Phase 1 Study to Evaluate the Safety and Tolerability of the CD40 Agonistic Monoclonal Antibody APX005M in Subjects with Solid Tumors

Marwan G. Fakih[1], David L. Bajor[2], Ronac Mamtani[3], Thomas M. Tremblay[4], Ovidiu C. Trifan[4], Robert H. Vonderheide[3]

[1] City of Hope, Duarte, CA; [2] Case Western Reserve University, Cleveland, OH
[3] University of Pennsylvania, Philadelphia, PA; [4] Apexigen, Inc., San Carlos, CA

P252

Background

APX005M is a humanized monoclonal IgG1 CD40 agonistic antibody developed by Apexigen, that mimics the natural ligand CD154. APX005M binds with high affinity to human CD40 leading to antigen presenting cell (APC) activation (Figure 2A) and subsequent T-cell activation. APX005M enhances T-cell proliferation (Figure 2B), IFN–γ production and T-cell response to tumor antigens. In comparison with other anti-human CD40 agonistic antibodies, such as CP-870,893/ RG7876, SGN-40, and ADC-1013/JNJ-64457107 analogs, APX005M is the most potent CD40 agonist and outperforms all others in many measures of immune activation (Figure 2C). In a first in human clinical trial (APX005M-001), APX005M was administered IV every 21 days and demonstrated a dose-dependent activation of APCs and T cells and increases in circulating levels of IL-12, IFN-γ, TN-α and IL-6. APX005M was escalated up to 1mg/kg with a good safety profile (abstract 036).
Study APX005M-001 was originally designed as a multicenter Phase 1 dose escalation study of APX005M administered every 3 weeks to subjects with solid tumors and was amended in March 2017 to introduce two new dosing schedules for APX005M (every 2 weeks and every 1 week) and limit the patient population to selected solid tumors.

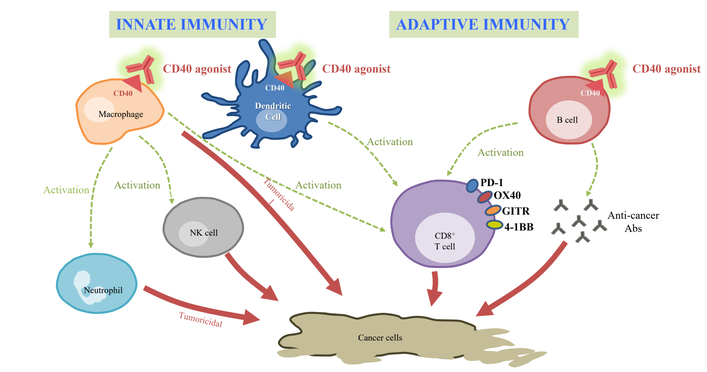


Figure 1: CD40 activated both innate and adaptive immunity playing a central role in the immune response against cancer

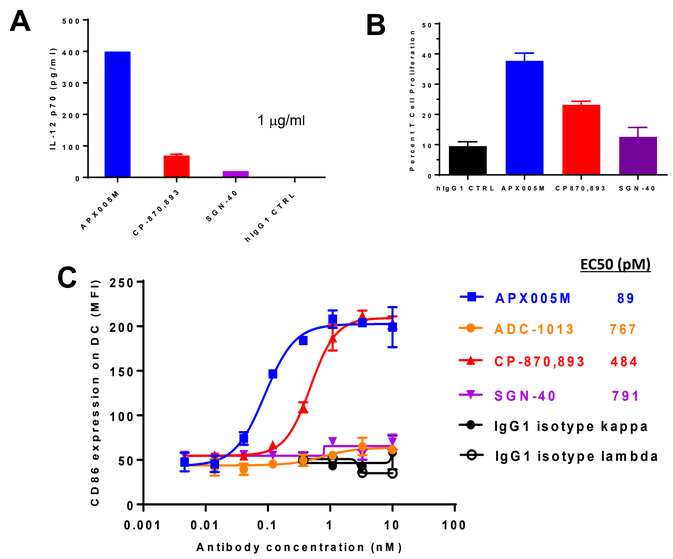
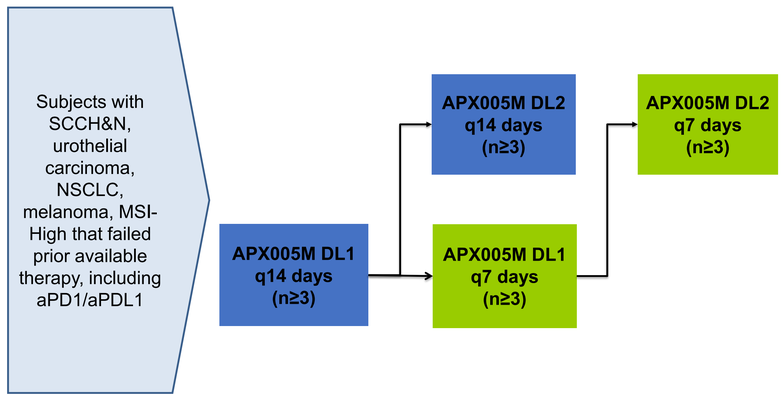


Figure 2: APX005M outperforms other anti-human CD40 agonistic antibody analogs. A) APX005M stimulates IL-12 production by dendritic cells B) APX005M enhances alloantigen-specific T cell proliferation C) APX005M is more potent than CP-870,893, ADC-1013 and SGN-40 analogs in activating human dendritic cells.

APX005M-001 Study Design



APX005M-001 is Phase 1 study following a 3+3 design. APX005M is administered IV every 2 weeks or every 1 week until disease progression, unacceptable toxicity, or up to 1 year.

APX005M-001 Study Objectives

Primary
- Evaluate the safety of APX005M administered IV on a every 2-week and 1-week schedule to subjects with selected solid tumors
- Determine the maximum tolerated dose and the recommended phase 2 dose of APX005M

Secondary
- Determine the PK of APX005M
- Assess the incidence of anti-drug antibodies
- Preliminary assessment of clinical efficacy in subjects with selected solid tumors

Exploratory
- Assess the time to subsequent treatment for each subject
- Determine the immune PDn of APX005M
- Identify tumor and blood efficacy and/or resistance biomarkers

APX005M-001 Study Population

Key Inclusion Criteria:

- Male or female 18 years and older
- Histologically or cytologically documented diagnosis of urothelial carcinoma, melanoma, squamous cell carcinoma of the head and neck, non-small cell lung cancer, or any solid tumor with high microsatellite instability status (MSI-high)
- No known effective therapy options are available
- Measurable disease by RECIST 1.1
- ECOG performance status of 0 or 1
- Adequate bone marrow, liver and kidney function
- No toxicities related to prior treatment with the exception of alopecia and neuropathy
- Negative pregnancy test for women of child bearing potential

Key Exclusion Criteria:

- History of or current hematologic malignancy
- Major surgery or treatment with any other investigational agent within 4 weeks
- Uncontrolled diabetes or hypertension
- History of arterial thromboembolic event
- History of congestive heart failure, symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction
- Active known clinically serious infections

Statistical Considerations

Cohorts of 3 to 6 subjects will be treated at each dose level. It is anticipated that approximately 18 subjects will be treated in this portion of the study depending on the actual rate of DLTs.

Correlative Analysis

Immune Pharmacodynamic Measurements

- Unmanipulated peripheral blood lymphocytes collected from participating 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.

APX005M-001 Participating Sites

City of Hope
Duarte, California

University Hospitals of Case Western Reserve University
Cleveland, Ohio

Abramson Cancer Center of the University of Pennsylvania
Philadelphia, Pennsylvania

ClinicalTrials.gov Identifier: **NCT02482168**