Therapeutic Advances in Metastatic Melanoma: TILs, ImmTACs, and Targeted Therapies

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Therapeutic options for metastatic melanoma have expanded dramatically over the past decade. Advances in tumor biology, immunotherapy, and adoptive cellular therapy are offering patients more options and requiring oncology advanced practitioners to develop familiarity with increasingly complex treatment modalities and care pathways. Speakers at JADPRO Live 2025 focused on extracutaneous melanoma—particularly mucosal and uveal melanoma—and highlighted novel immune-based therapies, including immune-mobilizing monoclonal T-cell receptors against cancer (ImmTACs) and tumor-infiltrating lymphocyte (TIL) therapy.

At the JADPRO Live 2025 educational session "Therapeutic Advances in Metastatic Melanoma: TILs, ImmTACs, and Targeted Therapies," held on October 25, 2025, **Alexandra Haugh, MD, MPH,** and **Krista M. Rubin, MS, FNP-BC** presented an overview of emerging treatment strategies for advanced melanoma. Dr. Haugh is a medical oncologist in both The Center for Melanoma and Skin Cancer as well as the Cellular Immunotherapy Program at Mass General Hospital, and Ms. Rubin is a nurse practitioner in the Center for Melanoma and Skin Cancer also at Mass General Hospital. With a focus on extracutaneous melanoma, including mucosal and uveal melanoma, the session highlighted the growing role of novel immune-based approaches such as immune-mobilizing monoclonal T-cell receptors against cancer (ImmTAC) therapies and tumor-infiltrating lymphocyte (TIL) therapy.

OVERVIEW OF MELANOMA

"Melanoma is more than just skin," started off Ms. Rubin. Although most patients present with skin-based melanoma, extracutaneous subtypes, including mucosal and uveal melanoma, are diseases with different sites of origin, molecular drivers, and clinical outcomes.

Mucosal melanoma represents approximately 1.4% of all melanomas,

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with roughly 50% arising in the head and neck region. Common primary sites also include the anorectal, urogenital, and gastrointestinal tracts. Clinical outcomes are worse than those seen with cutaneous melanoma, with a median overall survival of approximately 9 months and 23% of patients presenting with metastatic disease at diagnosis.

Uveal melanoma is the most common ocular malignancy and accounts for approximately 5% of all melanomas, with an incidence of about 2,000 cases annually in the United States. It primarily affects Caucasian patients and is most often diagnosed in the fifth to seventh decades of life, although younger patients may also be affected.

Approximately one-third of patients are asymptomatic at presentation, with tumors often detected incidentally during routine eye examinations. Most patients present with localized disease at diagnosis. Uveal melanoma lacks the common *BRAF* and *NRAS* mutations seen in cutaneous melanoma and instead is driven by mutations in *GNAQ*, *GNA11*, and *BAP1*. Approximately 40% to 50% of patients develop metastatic disease, and 85% of metastases are liver dominant. Once metastatic, outcomes are poor, with reported 1-year survival rates ranging from 3% to 25%.

"This is a challenging disease to manage," commented Ms. Rubin.

Targeted therapies do not seem to work well in this population, and there has been limited success with immunotherapy.

MOLECULAR PROGNOSTICATION AND RISK-STRATIFIED SURVEILLANCE

"What has evolved in the past 5 to 10 years is the importance of understanding the tumor biology and the molecular aspects of uveal melanoma," said Ms. Rubin.

The 15-gene expression profile (GEP) groups tumors into Class 1A, Class 1B, and Class 2 categories of risk. Over 5 years, Class 1A tumors carry an approximately 2% risk of metastasis, Class 1B tumors carry an approximately 21% risk of metastasis, and Class 2 tumors carry an approximately 72% risk of metastasis.

The biomarker PRAME can further refine prognosis, particularly within Class 1 tumors, identifying patients with higher metastatic risk. Next-generation sequencing provides insight into driver mutations. These molecular classifications inform surveillance intensity, with low-risk patients managed using annual imaging and/or liver function tests, and high-risk patients undergoing imaging and/or liver function tests every 3 to 6 months. Circulating tumor DNA (ctDNA) has emerged as a tool to monitor disease burden and response, and detect early metastatic progression in uveal melanoma.

IMMTACs

According to current National Comprehensive Cancer Network (NCCN) guidelines, participation in a clinical trial remains the preferred treatment strategy for patients with metastatic uveal melanoma. Tebentafusp (Kimmtrak) is recommended for those who are positive for the HLA-A*02:01 allele.

Tebentafusp is a first-in-class ImmTAC that redirects endogenous T cells to recognize and kill melanoma cells (Figure 1). It is the first systemic therapy to demonstrate an overall survival benefit in metastatic uveal melanoma, with reported median overall survival of 22 months compared with 16 months in control groups (Hassel et al., 2023).

Because tebentafusp is HLA-restricted, only patients with the HLA-A*02:01 allele are eligible for this therapy; therefore, patient selection is critical, with approximately 50% of Caucasian patients and approximately 35% of African Americans meeting eligibility criteria.

The safety profile of tebentafusp is generally manageable, with cytokine release syndrome (CRS) and rash being the most common treatment-related adverse events. These toxicities are typically low grade, and severe (grade 4) events are rare.

To mitigate the risk of CRS, tebentafusp is administered using a step-up dosing regimen, beginning with 20 µg in week one, followed by 30 µg in week two, and escalation to 68 µg in week three, after which treatment continues at the full dose. The first three doses are administered with inpatient observation given the risk of CRS.

"Generally, we see cytokine-mediated effects within 2 to 12 hours of administering the agent, and peaking 4 to 6 hours after the dose," said Ms. Rubin. These include pyrexia, chills and rigors, hypotension, and tachycardia.

"Supportive management is foundational to managing these patients," said Ms. Rubin.

Rigors are typically managed with meperidine, while fever and chills are treated with antipyretics such as acetaminophen or ibuprofen. Hypotension is most often responsive to intravenous fluid resuscitation, with intravenous corticosteroids and in some cases anti-IL-6 agents such as tocilizumab reserved for cases that are refractory to initial supportive measures. Dermatologic toxicities, particularly rash and pruritus, are managed with antihistamines, skin moisturizers, and topical agents such as menthol to alleviate erythema.

TIL THERAPY

Tumor-infiltrating lymphocyte (TIL) therapy differs from other cellular immunotherapies in that it relies on a polyclonal population of T cells that are already present within the tumor microenvironment. These T cells are believed to have intrinsic antitumor activity, as they have demonstrated the ability to traffic into the tumor and persist within an immunosuppressive environment.

After surgical harvest of at least 1.5 cm of tumor tissue, the specimen is processed to extract T cells, which are subsequently cultured in a growth medium enriched in IL-2.

"We essentially bathe them in IL-2 and 'feeder cells' and try to reverse some of the T-cell exhaustion that occurs in the tumor," described Dr. Haugh. "Then, we multiply the number of TIL by the billions in a process called rapid expansion."

The manufacturing process takes 5 to 6 weeks. Once the expanded T cells are ready, patients are generally admitted to receive lymphodepleting chemotherapy, although outpatient administration of chemotherapy is possible. Following lymphodepletion, the TIL product is infused, and patients receive up to six doses of high-dose IL-2 to further support T-cell persistence and expansion.

TIL therapy is an intensive treatment that typically requires hospitalization for approximately 2 to 3 weeks due to chemotherapy-related cytopenias, IL-2–related toxicities, and the need for close monitoring.

Place of TIL Therapy in Metastatic Melanoma

Long-term survival data demonstrate that while a substantial proportion of patients treated with first-line checkpoint inhibitors experience durable responses and long-term survival, nearly half of patients ultimately progress and have limited effective treatment options thereafter. For patients with *BRAF*-mutant disease, targeted therapy is an option; however, progression-free survival with BRAF/MEK inhibition is typically limited, with most patients progressing within 1 year.

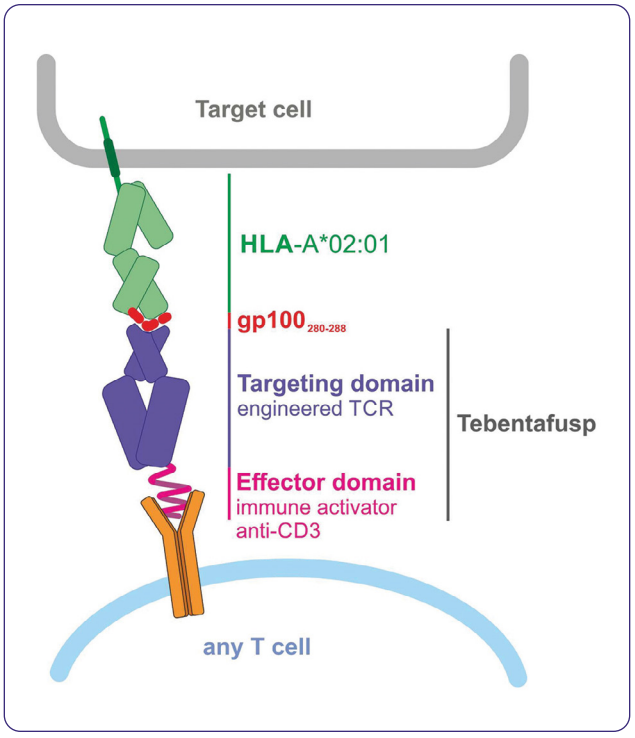

Figure 1. Mechanism of action tebentafusp. Adapted from Hassel et al. (2023).

Lifileucel (Amtagvi) was approved for patients who have progressed on prior immune checkpoint inhibition and, when applicable, prior BRAF/MEK–targeted therapy. Approval was based on a combined cohort trial that included 153 heavily pretreated patients with metastatic melanoma (Chesney et al., 2022). The median number of prior systemic therapies in this population was three, and although most patients had cutaneous melanoma, the cohort also included patients with mucosal melanoma, acral melanoma, and melanoma of unknown primary. Lifileucel demonstrated an overall response rate of 31%. The median duration of response exceeded 27 months.

"I think an interesting thing about TIL is that for patients who respond, the response tends to

deepen over time...Every time we see them on a scan, there's less and less melanoma until they get to a complete response," said Dr. Haugh.

Additional support for TIL therapy came from a randomized phase III trial conducted primarily in Europe that evaluated TIL therapy earlier in the treatment course (Rohaan et al., 2022). In this study, patients in the second-line setting were randomized to receive either TIL therapy or single-agent ipilimumab (Yervoy). The overall response rate was 50% in the TIL-treated group, and complete responses were observed in 20% of patients.

"That study has been criticized because we don't often use single-agent ipilimumab, but I think it is a good indicator of responses that you can get from TIL if you start using it earlier," commented Dr. Haugh.

Toxicities

"The dose of lymphodepleting chemotherapy that we use for TIL is a lot higher than what they use for lymphodepletion in the CAR-T world for hematologic malignancies," noted Dr. Haugh.

The primary concerns with high-dose cyclophosphamide are severe cytopenias and infection. To reduce infectious complications, patients admitted for TIL therapy are started on prophylaxis, including atovaquone, later transitioning to sulfamethoxazole and trimethoprim in the outpatient setting once blood counts recover, along with acyclovir. Acyclovir prophylaxis is typically continued for 1 year, while PJP prophylaxis is continued for at least 6 months.

Common side effects during lymphodepletion include nausea, diarrhea, and hair loss. A rare but serious complication is cyclophosphamide-related cardiotoxicity, which can be fatal. Because of this risk, clinicians monitor EKGs twice daily during hospitalization and pause treatment if any concerning changes are detected.

"TIL therapy is generally well tolerated," said Dr. Haugh. "After TIL infusion, patients get up to six doses of high dose IL-2. That has a lot of side effects, but usually they are transient and patients will recover from them within a week after they finish the IL-2."

These side effects include fevers/rigors, rash, shortness of breath, decreased urine output, diarrhea, hepatotoxicity, and hypotension.

FUTURE DIRECTIONS IN CELLULAR THERAPY

The presentation concluded by highlighting next-generation adoptive cell therapies, including IL-2–sparing engineered TIL products and novel TCR-based therapies targeting antigens such as PRAME, with the goal of reducing toxicity while preserving efficacy.

"I think there's going to be new future generations of TIL and adoptive cell therapy where we genetically modify the TIL," commented Dr. Haugh. ●

Disclosure

Ms. Rubin has served on the advisory board for ImmunoCore. Dr. Haugh has no relevant financial relationships to disclose.

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