Abstract # E1192

DOSE-CONFIRMATION STUDY OF ORAL ASTX727, A COMBINATION OF ORAL DECITABINE WITH A CYTIDINE DEAMINASE INHIBITOR (CDAI) E7727, IN SUBJECTS WITH MYELODYSPLASTIC SYNDROMES (MDS): PRELIMINARY RESULTS

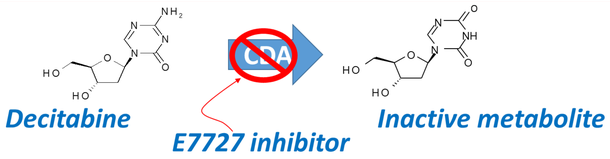
Guillermo Garcia-Manero[1], Elizabeth A. Griffiths[2], Gail Roboz[3], Julie Bergeron[4], Richard Wells[5], Olatoyosi Odenike[6], David Steensma[7], Karen Yee[8], Stefan Faderl[9], Philip Amrein[10], Laura Michaelis[11], Hagop Kantarjian[1], Aram Oganesian[12], James Lowder[12], Pietro Taverna[12], Mohammad Azab[12], Michael R. Savona[13]

[1]UT MD Anderson Cancer Center, Houston, [2]Roswell Park Cancer Institute, Buffalo, [3]Cornell University Medical Center, New York, [4]Hopital Maisonneuve-Rosemont, Montreal, 5Sunnybrook Medical Center, Toronto [6]University of Chicago, Chicago, [7]Dana Farber Institute, Boston, [8]Princess Margaret , Toronto, [9]Hackensack University Medical Center, Hackensack, [10]Massachussetts General Hospital, [11]Medical College of Wisconsin, Milwaukee, [12] Astex Pharmaceuticals Inc., Pleasanton, [13]Vanderbilt University Medical Center, Nashville.

INTRODUCTION

An oral hypomethylating agent which could be administered in 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 oral administration.[1] 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) should produce similar pharmacokinetics (PK) to decitabine administered intravenously at 20 mg/m^2 as a 1-hour infusion (DAC IV).[3] We tested this hypothesis in a randomized cross-over study of DAC IV vs ASTX727 and report the preliminary results here.

Figure 1. E7727 Blocks First Pass Metabolism of Decitabine Permitting Oral Administration



STUDY DESIGN

Figure 2. Study Schema

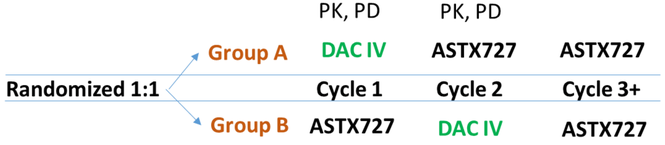


Table 1: Patient Demographics

	Group A DAC IV ➡ ASTX727 [N=25]	Group B ASTX727 ➡ DAC IV [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 (1.2-2)	2.1 (1.4-2.4)	2.0 (1.2-2.4)
ECOG			
1	13 (52%)	11 (44%)	24 (48%)
2	9 (36%)	13 (52%)	22 (44%)
3	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

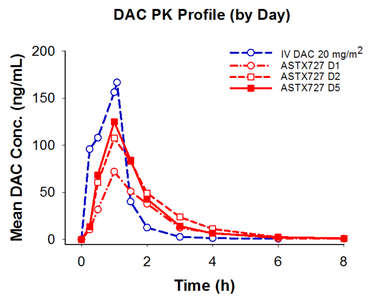


Figure 4. Decitabine AUC by Patient

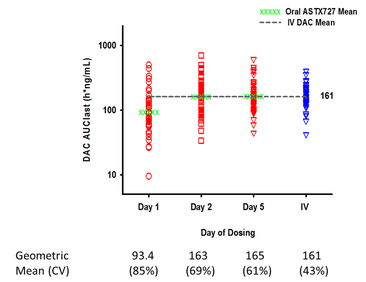


Table 2: Intrapatient AUC Equivalence Analysis Based on 5-day AUC Estimates

Treatment [N=43*]	Estimated Geometric Means of 5 Day Treatment	Ratio (80% CI)
ASTX727 35 mg DAC/100 mg E7727	769.2	0.955 (0.84-1.1)
DAC 20 mg/m^2 one hour IV infusion	805.1	

*43 Subjects completed PK for the first 2 cycles

Figure 5. E7727 PK Profile Similiar over Time Except for Presence of Trough Levels after Day 1

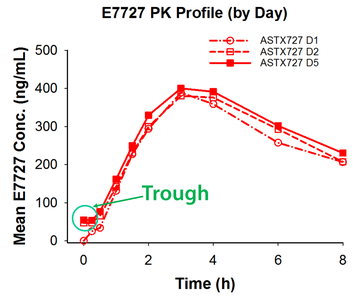
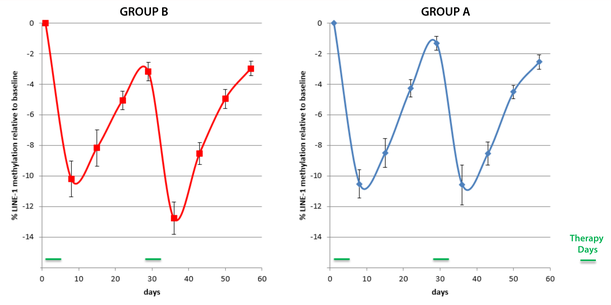


Figure 6: LINE-1 Demethylation Similar between DAC IV and ASTX727



Maximum LINE-1 Demethylation Analysis (n=46)

SAFETY

Table 3: Adverse Events Regardless of Relationship in ≥10% of Subjects

All TEAEs	Number (%) of Subjects [N=50 Treated]											
	DAC IV Cycle 1 or 2 [N=48]				ASTX727 Cycle 1 or 2 [N=49]				ASTX727 Cycle ≥3 [N=37]			
	All Grades		≥Grade 3		All Grades		≥Grade 3		All Grades		≥Grade 3	
Neutropenia	14	(29)	11	(23)	8	(16)	7	(14)	10	(27)	10	(27)
Thrombocytopenia	13	(27)	12	(25)	10	(20)	6	(12)	4	(11)	4	(11)
Febrile neutropenia	9	(19)	9	(19)	8	(16)	8	(16)	11	(30)	11	(30)
Fatigue	7	(15)	0	0	7	(14)	2	(4)	6	(16)	2	(5)
Constipation	6	(13)	0	0	5	(10)	0	0	3	(8)	0	0
Diarrhoea	6	(13)	0	0	3	(6)	0	0	6	(16)	1	(3)
Hypomagnesaemia	1	(2)	0	0	5	(10)	0	0	5	(14)	0	0
Nausea	5	(10)	0	0	3	(6)	0	0	4	(11)	0	0

Table 4: Related Adverse Events ≥ Grade 3 in >2% of Subjects

Related Grade ≥ 3 TEAEs	Number (%) of Subjects							
	DAC IV Cycle 1 or 2 [N=48]		ASTX727 Cycle 1 or 2 [N=49]		ASTX727 Cycle ≥3 [N=37]		ASTX727 Total [N=50]	
Neutropenia	1	(2)	4	(8)	8	(22)	11	(22)
Leukopenia	0		3	(6)	3	(8)	5	(10)
Thrombocytopenia	1	(2)	3	(6)	2	(5)	5	(10)
Febrile neutropenia	0		3	(6)	2	(5)	3	(6)
Fatigue	0		2	(4)	1	(3)	2	(4)

CLINICAL RESULTS

Table 5: Preliminary Response Data

Clinical Response	Best Response Rate, N (%) Total [N=50]	
Complete Response (CR)	5	(10)
Marrow Complete Response (mCR)	10	(20)
Hematologic Improvement	10	(20)
No Response	25	(50)
RBC Transfusion Dependence at Baseline, N	20	
RBC Transfusion Independence[a]	8	(40)

[a]Proportion based on patients transfusion dependent at baseline

Response data are preliminary as only 37 patients had received at least 3 cycles of treatment

CONCLUSIONS

- Oral ASTX727 successfully emulates DAC AUC exposures and LINE-1 pharmacodynamics (PD) of 20 mg/m^2 IV decitabine in a 5 consecutive day regimen
- Preliminary clinical response and safety data appear similar to that reported for 20 mg/m^2 IV
- A Phase 3 trial of DAC IV vs ASTX727 is being planned

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

Poster presented at: 22nd Congress of the European Hematology Association (EHA), June 22 – 25, 2017 Madrid, Spain

Poster can be downloaded from www.astx.com ASTX727-PB17(701)