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P253

Phase 1 Dose-Escalation Study of ASTX727, a Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine: Comparable Variability in Pharmacokinetics

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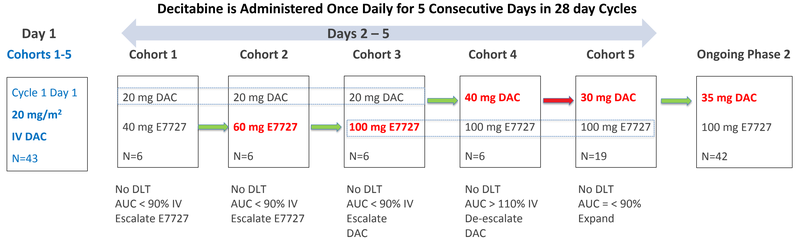
INTRODUCTION

Hypomethylating agents (HMA) are typically administered parenterally and adjusted to body surface area (BSA) in order to achieve target pharmacokinetic (PK) parameters associated with response. Much of the variation associated with administration of HMAs is related to the intrinsic activity of cytidine deaminase (CDA) an enzyme which rapidly metabolizes HMAs and is highest in the gut and liver. We report here intra- and inter-patient pharmacokinetic variation in patients from a study aiming to match PK parameters of BSA adjusted dosing with IV decitabine (DAC) with a novel fixed-dose oral combination (ASTX727), of DAC and E7727, a CDA inhibitor. Preliminary safety and clinical activity were previously reported and are updated here.[1]

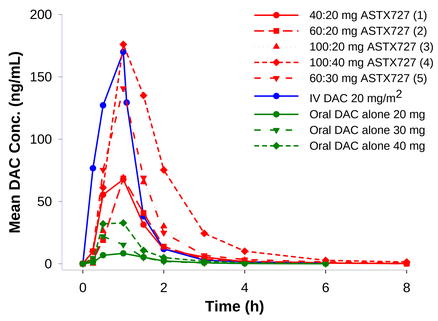
STUDY DESIGN

Figure 1: ASTX727-01: dose escalation schema



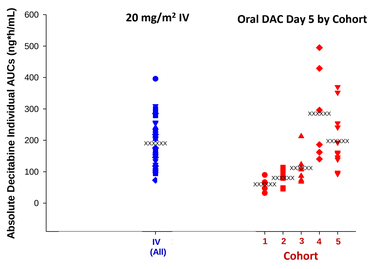
PHARMACOKINETICS

Figure 2: Decitabine PK profile, IV vs oral, without/with CDAi



Increases in the oral dose of E7727 and DAC, increase the peak serum concentration (C_{max}) and area under the curve (AUC_{last}) in a dose dependent manner.

Figure 3: Decitabine AUC_{last} comparison, by cohort



- Variability for fixed dose of oral decitabine (with E7727) is similar to IV (BSA dosing).
- Decitabine mean AUC in cohort 5 was slightly lower than the IV AUC (~80%) based on projection with 5-day dosing.

Table 1: Pharmacokinetics of IV decitabine

N	Dose mg/m^2	Actual Dose mg Mean [SD] (CV%)	AUC_{last} ng*hr/mL Geometric Mean (CV%)	C_{max} ng/mL Geometric Mean (CV%)
42	20	40.0 [5.6] (14%)	174 (43.4%)	183 (41.2%)

Table 2: ASTX727 decitabine PK summary

	Oral Dose (mg)			Day 5	Day 5	Projected 5 day sum
Cohort	DAC	E7727	N	AUC_{last} ng*hr/mL Geometric Mean (CV%)	C_{max} ng/mL Mean [SD] (CV%)	% IV AUC
1	20	40	5[a]	39.6 (119)	33.4 (134)	22%
2	20	60	6	75.3 (40.3)	82.4 (38.4)	37%
3	20	100	6	103 (162)	80.9 (157)	52%
4	40	100	6	232 (72.2)	161 (51.0)	125%
5	30	100	19	152 (50.1)	138 (54.7)	78%

[a]One significant outlier was eliminated from the analysis

Figure 4: Weight and BSA by cohort

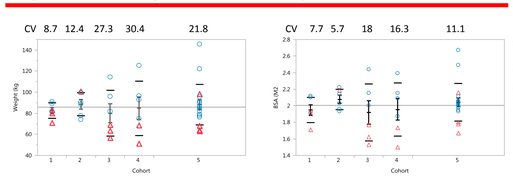
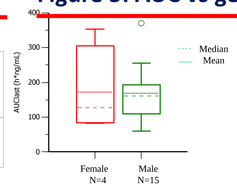
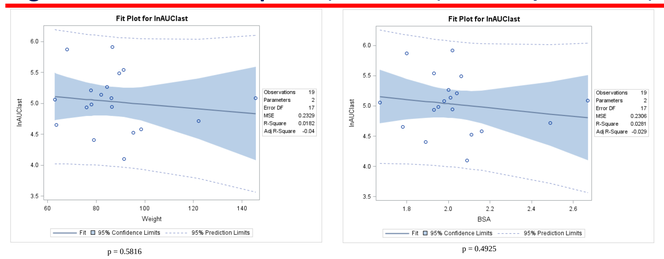


Figure 5: AUC vs gender



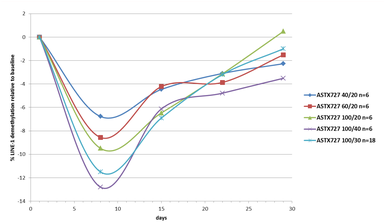
Substantial distribution differences in weight and BSA exist between cohorts, with ranges between 1.5 and 2.67 BSA and 51.1 and 145.6 kg. Females (Δ), who have been reported to have lower levels of CDA than males (●), are clustered at the lower end of the body mass scale.[2] The mean AUC in females is similar to males.

Figure 6: Decitabine PK profile, IV vs oral, without/with CDAi, cohort 5 day 5



No correlation was found between DAC exposure on C1D5 (100 mg E7727 + 30 mg DAC) and body weight or BSA

Figure 7: LINE-1 methylation change - cycle 1 overall summary for 5 cohorts (42 patients)



LINE-1 Methylation change - Cycle 1 Overall summary for 5 Cohorts (42 patients)

CLINICAL RESULTS

Table 3: Patient characteristics

	Cohort [n]					Total [n]
	1 [6]*	2 [6]	3 [6]	4 [6]	5^ [19]	[43]
Age						
Mean (SD)	70.5 (8.5)	72 (6.2)	74 (4.8)	75.2 (7.1)	71.6 (8.8)	72.3 (7.6)
Median (range)	68.5 (59-81)	71 (63-79)	72.5 (70-83)	76.5 (66-85)	73 (59-86)	72 (59-86)
Sex						
M n (%)	3 (50%)	5 (83%)	3 (50%)	4 (67%)	15 (79%)	30 (70%)
F n (%)	3 (50%)	1 (17%)	3 (50%)	2 (33%)	4 (21%)	13 (30%)
ECOG PS n (%)						
0	4 (67%)	3 (50%)	2 (33%)	2 (33%)	7 (37%)	18 (42%)
1/2	2 (33%)	3 (50%)	4 (67%)	4 (67%)	12 (63%)	25 (58%)
IPSS³/DX n (%)						
MDS INT-1	4 (67%)	2 (33%)	2 (33%)	2 (33%)	10 (53%)	20 (47%)
MDS INT-2	2 (33%)	1 (17%)		1 (17%)	3 (16%)	7 (16%)
MDS High Risk		1 (17%)	3 (50%)	2 (33%)	4 (21%)	10 (23%)
CMML		2 (33%)	1 (17%)	1 (17%)	2 (10%)	6 (14%)
Prior RX n (%)						
Yes [HMA]	1 [0] (17%)	2 [1] (33%)	1 [0] (17%)	6 [4] (100%)	12 [10] (63%)	22 [15] (51%)
No	5 (83%)	4 (67%)	5 (83%)	0	7 (37%)	21 (49%)

* One subject only treated in C1D3 is not included

^ Includes 13 from dose expansion

Table 4: Preliminary response assessment

Clinical Response / Cohort	1 (6)* n(%)	2 (6) n(%)	3 (6) n(%)	4 (6) n(%)	5 (19) N(%)	Total (43) n(%)
Complete Response (CR)	2 (33)	2 (33)	0	1 (17)	0	5 (12)
Marrow Complete Response (mCR)	1 (17)	0	0	1 (17)	1 (5.3)	3 (6.9)
Hematologic Improvement (HI)	0	1 (16.7)	2 (33.3)	0	1 (5.3)	4 (9.3)
Total Responders	**3 (50)**	**3 (50)**	**2 (33.3)**	**2 (33.3%)**	**2 (10.6)**	**12 (27.9)**
On Treatment	2 (33.3)	2 (33.3)	2 (33.3)	1 (16.7)	9 (47.3)	16 (18.6)
Median number of cycles	11	6.5	5	3.5	5	5

*One subject only treated in C1D3 is not included

- Responses seen in all cohorts including the lowest doses.
- All responses were in patients who were naïve to prior HMA except one patient in Cohort 2.

SAFETY

Table 5: Adverse events ≥ grade 3 > 5% incidence*

Adverse Event / Cohort	1 (6)* n(%)	2 (6) n(%)	3 (6) n(%)	4 (6) n(%)	5 (19) N(%)	Total (43) n(%)
Thrombocytopenia	4 (67)	1 (17)	4 (67)	1 (17)	6 (32)	16 (37)
Anemia	3 (50)	1 (17)	3 (50)	2 (33)	4 (21)	13 (30)
Neutropenia	3 (50)	2 (33)	2 (33)	1 (17)	4 (21)	12 (28)
Febrile Neutropenia	1 (17)	1 (17)	2 (33)	3 (50)	2 (11)	9 (21)
Pneumonia	0	1 (17)	0	2 (33)	3 (16)	6 (14)
Leukopenia	1 (17)	2 (33)	1 (17)	0	2 (11)	6 (14)
Sepsis	0	0	0	1	3 (16)	4 (9)

* Incidence by patient regardless of relationship to ASTX727

CONCLUSIONS

- Simultaneous oral administration of E7727, a CDA inhibitor, and DAC, increases DAC AUC in a dose dependent manner.
- The CV of ~50% for fixed dose oral ASTX727 is comparable to the ~40% CV for BSA adjusted IV DAC.
- ASTX727 is clinically active and induces potent DNA demethylation.
- A fixed oral dose of 35 mg decitabine and 100 mg E7727 is expected to result in DAC AUC. equivalent to 20 mg/m^2 IV DAC and is being further studied in a Phase 2 trial in HMA naïve MDS.

REFERENCES

1. Savona M, et al. Blood: 126(23);1683, 2015.
2. Mahfouz RZ et al Clin Cancer Res 19(4):938-948, 2013.
3. Cheson B, et al. Blood 108(2):419-425, 2006.

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