Abstract: #130

Selinexor Plus Ruxolitinib in JAK Inhibitor Treatment-Naïve Patients With Myelofibrosis: Long-Term Follow-up and Disease Modification From XPORT-MF-034

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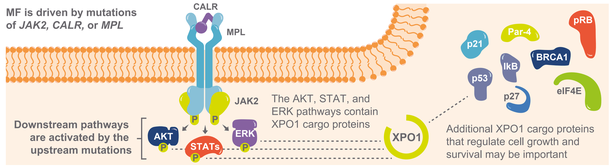
Introduction

- Myelofibrosis (MF) is a heterogenous, progressive, and fatal disease with the underlying biological hallmarks of aberrant blood and bone marrow differentiation, increased cytokine production and inflammation, bone marrow fibrosis with presence of driver mutations (e.g. *JAK2, CALR,* and *MPL)*, and dysregulated cell proliferation of megakaryocytes/granulocytes.[1,2]
- Current therapies, including ruxolitinib and other Janus kinase inhibitors (JAKis), primarily target the JAK/STAT pathway commonly overactivated in MF, but an urgent need remains for therapies with rapid, effective, and durable response that address underlying drivers of this disease.
  - <50% of patients achieve spleen volume reduction of 35% from baseline (SVR35) and total symptom score reduction of 50% from baseline (TSS50) with ruxolitinib at Week 24.[3]
  - Probability of maintaining response declines as early as Week 12 following response in patients who achieved SVR35 with ruxolitinib.[4]
- Selinexor is an investigational oral exportin 1 (XPO1) inhibitor with pro-apoptotic and anti-inflammatory properties that may impact both JAK and non-JAK pathways (**Figure 1**).[5,6]

Figure 1. Selinexor is a Targeted Oral XPO1 Inhibitor That Impacts Multiple Pathways Relevant in MF With Significant Treatment Potential



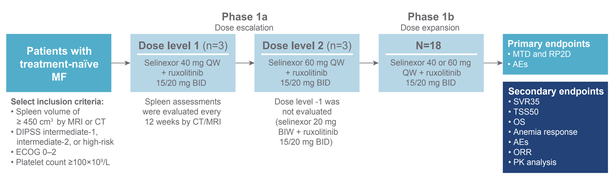
- Selinexor has single-agent antiproliferative activity in myeloproliferative cell lines and synergizes with other therapeutic agents, indicating its potential as a backbone for treatments for MF.
  - See the accompanying Poster 123: Maloof M, et al. Activity of Selinexor as a Single Agent and Synergistic Activity With Approved/Investigational Myelofibrosis Therapies in Vitro.
- Previously, both safety and efficacy data during Phase 1 of the XPORT-MF-034 trial (NCT04562389) were shown to support 60 mg as the dose to be used in the Phase 3 trial of selinexor plus ruxolitinib, with rapid, deep, and sustained spleen volume reduction and robust symptom improvement independent of ruxolitinib dose or baseline hemoglobin or platelet levels.[7]
- Here, we present long-term follow-up of these Phase 1 patients as well as exploratory data on clinical biomarkers of disease modification as of August 1, 2023, data cutoff.

Methods

Study Design

- Phase 1 of XPORT-MF-034 was an open-label study evaluating the safety and efficacy of selinexor (40 mg or 60 mg) once weekly plus ruxolitinib per standard of care in 28-day cycles in treatment-naïve patients with MF (**Figure 2**).

Figure 2. Study Design of Phase 1 of XPORT-MF-034



Cycle is defined as 28 days.

Study Populations

- Safety population: All patients in the 60 mg cohort who had at least one dose of selinexor.
- Durability analysis population: All patients treated with 60 mg selinexor who achieved response at Week 24 for SVR35 or TSS50, respectively.
- Biomarker analysis population: All patients who had at least one dose of selinexor (40 mg or 60 mg) and had longitudinal exploratory clinical biomarker data available, including variant allele frequency (VAF) at baseline and Week 24 or plasma cytokine levels at baseline and Week 4 (Cycle 2, Day 1) and end of treatment (EOT).

Results

- 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).

Table 1. Demographics and Baseline Disease Characteristics

	Selinexor 60 mg + ruxolitinib N=14
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)
Myelofibrosis type, n (%)	
PMF	7 (50.0)
PET-MF	4 (28.6)
PPV-MF	3 (21.4)
Mutations, n (%)	
JAK2	11 (78.6)
CALR	2 (14.3)
MPL	1 (7.1)
High-risk mutation*	5 (35.7)
DIPSS risk, n (%)	
Intermediate-1	3 (21.4)
Intermediate-2	8 (57.1)
High-risk	3 (21.4)
Hemoglobin (g/L) at baseline, n (%)	
<10	8 (57.1)
≥10	6 (42.9)
Platelet count (10^9/L) at baseline, n (%)	
100–<150	2 (14.3)
≥150	12 (85.7)
Baseline spleen volume (cm^3), median (min, max)	1961.6 (650.1, 3657.0)
Baseline TSS, median (min, max)†	12.0 (0, 54)

*High-risk genes include: *ASXL1, EZH2, IDH1, IDH2, SRSF2,* and *U2AF1*; †Based on the Myelofibrosis Symptom Assessment Form (MFSAF) version 4.0.

Table 2. Treatment-Emergent Adverse Events (TEAEs)

	Selinexor 60 mg + Ruxolitinib N=14
Any grade (≥25% 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)
Decreased appetite	4 (28.6)
Dysgeusia	4 (28.6)
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	1 (7.1)

- Most nausea events were Grade 1 (75%); one patient had Grade 3 nausea (no antiemetic prophylaxis).
- 64% of patients received one prophylactic antiemetic. Among the subgroup who received one prophylactic antiemetic, 67% of patients experienced nausea (Grade 1 only) compared with 100% of those who did not receive prophylactic antiemetic (Grades 1–3).
- Most vomiting events were Grade 1 and the only patient who experienced Grade 2 vomiting did not receive a prophylactic antiemetic.

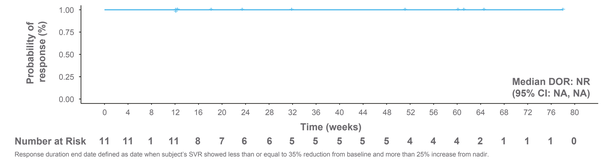
Time to Response and Durability

Table 3. SVR35 and TSS50 Responses

	Selinexor 60 mg + ruxolitinib N=14
Patients with SVR35 at Week 12, n (%)	10 (71)
Patients with SVR35 at Week 24, n (%)	11 (79)
Median time to SVR35 response, weeks	12.1
Median duration of SVR35 response, weeks	NR
Median follow-up time from SVR35 response, weeks	31.9 (18.1, NA)
Patients with TSS50 at Week 12, n (%)	8 (67)
Patients with TSS50 at Week 24, n (%)	7 (58)
Median time to TSS50 response, weeks	12.1
Median duration of TSS50 response, weeks	NR
Median follow-up time from TSS50 response, weeks	50.9 (12.1, NA)

- Treatment with selinexor plus ruxolitinib combination resulted in rapid and durable spleen response and symptom improvement (**Table 3**).

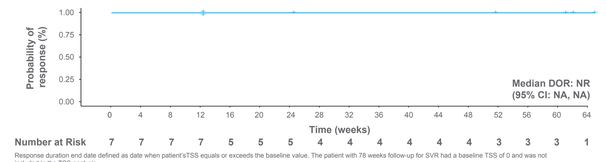
Figure 3. Duration of SVR Response in Patients Treated With Selinexor Plus Ruxolitinib Who Achieved SVR35 Response at Week 24 as of the Data Cutoff (August 1, 2023)



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.

- After up to 78 weeks of follow-up, the median duration of SVR response has not been reached.
- No responders have progressed; selinexor plus ruxolitinib treatment showed 100% probability of maintaining a SVR with a median follow-up time of 32 (12–78) weeks

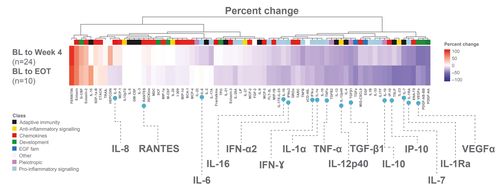
Figure 4. Duration of TSS Response in Patients Treated With Selinexor Plus Ruxolitinib Who Achieved TSS50 Response at Week 24 as of the Data Cutoff (August 1, 2023)



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.

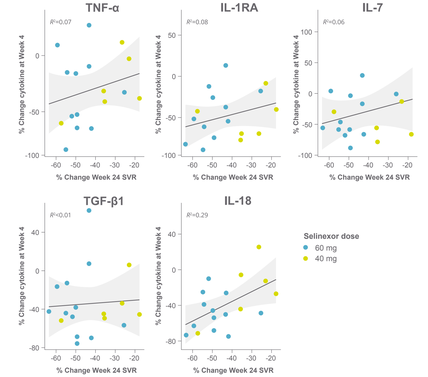
- After up to 64 weeks of follow-up, the median duration of TSS response has not been reached.
- Selinexor plus ruxolitinib treatment showed 100% probability of maintaining TSS50 with a median follow-up time of 51 (12–64) weeks.

Figure 5. Early, Rapid, and Sustained Reduction of Proinflammatory Cytokines Were Observed in Samples From Patients Receiving Selinexor Plus Ruxolitinib



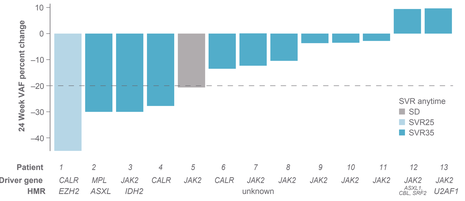
- In patients treated with selinexor plus ruxolitinib, early, rapid, and sustained reduction of proinflammatory cytokines was observed (**Figure 5**).
  - At baseline, 76% of the 75 cytokines analyzed were elevated in MF samples compared with healthy donor samples (data not shown).
  - In the majority of patients treated with selinexor plus ruxolitinib, early (by Week 4) and sustained (into EOT) decreases in proinflammatory MF-relevant cytokines were observed, including large decreases in TGF-β1, IFNγ, TNF-α, IL-7, IL-1Ra, and IL-16.

Figure 6. Associations Between Early Reduction (Week 4) in Plasma Cytokines and SVR at Week 24 Were Observed



- Rapid proinflammatory cytokine reduction was observed at Week 4 that correlated with spleen volume reduction (**Figure 6**).

Figure 7. Percent VAF Changes in Patients Treated With Selinexor Plus Ruxolitinib at Week 24 (N=13)



- Reduced allele burden regardless of MF driver gene mutations were observed with selinexor plus ruxolitinib (**Figure 7**).
  - VAF change ≥20% was observed in five patients; three of these patients 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 acheived SVR35 at any time.

Conclusions

- Selinexor plus ruxolitinib had a generally tolerable and manageable side-effect profile.
  - Nausea was mostly Grade 1 and transient and gastrointestinal toxicities were manageable with prophylactic antiemetics.
- Treatment with selinexor plus ruxolitinib resulted in rapid, deep, and sustained spleen response and robust symptom improvement.
  - 100% (11/11) of patients who achieved SVR35 response at Week 24 maintained response after a maximum of 78 weeks and a median of 32 weeks follow-up.
  - 100% (7/7) of patients who achieved TSS50 response at Week 24 maintained response after a maximum of 64 weeks and a median of 51 weeks follow-up.
- In this exploratory biomarker analysis, signals of promising efficacy were associated with evidence suggestive of disease modification, indicating that selinexor plus ruxolitinib has the potential to become a novel, first-line treatment for JAKi-naïve patients with MF.
  - Reduced VAF for all three MF driver genes and rapid and sustained reduction of pro-inflammatory cytokine production were observed with selinexor plus ruxolitinib treatment, suggestive of disease modification and impact on the biological hallmarks of MF.
  - Early cytokine reduction at Week 4 correlated with SVR35 achievement at Week 24 and was sustained to EOT.
- A double-blind, randomized, Phase 3 trial of selinexor 60 mg plus ruxolitinib vs placebo plus ruxolitinib in JAKi-naïve patients with MF is ongoing (NCT04562389).

Abbreviations

AE, adverse event; AKT, protein kinase B; BL, baseline; BID, twice-daily dosing; BIW, twice-weekly dosing; BRCA1, breast cancer gene 1; CALR, calreticulin; CBL, casitas B-lineage lymphoma; CI, confidence interval; CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGF, endothelial growth factor; EOT, end of treatment; eIF4E, eukaryotic translation initiation factor 4E; ERK, extracellular signal–regulated kinase; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; HMR, high molecular risk; IDH, isocitrate dehydrogenase; IFN, interferon; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; IP-10, interferon-10-inducible protein 10 kDA; IWG-MRT, International Working Group for Myelofibrosis, Research, and Treatment; JAK, Janus kinase; JAKi, Janus kinase inhibitor; max, maximum; MF, myelofibrosis; min, minimum; MPL, myeloproliferative leukemia virus; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; NA, not achieved; NR, not reached; OS, overall survival; ORR, overall response rate; p, phosphorylated; p21/27/53, tumor suppressor protein 21/27/53; Par-4, prostate apoptosis response 4; PET, post-essential thrombocythemia; PK, pharmacokinetics; PMF, primary myelofibrosis; PPV, post-polycythemia vera; pRB, RB protein; QW, once-weekly; RANTES, regulated on activation, normal T cell expressed and secreted; RP2D, recommended Phase 2 dose; STAT, signal transducer and activator of transcription; SD, stable disease; SRSF2, serine and arginine rich splicing factor 2; SVR, spleen volume reduction; SVR25, spleen volume reduction of 25% from baseline; SVR35, spleen volume reduction of 35% from baseline; TEAE, treatment-emergent adverse event; TGF, transforming growth factor; TNF, tumor necrosis factor; TSS, total symptom score; TSS50, total symptom score reduction of 50% from baseline; U2AF, U2 small nuclear RNA auxiliary factor 2; VAF, variant allele frequency; VEGF, vascular endothelial growth factor; XPO1, exportin 1.

References

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Disclosures

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