

Phase I Study to Evaluate the Safety and Tolerability of the CD40 Agonistic Monoclonal Antibody APX005M in Pediatric Subjects with Recurrent/Refractory Brain Tumors and Newly Diagnosed Brain Stem Glioma

Abstract

This is a multicenter phase 1 trial of APX005M for children with recurrent or refractory primary malignant CNS tumor or newly diagnosed DIPG.

APX005M is an IgG1 humanized mAb with the S267E mutation at the Fc region. APX005M binds with high affinity to human CD40 ($K_d = 1.2 \times 10^{-10}$ M) and monkey CD40 ($K_d = 3.5 \times 10^{-10}$ M), but does not cross-react with mouse or rat CD40. APX005M blocks the binding of CD40 to CD40L. It has been shown that CD40L-blocking antibodies tend to have more potent CD40 agonistic activities than CD40L-non-blocking antibodies.

Pre-clinical studies of APX005M in monkeys revealed the most significant toxicity to be a prolonged reduction (no recovery over 28 days) in the number of B-cells at doses > 3 mg/kg/dose. Apexigen notes that there was no evidence of hepatotoxicity and “no evidence of any other clinical pathology effects”.

Based on the pre-clinical observations, Apexigen initiated a first in human study for adults with solid tumors in 2015. APX005M induces a dose-dependent activation of antigen-presenting cells (as demonstrated by increases in expression of CD54, CD70, CD80, CD86, HLA-DR) and increases in circulating levels of IL12, interferon gamma, TNF-alpha and IL6. The most common symptoms observed during the first 48 hours following infusion of APX005M include: rigors/chills, fever, flushing, itching/pruritis, nausea/vomiting, headache, and rash, as well as hypotension/hypertension; the majority of these symptoms were mild (\leq Grade 2) and responded promptly to symptomatic treatment. Transient transaminase and total bilirubin elevations have been observed in several subjects with liver metastases or with pre-existing biliary tract stenosis due to the location of the tumor. A reversible decrease in peripheral blood lymphocyte counts in general, and B-cell count in particular, have been observed for APX005M and are believed to be a pharmacodynamic (PD) effect. Transient decreases in platelets with no clinical consequences were observed in some subjects.

Apexigen has declared the adult recommended phase 2 dose to be 0.3 mg/kg because no dose limiting toxicities were encountered at that dose and the pharmacodynamic profile was similar to the 1 mg/kg maximally tolerated dose.

The primary objectives of the study are to (1) evaluate the safety of APX005M administered intravenously every 3 weeks to children with central nervous system tumors; (2) determine the maximum tolerated dose and/or the recommended phase II dose of APX005M; (3) determine the pharmacokinetics of APX005M.

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Only patients with recurrent or refractory primary malignant CNS tumor will be enrolled initially, newly diagnosed DIPG patients will be on-hold until pediatric RP2D has been established in Stratum 1. APX005M dosing will begin at 0.1 mg/kg, which is one dose level below the adult recommended phase 2 dose. The APX005M dose will be increased in subsequent cohorts until the MTD is reached or until dose level 3 is complete without MTD being defined. APX005M will be administered at the assigned dose level by intravenous infusion in about 60 minutes every 21 days for 36 courses (2 year) or until disease progression, unacceptable toxicity or death, whichever occurs first.

The starting dose (dose level 1) is 0.1 mg/kg. The table below lists the proposed dose levels to be studied:

Dose Escalation Schedule	
Dose Level	Dose of APX005M (mg/kg, Q3 weeks, IV)
0	0.03 mg/kg
1* (starting dose level)	0.1 mg/kg
2	0.3 mg/kg
2.5	0.45 mg/kg
3	0.6 mg/kg

Note: Dose level 2.5 will only be studied if dose level 3 is deemed to be too toxic.

OBJECTIVES

Primary Objectives

- To evaluate the safety of APX005M administered intravenously every 3 weeks to children with central nervous system tumors.
- To determine the maximum tolerated dose and/or the recommended phase II dose of APX005M.
- To determine the pharmacokinetics of APX005M.

Secondary Objective

- To make a preliminary assessment of efficacy via overall response rate, duration of response, progression-free survival and overall survival for DIPG patients.

Exploratory Objectives

- To assess the incidence of anti-drug antibodies.
- To determine the immune pharmacodynamics of APX005M.
- To identify tumor and blood efficacy and/or resistance biomarkers.

PATIENT SELECTION

All subjects must meet the following inclusion and exclusion criteria. No exceptions will be given. Imaging studies to establish eligibility must be done within three weeks prior to enrollment. All other clinical evaluations to establish eligibility must be done within 7 days prior to enrollment.

Inclusion Criteria

➤ Diagnosis

Stratum 1: Recurrent or refractory primary malignant CNS tumor patients

Patients with a histologically confirmed diagnosis of a primary malignant non-brainstem CNS tumor (excluding DIPG patients) that is recurrent, progressive, or refractory. All tumors must have histologic verification at either the time of diagnosis or recurrence except patients with marker (+) CNS germ cell tumors.

Stratum 2: Newly diagnosed DIPG patients (on-hold until pediatric RP2D has been established in Stratum 1)

Patients with diffuse intrinsic pontine gliomas (DIPGs) will be eligible 6 to 14 weeks post-completion of radiation therapy if they do not have any evidence of progression. Patients with newly diagnosed DIPGs, defined as tumors with a pontine epicenter and diffuse involvement of 2/3 or more of the pons, are eligible without histologic confirmation. Patients with pontine tumors that do not meet these criteria or not considered to be typical intrinsic pontine gliomas will only be eligible if the tumors have been biopsied and (1) are proven to be an anaplastic astrocytoma,

glioblastoma multiforme, gliosarcoma, anaplastic mixed glioma or fibrillary astrocytoma or (2) have a histone mutation typically seen in DIPG. Patients with disseminated disease are not eligible, and MRI of spine must be performed if disseminated disease is suspected by the treating physician.

➤ Available Pre-trial Tumor Tissue

Stratum 1: Recurrent or refractory primary malignant CNS tumor patients must have adequate pre-trial frozen or FFPE tumor material (minimum of 10 unstained slides) available for use in the tumor mutation burden studies (section 9.1.5).

Stratum 2: Patients with DIPG who have pre-trial tumor tissue available are requested to submit tissue; however, this is not required for eligibility.

➤ Age

Patient must be ≥ 1 and ≤ 21 years of age at the time of enrollment.

➤ Prior Therapy

- Newly Diagnosed DIPG patients

Patients must have not received any prior therapy for treatment of their current CNS malignancy other than radiation therapy.

- Refractory/Recurrent patients

Patients must have recovered from the acute treatment related toxicities (defined as $<$ grade 1) of all prior chemotherapy, immunotherapy, radiotherapy or any other treatment modality prior to entering this study.

➤ Myelosuppressive chemotherapy

Patients must have received their last dose of known myelosuppressive anticancer therapy at least 21 days prior to enrollment or at least 42 days if nitrosourea.

➤ Biological Agent/Monoclonal Antibody

- Biological agent:

Patient must have recovered from any acute toxicity potentially related to the agent and received their last dose of the biologic agent ≥ 7 days prior to study enrollment.

- For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.

- Monoclonal antibody treatment and agents with known prolonged half-lives: At least three half-lives must have elapsed prior to enrollment.

Note: A list of the half-lives of commonly used monoclonal antibodies is available on the PBTC webpage under Generic Forms and Templates.

➤ Radiation

Patients must have had their last fraction of:

- Craniospinal irradiation (>24Gy) or total body irradiation or radiation to $\geq 50\%$ of pelvis > 3 months prior to enrollment.
- Focal irradiation >6 weeks prior to enrollment
- Local palliative irradiation (small port) ≥ 4 weeks

➤ Autologous Stem Cell Transplant

Patient must be ≥ 6 months since autologous bone marrow/stem cell transplant prior to enrollment and have CD4 counts above 200/mm³.

➤ Surgery

Patients must be at least 4 weeks (28 days) from major surgery and fully recovered from all acute effects of prior surgical intervention.

➤ Inclusion of Women and Minorities

Both males and females of all races and ethnic groups are eligible for this study

➤ Neurologic Status

- Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to enrollment.
- Patients with seizure disorders may be enrolled if seizures are well controlled.

➤ Performance Status

Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within two weeks of enrollment must be ≥ 60 . Patients who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

➤ Organ Function

Patients must have adequate organ and bone marrow function as defined below:

- Absolute Neutrophil Count (ANC) $\geq 1.0 \times 10^9$ cells/ L
- Platelets $\geq 100 \times 10^9$ cells/L (unsupported, defined as no platelet transfusion within 7 days)
- Hemoglobin ≥ 8 g/dL (may receive transfusions)
- Total bilirubin ≤ 1.5 times institutional upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) ≤ 3 x institutional upper limit of normal (ULN)
- Albumin ≥ 3 g/dl
- Serum creatinine based on age/gender as noted in Table1. Patients that do not meet the criteria in Table 1 but have a 24 hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 mL/min/1.73 m² are eligible.

Table 1

Serum Creatinine for age/gender	
Age	Maximum Serum Creatinine (mg/dL)
	Male Female

1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4
The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.		

- Cardiac Function:
 - Left Ventricular Ejection Fraction (LVEF) > 50%
 - ECG QTc ≤ 450 msec
- Pulmonary Function:
 - Oxygen saturation as measured by pulse oximetry is > 93% on room air and no evidence of dyspnea at rest

➤ Growth Factors

Patients must be off all colony- forming growth factor(s) for at least 1 week prior to enrollment (i.e., filgrastim, sargramostim or erythropoietin). 2 weeks must have elapsed if patients received PEG formulations.

➤ Pregnancy Status

Female patients of childbearing potential must have a negative serum or urine pregnancy test.

➤ Pregnancy Prevention

Female subjects with childbearing potential and male subjects should use effective contraception methods (or abstain from sexual activity) while being treated with APX005M and for 30 days following treatment.

➤ Informed Consent

The patient or parent/guardian is able to understand the consent and is willing to sign a written informed consent document according to institutional guidelines.

Exclusion Criteria

➤ Concurrent Illness

- Patients with any clinically significant unrelated systemic illness (serious infections Grade ≥ 2 or significant cardiac, pulmonary, hepatic or other organ dysfunction), that in the opinion of the investigator would compromise the patient’s ability to tolerate protocol therapy, put them at additional risk for toxicity or would interfere with the study procedures or results.
- Patients with a history of any other malignancy, except patients with a secondary brain tumor if the patient’s first malignancy has been in remission for at least 5 years from the end of treatment.

➤ Concurrent Therapy

- Patients who are receiving any other anticancer or investigational drug therapy.
- Patients requiring systemic treatment with either corticosteroids (greater than dexamethasone 0.75 mg/m²/day or the equivalent dose of other steroids) or other immunosuppressive medications within 14 days of study drug administration will be excluded. However, patients who require intermittent use of bronchodilators or local steroid injections will not be excluded from the study. Please see section 5.3 for a list of acceptable and unacceptable concomitant medications as well as reporting requirements.

➤ Presence of Bulky Tumor

Patients with bulky tumor on imaging are ineligible. Bulky tumor is defined as:

- Tumor with any evidence of uncal herniation or midline shift
- Tumor that in the opinion of the site investigator, shows significant mass effect

Treating physicians are encouraged to contact the Study Chair to request a rapid central imaging review to confirm fulfilment of these eligibility criteria, if they have concerns.

➤ Allergy

Patients with a history of severe (Grade \geq 3) hypersensitivity reaction to a monoclonal antibody are ineligible.

➤ Allogeneic Hematopoietic Stem Cell Transplantation

Patients who have received allogeneic hematopoietic stem cell transplantation are ineligible.

➤ Autoimmune Diseases

Patients with active autoimmune disease or documented history of autoimmune disease/syndrome that requires ongoing systemic steroids or systemic immunosuppressive agents, except

- Patients with vitiligo or well controlled asthma/atopy
- Patients with hypothyroidism stable on hormone replacement or Sjogren's syndrome

➤ Inability to Participate

Patients who in the opinion of the investigator are unwilling or unable to return for required follow-up visits or obtain follow-up studies required to assess toxicity to therapy or to adhere to drug administration plan, other study procedures, and study restrictions.

➤ Bleeding Disorder

Patients with a known coagulopathy or bleeding diathesis or require the use of systemic anticoagulant medication are not eligible.

➤ Lactation Status

Female patients must not be breast-feeding.