Abstract # 4274

A Phase 2 Dose-Confirmation Study of Oral ASTX727, a Combination of Oral Decitabine with a Cytidine Deaminase Inhibitor (CDAi) Cedazuridine (E7727), in Subjects with Myelodysplastic Syndromes (MDS)

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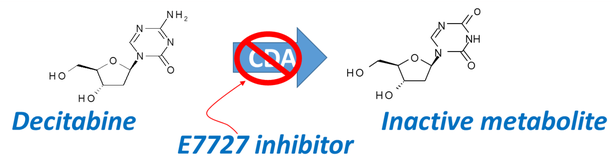
INTRODUCTION

An oral hypomethylating agent which could be administered at a dose which would emulate parenteral pharmacokinetics would be more convenient and potentially enhance adherence to treatment. Heretofore, rapid clearance by cytidine deaminase (CDA) during first pass has prevented good oral bioavailability for decitabine (DAC).[1] Cedazuridine (E7727), a novel CDAi, is orally bioavailable with a large safety margin and reproducible effectiveness in preclinical models.[2] A phase I dose finding study found that a fixed oral combination of 35 mg of decitabine and 100 mg of E7727 (ASTX727 with 35 mg decitabine/100 mg cedazuridine (ASTX727 35/100 mg) should produce similar PK to decitabine administered intravenously at 20 mg/m^2 as a 1-hour infusion.[3] We tested this hypothesis in a phase 2 cross-over study, and report the preliminary results here.

Figure 1. Cedazuridine Blocks First Pass Metabolism of Decitabine Permitting Oral Administration



STUDY DESIGN

Figure 2. Study Schema

	PK, PD	PK, PD	
Group A	20 mg/m^2 IV	ASTX727 35/100 mg	ASTX727 35/100 mg
Randomized 1:1	Cycle 1	Cycle 2	Cycle 3+
Group B	ASTX727 35/100 mg	20 mg/m^2 IV	ASTX727 35/100 mg

Table 1: Patient Demographics

	Group A [N=25]	Group B [N=25]	Total [N=50]
Age (y)			
Median (Range)	69 (32-87)	72 (41-86)	71.5 (32-87)
Gender			
Male	20 (80%)	21 (84%)	41 (82%)
Female	5 (20%)	4 (16%)	9 (18%)
Weight (kg)			
Median (Range)	81.8 (40-122)	87.3 (55-118)	84.75 (40-122)
BSA (m^2)			
Median (Range)	2.0 (1.3-2.4)	2.1 (1.6-2.4)	2.0 (1.3-2.4)
ECOG			
0	13 (52%)	9 (36%)	22 (44%)
1	9 (36%)	15 (60%)	24 (48%)
2	3 (12%)	1 (4%)	4 (8%)
Prior HMA			
No	23 (92%)	24 (96%)	47 (94%)
IPSS Class			
Int-1	10 (40%)	10 (40%)	20 (40%)
Int-2	6 (24%)	7 (28%)	13 (26%)
High Risk	4 (16%)	4 (16%)	8 (16%)
CMML	5 (20%)	4 (16%)	9 (18%)

RESULTS

Figure 3. Pharmacokinetics of Decitabine

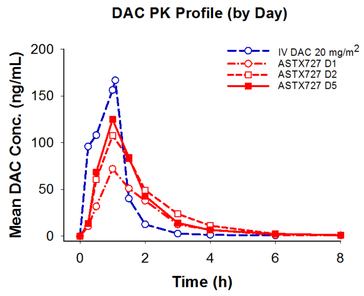
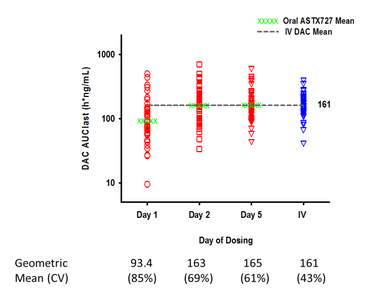


Figure 4. Decitabine individual AUC by Day



Geometric Mean (CV)	93.4 (85%)	163 (69%)	165 (61%)	161 (43%)

Table 2: AUC Equivalence Analysis Based on 5-day AUC Estimates

Treatment [N=43]	Adjusted Geometric Means of 5-Day AUC (ng*h/mL)	Ratio (80% CI)
ASTX727 35/100 mg	769.2	0.955 (0.80-1.13)
DAC 20 mg/m^2 one hour IV infusion	805.1	

Table 3: Cycles Administered

N=50	Median	Range
Cycles of Therapy	6.5	1-20

Figure 5. Cedazuridine Pharmacokinetics over 5 Days of Treatment

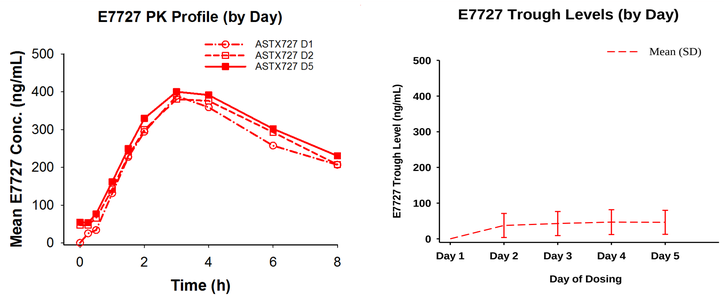
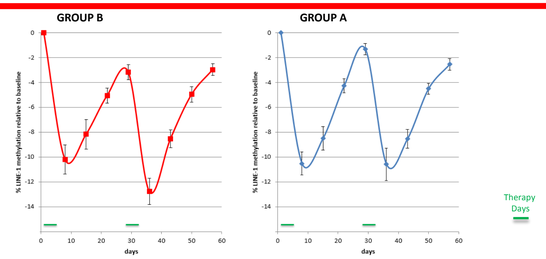


Figure 6: LINE-1 Demethylation Similar between IV-DAC and ASTX727



Maximum LINE-1 Demethylation Analysis (N=46)

SAFETY

Table 4: All Adverse Events Occurring in ≥25% of Subjects During Study

	Number (%) of Subjects [N=50 Treated]									
	IV Decitabine Cycle 1 or 2 [N=48]				Oral ASTX727 Cycle 1 or 2 [N=49]				Entire Study (n=50)	
	All Grades		≥Grade 3		All Grades		≥Grade 3		All Grades	≥Grade 3
Any event	46	(96)	30	(63)	45	(92)	29	(59)	50 (100)	46 (92)
Neutropenia	18	(38)	15	(31)	11	(22)	10	(20)	27 (54)	25 (50)
Thrombocytopenia	14	(29)	12	(25)	12	(25)	7	(14)	27 (54)	21 (42)
Fatigue	7	(15)	0	0	11	(22)	2	(4)	21 (42)	3 (6)
Febrile neutropenia	9	(19)	9	(19)	6	(12)	6	(12)	19 (38)	19 (38)
Diarrhoea	6	(13)	0	0	5	(10)	0	0	18 (36)	2 (4)
Constipation	6	(13)	0	0	8	(16)	0	0	16 (32)	0 0
Anemia	5	(10)	4	(8)	6	(12)	5	(10)	14 (28)	13 (26)
Nausea	5	(10)	0	0	5	(10)	0	0	14 (28)	1 (2)
Dyspnoea	1	(2)	1	(2)	7	(14)	3	(6)	13 (26)	5 (10)

CLINICAL RESULTS

Table 5: Clinical Response Data[a]

	Best Response Rate, N (%)	
Clinical Response	Total [N=50]	
Complete Response (CR)	8	(16)
Marrow Complete Response (mCR)	14	(28)
Hematologic Improvement	9	(18)
No Response	19	(38)
RBC Transfusion Dependence at Baseline, N	22	
RBC Transfusion Independence[b]	10	(45)

[a]Responses based on IWG.

[b]Proportion based on patients transfusion dependent at baseline.

CONCLUSIONS

- ASTX727 successfully emulates the AUC exposures and LINE-1 PD of 20 mg/m^2 IV decitabine in a 5 consecutive day regimen with a 5-day AUC ratio of 0.955.
- The 6-hour $T_{1/2}$ of cedazuridine produces steady state by Day 2 and subsequent trough levels of drug which facilitates consistent decitabine oral bioavailability on Days 2 to 5 of the cycle.
- Clinical response and safety data appear similar to that reported for 20 mg/m^2 IV

REFERENCES

1. Lowder JN et al. Epigenomics 7:1083-1088, 2015.
2. Oganesian A et al. Blood 122:2526 (abstract), 2013
3. Garcia-Manero G et al. ASH 114 (abstract), 2016

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Poster can be downloaded from www.astx.com