Biomarker study of vantictumab plus paclitaxel in HER2- breast cancer patients
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We have developed a monoclonal antibody, vantictumab, which blocks canonical Wnt5a-catenin signaling through binding of five FZD receptors (1, 2, 5, 7, and 8). This antibody inhibits the growth of several tumor types, including breast. Vantictumab reduces tumour cell frequency and exhibits synergistic activity with standard-of-care agents (Gurney et al, 2012). We previously identified a 6-gene Wnt pathway-related signature, FBXW2, CCND2, RHOU, CTBP2, WIF1, and DKK1, based on microarray gene expression data from 8 breast cancer patient derived xenograft (PDX) models with established in vivo response to vantictumab plus paclitaxel. This signature successfully predicted the response of 8 additional and independent PDX breast tumors.

We further developed a qPCR Research Use Only (RUO) assay for the 6-genes for use on FFPE breast tumor samples. This assay was evaluated in the Phase 1b study of vantictumab in combination with paclitaxel in locally recurrent or metastatic HER2-2 breast cancer (NCT01973309) and the signature score was refined using a Lasso model with overall survival as the outcome. A repeated 10 fold cross-validation was used to evaluate the performance of the gene signature. The association of the signature with progression free survival (PFS) and overall survival (OS) was examined (n=40 patients).

Pharmacodynamic (PD) biomarker analyses were performed on tumor biopsies and hair follicles by comparing gene expression data from post treatment time points versus baseline data (Affymetrix U133 plus 2 Microarrays).

RESULTS

Phase 1b clinical study: Dose escalation study for HER2-negative breast cancer with locally recurrent or metastatic disease with HER2+ prior chemotherapies. Total of 7 cohorts: 3.5, 7.0, 14.0 mg/kg QW; 3.0, 5.0, 8.0 mg/kg QW; and 8 mg/kg QW sequential dosing.

Primary Objectives:
- Maximum tolerated (or administered) dose.
- Safety, tolerability and recommended Phase 2 dose.

Secondary Objectives:
- Pharmacokinetics (PK) and immunogenicity of vantictumab.
- Preliminary efficacy.

Exploratory Objectives:
- PD and predictive biomarkers.

CONCLUSIONS

A 6-gene signature was identified and evaluated as a potential predictive biomarker for the response to vantictumab plus paclitaxel in HER2- breast cancer patients. The biomarker was tested in tumor samples from 40 patients in the Phase 1b trial of vantictumab with paclitaxel in HER2-negative breast cancer, and found to be significantly associated with both PFS and OS. PD biomarker analysis in hair follicles confirmed the mechanism of action of vantictumab plus paclitaxel in Phase 1b patient samples. Preliminary efficacy of vantictumab plus paclitaxel in the Phase 1b study was encouraging in breast cancer pts positive for the biomarker. Further biomarker validation is required in independent studies.