A Phase 1b Study of CD40 Agonistic Monoclonal Antibody APX005M Together with Gemcitabine and nab-Paclitaxel with or without Nivolumab in Untreated Metastatic Ductal Pancreatic Adenocarcinoma (PDAC) Patients

Mark H. O'Hara[1,*], Eileen O'Reilly[2,*], Rosemarie Mick[1], Gauri Varadhachary[3], Zev Wainberg[4], Andrew Ko[5], George Fisher[6], Osama Rahma[7], Jaclyn P. Lyman[8], Christopher R. Cabanski[8], Ovid C. Trifan[9], Ute Dugan[10], Vanessa Lucey[11], Robert H. Vonderheide[1,5,8]

*These two authors contributed equally
[1]Abramson Cancer Center of the University of Pennsylvania
[2]Memorial Sloan Kettering Cancer Center
[3]MD Anderson Cancer Center
[4]University of California, Los Angeles
[5]University of California San Francisco
[6]Stanford University
[7]Dana-Farber Cancer Institute
[8]Parker Institute for Cancer Immunotherapy
[9]Apexigen, Inc.
[10]Bristol-Myers Squibb
[11]Cancer Research Institute

Background: Checkpoint inhibitors such as αPD-1 have been ineffective for patients with PDAC. Preclinical data suggests that chemotherapy with agonist CD40 antibodies can be combined with αPD-1 to trigger effective T cell immunity. We conducted a multi-center, open label clinical trial to evaluate the combination of APX005M with nivolumab (Nivo) and standard chemotherapy (gemcitabine (Gem) and nab-paclitaxel (NP)). Here we report safety and efficacy from the ongoing study.

Methods: Adult patients with previously untreated PDAC were enrolled in 4 cohorts (see Table). Primary objectives were to evaluate safety and determine the Phase 2 dose of APX005M. Secondary objectives included tumor response and immune pharmacodynamics. Analyses were performed on DLT-evaluable subjects, defined as receiving 1 dose of APX005M and ≥ 2 doses of Gem/NP during Cycle 1 and remaining on study through Cycle 2 Day 1.

Cohort	1	2	3	4
Treatment	Gem/NP/APX005M 0.1 mg/kg	Gem/NP/APX005M 0.3 mg/kg	Gem/NP/Nivo/ APX005M 0.1 mg/kg	Gem/NP/Nivo/ APX005M 0.3 mg/kg
DLT	–	Grade 3 Febrile neutropenia	Grade 4 Febrile neutropenia	–

Results: Of 30 subjects enrolled and treated, 24 were DLT-evaluable (6 per cohort). Median follow up is 5.2 months. 22 (54%) subjects experienced a Grade 3/4 treatment-related AE. 8 (33%)

subjects experienced a serious AE and 8 (33%) discontinued treatment due to an AE. 2 dose limiting toxicities (DLTs) were observed (see Table). AE rates were similar across cohorts. 4 (17%) subjects died (2 each in Cohorts 1 and 3) due to disease progression (n=2) and AE (n=2, sepsis and septic shock in the setting of neutropenia). 21 (88%) subjects had ≥ 1 tumor assessment per RECIST v1.1. The best overall responses include 11 (52%) PR (3 confirmed, 8 unconfirmed), 9 (43%) SD and 1 PD (5%).

Conclusions: Gem/NP/APX005M +/- Nivo demonstrated manageable safety profiles and promising antitumor activity in untreated metastatic PDAC patients. APX005M 0.3 mg/kg was selected as the dose for a randomized Phase 2 study in which the primary endpoint is 1-year overall survival. Clinical trial information: NCT02482168.