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

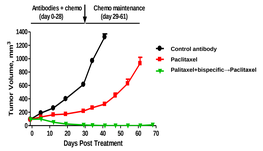
Inhibition of tumor angiogenesis has proven to be a successful approach to treating cancer and the two major ligands responsible for tumor angiogenesis are vascular endothelial growth factor (VEGF) and delta-like ligand 4 (DLL4) which is one of the 5 ligands in the Notch pathway. In addition, there is accumulating evidence from xenograft models that inhibition of DLL4 reduces the tumorigenicity of a tumor by reducing the number of tumor initiating cells or cancer stem cells. OMP-305B83 is an IgG_2 humanized bispecific monoclonal antibody directed against both human DLL4 and VEGF. OMP-305B83 was carefully designed such that the anti-VEGF and anti-DLL4 arms have roughly equivalent affinity for their respective ligands. Thus, the bispecific antibody should block signaling of both ligands at a fixed dose. OMP-305B83 was efficacious in all 11 of the human tumor xengraft models tested which included human breast, colon, gastric, glioblastoma, non-small cell lung cancer, pancreatic, ovarian and renal 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 dilution assays.

Nonclinical Xenograft Data

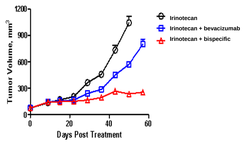
- Efficacious in 11/11 PDX tumor models tested (breast, colon, gastric, glioblastoma, non-small cell lung cancer, pancreatic, ovarian, renal)
- Reduces tumor growth and CSC frequency

Representative Xenograft Results

Ovarian - OV19



Colorectal – C8



Methods

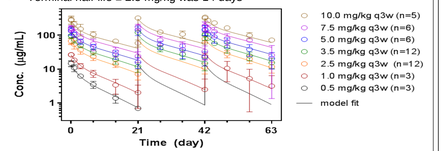
This is an ongoing open-label Phase 1a dose escalation and expansion study of OMP-305B83 in subjects with previously treated solid tumors. To be eligible patients must have no remaining standard curative therapy and no therapy with a demonstrated survival benefit or they must be ineligible to receive such therapy. Fifty-one patients have been enrolled in the dose escalation portion of the study and up to 70 subjects will be treated by the completion of the study at 4 centers. Subjects were assessed for safety, immunogenicity, PK, biomarkers, and efficacy. In the dose escalation portion of the study the dose levels of OMP-305B83 were 0.5, 1.0, 2.5, 3.5, 5, 7.5, 10 and 12.5 mg/kg administered IV once every 3 weeks. Three patients were treated at the 0.5 and 1 mg/kg dose and six subjects were treated at the 2.5, 3.5, 5, 7.5, 10 and 12.5 mg/kg dose levels. If 0 or 1 of 6 subjects in a cohort experienced a DLT, the dose was escalated to the next dose level. If 2 or more subjects experienced a DLT, no further subjects were dosed at that level and 3 additional patients were added to the preceding dose cohort unless 6 subjects had already been treated at that dose level. Patients were assessed for DLTs from the time of the first dose through Day 21. The maximum tolerated dose (MTD) was defined as the highest dose level at which 0–1 of 6 subjects experienced a DLT (i.e., 6 patients will ultimately be treated at the MTD dose level). Following completion of the dose escalation portion of the study, up to 14 patients will be enrolled in an expansion cohort and treated at the MTD or a lower dose. Data through October 17, 2016 are presented.

Patient Demographics (n=51)

Dose Level – mg/kg	0.5 every 3 weeks	1 every 3 weeks	2.5 every 3 weeks	2.5 every 3 weeks	3.5 every 3 weeks	3.5 every 3 weeks	5 every 3 weeks	7.5 every 3 weeks	10 every 3 weeks	12.5 every 3 weeks	Total
N	3	3	6	6	6	6	6	6	6	3	51
Median age (years)	75	59	64.5	53.0	60.5	60.0	43.0	52.5	63.0	61.0	60.0
Male/Female	0/3	0/3	3/3	1/5	2/4	4/2	3/3	2/4	2/4	1/2	18/33
Tumor Type Ovarian Uterine Breast Endometrial Pancreatic Renal Colorectal Other	2 0 0 1 0 0 0 0	0 1 1 0 0 0 0 0	1 0 0 2 0 1 0 2	2 0 1 1 0 0 0 2	0 1 1 0 0 0 1 3	1 1 0 0 0 1 0 3	0 1 0 0 0 0 0 5	1 0 1 0 2 0 0 2	1 0 1 0 0 0 1 3	2 0 0 4 0 0 1 2	10 4 4 4 3 2 2 22
Ongoing/ Discontinued	0/3	0/3	0/6	0/6	1/5	1/5	0/6	1/5	3/3	3/0	9/51

Pharmacokinetics/Immunogenicity

- Linear PK at ≥ 2.5 mg/kg
- Terminal half-life ≥ 2.5 mg/kg was 14 days



Dose Level (mg/kg)	0.5	1.0	2.5	3.5	5.0	7.5	10
Incidence of ADA*	3/3	1/3	6/12	2/12	0/6	0/6	1/4
Incidence of ADA with impact on PK	3/3	0/3	3/12	0/12	0/6	0/6	1**/4

* Frequency greatly reduced at doses > 3.5 mg/kg ** Patient experienced infusion reaction

Dose Limiting Toxicities

Dose Level – mg/kg	0.5 every 3 weeks	1 every 3 weeks	2.5 every 3 weeks	2.5 every 3 weeks	3.5* every 3 weeks	3.5* every 3 weeks	5* every 3 weeks	7.5* every 3 weeks	10* every 3 weeks	12.5 every 3 weeks
N	-	-	1*	-	-	-	-	-	-	-

* Diverticulitis resulting in a perforation which required a partial colectomy

Related AEs >10% Pts (n=51) All Grades by Dose Level (mg/kg)

Dose Level – mg/kg	0.5 every 3 weeks	1 every 3 weeks	2.5 every 3 weeks	2.5 every 3 weeks	3.5* every 3 weeks	3.5* every 3 weeks	5* every 3 weeks	7.5* every 3 weeks	10* every 3 weeks	12.5 every 3 weeks	Total
N	3	3	6	6	6	6	6	6	6	3	51
Hypertension	1	0	4	4	3	5	5	1	4	1	28 (54.9%)
Headache	1	0	1	1	0	3	2	1	4	1	14 (27.5%)
Pulmonary Hypertension	0	1	1	1	1	2	0	1	1	0	8 (15.7%)
Diarrhea	0	0	0	0	2	1	0	2	2	0	7 (13.7%)
Dyspnea	0	0	0	1	2	2	0	1	1	0	7 (13.7%)
Fatigue	1	1	0	1	2	2	0	1	2	0	10 (19.6%)
Anemia	0	1	0	1	2	1	1	0	0	0	6(11.8%)

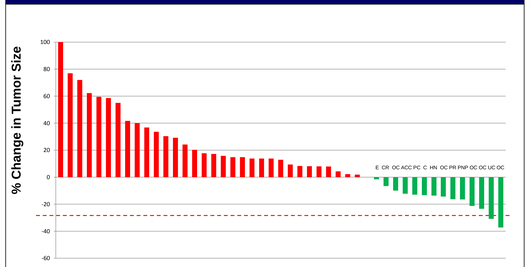
Toxicities of Interest (N=51)

Dose Level – mg/kg	0.5 every 3 weeks	1 every 3 weeks	2.5 every 3 weeks	2.5 every 3 weeks	3.5* every 3 weeks	3.5* every 3 weeks	5* every 3 weeks	7.5* every 3 weeks	10* every 3 weeks	12.5 every 3 weeks	Total
N	3	3	6	6	6	6	6	6	6	3	51
Pulmonary HTN (Reversible)	-	1 (G1)	1 (Gr1)	1 (Gr 2)	1 (Gr 1)	2 (Gr 1)	-	1 (Gr2)	1 (G3)	-	**8**
Heart failure (Reversible)	-	-	-	-	-	-	-	-	-	-	-
Proteinuria								1 (Gr 1)	2 (Gr 2)	-	**3**

RECIST Best Overall Response (n=51)

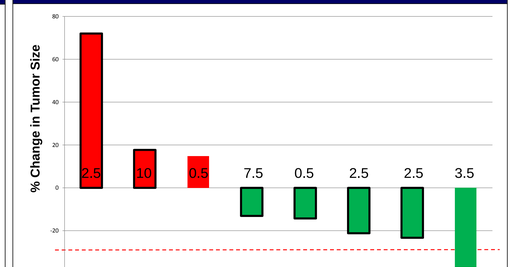
Dose Level – mg/kg	0.5 every 3 weeks	1 every 3 weeks	2.5 every 3 weeks	2.5 every 3 weeks	3.5* every 3 weeks	3.5* every 3 weeks	5* every 3 weeks	7.5* every 3 weeks	10* every 3 weeks	12.5 every 3 weeks	Total
Enrolled/ Evaluable	3/3	3/3	6/6	6/6	6/6	6/6	6/6	6/5	6/5	3/0	51/46
Partial Response	-	-			1	1					**2 (4%)**
Stable Disease	1	-	2	2	1	3	1	2	4	-	**16 (35%)**
Clinical Benefit Rate (PR + SD)	1	-	2	2	2	4	1	2	4	-	**18 (39%)**
Progressive Disease	1	-	2	2	4	2	5	3	1	-	**28 (61%)**
Not Evaluable	-	-	-	-	-	-	-	1	1	3	**5**

% Change in RECIST Target Lesion Size All Patients



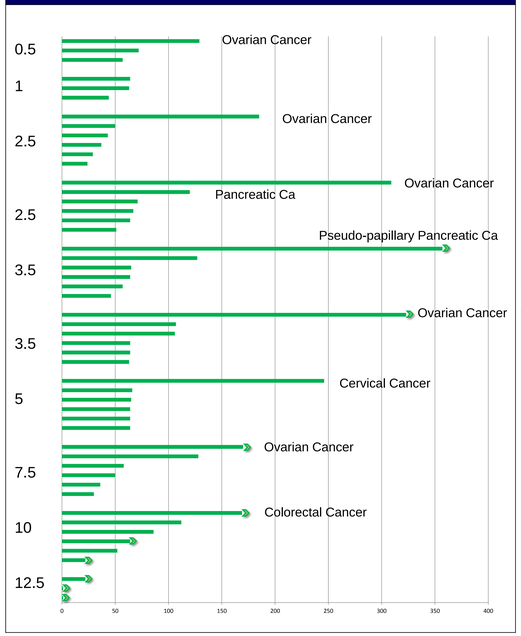
OV – Ovarian, UC = uterine carcinosarcoma, PNP = pseudo papillary neoplasm of the pancreas, PR = prostate, HN = head and neck, C = cervical, PC = pancreatic, ACC = adenocystic carcinoma, CR = colorectal, E = endometrial

% Change in RECIST Target Lesion Size Ovarian Cancer

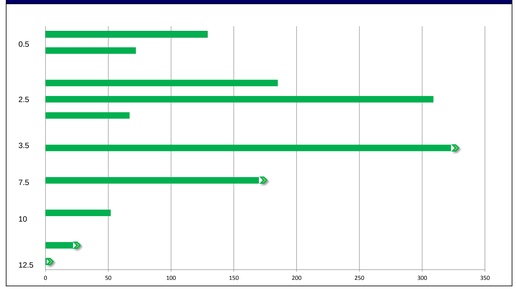


Outlined bar = prior bevacizumab

Duration On Study All Patients



Duration On Study Ovarian Cancer



Outlined bars = prior bevacizumab

Summary

- This was a Phase 1a dose escalation study of OMP-305B83, a bispecific monoclonal antibody (targeting the DLL4 ligand 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 impacted PK in some patients was observed at the lower dose levels, but was only observed in 1 patient receiving a dose > 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 leukoencehalopathy syndrome that occurred after the data cut-off) observed at 10 mg/kg resulted in stopping the dose escalation and initiating the 14 patient expansion cohort which is 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 asymptomatic Grade 1 pulmonary hypertension, two patients receiving 2.5 & 7.5 mg/kg developed Grade 2 pulmonary hypertension & one patient receiving 10 mg/kg developed Grade 3 pulmonary hypertension. The 2.5 mg/kg patient improved on sildenafil, but ultimately had treatment stopped for pulmonary hypertension on Day 309. The 7.5 mg/kg improved on sildenafil & is still on treatment on Day 170 & the 10 mg/kg patient had treatment terminated on Day 112 for pulmonary hypertension.
- Two of the 46 evaluable patients had a partial response & 16 had stable disease resulting in a clinical benefit rate of 39%. The partial responses occurred in patients with ovarian cancer and uterine carcinosarcoma.
- Five of 8 evaluable ovarian patients had reductions in tumor volume and remained on therapy for 129-323+ days. Four of these 5 patients had received prior bevacizumab.
- Phase 1b studies with OMP-305B83 in ovarian cancer and colorectal cancer are being initiated.