**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 human cancers. OMP-59R5 is a fully human IgG2 antibody originally identified by binding to Notch2. It inhibits the signaling of both Notch2 and Notch3 receptors. Mouse xenograft studies using minimally-passaged, patient-derived xenografts show that OMP-59R5 impedes tumor growth and eliminates cancer stem cells (CSC) in many tumor types. OMP-59R5 modulates the expression of stromal genes and genes associated with the function of tumor vascular pericytes. As such, OMP-59R5 is a novel anti-tumor agent that inhibits tumor growth through direct actions on tumor cells, including CSCs, and effects the stromas and vasculatures.

Methods: A phase I dose escalation study (3-3 design) was initiated in solid tumor patients. OMP-59R5 was administered to study safety, pharmacokinetics (PK), pharmacodynamics (PD), preliminary efficacy, and to determine the maximum tolerated dose (MTD).

Results: Thirty patients have been enrolled in 6 dose-escalation cohorts at doses of 0.5, 1, 2.5, and 5mg/kg administered weekly (QW) and 5 and 10mg/kg every other week (QoW). The most frequently reported drug-related adverse events were: mild to moderate diarrhea, fatigue, nausea, decreased appetite, and constipation. Diarrhea was dose related and occurred at doses ≥2.5mg/kg and appears less pronounced with every other week dosing. Four dose-limiting toxicities (grade 3 diarrhea (N=3) and grade 3 hypokalemia (N=1)) occurred at 5mg/kg QoW (N=2) and 10mg/kg QoW. Thus, 2.5mg/kg QW and 5mg/kg QoW were established as MTDs for the QW and QoW dosing schedules. The PK of OMP-59R5 is generally well tolerated. MTDs of 2.5mg/kg QW and 5mg/kg QoW were established as MTDs for the QW and QoW dosing schedules. The PK of OMP-59R5 in patients ranges from 0.5 day (at 1 mg/kg) to 1.5 days (at 10 mg/kg) and exposure increased proportionally by dose. In patients at ≥2.5mg/kg who had prolonged stable disease (SD) lasting ≥56 days (range 61-111 days); these tumor types include: Kaposi's Sarcoma, adenoid cystic carcinoma, rectal cancer and liposarcoma.

Conclusions: OMP-59R5 is generally well tolerated. MTDs of 2.5mg/kg QW and 5mg/kg QoW have been established. A phase II dose-escalation study is ongoing in patients with advanced solid tumors to further evaluate safety and anti-tumor activity.

**STUDY DESIGN**

- Safety study in pts with advanced solid tumors
- Repeat dose study, 3-6 cycles
- Dose levels:
  - 0.5, 1, 2.5, and 5mg/kg weekly (QW)
  - 5 and 10mg/kg every other week (QoW)
- Response assessment: D56, QBW
- Repeat cycle: 28 days

**PATIENT DEMOGRAPHIC**

- Number of Patients Enrolled (to date): 30
- Median Age: 59 (28-90)
- Gender: M: 14 (46%); F: 16 (52%)
- Tumor Types: Colorectal Cancer (8) + Adenoid Cystic Cancer (3) + Breast Cancer (3) + Pancreatic Cancer (3) + Chondrosarcoma (1) + Liposarcoma (2) + Prostate Cancer (2)

**DEOSE LIMITING TOXICITY (DLT) AND MAXIMUM TOLERATED DOSE (MTD)**

- **OMPA-59R5 PHARMACOKINETICS (PK):**
  - Max Tolerated Dose (QW): 8.4mg/kg
  - Max Tolerated Dose (QoW): 6.5mg/kg
- **OMPA-59R5 PHARMACODYNAMIC (PD):**
  - Max Tolerated Dose (QW): 8.4mg/kg
  - Max Tolerated Dose (QoW): 6.5mg/kg
- **TREATMENT RELATED ADVERSE EVENTS (AE)***
  - All Grades Related AEs
    - Diarrhea
    - Fatigue
    - Decreased Appetite
    - Dehydration
    - Anemia
    - Hypokalemia
    - Thrombocytopenia
    - Thrombocytopenia
- **FINDINGS**
  - Increased ALT (N=1)
  - Other: None
- **PHARMACODYNAMIC (PD):**
  - Surrogate Tissue
    - Effect of OMP-59R5 on Notch Biomarkers
      - Notch Target Gene, HES1, Levels in Whole Blood Significantly Decreased by OMP-59R5
      - Notch biomarkers in whole blood at doses of 1mg/kg and above
      - Significance correlation between diarrhea grade & dose (p-value = 0.01032)
      - Statistically significant overall
      - Notch signaling in patient cells
- **PHARMACODYNAMIC (PD):**
  - Tumor
    - OMP-59R5 induces Notch Pathway-Related microRNAs in Tumor
    - OMP-59R5 increases (≥14 fold) Notch pathway-related miRNAs
- **FINDINGS**
  - Increased ALT (N=1)
  - Other: None