A First-In-Human, Phase I Trial of the Anti-DLL4 Antibody (OMP-21M18) Targeting Cancer Stem Cells (CSCs) in Patients with Advanced Solid Tumors

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**BACKGROUND**

There is accumulating evidence that tumor cell types are heterogeneous and that only a subset of the cells retain the property to self-renew and give rise to more differentiated progeny. These cells, called cancer stem cells (CSCs) or tumor initiating cells, are involved in tumor growth and metastasis and are more resistant to chemotherapy and radiotherapy than the remainder of the tumor cells. The ability to characterize the CSC through surface markers and functional limiting tumor cell assays, using minimally passaged human tumors, has enabled the identification of novel agents that specifically target the CSC population.

**METHODS**

This was an open-label Phase I dose escalation trial of OMP-21M18 in patients with previously treated solid tumors for which there was no remaining standard curative therapy and no therapy with a demonstrated survival benefit. Prior to enrollment, patients underwent screening to determine study eligibility. The study endpoints included the determination of the safety profile, maximum tolerated dose (MTD), immunogenicity, pharmacokinetics, antitumor activity and biomarkers of Notch signaling and CSC in blood, hair and tumor tissue.

**RESULTS**

- **DLT**
  - GI bleeding (2), previously undiagnosed brain metastases (1)
- **No DLT**
  - Cough (6), nausea (6), fatigue (6), constipation (9), abdominal pain (11), diarrhea (16), hypertension (14), asthenia (10)

**Non-compartmental Pharmacokinetic Parameters – Every Week Dosing**

- **Mean Day 49**
  - OMP-21M18 (N = 39)
    - Area under the curve (AUC) = 13.3 ± 116
    - Maximum concentration (Cmax) = 0.1 ± 36
- **Mean Day 0**
  - OMP-21M18 (N = 39)
    - AUC = 4.3 ± 82
    - Cmax = 0.6 ± 16

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**Conclusions**

- **Significant Impact on Plasma Biomarkers**
  - **Significant Impact on Blood mRNA Biomarkers**

- **Significant Impact on Hair Follicle Biomarkers**

- **Significant Impact on Skin mRNA Biomarkers**

**Results**

- **Non-compartmental post-treatment half-life = 17.1 days**
- **Two compartment analysis**
  - alpha half-life = 1 day; beta half-life = 15 days

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**Deaths on Study**

- **No deaths in the study**
- **Not related to the tumor or study drug**
- **Related to the tumor or study drug**

**Related Adverse Events (All Grades) 25% by Dose Level (N = 39)**

- **Event**
  - **Event**
  - **Event**
  - **Event**
  - **Event**
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