Abs. #: MDS19-0166

Development of an oral hypomethylating agent (HMA) as a fixed dose combination (FDC) of decitabine and CDA inhibitor cedazuridine

Guillermo Garcia-Manero[1], Elizabeth A Griffiths[2], Olatoyosi Odenike[3], Amy DeZern[4], David P Steensma[5], Casey O'Connel[6], Gail Roboz[7], Richard Wells[8], Aram Oganesian[9], James N Lowder[9], Mohammad Azab[9], and Michael R Savona[10]

MD Anderson Cancer Center[1], Roswell Park Comprehensive Cancer Center[2], University of Chicago[3], Johns Hopkins University Hospital[4], Dana-Farber Cancer Institute[5], USC/Norris Comprehensive Cancer Center[6], Cornell University Medical Center, NY[7], Sunnybrook Medical Center, Toronto[8], Astex Pharmaceuticals, Inc.[9], Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center[10]

INTRODUCTION

- Hypomethylating Agents (HMAs) require parenteral (IV or SC) injections daily for 5-7 days every month for several months, and even years in patients having benefit.
- Oral bioavailability of HMAs is low due to degradation in the gut and liver by cytidine deaminase (CDA).
- We developed an oral, potent, and safe CDA inhibitor cedazuridine (E7727)
- Combining cedazuridine with decitabine (DAC) in an oral Fixed Dose Combination (FDC) tablet (ASTX727) should allow successful oral delivery as the first oral HMA to achieve equivalent AUC exposure to decitabine IV.

METHODS

Figure 1: ASTX727 Phase 1 Study Dose Escalation Design

The Phase 1 study was a dose escalation design to establish the recommended doses of E7727 (cedazuridine) and decitabine (DAC) likely to achieve AUC equivalence with standard dose decitabine IV (DAC 20 mg/m^2 IV).

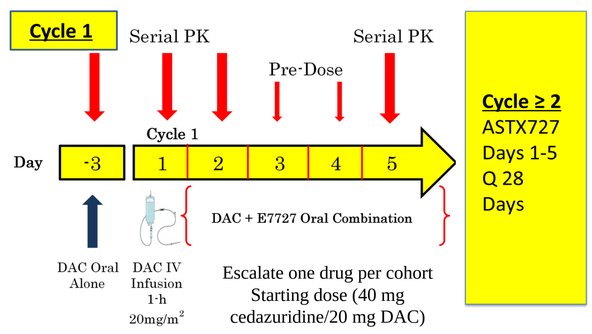
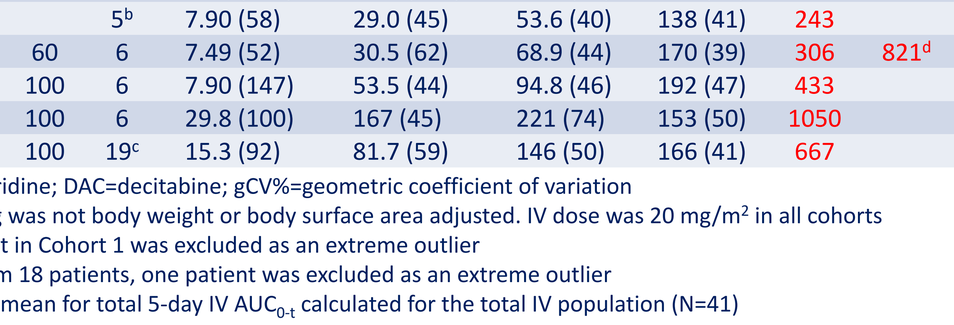


Figure 2: ASTX727 Phase 2 Study Dose Confirmation Design



Phase 2 was a randomized cross over design of DAC 20 mg/m^2 IV dailyx5 vs oral ASTX727 once dailyx5 in Cycle 1 with patients crossing over to the other drug in Cycle 2.
From Cycle 3 onwards all patients continued on oral ASTX727 once dailyx5 Q 28 Days until progression.

* ASTX727 was given as individual capsules of cedazuridine and decitabine in the first stage of Phase 2 then as a single FDC tablet of both cedazuridine and decitabine combined in the second stage of Phase 2

RESULTS

Table 1: Phase 1 Dose Escalation AUC

Subjects Who Completed Course 1 (N=43); Data are Geometric Mean (gCV%)

Oral Dose[a] (mg)				AUC$_{0-t}$ by Day (ng*h/mL) Geometric Mean (gCV%)				5-Days Total AUC$_{0-t}$		
Cohort	DAC	CED	N	D –3 (DAC alone)	D2 (ASTX727)	D5 (ASTX727)	IV D1	Oral	IV (N=41)	% of AUC (Oral/IV)
1	20	40	6	10.7 (108)	42.8 (136)	70.3 (86)	159 (53)	324		40
			5[b]	7.90 (58)	29.0 (45)	53.6 (40)	138 (41)	243		30
2	20	60	6	7.49 (52)	30.5 (62)	68.9 (44)	170 (39)	306	821[d]	37
3	20	100	6	7.90 (147)	53.5 (44)	94.8 (46)	192 (47)	433		53
4	40	100	6	29.8 (100)	167 (45)	221 (74)	153 (50)	1050		128
5	30	100	19[c]	15.3 (92)	81.7 (59)	146 (50)	166 (41)	667		81

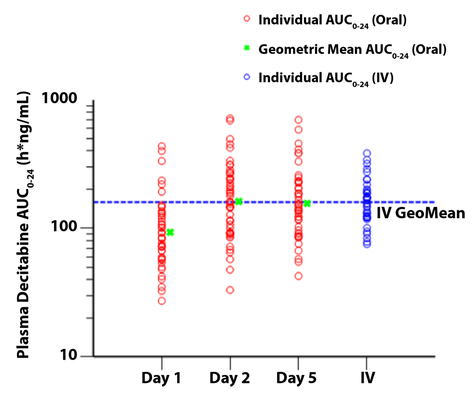
CED=cedazuridine; DAC=decitabine; gCV%=geometric coefficient of variation
[a] Oral dosing was not body weight or body surface area adjusted. IV dose was 20 mg/m^2 in all cohorts
[b] One subject in Cohort 1 was excluded as an extreme outlier
[c] IV data from 18 patients, one patient was excluded as an extreme outlier
[d] Geometric mean for total 5-day IV AUC$_{0-t}$ calculated for the total IV population (N=41)

- Oral doses of cedazuridine 100 mg and decitabine at 30 and 40 mg achieved decitabine AUC of 81 and 128% of decitabine 20 mg/m^2 IV AUC respectively
- Recommended dose for Phase 2 is 100 mg cedazuridine and 35 mg decitabine

Table 2: Phase 2 Patients Baseline Characteristics

Characteristic	Sequence A (N=41) ASTX727 → DAC IV	Sequence B (N=39) DAC IV → ASTX727
Median Age (min-max)	71 (32, 90) Years	71 (41, 86) Years
Sex Male/Female %	78/22%	74/26%
Median Weight (min-max)	78.8 (40-122) Kg	86.2 (42-118) Kg
Median BSA	1.96 (1.3-2.4) m^2	2.05 (1.3-2.4) m^2
ECOG PS		
0-1	93%	90%
2	7%	10%
IPSS		
Intermediate-1	46%	41%
Intermdiat-2 or High Risk	34%	36%
CMML	20%	23%
Median Hemoglobin (min-max)	8.75 (7.1-14.9) g/dL	9.25 (6.8-13.9) g/dL
Median Neutrophils (min-max)	0.94 (0.03-73.6) 10^9/L	0.76 (0.06-63.4) 10^9/L
Median Platelets (min-max)	58.5 (2-523) 10^9/L	60.0 (8-569) 10^9/L
RBCs Transfusion Dependence	48.8%	46.2%
Platelets Transfusion Dependence	19.5%	10.3%
Median BM Blasts (min-max)	7% (0-19%)	5% (0-17%)

Figure 3: Phase 2 PK (Individual and Mean Decitabine Levels)



Individual and geometric Mean Plasma decitabine AUC$_{0-24}$ following oral 100 mg cedazuridine and 35 mg decitabine vs a single IV infusion of decitabine 20 mg/m^2 – dose confirmation stage.

Table 3a: Phase 2 PK (Cedazuridine + Decitabine Capsules vs IV DAC)

Primary Analysis (Paired Population): Plasma (oral cedazuridine and decitabine capsules vs IV DAC)

	N	IV Geo. LSM	Oral Geo. LSM	Ratio of Geo. LSM Oral/IV (%)	(80% CI)	Intra-Subject (CV%)
5-day AUC$_{0-t}$ (h*ng/mL)	40	802.81	750.82	93.52	(82.10, 106.5)	47.0

IV = 20 mg/m^2 IV infusion (1h) of decitabine. Oral = 100 mg cedazuridine and 35 mg decitabine capsules
CI = Confidence interval; IV = intravenous; Geo. LSM= Geometric Least Squares Means; CV = coefficient of variation

Table 3b: Phase 2 PK (Single FDC tablet vs IV DAC)

Primary Analysis (Paired Population): Plasma (single FDC tablet vs IV DAC)

	N	IV Geo. LSM	Oral Geo. LSM	Ratio of Geo. LSM Oral/IV (%)	(80% CI)	Intra-Subject (CV%)
5-day AUC$_{0-t}$ (h*ng/mL)	24	745.26	727.29	97.59	(80.48, 118.3)	53.8

IV = 20 mg/m^2 IV infusion (1h) of decitabine. Oral = ASTX727 FDC tablet. (100/35 mg cedazuridine/decitabine)
CI = Confidence interval; IV = intravenous; Geo. LSM= Geometric Least Squares Means; CV=coefficient of variation

Figure 4a: Phase 2 PD (LINE-1 Demethylation): Sequence A

Sequence A: ASTX727 → IV DAC

Figure 4b: Phase 2 PD (LINE-1 Demethylation): Sequence B

Sequence B: IV DAC→ ASTX727

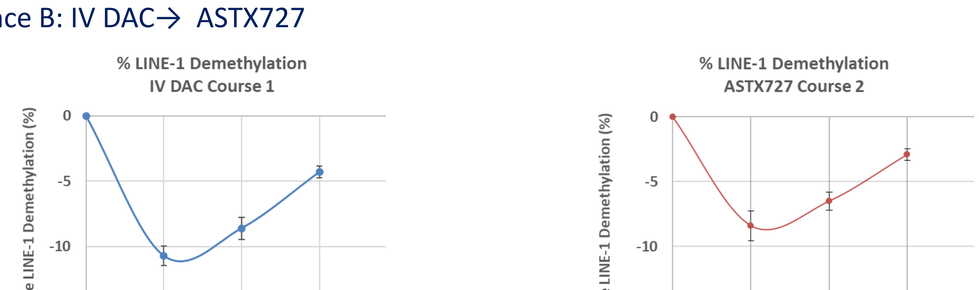


Table 4: Phase 2 Efficacy (Best Response[a] and Transfusion Independence[b])

Best Response (N=80)	%	95% CI
Complete Response (CR)	21.3%	13-32%
Partial Response	0	
Marrow Complete Response (mCR)	22.5%	14-32%
mCR+HI	7.5%	2.8-15.6%
Hematological Improvement (HI)	16.3%	9-26%
HI-E	10%	4-19%
HI-N	2.5%	0.3-8.7%
HI-P	13.8%	7-23%
Overall Response (CR+PR+mCR+HI)	60%	48-71%
RBCs Transfusion Independence (N=38)[b]	50%	33-67%
Platelets Transfusion Independence (N=12)[b]	50%	21-79%

[a] IWG 2006 criteria; [b] at least 8 weeks of transfusion independence in patients who were dependent at baseline

Table 5: Phase 2 Safety: Related AEs Grade ≥ 3 in ≥5% of Patients

	IV DAC (Cycle 1 or 2) N=75 n (%)	ASTX727 (Cycle 1 or 2) N=78 n (%)
Any Grade ≥ 3 Related AEs	24 (32%)	21 (27%)
Neutropenia	16 (21.3%)	11 (14.1%)
Thrombocytopenia	11 (14.7%)	9 (11.5%)
Leukopenia	6 (8.0%)	6 (7.7%)
Anemia	4 (5.3%)	5 (6.4%)
Febrile Neutropenia	4 (5.3%)	3 (3.8%)

SUMMARY

1. ASTX727 FDC tablet (cedazuridine/decitabine 100/35 mg) demonstrated decitabine AUC equivalence with decitabine IV 20 mg/m^2.
2. Efficacy and safety using ASTX727 were consistent with expected results from decitabine IV.

Poster presented at: 15th International Symposium on MDS May 8 – 11, 2019
Poster can be downloaded from www.astx.com
ASTX727-PB19(101)