MELANOMA IN FOCUS

Current Developments in Melanoma

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The Evolution of Treatment for Uveal Melanoma

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H&O What distinguishes uveal melanoma from cutaneous melanoma biologically?

SK Although these 2 tumors are both melanomas—they have the same cell of origin, the melanocyte—they are very different biologically. Cutaneous melanomas, which are typically driven by changes related to ultraviolet light, may have driver mutations in genes such as *BRAF* and *NRAS*. These mutations are not seen in uveal melanoma, which usually features mutations in *GNAQ* and *GNA11*. In addition to these foundational mutations in uveal melanoma, secondary mutations in genes such as *BAP1* and *SF3B1* can drive its behavior and determine how aggressively the tumor cells behave.

We also see differences in the tumor mutation burden. Cutaneous melanomas usually have a high tumor mutation burden, which is one of the reasons they respond well to immune checkpoint inhibitors. This stands in contrast to uveal melanoma, in which the tumor mutation burden is low and immune checkpoint inhibitors do not work as well.

Uveal melanoma is a rare cancer, which makes it difficult to perform large prospective clinical trials. As a result, we have often relied on treatment approaches that have been extrapolated from cutaneous melanoma. Because of the differences between these diseases, however, results have often been disappointing when the same treatments used in cutaneous melanoma are used in uveal melanoma.

H&O What new treatments have become available over the past few years?

SK The newest treatments we have for uveal melanoma are tebentafusp-tebn (Kimmtrak, Immunocore), which received US Food and Drug Administration (FDA) approval in 2022, and the melphalan hepatic delivery system (Hepzato Kit, Delcath), also known as percutaneous hepatic perfusion (PHP) with melphalan, which received approval in 2023. Both treatments are approved for use in patients with metastatic disease.

Tebentafusp is a bispecific molecule that binds to the GP100 protein on one end and to CD3 T cells on the other end. The GP100 protein is highly expressed on melanoma cells, including uveal melanoma cells, so binding to both this protein and T cells brings immune cells directly to the tumor. Patients must be positive for the human leukocyte antigen (HLA) A*02:01 serotype to be eligible for treatment.

Tebentafusp was approved on the basis of the results of a phase 3 trial in 378 patients positive for HLA-A*02:01 who had previously untreated metastatic uveal melanoma.[1] Patients were randomly assigned in a 2:1 ratio to tebentafusp or a control group treated with the investigator's choice of therapy: pembrolizumab (Keytruda, Merck), ipilimumab (Yervoy, Bristol Myers Squibb), or dacarbazine. After a minimum follow-up of 3 years, median overall survival (OS) was statistically significantly longer in the tebentafusp group than in the control group, at 21.6 vs 16.9 months.

It is interesting to note that even though tebentafusp produced a survival benefit, we did not see significant shrinkage of the tumors on imaging. Despite the absence of a visible tumor response, the behavior of the tumors clearly changed, and they did not grow as quickly. This finding represents a major step in the right direction, and

we are seeking to improve further on these results.

The FDA approved PHP with melphalan on the basis of the FOCUS trial.[2] The study was originally designed to assign patients randomly in a 1:1 ratio to receive up to 6 cycles of melphalan every 6 to 8 weeks by PHP or best alternative care, but the design was converted to a single-arm trial in 91 patients. The objective response rate (ORR) of 36.3% and the median duration of response of 14 months led to FDA approval despite the lack of a phase 3 study.

In October of 2025, we saw results presented at the European Society for Medical Oncology (ESMO) Congress for a combination of melphalan PHP and dual immune checkpoint inhibition. In the phase 2 CHOPIN study, 76 adults with unresectable metastatic uveal melanoma were randomly assigned to melphalan PHP plus ipilimumab and nivolumab (Opdivo, Merck) or melphalan alone.[3] After a median follow-up of 2 years, trends were seen toward improved PFS, OS, and ORR with the addition of melphalan PHP to dual immune checkpoint inhibition. These are early data based on a small number of patients, but they point to the potential of combination treatment with melphalan PHP plus systemic therapy.

H&O What is the rationale behind targeting the liver in patients with metastatic uveal melanoma?

SK Liver metastases are very common in patients with uveal melanoma. Metastatic recurrence develops in approximately 40% to 50% of people with a primary uveal melanoma tumor, and spread to the liver occurs in approximately 90% of patients with metastatic disease. As a result, much emphasis has been placed on efforts to control liver disease through liver-directed therapy.

Over the years, we have used various approaches to targeting liver metastases, including removing them surgically and irradiating them. These approaches can be viable options for people who have few sites of disease. For people who have more extensive metastases, we can use techniques such as bland embolization, in which an interventional radiologist blocks the blood supply to areas of metastasis. Embolization can be combined with other treatments. In immune embolization, embolization is combined with the administration of immune-stimulating drugs. In radioembolization, small radioactive beads are infused into areas of the liver that contain metastases. None of these approaches is curative, but we have found that they can benefit patients by controlling disease for short periods, and in some cases for prolonged periods.

Although the biggest advance has been the approval of melphalan PHP, a similar technique, called isolated hepatic perfusion (IHP), is also being tested. IHP is a more involved surgical technique than PHP; in IHP, the liver must be isolated from the body's main circulatory system while a high dose of chemotherapy is delivered directly to the liver. Several prospective trials have demonstrated benefits with this approach, including the phase 3 SCANDIUM trial from Sweden and Denmark.[4] In this open-label, randomized trial, ORR, hepatic progression-free survival (PFS), and PFS were statistically significantly better with IHP than with best alternative care.

> We are in a more exciting time in the therapeutic landscape for uveal melanoma than we have ever been before.

H&O Should all patients with uveal melanoma receive prognostic genetic testing at diagnosis?

SK This is a question with a nuanced answer. I think that genetic testing information is helpful, but obtaining this can be challenging. If the patient's primary tumor is going to be irradiated before radioactive plaque therapy, we would need the ocular oncologist to perform a biopsy of the tumor to get this information. If the surgeon does not think the procedure is safe, however, we do not want to do anything that will put the patient at risk. If the patient is going to undergo enucleation, which is less common, we can test the sample after the tumor has been removed. As long as obtaining the sample does not involve potential safety issues, genetic testing is helpful to understand the biology of the tumor, how aggressive the cancer may be, and how frequently we should conduct surveillance after treatment. For example, we know that the risk of recurrence is going to be elevated if the patient has a *BAP1* mutation.

We have a gene expression profiling tool, DecisionDx-UM (Castle Biosciences), that can classify patients into risk categories. We can also conduct cytogenetic testing if the patient has monosomy of chromosome 3, which is often accompanied by a *BAP1* mutation. Not only can we obtain a lot of information from upfront genetic testing that might be actionable in terms of surveillance, we also should eventually be able to select patients for treatment with specific adjuvant agents on the basis of whether they are likely to benefit from them.

H&O How often do you surveil for metastases, and what imaging tests do you use?

SK A lot of variance is seen in practice patterns depending on whether the patient lives in the United States or elsewhere in the world, but we generally like to conduct imaging every 3 to 6 months in patients we consider to be at high risk, whether according to clinical criteria, size, anatomic features, cytogenetics, or mutations on the gene expression profile. We continue that schedule for the first 3 to 5 years, followed by less-frequent imaging until the 10-year point. We want to detect any evidence of recurrence as early as possible because doing so maximizes our ability to step in with treatment as needed. Imaging should be conducted every 6 to 12 months in patients we consider to be at lower risk and should continue for 5 years.

Whenever possible, we prefer to surveil the liver with magnetic resonance imaging (MRI), which provides the highest sensitivity in terms of getting a close view of the liver. Ultrasound or computed tomography can be used when MRI is not feasible.

H&O What are the most promising therapies in development right now?

SK We are in a more exciting time in the therapeutic landscape for uveal melanoma than we have ever been before. Just during the 7 years that I have been in this field, I have witnessed a sea change in terms of what is available and what is in development.

The phase 1/2 OptimUM-01 trial is investigating a combination of crizotinib (Xalkori, Pfizer) and the investigational protein kinase C inhibitor darovasertib, with promising early results.[5] This is an encouraging combination because early results are showing efficacy in patients both with and without the HLA-A*02:01 serotype; the ongoing phase 2/3 OptimUM-02 study is looking specifically at this combination in the frontline setting in participants who are negative for HLA-A*02:01 (NCT05987332).

Tebentafusp is also being tested in combination with other agents, including other systemic treatments and liver-directed therapies. At the 2025 ESMO Congress, we saw a presentation on the use of an engineered T-cell therapy called anzutresgene autoleucel, or IMA203, which is directed toward an antigen called PRAME that is very highly expressed in melanoma, including uveal melanoma.[6] This agent produced a clinical response rate of 67% in a small phase 1 study of 16 patients with metastatic uveal melanoma, which is unheard of in this disease. The preliminary results are exciting, and this therapy is going to be studied further in a slightly larger cohort of people with uveal melanoma. I expect T cell–directed therapy to be a significant step forward in the overall landscape of uveal melanoma treatment.

Unfortunately, the treatments we use in the metastatic setting are not curative; they are palliative treatments, designed to provide disease control and alleviate symptoms. As a result, we are now looking to see what advances we can move up to the nonmetastatic setting. For example, the phase 3 ATOM trial is looking at the use of tebentafusp in the adjuvant setting for nonmetastatic uveal melanoma (NCT06246149). This study has opened in Europe and will be opening at selected sites in North America within the next several months.

We hope that by using these treatments earlier, we may be able to prevent recurrence and metastatic disease and increase the chances of a cure.

Disclosures

Dr Khan has served as an advisor or consultant to Regeneron, Ideaya Biosciences, Replimune, and Immunocore.

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