Antitumor Activity of Anti-RON Antibodies and Biomarker of Response

May Han, Kerry Whalen, Jamie Gifford, Andrea Boudrow, Kristian Meetze, Qing Liu, Ting Chen, William Winston, Sally Weiler, Jeno Gyuris

AVEO Pharmaceuticals, Inc., Cambridge, MA, USA.

Abstract

Receptors of Origin-Mediated RON (or MST1/2) receptor tyrosine kinases is a member of the c-Met family. Microarray stimulating proteins (MSP) cross-talk with c-Met to constitutively activate liganded RON. Overexpression of RON has been demonstrated in multiple solid tumor types, and it correlates with disease progression. A potentially oncogenic splice variant has also been observed in a subset of breast cancers. Inhibition of RON has been shown to induce tumor development and metastasis in animal models. Inhibition of RON kinase activity dominantly negative receptor, receptor-like kinase inhibitors, and monoclonal antibodies have shown limited effectiveness in several preclinical models. Investigating the antitumor therapeutic potential of an anti-RON antibody is warranted, and a predictive biomarker to guide the therapeutic development are important in this regard. Here, we identified two humanized derivatives, 29B06 and 07F01, with high binding affinity to the RON protein by Biacore and SPR. We have also identified a multi-parametric biomarker to identify tumor lines with potentially activated RON pathway, and it is being validated in a panel of xenograft studies. This signature may also help to predict which tumor lines or subtypes are more likely to respond to anti-RON antibody treatments.

In vitro, 29B06 and 07F01 are humanized, and the panel of functional anti-RON antibodies were identified by their ability to inhibit MSP-induced cell signaling, cell proliferation, migration, apoptosis (cleaved caspase-3 IHC), decreases angiogenesis (CD31 IHC), induces tumor regression in xenograft settings.

29B06 is efficacious in human cancer xenografts

29B06 is efficacious in human cancer xenografts

We have identified a panel of high-affinity anti-RON antibodies that inhibit MSP-induced cellular activities, such as p-RON, p-Erk, mobility, and invasion.

Summary

- A high-scored RON index is strongly correlated with tumor volume, suggesting that the cell line homogeneity is an important factor in predicting tumor response.
- A RON pathway index biomarker derived from human microarray datasets was shown to correlate with TROG response to 29B06.
- The same cancer types, such as pancreatic cancer and colorectal cancer, are highly enriched for samples with RON pathway index in human cell lines and xenografts, suggesting that the biomarker may be relevant in clinical development.
- The biomarker may help to identify tumor types or subtypes for clinical investigation.

Biomarker of 29B06 response

Cell lines with high RON index are highly enriched in certain cancer types

Human tumors with high RON index are highly enriched in certain cancer types

GeneLogic dataset: 660 tumors, 8 types

GSK cell line dataset: 316 cell lines, diverse types

Biomarker of RON response

GSK panel

- A gene set consists of the top-40 most correlated genes, with gene expression identified by 7 different human microarray datasets.
- The RON pathway index is the average of the expression scores of these genes in a given dataset.
- To date, 16 cell lines with RON expression (by FACS analysis) was tested for tumor growth inhibition (TGI). % by 29B06 in xenograft settings.
- There is a significant correlation between RON pathway index and TGI, with R = 0.56, P = 0.01
- Top 25% of cell lines have a high RON index value of ≥ 0.5 in GSK cell line dataset, top 25% of tumors have high RON index value ≥ 0.6 in GeneLogic dataset.
- The same cancer types are enriched for high RON index in both cancer cell line and human tumor dataset, suggesting that the cell line homogeneity may be applicable to human tumors.

Pharmacokinetic parameters of 29B06 and 07F01

- 29B06 is efficacious at inhibiting tumor growth in more than 10 xenograft models, including tumors expressing WT RON and RON(Δ160) iso.
- 29B06 treatment decreases proliferation (Ki-67 %), increases apoptosis (low level expression Ki-67), decreases angiogenesis (CD31 %), and induces receptor degradation (RON western) in xenografts.
- 29B06 was administered twice weekly at the indicated doses.

Inhibition of MSP-stimulated HPAF-II migration

Inhibition of MSP-stimulated HPAF-II invasiveness

Ant-RON mAbs bind to receptor

Ant-RON antibodies inhibit MSP-binding to RON

Pharmacokinetic parameters of 29B06 and 07F01

Pharmacokinetic parameters of 29B06 and 07F01

- Pharmacokinetic parameters of 29B06 are as follows: T1/2, 9.7 days; Cmax, 31.1 µg/ml; Vd, 23.9 ml/kg.
- Pharmacokinetic parameters of 07F01 are as follows: T1/2, 8.2 days; Cmax, 34.8 µg/ml; Vd, 20.0 ml/kg.
Antitumor Activity of Anti-RON Antibodies and Biomarker of Response

May Han, Kerry Whalen, Jamie Gifford, Andrea Boudrow, Kristan Meetze, Qing Liu, Ting Chen, William Winston, Solly Weiler, Jenő Gyuris

AVEX Pharmaceuticals, Inc., Cambridge, MA, USA.