Abstract: P1020

Selinexor plus ruxolitinib in JAK inhibitor treatment-naïve patients with myelofibrosis: Updated results from XPORT-MF-034

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INTRODUCTION

- Myelofibrosis (MF) is a myeloproliferative neoplasm that commonly harbors somatic gene driver-mutations in Janus kinase 2 (JAK2), calreticulin (CALR), and myeloproliferative leukemia virus (MPL) genes[1]
- Development of severe thrombocytopenia is a negative prognostic marker in MF and an early indicator of blast transformation. Furthermore, treatment-emergent thrombocytopenia is the leading cause of discontinuation of ruxolitinib, a JAK2 inhibitor (JAKi) that is standard-of-care[2-4]
- Other unmet needs persist with ruxolitinib for the treatment of JAKi-naïve patients with MF:
  - <50% of patients achieved SVR35 and TSS50 with ruxolitinib at Week 24 in the Phase 3 ruxolitinib trial[5] and male patients achieved an SVR35 of ~25% at Week 24[6]
  - Most real-world patients (~70%) are started at a dose ≤15 mg BID but at those doses <27% of patients achieve a spleen response[7]
  - Overall survival is short; SVR35 is correlated with overall survival[7,9]
- Selinexor is an investigational oral XPO1 inhibitor that may inhibit MF-relevant pathways including STAT, extracellular signal-regulated kinase (ERK), and protein kinase B (AKT).[10] Preclinical studies have shown potential synergy of selinexor and ruxolitinib treatment in vivo[11]
- Previously, both efficacy and safety data were shown to support the 60 mg dose of selinexor as the recommended Phase 3 selinexor dose in combination with ruxolitinib.[12] Updated results with subgroup analyses are presented here

METHODS

Trial Design

- XPORT-MF-034 (NCT04562389) is a Phase 1, open-label study evaluating safety and efficacy of selinexor at 40 mg and 60 mg once-weekly plus ruxolitinib per standard of care in 28-day cycles in patients with treatment-naïve myelofibrosis
- **Select inclusion criteria:** Spleen volume of ≥ 450 cm^3 by MRI or CT; DIPSS intermediate-1, intermediate -2, or high-risk; ECOG 0-2; Platelet count ≥ 100 x 10^9/L.
- **Primary endpoints:** MTD, RP2D, and adverse events (AEs)
- **Key secondary endpoints:** SVR35, TSS50, OS, anemia response, AEs, ORR, and PK analysis
- **Analysis populations**
  - **Safety population:** All patients who received at least one dose of selinexor
  - **Efficacy evaluable population (EE):** Spleen assessment: All patients who had at least one dose of selinexor and an evaluation at the timepoint (12 or 24 weeks): Symptom assessment; Patients who had symptoms at baseline and a TSS evaluation at the timepoint (12 or 24 weeks)
  - **Intent-to-treat (ITT) population (primary analysis population):** Spleen assessment: All patients who had at least one dose of selinexor; Symptom assessment: All patients who had at least one dose of selinexor but excludes those who had no symptoms at baseline (TSS=0)

RESULTS

Table 1. Baseline Characteristics

Characteristic	Selinexor 60 mg + ruxolitinib (N=14)	Characteristic	Selinexor 60 mg + ruxolitinib (N=14)
Age (years), median (range)	64.5 (58-77)	**Mutations, n (%)**	
Female, n (%)	5 (35.7)	*JAK2*	11 (78.6)
Baseline weight (kg), median (range)	77.5 (54.7-141.9)	*CALR*	2 (14.3)
Transfusion Status, n (%)		*MPL*	1 (7.1)
Transfusion-Dependent	1 (7.1)	High-risk mutation*	5 (35.7)
Transfusion-Independent	13 (92.9)	**Hemoglobin (g/dL), n (%)**	
MF type, n (%)		<10	8 (57.1)
Primary MF	7 (50.0)	≥10	6 (42.9)
Post-ET MF	4 (28.6)	**Platelets (10^9/L), n (%)**	
Post-PV MF	3 (21.4)	100 to <150	2 (14.3)
DIPSS risk, n (%)		≥150	12 (85.7)
Int-1	3 (21.4)	**Baseline spleen volume (cm^3), median (range)**	1961.6 (650.1-3657.0)
Int-2	8 (57.1)	1800 cm^3	7 (50)
High	3 (21.4)	>1800 cm^3	7 (50)

DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; PV, polycythemia vera. *High-risk genes include: *ASXL1, EZH2, IDH1, IDH2, SRSF2, U2AF1*

RESULTS

- Results are as of Apr 10, 2023 data cutoff

Table 2. SVR35

Population	Timepoint	Selinexor 60 mg +ruxolitinib, n (%)
Efficacy Evaluable	SVR35 at Week 12	10/12* (83.3)
	SVR35 at Week 24	11/12 (91.7)
	SVR35 at anytime	12/12 (100.0)
Intent-to-Treat	SVR35 at Week 12	10/14 (71.4)
	SVR35 at Week 24	11/14 (78.6)
	SVR35 at anytime	12/14 (85.7)

*One patient discontinued prior to Week 12; one patient with missing data at Week 12 who subsequently discontinued prior to Week 24

- TSS50 at Week 24 was achieved by 77.8% (7/9) in the EE population (2 patients discontinued prior to reaching Week 24 and 1 had missing data), and by 58.3% (7/12) in the ITT. Two patients with baseline TSS of 0 were excluded

Figure 1. Symptom scores at W12 & W24 in the 60 mg cohort

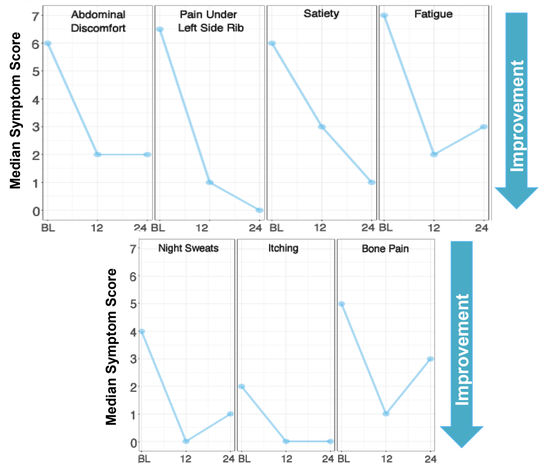
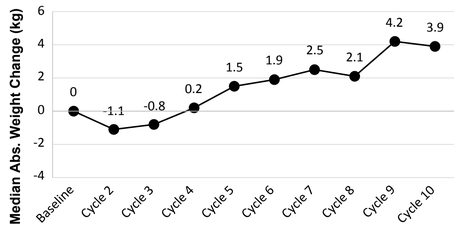


Table 3. Treatment-emergent adverse events (TEAE)

TEAEs	Selinexor 60 mg + ruxolitinib (N=14)	TEAEs	Selinexor 60 mg + ruxolitinib (N=14)
Any grade, >25% population		**Grade 3+, >10% population**	
Nausea	11 (78.6)	Anemia	6 (42.9)
Anemia	9 (64.3)	Thrombocytopenia	4 (28.6)
Thrombocytopenia	9 (64.3)	Back pain	2 (14.3)
Fatigue	8 (57.1)	**TRAEs leading to treatment discontinuations**	
Constipation	7 (50.0)	Thrombocytopenia, Grade 3	1 (7.1)
Vomiting	7 (50.0)	Peripheral Neuropathy	1 (7.1)
Headache	5 (35.7)		
Dyspnea	5 (35.7)		
Neutropenia	5 (35.7)		
Hyponatremia	5 (35.7)		
Leukopenia	5 (35.7)		
Decreased appetite	4 (28.6)		
Dysgeusia	4 (28.6)		
Back Pain	4 (28.6)		
Fall	4 (28.6)		
Myalgia	4 (28.6)		
Pain in Extremity	4 (28.6)		
Contusion	4 (28.6)		

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

Figure 2. Weight change in the 60 mg cohort



- Despite nausea and vomiting incidence, patients generally did not experience weight loss. Patient median weight increase at Week 24 was 2.5 kg

Table 4. SVR35 at Week 24 by subgroup in the 60 mg cohort

Subgroup	SVR35 at Week 24 for 60 mg cohort	
	n/N	Response Rate
Gender		
Female	4/5	80 (28.4-99.5)
Male	7/9	77.8 (40-97.2)
Age		
18-65	6/7	85.7 (42.1-99.6)
≥65	5/7	71.4 (29-96.3)
Ruxolitinib Starting Dose		
15/20 mg BID	6/8	75 (34.9-96.8)
5/10 mg BID	5/6	83.3 (35.9-99.6)
MF type		
Primary	6/7	85.7 (42.1-99.6)
Secondary	5/7	71.4 (29-96.3)
DIPSS Risk		
High Risk	2/3	66.7 (9.4-99.2)
Intermediate 1	2/3	66.7 (9.4-99.2)
Intermediate 2	7/8	87.5 (47.3-99.7)
JAK2 Mutation		
Yes	9/11	81.8 (48.2-97.7)
No	2/3	66.7 (9.4-99.2)
Baseline Platelet		
≤200 K	4/6	66.7 (22.3-95.7)
>200 K	7/8	87.5 (47.3-99.7)
Baseline Hemoglobin		
<10 g/dL	6/8	75.0 (34.9-96.8)
≥10 g/dL	5/6	83.3 (35.9-99.6)
Baseline Spleen Volume		
<1800 cm^3	5/7	71.4 (29-96.3)
≥1800 cm^3	6/7	85.7 (42.1-99.6)
Baseline TSS		
<20	7/9	77.8 (40-97.2)
≥20	4/5	80 (28.4-99.5)

CONCLUSIONS

- **The selinexor 60 mg dose was generally well tolerated and manageable allowing most patients to remain on therapy; most common AEs were nausea, anemia, thrombocytopenia, and fatigue**
  - For patients who received prophylactic anti-emetics, nausea and vomiting was limited to Grade 1, suggesting that nausea and vomiting may be able to be further managed with mandatory, dual antiemetics for the first two cycles
  - Median weight gain at Week 24 was 2.5 kg, despite the incidence of nausea and vomiting
- **In patients treated with 60 mg selinexor in combination with ruxolitinib, rapid, deep, and sustained spleen responses were observed across all subgroups**
  - SVR35 were observed in 100% of evaluable patients at anytime and SVR35 rates at Week 24 were consistent by gender and regardless of ruxolitinib starting dose
- **Robust symptom improvement was also observed with 77.8% of evaluable patients achieving TSS50 at anytime and improvements were observed across all spleen and cytokine related symptoms**
- **A double-blind, randomized, phase 3 trial of selinexor 60 mg + ruxolitinib vs placebo + ruxolitinib in JAKi treatment-naïve patients with MF planning to initiate 1H 2023**

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