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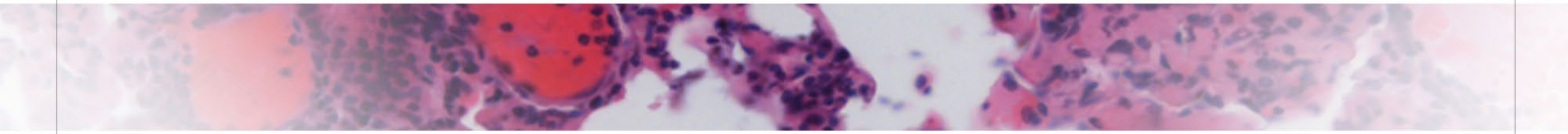

A Phase II Study to Evaluate the Efficacy and Safety of Selinexor in Patients with Myelofibrosis Refractory or Intolerant to JAK1/2 Inhibitors (ESSENTIAL study)

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Disclosures

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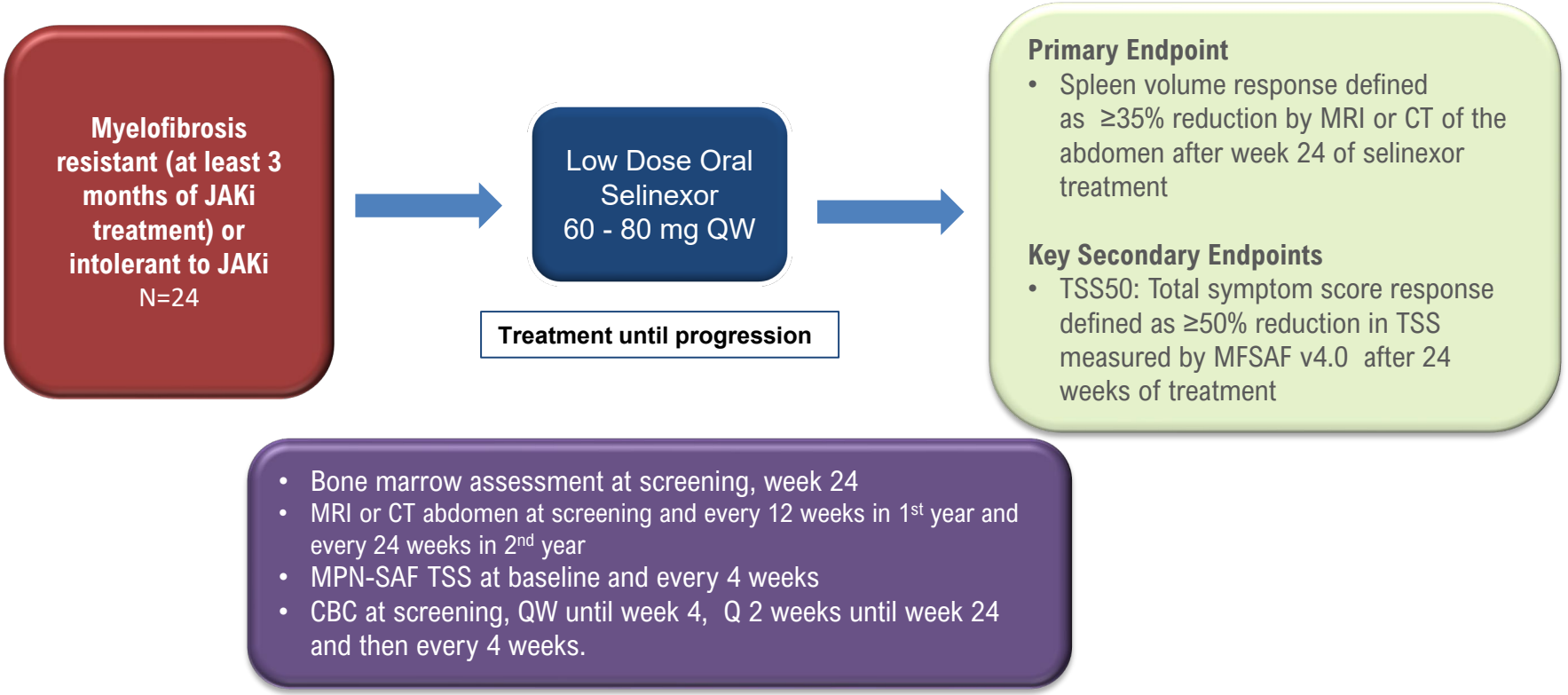
Background: Nuclear–Cytoplasmic Transport (NCT) is a Novel Therapeutic Target in Myelofibrosis (MF)

- JAK inhibitors (JAKi), ruxolitinib and fedratinib reduce spleen volume, alleviate constitutional symptoms and improve quality of life in MF patients
- However, some patients demonstrate inadequate response to JAKi or develop progressive increase in spleen size after an initial response
- Anemia and thrombocytopenia frequently limit JAKi dose intensity and renders many patients ineligible
- Novel approaches and new class of therapeutics are needed for patients with JAKi refractory or intolerant disease
- Selinexor is an oral, small molecule, selective inhibitor of nuclear export (SINE) compound that specifically blocks the karyopherin protein exportin 1 (XPO1)
- We have previously reported that *JAK2*^{V617F} mutant HEL and SET-2 cells are exquisitely sensitive to selinexor. Selinexor has selective activity against $CD34^{+}$ primary MF cells compared to normal cord blood cells (Yan et al, Clinical Cancer Research 2019)

ESSENTIAL Study Design



Key Eligibility Criteria

- Diagnosis of primary MF, post-essential thrombocytosis MF, or post-polycythemia-vera MF

- Prior treatment with JAKi with any of the following:
  - Resistance to JAKi after ≥ 3 months of treatment: palpable spleen ≥ 10 cm OR palpable spleen ≥ 5 cm with active symptoms of MF
  - Intolerance to JAKi treatment: ≥ 3 grade non-hematologic adverse events (AEs) or ≥ 2 AEs requiring JAKi discontinuation AND palpable spleen ≥ 5 cm

- Hemoglobin ≥ 7 g/dL, platelets > 30,000/µL and absolute neutrophil count > 500/µL
- No Prior exposure to a SINE compound, including selinexor
- Ruxolitinib or other JAKi discontinued at least 3 days (5 half-lives) prior to study treatment to reduce the risk of withdrawal symptoms

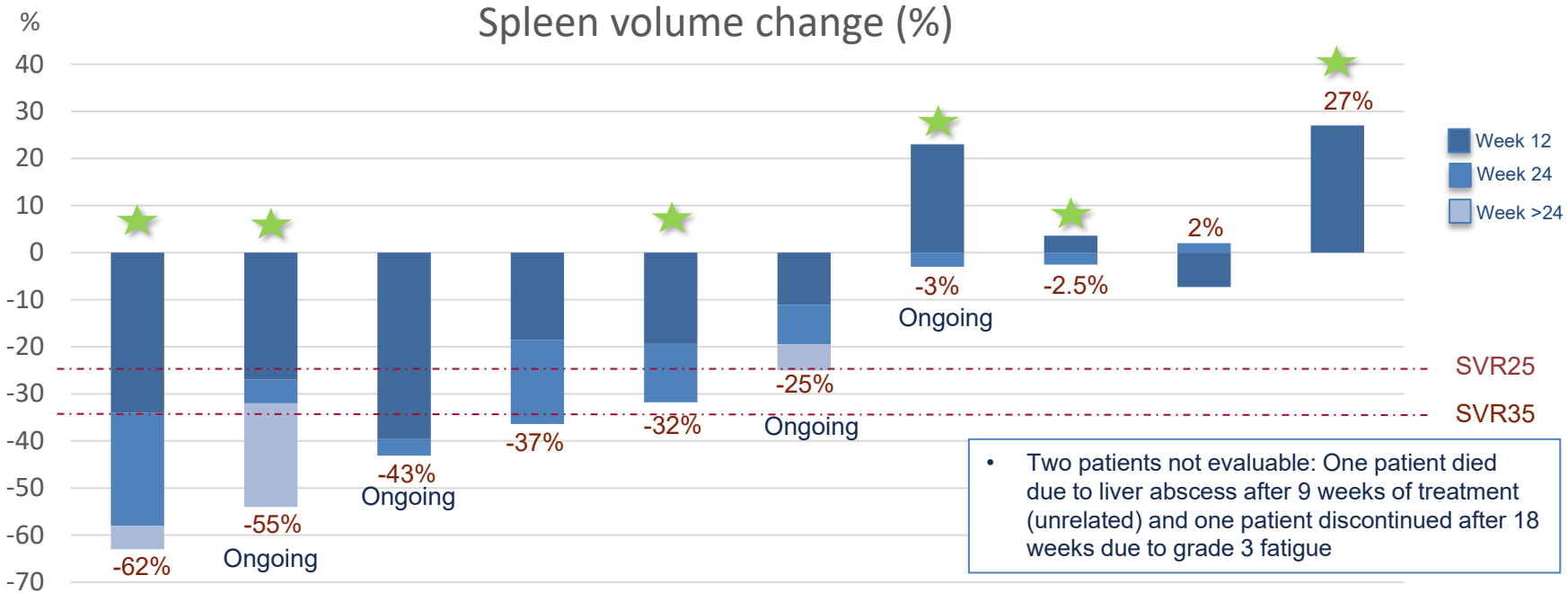
ESSENTIAL Baseline Demographics

- Between May 2019 and February 2021, 12 patients (pts) enrolled (7 men and 5 women)
- Median age 68 years (range 43 to 80)
- Median duration of JAKi therapy was 22 months (range 0.5 to 96 months)
- 92% (11 pts) had MF resistant to prior JAKi
- Median spleen volume at screening was 1454 cm^3 (range 835 to 5792 cm^3)
- Driver mutations were *JAK2* in 7 (58.3%), *CALR* in 4 (33.3%) and *MPL* in 1 (8.3%).
- 67% (8 pts) had at least one high risk molecular mutation
- Selinexor starting dose was 80 mg weekly in the first 6 pts and 60 mg for subsequent pts

ID	Driver mutation	Additional mutations	Prior treatments	Duration of prior JAKi therapy (months)	JAKi refractory or intolerant
01-001	JAK2	ASXL1, U2AF1	ruxolitinib, ruxolitinib + azacitidine	9	R
01-003	JAK2	IDH1	ruxolitinib	84	R
01-004	CALR	SF3B1, ASXL1	danazol ruxolitinib	3	R
01-005	JAK2	SF3B1	ruxolitinib danazol	20	R
01-006	MPL	SRSF2, RUNX1	pegylated interferon alfa, ruxolitinib, ruxolitinib + navitoclax, azacitidine	28	R
01-007	CALR	KRAS, SRSF2	ruxolitinib, pacritinib	84	R
01-008	JAK2	none	ruxolitinib	4	R
01-009	CALR	ASXL1, KRAS, DNMT3A, NRAS	ruxolitinib, ruxolitinib + navitoclax	96	R
01-010	CALR	SF3B1, ZRSR2	ruxolitinib	3	R
01-011	JAK2	SRSF2, GNAS	ruxolitinib	0.5	I
01-012	JAK2	TET2	ruxolitinib	24	R
01-013	JAK2	IDH1	ruxolitinib, ruxolitinib + navitoclax, navitoclax	46	R

Note: 01-002 was a screen failure.

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

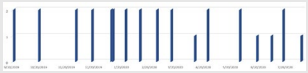
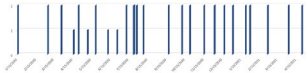


SVR35 at week 24 = 30%; SVR35 at ≥ week 24 = 40% (4/10 pts)

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)

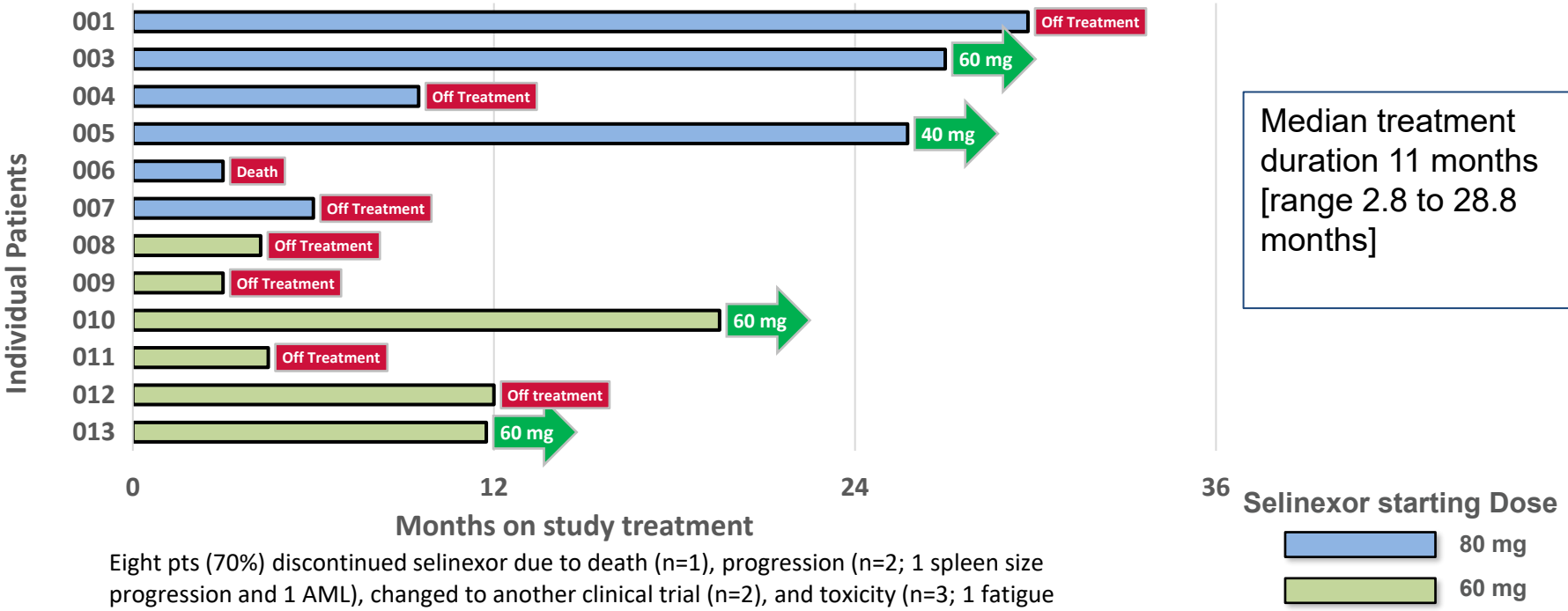
TD to TI occurred in 40%
(2 out of 5)

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)

TD = Transfusion Dependent ; TI = Transfusion Independent; Patient 006 is not evaluable due to discontinuation at 9 weeks; Patient 007, 009 and 013 had Hb >10 g/dL at baseline (Hgb 11.4, 12.8 and 10.6, respectively)

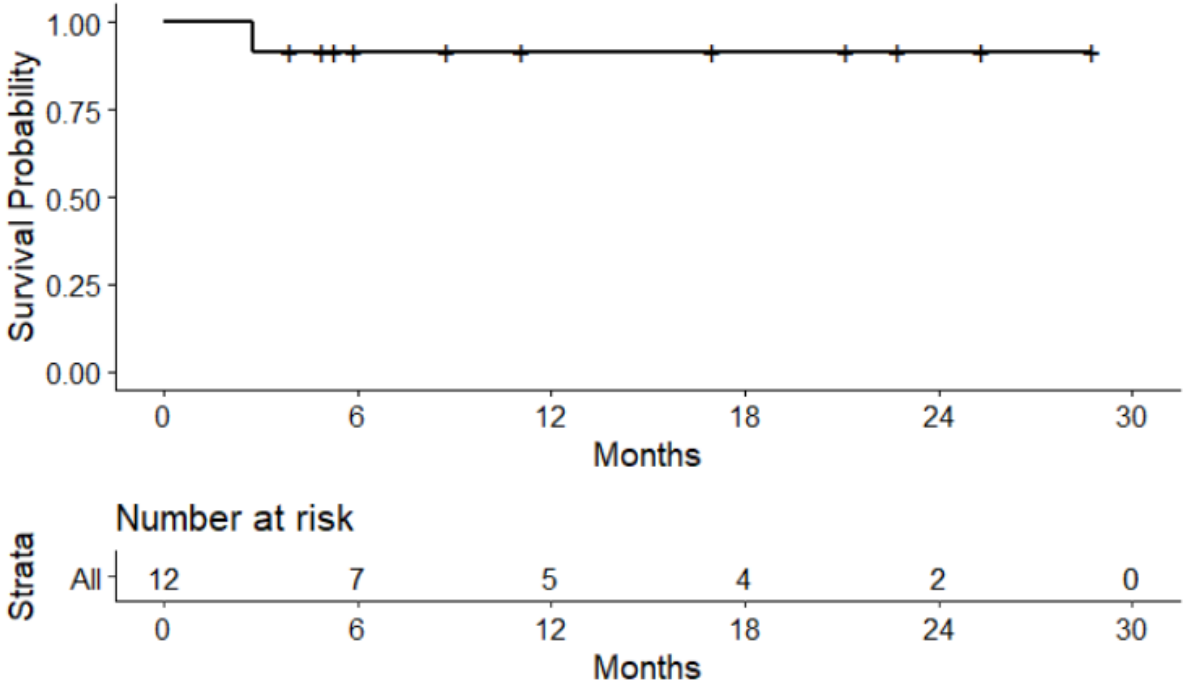
Swimmers Plot: Durable responses with long term therapy beyond 2 years



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)

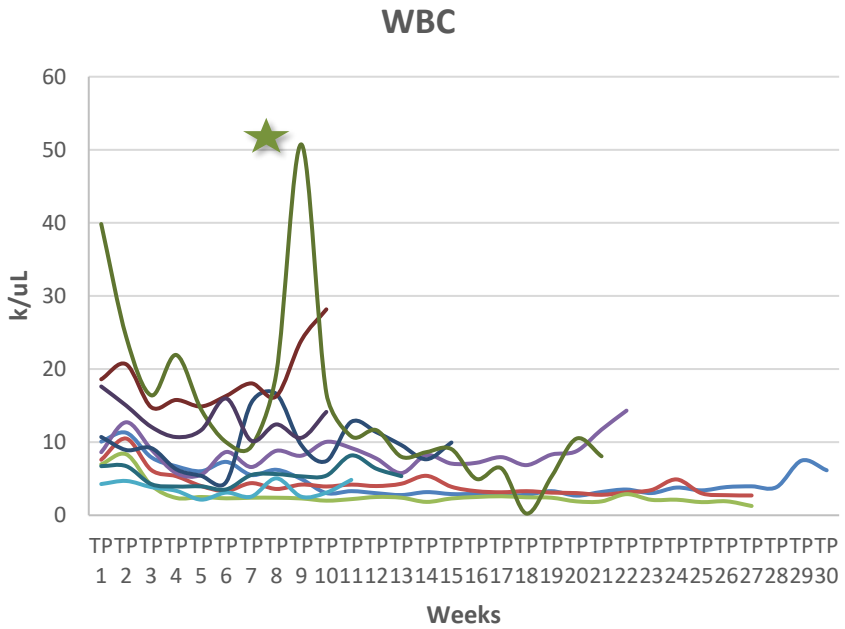
Overall Survival Status: current 2-year survival probability is 91.7%

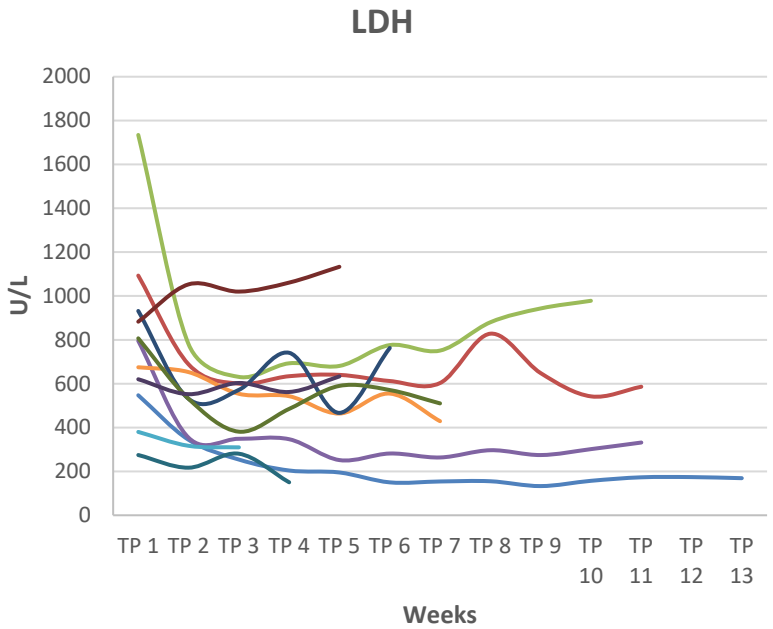


Median OS not reached after a median follow up of 11.1 months [range 3 to 30 months].

The 2-year survival probability is 91.7%

Selinexor treatment resulted in rapid decrease of total WBC and LDH concentrations

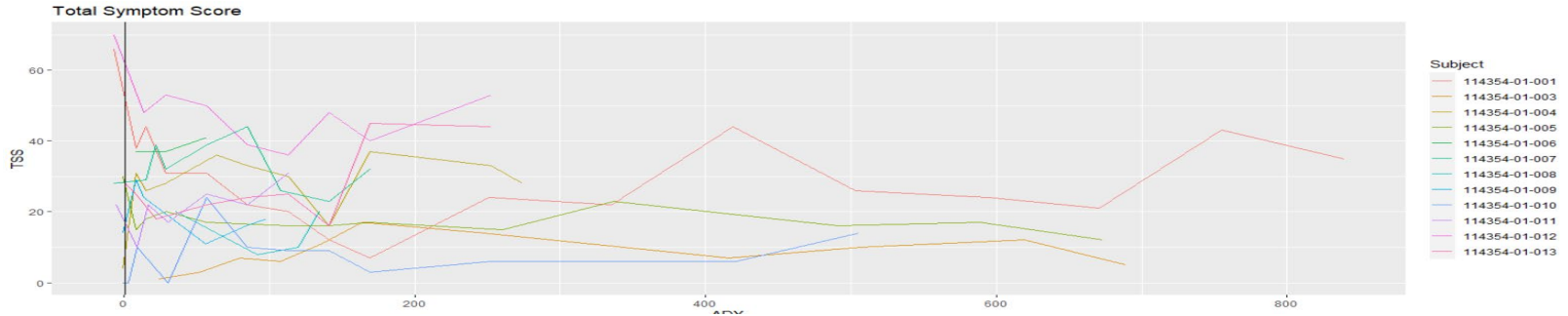




★ Patient 010: Reactive leukocytosis secondary to autoimmune hemolytic anemia (unrelated to selinexor)

MPN-SAF symptom score changes on selinexor

Patient	Score at screening	Best response
01-001	66	7
01-004	4	30
01-005	30	15
01-007	28	30
01-009	14	11
01-011	22	10
01-012	70	39
01-013	28	18



Patient 003, 006, 008 excluded due to missing TSS score at baseline. Patient 10 excluded due to score 0 at baseline

Safety

Treatment Emergent Adverse Events[1]	Selinexor 80 or 60 mg weekly (N = 12)		
Non-Hematologic	**Grade 1-2**	**Grade 3 and 4**	**Grade 5**
Weight loss	3 (25%)	1 (8%)	-
Fatigue	4 (33%)	4 (33%)	-
Dyspnea and Hypoxia	1 (8%)	2 (17%)	-
Hypertension	-	2 (17%)	-
Dizziness	3 (25%)	2 (17%)	-
Flu like symptoms	2 (17%)	2 (17%)	-
Sepsis	-	-	1 (8%)
Hematologic		**Grade 3 or 4**	**Grade 5**
Anemia	-	4 (33%)	-
Thrombocytopenia	-	2 (17%)	-

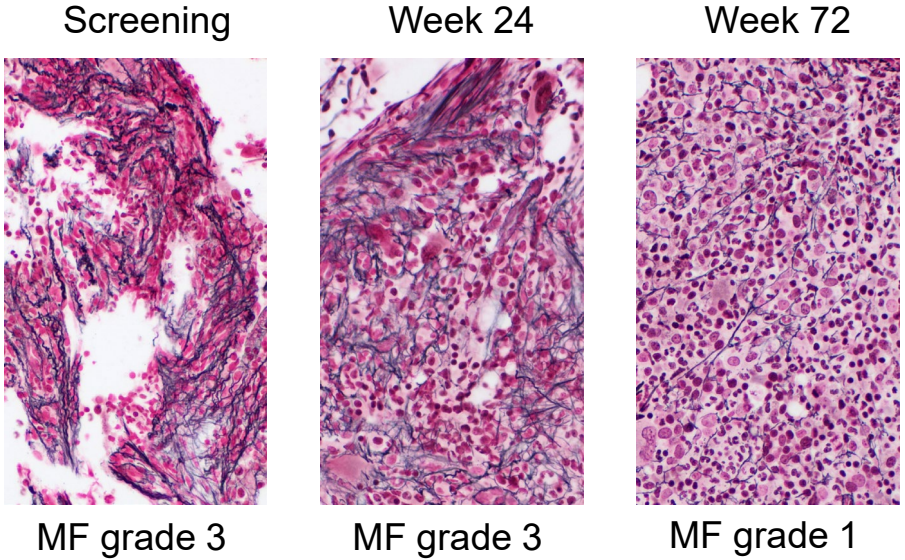
[1]**TEAE occurred in >1 patient**

- Ten pts required dose reduction due to fatigue (n=1), anemia (n=1), thrombo-cytopenia (n=2), abdominal pain (n=1) and weight loss (n=4)

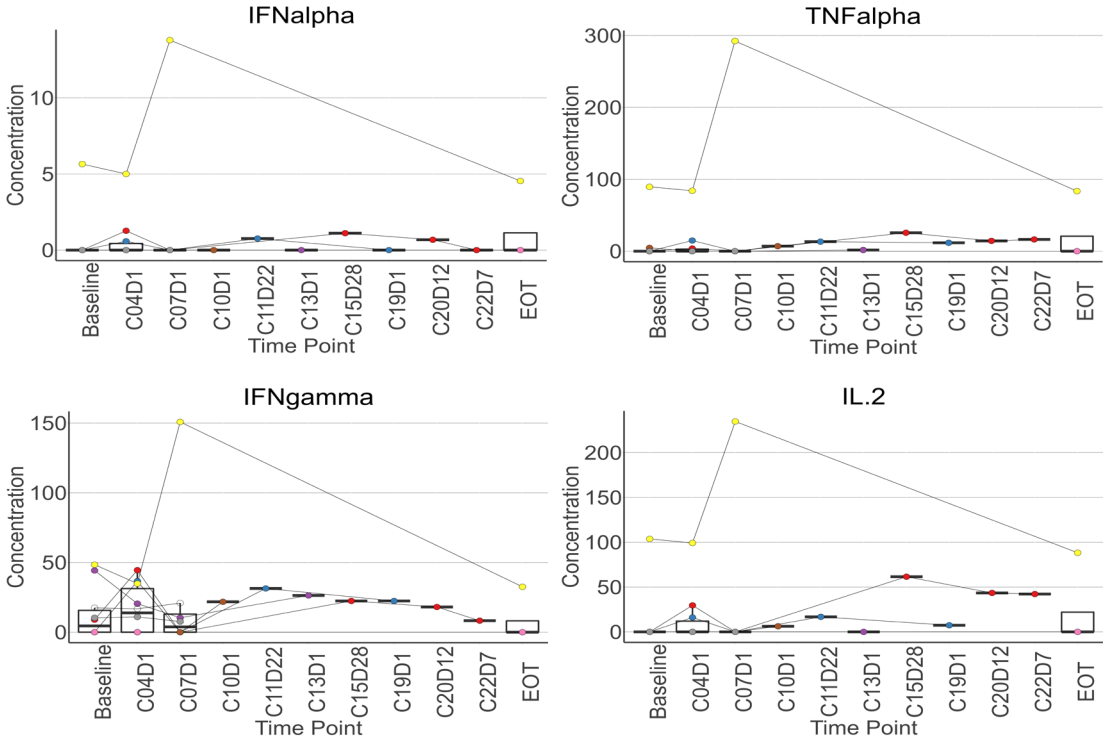
Reduction in marrow fibrosis at long term follow up supports potential disease modification

- 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)



Plasma inflammatory cytokines



Box plots demonstrating concentrations of representative cytokines at screening and during selinexor treatment.
Higher concentrations of cytokines were observed in pt 001-009 (yellow circle) who had progressive disease at week 12.

Conclusions

- Once weekly, low dose oral selinexor demonstrated robust single agent activity with sustained spleen responses in JAKi refractory MF
- Responses were durable with long term therapy beyond 2 years
- Improvement in anemia and symptom scores were observed
- Promising overall survival (median not reached and 2-year survival probability is 91.7%) in patients with historical poor OS
- Reduction in marrow fibrosis with long-term selinexor supports potential disease modification
- Long-term use of selinexor is safe with manageable side effect profile
- Two registration studies are currently underway in JAKi naïve (selinexor + ruxolitinib ; NCT04562389) and previously treated MF patients (selinexor alone; NCT04562870)