**A First-in-Man Phase 1a Study of the Bispecific Anti-DLL4/Anti-VEGF Antibody OMP-305B83 in Patients with Previously Treated Solid Tumors**

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**Background**

Inhibition of tumor angiogenesis has proven to be a successful approach to treating cancer and the two major ligands responsible for tumor angiogenesis are vascular endothelial growth factor (VEGF) and delta-like ligand 4 (DLL4) which is one of the 5 ligands in the notch pathway. In addition, there is accumulating evidence from xenograft models that inhibition of DLL4 reduces the hemorrhage is a tumor by reducing the number of tumor infiltrating cells or cancer stem cells. OMP-305B83 is an IgG2a, humanized bispecific monoclonal antibody directed against both human DLL4 and VEGF. OMP-305B83 was confluently designed such that DLL4 binding is not compromised by VEGF ligand binding; VEGF ligand binding is not compromised by DLL4 ligand binding. Thus, the bispecific antibody should block upregulation of both ligands at a fixed dose. OMP-305B83 was efficacious in xenograft models tested which included human breast, colon, gastric, glioblastoma, melanoma, small lung cancer, pancreatic, ovarian and melanoma cell carcinomas. In addition, inhibition of angiogenesis was documented in the xenograft models as well as a reduction in the frequency of CSCs by limiting axon growth.

**Nonclinical Xenograft Data**

- Efficacious in 11/11 PDX tumor models tested (breast, colon, gastric, glioblastoma, non-small cell lung cancer, pancreatic, ovarian, renal)
- Reduces tumor growth and CSC frequency

**Pharmacokinetics/ Immunogenicity**

- Terminal half life of 3.5 h ranging was 14 days
- Dose level
  - Colonel Cancer
  - Ovarian Cancer
- Representation Xenograft Results

**Dose Limiting Toxicities**

- Related AEs >10% Pts (n=51) All Grades by Dose Level (mg/kg)
- % Change in RECIST Target Lesion Size All Patients
- % Change in RECIST Target Lesion Size Ovarian Cancer

**Toxicities of Interest (N=51)**

- Diarrhea
- Dyspnea
- Nausea
- Rash
- Anemia
- Platelet
- Neutropenia

**Duration On Study Patients**

- Ovarian Cancer
- Colorectal Cancer
- Cervical Cancer

**Duration On Study Ovarian Cancer**

- Ovarian Cancer

**Summary**

- This was a Phase 1 dose escalation study of OMP-305B83, a bispecific monoclonal antibody (targeting DLL4 and VEGF) in the notch pathway and VEGF, in patients with previously treated solid tumors.
- OMP-305B83 had a half-life of 14 days. Anti-OMP-305B83 which peaked PI in some patients was observed at the lowest dose levels, but was only obtained in 1 patient receiving a dose of 3.5 mg/kg once every 3 weeks.
- One patient receiving 2.5 mg/kg had a DLT of diverticulitis requiring a partial colectomy. No other DLTs were observed, but chronic toxicity (pulmonary hypertension, proteinuria and a case of reversible posterior leukoencephalopathy syndrome that occurred after the dose cut 1.5 mg/kg at 10 mg/kg resulted in a faster expansion cohort which was ongoing at 7.5 mg/kg once every 3 weeks.
- OMP-305B83 was generally well tolerated with hypertension, headache and pulmonary hypertension being the most common drug-related toxicities.
- The hypertension was successfully managed with a protocol defined standard anti-hypertensive treatment algorithm.
- Eight patients developed pulmonary hypertension, five patients had symptomatic Grade 1 pulmonary hypertension, two patients were treated with 2.5 mg/kg and 3.5 mg/kg who developed Grade 2 pulmonary hypertension A 4 patients one patient receiving 0.5 mg/kg and 3 patients receiving Grade 3 pulmonary hypertension. The 2.5 mg/kg patient improved on oral sildenafil, but ultimately had receiving responded to OMP-305B83 alone. Two patients had pulmonary hypertension on Day 200. The 7.5 mg/kg improved on oral sildenafil but was on an expanded cohort that was ongoing at 1121 for pulmonary hypertension.
- Two of the 49 evaluable patients had partial response and 18 had stable disease resulting in clinical benefit rate of 50%. The partial response was noted in a patient with ovarian cancer and colorectal carcinoma.
- Five of 49 evaluable patients had reductions in tumor volume and remained on therapy for >120–320x days. Four of these 5 patients had received bevacizumab.
- Phase 1b studies with OMP-305B83 in ovarian cancer and colorectal cancer are being initiated.