Tebentafusp (uveal melanoma)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Tebentafusp (uveales Melanom)– Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
CAR T-cells	chimeric antigen receptor T-cells
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen protein 4
CRS	cytokine release syndrome
CSR	clinical study report
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HLA	human leukocyte antigen
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PT	Preferred Term
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAP	statistical analysis plan
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
ULN	upper limit of normal
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug tebentafusp. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 4 December 2023.

Research question

The aim of this report was to assess the added benefit of tebentafusp in comparison with treatment of physician's choice as the appropriate comparator therapy (ACT) in HLA (human leukocyte antigen)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of tebentafusp

Therapeutic indication	**ACT**[a]
HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma[b]	Treatment of physician's choice[c], taking into account ▪ dacarbazine ▪ ipilimumab ▪ lomustin ▪ nivolumab ▪ pembrolizumab
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, it is assumed that resection with a curative aim is not indicated for the patients in the present therapeutic indication. c. According to the G-BA, it is assumed that a local or targeted treatment of liver metastases, in particular transarterial chemoembolization (TACE) or transarterial radioembolization (TARE; or selective internal radiotherapy [SIRT]), can be performed in both study arms if indicated in the patients. However, this is not part of the ACT. A single-comparator study is typically insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HLA: human leukocyte antigen	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The IMCgp100-202 study was used for the benefit assessment.

The IMCgp100-202 study is an open-label RCT comparing tebentafusp versus a treatment of physician's choice with a choice of dacarbazine, ipilimumab and pembrolizumab. Adult HLA-A*02:01-positive patients with metastatic uveal melanoma were included in the study. Patients with unresectable, yet non-metastatic uveal melanoma according to the therapeutic indication were not included in the study population. Patients were not allowed to have received any prior systemic therapy in the metastatic or advanced stage. Enrolment was limited to patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1.

A total of 378 patients were randomly assigned in a 2:1 ratio to receive treatment with tebentafusp (N = 252) or treatment of physician's choice (N = 126, including N = 7 dacarbazine, N = 16 ipilimumab and N = 103 pembrolizumab). The randomization was stratified according to the lactate dehydrogenase status (≤ upper limit of normal [ULN] [250 U/L] vs. > ULN [250 U/L]).

Treatment with tebentafusp was largely in compliance with the specifications of the Summary of Product Characteristics (SPC).

Treatment with dacarbazine (7 patients) was carried out contrary to the SPC at a dosage of 1000 mg/m² body surface area (BSA) IV on day 1 of a 3-week cycle. According to the SPC, the dosage for metastatic melanoma for this 3-week therapy regimen is 850 mg/m² BSA. The S3 guideline on the diagnosis, therapy, and follow-up care of melanoma does not mention a dosage recommendation for dacarbazine. However, reference is made to publications in which a dosage of 1000 mg/m² BSA is recommended for dacarbazine monotherapy.

Ipilimumab was administered in accordance with the SPC.

During the course of the study, the dosing options for pembrolizumab were expanded from an initial 2 mg/kg body weight at baseline to a fixed dose of 200 mg (if locally approved). The fixed dose of 200 mg corresponds to the dose for advanced melanoma according to the current SPC. Studies comparing the equivalence of a weight-adapted dosage of 2 mg/kg body weight and a fixed 200 mg dosage are available. It is therefore assumed that the results of a treatment regimen with 2 mg/kg body weight every 3 weeks are transferable to a treatment regimen with a fixed 200 mg dosage every 3 weeks.

Treatment was continued until disease progression, unacceptable toxicity, reaching the maximum duration of therapy (4 cycles with ipilimumab), initiation of a new antineoplastic treatment, withdrawal of consent, or decision of the physician to discontinue therapy.

Patients in the intervention arm and patients in the comparator arm who received pembrolizumab or ipilimumab could continue treatment until further progression under certain conditions according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria after initial progression.

The study's primary outcome was overall survival. Patient-relevant secondary outcomes were those measuring morbidity, health-related quality of life, and adverse events (AEs).

Implementation of the ACT

In the IMCgp100-202 study, the study physicians in comparator arm 3 (dacarbazine, ipilimumab, pembrolizumab) had the options listed by the G-BA in the appropriate comparator therapy at their disposal. The medication used in the comparator arm of the study is considered to be an adequate implementation of the ACT.

Data cut-offs

in the present benefit assessment, the 13 October 2020 data cut-off is primarily used for the outcome of overall survival. On the one hand, this is due to the prespecification and, on the other hand, to the fact that no patients in the comparator arm had yet completed treatment switching by switching to treatment with tebentafusp at this data cut-off date. However, the June 2023 data cut-off is also taken into account due to its longer observation period.

For outcomes related to side effects, the 13 October 2020 data cut-off is used, which occurred before treatment switching was possible.

Risk of bias

The risk of bias across outcomes was rated as low.

The risk of bias of the results for the outcome "overall survival" was rated as low for the 13 October 2020 data cut-off. Up to this data cut-off, there was no switch from the comparator arm to treatment with tebentafusp. After this primary analysis and with amendment of the protocol (Version 6 dated 11 June 2021), switching to treatment with tebentafusp was permitted in the comparator arm. At the June 2023 data cut-off, 24 patients in the comparator arm (19.0%) had received subsequent therapy with tebentafusp. Due to this treatment switching and due to the potential lack of prespecification of the data cut-off, the risk of bias in the results for the outcome "overall survival" for the June 2023 data cut-off is rated as high.

For the outcome "discontinuation due to AEs", the risk of bias due to subjective decision to terminate therapy in the absence of blinding is rated as high. For all other outcomes related to side effects, the risk of bias of results is rated as high in each case due to incomplete

observations for potentially informative reasons, with median observation duration differing between the intervention and control arm.

Results

Based on the available information, at most indications, e.g. of an added benefit, can be derived for the outcome of overall survival, and at most one hint for the other outcomes due to the high risk of bias.

Mortality

Overall survival

For the outcome "overall survival", primarily the results of the first data cut-off from 13 October 2020 are used.

A statistically significant difference in favour of tebentafusp in comparison with treatment of physician's choice was shown for the outcome of overall survival as of the data cut-off date 13 October 2020. There is an indication of added benefit of tebentafusp in comparison with treatment of physician's choice. The statistically significant difference in favour of tebentafusp also remains at the June 2023 data cut-off.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 [EORTC QLQ-C30])

No suitable date were available for the symptoms outcomes, measured with the EORTC QLQ-C30. There is no hint of added benefit of tebentafusp in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health status (EQ-5D visual analogue scale [VAS])

No suitable data are available for the outcome of health status, measured with the EQ-5D VAS. There is no hint of added benefit of tebentafusp in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No suitable data are available for health-related quality of life, measured with the EORTC QLQ-C30. There is no hint of added benefit of tebentafusp in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Side effects

Serious AEs (SAEs) and discontinuations due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from tebentafusp in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Severe AEs

A statistically significant difference to the disadvantage of tebentafusp in comparison with treatment of physician's choice was shown for the outcome of severe AEs. There is a hint of greater harm from tebentafusp in comparison with treatment of physician's choice.

Cytokine release syndrome (CRS)

The data presented by the company for the outcome of CRS are not suitable for the benefit assessment; greater or lesser harm is therefore not proven. However, the events or symptoms underlying the outcome are recorded via the analyses of AEs (overall rates and specific AEs).

Skin reactions

For the outcome of skin reactions (operationalized via the System Organ Class [SOC] "skin and subcutaneous tissue disorders"), a statistically significant difference to the disadvantage of tebentafusp compared to treatment of physician's choice is observed. Due to the size of the effect, which was already evident at an early point in the course of the study, there is a high certainty of results for this outcome despite high risk of bias. There is an indication of greater harm from tebentafusp in comparison with treatment of physician's choice.

Severe skin reactions

For the outcome of severe skin reactions (operationalized by the SOC "skin and subcutaneous tissue disorders", severe AEs), the company did not provide information on hazard ratio (including 95% confidence interval) and p-value. In the present data constellation, with an event rate of 20% (n = 49) in the intervention arm vs. 0% (n = 0) in the comparator arm and with Kaplan-Meier curves clearly separating early in the course of the study, a statistically significant difference to the disadvantage of tebentafusp can be assumed. There is a hint of greater harm from tebentafusp in comparison with treatment of physician's choice.

Immune-mediated AEs

The outcome of immune-mediated AEs was not operationalized in the study, greater or lesser harm is therefore not proven.

Other specific AEs

Gastrointestinal disorders, eye disorders (each SOC, AEs), headaches, paraesthesia (each preferred term [PT], AEs), general disorders and administration site conditions, vascular disorders (each SOC, severe AEs)

For the outcomes “gastrointestinal disorders”, “eye disorders” (each SOC, AEs), “headaches”, “paraesthesia” (each PT, AEs), “general disorders and administration site conditions”, as well as “vascular disorders” (each SOC, severe AEs), a statistically significant difference to the disadvantage of tebentafusp compared to treatment of physician’s choice is evident. In each case, there is a hint of greater harm from tebentafusp in comparison with treatment of physician’s choice.

Respiratory, thoracic and mediastinal disorders (SOC, SAEs)

For the outcome “respiratory, thoracic and mediastinal disorders” (SOC, SAEs), there is a statistically significant difference in favour of tebentafusp in comparison with treatment of physician’s choice. There is a hint of lesser harm from tebentafusp in comparison with treatment of physician’s choice.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug tebentafusp in comparison with the ACT is assessed as follows:

Overall, both positive and negative effects of tebentafusp compared to a treatment according to physician’s choice are observed in HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. Data across the entire observation period are available only for overall survival. All effects of the outcome category of side effects are based exclusively on the shortened observation period.

An indication of a major added benefit was shown for the outcome "overall survival". In addition, on the positive effects side, there is a hint of lesser harm in the outcome of respiratory, thoracic, and mediastinal disorders (SAEs). On the side of the negative effects, in the outcome category of serious/severe adverse events there are hints of greater harm both in the overall rate of severe AEs (extent: "major") and in several specific severe AEs (extent:

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

"considerable" or "major"). In addition, for several specific AEs in the outcome category of non-serious/non-severe side effects, there are several hints or 1 indication of greater harm (extent: "considerable" for each).

There are no suitable data for the outcome categories of morbidity and health-related quality of life.

In summary, considering the positive and negative effects for HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma, there is an indication of considerable added benefit of tebentafusp compared to a treatment according to physician's choice.

Table 3 shows a summary of the probability and extent of added benefit of tebentafusp.

Table 3: Tebentafusp – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma[b]	Treatment of physician's choice[c], taking into account ▪ dacarbazine ▪ ipilimumab ▪ lomustin ▪ nivolumab ▪ pembrolizumab	Indication of considerable added benefit[d]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that resection with a curative aim is not indicated for the patients in the present therapeutic indication.
c. According to the G-BA, it is assumed that a local or targeted treatment of liver metastases, in particular transarterial chemoembolization (TACE) or transarterial radioembolization (TARE; or selective internal radiotherapy [SIRT]), can be performed in both study arms if indicated in the patients. However, this is not part of the ACT. A single-comparator study is typically insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study).
d. In accordance with the inclusion criteria, only patients with an ECOG PS of 0 or 1 were included in the IMCgp100-202 study. Furthermore, only HLA-A*02:01-positive patients with metastatic uveal melanoma were included. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or to HLA-A*02:01-positive patients with unresectable uveal melanoma.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HLA: human leukocyte antigen

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report was to assess the added benefit of tebentafusp in comparison with treatment of physician's choice as the appropriate comparator therapy (ACT) in HLA (human leukocyte antigen)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of tebentafusp

Therapeutic indication	**ACT**[a]
HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma[b]	Treatment of physician's choice[c], taking into account ▪ dacarbazine ▪ ipilimumab ▪ lomustin ▪ nivolumab ▪ pembrolizumab
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, it is assumed that resection with a curative aim is not indicated for the patients in the present therapeutic indication. c. According to the G-BA, it is assumed that a local or targeted treatment of liver metastases, in particular transarterial chemoembolization (TACE) or transarterial radioembolization (TARE; or selective internal radiotherapy [SIRT]), can be performed in both study arms if indicated in the patients. However, this is not part of the ACT. A single-comparator study is typically insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HLA: human leukocyte antigen	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on tebentafusp (status: 25 October 2023)
- bibliographical literature search on tebentafusp (last search on 25 October 2023)
- search in trial registries/trial results databases for studies on tebentafusp (last search on 25 October 2023)
- search on the G-BA website for tebentafusp (last search on 25 October 2023)

To check the completeness of the study pool:

- search in trial registries for studies on tebentafusp (last search on 18 December 2023); for search strategies, see I Appendix A of the full dossier assessment

The check of completeness of the study pool did not identify any additional relevant studies beyond the RCT IMCgp100-202 (see following section).

In the search for further studies, the company identified the single-arm IMCgp100-102 study [3] on tebentafusp in the present therapeutic indication. It states that the results of the study are listed as supporting evidence in the sense of a transparent information base. A completeness check of the search for further studies was waived, as the IMCgp100-202 study is already available as a comparative study for the benefit assessment.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: tebentafusp vs. treatment of physician's choice[a]

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication and other sources[d] (yes/no [citation])
IMCgp100-202	Yes	Yes	No	Yes [4]	Yes [5,6]	Yes [7-9]

a. Dacarbazin, ipilimumab, or pembrolizumab.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
d. Other sources: documents from the search on the G-BA website and other publicly available sources.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The IMCgp100-202 study was used for the benefit assessment. The study pool is consistent with that selected by the company. This study compared tebentafusp with treatment of physician's choice with a choice of dacarbazine, ipilimumab, and pembrolizumab. Consequently, the study lends itself only to drawing conclusions on the added benefit of tebentafusp in patients for whom dacarbazine, ipilimumab, or pembrolizumab represents a suitable treatment of physician's choice.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: tebentafusp versus treatment of physician's choice[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
IMCgp100-202	RCT, open-label, parallel-group	Adult HLA-A*02:01-positive patients with metastatic uveal melanoma ▪ without prior systemic therapy in the metastatic or advanced stage ▪ ECOG PS ≤ 1	Tebentafusp (N = 252) Treatment of physician's choice[c] (N = 126) ▪ dacarbazine (N = 7) ▪ ipilimumab (N = 16) ▪ pembrolizumab (N = 103)	Screening: 21 days Treatment: until disease progression[d], withdrawal of consent, unacceptable toxicity, in the comparator arm: reaching the maximum duration of therapy (4 cycles) (ipilimumab only), initiation of a new antineoplastic treatment, withdrawal of consent, decision of the physician to discontinue therapy Observation[ej]: outcome-specific, at most until death	58 centres in Australia, Belgium, Canada, France, Germany, Italy, , Netherlands, Poland, Russia, Spain, Switzerland, Ukraine, United Kingdom, United States 10/2017–ongoing <u>Data cut-offs:</u> ▪ 13 October 2020[f] (primary analysis for overall survival) ▪ 12 August 2021g (data cut-off requested by the EMA) ▪ 4 April 2022g ▪ June 2023 (final 3-year follow-up observation for overall survival)[h]	Primary: overall survival secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: tebentafusp versus treatment of physician's choice[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]

a. Dacarbazin, ipilimumab, or pembrolizumab.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
c. In the IMCgp100-202 study, the treatment options were dacarbazine, ipilimumab and pembrolizumab to choose from. The treatment options suitable for dossier assessment in terms of ACT are dacarbazine, ipilimumab, lomustine, nivolumab, and pembrolizumab.
d. Patients in the intervention arm and patients in the comparator arm who received pembrolizumab or ipilimumab could continue treatment until further progression according to RECIST 1.1 criteria after initial progression, provided that all of the following criteria were met: i) no signs or symptoms of clinically significant progression, ii) no deterioration of ECOG PS, iii) no imminent threat to vital organs/critical anatomical sites requiring urgent alternative medical intervention or where continuation of study medication would prevent such intervention, and iv) absence of criteria for discontinuation of study medication. In the event of further progression according to defined criteria, treatment had to be permanently discontinued.
e. Outcome-specific information is described in Table 8.
f. Originally planned 1st interim analysis after 150 deaths.
g. Non-prespecified data cut-off.
h. The exact date is not available. According to Hassel 2023 [8], the database lock for this data cut-off was 3 July 2023, after all patients had had the opportunity to be observed for at least 36 months; for further description of the data cut-off, see Section I 3.2 (Data cut-offs).

ACT: appropriate comparator therapy; AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; HLA: human leukocyte antigen; N: Number of randomized patients; RCT: randomized controlled study; RECIST: Response Evaluation Criteria in Solid Tumors

Table 7: Characteristics of the intervention – RCT, direct comparison: tebentafusp versus treatment of physician's choice[a] (multipage table)

Study	Intervention	Comparison
IMCgp100-202	Tebentafusp IV weekly on days 1, 8, and 15 of a 3-week cycle: ▪ cycle 1, day 1: 20 µg ▪ cycle 1, day 8: 30 µg ▪ cycle 1, day 15: 68 µg from cycle 2: 68 µg/day	Treatment of physician's choice[a, b]: ▪ dacarbazin: 1000 mg/m² BSA, IV, on day 1 of a 3-week cycle ▪ or ▪ ipilimumab: 3 mg/kg IV for a maximum of 4 cycles on day 1 of a 3-week cycle ▪ or ▪ pembrolizumab on day 1 of a 3-week cycle ▫ 200 mgc or ▫ 2 mg/kg (up to a maximum of 200 mg)c
	Dose adjustments ▪ Dose reduction from 68 µg to 54 µg or further reduction to 50 µg allowed in case of toxicityd ▪ treatment interruption or discontinuation allowed in case of toxicity	Dose adjustments ▪ no dose reduction allowed ▪ treatment interruption or discontinuation allowed in case of toxicity

Table 7: Characteristics of the intervention – RCT, direct comparison: tebentafusp versus treatment of physician's choice[a] (multipage table)

Study	Intervention	Comparison
	Disallowed pretreatment ▪ systemic therapy in metastatic or advanced stage, including chemotherapy, immunotherapy or targeted therapy ▪ regional therapy targeting the liver, including chemotherapy, radiotherapy or embolization ▪ major surgical procedures, radiotherapye, hematopoietic colony-stimulating growth factors (e.g G-CSF, GM-CSF, M-CSF) within 2 weeks prior to the first dose of the study medication ▪ systemic steroid therapy or other immunosuppressive therapy at the start of the study **Allowed pretreatment** ▪ surgical resection of oligometastatic disease ▪ neoadjuvant or adjuvant therapy in the curative setting for localized disease **Allowed concomitant treatment** ▪ tebentafusp arm premedication includes, among other things, fluid administration, paracetamol, and antihistaminesf ▪ supportive treatment deemed necessary for the patient's treatment and safety (e.g anti-emetics, antidiarrhoeal drugs or electrolyte supplementation ▪ supportive treatment of bone metastases, including bisphosphonates and denosumab ▪ palliative radiotherapy or surgery for pain reduction of tumours ▪ haematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF)g ▪ antihypertensive medicationsh ▪ anticoagulantsi ▪ systemic steroid therapyj ▪ treatment of acute allergic reactions according to guidelines **Disallowed concomitant treatment** ▪ other investigational preparations ▪ other therapies (e.g. chemotherapy) for cancer treatment ▪ monoclonal antibodiesk ▪ immunosuppressive drugs[j]	

Table 7: Characteristics of the intervention – RCT, direct comparison: tebentafusp versus treatment of physician's choice[a] (multipage table)

Study	Intervention	Comparison
a. Dacarbazin, ipilimumab, or pembrolizumab. b. Patients were not allowed to be treated with the same drug that was administered as adjuvant or neoadjuvant treatment. In addition, patients who had received nivolumab as prior adjuvant/neoadjuvant treatment were not allowed to receive pembrolizumab as treatment of physician's choice. c. At the start of the study (October 2017), a dose of 2 mg/kg pembrolizumab was planned. Due to the change in the approval of pembrolizumab to a fixed 200 mg dose (European approval for melanoma in August 2018), as of protocol version 4 dated 20 December 2018, in addition to 2 mg/kg, this fixed dose of 200 mg (if locally approved) was also possible. In addition, the weight-adapted dosage was limited to a maximum of 200 mg. With protocol version 5 of 31 March 2020, the switch from a weight-based to a fixed dose of 200 mg was additionally allowed. For assessment, see body of text below. d. Patients requiring ≥ 2 dose reductions should permanently discontinue therapy; after a dose reduction, the original dose could be increased again if no further toxicity occurred with subsequent doses; 18 patients (7.1%) in the intervention arm reduced their dose. e. With the exception of palliative radiotherapy in a limited area e.g. for the treatment of bone pain or a focally painful tumour mass. f. Fluid intake due to risk of hypotension, antihistamines due to skin toxicity, at least paracetamol and antihistamines due to infusion reactions; in case of insufficient effectiveness, secondary prophylaxis with corticosteroids was permitted. g. Not before cycle 2 in the tebentafusp arm. h. Dose reductions or administration should be considered only 24 hours before or after tebentafusp administration in at least the first 3 weeks. i. As long as patients were already on a stable dose of warfarin or low molecular weight heparin (> 2 weeks before first study medication). j. Only under certain circumstances, e.g. in the treatment of toxicities such as infusion reactions. k. With the exception of denosumab, tocilizumab, and SARS-CoV-2 monoclonal antibodies. BSA: body surface area; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IV: intravenous; M-CSF: macrophage colony-stimulating factor; RCT: randomized controlled trial; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2		

The IMCgp100-202 study is an open-label RCT comparing tebentafusp versus a treatment of physician's choice with a choice of dacarbazine, ipilimumab and pembrolizumab. Adult HLA-A*02:01-positive patients with metastatic uveal melanoma were included in the study. Patients with unresectable, yet non-metastatic uveal melanoma according to the therapeutic indication were not included in the study population. Patients were not allowed to have received any prior systemic therapy in the metastatic or advanced stage. Furthermore, regional therapies targeting the liver, including chemotherapy, radiotherapy, or embolization, were not allowed as pretreatment. However, local procedures for the treatment of liver metastases were not explicitly excluded during the study. Enrolment was limited to patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1.

A total of 378 patients were randomly assigned in a 2:1 ratio to receive treatment with tebentafusp (N = 252) or treatment of physician's choice (N = 126, including N = 7 dacarbazine, N = 16 ipilimumab and N = 103 pembrolizumab). The randomization was

stratified according to the lactate dehydrogenase status (≤ upper limit of normal [ULN] [250 U/L] vs. > ULN [250 U/L]).

Tebentafusp treatment was largely in compliance with the specifications of the SPC [10]. Contrary to the SPC, a dose reduction of tebentafusp from 68 µg to 54 µg or a further reduction to 50 µg in case of toxicity was allowed, with the possibility to increase back to the original dose if no further toxicity occurred with the following doses. Overall, the dose was reduced in only 18 patients in the intervention arm (7.1%). The deviation from the SPC therefore is of no consequence due to the low proportion of patients with a dose reduction.

Treatment with dacarbazine (7 patients) was carried out contrary to the SPC at a dosage of 1000 mg/m² body surface area (BSA) IV on day 1 of a 3-week cycle. According to the SPC, the dosage for metastatic melanoma for this 3-week therapy regimen is 850 mg/m² BSA [11]. The S3 guideline on the diagnosis, therapy, and follow-up care of melanoma [12] does not mention a dosage recommendation for dacarbazine. However, reference is made to publications in which a dosage of 1000 mg/m² BSA is recommended for dacarbazine monotherapy [13-15].

Ipilimumab was administered according to the SPC [16].

During the course of the study, the dosing options for pembrolizumab were expanded from an initial 2 mg/kg body weight at baseline to a fixed dose of 200 mg (if locally approved). The fixed dose of 200 mg corresponds to the dose for advanced melanoma according to the current SPC [17]. Studies comparing the equivalence of a weight-adapted dosage of 2 mg/kg body weight and a fixed 200 mg dosage are available [18,19]. It is therefore assumed that the results of a treatment regimen with 2 mg/kg body weight every 3 weeks are transferable to a treatment regimen with a fixed 200 mg dosage every 3 weeks.

Treatment was continued until disease progression, unacceptable toxicity, reaching the maximum duration of therapy (4 cycles with ipilimumab), initiation of a new antineoplastic treatment, withdrawal of consent, or decision of the physician to discontinue therapy. Patients in the intervention arm and patients in the comparator arm who received pembrolizumab or ipilimumab could continue treatment until further progression under certain conditions (see Table 6) according to RECIST 1.1 criteria after initial progression.

The study materials do not contain any information on restrictions regarding subsequent therapies. In the protocol version 6 from 11 June 2021, switching patients from the comparator arm to treatment with tebentafusp was allowed (see section “Data cut-offs”).

The study’s primary outcome was overall survival. Patient-relevant secondary outcomes were those measuring morbidity, health-related quality of life, and adverse events (AEs).

Implementation of the ACT

The G-BA designates a treatment of physician's choice as ACT, taking into account dacarbazine, ipilimumab, lomustine, nivolumab, and pembrolizumab. Based on the ACT information, the investigators are expected to have a choice between several treatment options (multicomparator study). In the IMCgp100-202 study, the study physicians in comparator arm 3 (dacarbazine, ipilimumab, pembrolizumab) had the options listed by the G-BA in the appropriate comparator therapy at their disposal. The company justified the selection of options in the study by providing one representative from each drug class (programmed cell death 1 [PD-1] inhibitor pembrolizumab, cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] inhibitor ipilimumab and alkylant dacarbazine). It assumed that pembrolizumab and nivolumab (both PD-1 inhibitors) or dacarbazine and lomustine (both alkylating agents) are interchangeable, and therefore only one of these options was included as an option in the comparator arm of the IMCgp100-202 study. There is no German guideline for uveal melanoma. In guidelines of the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), tebentafusp is mentioned as the treatment of choice for HLA-A*02:01-positive adult patients with metastatic uveal melanoma [20,21]. Other preferred treatment options include the combination of ipilimumab and nivolumab as well as monotherapy with pembrolizumab or nivolumab. In addition, therapy with ipilimumab and dacarbazine is listed under certain circumstances [21]. Overall, the medication used in the comparator arm of the study is considered to be an adequate implementation of the ACT.

Data cut-offs

The IMCgp100 study enrolled the first patient in October 2017. In Module 4 A, the company presents results on all outcomes of the outcome categories mortality, morbidity and adverse events for 2 data cut-offs:

Data cut-off 13 October 2020

The data cut-off 13 October 2020 is the predefined data cut-off for the interim analysis at 150 deaths. Since the predefined criteria of the effectiveness hypothesis for the outcome of overall survival had already been met for this data cut-off, this interim analysis was conducted as the primary analysis. The clinical study report (CSR) is available for this data cut-off.

Data cut-off June 2023

The data cut-off of June 2023 is the basis for the publication Hassel 2023 [8]. An exact date is not available, according to Hassel 2023, the database lock was on 3 July 2023. The data cut-off occurred after all female and male patients had had the opportunity to be observed for at least 36 months. The company refers to the data cut-off in the dossier as the "final 3-year follow-up observation" for overall survival. There was no prespecified criterion regarding a minimum 36-month follow-up observation period for conducting a data cut-off. Final analysis was to be prespecified at 250 deaths. The EMA has also recommended the submission of the

final analysis at 250 deaths [22]. As of the data cut-off in June 2023, there have already been 291 deaths. Overall, it can be assumed that the data cut-off is the originally planned final analysis of the study (however, with a deviation from the planned 250 deaths to the current 291 deaths). According to the company, the data will also be submitted to the EMA and a corresponding addendum to the CSR will be prepared.

After primary analysis and with amendment of the protocol (Version 6 dated 11 June 2021), switching from the comparator arm to treatment with tebentafusp was allowed. According to the company, treatment switching occurred in 16 patients in the comparator arm (12.7 %). According to Hassel 2023 [8], at the June 2023 data cut-off, a total of 24 patients in the comparator arm (19.0%) had received subsequent therapy with tebentafusp. in the present benefit assessment, the 13 October 2020 data cut-off is primarily used for the outcome of overall survival. On the one hand, this is due to the prespecification and, on the other hand, to the fact that no patients in the comparator arm had yet completed treatment switching [1] by switching to treatment with tebentafusp at this data cut-off date. However, the June 2023 data cut-off is also taken into account due to its longer observation period. This treatment switching and the possible lack of prespecification are taken into account in the risk of bias for the outcome of overall survival for this data cut-off (see Section I 4.2).

Regardless of the data cut-off, there are no usable data for outcomes on morbidity and health-related quality of life (see Section I 4.1).

For outcomes related to side effects, the 13 October 2020 data cut-off is used, which occurred before treatment switching was possible. This is because according to the study protocol (version 6), AEs were recorded differently in patients undergoing treatment switching compared to patients not undergoing treatment switching. For patients switching to tebentafusp treatment, all AEs should be recorded in the first 2 cycles of this subsequent therapy and from cycle 3 onwards only serious or clinically relevant events should be recorded for unscheduled visits. For all other patients, however, only an unscheduled survey of serious or clinically relevant events was carried out. The impact of the different survey methods on effect estimates after this protocol change is unclear. Irrespective of this, only a few events were added to the June 2023 data cut-off compared to the 13 October 2020 data cut-off (for a comparison of the overall adverse event rates, see Section I 4.3 for the 13 October 2020 data cut-off and I Appendix B of the full dossier assessment for the June 2023 data cut-off).

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: tebentafusp versus treatment of physician's choice[a]

Study outcome category outcome	Planned follow-up observation
IMCgp100-202	
Mortality	
Overall survival	Until death, withdrawal of consent, lost to follow-up, or end of study
Morbidity	
Symptoms (EORTC QLQ-C30[b])	Until treatment discontinuation due to progression or until progression in the context of a progression follow-up phase[c]
Health status (EQ-5D VAS[b])	Until death, withdrawal of consent, lost to follow-up, or end of study
Health-related quality of life	
EORTC-QLQ-C30[b]	Until treatment discontinuation due to progression or until progression in the context of a progression follow-up phase[c]
Side effects	
All outcomes in the side effects category	Until 90 days after the last dose of the study medication or until initiation of a subsequent cancer treatment, whichever occurs first

a. Dacarbazin, ipilimumab, or pembrolizumab.
b. Patients who did not complete a questionnaire at the start of the study should not receive a further questionnaire. After the primary analysis with data cut-off on 13 October 2020, patients in the comparator arm were allowed to switch to treatment with tebentafusp (see Section I 4.2). No further patient-reported outcomes were recorded for these patients after the switch. For all other patients, no further survey of patient-reported outcomes was conducted with protocol version 6 of 11 June 2021.
c. Patients who discontinued their treatment for reasons other than progression, death, lost to follow-up, withdrawal of informed consent or end of study entered a disease progression follow-up period. For these patients, the EORTC QLQ-C30 was followed up until progression.
d. After the primary analysis with data cut-off on 13 October 2020, patients in the comparator arm were allowed to switch to treatment with tebentafusp (see Section I 4.2). According to protocol version 6 of 11 June 2021, all AEs were additionally recorded for these patients in the first 2 cycles of their subsequent tebentafusp therapy (see section on data cut-offs).

AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

The observation times are systematically shortened for all outcomes except the outcome of overall survival and health status recorded via the EQ-5D visual analogue scale (VAS). Side effects were only recorded for the period of treatment with the study medication (plus 90 days or until the start of subsequent therapy). Outcomes on morbidity and health-related quality of life recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) were only recorded until the end of treatment or progression. Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Characteristics of the study population

Table 9 shows the characteristics of the patients in the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: tebentafusp vs. treatment of physician's choice[a] (multipage table)

Study characteristic category	Tebentafusp N = 252	Treatment of physician's choice[a] N = 126
IMCgp100-202		
Age [years], mean (SD)	61 (12)	64 (11)
Sex [F/M], %	49/51	51/49
Family origin, n (%)		
White	222 (88)	107 (85)
Native American or Alaska Native	0 (0)	1 (< 1)
Not reported/unknown	24 (10)[b]	15 (12)[b]
Not allowed according to local regulations[c]	5 (2)	3 (2)
Other	1 (< 1)	0 (0)
ECOG PS, n (%)		
0	192 (76)	85 (68)
1	49 (19)	31 (25)
2	0 (0)	1 (< 1)
Missing	11 (4)	9 (7)
Location of the original uveal melanoma, n (%)		
Iris	3 (1)	5 (4)
Ciliary body	25 (10)	13 (10)
Uvea (choroid)	193 (77)	93 (74)
Unknown/missing	31 (12)[b]	15 (12)[b]
Disease duration [years], median [min; max]	2.9 [0.1; 25.1]	2.4 [0.1; 36.1]
Largest metastatic lesion at baseline, n (%)		
≤ 3 cm	139 (55)	70 (56)
3.1–8.0 cm	92 (37)	46 (37)
≥ 8.1 cm	21 (8)	10 (8)
Stage at initial diagnosis, n (%)		
I	48 (19)	14 (11)
II	89 (35)	40 (32)
III	56 (22)	34 (27)
IV	23 (9)	7 (6)
Missing	36 (14)	31 (25)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: tebentafusp vs. treatment of physician's choice[a] (multipage table)

Study characteristic category	Tebentafusp N = 252	Treatment of physician's choice[a] N = 126
Metastases at initial diagnosis, n (%)		
Yes	17 (7)	10 (8)
No	234 (93)	115 (91)
Missing	1 (< 1)	1 (< 1)
LDH, n (%)		
≤ ULN (250 U/L)	162 (64)	80 (63)
> ULN (250 U/L)	90 (36)	46 (37)
Previous surgery for metastatic disease[d], n (%)	24 (10)	9 (7)
≥ 1 previous systemic cancer medication, n (%)	14 (6)	4 (3)
Treatment discontinuation, n (%)		
As per Data cut-off 13 October 2020	172 (68.3)[e]	100 (79.4)[b, e]
As per Data cut-off June 2023	232 (92.1[b])[f]	111 (88.1[b])[f]
Study discontinuation, n (%)		
As per Data cut-off 13 October 2020	96 (38.1)[g]	69 (54.8)[b, g]
As per Data cut-off June 2023	215 (85.3)[bh]	113 (89.7[b]) [h]

a. Dacarbazin, ipilimumab, or pembrolizumab.
b. Institute's calculation.
c. According to information from the study documents; this category is not specified in more detail.
d. Based on a medical review.
e. The most common reason for treatment discontinuation in the intervention arm vs. control arm was: progression (154 patients vs. 78 patients).
f. The most common reason for treatment discontinuation in the intervention arm vs. control arm was: progression (198 patients vs. 84 patients).
g. The most common reason for study discontinuation in the intervention arm vs. control arm was: death (87 patients vs. 63 patients).
h. The most common reason for study discontinuation in the intervention arm vs. control arm was: death (189 patients vs. 103 patients).

ECOG PS: Eastern Cooperative Oncology Group Performance Status; f: female; LDH: lactate dehydrogenase; m: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; ULN: upper limit of normal

The patient characteristics of the IMCgp100-202 study are balanced between the two treatment groups. The mean age of patients was 61 years in the intervention arm and 64 years in the comparator arm. The majority of patients were white (87%) and the proportion of women and men was balanced. With the exception of 1 patient with an ECOG PS of 2 and 20 patients (5.3%) with unknown status, all patients had an ECOG PS of 0 or 1. The median duration of disease in the intervention arm was slightly longer at 2.9 years (versus 2.4 years in the comparator arm).

At the data cut-off 13 October 2020, the proportion of patients who discontinued treatment was 68% in the intervention arm and 79% in the comparator arm (data cut-off June 2023: 92% vs. 88%). The proportion of patients discontinuing the study was 38% in the intervention arm compared to 55% in the comparator arm (data cut-off June 2023: 85% vs. 90%). The most common reason for study discontinuation was patient death.

Information on the course of the study

Table 10 shows the mean and median treatment durations of the patients and the median observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: tebentafusp versus treatment of physician's choice[a] (multipage table)

Study **duration of the study phase** **data cut-off** **outcome category**	**Tebentafusp** **N = 252**	**Treatment of physician's choice** **N = 126**
IMCgp100-202		
Treatment duration [months][b]		
Data cut-off 13 October 2020		
Median [min; max]	5.4 [0.03; 33.4]	2.1 [0.03; 21.6][c]
Mean (SD)	7.2 (6.3)	3.9 (4.3)[c]
Data cut-off June 2023		
Median [min; max]	5.7 [0.03; 56.4]	2.1 [0.03; 27.6][c]
Mean (SD)	10.7 (11.1)	4.6 (5.8)[c]
Observation period [months]		
Data cut-off 13 October 2020		
Overall survival[d]		
Median [95% CI]	14.1 [12.5; 16.1]	14.3 [10.9; 17.0]
Mean (SD)	ND	ND
Morbidity (EORTC QLQ-C30 and EQ-5D VAS)	ND	ND
Health-related quality of life (EORTC QLQ-C30)	ND	ND
Side effects	ND	ND
Median [min; max]		
Mean (SD)		

Table 10: Information on the course of the study – RCT, direct comparison: tebentafusp versus treatment of physician's choice[a] (multipage table)

Study **duration of the study phase** **data cut-off** **outcome category**	**Tebentafusp** **N = 252**	**Treatment of physician's choice** **N = 126**
Data cut-off June 2023		
Overall survival[d]		
Median [95% CI]	43.3 [40.0; 48.0]	41.7 [36.3; 46.5]
Mean (SD)	ND	ND
Morbidity (EORTC QLQ-C30 and EQ-5D VAS)	ND[e]	ND[e]
Health-related quality of life (EORTC QLQ-C30)	ND[e]	ND[e]
Side effects		
Median [min; max]	N D[f]	ND[f]
Mean (SD)	N D[f]	ND[f]

a. Dacarbazin, ipilimumab, or pembrolizumab.
b. Data are based on 245 vs. 111 patients of the intervention or the control arm.
c. No information is available on treatment durations separately for the drugs dacarbazine, ipilimumab or pembrolizumab.
d. Inverse Kaplan-Meier estimate.
e. The median observation period across both study arms was 33.7 months for EORTC QLQ-C30 and 43.3 months for EQ-5D VAS.
f. There is no data available for the data cut-off 13 October 2020 or for the data cut-off June 2023.

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

At the 13 October 2020 data cut-off, the median treatment duration in the intervention arm was 5.4 months, around 2.6 times longer than in the comparator arm (2.1 months). At the later data cut-off in June 2023, the treatment durations were comparable to those at the data cut-off 13 October 2020. The median observation period for overall survival was around 14 months in both study arms at the data cut-off 13 October 2020 and just over 40 months at the data cut-off in June 2023. For outcomes regarding morbidity, health-related quality of life, and side effects, no information on the observation period is available in the respective study arms. For these outcomes (with the exception of the EQ-5D VAS), the observation period was linked to the end of treatment or disease progression (see Table 8). Therefore, it is safe to assume that, for these outcomes, the observation duration is shortened with respect to overall survival.

Information on subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: tebentafusp versus treatment of physician's choice[a] (multipage table)

Study drug class drug	Patients with subsequent therapy, n (%)	
	tebentafusp N = 252	treatment of physician's choice[a] N = 126
IMCgp100-202, data cut-off 13 October 2020		
Total	ND	ND
Systemic therapy	109 (43.3)	55 (43.7)[b]
Chemotherapy	26 (10.3)	16 (12.7)[b]
Immunotherapy	99 (39.3)	39 (31.0)[b]
Anti-CTLA-4	64 (25.4)	25 (19.8)[b]
Other	7 (2.8)	4 (3.2)[b]
Anti-PD-1	88 (34.9)	29 (23.0)[b]
Anti-PD-1/other	1 (0.4)	0 (0)
Other	0 (0)	0 (0)
Targeted therapy	6 (2.4)	8 (6.3)[b]
Local therapy other than radiotherapy	15 (6.0)	16 (12.7)[b]
Radiotherapy	18 (7.1)	16 (12.7)[b]
Surgery	1 (0.4)	2 (1.6)[b]
Other treatments	2 (0.8)	2 (1.6)[b]
IMCgp100-202, data cut-off June2023		
Total	ND	ND
Systemic therapy	148 (59)	73 (58)
Chemotherapy	44 (18)	18 (14)
Immunotherapy	131 (52)	58 (46)
Anti-CTLA-4 monotherapy	16 (6)	9 (7)
Anti-PD-(L)1 monotherapy	62 (25)	21 (17)
Anti-PD-(L)1 + Anti-CTLA-4	72 (29)	20 (16)
Anti-PD-1/other[c]	1 (0)	2 (2)
Other immunotherapies	16 (6)	25 (20)
Tebentafusp	0 (0)	24 (19)
Other[c]	16 (6)	2 (2)
Targeted therapy	20 (8)	14 (11)
Other systemic therapies	4 (2)	2 (2)
Radiotherapy	35 (14)	23 (18)
Local therapy other than radiotherapy	27 (11)	22 (18)
Surgery	1 (0)	1 (1)
Other treatments	4 (2)	1 (1)

a. Dacarbazin, ipilimumab, or pembrolizumab.
b. Institute's calculation.
c. All other therapeutic products, antineoplastic and immunomodulatory drugs, CAR-T-cells, CDX-1140, antineoplastic study medications, M6223, relatlimab, talimogen laherparepvec, tiragolumab.

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: tebentafusp versus treatment of physician's choice[a] (multipage table)

Study drug class drug	Patients with subsequent therapy, n (%)	
	tebentafusp N = 252	treatment of physician's choice[a] N = 126
CAR: chimeric antigen receptor; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; n: number of patients with subsequent therapy; N: number of evaluated patients; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial		

The company did not provide any information on how many patients in total received subsequent therapy, nor are there any details available separated by drugs, in particular no information on the type of chemotherapy. At the data cut-off 13 October 2020, 43.3% of patients in the intervention arm and 43.7% in the comparator arm received systemic subsequent therapy; by the data cut-off June 2023, the corresponding proportions were 59% and 58%. Among systemic therapies, immunotherapies were the most commonly used subsequent therapies, followed by chemotherapies. In terms of patients who discontinued treatment due to disease progression, the proportions with subsequent therapy were 70.8% vs. 70.5% (data cut-off 13 October 2020) and 74.7% vs. 86.9% (data cut-off June 2023). Overall, the subsequent therapies used in both studies largely correspond to the drug classes mentioned in guidelines [21].

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: tebentafusp vs. treatment of physician's choice[a]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
IMCgp100-202	Yes	Yes	No	No	Yes	No	Low
a. Dacarbazin, ipilimumab, or pembrolizumab. RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low.

Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company states that in addition to Germany, the study was conducted in study centres in the United States, the UK, France, Poland, Canada, Australia, Belgium, Spain, Switzerland, Ukraine, Russia, Italy and the Netherlands. According to the company, there was no evidence of biodynamic or kinetic differences between the individual population groups or regarding Germany to an extent which would significantly impact study results. In addition, the treatments chosen by the investigator would be carried out in accordance with local regulatory information and in line with their use in Germany. Therefore, it could be assumed that the results, taking into account the uncertainty associated with the transferability of clinical data, are in principle transferable to the German health care context. Even the G-BA confirmed this in its benefit assessment of 1 August 2022. Furthermore, there is now sufficient experience with tebentafusp in the German healthcare context, and recommendations from experts in the treatment of uveal melanoma have already been published. Tebentafusp is the preferred treatment for the target population, which would be emphasised by the G-BA's request for a full assessment after exceeding the revenue threshold for an orphan medicinal product of 30 million in accordance with Section 35a SGB V.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Symptoms, recorded with the EORTC QLQ-C30
  - Health status, recorded with the EQ-5D VAS
- Health-related quality of life
  - Recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - Severe AEs (Common-Terminology-Criteria-for-Adverse-Events [CTCAE]-grade ≥ 3)
  - Discontinuation due to AEs
  - Cytokine release syndrome (CRS)
  - Skin reactions and severe skin reactions
  - Immune-mediated AEs
  - Other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 13 shows the outcomes for which data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: tebentafusp vs. treatment of physician's choice[a]

Study	Outcomes											
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Cytokine release syndrome	Skin reactions[c]	Severe skin reactions[b, c]	Immune-mediated AEs	Further specific AEs[d]
IMCgp100-202	Yes	No[e]	No[e]	No[e]	Yes	Yes	Yes	No[f]	Yes	Yes	No[g]	Yes

a. Dacarbazin, ipilimumab, or pembrolizumab.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized via the SOC "skin and subcutaneous tissue disorders"; see body of text below for explanation.
d. The following events are considered (MedDRA-coded): gastrointestinal disorders (SOC, AEs), eye disorders (SOC, AEs), headaches (PT, AEs), paraesthesia (PT, AEs), respiratory, thoracic, and mediastinal disorders (SOC, SAEs), general disorders and administration site conditions (SOC, severe AEs), vascular disorders (SOC, severe AEs).
e. No suitable data available; see body of text below for reasons.
f. The data presented by the company are unsuitable for the benefit assessment, but the events underlying the outcome have been recorded through the analyses of side effects; see body of text below for reasons.
g. Outcome not operationalized.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Patient-reported outcomes recorded using the EORTC QLQ-C30 and EQ-5D VAS

In Module 4 A, the company presented analyses on morbidity and health-related quality of life, recorded with the EORTC QLQ-C30 and the EQ-5D VAS. In the analyses presented by the company, less than 70% of patients are included (with the exception of a poorly described sensitivity analysis on mean differences in EQ-5D VAS) or the difference between treatment arms is > 15 percentage points. The analyses presented by the company are therefore not usable for benefit assessment. In addition, the company did not present complete results for the EORTC QLQ-C30 and, according to its own information, presented the diarrhoea scale as a substitute for the scales on symptoms and the global health status scale for the scales on health-related quality of life. Irrespective of the lack of usability of the results, the incomplete presentation is not appropriate.

Notes on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the company's Module 4 A presents both analyses on all AEs and post hoc analyses excluding disease-related events. The company defines disease-related events as events of the SOC "neoplasms benign, malignant and unspecified (incl. cysts and polyps)". Even if it is unclear whether this approach completely excludes events that can be attributed to the progression of the underlying disease, these analyses are used for benefit assessment.

In the dossier, the company presents frequent AEs that occurred in ≥ 10% of patients in one study arm. This means that results are not available for all AEs according to the module templates (≥ 10 patients in at least 1 study arm). The naive event rates for the missing AEs (n = 39 common Preferred Terms [PT] or system organ classes [SOC], see | Appendix D of the full dossier assessment) were taken from the CSR. Due to the lack of effect estimates and p-values for these AEs, the selection of specific AEs based on the AEs observed in the study is not fully possible (see Section I 5.2).

Cytokine release syndrome (CRS)

In the IMCgp100-202 study, CRS was investigated as an AE of special interest. In the intervention arm, patients had to be hospitalized overnight for at least 16 hours in the first 3 cycles of tebentafusp administration to monitor for signs of CRS; no such monitoring was performed in the comparator arm. Neither the study documents (including the case report form) nor Module 4 A contain any information on how a CRS was defined in the study. Only the classification of the severity of a CRS was defined and adjusted in the course of the study. With protocol version 4 of 20 December 2018, the CRS was subdivided into severity levels in accordance with Lee 2014 [23]. According to the statistical analysis plan (SAP; version 2 of 12 June 2020), the severity classification was adjusted according to the consensus criteria of the American Society for Transplantation and Cellular Therapy (ASTCT) according to Lee 2019 [24]. The severity classification according to Lee 2014 is based on different gradations of i) symptoms of CRS (such as fever, dizziness, and fatigue), ii) hypotension (with or without the need for vasopressors) as well as iii) hypoxia. The severity classification according to Lee 2019, on the other hand, is based solely on the presence of fever ≥ 38°C associated with different degrees of hypotension (with or without the need for vasopressors) and hypoxia.

The data on CRS presented by the company are not suitable for benefit assessment. This is primarily due to the differing CRS recording methods used in the intervention arm (monitoring for CRS) compared to the comparator arm (no monitoring) in an unblinded study design. Furthermore, it is unclear how CRS (regardless of severity) was defined in the IMCgp100-202 study. While the company states that the CRS is based on the criteria of Lee 2014 on the one hand and on a medical assessment using the criteria of Lee 2019 on the other, these publications only define the severity classification of the CRS (see above).

Overall, the analyses submitted by the company for the outcome “CRS” are not suitable for benefit assessment. However, typical symptoms that can occur in connection with a CRS (e.g. fever, hypotension, chills, nausea, vomiting, fatigue, headache) are recorded via the analyses of AEs (overall rates and specific AEs; see results in Section I 4.3 and I Appendix D of the full dossier assessment).

Skin reactions

The company defines the outcome "skin reactions" using a predefined procedure according to the SAP version 2 of 12 June 2020. To record skin reactions, a continuous list of PTs of the SOC “skin and subcutaneous tissue disorders” and other SOCs was developed as part of the tebentafusp study programme with the involvement of study physicians. In Module 4 A of the dossier, the company names the terms that were included in the final list for the IMCgp100-202 study. In addition, it also provides the frequencies of the respective terms that have been included in the analyses of skin reactions.

Defining and refining a list of PTs for the comprehensive recording of skin reactions is useful. Furthermore, it seems reasonable that not only PTs for the SOC “skin and subcutaneous tissue disorders”, but also other SOCs should be included. However, the analyses presented by the company will not be taken into account for the benefit assessment. This is mainly due to the fact that according to the information provided by the company in Module 4 A, important PTs from the SOC “skin and subcutaneous tissue disorders”, which are explicitly named as skin reaction symptoms with tebentafusp in the SPC [10] and are very common in the IMCgp100-202 study, are missing. These include, for example, the PT “pruritus” (69.0% vs. 23.4%) as well as the PT “erythema” (24.5% vs. 0.9%). It is unclear why these PTs are not included in the list. Moreover, it is unclear whether the terms listed in Module 4 A in the final PT collection are exclusively PTs, as some German terms do not correspond to PTs according to MedDRA (Version 23.1).

Due to the existing uncertainties, the outcomes “skin reactions” and “severe skin reactions” will be operationalized via the SOC “skin and subcutaneous tissue disorders” (AEs or severe AEs) – which also includes the above-mentioned missing PTs from the company's analysis. The use of the SOC “skin and subcutaneous tissue disorders” for the outcome “skin reactions” is also justified by the fact that, according to the comparison of the terms from the list used by the company, it can be assumed that only very few PTs from other SOCs can be assigned to skin reactions.

Immune-mediated AEs

A summarized analysis of immune-mediated AEs was not pre-specified in the IMCgp100-202 study according to the study documents. The company also does not operationalize immune-

mediated AEs post hoc for the benefit assessment. Thus, there is no operationalization for the outcome “immune-mediated AEs”.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: tebentafusp vs. treatment of physician’s choice[a]

Study	Study level	Outcomes											
		Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Cytokine release syndrome	Skin reactions[c]	Severe skin reactions[b, c]	Immune-mediated AEs	Further specific AEs[d]
IMCgp100-202	L	L/H[e]	-[f]	-[f]	-[f]	H[g]	H[g]	H[h]	–[i]	H[g, j]	H[g]	-[k]	H[g, j]

a. Dacarbazin, ipilimumab, or pembrolizumab.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized via the SOC "skin and subcutaneous tissue disorders"; see Section I 4.1.
d. The following events are considered (MedDRA-coded): gastrointestinal disorders (SOC, AEs), eye disorders (SOC, AEs), headaches (PT, AEs), paraesthesia (PT, AEs), respiratory, thoracic, and mediastinal disorders (SOC, SAEs), general disorders and administration site conditions (SOC, severe AEs), vascular disorders (SOC, severe AEs).
e. Low risk of bias for data cut-off 13 October 2020: at this data cut-off, no patients switched treatment from the comparator therapy to the intervention. High risk of bias for data cut-off June 2023: at this data cut-off, 19% of patients in the comparator arm received subsequent therapy with tebentafusp (see following body of text). Furthermore, the possible lack of prespecification of the data cut-off contributes to the high risk of bias.
f. No usable data available; see Section I 4.1 for reasons.
g. Incomplete observations for potentially informative reasons with different lengths of follow-up observation in the intervention and comparator arms.
h. Subjective decision to discontinue therapy in the absence of blinding.
i. The data presented by the company are unsuitable for the benefit assessment, but the events underlying the outcome have been recorded through the analyses of side effects; see Section I 4.1 for reasons.
j. Lack of blinding in the presence of subjective recording of outcomes; for other specific AEs, this applies to non-serious/non-severe side effects.
k. Outcome not operationalized.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results for the outcome "overall survival" was rated as low for the 13 October 2020 data cut-off. Up to this data cut-off, there was no switch from the comparator arm to treatment with tebentafusp. After this primary analysis and with amendment of the protocol (Version 6 dated 11 June 2021), switching to treatment with tebentafusp was permitted in the comparator arm. At the June 2023 data cut-off, 24 patients in the comparator arm (19.0%) had received subsequent therapy with tebentafusp [8]. Due to the treatment switching of patients in the comparator arm to a therapy with tebentafusp and the potential lack of prespecification of the data cut-off, the risk of bias in the results for the outcome “overall survival” for the June 2023 data cut-off is rated as high.

There are no suitable data for all outcomes on morbidity and health-related quality of life (see Section I 4.1). The same applies to the outcome “CRS” of the outcome category “side effects” (see Section I 4.1). The outcome “immune-mediated AEs” was not operationalized in the IMCgp100-202 study.

For the outcome “discontinuation due to AEs”, the risk of bias due to subjective decision to terminate therapy in the absence of blinding is rated as high.

For all other outcomes related to side effects, the risk of bias of results is rated as high in each case due to incomplete observations for potentially informative reasons, with median observation duration differing between the intervention arm and the control arm. There are no observation periods for the outcomes regarding side effects, but the duration of observation is linked to the duration of treatment (+90 days, see Table 8). Hence, the different median treatment durations (5.4 months in the intervention arm and 2.1 months in the control arm), also result in different median observation durations. For the specific AE “skin reactions” as well as other specific AEs of the category “non-serious/non-severe side effects”, the lack of blinding – in addition to incomplete observation for potentially informative reasons – is also seen as a distorting aspect.

I 4.3 Results

Table 15 summarizes the results of comparing tebentafusp with a treatment of physician’s choice with a choice of dacarbazine, ipilimumab, and pembrolizumab in HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

Kaplan-Meier curves on the presented time-to-event analyses can be found in I Appendix C of the full dossier assessment. Results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tebentafusp vs. treatment of physician's choice[a] (multipage table)

Study outcome category outcome	Tebentafusp		Treatment of physician's choice[a]		Tebentafusp vs. treatment of physician's choice[a]
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95 %-CI]; p-value[b]
IMCgp100-202					
Mortality					
Overall survival					
Data cut-off 13 October 2020	252	21.7 [18.6; 28.6] 87 (34.5)	126	16.0 [9.7; 18.4] 63 (50.0)	0.51 [0.37; 0.71]; < 0.001
Data cut-off June 2023	252	21.6 [19.0; 24.3] 189 (75.0)	126	16.9 [12.9; 19.5] 103 (81.7)	0.68 (0.54; 0.87); < 0.01
Morbidity					
Symptoms (EORTC QLQ-C30)	No suitable data[c]				
Health status (EQ-5D VAS)	No suitable data[c]				
Health-related quality of life					
EORTC QLQ-C30	No suitable data[c]				
Side effects (data cut-off 13 October 2020)					
AEs (supplementary information)[d]	245	ND 245 (100)	111	ND 105 (94.6)	–
SAEs[d]	245	ND 68 (27.8)	111	ND 24 (21.6)	1.35 [0.84; 2.15]; 0.21
Severe AEs[d, e]	245	ND 132 (53.9)	111	ND 38 (34.2)	2.01 [1.40; 2.88]; < 0.01
Discontinuation due to AEs	245	ND 8 (3.3)	111	ND 7 (6.3)	0.45 [0.16; 1.24]; 0.12
Cytokine release syndrome	No suitable data[f]				
Skin reactions[g]	245	ND 229 (93.5)	111	ND 51 (45.9)	6.26 [4.56; 8.6]; < 0.01
Severe skin reactions[e, g]	245	ND 49 (20.0)	111	ND 0 (0)	ND[h]
Immune-mediated AEs	Outcome not operationalized				
Gastrointestinal disorders (SOC, AEs)	245	ND 194 (79.2)	111	ND 66 (59.5)	1.68 [1.27; 2.23]; < 0.01
Eye disorders (SOC, AEs)	245	ND 79 (32.2)	111	ND 15 (13.5)	2.54 [1.46; 4.41]; < 0.01

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tebentafusp vs. treatment of physician's choice[a] (multipage table)

Study outcome category outcome	Tebentafusp		Treatment of physician's choice[a]		Tebentafusp vs. treatment of physician's choice[a]
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95 %-CI]; p-value[b]
Headache (PT, AEs)	245	ND 75 (30.6)	111	ND 11 (9.9)	3.22 [1.71; 6.06]; < 0.01
Paraesthesia (PT, AEs)	245	ND 27 (11.0)	111	ND 1 (0.9)	12.3 [1.67; 90.53]; 0.01
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	245	ND 4 (1.6)	111	ND 6 (5.4)	0.27 [0.08; 0.96]; 0.04
General disorders and administration site conditions (SOC, severe AEs[e])	245	ND 21 (8.6)	111	ND 2 (1.8)	4.76 [1.12; 20.31]; 0.04
Vascular disorders (SOC, severe AEs[e])	245	ND 28 (11.4)	111	ND 3 (2.7)	3.97 [1.2; 13.08]; 0.02

a. Dacarbazin, ipilimumab, or pembrolizumab.
b. Overall survival: Cox proportional hazards model, p-value from log-rank test, each stratified by LDH status; outcomes of the category "side effects": Cox proportional hazards model, no specification for stratification and calculation of the p-value.
c. See Section I 4.1 for reasons.
d. Without progression events recorded via the SOC "neoplasms benign, malignant and unspecified (incl. cysts and polyps)".
e. Operationalized as CTCAE grade ≥ 3.
f. The data presented by the company are unsuitable for the benefit assessment, but the events underlying the outcome have been recorded through the analyses of side effects; see Section I 4.1 for reasons.
g. Operationalized via the SOC "skin and subcutaneous tissue disorders".
h. The company did not present any information on HR (including 95% CI) and p-value. In the present data constellation, with an event rate of 20% (n = 49) in the intervention arm vs. 0% (n = 0) in the comparator arm and with Kaplan-Meier curves (see Figure 7 of the full dossier assessment) clearly separating early in the course of the study, a statistically significant difference to the disadvantage of tebentafusp can be assumed.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with (at least one) event; LDH: lactate dehydrogenase; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most indications, e.g. of an added benefit, can be derived for the outcome of overall survival, and at most one hint for the other outcomes due

to the high risk of bias. Despite the high risk of bias, the certainty of conclusions for results might not be downgraded for certain outcomes (see description of results below).

Mortality

Overall survival

For the outcome of overall survival, primarily the results of the first data cut-off from 13 October 2020 are used (see sections I 3.2 for data cut-offs and I 4.2 for risk of bias).

A statistically significant difference in favour of tebentafusp in comparison with treatment of physician's choice was shown for the outcome of overall survival as of the data cut-off date 13 October 2020. There is an indication of added benefit of tebentafusp in comparison with treatment of physician's choice. The statistically significant difference in favour of tebentafusp also remains at the June 2023 data cut-off.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30])

No suitable date were available for the symptoms outcomes, measured with the EORTC QLQ-C30 (see Section I 4.1) There is no hint of added benefit of tebentafusp in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No suitable data are available for the outcome of health status, measured with the EQ-5D VAS (see Section I 4.1). There is no hint of added benefit of tebentafusp in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No suitable data are available for health-related quality of life, measured with the EORTC QLQ-C30 (see Section I 4.1). There is no hint of added benefit of tebentafusp in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from tebentafusp in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Severe AEs

A statistically significant difference to the disadvantage of tebentafusp in comparison with treatment of physician's choice was shown for the outcome of severe AEs. There is a hint of greater harm from tebentafusp in comparison with treatment of physician's choice.

CRS

The data presented by the company for the outcome of CRS are not suitable for the benefit assessment (see Section I 4.1); greater or lesser harm is therefore not proven. However, the events or symptoms underlying the outcome are recorded via the analyses of AEs (overall rates and specific AEs) (see Section I 4.1).

Skin reactions

For the outcome of skin reactions (operationalized via the SOC "skin and subcutaneous tissue disorders"), a statistically significant difference to the disadvantage of tebentafusp compared to treatment of physician's choice is observed. Due to the size of the effect, which was already evident at an early point in the course of the study, there is a high certainty of results for this outcome despite high risk of bias (see Figure 6 of the full dossier assessment). There is an indication of greater harm from tebentafusp in comparison with treatment of physician's choice.

Severe skin reactions

For the outcome of severe skin reactions (operationalized by the SOC "skin and subcutaneous tissue disorders", severe AEs), the company did not provide information on hazard ratio (including 95% confidence interval) and p-value. In the present data constellation, with an event rate of 20% (n = 49) in the intervention arm vs. 0% (n = 0) in the comparator arm and with Kaplan-Meier curves (see Figure 7 of the full dossier assessment) clearly separating early in the course of the study, a statistically significant difference to the disadvantage of tebentafusp can be assumed. There is a hint of greater harm from tebentafusp in comparison with treatment of physician's choice.

Immune-mediated AEs

The outcome of immune-mediated AEs was not operationalized in the study, greater or lesser harm is therefore not proven.

Other specific AEs

Gastrointestinal disorders, eye disorders (each SOC, AEs), headaches, paraesthesia (each PT, AEs), general disorders and administration site conditions, vascular disorders (each SOC, severe AEs)

For the outcomes "gastrointestinal disorders", "eye disorders" (each SOC, AEs), "headaches", "paraesthesia" (each PT, AEs), "general disorders and administration site conditions", as well

as “vascular disorders” (each SOC, severe AEs), a statistically significant difference to the disadvantage of tebentafusp compared to treatment of physician’s choice is evident. In each case, there is a hint of greater harm from tebentafusp in comparison with treatment of physician’s choice.

Respiratory, thoracic and mediastinal disorders (SOC, SAEs)

For the outcome “respiratory, thoracic and mediastinal disorders” (SOC, SAEs), there is a statistically significant difference in favour of tebentafusp in comparison with treatment of physician’s choice. There is a hint of lesser harm from tebentafusp in comparison with treatment of physician’s choice.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)
- largest metastatic lesion (3.0 cm vs. 3.1-8.0 cm vs. ≥ 8.1 cm; corresponds to stage M1a vs. M1b vs. M1c of the TNM status according to the American Joint Committee on Cancer [AJCC] [25])

The above subgroup characteristics were defined a priori.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

For the outcome “severe skin reactions”, the company did not present any results of interaction tests. Therefore, no statement on possible effect modifications can be made for this outcome.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [26].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 16).

Table 16: Extent of added benefit at outcome level: tebentafusp vs. treatment of physician's choice[a] (multipage table)

Outcome category **outcome**	**Tebentafusp vs. treatment of physician's choice[a]** **median time to event (months)** **effect estimation [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival (13 October 2020 data cut-off)	21.7 vs. 16.0 HR: 0.51 [0.37; 0.71] p < 0.001 probability: "indication"	Outcome category: mortality CI_o < 0.85 added benefit, extent: "major"
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30)	No suitable data	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No suitable data	Lesser/added benefit not proven

Table 16: Extent of added benefit at outcome level: tebentafusp vs. treatment of physician's choice[a] (multipage table)

Outcome category **outcome**	**Tebentafusp vs. treatment of physician's choice[a]** **median time to event (months)** **effect estimation [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Side effects[d]		
SAEs[e]	ND vs. ND HR: 1.35 [0.84; 2.15] p = 0.21	Greater/lesser harm not proven
Severe AEs[e]	ND vs. ND HR: 2.01 [1.40; 2.88] HR: 0.50 [0.35; 0.71][f] p < 0.01 probability: "hint"	Outcome category: serious/severe side effects CI_o < 0.75; risk ≥ 5% greater harm, extent: "major"
Discontinuation due to AEs	ND vs. ND HR: 0.45 [0.16; 1.24] p = 0.12	Greater/lesser harm not proven
Cytokine release syndrome	No suitable data[g]	Greater/lesser harm not proven
Skin reactions[h]	ND vs. ND HR: 6.26 [4.56; 8.6] HR: 0.16 [0.12; 0.22][f] p < 0.01 probability: "indication"	Outcome category: non-serious/non-severe side effects CI_o < 0.80 greater harm; extent: "considerable"
Severe skin reactions[h]	ND vs. ND (Patients with event: 20% vs. 0%) HR: ND p = ND probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "major"
Immune-mediated AEs	Outcome not operationalized	Greater/lesser harm not proven
Gastrointestinal disorders (AEs)	ND vs. ND HR: 1.68 [1.27; 2.23] HR: 0.60 [0.45; 0.79][f] p < 0.01 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_o < 0.80 greater harm; extent: "considerable"
Eye disorders (AEs)	ND vs. ND HR: 2.54 [1.46; 4.41] HR: 0.39 [0.23; 0.68][f] p < 0.01 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_o < 0.80 greater harm; extent: "considerable"

Table 16: Extent of added benefit at outcome level: tebentafusp vs. treatment of physician's choice[a] (multipage table)

Outcome category **outcome**	**Tebentafusp vs. treatment of physician's choice[a]** **median time to event (months)** **effect estimation [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Headache (AEs)	ND vs. ND HR: 3.22 [1.71; 6.06] HR: 0.31 [0.17; 0.58][f] p < 0.01 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_o < 0.80$ greater harm; extent: "considerable"
Paraesthesia (AEs)	ND vs. ND HR: 12.3 [1.67; 90.53] HR: 0.08 [0.01; 0.60][f] p = 0.01 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_o < 0.80$ greater harm; extent: "considerable"
Respiratory, thoracic and mediastinal disorders (SAEs)	ND vs. ND HR: 0.27 [0.08; 0.96] p = 0.04 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_o < 1.00$ lesser harm, extent: "minor"
General disorders and administration site conditions (severe AEs)	ND vs. ND HR: 4.76 [1.12; 20.31] HR: 0.21 [0.05; 0.89][f] p = 0.04 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_o < 0.90$ greater harm; extent: "considerable"
Vascular disorders (severe AEs)	ND vs. ND HR: 3.97 [1.2; 13.08] HR: 0.25 [0.08; 0.83][f] p = 0.02 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_o < 0.90$ greater harm; extent: "considerable"

Table 16: Extent of added benefit at outcome level: tebentafusp vs. treatment of physician's choice[a] (multipage table)

Outcome category **outcome**	**Tebentafusp vs. treatment of physician's choice[a]** **median time to event (months)** **effect estimation [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
a. Dacarbazin, ipilimumab, or pembrolizumab. b. Probability provided if a statistically significant and relevant effect is present. c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u). d. No information is available on the median time to event. See Appendix C of the full dossier assessment for the respective Kaplan-Meier curves. e. Without progression events recorded via the SOC "neoplasms benign, malignant and unspecified (incl. cysts and polyps)". f. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. g. The data presented by the company are unsuitable for the benefit assessment, but the events underlying the outcome have been recorded through the analyses of side effects; see Section I 4.1 for reasons. h. Operationalized via the SOC "skin and subcutaneous tissue disorders". i. The company did not present any information on HR (including 95% CI) and p-value. In the present data constellation, with an event rate of 20% (n = 49) in the intervention arm vs. 0% (n = 0) in the comparator arm and with Kaplan-Meier curves (see Figure 7 of the full dossier assessment) clearly separating early in the course of the study, a statistically significant difference to the disadvantage of tebentafusp can be assumed. The extent is still assessed as "major". AE: adverse event; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR: hazard ratio; ND: no data; SOC: System Organ Class; SAE: serious adverse event; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of tebentafusp compared with treatment of physician's choice

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: indication of added benefit – extent: "major"	-
Outcomes with shortened observation period	
Serious/severe side effects ▪ respiratory, thoracic and mediastinal disorders (SAEs): hint of lesser harm – extent: "minor"	Serious/severe side effects ▪ severe AEs: hint of greater harm – extent: "major", including ▫ vascular disorders, general disorders and administration site conditions each a hint of greater harm – extent: "considerable" ▫ skin reactions: hint of greater harm – extent: "major"
-	Non-serious/non-severe side effects ▪ skin reaction: indication of greater harm – extent "considerable" ▪ further specific AEs hint of greater harm – extent "considerable": ▫ gastrointestinal disorders (AEs) ▫ eye disorders (AEs) ▫ headache (AEs) ▫ paraesthesia (AEs)
There are no suitable data for the outcome categories of morbidity and health-related quality of life.	
AE: adverse event; SAE: serious adverse event	

Overall, both positive and negative effects of tebentafusp compared to a treatment according to physician's choice are observed in HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. Data across the entire observation period are available only for overall survival. All effects of the outcome category of side effects are based exclusively on the shortened observation period.

An indication of a major added benefit was shown for the outcome "overall survival". In addition, on the positive effects side, there is a hint of lesser harm in the outcome of respiratory, thoracic, and mediastinal disorders (SAEs). On the side of the negative effects, in the outcome category of serious/severe adverse events there are hints of greater harm both in the overall rate of severe AEs (extent: "major") and in several specific severe AEs (extent: "considerable" or "major"). In addition, for several specific AEs in the outcome category of non-serious/non-severe side effects, there are several hints or 1 indication of greater harm (extent: "considerable" for each).

There are no suitable data for the outcome categories of morbidity and health-related quality of life.

Due to the lack of effect estimates and p-values for several frequently occurring AEs, the selection of specific AEs based on frequencies was not fully possible. These AEs all show a numerical disadvantage of tebentafusp. In the present data situation with almost exclusively disadvantages of tebentafusp in terms of side effects and an advantage in overall survival, the absence of effect estimates and thus the lack of selection of potential further specific AEs does not call into question the overall assessment. It can therefore not be assumed that the overall assessment will change as a result of the subsequent submission of this data.

In summary, considering the positive and negative effects for HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma, there is an indication of considerable added benefit of tebentafusp compared to a treatment according to physician's choice.

Table 18 summarizes the result of the assessment of the added benefit of tebentafusp in comparison with the ACT.

Table 18: Tebentafusp – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma[b]	Treatment of physician's choice[c], taking into account ▪ dacarbazine ▪ ipilimumab ▪ lomustin ▪ nivolumab ▪ pembrolizumab	Indication of considerable added benefit[d]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that resection with a curative aim is not indicated for the patients in the present therapeutic indication.
c. According to the G-BA, it is assumed that a local or targeted treatment of liver metastases, in particular transarterial chemoembolization (TACE) or transarterial radioembolization (TARE; or selective internal radiotherapy [SIRT]), can be performed in both study arms if indicated in the patients. However, this is not part of the ACT. A single-comparator study is typically insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study).
d. In accordance with the inclusion criteria, only patients with an ECOG PS of 0 or 1 were included in the IMCgp100-202 study. Furthermore, only HLA-A*02:01-positive patients with metastatic uveal melanoma were included. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or to HLA-A*02:01-positive patients with unresectable uveal melanoma.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HLA: human leukocyte antigen

The assessment described above concurs with that by the company.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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