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Marker may predict response to ipilimumab in advanced melanoma

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Among patients with advanced melanoma, presence of higher levels of the protein vascular endothelial growth factor (VEGF) in blood was associated with poor response to treatment with the immunotherapy ipilimumab, according to a study published in *Cancer Immunology Research*, a journal of the American Association for Cancer Research.

The study suggests combining immunotherapy with VEGF inhibitors, also known as angiogenesis inhibitors, may be a potential option for these patients.

The immune-checkpoint inhibitor ipilimumab works by boosting the body's immune system to combat melanoma. VEGF is a protein that promotes new blood vessel formation and growth, a process called angiogenesis, thus providing nutrients to the growing tumor. The study found that among patients who had late-stage melanoma, those who had high levels of VEGF in their blood prior to treatment with ipilimumab had decreased clinical benefit, poor overall survival outcomes, and were 60 percent more likely to die of their disease, compared with those who had lower levels of VEGF.

"VEGF is known to suppress the maturation of immune cells and their antitumor responses, and evidence points toward an association between high serum VEGF levels and poor prognosis in melanoma patients," said F. Stephen Hodi, M.D., director of the Melanoma Center at Dana-Farber Cancer Institute, and associate professor of medicine at Harvard Medical School in Boston, Mass. "VEGF has also been shown to be a potential

biomarker for other immunotherapies, thus it seemed logical to test the ability of VEGF to predict responses to ipilimumab.

"We found that VEGF may actually hinder some of the effects of the immune-checkpoint inhibitor," Hodi added. "We are beginning to better define predictive biomarkers for immune-checkpoint blockers, specifically ipilimumab. Our study further suggests that there is a potential interaction existing between the biology of angiogenesis and immune-checkpoint blockade."

Hodi and colleagues conducted retrospective analyses of blood samples collected from 176 patients with metastatic melanoma, before and after they were treated with ipilimumab, at Dana-Farber/Harvard Cancer Center and Memorial Sloan-Kettering Cancer Center. Patients were 16 to 91 years old, and the majority of them had stage 4 disease.

VEGF levels in patients' blood ranged from 0.1 to 894.4 picograms per milliliter (pg/ml). The investigators determined 43 pg/ml to be the cutoff value, and evaluated patient responses to treatment as those whose pretreatment VEGF levels were greater than (VEGF-high) or less than (VEGF-low) the cutoff value.

They found that at 24 weeks after starting ipilimumab treatment, 41 percent of the VEGF-low patients experienced clinical benefit, including partial or complete treatment responses; only 23 percent of the VEGF-high patients experienced a clinical benefit.

The median overall survival for VEGF-low patients was 12.9 months, compared with 6.6 months for VEGF-high patients.

The researchers found that while pretreatment VEGF levels had the potential to predict treatment outcomes, changes in VEGF levels during treatment were not linked to treatment outcomes.

"It may be worthwhile to investigate combining immune-checkpoint inhibitors and angiogenesis inhibitors in advanced melanoma with high serum VEGF levels," said Hodi. His team has initiated a randomized clinical trial to test ipilimumab in combination with bevacizumab, an angiogenesis inhibitor, in patients with advanced melanoma.

Provided by American Association for Cancer Research

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