Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Kimmtrak

Active ingredient: Tebentafusp

Sponsor: Adjutor Healthcare Pty Ltd

October 2022

TGA Health Safety Regulation

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Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer (United States of America)
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BAP1	BRCA1-associated protein 1
CD	Cluster of differentiation
CI	Confidence interval
CMI	Consumer Medicines Information
CRS	Cytokine release syndrome
CTLA4	Cytotoxic T-lymphocyte-associated antigen 4
CYP	Cytochrome P450
DLP	Data lock point
EU	European Union
FDA	Food and Drug Administration (United States of America)
gp100	Glycoprotein 100
GVP	Good Pharmacovigilance Practices
HLA	Human leukocyte antigen
ICH	International Council for Harmonisation

Abbreviation	Meaning
ITT	Intent(ion)-to-treat
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
Nab	Neutralising antibody
NCCN	National Comprehensive Cancer Network (United States of America)
OCE	Oncology Center of Excellence (Food and Drug Administration, United States of America)
PD(L)1	Programmed death (ligand)-1
PI	Product Information
PK	Pharmacokinetic(s)
PSUR	Periodic safety update report
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumours
RMP	Risk management plan
SAE	Serious adverse event
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
TMB	Tumour mutational burden
ULN	Upper limit of normal
US(A)	United States of (America)

Product submission

Submission details

Type of submission:	New biological entity
Product name:	Kimmtrak
Active ingredient:	Tebentafusp
Decision:	Approved
Date of decision:	27 May 2022
Date of entry onto ARTG:	3 June 2022
ARTG number:	375296
, *Black Triangle Scheme:*	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Adjutor Healthcare Pty Ltd 3 Grandview Avenue Point Cook, VIC 3030
Dose form:	Concentrated solution for infusion
Strength:	0.1 mg/0.5 mL
Container:	Vial
Pack size:	One
Approved therapeutic use:	*Kimmtrak is indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.*
Route of administration:	Intravenous infusion
Dosage:	Kimmtrak should be administered under the supervision of a physician experienced in the use of anti-cancer agents. Patients treated with Kimmtrak must have human leukocyte antigen (HLA)-A*02:01 genotype determined by any validated HLA genotyping assay. Kimmtrak is administered via continuous intravenous infusion. A two-step dilution process is required for preparation of the final Kimmtrak dose for infusion. The recommended dose and dose schedule of Kimmtrak is: • 20 µg on Day 1

- 30 µg on Day 8
- 68 µg on Day 15
- 68 µg once every week thereafter

The recommended infusion period is 15 to 20 minutes. Continue treatment with Kimmtrak until disease progression or unacceptable toxicity occurs.

First three treatment doses

The first three doses of Kimmtrak should be administered in a healthcare setting with adequate resources to manage cytokine release syndrome. Patients should be monitored for signs and symptoms of cytokine release syndrome during infusion and for at least for 16 hours after infusion is complete.

Subsequent treatment doses

If the patient does not experience hypotension that is Grade 2 or worse (requiring medical intervention) in association with the third infusion, subsequent doses can be administered in an appropriate out-patient or ambulatory care setting. Observe patients for a minimum of 30 minutes following each infusion.

Dose adjustments

Dose modifications for Kimmtrak for adverse reactions are summarised in Table 1 of the Product Information.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Adjutor Healthcare Pty Ltd (the sponsor) to register Kimmtrak (tebentafusp) 0.1 mg/0.5 mL, concentrated solution for infusion for the following proposed indication:

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

Uveal melanoma is the most common malignancy of the eye in adults and the most common non-cutaneous melanoma.[1,2] It represents around 5% of melanomas overall population.[3] Clinical presentation most commonly involves a new or changed lesion in the iris, visual acuity or field changes, or photopsia; however, around a third of cases are asymptomatic and diagnosed incidentally at routine ophthalmological examination for other conditions (such as screening for diabetic retinopathy).[4]

The mean age-standardised incidence of uveal melanoma in Australia between 1982 and 2014 was 7.6 cases per million, with a slight peak in 1993.[5] This is higher than the rate reported for a similar period in the United States of America (USA) of 5.1 per million per year, from 1973 to 2008.[3] European data (1983 to 1994) demonstrates age standardised incidence rates that follow a decreasing north-to-south gradient (from 2 per million per year in Spain and southern Italy to 8 per million per year in Norway and Denmark),[6] attributed to the protective effect of ocular pigmentation in populations who evolved at latitudes with higher exposure to ultraviolet light.

In addition to lighter ocular and skin pigmentation, the risk of uveal melanoma is higher with male sex (8.4 per million versus 6.9 per million for females in Australia),[5] and older age (50 to 70 years);[4] uveal melanoma is rare in children.[3] The median age of diagnosis in Australia is 63 years.[5] Younger median age of diagnosis is reported in Asian populations, from 45 years in China,[7] to 55 years in Japan.[8] Increased risk can also be conferred by the presence of a germline BRCA1-associated protein 1 gene (*BAP1*) mutation, which is usually associated with younger age of presentation (30 to 59 years).[9] Other risk factors include dysplastic naevus syndrome, sensitivity to sunburn, ocular melanocytosis, and xeroderma pigmentosum, however, there is not a clear causal association with ultraviolet exposure.[4,10,11]

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[1] Branisteanu, D.C. et al. Uveal Melanoma Diagnosis and Current Treatment Options (Review), *Exp Ther Med*, 2021; 22(6) :1428.
[2] Sayan, M. et al. Clinical Management of uveal Melanoma: a Comprehensive Review with a Treatment Algorithm, *Radiat Oncol J*, 2020; 38(3): 162-169.
[3] Kaliki, S. and Shields, C. Uveal Melanoma: Relatively Rare but Deadly Cancer, *Eye (Lond)*, 2017; 31(2): 241-257.
[4] Lamas, N.J. et al. Prognostic Biomarkers in Uveal Melanoma: the Status Quo, Recent Advances and Future Directions, *Cancers (Basel)*, 2021; 14(1): 96.
[5] Beasley, A.B. et al. Incidence and Mortality of Uveal Melanoma in Australia (1982–2014),. *Br J Ophthalmol*, 2021; bjophthalmol-2021-319700.
[6] Virgili, G. et al, EUROCARE Working Group. Incidence of Uveal Melanoma in Europe, *Ophthalmology*, 2007; 114: 2309-2315.
[7] Liu, Y.M. et al. Clinical Characteristics of 582 Patients with Uveal Melanoma in China, *PLoS One*, 2015; 10 (12): e0144562.
[8] Sakamoto, T. et al. Histologic Findings and Prognosis of Uveal Malignant Melanoma in Japanese Patients, *Am J Ophthalmol*, 1996; 121 (3): 276-283.
[9] Yang, J. et al. Treatment of Uveal Melanoma: Where are We Now? *Ther Adv Med Oncol*, 2018; 10: 1758834018757175.
[10] Elder, D.E. et al. The 2018 World Health Organization Classification of Cutaneous, Mucosal, and Uveal Melanoma: Detailed Analysis of 9 Distinct Subtypes Defined by Their Evolutionary Pathway, *Arch Pathol Lab Med*, 2020; 144(4): 500-522.
[11] Singh, A.D. et al. Sunlight Exposure and Pathogenesis of Uveal Melanoma, *Surv Ophthalmol*, 2004; 49: 419-428.

Factors associated with worse prognosis include location (ciliary body versus choroid, versus iris) and size of primary lesion (larger versus smaller).[12] Histopathological factors (cell type, mitotic activity, microcirculation architecture, tumour infiltrating lymphocytes and the presence of extrascleral extension) are also predictive, and are included in the American Joint Committee on Cancer (AJCC) classification system for uveal melanoma.[13] Cytogenic and molecular genetic prognostic markers have been identified more recently,[14] and a recent publication out of the Cancer Genome Atlas Project categorised uveal melanoma into four groups based on genetic abnormalities.[15] No prospective studies to support the prognostic or therapy selecting value of these groupings are yet available.

Despite melanocytes sharing a common embryonic origin, uveal melanoma is biologically, clinically, and genetically distinct from cutaneous melanoma.[16] Cutaneous melanoma is associated with mutations in the mitogen-activated protein kinase pathway (notably, *BRAF* and *NRAS*), lymphatic dissemination, and high tumour mutational burden (TMB).[17] By contrast, uveal melanoma tends to be associated with different genetic abnormalities (90% show a mutation in *GNA11* or *GNAQ*; other common mutations are *BAP1*, *EIF1AX*, and *SF3B1*), low average TMB scores,[18] and haematogenous spread (explained by a lack of lymphatics in the uveal tract).[16]

Metastatic uveal melanoma also differs from cutaneous melanoma in its striking liver tropism: around 90% of patients with metastatic uveal melanoma have hepatic metastases (compared to around 20% in cutaneous melanoma),[19] whilst lesions in lung, bone, brain and soft tissue are less common.[20] The cause of death in patients with uveal melanoma who have hepatic metastases is almost exclusively hepatic failure, even when other visceral sites are involved.[21]

Although, in general, uveal melanoma is considered to have low immunogenicity,[22] a subset of uveal melanoma liver metastases has been shown to harbour infiltrating T-cells with similar anti-tumour activity to those seen in cutaneous melanoma, suggesting this trait may be heterogeneous.[23]

Despite the success of sight conserving treatments, survival rates have remained stagnant over the past few decades.[24] The 5-year disease specific overall survival rate of uveal melanoma in Australia (1982 to 2011) has remained stable at around 81%;[5] (similarly to

[12] Singh, A.D. et al. Prognostic Factors in Uveal Melanoma, *Melanoma Res*, 2001; 11(3): 255-263.
[13] Kivela, T. et al. editors. AJCC Cancer Staging Manual. 8th ed. Springer Publishing Company; New York, NY, USA: 2017. pp. 805-817.
[14] Gajdzis, M. et al. Novel Prognostic Immunohistochemical Markers in Uveal Melanoma-Literature Review, *Cancers (Basel)*, 2021;13(16):4031.
[15] Robertson, A.G. et al. Integrative Analysis Identifies Four Molecular and Clinical Subsets in Uveal Melanoma, *Cancer Cell*, 2017; 32: 204-220.
[16] van der Kooij, M.K. et al. Uveal Versus Cutaneous Melanoma; Same Origin, Very Distinct Tumor Types, *Cancers (Basel)*, 2019; 11(6): 845.
[17] Jager, M.J. et al. Uveal Melanoma, *Nat Rev Dis Primers*, 2020; 6(1): 24.
[18] Yarchoan, M. etal. Tumor Mutational Burden and Response Rate to PD-1 Inhibition, *N Engl J Med*, 2017; 377(25): 2500-2501.
[19] Leiter, U. et al. The Natural Course of Cutaneous Melanoma, *J. Surg. Oncol*, 2004; 86: 172-178.
[20] Garg, G. et al. Patients Presenting with Metastases: Stage IV Uveal Melanoma, an International Study, *Br J Ophthalmol*, 2022; 106(4): 510-517.
[21] Tosi, A. et al. The Immune Cell Landscape of Metastatic Uveal Melanoma Correlates with Overall Survival, *J Exp Clin Cancer Res*, 2021; 40(1): 154.
[22] Pan, H. et al. Immunological Analyses Reveal an Immune Subtype of Uveal Melanoma with a Poor Prognosis, *Aging (Albany NY)*, 2020; 12(2): 1446-1464.
[23] Rothermel, L.D. et al. Identification of an Immunogenic Subset of Metastatic Uveal Melanoma, *Clin Cancer Res*, 2016; 22(9): 2237-2249.
[24] Singh, A.D. et al. Uveal Melanoma: Trends In Incidence, Treatment, and Survival, *Ophthalmology,* 2011; 118 (9): 1881-1885.

rates reported in the USA),[25] and the 15-year overall survival rate is around 55%.[9] Once a patient develops metastatic disease, the median overall survival is 13 months, [26,27] with a 2-year overall survival rate of 8%.[28] The median survival of patients with uveal melanoma who develop hepatic metastases is shorter (6 to 12 months) than for patients who first develop metastatic disease in other sites (19 to 28 months).[21]

Treatment of primary uveal melanoma aims for conservation of vision, and includes radiation followed by localised resection, or enucleation for larger or locally advanced tumours.[4] Local tumour control is achieved in the vast majority of cases (> 95%), but despite this, metastatic uveal melanoma develops in around half of patients with uveal melanoma within ten years of diagnosis.[4]

There are no registered systemic therapies for the treatment of uveal melanoma in Australia, and prior to the US Food and Drug Administration (FDA) approval of tebentafusp (in January 2021),[29] this was also the case in the USA.

The National Comprehensive Cancer Network (NCCN) guideline recommends participation in a clinical trial as the preferred management option, because existing therapies have shown limited efficacy (though there are isolated examples of patients who derived substantial benefit).[30] Outside of clinical trial enrolment, the guideline mentions a number of possible therapies which may be tried as monotherapies or in combination. These include liver directed therapies (such as ablative procedures, embolisation, isolation of perfusion, resection or radiation), systemic therapies (such as with immune-oncology agents, cytotoxic regimens or trametinib), resection or radiation treatment for limited or symptomatic extrahepatic disease, and supportive palliative care.[30]

Systemic chemotherapy is associated with significant toxicity, and efficacy has been generally disappointing both with conventional drugs (dacarbazine, temozolomide, fotemustine) and modern agents (paclitaxel, docosahexaenoic acid, liposomal vincristine).[31] Of these, treosulfan plus gemcitabine showed the most promise, with a median overall survival of 14 months.[32]

Various localised therapies to hepatic lesions have shown promise across a number of studies, but to date none have demonstrated a significant population survival advantage.[1,31,33]

Immunotherapies have been incredibly successful in the cutaneous melanoma setting, but in keeping with the scientific rationale for immunotherapy efficacy and the generally low TMB seen in uveal melanoma, results with immunotherapy in metastatic uveal melanoma

[25] Aronow, M.E. et al. Uveal Melanoma: 5-Year Update on Incidence, Treatment, and Survival (SEER 1973-2013), *Ocul Oncol Pathol*, 2018; 4: 145-151.
[26] Rantala, E.S. et al. Overall Survival after Treatment for Metastatic Uveal Melanoma: a Systematic Review and Meta-Analysis, *Melanoma Res*, 2019; 29: 561-568.
[27] Kuk, D. et al. Prognosis of Mucosal, Uveal, Acral, Nonacral Cutaneous, and Unknown Primary Melanoma From the Time of First Metastasis, *Oncologist*, 2016; 21(7): 848-854.
[28] Diener-West, M. et al. Development of Metastatic Disease after Enrollment in the COMS Trials for Treatment of Choroidal Melanoma: Collaborative Ocular Melanoma Study Group Report No. 26, *Arch Ophthalmol*, 2005; 123(12): 1639-1643.
[29] United States Food and Drug Administration (FDA) FDA Approval Press Release for Tebentafusp, 26 January 2022. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tebentafusp-tebn-unresectable-or-metastatic-uveal-melanoma (Accessed 14 February 2022).
[30] United States National Comprehensive Cancer Network (NCCN) NCCN Guidelines for Uveal Melanoma, Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf (Accessed 14 February 2022).
[31] Rodriguez-Vidal, C. et al. Treatment of Metastatic Uveal Melanoma: Systematic Review, *Cancers (Basel)*, 2020; 12(9): 2557.
[32] Pföhler, C. et al. Treosulfan and Gemcitabine in Metastatic Uveal Melanoma Patients: Results of a Multicenter Feasibility Study, *Anticancer Drug*,. 2003; 14: 337-340.
[33] Agarwala, S.S. et al. Metastatic Melanoma to the Liver: a Contemporary and Comprehensive Review of Surgical, Systemic, and Regional Therapeutic Options, *Cancer*, 2014; 120(6): 781-789.

have been disappointing. Monotherapy with either anti-programmed death (ligand)-1 (anti-PD(L)1)[34] or anti-cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA4)[35] treatment was associated with response rates of 4 to 5%, whilst combining both classes of agent gave response rates of 12 to 18%, without evidence of significant survival benefit.[16] Despite this, and in keeping with a subset of uveal melanoma being immunogenic, individual responses are on occasion striking, including complete responses, particularly amongst patients with unusually high TMB for uveal melanoma.[16,36]

Tebentafusp is a bispecific protein that was developed by Immunocore;[37] through their 'ImmTAC' platform.[38] ImmTAC molecules are based on a soluble human T-cell receptor and incorporate a non-native interchain disulfide bond to overcome the instability of T-cell receptors as soluble proteins.[38]

On the tumour facing side, tebentafusp has a binding site with high affinity for the glycoprotein 100 (gp100) peptide presented by human leukocyte antigen (HLA)-A*02:01, which is present in around 50% of Caucasian population.[39] Expression of the gp100 peptide is much higher in melanoma cells than normal melanocytes and is minimal in other histologies.[38]

At the other end of the tebentafusp molecule, the soluble T-cell receptor fragment is fused to an anti-cluster of differentiation 3 (anti-CD3) single chain variable fragment. This binds to the T-cell specific CD3 co-receptor, and thereby recruits and activates polyclonal T-cells to release cytokines and cytolytic mediators.[40] As formation of the active CD3 signalling complex is independent of native T-cell receptor specificity, ImmTAC molecules such as tebentafusp are said to 'redirect' T-cells to attack cells expressing a target antigen, independently of their native specificity.[38]

The proposed mechanism of action of tebentafusp is supported by pharmacodynamic observations in the submitted Phase I/II clinical Study IMCgp100-102 (also known as Study 102). Transient increases in serum inflammatory cytokines and chemokines were seen in patients within 24 hours after a dose, and increased levels of CD3+, CD4+ and CD8+ T-cells were seen in Day 16 tumour re-biopsy tissue (after three doses of drug) compared to baseline biopsies.

This evaluation was facilitated through Project Orbis, an initiative of the United States (US) Food and Drug Administration (FDA) Oncology Center of Excellence (OCE). Under this project, the FDA, Health Canada, Medicines and Healthcare products Regulatory Agency (MHRA; Great Britain) and the TGA collaboratively reviewed the submission. This evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

[34] Anti-programmed death (ligand)-1 or anti-PD-(L)1: medicines that target the programmed death 1 (PD-1) protein or its ligand (PD-L1).
[35] Anti-cytotoxic T-lymphocyte-associated antigen 4 or anti-CTLA4: medicines that target the cytotoxic T-lymphocyte-associated antigen-4 (CTLA4) protein.
[36] Pelster, M.S. et al. Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results from a Single-Arm Phase II Study, *J Clin Oncol*, 2021; 39(6): 599-607.
[37] Immunocore is a biotechnology company and innovator of tebentafusp.
[38] Damato, B.E. et al. Tebentafusp: T Cell Redirection for the Treatment of Metastatic Uveal Melanoma, *Cancers*, 2019; 11(7): 971.
[39] Gonzalez-Galarza, F.F. et al. Allele Frequency Net Database (AFND) 2020 Update: Gold-Standard Data Classification, Open Access Genotype Data and New Query Tools., *Nucleic Acids Res*, 2020; 48(D1): D783-D788.
[40] Nathan, P. et al. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma, *N Engl J Med*, 2021; 385(13): 1196-1206.

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

This product received orphan drug designation on 30 August 2021 for the following indication:

for the treatment of uveal melanoma

At the time the TGA considered this submission, similar submissions were under consideration in the USA (submitted on 23 June 2021), the Great Britain (submitted on 29 July 2021), and the European Union (submitted on 26 July 2021).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 1: Timeline for Submission PM-2021-04357-1-4

Priority review pathway

Description	Date
Designation (Orphan)	30 August 2021
Determination (Priority)	30 August 2021
Submission dossier accepted and first round evaluation commenced	26 October 2021
Evaluation completed	10 March 2022
Delegate's Overall benefit-risk assessment	19 April 2022
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	27 May 2022
Completion of administrative activities and registration on the ARTG	3 June 2022
Number of working days from submission dossier acceptance to registration decision*	120

*Target timeframe for priority submissions is 150 working days from acceptance for evaluation to the decision.

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- European Medicines agency (EMA), Committee for medicinal products for human use (CHMP), ICH Guideline S6 (R1) - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, EMA/CHMP/ICH/731268/1998, June 2011.
- National Comprehensive Cancer Network (NCCN) Guidelines for Uveal Melanoma, Version 2.2021.

Quality

Tebentafusp is a bispecific glycoprotein 100 (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*.

Tebentafusp is comprised of an affinity-enhanced soluble T-cell receptor domain fused to an anti-CD3 single-chain variable fragment. Tebentafusp is a heterodimeric protein consisting of an alpha and a beta sub-unit.

The finished product is a solution for infusion presented at the concentration of 0.2 mg/mL. The product is available in a 2 mL Type 1 clear glass injection vial with a bromobutyl, low siliconised rubber stopper and an aluminium overseal with a flip-off cap. Kimmtrak does not contain a preservative.

A two-step process is required for preparation of the final Kimmtrak dose for use in a patient, summarised as follows:[41]

- Step 1 requires preparation of the infusion bag. A calculated volume of human albumin (varying depending on the available concentration) is added to 100 mL 0.9% sodium chloride for injection.
- Step 2 requires preparation of Kimmtrak solution for infusion.

  The required volume of Kimmtrak (tebentafusp) 200 µg/mL as per the dose required is extracted and added to the prepared 100 mL infusion bag containing sodium chloride 9 mg/mL (0.9 %) solution for injection, plus human albumin.

The recommended shelf life is based upon stability data submitted by the sponsor. For the drug substance the recommended shelf life is 24 months at ≤ -60°C.

- For the drug product (that is Kimmtrak (tebentafusp), vial) the long-term shelf life is 18 months, to be stored at between 2°C to 8°C, and protected from light.
- When in use (that is, following dilution) the diluted solution for infusion may be stored below 30°C for 4 hours, or at 2°C to 8°C for 24 hours from the time of preparation which includes the time allowed for equilibration of the infusion bag to below 30°C and the duration of the infusion.
- 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

[41] See the Product Information for full.

Kimmtrak infusion bag should remain below 30°C. There are no allowable temperature excursions for the product.

- 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.

Conclusions and recommendation

The formulation development has been adequately described and the final formulation intended for marketing was used in the Phase III clinical trials.

Sufficient evidence was provided to demonstrate that the risks related to adventitious agents in the manufacturing of Kimmtrak have been managed to an acceptable level. An evaluation of sterility aspects concluded that there were no objections from a microbiological perspective for the application to register Kimmtrak (tebentafusp) 0.1 mg/0.5 mL concentrated solution for infusion vial. Container safety and bacterial endotoxin testing aspects were also found to be acceptable.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the PI, labels, Consumer Medicines Information (CMI) and the Australian Register of Therapeutic Goods (ARTG). Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. From quality perspective, compliance with Therapeutic Goods Legislations (Therapeutic Goods Act, Regulations and Orders) and relevant Therapeutic Goods Orders as well as consistency with relevant guidelines and the Australian Regulatory Guidelines for Prescription Medicines has been demonstrated.

Standard quality-related conditions of registration are proposed.

Nonclinical

The TGA toxicology evaluation concluded that the nonclinical data support the use of tebentafusp for the proposed indication. Potential areas of concern raised by the nonclinical data were considered during review of clinical data (See Sections Cytokine release syndrome, Skin toxicity, Eye toxicity, Infections and Drug-drug interaction with cytochrome P450 (CYP) substrates.[42]

Nonclinical data in this submission were limited to pharmacology studies with human cancer and cross reactivity with normal cells and tissues. The absence of nonclinical

[42] **Cytochrome P450 (CYP)** enzymes: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.
Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

toxicity studies in animal species was justified based on the human specificity of the tebentafusp molecule and the absence of equivalent targets in other species.

Tebentafusp was shown to bind to the human gp100 peptide presented by HLA-A*02:01 and human CD3 with picomolar affinity and shows specificity for the target human HLA-A*02. Tebentafusp redirects T-cell activity against HLA-A*02:01 and gp100-positive cancer cells (uveal melanoma and cutaneous melanoma) at clinically relevant concentrations (at pM) as demonstrated by T-cell activation and target cell killing. Tebentafusp also induced cytokine or chemokine release from T-cells from healthy donors or cancer patients. In a mouse xenograft model of human melanoma with human T-cell engraftment, tebentafusp reduced tumour growth compared to controls at doses comparable to human doses.

Tebentafusp binds to normal human epidermal melanocytes *in vitro* at 10 to 100 pM concentrations. CD3 specific tebentafusp binding was detected in membrane and cytoplasm of lymphocytes throughout the human tissue panel examined at clinically relevant concentrations. Tebentafusp did not display any other off target binding or alloreactivity against any common non-HLA-A*02 HLA types at clinically relevant concentrations.

The nonclinical pharmacokinetic data are limited and are not clinically relevant for the assessment of tebentafusp safety given the absence of appropriate animal models. Tebentafusp is expected to be eliminated by proteolytic enzymes, and excretion was primarily in the urine.

Based on nonclinical pharmacology data, skin, and eye (melanocyte) toxicity is considered the most likely on-target, off-tumour toxicity.

Based on the mechanism of action of tebentafusp, it may lower exposures to co-administered drugs that are CYP substrates due to changes in cytokine levels in clinical scenarios. A transient reduction in lymphocyte counts could also occur, with possible associated risk of infection.

Tebentafusp did not induce cytokine release or impairment of platelet function at < 1 nM of tebentafusp in whole blood assays; however, some cytokine release was noted in blood from one out of 3 donors at a tebentafusp concentration (250 pM) slightly above the expected clinical maximum plasma concentration. Based on the nature of the drug, potential anti-drug antibody (ADA) development affecting tebentafusp exposure and cytokine release syndrome (CRS) are expected in clinical scenarios.

Genotoxicity and carcinogenicity studies were not conducted, in line with International Council for Harmonisation (ICH);[43] guideline S6 (R1).[44]

In the absence of reproductive toxicity data, the sponsor provided an assessment based on published literature. Tebentafusp may affect embryofetal development based on target biology. The proposed Pregnancy Category C;[45] is appropriate.

[43] The **International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)** brings together regulatory authorities and the pharmaceutical industry. It makes recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration.
[44] European Medicines agency (EMA), Committee for medicinal products for human use (CHMP), ICH Guideline S6 (R1) - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, EMA/CHMP/ICH/731268/1998, June 2011.
[45] **Pregnancy Category C**: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines

One identified impurity was shown to impact tebentafusp activity and specificity at a concentration much higher than clinical concentrations, but with minimal effects at clinically relevant concentrations. The proposed specification limits are therefore adequate.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- three Phase I/II studies: Study IMCgp100-01, Study IMCgp100-102, Study IMCgp100-201 (abbreviated to Studies 01, 102 and 201 in this AusPAR);
- one Phase II study: Study IMCgp100-401 (or Study 401);
- one Phase III study: Study IMCgp100-202 (or Study 202).

Pharmacology

Dosing

The proposed dosing regimen follows a priming strategy: 20 µg on Day 1, 30 µg on Day 8, 68 µg on Day 15, and 68 µg once every week thereafter, via intravenous infusion over 15 to 20 minutes.

This regimen was used in the pivotal efficacy and safety study, Study 202 (see Section: *Efficacy*), and is supported by the following data from earlier Phase I/II studies:

- Study IMCgp100-01 (Study 01):
  - Weight based dosing was associated with more adverse events (AEs) in patients with higher body weight.
  - Weekly dosing was not associated with clinically meaningful differences in safety or efficacy compared to daily dosing.
- Study IMCgp100-102 (Study 102):
  - A higher 73 µg dose was associated with elevations in hepatic transaminases and concurrent low grade increases in bilirubin. No dose limiting toxicities nor significant liver enzyme elevations were observed at the maintenance dose of 68 µg.
  - Cytokine release syndrome (CRS) occurred in 89% of patients and led to permanent treatment discontinuation in 1.2%. The priming dosing strategy used in the pivotal study was adopted to mitigate CRS.

Pharmacokinetics

Non-compartmental population pharmacokinetic (PK) analysis of tebentafusp from Study 202 in metastatic uveal melanoma patients indicated dose proportional PK with a terminal half-life of 6.8 to 7.5 hours. The estimated systemic clearance and central volume of distribution of tebentafusp in melanoma patients were 4.33 L/d and 5.25 L, respectively.

during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

High-titre anti-drug antibodies (ADA) and renal function (estimated glomerular filtration rate) were identified as significant covariates impacting clearance. Age, sex, weight, and race had no impact on PK.

Exploratory exposure response analysis did not find clinically significant trends between tebentafusp exposure and key safety or efficacy endpoints over the dose range investigated (once weekly by intravenous infusion of 5 ng/kg to 68 µg of tebentafusp).

Renal function

Although tebentafusp clearance decreased slightly with decreasing renal function, it remained essentially within the range observed in patients with normal renal function, and no impact on safety or efficacy parameters was identified. Therefore, no dose adjustment is recommended in mild to moderate renal impairment. There are no data to support recommendations for patients with severe renal impairment to end stage renal disease (creatinine clearance < 30 mL/min), or moderate to severe hepatic impairment (total bilirubin > 3 to 10 x upper limit of normal (ULN), any aspartate aminotransaminase (AST)).

Pharmacokinetic impact of anti-drug antibodies

Treatment-emergent ADA against tebentafusp were detected in around 33% and 29% of tebentafusp treated patients in Study 102 and Study 202, respectively, with a median onset time of 6 to 9 weeks. High titre ADA positivity (above the median titre of 8192) was associated with a 33-fold increase in clearance and commensurate decreased tebentafusp plasma concentrations. (See Section: *Immunogenicity*)

Cytokine release and interactions with cytochrome P450 metabolised drugs

As tebentafusp can cause a transient release of cytokines after dosing, it was considered whether this could suppress CYP enzyme function and lead to drug-drug interactions.

Based on the totality of data, the risk is considered to be low:

- Tebentafusp has a short half-life (6 to 8 hours).
- Elevations of pro-inflammatory cytokines are transient following tebentafusp infusion.
- Elevations of pro-inflammatory cytokines are observed to attenuate with repeat dosing, such that the highest drug-drug interaction risk is following the first three doses.
- The dosing instructions recommend observation of patients for at least 16 hours after dosing, so that if drug interaction-related AEs occurred, they would be likely to receive prompt recognition and management.

The observed clinical data support an assessment of low risk. In Study 202, 20 (5.1%) of the tebentafusp treated patients with metastatic uveal melanoma had concomitant medications with a narrow therapeutic index within a 2-week period of a CRS episode. The rate of Grade 3 and 4 treatment-emergent adverse events (TEAEs) in that population was comparable to the overall tebentafusp population and none of these patients had QTcF (QT interval corrected for heart rate according to Fridericia's formula)[46] prolongation > 500 ms during the susceptible period.

[46] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
The corrected QT interval (**QTc**) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias. The **QTcF** is the QT interval corrected for heart rate according to Fridericia's formula.

Given the technical challenges of conducting a dedicated drug-drug interaction study to coincide with the peak of cytokine release and expected variance in degree of cytokine increase for individual patients, a formal drug-drug interaction study to assess the drug interaction potential due to cytokine release after tebentafusp treatment is not considered feasible.

Efficacy

Study IMCgp100-201 (Study 202, pivotal study)

The pivotal data supporting efficacy come from the Phase III Study 202. The design of Study 202 has been described in a peer-reviewed publication,[40] and is summarised in Figure 1 below, and in the publicly available FDA label.[47]

The submitted clinical study report presents data from the primary analysis, which was triggered by a recommendation from the Independent Data Monitoring Committee to unblind the study following the first prespecified interim analysis (at approximately 60% of the expected death events).

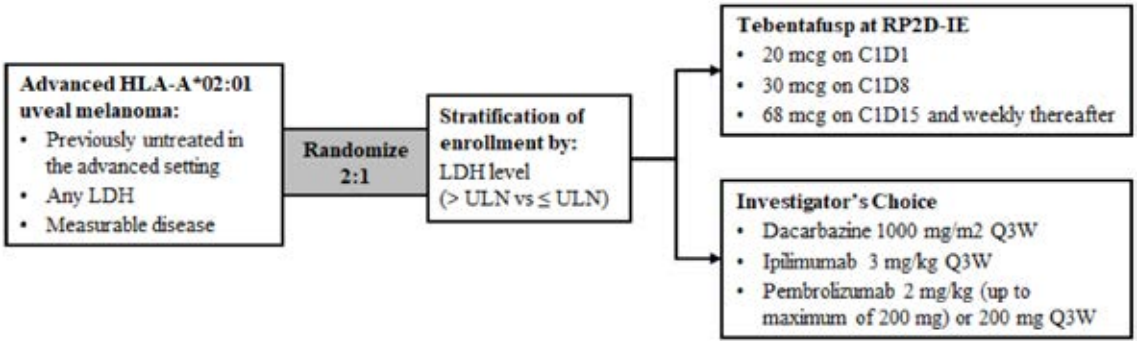
Study design

Study 202 was a randomised, controlled, open label, multi-centre trial that enrolled patients with metastatic uveal melanoma who were HLA-A*02:01 genotype-positive according to a central clinical trial assay (see Section: *Companion diagnostic considerations*). Key eligibility criteria are summarised in Table 2 below. Patients who had received prior systemic or localised liver directed treatment of metastatic uveal melanoma were excluded, but those who had received prior surgical resection of oligometastatic disease were not.

A total of 378 patients were randomised in 2:1 ratio to either receive tebentafusp weekly by intravenous infusion following the proposed tebentafusp dosing regimen (Arm 1, 252 patients); or investigator's choice of treatment (Arm 2, 126 patients in total), with 103 patients treated with pembrolizumab, 16 with ipilimumab, or 7 with dacarbazine. This comparator arm is considered appropriate, as it is in line with the current standard of care for metastatic uveal melanoma.

Figure 1 shown below, summaries the study design.

Figure 1: Study 202 Study design



Abbreviations: C = Cycle; D = Day; HLA = human leukocyte antigen; LDH = lactate dehydrogenase; Q3W = every 3 weeks; RP2D-IE = recommended Phase II dose intrapatient escalation regimen; ULN = upper limit of normal; vs = versus.

[47] United States Food and Drug Administration (FDA) Prescribing Information for Kimmtrak (Tebentafusp-tebn), Revised in January 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761228s000lbl.pdf (Accessed 14 February 2022).

Randomisation was stratified by lactate dehydrogenase (LDH) level at study entry, into those with baseline LDH below or equal to the ULN; or those with baseline LDH above the ULN (LDH measured centrally) to ensure adequate balance of this prognostic factor across arms.

Study treatment was ceased on disease progression per Response Evaluation Criteria In Solid Tumours (RECIST)[48] version 1.1 criteria;[49] or for unacceptable toxicity, however, treatment beyond initial progression was allowed in select settings in which it was considered the patient may still be benefiting. The rationale provided for this in the clinical study report was:

> There is accumulating evidence in the field of immuno-oncology that some patients treated with immunotherapy agents, such as tebentafusp, may develop initial progressive disease of the tumour prior to subsequent disease stabilisation or objective response.[50] Evidence of these phenomena were noted in the Phase I development of tebentafusp.[51,52] Given these data, patients receiving tebentafusp, ipilimumab, or pembrolizumab who demonstrated initial progressive disease by RECIST version 1.1 could have continued treatment beyond the initial progressive disease.

Patients experiencing progressive disease per RECIST version 1.1 criteria could therefore continue to be treated until meeting the criteria for unequivocal, confirmed progressive disease by immune-related RECIST.[53]

Inclusion and exclusion criteria.

Table 2, shown below, presents a summary of the key eligibility criteria for the pivotal study.

Table 2: Study 202 Key eligibility criteria

Inclusion criteria	Exclusion criteria
Consenting adults (≥ 18 years) with metastatic uveal melanoma (histology or cytology-confirmed)	Systemic or untreated central nervous system metastases Hypersensitivity to monoclonal antibodies or other biological medicines Inadequate cardiac health

[48] The **Response Evaluation Criteria In Solid Tumours (RECIST)** is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

[49] Eisenhauer, E.A. et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1), *Eur J Cancer*, 2009; 45(2): 228-247.

[50] Hodi, F.S. et al. Evaluation of Immune-Related Response Criteria and RECIST v1.1 in Patients with Advanced Melanoma Treated with Pembrolizumab, *J Clin Oncol*, 2016; 34(13): 1510-1517.

[51] Middleton, M. et al. A Phase I/IIa Study of IMCgp100: Partial and Complete Durable Responses with a Novel First-in-Class Immunotherapy for Advanced Melanoma, American Academy for Cancer Research Annual Meeting, Philadelphia, PA. April 2015.

[52] Middleton, M. et al. Safety, Pharmacokinetics and Efficacy of IMCgp100, a First-in-Class Soluble TCR-AntiCD3 Bispecific T Cell Redirector with Solid Tumour Activity: Results from the FIH Study in Melanoma, American Society for Clinical Oncology, 2016 Annual Meeting, Chicago, USA.

[53] Wolchok, J.D. et al. et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria, *Clin Cancer Res*, 2009; 15(23): 7412-7420.

Inclusion criteria	Exclusion criteria
Eastern Cooperative Oncology Group Performance Status score < 2;[54] No prior systemic therapy in the metastatic or advanced setting No regional liver-directed therapy Human leukocyte antigen-A*02:01 positive by central assay	Significant infection (systemic antibiotics, human immunodeficiency virus, active hepatitis B or C) or immunosuppression (including any dose systemic steroid) Adrenal insufficiency Interstitial lung disease, pneumonitis requiring corticosteroids Colitis/inflammatory bowel disease Radiotherapy within 2 weeks of first dose of study drug Use of haematopoietic colony-stimulating growth factors

Efficacy outcomes

The primary efficacy outcome was overall survival with tebentafusp versus investigator's choice of treatment (the intention-to-treat (ITT)[55] analysis set).[56] Additional efficacy endpoints included investigator assessed progression free survival, objective response rate and best overall response per RECIST version 1.1.

Statistical analysis

Type 1 error control was incorporated using sequential testing (overall survival, then progression free survival, then best overall response). The difference in overall survival between the treatment arms was tested using a 2-sided log-rank test;[57] stratified by LDH status. The overall survival hazard ratio was estimated using a stratified Cox-proportional hazards model,[58] using the Efron approach for handling ties,[59] along with corresponding 95% confidence intervals (CIs) for the hazard ratio. Kaplan Meier estimates and exploratory landmark rates were also generated.[60] The analysis method for progression free survival was the same as that of overall survival. A summary of best overall response and objective response rate was presented by treatment group, and objective response

[54] One patient with ECOG 2 was enrolled, in deviation from these criteria, and was randomised into the investigator's choice of treatment arm. This is unlikely to have meaningfully altered study outcomes.
[55] Randomised clinical trials analysed by the **intent-to-treat (ITT)** approach provide the unbiased comparisons among the treatment groups. In the ITT population, none of the patients are excluded and the patients are analysed according to the randomisation scheme.
[56] The study design incorporated a dual primary endpoint of overall survival in a subset of the intention-to-treat (ITT) (all patients randomised to tebentafusp who developed a rash during the first week of treatment) versus all patients randomised to investigator's choice (the randomised analysis set (RAS)). This endpoint was added to the protocol in response to single-arm data from Phase I Study IMCgp100-102 to suggest an association between rash (an early and on-target pharmacodynamic biomarker), and tebentafusp activity. This endpoint was prioritised in the statistical analysis, but the statistical design did not incorporate comparison between it and the other primary endpoint: overall survival in the ITT. Overall survival in the RAS analysis set may have been relevant to the Delegate's considerations if overall survival in the ITT had not reached statistical significance or had been unfavourable. As this was not the case, results in the RAS analysis set are not discussed further.
[57] Mantel, N. Evaluation of Survival Data and Two New Rank Order Statistics Arising in Its Consideration, *Cancer Chemother Rep*, 1966; 50(3): 163-170.
[58] Cox, D.R. Regression Models and Life-Tables, *J. R. Stat. Soc*, Series B, 1972, 34: 187-220.
[59] Efron, B. The Efficiency of Cox's Likelihood Function for Censored Data, *J Am Stat Assoc*, 1977; 72 (359): 557-565.
[60] Kaplan, E.L. and Meier, P. Nonparametric Estimation from Incomplete Observations, *J Am Stat Assoc*, 1958; 53(282); 457-481.

rate was compared between treatment arms using a stratified Cochran-Mantel-Haenszel test adjusting for baseline LDH status.[61,62]

The sample size in Study 202 was chosen based on 250 events (deaths) required in the all randomised population to provide 89% power to detect an overall survival hazard ratio of 0.645 at 2-sided significance level of 0.045. Assuming an exponential distribution and a median overall survival of 12 months in the investigator's choice of treatment arm, the hazard ratio of 0.645 corresponds to a median overall survival of 18.6 months in the tebentafusp arm and a difference of 6.6 months in median overall survival between the arms. Considering a non-uniform recruitment of about 33 months and 10% annual drop-out rate, 369 patients were to be randomised in a 2:1 ratio to observe 250 events after 51 months.

Two formal interim analyses of overall survival were planned, to be performed at approximately 60% (150 events) and 80% (200 events) of the total expected events. Analyses of overall survival were based on O'Brien-Fleming boundaries,[63] using the Lan-DeMets approach to adjust for situations where the actual number of events up to the data cut-off date for a given interim analysis did not match the planned number.[64]

The progression free survival analysis could be performed once 274 progression or death events had occurred. Assuming a median progression free survival of 5 months in the tebentafusp arm and 3.3 months in the investigator's choice of treatment arm, a hazard ratio of 0.66, and the same accrual and drop-out assumptions described above for overall survival, the analysis of progression free survival was expected to have 90% power to demonstrate a difference between arms. Due to the higher hazard of progression events relative to death events, the required number of progression free survival events was expected to (and did) occur prior to the first interim analysis of overall survival.

Protocol amendments and deviations were reviewed by the regulators and are considered unlikely to have altered study conclusions. Compliance with Good Clinical Practice;[65] was audited by the FDA.

Population demographics and baseline disease characteristics

Patients were randomised across 58 sites in 14 countries (US, Germany, France, United Kingdom, Poland, Canada, Australia, Belgium, Spain, Switzerland, Ukraine, Russia, Italy, and the Netherlands). In total, 17 patients were randomised at Australian sites: 9 patients to the tebentafusp-treatment arm and 8 to investigator's choice of treatment arm.

Demographics and baseline disease characteristics were generally similar between treatment arms, suggestive of intact randomisation, and in keeping with what would be expected for a first line metastatic uveal melanoma population in Australia. Amongst the ITT group, the median age was 64 years (range 23 to 92); 50% were female; 87% were Caucasian; 73% had a baseline Eastern Cooperative Oncology Group Performance Status;[66] of 0; 76% had a primary lesion derived from the choroid, around 7% had

[61] Cochran, W.G. Some Methods for Strengthening the Common $\chi 2$ Tests, *Biometrics*, 1954; 10(4): 417-451.
[62] Mantel, N. and Haenszel, W. Statistical Aspects of the Analysis of Data from Retrospective Studies of Disease, *J Natl Cancer Inst*, 1959; 22 (4): 719-748.
[63] O'Brien, P.C. and Fleming, T.R. A Multiple Testing Procedure for Clinical Trials, *Biometrics*, 1979; 35(3): 549-556.
[64] Lan, K.K. and DeMets, D.L. Discrete Sequential Boundaries for Clinical Trials, *Biometrika*, 1983; 70(3): 659-663.
[65] **Good Clinical Practice (GCP)** is a code of international standards and guidance following the International Council on Harmonisation (ICH) concerning the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials. Good Clinical Practice provides assurance that a study's results are credible and accurate and that the rights and confidentiality of the study subjects are protected.
[66] **ECOG Performance Status**: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the

metastatic disease at diagnosis, 36% had an elevated baseline LDH level; and 94% had liver metastasis. The rate of prior surgical management of oligometastatic disease was 7% in the investigator's choice of treatment arm and 10% in the tebentafusp-treatment arm. For the majority of patients (80%), the pre-randomisation choice of therapy was pembrolizumab.

Disposition

At the data cut-off for the interim overall survival analysis, the median duration of follow-up for all patients was 14 months (range 13 to 15). Some key patient disposition information for the ITT is summarised in Table 3 below.

There was an imbalance across the treatment arms in patients who were randomised but did not receive treatment. Of these patients, 3 in the tebentafusp arm and 10 in the investigator's choice of treatment arm were still being followed for survival at the data cut-off date for the primary analysis (13 October 2020). At least 6 patients randomised to the investigator's choice of treatment arm who then decided not to continue with the study subsequently received anti-PD(L)1 or anti-CTLA4 therapy (5 of these patients received both in combination).

Table 3: Study 202 Patient disposition (intention-to-treat analysis population; data cut-off date: 13 October 2020)

		Tebentafusp arm (n = 252)	Investigator's choice of treatment[a] (n = 126)
Patients randomised but not treated, n (%)		7 (3%)	15 (12%)
Reason for no treatment, n	Patient decision/withdrew consent	4	14
	Adverse event	2	0
	Didn't meet eligibility criteria and unsafe to continue	1	1
Patients who received treatment beyond RECIST progression, n (%)		109 (43%)	18 (14%)
Duration of treatment beyond progression (ITT)	Mean (standard deviation), months	3.5 (4.6)	2.3 (3.2)
	< 12 weeks, n (%)	70 (28%)	15 (12%)
	12-24 weeks, n (%)	25 (10%)	1 (1%)

daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

		Tebentafusp arm (n = 252)	Investigator's choice of treatment[a] (n = 126)
	> 24 weeks, n (%)	14 (6%)	2 (2%)
Patients still receiving study treatment at data cut-off, n (%)		73 (29%)	11 (9%)
Patients who discontinued study treatment, n (%)		172 (68%)	100 (79%)
Reason for study treatment discontinuation, n (%)	Progression of disease	154 (61%)	78 (62%)
	Adverse event	6 (2%)	5 (4%)
Patients who discontinued study altogether, n (%)		96 (38%)	69 (55%)
Reason for study discontinuation, n (%)	Death	87 (35%)	63 (50%)

Abbreviations: DCO = data cut-off date; IC = investigator's choice; ITT = intention-to-treat analysis population; n = number of subjects in group; RECIST = Response Evaluation Criteria In Solid Tumours.

a investigator's choice of treatment = pembrolizumab, ipilimumab, or dacarbazine.

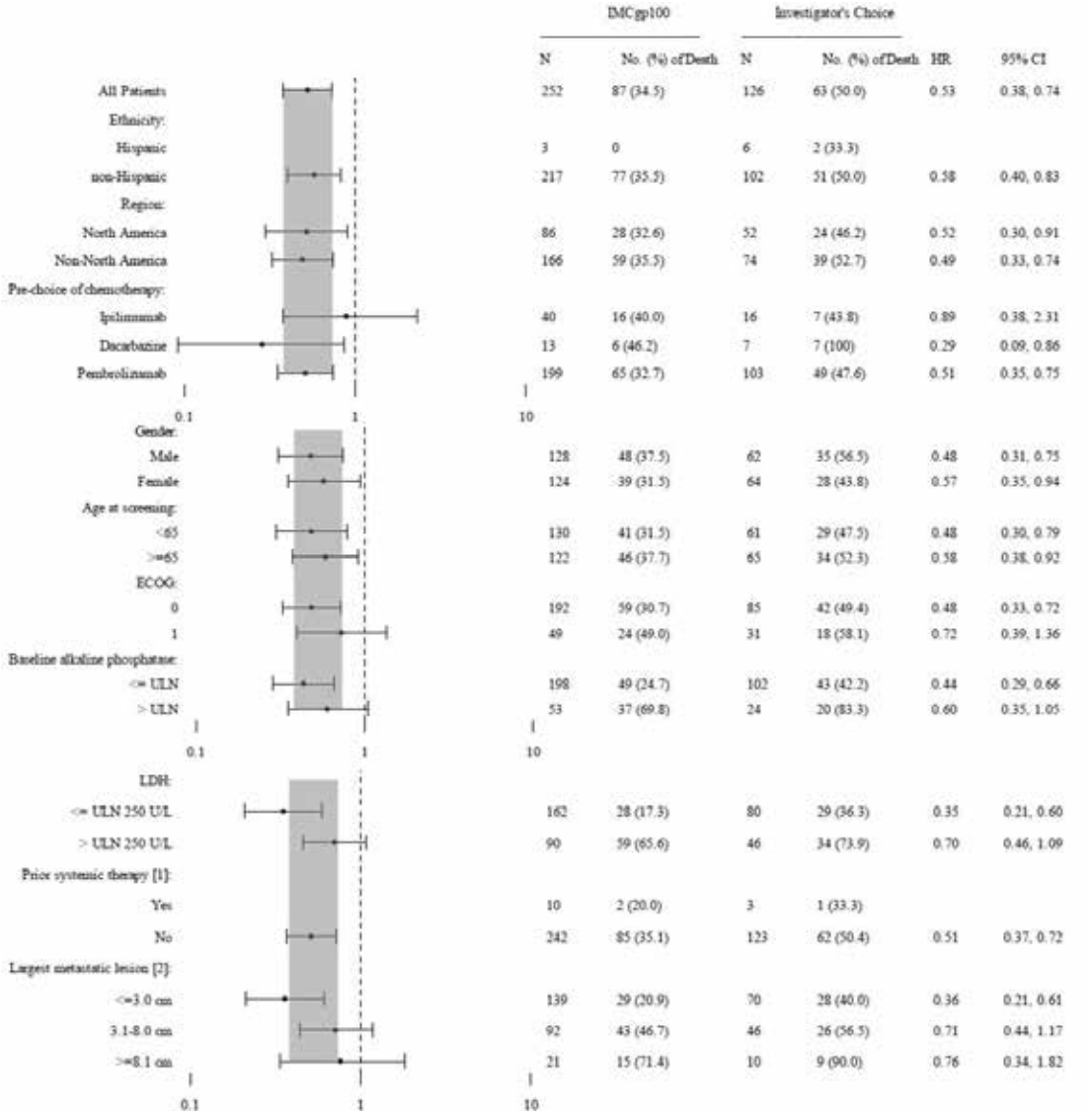
Results for the efficacy outcomes

Results (including some selected descriptive statistics and exploratory results) for Study 202 are summarised in Table 4, Figure 3 and Figure 4, below.

At the first interim analysis of overall survival, with a data cut-off date of 13 October 2020, which became the primary analysis at the recommendation of the Independent Data Monitoring Committee, a significant survival benefit of tebentafusp over investigator's choice of treatment was demonstrated, with a difference of 5.7 months in median overall survival, corresponding to a hazard ratio of 0.51 (95% CI: 0.37, 0.71, $p < 0.0001$), and meeting the stopping boundary of 0.006. Exploratory landmark analysis indicated an approximate 15% increase in the one-year overall survival rate.

Exploratory subgroup analyses indicated consistent overall survival findings for all subgroups with adequate sample size (see Figure 2 below). The greatest difference in hazard ratio for overall survival seen in subgroup analysis was between patients with an LDH above versus ≤ the upper limit of normal (250 U/L), which was a stratification factor for Study 202. The hazard ratio (95% CI) for overall survival was 0.35 (95% CI: 0.21, 0.60) in patients with LDH no higher than 250 U/L, and 0.70 (95% CI: 0.46, 1.09) in patients with LDH above 250 U/L.

Figure 2: Study 202 Forest plots representing exploratory subgroup analyses of overall survival (intention-to-treat analysis population)



Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IMCgp100 = tebentafusp; ITT = Intent-to-treat; LDH = lactate dehydrogenase; N = number of subjects; ULN = upper limit of normal.

Exploratory sensitivity analyses using an inverse probability of censoring weighting approach suggest that the overall survival benefit that was observed in the primary analysis was maintained after removing the effect of subsequent therapy.

With a total of 295 events and a median follow-up duration of 11.4 months, the median progression free survival was 3.3 months in the tebentafusp arm and 2.9 months in the investigator's choice of treatment arm, corresponding to a difference of 0.4 months (less than 2 weeks), and a hazard ratio of 0.73 (95% CI: 0.58, 0.94, p = 0.0139). Whilst this result reached statistical significance (within the specified alpha limit of 0.05), it does not represent a clinically meaningful difference based on magnitude, particularly in context of the 12 weekly tumour assessments. The lack of meaningful difference is also reflected by a lack of clear, maintained separation of Kaplan-Meier curves for progression free survival (see Figure 4 below).

Progression free survival results were consistent across prespecified sensitivity analyses assessing for evaluation-time bias and attrition bias. An exploratory analysis of *PFS2*

(defined as time from randomisation to a subsequent disease progression following initial RECIST version 1 .1 disease progression, or death; assessed using similar methodologies as for progression free survival) showed less than a month difference in medians (8.3 months with tebentafusp versus 9.2 months with investigator's choice of treatment), and a stratified hazard ratio of 0.79 (0.59, 1.06).

Objective response rate and best overall response were not formally analysed. Tumour response rates were low, and similar between arms. *Post-hoc* exploratory analyses of treatment beyond progression were provided, but are not of adequate statistical rigour to support regulatory approval of this approach to duration of therapy.

Table 4: Study 202 Summary of study results (intention-to-treat analysis population; data cut-off date: 13 October 2020)

	Tebentafusp (n = 252)	Investigator's choice of treatment* (n = 126)
Overall survival		
Median follow-up time for overall survival, months (95% CI)[a]	14.1 (12.5, 16.1)	14.3 (10.9, 17.0)
Patients with death events, n (%)	87 (35%)	63 (50%)
Median overall survival (95% CI), months	21.7 (18.6, 28.6)	16.0 (9.7, 18.4)
Overall survival hazard ratio (95% CI)[b] (p-value)[c]	0.51 (0.37, 0.71) (p < 0.0001)	
Survival probability, *% (95% CI)*		
6 months	88.8 (84.1, 92.2)	78.1 (69.6, 84.6)
9 months	81.1 (75.3, 85.7)	63.2 (53.4, 71.5)
12 months	73.2 (66.4, 78.8)	58.5 (48.3, 67.3)
18 months	61.5 (53.3, 68.7)	42.9 (31.5, 53.8)
24 months	44.8 (34.9, 54.2)	20.3 (9.1, 34.7)
30 months	33.6 (20.2, 47.6)	10.2 (1.1, 31.1)
Progression free survival		
Median follow-up time for progression free survival, months (95% CI)[a]	13.8 (10.9, 16.8)	11.3 (8.3, 16.9)
Combined median progression free survival follow-up time, months (95% CI)[a]	11.4 (11.1, 1.6)	
Patients with death or progression events, n (%)	198 (79%)	97 (77%)

	Tebentafusp (n = 252)	Investigator's choice of treatment* (n = 126)
Patients with progression events, n (%)	183 (73%)	83 (66%)
Patients who died without progression being recorded, n (%)	15 (6%)	14 (11%)
Median progression free survival (95% CI), months	3.3 (3.0, 5.0)	2.9 (2.8, 3.0)
Progression free survival hazard ratio (95% CI) (p-value)	0.73 (0.58, 0.94) (p = 0.0139)	
Best overall response/objective response rate		
Objective response rate (complete response + partial response) (95% CI)	9% (5.9, 13.4)	5% (1.8, 10.1)
Complete response, n (%)	1 (0.4%)	0
Partial response, n (%)	22 (8%)	6 (5%)
Stable disease, n (%)	92 (37%)	28 (22%)
Progressive disease, n (%)	131 (52%)	78 (62%)
Not evaluable, n (%)	6 (2%)	14 (11%)

Abbreviations: CI = confidence interval; n = number of subjects in group.

Objective response rate per Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1.

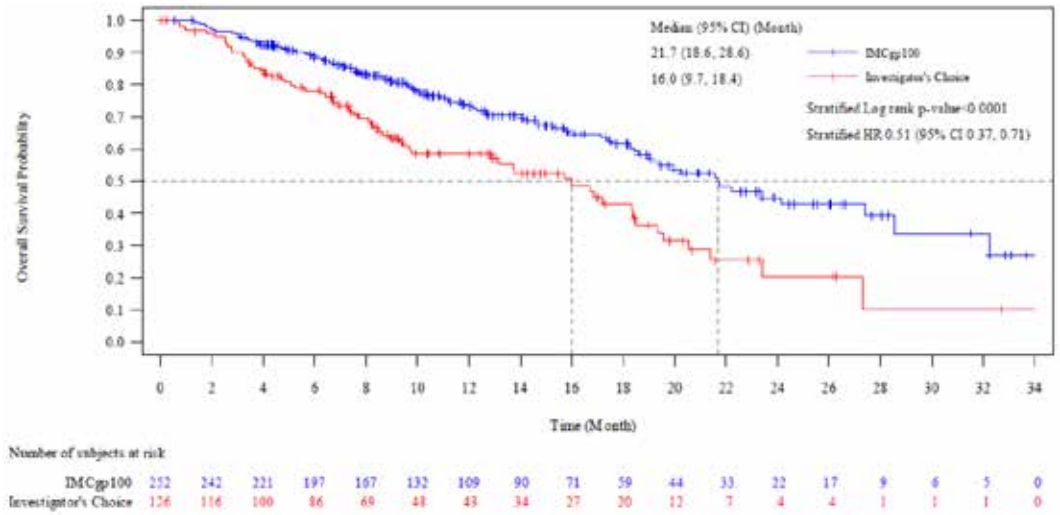
* Investigator's choice of treatment = pembrolizumab, ipilimumab, or dacarbazine.

a Reverse Kaplan-Meier estimate

b Cox-proportional hazards model stratified by lactate dehydrogenase status

c Log-rank test stratified by lactate dehydrogenase status

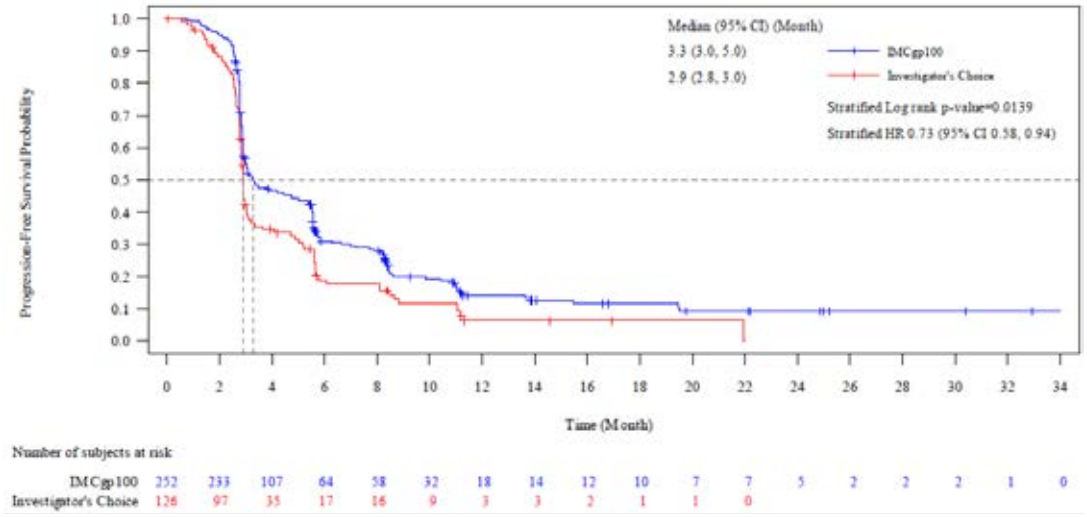
Figure 3: Study 202 Kaplan-Meier estimate of overall survival (intention-to-treat analysis population; data cut-off date: 13 October 2020)



Abbreviations: CI = confidence interval; HR = hazard ratio; IMCgp100 = tebentafusp.

Investigator's choice of treatment = pembrolizumab, ipilimumab, or dacarbazine.

Figure 4: Study 202 Kaplan-Meier estimate of progression free survival (intention-to-treat analysis population; data cut-off date: 13 October 2020)



Abbreviations: CI = confidence interval; HR = hazard ratio; IMCgp100 = tebentafusp.

Investigator's choice of treatment = pembrolizumab, ipilimumab, or dacarbazine.

Safety

Safety database

The sponsor's clinical development program for tebentafusp in melanoma includes two completed studies (Phase I Study 01 and Phase II rollover Study 401) and three ongoing studies (Phase I/II Study 102, Phase Ib/II Study 201, and Phase III Study 202). Across these clinical studies, 587 patients with melanoma, including 410 patients with uveal melanoma, have been exposed to tebentafusp (as monotherapy for 505 patients).

The regulatory safety review focussed primarily on the safety analysis population in Study 202, which consisted of all randomised patients who received at least one dose of study treatment: 245 patients in the tebentafusp arm and 111 in the investigator's choice of treatment arm. In addition, safety data from an integrated safety pool (505 patients with cutaneous or uveal melanoma, who received at least one dose of tebentafusp as monotherapy at any dose level across the clinical development program) were included in the submission.

The safety database was considered adequate in size and duration of exposure to provide a reasonable estimate of adverse reactions that may be observed with tebentafusp at the proposed dosage in the overall population of patients who are diagnosed with uveal melanoma.

Comparisons between the tebentafusp and the investigator's choice of treatment arm are exploratory and contextualised by a longer (approximately doubled) duration of 'at-risk' time and the more frequent opportunities for data collection (due to the more frequent dosing) in the tebentafusp arm, both of which predict a higher volume of safety data.

Protocol for dose modification in case of adverse events

The Study 202 protocol specified that the tebentafusp dose should be modified for specific adverse events (AEs), as outlined in Table 5 below.

Table 5: Study 202 Dose modifications specified by the protocol (version 5) for patients receiving tebentafusp

Adverse event	Grade 2	Grade 3	Grade 4
All unspecified	-	Hold tebentafusp until ≤ Grade 1	
Pruritis	-	Hold tebentafusp until ≤ Grade 1	
Rash/photosensitivity	Hold tebentafusp until ≤ Grade 1		Permanently discontinue
Hypotension	-	-	Dose reduce or permanently discontinue
Infusion-related reactions during infusion/anaphylaxis	Hold tebentafusp until resolution. May recommence within 4 hours. Recommence at 50% rate. If recurs: permanently discontinue.	If not improved by at least 1 grade within 6 hours with medical management: permanently discontinue	Permanently discontinue
Infusion-related reactions after infusion/cytokine release syndrome (based on Lee et al (2014) grading criteria)[67]	-	Hold tebentafusp until resolution of symptoms and restart after discussion and written approval of sponsor's Medical Monitor	Permanently discontinue

[67] Lee, D.W. et al. Current Concepts in the Diagnosis and Management of Cytokine Release Syndrome, *Blood*, 2014; 124(2): 188-195.

Adverse event	Grade 2	Grade 3	Grade 4
Hepatic function abnormalities	-	Hold tebentafusp until ≤ Grade 1	
Vomiting	-	Hold tebentafusp until ≤ Grade 1	

The protocol also specified the following dose reduction schedule:

- From a starting tebentafusp dose of 68 µg, the dose will be reduced to 54 µg for any toxicity requiring dose reduction.
- The dose may be reduced further to 50 µg for recurrent toxicity.
- Patients who require more than 2 dose reductions of tebentafusp should discontinue treatment.

Exposure

Exposure to study treatment for the safety analysis population at the primary data cut-off for the clinical study report (13 October 2020) is summarised in Table 6 below.

The median duration of exposure was 163 days (around 5.3 months, range 0.3 to 33 months) in patients receiving tebentafusp. A higher rate of dose interruptions was noted in the tebentafusp arm, consistent with the three times more frequent dosing regimen, interruptions in response to AEs (predominantly CRS, see Section: *Cytokine release syndrome*), and a longer duration of treatment exposure.

Table 6: Study 202 Exposure (safety analysis population; data cut-off date: 13 October 2020)

	Tebentafusp (n = 245)	Investigator's choice of treatment arm[a] (n = 111)
Exposure		
Median treatment duration, days (range)	163 (1, 1016)	65 (1, 658)
Mean treatment duration, days (standard deviation)	220 (192)	119 (130)
Mean relative dose intensity, % (standard deviation)	99.9 (0.4)	100 (0)

a Investigator's choice of treatment = pembrolizumab, ipilimumab, or dacarbazine.

Deaths

Deaths in the safety analysis population at the primary data cut-off for the clinical study report (13 October 2020) are summarised in Table 7 below.

There were two fatal AEs in the tebentafusp arm in Study 202 (pneumonia and pulmonary embolism), however, clinical review of the provided case narratives does not indicate that these were likely to be related to tebentafusp treatment. There were three fatal AEs in the investigator's choice of treatment arm (pulmonary embolism, sepsis and left ventricular dysfunction).

Table 7: Study 202 Deaths (safety analysis population; data cut-off date: 13 October 2020)

	Tebentafusp arm (n = 245)	Investigator's choice of treatment arm[a] (n = 111)
Deaths		
Total, n (%)	**84 (43)**	**57 (51)**
Within 30 days of last dose of study treatment, n (%)	5 (2.0)	5 (4.5)
Due to disease progression, n (%)	80 (33)	52 (47)
Due to adverse events, n (%)	2 (0.8)	3 (2.7)
Unknown, n (%)	2 (0.8)	1 (0.9)
'Other: subdural haematoma', n (%)	0	1 (0.9)

Abbreviation: n = number of subjects in group.

a Investigator's choice of treatment = pembrolizumab, ipilimumab, or dacarbazine.

Dose modifications and permanent discontinuations

Dose modifications and permanent discontinuations for the safety analysis population at the primary data cut-off for the clinical study report (13 October 2020) are summarised in Table 8 below.

Adverse events (AEs) for which tebentafusp causality could not be excluded led to permanent discontinuation in 3.3% of patients. These were events of anaphylactic reaction, brain oedema, cytokine release syndrome, fatigue, hepatotoxicity, hypotension, and nausea (one patient each).

Adverse events leading to dose interruption occurred in 25% of tebentafusp treated patients. Most commonly (≥ 2% of patients) these were fatigue (3.7%), lipase increased (2.9%), pyrexia (2.4%), alanine aminotransferase increase (2%) or aspartate aminotransferase increase (2%).

Adverse events leading to dose reduction occurred in 5% of patients who received tebentafusp. Most commonly (≥ 2% of patients) these were cytokine release syndrome (2.4%) or rashes (2%).

Table 8: Study 202 Dose modifications and permanent discontinuations according to the clinical study report (safety analysis population; data cut-off date: 13 October 2020)

		Tebentafusp (n = 245)	Investigator's choice of treatment arm* (n = 111)
Dose modifications			
Patients with least one dose interruption, n (%)		104 (42)	15 (14)
Reason for interruption, n	'Missed visit,' 'delayed administration' or 'scheduled visit not done'	135 (61% of interruptions)	3 (20% of interruptions)
	'Adverse event'	50 (23% of interruptions)	12 (80% of interruptions)
	'Other,' 'unknown' or 'missing'	37 (17% of interruptions)	0
Patients with at least one dose reduction, n (%)		18 (7)	2 (2)
More than one dose reduction required, n (%)		2 (0.8)	1 (0.9)
Reason for dose reduction, n	Adverse event	85% of reductions	100% of reductions
	Other	15% of reductions	0
Patients who permanently discontinued treatment, n (%)		172 (70)	100 (90)
Reason for discontinuation, n (%)	Adverse event	6 (2.4)	5 (4.5)
	Disease progression	154 (63)	78 (70)

Abbreviation: n = number of subjects in group.

a Investigator's choice of treatment = pembrolizumab, ipilimumab, or dacarbazine.

Common and high-grade adverse events

The FDA label approved at the time of this submission contains the following description of common AEs and laboratory abnormalities with tebentafusp in Study 202:

> 'The most common adverse events (≥ 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. Clinically relevant adverse reactions occurring in < 20% of patients who received Kimmtrak included back pain, decreased appetite, constipation, hypertension, tachycardia or sinus tachycardia, dyspnea, paresthesia, dizziness, flushing, muscle spasms, myalgia, pain in extremity, alopecia, skin hyperpigmentation, influenza-like illness, oropharyngeal pain and night sweats.

The most common (≥ 50%) laboratory abnormalities in patient who received Kimmtrak were decreased lymphocyte count, increased creatinine, increased glucose, increased AST, increased ALT, decreased hemoglobin, and decreased phosphate.'

An overview of the most common treatment-emergent adverse events (TEAEs) and Grade 3 to 4 TEAEs in Study 202 is provided in Table 9 below, using clinically rational groupings of Medical Dictionary for Regulatory Activities (MedDRA)[68] Preferred Terms defined as Grouped Terms in the TGA's clinical evaluation. While laboratory abnormalities were common in patients who received tebentafusp, most of these were Grade 1 or 2, and many were abnormalities associated with CRS.

Table 9: Study 202 The most common treatment-emergent adverse events (safety population; data cut-off date: 13 October 2020)

		Tebentafusp arm (n = 245)		Investigator's choice of treatment arm* (n = 111)	
CTCAE Grade;[69]		**All grades (%)**	**Grade ¾ (%)**	**All grades (%)**	**Grade ¾ (%)**
Patients with at least one TEAE, %		100	54	95	*34*
Most common TEAEs (any grade incidence ≥ 15% in the tebentafusp arm), %	Pyrexia (GT)[2]	78	4	7	0.9
	Fatigue (GT)	64	6	42	0.9
	Chills	48	0.4	4	0
	Oedema (GT)	40	0	7	0
	Rash (GT)	82	18	28	0
	Pruritus	69	4	23	0
	Dry skin	31	0	4	0
	Erythema	24	0	1	0
	Hair colour changes	20	0.4	0	0
	Vitiligo	16	0	4	0
	Nausea	49	2	26	0.9

[68] The **Medical Dictionary for Regulatory Activities (MedDRA)** is a single standardised international medical terminology, developed as a project of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) which can be used for regulatory communication and evaluation of data pertaining to medicinal products for human use. As a result, MedDRA is designed for use in the registration, documentation and safety monitoring of medicinal products through all phases of the development cycle (that is, from clinical trials to post-marketing surveillance). Furthermore, MedDRA supports ICH electronic communication within the ICH's Electronic Common Technical Document (eCTD) and the E2B Individual Case Safety Report.

[69] United States National Cancer Institute (NIH). Common Terminology Criteria for Adverse Events, Version 4.03. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_v40.

		Tebentafusp arm (n = 245)		Investigator's choice of treatment arm* (n = 111)	
	Abdominal pain (GT)	42	3	32	4
	Vomiting (GT)	30	1	9	0
	Diarrhoea (GT)	25	1	20	5
	Constipation	18	0	12	0
	Hypotension (GT)	40	4	3	0
	Hypertension (GT)	16	9	7	3
	Headache (GT)	32	0.4	10	0.9
	Musculoskeletal pain (GT)	43	1	31	0.9
	Decreased appetite	18	0.8	14	0
	Cough (GT)	19	0.4	11	0.9
	Cytokine release syndrome[3]	21	0.8	0	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events Version 4.03; GT = Grouped Medical Dictionary for Regulatory Activities (MedDRA) Terms; n = number of subjects in group; TEAE = treatment-emergent adverse event.

Grey shading proportionally indicates the most common Grade 3 to 4 TEAEs, in the tebentafusp arm only (darker shade = higher frequency).

Percentages below one are given to one decimal place.

* Investigator's choice of treatment = pembrolizumab, ipilimumab, or dacarbazine.

1 Does not include investigator reported laboratory abnormalities

2 Grouped MedDRA Preferred Terms

3 Based on investigator assessment using Lee et al. (2014) criteria,[59] see Section Cytokine release syndrome

Serious adverse events

A serious adverse events (SAE) was defined in the protocol as being any adverse event that:

- is fatal or life-threatening
- results in persistent or significant disability or incapacity
- constitutes a congenital anomaly or birth defect
- is medically significant, defined as an event that jeopardises the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- requires inpatient hospitalisation or prolongation of existing hospitalisation, unless hospitalisation is for:

  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- death due to progressive disease of malignancy should not be reported as an SAE, if documented by use of appropriate method (for example, as per RECIST version 1.1). Any AE that occurred as a result of the progressive disease should be reported in the appropriate manner.

The most common SAEs that occurred in Study 202 (see Table 10 below) were CRS (or events consistent with its clinical presentation: pyrexia and hypotension) and skin disorders. Other SAEs of clinical note included hepatotoxicity (2 patients) and tumour lysis syndrome (one patient).

In the broader integrated safety pool, multiple organ dysfunction syndrome was reported for two patients (0.4%). No narrative was available for one event that occurred in a 78-year-old male. The other occurred in a 53-year-old female: following her first and only dose of study drug she experienced CRS with Grade 4 hypotension that required aggressive resuscitation, was intubated and admitted to the intensive care unit. Eventually, after extubation, she was transitioned to haemodialysis. The event of multi-organ failure remained unresolved at the time that she died due to progression of uveal melanoma, 27 days after receiving tebentafusp.

Table 10: Study 202 Serious adverse events that occurred in at least 2% of tebentafusp treated patients (safety population; data cut-off date:13 October 2020)

		Tebentafusp arm (n = 245)	Investigator's choice of treatment arm* (n = 111)
Patients with at least one serious TEAE (SAE), %		28	23
SAEs that occurred in at least 2% of patients in the tebentafusp arm, %	Cytokine release syndrome	10	0
	Rash (GT)	4.5	0
	Pyrexia (GT)	2.4	1.8
	Hypotension (GT)	2.0	0

Abbreviations: GT = Grouped Medical Dictionary for Regulatory Activities (MedDRA) Terms; n = number of subjects in group; SAE = serious adverse events; TEAE = treatment-emergent adverse event.

Percentages below 5 are given to one decimal place.

* Investigator's choice of treatment = pembrolizumab, ipilimumab, or dacarbazine.

1 Does not include investigator reported laboratory abnormalities

2 Grouped MedDRA Preferred Terms

Adverse events of special interest

Cytokine release syndrome

Cytokine release syndrome (CRS) was considered an adverse event of special interest (AESI) for Study 202 based on prior clinical experience and mechanism of action and is the most important adverse reaction associated with tebentafusp use.

Cytokine release syndrome (CRS) is an expected class effect for biological products that engage T-cells. Drug-induced CRS is a clinical diagnosis based on fever ≥ 38°C with or without hypotension and/or hypoxia with a temporal relationship to treatment with a drug mechanistically known to provoke production of proinflammatory cytokines.[70] It can start within minutes or hours of the first dose and up to 14 days after infusion, depending on the specific drug product. Constitutional symptoms (headache, fatigue, arthralgias, myalgias, nausea or rash) are common but not required for diagnosis of CRS. Severe cases may include respiratory failure, hypotension requiring vasopressors, cardiac dysfunction, renal failure, elevated transaminases, and disseminated intravascular coagulation. CRS may result in fatal multiple system organ dysfunction. Laboratory findings can include cytopaenias, elevated creatinine and liver enzymes, abnormal coagulation parameters, and elevated C-reactive protein and ferritin. Laboratory abnormalities can be highly variable and nonspecific and may lag after clinical changes. A diagnosis of CRS does not rely on laboratory findings.

There are multiple grading systems for CRS in use. Initially, in Study 102 and Study 202, reporting of CRS was based on National Cancer Institute Common Terminology Criteria;[71] for Adverse Event version 4.03 criteria. In October 2017, the Lee et al (2014) CRS grading criteria was incorporated into both studies and used by investigators in reporting CRS as an AE.[59] To support a more complete analysis of CRS associated with tebentafusp, the sponsor performed a retrospective analysis of CRS in Study 202 based on AEs, concomitant medication and vital signs data, using the newer American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system published in Lee et al (2019).[72] Cases were adjudicated by a panel of oncologists.

The actual rate of CRS in Study 202 is unknown. The rate of CRS (all grades) reported by investigators as AEs in tebentafusp treated patients (21%) likely underestimates the true rate, while the retrospective analysis using ASTCT criteria, which found a rate of 89%, likely overestimates the frequency.

The regulatory clinical evaluation considered that the true frequency may be closer to 77%; this estimate was reached by only including events of Grade 2 or higher according to the retrospective ASTCT based analysis.

Transient changes in vital signs associated with CRS were frequently observed in patients receiving tebentafusp, however, analysis of vital signs did not identify changes in weight, pulse, or respiratory rate that persisted beyond resolution of CRS.

The main medical interventions used for CRS are oxygen, intravenous fluids, steroids, and vasopressor(s). The percentages of patients requiring these interventions for CRS in Study 202 were 8%, 40%, 24% and 1%, respectively.

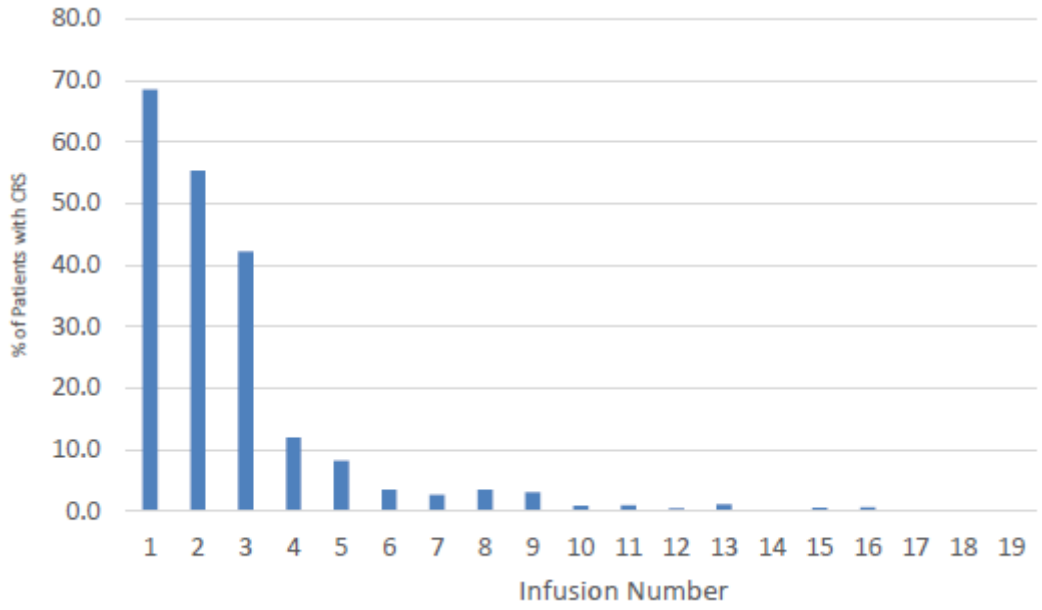
In Study 202, Grade ≥ 2 CRS (ASTCT criteria) was highest during the first 3 infusions with the frequency dropping to around 10% after infusion 3 (Cycle 1 Day 15) (see Figure 5

[70] Shimabukuro-Vornhagen, A. et al., Cytokine Release Syndrome, *J Immunother Cancer*, 2018; 6: 56.
[71] **Common Terminology Criteria (CTC)** is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.
[72] Lee, D.W. et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells, *Biol Blood Marrow Transplant*, 2019; 25: 25-38.

below). Considering only Grade ≥ 2 events, the median number of CRS events for an individual patient was 2 with a range of 1 to 12 events.

Grade 3 or higher events were rare. Four Grade 3 events were identified in Study 202. A single Grade 4 event of CRS occurred across Studies 102 and 202, and as described earlier (under Section: *Serious adverse events*), led to multi-organ failure, which was unresolved at time the patient died due to progression of melanoma. Whilst this is rare, it indicates the potential severity and sequelae of CRS.

Figure 5: Study 202 Percentage of tebentafusp treated patients with events of Grade 2 or higher cytokine release syndrome by infusion number (safety analysis population)



Abbreviation: CRS = cytokine release syndrome.

Skin toxicity

Acute skin reactions have been reported with tebentafusp infusion, likely related to its mechanism of action and gp100 expression in normal melanocytes in the skin. Acute skin reactions associated with tebentafusp include the subcategories of rash, pruritis, pigment change, erythema, oedema, and dry skin. Although common, skin toxicity did not result in treatment discontinuation or fatalities. While 3 patients (1.2%) had TEAEs of erythema multiforme, two were Grade 1 and one was Grade 2. There were no cases of Stevens-Johnson syndrome or drug rash with eosinophilia and systemic symptoms.

In Study 202, rash was seen in around 80% of tebentafusp treated patients, and around 30% of the investigator's choice of treatment arm. Rash was considered an SAE in around 5% of tebentafusp treated patients and was the most common Grade 3 AE in tebentafusp treated patients (18%). However, there were no Grade 4 or higher events. There were no Grade ≥ 3 rashes in the investigator's choice of treatment arm.

Rash led to tebentafusp dose interruption for 4 patients (1.6%) but did not lead to study discontinuation patient discontinued study treatment due to rash.

Hypopigmentation or hyperpigmentation was reclassified by the regulatory safety evaluation as follows:

- Skin hypopigmentation

  - Included skin depigmentation, skin hypopigmentation, vitiligo, and pigmentation disorder (for the latter, each case was determined to be hypo or hyper based on actual term reported by the investigator).
  - Skin hypopigmentation occurred in 28% of tebentafusp treated patients and 5% of the investigator's choice of treatment arm in Study 202.
- Skin hyperpigmentation
  - Included ephelides, lentigo, skin hyperpigmentation, solar lentigo, and pigmentation disorder (as above, each case of pigmentation disorder was determined to be hypo- or hyper- based on actual term reported by the investigator).
  - Skin hypopigmentation occurred in 12% of tebentafusp treated patients and 2% of the investigator's choice of treatment arm in Study 202.
- Hair colour changes
  - Included eyelash discolouration and hair colour change.
  - Skin hypopigmentation occurred in 20% of tebentafusp treated patients and zero patients in the investigator's choice of treatment arm in Study 202.

Skin toxicity warrants specific mention in the PI under Warnings and precautions, based on frequency. To provide more meaningful information to clinicians and patients, the grouped terms skin hypopigmentation, skin hyperpigmentation and hair colour changes should be incorporated into the adverse effects section of the Australian PI rather than hypopigmentation or hyperpigmentation.

Hepatotoxicity

Elevation of serum hepatic enzyme levels are not uncommon in metastatic uveal melanoma since the liver is the predominant site of metastasis and tumour progression within the liver can result in liver injury. Hepatocytes do not express gp100, and tebentafusp did not redirect T-cells against normal hepatocytes *in vitro*. However, treatment with tebentafusp may result in hepatocyte injury secondary to tebentafusp-induced inflammation in metastatic uveal melanoma liver lesions.

The great majority (> 95%) of patients in Study 202 had baseline liver metastases.

Drug-related hepatic disorders (Standardised MedDRA Query,[73] broad and narrow) were reported in 40% of tebentafusp treated patients and 29% of patients in the investigator's choice of treatment arm in Study 202. Grade 3 events occurred in 11% and 6%, respectively, and a single Grade 4 event occurred in the tebentafusp arm. In the tebentafusp arm, drug-related hepatic disorders were serious for 11 patients (4.4%), led to withholding of study drug for 13 patients (5%), and led to permanent discontinuation of study treatment for one patient (0.4%).

Worsening laboratory assessments from Baseline for markers of liver function were common in patients receiving tebentafusp, with about half experiencing worsening of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT). This may have been due to CRS or underlying liver metastases. Overall, however, the abnormalities were mild (Grade 3 AST or ALT increases occurred in 12% and 8% of patients, respectively, and Grade 4 AST or ALT increases occurred in 0.4% and 0.8% of patients, respectively) and did not require discontinuation of study treatment.

[73] **Standardised MedDRA Queries (SMQs)** are groupings of terms from one or more MedDRA System Organ Classes (SOCs) that relate to a defined medical condition or area of interest. They are intended to aid in case identification.

Liver enzyme elevation warrants specific mention in the PI under Warnings and precautions, based on frequency, and due to the potential for serious outcomes.

Eye disorders

Patients with uveal melanoma are likely to have baseline recurrent or persistent local ocular events relating to their primary treatment (for example., enucleation, complication of radiotherapy, intravitreal anti-vascular endothelial growth factor therapy). In addition, eye disorders were initially identified as a potential risk with tebentafusp since gp100-positive intra-ocular melanocytes could serve as a target for tebentafusp which in theory may lead to uveitis or vision changes.

Detailed baseline and on-study ophthalmologic exams were incorporated into the Phase I Study 01 (n = 84). No concerning intra-ocular findings or overt vision changes were identified. A number of low grade (Grade 1 or 2) extra-ocular AEs were reported, including periorbital oedema (49%), eye pain (4%), and eye pruritus (4%).

In Study 202, 32% of patients in the tebentafusp arm and 14% of patients in the investigator's choice of treatment arm had events in the MedDRA System Organ Class (SOC) of eye disorders. The most common events (≥ 3% incidence in either arm) were periorbital oedema (11% with tebentafusp versus 1% with investigator's choice of treatment) and lacrimation increased (3% versus 2%, respectively).

There were a total of 5 higher grade (≥ 3) events reported in Study 202: cataract, eye pain, and glaucoma (one patient each) were reported in the tebentafusp arm (1.2% total) and retinal detachment and uveitis (one patient each) were reported in the investigator's choice of treatment arm (1.8% total).

Serious eye disorders were reported in 2 patients (0.8%) in the tebentafusp arm (diplopia and periorbital oedema) and one patient (0.9%) in the investigator's choice of treatment arm who received pembrolizumab (uveitis). Review of case narratives indicates the event of diplopia was associated with dizziness, elevated transaminases, hyperbilirubinaemia, and a computerized tomography scan the following day that indicated disease progression, with target lesions in the liver having more than doubled in size. A true ophthalmological drug effect is considered very unlikely.

The periorbital AEs are consistent with tebentafusp redirecting T-cells to gp100-positive melanocytes in the skin, do not impact vision, are reversible and have been observed in tebentafusp treated patients in all studies.

No specific Australian PI text (outside the usual 'Adverse Events' listings) is warranted for eye disorders.

Neurotoxicity

Neurotoxicity, including potentially life-threatening or fatal events, is an identified complication associated with T-cell engager therapies, including anti-CD19 CAR-T-cells and bi-specific T-cell engagers.[74] Although neurotoxicity was not considered an AESI for Study 202 based on prior clinical experience, the regulatory safety review included a separate assessment of the risks of neurotoxicity for Study 202, based on tebentafusp mechanism of action.

Neurotoxicities were assessed using all Preferred Terms in the SOC nervous system disorders, with the exclusion of terms clearly related to structural pathology, for example, carpal tunnel syndrome, cerebral cyst, cerebrospinal fluid circulation disorder, intracranial aneurysm, intracranial mass, perineurial cyst, sciatica, and spinal cord compression.

[74] Zheng, P.P. et al. Elusive Neurotoxicity in T Cell-Boosting Anticancer Therapies, *Trends Immunol*, 2019: 274-278.

Events fitting this category occurred in 51% of tebentafusp treated patients and 24% of the investigator's choice of treatment arm, were Grade 3 to 4 in 2.4% and 3.6%, and were considered serious in 1.6% and 0.9%, respectively. There were no fatal neurotoxicity TEAEs in the study. The SAEs in the tebentafusp arm were motor dysfunction (due to progressive disease in the spine), dizziness, brain oedema (due to cerebral metastases), and presyncope. The most common event in both arms was headache.

No specific Australian PI text (outside the usual 'Adverse Events' listings) is warranted for events under the category of neurotoxicity.

Infections

Events in the infections and infestations MedDRA SOC were reported in 31% of tebentafusp treated patients and 21% of those who received investigator's choice of treatment. These equate to exposure adjusted incidence rates of 58 and 54 (per 100 patient years), respectively. Within this SOC, events of Grade 3 or higher occurred at incidences of 4% and 2%, respectively, and serious events occurred at 2% incidence in each arm.

Pyrexia occurred in 76% of the tebentafusp arm and 7% of the investigator's choice of treatment arm, however, the differential reporting of this term is very likely to be attributable to CRS, as infections were not notably more frequent or severe in the tebentafusp arm.

Cardiac safety

Electrocardiogram analyses in Study 202 demonstrated no meaningful or persistent QT;[46] prolongation with tebentafusp treatment.

Immunogenicity

Anti-drug antibodies

Treatment-emergent ADAs against tebentafusp were detected in around 30% of tebentafusp treated patients in Study 102 and Study 202, with a median onset time of 6 to 9 weeks:

- The rate of ADA positivity was 29% (n = 63) in Study 202 and 33% (n = 48) in Study 102.
- The median time to onset of ADA positivity was 8 weeks (range: 1 to 30 weeks).
- The ADA-positive rate was 14% (n = 30) at the Week 8 landmark in Study 202.
- The median ADA titre in Study 202 was 8192, and around 13% of patients developed an ADA titre of at least 8192.

Impact of immunogenicity on PK:

- Clearance increases by 33-fold in patients with high titre ADA (defined as above the median of 8192).
- As a consequence, the terminal half-life reduced from 6 to 7 hours to 10 to 14 minutes in this subgroup of patients.

Exploratory exposure response analyses were conducted, using ADA status at the 8-week landmark (that is, the median time to onset) in Study 202:

- Efficacy was compared between patients who were ADA-positive and those who were not. A significant difference couldn't be detected, but the analysis was limited by the number of patients (n = 30) who were ADA-positive at 8 weeks. The overall survival hazard ratio in these subgroups were as follows:
  - ADA-positive subgroup (n = 30): 0.65 (0.36, 1.16)

  - ADA-negative subgroup (n = 178): 0.44 (0.3, 0.64)

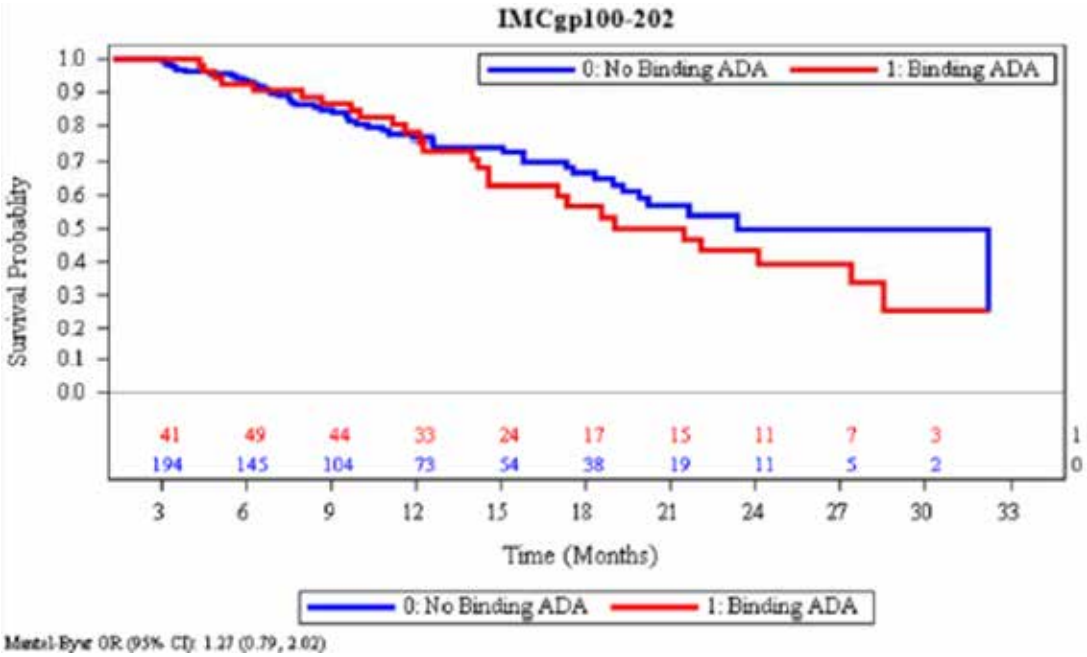
- Efficacy was also compared between patients who had an ADA titre higher than the median (128) at the 8-week landmark and those who did not. Again, a significant difference couldn't be detected but the analysis was limited by the subgroup size (n = 11). Overall survival hazard ratio in these subgroups were as follows:
  - High titre (> 128) subgroup (n = 11): 0.41 (0.15, 1.13)
  - ADA-negative or low titre subgroup (n = 197): 0.48 (0.33, 0.69)

Similarly, a Simon-Makuch estimate of overall survival by ADA status at the landmark time of 3 months did not detect a significant difference (see Figure 6 below).[75]

Exploratory exposure-safety analyses were also conducted on data from studies 102 and 202, considering frequency and grade of hypersensitivity AEs before and after ADA onset, as ADA formation has the potential to induce type I to III hypersensitivity events. No clinically relevant association was identified between hypersensitivity AEs and ADA onset, noting the limitations of analysis and possibility of confounders.

Considering the totality of data, there is insufficient evidence of an association between ADAs and efficacy or safety to warrant ADA monitoring, or dose adjustment for patients who develop ADAs.

Figure 6: Study 202 Simon-Makuch estimate of overall survival by anti-drug antibody status (any binding positivity) at the landmark time of 3 months



Abbreviations: ADA = anti-drug antibody; CI = confidence interval; OR = overall survival.

[75] Simon, R.M. and Makuch, R.W. A Non-parametric Graphical Representation of the Relationship between Survival and the Occurrence of an Event: Application to Responder versus Non-responder bias, *Stat Med*, 1984; 3(1), 35-44.

Neutralising anti-drug antibodies

Information regarding the presence and impact of neutralising ADA on PK, safety and efficacy was not included in the submission reviewed under Project Orbis and was the subject of an FDA post-marketing commitment.[76]

The report was submitted to the TGA in March 2022 at the Delegate's request, as it became available towards the end of the TGA regulatory process. The sponsor's analyses were not repeated by the TGA, and formal PK modelling was not provided.

The report states that of the patients who were ADA-positive, 60% of those in Study 102 and 65% of those in Study 202 also had neutralising antibodies (NAbs). In total, NAbs against tebentafusp were detected in around 19% and 15% of tebentafusp treated patients in Study 102 and Study 202, respectively, with a median onset time of 12 to 16 weeks.

The report states that tebentafusp exposure was persistently reduced after NAb onset in 67% (Study 102) and 79% (Study 202) of NAb-positive patients.

An assessment is provided of hypersensitivity AEs before and after the onset of NAbs. There were no reported hypersensitivity events after NAb onset in Study 202, and one hypersensitivity event (allergic rhinitis; Grade 2) after NAb onset for a patient in Study 102 who had the same grade of allergic rhinitis before NAb onset.

The sponsor provides exploratory analyses of overall survival comparing NAb-positive versus NAb-negative patients, and comparing patients with NAb titre above versus below the median, per study (100 in Study 102 and 2560 in Study 202). These do not indicate a difference in overall survival based on NAb status in either study (Mantel-Byar odds ratio (95% CI), Study 102: 0.88 (0.47, 1.66); Study 202: 1.05 (0.57, 1.91)).[77] However, these analyses are limited by the small numbers of patients with titres above median (n = 9 in Study 102, n = 6 in Study 202).

Companion diagnostic considerations

A clinical trial assay was used to select patients with HLA-A*02:01 for eligibility for the pivotal trial. A post-marketing commitment regarding a companion diagnostic is in place between the USA sponsor and the FDA. Submission of the final report to the FDA is anticipated in June 2022.

Risk management plan

The sponsor has submitted European Union (EU)-risk management plan (RMP) version 0.1 (9 July 2021; data lock point (DLP) 13 October 2020) and Australia specific annex (ASA) version 0.1 (13 September 2021) in support of this application. In response to the rolling questions sent on 3 February 2022, the sponsor has provided EU-RMP version 0.3 (28 January 2022, DLP 13 October 2020) and ASA version 0.2 (15 February 2022).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 11. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

[76] European Medicines Agency (EMA) Kimmtrak (Tebentafusp) An Overview of Kimmtrak and Why It is Authorised in the EU, EMEA/H/C/004929, EMA/128686/2022. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/kimmtrak.
[77] Mantel, N. and Byar, D.P. Evaluation of Response-Time Data Involving Transient States: an Illustration Using Heart-Transplant Data, *J Am Stat Assoc*, 1974; 69(345): 81-86.

Table 11: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Cytokine release syndrome	ü*	ü^	ü	ü#¶
	Acute skin reactions	ü*	–	ü	ü#
Important potential risks	None	–	–	–	–
Missing information	Use in pregnancy and lactation	ü†	–	ü	–
	Use in patients with clinically significant cardiac disease	ü	–	ü	–

* Specific follow-up forms (Australia specific annex only)

† Specific follow-up form for pregnancy only (Australia specific annex only)

Dear Healthcare Professional Letter and Pharmacist Guide (Australia specific annex only)

¶ Treatment Guide for Healthcare Professionals and Patient Guide (European Union only)

^ Physician survey to assess effectiveness of educational materials for cytokine release syndrome (European Union only)

- The summary of safety concerns is acceptable.
- Only routine pharmacovigilance activities have been proposed which include specific follow-up forms for cytokine release syndrome, acute skin reactions and use in pregnancy in Australia. This is acceptable.
- The sponsor has proposed routine risk minimisation activities for all safety concerns as well as a Dear Healthcare Professional Letter and Pharmacist Guide as additional risk minimisation activities to address the important identified risks. This is acceptable.

Risk-benefit analysis

Delegate's considerations

Uveal melanoma is a serious and life-threatening condition. Metastatic uveal melanoma carries a poor prognosis with median survival of 13 months. Uveal melanoma demonstrates different genetics, pathology and clinical behaviour to cutaneous melanoma and shows poor susceptibility to systemic treatments that are effective against the latter.

There are no therapies that are registered in Australia specifically for uveal melanoma.

Tebentafusp is a bispecific protein that binds to a gp100 peptide presented by human leukocyte antigen (HLA)-A*02:01 on the cell surface of uveal melanoma tumour cells, and also binds to CD3+ on T-cells, redirecting them to attack gp100-expressing cells.

Study 202 is an ongoing, open label, randomised, multi-centre study in 378 adult HLA-A*02:01-positive patients with unresectable or metastatic uveal melanoma, who had not received prior systemic therapy in the metastatic setting or regional liver directed therapy. Patients were randomised 2:1 to receive tebentafusp or investigator's choice of

therapy (dacarbazine, ipilimumab, or pembrolizumab) until radiographic progression (for a maximum of four doses if receiving ipilimumab), unacceptable toxicity, investigator decision, or patient withdrawal of consent.

Study 202 demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint (overall survival in patients treated with tebentafusp compared to investigator's choice of treatment (hazard ratio of 0.51 (95% CI: 0.37, 0.71), $p < 0.0001$). The difference in median overall survival between arms was 5.7 months.

The safety profile of tebentafusp for the treatment of HLA-A*02:01-positive metastatic or unresectable uveal melanoma appears acceptable for a therapy used for the treatment of a serious and life-threatening disease. The most important adverse effect caused by tebentafusp is cytokine release syndrome (CRS), which was associated with two cases of multi-organ failure in the clinical development program. The first three doses of tebentafusp carry the greatest risk of CRS, and must be given in an appropriate setting. A black box warning is required in the Australian PI to highlight this potentially fatal reaction. A communication plan should also be in place to educate Australian clinicians who will prescribe tebentafusp regarding the risk of CRS.

Tebentafusp also commonly causes skin toxicity and hepatic enzyme elevation, but such reactions are generally low grade. Immunogenicity appears to occur in around 30% of patients, but does not appear to affect safety or efficacy, based on the available evidence.

Proposed action

Overall, tebentafusp has demonstrated a survival advantage and an acceptable toxicity profile for patients with a dire prognosis who have no other registered treatment option. The benefit-risk balance of tebentafusp for the proposed usage, taking into account the uncertainties, is positive.

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Kimmtrak (tebentafusp) 0.1 mg/0.5 mL, concentrated solution for infusion, vial, indicated for:

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

Specific conditions of registration applying to these goods

- Kimmtrak (tebentafusp) is to be included in the Black Triangle Scheme. The PI and CMI for Kimmtrak must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Kimmtrak EU-risk management plan (RMP) (version 0.3, dated 28 January 2022, data lock point 13 October 2020), with Australian specific annex (version 0.2, dated 15 February 2022), included with Submission PM-2021-04357-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Kimmtrak approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

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