# Trial stopped early: Giving immunotherapy before targeted therapy improves survival in advanced melanoma

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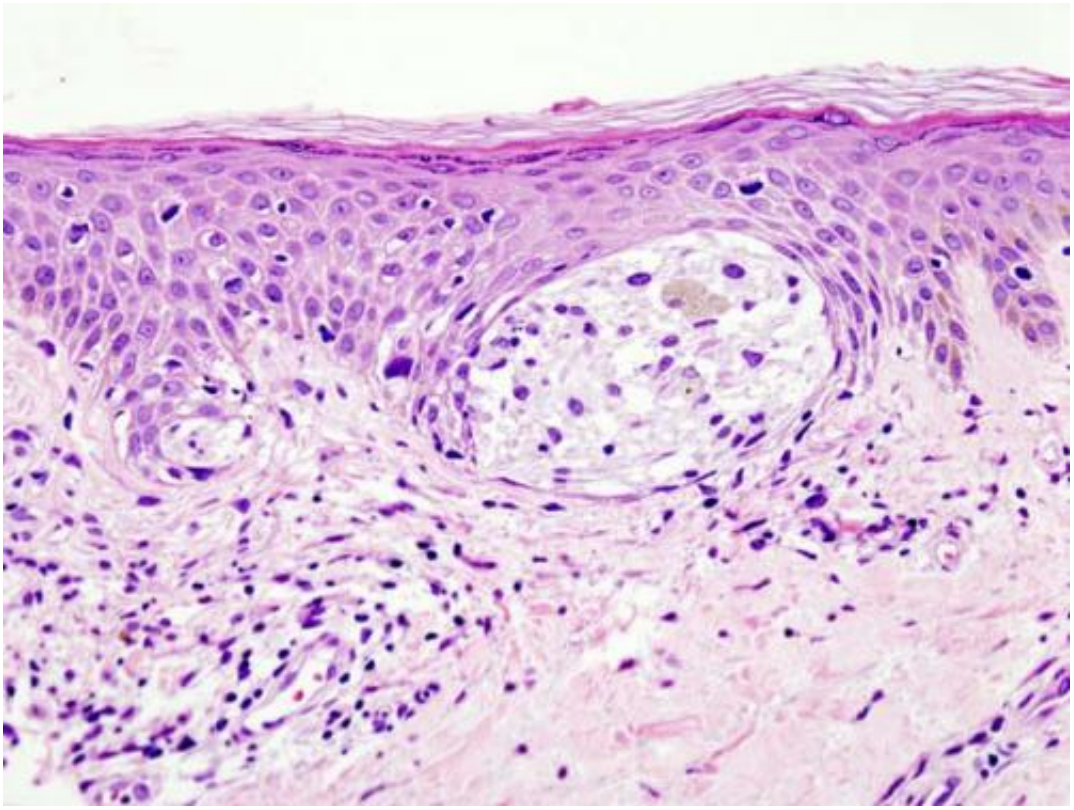

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

More people with advanced melanoma survive for two years or more when they receive a combination of two immunotherapy drugs given

before a combination of two targeted therapies, if needed, compared to people who start treatment with targeted therapies. The finding comes from a clinical trial that was stopped early because definitive results became apparent sooner than expected. It provides strong evidence for how best to treat patients with melanoma that has a specific mutation: immunotherapy is the better initial approach even for people whose tumors have a mutation that could be treated by targeted therapies.

DREAMseq, a phase III, randomized clinical trial conducted at 849 U.S. locations, was led by oncology professor Michael Atkins, MD, at the Georgetown Lombardi Comprehensive Cancer Center, on behalf of the ECOG-ACRIN Cancer Research Group and sponsored by the National Cancer Institute. The findings were presented November 16, 2021, at the inaugural American Society of Clinical Oncology (ASCO) Virtual Plenary Series.

An estimated 106,000 new melanomas cases will be diagnosed and over 7,000 people will die of the cancer in 2021, according to the National Cancer Institute. While melanoma rates rose rapidly over the past few decades, the latest Annual Report to the Nation on the Status of Cancer noted that mortality rates are now declining, reflecting a significant increase in survival due to improved treatment options, among other factors.

"The drug combinations tested in this trial all improve survival compared to prior standards of care, but we now know which combination should be administered first to achieve maximum benefit for the vast majority of our patients," says Atkins. "This trial should provide clearer guidance to clinicians on when to administer particular treatments."

Starting in 2015, 265 trial participants with metastatic melanoma were randomly assigned to two groups; each group received one drug combination followed by the other combination if their cancer resisted

the first combination.

Each regimen had its own distinct method of combating melanoma. One worked by targeting the effects of a mutation in the *BRAF* gene with the drugs dabrafenib and trametinib, which are taken in pill form. Everyone in the trial had a melanoma that contained a *BRAF* V600 mutation that is known to drive tumor proliferation. Working together, the two targeted drugs inhibit the function of the proteins associated with the *BRAF* mutation, leading to direct tumor cell killing.

The other two-drug combination utilized the immunotherapy drugs ipilimumab and nivolumab. They were given intravenously and function by disabling the cancer's defense mechanisms, thereby unleashing the body's antitumor immunity.

The trial outcomes were definitive enough that the trial is being stopped and reported early, with 59 percent of patients having been on the trial for two years. The two-year overall survival rate for people who first received the immunotherapies was 72 percent versus 52 percent for those who initially got the targeted therapies. Progression-free survival, where the cancer is stable or improving, was also trending in favor of those who started on the immunotherapies.

Other trial findings are intriguing but point to uncertainties that will need to be teased out in future analyses or studies. Overall response rates, which indicate who had a partial or complete response to the drugs, were similar for all permutations of drug administration except for patients who received targeted therapies first and then got immunotherapy, indicating that immunotherapy may not work well after targeted therapy.

"One conundrum in the data showed that some patients don't do well on initial immunotherapy treatments and for some reason switching to targeted therapies did not help," says Atkins. "We are focusing on trying

to determine why there was no benefit for this small group of patients."

Given the clearer advantage for starting with immunotherapy, which is not dependent on having a *BRAF* mutation, the researchers believe all patients with metastatic melanoma who don't have other complicating factors should now be treated first with immunotherapy. What this study does not resolve is what immunotherapy regimen is the best initial treatment. That question is continuing to be addressed in other clinical trials.

"While this trial focuses on melanoma, it could have significant implications for the treatment of other forms of cancer where immunotherapies are increasingly part of treatment regimens," says Atkins.

**More information:** clinicaltrials.gov/ct2/show/NC … EAMSeq&draw=2&rank=1

Provided by Georgetown University Medical Center

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