Treatment Guide

KIMMTRAK® Dosing and AE Management

KIMMTRAK (tebentafusp-tebn)
Injection for Intravenous Use 100 mcg/0.5 mL

INFORMATION AT A GLANCE

Use this guide when treating patients prescribed KIMMTRAK. More details can be found inside.

KIMMTRAK is indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

Cytokine Release Syndrome (CRS), which may be serious or life-threatening, occurred in patients receiving KIMMTRAK. Monitor for at least 16 hours following the first three infusions and then as clinically indicated.

Please see the Important Safety Information, including **BOXED WARNING for CRS** on page 7 and click here for full Prescribing Information.

Patients should be monitored during and after KIMMTRAK infusion for the following[1]:

Cytokine Release Syndrome (T cell activation)

- Fever
- Hypotension
- Hypoxia
- Chills
- Nausea
- Vomiting
- Rash
- Elevated Transaminases
- Fatigue
- Headache

Some of these symptoms may be associated with cytokine release syndrome OR may be isolated events.

Skin Reactions (gp100 expression in normal melanocytes)

- Rash
- Pruritus
- Skin hypopigmentation
- Edema
- Dry Skin
- Erythema
- Hair color changes

Elevated Liver Enzymes

Reminders

- Discuss with patients the frequency of monitoring and the possible side effects that can occur
- Emphasize to patients the importance of keeping their weekly infusion schedule to maximize the clinical effectiveness of their treatment
- Communication across the care team is important to make sure that KIMMTRAK side effects are recognized and treated as early as possible

KIMMTRAK Dosing and Patient Monitoring[1]

Adequate hydration/euvolemic status prior to starting KIMMTRAK is advised

KIMMTRAK is given as a 15-20 minute infusion

	Week 1	Week 2	Week 3	Week 4 and beyond
Dosing schedule	20 mcg	30 mcg*	68 mcg*	68 mcg
Patient monitoring requirement	16 hours after administration			A minimum of 30 minutes after administration†
Monitor‡: temperature pulse rate respiratory rate blood pressure	At least every 4 hours			Twice post infusion

* If patient has not had a ≥ grade 2 cytokine release syndrome adverse event with their previous dose (see CRS grading and management guidance on page 5 for specific recommendations).

† If patient has not had hypotension requiring medical intervention with their most recent dose.

‡ 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.

KIMMTRAK Dosing[1]

The recommended dosage of KIMMTRAK administered intravenously is 20 mcg on day 1, 30 mcg on day 8, 68 mcg on day 15, and 68 mcg once every week thereafter. In clinical trials, patients stopped treatment for disease progression, unless the patient was otherwise deriving benefit, or for unacceptable toxicity.

- Dose of KIMMTRAK is generally based on how many infusions have been received
- Verify patient dose prior to each infusion
- Patients must be monitored at baseline, during, and after each infusion for side effects

KIMMTRAK Administration[1]

Prior to administering KIMMTRAK:

- No standard premedications are required
- Ensure patients are euvolemic prior to initiating the infusions. Administer intravenous (IV) fluids based on clinical evaluation, baseline vital signs, and the volume status of the patient, as assessed by the treating physician, to minimize the risk of hypotension associated with CRS
- Patients who may be sensitive to manifestations of CRS, such as hypotension, tachycardia, or hypoxia, or the use of intravenous fluids to manage CRS, should be carefully assessed prior to starting KIMMTRAK. Ensure patients are euvolemic prior to initiating KIMMTRAK infusions
- For patients on maintenance systemic corticosteroids, consider adjusting the corticosteroid dose given the risk of hypotension

For at least the first 3 infusions, patients should be monitored during infusion and at least for 16 hours after the infusion is complete.

To administer KIMMTRAK:

- Administer the diluted solution via intravenous infusion over 15-20 minutes through a dedicated IV line
  - A sterile, non-pyrogenic, low protein binding 0.2 micron in-line filter infusion set should be used
  - Administer the entire contents of the KIMMTRAK infusion bag to the patient
- Upon completion of KIMMTRAK infusion, flush the infusion line with adequate volume of sterile 0.9% Sodium Chloride Injection, USP to ensure that the entire contents of the infusion bag are administered
  - DO NOT mix KIMMTRAK with drugs other than albumin used during preparation or administer other drugs through the same IV line. Compatibility with other medications and fluids has not been established

Low 3.3% discontinuation rate due to treatment-related adverse events[1]

Please see the Important Safety Information, including **BOXED WARNING for CRS** on page 7 and click here for full Prescribing Information.

Possible Adverse Reactions[1]

In clinical trials, CRS, skin reactions, and elevated liver enzymes have occurred following KIMMTRAK infusion. These events decreased in frequency and severity following each subsequent KIMMTRAK infusion

- KIMMTRAK commonly causes mild to moderate **CRS**, which if not identified and treated appropriately, may become life-threatening or fatal
- Most patients typically experienced CRS following each of the first 3 infusions. The majority (84%) of episodes of CRS started the day of infusion

Discontinuation Rate	All Grades	Grade 1	Grade 2	Grades 3 or 4
1.2%	89%	12%	76%	0.8%

- A rise in temperature is generally the first sign of CRS, occurring earlier than drops 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. Consider managing symptoms early to help prevent CRS from escalating
- CRS symptoms were generally reversible and were mostly managed with IV fluids, NSAIDs, or a single dose of systemic corticosteroids

Systemic Corticosteroids*	Supplemental Oxygen*	Vasopressor*
23%	8%	0.8%

* For at least one infusion.

Skin Reactions: Typically occurred following each of the first 3 infusions. Median time to onset was one day, with most resolved to ≤ grade 1 between doses.

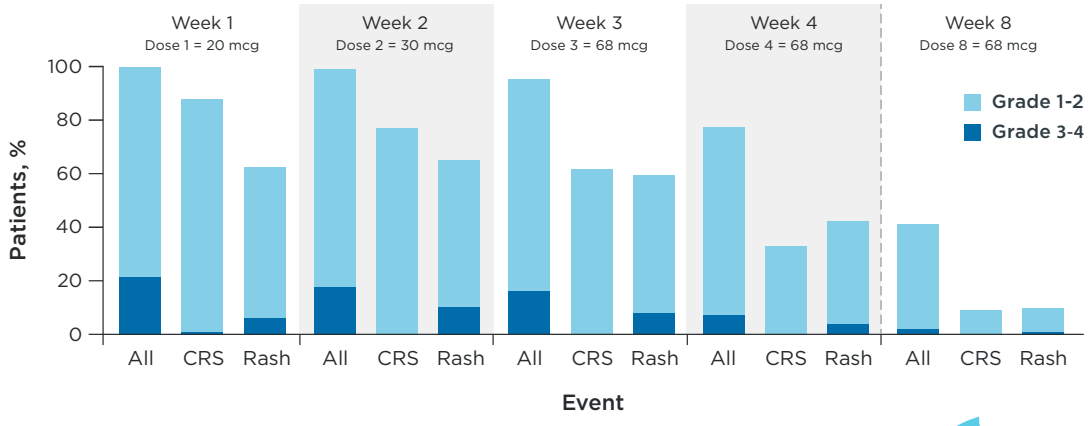
Discontinuation Rate	All Grades	Grade 1	Grade 2	Grade 3	Grades 4 or 5
0.00%	91%	26%	44%	21%	NONE

- Rash occurred in 83% of patients. Rash was often described as closer to symptoms of a sunburn than a typical rash. It could cause all or more of the body to turn red, and the skin to be sore, itchy, and peel. It can manifest differently in different patients
- Monitor patients for skin reactions. If skin reactions occur, treat with antihistamines and topical or systemic steroids based on persistence and severity of symptoms
- Most systems resolved without any long-term sequelae. Withhold or permanently discontinue KIMMTRAK depending on the severity of skin reactions

Elevated Liver Enzymes: The majority (73%) of ALT or AST elevations occurred within the first 3 infusions. Most patients experiencing grade 3 or 4 ALT/AST elevations had improvement to ≤ grade 1 within 7 days.

Discontinuation Rate	All Grades	Grades 3 or 4
0.4%	65%	8%

Incidence of Treatment-Related AEs by Week During Treatment with KIMMTRAK[2]



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Patient Monitoring[1]

For at least the first 3 infusions, patients should be monitored during infusion and at least for 16 hours after infusion is complete

- Based on clinical trials, 16 hours is the likely time frame for presentation of cytokine release syndrome (CRS) symptoms
- A rise in temperature is generally the first sign of CRS, occurring earlier than drops 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. Consider managing symptoms early to help prevent CRS from escalating
- Ensure that healthcare providers administering KIMMTRAK have immediate access to medications and resuscitative equipment to manage CRS
- After infusion 3, and once the patient tolerates the most recent infusion without hypotension requiring medical intervention (eg, giving IV fluids), subsequent doses can be administered in appropriate ambulatory care settings (eg, infusion center)

Starting with the fourth infusion of KIMMTRAK, patients should be monitored for a minimum of 30 minutes following each infusion.

The below monitoring reflects what was done in the clinical trials. Adjustment in what to monitor and at what frequency should be made using clinical judgment or by institutional standards.

First 3 Infusions of KIMMTRAK: 16-hour monitoring

Before dosing and every 4 hours (at a minimum), check vital signs:

- temperature
- pulse rate
- respiratory rate
- blood pressure

In cases of hypotension requiring medical intervention, consider vital sign monitoring at least every 2 hours or more frequently, as necessary. In cases of severe hypotension, consider vital sign monitoring every hour until resolved.

Starting with the Fourth Infusion: 30-minute monitoring

If the third infusion or most recent infusion was well tolerated

Before dosing and at least twice after infusion, check vital signs:

- temperature
- pulse rate
- respiratory rate
- blood pressure

If the third dose or most recent infusion was not well tolerated, monitoring vital signs more frequently and for longer than a 30-minute monitoring period should be considered starting with the fourth infusion.

- Elevated liver enzymes have occurred following KIMMTRAK Infusion
  Prior to the start of and during KIMMTRAK, monitor:
  - Alanine aminotransferase (ALT)
  - Aspartate aminotransferase (AST)
  - Total blood bilirubin

Please see the Important Safety Information, including **BOXED WARNING for CRS** on page 7 and click here for full Prescribing Information.

Adverse Event (AE) Management[1]

No dosage reduction for KIMMTRAK is recommended. For specific dosage modifications please refer to Section 2.3, Table 1 in full Prescribing Information.

CRS Grading and Management Guidance

Temperature ≥38 °C (100.4 °F) with:	CTCAE Grade*	Hold KIMMTRAK?	Treat with corticosteroids?	Corticosteroid premedication 30 minutes prior to next dose?	Can escalate to next dose?
• No hypotension or hypoxia	≤ **Grade 1**	NO	NO	NO	**YES**
• Hypotension that responds to fluids (does not require vasopressors) • Or hypoxia requiring low flow nasal cannula (≤6 L/min) or blow by oxygen	**Grade 2** lasting <2 hours	NO	NO	NO	**YES**
	lasting 2-3 hours or recurrent	NO	**YES**†	**YES**	**YES**
	lasting >3 hours & not responding to therapy	**YES**	**YES**†	**YES**	NO
• Hemodynamic instability requiring vasopressor (with or without vasopressin) • Or worsening hypoxia or respiratory distress requiring high flow nasal cannula (≥6 L/min) or face mask	**Grade 3**	**YES**	**YES**†	**YES**	NO
• Hemodynamic instability requiring multiple vasopressors (excluding vasopressin) • Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure	**Grade 4**	**Permanently discontinue KIMMTRAK and treat with corticosteroids**†			

* Based on ASTCT consensus grading of CRS criteria (Lee et al. 2019).

† If hypotension is not rapidly resolved (ie, within 2–3 hours of onset) with intravenous crystalloid therapy, intravenous corticosteroid therapy of methylprednisolone 2 mg/kg initial dose or equivalent and/or tocilizumab 8 mg/kg IV (not to exceed 800 mg/infusion) per institutional guidelines should be administered until symptoms (eg, hypotension) resolve.[3]

Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Potentially life threatening

Skin Reaction Management and Dose Modifications

Severity	KIMMTRAK Dosage Modifications
Grade 1[a]	• Treat symptomatically with antihistamines, oral analgesics, and topical steroids, as needed
Grade 2 or 3[a]	• Withold KIMMTRAK until ≤ grade 1 or baseline • Resume KIMMTRAK at same dose level (ie, 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 (eg, 2 mg/kg/day methylprednisolone or equivalent)
Grade 4[a]	• Permanently discontinue KIMMTRAK • Administer intravenous corticosteroid (eg, 2 mg/kg/day methylprednisolone or equivalent)

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (NCI CTCAEv4.03).

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Elevated Liver Enzymes Management and Dose Modifications

Severity	KIMMTRAK Dosage Modifications
Grade 3 or 4[a]	• Withhold KIMMTRAK until ≤ grade 1 or baseline • Resume KIMMTRAK at same dose level if the elevated liver enzymes occur in the setting of grade 3 CRS; resume escalation if 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 mcg, - or resume at same dose level if dose escalation has completed • Administer intravenous corticosteroids if no improvement within 24 hours

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (NCI CTCAEv4.03).

Other Adverse Reactions* Management and Dose Modifications

Severity	KIMMTRAK Dosage Modifications
Grade 3[a]	• Withhold KIMMTRAK until ≤ grade 1 or baseline • Resume KIMMTRAK 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)
Grade 4[a]	• Permanently discontinue KIMMTRAK

* Other adverse reactions as found in Section 6.1, Table 4 of full Prescribing Information.
[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (NCI CTCAEv4.03).

Reminders for Patients[1]

Consider discussing with patients the frequency of monitoring and the possible side effects that can occur. Remind the patient to alert the provider or nursing staff if they have:

- Fever
- Tiredness or weakness
- Vomiting
- Chills
- Nausea
- Low blood pressure
- Dizziness and light headedness
- Headache
- Wheezing and trouble breathing
- Rash
- Patchy or extensive redness, pain, itching or swelling of skin (rash)
- Redness, pain, or swelling around the eye, eyelid, or inner lining of the eyelid
- Dry skin and skin peeling
- Right-sided abdominal pain or yellowing of the skin or eyes (ie, abnormal liver blood tests)

Importance of patients keeping their infusion appointments

- Emphasize to patients the importance of keeping their weekly infusion schedule. To maximize the patient's opportunity to experience the overall survival benefit seen in clinical trials, patients must receive KIMMTRAK weekly, as prescribed
- Breaks in treatment, if needed, were allowed in the clinical trials for up to 2 weeks. Breaks for more than 2 weeks are not recommended
  - Side effects may occur at the same frequency and severity as a patient who is initiating treatment (first 3 infusions)
  - The impact on outcomes for breaks longer than 2 weeks has not been evaluated

If KIMMTRAK is well tolerated during the first 3 infusions, the patient may be able to continue weekly treatments in an appropriate healthcare setting closer to home

- KIMMTRAK CONNECT® can help the patient find closer to home options

KIMMTRAKCONNECT.com
844-775-CARE (844-775-2273)

KIMMTRAK CONNECT®

Please see the Important Safety Information, including **BOXED WARNING for CRS** on page 7 and click here for full Prescribing Information.

Indication and Important Safety Information Including Boxed Warning

Indication

KIMMTRAK is a bispecific gp100 peptide-HLA-directed CD3 T cell engager indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

Important Safety Information Including Boxed Warning

WARNING: CYTOKINE RELEASE SYNDROME

Cytokine Release Syndrome (CRS), which may be serious or life-threatening, occurred in patients receiving KIMMTRAK. Monitor for at least 16 hours following first three infusions and then as clinically indicated. Manifestations of CRS may include fever, hypotension, hypoxia, chills, nausea, vomiting, rash, elevated transaminases, fatigue, and headache. CRS occurred in 89% of patients who received KIMMTRAK with 0.8% being grade 3 or 4. Ensure immediate access to medications and resuscitative equipment to manage CRS. Ensure patients are euvolemic prior to initiating the infusions. Closely monitor patients for signs or symptoms of CRS following infusions of KIMMTRAK. Monitor fluid status, vital signs, and oxygenation level and provide appropriate therapy. Withhold or discontinue KIMMTRAK depending on persistence and severity of CRS.

Skin Reactions

Skin reactions, including rash, pruritus, and cutaneous edema occurred in 91% of patients treated with KIMMTRAK. Monitor patients for skin reactions. If skin reactions occur, treat with antihistamine and topical or systemic steroids based on persistence and severity of symptoms. Withhold or permanently discontinue KIMMTRAK depending on the severity of skin reactions.

Elevated Liver Enzymes

Elevations in liver enzymes occurred in 65% of patients treated with KIMMTRAK. Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total blood bilirubin prior to the start of and during treatment with KIMMTRAK. Withhold KIMMTRAK according to severity.

Embryo-Fetal Toxicity

KIMMTRAK may cause fetal harm. Advise pregnant patients of potential risk to the fetus and patients of reproductive potential to use effective contraception during treatment with KIMMTRAK and 1 week after the last dose.

The most common adverse reactions (≥30%) in patients who received KIMMTRAK were cytokine release syndrome, rash, pyrexia, pruritus, fatigue, nausea, chills, abdominal pain, edema, hypotension, dry skin, headache, and vomiting. The most common (≥50%) laboratory abnormalities were decreased lymphocyte count, increased creatinine, increased glucose, increased AST, increased ALT, decreased hemoglobin, and decreased phosphate.

Please see full Prescribing Information, including **BOXED WARNING for CRS**.

For questions or to report adverse events

For more information or to report suspected adverse reactions, contact the Immunocore Medical Information Center at 1-844-IMMUNO-1 (1-844-466-8661).

For patient assistance, contact:

KIMMTRAK CONNECT®

KIMMTRAKCONNECT.com
844-775-CARE (844-775-2273)

References: 1. Kimmtrak. Package Insert. Immunocore Ltd; 2022. **2.** Nathan P, Hassel JC, Rutkowski P, et al; IMCgp100-202 Investigators. Overall survival benefit with tebentafusp in metastatic uveal melanoma. *N Engl J Med*. 2021;385:1196-206. doi:10.1056/NEJMoa2103485 **3.** Protocol for: Nathan P, Hassel JC, Rutkowski P, et al; IMCgp100-202 Investigators. Overall survival benefit with tebentafusp in metastatic uveal melanoma. *N Engl J Med*. 2021;385:1196-206. doi:10.1056/NEJMoa2103485

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