Abstract # 1245

A Phase 1 Study Evaluating ASTX727 (Decitabine and Cedazuridine) and Venetoclax Combination Therapy in Newly Diagnosed AML Patients Unfit for Intensive Induction Chemotherapy

Gabriel N. Mannis, MD[1], Elizabeth A. Griffiths, MD[2], Michael R. Savona, MD[3], Olatoyosi Odenike[4], Gail J. Roboz[5], Casey L. O'Connell[6], Jacqueline Dillingham[7], Prieya Wason[7], Lixia Zhu[7], Danna Chan[7], Harold N. Keer[7], Aram Oganesian[7], Kim-Hien Dao[7] and Courtney D. DiNardo[8]

[1]Department of Medicine, Division of Hematology, Stanford University School of Medicine, Stanford, CA; [2]Roswell Park Comprehensive Cancer Center, New York, NY; [3]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN; [4]University of Chicago, Chicago, IL; [5]Weill Cornell Medicine, The New York Presbyterian Hospital, New York, NY; [6]USC Keck School of Medicine, University of Southern California, Los Angeles, CA; [7]Astex Pharmaceuticals, Inc., Pleasanton, CA; [8]The University of Texas MD Anderson Cancer Center, Houston, TX

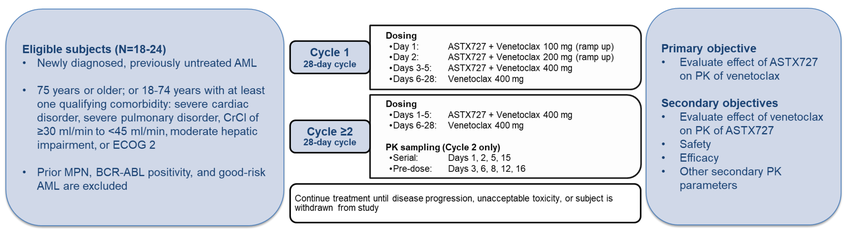
BACKGROUND

- The combination of a DNA methyltransferase inhibitor (DNMTi; parenteral azacitidine or decitabine) with the BCL2 inhibitor venetoclax is a newly established standard-of-care regimen for patients with newly diagnosed acute myeloid leukemia (AML) ineligible to receive intensive induction chemotherapy (DiNardo et al, 2020).
- Replacing the parenteral DNMTi with oral ASTX727 (a fixed-dose combination of decitabine 35 mg and cedazuridine 100 mg) with equivalent exposure may provide the benefit of reducing patient and caregiver burden of chronic parenteral therapy and may help responding patients stay on treatment longer (Savona et al, 2019; Garcia-Manero et al, 2020).

METHODS

- This is an ongoing single-arm, non-randomized Phase 1 study at 7 US medical centers evaluating ASTX727 and venetoclax combination therapy in newly diagnosed AML ineligible to receive intensive induction chemotherapy.
- Study schema and objectives are summarized in Figure 1.
- Delay of subsequent cycles and venetoclax dose modifications follow the Venclexta USPI for hematologic toxicities and anti-fungal concomitant medications.
- Response assessments are evaluated using the 2017 ELN criteria (Döhner et al, 2017).
- 25 subjects have received at least one dose of study medication as of the data cut-off date November 4, 2021.

Figure 1: Study Schema – ClinicalTrials.gov identifier: NCT04657081



Note: Subjects are instructed to take ASTX727 with water on an empty stomach with no food for 2 hours after administration and venetoclax with a meal and water (Venclexta® USPI) at least 2 hours after ASTX727 administration.

RESULTS

Table 1: Demographics and Baseline Disease Characteristics

- 25 subjects dosed as of the data cut-off
- Median age is 78.1 years (range 66 - 87)
- 19 (76%) subjects were ineligible to receive intensive chemotherapy due to age 75 years or older

Characteristic		n (%)
Sex	Male	14 (56)
	Female	11 (44)
Diagnosis	AML with myelodysplasia-related changes	9 (36)
	AML NOS	13 (52)
	AML, therapy-related	1 (4)
	Other/Missing	2 (8)
ELN Risk Category	Favorable	5 (20)
	Intermediate	9 (36)
	Adverse	7 (28)
	Missing	4 (16)
Eligible Comorbidity	≥75yo	19 (76)
	<75 with comorbidity	6 (24)

Table 2: Treatment Exposure

- The mean, median, and minimum-maximum number of dosing days of ASTX727 and venetoclax by cycle are indicated
- Subjects completed a median of 3.0 cycles (range 1-7); the median duration on treatment was 3.1 months (range 0.1-8.8) as of the data cut-off
- 9 (36%) subjects had a delay of the start of Cycle 2 for myelosuppression

Drug		Dosing Days by Cycle			
		1	2	3	4
ASTX727	No. Subjects	25	16	14	7
	Mean	4.8	5.0	4.9	4.7
	Median	5.0	5.0	5.0	5.0
	Min - Max	1 - 5	5 - 5	4 - 5	3 - 5
Venetoclax	No. Subjects	25	18	13	8
	Mean	24.1	23.9	19.4	14.5
	Median	28.0	28.0	21.0	12.0
	Min - Max	4 - 29	1 - 30	14 - 28	7 - 28

Note: The study is ongoing with 14 subjects continuing to receive study drugs, and up to 18 subjects completed Cycle 2 as of the data cut-off

Table 3: AUC at Steady-State for Venetoclax (D5, 15) and Decitabine (D5)

- Preliminary PK data are available from 19 subjects
- Venetoclax AUC seem to not be affected by coadministration of ASTX727 (C2D5 vs. C2D15) and are comparable to published data (32,800 [52%] ng*hr/ml) (Venclexta USPI)
- Decitabine AUC are slightly higher than observed in the Phase 3 study (ASTX727-02) with higher variability, but still within range of exposures seen in previous studies (189 [55%] ng*hr/ml at steady state; ASTX727-02 Clinical Study Report)

$AUC_{0\text{-}24h}$ (NG*HR/ML)	n	C2D5 (ASTX727+ venetoclax)	C2D15 (venetoclax)
Venetoclax	19	24,697 (84%)	19,087 (61%)
Decitabine	19	277 (63%)	*not applicable*

Figure 2: Preliminary Efficacy – Swimmer's Plot of Best Response

- 20 evaluable subjects were available for response assessment as of the data cut-off
- 9 (45%) achieved CR and 4 (20%) achieved CRi, for a composite CR+CRi rate of 65% (95% CI 40.8 to 84.6)

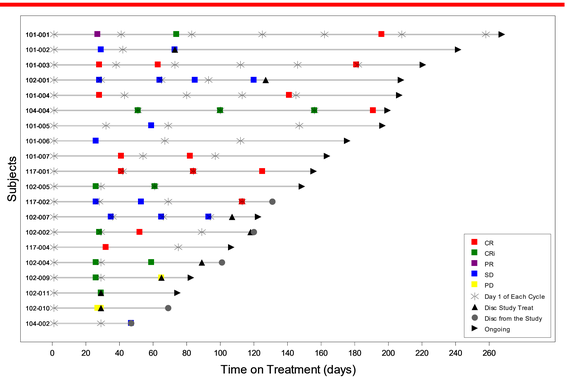


Table 4: AEs Occurring at ≥15% Regardless of Relationship to Study Drug

- No deaths occurred within the first 30 days of study treatment
- There were 32 SAEs, 7 were related to study drugs including: Grade 5 sepsis (2 subjects), Grade 3 pneumonia (3 subjects), and Grade 3 sepsis (2 subjects)
- 6 of 10 (60%) subjects discontinued treatment primarily due to a lack of response (stable disease, refractory disease, or progressive disease)
- There were 5 deaths before treatment discontinuation or within the 30-day safety follow-up: Grade 5: sepsis, C3D32; sepsis, C4D19; respiratory failure, C1D31; one death due to multiple myeloma progression; one death due to AML progression

Preferred Term*	Grade 1/2 (n, %)	Grade ≥3 (n, %)	All grades (n, %)
Diarrhea	10 (40.0)	0	10 (40.0)
Edema peripheral	9 (36.0)	1 (4.0)	10 (40.0)
Hyponatremia‡	8 (32.0)	0	9 (36.0)
Neutrophil count decreased	0	9 (36.0)	9 (36.0)
Hypokalemia	8 (32.0)	0	8 (32.0)
Constipation	7 (28.0)	0	7 (28.0)
Fatigue	7 (28.0)	0	7 (28.0)
Dyspnea	6 (24.0)	0	6 (24.0)
Nausea	6 (24.0)	0	6 (24.0)
Platelet count decreased	0	6 (24.0)	6 (24.0)
Vomiting	6 (24.0)	0	6 (24.0)
Anemia	0	5 (20.0)	5 (20.0)
Cough	5 (20.0)	0	5 (20.0)
Pain in extremity	5 (20.0)	0	5 (20.0)
Pneumonia	0	5 (20.0)	5 (20.0)
Pyrexia	5 (20.0)	0	5 (20.0)
Sepsis	0	5 (20.0)	5 (20.0)
Stomatitis	5 (20.0)	0	5 (20.0)
Febrile neutropenia	0	4 (16)	4 (16)
Hypotension	2 (8.0)	2 (8.0)	4 (16.0)
Infusion related reaction	3 (12.0)	1 (4.0)	4 (16.0)
Vascular access complication	2 (8.0)	2 (8.0)	4 (16.0)

*The following AEs occurred as Grade 1 or 2 and at a frequency of 4 (16%) but were not included in the table: anxiety, arthralgia, dizziness, dyspepsia, epistaxis‡, headache, hyperbilirubinemia, hyperuricemia, hypocalcemia, insomnia‡, and mouth hemorrhage. ‡Data not clean. Grade missing for 1 subject.

Summary

- This is an ongoing single-arm, non-randomized Phase 1 study investigating ASTX727 and venetoclax combination therapy in subjects with newly diagnosed AML unfit for intensive induction chemotherapy.
- These preliminary results indicate no apparent drug interactions between ASTX727 and venetoclax when compared to intra-study and historical venetoclax PK data and historical ASTX727 PK data (ASTX727-02 study).
- The CR rate is 45% and CR+CRi rate is 65% in 20 evaluable subjects and are comparable to the VIALE-A results for SQ/IV azacitidine and venetoclax combination therapy (DiNardo et al, 2020).
- The AEs observed are expected for the study population undergoing combination anti-leukemia therapy.
- These data suggest that an all-oral regimen of a DNMTi in combination with venetoclax is feasible and should be investigated further. This study has an expected completion date of February 2022. The Phase 2 study is ongoing.

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Conflict-of-interest statement:

GNM has research funding from Astex Pharmaceuticals, Inc., Forty Seven Inc/Gilead, Glycomimetics & Jazz; consultancy from Abbvie, Agios, Astellas Pharma, Bristol Myers Squibb, Genentech, MacroGenics, & Stemline
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Off-label disclosure:
This presentation contains information about the investigational use of decitabine + cedazuridine (ASTX727) in combination with venetoclax. Safety and efficacy have not been determined by any regulatory agency in this combination. Decitabine + cedazuridine is a prescription medicine approved in the United States and Canada to treat adults with myelodysplastic syndromes and chronic myelomonocytic leukemia. Venetoclax is a prescription medicine approved in the United States for multiple indications, including adults with newly diagnosed acute myeloid leukemia 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy in combination with azacitidine, decitabine, or low-dose cytarabine.

Abstract 1245

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