

651 PHASE 2 TRIAL OF AGEN1423, AN ANTI-CD73-TGF β -TRAP BIFUNCTIONAL ANTIBODY, IN COMBINATION WITH BALSTILIMAB, WITH OR WITHOUT CHEMOTHERAPY IN SUBJECTS WITH ADVANCED PANCREATIC CANCER

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Background Immunotherapy has made relatively few inroads in pancreatic ductal adenocarcinoma (PDAC) due to its non-redundant mechanisms of resistance, underscoring the need to target alternative immune pathways using a multi-faceted approach. Transforming growth factor-beta (TGF β) plays an important role in mediating primary resistance to programmed cell death protein/ligand 1(PD-1)/PD-(L)1 blockade. Active adenosine signaling and high basal CD73 expression (an enzyme involved in adenosine metabolism), represent another established resistance mechanism in PDAC and other solid tumors. AGEN1423 is a bifunctional humanized immunoglobulin (IgG1) antibody designed to target both CD73 and TGF β with a unique mechanism of action featuring (1) preferential localization within the tumor microenvironment (TME) via its CD73 targeting moiety; (2) ability to reduce the concentration of adenosine in the TME by blocking CD73 enzymatic activity; and (3) inhibition the immunosuppressive effect of TGF β via intracellular trapping. A Phase 1 dose escalation study of AGEN1423 monotherapy was already conducted in patients with advanced solid tumors. Collectively, AGEN1423 is a promising therapeutic investigational candidate designed to address two unique immunosuppressive resistance mechanisms in PDAC simultaneously.

Methods This open-label, two-cohort Phase 2 clinical trial was designed to assess the safety and efficacy of AGEN1423 plus balstilimab with or without chemotherapy in advanced PDAC. Eligible patients include individuals ≥ 18 years with histologically or cytologically confirmed metastatic or locally advanced PDAC, Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ and bone marrow function. In cohort 1, twelve patients with advanced PDAC with progression after ≥ 1 prior lines of therapy will be enrolled to receive AGEN1423 30mg/kg plus balstilimab 3mg/kg on day 1 of a 14-day cycle. In cohort 2, twelve patients with metastatic PDAC following disease progression on fluorouracil-based therapy will be enrolled to receive AGEN1423 30mg/kg plus balstilimab 3mg/kg on days 1 and 15 of a 28-day cycle in combination with gemcitabine 1000 mg/m² plus nab-paclitaxel 125 mg/m² on days 1, 8 and 15 of a 28-day cycle. The primary endpoint is to assess the objective response rate (ORR) according to RECISTv1.1. Secondary endpoints include disease control rate (stable disease or a complete or partial response), overall survival and progression-free survival, and to evaluate safety and tolerability. Biopsies will be obtained at baseline and on-treatment for multiplex immunohistochemistry and additional genomic analyses to better understand changes in the tumor microenvironment following AGEN1423 and balstilimab treatment. Recruitment is anticipated to commence in Q3 2022.

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