Tebentafusp-tebn: A Novel Bispecific T-Cell Engager for Metastatic Uveal Melanoma

GWEN HUA,[1] PharmD, DANIEL CARLSON,[2] DO, and JACQUELINE R. STARR,[1] PharmD, BCOP

From [1]Geisinger Enterprise Pharmacy, Danville, Pennsylvania; [2]Geisinger Cancer Institute, Danville, Pennsylvania

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

Correspondence to: Gwen Hua, PharmD, 100 N Academy Ave, Danville, PA 17822
E-mail: ghua@geisinger.edu

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Abstract

Uveal melanoma is the most common intraocular cancer in adults. Metastatic uveal melanoma has a poor prognosis. Tebentafusp-tebn is the first drug in the new immune mobilizing monoclonal T-cell receptors against cancer (ImmTAC) class of T cell–directed therapy. Tebentafusp-tebn has been shown in a randomized phase III clinical trial to lead to improved overall survival and progression-free survival when compared with single-agent pembrolizumab, ipilimumab, or dacarbazine in previously untreated human leukocyte antigen (HLA)-A*02:01-positive metastatic uveal melanoma patients. Tebentafusp-tebn is now approved by the US Food and Drug Administration in HLA-A*02:01-positive uveal melanoma patients as first-line therapy in the metastatic setting.

Uveal melanoma is the most common intraocular cancer in adults, representing approximately 3% to 5% of all melanomas (Jager et al., 2020). The annual incidence of uveal melanoma in Europe and the US is approximately 6 cases per million population per year (Jager et al., 2020). The incidence of uveal melanoma is low in Africa and Asia, with an incidence rate of 0.2 to 3 cases per million per year (Kaliki & Shields, 2017). Risk factors for developing uveal melanoma include fair skin, light-colored eyes, inability to tan, and ocular or oculodermal melanocytosis (Kaliki & Shields, 2017). While uveal melanomas also arise from melanocytes, they are a distinct entity from cutaneous melanomas, with different drivers and a different microenvironment (Coupland et al., 2013; van der Kooij et al., 2019). Unfortunately, these differences lead uveal melanoma patients to worse outcomes with systemic therapy, including immunotherapy (Buder et al., 2013; Rantala et al., 2019). Around 50% of patients with uveal melanoma will present with metastatic disease, and the prognosis in these patients is poor, with a median overall survival of approximately 1 year (Rantala et al., 2019; Kujala et al., 2003; Weis et al., 2016). There is a paucity of data in this setting with systemic therapy.

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The presence of human leukocyte antigen (HLA)-A*02:01 is seen in approximately 45% of individuals with uveal melanoma in the United States and Europe (Nathan et al., 2021). Metastatic uveal melanoma is a historically treatment-refractory tumor with a high expression of glycoprotein 100 (gp100; Khoja et al., 2019). Molecules called immune mobilizing monoclonal T-cell receptors against cancer (ImmTAC) are a new class of T cell–redirecting bispecific fusion proteins that use an engineered high-affinity T-cell receptor to target a specific protein, including intracellular antigens, that is presented as a peptide–HLA complex on the target-cell surface (Liddy et al., 2012; Lowe et al., 2019). Once ImmTAC molecules are bound to their specific peptide–HLA complexes on the target-cell surface, they recruit and activate polyclonal T cells through CD3 to release cytokines and cytolytic mediators against target cells (Liddy et al., 2012; Bossi et al., 2014). Tebentafusp-tebn (Kimmtrak) is currently the first and only drug in the new ImmTAC class.

PHARMACOLOGY AND MECHANISM OF ACTION

Tebentafusp-tebn is a T cell–redirecting bispecific fusion protein that redirects the immune system to target gp100-expressing uveal melanoma tumor cells. Tebentafusp-tebn is comprised of a soluble HLA-A*02:01-restricted T-cell receptor that is specific for the gp100 peptide and is fused to an anti-CD3 single-chain variable fragment (Nathan et al., 2021). Tebentafusp-tebn has a 1-million-fold greater affinity for gp100 presented by HLA-A*02:01 than natural T-cell receptors. Once bound to HLA-A*02:01-positive uveal melanoma cells, tebentafusp-tebn recruits and activates polyclonal T cells (via CD3) to release inflammatory cytokines and cytotoxic proteins, resulting in direct lysis of uveal melanoma tumor cells (Boudousquie et al., 2017; Middleton et al., 2020). The steady-state volume of distribution of tebentafusp-tebn is 7.56 liters (Immunocore Ltd., 2022). Tebentafusp-tebn is expected to be catabolized into small peptides and amino acids. The geometric mean clearance of tebentafusp-tebn is 16.4 liters per day with the median terminal half-life of 7.5 hours (range 6.8 to 7.5 hours).

CLINICAL TRIALS

The approval of tebentafusp-tebn was based on IMCgp100-202, a randomized, open-label, multicenter, phase III clinical trial of 378 patients with metastatic uveal melanoma. Patients were required to be HLA-A*02:01 genotype positive as identified by a central assay. Patients with prior surgical resection of oligometastatic disease were permitted in the study. Exclusion criteria included patients who received prior systemic therapy or localized liver-directed therapy and those with clinically significant cardiac disease or symptomatic, untreated brain metastases (Nathan et al., 2021).

Patients were randomized in a 2:1 ratio to receive weekly tebentafusp-tebn (N = 252) or investigator's choice (N = 126) of pembrolizumab (Keytruda), ipilimumab (Yervoy), or dacarbazine. Randomization was stratified by lactate dehydrogenase level at study entry. Patients in the tebentafusp-tebn group received a dose-escalation regimen starting with 20 µg on day 1 and 30 µg on day 8, followed by 68 µg on day 15 and weekly thereafter. For the investigator's choice, pembrolizumab was dosed at 2 mg/kg up to a maximum of 200 mg administered intravenously or 200 mg fixed dose every 3 weeks (82%). Ipilimumab was given at 3 mg/kg every 3 weeks (12%). A small number of patients received dacarbazine 1,000 mg/m^2 every 3 weeks (6%).

The major efficacy outcome was overall survival (OS). Additional efficacy outcomes were investigator-assessed progression-free survival (PFS) and objective response rate (ORR) per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The baseline demographic and clinical characteristics of the two groups were well balanced. The median OS was 21.7 months (95% confidence interval [CI] = 18.6–28.6) for patients treated with tebentafusp-tebn and 16 months (95% CI = 9.7–18.4) in the investigator's choice arm (hazard ratio [HR], 0.51, 95% CI = 0.37–0.71, $p < .0001$) in the intention-to-treat population. Moreover, PFS was 3.3 months (95% CI = 3–5) in the tebentafusp-tebn arm and 2.9 months (95% CI = 2.8–3) in the investigator's choice arm (HR, 0.73, 95% CI = 0.58–0.94, $p = .0139$). The ORR was 9.1% (95% CI = 5.9–13.4) in the tebentafusp-tebn arm compared with 4.8% (95% CI = 1.8–10.1) in the investigator's choice arm.

ADVERSE EFFECTS

Based on the pivotal phase III clinical trial, the most common treatment-related adverse events (≥ 30%) in patients who received tebentafusp-tebn were cytokine release syndrome (89%), rash (83%), pyrexia (76%), pruritus (69%), chills (47%), nausea (43%), fatigue (41%), and hypotension (38%; Nathan et al., 2021). The most common laboratory abnormalities (≥ 50%) were decreased lymphocyte count, increased creatinine, increased glucose, increased aspartate aminotransferase, increased alanine aminotransferase, decreased hemoglobin, and decreased phosphate. Adverse events due to tebentafusp-tebn led to 3.3% of patients discontinuing treatment. The frequency and severity of adverse events such as cytokine release syndrome, skin reactions, and elevated liver enzymes were seen most often with the first three doses and decreased with subsequent infusions (Nathan et al., 2021).

A list of treatment-related adverse events occurring in more than 20% of patients from the IMCgp100-202 trial is summarized in Table 1. Additionally, significant laboratory abnormalities (≥ 10%) worsening from baseline are listed in Table 2. Other clinically relevant adverse events occurring in less than 20% of patients who received tebentafusp-tebn included back pain, anorexia, constipation, hypertension, tachycardia, dyspnea, paresthesia, dizziness, flushing, muscle spasms, myalgia, pain in extremity, alopecia, skin hyperpigmentation, influenza-like illness, oropharyngeal pain, and night sweats (Nathan et al., 2021).

DOSING AND ADMINISTRATION

Tebentafusp-tebn is indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma (Immunocore Ltd., 2022). Tebentafusp-tebn is administered once weekly via continuous intravenous infusion over 15 to 20 minutes. The recommended starting dose is 20 µg for week 1. The dose is increased to 30 µg for week 2 and 68 µg for week 3 and beyond. Patients are treated until unacceptable toxicity or disease progression. The first three infusions are

Table 1. Treatment-Related Adverse Events Occurring in ≥ 20% of Patients

Adverse reactions		All grades, %	Grades 3–4, %
Immune system disorders	Cytokine release syndrome	89	0.8
Skin and subcutaneous tissue disorders	Rash	83	18.0
	Pruritus	69	4.5
	Dry skin	31	0
	Skin hypopigmentation	28	NA
	Erythema	24	0
	Hair color changes	20	NA
General disorders and administration site conditions	Pyrexia	76	3.7
	Fatigue	64	6.0
	Chills	48	0.4
	Edema	45	0
Gastrointestinal disorders	Nausea	49	2.0
	Abdominal pain	45	2.9
	Vomiting	30	1.2
	Diarrhea	25	1.2
Vascular disorders	Hypotension	39	3.3
Nervous system disorders	Headache	31	0.4
Musculoskeletal and connective tissue disorders	Arthralgia	22	0.8

Note. Information from Immunocore Ltd. (2022).

Table 2. Select Laboratory Abnormalities Occurring in ≥ 10% of Patients

Adverse reactions		Grades 1–4, %	Grades 3–4, %
Hematology	Lymphocyte count decreased	91	56.0
	Hemoglobin decreased	51	0.8
	Platelet count decreased	16	0
	Neutrophil count decreased	14	2.0
Chemistry	Creatinine increased	87	0.4
	Glucose increased	66	3.3
	Aspartate aminotransferase increased	55	13.0
	Alanine aminotransferase increased	52	9.0
	Phosphate decreased	51	11.0
	Albumin decreased	47	2.1
	Calcium decreased	45	2.1
	Lipase increased	37	15.0
	Magnesium decreased	34	0
	Alkaline phosphatase decreased	34	2.9
	Sodium decreased	30	2.9
	Potassium increased	29	1.6
	Bilirubin increased	27	4.1
	Amylase increased	23	4.1
	Glucose decreased	18	0.4
	Potassium decreased	17	0.8
	Calcium increased	13	0

Note. Information from Immunocore Ltd. (2022).

given in an appropriate health-care setting with immediate access to medications and resuscitation equipment to manage cytokine release syndrome. Patients should be monitored during the infusion and for at least 16 hours after the completion of each dose.

Tebentafusp-tebn can be administered in the outpatient setting starting at the fourth dose in the absence of any hypotension requiring medical intervention with the most recent dose. Additionally, patients are required to be monitored for a minimum of 30 minutes with subsequent doses in an appropriate ambulatory care setting. A summary of recommended monitoring parameters is provided in Table 3.

There are no dosage adjustments provided in the prescribing information for altered kidney function or hepatic impairment before treatment with tebentafusp-tebn. The prescribing information does provide dosing modifications for adverse events occurring during treatment. These recommendations are summarized in Table 4.

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

As the first ImmTAC, tebentafusp-tebn provides a new treatment option for select patients with unresectable or metastatic uveal melanoma. T cell–engaging immunotherapeutic agents signify impressive progress in our ability to target previously untreated diseases; however, serious and potentially fatal adverse events should be noted, especially with cytokine release syndrome. Tebentafusp-tebn has a boxed warning for cytokine release syndrome, requiring monitoring for at least 16 hours following the first three infusions. Cytokine release syndrome may manifest with fevers, hypotension, hypoxia, chills, nausea, vomiting, rash, elevated transaminases, fatigue, and headache (Immunocore Ltd., 2022).

Table 3. Monitoring Parameters and Frequency of Monitoring

Monitoring parameter(s)		Frequency of monitoring
Vital signs	Temperature Pulse rate Respiratory rate Blood pressure	At least every 4 hours during the first three doses; twice post-infusion starting at the fourth dose
Labs	Complete metabolic panel	Prior to initiation; duration of treatment
	Complete blood count (with differential)	Prior to initiation; duration of treatment
	Pregnancy status	Prior to treatment

Note. Information from Immunocore Ltd. (2022).

Based on the IMCgp100-202 trial, 60% of patients experienced grade 2 or higher cytokine release syndrome with more than one infusion (Nathan et al., 2021). The median number of cytokine release syndrome events was two (range 1–12). Approximately 84% of cytokine release syndrome episodes started the day of the infusion. The median time to resolution was 2 days among cases where cytokine release syndrome was resolved. Special precautions must be taken to prevent life-threatening complications. The advanced practitioner should ensure that immediate access to medications and resuscitative equipment is available to manage cytokine release syndrome. Patients should be euvolemic prior to the initiation of the infusions. Patients should also be closely monitored for signs and symptoms of cytokine release syndrome following infusions.

There are no contraindications listed in the prescribing information; however, tebentafusp-tebn does carry warnings and precautions for skin reactions, elevated liver enzymes, and embryo-fetal toxicity (Immunocore Ltd., 2022). Dermatologic toxicity such as rash, pruritus, and cutaneous edema have been reported with a median time to onset of 1 day (range 1 to 55 days). In the IMCgp100-202 trial, skin reactions occurred in 91% of treated patients with a high incidence of grade 2 (44%) and grade 3 (21%) adverse events. The median time to improvement in skin reactions (grade 1 or less) was 6 days. Patients should be monitored for skin reactions and be treated with supportive care therapies such as an antihistamine, or topical or systemic steroids, as clinically indicated.

In the IMCgp100-202 trial, the majority (65%) of patients experienced elevated liver enzymes (Nathan et al., 2021). Of those who experienced elevated liver enzymes, 73% occurred within the first three infusions, noted as part of a clinical manifestation of cytokine release syndrome. Fortunately, most patients who experienced grade 3 or 4 elevated liver enzymes had improvement within 7 days (grade 1 or less). Grade 3 or higher elevation in liver enzymes outside of cytokine release syndrome was less common, occurring in 8% of patients (Nathan et al., 2021). Patients should be monitored with liver function panels prior to starting and during treatment with tebentafusp-tebn.

There are no available data regarding the use of tebentafusp-tebn in pregnant women. Animal reproductive and developmental toxicity studies are also not available. Based on the mechanism of action, tebentafusp-tebn is postulated to cause fetal harm to pregnant women. Women with reproductive potential should use effective contraception during and for 1 week after the last treatment dose. Tebentafusp-tebn may be excreted in human milk. Thus, patients should be advised not to breastfeed while receiving treatment with tebentafusp-tebn.

Tebentafusp-tebn is currently only available as a single-dose, preservative-free vial of 100 µg/0.5 mL (Immunocore Ltd., 2022). The estimated average wholesale price (AWP) for one vial is $22,512 (Lexicomp, n.d.). Based on the AWP and current dosing schedule, the cost of tebentafusp-tebn for each patient will exceed $1.1 million per year. The rising cost of cancer care, especially for new oncology treatment options, poses financial toxicity to patients (Shah et al., 2022). The advanced practitioner should routinely screen for financial toxicity and discuss costs with patients. The American Society of Clinical Oncology recommends that clinicians discuss the cost of cancer care with patients to enhance shared decision-making (Agarwal et al., 2021). The opportunity to meet with a financial counselor may

Table 4. Tebentafusp Dosing Modification for Adverse Events

Adverse reaction	Severity	Dosing modifications
Cytokine release syndrome	Moderate is defined as temperature ≥ 38°C with: • Hypotension that responds to fluids (does not require vasopressors) or • Hypoxia requiring low flow nasal cannula (≤ 6 L/min) or blow-by oxygen	• If hypotension and hypoxia do not improve within 3 hours or CRS worsens, escalate care and manage according to the next high level of severity • For moderate CRS that is persistent (lasting 2–3 hours) or recurrent, administer corticosteroid premedication (e.g., dexamethasone 4 mg or equivalent) at least 30 minutes prior to the next dose
	Severe is defined as temperature ≥ 38°C with: • Hemodynamic instability requiring a vasopressor (with or without vasopressin) or • Worsening hypoxia or respiratory distress requiring high flow nasal cannula (> 6 L/min oxygen) or face mask	• Withhold until CRS and sequelae have resolved • Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent) • Resume therapy at the same dose level (i.e., do not escalate if severe CRS occurred during initial dose escalation; resume escalation once dosage is tolerated) • For severe CRS, administer corticosteroid premedication (e.g., dexamethasone 4 mg or equivalent) at least 30 minutes prior to the next dose
	Life-threatening is defined as temperature ≥ 38°C with: • Hemodynamic instability requiring multiple vasopressors (excluding vasopressin) • Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure	• Permanently discontinue • Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)
Skin reactions[a]	Grade 2 or 3	• Withhold until ≤ grade 1 or baseline • Resume at the same dose level (e.g., do not escalate if grade 3 skin reactions occurred during initial dose escalation; resume escalation once dosage is tolerated) • For persistent reactions not responding to oral steroids, consider intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)
	Grade 4	• Permanently discontinue • Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)
Elevated liver enzymes[a]	Grade 3 or 4	• Withhold until ≤ grade 1 or baseline • Resume at the same dose level if the elevated liver enzymes occur in the setting of grade 3 CRS; resume escalation if the next administration is tolerated • If the elevated liver enzymes occur outside the setting of grade 3 CRS, resume escalation if the current dose is less than 68 micrograms, or resume at the same dose level if dose escalation has been completed • Administer corticosteroids if no improvement within 24 hours
Other adverse reactions[a]	Grade 3	• Withhold until ≤ grade 1 or baseline • Resume at the same dose level (i.e., do not escalate if other grade 3 adverse reactions occurred during initial dose escalation; resume escalation once the dosage is tolerated)
	Grade 4	• Permanently discontinue

Note. CRS = cytokine release syndrome. Information from Immunocore Ltd. (2022).
[a]Grading based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

alleviate anxiety and cost concerns before beginning therapy (Coughlin et al., 2021). The patient's out-of-pocket expense for this therapy will depend on the individual's insurance coverage. Copay support of $7,500 is currently available to commercially insured patients, whereas patients insured through governmental programs such as Medicare, Medicaid, and Tricare may be eligible for foundation support. A Prescription Assistance Program is available from the manufacturer for uninsured or underinsured patients. Early discussions and possible financial solutions and support will help the patient navigate their care and financial responsibilities.

CONCLUSION

Historically, patients with metastatic uveal melanoma have had a poor prognosis and limited treatment options. Tebentafusp-tebn is the first drug in the new ImmTAC class of T cell–directed therapy. Tebentafusp-tebn has been demonstrated to lead to significantly improved overall survival and progression-free survival in select (HLA-A*02:01-positive) metastatic uveal melanoma patients. As with other forms of T cell–directed therapy, cytokine release syndrome remains a treatment-related adverse event seen in patients with tebentafusp-tebn administration. The approval of the novel agent, tebentafusp-tebn, represents a major paradigm shift in the treatment of metastatic uveal melanoma.

Disclosure

The authors have no conflicts of interest to disclose.

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