TPS4227 Poster Session

An open-label, dose-finding, phase Ib study to assess the safety, tolerability of nesuparib (JPI-547), a dual inhibitor of PARP/TNKS, in combination with modified FOLFIRINOX (mFOLFIRINOX) and gemcitabine-nab-paclitaxel (GemAbraxane) in patients with locally advanced and metastatic pancreatic cancer.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer deaths, with most cases diagnosed at advanced stages. Current maintenance therapy with the PARP inhibitor, olaparib, benefits only patients with germline BRCA1/2 mutations (Approximately 5-7 % of PDAC cases). However, homologous recombination deficiency (HRD)-related mutations occur in ~15% of PDACs, potentially expanding the utility of PARP inhibitors. Nesuparib, a next-generation PARP inhibitor, also targets tankyrase, disrupting WNT and Hippo signaling pathways which are critical for homologous recombination repair. This dual mechanism mimics BRCA loss (''BRCAness''), sensitizing HRD-positive tumors without BRCA mutations to PARP inhibition, broadening therapeutic options. Combining PARP inhibitors with chemotherapy (e.g., irinotecan or platinum-based drugs) enhances sensitivity to DNA damage. Preclinical studies showed nesuparib inhibited tumor growth as monotherapy and achieved higher efficacy in combination with standard treatments. In a prior phase I trial, nesuparib showed promising antitumor activity, with overall response rate of 28.2% and disease control rate of 64.1%. This Phase Ib study aims to evaluate the efficacy of nesuparib in combination with standard chemotherapy for advanced PDAC using a 3+3 dose-escalation design. **Methods:** This multicenter, open-label, Phase Ib, dose-finding study will enroll 24–48 patients with locally advanced or metastatic PDAC. Two arms are included: Arm A (mFOLFIRINOX combination) and Arm B (GemAbraxane combination), each with 12–24 subjects across four dose groups (3–6 patients per group). Nesuparib is administered orally under fasting conditions ranging from Dose Levels -2 (12.5 mg qd) to 4 (100 mg qd), starting at Dose Level 1 (25 mg qd) with a 5 days on/2 days off schedule. Based on the occurrence of dose-limiting toxicities (DLTs), the dose may be escalated to higher levels (Dose Levels 2, 3, or 4) or reduced to lower levels (Dose Levels -1 or -2) with a 5 days on/2 days off or 3 days on/4 days off schedule. Arm A includes mFOLFIRINOX chemotherapy with biweekly oxaliplatin (65 mg/m^2), leucovorin (400 mg/m^2), irinotecan (135 mg/m^2), and 5-FU (2,400 mg/m^2). Arm B involves gemcitabine (1,000 mg/m^2) and nab-paclitaxel (125 mg/m^2) on Days 1, 8, and 15 of a 28-day cycle. Primary objectives are to determine the maximum tolerable dose (MTD) and recommended Phase II dose (RP2D) and to identify the optimal combination regimen based on safety. Secondary objectives include evaluating safety and antitumor activity. Enrollment began in Q1 2022. ClinicalTrials.gov ID: NCT05257993. Clinical trial information: NCT05257993. Research Sponsor: Onconic Therapeutics.