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
• Frizzled is a large family of G-protein-coupled receptors (GPCRs) that 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 binding to Frizzled 7.
• Vantictumab blocks five Frizzled receptors (1, 3, 5, 7, and 8) and inhibits Wnt signaling.
• Vantictumab has broad anti-tumor activity in patient-derived xenograft (PDX) models, and in particular when combined with standard of care chemotherapies, 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 119, 11717 (2012)

BASELINE CHARACTERISTICS

| Number of patients | 23 |
| Gender (male/female) | 15 (65%) |
| ECOG score | 1 (77%) |
| Number of prior systemic therapies (median) | 3 (9) |

PHARMACODYNAMICS

Vantictumab affects Wnt-related gene expression patterns in hair follicles
• Vantictumab causes increased expression of Wnt pathway target genes and increased expression of differentiation genes (VanhN18R5; in red).
• Hair biopsies taken in triplicate in each cohort show no significant changes in the same genes (Vanh; in grey).
• Tumors complete analyzed ≥3 collected 1 week after initiation 1 collected 3 weeks after initiation.

SAFETY

Related adverse events observed in >5% of patients

PHARMACOKINETICS

NONCLINICAL EFFICACY DATA

Activity of vantictumab in patient-derived pancreatic cancer xenografts

SCHEDULED AND ASSESSMENTS

STUDY OVERVIEW
• Patients with advanced solid tumors
• 3+ dose escalation
• Dose levels:
  • 0.5 mg/kg every two weeks
  • 1.25, 5 and 10 mg/kg every three weeks
  • DIC assessment window: 28 days
• Pharmacokinetic: blood RNA, total bilirubin, tumor (optional)
• Tumor assessments: every 8 weeks

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TIME ON STUDY

NEUROENDOCRINE TUMORS

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 B-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.

ACKNOWLEDGMENTS
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