POSTER #1734

A PHASE 1, OPEN-LABEL, DOSE-ESCALATION STUDY OF SELINEXOR PLUS RUXOLITINIB IN PATIENTS WITH TREATMENT-NAÏVE MYELOFIBROSIS

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INTRODUCTION

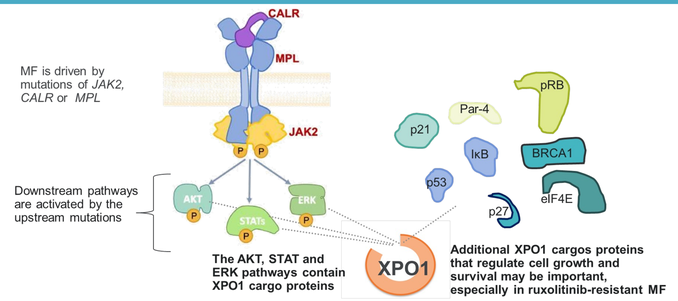
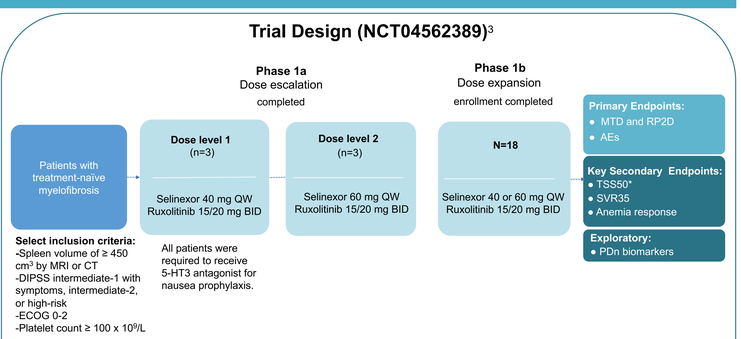


Figure 1. Selinexor mechanism of action. Adapted from Green et al, *Exp Hematol,* 2022

- Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by unregulated, clonal proliferation of a hematopoietic stem cells in the bone marrow that is commonly associated with gene mutations in JAK2, CALR, or MPL
- Selinexor is an oral XPO1 inhibitor with approved indications in multiple myeloma and diffuse large B-cell lymphoma and additionally is being studied in combination with ruxolitinib for treatment-naïve myelofibrosis
- XPO1 is a RAN-dependent nuclear export factor that facilitates the non-redundant nuclear to cytoplasmic transport of many cargo proteins and protein-RNA complexes, including tumor suppressors proteins and oncogene RNAs
- RAN and XPO1, key proteins of nucleocytoplasmic transport, are important for the survival and proliferation of cellular MF models with aberrant activation of JAK/STAT signaling[1] (Figure 1)
- Selinexor in combination with ruxolitinib significantly reduced white blood cells, granulocytes, spleen GFP+ cells, and spleen weight on day 28 ($p<0.05$) in JAK2V617F-driven MPN mouse models
- We previously reported clinical activity of selinexor in combination with ruxolitinib in treatment-naïve MF where at week 12, 75% of evaluable patients achieved a spleen volume reduction of 35% or more (SVR35)[2]
- Here we report updated data of the ongoing phase 1, open-label, dose-escalation study of selinexor in combination with ruxolitinib in treatment-naïve MF

STUDY DESIGN

Trial Design (NCT04562389)[3]



Select inclusion criteria:
-Spleen volume of ≥ 450 cm^3 by MRI or CT
-DIPSS intermediate-1 with symptoms, intermediate-2, or high-risk
-ECOG 0-2
-Platelet count ≥ 100 x 10^9/L

All patients were required to receive 5-HT3 antagonist for nausea prophylaxis.

AE, adverse event; BID, twice a day; BIW, twice a week; MTD, maximum tolerated dose; QW, once weekly; PDn, pharmacodynamic; RP2D, recommended phase 2 dose; SVR35, spleen volume reduction of at least 35%; TSS50, total symptom score reduction ≥ 50%
*Scores from the Myelofibrosis Symptom Assessment Form were collected daily for 5-7 days prior to the start of each cycle.

As of Oct 21, 2022, 24 patients have been dosed in one of two dose levels selinexor 40 mg (n=10), and 60 mg (n=13) weekly in combination with ruxolitinib daily as per standard of care. One patient received 20 mg for 3 cycles then switched to 60 mg and was included in the 40 mg group for the purpose of this analysis.

RESULTS

Table 1. Patient characteristics

	Overall (N=24)	Selinexor 40 mg PO QW + Ruxolitinib PO BID (N=11)*	Selinexor 60 mg PO QW + Ruxolitinib PO BID (N=13)
Age (years), median (range)	64.0 (44-77)	58.0 (44-71)	65.0 (58-77)
Female, n (%)	8 (33.3)	4 (36.4)	4 (30.8)
Transfusion Status, n (%)			
Transfusion-Dependent	1 (4.2)	0	1 (7.7)
Transfusion-Independent	23 (95.8)	11 (100.0)	12 (92.3)
MF type, n (%)			
Primary MF	11 (45.8)	5 (45.5)	6 (46.2)
Post-ET MF	6 (25.0)	2 (18.2)	4 (30.8)
Post-PV MF	7 (29.2)	4 (36.4)	3 (23.1)
DIPSS risk, n (%)			
Int-1	7 (29.2)	4 (36.4)	3 (23.1)
Int-2	11 (45.8)	4 (36.4)	7 (53.8)
High	6 (25.0)	3 (27.3)	3 (23.1)
Driver Mutation, n (%)			
JAK2	18 (75.0)	7 (63.6)	11 (84.6)
CALR	5 (20.8)	3 (27.3)	2 (15.4)
MPL	1 (4.2)	1 (9.1)	0

DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; MF, myelofibrosis; MPL, myeloproliferative leukemia virus; PV, polycythemia
*One patient received 20 mg for 3 cycles then 60 mg for 3 cycles and was included in the 40mg group for the purpose of this analysis

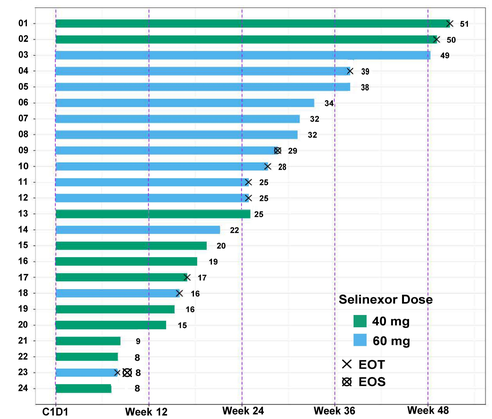
Evaluated populations

Safety population:
- All patients who received at least one dose of selinexor (n=24)

Efficacy population:
- Spleen evaluable: Patients who had a spleen assessment available at baseline and the timepoint (12/24 week)
- Symptom evaluable: Patients who had at least 1 symptom score available at baseline and the timepoint (12/24 week)

Primary analysis population:
- Patients who had available baseline assessment and have been treated until the timepoint (12/24 week) or discontinued before the timepoint. Patients with missing data at the timepoint were considered as non-responders

Figure 2. Treatment duration and disposition



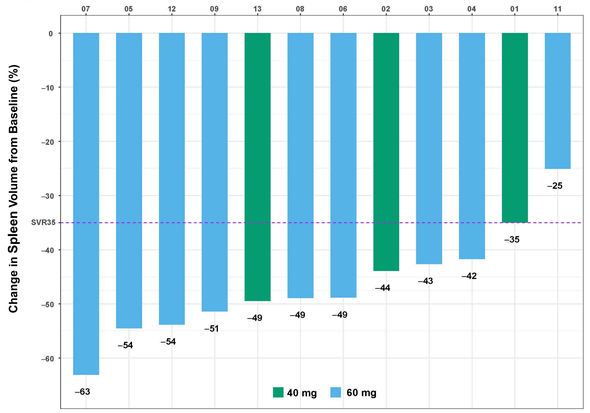
EOT, end of treatment; EOS, end of study
One patient received 20 mg for 3 cycles then 60 mg for 3 cycles and was included in the 40 mg group for the purpose of this analysis
Ten patients discontinued treatment due to: Clinical progression/Transformation to AML (n=3), Treatment related adverse events (n=2), Stem Cell Transplant (n=2), Withdrawal by patient (n=1), Physician decision (n=1), Unrelated death (n=1)

Table 2. TSS50 response and SVR35 at week 24

Time point	Endpoint	Efficacy Evaluable** n (%)
Week 24	SVR35	11/12 (92)
	TSS50*	4/6 (67)

TSS, total symptom score; SVR, spleen volume reduction
Six patients with missing data were considered as non-responders
*Median TSS was calculated for each cycle, regardless of number of scores collected per cycle
**Primary analysis population: week 24 SVR35 11/16 (69%), TSS50 4/12 (33%)

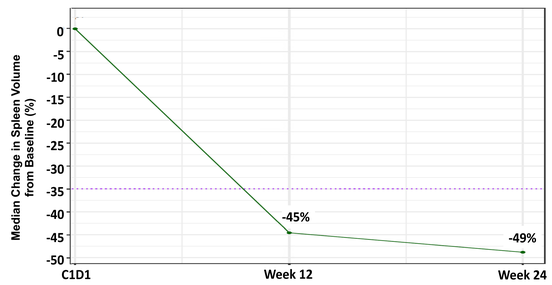
Figure 3. Spleen volume reduction at 24 weeks



One patient received 20 mg for 3 cycles then 60 mg for 3 cycles and was included in the 40 mg group for the purpose of this analysis

- No patient had an increase in spleen volume from baseline

Figure 4. Median change in spleen volume from baseline (%)



- Selinexor and ruxolitinib combination induced rapid spleen responses at week 12 and 24
- Responses were also observed in patients who received low doses of ruxolitinib (5mg BID)

Table 3. Hemoglobin Stabilization

Transfusion-independent Patients	Overall n/N (%) patients with <2 g/dL decrease in HGB	Selinexor 40 mg PO QW + Ruxolitinib PO BID*	Selinexor 60 mg PO QW + Ruxolitinib PO BID
Baseline HGB <10 g/dL	9/11 (81.8)	4/4 (100.0)	5/7 (71.4)
Total	13/23 (56.5)	7/11 (63.6)	6/12 (50.0)

HGB, hemoglobin

Figure 5. Change in median hemoglobin over time

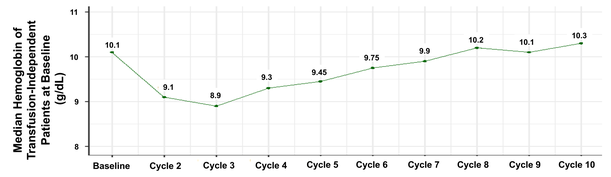


Table 4. Treatment-emergent adverse events (TEAE)

Treatment Emergent Adverse Events	Selinexor 40 mg PO QW + Ruxolitinib PO BID (N=11)*	Selinexor 60 mg PO QW + Ruxolitinib PO BID (N=13)	Overall (N=24)
Any grade, >25%			
Nausea	8 (72.7)	10 (76.9)	18 (75.0)
Anemia	5 (45.5)	10 (76.9)	15 (62.5)
Fatigue	7 (63.6)	7 (53.8)	14 (58.3)
Thrombocytopenia	5 (45.5)	8 (61.5)	13 (54.2)
Constipation	2 (18.2)	7 (53.8)	9 (37.5)
Headache	5 (45.5)	4 (30.8)	9 (37.5)
Vomiting	3 (27.3)	6 (46.2)	9 (37.5)
Neutropenia	2 (18.2)	6 (46.2)	8 (33.3)
Dyspnea	2 (18.2)	5 (38.5)	7 (29.2)
Decreased appetite	2 (18.2)	4 (30.8)	6 (25.0)
Dysgeusia	2 (18.2)	4 (30.8)	6 (25.0)
Hyponatremia	1 (9.1)	5 (38.5)	6 (25.0)
Grade 3+, >5%			
Anemia	3 (27.3)	6 (46.2)	9 (37.5)
Thrombocytopenia	1 (9.1)	4 (30.8)	5 (20.8)
Neutropenia	2 (18.2)	2 (15.4)	4 (16.7)
Atrial fibrillation	2 (18.2)	1 (7.7)	3 (12.5)
Back pain	0	2 (15.4)	2 (8.3)

BID, twice daily; PO, orally; QW, once weekly
There was one grade 5 event following abdominal paracentesis that was deemed not related to study treatment
*One patient received 20 mg for 3 cycles then 60 mg for 3 cycles and was included in the 40 mg group for the purpose of this analysis

- The most common TEAE is nausea with 50% of the events grade 1; only 1 grade 3 nausea was observed
- Two cases of grade 4 thrombocytopenia occurred in the 60 mg dose level
- Thrombocytopenia was not clinically relevant with no bleeding events observed

CONCLUSIONS

- **The novel combination of selinexor and ruxolitinib demonstrates meaningful efficacy across the relevant efficacy endpoints of SVR35 (92%), TSS50 (67%), and hemoglobin stabilization**
- **AEs were generally manageable; grade 3-4 AEs were not clinically relevant with no bleeding, serious infections or clinical sequalae**
- **The 40 mg and 60 mg dose level were generally well tolerated; most common AEs were nausea, fatigue, anemia, and thrombocytopenia**
- **The combination of selinexor with ruxolitinib achieved a rapid and sustained spleen response in treatment-naïve patients with myelofibrosis**
- **These data demonstrate that the combination of selinexor and ruxolitinib has the potential to be a novel first-line treatment for MF patients**

REFERENCES:[1]**Yan et al**, *Clin Cancer Res* 2019;25(7): 2323–2335; [2]**Ali et al**, Poster presented at: 2022 American Society of Clinical Oncology Annual Meeting; June 3-6, 2022; Chicago, IL. Abstract 7060; [3]**ClinicalTrials.gov. NCT04562389**. https://clinicaltrials.gov/ct2/show/NCT04562389. Accessed October 21, 2022.

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