TPS6585 **Poster Session**

Phase II study evaluating olutasidenib in patients with *IDH1*-mutated clonal cytopenia of undetermined significance or lower-risk myelodysplastic syndromes/ chronic myelomonocytic leukemia.

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Background: Observational studies have demonstrated that individuals with clonal cytopenia of undetermined significance (CCUS) involving high-risk mutations, such as *IDH1*, are more likely to transform to acute myeloid leukemia (AML), with one study showing a progression rate of 100% in *IDH1*/2-mutated patients after 5 years of follow-up. However, there are no Food and Drug Administration (FDA)-approved strategies for the prevention of hematologic malignancies in the setting of CCUS. *IDH1* mutations are detected in 3-4% of patients with myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML). Despite the safety and efficacy of IDH1 inhibitors in acute myeloid leukemia and the recent FDA approval of ivosidenib for relapsed/refractory *IDH1*-mutated MDS, no IDH1-directed therapies are approved in lower-risk, treatment-naïve MDS/CMML. Olutasidenib, an FDA-approved oral, highly selective, potent inhibitor of mutant IDH1, is well-tolerated, non-cytotoxic and effective, with overall response rates in relapsed/refractory AML of 48% as monotherapy. We consequently hypothesize olutasidenib to be effective in both improving hematologic parameters and decreasing the risk of progression to high-risk MDS/CMML and AML in *IDH1*-mutated patients. **Methods:** This multicenter investigator-initiated study under the MDACC-Rigel Research Alliance is a phase II single-arm study evaluating the efficacy of olutasidenib monotherapy in patients with *IDH1*-mutated CCUS or lower-risk MDS/CMML. Eligibility includes adult patients with acceptable organ function and confirmed *IDH1* mutation with CCUS (by World Health Organization criteria) or lower-risk MDS/CMML (by Revised International Prognostic Scoring System [IPSS-R] and Molecular International Prognostic Scoring System [IPSS-M] criteria). The primary objective of the study is to determine the response rate by International Working Group 2018 criteria. Secondary objectives include rates of transfusion independence, safety and tolerability, overall survival, progression-free survival, duration of response, rates of leukemic transformation, and changes in *IDH1* clone size. All patients will receive olutasidenib 150 mg orally twice daily. CCUS patients will receive up to 18 months of olutasidenib, while lower-risk MDS/CMML patients can receive olutasidenib indefinitely. Response assessments will be performed approximately every 3 months for the first year, then yearly thereafter. Once off treatment, survival follow-up will occur every 3 months for 3 years. The goal enrollment is 15 total patients with at least 8 CCUS patients across 5-6 centers in the United States. The study was activated and enrollment began in December 2024. Clinical trial information: NCT06566742. Research Sponsor: None.