Phase I/II Dose Escalation and Expansion Study of Image Guided Intratumoral APX005M in Combination with Systemic Pembrolizumab in Treatment Naive Metastatic Melanoma Patients

Daniel H Johnson[1], Salah Eddine Bentebibel[1], Srisuda Lecagoonporn[1], Chantale Bernatchez[1], Cara Haymaker[1], Ravi Murthi[1], Alda Tam[1], Marc Uemura[1], Cassian Yee[1], Rodabe Amaria[1], Sapna Patel[1], Hussein Tawbi[1], Isabella Glitza[1], Michael A. Davies[1], Michael K. Wong[1], Wen-Jen Hwu[1], Patrick Hwu[1], Willem Overwijk[1], Adi Diab[1]

1 The University of Texas MD Anderson Cancer Center, Houston, TX, United States of America

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

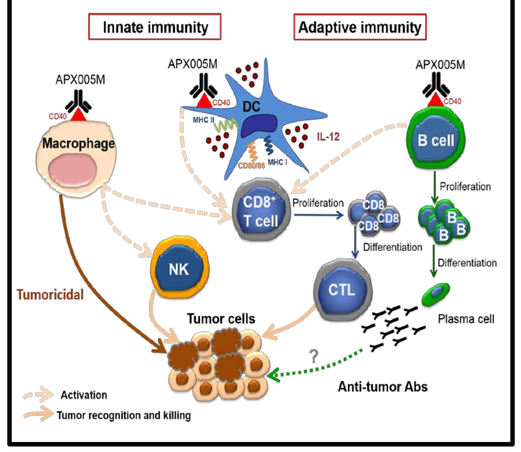
Making Cancer History®

BACKGROUND

- Checkpoint blockade (CPI) has become a major modality in the treatment of metastatic melanoma (MM).
- However, long-term survival and durable remission rates remain low.

- CD40 activation on antigen presenting cells (APCs) initiates priming of tumor specific CD8+ T cells by upregulation of:
  1. Co-stimulatory molecules (CD80, CD86, CD70, 4-1BBL, OX40L)
  2. Expression of effector cytokines (IL-12) [1]
- Furthermore, CD40 activation enhances tumoricidal effects of macrophages and other cells of the innate immune system [2].

Figure.1 APX005 Mechanism of Action



APX005M

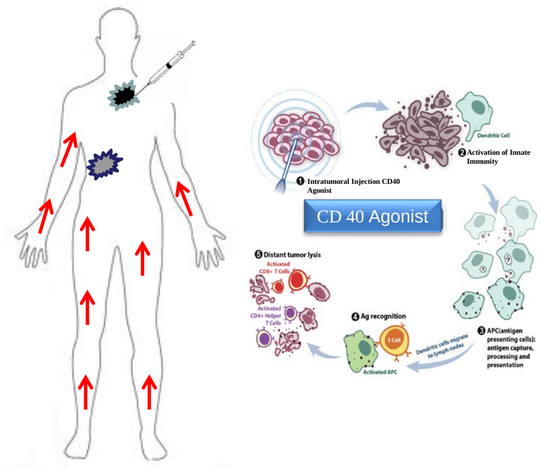
- APX005M is a novel, potent IgG1 CD40 agonistic monoclonal antibody (mAb) that activates B-cells, monocytes, and dendritic cells **(Figure 1).**

Tumor as "Vaccine Site"

- Ligation of the CD40 receptor on antigen presenting cells (APCs) is important for activation of tumor-specific T-cells [3].

- Intratumoral (IT) injection of a CD40 agonist activates innate immunity and may "immunize" patients against their own unique mutated tumor antigens **(Figure 2)**.

- IT administration of a recombinant adenovirus encoding CD40L in mice induces T-cell-mediated **systemic** activity against B16 melanoma. Importantly, IT rAdCD40L also augmented the activity of anti-PD-1 [4]



- We hypothesize IT APX005M can synergize with systemic PD-1 blockade resulting in superior anti-melanoma activity.

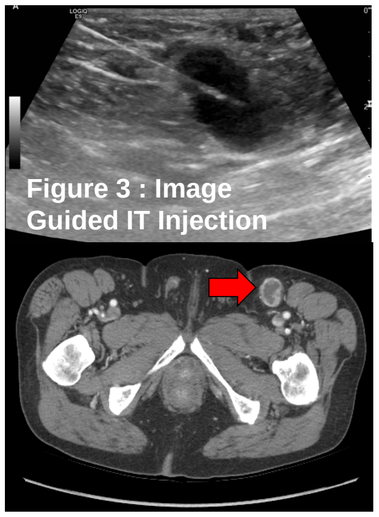


Image Guided Intratumoral Injections

- Injectable lesions: cutaneous, SC, nodal, or visceral tumors ≥ 10 mm amenable for direct injection or US vs CT guidance **(Figure 2)**.

- Same tumor site for each of 4 IT injections of APX005M.

- Volume of injection dependent on tumor size.

INTRATUMORAL APX005M WITH PEMBROLIZUMAB

Study Objectives

Primary Objectives

- Safety and Tolerability
- Define the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) [Figure 3]
- Assess objective response rate (ORR) at 12 weeks based on RECIST 1.1 at RP2D.

Secondary Objectives

- Quantify tumor infiltrated CD8+ T-cells pre/post IT APX005M + IV pembrolizumab both in injected and non-injected tumors

Exploratory Objectives

- Associations between biomarker measures and anti-tumor activity
- Overall survival and Progression Free Survival at 1 year and 2 years.

Eligibility

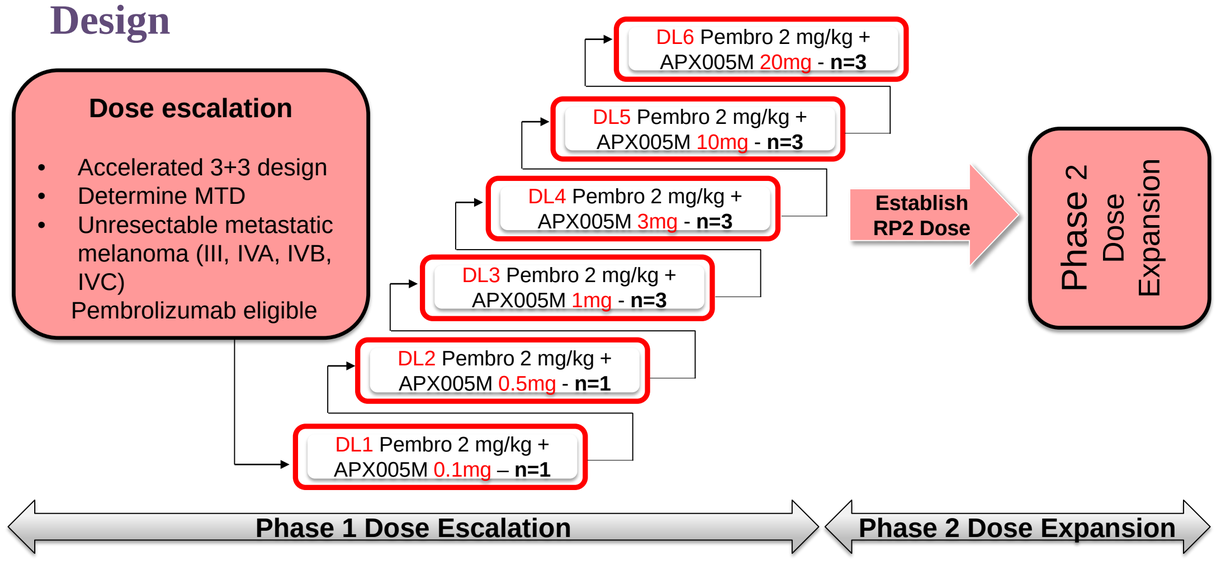
Key Inclusion Criteria

- Histologically or cytologically confirmed cutaneous or mucosal melanoma (i.e., ocular melanoma subjects are not eligible)
- Measurable, unresectable stage III or IV disease.
- At least 2 injectable melanoma lesions (amenable for direct injection or through the use of image guidance such ultrasound [US], CT or MRI) ≥ 10 mm in longest diameter.
- ECOG performance status of 0 or 1

Key Exclusion Criteria

- Prior CPI therapy, anti-CD40, IT oncolytic therapy or TLR agonist.
- Uveal melanoma
- Active autoimmune disease requiring disease-modifying therapy
- Concurrent systemic steroid therapy (> 7.5 mg prednisone or equivalent)
- Patients with untreated symptomatic brain metastases
- Active immunodeficiency

Design



Status

- 10 patients have been enrolled in the dose escalation phase currently at DL5
- Dose escalation continues to enroll

Acknowledgements

This study is partially funded by the American Society for Clinical Oncology Conquer Cancer Foundation and the Melanoma Research Alliance.

References

1. Summers deLuca L, Gommerman JL: Fine-tuning of dendritic cell biology by the TNF superfamily. Nature reviews Immunology 2012, 12(5):339-351.
2. Khong A, Nelson DJ, Nowak AK, Lake RA, Robinson BW: The use of agonistic anti-CD40 therapy in treatments for cancer. International reviews of immunology 2012, 31(4):246-266
3. Sotomayor EM, Borrello I, Tubb E, Rattis FM, Bien H, Lu Z, Fein S, Schoenberger S, Levitsky HI: Conversion of tumor-specific CD4+ T-cell tolerance to T-cell priming through in vivo ligation of CD40. Nature medicine 1999, 5(7):780-787.
4. Singh, M., Vianden, C., Diab, A., Hwu, P., & Overwijk, W. W. (2016). Abstract LB-096: Induction of systemic immunity through single-site intratumoral CD40 activation and checkpoint blockade eradicates melanoma in the brain.