Uveal Melanoma: Current Treatments & New Approaches on the Horizon

BY CATLIN NALLEY

Uveal melanoma—a rare cancer that forms in the eye—remains a challenge for the field of oncology. Approximately 50 percent of patients will develop metastatic disease, facing poor survival outcomes due to a lack of effective treatment options.

With no current standard of care, metastatic uveal melanoma represents a significant area of unmet need. However, there is reason for hope, according to Sapna Patel, MD, Associate Professor and Director of the Uveal Melanoma Program in the Department of Melanoma Medical Oncology at The University of Texas MD Anderson Cancer Center, Houston.

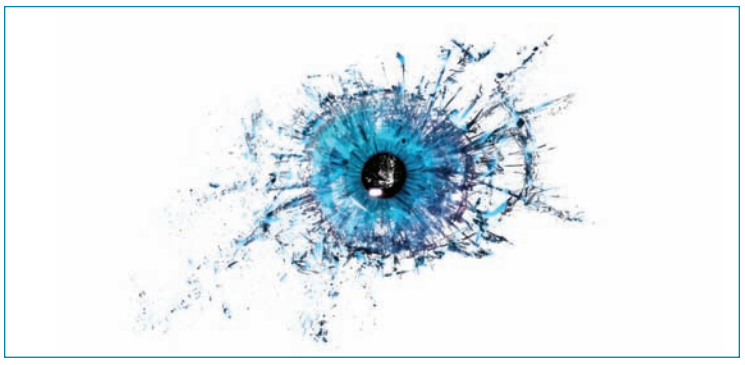
"Outcomes are improving," noted Patel, a specialist in uveal melanoma with an active clinical practice and research program. "The most recent clinical trial data and even some aggregate data of individuals who do not go on clinical trials show that patients are living past a year, which is a striking improvement from just a decade ago.

"We're not at the point where we are giving patients 2 or 5 years of survival, but this extra time is invaluable to patients and progress continues," she said.

Current Approaches & Challenges

Since there is currently no standard of care, expert guidelines recommend that patients with uveal melanoma start treatment on a clinical trial, if possible, according to Patel. However, therapeutic choices remain limited for patients who do not have access to this option.

"Today, a lot of what we use to treat melanoma of the eye is borrowed from melanoma of the skin, but it's not a good fit," explained Patel, noting there are two reasons for this. "For one, uveal melanoma patients have been excluded from all of the Phase III studies in skin melanoma that have led to or are in the process of being evaluated for approval.



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"However, when these drugs receive approval, the language doesn't necessarily exclude these patients from receiving treatment," she elaborated. "That leaves us with a caveat noting that the effect of this therapy in uveal melanoma is unknown."

Patel emphasized the importance of including uveal melanoma in these larger studies, pointing out the FDA Oncology Center of Excellence is attuned to the efforts in rare cancers. "This involves including cohorts of rare cancers such as uveal melanoma in registrational study efforts that can be separated from the main skin melanoma cohort at the end for evaluation without penalizing the endpoint.

"However, this message has not translated over to pharmaceutical companies, and large trials continue to be run without these patient cohorts," Patel said. "As a result, we have the uveal melanoma community wondering if a treatment will work for this patient population. Without inclusion in these larger trials, it is a challenge to amass data other than inherently biased retrospective series or case studies."

CME/NCPD

Another problem with borrowing treatments from skin melanoma are the intrinsic differences between the two diseases. "Skin melanoma and uveal melanoma have different pathobiology," Patel noted. "Therefore, any therapies that target cancer-specific genes in skin melanoma would not work for patients with uveal melanoma."

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> *—Sapna Patel, MD, at The University of Texas MD Anderson Cancer Center*

Recent Research

Despite these ongoing challenges, researchers continue to dedicate significant time and effort to find a standard of care and improve outcomes for this rare disease. Patel and colleagues performed the only Phase II study in the U.S. exploring nivolumab plus ipilimumab for metastatic uveal melanoma. The findings were recently published in the *Journal of Clinical Oncology* (2020; doi:10.1200/JCO.20.00605).

The study included 35 patients with metastatic uveal melanoma; 33 were evaluable for efficacy. Patients received nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) for 4 cycles, followed by nivolumab maintenance therapy for up to 2 years. Overall response rate (ORR) was the primary outcome and data showed an ORR of 18 percent, including one confirmed complete response and five confirmed partial responses. The researchers reported a median progression-free survival of 5.5 months and a median overall survival of 19.1 months.

Another trial, led by the Spanish Multidisciplinary Melanoma Group, recently released their Phase II data on nivolumab plus ipilimumab among treatment-naïve metastatic uveal melanoma patients (*J Clin Oncol* 2021; doi:10.1200/JCO.20.00550). Fifty-two patients were included in the study and the ORR was 11.5 percent. The median progression-free survival and overall survival were 3.0 months and 12.7 months, respectively.

"These two studies validate each other," Patel noted. "We now have prospective clinical trial data using these immune agents, and that is a start. We can now comfortably say that, if a patient cannot join a clinical trial, nivolumab plus ipilimumab is a standard of care combination that has some efficacy. While I don't think anybody would say 18 percent ORR is where we want to be, it shows promise."

Patel and colleagues are currently taking a deeper look at the responding patients in their trial, as well as the study out of Spain. "What differentiates the responders? Did their tumors at the start of treatment have a different characteristic signature?" she queried. "A deeper understanding will help us identify future patients who may or may not benefit from this treatment approach."

Ongoing Avenues of Exploration

While continued study of cancer genes and the immune system are crucial to ongoing treatment advances, Patel noted that there are two other areas that should not be overlooked.

First is the use of a patient's autologous T cells, according to Patel. "This comes in many different flavors, such as tumor infiltrating lymphocytes," she said, noting the promising research in this area. At the University of Pittsburgh Medical Center, researchers are recruiting patients for a Phase II study exploring the adoptive transfer of tumor infiltrating lymphocytes for metastatic uveal melanoma (NCT03467516).

Intratumoral therapy is another interesting area of study. "Improvements over the years have generated a pretty effective response in the injected tumor, but that doesn't help the patient who might have tumor in multiple locations or multiple tumors in an organ," Patel explained. "And so, there are strategies to enhance intratumoral therapy by either changing how you deliver it, such as with a side-hole or multi-pronged needle or pressure-enabled delivery device to enhance vascular drug delivery to a tumor, or giving it with systemic checkpoint blockade or an immune-stimulating agent to enhance the benefit beyond the treated tumor(s)."

These two strategies, Patel told *Oncology Times*, "are very exciting and can turn on that immune response for cancers like uveal melanoma where the tumor environment is not exactly an immune desert, but rather immune paralyzed."

Looking to the future, Patel is optimistic. "I've been working in uveal melanoma for over a decade, and where you used to get no attention at meetings or from pharmaceutical companies, we are now seeing more focus on this area of study," she said, noting that the uveal melanoma TCGA has helped raise awareness of this disease and potential drug targets. "I am very optimistic and hopeful that we are on a path to make meaningful progress for these patients." OT

Catlin Nalley is a contributing writer.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to: 1. Explain research challenges to establishing a standard of care for the treatment of patients with uveal melanoma.

2. Analyze results from two phase II clinical trials evaluating the use of nivolumab and ipilimumab in the treatment of uveal melanoma.

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