A Phase Ia study in patients with advanced solid tumors for the human monoclonal antibody vantictumab (OMP-18R5; anti-Frizzled) targeting the WNT pathway

Kyrillos Papadopoulos,1 Lee Rosen,2 Rashmi Chugh,3 Jonathan Goldman,2 Wan-Ching Yen,4 Pete Yeung,4 Lu Xu4, Ann M. Kapoun,4 Rainer K. Brachmann,5 Robert Stagg,4 Tony Tolcher,1 David Smith3 1START, San Antonio, TX, USA; 2University of California, Los Angeles, CA, USA; 3University of Michigan, Ann Arbor, MI, USA; 4OncoMed Pharmaceuticals, Redwood City, CA, USA

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 IgG1 monoclonal antibody that was identified by screening a F7.
• 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 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 Gumeu et al., PNAS 109, 11717 (2012).

NONCLINICAL EFFICACY DATA
Dose-ranging experiment in patient-derived breast cancer xenograft.
Established UMP-F13 tumors (triple-negative breast) were treated with various doses of vantictumab (OMP-18R5) in combination with paclitaxel. 5 mg/kg every 3 weeks (q3w) of vantictumab resulted in a reduction in relative to vehicle alone and established the minimum efficacious dose. Treatment at 25 mg/kg q3w resulted in tumor regression and corresponded to the minimum efficacious dose.

PHARMACOKINETICS
Dose-partitioning experiment in patient-derived breast cancer xenograft to determine PK driver of efficacy.
The top graph shows the PK parameters associated with the various doses and schedules of vantictumab. The bottom graph shows tumor growth rates for these treatment regimens. Established OMP-B60 tumors (triple-negative breast) were treated with vantictumab (OMP-18R5) in combination with paclitaxel. The same amount of vantictumab was administered with different schedules. The 10 mg/kg q3w regimen (tumor Cmax and high Cmin) was efficacious; however, this was the least efficacious regimen. Higher plasma given less frequently produced greater anti-tumor efficacy supporting Cmax as the PK driver for anti-tumor efficacy.

TIME ON STUDY

SAFETY
Related adverse events observed in >5% of patients

PHARMACODYNAMICS
Vantictumab affects Wnt-related gene expression patterns in hair follicles

Bone turnover
Patient 003 experienced Grade 3 compression fracture after minor fall on Day 110.

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.
• Prolonged stable disease in 3 patients with neuroendocrine tumors may represent single-agent activity.

Acknowledgements
We thank all patients who participated in this study and their families. Vantictumab is part of OncoMed’s Wnt pathway collaboration with Bayer Pharma AG.

European Cancer Congress 2013 (ECCO-ESMO-ESTRO), Amsterdam, 29 September 2013