

Tebentafusp-tebn

An HCP Tool From AIM with Immunotherapy

Tebentafusp-tebn (Kimmtrak[®]) is cellular immunotherapy for use in unresectable or metastatic (advanced) uveal melanoma in patients who are *HLA-A*02:01*-positive. It is the first FDA-approved treatment for advanced uveal melanoma and the only treatment that has been shown to improve survival.

Tebentafusp-tebn is a bispecific T-cell engager that targets the *HLA-A*02:01/gp100* complex, a marker (antigen) frequently found on uveal melanoma tumor cells and melanocytes. Bispecifics are antibodies designed to simultaneously bind to T cells and tumor-cell antigens. Tebentafusp-tebn consists of a T-cell receptor precisely engineered to bind to cells with the *HLA-A*02:01/gp100* marker and cytotoxic T cells, activating T cells to recognize and kill tumor cells. It can also target normal melanocytes.

In a phase 3 study, tebentafusp-tebn was shown to significantly improve overall survival vs standard treatments (control group) in patients with *HLA-A*02:01*-positive advanced uveal melanoma who were previously untreated.

- There was a 6-month improvement in survival in patients treated with tebentafusp-tebn vs that in those who received standard therapies (21.7 months with tebentafusp-tebn vs 16.0 months with standard therapies)
- There was a clinically meaningful benefit in some patients who continued to receive treatment with tebentafusp-tebn after disease progression. These patients had longer survival than those who received standard therapies.

Patient eligibility for tebentafusp-tebn

Only patients who are *HLA-A*02:01*-positive eligible for tebentafusp-tebn. *HLA-A*02:01* status is determined by a simple blood test (high-resolution HLA test). Biopsy tissue samples should not be used. Tissue testing yields inaccurate results because of intratumoral heterogeneity and because HLA can be downregulated in tumor tissue.

Patients should be tested as soon as possible after diagnosis, since it can take up to 1 to 2 weeks to receive the results back.

This document is intended to assist providers in optimizing the management of uveal melanoma with this treatment.

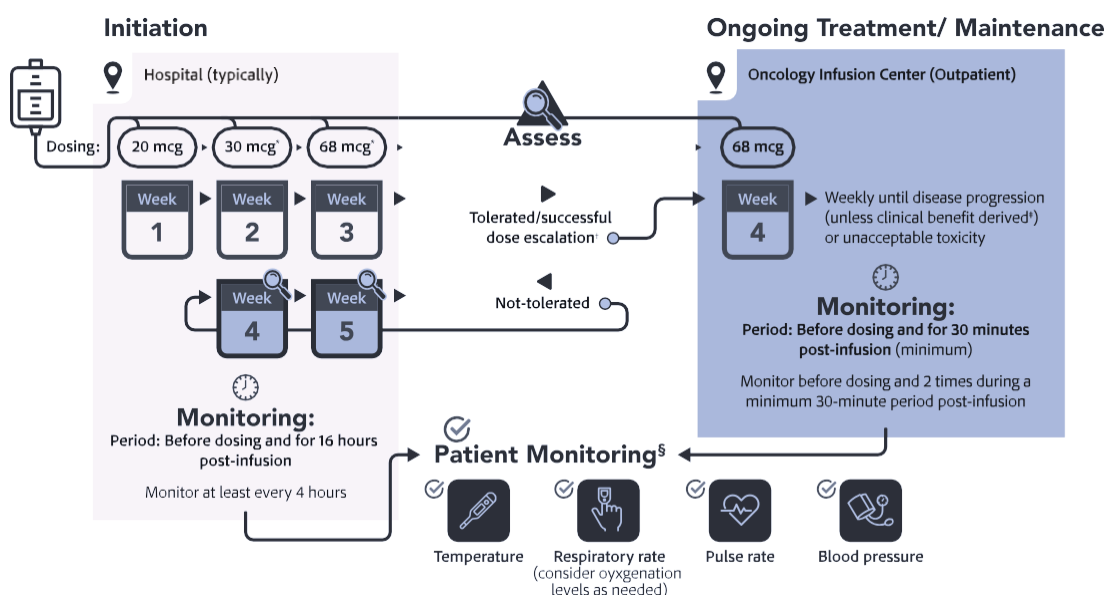
DRUG DOSING AND ADMINISTRATION

As a precaution, the initial infusions (induction) of tebentafusp-tebn are typically administered in the hospital to facilitate monitoring and management of toxicities. The most common side effects of tebentafusp-tebn are cytokine release symptom (CRS) and skin reactions. Among other drug-related adverse effects, elevated liver enzymes are also important to address. Toxicities are generally milder than those seen with other cellular therapies and are more common within the first 3-4 doses.

Patient monitoring periods:

Prior to Infusion

- Adequate hydration/euvolemic status
- Adequate liver function (labs prior to initiation and q3 wk throughout treatment)
- For patients on maintenance systemic corticosteroids, consider adjusting the corticosteroid dose given the risk of hypotension



* If patient has not had a \geq grade 2 cytokine release syndrome adverse event with their previous dose. See [CRS Care Step Pathway](#) for CRS grading and management).

† Transition to outpatient, if no hypotension requiring medical intervention during or after dose 3

‡ Determination of clinical benefit in patients with progressive disease is based on clinical judgement

§ Adjustment in what to monitor and at what frequency should be made using clinical judgment or by institutional standards.

Recommendations above based on clinical trial protocol.

Note: Adjustment in the corticosteroid dose, for patients who are on maintenance corticosteroids (adrenal insufficiency) is based on company materials not included in the prescribing information

- Tebentafusp-tebn is given as a 15-20-minute IV infusion
- Premedication of the first dose is not required, but institutional practices vary. Examples of potential premedications include acetaminophen 650 mg PO, ondansetron 8 mg PO, diphenhydramine 25 mg PO, and famotidine 20 mg
- Tebentafusp-tebn is administered weekly until disease progression (unless the patient is otherwise deriving clinical benefit) or unacceptable toxicity
- The majority of patients can transition to outpatient administration (infusion center) for ongoing maintenance therapy after the first 3 doses
- Patients can transition to outpatient administration, as long as there is no hypotension during or after the 3rd dose and the dose is otherwise well tolerated. Although uncommon, some patients may require hospitalization for their 4th or 5th dose

SIDE EFFECTS AND MANAGEMENT

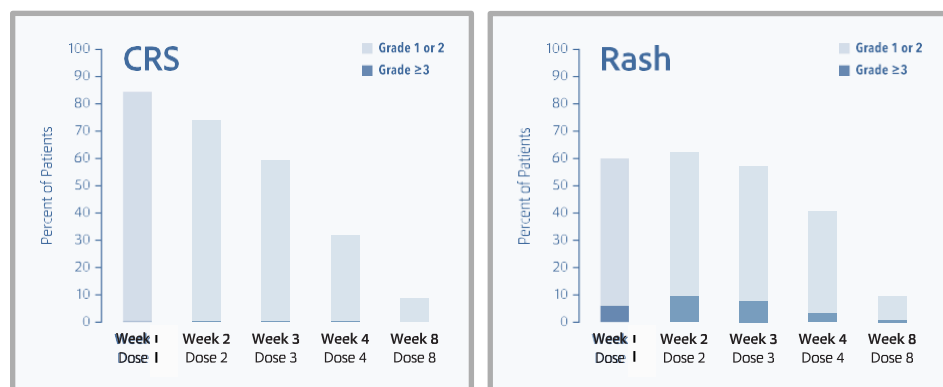
The most common side effects of tebentafusp-tebn are cytokine release syndrome (CRS) and skin reactions, which are related to the mechanism of action of tebentafusp-tebn. As shown in Figure 1, most of the adverse events are mild to moderate and occur within the first 3-4 doses (induction).

Cytokine release syndrome

CRS occurs in most patients during the initial induction, because tebentafusp-tebn is an immunotherapy that activates the T cells and enhances the body's immune system. CRS toxicities are generally milder than those seen with some other cellular-based therapies (eg, CAR-T), are usually Grade 1-2, and are reversible.

As shown in the chart below, the frequency of CRS in the clinical trial declined dramatically after the 3rd dose.

Figure 1. Incidence and severity of CRS over time in the clinical trial.



8 Hours Typical time to onset* of skin toxicity post infusion

*Based on onset of fever associated with CRS

See the Care Step Pathway for detailed discussion of grading and management of CRS

Tebentafusp-tebn Care Step Pathway – Cytokine Release Syndrome

Skin toxicities

Skin reactions, such as rash, are common during the induction phase. Since tebentafusp-tebn can recognize gp100 on melanocytes in the skin, normal cells may be affected.

While the frequency and severity of skin reactions typically decrease following each subsequent tebentafusp-tebn infusion, and usually drop dramatically after the first 3-4 doses, this is not always the case. In some cases, in some cases, skin toxicities can limit the ability to escalate the dosage, necessitating continued hospitalizations for infusions, including the 4th or 5th doses.

See the Care Step Pathway for a detailed discussion of the management of skin toxicities

24 Hours Typical time to onset of skin toxicity post infusion

Tebentafusp-tebn Care Step Pathway – Skin Toxicities

Other side effects

The table below shows management strategies for other side effects associated with tebentafusp-tebn.

Management of other notable side effects of tebentafusp-tebn

Adverse event	Common management/anticipatory guidance
Elevated liver enzymes	<p>Testing should be repeated throughout treatment</p> <p>For Grade 3 or Grade 4 liver enzyme elevations, withhold tebentafusp-tebn until Grade 1 or lower (or baseline)</p> <p>Then</p> <p><u>In the setting of Grade 3 CRS:</u></p> <ul style="list-style-type: none"> Resume tebentafusp-tebn at the same dose level; resume escalation if next administration is tolerated <p><u>Outside the setting of Grade 3 CRS:</u></p> <ul style="list-style-type: none"> Resume escalation if the current dose is less than 68 mcg Or resume at the same level if dose escalation has completed For all patients: Consider intravenous corticosteroids if no improvement in liver enzymes within 24 hours
Embryo-fetal toxicity	<p>May cause fetal harm. Advise females of reproductive potential to use effective contraception during treatment with tebentafusp-tebn and for 1 week after the last dose</p>
Other side effects (for example, diarrhea, fatigue, joint pain, and swelling of the stomach or skin)	<p>The general recommendation for remaining side effects:</p> <p><u>Grade 3</u></p> <ul style="list-style-type: none"> Withhold tebentafusp-tebn until Grade 1 or lower (or baseline) Resume tebentafusp-tebn at same dose level (ie, do not escalate if other Grade 3 adverse reaction occurred during initial dose escalation; resume escalation once dosage is tolerated) <p><u>Grade 4</u></p> <ul style="list-style-type: none"> Permanently discontinue tebentafusp-tebn

KEY TAKEAWAYS ABOUT TEBENTAFUSP-TEBN ADMINISTRATION

- HLA should be tested on the blood
- Tebentafusp-tebn is administered under long observation, typically for the first 3 doses
- Premedication may be considered during the initial doses but is frequently not needed subsequently
- Most side effects occur during the initial doses and are not likely to lead to discontinuation
- CRS occurs in the majority of patients; fever is usually the first sign
- Skin toxicities, such as rash, are also more common with the initial dosages and typically improve over time
- Due to the risk of hypotension, consider adjusting the corticosteroid dose given in patients on maintenance systemic corticosteroids, including patients with adrenal insufficiency
- Educate patients and caregivers about side effects and the importance of reporting symptoms as soon as possible. Remind patients about the importance of staying on schedule with their weekly infusions of tebentafusp-tebn
- Advise patients to take pictures of any skin changes for documentation

QUESTIONS & ANSWERS

Q. How long will patients stay on tebentafusp-tebn?

A. The prescribing information indicates until disease progression (unless the patient is otherwise deriving clinical benefit) or unacceptable toxicity. In the clinical trial, some patients with progressive disease continued to benefit. There is currently no consensus on strategies for treatment past progression or at which point the patient should be switched to an alternative treatment

Q. Are there standard dose reductions for adverse events?

A. There are no dosage reductions for AEs associated with tebentafusp-tebn. The dose is either held until the AE resolves sufficiently (typically to Grade 0 or Grade 1) or, if the AE is severe enough, tebentafusp-tebn is discontinued permanently.

Q. How do you dose escalate in a patient experiences a severe adverse event?

A. Patients who experience severe (Grade 3) CRS can be restarted at the same dose following resolution of symptoms, but the next dose should not be escalated. Dose escalation can resume once tebentafusp-tebn is tolerated.

For all other toxicities, tebentafusp-tebn can be restarted at the same dose following resolution to < Grade 1 or baseline. If Grade 3 reactions occurred with the first dose, dose escalation should only be resumed once the dose is tolerated.

Q. How often do patients discontinue tebentafusp-tebn due to adverse events?

A. There is a low rate of discontinuation due to adverse events. In the clinical trial, 3.3% of patients discontinued tebentafusp-tebn due to treatment-related adverse events. Reasons for discontinuation of tebentafusp-tebn were anaphylactic reaction, brain edema, CRS, fatigue, hepatotoxicity, hypotension, and nausea.

The majority of adverse events with tebentafusp-tebn are Grade 1-2 and occur most often with the first 3 doses while patients are in the hospital. They are manageable, reversible, and decrease in severity and frequency over time. Less than 10% of patients experience CRS or a skin reaction after 8 weeks of treatment.

Q. When do patients need to be hospitalized for 4th or 5th doses of tebentafusp-tebn?

A. Patients who experience Grade 2 or worse hypotension requiring medical intervention during or after dose 3 should receive tebentafusp-tebn in the hospital. The majority of patients can receive tebentafusp-tebn outpatient (infusion center) after the initial 3 doses. There may also be instances in which the dose could not be escalated during the first 3 doses, those patients may be required to receive additional doses in the hospital.

PATIENT RESOURCES

ADDITIONAL INFORMATION RESOURCES

AIM at Melanoma Foundation (Ask an Expert program, patient symposia, drug resources, etc)
<https://www.aimatmelanoma.org/>

American Cancer Society: Immunotherapy and Targeted Drugs for Eye Cancer
<https://www.cancer.org/cancer/types/eye-cancer/treating/targeted-therapy.html>

FINANCIAL ASSISTANCE

KIMMTRAK CONNECT®

Financial assistance and personalized care coordination for patients taking Kimmtrak.

www.kimmtrakconnect.com/

844-755-2273

Cancer Financial Aid Coalition

Facilitates communication, educates and advocates for patients.

www.cancerfac.org

Centers for Medicare and Medicaid Services (CMS)

Apply to determine if you are eligible for government assistance.

www.cms.gov or www.medicare.gov

800-633-4227

Lazarex Foundation

Provides assistance with travel costs for clinical trial participation. Ask your social work counselor for a referral if you have been consented to a clinical trial for melanoma.

www.lazarex.org

Needymeds

Database to search for free or low-cost medications, help with medical transportation and other resources.

www.needymeds.org

Patient Advocate Foundation

Provides assistance with mediation, financial stability, and other assistance. Funds subject to availability. Patient must meet their eligibility for financial assistance.

www.patientadvocate.org

800-532-5274

The Sam Fund for Young Adult Survivors of Cancer

Assists cancer survivors ages 21-39 with their transition into post-treatment life. This program distributes grants and scholarships in an effort to enable survivors to pursue goals.

www.thesamfund.org

info@thesamfund.org

Continue on next page

PRESCRIPTION ASSISTANCE

CancerCare Co-Payment Assistance Foundation

Helps with the cost of medication. Availability of funds for patients with Stage IV melanoma subject to availability.

www.cancercapecopay.org

1-866-552-6729

Medicine Assistance Tool

Database to search for patient assistance resources offered by pharmaceutical companies.

www.medicineassistancetool.org/

Patient Advocate Foundation Co-Pay Relief

Provides direct financial support to patients who medically qualify. Availability of funds for patients with Stage IV melanoma subject to availability.

www.copays.org

1-866-512-3861

Good Days

Formerly known as the Chronic Disease Fund. Provides assistance with insurance co-pays, and prescription medications. Availability of funds for patients with Stage IV melanoma subject to availability.

www.mygooddays.org

HealthWell Foundation

For patients who cannot afford insurance premiums, co-payments, co-insurance, or other out-of-pocket health care costs. Availability of funds for patients with Stage IV melanoma subject to availability. Patient must also meet eligibility for financial assistance.

www.healthwellfoundation.org or grants@healthwellfoundation.org

1-800-675-8416

The Assistance Fund, Inc

Provides prescription copay and financial assistance, including health insurance premiums. Availability of funds for patients with Stage IV melanoma subject to availability.

www.theassistancefund.org

1-855-845-3663

PAN Foundation

Provides financial assistance to cover out-of-pocket treatment costs. Availability of funds for patients with Stage IV melanoma subject to availability.

www.panfoundation.org

1-866-316-PANF (7263)

Patient Assistance Program

Comprehensive database of patient assistance programs offering free medications.

www.rxassist.org

info@rxassist.org

HOUSING

American Cancer Society – Hope Lodge

Provides free housing during treatment appointments. Requires a referral from your social worker.

www.cancer.org/

1-800-227-6333

TRANSPORTATION (AIR AND GROUND)

Medicaid

Ground transportation only. Sets up rides and provides mileage reimbursement for Medicaid patients only.

1-877-633-8747

Mercy Medical Angels

Provides free medical transportation (flights, gas cards, bus and train tickets) for patients with financial needs who need to travel more than 50 miles. Patients must meet their eligibility for financial assistance.

www.mercymedical.org/

Pilots for Patients

Provides free flights to people in need of medical treatment. Patient must be medically stable to fly and be ambulatory. Ask your social worker about a referral.

www.pilotsforpatients.org

318-322-5112

ADDITIONAL RESOURCES

- Carvajal RD, Butler MO, Shoushtari AN, et al. Clinical and molecular response to tebentafusp in previously treated patients with metastatic uveal melanoma: a phase 2 trial. *Nat Med*. 2022;28(11):2364-2373. doi: 10.1038/s41591-022-02015-7
- Carvajal RD, Nathan P, Sacco JJ, Orloff M, et al. Phase I study of safety, tolerability, and efficacy of tebentafusp using a step-up dosing regimen and expansion in patients with metastatic uveal melanoma. *J Clin Oncol*. 2022;40(17):1939-1948. doi: 10.1200/JCO.21.01805
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