TPS4219 Poster Session

A phase 1b/2, safety lead-in and dose-expansion trial of ivosidenib plus durvalumab and gemcitabine/cisplatin as first-line therapy in patients with locally advanced, unresectable or metastatic cholangiocarcinoma with an IDH1 mutation.

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Background: Cholangiocarcinomas (CCAs) are often advanced and incurable at the time of diagnosis. The phase 3 TOPAZ-1 trial showed improved OS and ORR with gemcitabine/cisplatin (GEM/CIS) and durvalumab (DURVA) vs GEM/CIS in unresectable advanced or metastatic biliary tract cancers. The phase 3 ClarIDHY trial demonstrated that the mIDH1 inhibitor ivosidenib (IVO) improved progression-free survival in CCA patients who have progressed from first or second-line chemotherapy and who have activating mutations in isocitrate dehydrogenase-1 (mIDH1). Additionally, mIDH1 suppresses key immune-related genes, with reversal of this effect when mIDH1 inhibitors are administered in preclinical CCA models. Finally, encouraging activity has been observed in treatment-naive mIDH1 patients administered with the mIDH1 inhibitor LY3410738 in combination with GEM/CIS. Given the ability of ivosidenib to stabilize advanced CCA, ability of IDH1 inhibition to restore immune activity, promising clinical activity of an mIDH1 inhibitor in combination with GEM/CIS, and the limited overlapping toxicities of these treatments, this study seeks to explore safety and preliminary activity of the quadruplet combination. **Methods:** This is a phase 1b/2, multicenter, safety lead-in and dose expansion, open-label study of IVO in combination with DURVA/GEM/CIS in first-line therapy of locally advanced, unresectable, or metastatic CCA with mIDH1. Treatment with up to one cycle of DURVA/GEM/CIS is permitted before initiation of study treatment. Key eligibility criteria include: a histopathological diagnosis; tumor mIDH1 based on local or centralized tissue testing (local testing by plasma ctDNA may be used); at least 1 measurable lesion as defined by RECIST v1.1; and adequate bone marrow, hepatic, and renal function. The study has a safety lead-in phase where IVO will be administered orally to the first 6 patients at a starting dose of 500 mg QD on every day of the 21-day cycle, plus DURVA 1500 mg IV infusion every 3 weeks for up to 8 cycles, plus GEM 1000 mg/m2 IV and CIS 25 mg/m2 IV on days 1 and 8 of each 21-day cycle, followed by IVO 500 mg QD and DURVA 1500 mg every 4 weeks of a 28-day cycle. Dose-limiting toxicities (DLTs) will be evaluated during the first cycle of quadruplet treatment. 6 additional patients may be enrolled to evaluate an alternative reduced dose of IVO 250 mg QD. The primary objective is to evaluate the safety and tolerability of the quadruplet combination, and to determine the recommended combination dose (RCD). The expansion phase will enroll approximately 40 patients who will be treated with the RCD, with the primary objective being to assess the clinical activity of the combination, as determined by a primary endpoint of confirmed complete or partial response using RECIST v1.1 criteria. Clinical trial information: NCT06501625. Research Sponsor: Servier.