Reprogramming myeloid cells in TME with first-in-class Semaphorin 4D Mab enhances combination immunotherapy.


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Abstract

Purpose: Tumor growth inhibition by anti-semaphorin 4D (SEMA4D) antibody enhances antitumor immunity in preclinical models of advanced cancer. In this dose escalation trial, we examined the safety, tolerability, and anti-tumor effects of avelumab (4D Mab), an advanced anti-sema4d antibody, in patients with advanced melanoma or non-small cell lung cancer (NSCLC).

Methods: This was a phase 1 study for subjects with advanced melanoma or NSCLC, who had progressed following immunotherapy. Subjects were stratified into 3 cohorts of 6 subjects each, per NCI Cancer Therapy Evaluation Program dose-finding design, based on avelumab PK/PD, and the dose of ipilimumab. Subjects were treated with avelumab 10 mg/kg or 100 mg/kg, and ipilimumab 3 mg/kg Q3W x 4. Immune effects were assessed through immune infiltration in tumor biopsies, and biomarkers including immune infiltration in tumor biopsies, and biomarkers including immune infiltration in tumor biopsies.

Results: Of 18 patients, 17 were evaluable for safety, tolerability, and anti-tumor effects. Avelumab was well tolerated with only 5 grade 3 or 4 adverse events (AEs) from avelumab-monotherapy, and no significant new safety signals. Consistent with preclinical results, avelumab induced PD-L1 upregulation on tumor-infiltrating leukocytes, and increased TME infiltration with cytotoxic T cells. Anti-SEMA4D reversed MDSC suppression of T cell activity.

Conclusions: Avelumab is safe to administer with ipilimumab, with grade 3 or 4 AEs consistent with the overall safety profile of avelumab. TME infiltration with cytotoxic T cells was consistent with preclinical studies of avelumab + ipilimumab. The addition of avelumab to ipilimumab enhances immunotherapy.

Anti-SEMA4D reverses immune suppression and regulates recruitment of myeloid cells to enhance T cell infiltration and activity within TME

Combination Immunotherapy – Preclinical Models

- **SEMA4D regulates migration and polarization of tumor-associated macrophages
  - SEMA4D decreases expression of M2 polarization markers in tumor-associated macrophages. SEMA4D treatment of M2 macrophage.**

- **Anti-SEMA4D inhibits tumor production of chemokines that recruit MDC and M2 TAMs
  - Anti-SEMA4D reduces expression of CCL2, CCL5, and CXCL1 in tumor cells.**

- **Anti-SEMA4D reverses M2D macrophage suppression of T cell activity
  - Anti-SEMA4D treatment of M2D macrophages restores T cell activity.**

Pepinemab (VX15/2503) Combination with Nivolumab or Ipilimumab in Patients with Advanced Solid Tumors

- **Pepinemab (VX15/2503) in combination with nivolumab or ipilimumab in patients with advanced solid tumors**

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Phase 1 Evaluation of Safety, Tolerability, PK & PD of Intravenous VX15/2503 in Patients With Advanced Solid Tumors

- **A Phase 1/2 trial of Pepinemab (VX15/2503) in patients with advanced solid tumors**

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