

Immune booster combined with checkpoint blocker improves survival in metastatic melanoma

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Patients with metastatic melanoma who were treated with ipilimumab, an immune checkpoint blocker, survived 50 percent longer – a median 17.5 months vs. 12.7 months – if they simultaneously received an immune stimulant, according to a study led by Dana-Farber Cancer Institute scientists.

Patients in the clinical trial who got the combined therapies also had fewer serious adverse side effects than those who received only [ipilimumab](#), the researchers report in the *Journal of the American Medical Association*.

The group treated with both ipilimumab and the immune stimulant, called sargramostim, had a one-year survival rate of 68.9 percent vs. 52.9 percent in the ipilimumab-only group. In both groups, however, the median progression-free survival (the length of time before the cancer began to grow) was similar – 3.1 months.

The two drug combination "reveals the possibilities of combining an immune signaling molecule with taking the brakes off at the same time," said F. Stephen Hodi, MD, first author on the clinical trial report. Hodi is director of the Melanoma Treatment Center and director of the Center for Immuno-Oncology at Dana-Farber.

Ipilimumab, sold as Yervoy, is an immunotherapy drug consisting of a

monoclonal antibody that targets a protein receptor, CTLA-4. Because CTLA-4 acts like a brake on the immune system, it prevents the body's defenses from attacking [cancer cells](#). By blocking CTLA-4, ipilimumab releases the brake, allowing cell-killing T cells to assault the cancer cells. It is sold for treatment of melanoma and is in [clinical trials](#) for lung and other cancers.

Sargramostim is a form of GM-CSF (granulocyte-macrophage colony-stimulating factor), a natural protein that spurs the growth of [white blood cells](#) in the immune system. It is used, among other things, to restore white blood cells following a stem cell transplant for cancer.

Hodi designed this investigator-initiated clinical trial to find out if giving sargramostim along with ipilimumab would have a synergistic effect against the melanoma – like pressing the immune system's accelerator while releasing the brake. He had reason to think so, because clinical benefits had been seen in cancer patients who received ipilimumab along with cancer vaccines that pumped out GM-CSF.

The phase 2 randomized clinical trial was conducted by the Eastern Cooperative Oncology Group, enrolling 245 patients with stage 3 or stage 4 [metastatic melanoma](#) who had been treated with other drugs. The patients were followed for a median of 13.3 months.

The advantage in overall survival of nearly five months in the group receiving sargramostim was significant, as was the lower toxicity in that group. Why the drug combination did not prolong the time before the disease progress – as might be expected, because it did extend overall survival – is not clear, the researchers said. "It could be that the treatment is causing inflammation that that looked like early disease progression, but we won't know without further studies," Hodi said.

Larger trials and longer follow-up will be needed to confirm the results,

he added. "But this opens the possibility of improving clinical outcomes and decreasing serious side effects in treating advanced melanoma with ipilimumab."

More information: *Journal of the American Medical Association*, doi:10.1001/jama.2014.13943

Provided by Dana-Farber Cancer Institute

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