Abst. No. 1683

Results of First in Human (FIH) Phase 1 Pharmacokinetic (PK) Guided Dose-Escalation Study of ASTX727, a Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine, in Subjects with Myelodysplastic Syndromes (MDS)

Michael R Savona[1], Olatoyosi Odenike[2], Philip C Amrein[3], David P Steensma[4], Amy E DeZern[5], Laura C Michaelis[6], Stefan Faderl[7], Elizabeth Griffiths[8], Wael A Harb[9], Raoul Tibes[10], Casey O'Connell[11] Sanjeev Redkar[12], James N Lowder[12], Pietro Taverna[12], Aram Oganesian[12], Roya Nawabi[12], Mohammad Azab[12], Guillermo Garcia-Manero[13]

Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center[1], University of Chicago[2], Massachusetts General Hospital[3], Dana Farber Cancer Institute[4], Johns Hopkins University Hospital[5], Medical College of Wisconsin[6], Hackensack University Medical Center[7], Roswell Park Memorial Institute[8], Horizon Oncology Center[9], Mayo Clinic Scottsdale[10], University of Southern California[11], Astex Pharmaceuticals[12], MD Anderson Cancer Center[13]

Introduction

Treatment of MDS patients with parenteral hypomethylating agents (HMA) such as decitabine (DAC) requires frequent visits to the physician. An orally administered HMA would provide significant patient convenience, potentially enhance adherence to treatment, and permit the exploration of extended treatment schedules with lower doses of DAC. Neither DAC nor azacitidine is readily bioavailable in oral form due to rapid clearance by cytidine deaminase (CDA) present in the gut and liver[1]. E7727, a novel CDAi, is orally bioavailable with a large safety margin and reproducible effectiveness in preclinical models.[2] We report here the first in human Phase 1 results of a PK-guided dose escalation trial of ASTX727 (the orally administered combination of DAC and E7727).

Study Design

Figure 1: ASTX727-01: Phase 1 Dose Escalation Cohorts

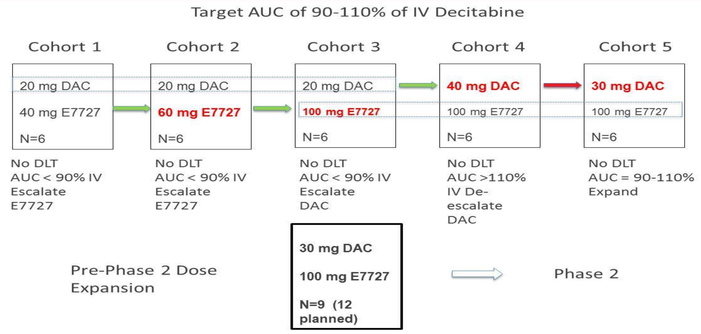
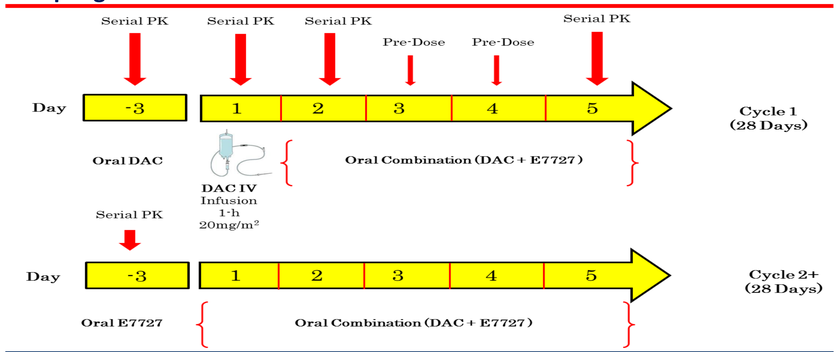


Figure 2: ASTX727-01: DAC IV; oral CDAi (E7727); and DAC oral Dosing and PK sampling schedule



Patient Characteristics (Table 1)

	Cohort [n]					Total [n]
	1 [6]	2 [6]	3 [6]	4 [6]	5^ [15]	[39]
Age						
Mean (SD)	70.5(8.5)	71(6.2)	74(4.8)	75.2(7.1)	70.2(7.9)	71.9 (7.2)
Median (range)	68.2(59-81)	79(63-79)	72.5(70-83)	76.5(66-85)	69(59-82)	71 (59-85)
Sex						
M n (%)	3 (50%)	5 (83%)	3 (50%)	4 (67%)	11 (73%)	26 (67%)
F n (%)	3 (50%)	1 (17%)	3 (50%)	2 (33%)	4 (27%)	13 (33%)
ECOG PS n (%)						
0	4 (67%)	3 (50%)	2 (33%)	2 (33%)	5 (33%)	16 (41%)
1/2	2 (33%)	3 (50%)	4 (66%)	4 (67%)	10 (67%)	23 (59%)
IPSS#/DX n (%)						
MDS INT-1	4 (67%)	2 (33%)	2 (33%)	2 (33%)	9 (60%)	19 (49%)
MDS INT-2	2 (33%)	1 (17%)		1 (17%)	4 (27%)	8 (21%)
MDS High Risk		1 (17%)	3 (50%)	2 (33%)	1 (7%)	7 (18%)
CMML		2 (33%)	1 (17%)	1 (17%)	1 (7%)	5 (13%)
Prior RX n (%)						
Yes [HMA]	1 [0] (17%)	2 [1] (33%)	1 [0] (17%)	6 [4] (100%)	10 [10] (67%)	20[15) (51%)
No	5 (83%)	4 (67%)	5 (83%)	0	5 (33%)	19 (49%)

^Includes 9 from dose expansion #International Prognostic Scoring System for MDS Cheson Blood 2000

Pharmacokinetics

Figure 3: Decitabine PK profile, IV vs oral, without/with CDAi

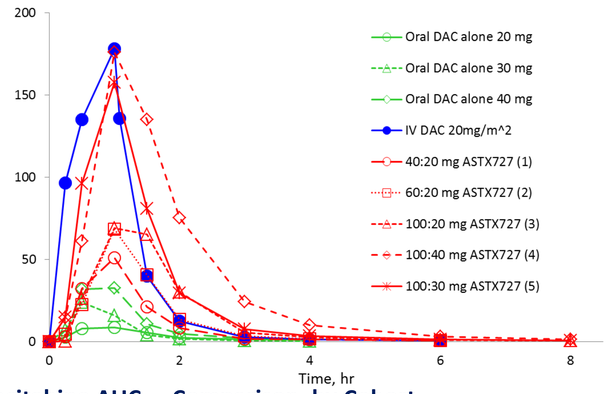
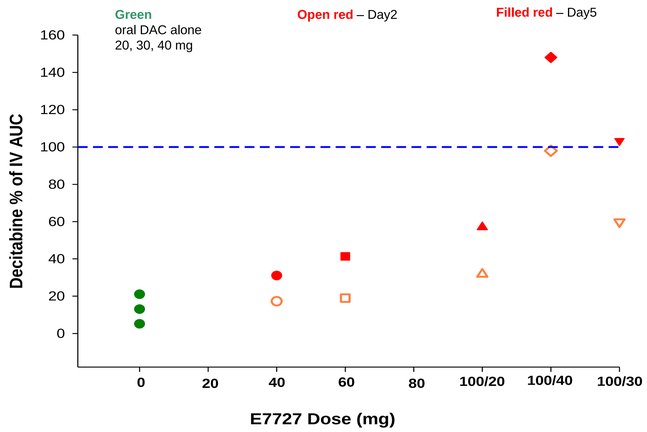


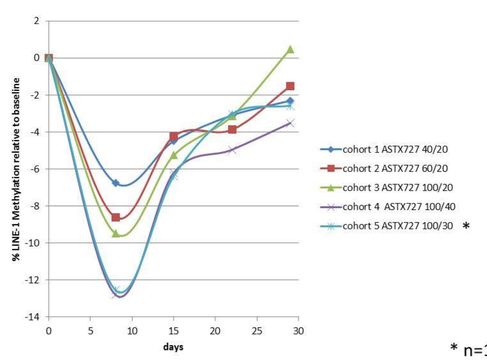
Figure 4: Decitabine AUC_{last} Comparison, by Cohort



- Decitabine AUC increased with increasing doses of CDAi E7727 when administered orally
- Decitabine AUC from 20 mg/m^2 IV was met (Cohort 5) or exceeded (Cohort 4) by the oral combination
- Oral fixed dose DAC AUC variability was similar to IV (BSA-adjusted)

Pharmacodynamics

Figure 5: ASTX727-01 LINE-1 Demethylation: Overall Summary for 5 Cohorts



* n=12

- ASTX727 cohorts 4 and 5 achieve LINE-1 demethylation > 10%

Clinical Activity

Figure 6: Time on Study and to Response

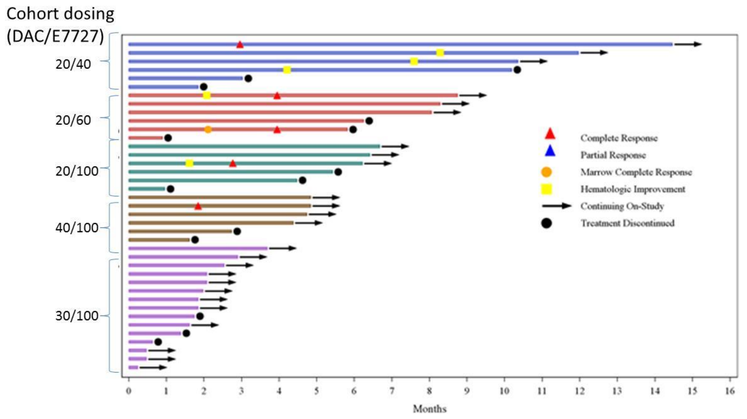


Table 2: Preliminary response assessment*

Cohort / Clinical Response	1 (6) n(%)	2 (6) n(%)	3 (6) n(%)	4 (6) n(%)	Sum(24) n(%)
Complete Response (CR)	1(17%)	2(33%)	1(17%)	1(17%)	5(21%)
Marrow Complete Response (mCR)	0	0	0	0	0
Hematologic Improvement (HI)	3(50%)	0	0	0	3(12%)
Total Responders	**4(67%)**	**2(33%)**	**1(17%)**	**1(17%)**	**8(33%)**
On Treatment	3(50%)	3(50%)	3(50%)	3(50%)	12 (50%)

- Responses seen in low dose (oral decitabine 20mg and 40-60mg E7727) cohorts
- 50% of responses seen in patients with prior treatment with HMAs

*Clinical response cannot yet be assessed in cohort 5

Safety

Table 3: Safety Summary Adverse Events [1] ≥ Grade 3

Cohort / Adverse Event	1 n(%)	2 n(%)	3 n(%)	4 n(%)	5 n(%)	Total n(%)
Thrombocytopenia	4(67%)	1(17%)	4(31%)	1(17%)	4(27%)	14(36%)
Anemia	3(50%)	1(17%)	3(50%)	2(33%)	2(13%)	11(31%)
Neutropenia	3(50%)	2(33%)	2(33%)	1(17%)	1(7%)	9(23%)
Febrile Neutropenia	1(17%)	1(17%)	1(17%)	2(33%)	1(7%)	6(15%)
Leukopenia	1(17%)	2(33%)	1(17%)	0	1(7%)	5(13%)

[1] Incidence by patient regardless of relationship to ASTX727

Conclusions

- ASTX727, a fixed dose oral combination of E7727, a CDA inhibitor, with low doses of decitabine, increases decitabine AUC in a dose dependent manner with similar variability to IV decitabine
- AEs are consistent with IV decitabine with no GI toxicity
- ASTX727 is clinically active and induces potent DNA demethylation
- The fixed oral dose of 30 mg decitabine and 100 mg E7727 results in decitabine AUC equivalent to 20 mg/m^2 IV and will be further studied in a Phase 2 trial in HMA naïve MDS

References

1. Lowder JN, Taverna P, and Issa J-P. Epigenomics [Epub ahead of print] 2015.
2. Oganesian A et al. Blood 122(21), Abstract 2526 (2013)

Disclosures

S Redkar, JN Lowder, P Taverna, A Oganesian, R Nawabi, and M Azab are employees of Astex Pharmaceuticals, Inc. which funded the study. MR. Savona: Advisory: Ariad, Astex, Celgene, CTI Pharma, Gilead, Karyopharm; Research Funding: Astex, TG Therapeutics, Sunesis Consulting: Karyopharm. D Steensma: Consultancy or Data Safety Monitoring Committee: Celgene, Onconova, Incyte, Novartis, Amgen. O Odenike: Incyte, Celgene, CTI/ Baxalta, Sanofi-Aventis, Spectrum Pharmaceuticals and Sunesis. There are no relevant conflicts of interest to disclose for : P Amrein, W Harb, A DeZern, LC. Michaelis, S Faderl, and G Garcia-Manero.

Poster presented at: American Society of Hematology Annual Meeting, Orlando, FL Dec 5 – 8, 2015

Poster can be downloaded from www.astx.com

15PB-129(1201)