TPS6586 **Poster Session**

Phase II study evaluating olutasidenib and azacitidine in patients with *IDH1*-mutated higher-risk myelodysplastic syndromes, chronic myelomonocytic leukemia, or advanced myeloproliferative neoplasms.

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Background: *IDH1* mutations are detected in 3-4% of patients with myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML) and approximately 9% of patients with myeloproliferative neoplasms (MPN). *IDH1* mutations have been associated with shortened survival and increased rates of transformation to acute myeloid leukemia (AML). Despite the use of IDH1 inhibitors in AML and the recent FDA approval of ivosidenib for relapsed/refractory *IDH1*-mutated MDS, no IDH1-directed therapies are approved in MPN or treatment-naïve MDS/CMML, and no combination treatment regimens are commercially available. 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 51% in combination with azacitidine. Olutasidenib alone or with azacitidine demonstrated overall response rates of 86% in treatment-naïve and 47% in relapsed/refractory MDS. We consequently hypothesize olutasidenib to be effective in patients with *IDH1*-mutated higher-risk MDS/CMML or advanced MPN. **Methods:** This multicenter investigator-initiated study under the MDACC-Rigel Research Alliance is a phase II non-randomized study evaluating the efficacy of olutasidenib in combination with azacitidine in patients with *IDH1*-mutated higher-risk MDS/CMML or advanced MPN. Patients will be divided into 2 arms: treatment naïve and previously treated. Eligibility includes adult patients with acceptable organ function and confirmed *IDH1* mutation with higher-risk MDS/CMML (by International Prognostic Scoring System [IPSS], Revised IPSS [IPSS-R], or Molecular IPSS [IPSS-M] criteria) or advanced MPN (with bone marrow blast percentage $\geq 10\%$). The primary objective of the study is to determine the overall response rate by International Working Group 2023 criteria (MDS), 2015 MDS/MPN uniform response criteria (CML), and European Leukemia Network 2017 AML criteria (advanced MPN). Secondary objectives include rates of complete remission, safety and tolerability, overall survival, progression-free survival, duration of response, and changes in *IDH1* clone size. All patients will receive azacitidine 75 mg/m^2 intravenously or subcutaneously daily on days 1-7 of each treatment cycle and olutasidenib 150 mg orally twice daily. Response assessments will be performed after cycle 1, then every 3 cycles up through cycle 12, then every 12 cycles thereafter. Once off treatment, survival follow-up will occur every 3 months for 3 years. The goal enrollment is 45 patients (25 treatment-naïve and 20 previously-treated with no more than 5 MPN patients in each arm) across 5-6 centers in the United States. The study was activated and enrollment began in January 2025. Clinical trial information: NCT06597734. Research Sponsor: None.