

Treatment Guide

KIMMTRAK® Dosing and AE Management

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:

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

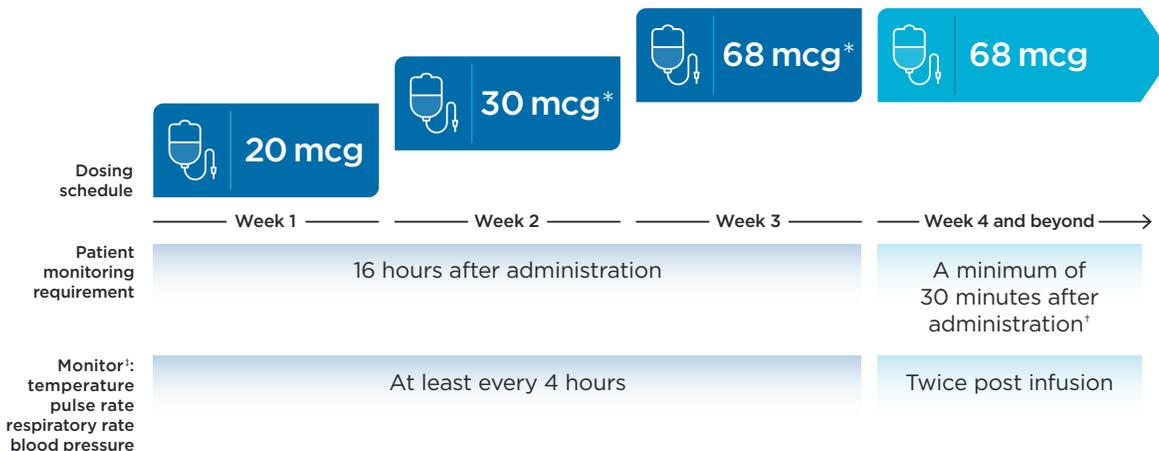
Elevated Liver Enzymes

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

KIMMTRAK is given as a 15-20 minute infusion



* If patient has not had a \geq 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

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

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
- 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.

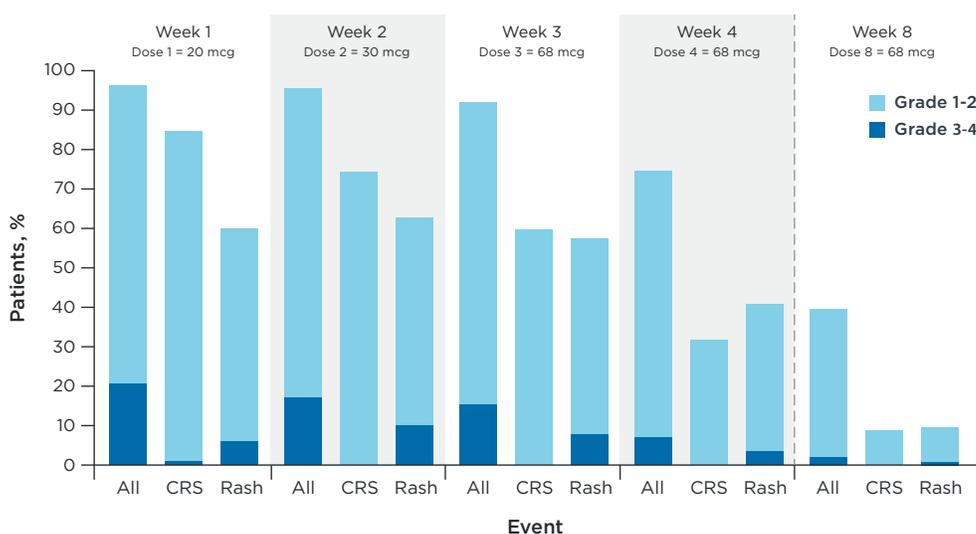
Low 3.3% discontinuation rate due to treatment related adverse events

Possible Adverse Reactions

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 KIMMTRAK infusions with decreasing severity and frequency.
 - The majority (84%) of episodes of CRS started the day of infusion
- CRS (Grades 2-4) occurred in 77% of patients (0.8% had Grade 3 or 4) in clinical trials who received KIMMTRAK.
 - CRS led to permanent discontinuation in 1.2% of patients
 - CRS symptoms were generally reversible and were mostly managed with IV fluids, NSAIDs, or a single dose of systemic corticosteroids
 - Among patients who received KIMMTRAK, 23% received systemic corticosteroids for at least 1 infusion, 8% received supplemental oxygen during at least 1 infusion, and 0.8% received a vasopressor for at least 1 infusion
 - Pyrexia was noted in nearly all cases of CRS
 - An increase in body temperature generally occurred within the first 8 hours after KIMMTRAK infusion
- Skin reactions typically occurred following each of the first 3 KIMMTRAK infusions, with decreasing severity and frequency.
 - In clinical trials, skin reactions occurred in 91% of patients treated with KIMMTRAK: Grade 1 (26%), Grade 2 (44%), and Grade 3 (21%) events. No Grade 4 or Grade 5 events were observed
 - Median time to onset of skin reactions was 1 day, with most resolved to ≤ Grade 1 between doses
 - The majority of symptoms resolved without any systemic corticosteroid or any long term sequelae
 - Skin reactions did not lead to any KIMMTRAK discontinuations
- In patients experiencing ALT/AST elevations, 73% initially occurred within the first 3 infusions of KIMMTRAK.
 - Increases in ALT or AST were observed in 65% of patients treated with KIMMTRAK
 - Most patients experiencing Grade 3 or 4 ALT/AST elevations had improvement to ≤ Grade 1 within 7 days
 - Elevations in liver enzymes led to permanent discontinuation in 0.4% of patients receiving KIMMTRAK

Incidence of Treatment-Related AEs by Week During Treatment with KIMMTRAK



Patient Monitoring

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.
- 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 (e.g., giving IV fluids), subsequent doses can be administered in appropriate ambulatory care settings (e.g., infusion center).

Starting with the 4th 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 4th 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 4th 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

Adverse Event (AE) Management

No dosage reduction for KIMMTRAK is recommended. Dosage modifications for KIMMTRAK for adverse reactions are summarized below.

CRS Grading and Management Guidance

CRS Grade*	Severity	KIMMTRAK Dosage Modifications
Grade 1	Mild defined as temperature $\geq 38^{\circ}\text{C}$ (100.4°F) AND No hypotension or hypoxia	<ul style="list-style-type: none"> Monitor for escalation in CRS severity Treat for symptoms as appropriate
Grade 2	Moderate defined as temperature $\geq 38^{\circ}\text{C}$ (100.4°F) with <ul style="list-style-type: none"> Hypotension that responds to fluids (does not require vasopressors) or Hypoxia requiring low flow nasal cannula ($\leq 6\text{L}/\text{min}$) or blow-by oxygen 	<ul style="list-style-type: none"> If hypotension and hypoxia do not improve within 3 hours or CRS worsens, escalate care and manage according to next higher level of severity For moderate CRS that is persistent (lasting 2-3 hours) or recurrent, administer corticosteroid premedication (e.g. dexamethasone 4mg or equivalent) at least 30 minutes prior to next dose
Grade 3	Severe defined as temperature $\geq 38^{\circ}\text{C}$ (100.4°F) with <ul style="list-style-type: none"> Hemodynamic instability requiring a vasopressor (with or without vasopressin) or Worsening hypoxia or respiratory distress requiring high flow nasal cannula ($> 6\text{L}/\text{min}$ oxygen) or face mask 	<ul style="list-style-type: none"> Withhold KIMMTRAK until CRS and sequelae have resolved Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent) Resume KIMMTRAK at 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 4mg or equivalent) at least 30 minutes prior to next dose
Grade 4	Life threatening defined as temperature $\geq 38^{\circ}\text{C}$ (100.4°F) <ul style="list-style-type: none"> Hemodynamic instability requiring multiple vasopressors (excluding vasopressin) Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure 	<ul style="list-style-type: none"> Permanently discontinue KIMMTRAK Administer intravenous corticosteroid (e.g., 2mg/kg/day methylprednisolone or equivalent)

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

Skin Reaction Management and Dose Modifications

Severity	KIMMTRAK Dosage Modifications
Grade 2 or 3 ^a	<ul style="list-style-type: none"> Withhold KIMMTRAK until \leq Grade 1 or baseline Resume KIMMTRAK at same dose level (i.e., 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 ^a	<ul style="list-style-type: none"> Permanently discontinue KIMMTRAK Administer intravenous corticosteroid (e.g., 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)

Elevated Liver Enzymes Management and Dose Modifications

Severity	KIMMTRAK Dosage Modifications
Grade 3 or 4 ^a	<ul style="list-style-type: none">Withhold KIMMTRAK until \leq Grade 1 or baselineResume KIMMTRAK at same dose level if the elevated liver enzymes occur in the setting of Grade 3 CRS; resume escalation if next administration is toleratedIf the elevated liver enzymes occur outside the setting of Grade 3 CRS<ul style="list-style-type: none">- resume escalation if the current dose is less than 68 mcg,- or resume at same dose level if dose escalation has completedAdminister 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	<ul style="list-style-type: none">Withhold KIMMTRAK until \leq Grade 1 or baselineResume KIMMTRAK at same dose level (i.e., do not escalate if other Grade 3 adverse reaction occurred during initial dose escalation; resume escalation once dosage is tolerated)
Grade 4 ^a	<ul style="list-style-type: none">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

! 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
- Right-sided abdominal pain or yellowing of the skin or eyes (i.e. abnormal liver blood tests)
- 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

! 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 (2273)



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 ($\geq 30\%$) 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 ($\geq 50\%$) laboratory abnormalities were decreased lymphocyte count, increased creatinine, increased glucose, increased AST, increased ALT, decreased hemoglobin, and decreased phosphate.



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:



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KIMMTRAKCONNECT.com
844-775-CARE (2273)



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

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