TPS4231 Poster Session

A phase 2 study of botensilimab and AGEN1423, an anti-CD73-TGFβ-trap bifunctional antibody, with or without chemotherapy in subjects with advanced pancreatic cancer.

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Background: Traditional immune checkpoint inhibitors have shown limited benefit in pancreatic ductal adenocarcinoma (PDAC) owing to non-redundant immune resistance mechanisms dominating the tumor microenvironment (TME). Transforming growth factor (TGF)-β and cluster of differentiation (CD)73-adenosine represent two major immunoregulatory and pro-tumorigenic pathways responsible for therapeutic resistance and progressive disease in PDAC. AGEN1423 (also known as dalutrafusp alfa and GS-1423) is a bifunctional, humanized, aglycosylated immunoglobulin G1 kappa antibody that selectively inhibits CD73-adenosine production and neutralizes active TGF-β signaling. Botensilimab (BOT) is an Fc-enhanced multifunctional anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody. We hypothesize that the combination of AGEN1423 with BOT can rescue T-cell functional activity leading to responses in advanced PDAC. **Methods:** An investigator-initiated open label Phase 2 study to evaluate the safety, tolerability, and initial efficacy of BOT + AGEN1423 +/- chemotherapy in patients with metastatic PDAC (NCT05632328). In cohort 1, 12 patients with metastatic PDAC with disease progression to at least one line of treatment will receive AGEN1423 30mg/kg IV Q2W for 4 doses + BOT 150mg IV Q6W ongoing for up to 2 years. If the combination is considered safe and tolerable, and objective response is achieved in at least 1 subject, the study will proceed to Cohort 2. In Cohort 2, 12 additional patients with disease progression on first-line fluorouracil-based chemotherapy will be enrolled to receive second-line gemcitabine and nab-paclitaxel in combination with AGEN1423 30mg/kg IV Q2W for 4 doses + BOT 150mg IV Q6W. Key eligibility criteria include histologically or cytologically confirmed metastatic pancreatic adenocarcinoma, age ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤1, adequate organ function, and measurable disease by RECISTv1.1. A pre-treatment and on-treatment tumor biopsy will be obtained for translational studies. The primary endpoint is to estimate the objective response rate (ORR) according to RECISTv1.1 criteria. Secondary endpoints include safety and tolerability as defined by the incidence of AEs as assessed according to CTCAE v5, disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Translational endpoints include the characterization of the transcriptional signatures in paired biopsies obtained before and on-treatment with BOT + AGEN1423, as well as the changes in cell composition of the TME following treatment using multiplexed immunofluorescence spatial technology. Enrolment has started and accrual is anticipated to complete in Q4 2025. Clinical trial information: NCT05632328. Research Sponsor: Agenus, Inc.