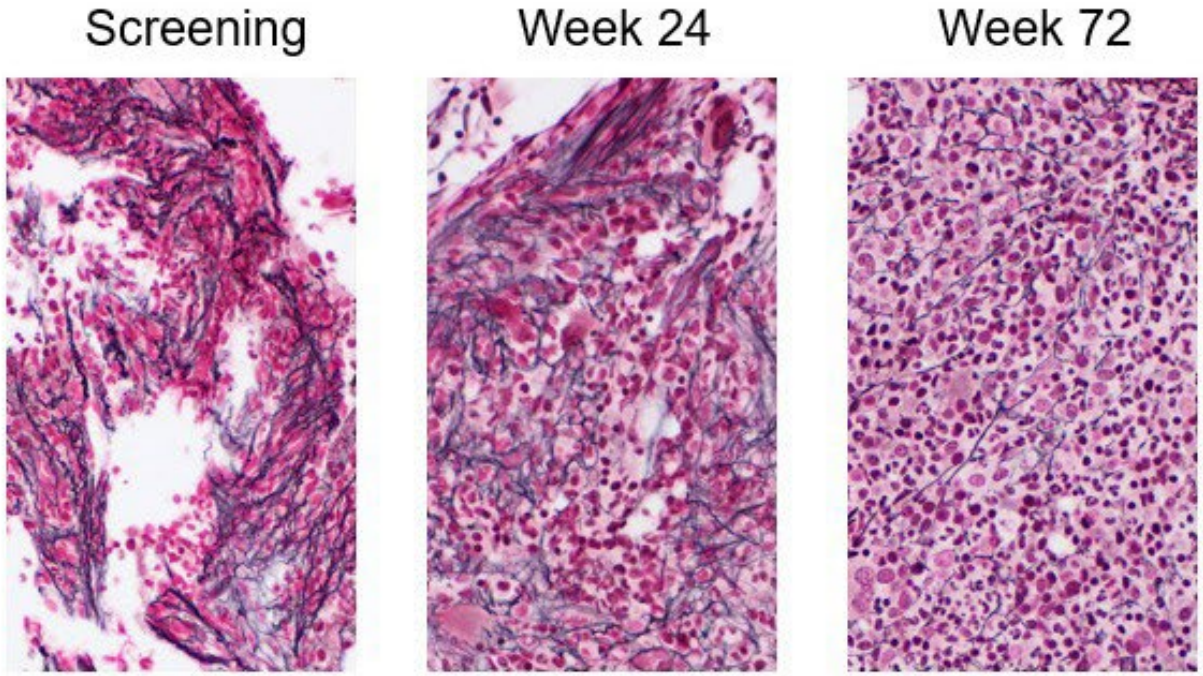
Median OS not reached after a median follow up of 11.1 months [range 3 to 30 months].

The 2-year survival probability is 91.7%

Reduction in marrow fibrosis at long term follow up supports potential disease modification

- Reduction in marrow reticulin fibrosis from **MF grade 3 to MF grade 1** at week 72 (patient 001-005)
- No change in marrow reticulin or collagen fibrosis grade was observed at week 24 (n=10)
- No changes in *JAK2*^{V617F} allele burden was observed in pts with *JAK2* mutated MF at week 24

001-005: Reticulin Fibrosis (reticulin special stain, 200X)



How do these drugs stack up? Which combinations might be effective?

	NL BLD	IM TSS	SPL 35	Tolerable	Dec Allele burden	Increase PFS & OS	Hb improve
Rux		x	x	x			
LSD1		x	x	dysgeusia	x		X (stable)
CD123/DP		x	x	Low alb		x	
Bet inhibitor		x	x	x			
SINE INH			x	fatigue		x	x

Endpoints for the clinical trials looking at MF treatment need to be standardized and more emphasis on the most meaningful parameters such as blood count normalization, PFS & OS, tolerability.

The Future: Drug combinations to try and achieve all parameters

- *JAK2* inhibitors: ruxolitinib/pacritinib in combination with drugs under investigation to tick off all the boxes
- Drugs which improve hemoglobin and decrease marrow fibrosis are obvious candidates
- Drugs which increase overall survival often are improving blood counts and fibrosis
- Combination therapy more difficult because of toxicities. For chronic use, drugs with even grade one and two toxicities may not be tolerable.