New Era for Treating Metastatic Uveal Melanoma

Last January, the FDA approved tebentafusp (Kimmtrak, Immunocore) for the treatment of unresectable or metastatic uveal melanoma in human leukocyte antigen (HLA)-A*02:01–positive adults. And the drug—which is designed to mobilize and activate T cells to fight uveal melanoma tumor cells—represents a new era in the treatment of the disease.

A breakthrough. "For the first time, we are seeing a targeted medication leading to an overall survival benefit in patients with metastatic uveal melanoma," said Andrew W. Stacey, MD, at the University of Washington in Seattle. Specifically, the drug offers prolongation of survival by about six months compared to single-agent checkpoint blockade or chemotherapy, said Sapna Patel, MD, at MD Anderson Cancer Center in Houston.

Moreover, in addition to being the first and only drug approved for metastatic uveal melanoma, tebentafusp is "the first-in-class approved T-cell redirection molecule in all of oncology," Dr. Patel said.

But not a slam dunk. Despite these firsts, tebentafusp is not a wonder drug. As Dr. Stacey noted, "The benefit is modest, and there are reasons to be cautious and not overly optimistic." However, he said, "It is still very exciting to have an option with survival benefit to offer patients."

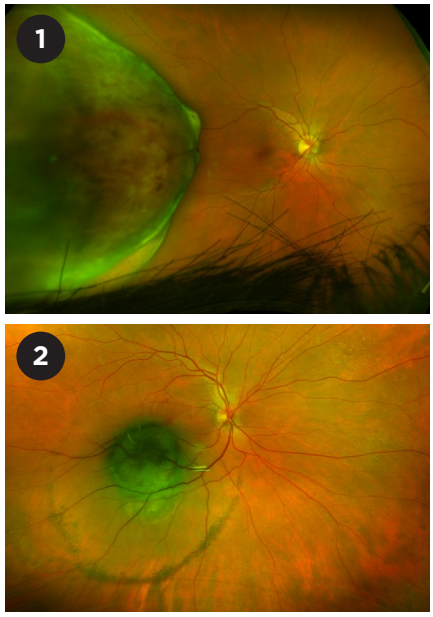
Before Tebentafusp: Few Options

Until recently, treatment options for metastatic uveal melanoma were limited. "There's a long track record of trying various treatment approaches with very poor to limited response," said Dan S. Gombos, MD, also at MD Anderson Cancer Center. "Once patients developed metastatic disease, their prognosis was generally poor and, historically, [life expectancy was] less than a year."

"We all hoped that the revolution of immunotherapy seen by our colleagues who take care of cutaneous melanoma would translate to the world of uveal melanoma. Unfortunately, it has not," said Dr. Stacey.

Although both cutaneous melanoma and uveal melanoma arise from melanocytes, the two diseases are different entities with vastly different mutational landscapes, Drs. Gombos and Stacey said. "Because of this, the medications that have changed the world of metastatic cutaneous melanoma have had little effect in our world of uveal melanoma," Dr. Stacey noted.

Dr. Gombos added, "Although targeted agents like pembrolizumab, ipilimumab, and nivolumab are very effective in cutaneous melanomas, they're far less effective in uveal melanomas." In addition, he pointed out, these drugs were never specifically FDA-approved for uveal melanoma.



DIAGNOSIS. *While the diagnosis of large lesions (1) is relatively straightforward, it is less so for smaller ones (2).*

Andrew W. Stacey, MD

Enter Tebentafusp

Unique mechanism of action. Tebentafusp is a bispecific fusion antibody, meaning that it binds to two different molecules at the same time: CD3 (a cluster of differentiation) on the T cell receptor and a molecular complex called gp100–HLA-A*02:01, a tumor-associated antigen.[1]

Glycoprotein-100 (gp100) is a molecule present in high amounts on the surface of certain cells, including uveal melanoma tumor cells and healthy melanocytes. Gp100 is presented by HLA-A*02.[2]

Tebentafusp is unique in that it functions as a bridge, bringing melanoma cells and T cells into close

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proximity. The drug activates T cells upon binding to CD3, stimulating an immune response. This leads to cytokine release, which attracts more T cells and other immune system cells to attack and kill tumor cells. Because of its affinity for gp100, tebentafusp may also affect normal melanocytes.

What led to FDA approval. A randomized, open-label, phase 3 trial assessed the overall survival benefit of tebentafusp in HLA-A*02:01–positive, previously untreated patients with metastatic uveal melanoma.[2]

All told, 252 patients received tebentafusp, while 126 patients received the investigator's choice of one of three other anticancer drugs. The results: tebentafusp was associated with improved one-year overall survival of 73%, versus 59% for those who received another agent. Patients who received tebentafusp also had improved progression-free survival of 31% at six months, versus 19% for controls. The most common adverse effects in tebentafusp-treated patients were cutaneous rash and cytokine-release syndrome.

Promises and Limitations

Limited patient selection. The study's results should be interpreted with caution, as less than half of all uveal melanoma patients with metastatic disease will be eligible to receive tebentafusp, Dr. Gombos noted.

"The main issue with tebentafusp is that a large percentage of the time, the patient is not biologically eligible for the medication," Dr. Stacey said. For instance, at MD Anderson, the HLA-A*02:01 haplotype—which must be present for the drug to bind to the melanoma cell—is expressed in "approximately a quarter to one-third of our patients," Dr. Patel said.

Risks and benefits. Tebentafusp's survival benefits must be weighed against the drug's downsides, which include the weekly dosing schedule—and the fact that "the first three doses require a 16-hour monitoring period, which usually leads to an overnight stay in the hospital," said Dr. Patel.

Side effects include cytokine release syndrome, "which can present as fever, racing heart, shortness of breath, hypotension, skin redness, and rashes," Dr. Patel added. As Dr. Gombos put it, the drug is "not a walk in the park."

Learning curve and other challenges. Dr. Patel noted that testing for the HLA-A*02:01 haplotype is not routine in clinical practice at this point. As a result, the introduction of tebentafusp has been accompanied by a learning curve, in which oncologists need to be taught how to order the test as well as how to interpret the results, she said.

Diagnostic Quandaries and Advancements

Ocular oncologists are very good at diagnosing uveal melanoma when lesions are medium or large in size (Fig. 1), said Dr. Stacey. "However, the dilemma occurs when there is an 'indeterminate' lesion that is small (Fig. 2). These lesions might be atypical nevi, or they may be showing very early signs of malignant transformation."

While some prognostic clues exist, there is no perfect way to know what each lesion will do, he said. "So, we either watch these lesions and let them grow before treating them, or we treat them with radiation. If we watch them, we might miss a window to treat them early. But if we treat them early, we might be destroying vision in an eye that was never going to develop a true melanoma."

Current research directions. One hot area of research involves figuring out how to find additional information about the malignancy without a direct biopsy of the tumor itself, Dr. Gombos said. At MD Anderson, Dr. Patel and Dr. Gombos' team have demonstrated the presence of circulating melanoma tumor cells in patients without gross disease. "So, there is definitely the potential to biopsy the blood or even the aqueous humor as a surrogate for the eye itself."

In Seattle, Dr. Stacey's team has investigated the use of small-gauge fine-needle aspiration in the diagnosis of uveal melanoma in cases of choroidal hemorrhage from an unknown source.[1] In another study, they found that the prognosis of metastatic disease in uveal melanoma can be enhanced by combining molecular prognostic markers with the tumor stage at the time of diagnosis.[2]

And there has been an explosion of research looking at the aqueous humor (AH) as a liquid biopsy for various intraocular malignancies, including uveal melanoma, said Jesse L. Berry, MD, at the University of Southern California in Los Angeles.

Dr. Berry's laboratory was the first to publish and present on the potential of AH as a liquid biopsy for ocular tumors.[3] Last year, her team published a report on the technique's application to uveal melanoma.[4] Dr. Berry said that she doesn't think liquid biopsy will completely replace tumor biopsy for uveal melanoma. But, she said, the 2022 study is the "very first step in showing that, in certain instances, particularly with larger tumors, post-radiation, you can detect these molecules in the AH."

Small lesions, big risks. The stakes are high, Dr. Berry emphasized. Of note, results of a study presented last year indicate that the risk of metastatic disease in patients with very small uveal melanoma tumors may be higher than previously understood.[5] Thus, Dr. Berry said, if ophthalmologists see a lesion in clinic, "even if it's small, refer the patient to your local ocular oncologist, because more and more data suggest these small lesions are risky."

1 Chee YE at al. *Am J Ophthalmol Case Rep.* 2021;23:101173.
2 Stacey AW et al. *Ocul Oncol Pathol.* 2022;8(1):35-41.
3 Berry JL et al. *JAMA Ophthalmol.* 2017;135(11):1221-1230.
4 Im DH et al. *Int J Mol Sci.* 2022;23(11):6226.
5 Garg G et al. *Indian J Ophthalmol.* 2022;70(1):271-274.

And tebentafusp's potential impact remains to be clarified, Drs. Gombos and Patel said. For instance, will the drug be beneficial if given in an adjuvant setting to patients known to be at high risk for developing metastatic disease?

A Bright Future

While tebentafusp is not a "slam dunk," Dr. Gombos said, it's "definitely an incremental—and important—step forward." Dr. Stacey agreed, noting that tebentafusp is "the first systemic medication created with uveal melanoma as its target. It is an exciting time."

Dr. Stacey added, "For decades we have been doing our best to take care of patients with uveal melanoma, and for decades we have made little progress in the overall survival of these patients. But I am optimistic. We are learning more about this disease. We know the mutations required for metastatic potential. We are developing more effective and less invasive treatments. I am confident that we are now at the doorstep of a revolution for uveal melanoma."

1 www.accessdata.fda.gov/drugsatfda_docs/label/2022/761228s000lbl.pdf. Accessed Nov. 8, 2022.
2 Nathan P et al. *N Engl J Med.* 2021;385(13):1196-1206.

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