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ORAL ABSTRACTS

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

Early Results of the Phase I/II Study Investigating the All-Oral Combination of the Menin Inhibitor Revumenib (SNDX-5613) with Decitabine/Cedazuridine (ASTX727) and Venetoclax in Acute Myeloid Leukemia (SAVE)

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Background: The interaction of menin with lysine methyltransferase 2A (KMT2A) is a dependency in acute leukemia caused by either rearrangement of the *KMT2A (KMT2Ar)* or *Nucleoporin 98* (*NUP98r*) genes, or mutation of the *Nucleophosmin 1* gene (*NPM1mt*). The menin inhibitor revumenib (previously SNDX-5613), is a potent, oral, selective inhibitor of the menin-KMT2A interaction with demonstrated safety and clinical activity in highly refractory acute leukemias (Issa GC, Nature 2023). *KMT2Ar* or *NPM1mt* leukemias are highly susceptible to induction of apoptosis through BCL2 inhibition, and dual Bcl-2 and menin inhibition led to synergistic activity in *KMT2Ar* or *NPM1mt* leukemia models (Carter BZ, Blood 2021). Therefore, we designed a phase I/II, investigator-initiated trial of the all-oral combination of revumenib, venetoclax and the hypomethylating agent ASTX727 in children and adults with relapsed/refractory (R/R) acute myeloid leukemia (AML) (NCT05360160).
Methods: Patients (pts) with R/R AML or myeloid mixed-lineage acute leukemia (MPAL) aged 12 years and older were eligible.Dose escalation followed a 3+3 design. ASTX727 (decitabine/ cedazuridine) was administered at 35 mg/100 mg PO daily days 1-5, venetoclax at 400 mg (target dose) PO daily days 1-14, and revumenib 113 mg PO Q12h (dose level [DL] 0) or 163 mg PO Q12h (DL 1, used in phase II monotherapy), days 1-28 with either posaconazole or voriconazole (strong CYP3A4 inhibitors, for antifungal prophylaxis). Maintenance with revumenib monotherapy is planned following hematopoietic stem cell transplant (HSCT) for 1 year. For the first pt cohort, bone marrow examination was performed on cycle 1 day 14 and at the end of the cycle to assess for early morphologic remission and to inform future dose adjustments.
Results: As of 7/20/2023, 8 pts were enrolled, 6 at DL0, and 2 at DL1. The median age was 27 years (range, 12-62 years), including 2 children (ages 12 and 16), 5 with *KMT2Ar*, 2 with *NUP98r* and 1 with *NPM1mt*. One pt had MPAL, and one had bone marrow and extramedullary disease. The median prior lines of therapy was 2.5 (range 1-4), 5 pts (63%) had prior venetoclax, 5 pts (63%) had a prior hypomethylating agent, 5 pts (63%) had prior HSCT, and one had prior menin inhibitor. The most common all-grade treatment-related adverse events (TRAEs) in ≥25% of pts were febrile neutropenia (63%), hyperphosphatemia (63%), nausea (63%), and AST/ALT elevation (25%). Grade ≥ 3 TRAEs were febrile neutropenia (63%), decreased platelets count (25%), and decreased neutrophil count (25%). There was 1 dose-limiting toxicity (DLT), grade 4 prolonged thrombocytopenia and neutropenia, at DL0 (resolved after dose hold), prompting enrollment of 3 additional pts, and escalation to DL1 when no additional DLTs were noted (1/6 pts with DLT). Pts at DL1 (N=2) have not completed the DLT period. There were no deaths due to TRAEs. No grade 3 or higher QTc prolongation occurred. Two pts had grade 2 differentiation syndrome (bone pain only), resolved with steroids. One pt (*NUP98r*) had asymptomatic leukocytosis at the end of cycle 1 with neutrophilia, monocytosis, decrease in peripheral blasts, decrease in bone marrow blasts from 66% to 8%, and persistence of *NUP98r* by fluorescence in situ hybridization at 90% indicating differentiation.

Seven of 8 pts are response-evaluable, and all 7 attained a morphologic remission (overall response rate of 100%) (Figure 1). Best responses achieved included a complete remission (CR) in 1 pt (including resolution of extramedullary disease), CR with partial hematologic recovery (CRh) in 1 pt, CR with incomplete platelet count recovery (CRp) in 3 pts, partial response (PR) in 1 pt, and 1 pt with morphologic leukemia free state (MLFS). Measurable residual disease was undetectable by flow (sensitivity at 10^{-4}) in 3 of 7 pts (43%). Three pts transitioned to HSCT following response, 2 are in continued remission, 1 has started maintenance and 1 pt died of transplant complications prior to starting maintenance. Enrollment is ongoing and updated data will be presented.

Conclusions: Early results indicate acceptable safety and high efficacy of this combination in R/R myeloid leukemias with either *KMT2Ar* or *NPM1mt or NUP98r.* This study is ongoing with plans to establish the recommended phase 2 dose and optimize delivery of this combination.

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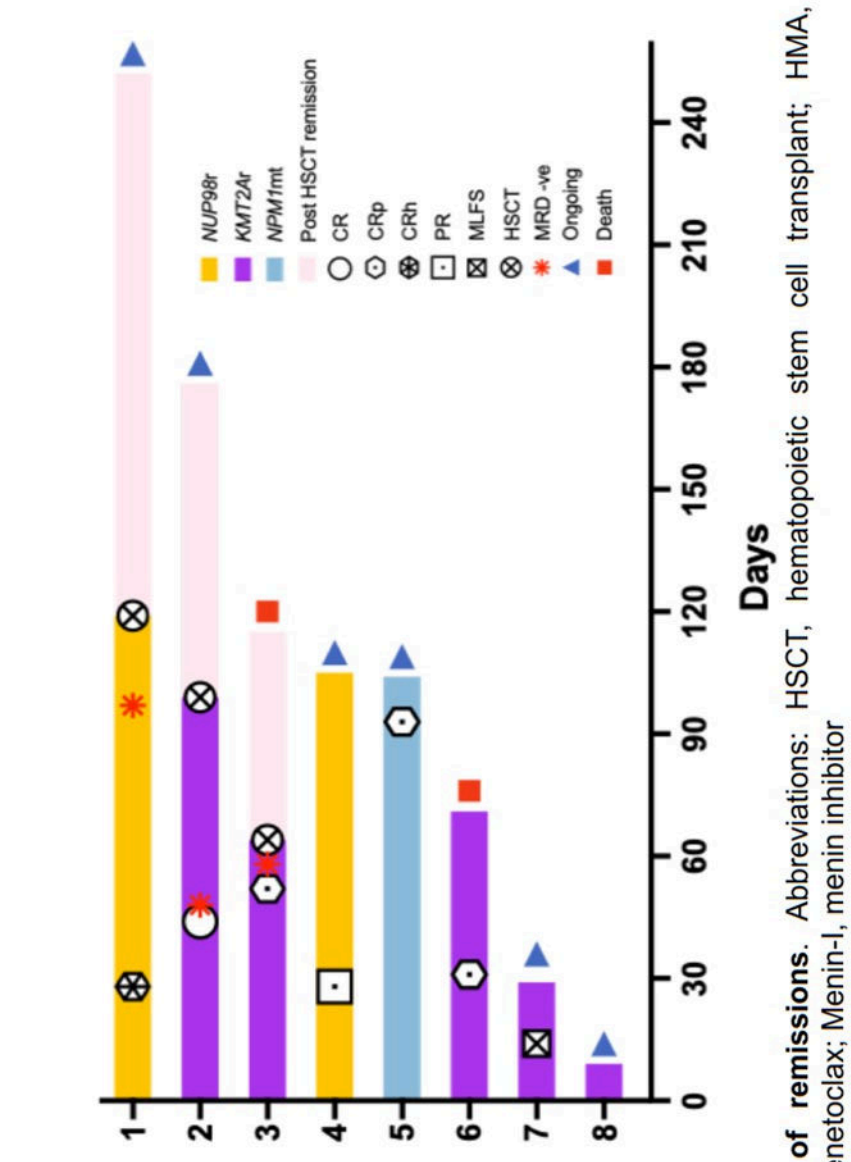

Figure 1: Characterization of remissions. Abbreviations: HSCT, hematopoietic stem cell transplant; HMA, hypomethylating agent; Ven, venetoclax; Menin-I, menin inhibitor

Figure 1