Selinexor Plus Ruxolitinib in JAK Inhibitor (JAKi)-Naïve Patients With Myelofibrosis: Long-Term Follow-up From XPORT-MF-034 Suggestive of Disease Modification

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The use of selinexor in myelofibrosis is investigational and not approved by any regulatory authority; the safety and efficacy of selinexor in myelofibrosis has not been established.

A Wide Range of Unmet Needs Persist in Myelofibrosis (MF)

MF is a heterogenous, progressive, and fatal disease characterized by splenomegaly and dysregulated Janus kinase/signal transducer and activator of transcription (JAK/STAT) and non-JAK/STAT pathways[1-3]

Underlying biological hallmarks of MF[1]:

- Aberrant blood and bone marrow differentiation: Dysregulated megakaryocyte/granulocyte proliferation
- Cytokine production and inflammation
- Bone marrow fibrosis and extramedullary hematopoiesis

An urgent need for therapies beyond JAK inhibitors (JAKi; e.g., ruxolitinib) persists due to:

Limited responses[2,3]

- < 50% of patients achieve Week 24 spleen volume reduction of 35% from baseline (SVR35) and total symptom score reduction of 50% from baseline (TSS50) with ruxolitinib[2]
- Probability of maintaining SVR35 decreases as early as Week 12 response in patients who achieved SVR35 with ruxolitinib[3]

Lack of evidence of disease modification[2,4]

- JAKi have limited ability to alter inflammation, bone marrow fibrosis, or prevent disease progression

Treatments for patient with cytopenic MF[2,5]

- Patients with anemia and thrombocytopenia have limited treatment options and may require suboptimal doses of ruxolitinib

Improved outcomes[2]

- MF continues to be a disease of decreased survival and significant morbidity

JAK, Janus kinase; JAKi, Janus kinase inhibitor; MF, myelofibrosis; SVR35, spleen volume reduction of 35% from baseline; TSS50, total symptom score reduction of 50% from baseline.

1. Tefferi A. *Am J Hematol*. 2023;98(5):801-821. **2.** Levavi H, et al. *Clin Adv Hematol Oncol*. 2022;20(7):456-467. **3.** Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):55. **4.** Fisher AC, et al. *Leukemia*. 2019;33(8):1978-1995. **5.** Maffioli M, et al. *Blood Adv*. 2022;6(6):1855-1864.

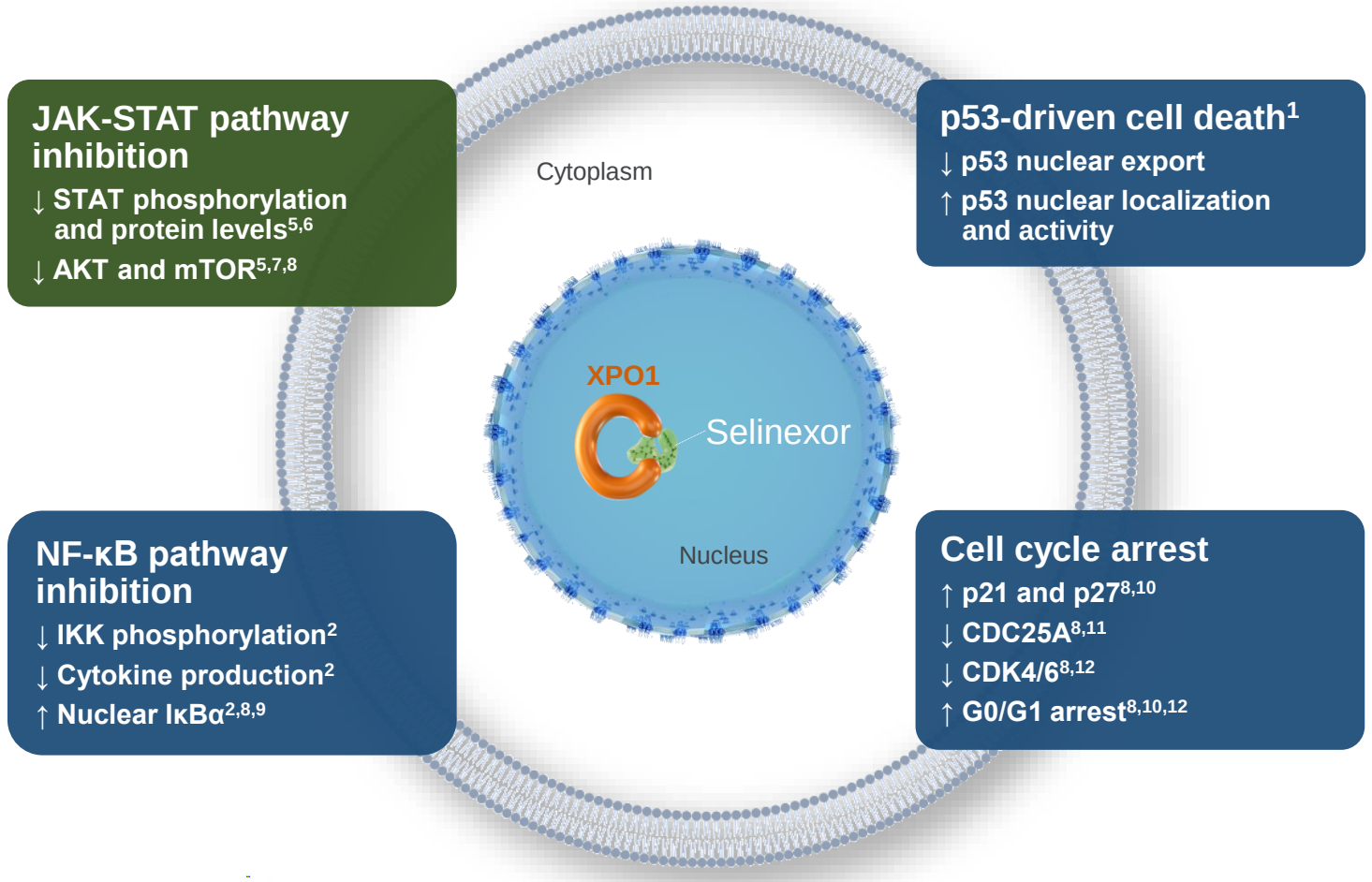
Selinexor is an Investigational Targeted Oral Exportin 1 (XPO1) Inhibitor

XPO1 Inhibition is a fundamental mechanism of action that may target both JAK/STAT and non-JAK/STAT pathways in MF

Selinexor inhibits XPO1-mediated nuclear cargo protein export that may lead to:

- Increased malignant cell death[1]
- Reduced inflammation[2]
- Apoptosis of *JAK2*-mutated MF CD34+ cells but not healthy donor cells[3]
- Synergism with ruxolitinib and other therapeutic agents in cell lines with or without *JAK2*^{V617F} and *TP53* mutations[4]

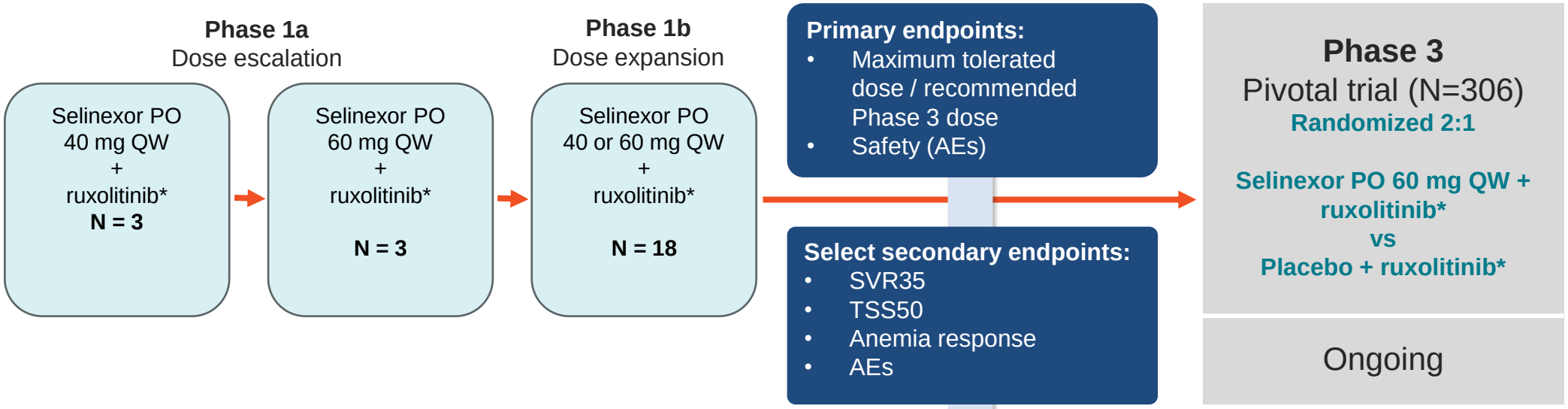
Poster 1792
Lu M, et al. Use of Combination Therapies Including the XPO1 Inhibitor Selinexor Is a Potential Effective Therapeutic Strategy to Treat Myelofibrosis Patients
Saturday, December 9, 2023: 6:00 PM–8:00 PM
Halls G–H (San Diego Convention Center)



AKT, protein kinase B; CD, cluster of differentiation; CDC, cell division cycle; CDK, cyclin-dependent kinase; IκBα, inhibitor of nuclear factor kappa-B kinase subunit alpha; IKK, inhibitor of nuclear factor-κB kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; pXX, tumor suppressor protein XX; XPO1, exportin 1.

1. Yan D, et al. *Clin Cancer Res*. 2019;25(7):2323-2335. **2.** Kashyap T, et al. *Oncotarget*. 2016;7(48):78883-78895. **3.** Lu M, et al. Poster presented at: 65th ASH Annual Meeting and Exposition; December 9–12, 2023; San Diego, CA. Abstract 1792. **4.** Maloof M, et al. Poster presented at: 15th International Congress for Myeloproliferative Neoplasms (MPN); November 2–3, 2023; Brooklyn, NY. **5.** Walker CJ, et al. *Blood*. 2013;122(17):3034-3044. **6.** Cheng Y, et al. *Mol Cancer Ther*. 2014;13(3):675-686. **7.** Argueta C, et al. *Oncotarget*. 2018;9(39);25529-25544. **8.** Gandhi UH, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(5):335-345. **9.** Turner JG, et al. *Oncotarget*. 2016;7(48):78896-78909. **10.** Gravina GL, et al. *BMC Cancer*. 2015;15:941. **11.** Garg M, et al. *Oncotarget*. 2017;8(5):7521-7532. **12.** Tan M, et al. *Am J Physiol Renal Physiol*. 2014;307(11):F1179-F1186.

XPORT-MF-034: A Phase 1/3 Study of Selinexor Plus Ruxolitinib for JAKi-Naïve Patients With MF (NCT04562389)



Select inclusion criteria:

- Spleen volume of ≥ 450 cm^3 by magnetic resonance imaging or computed tomography
- Dynamic International Prognostic Scoring System (DIPSS) intermediate-1 and symptomatic, intermediate-2, or high risk
- Eastern Cooperative Oncology Group 0–2
- Platelet count ≥ 100×10^9/L

AE, adverse event; DIPSS, Dynamic International Prognostic Scoring System; PO, by mouth; QW, once-weekly dosing; VAF, variant allele frequency.
*Ruxolitinib dosing per label

Patient Demographics and Baseline Characteristics of Selinexor 60 mg QW Cohort*

	Selinexor 60 mg QW + ruxolitinib (N = 14)
Demographics	
Age (years) median (min, max)	64.5 (58, 77)
Sex (female), n (%)	5 (35.7)
Weight (kg), median (min, max)	77.5 (54.7, 141.9)
Transfusion status, n (%)	
Transfusion independent	13 (92.9)
Transfusion dependent	1 (7.1)
MF type, n (%)	
Primary MF	7 (50.0)
Post-essential thrombocythemia MF	4 (28.6)
Post polycythemia vera MF	3 (21.4)
Mutations, n (%)	
JAK2	11 (78.6)
CALR	2 (14.3)
MPL	1 (7.1)
HMR†	5 (35.7)

	Selinexor 60 mg QW + ruxolitinib (N = 14)
DIPSS risk, n (%)	
Intermediate-1	3 (21.4)
Intermediate-2	8 (57.1)
High risk	3 (21.4)
Hemoglobin (g/dL) at baseline, n (%)	
< 10	8 (57.1)
≥ 10	6 (42.9)
Platelet count (10^9/L) at baseline, n (%)	
100 to < 150	2 (14.3)
≥ 150	12 (85.7)
Baseline spleen volume (cm^3), median (min, max)	1961.6 (650.1, 3657.0)
Baseline TSS, mean (SD)‡	21.6 (18.1)

As of August 1, 2023, a total of 24 patients received at least one dose of selinexor (40 mg: n = 10; 60 mg: n = 14)

CALR, calreticulin; HMR, high-molecular risk; max, maximum; min, minimum; MPL, myeloproliferative leukemia virus; TSS, total symptom score.

*Data cutoff date: August 01, 2023; †High-molecular risk genes include: *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SRSF2*, and *U2AF1*; ‡Based on the Myelofibrosis Symptom Assessment Form version 4.0 in patients with nonzero baseline score (N=12).

Treatment-Emergent Adverse Events (TEAEs) of Selinexor 60 mg QW Cohort*

TEAEs	Selinexor 60 mg QW + ruxolitinib (N = 14)
Any grade (≥ 30% overall), n (%)	
Nausea	11 (78.6)
Anemia	9 (64.3)
Thrombocytopenia	9 (64.3)
Fatigue	8 (57.1)
Constipation	7 (50.0)
Vomiting	7 (50.0)
Dyspnea	5 (35.7)
Headache	5 (35.7)
Hyponatremia	5 (35.7)
Leukopenia	5 (35.7)
Neutropenia	5 (35.7)
Grade 3+ (> 5%), n (%)	
Anemia	6 (42.9)
Thrombocytopenia	4 (28.6)
Back pain	2 (14.3)
Neutropenia	1 (7.1)
Atrial fibrillation	1 (7.1)
Leukopenia	1 (7.1)
Treatment-related AEs leading to treatment discontinuations, n (%)	
Thrombocytopenia, Grade 3	1 (7.1)
Peripheral neuropathy, Grade 3	1 (7.1)

Prophylactic Antiemetic use Reduced the Incidence and Severity of Nausea

Nausea was transient in nature with a median duration ~2 cycles

64% Patients in the 60 mg cohort received one prophylactic antiemetic

67% Of these patients had nausea (Grade 1 only)

Versus

100% Patients without antiemetic prophylaxis had nausea (Grades 1–3)

2.5 kg Median weight gain at Week 24

Median Hemoglobin (Hgb) Levels and Platelet Counts Were Generally Stable

46% Transfusion-independent patients had stable Hb levels†

Median Hgb levels (g/dL): **9.9** Baseline → **8.8** Week 12 → **9.1** Week 24

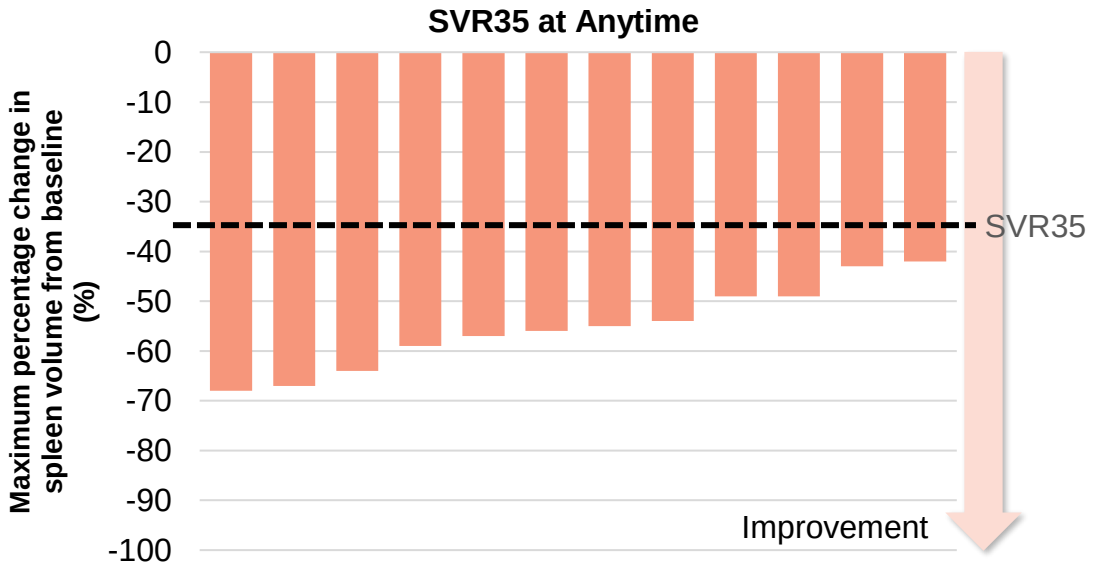
Median platelet levels ($\times 10^9$/L): **220** Baseline → **135** Week 12 → **137** Week 24

AE, adverse event; Hb, hemoglobin; TEAE, treatment-emergent adverse event.

*Data cutoff date: August 01, 2023; †Patients who do not have Hb level decreased by > 2 g/dL from baseline over the entire treatment duration and who remained transfusion independent.

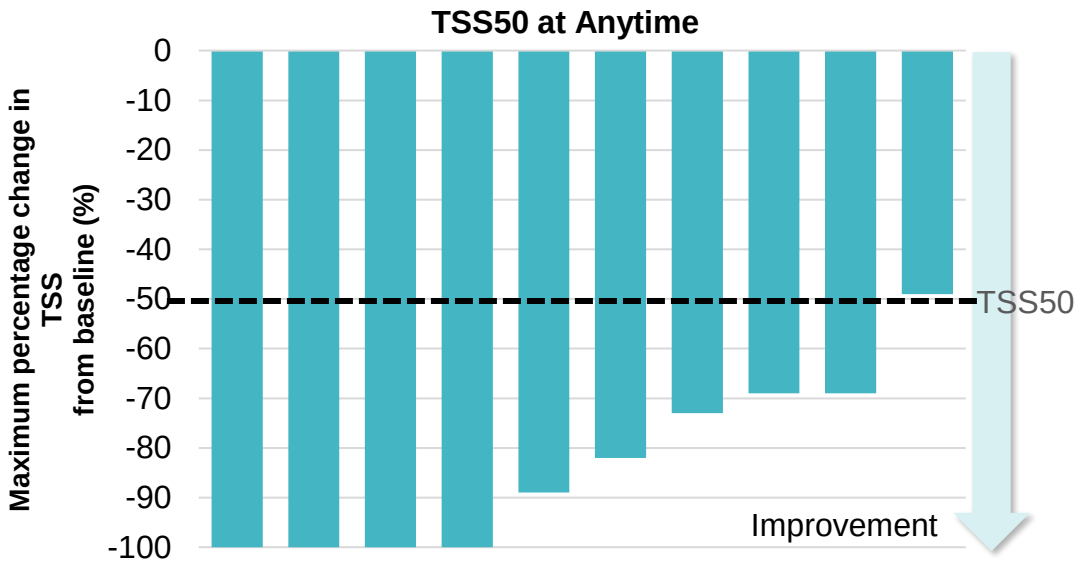
Spleen Volume Reduction (SVR) and Total Symptom Score (TSS) With Selinexor (60 mg QW) Plus Ruxolitinib*

		SVR35
Population	Timepoint	Selinexor 60 mg QW + ruxolitinib n (%)
Efficacy evaluable	Week 12	10/12† (83)
	Week 24	**11/12 (92)**
Intent-to-treat	Week 12	10/14 (71)
	Week 24	**11/14 (79)**



All patients in the efficacy evaluable population treated with selinexor 60 mg QW achieved an SVR35 at anytime

		TSS50
Population	Timepoint	Selinexor 60 mg QW + ruxolitinib n (%)
Efficacy evaluable	Week 12	8/10‡ (80)
	Week 24	**7/9§ (78)**
Intent-to-treat	Week 12	8/12 (67)
	Week 24	**7/12 (58)**



90% of patients in the efficacy evaluable population treated with selinexor 60 mg QW achieved an TSS50 at anytime

SVR, spleen volume reduction; TSS, total symptom score.

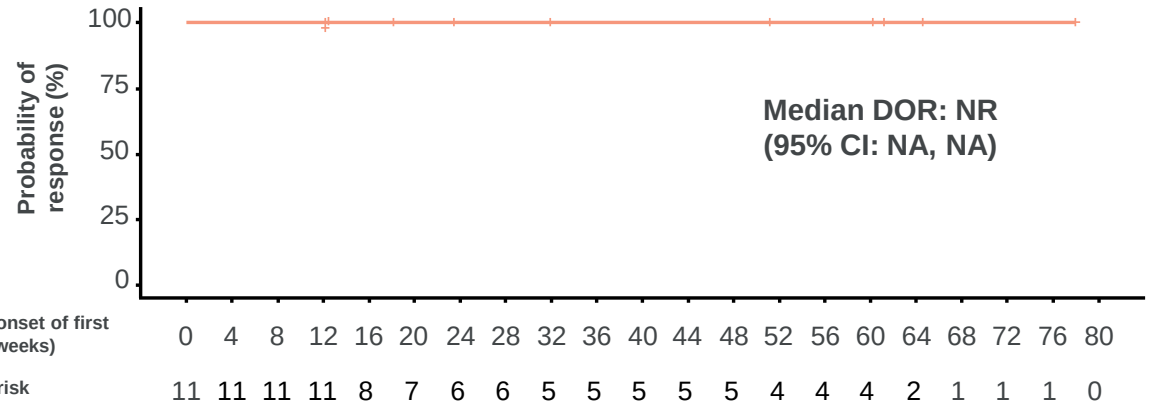
*Data cutoff date: August 01, 2023; †Two patients discontinued prior to Week 24; ‡One patient discontinued prior to Week 12; one patient with missing data at Week 12, who subsequently discontinued prior to Week 24; §Two patients discontinued prior to Week 24, and one had missing data.

Durability of SVR and TSS Responses With Selinexor (60 mg QW) Plus Ruxolitinib*

Duration of SVR Response†

in Patients Treated With Selinexor 60 mg QW Plus Ruxolitinib who Achieved SVR35 Response at Week 24 as of the Data Cutoff (August 1, 2023)

11 of 14 (79%) patients achieved SVR35 at Week 24



Median time to SVR35 response: 12.1 weeks
Median duration of follow-up: 32 weeks (range, 12–78)

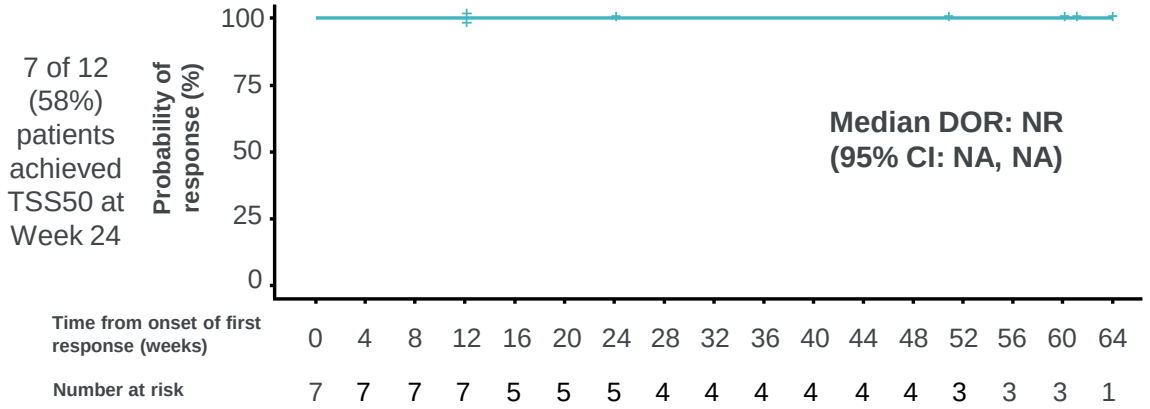
Change in Spleen Volume

- After the maximum 78 weeks of follow-up, median duration of SVR response has not been reached
- 100% probability of maintaining a SVR with a median follow-up time of 32 weeks (range, 12–78)

Duration of TSS Response‡

in Patients Treated With Selinexor 60 mg QW Plus Ruxolitinib who Achieved TSS50 Response at Week 24 as of the Data Cutoff (August 1, 2023)

7 of 12 (58%) patients achieved TSS50 at Week 24



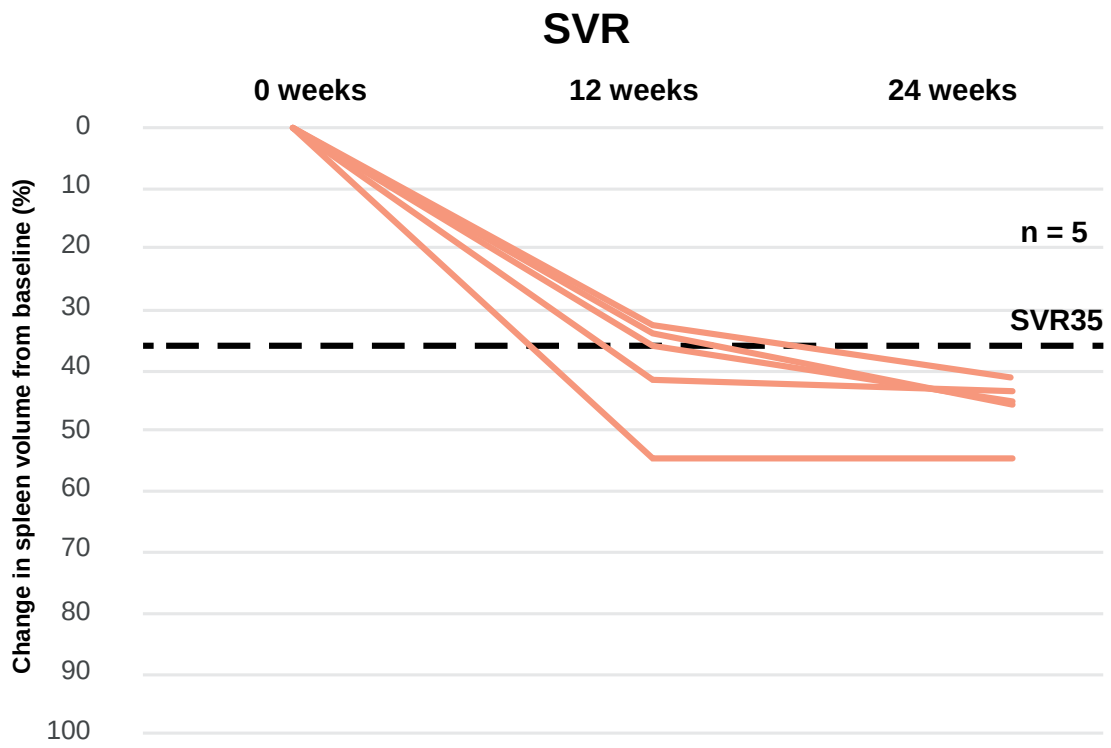
Median time to TSS50 response: 12.1 weeks
Median duration of follow-up: 51 weeks (range, 12–64)

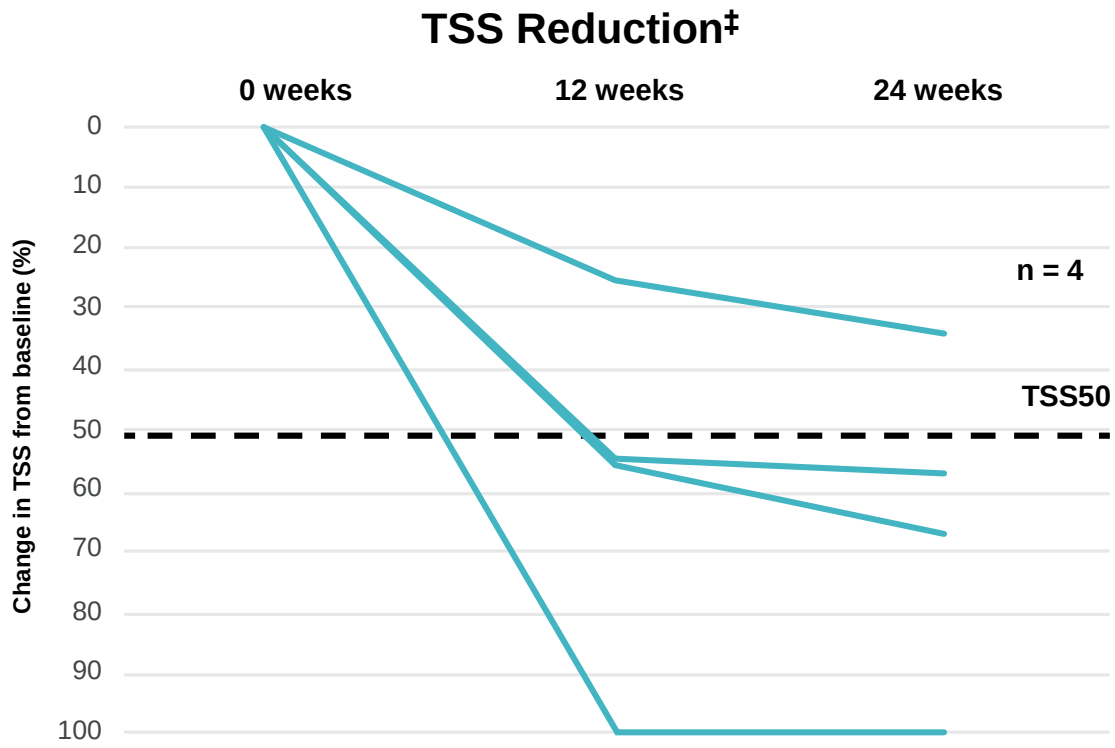
Change in TSS

- After up to 64 weeks of follow-up, the median duration of TSS response has not been reached
- 100% probability of maintaining TSS50 with a median follow-up time of 51 weeks (range, 12–64)

CI, confidence interval; DOR, duration of response; NA, not available; NR, not reached.
*Data cutoff date: August 01, 2023; †Response duration end date defined as date when subject's SVR showed less than or equal to 35% reduction from baseline and more than 25% increase from nadir; ‡Response duration end date defined as date when patient's TSS equals or exceeds the baseline value. The patient with 78 weeks follow-up for SVR had a baseline TSS of 0 and was not included in the TSS analysis.

SVR and TSS With Selinexor (60 mg QW) and Suboptimal Dose of Ruxolitinib (≤5 mg)*,†



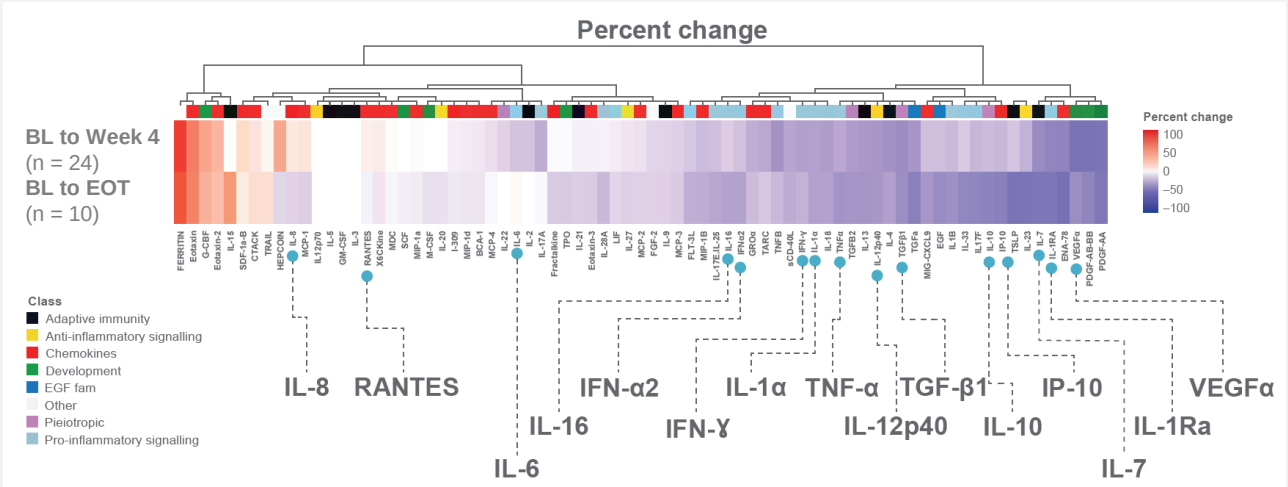


*Patients received ruxolitinib at ≤ 5 mg BID for at least five out of the first six cycles

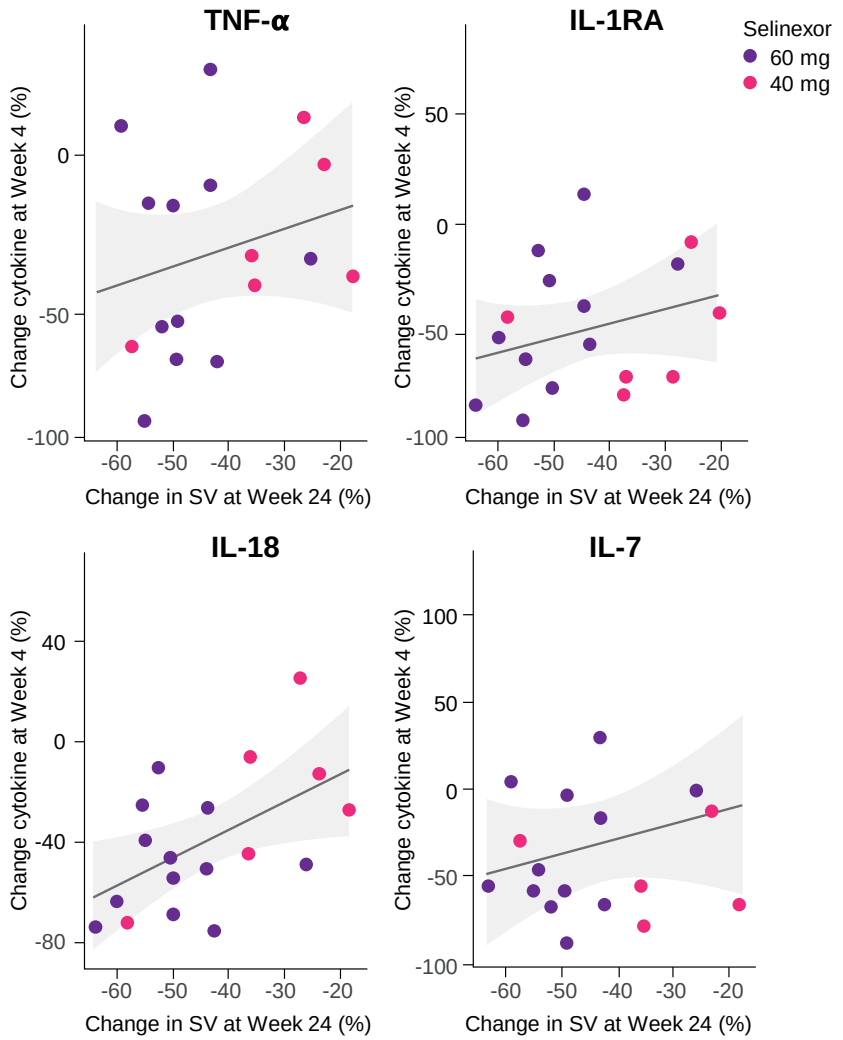
†Data cutoff date: August 01, 2023; ‡One patient with missing TSS50 score.

Cytokine Reduction and Correlation With SVR After Selinexor (40 or 60 mg QW) Plus Ruxolitinib

Early decreases in proinflammatory cytokines observed by Week 4 in evaluable patients and sustained to end of treatment (EOT) in evaluable patients*

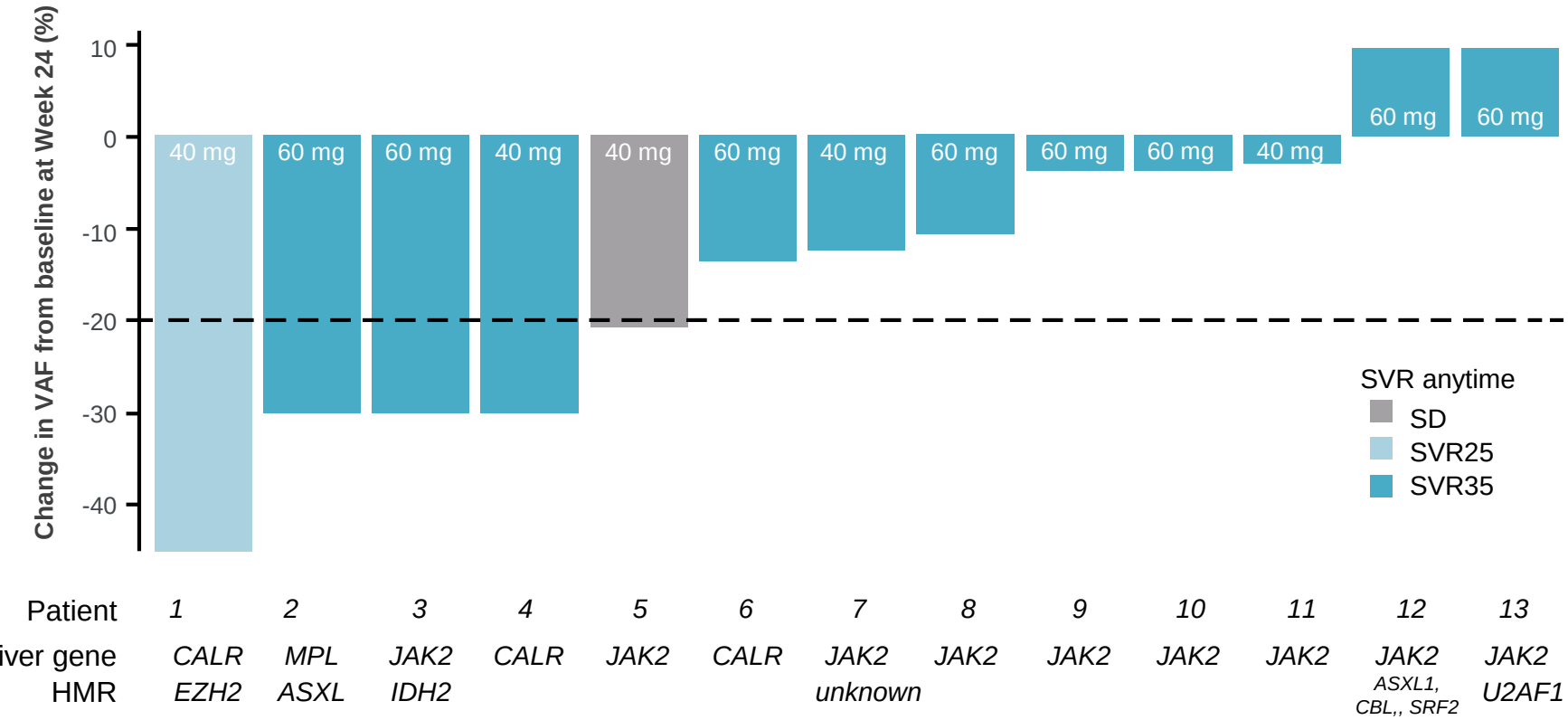


Cytokine changes at Week 4 associated with SVR at Week 24



BL, baseline; EGF, endothelial growth factor; EOT, end of treatment; IFN, interferon; IL, interleukin; IP-10, interferon-10-inducible protein 10 kDA; RANTES, regulated on activation, normal T-cell expressed and secreted; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.
*Analysis includes all patients who had at least one dose of selinexor (40 mg or 60 mg) and had cytokine levels at baseline and Week 4 and EOT.

Variant Allele Frequency (VAF) at Week 24 With Selinexor (40 or 60 mg QW) Plus Ruxolitinib



Reduced allele burden regardless of driver gene mutations were observed in 13 evaluable patients*

- ≥ 20% decreases in VAF were observed in five patients
  - Three of whom had ≥ 50% VAF at baseline and were high molecular risk (HMR)
- 13 of 24 patients had VAF values at baseline and Week 24; 11 of these 13 achieved SVR35 at any time

CALR, calreticulin; HMR, high molecular risk; MPL, myeloproliferative leukemia virus; SD, stable disease; SVR25, spleen volume reduction of 25% from baseline; VAF, variant allele frequency.
*Analysis includes all patients who had at least one dose of selinexor (40 mg or 60 mg) and had VAF values at baseline and Week 24.

Conclusions

- In the Phase 1 portion of XPORT-MF-034, selinexor plus ruxolitinib had a generally tolerable and manageable side-effect profile, most common adverse events were nausea, anemia, thrombocytopenia, and fatigue
- Encouraging signals of durable SVR and symptom improvement were observed with selinexor 60 mg QW plus ruxolitinib
  - 100% probability of maintaining SVR after a median follow-up of 32 weeks (range, 12–78)
  - 100% probability of maintaining TSS after a median follow-up of 51 weeks (range,12–64)
  - Rapid and deep SVR and robust symptom improvement at Weeks 12 and 24, even in patients receiving suboptimal doses of ruxolitinib
- The exploratory analysis of biomarkers impacting biological MF hallmarks was suggestive of disease modification
  - Reduced VAF for all three MF driver genes and rapid and sustained reduction of proinflammatory cytokine production were observed
  - Early cytokine reduction at Week 4 correlated with SVR at Week 24 and was sustained to EOT; patients receiving selinexor 60 mg QW were generally characterized by more profound reduction in cytokine levels
- Selinexor 60 mg QW plus ruxolitinib has the potential to become a novel, first-line treatment for JAKi-naïve patients with MF, which is being assessed in the ongoing Phase 3 trial

AE, adverse event.

Acknowledgments

Thank you to the patients, caregivers, study sites, and study investigators

To learn more about the ongoing clinical studies of selinexor in MF:

Phase 3 part of the XPORT-MF-034: Study design poster

Maher K, Rampal RK, Bose P, et al. A Global, Phase 3, Randomized, Double-blind Study to Evaluate Safety and Efficacy of Selinexor, an XPO1 Inhibitor, in Combination With Ruxolitinib in JAK-Inhibitor-Naïve Myelofibrosis (XPORT-MF-034) [abstract]. *Blood*. 2023. Abstract 3209

Study details on clinicaltrials.gov

Phase 2 selinexor monotherapy for patients with MF and moderate thrombocytopenia: Study design poster

Scandura JM, Gerds AT, Ritchie EK, et al. A Phase 2 Study to Evaluate the Efficacy and Safety of Selinexor Monotherapy in Patients With JAK Inhibitor-Naïve Myelofibrosis and Moderate Thrombocytopenia (XPORT-MF-044). [abstract]. *Blood*. 2023. Abstract 3211

Study details on clinicaltrials.gov

Sunday, December 10, 2023: 6:00 PM–8:00 PM Halls G–H (San Diego Convention Center)

- This study was funded by Karyopharm Therapeutics
- Medical writing support for this presentation was provided by dna Communications, funded by Karyopharm Therapeutics