#738

A first-in-human phase I study of the novel cancer stem cell (CSC) targeting antibody OMP-52M51 (anti-Notch1) administered intravenously to patients with certain advanced solid tumors

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Abstract

Background: The Notch pathway plays a central role in embryonic development, the regulation of stem and progenitor cells, and is implicated centrally in many forms of human cancer. Notch1 is known to be frequently activated in certain solid tumor types. OMP-52M51 is a humanized IgG2 antibody that inhibits the signaling function of the Notch1 receptor. Mouse xenograft studies using minimally-passaged, patient-derived xenografts have shown that OMP-52M51 impedes tumor growth and selectively eliminates CSCs in a range of tumor types particularly in tumors with activated Notch1 signaling. In these models, anti-Notch1 antibody also has anti-angiogenic effects leading to tumor growth inhibition. As such, OMP-52M51 is a novel anti-cancer agent that inhibits tumor growth through direct actions on tumor cells, including CSCs, and effects on tumor angiogenesis.

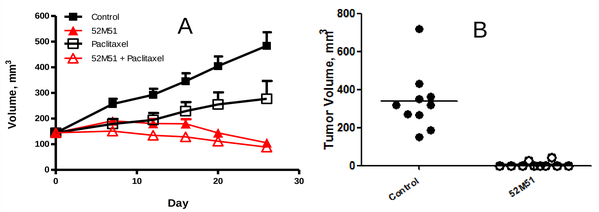
Methods: A phase I dose escalation and expansion study was initiated in patients with certain advanced solid tumor indications (cholangiocarcinoma, breast, colorectal, esophageal, gastric, pancreatic, and small cell lung cancers) that have frequencies of Notch1 activation of 12-29% (AACR 2013; #3728). OMP-52M51 was administered intravenously to study safety, pharmacokinetics (PK), pharmacodynamics (PD), preliminary efficacy, and to determine the maximum tolerated dose (MTD). The trial has a Notch1 IHC biomarker selected expansion cohort to test for single-agent response.

Results: Eleven patients have been enrolled in 4 dose-escalation cohorts at doses of 0.25, 0.5, 1, and 2.5mg/kg administered every 4 weeks (Q4W). The most frequently reported drug-related adverse events were: mild to moderate diarrhea (63%), nausea (27%), fatigue (18%), and rash (18%). One patient developed grade 3 diarrhea for 24 hours controlled with Imodium. One dose-limiting toxicity (DLTs) of grade 3 fatigue has occurred at 2.5mg/kg, and dose escalation continues. The PK of OMP-52M51 is characterized by dose-dependent clearance and the half-life at 2.5mg/kg is about 4 days. Two patient with have had stable disease > 100 days: one with refractory colorectal cancer and one with refractory HER2- breast cancer. Biomarker analyses reveal potential reductions in circulating tumor cells (CTCs) with OMP-52M51 treatment.

Conclusions: OMP-52M51 is generally well tolerated. Diarrhea is the primary toxicity of this antibody and potential biomarker effects on CTC with OMP-52M51 treatment and potential early efficacy is noted. Dose escalation continues and the predictive biomarker hypothesis will be tested in the expansion cohort of this study.

Pre-Clinical Data

Patient-Derived Primary Refractory Triple Negative Breast Cancer (Notch1 Mutation)



A: Anti-Tumor Activity of OMP-52M51 in a Basal, Triple Negative Breast Tumor Xenograft Model, OMP-B40. Mean±SEM, n=10 animals per group.
B: OMP-52M51 decreases tumorigenic potential of OMP-B40 tumors. Following treatment, 1000 tumor cells from each group were serially transplanted into ten mice each for each group and allowed to grow for 92 days without treatment. Tumor volumes in the individual mice on day 92 after cell injection are shown.

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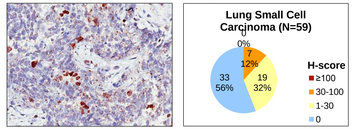
BioMarker Data

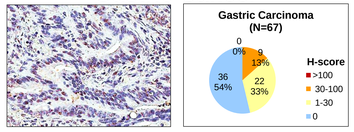
Notch1 IHC

Primary tumors sourced from patients

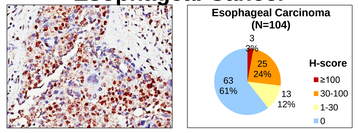
Small Cell Lung Cancer



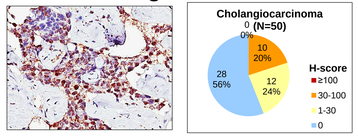
Gastric Cancer



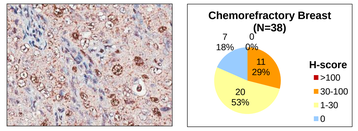
Esophageal Cancer



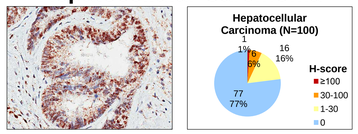
Cholangiocarcinoma



Refract. HER2- Breast Cancer



Hepatocellular Carcinoma



Notch1 over-expression also noted for: Pancreatic Cancer and Colorectal Cancer

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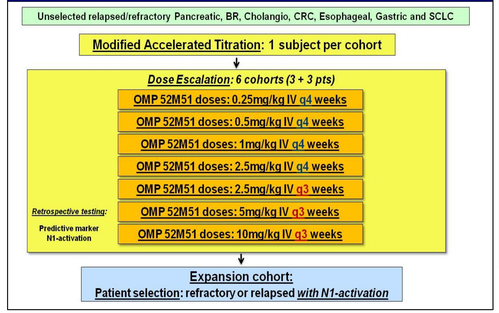
Study Schema



Patient Demographics

Dose Level – mg/kg	0.25	0.5	1	2.5	Total
N	1	3	3	4	11
Median age (years)	46 (38-74)				
Male/Female (%)	55/45				
Tumor Types					
Colorectal	5				
CholangioCarcinoma	2				
Breast Cancer	2				
Gastric Cancer	1				
Esophageal Cancer	1				

OMP-52M51 Related AEs (All Grades) in >10% of Pts (N = 11)

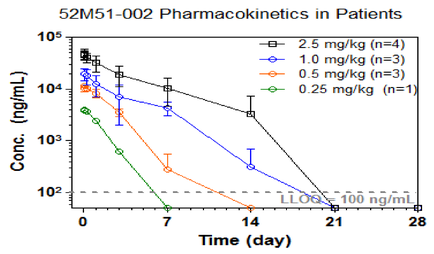
Dose Level – mg/kg	0.25	0.5	1	2.5	Total (%)
N (Patients)	1	3	3	4	11
Diarrhea	1	2	2	2	7 (64%)
Nausea	-	2	1	-	3 (27%)
Fatigue	-	1	-	1	2 (18%)
Rash	-	1	1	-	2 (18%)

OMP-52M51 Related AEs (Grades ≥3) (N = 11)

Dose Level – mg/kg	0.25	0.5	1	2.5	Total (%)
N	1	3	3	4	11
Events	0	1	1	1	3 (27%)
Hypertension	-	1 (Gr3)	-	-	1
Diarrhea	-	-	1 (Gr3)	-	1
Fatigue	-	-	-	1 (Gr3)*	1

* Gr3 Fatigue was DLT as this occurred in DLT window (D0-28); thus, cohort expanded

Pharmacokinetic Data

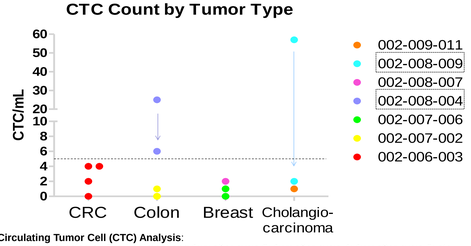


Non-Compartmental PK Analysis Parameter Summary

Dose (mg/kg Q4W)		$T_{1/2}$ (day)	C_{max} (µg/mL)	AUC_{last} (day*µg/mL)	$AUC_{0-\infty}$ (day*µg/mL)	AUC Extrap (%)	CL (mL/day/kg)	V_{ss} (mL/kg)
0.25	N	0	1	1	0	0	0	0
	Mean	- [a]	4.02	5.79	-	-	-	-
	SD	-	-	-	-	-	-	-
0.5	N	2	3	3	2	2	2	2
	Mean	1.37	11.38	24.30	25.87	3.11	19.87	36.50
	SD	-	0.73	4.03	-	-	-	-
1.0	N	2	3	3	2	2	2	2
	Mean	2.72	20.01	57.41	86.08	9.31	11.62	44.03
	SD	-	5.48	36.24	-	-	-	-
2.5	N	4	4	4	4	4	4	4
	Mean	3.91	48.26	175.10	211.61	16.62	14.44	66.08
	SD	1.30	10.07	94.30	113.72	9.79	7.13	11.72

- Non-linear PK, likely due to target-mediated clearance
- Exposure (measured by AUC) increases over-proportionally as dose increases
- Half-life averages 3.91 days at 2.5 mg/kg and is expected to increase as dose escalates
- Immunogenicity analysis is on-going

Biomarker Data: Circulating Tumor Cells



Circulating Tumor Cell (CTC) Analysis:
- Samples collected at: Pre-treatment and 1wk after cycle 2; 1wk after cycle 4; 1wk after cycle 6; etc.

CTCs were analyzed by Epic Sciences using their proprietary platform:
- Nucleated cells were plated on slides and subjected to immunofluorescent staining
- Slides scanned using Pyxis™ Scanner & CTCs identified as CK+/CD45-/DAPI+ using Atlas™ Software

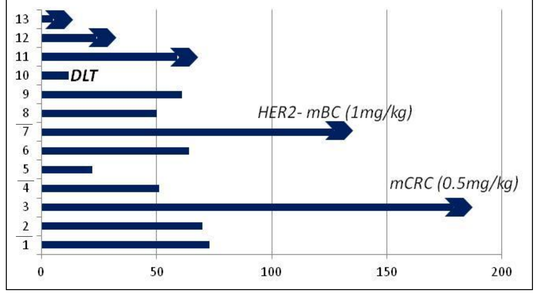
Most samples tested had < 5 CTC/mL
- Pts 002-008-009 & 002-008-004 with significant drop in CTC count between serial draws:
  - Pt 002-008-009 (Cholangio: OMP-52M51: 2.5mg/kg Q3W): Day 0: 57 CTC/mL: Day 35: 2 CTC/mL
  - Pt 002-008-004 (mCRC: OMP-52M51: 0.5mg/kg Q4W): Day 0: 25 CTC/mL; Day 28: 6 CTC/mL

RECIST (1.1) Best Overall Response (N=11)

Dose Level - mg/kg	0.25	0.5	1	2.5	Total
Partial Response	-	-	-	-	-
Stable Disease	-	1**	1	-	2 (18%)
Progressive Disease	1	2	1	2	6 (55%)
Not Evaluable	-	-	1	1	2 (18%)
Ongoing	-	1	1	3	5*

* 2 pts ongoing with SD; 3 pts ongoing at 2.5mg/kg without tumor assessment yet
** mCRC pt: RECIST SD and CEA tumor marker declining from: **62 → 51 → 46 → 43ng/mL**

Time on Study



Tumor Assessments at: Day 70; Day 126; and every 56 days thereafter

Conclusions

- This is an ongoing Phase 1a dose escalation study of OMP-52M51, a cancer stem cell targeting monoclonal antibody, targeting the Notch1 receptor in patients with certain refractory solid tumors
- The primary on target toxicity of OMP-52M51 is diarrhea
- The MTD of single agent OMP-52M51 has not been reached and dose escalation continues
- Thus far the half life of OMP-52M51 is approximately 4 days (at 2.5mg/kg Q4W), PK data supports change from a q 28 to q 21 day dosing
- There is potential evidence of CTC reduction in two patients with baseline >20 CTCs/mL (mCRC and cholangiocarcinoma) with OMP-52M51 treatment
- Some suggestion of single agent activity has been noted in a patient with mCRC and a patient with HER2- mBC both with stable disease >120 days.
- In the expansion cohort of this study, patients with tumors that have Notch1 activation, as determined using a CLIA certified predictive biomarker test, will be selected and treated with the single agent MTD dose and schedule of OMP-52M51
- Clinical trials of OMP-52M51 continue in patients with certain solid tumors (colorectal, esophageal, gastric, HER2- breast, pancreatic, small cell lung cancers and cholangiocarcinoma), as well as, certain lymphoid malignancies
- OMP-52M51 is developed in partnership with GlaxosmithKline (GSK)

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