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POSTER ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Decitabine/Cedazuridine (ASTX727) Combined with a Molecularly-Targeted Agent (Venetoclax, Gilteritinib, Ivosidenib, or Enasidenib) As Personalized Maintenance Therapy in Acute Myeloid Leukemia: First Results from a Phase 1b Study

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Background: Disease relapse is the major cause of treatment failure and death in acute myeloid leukemia (AML). Currently, oral azacitidine (CC-486) is the only drug approved in the maintenance setting in patients with AML who are unable to complete standard therapy. The ECOG ACRIN E2906 trial suggested an overall survival (OS) benefit with 3-day IV decitabine maintenance. Decitabine/cedazuridine (ASTX727) is an oral formulation of decitabine that achieves systemic exposures as seen with IV decitabine. Multiple small-molecule agents are now available targeting key leukemic drivers (BCL-2, FLT3, and IDH1/IDH2 inhibitors). We developed a multi-arm phase 1b study (NCT05010772) to evaluate an oral maintenance regimen composed of an ASTX727 backbone combined with a molecularly-targeted agent (venetoclax, gilteritinib, ivosidenib, or enasidenib).

Methods: Patients ≥ 18 years with AML in first complete remission (CR) or CR with incomplete blood count recovery (CRi) not currently eligible for stem cell transplantation (SCT) and unable/unwilling to complete standard therapy were eligible. Patients having received either intensive induction (at least 2 cycles of therapy based on intermediate to high dose cytarabine) or low-intensity induction (at least 3 cycles based on low-dose cytarabine or a hypomethylating agent) were permitted. Other inclusion criteria were ECOG ≤ 3, adequate hepatic/renal function, absolute neutrophil count > 0.5 x 10^9/L, and platelets > 50 x 10^9/L. Patients were enrolled in one of five arms per physician choice based on molecular profile. Arm A consisted of ASTX727 35/100 mg PO on D1-3. All other arms combined this ASTX727 backbone with either venetoclax 400 mg (adjusted for azoles) PO on D1-5 (arm B), gilteritinib 120 mg PO on D1-28 (arm C), enasidenib 100 mg PO on D1-28 (arm D), or ivosidenib 500 mg PO on D1-28 (arm E). Treatment was administered in 4-week cycles, up to 24 cycles. Each arm initially consisted of a safety lead-in cohort with predetermined dose reductions for dose-limiting toxicity (DLT) per a 3+3 dose de-escalation design. Prophylactic antibiotics, antifungals, and antivirals were encouraged. The primary objective was safety and tolerability. Secondary objectives included relapse-free survival (RFS) and OS. Patients becoming eligible for SCT were taken off study and censored at the time of SCT for time-to-event endpoints.

Results: 23 patients, with a median age of 68 years (range 33-83), have been enrolled (3 on arm A, 19 on arm B, and 1 on arm C). 12 (52%) were enrolled following intensive induction and 11 (48%) after low-intensity induction. 16 (70%) had prior venetoclax. Best response at enrollment was CR in 22 (96%) patients and CRi in 1 (4%). 6/22 (27%) patients with available testing were measurable residual disease (MRD)-positive. 2 (9%) patients had antecedent myelodysplastic/myeloproliferative neoplasms and 1 (4%) had therapy-related AML. ELN 2022 risk was favorable in 10 (43%), intermediate in 3 (13%), and adverse in 10 (43%) patients.

The most common grade 3/4 adverse events were neutropenia (96%), thrombocytopenia (74%), anemia (39%), lung infection (22%), hypertension (17%), and neutropenic fever (17%). Cycle 2 dose reductions due to myelosuppression occurred in 5/23

(22%) patients. No DLTs were observed. No deaths occurred on protocol. Two patients died in remission from SCT-related complications after going off maintenance.
The current median follow-up time is 5.3 months (m). The median number of cycles given is 3 (1-15). Three relapses have occurred to date (1 in arm A, 2 in arm B). The median RFS for the full cohort is not reached (NR, 1-year 71%). The median OS for the full cohort (figure 1A) is NR (1-year 100%). The median RFS for arms A, B, and C are NR (1-year 67%), NR (1-year 84%), and NR, respectively (figure 1B). The median RFS is 14.5 m (1-year 50%) for patients who received intensive induction and NR (1-year 75%) for those who received low-intensity induction. The median RFS for patients who were MRD-negative and MRD-positive at enrollment were NR (6-month 93%) and NR (6-month 75%), respectively (p=0.50). Of the 6 MRD-positive patients, 2 (33%) cleared their MRD while on maintenance (both patients in arm B).
Conclusions: A fully oral, targeted maintenance regimen is feasible in AML. Early results show encouraging RFS and OS. Further enrollment and follow-up are required to better assess the safety and efficacy of these regimens.

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OffLabel Disclosure: ASTX727 is not currently approved for AML.

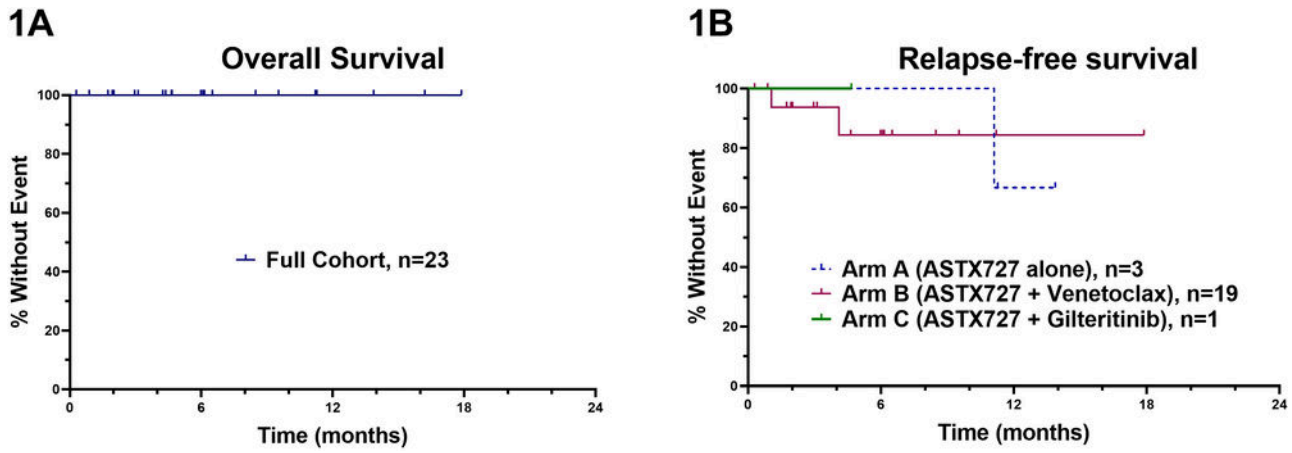

Figure 1

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