A Study to Evaluate the Safety and Efficacy of the CD40 Agonistic Antibody APX005M Administered in Combination with Nivolumab in Subjects with Non-small Cell Lung Cancer and Subjects with Metastatic Melanoma

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Background

Blocking immune checkpoint PD-1, PD-L1 and CTLA-4 function enhances anti-tumor immunity, leading to durable clinical responses for a subset of patients with melanoma, lung cancer and other tumor types. However, the majority of patients with melanoma or lung cancer continue to have short or no response to checkpoint blockade therapies and thus require novel approaches to stimulate the anti-tumor immune response such as immune stimulatory antibodies. Recently, Zippelius and co-authors [1] showed in preclinical models that CD40 engagement with an agonistic mAb leads to a T cell and IFN-g dependent upregulation of PD-L1 on tumor infiltrating monocytes and macrophages, thereby feeding into a negative feedback loop, which hampers CD40 induced T-cell responses. This resistance mechanism was successfully circumvented by co-administration of PD-1/PD-L1 blocking antibodies. To this end, Apexigen Inc., is developing APX005M, a humanized monoclonal IgG1 CD40 agonistic antibody, that stimulates both innate and adaptive immune response (Figure 1). APX005M recognizes a unique epitope that overlaps with the CD40 ligand binding sites (Figure 2a) and uses FcRγIIb to cluster CD40 (Figure 2 b) thus mimicking CD40L engagement. As a result of antigen presenting cell (APC) activation, APX005M enhances T-cell response to tumor antigens. APX005M combined with antibodies against PD-1 or PD-L1 synergistically enhances T-cell responses (Figure 2c). In a phase 1 trial, APX005M was administered IV every 21 days to human subjects up to 1mg/kg with an acceptable safety profile and has demonstrated a dose-dependent activation of APCs and T cells and increases in circulating levels of cytokines (Abstract 036).

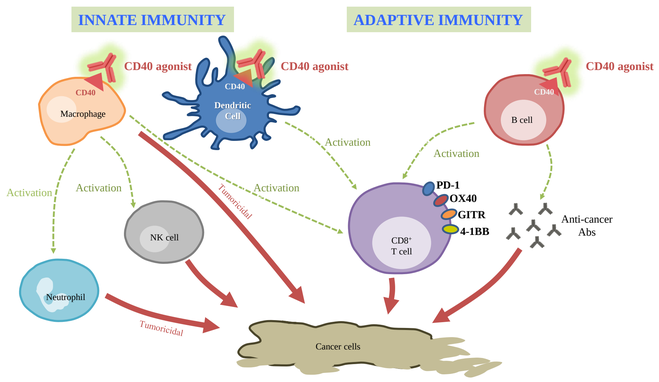


Figure 1: CD40 activated both innate and adaptive immunity playing a central role in the immune response against cancer

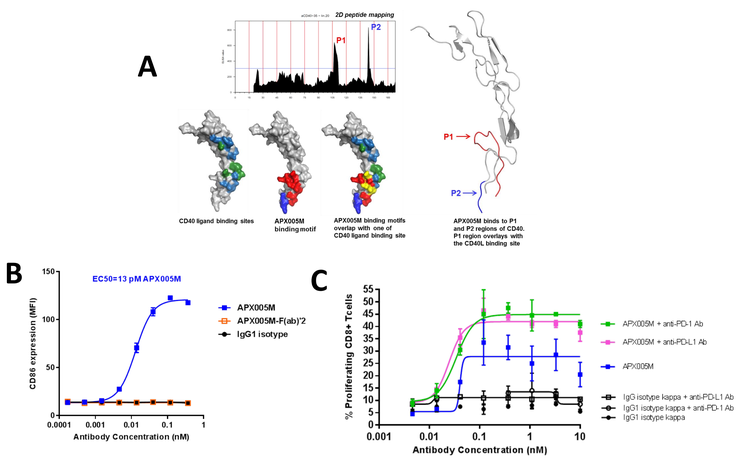
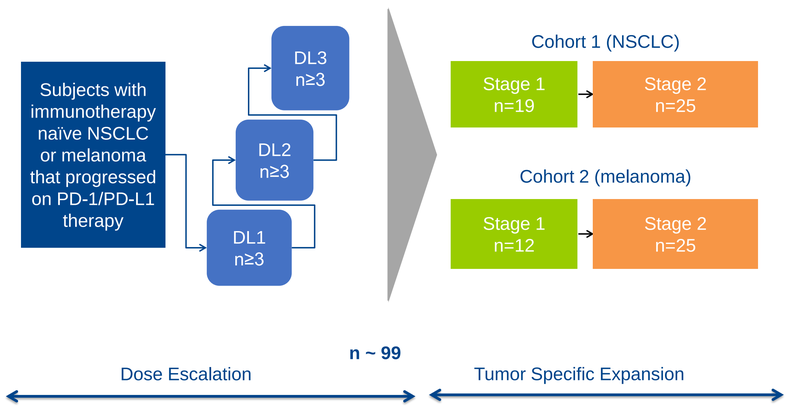


Figure 2: APX005M is a humanized IgG1 mAb against human CD40. A) The Fab domain binds to CD40 ligand binding domain with high affinity, B) CD40 agonistic activity of APX005M depends on cross-linking with FcγRIIb, C) APX005M enhances anti-PD-1 or anti-PD-L1 antibody-mediated T cell proliferation.

APX005M-002 Study Design



APX005M-002 is Phase 1b-2 study. Phase 1b follows a 3+3 design with 3 dose levels (DL) of APX005M administered in combination with nivolumab every 3 weeks (21-day cycle). Phase 2 will enroll subjects with immunotherapy naïve NSCLC or melanoma that progressed on anti-PD-1/PD-L1 therapy in two parallel disease specific cohorts.

APX005M-002 Study Population

Tumor Specific Inclusion Criteria:

- Histologically or cytologically confirmed immunotherapy naïve, metastatic or locally advanced non-small cell lung cancer (NSCLC) not amenable to curative treatment. Subjects must have received one prior platinum based chemotherapy for non-small cell lung cancer and subjects with a documented activating mutation (EGFR, ALK or ROS) must also have received the appropriate therapy and progressed

- Histologically or cytologically confirmed unresectable or metastatic melanoma that progressed during treatment with anti-PD-1 /PD-L1 therapy. Subjects with BRAF activating mutation could have also received a BRAF inhibitor and/or MEK inhibitor regimen prior to anti-PD-1/PD-L1 therapy. Subjects with ocular melanoma are excluded.

General inclusion criteria include:

- Age ≥ 18 years
- Measurable disease by RECIST 1.1
- ECOG performance status of 0 or 1
- Adequate bone marrow, liver and kidney function
- Negative pregnancy test for women of child bearing potential
- Agreement to use effective methods of contraception per the protocol requirements

General exclusion criteria include:

- Previous exposure to anti-CD40, CTLA-4, PD-1/PD-L1 or any other immunomodulatory agent (except PD-1/PD-L1 in subjects with metastatic melanoma)
- Second malignancy (solid or hematologic) within the past 5 years except locally curable cancers that have been apparently cured
- Active, known, clinically serious infections within the 14 days prior to first dose of investigational product
- Use of systemic corticosteroids or other systemic immunosuppressive drugs
- Active, known or suspected autoimmune disease
- History of (non-infectious) pneumonitis that required corticosteroids or current pneumonitis
- History of interstitial lung disease
- History of life-threatening toxicity related to prior anti-PD-1/PD-L1 treatment for subjects with metastatic melanoma
- Uncontrolled intercurrent illness

Study Objectives

Primary

- Phase 1b:
  - Determine the MTD and the RP2D of APX005M when given in combination with nivolumab
- Phase 2:
  - Evaluate the ORR by RECIST 1.1 in each population

Secondary

- Evaluate safety of the APX005M and nivolumab combination
- Evaluate the ORR by irRECIST
- Determine the PK of APX005M
- Assess incidence of APX005M ADA
- Evaluate the DOR and median PFS by RECIST 1.1

Statistical Considerations

Cohorts of 3 to 6 subjects will be treated at each DL during dose escalation portion of the study. It is anticipated that approximately 18 subjects will be treated in this portion of the study depending on the actual rate of DLTs.
Sample size for Phase 2 is calculated using the Simon optimal 2-stage design [2]:
Cohort 1 (NSCLC): Assuming a false positive rate (α) of 0.1, a false negative rate (β) of 0.1, a response probability of poor drug (P0) of 17% and a response probability of good drug (P1) of 35%, first stage sample size (n1) is 19 and the maximum sample size (n) is 44 response evaluable subjects.
Cohort 2 (melanoma): Assuming α of 0.1, β of 0.1, P0 5% and P1 of 20%, n1 is 12 and n is 37 response evaluable subjects.

Correlative Analyses

Immune Pharmacodynamic Measurements

- PBMCs collected from participating subjects before treatment and during the study will be analyzed using flow cytometry to measure cell surface immune markers of antigen-presenting cells (dendritic cells, B cells and monocytes).
- Together with complete blood count differentials, flow cytometry of peripheral blood will be used to characterize important T cell subsets. For each subset, differentiation status (e.g. naïve, central memory, effector memory) or activation status will be assessed using additional markers.

Tumor Biopsy

- Archived and fresh tumor tissue obtained prior to and after receiving APX005M will be analyzed by H&E, by Masson's trichrome, and by immunohistochemistry (IHC) for markers such as but not limited to immune, tumor, vascular and stromal markers.
- Tumor samples and peripheral blood may also be examined for gene expression (e.g., Quantigene), T and B cell receptor repertoire assessment by deep sequencing, and somatic tumor mutations.

Participating Sites

Site 0001: Abramson Cancer Center, U. Penn, Philadelphia, PA
Site 0002: Fox Chase Cancer Center, Philadelphia, PA
Site 0003: Karmonas Cancer Center, Detroit, MI
Site 0004: City of Hope, Duarte, CA
Site 0006: Tennessee Oncology, Nashville, TN
Site 0007: University of Arizona, Tucson ,AZ
Site 0008: Yale University, New Haven, CT

References: 1. Zippelius et al, Cancer Immunol Res 2015;3:236-44
2. Simon R, Control Clin Trials 1989;10:1-10