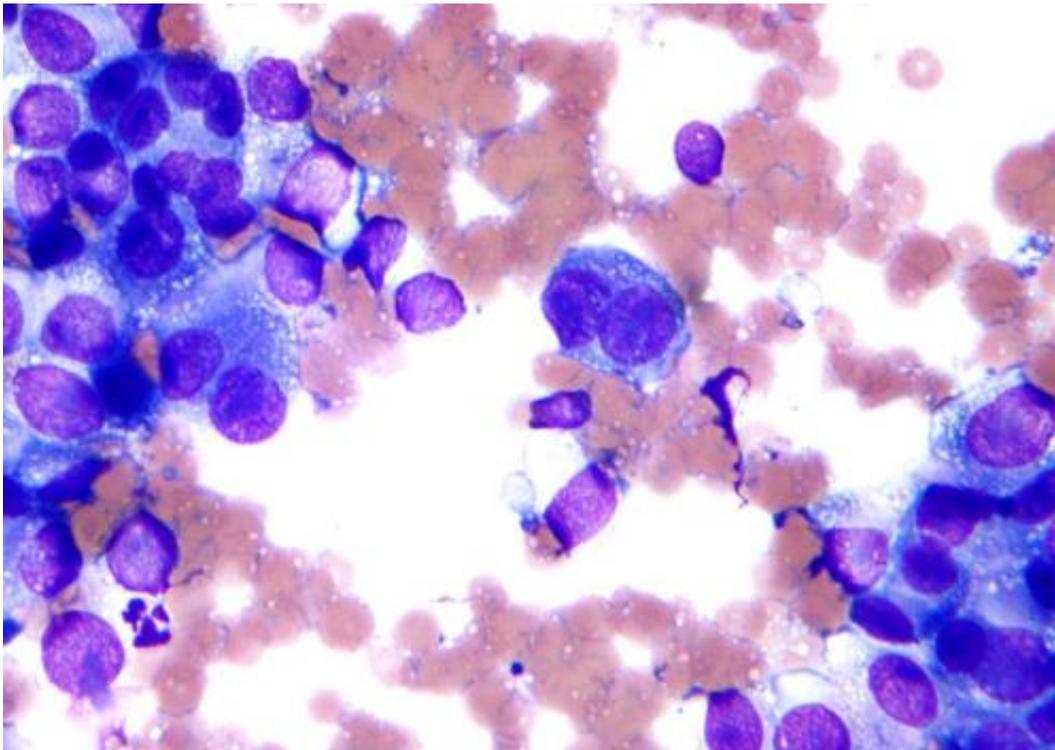


Three-drug combination helps curb the growth of deadly type of skin cancer

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Micrograph of malignant melanoma. Cytology specimen. Field stain. Credit: Nephron/Wikipedia

A UCLA-led research team has pinpointed a three-drug combination that could prove to be an effective new therapy for people with a specific type of advanced melanoma.

The approach shows promise for extending the lives of people with a

type of melanoma that contains a potent gene mutation, BRAF V600E. In [clinical trials](#), it appeared not to cause the debilitating side effects that are caused by a combination of one targeted drug and an [immunotherapy drug](#).

The researchers found that people with the melanoma survived longer without the cancer progressing or growing when they received a combination of two targeted inhibitors that block the BRAF mutation (dabrafenib and trametinib) and an immune checkpoint inhibitor drug (pembrolizumab) as the [initial treatment](#) for their disease.

"Utilizing the three drugs together sensitized the patient's own immune system to bolster the power of immunotherapy and block the growth of two genes—BRAF and MEK—that cause cancer cells to reproduce and grow out of control," said Dr. Antoni Ribas, the paper's senior author, a professor of medicine at the David Geffen School of Medicine at UCLA and director of the UCLA Jonsson Comprehensive Cancer Center's Tumor Immunology Program.

The results of phase one and phase two clinical trials were published today in two papers in the journal *Nature Medicine*.

In the phase two trial, those who received the three-drug combination had progression-free survival—meaning that the disease did not worsen or progress—for an average of 16 months. Those who received trametinib, dabrafenib and a placebo lived for an average of 10.3 months without the disease progressing.

Approximately 94,000 Americans are diagnosed with melanoma annually, and around 7,000 people die of the disease each year. About half of the people who are diagnosed with metastatic melanoma carry the BRAF mutation.

Previous studies have found that using one of the three drugs alone can dramatically shrink tumors in a small percentage of people with melanoma. A majority of people on the treatment, however, do not see any benefit or end up experiencing a relapse. Two-drug combinations also have been tested, but they, too, have had limited success.

"Earlier attempts to combine a targeted agent with an immune checkpoint inhibitor as a double-combination therapy had debilitating side effects for patients, and it was just too toxic to continue testing, so we went back to the drawing board," said Ribas, who is also the director of the Parker Institute for Cancer Immunotherapy Center at UCLA. "We found that by using two targeted inhibitors, instead of just one, in combination with a checkpoint inhibitor, we could safely and effectively treat the cancer."

In the phase one trial, the scientists tested the three-drug combination for safety in 15 people with BRAF-mutated metastatic melanoma. In 11 of them, the tumors shrank and remained stable and did not grow again for 12 to 27 months.

One of the participants in that trial was Joanna, a former Wall Street trader and veteran hiker and snowboarder. In 2014, Joanna had golf ball-sized tumors throughout her body, and she was diagnosed with BRAF-mutated advanced melanoma. By the time the clinical trial began, she needed a wheelchair to get around, a far cry from the active life she was accustomed to.

"I was in really bad shape," Joanna said. "I was bedridden and on pain killers, and I couldn't really move. It's no way to live. I was obviously scared, yet surprisingly optimistic before starting the treatment."

Just days after she began the therapy, Joanna's tumors began to disappear.

"I could actually see it working," she said. "The tumors started dissolving and getting smaller almost immediately. Within a month I was back walking on my own, and three months later I was on a plane to the Canadian Rockies for a vacation with one of my best friends."

Five years later, Joanna still has no evidence of the disease.

After the study's first phase proved the drug combination to be safe, the next phase incorporated 120 people at 22 sites around the world. Half of the patients received the three-drug combination, and the other half received the two targeted drugs and a placebo instead of the immunotherapy drug.

Even though the trial was randomized, the three-drug group had more patients with a poorer prognosis than the placebo arm. Regardless, people in the three-drug group fared better, with their [progression-free survival](#) lasting an average of nearly six months longer than the average for those in the placebo arm.

"The results of the triple therapy is so much more encouraging than double-therapy combinations with these [drug](#) agents," Ribas said. "With this triple [combination](#), we're doing two things at once: using the two inhibitors to block the cancer from spreading, and stimulating the immune system. An immune response has the ability to remember foreign invaders and help protect the body from similar infections in the future, so enlisting an [immune response](#) to the cancer is aimed at having more durable responses to the therapy."

More information: Paolo Antonio Ascierto et al. Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma, *Nature Medicine* (2019). DOI: 10.1038/s41591-019-0448-9 , www.nature.com/articles/s41591-019-0448-9

Antoni Ribas et al. Combined BRAF and MEK inhibition with PD-1 blockade immunotherapy in BRAF-mutant melanoma, *Nature Medicine* (2019). DOI: 10.1038/s41591-019-0476-5 , www.nature.com/articles/s41591-019-0476-5#article-info

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