TPS4233 Poster Session

Phase I trial of MK2 inhibitor in combination with mFOLFIRINOX for untreated metastatic pancreatic ductal adenocarcinoma.

Moh'd M. Khushman, Patrick Grierson, Nikolaos Trikalinos, Benjamin R. Tan, Olivia Aranha, Rama Suresh, Michael Iglesia, Nikolaos Andreatos, Caron E. Rigden, Jingxia Liu, Kian-Huat Lim; Washington University School of Medicine, St. Louis, MO; Washington University in St. Louis, St. Louis, MO; Washington University School of Medicine in St. Louis, St. Louis, MO; Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; Department of Medicine, Washington University School of Medicine, St. Louis, MO; Washington University, St. Louis, MO; Washington University in St. Louis/Siteman Cancer Center, St. Louis, MO

Background: Zunsemetinib (also known as ATI-450) is an investigational small molecule inhibitor targeting MAPK-Activated Protein Kinase (MAPKAPK2, or MK2). Preclinical work conducted by the Lim Lab at Washington University in St. Louis demonstrated that FOLFIRINOX activates heat shock protein 27 (Hsp27), a molecule with pleiotropic pro-survival properties, and beclin1, a key mediator of autophagy, in pancreatic ductal adenocarcinoma (PDAC) models. In an autochthonous PDAC (KPC) mouse model, zunsemetinib synergized with FOLFIRINOX, resulting in near-complete ablation of all PDAC foci and significantly improved mouse survival. Additionally, mice treated with zunsemetinib experienced significantly less intestinal damage and weight loss—common concerns associated with FOLFIRINOX. These preclinical data support the rationale for combining zunsemetinib with FOLFIRINOX in PDAC patients. **Methods:** We are conducting a phase I, single-arm, open-label study of zunsemetinib in combination with mFOLFIRINOX in patients with untreated metastatic PDAC. The study consists of two phases: a dose escalation phase and an expansion phase. During the dose escalation phase, zunsemetinib dosing will proceed according to the BOIN design with a cohort size of 3. A total of 6–21 patients will be enrolled at Washington University. Patients will receive zunsemetinib starting at Dose Level 1 (40 mg twice daily), with dose escalation continuing until the recommended phase 2 dose (RP2D) is determined. Patients will remain in the study until disease progression or treatment intolerance. In the expansion phase, up to 30 additional patients will be enrolled to further assess the toxicity profile of zunsemetinib in combination with mFOLFIRINOX. These patients will begin at the RP2D and continue on study treatment until disease progression or treatment intolerance. Eligible patients must be treatment-naïve, newly diagnosed, and have histologically or cytologically confirmed PDAC for which mFOLFIRINOX is deemed a suitable treatment option. The primary objective is to determine the dose-limiting toxicities (DLTs) and RP2D of zunsemetinib in combination with mFOLFIRINOX. Secondary objectives include assessing toxicity profiles, progression-free survival (PFS) at six months and overall PFS, disease control rate, overall response rate, overall survival, CA 19-9 response at the RP2D, and pharmacokinetics of zunsemetinib in PDAC treated with mFOLFIRINOX. Exploratory objectives include evaluating pharmacodynamic markers via immunohistochemistry (e.g., phospho-Hsp27 to assess pharmacodynamics of zunsemetinib, LC3B to assess autophagy, and TUNEL staining to evaluate DNA damage) and analyzing pathway suppression through RNA sequencing. Pre- and post-treatment serum samples will also be collected for the analysis of inflammatory cytokines. Clinical Trial Registration: NCT06648434. Clinical trial information: NCT06648434. Research Sponsor: Pancreatic SPORE (P50 CA272213); Aclaris.