TPS6582 **Poster Session**

Tagraxofusp and low-intensity chemotherapy for the treatment of CD123-positive relapsed or refractory acute myeloid leukemia.

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Background: The combination of venetoclax and a hypomethylating agent (Ven/HMA) is the standard frontline (1L) therapy for patients with acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy (IC). However, outcomes after Ven/HMA failure are poor, with a median overall survival of only 2-3 months. Cladribine (CLAD) with LDAC has previously been shown to be well-tolerated and effective in IC-ineligible patients with newly diagnosed AML. Resistance to Ven/HMA is commonly driven by mutations in the RAS/MAPK pathway and the presence of monocytic subclones that are less dependent on BCL2, both of which may retain sensitivity to cladribine-based therapy following 1L Ven/HMA. Tagraxofusp (TAG), a CD-123 targeted therapy, selectively induces apoptosis in CD123-expressing cells by irreversibly inhibiting protein synthesis through EF-2 inactivation. CD123 is highly expressed on AML blasts and leukemia stem cells compared to normal hematopoietic stem cells in the majority of AML patients. TAG in combination with Ven/HMA has shown efficacy in 1L adverse-risk AML. With its minimal additive myelosuppression and targeted specificity, TAG represents an ideal partner to combine with traditional cytotoxic chemotherapies such as CLAD and LDAC. This investigator-initiated study aims to determine the safety and tolerability of TAG in combination with CLAD and LDAC for IC-ineligible patients with relapsed or refractory (R/R) CD123 positive AML after 1L treatment with Ven/HMA. **Methods:** This single-center, open-label Phase 1b/2 trial will enroll up to 20 patients. Key inclusion criteria are: age≥18 years, R/R AML after 1L Ven/HMA with no prior salvage therapies with the exception of monotherapy with targeted inhibitors, ECOG 0-2; serum albumin≥3.2g/dL; and adequate cardiac, renal, and liver function. The phase 1b dose-exploration will determine the safety and tolerability of CLAD, LDAC, and TAG. The first 3 patients will all be treated at Dose Level 1, consisting of CLAD 5mg/m2 IV daily on days 1-3, LDAC 20mg/m2 IV daily days 1-5, TAG 12mcg/kg IV daily days 4-6. Dose escalation will proceed as tolerated to a target dose level of Dose Level 3, consisting of CLAD 5mg/m2 IV daily on days 1-5, LDAC 20mg/m2 IV daily days 1-10, TAG 12mcg/kg IV daily days 4-6. Dose-escalation and de-escalation will be determined by the BOIN design. The primary objective is determination of the RP2D based on the safety of TAG+CLAD+LDAC, as assessed by DLT evaluation. Secondary objectives include ORR, CR, composite CR (CR+CRi+CRh), and rate of MRD negativity in responders. Duration of RFS, OS, and responses according to mutational profile, karyotype, CD123 expression, and patient demographics will be reported. Once the RP2D is determined, a dose expansion cohort will begin enrolling. The study began enrolling patients in January 2025 and is actively recruiting. Clinical trial information: NCT06561152. Research Sponsor: None.