Phase 1 Study of VGX-100, an anti-VEGF-C monoclonal antibody, with or without Bevacizumab in Patients with Advanced Solid Tumors

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INTRODUCTION / BACKGROUND

- VGX-100 is an investigational, novel fully human IgG1k neutralizing monoclonal antibody that selectively targets vascular endothelial growth factor C (VEGF-C), inhibiting its signaling through VEGF-R2 and VEGF-R3 receptor pathways.
- VGX-100 has the potential to inhibit not only primary tumor growth through its anti-angiogenic and anti-lymphangiogenic activities, but also to inhibit metastasis via the lymphatic vessels. Lymphatic metastasis is associated with poor prognosis that is not effectively blocked by anti-VEGF-A or anti-VEGF-R2 therapeutics.

Over-expression of VEGF-C has been shown in human tumors, including cancers of the colon, stomach, breast, ovary and prostate. Elevated levels of intra-tumor and circulating VEGF-C often correlate with poor outcomes and features associated with tumor aggression (e.g. tumor depth, size, lymphatic invasion and lymph node metastasis).

Tumoral escape and relapse following VEGF-A inhibition with bevacizumab (a humanized monoclonal antibody that binds to and inhibits the biologic activity of human VEGF-A), may in part be due to increased VEGF-C that signals through VEGF-R2 and VEGF-R3.

Primary objectives:
- To evaluate the safety and establish the recommended dose of VGX-100 alone and in combination with bevacizumab.

Secondary objectives:
- To assess:
  - The pharmacokinetic profile of VGX-100 alone and co-administered with bevacizumab
  - The incidence of anti-VGX-100 antibody formation
  - Potential biomarkers of VGX-100 alone and co-administered with bevacizumab
  - Preliminary tumor response to VGX-100 alone and co-administered with bevacizumab

Efficacy of VGX-100 alone or in combination with anti-angiogenic agents / chemotherapy in murine models of cancer

- The combination of VGX-100 with bevacizumab may result in synergistic antitumor effects by targeting multiple VEGF signaling pathways that mediate tumor angiogenesis and lymphangiogenesis.

- Here we describe the ongoing first-in-human, Phase 1 clinical study design of the anti-VEGF-C human monoclonal antibody VGX-100 administered alone and in combination with bevacizumab in adult patients with advanced or metastatic solid tumors.

ENDPOINTS

Primary endpoint:
- Safety will be assessed by incidence and severity of adverse events (including DLTs) and clinically significant changes in vital signs, EKGs and clinical lab tests.

The recommended dose of VGX-100 alone and in combination with bevacizumab will be determined by the observed safety profile and incidence of DLTs during the 28-day DLT period from Arm A and Arm B, respectively.

Secondary endpoints:
- Serum concentrations of VGX-100 and bevacizumab including Cmax, Cmin, AUC, and half-life (t1/2).
- The development of serum anti-VEGF-100 antibodies
- Selected biomarkers including VEGF-A, VEGF-C, VEGF-D, sVEGFR-2, and sVEGFR-3, will be determined from serum and other tissue samples.
- Tumor response measured by CT or MRI and using RECIST 1.1 criteria.

PHASE 1 STUDY DESIGN

- Ongoing, open label, phase 1a / 1b dose escalation study.

- Study design with a standard 3+3 design.

- The study has an accelerated two arm design:
  - Arm A: VGX-100 monotherapy
  - Arm B: VGX-100 in combination with bevacizumab

- Dose escalation occurs if none of the initial 3 patients enrolled experience dose limiting toxicities (DLTs) per protocol definition during the first 28 days of the study.

- 28 day DLT safety period from Arm A will be available prior to starting the equivalent dose level in Arm B.

- Arm A (VGX-100 mono-therapy): 28 day treatment cycle of 4 administrations of VGX-100 by iv infusion at D1, D8, D15 and D22.

- Arm B (VGX-100 plus bevacizumab):
  - At each administration, treatment with bevacizumab will be administered first, followed by VGX-100.
  - For each subject, the 28 day treatment cycle will consist of:
    - Two administrations of bevacizumab, iv infusion at D1 and D15.
    - Four administrations of VGX-100, given as an iv infusion over approximately 60 minutes 7 days apart at D1, D8, D15 and D22.

- Patients received treatment until disease progression or intolerable toxicity.

- The safety follow-up period was 28 days after the last dose.

Key Eligibility Criteria:
- Adult (<18 years) patients with advanced solid tumors refractory to standard treatment or for which no curative therapy is available.
- Adequate hematologic, renal and hepatic function.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 and life expectancy >3 months.
- Evaluable or progressive disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.

- Patients are excluded with central nervous system or cerebrovascular haemorrhage, myocardial infarction or reversible posterior leucoencephalopathy syndrome associated with prior anti-VEGF-A/VEGF-B therapy.

SUMMARY

- Cohorts A1 to A5 of VGX-100 at weekly doses up to 20 mg/kg have completed accrual without any DLTs. In addition, cohorts B1 to B4 of VGX-100 at weekly doses of 2.5, 5 or 10 mg/kg in combination with bevacizumab given every 2 weeks at doses of 5 or 10 mg/kg have completed with 2 DLT observed in cohort B1B.
- The combination of inhibiting the VEGF-A and VEGF-C signaling pathways with VGX-100 + bevacizumab appears promising.
- Patient accrual for remaining cohorts A6 and B5 is near completion and further evaluation of VGX-100 alone or in combination with bevacizumab is ongoing.

References