New immunotherapy delivery approach safe and beneficial for some melanoma patients with leptomeningeal disease

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A novel approach to administer intrathecal (IT) immunotherapy (directly into the spinal fluid) and intravenous (IV) immunotherapy was safe and

improved survival in a subset of patients with leptomeningeal disease (LMD) from metastatic melanoma, according to interim analyses of a Phase I/Ib trial led by researchers at The University of Texas MD Anderson Cancer Center.

The study, published today (March 30) in *Nature Medicine*, represents the first-in-human trial of concurrent IT and IV nivolumab (anti-PD-1) in melanoma patients with LMD. Across 25 patients, the median overall survival (OS) was 4.9 months, with OS rates of 44% at 26 weeks and 26% at 52 weeks. Four patients survived to 74, 115, 136 and 143 weeks after their first IT dose, which is significantly longer than expected.

"This represents a major path forward for our patients, as there is a crucial unmet clinical need for better treatments for patients with LMD," said corresponding author Isabella Glitza Oliva, M.D., Ph.D., associate professor of Melanoma Medical Oncology. "We are encouraged by these preliminary results for a disease that has been notoriously difficult to study due to its highly aggressive nature. This approach is safe, and we're seeing a small subset of our patients who have had outstanding results, so we hope to learn from each and every one of them."

Leptomeningeal disease is a complication of cancer that occurs when cancer cells from primary tumors migrate into the cerebrospinal fluid (CSF) and leptomeninges, the outer lining of the brain and spinal cord. These cells can quickly spread throughout the CSF and cause a wide variety of neurological symptoms. Roughly 10% of patients with stage IV melanoma will be diagnosed with LMD, which also commonly derives from metastatic lung cancer and breast cancer.

There is no cure for LMD, but treatments such as targeted therapy and immunotherapy may improve quality of life. While immune checkpoint inhibitors are beneficial in patients with metastatic melanoma, little is known about their potential use for treating LMD.

Intrathecal administration has been studied in other settings. A previous proof-of-concept study by Glitza Oliva and colleagues at MD Anderson demonstrated that IT administration of interleukin-2 in patients with LMD had encouraging results but was associated with serious side effects. This new study showed that injecting nivolumab directly into the spinal fluid increases its concentration within the CSF, since these antibodies cannot otherwise easily penetrate the blood-brain barrier.

The current trial enrolled 25 patients with a median age of 43 and all but two had received prior systemic therapy, including immune checkpoint inhibitors (84%), BRAF/MEK inhibitors (64%) and chemotherapy (12%). The dose-expansion cohort evaluated four doses of IT nivolumab concurrent with a flat dose of IV nivolumab.

The drug was well tolerated at the highest IT nivolumab dose, with only mild grade 1 or 2 side effects and no dose-limiting toxicities. The most common treatment-related adverse events were nausea, dizziness and vomiting.

"Until recently there have been limited resources to develop clinical trials in this space, but we owe it to patients with very challenging diseases to push the unknown and to advocate for them when they don't have many options," Glitza Oliva said. "We are optimistic that these results, along with further clinical trials, will lead us to a better understanding of LMD and, ultimately, more effective ways of helping our patients."

Recently, the study completed enrollment for the dose-expansion cohort; analysis is underway to provide an opportunity for further insights. Ongoing research will seek to identify biomarkers that may predict patients most likely to benefit from this treatment approach.

More information: Isabella Glitza Oliva, Concurrent intrathecal and

intravenous nivolumab in leptomeningeal disease: phase 1 trial interim results, *Nature Medicine* (2023). DOI: 10.1038/s41591-022-02170-x. www.nature.com/articles/s41591-022-02170-x