Relatlimab plus nivolumab improves progression-free survival in metastatic melanoma

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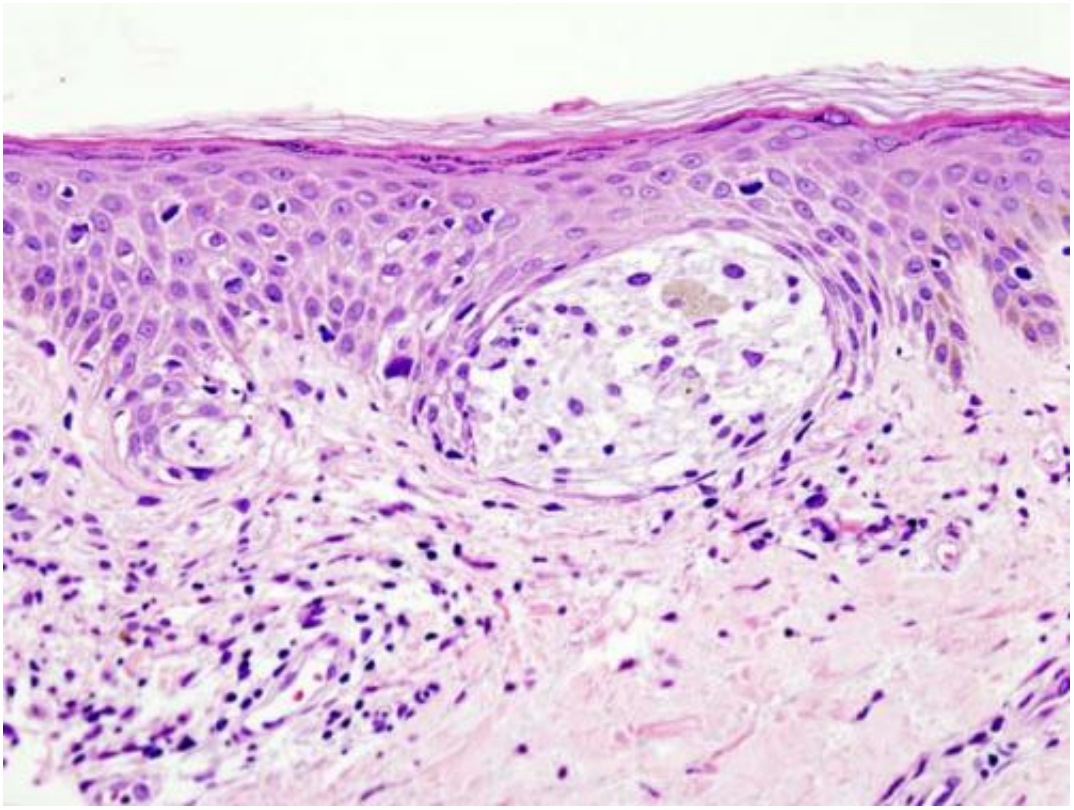

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

In patients with untreated, advanced melanoma, the combination of immune checkpoint inhibitors relatlimab and nivolumab doubled the

progression-free survival benefit compared to nivolumab alone, with a manageable safety profile, according to the results of the Phase II/III RELATIVITY-047 clinical trial reported by The University of Texas MD Anderson Cancer Center today in the *New England Journal of Medicine*.

Median progression-free survival was 10.1 months in the combination arm and 4.6 months in the monotherapy arm. After 12 months' follow-up, progression-free survival rates were 47.7% in the combination arm versus 36% in the monotherapy arm, with a 25% lower risk of disease progression or death in the combination arm. The benefit of the combination therapy was observed across pre-specified subgroups. The Food and Drug Administration granted priority review to the combination in September 2021 based on the results of this study.

"The results from this global effort advance the field of immunotherapy by establishing a third class of immune checkpoint inhibitors through the LAG-3 pathway and have the potential to be practice-changing," said lead author Hussein Tawbi, M.D., Ph.D., professor of Melanoma Medical Oncology. "We've seen historic developments in melanoma treatment over the last decade with the combination of PD-1 and CTLA-4 inhibitors, which work well but also carry substantial toxicity. This study represents a significant and long-awaited next step toward providing patients with effective and safer treatment options."

Relatlimab is a novel antibody that blocks lymphocyte-activation gene 3 (LAG-3), an immune checkpoint found on the surface of T cells. LAG-3 is often upregulated in melanoma, as is programmed death-1 (PD-1), the immune checkpoint inhibited by nivolumab. These data represent the first Phase II/III clinical trial results of a third-generation checkpoint inhibitor and the first clinical trial designed to compare combination checkpoint inhibitor therapy versus nivolumab monotherapy in melanoma.

Currently, PD-1 and CTLA-4 inhibitor monotherapy and combination therapy are approved frontline treatment options for metastatic melanoma. The combination therapies benefit more patients than monotherapy, but also greatly affect quality of life, with toxicity rates of more than 50%.

In this study, grade 3 or 4 treatment-related adverse events occurred in 18.9% of patients in the combination arm and 9.7% in the monotherapy arm. The most common grade 3 or 4 events included increased levels of pancreatic and liver enzymes, and fatigue. Investigators determined three deaths in the combination arm and two deaths in the monotherapy arm were treatment-related. Immune-mediated adverse events included hypothyroidism/thyroiditis, rash and colitis. No new safety signals were identified, and patients rated their health-related quality of life similarly across both treatment arms.

The trial enrolled 714 patients with untreated, unresectable stage III or IV melanoma across 111 international sites between May 2018 and December 2020. Patients were randomized to receive relatlimab and nivolumab or nivolumab alone once every four weeks. Sixty patients (8.4%) received prior targeted therapy or immunotherapy as adjuvant therapy at least six months before recurrence, or received interferon six weeks before randomization. The median age of participants was 63; 41.7% were female and 96% were white.

At the time of data cutoff (March 9, 2021), median follow-up was 13.2 months, with 470 patients (65.8%) having discontinued treatment. The top reason for discontinuation was disease progression (36.3% in the combination arm and 46% in the monotherapy arm).

The study met its primary endpoint of blinded independent central review-assessed progression-free survival, with progression defined as tumor growth or death due to any cause. The benefit was sustained

across pre-defined subgroups, including BRAF status, tumor stage, lactate dehydrogenase (LDH) levels and LAG-3 and PD-1 expression.

"We now have evidence of a clear benefit for combination therapy compared to single-agent PD-1 inhibitors, and we're looking forward to seeing response and overall survival data," Tawbi said. "We're also thinking about the populations that were excluded from this trial, including those with untreated brain metastases and uveal melanoma, so that all patients can have a chance to take advantage of the progress we're making against melanoma."

More information: Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma, *New England Journal of Medicine* (2022). DOI: 10.1056/NEJMoa2109970 , www.nejm.org/doi/full/10.1056/NEJMoa2109970

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