Abstract #7060

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

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Introduction

- Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by unregulated, clonal proliferation of a hematopoietic stem cells in the bone marrow and is commonly associated with gene mutations in JAK2, CALR, or MPL
- Selinexor is an oral Selective Inhibitor of Nuclear Export (SINE) compound that inhibits the karyopherin protein XPO1 (CRM1)

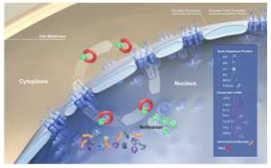


Figure 1. Selinexor mechanism of action

- Selinexor is approved for use in patients with multiple myeloma and diffuse large B-cell lymphoma
- Selinexor-mediated inhibition of XPO1 leads to nuclear retention and activation of tumor suppressor proteins (e.g., TP53, IkB, p21), reduction in oncoprotein mRNAs (c-Myc, Bcl-2, Bcl-6, cyclin D) and selective apoptosis of cancer cells (Figure 1)
- RAN and RANBP2 genes, which are involved in the nucleo-cytoplasmic transportation (NCT) pathway, were identified in a functional short hairpin RNA (shRNA) library screen among the top 20 genes involved in the survival of JAK2V617F mutant HEL cells[1]
- Inhibition of NCT by selinexor reduced the survival of HEL and SET-2 cell lines expressing JAK2V617F. Importantly, the JAK inhibitor-resistant cell line HEL-R remained highly sensitive to the effect of both selinexor and another SINE compound[1]
- Selinexor + ruxolitinib combination significantly reduced WBCs, granulocytes, spleen GFP+ cells, and spleen weight on day 28 ($p<0.05$) of mouse model of JAK2V617F-driven MPN (Figure 2)[1]
- Selinexor monotherapy in patients with MF refractory to JAK inhibitors demonstrated robust clinical activity with 40% SVR35 at ≥24 weeks and a tolerable safety profile[2]

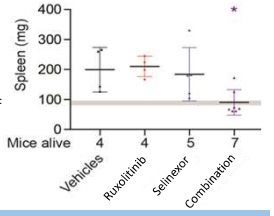
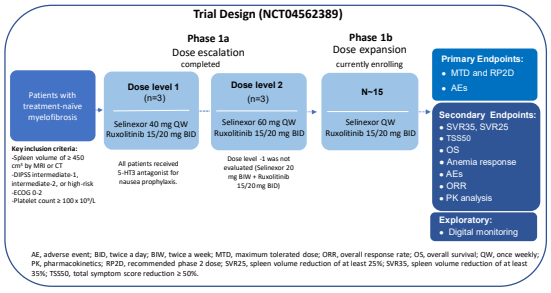


Figure 2. Spleen weights after selinexor and/or ruxolitinib treatment

Methods



- Exploratory remote digital monitoring is performed using a smart scale and a smart watch to evaluate QoL. Measurements include weight, body composition, activity, and sleep quality

Results

- As of 01 May 2022, 15 patients have been dosed in one out of two dose levels selinexor 40 mg (n=3), and 60 mg (n=12) weekly in combination with ruxolitinib daily as per standard of care

Table 1. Patient Baseline Demographics

Age	Gender	Baseline Spleen Volume (cm³)	Type of MF	DIPSS risk	Driver mutation	Transfusion Dependence
45	M	1077.1	Post-ET MF	Int-1	CALR	N
58	F	852	Primary MF	Int-1	JAK2	N
54	M	1914.5	Primary MF	Int-2	CALR	N
61	M	2413	Post-ET MF	Int-1	JAK2	N
65	M	1390	Primary MF	Int-2	JAK2	N
63	M	2431.2	Primary MF	Int-2	JAK2	N
68	M	1652	Primary MF	High	JAK2	Y
76	M	2502.8	Primary MF	Int-1	JAK2	N
76	F	1089	Primary MF	Int-2	JAK2	N
74	M	650.11	Post-ET MF	High	CALR	Y
64	F	790	Post-ET MF	Int-2	JAK2	N
65	M	2155.1	Primary MF	Int-1	JAK2	N
60	F	2748	Post-PV MF	Int-2	JAK2	N
77	F	1700	Post-PV MF	Int-2	JAK2	N
64	M	2315	Post-PV MF	High	JAK2	N

DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; F, female; M, male; MF, myelofibrosis; PV, polycythemia.

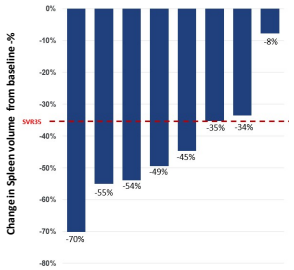
- Median age: 64 (range 45-76)

Evaluated populations

Safety population:
- All patients who received at least one dose of selinexor (n=15)

Efficacy population:
- Spleen evaluable: All patients who had at least one spleen assessment post baseline (n=8). One patient excluded due to discontinuation prior to week 12
- Symptom evaluable: All patients with available data AND at least 12 weeks of treatment (n=7). One patient excluded due to missing data
- Anemia evaluable: All patients who were transfusion independent at baseline and had at least 8 weeks of treatment (n=10)

Figure 3. Selinexor and ruxolitinib combination induced rapid spleen responses at week 12



Spleen Volume Reduction of ≥35% (SVR35)

- **75% of evaluable patients achieved SVR35 at week 12**
- 8 patients who reached week 12 spleen volume assessment post baseline are included

Figure 4. Treatment Duration

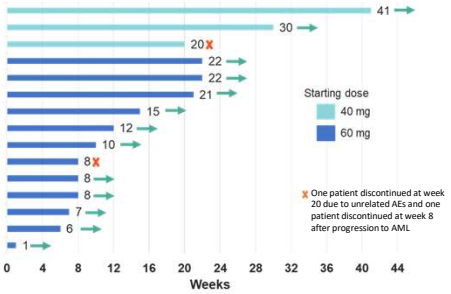
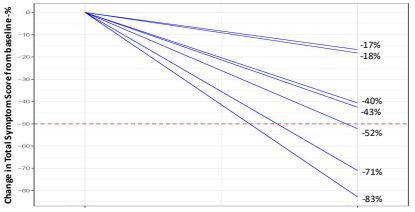
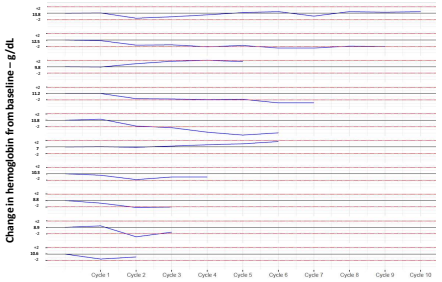


Figure 5. Selinexor and ruxolitinib combination induced rapid reduction in Total Symptom Score at week 12



Scores from the Myelofibrosis Symptom Assessment Form were collected daily for 5-7 days prior to the start of each cycle. Median score was calculated for each cycle

Figure 6. Stable or improving hemoglobin levels in some patients



5 out of 10 transfusion independent patients who had at least 8 weeks of treatment maintained stable hemoglobin (± 2g/dL) or improved hemoglobin level (>2g/dL increase) at last follow up Variation in hemoglobin level over time for each patient (blue line). Upper and lower red lines represent a 2g/dL absolute increase or decrease from baseline, respectively

Table 2. Treatment-emergent adverse events (TEAE)

Treatment Emergent Adverse Events*	Selinexor 40 mg or 60 mg PO QW + Ruxolitinib PO BID (N=15)		
Non-Hematologic	**Grade 1**	**Grade 2**	**Grade 3-4*** **
Nausea	4 (27%)	1 (7%)	1 (7%)
Dysgeusia	3 (20%)	1 (7%)	-
Hyponatremia	3 (20%)	-	-
Dizziness	3 (20%)	-	-
Vomiting	2 (13%)	1 (7%)	-
Headache	1 (7%)	2 (13%)	-
Anorexia	1 (7%)	-	1 (7%)
Atrial Fibrillation	-	-	3 (20%)
Failure to thrive**	-	-	1 (7%)
Pulmonary hypertension	-	-	1 (7%)
Tumor lysis syndrome	-	-	1 (7%)
Hematologic			
Neutropenia	2 (13%)	-	3 (20%)
Anemia	1 (7%)	2 (13%)	3 (20%)
Thrombocytopenia	1 (7%)	1 (7%)	4 (27%)

BID, twice daily; PO, orally; QW, once weekly.
*TEAEs grade 1-2 that occurred in > 2 patients and TEAEs grade ≥ 3 that occurred in at least 1 patient.
**SAE of "failure to thrive" (related to study treatment) occurred at time of progression to AML and includes other grade 3 AEs deemed not related to selinexor or ruxolitinib: abdominal pain, atrial fibrillation, delirium, dysphagia, muscle weakness
***No grade 4 AEs except one grade 4 thrombocytopenia

- No dose limiting toxicities are reported at either dose level
- The most common TEAE is nausea (40%), the majority of which are grade 1/2
- The 40 mg dose level was well tolerated, with the most common reported TEAEs of mild nausea and headache
- The 60 mg dose level was well tolerated overall, with the most common TEAEs of thrombocytopenia (40%) and anemia (33%)
- Hematologic adverse events were reversible with dose interruptions and reductions.
- One patient discontinued after 5 months of therapy due to unrelated AEs (dizziness, atrial fibrillation, and pulmonary hypertension)
- One patient discontinued after 8 weeks of therapy due to progression to AML.
- At last follow-up, ruxolitinib dose was reduced in 53% of patients, and selinexor dose was reduced in 20% of patients

Conclusions

- **The combination of selinexor and ruxolitinib has been well-tolerated and with a manageable side effect profile**
- **No dose limiting toxicities were observed in patients with treatment-naïve MF who received once weekly oral selinexor 40 or 60 mg in combination with standard dose ruxolitinib**
- **75% of evaluable patients achieved SVR35 at week 12**
- **Rapid reduction in symptom scores was observed at week 12**
- **Promising activity in overcoming the anemia caused by ruxolitinib**

This trial is currently enrolling

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References

[1]Yan et al, Clinical Cancer Research 2019 ; [2]Tantravahi et al, ASH 2021

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