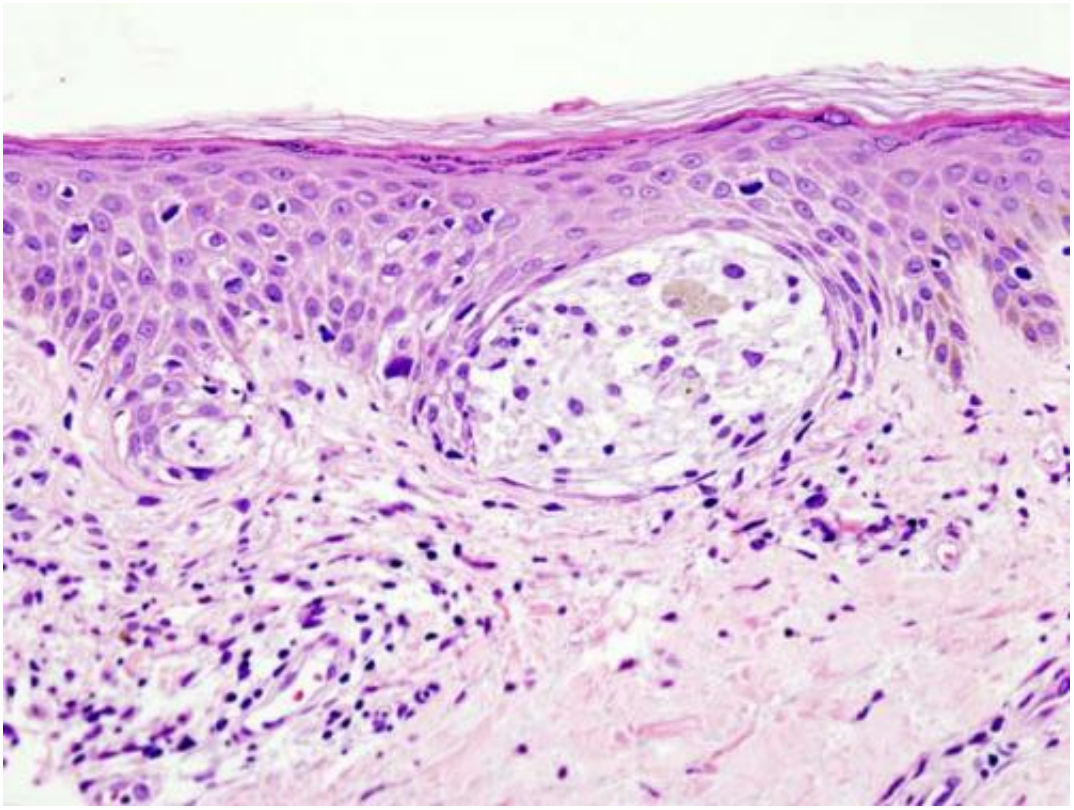
# Neoadjuvant combination checkpoint blockade trial yields high response rates for patients with stage 3 melanoma

October 8 2018



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

Combination checkpoint blockade before surgery (neoadjuvant therapy) produced a high response rate among patients with high-risk stage 3

melanoma, with nearly half having no sign of disease at surgery, but a high incidence of side effects caused the trial to be closed early.

The phase II study was led by researchers at The University of Texas MD Anderson Cancer Center. Results of the study, the first randomized neoadjuvant clinical trial of immune checkpoint blockade for melanoma patients, are reported in *Nature Medicine*.

Patients received either the PD-1 inhibitor nivolumab or the combination of nivolumab and the CTLA-4 checkpoint inhibitor ipilimumab. Each drug blocks a separate off-switch on T cells, freeing the immune system to attack cancer. All patients received nivolumab after surgery.

On the combination arm, 8 of 11 (73 percent) patients had their tumors shrink, 5 (45 percent) had no evidence of disease at surgery (pathological complete response), and 73 percent had grade 3 side effects, causing dose delays in 64 percent and delaying surgery for some. There were no grade 4 side effects.

In the nivolumab arm, 3 of 12 (25 percent) had their tumors shrink and had pathological complete response, only 8 percent had grade 3 side effects. Two patients progressed to stage 4 metastatic disease before they could get to surgery.

"In this trial, treatment with single-agent anti-PD-1 was associated with modest response rates, and we were concerned that two patients on that arm progressed and could not go to surgery," said co-first author Rodabe Amaria, M.D., assistant professor of Melanoma Medical Oncology. "Treatment with combined checkpoint blockade was much more effective, but at the expense of significant toxicity. It is clear from this trial that we need to further optimize this treatment approach."

All of those who achieved pathological complete response in either arm remain without evidence of disease recurrence. Overall survival was 100 percent at 24 months in the combination arm and 75 percent in the nivolumab arm.

"The advantage of a neoadjuvant approach in this setting is that it enables an interval evaluation of the tumor cells after therapy to determine the extent to which those tumor cells responded to the therapy in real time and predict which patients are likely to experience durable responses going forward. It also provides us the tissue resources to determine why tumors may not respond to therapy and thus tailor therapies going forward as we learn more about resistance," said co-senior author on the study, Michael Tetzlaff, M.D. Ph.D., associate professor of Pathology and Translational and Molecular Pathology.

Checkpoint blockade has been effective against metastatic melanoma and in reducing the risk of relapse after surgery for high-risk stage 3 disease. However, there is evidence in preclinical models that treatment before surgery may be superior to giving these agents in the adjuvant setting (after surgery).

Amaria and senior author Jennifer Wargo, M.D., associate professor of Surgical Oncology and Genomic Medicine, launched the investigator-initiated trial through MD Anderson's Moon Shots Program, a collaborative effort to accelerate the development of scientific discoveries into clinical advances that save patients' lives.

Due to the results of this study, the team re-designed the study to explore the safety and efficacy of nivolumab plus relatlimab, an inhibitor of the LAG3 immune checkpoint, a combination that Amaria notes thinks may be more effective than nivolumab alone with a better side effect profile than treatment with combined CTLA-4 and PD-1 blockade.

## Identifying biomarkers of response and resistance

"This presurgical platform provides an ideal setting to study biomarkers of response, mechanisms of resistance, and differential effects of these two commonly used treatment regimens," said co-first author Sangeetha Reddy, M.D., instructor in Cancer Medicine. "In this study we confirmed known biomarkers of response and observed novel biomarkers of therapeutic response that we are now studying further".

Analysis of biopsies and blood samples taken at multiple time points during the trial revealed:

- Baseline infiltration of tumors by lymphoid cells and total mutational burden were associated with response to therapy.
- Early on-treatment biopsies were better predictive of who would respond to both therapies compared to baseline biopsies.
- Molecular analyses using a novel spatial profiling technology identified differential abundance of multiple immune markers that correlated with response and/or resistance to neoadjuvant immune checkpoint blockade.
- T cell receptor sequencing identified differential patterns in responders versus non-responders to anti-PD-1 therapy versus combined CTLA-4 and PD-1 blockade. Responders to PD-1 monotherapy showed evidence of a pre-existing but inhibited T cell repertoire that further expanded during treatment, while treatment with combination therapy was associated with more variable changes in the T cell repertoire.

This trial was performed in parallel to a trial co-led by Christian Blank, M.D., Ph.D., and Ton Schumacher, Ph.D. of the Netherlands Cancer Institute—who tested the use of neoadjuvant versus adjuvant (post-surgical) treatment with combined CTLA-4 and PD-1 blockade in a similar patient population.

"The findings in their trial are provocative, demonstrating that a higher number of tumor-resident TCRs expanded in the peripheral blood of patients receiving neoadjuvant as opposed to adjuvant checkpoint blockade—supportive of what was seen in preclinical models—and suggests that the neoadjuvant approach may be superior." Wargo said.

This MD Anderson-led team is now working with others worldwide in an international neoadjuvant melanoma consortium to harmonize these efforts.

**More information:** Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma, *Nature Medicine* (2018). DOI: 10.1038/s41591-018-0197-1 , www.nature.com/articles/s41591-018-0197-1

Provided by University of Texas M. D. Anderson Cancer Center