Biomarker analysis in the first-in-human OMP-59R5 (anti-Notch2/3) phase I study demonstrates pharmacodynamic (PD) modulation of the Notch Pathway in patients with advanced solid tumors

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ABSTRACT

Background: The Notch pathway plays a central role in embryonic development, the regulation of stem and progenitor cells, and is implicated in many human cancers. OMP-59R5 is a fully human IgG2 which inhibits the signaling of both Notch2 and Notch3 receptors. Mouse xenograft studies using minimally-paissaged, patient-derived xenografts show that OMP-59R5 impedes tumor growth and reduces cancer stem cell (CSC) frequency in multiple tumor types. OMP-59R5 modulates gene expression in tumor associated with stem cell pathways and down-regulates stromal genes indicative of inhibiting the function of paracites in tumor vasculature. As such, OMP-59R5 is a novel anti-cancer agent that inhibits tumor growth through direct actions on tumor cells, reducing CSCs, and effects on the stroma and vasculature. We sought to determine the PD effects of various doses of OMP-59R5 on Notch signaling, stem cell pathways, and other aspects of the mechanism of action by examining surrogate tissues (hair follicles and blood cells) and also serial tumor biopsies from Phase I patients.

Methods and Results: PD biomarker analysis of surrogate tissues and tumors was performed in the OMP-59R5 phase Ia dose escalation study in patients with solid tumors. Thirty-two patients enrolled in 7 dose-escalation cohorts at 0.5, 1, 2, 5, and 10mg/kg administered weekly (QW), 5 and 7.5mg/kg administered every other week (Q2W), and 7.5mg/kg administered every three weeks (Q3W) were analyzed for biomarkers. Notch pathway-related genes including HES1, NEURL, MAML2, and POFUT1 were found to be regulated in blood cells at doses of 1mg/kg and above. OMP-59R5 plasma biomarkers were also modulated by OMP-59R5, as were stem cell and differentiation markers in hair follicles, including KITLG. In tumors, Notch pathway regulated microRNA150 (mir150) was induced post-treatment consistent with suppression of the Notch pathway by OMP-59R5.

Conclusions: The PD effects of OMP-59R5 on Notch targets, stem cell pathways in surrogate tissues and in tumor tissue on serial biopsy were clearly established in this first-in-human study.

STUDY DESIGN

Patient Samples: Safety study in patients with advanced solid tumors. Pharmacodynamic (PD) readouts: Whole blood RNA, hair follicles, plasma, and tumors

Microarray Analysis: RNAs were isolated from the whole blood, hair follicles, and biopsied tumors and gene expression profiles were assayed using Affymetrix HG-U1133 (plz2). GCRMA was used to normalize the arrays and summarize the signals. Empirical Bayes analysis (LIMMA) identified the genes differentially expressed in the samples between pre-dose and post-dose time points, or between different dosing groups. Gene Set Enrichment Analysis (GSEA) was performed to identify the biological processes affected by OMP-59R5 in the biopsied tumors

Plasma data analysis: Patient plasma samples were assayed using Myriad RMB HumanMap v1.6 platform or ELISA. The significance of protein differences in samples between pre-dose or post-dose time points was determined by paired-sample Student t-tests.

qPCR: qPCR was performed for NOTCH3 and human mir150 using AB human specific probes. Ct values were normalized to GUSB (NOTCH3) or U48 (mir150) to obtain the relative expression values.

PHARMACODYNAMIC (PD) DATA: Whole Blood

PHARMACODYNAMIC (PD) DATA: Blood Plasma

PHARMACODYNAMIC (PD) DATA: Hair Follicles

PHARMACODYNAMIC (PD) DATA: Tumors

SUMMARY OF FINDINGS

• OMP-59R5 modulated Notch pathway biomarkers in surrogate tissues and tumors in advanced solid tumor phaseIa study
• Pharmacodynamic modulation of Notch pathway observed at ≥1mg/kg QoW
• MicroRNA150, target of the NOTCH pathway, was significantly up-regulated by OMP-59R5 in the tumors, consistent with the down-regulation of Notch3
• Stem cell-related genes and CSC gene signatures were reduced by OMP-59R5 in hair follicles and tumors