

## **Novel biomarker may predict response to new VEGF receptor inhibitor**

EurekaAlert

DENVER ? Researchers believe there may be a way to predict, based on individual tumors, those patients that are more likely to respond to the investigational new drug tivozanib.

This is possible, the researchers from AVEO Pharmaceuticals, Inc. said, because they have used a new way of creating animal tumor models that mimic tumor variation seen in human. Based on the results of these studies, they have found a single biomarker that may predict resistance to tivozanib, an oral, triple VEGF (vascular endothelial growth factor) receptor inhibitor.

Tivozanib is in an ongoing Phase III registration trial in kidney cancer, which recently completed enrollment of 500 patients ahead of schedule, and is in multiple early trials in patients with breast, colon and lung cancer.

In a study being presented at the Fourth AACR International Conference on Molecular Diagnostics in Cancer Therapeutic Development, the researchers said that the biomarker reflects the presence of certain white blood cells inside a tumor.

"Predictive biomarkers that can be used to assess activity of treatments are what we are all striving for in cancer therapy today," said Murray Robinson, Ph.D., senior vice president, translational medicine, at AVEO Pharmaceuticals, Inc., in Cambridge, Mass. "We want to know in advance which patients are most likely to respond to an anticancer therapy, and in this way, spare patients who cannot respond from ineffective therapy."

In its ongoing trials, the company is collecting biomarker data in order to correlate the presence of the biomarker with clinical activity. "This is a necessary step that we must do to validate the predictive value of the biomarker," Robinson said.

To date, the researchers have evaluated 600 human tumor samples across eight different tumor types.

"We saw the biomarker in subsets of all the human tumor types we looked at. Based on these findings, we believe that the biomarker discovered in our animal models may be replicated in human tumors, and may be an important discovery relevant to patient care," said Robinson.

At the AACR conference, Robinson showed that the same biomarker identified in AVEO's breast tumor model was associated with clinical activity in a set of kidney tumor patients from a previous Phase II kidney cancer trial. This biomarker is associated with white blood immune cells that are recruited into the tumor to

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produce angiogenic growth factors.

"This produces an intrinsic resistance to tivozanib, which is an anti-angiogenesis agent," Robinson said.

The researchers inserted specific oncogenes and other engineered genes altered in numerous cancer types into the tissue of animals and then studied the variety of tumors that were produced. For example, genetically altering the HER2 gene resulted in tumors that naturally expressed different pathways for growth, Robinson said.

"That mimics what happens in women with HER2-positive breast cancer because across patients, there is a significant variation in these HER2 tumors that dramatically alters their response to treatment," he said.

After molecularly characterizing each tumor, they tested what happened when the cancer was treated.

"Because we have the molecular character of the tumor, we can associate biology with response. We have an ongoing effort to discover and develop predictive biomarkers that will aid our clinical development strategies and, we believe, maximize the benefit for specific patient populations," Robinson said.

In this way the researchers isolated tumors that do not respond to tivozanib, and from this they were able to identify the resistant biological phenotype. Further study revealed a correlation between the biomarkers and tivozanib clinical activity.

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