First-in-human evaluation of the human monoclonal antibody vantictumab (OMP-18R5; anti-Frizzled) targeting the WNT pathway in a Phase I study for patients with advanced solid tumors

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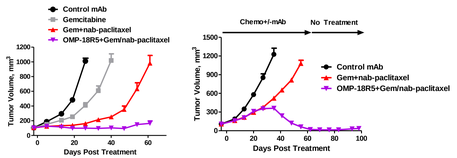
BACKGROUND

- Failure to effectively target Cancer Stem Cells (CSCs) may be responsible for the limited success of systemic therapies in the metastatic setting.
- The activated Wnt pathway is strongly associated with CSCs.
- Vantictumab is a fully human IgG_2 monoclonal antibody that was identified by binding to Frizzled 7.
- Vantictumab binds five Frizzled receptors (1, 2, 5, 7, and 8) and inhibits Wnt signaling.
- Vantictumab has broad anti-tumor activity in patient-derived xenograft models, in particular when combined with standard-of-care chemotherapy, such as taxanes.
- Vantictumab selectively reduces the frequency of CSCs in these models.
- Vantictumab can also promote widespread tumor cell differentiation, as shown for pancreatic cancer models.

For more details, see Gurney et al., PNAS 109, 11717 (2012)

NONCLINICAL EFFICACY DATA

Activity of vantictumab in patient-derived pancreatic cancer xenografts



Established OMP-PN13 tumors (left panel) or OMP-PN17 tumors (right panel) were treated with vantictumab (OMP-18R5) in combination with gemcitabine plus nab-paclitaxel. Vantictumab significantly inhibited tumor growth in both models. Doses used – Gemcitabine: 10 mg/kg weekly, nab-paclitaxel: 30 mg/kg weekly, OMP-18R5: 25 mg/kg every two weeks.

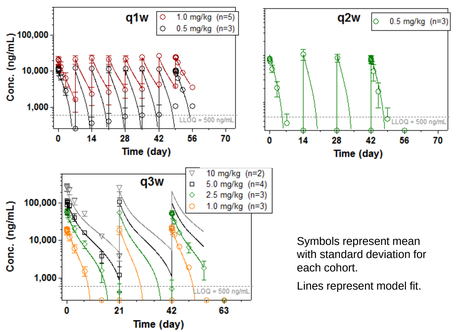
STUDY OVERVIEW

- Patients with advanced solid tumors
- 3+3 dose escalation
- Dose levels
  - 0.5 and 1 mg/kg every one week
  - 0.5 mg/kg every two weeks
  - 1, 2.5, 5 and 10 mg/kg every three weeks
- DLT assessment window: 28 days
- Pharmacodynamics: blood RNA, hair follicles, tumor (optional)
- Tumor assessments: every 8 weeks

BASELINE CHARACTERISTICS

Number of patients	23
Median age, yr (range)	59 (38-77)
Gender (female)	15 (65%)
ECOG score	
0	6 (26%)
1	17 (74%)
Number of prior systemic therapies, median (range)	3 (0-8)
Tumor types	
Colorectal	8
Neuroendocrine	3
Breast	2
Sarcoma	2
Other	8

PHARMACOKINETICS



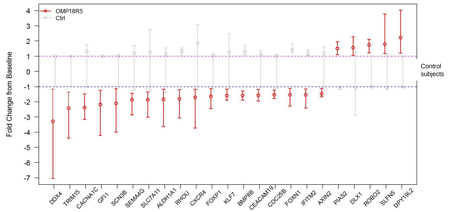
Symbols represent mean with standard deviation for each cohort.

Lines represent model fit.

At current dose levels:
- Apparent clearance (CL) ranges from 0.50 to 1.2 mL/hr/kg.
- Dose-dependent CL suggests target-mediated clearance plays a major role.
- Terminal $T_{1/2}$ ranges from 1.5 to 3.7 days.
- Anti-drug antibody formation in 5 of 21 patients did not affect PK.

PHARMACODYNAMICS

Vantictumab affects Wnt-related gene expression patterns in hair follicles



- Vantictumab causes decreased expression of Wnt pathway target genes and increased expression of differentiation genes ('OMP18R5;' in red)
- Hair follicles of control subjects not treated with vantictumab show no significant changes in the same genes ('Ctrl;' in gray)
- 10 patient samples analyzed: 9 collected 1 week after infusion; 1 collected 2 weeks after infusion

SAFETY

Related adverse events observed in >5% of patients

Cohort	1 (n=3)	2 (n=5)	3 (n=3)	4 (n=4)	5 (n=3)	6 (n=3)	7 (n=2)	Total (n=23)
Dose level	0.5 q1w	1 q1w	0.5 q2w	1 q3w	2.5 q3w	5 q3w	10 q3w	
Grade	1/2/3	1/2/3	1/2/3	1/2/3	1/2/3	1/2/3	1/2/3	
Fatigue	-/1/-	-/1/-	3/-/-	-/-/-	-/-/-	-/1/-	1/-/-	7
Nausea	-/-/-	-/1/-	2/-/-	-/-/-	1/-/-	1/-/-	-/-/-	5
Vomiting	1/-/-	1/-/1*	-/-/-	-/-/-	1/-/-	-/-/-	-/-/-	4
Alkaline phos-phatase increased	-/-/-	2/-/-	-/-/-	-/-/-	-/-/-	1/-/-	-/-/-	3
Constipation	-/-/-	-/-/-	1/-/-	1/-/-	-/-/-	-/-/-	1/-/-	3
Decreased appetite	-/-/-	-/1/-	-/-/-	1/-/-	-/-/-	-/1/-	-/-/-	3
Hypercalcemia	-/-/-	-/-/-	-/-/-	-/-/-	1/-/-	-/2/-	-/-/-	3
Abdominal pain	1/-/-	-/-/-	1/-/-	-/-/-	-/-/-	-/-/-	-/-/-	2
Anemia	-/-/-	-/1/-	-/-/-	-/1/-	-/-/-	-/-/-	-/-/-	2
Diarrhea	1/-/-	-/-/1*	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	2

Data as of 8 May 2013
q1w = every 1 week; q2w = every 2 weeks; q3w = every 3 weeks
* Grade 3 vomiting and diarrhea of patient 004 were the only Grade ≥3 adverse events and were considered dose-limiting toxicities for Cohort 2.

BONE TURNOVER

- Patient 003 experienced Grade 2 compression fracture after minor fall on Day 110.
- Review of program for bone toxicity resulted in revised safety plan.
  - More stringent exclusion criteria
    (e.g. chronic glucocorticoid use, high β C-terminal telopeptide [β -CTX, serum marker of bone turnover], and known insufficiency fracture)
  - Prophylactic Vitamin D and calcium carbonate
  - Less frequent dosing
  - Zoledronic acid for the following criteria
    - Doubling of β-CTX, serum marker for bone turnover
    - T-score decline to <-2.5 as measured by DEXA

Dose (mg/kg)	Pt	Day	β-Ctx (pg/mL)	T-score
0.5 q1w	1	0	570	-1.8
		Term		-2.2
	2	0	196	-1.0
		28	308	
		Term	217	ND
	3	0	219	-0.1
		28	825	
		56	896	
		Term	708	0.2
1 q1w	4	0	298	-1.3
		Term	401	ND
	5	0	229	-1.2
		28	681	
		Term	370	-1.0
	6	0	162	-0.4
		28	598	
	7	0	144	0.9
		28	301	
		Term		0.7
	8	0	406	-1.6
		28	551	
0.5 q2w	9	0	203	-0.7
		28	195	
		Term	287	-0.9

Dose (mg/kg)	Pt	Day	β-Ctx (pg/mL)	T-score
0.5 q2w	10	0	306	-1.4
		28	286	
		56	304	-1.0
		84	664	
		112	270	-0.9
		140	288	
		168	413	-1.0
		196	372	
		224	377	-0.9
		252	363	
		280	424	-1.0
		308	505	
		336	499	-1.2
		364	420	
	11	0	308	0.9
		42	358	
		Term	327	0.9

Dose (mg/kg)	Pt	Day	β-Ctx (pg/mL)	T-score
1 q3w	12	0	689	-1.4
		28	846	
		56	707	-1.3
		84	350	
		112	759	-1.4
		140	526	
		168	967	-1.8
		196	688	
		224	*1216*	-1.7
		252	*1174*	
		280	*1223*	-1.7
		308	1045	
	13	0	618	-0.9
		Term	876	-1.2
	14	0	471	2.4
		28	760	
		Term	688	2.2
	15	0	340	-0.7
		28	469	
		56	*586*	-0.8
		Term	156	ND

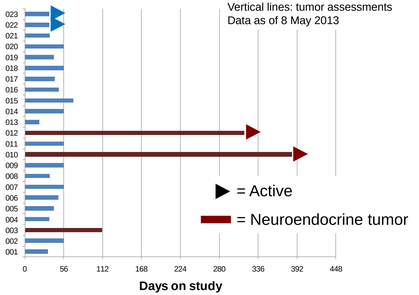
Dose (mg/kg)	Pt	Day	β-Ctx (pg/mL)	T-score
2.5 q3w	16	0	386	-0.7
		28	805	
		Term	345	-0.8
	17	0	232	-1
		28	309	
	18	0	607	-0.9
		28	555	
		Term	824	-1.0
5 q3w	19	0	648	0.1
		28	811	
		Term	1336	-0.1
	20	0	561	-1.0
		28	665	
		56	*1111*	-1.0
	21	0	629	-0.13
10 q3w	22	0	367	-1.2
		28	*697*	
	23	0	568	-1.3
		28	1449	

Active patients

Zoledronic acid administered

Red bold: Initial β-CTX doubling by Day 28; green bold: β-CTX doubling > Day 28
Blue italics: β-CTX values ≥1.7-fold of baseline
Data as of 8 May 2013; ND = not done;
Termination visit has to occur ≤30 days after last study drug dosing.
Lowest T-score is shown, regardless of location (hip, femur or lumbar spine).

TIME ON STUDY



NEUROENDOCRINE TUMORS

003 (59 yo female)
Carcinoid

Diagnosis:
2004: resection (curative intent)

Systemic Therapy:
1. **MEK inhibitor + AKT inhibitor**
   - **PD confirmed (+26%)**
2. **Vantictumab (SD)**

010 (69 yo female)
Pancreatic neuroendocrine tumor

Diagnosis:
2001: resection (curative intent)
2006: liver mets

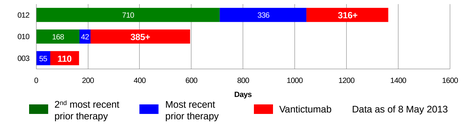
Systemic Therapy:
1. Regorafenib (1093 days)
2. **αLOXL2**
3. **αCSFR1**
   - **PD confirmed (+45%)**
4. **Vantictumab (SD)**

012 (77 yo female)
Carcinoid

Diagnosis:
2006: liver mets

Systemic Therapy:
1. Sandostatin (569 days)
2. **HSP90 inhibitor**
3. **αAng2**
   - **PD confirmed (+20%)**
4. **Vantictumab (SD)**

Time on study with stable disease



CONCLUSIONS

- Vantictumab is well tolerated.
  - Further dose escalation is ongoing.
- Vantictumab clearance is dose-dependent, consistent with target-mediated disposition.
- Vantictumab has pharmacodynamic (PD) effects on hair follicles.
  - PD effects are consistent with Wnt biology.
  - PD effects extend beyond serum exposure.
- Vantictumab has PD effects on bone, as evidenced by β-CTX increases.
- Increased bone turnover can be safely managed through careful monitoring, prophylactic Vitamin D and calcium carbonate, and administration of zoledronic acid, if indicated.
- Prolonged stable disease in 3 patients with neuroendocrine tumors may represent single-agent activity.

ACKNOWLEDGEMENTS

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