

Combating Melanoma Brain Metastases and Leptomeningeal Disease

Melanoma skin cancer cells may spread, or metastasize, in the brain and cerebrospinal fluid. Here's a roundtable discussion on the topic.

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Melanoma is the third most common source of brain metastases, exceeded only by lung and breast cancer. In addition, metastatic melanoma cells have the highest propensity for settling in the brain out of any solid tumor. Melanoma also has one of the highest rates of leptomeningeal disease (LMD), a cancer in the cerebrospinal fluid (CSF) and the membranes that surround the brain and spinal cord.

With the advent of [targeted drug therapy](#), [checkpoint immunotherapy](#), and targeted radiation therapy the median survival of patients with melanoma who have central nervous system (CNS) metastases (inclusive of both brain metastases and LMD) has improved. However, only certain groups of patients respond. "About half of the patients with metastatic melanoma are still dying and the majority of them have died because of uncontrolled CNS disease," said Dr. Michael B. Atkins, of the Georgetown-Lombardi Comprehensive Cancer Center and Chair of MRA's [Medical Advisory Panel](#). "CNS disease represents a principal unmet need in our treatment armamentarium for patients with metastatic melanoma."

Considerable work is still needed to fully understand where CNS metastases originate and how they progress, in order to identify better treatment strategies. To address these issues, MRA convened a roundtable discussion of approximately 35 representatives from industry, academia, and the US Food and Drug Administration (FDA) during MRA's 2023 Scientific Retreat that was co-chaired by Dr. Atkins and MRA's Chief Science Officer, Dr. Joan Levy. The participants were charged with evaluating the current standard of care for melanoma patients with CNS metastases, identifying compelling basic and translational science questions to address to improve our understanding of CNS metastasis, and proposing inclusive clinical studies to advance new treatment options for patients with these tumors.

Treatment of Melanoma Brain Metastases: What We Know & Remaining Questions

"Patients who have brain metastases, who have no neurologic symptoms and have small tumors that are not in critical parts of the brain, may be treated with systemic therapy," said Dr. Harriet Kluger of Yale University. "We often will treat these patients with the combination of [ipilimumab + nivolumab](#) based on the high response rate and clinical benefit observed in two Phase II multi-

center trials, one led by Drs. Hussein Tawbi of MD Anderson and Kim Margolin of the St. John's Cancer Center, and the other led by Dr. Georgina Long of the Melanoma Institute of Australia," added Dr. Kluger.

However, for patients with symptomatic brain metastases, the standard of care is far less clear. Many of these patients are treated with steroids to reduce swelling in the brain and manage any adverse events. This is a delicate balance, because steroids and immunotherapies have conflicting therapeutic actions. Steroids are used for their anti-inflammatory activity while immunotherapies act to ramp up an immune response. The typical approach has been to get patients off steroids before using immunotherapy, but there is a lack of data to support this, said Dr. Allison Betof Warner of Stanford University. "There is something different about patients with symptomatic brain metastases, and just getting off steroids and treating them like an asymptomatic patient is not the only solution."

Dr. Margolin added, "In the first line of treatment you approach symptomatic brain metastatic patients in a highly individualized manner depending on what treatments they have had before, what tumors they have in the brain and in other areas of the body, and how symptomatic these tumors are."

Can Brain Metastases Be Prevented?

Dr. Eva Hernando of the New York University School of Medicine commented that we used to think that we could go to the primary tumor and develop ways to stop them from spreading to other places in the body. However, emerging data suggests that most primary tumor cells can spread right away and can remain dormant in the brain for long periods of time. "One of the major challenges is the need to stop the melanoma tumor cells that have already reached the brain before they come out of dormancy and become actively metastatic tumors," said Dr. Hernando. "This is a tall task, but it is important for the research community to focus on this unmet need."

Leptomeningeal Disease Needs Better Criteria for Diagnosing and Treating

Just as with brain metastases, melanoma also has one of the highest incidences of LMD among solid tumors. Overall survival for patients with melanoma who have been diagnosed with LMD is measured in weeks to a few months.

"The biology of LMD is fundamentally different from that of brain metastases, and we need to think about that distinction. They are not the same," said Dr. Betof Warner. A major challenge in treating patients with LMD, she added, is just getting a reliable diagnosis, due to a lack of clear diagnostic and response criteria. "Part of that challenge is getting all of us—medical oncologists, neurologists, radiation oncologists—to agree that the patient has LMD so we can actually treat them," she said.

Responses to treatment may be very different between patients that have brain metastases and those with LMD. The microenvironments are quite distinct and therefore we should not think of the two as the same diseases. "LMD is a much smaller group of patients with a fundamentally distinct biology," said Dr. Georgina Long of Melanoma Institute of Australia. "It's harder to study because

it's almost like a different organ site than CNS metastasis to the brain. We need more biological information to be able to distinguish between the two."

Clinical Trials Need to Include More Patients with CNS Metastases

The roundtable participants agreed that more patients with CNS metastases must be included in [melanoma clinical trials](#), and that trial designs need improvements to make them more inclusive. The FDA did a review and the agency concluded that many of the common clinical trial eligibility exclusion criteria for cancer trials were historical in nature, and unnecessarily restrictive. So, in 2020 and 2021 the FDA issued broad guidance on how trial sponsors could change clinical trial inclusion criteria to be more inclusive to patients with CNS metastases. The FDA recognized that this is a special patient population that has not been historically included in clinical trials due to a hesitancy of including them in a primary analysis based on how they do clinically. However, the agency notes to sponsors that by including these patients we are able to capture really important information that is contributing to our growing understanding of how to address this population with unmet needs.

Due in part to this new guidance from the FDA, trial sponsors are now including patients with both asymptomatic and symptomatic brain metastases in clinical trials through separate subgroups with customized endpoints. Dr. Rohini Singh of Merck commented that their melanoma umbrella trial (KEYMAKER-U02) is evaluating immune checkpoint inhibitor pembrolizumab-based combinations in various patient settings. The brain metastasis sub-study is testing pembrolizumab in combination with lenvatinib (which inhibits the formation of new blood vessels) and MK-1308 (a CTLA-4 checkpoint inhibitor) in patients with metastatic melanoma with "active" brain metastases. "To enroll more patients with symptomatic brain metastases," noted Dr. Singh, "we had to revise and broaden the inclusion criteria to accommodate patients that were either [treatment] naïve or exposed to immune checkpoint therapies to be able to better evaluate the effectiveness of these novel combinations across different settings."

Several academic investigators and company representatives described trials that are ongoing or soon to launch which are inclusive of melanoma patients with brain metastases, both asymptomatic and symptomatic. Highlights of such studies include next generation checkpoint immunotherapies, TIL therapies, and different types of targeted therapies. As Dr. Suzanne Topalian of Johns Hopkins Medical Center and Chair of MRA's Scientific Advisory Panel suggested, "it would be useful to hear more about kinase inhibitors that are able to cross the blood brain barrier, as this would be potentially important for patients whose melanomas have targetable mutations."

Both Dr. Betof Warner and Dr. Richard Williams of Kinnate Biopharma agreed, but having the ability to measure drug concentrations in the CSF or CNS tissue would be useful when pursuing targeted therapy approaches especially with kinase inhibitors. "We don't know why these patients are developing resistance so early if we don't know what the concentration of the drug is in the CSF," said Dr. Betof Warner.

Dr. Levy also reminded participants that MRA's [Clinical Trial Navigator](#) is a great resource to identify trials that include patients with brain metastases.

Basic and Translational Research Can Improve Treatment for Patients with CNS Metastases

Basic and translational researchers are continuing to explore solutions to better understand the biological distinctions between metastases in the CNS and other sites. They are also hard at work identifying new targets and better treatment options for patients with CNS metastases. Dr. Keiran Smalley of the H. Lee Moffitt Cancer Center said that it is important to understand how the CNS microenvironment influences therapeutic responses. For example, he noted far lower immune infiltrates and clearance of immune cells in the brain.

Dr. Hernando added that a potential source of new targets can emerge from studies of other cancer types. "We're seeing certain shared mechanisms between different cancer types that also metastasize to the brain," she said. Dr. Hernando also emphasized the need for researchers to share their study models, "there are not many faithful models of brain metastasis."

Dr. Benjamin Izar of Columbia University said that there are genomic features that can vary between metastases to the brain compared to other parts of the body. Brain metastases have more unstable chromosomes—a hallmark of cancer that is associated with aggressive behavior and immune evasion. The brain microenvironment may be particularly susceptible to this process. "So far it is just an association," he commented. He also agreed with the need to support more work to create models of brain metastases, noting that they are very difficult to develop. He concluded by adding that the models would be useful to validate some of the interesting genomic and non-genomic findings and potential targets identified in CNS metastases from his and other studies.

Dr. Levy concluded the session by noting that MRA has awarded close to \$9M for basic and translational research on CNS metastases across all types of MRA grant mechanisms in the U.S. and abroad. She will bring back insight from this panel to inform future MRA funding opportunities to continue to support more research in this critically important area.

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