TPS4234 Poster Session

An open-label, phase 1 trial with expansion cohort of botensilimab (AGEN1181) + balstilimab (AGEN2034) + nab-paclitaxel + gemcitabine + cisplatin + chloroquine + celecoxib in adult patients with previously untreated metastatic pancreatic cancer.

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Background: The unfolded protein response (UPR) is an adaptive endoplasmic reticulum (ER) stress pathway that and can prevent cellular death under moderate stress conditions or promote apoptosis under severe stress. The UPR is often upregulated in pancreatic cancer cells and has been identified as a promising target for therapeutic intervention. We hypothesize that inducing severe ER stress by combining multiple chemo and immunotherapy agents will cause pancreatic cancer cells to enter the apoptotic UPR pathway, destroying these cells and improving patient survival. Prolonged ER stress is achieved in this study by using chemotherapy (nab-paclitaxel + gemcitabine + cisplatin) in combination with 2 immunotherapy agents: botensilimab (AGEN1181), an Fc-engineered anti-CTLA-4 monoclonal antibody, and balstilimab (AGEN2034), a human monoclonal immunoglobulin (Ig) G4 (IgG4) antibody designed to block programmed cell death protein (PD-1) binding by PD-L1 and PD-L2. Additionally, 2 agents are included to help block apoptosis escape routes: chloroquine to inhibit autophagy and celecoxib to reduce tumor microenvironment inflammation. **Methods:** This single-center, open-label, phase 1 study evaluates the safety, tolerability, and preliminary efficacy of two botensilimab doses in combination with fixed doses of balstilimab (240 mg) + nab-paclitaxel (125 mg/m^2) + gemcitabine (1000 mg/m^2) + cisplatin (25 mg/m^2) + chloroquine (500 mg) + celecoxib (200 mg) in adult patients with previously untreated metastatic pancreatic cancer (NCT06076837). The study design consists of 6 patients in a dose 1 cohort at 50 mg botensilimab + combination regimen and an escalated dose 2 cohort of 6 patients at 75 mg botensilimab + combination regimen (pending dose 1 cohort safety signals), with an additional 6 patients in an expansion cohort treated at the determined maximum tolerated dose (MTD) of botensilimab (Total N = 18). Adverse events (AEs) are evaluated according to NCI CTCAE v5.0 and tumor response is assessed by RECIST v1.1. Key eligibility criteria include 1) histologically confirmed diagnosis of metastatic pancreatic ductal adenocarcinoma with measurable disease on baseline imaging, 2) life expectancy of at least 3 months, 3) no previous radiotherapy, surgery, chemotherapy, or investigational therapy for the treatment of metastatic disease, and 4) no prior immune checkpoint inhibitor therapy. Enrollment began in January 2025 at the HonorHealth Research Institute. Clinical trial information: NCT06076837. Research Sponsor: TGen Foundation; Purple Pansies Foundation.