Integrated biomarker trials of VX15/2503 (pepinemab) in combination with checkpoint inhibitors in window of opportunity studies in solid tumors

*Winship Cancer Institute of Emory University (Atlanta, GA) and **VaccineX, Inc. (Rochester, NY)

Abstract

Interrogation of the human immunome in solid tumors to gain insight into immune contexture and develop rational combination strategies is key for successful clinical translation of immunotherapy. VX15/2503 (pepinemab) is a novel bivalent protein that engages SEMA4D-αPD-1/2 signaling and has demonstrated clinical efficacy for treatment resistant solid tumors. A number of preclinical and clinical studies have established a broad role for SEMA4D in immune modulation, and have demonstrated clinical efficacy for treatment resistant solid tumors. VX15/2503 (pepinemab) is designed to engage both αPD-1 and αPD-2, increase PD-1 expression, and synergize with various immunotherapies, including checkpoint inhibitors (PD-1, PD-L1), cancer vaccines, and CAR-T cell therapy. This biomarker analysis is designed to investigate novel combinations of pepinemab with anti-PD-1 and anti-CTLA-4 agents and among intraregional (RMP) treatment arms in an ongoing clinical trial (NCT03690986) for head and neck squamous cell carcinoma (HNSCC). Herein, we describe a novel combination strategy to engage both αPD-1 and αPD-2, and evaluate its ability to increase PD-1 expression and enhance tumor regression with anti-PD-1 agents.

Biomarker Analysis of Clinical Samples: Distribution of T cells and MDCS

The key biomarkers to determine distribution of T cells and MDCS. Schematic overview of biomarker analysis in combination with clinical samples. FACS analysis of clinical samples to investigate novel combinations of pepinemab with anti-PD-1 and anti-CTLA-4 agents and among intraregional (RMP) treatment arms in an ongoing clinical trial (NCT03690986) for head and neck squamous cell carcinoma (HNSCC). Herein, we describe a novel combination strategy to engage both αPD-1 and αPD-2, and evaluate its ability to increase PD-1 expression and enhance tumor regression with anti-PD-1 agents.

Preliminary Rationale: Immune Checkpoint Combinations

A. Galunisertib anti-PD-1 Combination  
B. MOCD1 HNSCC anti-CTLA-4 Combo  
C. Panimab/Sema4D anti-CTLA-4 Combo

Immuno-oncology effects of Sema4D blockade can enhance other immunotherapies. A) Colon26 (300x300) cells were subcutaneously injected in BALB/c. Mice were treated twice-weekly with DTX (15 mg/kg, i.p., and 1 h.i.p.) alone or Sema4D (25 mg/kg, i.p., and 1 h.i.p.) alone or Sema4D (25 mg/kg, i.p., and 1 h.i.p.) alone or (Sema4D + DTX) (25 mg/kg, i.p., and 1 h.i.p.). B) MOC1 (MOC1 HNSCC) were subcutaneously injected in BALB/c. Tumor mass was assessed 4 days post tumor implantation. C) Colon26 and Panc1 (7894) cell lines were subcutaneously injected in NOD/SCID mice. Tumor mass was assessed 4 days post tumor implantation. D) Galunisertib and/or Pepinemab were administered at doses of 20 mg/kg and/or 20 mg/kg. E) Pepinemab was administered at doses of 20 mg/kg and/or 10 mg/kg. F) Tumors were collected 24 hours after the final dose of Galunisertib.

Visual abstract of the clinical trial. 

Keywords: Immuno-oncology, Sema4D, anti-PD-1, anti-CTLA-4, Pepinemab, Galunisertib, PD-1, CD38, Ki67, MDCS, M1/M2, M1/Cytotoxic, M2/Cytotoxic.

Analysis of subcutaneous tumor sample stained for Ki67, CD11b, and CD11c.