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

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Abstract

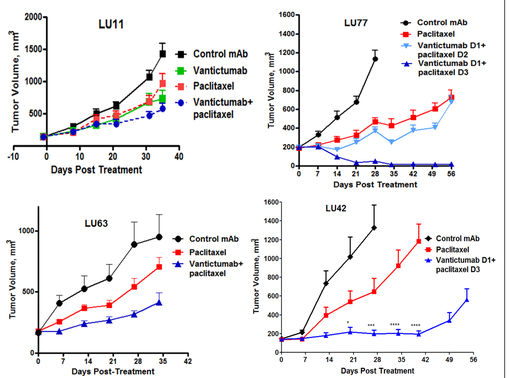
Background: Vantictumab is a monoclonal antibody that blocks canonical WNT/β-catenin signaling through binding of five FZD receptors (1, 2, 5, 7, 8). This antibody inhibits the growth of several tumor types, reduces tumor-initiating cell frequency (TIC) and exhibits synergistic activity with standard-of-care (SOC) chemotherapeutic agents[1]. 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 patients, gene expression data from 7 NSCLC patient derived xenograft (PDX) models was analyzed. We utilized support vector machine-recursive feature elimination (SVM-RFE[2]) 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 mitosis. PD biomarker analysis confirmed inhibition of 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 performance 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 response to vantictumab in 2 independent NSCLC PDX models. Prevalence estimation for LEF1 ranged from 35% to 50% based on public microarray datasets. LEF1 was also found to be significantly correlated with the response to vantictumab in combination with paclitaxel in 12 NSCLC PDX models (p=0.0162), indicating LEF1 as a potential predictive biomarker of the response to vantictumab as a single agent and in combination with SOC in NSCLC.

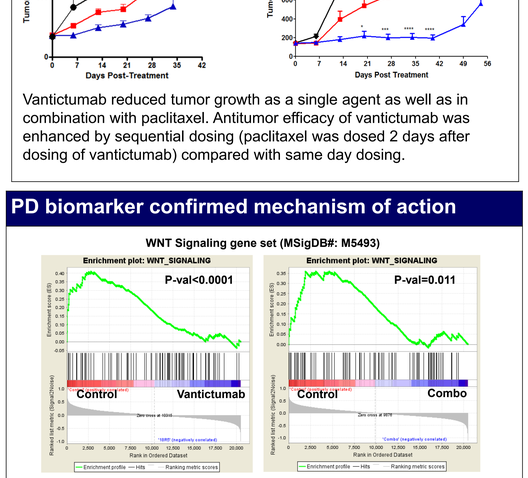
Conclusions: A biomarker study for the pharmacodynamics and response to vantictumab was performed using a series of PDX NSCLC models. PD biomarkers were identified which confirmed the mechanism of action of vantictumab. LEF1 was identified as a predictive biomarker and is being evaluated in the Phase 1b study of vantictumab in combination with SOC in previously treated NSCLC: NCT01957007. Comprehensive PD and predictive biomarker data will be presented.

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 by sequential dosing (paclitaxel was dosed 2 days after dosing of vantictumab) compared with same day dosing.

PD biomarker confirmed mechanism of action



GSEA[3,4] analysis showed the inhibition of Wnt signaling genes in tumors by vantictumab single agent and combo treatments (vantictumab + paclitaxel), but not paclitaxel (p-val=0.119).

Representative Wnt pathway genes inhibited in LU77 by vantictumab in combination with paclitaxel with both same day and sequential dosing. Wnt genes with a fold change < -1.2 and p-value < 0.05 in same day and sequential treatments vs control or paclitaxel are shown.

Predictive biomarker identification

Data preprocessing:
- GCRMA was used to process CEL files to probe set level expressions.
- Probe sets which potentially cross-hybridize to mouse were removed.
- Probe sets were collapsed to genes by using maximum gene expression over all probe sets mapping to one gene.

Feature selection:
- Used ~80 WNT pathway related genes.
- Removed genes with low expression/near-zero variance.
- Ranked features by using Support Vector Machine – Recursive Feature Elimination (SVM-RFE)[2].

Classification: Linear Kernel Support Vector Machine (SVM).

Performance measurement and model selection:
- PPV, NPV, sensitivity, specificity were calculated during leave-one-out cross validation (LOOCV).

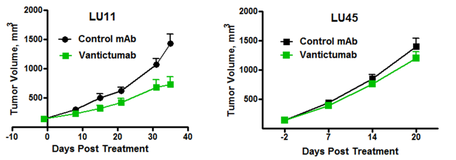
Training data for predictive biomarker discovery

Tumor	Subtype	Classification
LU11	Squamous	Responder
LU24	Squamous	Responder
LU33	Carcinoma	Responder
LU45	Adenocarcinoma	Non-responder
LU02	Adenocarcinoma	Non-responder
LU25	Large cell	Non-responder
LU56	Carcinoma	Non-responder

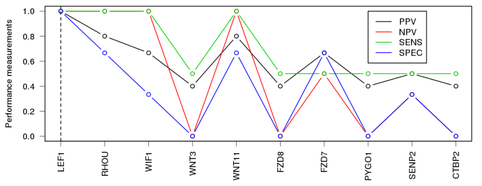
7 minimally passaged NSCLC PDX models from OncoMed tumor bank.

Microarray gene expression data (Affymetrix U133 plus 2) from baseline tumors.

Responder: tumor with greater inhibition by vantictumab vs. control.

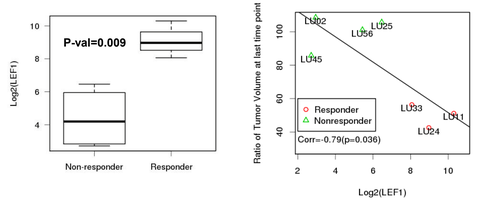


Performance of LEF1 gene



PPV: proportion of true positives in identified positives
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

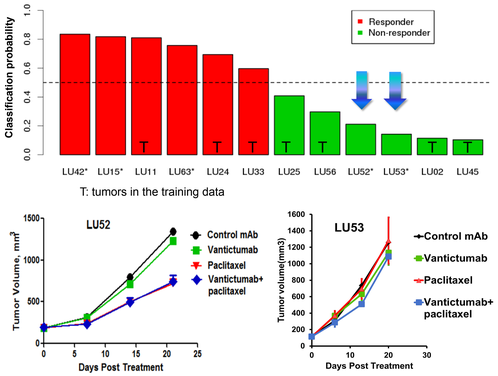
LEF1 correlation with single agent response



Responder: tumor with significant inhibition (pval<0.05) by vantictumab vs. control

$$RTV = \frac{TumorVolume_{combo}}{TumorVolume_{chemo}}$$

Prediction of response in PDX models

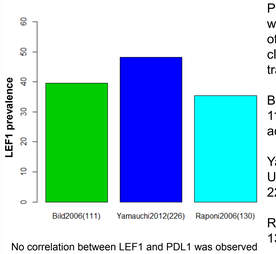


LEF1 gene expression levels correctly predicted efficacy of LU52 and LU53, previously untested tumors. LU52 and LU53 are both non-responders to vantictumab as a single agent and also in combination with paclitaxel.

References:

1. Gurney A, et al. *Proc Natl Acad Sci USA. 2012;109(29):11717–11722.*
2. Guyon I, et al. *Machine Learning, 46:389-422, 2002.*
3. Tamayo, et al. *PNAS 2005,102, 15545-15550*
4. Mootha, Lindgren, et al. *Nat Genet 2003, 34:267-273.*
5. Bild AH, et al. *Nature 2006 Jan 19;439(7074):353-7.*
6. Yamauchi M, et al. *PLoS One 2012;7(9):e43923.*
7. Raponi M, et al.. *Cancer Res 2006 Aug 1;66(15):7466-72.*

Prevalence estimation of LEF1



Prevalence of *LEF1* gene expression was estimated to be the percentage of responders based on the classification model built on the training data using *LEF1*.

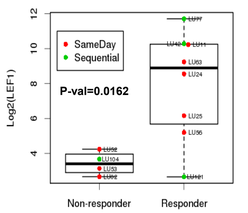
Bild2006[5]: Affymetrix U133plus2
111 NSCLC (54 Squamous, 57 adenocarcinoma).

Yamauchi2012[6]: Affymetrix U133plus2
226 lung adenocarcinoma.

Raponi2006[7]: Affymetrix U133plus2
130 squamous.

No correlation between LEF1 and PDL1 was observed

LEF1 correlation with combination response



Tumor	Subtype	Classification
LU11	Squamous	Responder
LU24	Squamous	Responder
LU25	Large cell	Responder
LU56	Carcinoma	Responder
LU02	Adenocarcinoma	Non-responder
LU52	Large Cell Neuroendocrine	Non-responder
LU53	Squamous	Non-responder
LU63	Large Cell Neuroendocrine	Responder
LU42	Squamous	Responder
LU121	Adenocarcinoma	Responder
LU104	Adenocarcinoma	Non-responder
LU77	Adenosquamous Cell Carcinoma	Responder

LEF1 is significantly correlated with response to vantictumab combined with paclitaxel. Responder = significant inhibition (pval<0.05) by vantictumab combined with paclitaxel compared to paclitaxel.

Summary

- Vantictumab reduced tumor growth as a single agent and in combination with paclitaxel. Sequential dosing for the combination treatment (vantictumab administered 2 days prior to paclitaxel) was more efficacious than same day dosing.
- PD biomarkers were identified and confirmed the mechanism of action of vantictumab.
  - Vantictumab inhibited genes in Wnt, Notch and stem cell pathways.
  - PD biomarkers were modulated by both same day and sequential dosing for the combination treatment.
- *LEF1* was identified as a predictive biomarker for response to vantictumab as a single agent in PDX models. *LEF1* was also found to correlate with response to vantictumab when combined with paclitaxel.
- Prevalence of *LEF1* in NSCLC was estimated ~35%--50%.
- *LEF1* as a predictive biomarker is being evaluated in the Phase 1b study of vantictumab combined with SOC in previously treated NSCLC: NCT01957007.