

Combination immunotherapy improves survival for patients with asymptomatic melanoma brain metastases

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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

Combination treatment with immune checkpoint inhibitors nivolumab and ipilimumab demonstrates overall survival for patients with

melanoma that has spread to the brain, according to Phase II study results published today in *The Lancet Oncology* by researchers from The University of Texas MD Anderson Cancer Center.

Final results from the CheckMate 204 study confirm durable responses from the [combination therapy](#)—which became first-line standard of care in this population based on the [Phase II study results](#)—with an overall survival rate of 71.9% in asymptomatic patients at three years. Among those whose cancer responded to treatment within 12 weeks, overall survival was 92%. In patients with symptomatic brain metastases or on corticosteroid therapy, responses were lower but remained durable, with 36.6% overall survival.

"Inducing an intracranial response with combination immunotherapy has a direct and lasting impact on survival for patients whose melanoma has spread to the brain," said lead author Hussein Tawbi, M.D., Ph.D., professor of Melanoma Medical Oncology and co-director of the Brain Metastasis Clinic at MD Anderson. "We've shown that this treatment offers a chance of long-term survival to patients with a historically dire prognosis."

About 40% of patients with stage IV melanoma have brain metastases at diagnosis, while 75% develop brain metastases at some point. Before this combination was introduced, the one-year survival rate for patients with melanoma brain metastases was about 20%.

The primary endpoint of the study was intracranial clinical benefit rate, defined as complete and partial responses and stable disease lasting at least six months. The investigator-assessed clinical benefit rate was 57.4% and objective response rate was 53.5% in asymptomatic patients. These results are similar to response rates in metastatic melanoma patients without brain metastases.

The investigator-assessed clinical benefit and objective response rates were both 16.7% in symptomatic patients. Intracranial progression-free survival at three years was 54.1% in asymptomatic patients and 18.9% in symptomatic patients.

Responses also were assessed by blinded independent central review (BICR), which is recommended for studies evaluating cancer drugs in patients with central nervous system metastasis. Overall, the BICR and investigator assessments had a high concordance.

Some patients who did not respond to the therapy still had favorable overall survival, which the researchers suggest could be due to subsequent radiation or systemic therapy and may indicate that response to combination immunotherapy is not fully or accurately assessed by current imaging techniques.

"These results confirm that combination immunotherapy is effective and should be considered as a front-line option for asymptomatic patients with melanoma brain metastases," Tawbi said. "The study also highlights the ongoing need for effective options for symptomatic patients, and the opportunity to help this population further by working on ways to eliminate the need for steroids."

The single-arm study began with enrollment of [asymptomatic patients](#) with melanoma brain metastases (Cohort A) and was later amended to allow enrollment of patients with neurological symptoms or baseline corticosteroid use (Cohort B), which is often prescribed to help control symptoms in patients with brain metastases.

A total of 101 patients were enrolled to Cohort A and 18 patients to Cohort B across 28 study sites in the United States. Median follow-up time was 34.3 months in Cohort A and 7.5 months in Cohort B. Patients in Cohort A had a median age of 59, were 67.3% male and 98% white.

Patients in Cohort B had a median age of 59.5, were 72.2% male and 94.5% white. Patients received nivolumab plus ipilimumab every three weeks for four doses, followed by a maintenance phase of nivolumab every two weeks for up to two years.

No new safety concerns were identified, and toxicity for the combination was similar to previous trials in advanced melanoma patients without brain metastases. In Cohort A, 55.4% of patients had grade 3 or 4 treatment-related adverse effects, leading to discontinuation of treatment in 28.7%. In Cohort B, 66.7% of patients had grade 3 treatment-related adverse effects, and 16.6% discontinued treatment. No grade 4 events were reported in Cohort B.

The most common serious treatment-related adverse events were colitis, diarrhea, pituitary inflammation and elevated liver enzymes. Immune-mediated events included hepatitis, rash and hypothyroidism. One patient death due to treatment-related myocarditis was previously reported.

"Combination immunotherapy remains a highly toxic treatment regimen, so one of our next areas of focus is developing treatments that are safer for patients and still just as effective," Tawbi said. "Historically, many patients with brain metastases have been excluded from clinical trials. Now, we're showing that it's possible to run trials specifically dedicated to this population."

MD Anderson's multidisciplinary Brain Metastasis Clinic, which Tawbi co-directs with Frederick Lang, M.D., chair of Neurosurgery, and Jing Li, M.D., Ph.D., associate professor of Radiation Oncology, opened in 2019 to expedite time to treatment and provide a hub for conducting clinical trials for [patients](#) with [brain](#) metastases.

More information: Hussein A Tawbi et al, Long-term outcomes of

patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study, *The Lancet Oncology* (2021). [DOI: 10.1016/S1470-2045\(21\)00545-3](https://doi.org/10.1016/S1470-2045(21)00545-3)

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