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Positive Quality Intervention: Tebentafusp-tebn (Kimmtrak®) for Patients with Unresectable or Metastatic Uveal Melanoma

Description:
The purpose of this PQI is to discuss clinical considerations surrounding the use of tebentafusp-tebn for patients with uveal melanoma and to review possible adverse events.

Background:
Uveal melanoma (UM) is the most common primary intraocular malignancy in adults. The annual incidence in Europe and the US is ~6 cases per million population per year [1] Tebentafusp-tebn is a bispecific CD3 T cell engager that combines a T cell receptor (TCR) with an anti-CD3 binding domain. The TCR binds to the gp100 peptide/human leukocyte antigen-A*02:01 (gp100/HLA-A*02:01) complex on UM tumor cells, while the CD3 domain recruits and activates polyclonal T cells to release cytokines leading to cell death.[2,3] It has been FDA approved for treatment of HLA-A*02:01-positive unresectable or metastatic UM in adult patients (NCCN® Category 1 recommendation in these patients). [2] Approval was based on the IMCgp100-202 trial which randomized (2:1) patients with previously untreated, unresectable or metastatic, HLA-A*02:01 genotype positive uveal melanoma to either tebentafusp-tebn or investigator's choice (IC) of single-agent pembrolizumab, ipilimumab, or dacarbazine. Patients were excluded if they had received prior systemic therapy or localized liver-directed therapy, had clinically significant cardiac disease, or symptomatic, untreated brain metastases. Tebentafusp-tebn was administered by intravenous infusion using weekly dose escalation starting with 20 mcg on day 1, 30 mcg on day 8, then 68 mcg on day 15 and once weekly thereafter. The primary endpoint of overall survival (OS) at 1 year was 21.7 months (95% CI: 18.6-28.6) for patients treated with tebentafusp-tebn and 16 months (95% CI: 9.7-18.4) in the IC arm (HR=0.51, 95% CI: 0.37-0.71, p<0.0001). Progression-free survival (PFS) was 3.3 months (95% CI: 3-5) for those receiving tebentafusp-tebn and 2.9 months (95% CI: 2.8-3) in the IC arm (HR=0.73, 95% CI: 0.58-0.94, p=0.0139).[3] An additional 3-year follow-up found OS was 21.6 months in the tebentafusp-tebn group and 16.9 months in the control group (HR, 0.68; 95% CI, 0.54-0.87).[4]
The most common adverse reactions (≥30%) in patients who received tebentafusp-tebn were cytokine release syndrome (CRS), rash, pyrexia, pruritus, fatigue, nausea, chills, abdominal pain, edema, hypotension, dry skin, headache, and vomiting. CRS (identified based on the presence of pyrexia, hypotension, and hypoxia) occurred in 89% of tebentafusp treated patients. It usually occurred within a few hours after the first three doses were administered, and the maximum grade of this event was typically grade 1 (12%) or grade 2 (76%). The majority (84%) of episodes of CRS started the day of infusion. Among cases that resolved, the median time to resolution of CRS was 2 days.[2]

PQI Process:

- Tebentafusp is indicated HLA-A*02:01-positive adult patients with unresectable or metastatic UVEAL melanoma
- HLA-A*02:01 status does not change over a person's life, and can be tested/assessed at any time—so consider it early[8]
- HLA Testing:
    - Prior to tebentafusp start, order HLA testing on BLOOD specimen to confirm HLA-A*02:01-positivity
    - Provide a whole blood specimen to your lab and request a high-resolution HLA test (ie, to the fourth digit)[8]. This test provides the necessary specificity, showing both the *02 and :01 portions. Low or intermediate resolution HLA testing only shows the *02 portion.
    - Do not use a biopsy tumor sample test for HLA[6,7] (tumor chromosomal alterations may cause

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discrepancy in the results based on tumor heterogeneity)
    - FDA approved companion diagnostic: SeCore CDx HLA Sequencing System (One Lambda Inc.)
- Black box warning: cytokine release syndrome
    - CRS occurred in 89% of patients who received tebentafusp with 0.8% being grade 3 or 4.
    - Monitor for at least 16 hours following the first three infusions and then as clinically indicated.
    - Fever is generally the first sign of CRS, occurring earlier than changes in blood pressure. Once fever is detected, patients should be monitored more closely for changes in other vital signs like pulse rate, respiratory rate, and blood pressure.[3] Consider managing symptoms early to help prevent CRS from escalating
- Dosing: 20 mcg intravenously on Day 1, 30 mcg intravenously on Day 8, 68 mcg intravenously on Day 15, and 68 mcg intravenously once every week thereafter
    - First three doses require 16-hour post infusion observation due to risk of CRS
- Pre-Medication for first 3 induction doses is not required but make sure patient is euvolemic to start and consider starting IVF at 150 cc/hr prior to infusion and continue during 16-hour observation period
- Managing Side Effects:
    - CRS: CRS symptoms should be managed with IV fluids, acetaminophen, or a single dose of systemic corticosteroids [see Table 1]
    - Rash: Treat with antihistamines and topical or systemic steroids based on persistence and severity of symptoms

Table 1. CRS Management[5]

Temperature ≥ 100.4ºF with:	**CTCAE Grade**	**Acute Management**	**Treat with corticosteroids?**	**Corticosteroid premedication 30 mins prior to next dose?**	**Can escalate to next dose?**
• No hypotension or hypoxia	≤ Grade 1	IV fluids, symptomatic support	NO	NO	**YES**
• Hypotension responsive to fluids (no vasopressors) • Or hypoxia requiring low flow nasal cannula	Grade 2 lasting < 2 hours	IV fluids, symptomatic support	NO	NO	**YES**
	lasting 2-3 hours/recurrent	**Above + Corticosteroids**	**YES**	**YES**	**YES**
	lasting > 3 hours/ non-responsive to therapy	**Above + Corticosteroids**	**YES**	**YES**	NO
• Vasopressor required • Or worsening hypoxia/respiratory distress/high flow nasal canula required	Grade 3	**Above + Corticosteroids**	**YES**	**YES**	NO
• Multiple vasopressors required • Worsening hypoxia despite requiring positive pressure	Grade 4	**Permanently discontinue tebentafusp and treat with steroids**			

No dosage reduction for tebentafusp is recommended; for specific dosage modifications, refer to USPI, section 2.3, table 1

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Patient-Centered Activities:

- Advise patients that for at least the first 3 infusions, they will be monitored in the hospital during the infusion and for 16 hours after. After the first 3 infusions, if tebentafusp was tolerated well, weekly treatments are given in an outpatient setting by IV infusion over 15-20 minutes and patients are typically monitored for 30 minutes after infusion.
- Advise patients that before the infusion, the healthcare provider may adjust or hold other medications such as blood pressure medication.
- Educate patient on expected side effects that can occur during the first 3 treatments including CRS, skin reactions, and liver issues. These side effects typically resolve after the first 3 treatments.
    - CRS: fever, chills, tiredness, weakness, nausea, vomiting, low blood pressure, dizziness, lightheadedness, headache, wheezing and trouble breathing, rash
    - Skin reactions: redness, burning, pain, itching, peeling or swelling of the skin
    - Liver issues: right-sided abdominal pain, yellowing of the skin or eyes
- Patient assistance: KimmtrakConnect

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