TPS6584 Poster Session

Phase 3 study of either ivosidenib monotherapy or azacitidine monotherapy in patients with IDH1-mutant myelodysplastic syndromes who are hypomethylating agent naive (PyramIDH).

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Background: Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal myeloid disorders that occur predominantly in older patients with variable risk of progression to acute myeloid leukemia (AML). According to International Prognostic Scoring Systems, patients with lower-risk MDS (LR-MDS) and cytopenias can be treated with different drugs and in some cases hypomethylating agents (HMAs). However, in higher-risk MDS (HR-MDS), HMAs are the only available standard of care therapy. The complete response (CR) + partial response (PR) rate of azacitidine in treatment-naive MDS ranges between 16% and 22%. These low response rates, combined with the short duration of responses observed with these approaches highlight an unmet medical need for this population. Ivosidenib (IVO) is an oral, targeted small molecule inhibitor of mutant IDH1 that is currently FDA approved in relapsed/refractory MDS with a complete remission (CR) + partial remission (PR) rate of 38.9% (95% CI: 17.3%, 64.3%) with all responses being CR. In the phase 2 IDIOME study, 72% of patients with previously untreated *mIDH1* HR-MDS obtained CR+PR with IVO monotherapy; median OS and DOR were not reached after median follow-up of 25.2 months. The aim of PyramIDH is to confirm the safety and clinical activity of IVO monotherapy in HMA–naive *mIDH1* MDS in a larger cohort. **Methods:** PyramIDH (NCT06465953) is a phase 3, multicenter, open-label, randomized, non-comparative two-arm study of IVO or azacitidine (AZA) monotherapy in patients with HMA-naive *mIDH1* MDS. Key eligibility criteria include diagnosis of HMA-naive *IDH1 R132* mutated MDS. HR-MDS (moderate high-, high- and very-high-risk MDS per IPSS-Molecular (IPSS-M) score), will be eligible if the bone marrow blast count is <20% regardless of blood cell counts. LR-MDS (low- and moderate-low-risk MDS per IPSS-M score), must have cytopenias related to MDS, defined as: <100 platelets/μL, or absolute neutrophil count (ANC) <1000/mm^3, or hemoglobin <10g/dL, have a blast count between 5% and 19%, and be eligible for HMA therapy. Very-low-risk MDS per IPSS-M will not be eligible for enrollment. Enrolled patients (n=~48) will be randomized (2:1) to IVO or AZA monotherapy and they will be stratified by IPSS-M risk status (HR versus LR). The primary endpoint is CR+PR at 4 months as per IWG 2006 criteria. Key secondary endpoints include duration of CR+PR per IWG 2006 criteria, time to CR+PR per IWG 2006 criteria, transfusion independence rate, AML transformation rate, and number of patients going to transplant. Other secondary endpoints are CR+PR at 6 months per IWG 2006 criteria; CR+PR at 4 and 6 months per IWG 2023 criteria; overall response rate per IWG 2023 criteria, duration of response, EFS, OS, duration of transfusion independence (TI), time to TI, AML transformation, quality of life, PK/PD, and safety. Clinical trial information: NCT06465953. Research Sponsor: Servier.