A Phase Ib/II Study of CD40 Agonistic Monoclonal Antibody (APX005M)

Together with Gemcitabine and nab-Paclitaxel with or without Nivolumab in Untreated Metastatic Pancreatic Adenocarcinoma Patients

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BACKGROUND

- Pancreatic cancer is one of the most lethal malignancies of the gastrointestinal tract, with a 5-year survival of about 8%.
- While checkpoint inhibitors (CPI) have yielded remarkable activity in several solid tumors, CTLA4 and PD-1 monoclonal antibodies (mAb) have not yielded clinical benefit in pancreatic cancer patients.[1,2]
- Activation of the CD40 signaling pathway plays an important role in immune activation (Figure 1), especially for crosstalk between T cells and antigen presenting cells (APCs).[3]
- APX005M is a potent anti-CD40 agonistic mAb (Figure 2), and is showing promising results as a single agent in a Phase 1 clinical trial (NCT02482168).
- In preclinical studies using a mouse model of pancreatic ductal adenocarcinoma (PDA) combination treatment with anti-CD40 agonistic mAb, gemcitabine (Gem) and nab-paclitaxel (NP), and anti-PD1 mAb result in T cell immunity and significant increase in survival compared to any of the other treatment groups (Figure 3A).[4]
- An anti-CD40 agonistic mAb demonstrated a clinical response in a pancreatic cancer patient when administered in combination with chemotherapy (Figure 3B).[5]
- Both preclinical and clinical data support the design of the combination strategy of Gem, NP, nivolumab and APX005M for previously untreated metastatic pancreatic cancer (Figure 4).

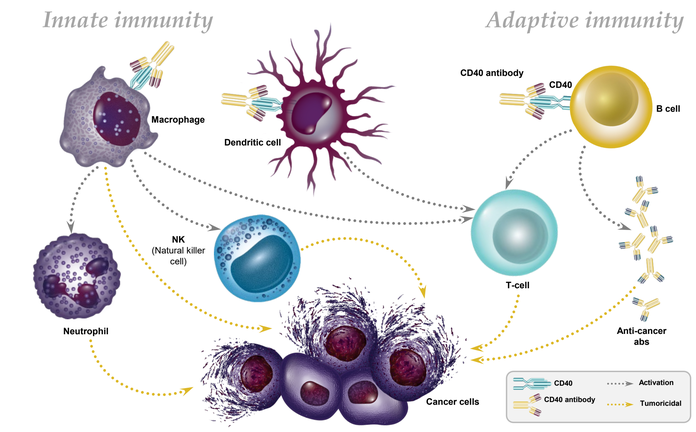

Figure 1: CD40 activation potentiates T-cell response and elicits both innate and adaptive immune cells.

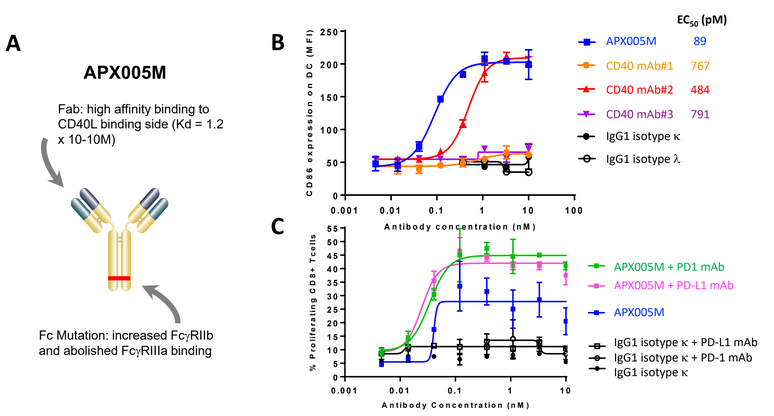

Figure 2: APX005M is a potent anti-CD40 agonist mAb. A) APX005M is a humanized IgG1 mAb against human CD40. The Fab domain binds to CD40 ligand binding domain with high affinity, and Fc domain has mutation which allows more favorable binding with Fcγ receptor. B) APX005M is more potent than other anti-CD 40 mAbs in activating human DCs by measuring CD86 activation. C) APX005M enhances anti-PD-1 or anti-PD-L1 antibody-mediated T cell responses. APX005M and PD-1 antibody, or PD-L1 antibody were added to co-culture of CD8 T cell and DC cells. T cell response was assessed by measuring T cell proliferation.

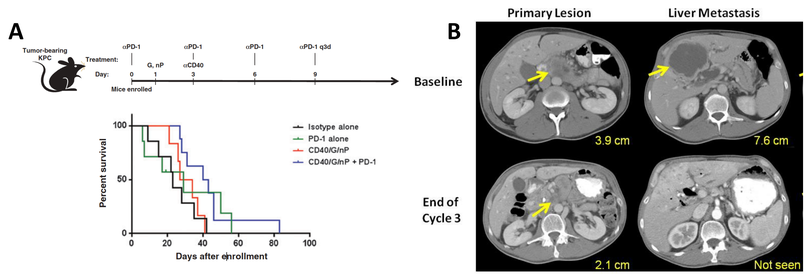

Figure 3. Rationale of the proposed study was supported both pre-clinically and clinically. A) Combination of anti-CD40 mAb, chemotherapy and PD-1 blockade improves survival in KPC tumor model of PDA.[4] B) Agonist CD40 mAb in combination with gemcitabine induces clinical responses in a patient with surgically incurable PDA. CT imaging obtained at baseline and end of cycle 3.[5]

COMBINATION RATIONALE

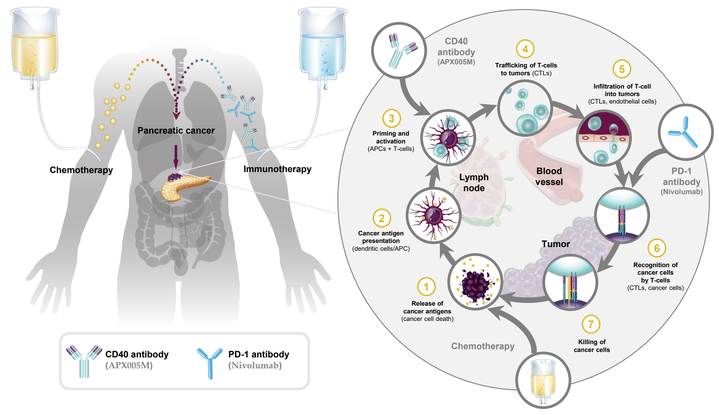

Figure 4. Proposed mechanism of action for combination treatment of pancreatic cancer patients With Gem, NP, nivolumab, and APX005M. CD40 mAb promotes T cell priming and early activation with APC, while PD1 mAb activates T cells in late stage at the tumor microenvironment. The addition of chemotherapy prior to APX005M not only kills the tumor cells directly, but also induces infiltration of T-cells, with skewing toward Th1 (and M1) immunity.[6]

STUDY OBJECTIVES

Phase Ib:

Primary Objectives:

- Feasibility, safety, and DLTs The recommended Phase II dose (RP2D) of APX005M with Gem/NP ± nivolumab

Secondary Objectives:

- Objective response rate (ORR) and duration of responses (DOR)

Exploratory Objectives:

- Pharmacokinetics (PK) of APX005M
- Immune biomarkers, in both blood and tumor tissue

Please visit clinicaltrials.gov for more details

Phase II:

Primary Objectives:

- Overall survival (OS) of each treatment arm
- To compare 1-year OS with the historical rate for Gem/NP

Secondary Objectives:

- ORR, DOR, disease control rate (DCR), and progression free survival (PFS)
- To further characterize the feasibility and safety of each treatment arm

Exploratory Objectives:

- PK of APX005M
- Immune pharmacodynamic, in both blood and tumor tissue
- Associations between immune biomarkers and clinical outcomes
- To construct multivariable linear models to dissect the pharmacodynamic effects of APX005M and nivolumab on immune biomarkers

STUDY SCHEMA

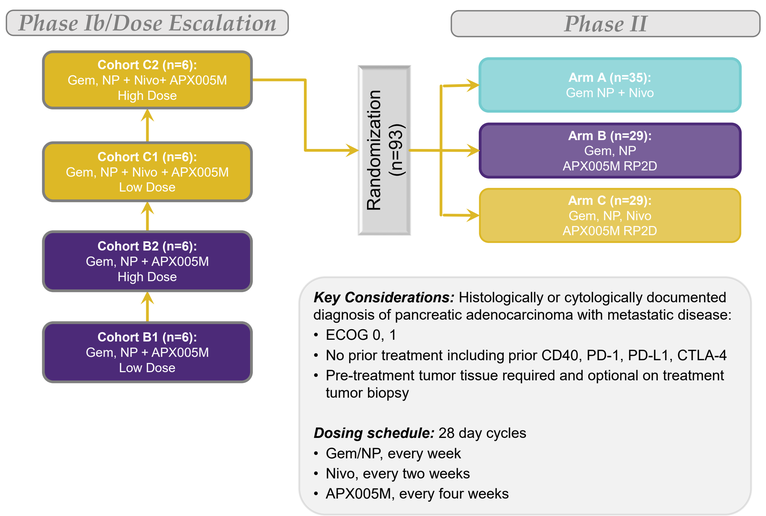

Figure 5. Study scheme: a phase Ib lead in followed by phase II. Phase Ib - 4 sequential treatment cohorts, to define the RP2D; Phase II - randomization to 3 treatment arms using a single APX005M dose (low or high for Arms B and C). (RP2D: recommended phase II dose).

DEEP IMMUNE PROFILING

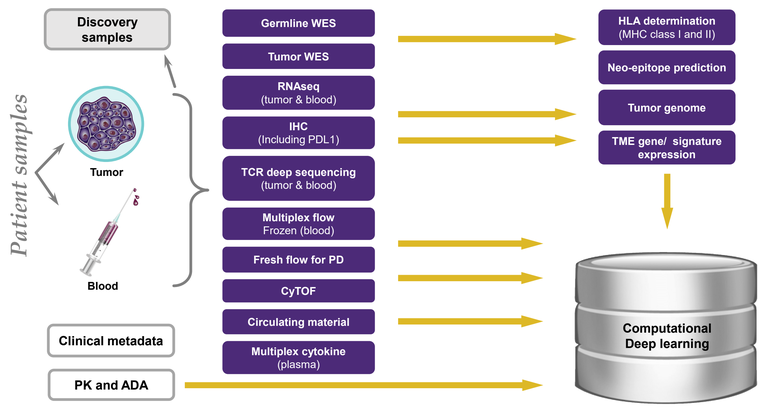

Figure 6. Exploratory correlative immune tumor biomarkers from tumor tissue and blood. Comprehensive immune biomarker assessment using Parker Institute for Cancer Immunotherapy (PICI) central collection, harmonization of sample processing and PICI network of biomarker technologies and bioinformatics to provide a data rich clinical study.

STATISTICAL CONSIDERATIONS

- **Phase Ib:** Assuming 4 treatment cohorts will be evaluated sequentially for feasibility, safety, and dose-limiting toxicities, up to 24 DLT evaluable subjects will be enrolled. A maximum sample size of 27 subjects may be needed, if 10% to 15% of Phase 1 subjects are not DLT evaluable.
- **Phase II:** Ninety-three subjects will be enrolled in Phase 2; all subjects will be included in the primary efficacy analysis following an intent-to-treat approach. This is a screening study, such that for each treatment arm, the 1-year OS rate will be estimated and compared with a historical value of 35% for Gem/NP. The study is not powered to detect a meaningful difference in OS among the 3 arms, since these are novel experimental arms and OS is unknown. A sample size of 35 subjects on each arm provides 90% power to statistically test the null hypothesis of historical 1-year OS rate of 35% versus the alternative hypothesis of 1-year OS rate of 58%, a hazard ratio = 0.52. This calculation assumes exponential survival, 1-sided 5% type I error rate, enrollment of subjects for 18 months with an additional 6 months of follow-up prior to conducting the final analysis.

STUDY STATUS + REFERENCES

Study Status

- **First patient enrolled in August 2017**
- **6 participating sites:**
  - Open: University of Pennsylvania
  - To open by end 2017/early 2018:
    - MSKCC
    - UCLA
    - UCSF
    - MD Anderson Cancer Center
    - Stanford University
- **Clinicaltrials.gov identifier: NCT02482168**

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