Abstract: S139

Title: PHASE 1/2 STUDY OF ORAL DECITABINE/CEDAZURIDINE WITH VENETOCLAX AND GILTERITINIB IN PATIENTS WITH NEWLY DIAGNOSED AND RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA

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Session Title: Acute myeloid leukemia - Clinical 2 - Ven/Aza

Background:

Hypomethylating agents (HMA) combined with venetoclax (VEN) is the standard of care for patients (pts) with acute myeloid leukemia (AML) ineligible for intensive chemotherapy. *FLT3* activating mutations occur in 30% of AML pts. Gilteritinib (GILT) is a second generation *FLT3* inhibitor approved for relapsed/refractory (R/R) *FLT3* mutated (*FLT3*mut) pts. ASTX727 (decitabine/cedazuridine;) is an oral fixed-dose combination of decitabine/cedazuridine (35/100 mg). We present the results of a phase 1/2 clinical trial of a total oral combination of ASTX727 with VEN and GILT in pts with *FLT3*mut AML.

Aims:

Determine the safety and efficacy of ASTX727 with VEN and GILT in pts with newly diagnosed (ND) and R/R AML or myelodysplastic syndrome (MDS) with *FLT3* mutation.

Methods:

This is a phase I/II open-label, single center clinical trial (NCT05010122). Eligibility criteria included pts with AML (ND and RR) or high-risk MDS with *FLT3* mutation. The phase 1 portion (dose escalation) used a Bayesian optimal interval (BOIN) design to identify the recommended phase II dose (RP2D) and included only R/R AML or MDS pts. In the phase 2 portion (dose expansion) two cohorts were defined (ND and R/R AML/MDS) in which efficacy endpoints were evaluated.**

Results:

Between November 2021 and February 2024, 26 pts were enrolled. Twelve in the phase 1 portion: 9 pts received GILT 80 mg on days 1-28 and 3 pts GILT 120 mg on days 1-28, all with ASTX727 on days 1-5 and VEN at 400 mg on days 1-21/28 (a bone marrow exam was performed on day 21 and VEN was held if <5% blasts). No dose-limiting toxicities occurred with any dose level, but myelosuppression was frequent. The RP2D was established as GILT 80 mg based on a better tolerance. Fourteen pts were included in the phase 2 portion.

The median age of the entire cohort was 70 years old (38-84), with 58% male. Phase 1 included 11 pts with R/R AML and 1 with R/R chronic myelomonocytic leukemia (CMML). Phase 2 included 7 and 7 pts with R/R and ND AML. Among R/R pts, the median number of previous lines of therapy was 1 (range, 1-12). 15 (79%) and 8 (42%) pts were previously exposed to VEN and a FLT3 inhibitor, respectively. 22 pts had a *FLT3* internal tandem duplication (ITD, median VAF 0.2, range 0.01-10.6) and 6 pts had a *FLT3* tyrosine kinase domain (TKD) mutation. The most frequent co-mutated genes were *DNMT3A* (50%), *NPM1* (38%), and *IDH2* (27%).

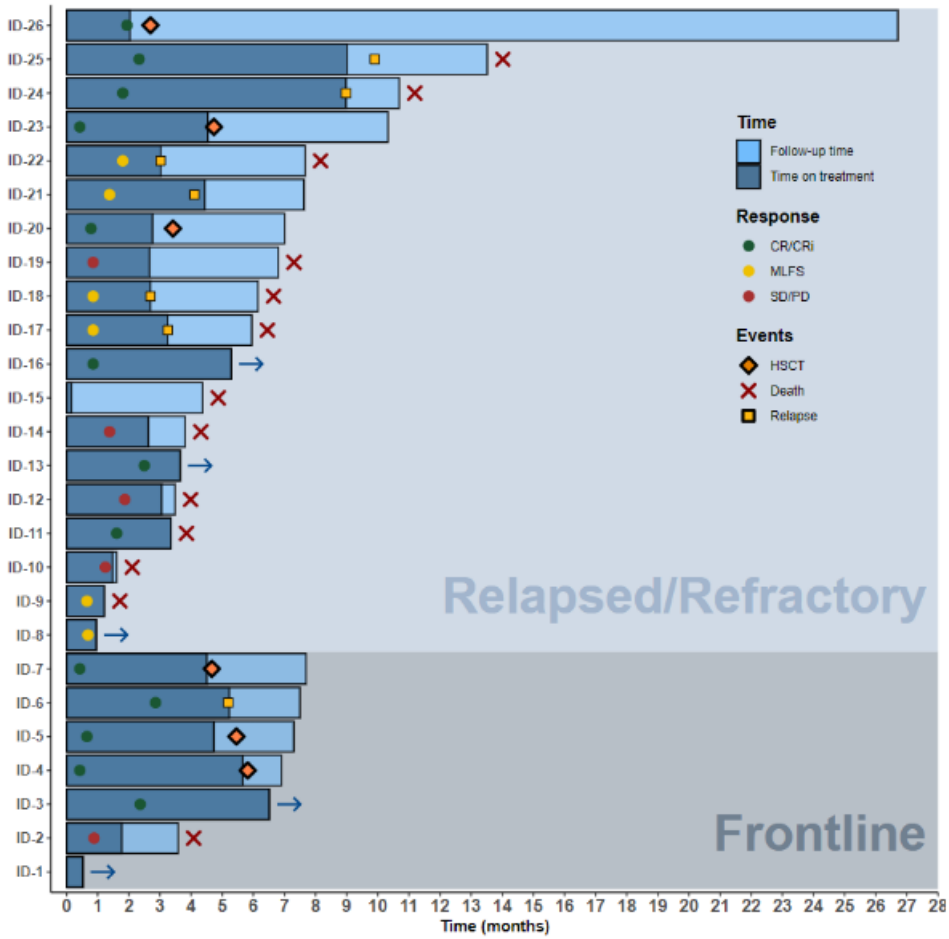
The median number of cycles received was 2 (range, 1-8). Among pts with evaluable response, the overall response rate (complete remission [CR] or CR without count recovery [CRi]) was 83% (n=5/7, CR=4 and CRi = 1) in the ND cohort and 44% (n=8/18, CR=3, CRi = 5) in the R/R cohort. 1 and 7 pts of the R/R and ND cohorts, respectively, achieved a morphologic leukemia-free status (MLFS). Two pts were not evaluable for response (one recently enrolled, other withdrew from study). The median number of cycles to best response was 1 (range 1-2). The median duration of response was 6.5 months (range, 1.2-25). Reasons for treatment discontinuation were alloSCT (n=6, 29%), relapse (n=6, 29%), no response (n=5, 24%), death (n=2, 10%), persistent residual disease (n=1, 5%) and patient decision (n=1, 5%). At the time of data cutoff, 5 pts remained on study drugs.

The median follow-up is 7.5 months. The median overall survival was not achieved (NA) and 6.8 months for the ND and R/R cohorts, respectively. The median relapse-free survival was not achieved and 7.8 months for the ND and R/R cohorts, respectively. Each patient evolution is described in **Figure 1**.

Nineteen pts (73%) experienced an adverse event of grade 3 or higher. The most common grade 3-4 TEAEs were sepsis (n=8, 31%), febrile neutropenia (n=5, 19%) and lung infection (n=5, 19%). Two deaths occurred while on study drugs due to sepsis after cycle 1 and 2, respectively. The 4-weeks and 8-weeks mortality was 0 and 8%, respectively. Myelosuppression was an expected effect of the treatment and was managed either with a delay of the following cycle and/or dose reductions. The median time to platelet (>50x109/L) and neutrophil count (>1x109/L) recovery after cycle 1 was 28 (17-52) and 52 (19-78) days, respectively.

Summary/Conclusion:

The combination of ASTX727 with VEN and GILT is a feasible fully oral combination for pts with *FLT3*mut AML and MDS.



Keywords: Acute myeloid leukemia, Venetoclax, decitabine, flt3 inhibitor