Phase 1 Study of VX15/2503, a humanized IgG4 anti-SEMA4D antibody, in advanced cancer patients (pts)

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Abstract (Number 128851)

Background: Semaphorin 4D (SEMA4D) regulates cellular adhesion, motility and activation of cells of the nervous, vascular and immune systems; it also promotes tumor progression and metastasis. SEMA4D and its receptor plexin B1 are widely expressed in human tumors; the interaction of plexin B1 with MET & ERBB2 leads to SEMA4D-mediated transactivation of these membrane receptor kinases promoting tumor cell migration and invasive growth. The murine progenitor of VX15/2503 suppressed tumor growth in syngeneic and transgenic tumors. No toxicologic effects were noted in studies of VX15/2503 using rats and primates and PK/PD profiles were generally predictive of data from clinical trial subjects.

Methods: A multiple ascending dose trial was initiated in adult pts with advanced refractory solid tumors; pts were administered weekly IV doses of VX15/2503 until progression. Dose levels were 0.3 to 20 mg/kg. Tumors were assessed by RECIST 1.1 after each 8 dose cycle. Biomarkers assessed were SEMA4D, VEGF, HGF, PLGF and MET.

Results: Enrollment has been concluded (n=42 Pts); sex 40.5%M/59.5%F. Mean age (yrs) 64.8; ECOG 0/1/2 are 28.6% /69%/2.4%. No MTD was found. One DLT (grade 3 GGT elevation; 15 mg/kg) was reported in a pancreatic cancer pt with disease progression. As of 12/16/2013 the most frequent treatment-related AE's (n=42 pts) included grade 1/2 nausea (19.0%), arthralgia (11.9%), decreased appetite (11.9%), and fatigue (11.9%); 15 drug unrelated SAE's were reported in 11 pts. No CR/PR were observed. Thirteen of 42 pts at all dose levels exhibited stable disease for at least 8 weeks. Pts with the longest duration of treatment included: 48-55 weeks (colorectal; 9 mg/kg) (breast; 15 mg/kg) (papillary thyroid; 20 mg/kg); these pts had relatively high T or B cell levels. VX15/2503 serum concentrations of ≥ 0.3 µg/mL produced complete T cell SEMA4D saturation. HAHA responses (titer > 100) with possible effects on PK were observed in 4 of 41 pts (10%); in only 1 pt (2%) was an effect of HAHA on PD observed. VX15/2503 half-life was roughly 4-5 days at doses ≥1.0 mg/kg.

Conclusion: VX15/2503 was well tolerated at dose levels up to 20 mg/kg, with 450 doses administered to 42 pts. Future studies will be combination trials in selected tumor types. **ClinicalTrials.gov identifier NCT01313065**

Rationale for Targeting SEMA4D

SEMA4D

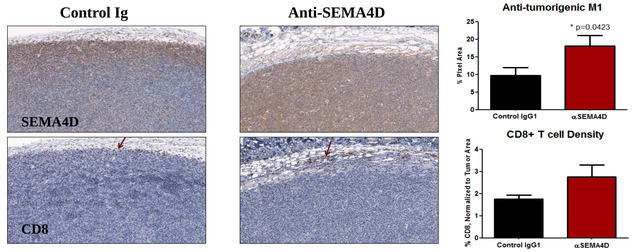
- Expressed on T & B lymphocytes, monocytes and dendritic cells
- Exists as cell-surface homodimer and soluble forms; both are active
- Binds to PLXNB1 (high affinity); PLXNB2 (intermediate affinity); CD72 (low affinity)
- Binding to PLXNB1 transactivates MET and ErbB2, stimulating invasive growth
- SEMA4D overexpressed in human tumors including breast, pancreatic, colon, ovarian, urogenital and sarcoma
- SEMA4D appears to regulate balance and localization of inflammatory M1 and tolerance-inducing M2 macrophages (MΦ) in tumor stroma; stimulates recruitment and activity of cytotoxic CD8+ T lymphocytes into stroma

VX15/2503, a humanized, IgG4 anti-human SEMA4D antibody

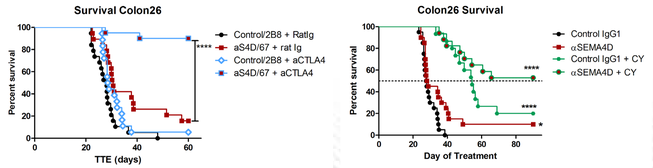
- Neutralizes both cellular and soluble forms of SEMA4D
- Blocks binding of human SEMA4D to its receptors
- Affinity for native human T cell SEMA4D is roughly 0.4 nM (Scatchard)
- Following binding to cellular SEMA4D roughly 60% of the antibody-antigen complex is internalized

Anti-SEMA4D Preclinical Tumor Model Data – MAb 67-1

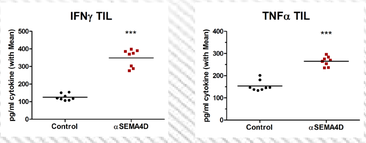
In vivo neutralization of SEMA4D by anti-SEMA4D allowed migration of MΦ and CD8⁺ T cells into tumor



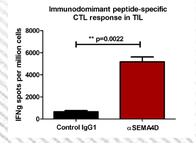
Anti-SEMA4D antibody improves anti-tumor effects of anti-CTLA-4 and cyclophosphamide in Colon26



Cytokine Secretion: CD45+ Tumor Infiltrating Lymphocytes (TIL)



Frequency of Tumor-Specific CD8+ T Cells



VX15/2503 Phase 1 Study Design, Objectives and Eligibility

Study Design:

- Nonrandomized, open-label, multiple dose, dose escalation study in patients with advanced solid tumor disease
- Standard 3 + 3 dose escalation
- Dose levels: 0.3, 1, 3, 6, 9, 15 and 20 mg/kg; weekly IV; expansion cohort (8 patients) treated at 20 mg/kg
- DLT defined as an adverse event during cycle 1 not definitely related to the underlying disease; NCI CTCAE, v4.03

Study Objectives:

- **Primary -** Safety and tolerability of VX15/2503 weekly IV infusion; Determine MTD
- **Secondary -** Evaluate PK
- **Exploratory Objectives**
  - Evaluate PD (T cell SEMA4D; soluble SEMA4D); Immunogenicity
  - Explore anti-tumor activity of IV infusions of VX15/2503
  - Serum VEGF, HGF, PLGF, and MET Levels

Main Inclusion Criteria:

- Adult patients with confirmed advanced tumor disease, relapsed or refractory to SOC
- Measureable disease by RECIST 1.1
- Life expectancy of ≥ 3 months; ECOG score 0-2; Adequate marrow, renal and liver function

Patient Demographics

Patients Treated	**N = 42 (8 in Expansion Cohort)**
Total No Infusions	**459 (Range = 1 to 54)**
Mean Age, Yrs	**64.8**
Gender N (%)	**F: 25 (60%)** **M: 17 (40%)**
Tumor Types (N)	**Colon; Rectal (14)** **Breast (5)** **Pancreatic (4)** **Adenocarcinoma Unknown Origin (4)** **Leiomyosarcoma (4)** **Lung (2)** **Gstroesopageal (1)** **Hepatocellular (1)** **Intrahepatic Cholangiocarcinoma (1)** **Ovarian (1)** **Prostate (1)** **Thyroid (1)** **Transitional Cell Ureter (1)** **PNET (1)** **Endometrial Stromal Sarcoma (1)**

Safety – VX15/2503

- **1 DLT:** Gr3 GGT elevation in a patient with pancreatic cancer concomitant with progressive disease in Cohort 6 (15mg/kg; 3 doses); exited study after completing F/U
- **7 deaths** in Safety Population; all due to disease progression
- **15 SAEs** in 12 patients, all assessed as UNRELATED to study drug
- **342 Treatment-Emergent AE's –** no apparent trends observed
- **TEAEs by CTCAE Grade:** 89% Grade 1/2; 9% Grade 3/4; 1.5% Grade 5
- **Discontinuations -** Six patients stopped treatment due to AE; Cohorts: 1 (1 pt); 6 (1 pt); 7/8 (4 pts)

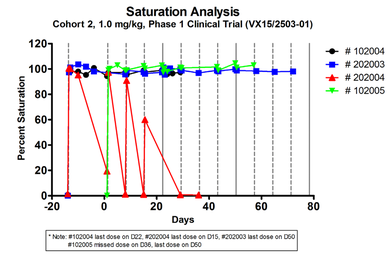
Frequency of Treatment-Related AE's Reported in Two or more Pts

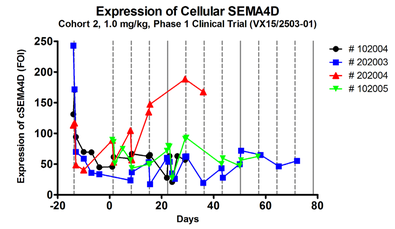
Adverse Event	0.3 mg/kg N= 4	1.0 mg/kg N= 4	3.0 mg/kg N= 3	6.0 mg/kg N= 4	9.0 mg/kg N= 4	15.0 mg/kg N= 8	20.0 mg/kg N=15	Total N = 42
Nausea				1 (25%)	1 (25%)		4 (26.7%)	6 (14.3%)
Fatigue	1 (25%)			1 (25%)	1 (25%)		2 (13.3%)	5 (11.9%)
Arthralgia					1 (25%)	2 (25%)		3 (7.1%)
Decreased Appetite		1 (25%)	1 (33.3%)			1 (12.5%)		3 (7.1%)
Infusion Related Reaction		1 (25%)				1 (12.5%)	1 (6.7%)	3 (7.1%)
Pyrexia				1 (25%)			2 (13.3%)	3 (7.1%)

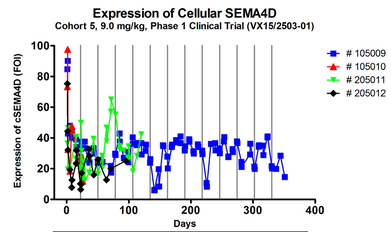
Pharmacokinetic/Pharmacodynamic Data – VX15/2503

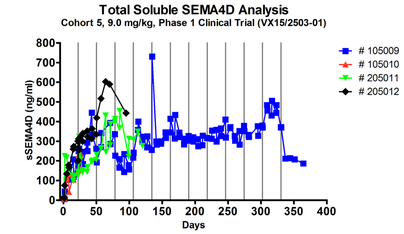
- VX15/2503 half-life was roughly 4 days from 1 mg/kg dose level through 20 mg/kg
- C_{max} increased with dose level from 3 µg/mL at 0.3 mg/kg to 286 µg/mL at 15 mg/kg; C_{max} at 20 mg/kg was similar to that at 15 mg/kg
- $AUC_{0-\infty}$ ranged from 123 µg/mL· Hr at 0.3 mg/kg to 20,507 µg/mL· Hr at 15 mg/kg; AUC at 20 mg/kg was similar

NB: Values from non-compartmental analysis of data from first dose; only a limited sampling of patients in each dose cohort occurred

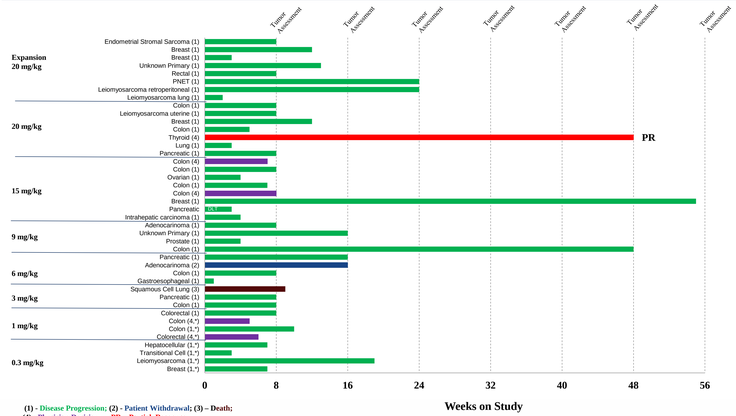








Patient Time on Study Profile – VX15/2503



(1) - Disease Progression; (2) - Patient Withdrawal; (3) – Death;
(4) - Physician Decision; PR – Partial Response
* includes sentinel dose,

Conclusions – VX15/2503

- **VX15/2503 was well tolerated when administered as a weekly infusion at doses up to and including 20 mg/kg; no MTD was determined**
- **459 doses administered to 42 patients; one DLT occurred at 15 mg/kg**
- **Immunogenicity reduced exposure in some patients, primarily at dose levels of 3 mg/kg and below**
- **Five patients (Cohorts 4 – 7) with SD for ≥ 15 weeks had relatively elevated T or B cell levels at enrollment**
- **Best overall response: 1 PR; 1.5 cm hilar LN decreased to 0.8 cm; cycle 2 through EOT; papillary thyroid; cohort 7 (20 mg/kg) (ORR 2.4%)**
- **Future trials of VX15/2503 will be combination studies in selected tumor types**