#3129

Predictive biomarker identification for response of vantictumab (OMP-18R5; anti-Frizzled) using primary patient-derived human pancreatic tumor xenografts

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ABSTRACT

Background: The Wnt/β-catenin signaling pathway has been shown to play a key role in both normal development and tumorigenesis[1,2]. We have developed a monoclonal antibody, vantictumab, 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, including pancreas, breast, colon and lung. Furthermore, our studies showed that vantictumab reduces tumor-initiating cell frequency and exhibits synergistic activity with standard-of-care (SOC) chemotherapeutic agents[3].

Material and methods: We set out to identify a predictive biomarker for the response of vantictumab in pancreatic cancer patients by analyzing mRNA-seq gene expression data from 14 patient-derived xenograft (PDX) models. These 14 minimally passaged pancreatic xenograft tumors were tested *in vivo* and their responses to vantictumab, in combination with the current SOC gemcitabine and *nab*-paclitaxel were established. Samples from these experiments were collected for pharmacodynamic (PD) biomarker analysis. We utilized a two-sample Welch's t-test to identify genes that can distinguish between responders and non-responders and the K-nearest neighbor (KNN[4]) algorithm for classification. A leave-one-out cross-validation was used to measure area under the ROC curve[5] (AUC), accuracy (ACC), positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity of the model.

Results: PD biomarker analysis confirmed inhibition of genes in Wnt and stem cell pathways by vantictumab in combination with gemcitabine as well as gemcitabine plus *nab*-paclitaxel. The selected 3-gene signature comprising *TGFB3, IGF2* and *SMO* achieved the best performance (AUC = 0.875, ACC = 0.93, PPV=0.91, NPV=1, sensitivity=1, specificity=0.75) in the 14 PDX pancreatic tumor models. In addition, a strong correlation between the gene signature biomarker and the ratio of tumor inhibition (RTI) in the pancreatic xenograft experiments was observed. The identified 3-gene biomarker was used to predict the response to vantictumab in combination with gemcitabine and *nab*-paclitaxel in three additional pancreatic PDX tumor models. The efficacy in the three models was successfully predicted by the biomarker.

Conclusions: The 3-gene biomarker is being evaluated in a Phase 1b study of vantictumab in combination with gemcitabine and *nab*-paclitaxel in previously untreated stage IV pancreatic cancer (NCT02005315).

MATERIALS AND METHODS

Training data for gene signature discovery:

- Baseline mRNAseq gene expression data from 14 minimally passaged pancreatic PDX tumors from OncoMed tumor bank.
- Responder: a tumor with significant inhibition by vantictumab combined with gemcitabine plus *nab*-paclitaxel compared to gemcitabine plus *nab*-paclitaxel alone.

Data preprocessing:

- RPKM was used for normalization of mRNAseq data.
- 420 curated Wnt pathway genes were used for analysis.

Feature selection: Two sample Welch's t-test.

Classification: K nearest neighbor (KNN) algorithm.

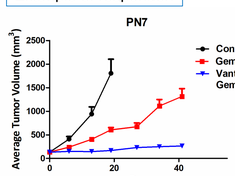
Performance measurement and model selection:

- AUC, ACC, PPV, NPV, sensitivity, specificity were calculated during leave-one-out cross validation.

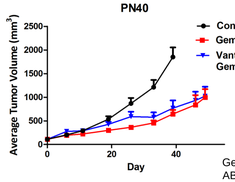
Tumor	Response
PN4	R
PN13	R
PN21	R
PN23	R
PN17	R
PN9	R
PN16	R
PN25	R
PN7	R
PN18	R
PN31	NR
PN38	NR
PN40	NR
PN33	NR

R: responder
NR: non-responder

Example of responder:



Example of non-responder:



Gem: gemcitabine
AB: *nab*-paclitaxel

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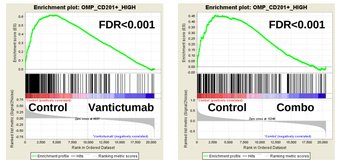
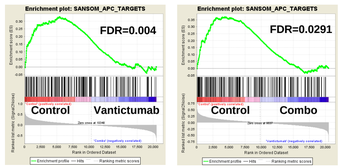
7 Mootha, L, et al. *Nat Genet 2003; 34:267-273*.

PD BIOMARKERS

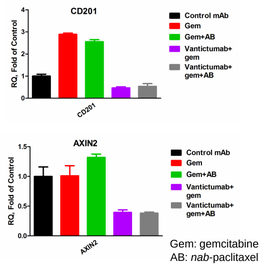
Pancreatic-specific cancer stem cell gene set OMP_CD201+_High: down-regulated by vantictumab and combo.



Wnt gene signature SANSOM_APC_TARGETS: down-regulated by vantictumab and combo.



5 PDX tumors PN7, PN8, PN11, PN23 and PN25 were used in the GSEA[6,7] analysis.



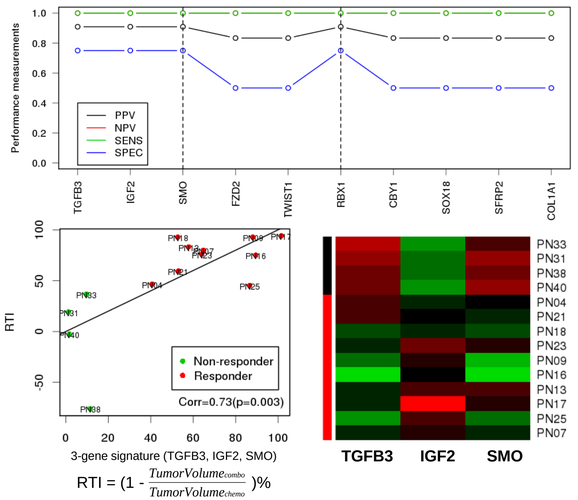
Gem: gemcitabine
AB: *nab*-paclitaxel

Taqman was performed with PN13. RNA samples were taken at the end of the treatment. Wnt target *AXIN2* and cancer stem cell gene *CD201* were down-regulated by both vantictumab + gemcitabine and vantictumab + gemcitabine + *nab*-paclitaxel respectively.

Combo: vantictumab+gemcitabine

GENE SIGNATURE DISCOVERY

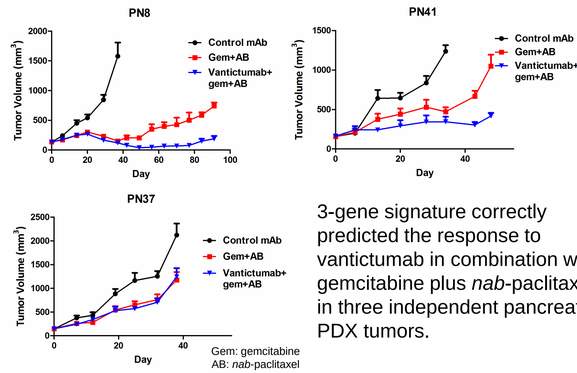
3-gene signature (TGFB3, IGF2, SMO) achieved the best performance.



RTI = (1 - $\frac{TumorVolume_{combo}}{TumorVolume_{chemo}}$)%

EVALUATION OF THE 3-GENE BIOMARKER

Tumor	Prediction	In vivo efficacy response
PN8	Responder	Responder
PN41	Responder	Responder
PN37	Non-responder	Non-responder



Gem: gemcitabine
AB: *nab*-paclitaxel

3-gene signature correctly predicted the response to vantictumab in combination with gemcitabine plus *nab*-paclitaxel in three independent pancreatic PDX tumors.

CONCLUSIONS

PD biomarkers were identified and confirmed mechanism of action of vantictumab in pancreatic tumors.

- Wnt gene signature and pancreatic tumor-specific cancer stem cell genes were down-regulated by vantictumab as a single agent and also in combination with gemcitabine.
- Wnt target AXIN2 and cancer stem cell gene CD201 were down-regulated by vantictumab combined with gemcitabine and *nab*-paclitaxel.

The 3-gene signature *TGFB3, IGF2, SMO* was identified as a predictive biomarker for response to vantictumab combined with gemcitabine plus *nab*-paclitaxel and it has been validated in three independent pancreatic PDX tumors.

The 3-gene signature as a predictive biomarker is being evaluated in the phase 1b study of vantictumab in combination with gemcitabine and *nab*-paclitaxel in patients with previously untreated stage IV pancreatic cancer (NCT02005315).

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