Abstract: CT261

A phase 1, open-label, dose-escalation study of selinexor plus ruxolitinib in patients with treatment-naïve myelofibrosis

H. Ali[1], A. Kishtagari[2], K. Maher[3], S. Mohan[2], K. Ansaldo[4], X. Wang[4], K. Chamoun[4], J. T. Prchal[5], S. K. Tantravahi[5]

1. City of Hope Comprehensive Cancer Center, 2. Vanderbilt Ingram Cancer Center, 3. VCU Massey Cancer Center, 4. Karyopharm Therapeutics, 5. Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, University of Utah

INTRODUCTION

- Myelofibrosis (MF) is a myeloproliferative neoplasm that commonly harbors acquired somatic gene mutations in *JAK2*, *CALR*, or *MPL*[1]
- Despite treatment with the current standard of care, ruxolitinib, significant unmet need remains for treatment naïve MF patients
  - <50% of patients achieved SVR35 and TSS50 with ruxolitinib at Week 24 in the Phase 3 ruxolitinib trial[2]
  - The leading cause of ruxolitinib discontinuations is thrombocytopenia, which is associated with shorter survival[3,4,5]
  - Overall survival is short; SVR35 is correlated with overall survival[6,7]
- Selinexor is an oral XPO1 inhibitor that may inhibit multiple pathways relevant in MF including STAT, ERK, and AKT. Preclinical studies have shown potential synergy of selinexor and ruxolitinib treatment *in vivo*[8]

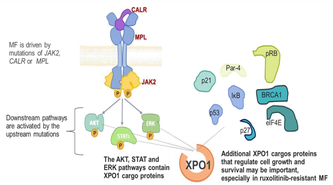


Figure 1. Proposed mechanism of action of selinexor in myelofibrosis. Adapted from Green et al.[9]

METHODS

XPORT-MF-034 Trial Design (NCT04562389)

Phase 1a
Dose escalation
completed

Phase 1b
Dose expansion
enrollment completed

Patients with treatment-naïve myelofibrosis

Dose level 1 (n=3)
Selinexor 40 mg QW + Ruxolitinib 15/20 mg BID

Dose level 2 (n=3)
Selinexor 60 mg QW + Ruxolitinib 15/20 mg BID

N=18
Selinexor 40 or 60 mg QW + Ruxolitinib 15/20 mg BID

Primary Endpoints:
- MTD and RP2D
- AEs

Key Secondary Endpoints:
- SVR35
- TSS50
- OS
- Anemia response
- AEs
- ORR
- PK analysis

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

Spleen assessments were evaluated every 12 weeks by CT/MRI

Dose level -1 was not evaluated (Selinexor 20 mg BIW + Ruxolitinib 15/20 mg BID)

AE, adverse event; BID, twice a day; BIW, twice a week; DIPSS, Dynamic International Prognostic Scoring System; ECOG, Eastern Cooperative Oncology Group; MTD, maximum tolerated dose; ORR, overall response rate; QW, once weekly; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SVR35, spleen volume reduction of at least 35%; TSS50, total symptom score reduction ≥ 50%.
Cycle is defined as 28 days.

Efficacy and Safety 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; excludes those who had no symptoms at baseline (TSS=0).

RESULTS

Table 1. Patient baseline characteristics

	Selinexor 40mg + ruxolitinib (N=10)	Selinexor 60mg + ruxolitinib (N=14)
Age (years), median (range)	57.5 (44-71)	64.5 (58-77)
Female, n (%)	3 (30.0)	5 (35.7)
Baseline weight (kg), median (range)	83.6 (53.0-94.4)	77.5 (54.7-141.9)
Transfusion Status, n (%)		
Transfusion-Dependent	0	1 (7.1)
Transfusion-Independent	10 (100.0)	13 (92.9)
MF type, n (%)		
Primary MF	4 (40.0)	7 (50.0)
Post-ET MF	2 (20.0)	4 (28.6)
Post-PV MF	4 (40.0)	3 (21.4)
DIPSS risk, n (%)		
Int-1	4 (40.0)	3 (21.4)
Int-2	3 (30.0)	8 (57.1)
High	3 (30.0)	3 (21.4)
Mutations, n (%)		
JAK2	7 (70.0)	11 (78.6)
CALR	3 (30.0)	2 (14.3)
MPL	0	1 (7.1)
High-risk mutation*	6 (60)	5 (35.7)
Hemoglobin (g/dL), n (%)		
<10	4 (40)	8 (57.1)
≥10	6 (60)	6 (42.9)
Platelets (10^9/L), n (%)		
100 to <150	1 (10.0)	2 (14.3)
≥150	9 (90.0)	12 (85.7)
Baseline spleen volume (cm^3), median (range)	1540.3 (660.0-2383.0)	1961.6 (650.0-3657.0)
Baseline TSS, median (range)	17.3 (7-29)	12.0 (0-54)

ET, essential thrombocythemia; PV, polycythemia vera
*High-risk genes include: *ASXL1, EZH2, IDH1, IDH2, SRSF2, U2AF1*

- The median duration of selinexor treatment as of the data cutoff in the 40mg cohort was 31.5 weeks (range 12-52 weeks), and in the 60mg cohort was 38 weeks (range 9-68 weeks).

Figure 2. Selinexor treatment duration as of the data cutoff (Feb 24, 2023)

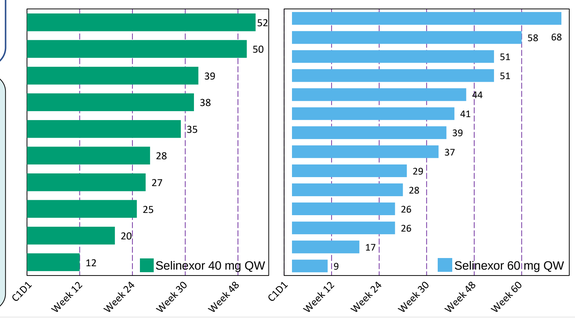


Table 2. SVR35

Population	Timepoint	Selinexor 40mg +ruxolitinib n (%)*	Selinexor 60mg +ruxolitinib n (%)
Efficacy Evaluable	SVR35 at Week 12	3/10 (30.0)	10/12** (83.3)
	SVR35 at Week 24	4/8* (50.0)	11/12 (91.7)
	SVR35 at anytime	4/10 (40.0)	12/12 (100.0)
Intent-to-Treat	SVR35 at Week 12	3/10 (30.0)	10/14 (71.4)
	SVR35 at Week 24	4/10 (40.0)	11/14 (78.6)
	SVR35 at anytime	4/10 (40.0)	12/14 (85.7)

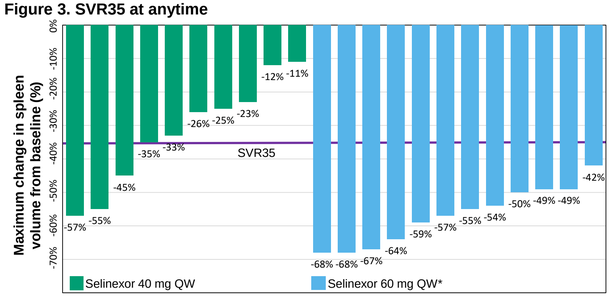
*Two patients discontinued prior to Week 24. ** one patient discontinued prior to week 12; one patient with missing data at week 12 who subsequently discontinued prior to week 24.

Table 3. TSS50

Population	Timepoint	Selinexor 40mg +ruxolitinib n (%)	Selinexor 60mg +ruxolitinib n (%)
Efficacy Evaluable	TSS50 at Week 12	6/9**** (66.7)	8/10** (80.0)
	TSS50 at Week 24	4/7* (57.1)	7/9*** (77.8)
	TSS50 at anytime	8/10 (80.0)	9/10 (90.0)
Intent-to-Treat	TSS50 at Week 12	6/10 (60.0)	8/12 (66.7)
	TSS50 at Week 24	4/10 (40.0)	7/12 (58.3)
	TSS50 at anytime	8/10 (80.0)	9/12 (75.0)

Note: Median TSS was calculated for each cycle, regardless of number of scores collected per cycle. *Two patients discontinued prior to Week 24 and 1 had missing data. ** 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 1 had missing data.**** One patient with missing data

Figure 3. SVR35 at anytime



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

Figure 4. Median platelet levels

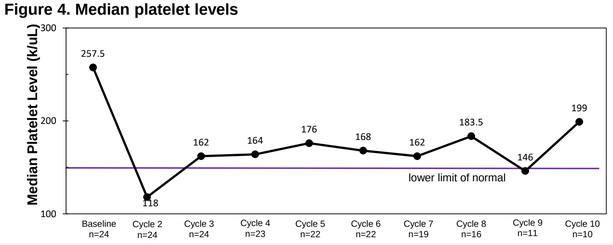


Table 4. Treatment-emergent adverse events (TEAE)

Treatment Emergent Adverse Events	Selinexor 40mg + ruxolitinib (N=10)	Selinexor 60mg + ruxolitinib (N=14)
Any grade, >25% overall		
Nausea	7 (70.0)	11 (78.6)
Anemia	4 (40.0)	9 (64.3)
Fatigue	6 (60.0)	8 (57.1)
Thrombocytopenia	4 (40.0)	9 (64.3)
Constipation	2 (20.0)	7 (50.0)
Headache	4 (40.0)	5 (35.7)
Vomiting	2 (20.0)	7 (50.0)
Neutropenia	2 (20.0)	5 (35.7)
Dyspnea	2 (20.0)	5 (35.7)
Decreased appetite	2 (20.0)	4 (28.6)
Dysgeusia	2 (20.0)	4 (28.6)
Hyponatremia	1 (10.0)	5 (35.7)
Grade 3+, >5%		
Anemia	3 (30.0)	6 (42.9)
Thrombocytopenia	1 (10.0)	4 (28.6)
Neutropenia	2 (20.0)	1 (7.1)
Atrial fibrillation	2 (20.0)	1 (7.1)
Back pain	0	2 (14.3)
Treatment-related adverse events leading to treatment discontinuations		
Thrombocytopenia, Grade 3	0	1 (7.1)
Peripheral Neuropathy	0	1 (7.1)

- 75% of nausea events were grade 1; 1 patient experienced grade 3 nausea (no anti-emetic prophylaxis)
- In the 60 mg cohort, 64% of patients received one prophylactic anti-emetic. Amongst the subgroup who received 1 prophylactic anti-emetic, 67% of pts experienced nausea (Grade 1 only) compared to 100% of those who did not receive prophylactic anti-emetics (Grades 1-3).
- Despite nausea and vomiting incidence, patients generally did not experience weight loss. Patients' mean weight increase at Week 24 was 2.5 kg in the 40mg cohort and 1.3 kg in the 60mg cohort.

CONCLUSIONS

- **Selinexor 40 mg and 60 mg dose levels were generally well tolerated and manageable allowing most patients to remain on therapy (up to 68 weeks as of data cutoff); most common AEs were nausea, fatigue, anemia, and thrombocytopenia**
  - Treatment related discontinuations due to cytopenias were low (n=1)
  - For patients who received prophylactic anti-emetics, nausea was transient and limited to Grade 1, suggesting that nausea can be further optimized with mandatory, dual antiemetics for the first two cycles
  - Meaningful weight gain was observed at week 24 despite incidence of nausea
- **Rapid, deep, and sustained spleen response, and robust symptom improvement were observed in patients treated with 60 mg selinexor in combination with ruxolitinib: 78.6% ITT (91.7%, EE) achieved SVR35 and 58.3% ITT (77.8%, EE) achieved TSS50 at Week 24**
  - Responses were observed in 100% of evaluable patients anytime with selinexor 60mg, including patients with high-risk mutations
- **Disease modification was observed as evidenced by rapid normalization of platelet levels**
- **Both efficacy and safety data support the 60 mg dose of selinexor as the recommended dose in combination with ruxolitinib**
- **Selinexor's fundamental mechanism of XPO1 inhibition is potentially synergistic with ruxolitinib and may be a novel, first-line treatment for patients with MF**
- **A double-blind, randomized, phase 3 trial of selinexor 60 mg + ruxolitinib vs placebo + ruxolitinib in JAKi treatment-naïve patients with MF is planned to initiate in 1H 2023**

REFERENCES: 1. O'Sullivan JM, Harrison CN. *Clin Adv Hematol Oncol.* 2018;16(2):121–31. **2.** Verstovsek S, et al. *N Engl J Med*. 2012;366(9)799-907. **3**. Sastow D, et al. *Clin Lymphoma, Myeloma Leuk*. 2022;22(7):e507–20. **4.** Masarova, et al. *Eur J Haematol*. 2018;100(3):257-263. **5.** Al-Ali, et al. *Hematologica*. 2016;101(9):1065. **6.** Vannuchi et al. *Haematologica*. 2015;100(9): 1139– 1145. **7.** Palandri et al. *Leuk Res*. 2018;74:86-8. **8.** Yan et al. *Clin Cancer Res*. 2019;25(7): 2323–2335. **9.** Green T. *Exp Hematol*. 2022;105:2–9.

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