Predictive and pharmacodynamic biomarkers of vantictumab (OMP-18R5; anti-Frizzled) in non-small cell lung cancer

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Abstract

Background: Vantictumab is a monoclonal antibody that blocks canonical WNT/β-catenin signaling through binding of free FZD receptors (1, 2, 5, 7, 8). This antibody inhibits the growth of several tumor types by reducing tumor-inhibiting cell frequency (TIC) and exhibits a synergistic activity with standard-of-care (SOC) chemotherapeutic agents. To target responsive patients and understand the mechanism of action of the drug, we set out to identify predictive and pharmacodynamic (PD) biomarkers of vantictumab in non-small cell lung cancer (NSCLC).

Materials and methods: The response to vantictumab was established from in vivo efficacy experiments including different treatment groups (control, vantictumab, paclitaxel, and vantictumab in combination with paclitaxel). For combination treatment, same day dosing and sequential dosing (paclitaxel dosed 2 days after the antibody) were compared. Samples were collected for PD biomarker analysis. To identify a predictive biomarker for the response to vantictumab in NSCLC PDX models, gene expression data from 7 NSCLC patient-derived xenograft (PDX) models was analyzed. We utilized support vector machine-receptor feature elimination (SVM-RFE) to select genes and support vector machine (SVM) for classification.

Results: Vantictumab showed significant tumor growth inhibition as a single agent as well as in combination with paclitaxel. The reduction of TIC and the antitumor efficacy of vantictumab were significantly enhanced with sequential dosing compared with same day dosing. These findings suggested that optimal synergy occurs using sequential dosing, likely due to enhanced blockade of cell cycle progression at micromolar concentrations. PD biomarker analysis confirmed inhibition of Wnt signaling genes in Wnt, Notch, and stem cell pathways by vantictumab both as a single agent and also in combination with paclitaxel. Wnt pathway targets including AXIN2 and LEF1 were down-regulated significantly by vantictumab in both sequential dosing and same day dosing. Confirming the mechanism of action. From a series of 7 in vivo efficacy PDX experiments, LEF1 was identified as a predictive biomarker of vantictumab response and achieved the best predictive power with cross-validated positive predictive value (PPV) = negative predictive value (NPV) = sensitivity = specificity = 100%.

Strong correlation was also observed between LEF1 gene expression and the ratio of tumor volume. Furthermore, LEF1 was able to successfully predict the antitumor efficacy of vantictumab in 2 independent NSCLC PDX models. Prevalence estimation for LEF1 ranged from ~25%--50% for LEF1 in NSCLC was estimated ~35%--50%.

Conclusions: A biomarker study for the pharmacodynamics and response to vantictumab was performed using a series of PDX NSCLC models. PD biomarkers were identified which confirmed the mechanism of action of vantictumab. LEF1 was identified as a predictive biomarker and is being evaluated in the Phase 1b study of vantictumab in combination with SOC in previously treated NSCLC.

Efficacy of vantictumab in PDX models

Vantictumab reduced tumor growth as a single agent as well as in combination with paclitaxel. Antitumor efficacy of vantictumab was enhanced with sequential dosing compared with same day dosing of vantictumab (p=0.0162).

Materials and methods

Performance of LEF1 gene

Prevalence estimation of LEF1

LEF1 is significantly correlated with response to vantictumab and achieved the best predictive power with cross-validated positive predictive value (PPV) = negative predictive value (NPV) = sensitivity = specificity = 100%.

PPV proportion of true positives in identified negatives

NPV proportion of true negatives in identified negatives

Sensitivity: proportion of correctly identified positives in known positives

Specificity: proportion of correctly identified negatives in known negatives

References: