Initial results from a phase 1a/b study of OMP-131R10, a first-in-class anti-RSPO3 antibody, in advanced solid tumors and previously treated metastatic colorectal cancer (CRC)

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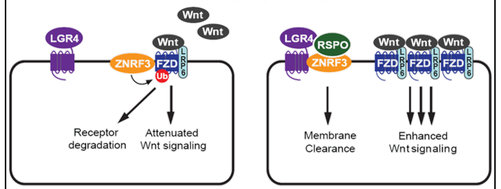
Background

- The R-spondin (RSPO) pathway plays a crucial role in regulating stem cell maintenance and renewal. RSPOs act to potentiate signaling by WNT ligands.



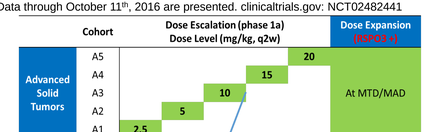
HX Hao, Nature 2012

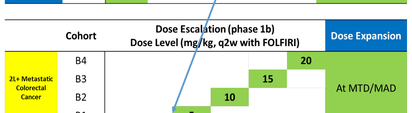
- RSPO translocations occur in CRC.
- OMP-131R10 is a novel IgG1 that targets RSPO3 ligand.
- Inhibition of RSPO3 binding to its receptor by OMP-131R10 demonstrates anti-tumor effects in patient derived xenograft models as a single agent and with chemotherapy.
- Here we present initial results from the ongoing Ph 1a/b study of OMP-131R10.

Methods, Study Schema, and Objectives

Study Design:

- Open-label Phase 1a/b dose-escalation study to assess the safety, tolerability, and PK of OMP-131R10 as a single agent for advanced solid tumors and in subjects with metastatic colorectal cancer.
- OMP-131R10 will be administered day 1 of each 14-day cycle.
- Treatment until progressive disease or unacceptable toxicity.
- In Phase 1b OMP-131R10 will be given in combination with FOLFIRI (5-FU, irinotecan, leucovorin).
- RECIST assessment every 8 weeks
- Data through October 11th, 2016 are presented. clinicaltrials.gov: NCT02482441





Objectives

Primary

• Maximum tolerated dose (MTD) or maximum administered dose (MAD) of OMP-131R10 as single agent and with FOLFIRI

• Recommended Phase 2 dose of OMP-131R10 as a single agent and with FOLFIRI

Secondary

•Pharmacokinetics (PK) and immunogenicity of OMP-131R10 as a single agent and in combination with FOLFIRI

•Preliminary assessment of the efficacy of OMP-131R10 as a single agent and in combination with FOLFIRI

Baseline Characteristics

	Study Part / Dose						
	1a				1b	Total	
	2.5 mg/kg	5 mg/kg	10 mg/kg	15 mg/kg	5 mg/kg		
n	3	3	3	7	7	23	
Age (years)							
Mean (SD)	66.7 (14.43)	55.7 (12.58)	62.0 (11.27)	61.9 (8.21)	51.7 (5.99)	58.6 (10.16)	
Median	75	54	56	59	52	55	
25th, 75th Percentile	50.0, 75.0	44.0, 69.0	55.0, 75.0	55.0, 70.0	45.0, 55.0	51.0, 69.0	
Min, Max	50, 75	44, 69	55, 75	51, 73	44, 61	44, 75	
<18	-	-	-	-	-	-	
18-65	1 (33.3%)	2 (66.7%)	2 (66.7%)	4 (57.1%)	7 (100%)	16 (69.6%)	
>65	2 (66.7%)	1 (33.3%)	1 (33.3%)	3 (42.9%)	-	7 (30.4%)	
Sex							
Male	1 (33.3%)	-	3 (100%)	5 (71.4%)	3 (42.9%)	12 (52.2%)	
Female	2 (66.7%)	3 (100%)	-	2 (28.6%)	4 (57.1%)	11 (47.8%)	

Diagnosis	CRC	ACC	Breast	GIST	Ovarian	Peritoneal	SCC	Small Bowel
n	16	1	1	1	1	1	1	1

Disposition and DLTs

	Phase 1a Dose Escalation					Phase 1b Dose Escalation	
	2.5 mg/kg Q2W (N=3)	5.0 mg/kg Q2W (N=3)	10.0 mg/kg Q2W (N=3)	15.0 mg/kg Q2W (N=7)	5.0 mg/kg Q2W with FOLFIRI (N=7)	Overall (N=23)	
DLT	-	-	-	-	-	-	-
Primary Reason for Ending OMP-131R10 Treatment							
Lost to Follow-Up	-	-	-	-	-	-	-
Withdrawal of Consent / Patient Decision	-	-	-	-	-	-	-
Death	-	-	-	1 (14.3%)	-	1 (4.3%)	
Adverse Event	-	-	-	-	-	-	-
Allergic Reaction	-	-	-	-	-	-	-
Disease Progression	2 (66.7%)	2 (66.7%)	2 (66.7%)	3 (42.9%)	3 (42.9%)	12 (52.2%)	
Intercurrent Illness that Prevents Further Administration of Treatment	-	-	-	-	-	-	-
Dose Delay Greater Than 14 days (Phase 1a)	-	-	-	-	-	-	-
Dose Delay Greater Than 28 days (Phase 1b)	-	-	-	-	-	-	-
Use of Non-Protocol Anti-cancer Therapy	-	-	-	-	-	-	-
Investigator Decision Based on Patient's Best Interest	-	-	-	-	-	-	-
Protocol Non-Compliance	-	-	-	-	-	-	-
Other: CLINICAL PROGRESSION	1 (33.3%)	1 (33.3%)	1 (33.3%)	-	-	3 (13.0%)	

Treatment Exposure

	Phase 1a Dose Escalation				Phase 1b Dose Escalation					
	2.5 mg/kg Q2W (N=3)	5.0 mg/kg Q2W (N=3)	10.0 mg/kg Q2W (N=3)	15.0 mg/kg Q2W (N=7)	5.0 mg/kg Q2W with FOLFIRI (N=7)					Overall (N=23)
Total Number of Infusions Administered per Patient	OMP-131R10				Irinotecan	5-FU Bolus	5-FU Infusion	Leucovorin		
n	3	3	3	7	7	7	7	7	7	23
Mean (SD)	7.0 (2.65)	9.0 (9.54)	7.3 (6.66)	2.9 (1.07)	6.4 (5.32)	6.0 (5.00)	5.7 (4.92)	6.4 (5.32)	5.9 (4.81)	5.9 (5.07)
Median	8.0	4.0	4.0	2.0	4.0	4.0	4.0	4.0	4.0	4.0
Total Dose Administered (mg) per Patient										
Mean (SD)	1344.3 (438.06)	3196.7 (3470.02)	6361.7 (5663.01)	3179.7 (1852.53)	2293.0 (1951.27)	1813.3 (1468.36)	3854.7 (3288.73)	25983.1 (21380.05)	4036.0 (3198.33)	3087.7 (2843.10)
Median	1413.0	1340.0	3656.0	2160.0	1480.0	1352.0	3008.0	18048.0	3008.0	2110.0
Duration of Treatment (days) [1]										
Mean (SD)	85.0 (37.04)	112.3 (132.40)	89.0 (93.79)	29.4 (16.18)	83.1 (79.71)	75.0 (71.22)	70.1 (68.92)	83.1 (79.71)	73.0 (68.75)	71.6 (72.27)
Median	99.0	43.0	42.0	22.0	44.0	44.0	44.0	44.0	44.0	43.0

AEs Considered Related to OMP-131R10 Occurring in > 10% of Pts

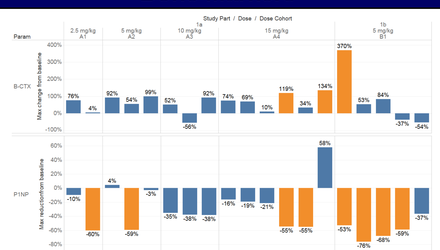
	Phase 1a Dose Escalation					Phase 1b Dose Escalation	
	2.5 mg/kg Q2W (N=3)	5.0 mg/kg Q2W (N=3)	10.0 mg/kg Q2W (N=3)	15.0 mg/kg Q2W (N=7)	5.0 mg/kg Q2W with FOLFIRI (N=7)	Overall (N=23)	
Preferred Term	Number of Patients [1]	Number of Events	Number of Patients [1]	Number of Events	Number of Patients [1]	Number of Events	Number of Patients [1]	Number of Events	Number of Patients [1]	Number of Events	Number of Patients [1]	Number of Events	Number of Patients [1]	Number of Events
Fatigue	1 (33.3%)	1	2 (66.7%)	2	-	-	3 (42.9%)	3	1 (14.3%)	2	7 (30.4%)	8		
Nausea	1 (33.3%)	1	2 (66.7%)	2	1 (33.3%)	1	2 (28.6%)	3	-	-	6 (26.1%)	7		
Weight decreased	-	-	-	-	1 (33.3%)	1	1 (14.3%)	1	1 (14.3%)	1	3 (13.0%)	3		
Decreased appetite	2 (66.7%)	2	-	-	-	-	1 (14.3%)	1	-	-	3 (13.0%)	3		

Grade 3 or higher AEs

	Phase 1a Dose Escalation					Phase 1b Dose Escalation	
	2.5 mg/kg Q2W (N=3)	5.0 mg/kg Q2W (N=3)	10.0 mg/kg Q2W (N=3)	15.0 mg/kg Q2W (N=7)	5.0 mg/kg Q2W with FOLFIRI (N=7)	Overall (N=23)	
Preferred Term	Number of Patients [1]	Number of Events	Number of Patients [1]	Number of Events	Number of Patients [1]	Number of Events	Number of Patients [1]	Number of Events	Number of Patients [1]	Number of Events	Number of Patients [1]	Number of Events	Number of Patients [1]	Number of Events
Small intestinal obstruction	-	-	-	-	1 (33.3%)	1	2 (28.6%)	2	1 (14.3%)	1	4 (17.4%)	4		
Nausea	-	-	-	-	1 (33.3%)	1	-	-	1 (14.3%)	1	2 (8.7%)	2		
Diarrhoea	-	-	-	-	-	-	-	-	1 (14.3%)	1	1 (4.3%)	1		
Neutropenia	-	-	-	-	-	-	-	-	2 (28.6%)	2	2 (8.7%)	2		
Anaemia	1 (33.3%)	1	-	-	-	-	-	-	-	-	1 (4.3%)	1		
Chest pain	-	-	-	-	-	-	1 (14.3%)	1	-	-	1 (4.3%)	1		
Fatigue	-	-	-	-	-	-	-	-	1 (14.3%)	2	1 (4.3%)	2		
Hypokalaemia	-	-	1 (33.3%)	1	-	-	-	-	-	-	1 (4.3%)	1		
Hyponatraemia	-	-	-	-	-	-	1 (14.3%)	4	-	-	1 (4.3%)	4		
Renal failure acute	-	-	-	-	-	-	1 (14.3%)	1	-	-	1 (4.3%)	1		
Ureteric obstruction	1 (33.3%)	1	-	-	-	-	-	-	-	-	1 (4.3%)	1		
Supraventricular tachycardia	-	-	-	-	-	-	1 (14.3%)	1	-	-	1 (4.3%)	1		
Neutrophil count decreased	-	-	-	-	-	-	-	-	1 (14.3%)	2	1 (4.3%)	2		
Anhedonia	-	-	-	-	-	-	-	-	1 (14.3%)	1	1 (4.3%)	1		
Failure to thrive in adult, volume overload, sirs, metastatic colon cancer	-	-	-	-	-	-	1 (14.3%)	1	-	-	1 (4.3%)	1		

No Grade 3 or higher AEs were considered related to OMP-131R10

Bone Markers

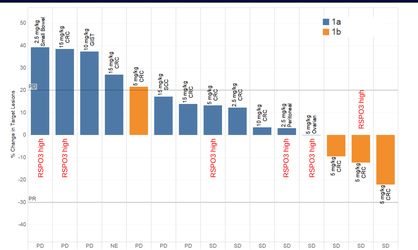


- Orange bars represent substantial changes from baseline (doubling or more for B-CTX, halving or more for P1NP)
- Markers of bone metabolism were monitored throughout the study and revealed dose-dependent changes
- Based on target modulation shown by changes in bone markers, 15 mg/kg Q2W was chosen as the top dose for Phase 1a and selected for the dose expansion cohort

Best Objective Responses (n=15 Evaluable)

	Phase 1a Dose Escalation					Phase 1b Dose Escalation	
	2.5 mg/kg Q2W (N=3)	5.0 mg/kg Q2W (N=3)	10.0 mg/kg Q2W (N=3)	15.0 mg/kg Q2W (N=7)	5.0 mg/kg Q2W with FOLFIRI (N=7)	Overall (N=23)	
Best Overall Tumor Response [1]							
Complete Response (CR)	-	-	-	-	-	-	
Partial Response (PR)	0	-	-	-	-	-	
Stable Disease (SD)	2 (66.7%)	2 (66.7%)	1 (33.3%)	-	3 (42.9%)	8 (34.8%)	
Progressive Disease (PD)	1 (33.3%)	1 (33.3%)	1 (33.3%)	3 (42.9%)	1 (14.3%)	7 (30.4%)	
Not Evaluable (NE)	-	-	1 (33.3%)	4 (57.1%)	3 (42.9%)	8 (34.8%)	
Overall Response Rate (CR or PR) [2]	-	-	-	-	-	-	
Clinical Benefit Rate (CR or PR or SD) [2]	2 (66.7%)	2 (66.7%)	1 (33.3%)	-	3 (42.9%)	8 (34.8%)	

% Change in RECIST Target Lesion Size (n=15)

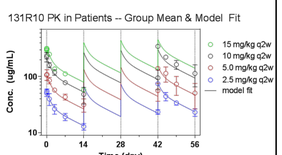


All subjects with post-baseline assessment and measurable disease

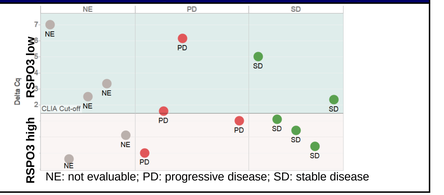
PD: progressive disease; SD: stable disease; CRC: colorectal ca; GIST: gastrointestinal stromal tumor; SCC: squamous cell carcinoma;

Pharmacokinetics

- OMP-131R10 exhibits regular Mab PK in patients
- Linear PK with slow clearance
- Half-life preliminarily estimated to be 13 days
- Primarily distributed within the blood space with modest extravasation

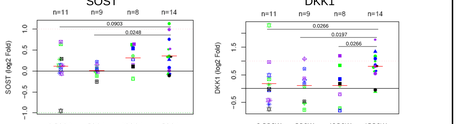


RSPO3 Gene expression and Best Objective Response (Ph1a only)

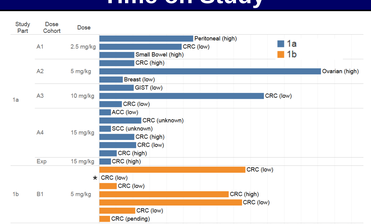


NE: not evaluable; PD: progressive disease; SD: stable disease

SOS and DKK1 regulated by OMP-131R10 (Ph1a only)



Time on Study



* This subject had small bowel obstruction on study day 1 and was withdrawn from study

Summary

- This is the first-in-human study of an anti-RSPO3 inhibitor
- The MTD has not been reached, but the maximum administered dose based on target engagement was 15 mg/kg Q2W
- OMP131-R10 was well tolerated
- There were signs of target engagement with evidence of changes in serum bone markers
- 3 subjects in the phase 1a portion have had prolonged stable disease (>112 days) as best objective response
- The study continues to enroll