Pharmacist Guide

KIMMTRAK® Dosing, Preparation, and Adverse Event Management

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

INFORMATION AT A GLANCE

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

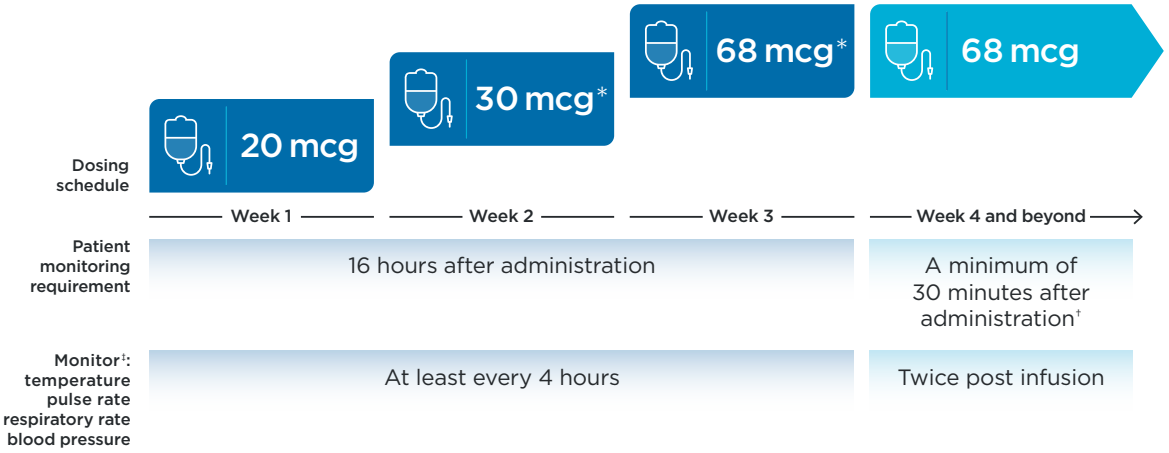
KIMMTRAK is indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

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 9 and click here for full Prescribing Information.

KIMMTRAK Dosing and Patient Monitoring

KIMMTRAK is given as a 15-20 minute 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.

What You Need to Prepare KIMMTRAK

Before you begin have the following available:

- KIMMTRAK comes in a 100 mcg / 0.5 mL clear, colorless to slightly yellowish solution in a 0.5 mL single-dose vial
- 1 mL sterile syringes with graduations of 2 decimal places (e.g., TB syringe)
- Sterile needles: 18-gauge to 21-gauge sterile needles commonly used in aseptic compounding are recommended
- Albumin (Human); use concentration as per local availability. Examples include but are not restricted to the following strengths: 5%, 20% or 25%

Human albumin is important to ensure that the active ingredient does not adhere to the bag and result in underdosing the patient.

- A 100 mL 0.9% Sodium Chloride Injection, USP infusion bag
  - The infusion bag should be constructed of polyolefins (PO) (such as polyethylene (PE) and polypropylene (PP)) or polyvinyl chloride (PVC)
- A sterile, non-pyrogenic, low protein binding 0.2 micron in-line filter infusion set for administration of the final infusion bag
- Inspect the parenteral drug products and infusion bags for particulate matter and discoloration

Reminders

- **KIMMTRAK is not a hazardous drug under NIOSH**
- **Before preparation and administration of KIMMTRAK, verify the dose of KIMMTRAK**
  - See directions within this guide or the KIMMTRAK Prescribing Information.
- **KIMMTRAK must be diluted prior to intravenous (IV) administration**
- If not used immediately, store the KIMMTRAK infusion bag in a refrigerator at 2°C to 8°C (36°F to 46°F) and **infuse within 24 hours from the time of preparation**

Scan and Watch!

Access a video showing the preparation of KIMMTRAK by scanning the QR code or visiting www.KIMMTRAKhcp.com.

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.

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.
- 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.

- 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

Preparation of KIMMTRAK

- KIMMTRAK is to be administered intravenously as IV infusion only.
- **Before preparation and administration of KIMMTRAK, verify the dose of KIMMTRAK.**
  - 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.
- KIMMTRAK must be diluted prior to IV administration.
- Each vial of KIMMTRAK is intended as single-dose only. DO NOT SHAKE the KIMMTRAK vial.

What You Need to Prepare KIMMTRAK

Before you begin, have the following available:

- KIMMTRAK comes in a 100 mcg / 0.5 mL clear, colorless to slightly yellowish solution in a 0.5 mL single-dose vial
- 1 mL sterile syringes with graduations of 2 decimal places (e.g., TB syringe)
- Sterile needles: 18-gauge to 21-gauge sterile needles commonly used in aseptic compounding are recommended
- Albumin (Human); use concentration as per local availability. Examples include but are not restricted to the following strengths: 5%, 20% or 25%

KIMMTRAK is not a hazardous drug under NIOSH

- A 100 mL 0.9% Sodium Chloride Injection, USP infusion bag
  - The infusion bag should be constructed of polyolefins (PO) (such as polyethylene (PE) and polypropylene (PP)) or polyvinyl chloride (PVC)
- A sterile, non-pyrogenic, low protein binding 0.2 micron in-line filter infusion set for administration of the final infusion bag
- Inspect the parenteral drug products and infusion bags for particulate matter and discoloration

Human albumin is important to ensure that the active ingredient does not adhere to the bag and result in underdosing the patient.

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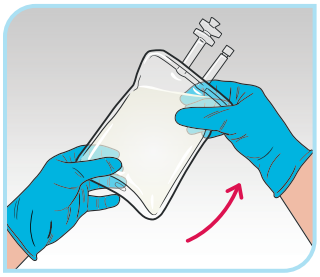
To dilute KIMMTRAK:

Step 1- Prepare the infusion bag, using aseptic technique

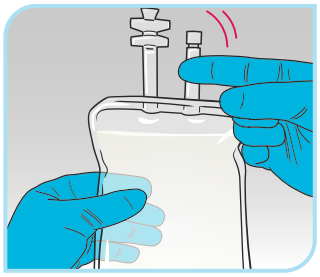
Using a 1 mL syringe with graduations of 2 decimal places and a sterile needle, withdraw the calculated volume of Albumin (Human) into the syringe and add to the 100 mL 0.9% Sodium Chloride Injection, USP bag to make a final Albumin (Human) concentration of 250 mcg/mL

Gently homogenize the prepared solution by completing the following steps:



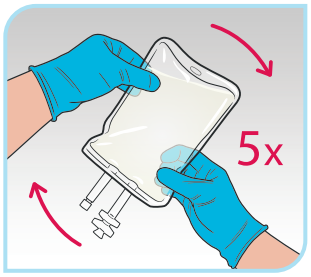
Step 1a

Invert the infusion bag so that the bag is upside down with the entry port positioned on top.



Step 1b

Tap the side of the port tubing to ensure that any residual solution is released into the bulk solution.



Step 1c

Mix the prepared solution by gently rotating the bag lengthwise at least 5 times.

Step 1d

DO NOT SHAKE the infusion bag.

Repeat the above steps an additional 3 times.

Before preparing KIMMTRAK remember to verify the dose for the patient.

Homogenous mixing is essential to prevent adsorption of drug to the infusion bag and other components of the drug delivery system.

Step 2: Preparation of KIMMTRAK Solution for Infusion.

a. Do not shake the KIMMTRAK vial

b. Using a 1 mL syringe with graduations of 2 decimal places and a sterile needle, withdraw the required volume of KIMMTRAK 100 mcg/0.5 mL as per the dose required (as shown in the table on right) and add to the prepared 100 mL infusion bag containing 0.9% Sodium Chloride Injection, USP plus Albumin (Human)

c. Discard the single dose vial containing the unused portion of KIMMTRAK in accordance with local requirements. DO NOT prepare more than one dose from the vial

d. Mix the infusion bag by following the same procedure as outlined in Steps 1a through 1d

Examples of Albumin (Human) Concentration and Volumes

Albumin (Human) concentration	Albumin (Human) volume for addition to a 100 mL 0.9% Sodium Chloride Injection, USP Infusion Bag to prepare a concentration of 250 mcg/mL Albumin (Human) in 0.9% Sodium Chloride Injection, USP
5% (50 g/L)	0.5 mL
20% (200 g/L)	0.13 mL
25% (250 g/L)	0.1 mL

KIMMTRAK Volumes Required for Addition to the Infusion Bag

Day of treatment	Dose (mcg) of KIMMTRAK	Volume (mL) of KIMMTRAK
Day 1	20	0.1
Day 8	30	0.15
Day 15 and weekly thereafter	68	0.34

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Prior to administering KIMMTRAK:

- No standard premedications are required
- Ensure patients are euvolemic prior to initiating the infusions. Administer 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 cytokine release syndrome (CRS)
- For patients on maintenance systemic corticosteroids, consider adjusting the corticosteroid dose given the risk of hypotension

To administer KIMMTRAK:

- Immediately 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.

KIMMTRAK Storage

- Store KIMMTRAK vials in the original carton refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light until time of use.
  - Do not freeze. DO NOT SHAKE.
- KIMMTRAK does not contain a preservative.
  - KIMMTRAK is stable for 4 hours if kept at room temperature. Administer the prepared infusion bag within 4-hours from the time of preparation including the duration of infusion (if kept at room temperature).
  - If not used immediately, store the KIMMTRAK infusion bag in a refrigerator at 2°C to 8°C (36°F to 46°F) **and infuse within 24 hours from the time of preparation**, which includes the storage time in the refrigerator, the time allowed for equilibration of the infusion bag to room temperature, and the duration of the infusion.
  - Once removed from the refrigerator, do not refrigerate the KIMMTRAK infusion bag again.
  - DO NOT freeze.
  - Discard unused KIMMTRAK solution beyond the recommended storage time.

Scan and Watch!

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Reminders

- **KIMMTRAK is not a hazardous drug under NIOSH**
- **Before preparation and administration of KIMMTRAK, verify the dose of KIMMTRAK**.
  - 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.

Patient Monitoring

Cytokine release syndrome (CRS), skin reactions, and elevated liver enzymes have occurred following KIMMTRAK infusion.

During the infusion and after KIMMTRAK administration, patients must be monitored for side effects.

CRS (T cell activation)

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

Some of these symptoms may be associated with CRS 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

Prior to the start of and during KIMMTRAK, monitor:

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total blood bilirubin

NDC 80446-401-01

Low 3.3% discontinuation rate due to treatment related adverse events

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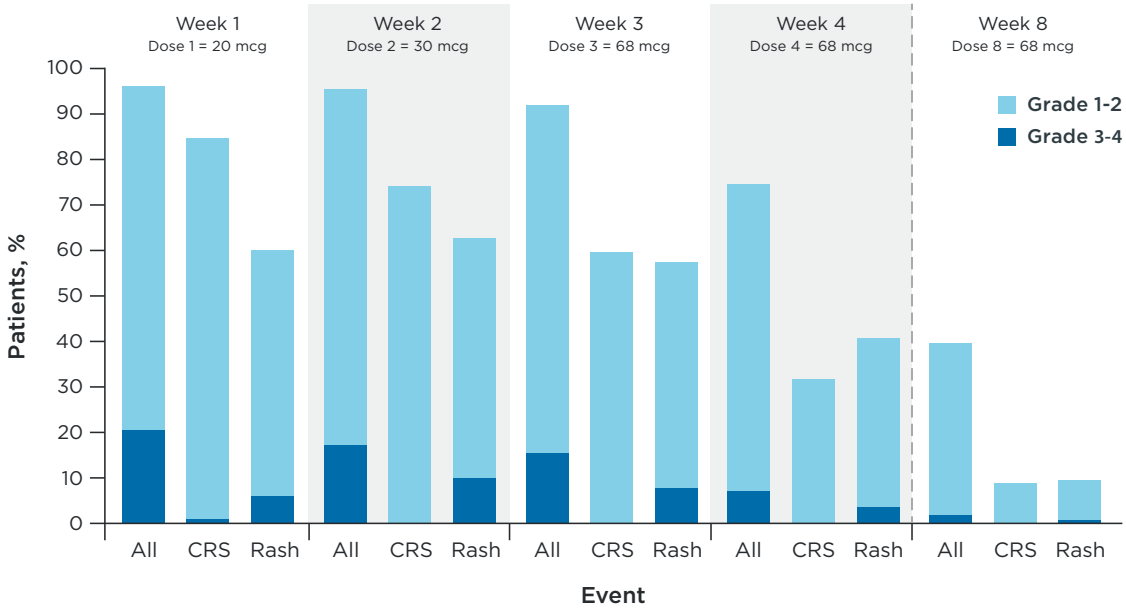
Possible Adverse Reactions

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 treatment 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 sequalae
    - 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



Please see the Important Safety Information, including **BOXED WARNING for CRS** on page 9 and click here for full Prescribing Information.

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 ≥ 38°C (100.4°F) AND No hypotension or hypoxia	• Monitor for escalation in CRS severity • Treat for symptoms as appropriate
Grade 2	Moderate defined as temperature ≥ 38°C (100.4°F) with • Hypotension that responds to fluids (does not require vasopressors) or • Hypoxia requiring low flow nasal cannula (≤ 6L/min) or blow-by oxygen	• 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 ≥ 38°C (100.4°F) with • Hemodynamic instability requiring a vasopressor (with or without vasopressin) or • Worsening hypoxia or respiratory distress requiring high flow nasal canula (> 6L/min oxygen) or face mask	• 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 ≥ 38°C (100.4°F) • Hemodynamic instability requiring multiple vasopressors (excluding vasopressin) • Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure	• 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]	• Withhold KIMMTRAK until ≤ 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]	• 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)

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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 (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]	• 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
- 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 (i.e. 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 (2273)

KIMMTRAK CONNECT®

Please see the Important Safety Information, including **BOXED WARNING for CRS** on page 9 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.

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:

KIMMTRAKCONNECT®

KIMMTRAKCONNECT.com
844-775-CARE (2273)

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