APX005M

BRIEFING MATERIALS

ONCOLOGIC DRUGS ADVISORY COMMITTEE

PEDIATRIC SUBCOMMITTEE

APEXIGEN, INC.

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List of Abbreviations

Abbreviation	Definition
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
ALT	Alanine aminotransferase
Ang2	Angiopoietin-2
APCs	Antigen-presenting cells
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the curve at the last measurable time point
CD	Cluster of differentiation
CD40L	CD40 ligand
C_{max}	Maximum serum concentration
CNS	Central nervous system
CSF-1R	Colony stimulating factor 1 receptor
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DCs	Dendritic cells
DIPG	Diffuse intrinsic pontine glioma
DLT	Dose-limiting toxicity
ICH	International Conference on Harmonisation
Fc	Fragment crystallizable region of an antibody
FcγRIIb	Fc gamma receptor IIb
FcγRIIIa	Fc gamma receptor IIIa
Ig	Immunoglobulin
GLP	Good Laboratory Practice
HLA-DR	Human leukocyte antigen - antigen D related

Abbreviation	Definition
IL	Interleukin
IND	Investigational New Drug application
INF	Interferon
IV	Intravenous
K_d	Dissociation constant
mAb	Monoclonal antibody
mL	Milliliter
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
PBMCs	Peripheral blood mononuclear cells
PBTC	Pediatric Brain Tumor Consortium
PD-1	Programmed death receptor-1
PD-L1	Programmed death-ligand 1
PK	Pharmacokinetics
RP2D	Recommended phase 2 dose
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor
VEGF	Vascular endothelial growth factor

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1. Summary

APX005M is a humanized immunoglobulin (Ig)G1κ-agonistic monoclonal antibody (mAb) that binds to CD40. APX005M binds to both human and cynomolgus monkey CD40 with high affinity, triggering activation of antigen-presenting cells (APCs) (including B cells, monocytes, and dendritic cells [DCs]) and T cells, as well as stimulating cytokine release from both human and monkey lymphocytes and monocytes. APX005M does not bind to rodent CD40. Through activation of APCs, APX005M is capable of stimulating antigen-specific T-cell responses to alloantigens, viral antigens, and tumor antigens. APX005M can also trigger antitumor activity in multiple human CD40-expressing lymphoma xenograft models.

In humans, APX005M is generally well tolerated and elicits a dose-dependent activation of APCs and T cells and dose-dependent increases in circulating levels of cytokines such as interleukin (IL)-12 and INF-γ. APX005M is currently being developed for the treatment of malignant solid tumors in adults.

Developing effective treatments for central nervous system (CNS) tumors arguably represents the major remaining unmet need in pediatric oncology. CNS tumors, as a group, are the second most frequently encountered pediatric malignancy, the most common solid tumor in children, and the leading cause of cancer-related death in children. Immunotherapy is currently considered a promising area of investigation in clinical oncology and it is expected that novel immune-activating agents will provide the next wave of improvements over immune checkpoint inhibitors.

Apexigen is partnering with the Pediatric Brain Tumor Consortium (PBTC) for an early phase, multicenter, open-label study designed to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, and preliminary efficacy of APX005M in children and young adults with malignant brain tumors.

If preliminary evidence of efficacy is observed in any type of pediatric brain tumor, and if the overall safety profile of APX005M in pediatric subjects is acceptable, proper confirmatory studies will be considered. The results of this study will also inform the possible development of APX005M in other pediatric solid tumors and/or in combination with other treatment modalities including immunotherapy.

2. Characterization of CD40

CD40 is a member of the tumor necrosis factor receptor (TNFR) superfamily and plays an important role in induction of tumor apoptosis and regulation of immune activation, especially in crosstalk between T cells and APCs (Aggarwal, 2003). CD40 is a 48 kDa transmembrane glycoprotein surface receptor that comprises a 171-amino acid extracellular domain, a 22-amino acid single transmembrane domain, and a 62-amino acid cytoplasmic domain. Like other TNFR superfamily members, CD40 forms a trimer on the cell surface. CD40 ligand (CD40L), also

known as CD154, is the chief ligand described for CD40 and is expressed primarily by activated T lymphocytes and platelets (Grewal and Flavell, 1998).

CD40 is expressed on APCs such as DCs, B cells, monocytes (Figure 1), and other nonlymphoid cells (Banchereau et al, 1994). CD40-agonistic antibodies can substitute for CD40L/CD154 on activated T cells to boost immunity. Signaling through CD40 on APCs, including DCs, B cells, and monocytes, results in improved antigen processing and presentation, and cytokine release from activated APCs, which in turn enhance the T-cell response (Clark and Ledbetter, 1994; Grewal and Flavell, 1998). Therefore, a CD40-agonistic antibody can activate and stimulate both innate and adaptive immunity. It is important to note that these mechanisms do NOT require CD40 expression on the tumor cells.

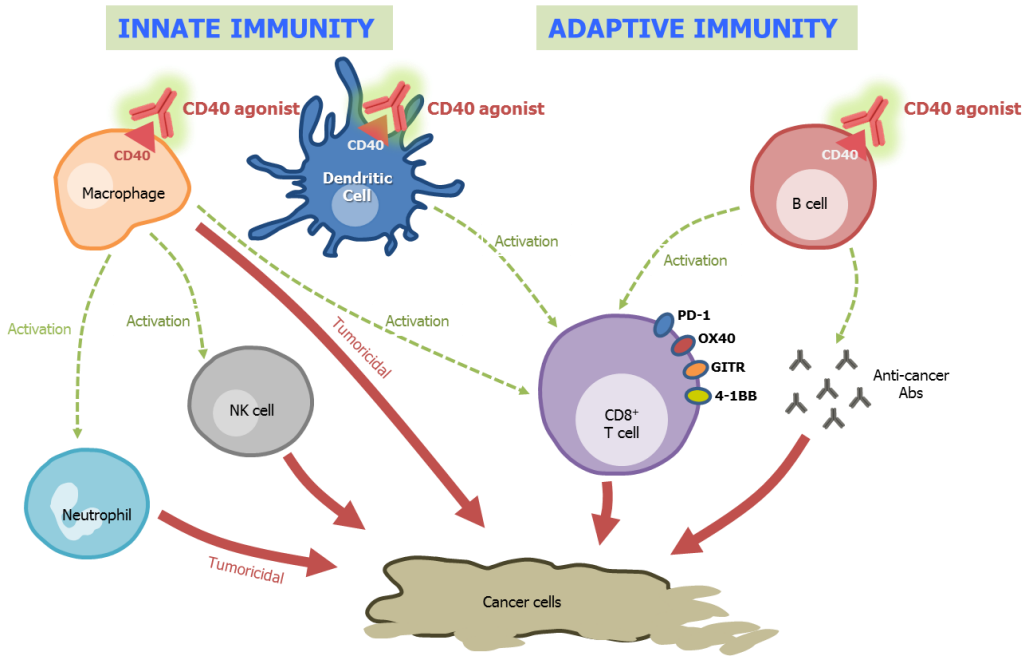

Figure 1: Among the immune activating molecules, CD40 is particularly important due to its key role in the control and activation of both innate and adaptive immunity against cancer. CD40 activation could lead to a strong and multifaceted antitumor immune response by activated APCs and T cells.

CD40 is also expressed on many tumor cells and can mediate an antibody-directed cytotoxic effect. In addition to B-cell lymphoma, CD40 expression has been reported in 30−70% of primary human solid tumor samples, including melanoma and carcinomas (Eliopoulos and Young, 2004). Patients with malignant glioma exhibit a variety of immune defects, many of which are related to impaired T cell function (Vega, 2008). Recent publications show that CD40/CD40L expression correlates with survival of patients with glioblastomas (Chonan, 2015). and activation of CD40 augments the efficacy of vaccinations against glioma models (Chonan, 2015; Derouazi, 2015) or can exert immune mediated anti-glioma effects in combination with

COX-2 inhibitors (Kosaka, 2014). Moreover, ligation of CD40 can also inhibit human glioma cell proliferation via the nuclear factor-κB signaling pathway (Zhang, 2012). Activation of CD40 on tumor cells results in tumor cell apoptosis and inhibition of tumor growth (Hess and Engelmann, 1996). CD40-agonistic antibodies have demonstrated potent antitumor immune response in both animal models and cancer patients (Khong, 2012; Law, 2009, Rakhmilevich, 2012; Tong, 2003). Due to its action on both immune and tumor cells, CD40 is being studied as a target for the treatment of cancer.

2.1 CD40 Agonistic Antibodies

While we are not aware of any experience investigating CD40 agonistic antibodies as antitumor agents in children, several such antibodies (APX005M [Apexigen], CP-870,893/RG-7876 [Pfizer/Roche], SGN-40 and SEA-CD40 [Seattle Genetics], ADC1013/JNJ-64457107 [Alligator Biosciences/Johnson and Johnson], Chi Lob 7/4 [University of Southampton]) have been investigated in adults with cancer. In general, these agents have been well-tolerated and have demonstrated some evidence of efficacy.

CP-870,893/RG-7876 seems to be the agent that has been most studied. A report of the first in human, Phase 1 study included 29 adults with advanced solid tumors (Vonderheide et al, 2007). They received single doses of the agent intravenously (IV), at doses ranging from 0.01 to 0.3 mg/kg. The maximum tolerated dose (MTD) was considered to be 0.2 mg/kg because 2/7 subjects treated at the 0.3 mg/kg dose level experienced dose limiting toxicity (DLT) (venous thromboembolism, Grade 3 headache). The most common adverse event (AE) was transient Grade 1 or Grade 2 cytokine release syndrome (chills, rigors, fever, rash, nausea, vomiting, muscle aches, back pain) associated with the infusion and elevated of serum TNF-α and IL-6. Other non-DLT toxicities included Grade 3 or 4 lymphopenia, Grade 2 thrombocytopenia (at the 0.3 mg/kg dose level), Grade 3 AST/ALT elevations, Grade 1 or 2 hyperbilirubinemia, and Grade 1 or 2 proteinuria. Antitumor activity was demonstrated in 4 patients with melanoma (14% of all subjects; 27% of melanoma subjects) who achieved partial response at day 43 after a single dose of CP-870,893. One of these patients received 9 subsequent doses (about every 8 weeks) and was in complete remission more than 9 years later (Bajor et al, 2014). CP-870,893 was subsequently used in combination with carboplatin and paclitaxel for patients with advanced cancer (Vonderheide et al, 2013), with gemcitabine for patients with metastatic pancreatic carcinoma (Beatty et al, 2011) with response rates of about 20% (thought to be promising in the context of these patients), and with cisplatin and pemetrexed for advanced mesothelioma (Nowak et al, 2015). Trials also have been initiated in combination with an anti-CTLA-4 antibody (tremelimumab), an anti-PD-L1 antibody (atezolizumab), an anti-CSF-1R antibody (emactuzumab), and an anti-Ang2-VEGF bispecific antibody (vanucizumab).

SGN-40 is a humanized IgG1 CD40-agonistic antibody tested in hematological malignancies as monotherapy or in combination with rituximab and chemotherapy (Forero-Torres et al, 2013; Lewis et al, 2011). The major adverse effects of SGN-40 were anemia, pleural effusion, and

thrombocytopenia. **SEA-CD40** is an engineered version of SGN-40. SEA-CD40 and SGN-40 have the same amino acid sequences but the fragment crystallizable (Fc) region of SEA-CD40 is defucosylated, leading to increased binding to and crosslinking by FcγRIIIa which in turn induces antibody-dependent cytotoxicity (ADCC), and could inhibit the proliferation of CD40-expressing cells. SEA-CD40 is currently being studied in a Phase 1 trial in metastatic or unresectable solid tumors and hematologic malignancies.

ADC-1013/ JNJ-64457107 is a fully human IgG1 CD40-agonistic antibody in Phase 1 clinical trial for treatment of solid tumors (Mangsbo et al, 2014). ADC-1013 was originally intended for intratumoral delivery and is currently being studied with IV administration to subjects with advanced stage solid tumors (with a focus on non-small cell lung cancer [NSCLC], pancreatic cancer and cutaneous melanoma).

ChiLob 7/4 is an IgG1 chimeric CD40 agonistic antibody that has been tested in a Phase 1 clinical trial in subjects with solid tumors. The MTD of ChiLob 7/4 is 200 mg/weekly × 4, and the major DLT was reversible liver enzyme elevation (Johnson et al, 2015). Significant anti-drug antibodies (ADA) were detected in patients treated with Chi Lob 7/4 due to its mouse-human chimeric structures.

Theoretical concerns associated with CD40 agonists beyond cytokine release include autoimmune reactions, thromboembolic phenomena (CD40 is expressed on platelets and endothelial cells), hyperimmune stimulation leading to cell death or tolerance, and tumor angiogenesis; however, Vonderheide and Glennie note in their 2013 review article that "overall, toxicity has not been a major issue with CD40 agonists in the clinic" (Vonderheide and Glennie, 2013).

Although CP-870,893 has potent CD40-agonistic activities, it is an IgG2 antibody and thus its CD40-agonistic activity is independent of Fc receptor crosslinking (Richman and Vondeheide, 2014). SGN-40 is an IgG1 antibody, but a weak CD40 agonist. Due to its chimeric structure, Chi Lob 7/4 may potentially be more immunogenic considering that the immune response may be boosted by its CD40-agonistic effects. ADC-1013 has similar binding affinity as APX005M but is a weaker CD40-agonistic antibody likely due to its lack of binding to FcγRIIb. Although SEA-CD40 has increased potency compared with SGN-40, its high affinity binding to FcγRIIIa may lead to enhanced antibody effector functions such as ADCC on CD40-expressing cells such as DCs and B cells.

A human or humanized IgG1 antibody that can utilize Fc receptors to cluster CD40 and enhance CD40-agonistic effects, like APX005M, might be preferable both in terms of potential decreased immunogenicity and increased antitumor activity for use in cancer immunotherapy.

3. APX005M

3.1 Pharmacology

APX005M is an humanized immunoglobulin (Ig)G1κ-agonistic mAb with mutation at the Fc region. APX005M binds with high affinity to human CD40 (K_d = 1.2 × 10^{-10} M) and monkey CD40, but does not cross-react with mouse or rat CD40. APX005M blocks the binding of CD40 to CD40L. In contrast, CP-870,893 and SGN-40 failed to block CD40 binding to CD40L suggesting that APX005M binds to an epitope that is different from the CP-870,893 and SGN-40 binding site(s). The APX005M binding epitope has been mapped to 2 specific regions on CD40:P1 region (92TSEACESCVLHRSCSP107) and P2 region (125PCPVGFFSNVSSAFEKCHPW144). The region 92TSEACESCVLHRSCSP107 is known as a CD40L binding domain (Figure 2). It has been shown that CD40L-blocking antibodies tend to have more potent CD40 agonistic activities than CD40L-non-blocking antibodies (Barr and Heath, 2001).

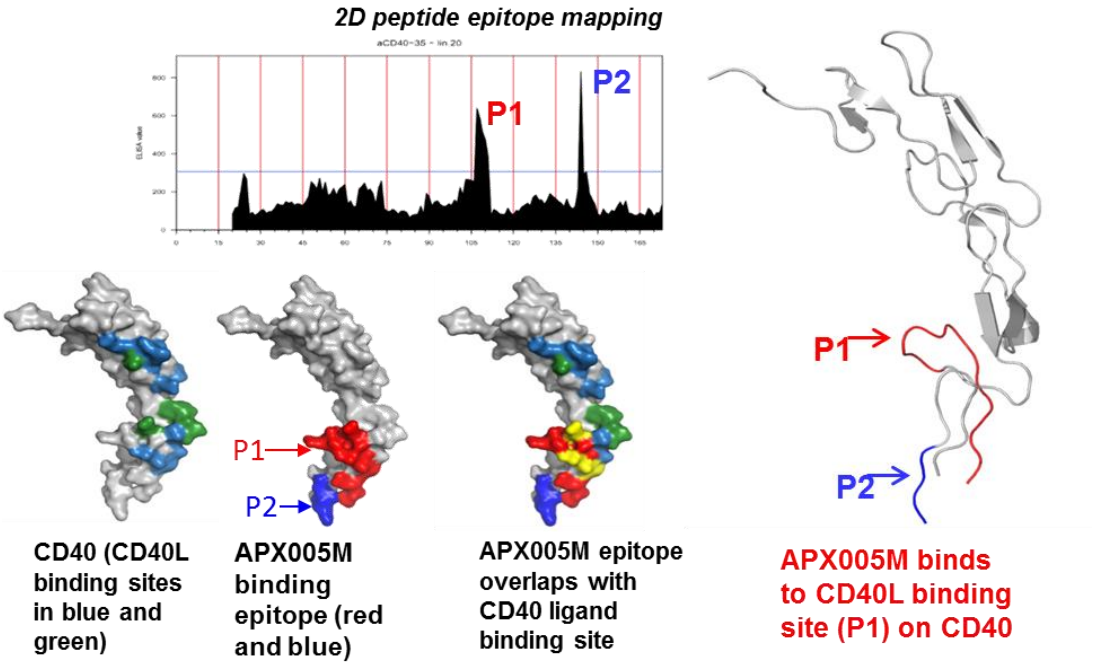

Figure 2: The APX005M binding epitope has been mapped to 2 specific regions on CD40. These are P1 region (92TSEACESCVLHRSCSP107) and P2 region (125PCPVGFFSNVSSAFEKCHPW144). The region 92TSEACESCVLHRSCSP107 is known as a CD40L binding domain.

Preclinical experiments with APX005M showed that it activates the CD40 signaling pathway, leading to APC activation, as demonstrated by an increased expression of CD80, CD83, and CD86 and by expression and release of cytokines from human DCs and lymphocytes. As a result of APC activation, APX005M enhances T cell proliferation to alloantigen, triggers production of

IFN-γ in response to viral antigens, and enhances T-cell response to tumor antigens. APX005M combined with a TLR 4 agonist or an antibody against programmed death ligand 1 (PD-L1) synergistically enhances T-cell responses. In comparison with other CD40-agonistic antibodies, such as CP-870,893, SGN-40, and ADC-1013 analogs, APX005M is the most potent CD40 agonist.

The potential for APX005M to induce expression of cytokines was evaluated with peripheral blood mononuclear cells (PBMCs) obtained from humans and treatment naïve cynomolgus monkeys. Cytokine secretion differed significantly between species, with much less secretion from monkey PBMCs compared with human PBMCs. The level of secretion varied between cytokines and between platforms. APX005M induced secretion of IL-12, TNF, IL-6, and TGF-β from PBMCs suggesting that APX005M is a strong CD40 agonistic antibody that can activate APCs. APX005M also stimulated IFN-γ secretion, indicating that APX005M has the potential to activate T cell and/or natural killer (NK) cells indirectly through APCs. These data suggest that APX005M is a strong CD40-agonistic antibody that can activate APCs (DCs, B cells, and monocytes) and in turn stimulate T-cell response.

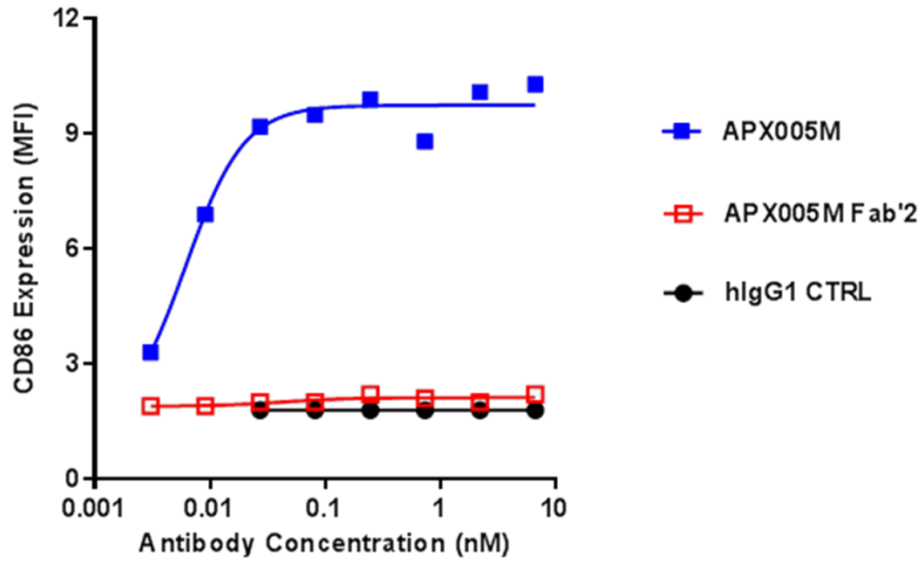

Figure 3: APX005M is engineered to bind with higher affinity to FcgRIIb expressed on B cells and other lymphoid cells. Removal of the Fc portion of APX005M results in loss of CD40 agonistic activity on human B cells.

APX005M's CD40-agonistic activity depends on its ability to bind FcγRs (Figure 3). In in vitro cultures with T cells and DCs, APX005M was able to enhance antigen-specific T cell proliferation and promote interferon (IFN)-γ secretion. In combination with an antibody against programmed cell death receptor-1 (PD-1) or programmed cell death ligand-1 (PD-L1), APX005M synergistically enhances antigen-specific T-cell responses. Upon binding to CD40-

expressing tumor cells, APX005M was capable of inducing ADCP and tumor cell apoptosis (Figure 4). APX005M did not appear to have a substantive effect on normal human DC and T cell counts, but could partially reduce B-cell counts in vitro.

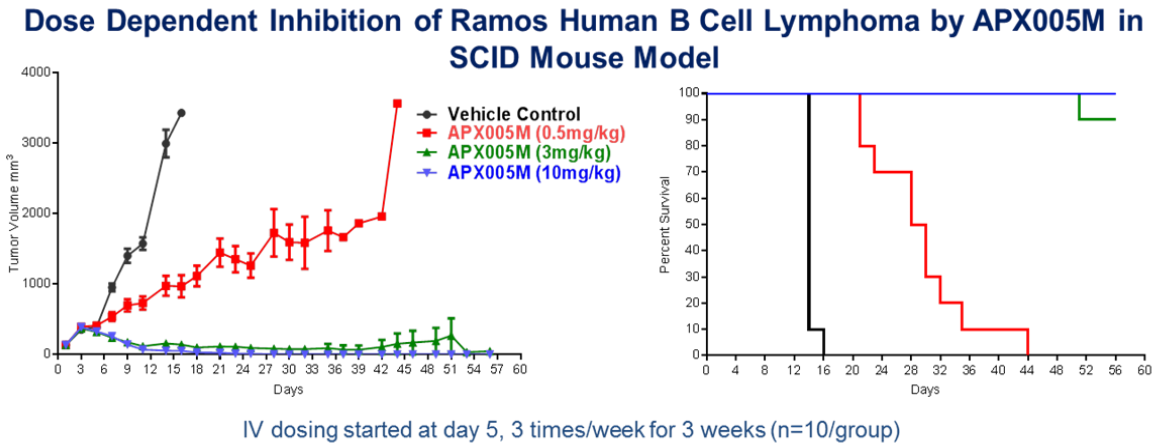

Figure 4: APX005M can trigger direct ADCP and apoptosis in CD40 expressing tumor cells (e.g., Ramos B-cell lymphoma cells). In a SCID mouse APX005M can inhibit growth in a dose-dependent manner of a Ramos human B-cell lymphoma implanted subcutaneously.

3.2 Nonclinical Data Supporting Pediatric Development

The pharmacology, PK, and toxicology of APX005M have been investigated in adult primate nonclinical studies. No specific toxicities have been identified that could raise concerns for pediatric patients or that could be further informed by juvenile animal studies. All animals survived, and there were no effects on clinical observations, body weight, appetite, ophthalmoscopy, cardiovascular and respiratory parameters, cytokines, and anatomical pathology attributable to APX005M. APX005M-related findings were limited to reduced B lymphocytes detected using flow cytometry. The reduction in peripheral B lymphocytes observed is an anticipated pharmacological response associated with upregulation of immune co-stimulatory molecules (Vonderheide and Glennie, 2013). The currently available nonclinical data are considered to be sufficient to support initiation of pediatric development of APX005M.

Genotoxicity and carcinogenicity studies with APX005M have not been conducted, consistent with the recommendations in International Committee on Harmonisation (ICH) S6(R1) (Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, 2011). APX005M, a mAb that binds specifically to CD40, is not expected to interact directly with DNA or other chromosomal material, therefore the use of standard genotoxicity or carcinogenicity studies is not appropriate. Similarly, reproductive/developmental toxicology studies have not been

performed with APX005M, consistent with the expectations for this early phase of clinical development and in accordance with ICH S6(R1) and M3(R2) (Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, 2009).

3.3 Pharmacokinetics

Nonclinical PK parameters of APX005M were determined in a Good Laboratory Practice (GLP) repeat-dose toxicology study using cynomolgus monkeys. Weekly IV administration of 5 doses of APX005M was well tolerated up 30 mg/kg. The PK properties of APX005M are typical of other mAbs and comprise low clearance, small volume of distribution, and long terminal half-life. Positive ADA titers were observed in all animals except in the high-dose group. Based on these results, the no observed adverse effect level (NOAEL) was considered 30 mg/kg.

There are limited human PK data with APX005M at this time. Increases in the dose of APX005M led to approximately dose-proportional increases in maximum serum concentration (C_{max}) and area under the curve at the last measurable time point (AUC_{0-t}). No accumulation of APX005M was observed with every 21 day dosing.

3.4 Clinical Experience

APX005M had been administered to 30 adult subjects with solid tumors in a Phase 1 dose-escalation clinical study. To date, APX005M has been well tolerated; the majority of AEs have been mild to moderate in severity, and the majority of serious AEs have been considered unrelated to APX005M.

As of 29 November 2016, infusion-related reactions including cytokine release syndrome have been reported in 10/30 (33%) of subjects (all grades). There has been one Grade 4 event of cytokine release syndrome that was considered related to APX005M. Three other subjects receiving APX005M experienced Grade 3 infusion-related reactions. All of these events occurred in subjects receiving APX005M at doses ≥ 0.6 mg/kg. The most common AEs observed during the first 48 hours following infusion of APX005M include: rigors/chills, fever, flushing, itching/pruritis, nausea/vomiting, headache, and rash; the majority of these symptoms were mild (≤ 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 effect. Transient decreases in platelets with no clinical consequences were observed in some subjects.

In adult cancer patients APX005M has demonstrated a dose-dependent activation of APCs (as demonstrated by increases in expression of activation markers such as CD54, CD70, CD80, CD86, HLA-DR), T cell activation and increases in circulating levels of IL-12, INF-γ, TNF-α and IL-6.

3.5 Formulation

APX005M is intended for IV or subcutaneous administration in adult and pediatric patients. APX005M investigational product is supplied in Type 1 clear glass vials intended for single use. Each depyrogenated vial contains 10 mg/mL APX005M in a sterile, preservative-free solution (pH 5.5) containing 25 mM sodium acetate, 248 mM trehalose, and 0.02% polysorbate 20 in water for injection.

4. Clinical Development Plan

Safety of single-agent APX005M administered on an every 3 week schedule has been explored in adult subjects with solid tumors who failed available therapy. In an expansion of the first in human Phase 1 study, single-agent safety of APX005M administered on a every 2 week and every 1 week schedule is currently being explored in adult subjects with urothelial carcinoma, melanoma, squamous cell carcinoma of the head and neck, NSCLC, or any solid tumor with high microsatellite instability status (MSI-high) who failed available therapy.

A Phase 1b–2 study of APX005M administered in combination with nivolumab to adult subjects with NSCLC or metastatic melanoma was initiated in May 2017. The Phase 1 portion is intended to establish the MTD and the recommended Phase 2 dose (RP2D) of APX005M when administered in combination with nivolumab. The Phase 2 portion of the study will evaluate safety and efficacy of the combination.

Additional investigator-sponsored Phase 1b–2 trials exploring the safety and preliminary efficacy of APX005M administered in combination with checkpoint inhibitors and/or chemo(radio)therapy to adult subjects with metastatic melanoma, metastatic pancreatic cancer and neoadjuvant gastric and gastro-esophageal junction cancers are about to be initiated.

No Phase 3 studies with APX005M are being planned at this time.

5. Regulatory History

Apexigen is currently conducting 2 studies in adults under 1 active investigational new drug (IND) application. A proposed pediatric study request (PPSR) summarizing Study PBTC-051 below was considered a pre-IND submission to a second IND.

6. Pediatric Development Plan

6.1 Overview

Pediatric oncology trials are inherently difficult because of the rarity of childhood cancers (Adamson et al. 2014); therefore, Apexigen is partnering with PBTC to conduct a safety and dose-finding study in subjects with malignant pediatric brain tumors, the subject of Apexigen's proposal for a pediatric development plan. The PBTC was formed by the National Cancer Institute (NCI) in 1999 to improve the treatment of primary brain tumors in children. The participating academic centers and children's hospitals are responsible for the diagnosis and treatment of the majority of children with primary brain tumors in the United States.

6.2 Pediatric Brain Tumors

Developing effective treatments for CNS tumors arguably represents the major remaining unmet need in pediatric oncology. CNS tumors, as a group, are the second most frequently encountered pediatric malignancy, the most common solid tumor in children, and the leading cause of cancer-related death in children. In the US, approximately 4,300 children younger than 20 years of age were diagnosed with a CNS tumor in 2013.

Pediatric CNS tumors include a relatively wide variety of specific tumor types with the most common being high- and low-grade gliomas, medulloblastoma, and ependymoma. In general, pediatric patients with CNS tumors do not share the favorable prognosis of those with other common pediatric malignancies. Patients with newly diagnosed diffuse intrinsic pontine gliomas (DIPGs) or high-grade astrocytomas essentially do not have any curative treatment options, and most patients with recurrent malignant brain tumors such as ependymoma, medulloblastoma, and others will die of their disease.

Immunotherapy is currently considered a promising area of investigation in clinical oncology. Checkpoint inhibitors such as ipilimumab (anti-CTLA-4), pembrolizumab (anti-PD-1) and nivolumab (anti-PD-1) have revolutionized the treatment of adults with advanced melanoma and have also demonstrated efficacy for other high-risk malignancies in adults such as NSCLC, renal cell or urothelial cell carcinoma. There is only limited experience with these agents in pediatric patients. A pediatric Phase 1 trial of ipilimumab monotherapy concluded that ipilimumab may be

safely administered to pediatric patients (Merchant et al, 2016) and a Phase 1 study of nivolumab ± ipilimumab is ongoing through the Children's Oncology Group (COG ADVL 1412). Both of these studies excluded children with brain tumors. A recently opened study (PBTC-045) is exploring the safety and preliminary efficacy of the anti-PD-1 agent pembrolizumab for children with recurrent/refractory high-grade astrocytoma or DIPG.

Although antibodies are not thought the cross the blood-brain barrier, APX005M activates T cells, which are capable of entering the CNS. The potential of the immunotherapy approach for brain tumor treatment is supported by the evidence of activity of ipilimumab in adult melanoma patients with CNS lesions (Margolin et al, 2012) and by the preliminary evidence of safety and efficacy of nivolumab ± ipilimumab in adults with recurrent glioblastoma multiforme (Sampson et al, 2015).

6.3 Proposed Evaluation of APX005M in Children (Study PBTC-051)

Study PBTC-051 is planned as an early phase, multicenter, open-label study designed to evaluate the safety, tolerability, PK, immunogenicity, and preliminary efficacy of APX005M in children and young adults with malignant brain tumors.

6.3.1 Study Population

Stratum 1: Histologically confirmed diagnosis of a primary malignant CNS tumor that is recurrent, progressive, or refractory to available treatment.

Stratum 2: Newly diagnosed with DIPG, 6 to 14 weeks post-completion of radiation therapy if without evidence of progression. Stratum 2 will open only once the pediatric RP2D has been established in Stratum 1 (see Section 7.3.2).

6.3.1.1 Main Inclusion Criteria

- Age ≥ 1 and ≤ 21 years at the time of enrollment
- Bi-dimensionally measureable disease
- Adequate time from last dose of known myelosuppressive anticancer therapy
- Adequate time from last dose of radiation therapy
- Stable neurological status
- Karnofsky Performance Scale (> 16 years of age) or Lansky Performance Score (≤ 16 years of age) must be ≥ 60

- Adequate organ function

6.3.1.2 Main Exclusion Criteria

- Any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that 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
- History of any other malignancy, except a secondary brain tumor if the first malignancy occurred in the distant past (such as acute lymphoblastic leukemia)
- Receiving any other anticancer or investigational drug therapy
- Presence of bulky or multi-focal tumor on imaging
- Known coagulopathy or bleeding diathesis or requirement for the use of systemic anticoagulant medication
- Inability to participate in study procedures (unable or unwilling 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).

6.3.2 Study Objectives

6.3.2.1 Primary Objectives:

- To evaluate the safety of APX005M administered IV every 3 weeks to children with CNS tumors
- To determine the MTD and/or the RP2D of APX005M.

6.3.2.2 Secondary Objectives:

- To determine the PK of APX005M in pediatric subjects
- To assess the incidence of ADA
- To make a preliminary assessment of efficacy via overall response rate, duration of response, progression-free survival and overall survival for subjects with DIPG.

6.3.3 Study Design

Study will start in Stratum 1 with a 3+3 dose escalation of APX005M administered on an every 3 week schedule (Figure 5). The DLT observation period will be the first 2 cycles (42 days). No intra-patient escalation will be allowed and dose escalation will not be considered until toxicity information is available from at least 3 evaluable patients at the current dose level. The MTD will be empirically defined as the highest dose level with less than 33% of subjects experiencing a DLT during the DLT observation period. If all of the pre-planned dose levels are investigated with acceptable toxicity, consideration may be given to investigating higher dose levels. If a decision is made to not study higher doses and at least 6 subjects have been treated safely at the highest dose level, then the highest dose level may be recommended for further study in Phase 2 trials.

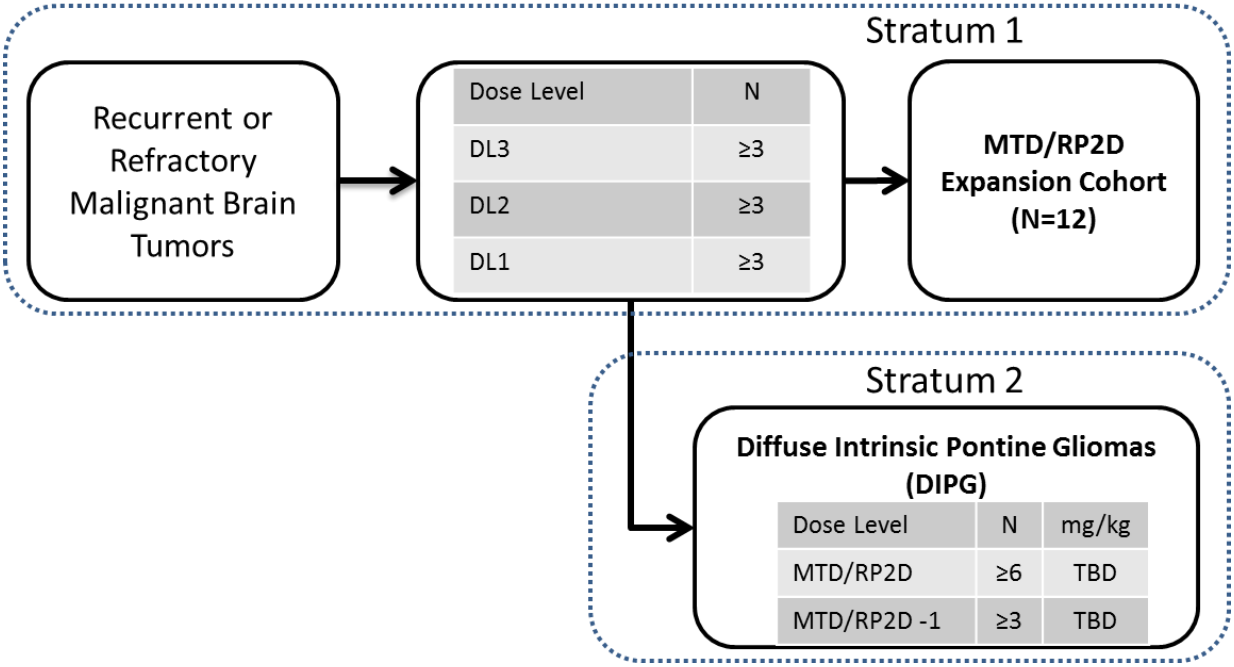

Figure 5: Design of the proposed safety and dose finding study in pediatric subjects with malignant brain tumors.

The RP2D will be based on the MTD and the totality of the safety/efficacy data. Once the MTD or a RP2D is identified, the total number of patients treated at the MTD/RP2D will be increased to 12 to further define the toxicity profile. In the event that excessive toxicities are observed in these additional patients, the MTD/RP2D may be revised and de-escalation to a lower dose level may occur.

Barring excessive toxicity, approximately 12 evaluable DIPG subjects will be enrolled in Stratum 2 after pediatric RP2D has established in Stratum 1 to assess the safety of this agent in

patients with non-progressive DIPG post radiation therapy. The first dose level used for the first DIPG cohort will be one dose level below the RP2D determined in non-DIPG subjects where 3 subjects will be enrolled. If no DLTs are observed then APX005M dose will be escalated to the RP2D where 6 additional subjects with DIPG will be treated. If 1 DLT is observed in first 3 subjects then 3 additional subjects will be enrolled at the starting dose level. If 2 or more DLTs are observed at the starting dose level then de-escalation to a lower dose level will be considered and a similar approach will be repeated.

6.4 Confirmatory Study

If preliminary evidence of efficacy is observed in any type of pediatric brain tumor, and if the overall safety profile of APX005M in pediatric subjects is acceptable, Apexigen will develop in collaboration with the appropriate health authorities and academic collaborators proper confirmatory studies. The results of this study will also inform the possible development of APX005M in other pediatric solid tumors and/or in combination with other treatment modalities including immunotherapy.

7. References

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