Tebentafusp (Kimmtrak®) as monotherapy for the treatment of human leukocyte antigen (HLA) A*02:01 positive patients with unresectable or metastatic uveal melanoma

General information [1]

Drug description	Indication
Tebentafusp (Kimmtrak®) is an antineoplastic agent with bispecific affinity, targeting the CD_3 T cells and a gp100 peptide on the surface of uveal melanoma tumour cells. This redirects and activates T cells and results in direct lysis of uveal melanoma tumour cells.	Tebentafusp (Kimmtrak®) is indicated as monotherapy for the treatment of HLA A*02:01 positive adult patients with unresectable or metastatic uveal melanoma.

Current treatment [2]

- ❖ The rarity of uveal melanoma and lack of close surveillance for secondary tumours have limited the evidence for treatment of metastases.
- ❖ There is no effective, systemic, cytotoxic chemotherapy for metastatic uveal melanoma.
- ❖ Resection of uveal melanoma liver metastases is proven to prolong survival when technically possible.
- ❖ In recent years there has been development in the use of liver-directed therapies, such as liver surgery, transcatheter arterial chemoembolisation, selective internal radioembolisation and percutaneous hepatic perfusion. Immunotherapy is also an option, although it must be given early enough to allow it to work (12 weeks to 1 year). The genetic mutations thought to initiate uveal melanoma (GNAQ and GNA11) are not currently therapeutically targetable. However, it is possible that biological therapies that target the same pathway, such as MEK inhibitors, could be useful in uveal melanoma.
- ❖ For metastatic disease, national guidelines for uveal melanoma recommend:
  - Patients with systemic disease should be considered for clinical trials wherever possible and should be offered systemic treatments if not placed in a clinical trial.
  - Patients with liver predominant disease should be considered for regional therapy. Loco-regional treatment for the management of oligometastatic disease (i.e. when metastases are limited to a single or limited number of organs) should be considered. This may include surgery, stereotactic treatment, or other forms of ablation.
  - Ipilimumab can be offered following NICE approval of this drug for use in melanoma generically.
  - For patients with technically resectable liver metastases, assessment for curative intent hepatic resection should be offered.
  - Regional or systemic treatments may be considered in patients with liver dominant disease where resection is not suitable.

Regulatory status

EMA [1]	FDA [3]
Approval status for this indication: On 24 February 2022, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Kimmtrak®. **UPDATE**: Date of issue of marketing authorisation valid throughout the European Union: 01/04/2022 <u>The full indication is:</u> ❖ Kimmtrak® is indicated as monotherapy for the treatment of HLA A*02:01 positive adult patients with unresectable or metastatic uveal melanoma. **Other indications**: none ✓ **Orphan status** ✓ **Medicine is under additional monitoring** ✓ **Accelerated assessment**[1]	**Approval status for this indication**: On 25 January 2022, the FDA approved tebentafusp-tebn (Kimmtrak®), a bispecific gp100 peptide-HLA-directed CD_3 T cell engager, for HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. ✓ Priority review ✓ Breakthrough designation ✓ Orphan drug designation **Other indications**: none

Costs

[1] This medicine had an accelerated assessment, meaning that it is a medicine of major interest for public health, so its timeframe for review was 150 evaluation days rather than 210.

Kimmtrak® concentrate for solution for infusion 100 MCG/0.5ml = € 13,264.00 (ex-factory price) [4].

Premedication [5]

- To minimise the risk of hypotension associated with cytokine release syndrome (CRS), intravenous fluids should be administered 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, adjusting the corticosteroid dose should be considered to manage the risk of hypotension.

Warnings and precautions

- **CRS**
  - 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.
- **Skin reactions**
  - Rash, pruritus, and cutaneous edema occurred in patients treated with Kimmtrak®.
  - If skin reactions occur, treat based on persistence and severity of symptoms.
- **Elevated liver enzymes**
  - Elevations in liver enzymes occurred in patients treated with Kimmtrak®.
  - Monitor ALT, AST, and total bilirubin.
- **Cardiac disease**
  - Cardiac events such as sinus tachycardia and arrhythmia have been observed in patients who have received tebentafusp treatment.
  - 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.
  - 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 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.
- **Embryo-foetal toxicity**
  - May cause foetal harm.
  - Advise patients of reproductive potential of the potential risk to the foetus and to use effective contraception.

Study characteristics [6-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
IMCgp100-202 NCT03070392	378 (2:1)	tebentafusp IV at a dose of 20 µg on day 1, 30 µg on day 8, and 68 µg weekly thereafter	investigator's choice of treatment with single-agent	OS	**ongoing**[3], open-label, multicenter, randomised, phase 3 trial	HLA A* 02:01	Immunocore	[8]

[3] The IMCgp100-202-trial is currently ongoing; estimated study completion date is 03/2023.

			pembrolizumab, ipilimumab, or dacarbazine[2]					

Efficacy (I vs. C), interim analysis data	**Safety** (I vs. C), interim analysis data
Median duration of follow-up at the time of the clinical data cut-off for the first interim analysis (October 13, 2020): 14.1 months **Estimated OS at 1 year**: 73% (95% CI, 66-79) vs. 59% (95% CI, 48-67) **Estimated median duration of OS**: 21.7 months (95% CI, 18.6-28.6) vs. 16.0 months (95% CI, 9.7-18.4); stratified HR for death: 0.51, 95% CI, 0.37-0.71; p<0.001 **Estimated PFS at 6 months**: 31% vs. 19%; stratified HR for disease progression or death: 0.73; 95% CI, 0.58-0.94; p=0.01 **Objective response**: 9% (95% CI, 6-13) vs. 5% (95% CI, 2-10) **Median duration of response**: 9.9 months vs. 9.7 months **Patients who had disease control** (complete response, partial response, or stable disease for ≥12 weeks): 46%; 95% CI, 39-52 vs. 27%; 95% CI, 20-36 **Estimated median duration of OS in a landmark-based analysis among patients who had disease progression as the best response before day 100**: 15.3 months (95% CI, 12.0-not reached) vs. 6.5 months (95% CI, 4.9-13.4); HR for death: 0.43; 95% CI, 0.27-0.68) **UPDATE [5]:** ❖ After completion of the primary efficacy analysis, patients from the investigator's choice arm were permitted to **crossover** to the tebentafusp treatment. ❖ With a median duration of follow up of 22.4 months, the updated OS continued to favour the tebentafusp arm (HR= 0.58; 95% CI: 0.44, 0.77). ❖ At the time of analysis, 16 patients had crossed over to tebentafusp treatment.	**Any treatment-related AEs of grade 3 or 4:** n=109/245 (44%) vs.19/111 (17%) **Patients with any serious treatment-emergent AE:** n=69/245 (28%) vs. n=26/111 (23%) **Discontinuation due to treatment-related AEs:** 2% vs. 5% **Treatment-related deaths:** 0 vs. 0

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	>12 months ≤24 months	OS: +5.7 months	0.51 (0.37-0.71)	HR ≤0.70 AND gain ≥5 months	4	+27% treatment-related AEs grade 3 or 4	NA	-	4
Adapted	NC	2A	>12 months ≤24 months	OS: +5.7 months	0.51 (0.37-0.71)	HR ≤0.70 AND gain ≥5 months	4	+27% treatment-related AEs grade 3 or 4	NA	-1	3

Risk of bias (RCT) [11]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	-	no, open-label	unclear[4]	yes[5]	unclear

[2] Pembrolizumab was administered IV at a dose of 2 mg per kilogram of body weight to a maximum of 200 mg per dose or (where approved locally) at a fixed dose of 200 mg on day 1 of each 21-day cycle. Ipilimumab was administered IV at a dose of 3 mg per kilogram on day 1 of each 21-day cycle for a maximum of four doses. Dacarbazine was administered IV at a dose of 1000 mg per square meter of body-surface area on day 1 of each 21-day cycle.

[4] Currently only interim analysis data available; IMCgp100-202-trial is ongoing. Data not yet available for all predefined endpoints.

[5] The sponsor and a steering committee designed the trial and analysed the data, with the participation of all the authors.

Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine transaminase, AST=aspartate aminotransferase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CRS=cytokine release syndrome, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HLA=human leukocyte antigen, HR=hazard ratio, I=intervention, Int.=intention, IV=intravenously, MEK=mitogen-activated protein kinase, MG=median gain, n=number of patients, NICE=National Institute for Health and Care Excellence, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

References:

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[11] European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].