Abstract
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Prolonged Survival Observed in 133 MDS Patients Treated with Oral Decitabine/Cedazuridine

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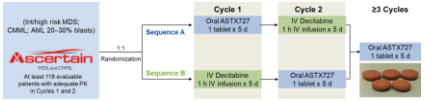
BACKGROUND

- DNA methyltransferases (DNMTi), also often called hypomethylating agents (HMAs), have historically been administered parenterally due to limited and variable oral availability.
- Cedazuridine is a novel, potent, and safe inhibitor of cytidine deaminase and when given in combination with decitabine, enables efficient oral availability[1]
- A fixed dose combination of 35 mg decitabine/100 mg cedazuridine (ASTX727) was shown to provide decitabine PK AUC exposures equivalent to decitabine 20 mg/m^2 IV when given on Days 1-5 of an every 28-day regimen[2] and patients had the ability to continue to receive oral decitabine/cedazuridine as treatment.
- Efficacy and long term follow up (survival) data are presented here.

ASCERTAIN STUDY DESIGN

- Subjects with MDS or CMML eligible to receive IV decitabine.
- Randomized crossover design was used where subjects serve as their own control.
- Pharmacokinetics: decitabine 5-day exposure (AUC) for IV vs. oral was compared between cycle 1 and 2.
- Pharmacodynamics: LINE-1 demethylation was compared between cycle 1 and 2.
- Subjects received oral decitabine/cedazuridine for cycles 3 onward and subjects were followed for safety and efficacy until progression, toxicity, or withdrawal.



Major entry criteria
- Candidates for IV decitabine
- ECOG PS 0 – 1
- Life expectancy of ≥3 months
- Adequate organ function

Primary endpoint
- Total 5-day decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

Secondary endpoints
- Efficacy: Response rate; transfusion independence; duration of response; leukemia-free and overall survival
- Safety of ASTX727
- Maximum LINE-1 demethylation

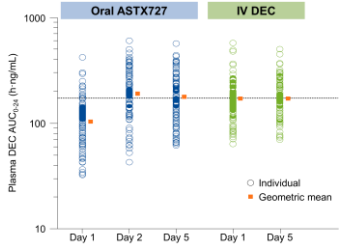
Table 1. Study Population

Characteristics		Total Treated N=133
Median age, years (range)		71 (44–88)
Sex	Male	87 (65%)
	Female	46 (35%)
Median weight, kg (range)		83 (45 -158)
Median BSA, m^2 (range)		1.98 (1.4 - 2.9)
CMML		16 (12%)
MDS, IPSS classification	High risk	21 (16%)
	Int-1 and 2	90 (68%)
	Low risk	6 (5%)
Transfusion dependent	RBCs	53 (40%)
	Platelets	12 (9%)
ECOG PS	0	55 (41%)
	1	78 (59%)

RESULTS

Results: Pharmacokinetics and Pharmacodynamics

- Compared to baseline, the median maximum LINE-1 methylation decrease (demethylation) in cycle 1 was 13.7%.
- The change in LINE-1 demethylation between oral vs. IV decitabine was less than 1% for both cycles 1 and 2 with overlapping 95% confidence intervals suggesting similar biologic effect.



- Individual decitabine exposures from oral fixed-dose decitabine/cedazuridine dosing overlapped with IV decitabine BSA-based dosing.
- The study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106% (N=123).
- All sensitivity (N=131) and secondary PK AUC analyses confirmed findings from primary analysis.

Decitabine 5-day AUC$_{0-24}$ (h·ng/mL)		IV DEC N	IV DEC Geo. LSM	Oral ASTX727 N	Oral ASTX727 Geo. LSM	Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
Primary Analysis	Paired[1]	123	864.9	123	855.7	98.9 (92.7, 105.6)	31.7

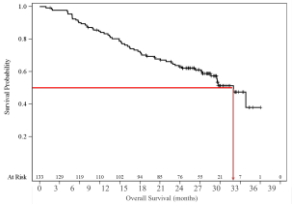
Table 2. Results: Responses

Response category	Treated Patients (N=133), n (%)	95% CI
Complete response (CR)	29 (22%)	(15.1,29.8)
Partial response (PR)	0	
Marrow CR (mCR)	43 (32.3%)	(24.5,41.0)
mCR with hematologic improvement	22 (16.5%)	(10.7,24.0)
Hematologic improvement (HI)	10 (7.5%)	(3.7,13.4)
HI-erythroid	2 (1.5%)	(0.2,5.3)
HI-neutrophils	1 (0.8%)	(0.0,4.1)
HI-platelet	7 (5.3%)	(2.1,10.5)
Overall response (CR + PR + mCR + HI)	82 (61.7%)	(52.8,69.9)
Progressive Disease	6 (4.5%)	(1.7,9.6)
No Response	28 (21.1%)	(14.5, 29.0)
Non-evaluable	17 (12.8%)	(7.6, 19.7)

- Median CR duration was 14.0 months. (range 2-29 months)
- Median duration of best response was 12.7 months. (range 1-33 months)
- 34 (26%) of subjects proceeded to HCT.
- No survival difference was seen between subjects proceeding to HCT vs. others.
- Subjects received median 9 cycles of treatment

RESULTS

Results: Responses



- Median follow up is approximately 32 months.
- mOS for the 133 patients is 31.7 months (95% CI: 28.0, NE).
- Leukemia-free survival is 29.1 months (95% CI:22.1, NE).

Table 3. Results: Safety - Treatment Emergent Adverse Events in >10% of Patients*

Preferred Term	Phase 3 Total (N=133, n (%))	Phase 3 Total Grade 3 or higher
Neutropenia	68 (51%)	65 (49%)
Thrombocytopenia	71 (53%)	62 (47%)
Anaemia	55 (41%)	47 (35%)
Leukopenia	33 (25%)	29 (22%)
Febrile Neutropenia	18 (14%)	17 (13%)
Fatigue	32 (24%)	3 (2%)
Diarrhea	22 (17%)	2 (2%)
Nausea	33 (25%)	0 (0%)
Decreased Appetite	19 (14%)	0 (0%)
Constipation	18 (14%)	0 (0%)

*Events attributable to oral decitabine/cedazuridine

- Safety profile consistent with that of IV decitabine.
- No new safety concerns with longer follow up.

CONCLUSIONS

- **Oral decitabine/cedazuridine demonstrates:**
  - PK AUC equivalence to IV decitabine.
  - Similar pharmacodynamic activity (LINE-1 demethylation).
- **Updated long term results with median follow up of ~32 months show:**
  - Median Overall Survival of 31.7 months.
  - CR rate of 22% and ORR of 62%.
  - 26% of subjects have been able to proceed to HCT.
    - No apparent difference between survival of those transplanted vs. continued oral decitabine/cedazuridine treatment.
  - No new noteworthy safety signals have emerged.
- **Oral decitabine (35 mg)/cedazuridine (100 mg) is the only approved oral HMA providing equivalent exposure as compared to its injectable form.**

References
1. Garcia-Manero, et al, Blood 2019; 134 (Supplement_1): 846. doi: https://doi.org/10.1182/blood-2019-122980
2. Savona, et al, Blood 2020; 136 (Supplement 1): 37–38. doi: https://doi.org/10.1182/blood-2020-133855

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