Pilot Integrated Biomarker Study of VX15/2503 in Combination with Ipilimumab and/or Nivolumab in Patients with Resectable Metastatic Melanoma

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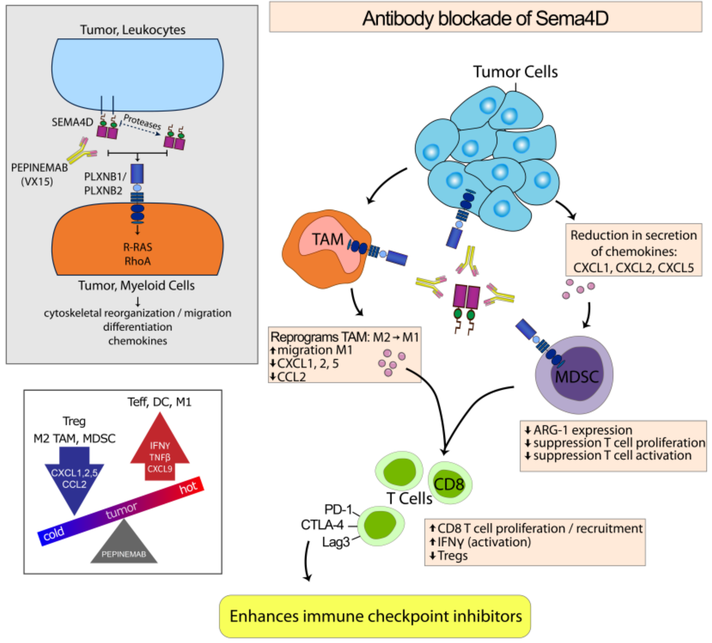
Abstract

Background: Interrogation of the tumor microenvironment (TME) is crucial to provide insight into biological activity, resistance mechanisms and implementation of rational combination immunotherapies. Semaphorin 4D (SEMA4D, CD100) has broad immunomodulatory effects in the TME. In preclinical models, blockade of SEMA4D promoted immune infiltration and reduced recruitment of immunosuppressive myeloid cells. Preclinical combinations of anti-SEMA4D with immune checkpoint inhibitors (ICIs) enhanced T cell activity and tumor regression. VX15/2503 (pepinemab), an IgG4 humanized monoclonal antibody targeting SEMA4D, is being evaluated in an integrated biomarker trial to characterize immunomodulatory effects in melanoma (NCT03769155).

Methods: Patients with biopsy-proven stage IIIB, C, and D melanoma are eligible. Prior to curative-intent surgery, patients receive pepinemab alone or in combination with nivolumab and/or ipilimumab every three weeks for two doses. A control cohort proceed directly to surgery. Resection specimens will be collected for comparison across treatment groups and with a pre-treatment biopsy. Blood will be collected for PK, PD, and correlative biomarker assessments. The primary objective is to evaluate effects on the immune profile in TME and peripheral blood. Additional objectives include safety of pepinemab (alone and in combination with ICI), and pathologic and radiographic responses.

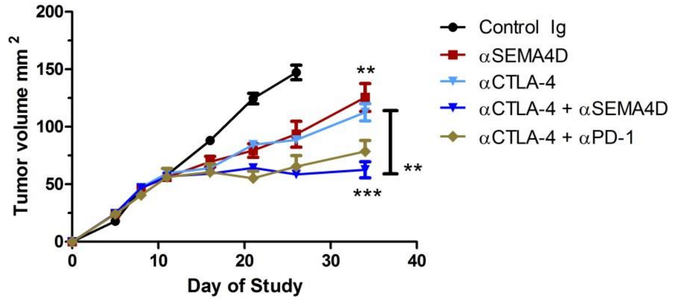
Multiplex flow cytometry panels were created to phenotype cells in the TME and periphery. A multiplex IHC assay utilizing a sequential probe and strip procedure has been qualified that allows co-localization, orientation, and quantification of multiple immune markers. Analysis of immune subsets include cytotoxic T cells, neutrophils, Tregs, DCs, monocytes, macrophages, and myeloid-derived suppressor cells. Target engagement and expression of SEMA4D and its receptors will be evaluated. As of 01 May 2019, 10 of 36 patients have been enrolled. This trial will provide the first biomarker-driven clinical assessment of anti-SEMA4D antibody activity to reprogram the TME.

Preclinical Rationale



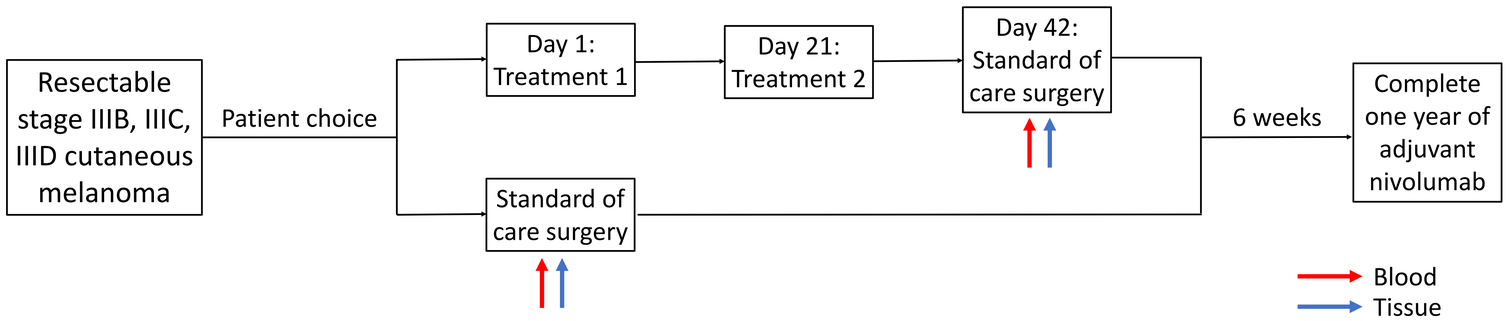
Anti-SEMA4D Mab blocks binding to receptor and signaling activity. SEMA4D blockade inhibits differentiation of MDSC, M2 TAM, and Treg and promotes infiltration of APC and T cells into the tumor microenvironment.

YUMM2.1 Melanoma and aCTLA-4 combination



Immunomodulatory effects of SEMA4D blockade can enhance other immunotherapies; activity of anti-SEMA4D plus anti-CTLA-4 is comparable to combination of anti-PD-1 plus anti-CTLA4. YUMM2.1 melanoma were implanted into C57Bl/6 mice and treated with αSEMA4D/MAb67 (10 mg/kg, weekly IP) 10, αCTLA-4 / MAb UC10-4F10 (5 mg/kg 2x/wk X3 doses), αPD-1 / MAb RMP1-14 (mg/kg 3x/week); n=8.*

Trial Design: window of opportunity, integrated biomarker phase II trial



Cohort	Treatment	Patients
A	VX15/2503 (15mg/kg) Nivolumab 360mg	8
B	VX15/2503 (15mg/kg) Ipilimumab (3mg/kg)	8
C	VX15/2503 (15mg/kg) Nivolumab 360mg Ipilimumab (3mg/kg)	8
D	VX15/2503 (15mg/kg)	8
E	No treatment	6

Enrollment

- Upon signing consent, patients choose to receive two doses of neoadjuvant therapy prior to surgery (cohorts A-D) or to proceed directly to standard of care surgery (cohort E)
- If treatment is chosen, patients are enrolled in sequential cohorts (A through D) in order until each cohort is filled
- To date all patients that have signed consent have chosen to undergo neoadjuvant therapy prior surgery (cohorts A-D)
- Enrollment in cohort A is complete and two patients have enrolled in cohort B

Objectives

- **Primary Objective**:
  - Evaluate the effect of VX15/2503 in combination with checkpoint inhibitors on T cell infiltrate into the tumor microenvironment in lymph nodes and peripheral blood
- **Secondary Objectives**:
  - Assess safety and tolerability of single agent VX15/2503 and the combination of VX15/2503 with checkpoint inhibitors in patients with resectable stage III melanoma
  - Document pathologic response rates of single agent VX15/2503 and the combination of VX15/2503 with checkpoint inhibitors
  - Compare pathologic response to radiographic response using RECIST criteria in patients receiving single agent VX15/2503 and the combination of VX15/2503 with checkpoint inhibitors

Correlative Studies

TIL and PBMC Evaluation by Flow cytometry

- Target (SEMA4D) saturation
- $CD3^+$ $CD4^+/CD8^+$ T cells
- $CD19^+$ B cells
- $CD56^+$ NK-T and NK cells
- $CD3^+$ $CD4^+/CD8^+$ $HLA\text{-}DR^+$ $CD38^+$ $Ki67^+$ stem-like PD-1 responsive T cell population
- PD-1, Tim3 and CD28 expression
- Tregs ($CD3^+$ $CD4^+$ $CD25^+$ $GITR^+$ $CD127^-$)
- SEMA4D, Plexin B1/B2 and PD-L1 expression

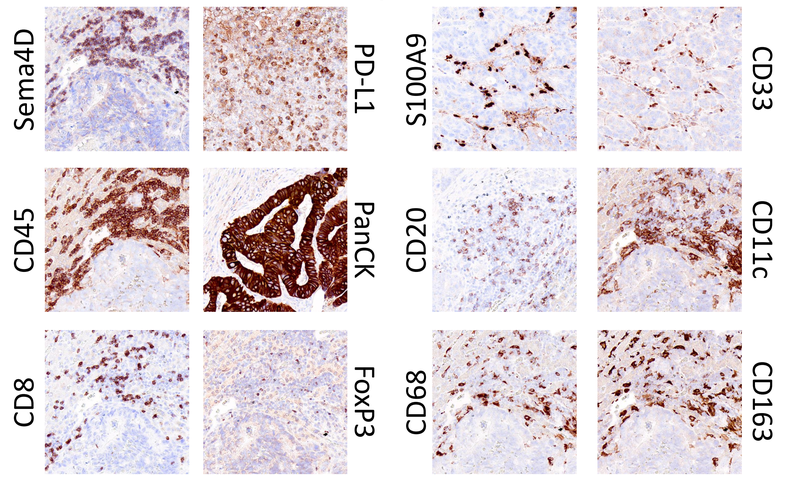
Analysis of T cell receptor diversity and clonality

- Illumina sequencing of the TCRβ gene and ImmunoSEQ analysis

Phenotypic analysis of immunomodulatory cytokines and immune suppressor cell populations

- Serum cytokine and chemokine analysis
- Analysis of effects of VX15/2503 on Th subsets
- *Ex vivo* analysis utilizing ICCS and Ki67 staining following stimulation

Multiplex IHC



Tumor tissue can be assessed for various cell types using sequential serial stains on the same section to allow multiplex IHC and colocalization of markers for various immune cell subsets. This allows for evaluation of spatial and cell-specific expression of SEMA4D and its cognate receptors.

*Work done in collaboration with Vaccinex, Inc., and Toni Ribas and Siwen Hu-Lieskovan, UCLA

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