Abstract #124136

Eltanexor (KPT-8602), a Second-Generation Selective Inhibitor of Nuclear Export (SINE) Compound, in Patients with Hypomethylating Agent (HMA) Refractory Myelodysplastic Syndrome

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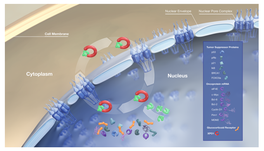
INTRODUCTION

- Patients with myelodysplastic syndrome (MDS) that is refractory to hypomethylating agents (HMAs) have limited treatment options and a median overall survival (OS) of 4-6 months[1,2]
- Recent studies have demonstrated that selinexor, a selective inhibitor of exportin 1 (XPO1, CRM1) mediated nuclear export (SINE), is efficacious in patients with HMA refractory MDS[3]



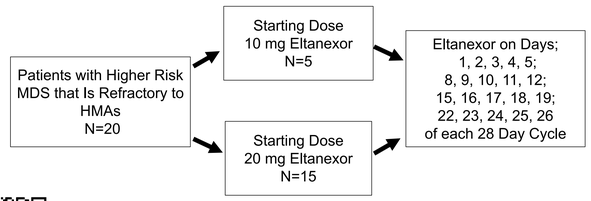
- Inhibition of XPO1 leads to nuclear retention and activation of tumor suppressor proteins (e.g. p53, IkB, p21), reduction in oncoprotein mRNAs (c-Myc, Bcl-2, Bcl-6, cyclin D) and selective apoptosis of cancer cells[4]
- Eltanexor is a second-generation, oral, SINE compound with low brain penetration and good tolerability in non-clinical animal models[5,6]
- Eltanexor has demonstrated preliminary anti-tumor activity in clinical trials of hematologic and solid tumor malignancies[7,8]

Study Design and Treatment Schema

Phase 1/2 Open-Label Study of the Safety, Tolerability, and Efficacy of Eltanexor in Multiple Myeloma, Colorectal Cancer, Metastatic Castrate Resistant Prostate Cancer and Higher Risk MDS (KCP-8602-801)

For the MDS cohort, patients must have documented diagnosis of progressing MDS with 5-19% myeloblasts

Patients should have intermediate-2 or high-risk MDS by International Prognostic Scoring System (IPSS)



Demographics

	N=20
Age	
Median (range)	77 (62 - 89)
< 75	7 (35%)
≥ 75	13 (65%)
Sex	
Male	11 (55%)
Female	9 (45%)
Race	
White	13 (65%)
Black or African American	1 (5%)
Asian	1 (5%)
Other/Not Reported	5 (25%)
ECOG Performance Status at Screening	
0	3 (15%)
1	16 (80%)
2	1 (5%)
IPSS Risk at Screening	
Intermediate I	1 (5%)
Intermediate II	7 (35%)
High	12 (60%)
Median Time Since Initial Diagnosis of MDS	
Years (range)	2.4 (0.6 - 9)
MDS Subtype	
De Novo	16 (80%)
Secondary	4 (20%)
Prior Therapies	
Median (range)	2 (1 - 3)
Azacitidine	15 (75%)
Decitabine	9 (45%)
Lenalidomide	3 (15%)
Chemotherapy	2 (10%)
Investigational Agent	4 (20%)
Blood Counts on Cycle 1 Day 1	
Platelets (K/μL): Median (range)	26 (12 – 88)
Hemoglobin (g/dL): Median (range)	8.3 (7.0 – 9.3)
Neutrophils (K/μL): Median (range)	1.2 (0.1 – 9.0)
Cytogenetics and Mutational Status*	
TET2	7 (35%)
ASXL1	5 (25%)
del (5q)	4 (20%)
EZH2	3 (15%)
DNMT3A	3 (15%)
IDH1	2 (10%)
p53	1 (5%)
SF3B1	1 (5%)
KRAS	1 (5%)
Normal	5 (25%)
Unknown	1 (5%)

ECOG – Eastern Cooperative Oncology Group, IPSS – International Prognostic Scoring System
* Patients may have more than one mutation or cytogenetic abnormality

Treatment Related Adverse Events (AEs)

Adverse Event	10 mg Eltanexor (N = 5)				20 mg Eltanexor (N = 15)				All Patients (N=20)
Non-Hematologic	G1	G2	G3	G4	G1	G2	G3	G4	All Grades
Nausea	-	-	-	-	3 (20.0)	6 (40.0)	-	-	9 (45.0)
Decreased appetite	-	-	1 (20.0)	-	3 (20.0)	4 (26.7)	-	-	8 (40.0)
Fatigue	-	2 (40.0)	-	-	-	3 (20.0)	2 (13.3)	-	7 (35.0)
Diarrhea	2 (40.0)	-	-	-	3 (20.0)	1 (6.7)	1 (6.7)	-	7 (35.0)
Dysgeusia	2 (40.0)	-	-	-	2 (13.3)	1 (6.7)	-	-	5 (25.0)
Vomiting	1 (20.0)	-	-	-	2 (13.3)	1 (6.7)	-	-	4 (20.0)
Weight decreased	-	-	1 (20.0)	-	3 (20.0)	-	-	-	4 (20.0)
Constipation	-	-	-	-	-	1 (6.7)	1 (6.7)	-	2 (10.0)
Vision blurred	-	-	-	-	1 (6.7)	1 (6.7)	-	-	2 (10.0)
Failure to thrive	-	-	1 (20.0)	-	-	1 (6.7)	-	-	2 (10.0)
Hyponatremia	-	-	1 (20.0)	-	-	-	1 (6.7)	-	2 (10.0)
Sepsis	-	-	-	1 (20.0)	-	-	-	1 (6.7)	2 (10.0)
Hematologic	G1	G2	G3	G4	G1	G2	G3	G4	All Grades
Anemia	-	-	2 (40.0)	-	-	-	3 (20.0)	1 (6.7)	6 (30.0)
Neutropenia	-	-	-	2 (40.0)	-	1 (6.7)	-	3 (20.0)	6 (30.0)
Thrombocytopenia	-	-	-	1 (20.0)	-	-	1 (6.7)	2 (13.3)	4 (20.0)
Leukopenia	-	-	-	1 (20.0)	1 (6.7)	-	1 (6.7)	1 (6.7)	4 (20.0)

Treatment related AEs in ≥10% of the patients. Data are N (%). G = grade. There were five serious AEs (SAEs) determined by the treating physician to be related to study drug reported in three patients: grade 3 diarrhea (20 mg dose), grade 2 failure to thrive (20 mg dose), grade 3 and grade 4 fatigue and sepsis (20 mg dose), grade 4 sepsis (20 mg dose) and grade 3 failure to thrive (10 mg dose).

Dose Reductions

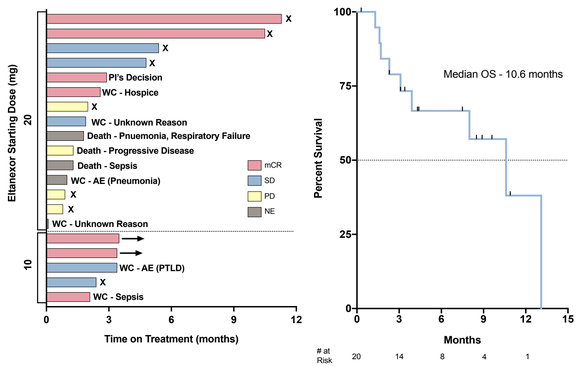
Eltanexor Starting Dose	Number of Patients Per Dose Level	Number of Patients Requiring a Dose Reduction	Median Time to Dose Reduction
(mg)	N	N (%)	(Days, Range)
10	5	0 (0%)	Not Applicable
20	15	7 (47%)	42 (21-89)

Best Overall Response

Patients	(N)	ORR	mCR	SD	PD	NE
All Patients	20	7 (35%)	7 (35%)	5 (25%)	4 (20%)	4 (20%)
Starting Eltanexor Dose						
10 mg	5	3 (60%)	3 (60%)	2 (40%)	0 (0%)	0 (0%)
20 mg	15	4 (27%)	4 (27%)	3 (20%)	4 (27%)	4 (27%)
Cytogenetics						
Good	8	2 (25%)	2 (25%)	2 (25%)	1 (13%)	3 (38%)
Intermediate	7	2 (29%)	2 (29%)	2 (29%)	2 (29%)	1 (14%)
Poor	4	3 (75%)	3 (75%)	0 (0%)	1 (25%)	0 (0%)
Unknown	1	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)

Overall response rate (ORR) includes complete response (CR) [not observed], complete response without marrow recovery (mCR), and hematologic improvement (HI) [not observed]. Stable disease (SD). Progressive disease (PD). Four patients were considered non-evaluable (NE) per the 2006 International Working Group (IWG) Response Criteria for MDS; however were included in the denominator of all response assessments based on an intent-to-treat.

Time on Treatment and Overall Survival



Time on Treatment Plot: mCR = marrow complete response, SD = stable disease, PD = progressive disease, NE = non-evaluable; X: off study for disease progression; arrows: patient continuing on treatment; WC: withdrawal of consent; PTLD = post transplant lymphoproliferative disorder. **Overall Survival Plot:** black tick marks indicate censored patient. OS = overall survival

Conclusions

- In patients with HMA-refractory, higher risk MDS and short expected survival, oral eltanexor demonstrated anti-tumor activity with mCRs, as well as SD
- Side effects were dose-dependent and reversible, and primarily gastrointestinal, constitutional, and hematologic
- Based on safety and efficacy, the recommended phase 2 dose (RP2D) is 10 mg eltanexor Days 1 through 5 each week
- Further evaluation of eltanexor in MDS as a single agent and in combination is warranted

References and Acknowledgements

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