SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

KIMMTRAK 200 micrograms/ mL concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One 0.5 mL vial contains 100 micrograms of tebentafusp, corresponding to a concentration before dilution of 200 mcg/mL

Tebentafusp is a bispecific gp100-targeted T cell receptor fusion protein with an approximate molecular weight of 77 kDa. Tebentafusp is produced by recombinant DNA technology in *Escherichia coli* cells.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear, colourless to slightly yellowish solution in a single-dose vial.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

KIMMTRAK is indicated as monotherapy for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

4.2 Posology and method of administration

KIMMTRAK should be administered under the supervision of a physician experienced in the use of anti-cancer immunotherapy agents. Appropriate medicinal products, including anti-IL-6 treatment and resuscitation equipment should be available.

Posology

Patients treated with KIMMTRAK must have HLA-A*02:01 genotype determined by a validated HLA genotyping assay.

The recommended dose of KIMMTRAK is:

20 micrograms on Day 1

30 micrograms on Day 8

68 micrograms on Day 15

68 micrograms once every week thereafter (see section 6.6).

Continue treatment until disease progression or unacceptable toxicity. Atypical responses similar to immune checkpoint inhibitors have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

First three treatment doses

First three doses of KIMMTRAK should be administered in a hospital setting with overnight monitoring for signs and symptoms of CRS for at least 16 hours. Vital signs should be monitored pre-dose and at a minimum of every 4 hours until resolution of symptoms. If clinically indicated, more frequent monitoring or prolongation of hospitalisation should occur.

If patients experience Grade 3 or 4 hypotension during any of the first three KIMMTRAK infusions, patients should be monitored every hour for at least 4 hours in an outpatient setting for the next three infusions.

Subsequent treatment doses

After 68 mcg dose level is tolerated (i.e., absence of Grade ≥ 2 hypotension requiring medical intervention), subsequent doses can be administered in appropriate out-patient ambulatory care setting. Observe patients for a minimum of 30 minutes following each infusion.

Pre-medication

To minimize the risk of hypotension associated with cytokine release syndrome (CRS), administer intravenous fluids prior to starting KIMMTRAK infusion based on clinical evaluation and the volume status of the patient.

For patients with pre-existing adrenal insufficiency on maintenance systemic corticosteroids, consider adjusting the corticosteroid dose to manage the risk of hypotension.

Dose adjustments

Evaluate for and treat other causes of fever, hypoxia and hypotension. If CRS is suspected, identify and manage according to recommendations in Table 1.
See Table 2 for management guidelines for acute skin reactions.

Table 1: CRS Grading and Management Guidance

CRS Grade*	Management
Grade 1 Temperature ≥ 38°C No hypotension or hypoxia	Treat for symptoms as appropriate. Monitor for escalation in CRS severity
Grade 2 Temperature ≥ 38°C Hypotension that responds to fluids and does not require vasopressors. Oxygen requirement includes low flow nasal cannula (delivery of oxygen ≤ 6 L/min) or blow-by	Symptom management as per Grade 1 in addition to the following measures: Administer bolus intravenous fluids as needed for hypotension Manage oxygen requirement with supplemental oxygen and additional respiratory support as needed. Increase monitoring to determine resolution or escalation in severity If Grade 2 CRS symptoms do not rapidly improve to Grade ≤ 1 within 2-3 hours, then treat as Grade 3 For Grade 2 CRS that is persistent (lasting 2-3 hours) or recurrent (occurrence of ≥ Grade 2 CRS with more than one dose), administer corticosteroid premedication (e.g. dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose
Grade 3 Temperature ≥ 38°C Require a vasopressor with or without vasopressin. Require high flow nasal cannula (delivery of oxygen > 6 L/min), face mask or non-rebreather mask or Venturi mask	Management per Grade 2 and include the following measures: Administer high-dose intravenous corticosteroid (e.g. 2 mg/kg/day methylprednisolone or equivalent) Increase monitoring to determine resolution or escalation in severity Consider administering tocilizumab. Withhold KIMMTRAK until Grade ≤ 1. At next treatment, resume KIMMTRAK at same dose level (i.e. do not escalate) after appropriate risk versus benefit assessment and monitor patient accordingly. Once dose level is tolerated, can resume pre-planned dosing schedule For Grade 3 CRS, administer corticosteroid premedication (e.g. dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose
Grade 4 Temperature ≥ 38°C Require multiple vasopressors. Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation).	Permanently discontinue KIMMTRAK Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)

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

Table 2: Recommended Management and Dose Modifications for Acute Skin Reactions and Elevated Liver Enzymes

Adverse Reactions	Severity[a] of Adverse Reaction	Management
Acute skin reactions (see section 4.4)	Grade 2 or 3	Use local skin management and systemic antihistamine regimen. Topical corticosteroid treatment can be considered for symptomatic rash that does not respond to anti-pruritic regimen. Consider systemic steroids for persistent or severe symptoms. Withhold KIMMTRAK until Grade ≤ 1 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)
	Grade 4	Permanently discontinue KIMMTRAK Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)
Elevated liver enzymes (see section 4.4)	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
Other clinically relevant adverse reactions	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

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

Special populations

Paediatric population

The safety and efficacy of KIMMTRAK in children under the age of 18 years has not been established.

No data are available.

Elderly

No dose adjustment is required for elderly patients (≥ 65 years of age).

Renal impairment

Based on pharmacokinetic analyses, dose adjustment is not necessary in patients with mild to moderate renal impairment (see section 5.2). Patients with severe renal impairment have not been evaluated and should be treated with caution. No dose recommendations can be made for patients with severe renal impairment because of the lack of pharmacokinetic data.

Hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment. KIMMTRAK has not been studied in patients with moderate or severe hepatic impairment at baseline (see section 5.2).

Cardiac disease

Patients with significant history of cardiac disease have not been evaluated. Patients with cardiac disease, QTc prolongation, or risk factors for cardiac failure should be monitored carefully.

Method of administration

KIMMTRAK is for intravenous use. The recommended infusion period is 15-20 minutes.

KIMMTRAK requires dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection containing human albumin for IV infusion. Each vial of KIMMTRAK is intended for use as single-dose only. Do not shake the KIMMTRAK vial.

Use aseptic technique for dilution and preparation of dosing solutions.

Closed system transfer devices (CSTDs) must not be used for dose preparation of solution for infusion.

For instructions on dilution and administration of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patient selection

When considering the use of KIMMTRAK as a monotherapy for unresectable or metastatic uveal melanoma, it is important that the HLA-A*02:01 positive status of a patient is determined.

Cytokine release syndrome (CRS)

CRS has occurred following KIMMTRAK infusions. Diagnosis of CRS following KIMMTRAK infusion was most frequently based on pyrexia followed by hypotension and infrequently hypoxia. Other commonly observed symptoms with CRS included chills, nausea, vomiting, fatigue, and headache.

Most patients experienced CRS following each of first three KIMMTRAK infusions, with decreasing severity and frequency. Nearly all cases of CRS started on the day of infusion. Early signs of CRS include increase in body temperature and hypotension which occur within the first 16 hours after KIMMTRAK infusion.

Monitor patients for signs or symptoms of CRS for at least 16 hours following first three infusions of tebentafusp in hospital setting with immediate access to medicinal products and resuscitative equipment to manage CRS. If CRS is observed, prompt treatment with supportive care including antipyretics, intravenous fluids or corticosteroids should be initiated to avoid escalation to severe or life-threatening events and monitoring should be continued until resolution (see section 4.2).

At subsequent doses, patients should be closely monitored for at least 30 minutes after treatment for early identification of signs and symptoms of CRS. Patients with co-morbidities, including certain cardiovascular disorders, may be at increased risk for sequalae associated with CRS.

Withhold or discontinue tebentafusp depending on persistence and severity of CRS (see section 4.2, Table 1).

Acute skin reactions

Acute skin reactions have been reported with KIMMTRAK infusion, which may be based on its mechanism of action and gp100 expression in normal melanocytes in the skin. Acute skin reactions mainly included rash, pruritus, erythema and cutaneous oedema.

Acute skin reactions typically occur following each of the first three KIMMTRAK infusions and decrease in severity and frequency with subsequent doses. No cases of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported.

Acute skin reactions can be managed with antihistamine and topical corticosteroids. Consider systemic steroids for persistent or severe symptoms. For additional details on management of acute skin reaction, refer to clinical management as outlined in section 4.2, Table 2.

Elevated liver enzymes

Transient elevations in liver enzymes including aspartate transaminase/alanine aminotransferase (AST/ALT) and bilirubin have occurred following KIMMTRAK treatment. These elevations mainly occurred secondary to a CRS event and may also be attributed to underlying disease, liver metastasis, or disease progression. Cases of liver enzyme increase can be asymptomatic.

Monitor AST, ALT and total blood bilirubin prior to the start of and during treatment with KIMMTRAK. Withhold KIMMTRAK according to severity (see section 4.2, Table 2).

Cardiac Disease

Cardiac events such as sinus tachycardia and arrhythmia have been observed in patients who have received tebentafusp treatment (see section 4.8). Patients with

pre-existing cardiovascular disorders may be at increased risk for sequalae associated with CRS and should be monitored carefully. Any patient with signs or symptoms consistent with cardiac events should be evaluated and promptly treated. In addition, appropriate treatment should be administered for any underlying CRS as a precipitating factor.

Cases of QT interval prolongation were reported following tebentafusp treatment (see section 4.8). Tebentafusp treatment should be administered with caution in patients with history of or predisposition to QT interval prolongation and in patients who are taking medicinal products that are known to prolong QT interval.

An electrocardiogram (ECG) should be performed in all patients before and after tebentafusp treatment during the first 3 weeks of treatment and subsequently as clinically indicated. If QTcF exceeds 500 msec or increases by ≥ 60 msec from baseline value, tebentafusp treatment should be withheld and patients should be treated for any underlying precipitating factors including electrolyte abnormalities. Tebentafusp treatment should be resumed once QTcF interval improves to <500 msec or is < 60 msec from baseline value. Depending on persistence and severity of the cardiac event and any associated CRS, tebentafusp treatment should be withheld or discontinued (see section 4.2, Table 1).

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed with tebentafusp.

Initiation of KIMMTRAK treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug-drug interaction risk is during the first 24 hours of the first three doses of KIMMTRAK in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (e.g., warfarin) or drug concentrations (e.g., cyclosporine). Adjust the dose of the concomitant drug as needed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with tebentafusp and for at least 1 week after last dose of tebentafusp.

Verify pregnancy status in females of reproductive potential prior to initiating tebentafusp treatment.

Pregnancy

There are no data from the use of tebentafusp in pregnant women. Animal reproduction studies have not been conducted with tebentfusp (see section 5.3). Tebentafusp is not recommended during pregnancy and in women of childbearing potential not using contraception. The pregnancy status in females of reproductive potential should be verified prior to initiating tebentafusp treatment.

Breastfeeding

There is insufficient information on the excretion of tebentafusp/metabolites in human milk. A risk to the new-borns /infants cannot be excluded. Breast-feeding should be discontinued during treatment with tebentafusp.

Fertility

No fertility studies have been conducted with tebentafusp (see section 5.3). There are no data on the effect of tebentafusp on human fertility.

4.7 Effects on ability to drive and use machines

KIMMTRAK has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The most common adverse drug reactions (≥ 30 %) in patients treated with KIMMTRAK were cytokine release syndrome (89 %), rash (83 %), pyrexia (76 %), pruritus (69 %), fatigue (64 %), nausea (49 %), chills (48 %), hypo/hyperpigmentation (47 %), abdominal pain (45 %), oedema (45 %), hypotension (39 %), dry skin (31 %), headache (31 %) and vomiting (30 %).

The most common serious adverse reactions (≥ 2 %) in patients treated with KIMMTRAK were cytokine release syndrome (10 %), rashes (4.5 %), pyrexia (2.4 %), and hypotension (2 %).

The most common ≥ Grade 3 adverse reactions (≥ 2 %) in KIMMTRAK treated patients were rash (18 %), hypertension (8 %), hypotension (7 %), aspartate aminotransferase increased (6 %) blood phosphate decreased (5 %), pruritus (4.8 %), lipase increased (4.2 %), pyrexia (4 %), abdominal pain (3.7 %), blood bilirubin increased (3.4 %), lymphocyte count decreased (3.4 %), alanine aminotransferase increased (3.4 %), cytokine release syndrome (2.6 %), and gamma-glutamyltransferase increased (2.4 %).

The frequency of treatment discontinuation due to adverse reactions was 4 % in patients who received KIMMTRAK. The most common adverse reactions leading to discontinuation were cytokine release syndrome (0.4 %). No treatment-related deaths were reported.

Adverse reactions resulting in dose interruption occurred in 26 % of patients who received KIMMTRAK. The most common adverse reactions leading to dose interruption (≥ 2 %) included fatigue (3 %), pyrexia (2.7 %), alanine aminotransferase increase (2.4 %), aspartate aminotransferase increase (2.4 %). abdominal pain (2.1 %) and lipase increased (2.1 %).

Adverse reactions leading to dose reduction occurred in 4.3 % of patients who received KIMMTRAK. The most common adverse reactions (≥1 %) leading to dose reduction were cytokine release syndrome (1.9 %), and hypotension (1.1 %).

Tabulated list of adverse reactions

Table 3 summarizes adverse reactions that occurred in 378 metastatic uveal melanoma patients from two clinical studies (IMCgp100-102 and IMCgp100-202) that received the recommended dosing KIMMTRAK dosing regimen of 20 micrograms on Day 1, 30 micrograms on Day 8 and 68 micrograms on Day 15 and 68 micrograms weekly thereafter.

The adverse drug reaction frequency is listed by MedDRA System Organ Class (SOC) at the preferred term level. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse Reactions in Patients Treated with KIMMTRAK Monotherapy

	Adverse Reactions
Infections and infestations	
Common	Nasopharyngitis
Immune system disorders	
Very common	Cytokine release syndrome[1]
Metabolism and nutrition disorders	
Very common	Decreased appetite, hypomagnesaemia, hyponatraemia, hypocalcaemia, hypokalaemia
Uncommon	Tumour lysis syndrome
Psychiatric disorders	
Very Common	Insomnia
Common	Anxiety
Nervous system disorders	
Very common	Headache[2], dizziness, paraesthesia
Common	Taste disorder
Cardiac disorders	
Very common	Tachycardia[9]
Common	Arrhythmia[2]
Uncommon	Angina pectoris[2]
Vascular disorders	
Very common	Hypotension[2], flushing, hypertension
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, dyspnoea
Common	Oropharyngeal pain, hypoxia[10]
Gastrointestinal disorders	
Very common	Nausea[2], vomiting[2], diarrhoea, abdominal pain[6], constipation, dyspepsia
Skin and subcutaneous tissue disorders	
Very common	Rash[3], pruritus, dry skin, hypo-/ hyperpigmentation[5], erythema
Common	Alopecia, night sweats
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, back pain, myalgia, pain in extremity
Common	Muscle spasm
General disorders and administration site conditions	
Very common	Pyrexia[2], fatigue[4], chills[2], oedema[7], influenza like illness
Investigations	
Very common	Aspartate aminotransferase increased[8], alanine aminotransferase increased[8], blood bilirubin increased[8], lipase increased[8], anaemia[8], lymphopenia[8], hypophosphataemia[8]
Common	Amylase increased[8], blood creatinine increased[8], gamma glutamyl transferase increased[8], white blood cell count increased[8], blood alkaline phosphatase increased[8]

[1] CRS was adjudicated using the ASTCT consensus grading of CRS criteria (Lee et.al 2019). Adjudicated CRS is provided in lieu of investigator reported CRS.
[2] Some of the events may be associated with CRS or may be isolated reported events.
[3] Includes blister, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatosis, drug eruption, eczema, eczema eyelids, erythema multiforme, exfoliative rash, interstitial granulomatous dermatitis, lichenification, lichenoid keratosis, palmar-plantar erythrodysaesthesia syndrome, papule, psoriasis, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, seborrhoea, seborrhoeic dermatitis, skin abrasion, skin erosion, skin exfoliation, skin irritation, skin plaque, solar dermatitis, toxic skin eruption, urticaria.
[4] Includes fatigue and asthenia.
[5] Includes achromotrichia acquired, ephelides, eyelash discolouration, eyelash hypopigmentation, hair colour changes, lentigo, pigmentation disorder, retinal depigmentation, skin depigmentation, skin discolouration, skin hyperpigmentation, skin hypopigmentation, solar lentigo, vitiligo.
[6] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, flank pain, gastrointestinal pain and hepatic pain.
[7] Includes eye oedema, eye swelling, eyelid oedema, periorbital swelling, periorbital oedema, swelling of eyelid, pharyngeal oedema, lip oedema, lip swelling, face oedema, generalized oedema, localised oedema, oedema, oedema peripheral, peripheral swelling, swelling, swelling face.
[8] Based on laboratory values; not all were reported as adverse events.
[9] Includes tachycardia and sinus tachycardia.
[10] Includes hypoxia and oxygen saturation decrease.

Description of selected adverse reactions

Cytokine release syndrome (CRS)
In clinical trial Study IMCgp100-202, cytokine release syndrome (adjudicated based on ASTCT consensus grading 2019) occurred in 89 % of KIMMTRAK-treated patients. The overall incidence of CRS included 12 % Grade 1, 76 % Grade 2 and 0.8 % Grade 3 events. The majority (84 %) of episodes of CRS started the day of infusion. The median time to resolution of CRS was 2 days.

CRS rarely (1.2 %) led to treatment discontinuation. All CRS symptoms were reversible and were managed with intravenous fluids, antipyretics, or a single dose of corticosteroid. Two patients (0.8 %) received tocilizumab.

For clinical management of CRS, see section 4.2, Table 1.

Acute skin reactions
In Study IMCgp100-202, acute skin reactions occurred in 91% of patients treated with KIMMTRAK including any grade rash (83 %), pruritus (69%), erythema (25 %) and cutaneous oedema (27 %). Most skin reactions were Grade 1 (28 %) or 2 (44 %) and some KIMMTRAK-treated patients experienced Grade 3 (21 %) events.

Acute skin reactions typically occurred following each of the first three KIMMTRAK infusions, with decreasing frequency of ≥ Grade 3 reactions (dose 1; 17 %, dose 2; 10 %, dose 3; 8 %, dose 4; 3 %). The median time to onset of acute skin reactions was 1 day in the KIMMTRAK-treated patients and median time to improvement to ≤ Grade 1 was 6 days. There were no discontinuations of KIMMTRAK due to acute skin reactions.

For clinical management of acute skin reactions, see section 4.2, Table 2.

Elevated liver enzymes
In Study IMCgp100-202 where 95 % of patients had pre-existing liver metastasis, ALT/AST increase to ≥ Grade 1 were observed in 65 % of patients treated with KIMMTRAK. More than 90 % of patients were able to continue treatment beyond worst grade ALT/AST elevation. In patients experiencing ALT/AST elevations, 73 % initially occurred within the first 3 infusions with KIMMTRAK. Most patients experiencing Grade 3 or 4 ALT/AST elevations had improvement to ≤ Grade 1 within 7 days.

Elevations in bilirubin have been reported in 27 % of patients and these were primarily associated with an increase in size of liver metastasis.

For clinical management of elevated liver enzymes, see section 4.2, Table 2.

Other laboratory abnormalities
In Study IMCgp100-202, decreased lymphocytes were reported in 91 % of patients treated with KIMMTRAK. Decreased lymphocytes Grade ≥ 3 was reported in 56 % of patients treated with KIMMTRAK. Decreases in lymphocytes count were transient and were most commonly (> 95% of cases) observed the day after the initial 3 KIMMTRAK doses.

The proportion of patients (≥ 3 %) who experienced a shift from baseline to a Grade 3 or 4 of other laboratory abnormalities were as follows: 3 % haemoglobin decreased, 4 % for amylase increased, 15 % for lipase increased.

Immunogenicity
Treatment-emergent anti-drug antibodies (ADA) against tebentafusp were detected in 33 % and 29 % of patients receiving tebentafusp across all doses in study IMCgp100-102 and study IMCgp100-202, respectively. The median onset time to ADA formation was 6 to 9 weeks after start of tebentafusp treatment. There was no evidence of ADA impact on safety or efficacy of tebentafusp, although the small number of patients who developed high titre ADA precludes firm conclusions regarding their clinical impact.

Neutralizing antibodies (Nab) against tebentafusp were detected in 19 % and 15 % of patients from studies IMCgp100-102 and IMCgp100-202, respectively, with a median time to onset of 12-16 weeks. NAb responses were generally persistent, lasting longer than 20 weeks from first detection. The majority of NAb responses occurred in high titre ADA positive patients: 24/27 (89 %) patients with ADA titres greater than the median in study IMCgp100-102 and 29/34 (85 %) patients with ADA titres greater than the median in study IMCgp100-202. No association between NAb onset or titre and the safety or efficacy of tebentafusp was identified in either study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no information on overdose with tebentafusp. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment should be instituted immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents; other antineoplastic agents,
ATC code: L01XX75

Mechanism of action

Tebentafusp is a bispecific fusion protein, comprised of a T cell receptor (TCR; targeting domain) fused to an antibody fragment targeting CD3 (cluster of differentiation 3; effector domain). The TCR end binds with high affinity to a gp100 peptide presented by human leukocyte antigen – A*02:01 (HLA-A*02:01) on the cell surface of uveal melanoma tumour cells, and the effector domain binds to the CD3 receptor on the polyclonal T cell.

An immune synapse is formed when the TCR targeting domain of tebentafusp binds to uveal melanoma cells and the CD3 effector domain binds to polyclonal T cells. This immune synapse results in redirection and activation of polyclonal T cells regardless of their native TCR specificity. Tebentafusp-activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of uveal melanoma tumour cells.

Pharmacodynamic effects

Transient and clinically non-significant reduction in lymphocyte counts in blood was observed after treatment with tebentafusp. Lymphocytes decreased the day after the first 3 doses and returned to baseline prior to subsequent doses.

After treatment with tebentafusp, transient increases in serum levels of proinflammatory cytokines and chemokines were observed in samples collected after the first three doses. Peak levels were observed between 8 to 24 hours after treatment with tebentafusp and levels returned to baseline prior to subsequent doses.

Clinical efficacy and safety

Study IMCgp100-202: Previously untreated metastatic uveal melanoma
Study IMCgp100-202 was a randomised, open-label, multicentre trial that enrolled HLA-A*02:01 positive metastatic uveal melanoma patients who were naïve to systemic therapy. Patients could not have received previous systemic treatment or localized (liver-directed) therapy for metastatic uveal melanoma except for a prior surgical resection of oligometastatic disease. Patient were excluded for clinically significant cardiac disease and presence of symptomatic or untreated brain metastasis.

Patients were randomised (2:1) to receive KIMMTRAK weekly by intravenous infusion according to the recommended intra-patient dosing regimen section 4.2 or investigator's choice treatment (pembrolizumab, ipilimumab, or dacarbazine) at the approved doses of these agents until disease progression or unacceptable toxicity.

Patients could receive KIMMTRAK, pembrolizumab, or ipilimumab treatment beyond disease progression if the patients were clinically stable, deriving clinical benefit and showed no signs of unacceptable toxicity as determined by the investigator. Randomisation was stratified by lactate dehydrogenase (LDH) status, a known prognostic factor for unresectable or metastatic UM.

The primary efficacy outcome was overall survival (OS) in all patients randomised in the trial. Tumour assessments were conducted every 12 weeks. Additional efficacy outcomes were investigator-assessed progression free survival (PFS)

and disease control rate (DCR). A total of 378 patients were randomised; 252 to KIMMTRAK-treated group and 126 to the investigator's choice-treated group (pembrolizumab: 82 %; ipilimumab: 12 %; or dacarbazine: 6 %). The median age was 64 years (range 23 to 92 years); with 49.5 % of patients ≥ 65 years, 87 % were white, 50 % were female. Baseline ECOG performance status was 0 (72 %) or 1 (20.4 %) or 2 (0.3 %), 36 % had elevated LDH level, and 95 % had liver metastasis.

In this study, 43 % of patients received treatment beyond initial progression with KIMMTRAK with no new safety signals identified. Median duration of KIMMTRAK-treatment beyond initial progression was 8 weeks. Of the total KIMMTRAK infusions during the study, 21.5 % was administered after initial progression.

The efficacy results are summarized in Table 4 and Figure 1.

Table 4: Efficacy results in study IMCgp100-202

Primary and secondary endpoints	**KIMMTRAK (N = 252)**	**Investigator`s choice therapy (N = 126)**
Overall survival (OS) [1]		
Number of deaths	87 (34.5 %)	63 (50 %)
Median months (95 % CI)	21.7 (18.6, 28.6)	16.0 (9.7, 18.4)
HR (95 % CI)[2, 4]	0.51 (0.37, 0.71)	
Stratified log-rank p-value[2]	p = <0.0001	
Progression free survival (PFS)[3, 4]		
Number (%) of patients with event	200 (79.4 %)	101 (80.2 %)
Median in months (95 % CI)	3.3 (3.0, 5.0)	2.9 (2.8, 3.0)
HR (95 % CI)[4]	0.77 (0.60, 0.98)	
Stratified log-rank p-value[2]	p = 0.0310	
Objective response rate (ORR)[6]		
n (%)	26 (10.3)	6 (4.8)
95% CI	6.9, 14.8	1.8, 10.1
Complete Response (CR)	1 (0.4)	0
Partial Response (PR)	25 (9.9)	6 (4.8)
Stable Disease (SD)[5]	52 (20.6)	16 (12.7)
Median duration of response		
Months (95% CI)	9.9 (5.6, 22.1)	9.7 (2.7, --)

CI = Confidence interval, HR = Hazard ratio

1 At a prespecified interim analysis, 150 OS events were observed, and a p-value boundary for declaring efficacy (0.006) was determined by a Lan-Demets alpha spending function with O'Brien Fleming type boundary.

2 Two-sided p-value based on log rank test stratified by LDH.

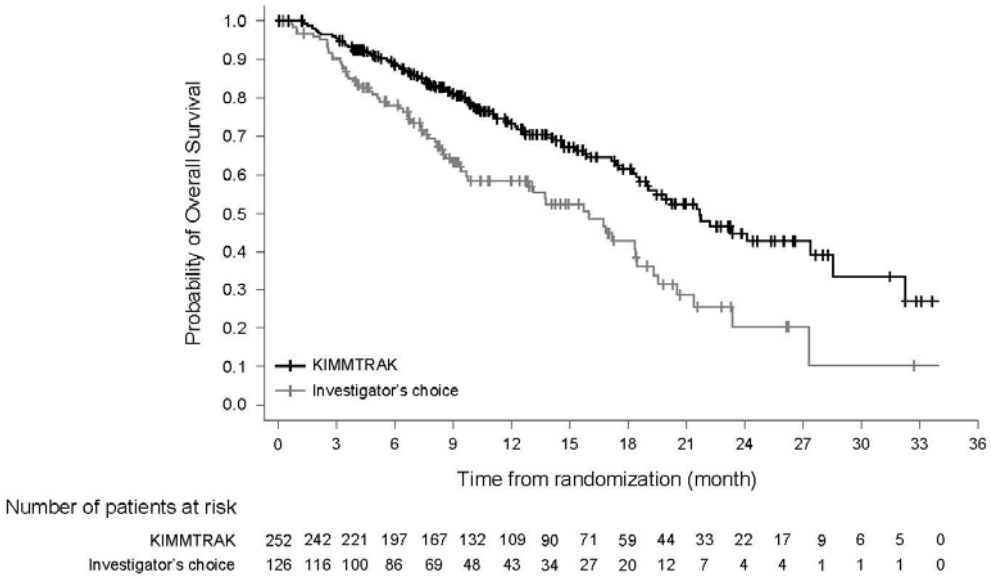
3 As assessed by investigator using RECIST v1.1 criteria.

4 Hazard ratio is from a proportional hazards model stratified by LDH status

5 Based on ≥24 weeks.

6 Updated based on all patients having opportunity for at least 3 radiological assessments

Figure 1: Kaplan-Meier curves of overall survival in the study IMCgp100-202



Number of patients at risk

KIMMTRAK	252	242	221	197	167	132	109	90	71	59	44	33	22	17	9	6	5	0
Investigator's choice	126	116	100	86	69	48	43	34	27	20	12	7	4	4	1	1	1	0

Patient Reported Outcomes
Health-related quality-of-life data were collected using the European Organization of Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D, 5L PRO instruments. No differences in overall scores were observed between the treatment arms.

Study IMCgp100-102: Previously treated metastatic uveal melanoma

Study IMCgp100-102 was an open-label, Phase 2 multicentre study conducted in 127 patients. Patients were required to be HLA-A*02:01 positive. Patients were eligible if they had experienced disease progression following at least 1 or more prior lines of liver directed therapy or systemic therapy including immune check point inhibitors in the metastatic setting. Patients were excluded for clinically significant cardiac disease and presence of symptomatic or untreated brain metastasis.

Patients were enrolled to receive KIMMTRAK administered intravenously using an intra-patient dose escalation scheme as recommended in section 4.2. Patients received KIMMTRAK until unacceptable toxicity or disease progression. Patients could receive KIMMTRAK treatment beyond disease progression if the patient was clinically stable, deriving clinical benefit and showed no signs of unacceptable toxicity as determined by the investigator.

Tumour assessments were conducted every 2-3 months. Major efficacy outcome measures included confirmed ORR as assessed by Independent Central Review (ICR) using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. Secondary efficacy outcomes included PFS, DCR, DOR and OS.

A total of 127 patients were enrolled into the Phase 2 expansion cohort. In the Phase 2 cohort of the study, the median age was 61 years, 50 % were female, 99 % were white, the ECOG performance score was 0 (70 %) or 1 (29 %) and 96 % of patients had liver metastasis. Prior treatments included immunotherapy (73 % of patients) including immune checkpoint inhibitors (PD-1/PD-L1; 65 %; CTLA-4; 31 %) and liver directed therapy 45 %.

In the Phase 2 expansion cohort, the ORR was 4.7 % (95 % CI: 1.8 %, 10 %), consisting of no complete and 6 partial responses in KIMMTRAK-treated patients. The median duration of response was 8.7 months (95% CI: 5.6, 24.5). The DCR was 22.8 % (95 % CI: 15.9 %, 31.1 %).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with KIMMTRAK in all subsets of the paediatric population in the treatment of ocular melanoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of tebentafusp appear linear and dose-proportional over a dose range of 20 mcg to 68 mcg. Following weekly intravenous infusion in metastatic uveal melanoma patients, the maximum plasma concentrations (C_{max}) reached 4.2 ng/mL - 13.7 ng/mL immediately at the end of infusion (T = 0.5 hours). No accumulation was observed with a weekly dosing regimen at the target therapeutic doses.

Distribution

Tebentafusp did not distribute extensively and displayed a volume of distribution comparable to blood volume (5.25 L).

Biotransformation

The metabolic pathway of tebentafusp has not been characterised. Like other protein therapeutics, tebentafusp is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination

The excretion of tebentafusp is not fully characterised.

Following administration of tebentafusp in metastatic uveal melanoma patients the estimated systemic clearance was 4.29 L/d, with a terminal half-life of 6 to8 hours.

Special populations

Population pharmacokinetic analysis indicated that there was no significant effect of weight (43 to 163 kg), gender, race, and age (23 to 91 years) on tebentafusp clearance.

Renal impairment

No formal pharmacokinetic studies of tebentafusp have been conducted in patients with renal impairment.

No impact on safety or efficacy parameters was identified in patients with mild (creatinine clearance [CrCL] ranging 60 to 89 mL/min) to moderate (CrCL ranging 30 to 59 mL/min) renal impairment and no dose adjustments are recommended. There are limited data from patients (< 5 %) with moderate renal impairment and there is no information available from patients with severe renal impairment (CrCL < 30 mL/min).

Hepatic impairment

No formal pharmacokinetic studies of tebentafusp have been conducted in patients with hepatic impairment. Baseline and on treatment ALT/AST elevations did not impact tebentafusp pharmacokinetics. There was no impact on pharmacokinetics in patients with mild hepatic impairment at baseline. The effect of moderate [total bilirubin (TB) >1.5 to 3x ULN, any AST] to severe (TB > 3 to 10x ULN, any AST) baseline hepatic impairment on tebentafusp pharmacokinetics has not been studied.

Immunogenicity

In the subset of patients with ADA titres above the median of 8192 (n=48), the exposure (AUC_{0-7} days) of tebentafusp decreased by 97 % and terminal half-life decreased to 10-14 minutes. Neutralizing antibodies developed in a subset of patients with high titre ADA and was associated with reduced tebentafusp C_{max} values (see section 4.8). No impact on efficacy or safety was observed.

5.3 Preclinical safety data

Tebentafusp is a human-specific protein and there are no relevant animal species in which non-clinical toxicology of tebentafusp could be tested.

No carcinogenicity or genotoxicity studies have been conducted with tebentafusp.

No studies have been conducted to evaluate the effects of tebentafusp on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate

Di-sodium hydrogen phosphate

Mannitol

Trehalose

Polysorbate 20

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years

After opening

Once opened, the medicinal product should be diluted and infused immediately.

After preparation of solution for infusion

Diluted solution for infusion may be stored at room temperature for 4 hours or at 2°C to 8°C for 24 hours (times are inclusive of the administration period, see Section 6.6).

6.4 Special precautions for storage

Store and transport refrigerated (2 °C – 8 °C)
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with a bromobutyl rubber stopper and an aluminium/plastic flip-off seal, containing 0.5 mL concentrate.

Pack size of 1 vial

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

General precautions

The solution for infusion should be prepared by a healthcare professional using proper aseptic technique throughout the handling of this medicinal product.

Closed system transfer devices (CSTDs) must not be used for dose preparation of KIMMTRAK solution for infusion.

Parenteral drug products and infusion bags should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Preparation

KIMMTRAK must be diluted prior to intravenous administration.

Ensure the following supplies are available prior to preparing KIMMTRAK for administration:

1 mL sterile syringes with graduations of 2 decimal places.

Sterile needles.

Human Albumin; use concentration as per local availability. Local concentrations include but not restricted to 4 % (40 g/L, 5 % (50 g/L), 20 % (200 g/L), 25 % (250 g/L).

A 100 mL infusion bag containing sodium chloride 9 mg/mL (0.9 %) solution for injection:

- 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.

Dilution and Administration

A 2-step process is required for preparation of the final KIMMTRAK dose:

Step 1: Prepare the infusion bag

Using aseptic technique, prepare the infusion bag as follows:

a. Using a 1 mL syringe and a sterile needle, withdraw the calculated volume of human albumin into the syringe (see Table 5 below) and add to the 100 mL 0.9 % sodium chloride injection bag to make a final human albumin concentration between 225 mcg/mL and 275 mcg/mL.

Table 5: Examples of Human Albumin Concentration and Acceptable Withdrawal Volumes

Human albumin concentration	Acceptable volume range for addition to 100 mL infusion bag for human albumin concentration between 225 mcg/mL to 275 mcg/ mL
4 % (40 g/L)	0.63 mL (0.57 mL to 0.69 mL)
5 % (50 g/L)	0.50 mL (0.45 mL to 0.55 mL)
20 % (200 g/L)	0.13 mL (0.12 mL to 0.14 mL)
25 % (250 g/L)	0.10 mL (0.09 mL to 0.11 mL)

b. Gently homogenize the diluted solution by completing the following steps:

i. Invert the infusion bag so that the entry port is positioned at the top of the bag and tap the side of port tubing to ensure that any residual solution is released into the bulk solution.

ii. Mix by gently rotating the bag lengthwise 360 degrees from the inverted position at least 5 times. Do NOT shake the infusion bag.

iii. Repeat (i) and (ii) an additional three times.

Step 2: Preparation of KIMMTRAK solution for infusion

c. Using a 1 mL syringe and a sterile needle, withdraw the required volume of KIMMTRAK 200 micrograms/mL as per the dose required (shown in Table 6 below) and add to the prepared 100 mL infusion bag containing sodium chloride 9 mg/mL (0.9 %) solution for injection, plus human albumin.

d. Do NOT flush the needle and syringe on transfer. Discard the vial containing the unused portion of KIMMTRAK in accordance with local requirements. Do not prepare more than one dose from the vial.

Table 6: KIMMTRAK Volumes Required for Addition to Infusion Bag

Day of treatment	Dose (mcg) of KIMMTRAK	Volume (mL) of KIMMTRAK
Day 1	20	0.10
Day 8	30	0.15
Day 15 and weekly thereafter	68	0.34

e. Mix the infusion bag by following the same procedure outlined in Step 1b.

Administration

Administer KIMMTRAK as intravenous infusion only.

Immediately administer the infusion over 15-20 minutes through a dedicated intravenous 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 sodium chloride 9 mg/mL (0.9 %) solution for injection, to ensure that the entire contents of the infusion bag are administered. Do not administer KIMMTRAK as an intravenous push or bolus. Do not mix KIMMTRAK with other drugs or administer other drugs through the same intravenous line.

Storage of prepared infusion bag

KIMMTRAK does not contain a preservative. The prepared infusion bag should be administered within 4 hours from the time of preparation including the duration of

infusion. During the 4 hour window, the KIMMTRAK infusion bag should remain at room temperature.

If not used immediately, store the KIMMTRAK infusion bag in a refrigerator at 2 °C to 8 °C for up to 24 hours from the time of preparation which includes the time allowed for equilibration of the infusion bag to room temperature and the duration of the infusion.

Once removed from the refrigerator, KIMMTRAK infusion bag must not be refrigerated again. Do not freeze. Discard unused KIMMTRAK solution beyond the recommended storage time.

7 MARKETING AUTHORISATION HOLDER

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