# Promising Advances in Eye Melanoma Research

There's no FDA-approved treatment for uveal, or eye, melanoma, but a new immunotherapy and molecular therapy show encouraging results.

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Uveal melanoma, often called ocular melanoma or just eye melanoma, is a rare melanoma subtype that affects about 2,500 people each year in the United States. As is true with other rare subtypes, we know far less about what causes uveal melanoma, how it progresses, and how it can be effectively treated. Research focused on rare subtypes is urgently needed and this is why the flurry of recent advances focused on uveal melanoma are so exciting.

"Other than the fact that [uveal melanoma and cutaneous melanoma cells] look the same under a microscope, they couldn't be more different," says Dr. Marlana Orloff, a medical oncologist from Thomas Jefferson University and MRA-funded investigator on the new Helman Family-MRA Team Science Award. "In the way that they present, spread, and are treated – uveal melanoma is a distinctly different disease."

Just like melanoma of the skin, treatment for uveal melanoma depends greatly on whether or not the tumor has spread beyond its site of origin (what researchers call the primary site or tumor). Uveal melanoma that has not metastasized beyond the eye is often treated effectively with radiation therapy. However, uveal melanoma that has spread to other parts of the body is far more difficult to treat.

That's because existing checkpoint immunotherapies and BRAF-focused targeted therapies haven't proved as effective in uveal melanoma.

"Even though people want to lump uveal in with skin melanoma, we know that it's a very different disease, and a lot of the treatments for skin melanoma don't work for eye melanoma. There's really nothing officially FDA-approved to treat eye melanoma," says Orloff.

Uveal melanoma — and its lack of effective treatment options — represents a huge area of unmet patient need and researchers are working every day to better understand the unique biology of rare melanoma subtypes needed to devise new treatment strategies.

## On the Horizon: Tebentafusp

Late last month, researchers published encouraging results from the Phase 3 clinical trial of tebentafusp, a new type of immunotherapy being developed by Immunocore, in the New England Journal of Medicine (NCT03070392). Tebentafusp is a new class of immunotherapy that works by bridging together tumor and T cells, which helps the body's immune system to locate and kill the melanoma cells.

In the study of 378 patients with uveal melanoma, researchers determined that tebentafusp improved overall survival (OS) compared to the investigator's choice of therapy in previously untreated patients who have the HLA-A*02:01 biomarker (which is found in about 50% of patients with uveal melanoma). The one-year OS was found to be 73.2% in the tebentafusp arm versus 58.5% in the comparator arm, with patients in the control arm receiving either Keytruda (pembrolizumab) (82%), Yervoy (ipilimumab) (12%), or dacarbazine (6%).

Tebentafusp is the first systemic treatment to ever show a survival benefit among patients with metastatic uveal melanoma. The U.S. Food and Drug Administration (FDA) granted tebentafusp priority review for the treatment of patients with uveal melanoma. Full FDA approval could come as early as next February.

## A Clinical trial to Watch: Phase 2 PEMDAC Study of Pembro + Entinostat

Last month, researchers also provided an update on the ongoing Phase 2 clinical trial of pembrolizumab combined with entinostat, an experimental molecular therapy developed by Syndax Pharmaceuticals (NCT02697630). Entinostat works by binding to and stopping specific members of the histone deacetylase family of enzymes, which regulate gene expression. Researchers believe that this helps increase the effectiveness of pembrolizumab in several ways, including reducing the number and function of several immune-suppressing cells within the body.

In the study, 29 patients with uveal melanoma received a standard infusion of 200 mg of pembrolizumab every three weeks in combination with a weekly 5 mg dose of entinostat taken orally. The patients were then followed for up to two years or until disease progression, intolerable side effects, patient withdrawal of consent, or clinician decision to discontinue treatment. Ultimately, the researchers reported response rates of 14%, a clinical benefit rate of 28% at 18 weeks, progression free survival (PFS) of 2.1 months, and overall survival (OS) of 13.4 months.

Despite being a small clinical trial, the results from this trial are encouraging because this is the first trial to demonstrate that combined epigenetic and immunotherapy can cause tumor regression. The next step for this combination is a larger, randomized clinical trial.

## Why Some Uveal Melanomas Metastasize

In addition to these clinical trial developments, researchers in the lab have also been busy

unraveling the many mysteries surrounding uveal melanoma. MRA-funded investigator Dr. Ashley Laughney, assistant professor of physiology and biophysics at Weill Cornell, and her team recently published work that explains why some uveal melanomas metastasize.

Due to the tendency of uveal melanoma to rapidly metastasize — and the very poor patient prognosis once this occurs — identifying patients at high risk of developing metastatic uveal melanoma is critical to allow for early intervention. Dr. Laughney's work is significant because it underlines a key mechanism in this process – and suggests ways in which it could be disrupted via future therapies.

In this MRA-funded study published by Nature Communications, researchers studied 17,074 individual uveal melanoma cells donated by six patients. They performed single-cell genomic analysis of each cell and found that melanomas evolve into a metastatic state after losing function of a molecular machine called Polycomb Repressive Complex 1 (PRC1). PRC1 normally helps control DNA folding and gene activity. This loss then leads to increased risk of the tumor metastasizing.

"The discovery of these key steps in uveal melanoma progression gives us an opportunity to target them with therapies to suppress tumor evolution toward metastasis," said Dr. Ashley Laughney. "It also represents a significant conceptual advance in cancer research, because it shows how epigenetic alterations can lead to chromosomal instability and metastasis."

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Want to help accelerate uveal melanoma research? Our partner organizations the Melanoma Research Foundation and A Cure in Sight (ACIS) have sponsored two distinct direct-to-patient registries for patients with uveal melanoma. Check out MRF's Vision Registry and ACIS's INSIGHT Registry to enroll or learn more.

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