

# **APX005M**

*A CD40 Agonistic Monoclonal Antibody*

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ONCOLOGIC DRUGS ADVISORY COMMITTEE  
PEDIATRIC SUBCOMMITTEE

*June 21, 2017*

# Presentation Overview

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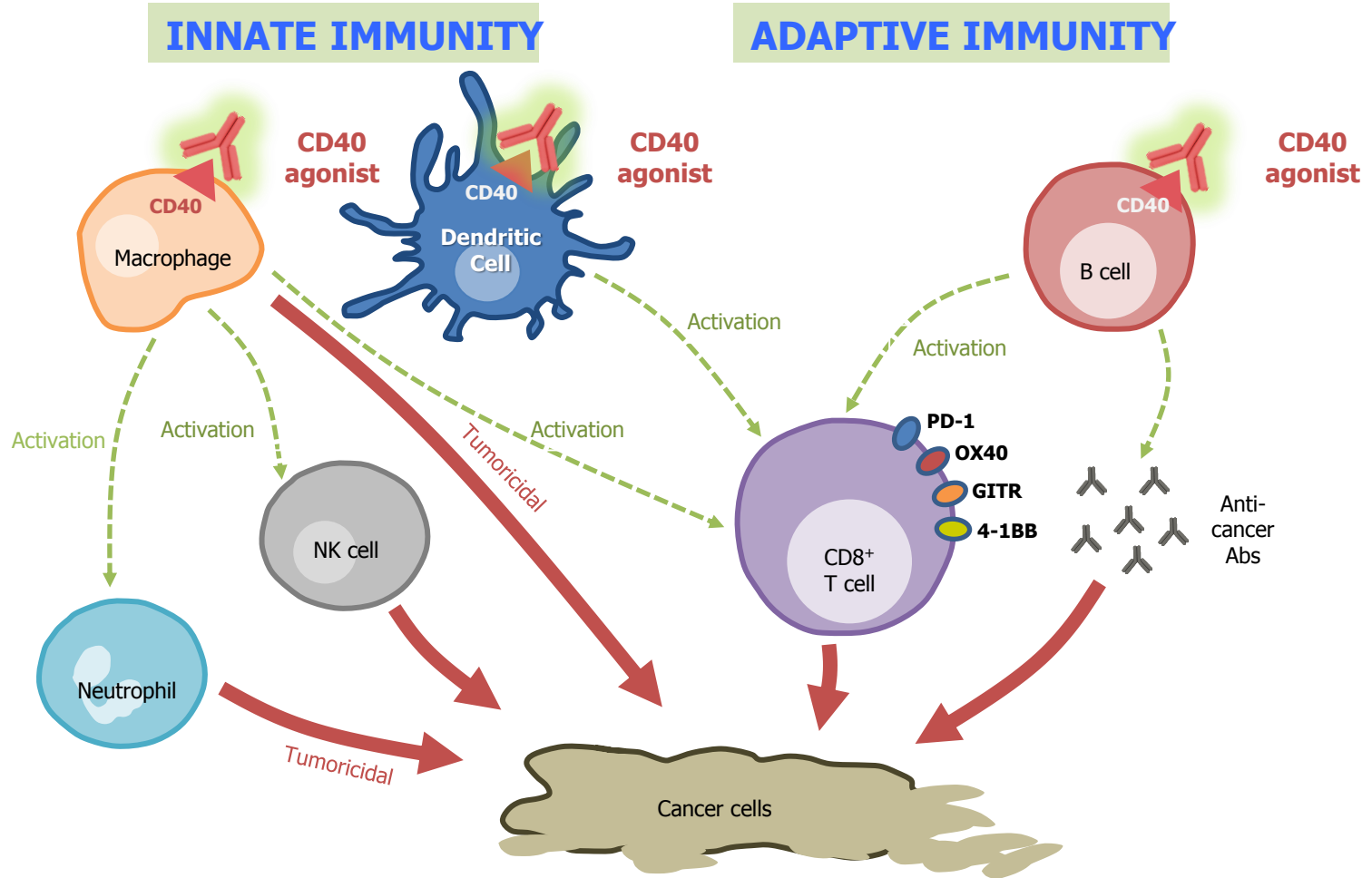
Role of CD40 in the Immune System

Therapeutic Effects of Targeting CD40

CD40 Agonistic Antibody APX005M

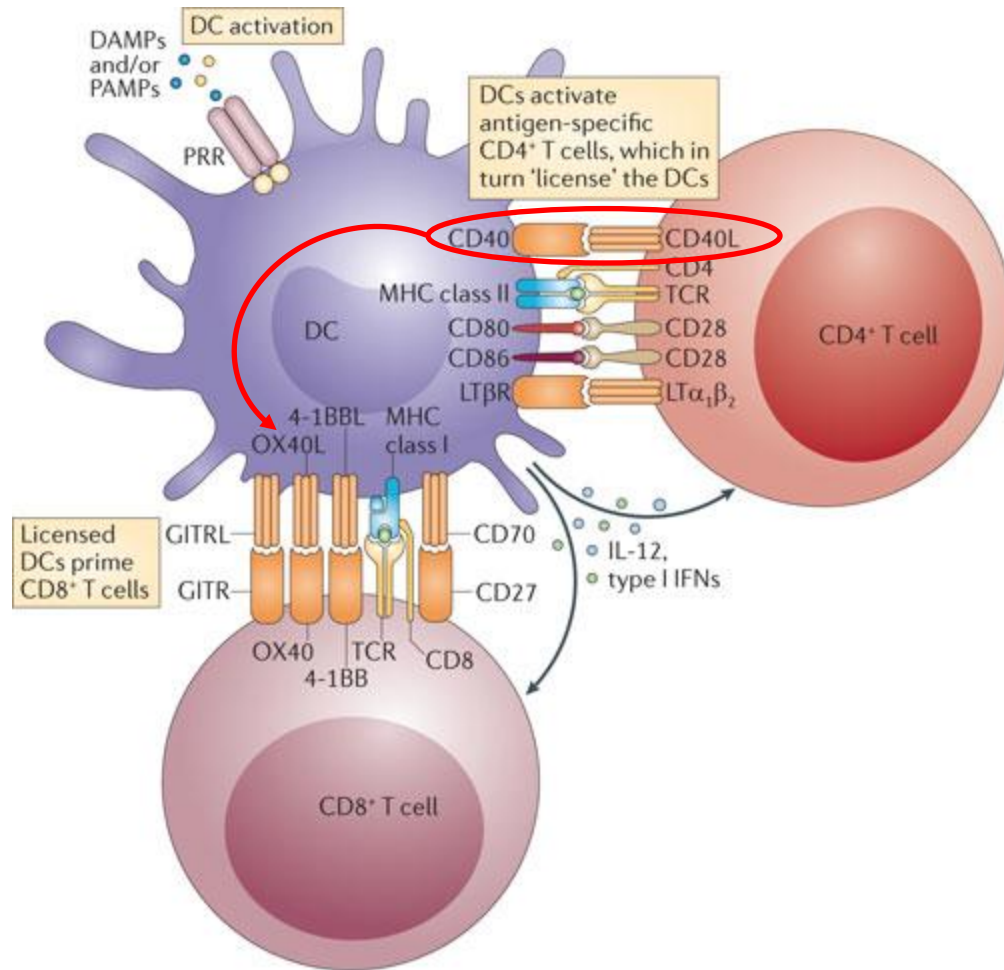
Proposed Pediatric Development

# CD40 Plays a Central Role in the Immune Response Against Cancer



CD40 activates both innate and adaptive immunity and the potential to complement direct T-cell targeting

# CD40 Signaling Results in the Production of IL-12 and the Upregulation of CD70, CD86, 4-1BBL, OX40L and GITRL



## CD40 is an upstream regulator of anti-tumor CD8+ T cells

CD40 signaling triggers the production of IL-12 and the upregulation of CD70, CD86, 4-1BB ligand, OX40 ligand and GITR ligand. Stimulation of the corresponding receptors on CD8+ T cells, in combination with IL-12 and type I IFNs, results in robust CD8+ T cell activation, proliferation and effector function, as well as the formation and maintenance of tumor-specific CD8+ T cell memory.

deLuca & Gommerman, 2012  
Nature Reviews | Immunology

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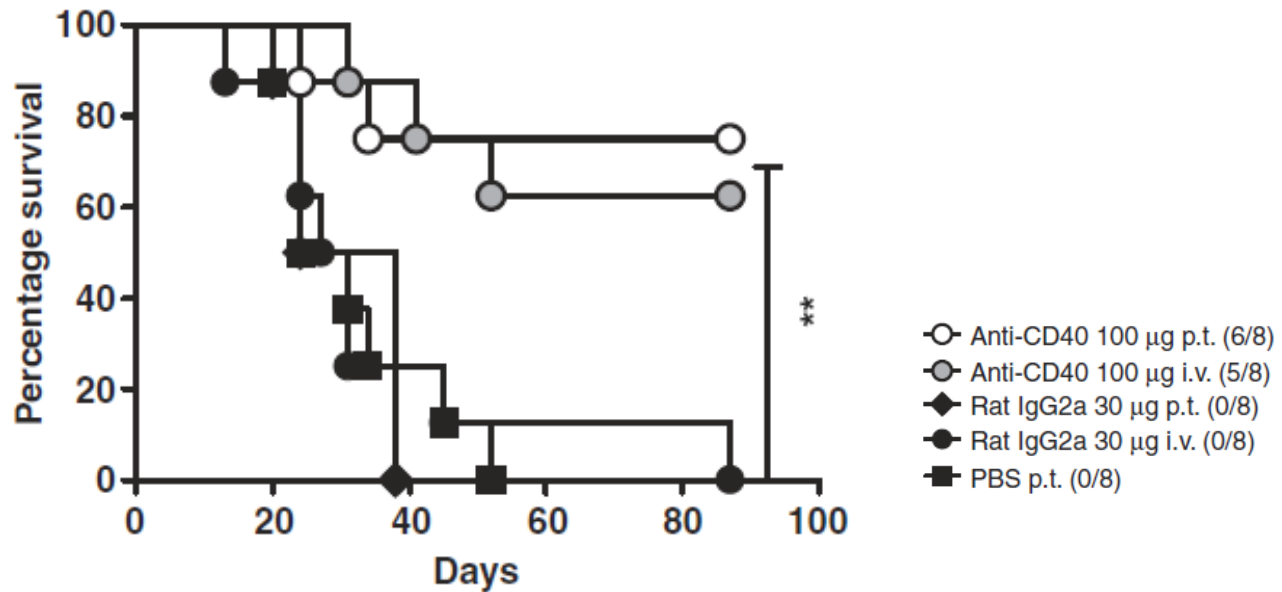
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# CD40 Agonistic mAbs Have Single Agent Activity in Pre-clinical Tumor Models

## C57BL6 Mice Carrying MB49 Bladder Tumors



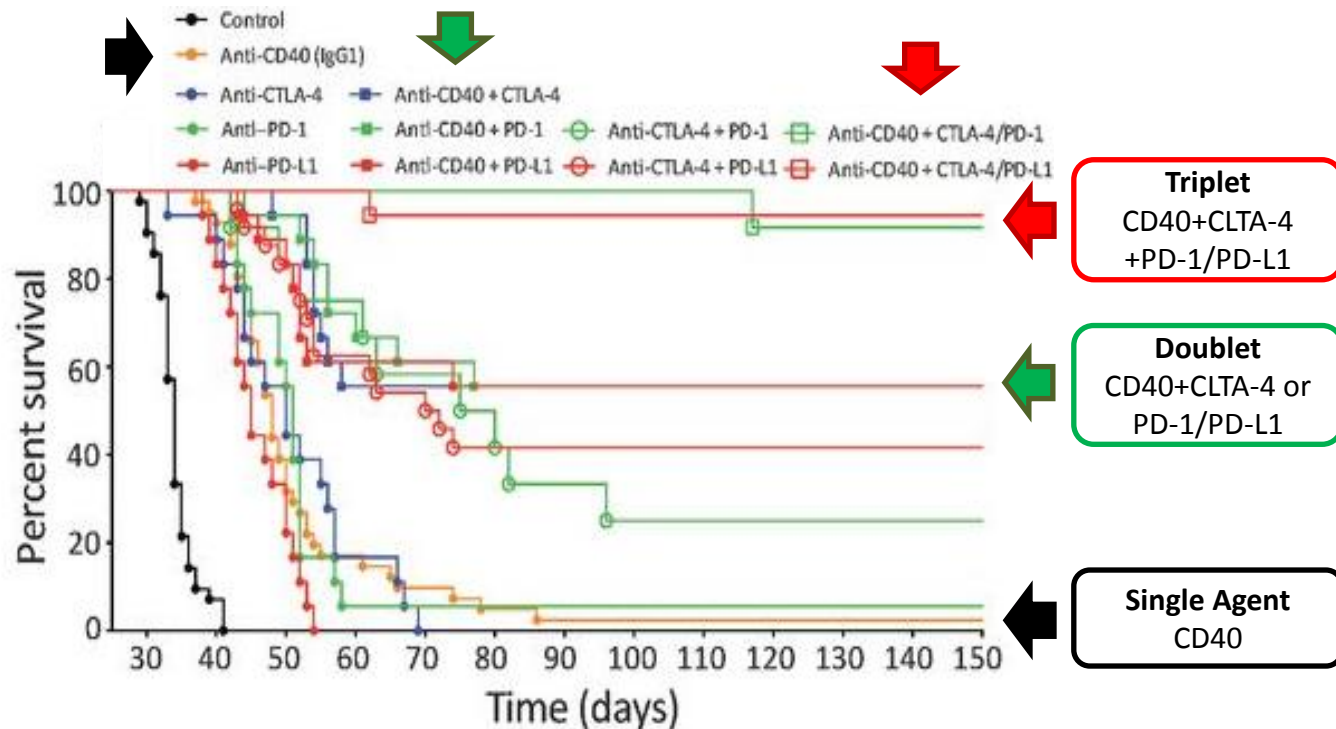
Sandin et al, Cancer Immunol Res, 2014

**CD40 agonistic mAb: FGK45**

These effects have been recapitulated across multiple pre-clinical tumor models, including melanoma, pancreatic, and lung cancers.

# CD40 Agonistic mAbs Synergize with Checkpoint Inhibitors in Multiple Pre-clinical Tumor Models

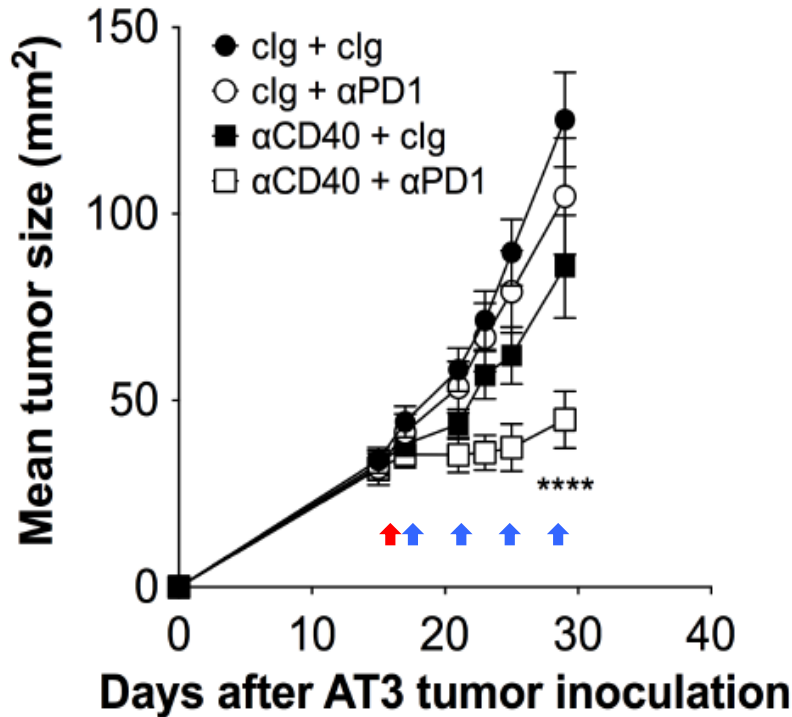
## MC38 Mouse Colon Carcinoma Model



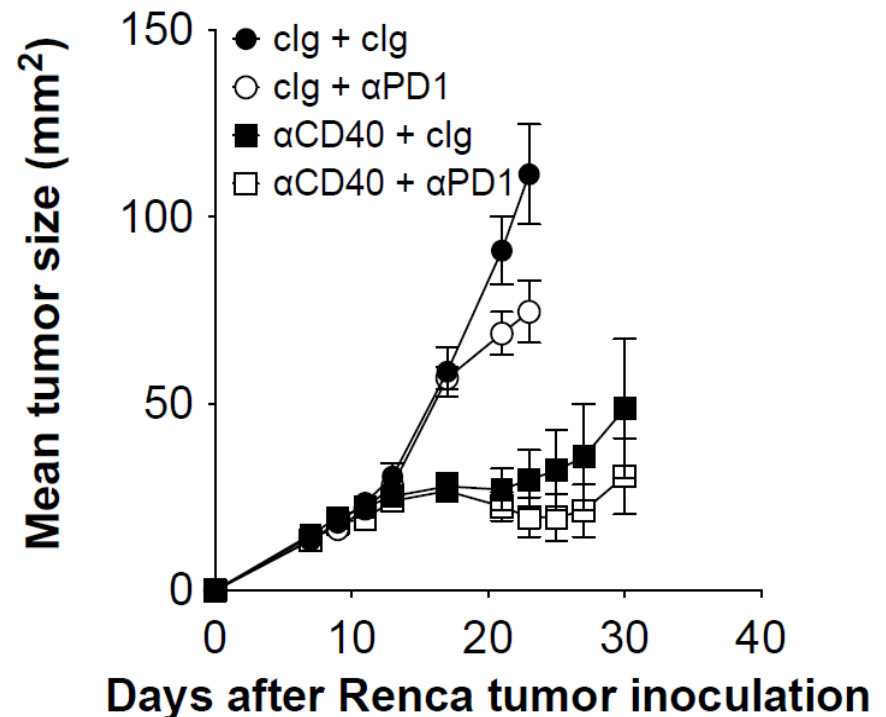
Zippelius, Cancer Immunol Res, 2015

**CD40 agonistic mAb: 1C10**

# Reversal of Resistance to Anti-PD1 by CD40 Agonistic mAb



**αCD40 agonistic mAb: FGK45**



**αPD-1 antagonist mAb**

CD40 agonistic mAb can condition tumors to respond to anti-PD-1 and reverse resistance to anti-PD-1 via stimulation of IL-12 production from APC





# FGK45, 1C10, 3/23 as Surrogates for APX005M

| Antibody       | Specificity   | Activity | Isotype | Epitope                                  |
|----------------|---------------|----------|---------|------------------------------------------|
| <b>FGK45</b>   | Mouse<br>CD40 | Agonist  | IgG2a*  | Blocks binding of<br>CD40 to CD40 ligand |
| <b>1C10</b>    | Mouse<br>CD40 | Agonist  | IgG2a*  | Blocks binding of<br>CD40 to CD40 ligand |
| <b>3/23</b>    | Mouse<br>CD40 | Agonist  | IgG2a*  | Blocks binding of<br>CD40 to CD40 ligand |
| <b>APX005M</b> | Human<br>CD40 | Agonist  | IgG1    | Blocks binding of<br>CD40 to CD40 ligand |

**FGK45, 1C10, 3/23 are widely-used anti-mouse CD40 agonistic mAbs and are surrogate mAbs for APX005M based on isotype and binding epitope**

\* Rat isotype IgG2a is equivalent to human IgG1

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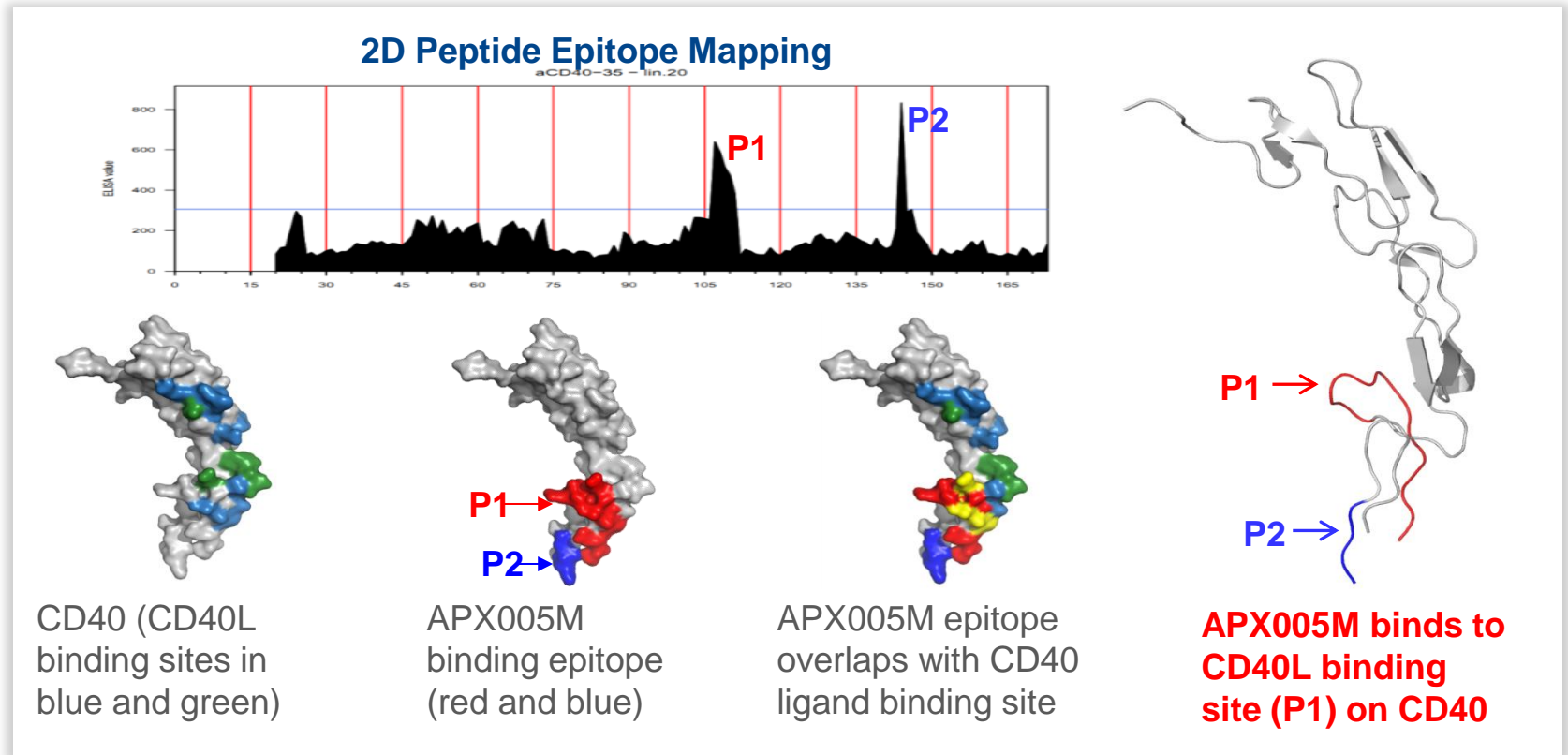
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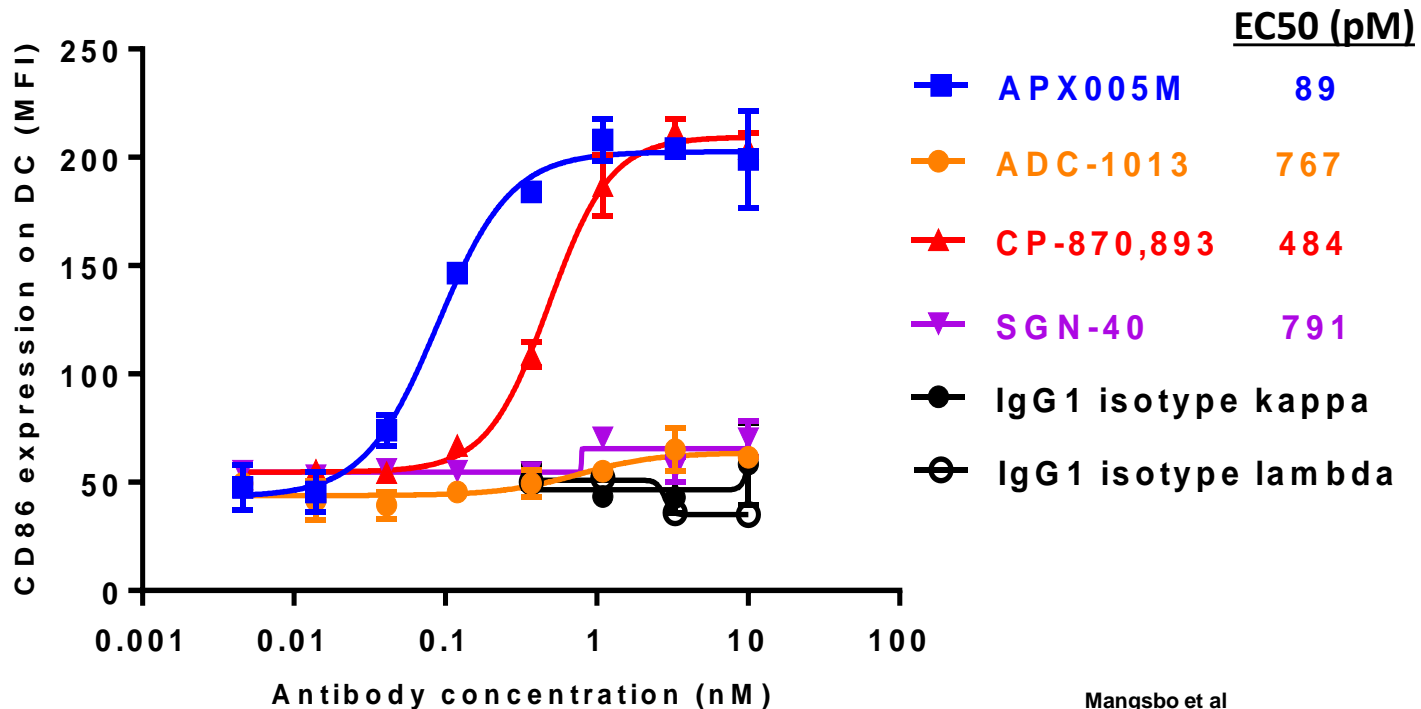
# APX005M Binds The CD40L Binding Site on CD40



Antibodies which bind to CD40 ligand (CD40L) binding sites demonstrated more potent CD40 agonistic activities\*

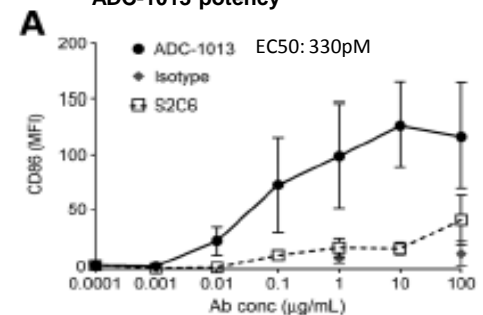
\*Source: Barr & Heath, Immunol, 2001

# APX005M Activates Human Dendritic Cells



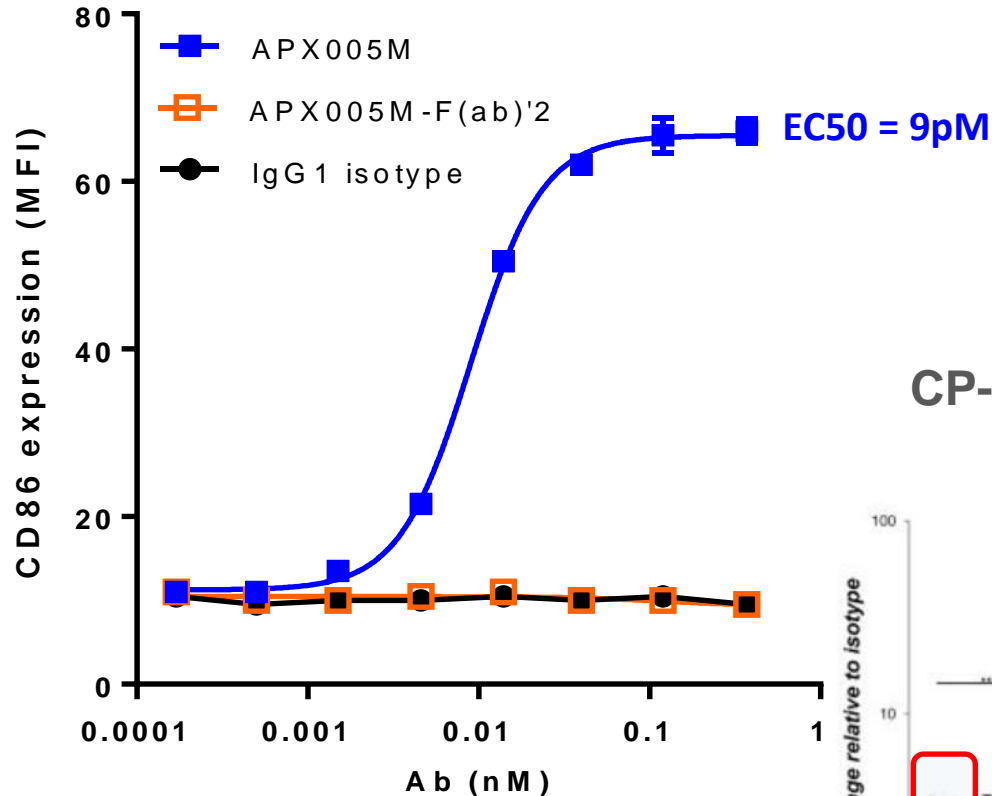
APX005M is more potent than CP-870,893, ADC-1013 and SGN-40 in activating human DCs

Mangsbo et al  
Clin Cancer Res 2014; 21:1115.  
ADC-1013 potency

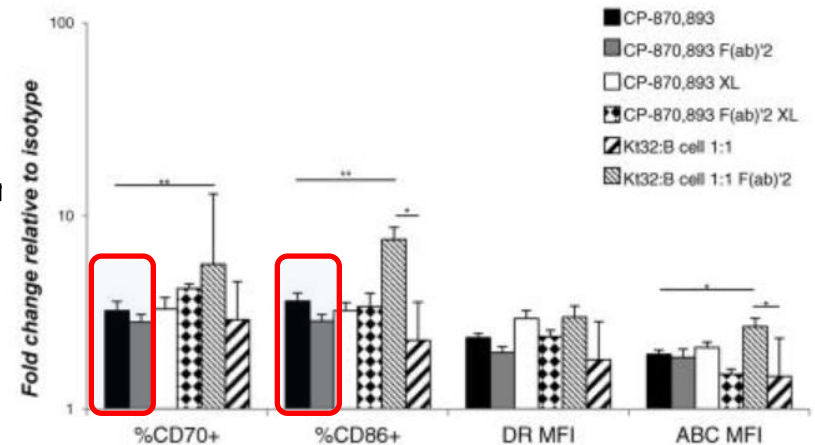


# APX005M Activates CD40 Signaling Pathway Through Fc $\gamma$ R Crosslinking

APX005M F(ab)'2 has no CD40 agonistic activity

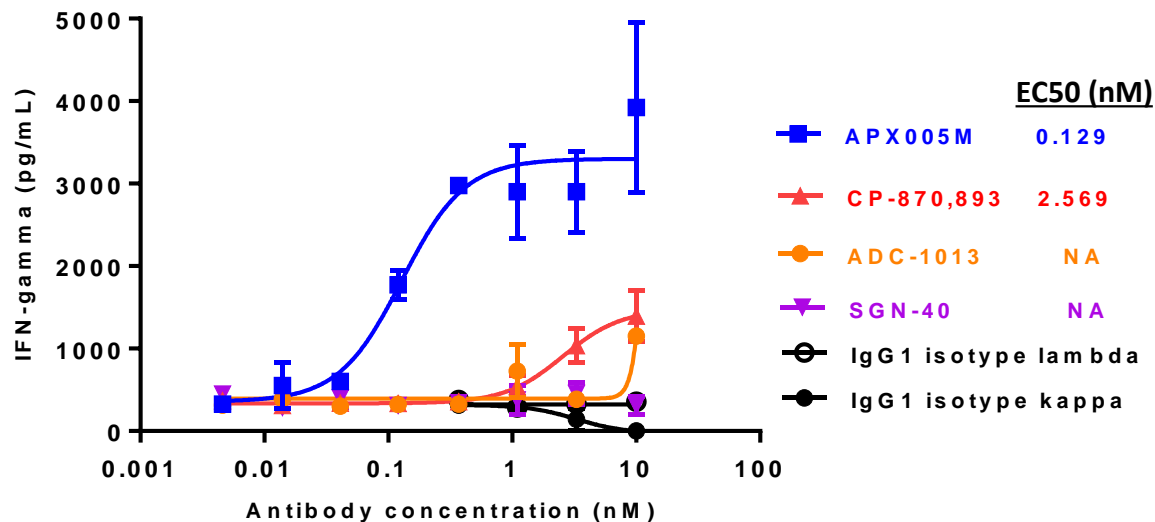
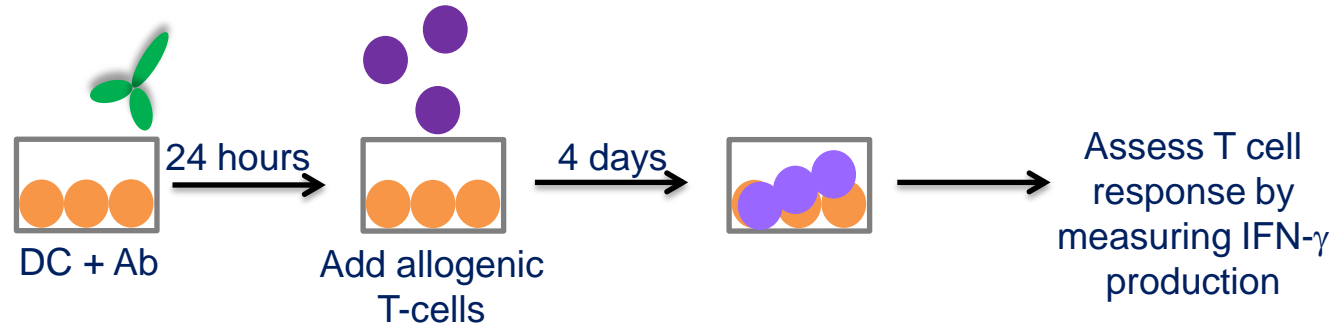


CP-870,893 F(ab)'2 is as active as the intact antibody



Richman & Vondeheide, *Cancer Immunol Res*, 2014

# APX005M Is Stimulating T cell Response in Mixed Lymphocyte Reaction



APX005M is more potent in stimulating T cell response to alloantigens than CP-870,893, ADC-1013 and SGN-40.

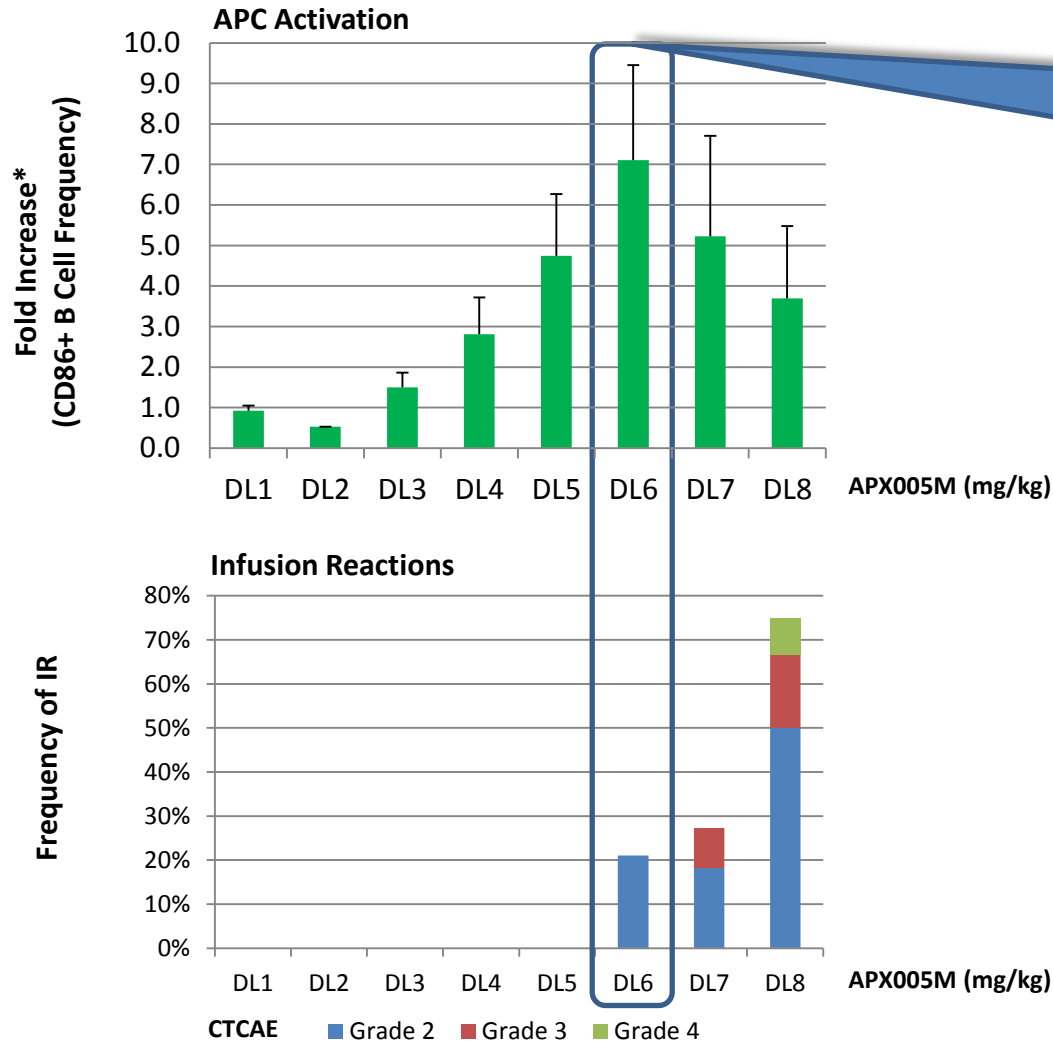
# Clinical Experience

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- APX005M had been administered to 30 adult subjects with solid tumors in a Phase 1 dose-escalation clinical study (every 3 week schedule). The majority of AEs have been mild to moderate in severity, and considered unrelated to APX005M
- Infusion-related reactions including cytokine release syndrome have been reported in 10/30 (33%) of subjects (all grades)
  - one Grade 4 and 3 Grade 3 infusion-related reactions/cytokine release syndrome occurred in subjects receiving highest doses of APX005M
- The most common AEs observed during the first 48 hours following infusion of APX005M include: rigors/chills, fever, flushing, itching, nausea/vomiting, headache, and rash; the majority of these symptoms were mild ( $\leq$  Grade 2) and responded promptly to treatment with antihistamine, antiemetic and antipyretic drugs
- A reversible decrease in peripheral blood lymphocyte counts in general, and B-cell count in particular, have been observed (believed to be a pharmacodynamic effect)
- 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- $\gamma$ , TNF- $\alpha$  and IL-6.



# Single Agent APX005M Recommended Phase 2 Dose for Every 3 Weeks Administration



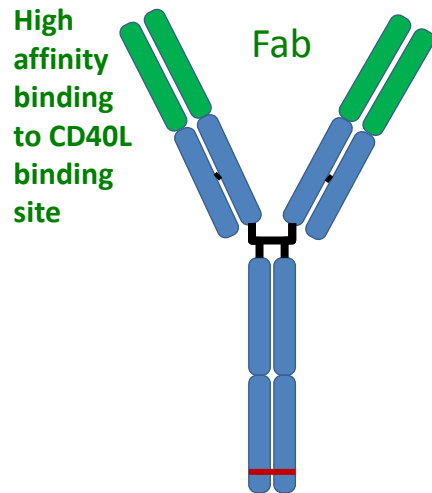
Recommended Phase 2 Dose of APX005M is the dose with maximum pharmacodynamics effect and low grade ( $\leq 2$ ) toxicity

# Development of APX005M in Adults with Cancer

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- Study NCT02482168 (APX005M-001) explores the single agent safety of APX005M administered IV on a every 2 week and every 1 week schedule to subjects with urothelial carcinoma, melanoma, squamous cell carcinoma of the head and neck, NSCLC, or any solid tumor with MSI-high status who failed available therapy
- Study NCT03123783 (APX005M-002) explores the safety and efficacy of APX005M administered IV in combination with nivolumab to subjects with NSCLC or metastatic melanoma
- Study NCT02706353 explores the safety and efficacy of APX005M administered intratumorally in combination with systemic pembrolizumab to subjects with metastatic melanoma
- Study NCT03165994 explores the safety and the effect on tumor immune microenvironment of APX005M administered IV with concurrent chemoradiation for resectable esophageal and gastroesophageal junction cancers
- Additional studies in adult subjects with solid tumors are currently under consideration

# Summary of APX005M Profile



High affinity binding to CD40L binding site

**Fc Mutation**  
-increased binding to FcγRIIb  
-abolished binding to FcγRIIIa

- Humanized IgG1/k mAb against human CD40
  - Binds with high affinity ( $K_d = 1.2 \times 10^{-10}M$ ) to CD40 ligand binding domain on CD40
- Fc mutation
  - Increased binding affinity to FcγIIb receptor
  - Decreased binding affinity to FcγIIIa receptor
- Immune activation
  - Enhanced CD40 agonistic activity via FcR crosslinking
  - Increased T cell response
  - Abolished NK cell mediated ADCC
- Anti-tumor effect
  - Surrogate rat anti-mouse CD40 mAbs showed potent immune activation and anti-tumor efficacy in pre-clinical models as single-agent and in combination therapy
- Better than expected safety profile at doses explored to date
- APX005M induced dose-dependent immune activation in cancer patients

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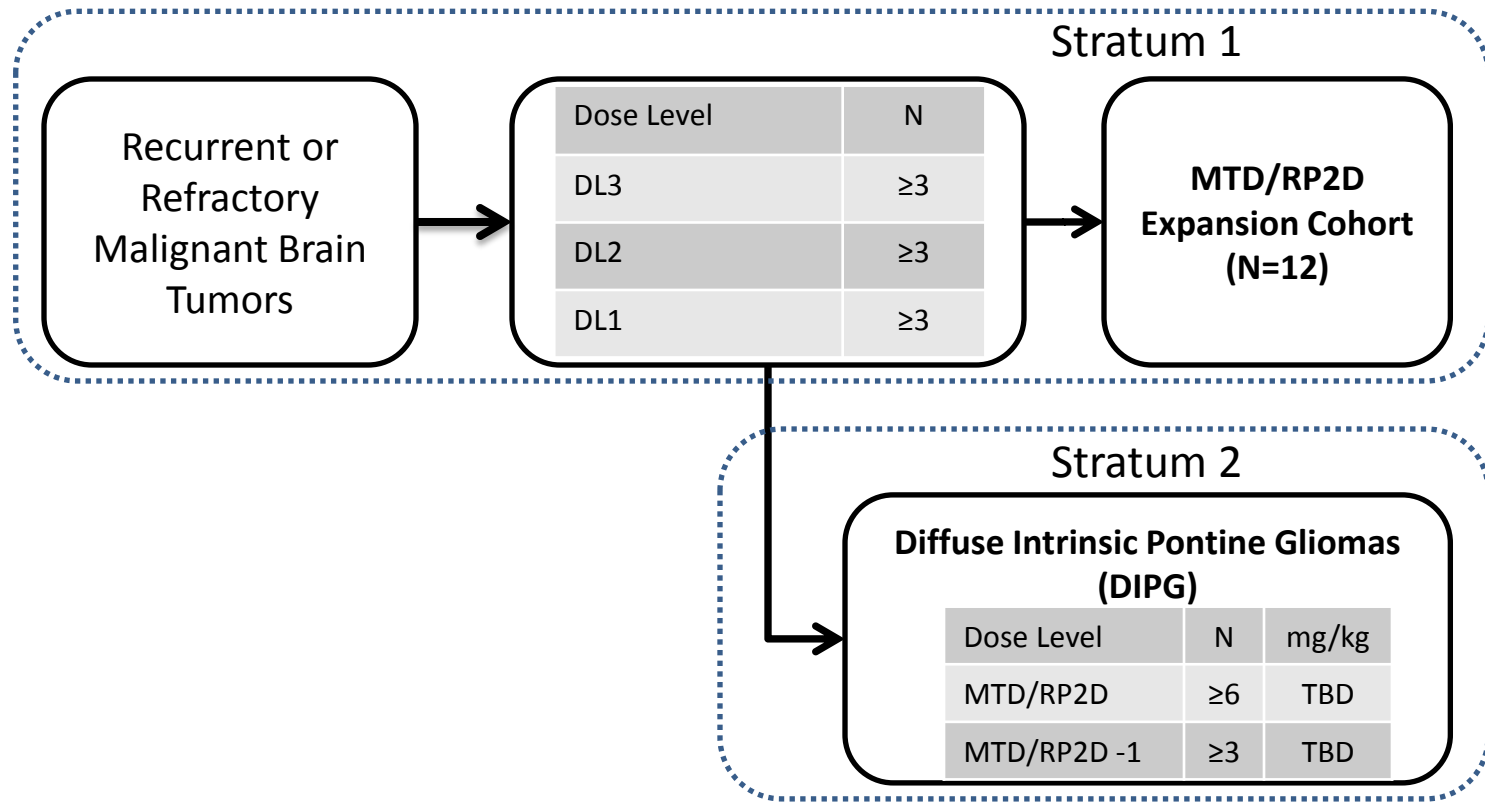
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# Proposed Study in Pediatric Subjects with Brain Tumors

## Study PBTC-051



### 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

# Study Objectives

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## Primary:

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

## 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

# Main Eligibility Criteria

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## Inclusion:

- Age  $\geq 1$  and  $\leq 21$  years at the time of enrollment
- Bi-dimensionally measurable 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 or Lansky Performance Score  $\geq 60$
- Adequate organ function

## Exclusion:

- Any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction)
- History of any other malignancy, except a secondary brain tumor if the first malignancy occurred in the distant past (such as ALL)
- 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

# Confirmatory Study

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- 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 populations solid tumors and/or in combination with other treatment modalities including immunotherapy



# Conclusions

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- CD40 is a promising I-O target
- APX005M:
  - Binds to the CD40L binding site with high affinity
  - Activates CD40 via FcR crosslinking
  - In pre-clinical setting outperforms CP-870,893, ADC-1013 and SGN40
  - Has a good safety profile at doses explored to date
  - Triggers immune activation in clinical setting
- Apexigen is teaming with PBTC to investigate the safety and efficacy of APX005M in pediatric subjects with brain tumors
- Additional confirmatory or combination studies might be considered