Pilot integrated biomarker study of VX15/2503 in combination with ipilimumab and/or nivolumab in patients with resectable metastatic melanoma

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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 Feb 2019, 8 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.