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


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 belong to the EPH/plexin superfamily of transmembrane receptors; these membrane receptor kinases promote 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-PF profiles were generally predictable from data of clinical trial subjects.

Methods: A multiple ascending dose trial was initiated in pts with advanced refractory solid tumors; pts were administered weekly IV doses of VX15/2503 until progression. Dose levels ranged from 0.3 to 20 mg/kg. Tumors were assessed by RECIST 1.1 after each cycle of therapy. No MTD was found. One DLT (grade 3 GGT elevation; 15 mg/kg) was reported in a pancreatic cancer pt with disease progression.

Results: 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.

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.

Pharmacokinetic/Pharmacodynamic Data – VX15/2503

- VX15/2503 half-life was roughly 4 days from 0.3 mg/kg dose through 20 mg/kg
- Cmax increased with dose level from 0.3 µg/mL to 282 µg/mL at 15 mg/kg, Cmax at 20 mg/kg was similar to that at 15 mg/kg
- AUC12h ranged from 12 µg*h to 15 µg*h at 15 mg/kg
- PK at 20 mg/kg was similar

VX15/2503 Phase 1 Study Design, Objectives and Eligibility

Study Design:
- Traditional, open-label, multiple dose, dose escalation study in patients with advanced solid tumor disease
- Standard 3 + 3 dose escalation
- 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 plexin D1 cell SEMA4D: soluble SEMA4D, Immunogenicity
- Explore antitumor activity of IV infusions of VX15/2503
- Safety VEGF, HGF, Flt-3, and MET

Main Inclusion Criteria:
- Adults patients with confirmed advanced tumor disease, relapsed or refractory to SOC
- Adult patients with solid tumors not amenable to surgical resection
- No prior anti-angiogenesis therapy; no prior chemotherapy
- ECOG 0/1/2 are 28.6% /69%/2.4%
- Sex 40.5%M/59.5%F
- Mean age (yrs) 64.8
- Normal liver function: ALT, AST ≤ 2.5 x ULN or ≤ 1.5 x ULN

Patient Demographics

<table>
<thead>
<tr>
<th>Tumor Types</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Colorectal (14)</td>
<td>33.3</td>
</tr>
<tr>
<td>Breast (5)</td>
<td>11.9</td>
</tr>
<tr>
<td>Pancreatic (1)</td>
<td>2.4</td>
</tr>
<tr>
<td>Other (9)</td>
<td>21.4</td>
</tr>
<tr>
<td>Total</td>
<td>42 (100)</td>
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Safety – VX15/2503

- 1 DLT (grade 3 GGT elevation; 15 mg/kg) in a pancreatic cancer pt with disease progression
- No MTD was found
- Safety profile was predictable
- Exposure to VX15/2503 at doses ≥ 0.3 µg/mL produced complete T cell SEMA4D saturation
- HAHA responses (titer > 100) with doses ≥ 0.3 µg/mL produced complete T cell SEMA4D saturation
- VX15/2503 half-life was roughly 4 days at doses ≥ 0.3 µg/mL

Conclusions – VX15/2503

- VX15/2503 was well tolerated when administered as a weekly infusion at doses up to and including 20 mg/kg; MTD was determined
- 459 (Range = 1 to 54)
- 89% Grade 1/2; 9% Grade 3/4; 1.5% Grade 5
- No apparent trends observed
- 15 SAEs
- TEAEs by CTCAE Grade:
  - Grade 1/2: 81.5%
  - Grade 3/4: 13.8%
  - Grade 5: 4.7%
- No toxicologic effects were noted in studies of VX15/2503 using rats and primates and PK-PF profiles were generally predictable from data of clinical trial subjects.