Abstract # 3676

Updated Efficacy of Eltanexor Monotherapy in Patients with Higher Risk Myelodysplastic Syndrome Primary Refractory to Hypomethylating Agents

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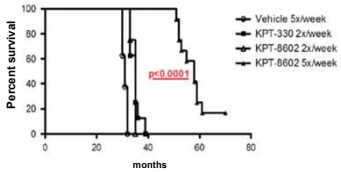
Introduction

- 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]
- Inhibition of XPO1 leads to nuclear retention and activation of tumor suppressor proteins (eg, p53, IkB, p21), reduction in oncoprotein mRNAs (c-Myc, Bcl-2, Bcl-6, cyclin D) and selective apoptosis of cancer cells.[3]
- Recent studies have demonstrated that inhibition of XPO1 with selinexor, a first-generation selective inhibitor of nuclear export (SINE), is efficacious in patients with HMA refractory MDS.[4]
- Eltanexor is an investigational, second innovative oral SINE compound with minimal penetration of the blood brain barrier. The reduced CNS infiltration observed with eltanexor across nonclinical species **may confer** lower rates of CNS-mediated gastrointestinal toxicity in patients relative to selinexor.
- Following oral administration, animals treated with eltanexor show lower percentage of body weight loss and improved food consumption than animals similarly treated with selinexor. This allows more frequent dosing of eltanexor, enabling a longer period of exposure at higher levels than possible with selinexor.
- In leukemia cells lines, the half-maximal inhibitory value (IC50) is consistently 30% to 50% lower for eltanexor than for selinexor, indicating eltanexor is more active than the first generation XPO1 inhibitor in this setting.
- Eltanexor dosed at 5x/week improved survival relative to selinexor dosed 2x/week in patient-derived xenograft of AML in mouse models (Figure 1).

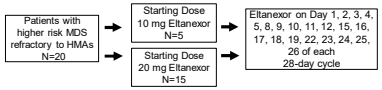
Figure 1. Non-clinical Model of AML and Eltanexor



- Eltanexor (KPT-8602) dosed 2x/week showed **similar** efficacy compared to selinexor (KPT=330).
- Eltanexor dosed 5 days/week showed **improved** efficacy to selinexor.

Methods

- Phase 1/2 open-label study of the safety, tolerability, and efficacy of eltanexor in multiple myeloma, colorectal cancer, metastatic castration resistant prostate cancer, and higher risk MDS (NCT02649790)
- In 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)



Results

MDS cohort enrolled 20 patients with primary HMA-refractory MDS

Starting Dose:
- **15 patients on 20 mg eltanexor**
- **5 patients on 10 mg eltanexor**

Evaluations:
- **20 patients were evaluable for safety**
- **15 patients were evaluable for efficacy**

Table 1. Patient Demographics and Disease Characteristics

Characteristic	Total (N=20)	Characteristic	Total (N=20)
Age		**Cytogenetic Abnormalities, n (%)**	
Years: Median (range)	77 (62 - 89)	Complex Karyotype	5 (25)
<75, n (%)	7 (35)	Del(7) or Del(7q)	3 (15)
≥75, n (%)	13 (65)	Del(5q)	1 (5)
ECOG Performance Status, n (%)		Other	2 (10)
0	4 (20%)	**Prior Therapies, median (range)**	2 (1 - 4)
1	13 (65%)	Azacitidine, n (%)	14 (70)
2	3 (15%)	Decitabine/ASTX727, n (%)	11 (55)
HMA Refractory, n (%)		Lenalidomide, n (%)	4 (20)
Primary	20 (100%)	Chemotherapy, n (%)	2 (10)
Secondary	0	Investigational Agent, n (%)	3 (15)
IPSS Risk Score, n (%)		Other, n (%)	4 (20)
Intermediate-1	1 (5)	**Blood Counts on Cycle 1 Day 1, median (range)**	
Intermediate-2	7 (35)	Platelets (K/μL)	26 (12–88)
High	12 (60)	Hemoglobin (g/dL)	8.3 (7.0–9.3)
North American MDS Consortium Risk Score, n (%)		Neutrophils (K/μL)	1.2 (0.1–9.0)
Low Risk	9 (45)	Bone marrow blasts (%)	10 (6-18)
High Risk	11 (55)	**Mutational Status*, n (%)**	
Median Time Since Initial Diagnosis of MDS		TET2	8 (40)
Years (range)	2.5 (0.6 – 8.9)	ASXL1	7 (35)
MDS Subtype, n (%)		EZH2	4 (20)
De novo	16 (80)	DNMT3A	3 (15)
Secondary	4 (20)	TP53	2 (10)
		KRAS	2 (10)
		IDH1	2 (10)
		N-RAS	1 (5)
		SF3B1	1 (5)
		Normal	5 (25)

ECOG=Eastern Cooperative Oncology Group, HMA=hypomethylating agent, IPSS=International Prognostic Scoring System, MDACC=MD Anderson Cancer Center, MDS=myelodysplastic syndrome
*Patients may have more than one mutation or cytogenetic abnormality

Table 2. Efficacy (reported as of data cut, September 15, 2021)

	Eltanexor (10mg) n=5	Eltanexor (20mg) n=10	Total N=15
ORR (mCR + HI) n (%)	3 (60)	5 (50)	8 (53.3)
mCR, n (%)	3 (60)	4 (40)	7 (46.7)
HI (with and without mCR) n (%)	1 (20)	2 (20)	3 (20)
SD, n (%)	2 (40)	2 (20)	4 (26.7)
PD, n (%)	0	3 (30)	3 (20)
Treatment Duration, weeks	15	12.5	13
Median Time to Response, weeks	8.1	9.1	8.4
Median Duration of Response, weeks, (95% CI)	7.9 (NE, NE)	25.3 (13.1, NE)	19.2 (7.9, NE)

ORR=overall response rate including CR (complete response), PR, mCR and HI, mCR=marrow complete response, HI=hematologic improvement (minimum of 8 weeks), SD=stable disease, PD=progressive disease, NE=non-evaluable

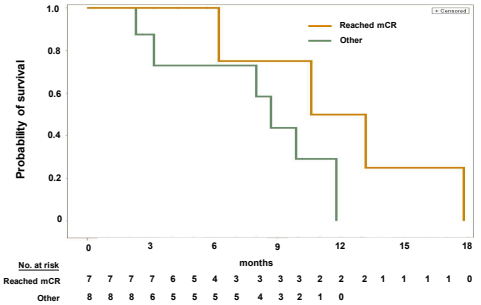
- Of the 7 patients who achieved mCR, 3 had reduced transfusion-dependence including 3 with complete TI for 5-10 cycles.
  - Median blast reduction was 78.6%
- Notably, mCR was observed in the 3 patients treated with >2 prior therapies and/or with secondary MDS

Recommended Phase 2 Dose (RP2D)
- **8 (53.3%) patients on 20mg eltanexor required a dose reduction, while no patients needed a reduction with 10mg eltanexor**
- **Due to better tolerability and at least comparable efficacy, the RP2D is 10mg**

Table 3. Treatment-Emergent Adverse Events (≥25%)

Adverse Event, n (%)	10 mg Eltanexor (N=5)				20 mg Eltanexor (N=15)			
Non-Hematologic	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**
Diarrhea	3 (60)	-	-	-	8 (53.3)	1 (6.7)	2 (13.3)	-
Nausea	1 (20)	-	1 (20)	-	4 (26.7)	6 (40)	-	-
Dyspnea	1 (20)	1 (20)	-	-	5 (33.3)	2 (13.3)	-	1 (6.7)
Fatigue	-	3 (60)	-	-	1 (6.7)	3 (20)	3 (20)	-
Constipation	1 (20)	2 (40)	-	-	2 (13.3)	4 (26.7)	-	-
Decreased appetite	1 (20)	-	1 (20)	-	3 (20)	4 (26.7)	-	-
Abdominal pain	3 (60)	-	-	-	3 (20)	2 (13.3)	-	-
Dizziness	1 (20)	-	1 (20)	-	3 (20)	2 (13.3)	1 (6.7)	-
Weight decreased	1 (20)	-	1 (20)	-	4 (26.7)	1 (6.7)	-	-
Fall	1 (20)	-	-	-	3 (20)	1 (6.7)	1 (6.7)	-
Anxiety	1 (20)	1 (20)	-	-	1 (6.7)	2 (13.3)	-	-
Back pain	1 (20)	-	1 (20)	-	3 (20)	-	-	-
Dysgeusia	2 (40)	-	-	-	2 (13.3)	1 (6.7)	-	-
Vomiting	1 (20)	-	-	-	3 (20)	1 (6.7)	-	-
Hematologic	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**
Anemia	-	-	2 (40)	-	-	-	5 (33.3)	1 (6.7)
Febrile neutropenia	-	-	2 (40)	-	-	-	5 (33.3)	-
Neutropenia	-	-	-	2 (40)	-	1 (6.7)	1 (6.7)	3 (20)
Thrombocytopenia	-	-	-	2 (40)	-	-	1 (6.7)	3 (20)
Leukopenia	-	-	1 (20)	1 (20)	2 (13.3)	-	1 (6.7)	1 (6.7)

Figure 2. Overall Survival Based on Response of All Evaluable Patients



- Median OS mCR vs Other: 11.86 vs 8.67 months (HR=0.27, p=0.05)
- Median OS mCR vs PD: 11.86 vs 3.15 months (HR=0.23, p=0.04)

Conclusions

- **Single-agent oral eltanexor was active in patients with high-risk MDS that is primary refractory to HMAs.**
- **Patients with mCR had significantly longer mOS than patients without mCR or with PD (including those with HI without mCR, SD or PD)**
- **Based on the results, the trial is being expanded at the RP2D of 10mg.**
- **Further evaluation of eltanexor in MDS as a single agent and in combination with other agents is ongoing.**

References

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