

Novel monoclonal antibody offers potential treatment for tumors resistant to VEGF therapy

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Despite the widespread use of current antiangiogenic cancer therapies, many tumors escape this blockade, which is designed to shut down growth of new blood vessels that feed tumors and spread cancer cells. Now, a study reported at the AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics suggests that targeting a novel antiangiogenic receptor may help patients whose cancer does not respond to existing agents.

The experimental agent, PF-03446962, targets activin receptor-like [kinase 1](#) (ALK-1), which is part of the transforming growth factor β (TGF β) superfamily of receptors that potentially regulate cell growth and differentiation. Known as a [tumor](#) suppressor, TGF β can conversely promote invasion and metastasis during the later stages of [cancer](#) progression, said Filippo de Braud, M.D., who was director of new drugs at the European Institute of Oncology when the study was conducted and is now chief of the Medical Oncology Department at the National Tumor Institute in Milan, Italy.

Tumor cells frequently lose the growth inhibitory response to TGF β , which makes it a prime target for cancer treatment, he said. PF-03446962, a fully humanized monoclonal antibody, specifically inhibits the activity of ALK-1, which the researchers said is in part regulated by vascular endothelial growth factor (VEGF), the protein that activates angiogenesis and other proangiogenic factors. Shutting down

ALK-1 inhibits the VEGF pathway in a manner different from other antiangiogenic treatments now on the market, de Braud said.

Researchers tested PF-03446962 in a phase 1 clinical trial, which demonstrated that the agent exerted anticancer activity in tumors already resistant to VEGF treatment.

De Braud and his colleagues tested eight different doses of PF-03446962 in 44 patients with solid tumors. Results showed a partial response in three patients and stable disease lasting at least four months in seven patients. Most of the patients who benefitted had previously been treated with prior antiangiogenic therapy for lung, renal or liver cancer. Some of these patients did not achieve remission with previous antiangiogenic therapy, "suggesting that ALK-1 can operate as an escape mechanism to VEGF," de Braud said.

The two patients with the longest response (stable disease for about a year) had been diagnosed with adrenocortical cancer and mesothelioma.

The researchers noted that three patients developed telangiectasia, which is dilation of [blood vessels](#) near the skin. This disorder is known to be caused by a mutation in the ALK-1 gene, and development of this mild side effect in these patients demonstrates PF-03446962 is affecting ALK-1 function.

"Based on this clinical activity, anti-ALK-1 may be a promising novel strategy to help patients who have failed previous VEGF therapy," de Braud said. The agent might be used on its own or in combination with current antiangiogenic therapy to strengthen inhibition of the VEGF pathway.

Toxicities seen in the phase 1 trial were manageable, a finding that demonstrates that the agent is safe to use, he said.

Provided by American Association for Cancer Research

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