ABSTRACT #177

PHASE 2 SURVIVAL AND SAFETY OF ELTANEXOR MONOTHERAPY IN RELAPSED/REFRACTORY MYELODYSPLASTIC SYNDROMES

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INTRODUCTION

- Currently, there are limited options for MDS patients who are relapsed and/or refractory to hypomethylating agents (HMA), median overall survival (mOS) of 4-6 months have been reported in these patients.[1,2] Approximately half of MDS patients are primary refractory to HMAs.[2,3]
- HMA monotherapy remains the standard of care in frontline MDS.[4] Patients with relapsed and/or refractory MDS (R/R MDS) lack a standard of care and have limited treatment options; ~80% of patients in the community setting do not receive a second line treatment.[5]
- Eltanexor is a novel, investigational, oral exportin 1 (XPO1) inhibitor of the nuclear export of Tumor Suppressor Proteins (TSP) relevant in MDS[6]
  - Preclinical studies have shown minimal blood brain barrier penetration in preclinical models, lower IC_{50} compared to selinexor in leukemia cell lines, and improved survival in a myeloid xenograft mouse model.[7,8]
  - XPO1 overexpression is an independent predictor of poor outcomes in myeloid malignancies[9]
- A Phase 1 dose-escalation trial in patients with primary HMA-refractory MDS treated with eltanexor 20mg (n=15) or 10mg (n=5) on days 1-5 of each week of each 28-day cycles showed a generally manageable tolerability profile and encouraging efficacy signals[10]

STUDY DESIGN

- Phase 2 open-label study of the safety, tolerability, and efficacy of eltanexor in multiple cancer indications, including R/R MDS (NCT02649790)
  - Eltanexor was administered on Days 1 through 5 each week of each 28-day cycle
  - One prophylactic anti-emetic required prior to first dose during first treatment cycle
  - The intent-to-treat (ITT) population consisted of all patients who received at least 1 dose at the RP2D (10 mg eltanexor). This population will be used for primary analyses of efficacy.
  - The efficacy evaluable (EE) population consisted of patients who had at least one response assessment.

Phase 2, Part F

n=30 enrolled

10 mg Eltanexor

Primary Objective:
- Overall response Rate (ORR) as defined by 2006 IWG MDS response criteria[11]

Select Secondary Objectives:
- Overall Survival (OS)
- 6-month OS
- Disease Control Rate (DCR)
- Rate of transfusion dependence
- Duration of response

Select Inclusion Criteria:
- Documentation of progressing MDS with 5%-19% myeloblasts in the bone marrow
- Intermediate, high- or very-high-risk MDS by Revised International Prognostic Scoring System (IPSS-R)
- R/R MDS, as defined*
- Eastern Cooperative Oncology Group (ECOG) performance status <2

*R/R MDS defined as having one of the following: ≥2 cycles of GMA agents with clear PD (pancytopenia with ≥50% increase in bone marrow blasts) OR patient progressed to a higher risk category of MDS, OR ≥4 cycles of HMA therapy with SD/lack of improvement per IWG 2006 criteria, OR intolerance to treatment (≥6 cycles of Aza if required per local SOC guidelines to establish lack of improvement/response to Aza, OR Relapse or disease progression after an initial response to HMA per IWG 2006 criteria).
IWG, International Working Group; RP2D, recommended phase 2 dose

RESULTS

- Here we report an update of the Phase 2 results of the MDS cohort (Part F) with the eltanexor RP2D dose
- As of the data cutoff date (Feb 8, 2023), 30 patients were enrolled, and median follow up was 9.5 months (95% CI 8.0-NR)
- Median treatment duration was 3.6 months (0.5-10.6) for ITT and 4.3 months (0.9-10.6) for EE.

Table 1. Patient Demographics and Disease Characteristics

Characteristic	Total (N=30)	Characteristic	Total (N=30)
Age		**Prior Therapies, n (%)**	
Years: Median (range)	76 (56 - 91)	Azacitidine	29 (96.7)
<75, n (%)	14 (46.7)	Venetoclax	9 (30.0)
≥75, n (%)	16 (53.3)	Decitabine	2 (6.7)
ECOG Performance Status, n (%)		Lenalidomide	2 (6.7)
0	11 (36.7)	Cytarabine-based chemotherapy	2 (6.7)
1	19 (63.3)	Other*	11 (36.7)
HMA Refractory, n (%)		**Baseline cytopenias on Cycle 1 Day 1, median (range)**	
Primary	27 (90.0)		
Secondary	3 (10.0)	Platelets (K/µL)	33 (5 - 163)
Investigator Reported IPSS-R Risk Score, n (%)		Hemoglobin (g/dL)	8.6 (6.5 - 10.6)
Intermediate	5 (16.7)	Neutrophils (K/µL)	0.9 (0.1 - 19.0)
High	16 (53.3)	**Cytogenetic Abnormalities, n (%)**	
Very High	9 (30.0)	Del(5q)	8 (26.7)
Median Time From Initial Diagnosis of MDS to Informed Consent Date		**Mutational Status**, n (%)**	
Years (range)	2.9 (0.5 - 6.3)	*ASXL1*†	7 (23.3)
MDS Subtype, n (%)		*TET2*	6 (20.0)
De novo	28 (93.3)	*SF3B1*	5 (16.7)
Secondary	2 (6.7)	*TP53*†	4 (13.3)
Prior lines of therapy, median (range)	1 (1 - 5)	*EZH2*†	4 (13.3)
		DNMT3A†	3 (10.0)
Bone marrow blasts (%), n (%)		*NRAS*	2 (6.7)
≤5%	4 (13.3)	*KRAS*	0
>5%	26 (86.7)	*IDH1*	0

ECOG, The Eastern Cooperative Oncology Group; HMA, hypomethylating agent; IPPS-R, Revised international prognostic scoring system; MDS, myelodysplastic syndrome.
*Consists of any drug not listed above, regardless of whether a patient also received any of those listed that include ALRN 6924, canakinumab, cedazuridine and decitabine, evorpacept, gilteritinib, imetelstat, investigational antineoplastic drugs, onametostat, other antineoplastic drugs, pevonedistat, and PLX51107
**Patients may have more than one mutation or cytogenetic abnormality †Mutations known to be associated with poorer prognosis[12]

RESULTS

Table 2. Efficacy

	Eltanexor (ITT) n=30	Eltanexor (EE) n=26
Overall Response Rate* (ORR = mCR + HI), n (%)	8 (26.7)	8 (30.8)
Marrow Complete Response (mCR), n (%)	8 (26.7)	8 (30.8)
Hematologic Improvement (± mCR) n (%)	2 (6.7)	2 (7.7)
HI-Erythroid	1 (3.3)	1 (3.8)
HI-Platelet	1 (3.3)	1 (3.8)
Stable Disease (SD), n (%)	13 (43.3)	13 (50.0)
Progressive Disease (PD), n (%)	5 (16.7)	5 (19.2)
Overall Survival, months, median (95% CI)	8.7 (6.6-NE)	8.7 (7.0-NE)
Disease Control Rate, n (%)	21 (70.0)	21 (80.8)
Median Time to Response, months (range), (based on number of responders; n=8)	1.8 (0.9 - 5.9)	1.8 (0.9 - 5.9)
Median Duration of Response, months, (95% CI)	NR (NE-NE)	NR (NE-NE)

CI, confidence interval; HI, hematologic improvement; mCR, marrow complete response; NR, not reached; ORR, overall response rate; PD, progressive disease; SD, stable disease.
*ORR as reported by Investigators.

- Then mCR was seen in the 8 patients treated with >2 prior therapies and/or with secondary MDS
  - Median blast reduction was 75.0% in the 8 mCR responders
- Investigator reported RBC transfusion independence was seen in 9/25 (36%) patients*
- Investigator reported Platelet transfusion independence was seen in 3/15 (20%) patients*
- Investigator reported Overall transfusion independence was seen in 8/28% (28.6%) patients**

* The transfusion independence is determined in patients who were dependent of RBC or Platelet transfusion and then became independent for a minimum of 8 consecutive weeks.
**The overall transfusion independence is determined in patients who were dependent of RBC and/or platelet at baseline and then became independent of both RBC and platelet.

Figure 2. Overall Survival (ITT)

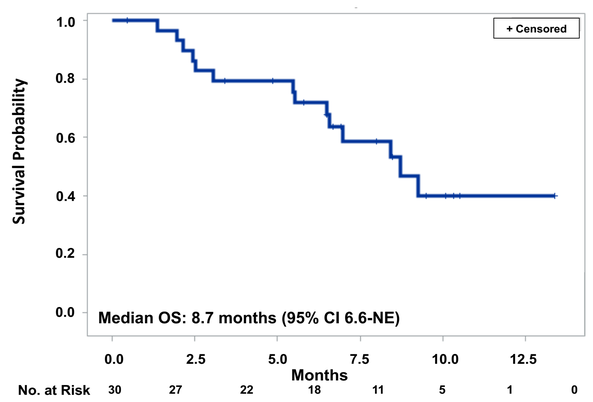

Figure 3. Overall Survival (EE)

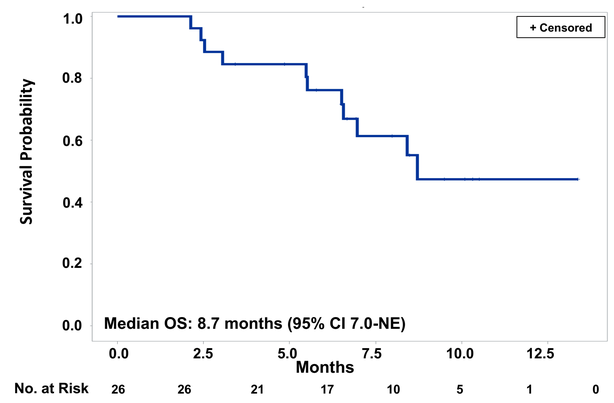

Table 3. Treatment-Emergent Adverse Events (TEAE)

Treatment Emergent Adverse Events	Eltanexor (N=30)	Treatment Emergent Adverse Events	Eltanexor (N=30)
Any grade, ≥20% overall		**Grade 3+, ≥10%**	
Asthenia	14 (46.7)	Neutropenia	9 (30.0)
Diarrhea	13 (43.3)	Thrombocytopenia	8 (26.7)
Nausea	10 (33.3)	Asthenia	5 (16.7)
Constipation	9 (30.0)	Anemia	4 (13.3)
Neutropenia	9 (30.0)	Febrile neutropenia	4 (13.3)
Thrombocytopenia	8 (26.7)	Leukopenia	3 (10.0)
Decreased appetite	7 (23.3)	Epistaxis	3 (10.0)
Weight decreased	7 (23.3)	Fall	3 (10.0)
Contusion	6 (20.0)		
Epistaxis	6 (20.0)		
Oedema peripheral	6 (20.0)		

- There were 4 TEAEs leading to death: lung neoplasm malignant, multiple organ dysfunction syndrome, septic shock, subdural hematoma
- There were no treatment-related AEs (TRAEs) leading to death.
- There were 3 patients that discontinued treatment due to TRAEs: alanine aminotransferase increase (ALT), aspartate aminotransferase (AST) increase, asthenia, and hemorrhagic diarrhea (increases in ALTs and ASTs were experienced by one patient).

CONCLUSIONS

- **Eltanexor has a promising single agent efficacy signal in a higher-risk R/R MDS patient population, including those with poor prognostic features (high and very high-risk IPSS-R scores, adverse prognosis mutations, higher baseline blasts >5%)**
  - ORR was 26.7% ITT (30.8%, EE); mOS was 8.7 mos, ITT (8.7 mos, EE)
- **Single agent eltanexor was generally well tolerated**
  - The most common AEs were asthenia (46.7%), diarrhea (43.3%), and nausea (33.3%) which were limited to Grades 1 and 2 and generally manageable
  - Grade ≥3 AEs were neutropenia (30%), thrombocytopenia (26.7%), and asthenia (16.7%)
- **Eltanexor's inhibition of XPO1, which blocks the nuclear export of TSPs relevant to MDS, warrants further evaluation in this hard-to-treat patient population in which no standard of care has been identified**

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17th International Congress on Myelodysplastic Syndromes
May 3-6, 2023• Marseille, France