ABSTRACT

The Wnt8-Cat signaling pathway has previously shown to play key roles in both normal development and tumorigenesis1,2. We developed a monoclonal antibody, vantictumab, that blocks canonical WNT8-Cat signaling through binding of five Fzd receptors (1, 2, 5, 7, 8) at a conserved epitope within the extracellular domain. This antibody inhibits the growth of several tumor types, including breast, pancreas, colon and lung. Furthermore, studies also showed that vantictumab reduces tumor-initiating cell frequency and exhibits synergistic activity with standard-of-care chemotherapeutic agents3-6.

Predictive biomarkers are central to maximizing clinical benefit by targeting breast cancer patients most likely to respond to vantictumab. We analyzed microarray gene expression data from 8 minimally passaged breast cancer xenograft models (mostly triple-negative) with established in vivo responses to vantictumab combined with paclitaxel (4 responders, 4 non-responders). We utilized support vector machine—recursive feature elimination (SVM-RFE) to identify genes that can distinguish between responder and non-responders and SVM for classification. Leave-one-out cross-validation was used to measure positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity of the models. The selected 6-gene signature achieved the best performance with PPV-NPV-sensitivity-specificity=100% in the 8 breast cancer models. In addition, we observed a strong correlation between the gene signature biomarker and the ratio of tumor volume (RTV) observed in the breast xenograft experiments.

The identified 6-gene biomarker was used to predict the response to vantictumab in combination with paclitaxel in 6 additional, HER2-negative breast cancer xenograft models. The efficacy in all 6 models was predicted successfully by the biomarker. Prevalence data for the biomarker will be presented for both HER2-positive and triple-negative breast cancers. The 6-gene biomarker is currently being evaluated in a Phase Ib study of vantictumab in combination with paclitaxel in patients with locally recurrent or metastatic HER2-negative breast cancer.

METHODS

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:

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).

Correlation with Ratio of Tumor Volume

Prediction Of The Response In Primary Human Xenografts

Prevalence Estimation Of The 6-gene Signature

SUMMARY

- 6-gene predictive biomarker of response to vantictumab in breast cancers was identified.
- The 6-gene biomarker predicted response to vantictumab in 6 independent patient derived breast xenograft models.
- Prevalence of the 6-gene biomarker in HER2- and TNBC populations was estimated to be ~60% and 55%, respectively.

REFERENCES:
2. Wang2010: Affymetrix U133plus2, 226 patients (145 HER2-, 51 TNBC)
3. Cremoux2011: Affymetrix U133plus2, 92 patients (79 HER2-, 28 TNBC)
5. Wang2010: Affymetrix U133plus2, 115 patients (79 HER2-, 28 TNBC)