Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende tebentafusp til behandling af metastatisk uvealt melanom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. tebentafusp
2. Forhandlingsnotat fra Amgros vedr. tebentafusp
3. Ansøgers endelige ansøgning vedr. tebentafusp

Medicinrådets udkast til rapporten for tebentafusp til behandling af metastatisk uvealt melanom

Document number 164311

Dear Danish Medicines Council,

Immunocore would like to thank you for the assessment of KIMMTRAK® (tebentafusp) in the indication of metastatic uveal melanoma, which has been well received.

Based on the assessment report on tebentafusp from DMC, concerns regarding the uncertainties associated with OS extrapolations and MAIC were raised and Immunocore wishes to comment on these concerns of uncertainty.

The extrapolation of OS preferred by the DMC does not capture the survival benefit of tebentafusp. Immunocore submitted the health economic assessment documentation as early as beginning of March 2022, and the submitted cost-effectiveness analysis was based on IMCgp100-202 with a data cut-off (DCO) from October 2020 and a median follow-up time of 14.1 months. However, during the course of assessment of tebentafusp by the DMC, an updated DCO [redacted] of study IMCgp100-202 with a median follow-up time of [redacted] became available [redacted]. Based on the survival data for tebentafusp from the latest DCO, the survival modelling by the DMC significantly underestimates the longer-term survival of tebentafusp. The DMC base case calculates a 5-year OS of [redacted] for tebentafusp which is significantly below the KM estimates from the latest dataset [redacted] Data for [redacted] and be published later this year. Survival data from the 3-year follow-up will address the key uncertainty in modelling survival beyond two years highlighted by the DMC.

Immunocore also acknowledges the uncertainties associated with conducting a MAIC to compare the efficacy of tebentafusp and ipilimumab/nivolumab as pointed out by DMC in the assessment report. However, Immunocore recently published [1] an indirect comparison using the individual patient data (IPD) from the same study [2] used for the MAIC. This alternative indirect comparison employed a propensity score analysis that is a more robust method than the MAIC. The results from the indirect comparison using IPD for the ipilimumab/nivolumab study [2] were not significantly different from the MAIC approach (see addendum Table 1). Therefore, it is the company's view that the impact of the uncertainty for the comparison of tebentafusp and ipilimumab/nivolumab is overstated.

[redacted]

Best regards,
Immunocore

References

1. Piulats Rodriguez JM, Piperno-Neumann S, Rutkowski P, Nathan P, Hassel JC, Espinosa E, et al. 823P A propensity score weighted comparison of tebentafusp or pembrolizumab versus combination ipilimumab and nivolumab in untreated metastatic uveal melanoma. Ann Oncol. 2022;33:S924.

2. Piulats JM, Espinosa E, de la Cruz Merino L, Varela M, Alonso Carrión L, Martín-Algarra S, et al. Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402). J Clin Oncol. 2021;39(6):586–98.

Addendum

[redacted]

[redacted]

Table 1. OS results from the MAIC vs indirect comparison using IPD.

MAIC results	Results based on IPD
OS HR = 0.51	OS HR = 0.43

Source: [1]

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27.02.2023

MGK/BMC

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.03.2023
Leverandør	Immunocore
Lægemiddel	Kimmtrak (tebentafusp)
Ansøgt indikation	Monoterapi til behandling af human-leokocyt-antigen-(HLA) A*02:01-positive voksne patienter med ikke-resektabel eller metastatisk uvealt melanom.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Kimmtrak (tebentafusp):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Kimmtrak	100 mikrogram/0,5 ml	1 stk.	98.684,16	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

Aftaleforhold

Amgros har indgået en aftale med leverandøren, som gælder fra [redacted]. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ikke en etableret standardbehandling af metastatisk uvealt melanom i dansk klinisk praksis.

[redacted] Tabel 3 nedenfor viser lægemiddeludgifter for Kimmtrak:

Tabel 2: Årlige lægemiddeludgifter Kimmtrak

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Antal pakninger pr. år	Lægemiddeludgift pr. år (SAIP, DKK)
Kimmtrak	100 mikrogram/ 0,5 ml	1 stk.	Dosis i første cyklus: Dag 1: 0,02 mg IV Dag 8: 0,03 mg IV Dag 15: 0,068 mg IV Dosis efterfølgende: 0,068 mg IV per uge	[redacted]	Opstartsår: ≈ 34,62 Vedligeholdelses år: ≈ 35,36	Opstart: [redacted] Vedligeholdelse: [redacted]

Status fra andre lande

Land	Status	Link
Norge	Under vurdering	https://nyemetoder.no/metoder/tebentafusp
Sverige	Under vurdering	Kimmtrak (tebentafusp) vid uvealt melanom (janusinfo.se)
England	Under vurdering	https://www.nice.org.uk/guidance/indevelopment/gid-ta10428

Konklusion

[redacted]

Application for the assessment of tebentafusp (KIMMTRAK®) for HLA-A*02:01 positive adults with metastatic uveal melanoma

Refences were made using Vancouver style. A reference placed before a full stop refers to the sentence just ended. A reference placed after a full stop refers to the just ended paragraph or until the previous placed reference. Any information that are unpublished/confidential is highlighted in [redacted] throughout this application and appendix. Immunocore has given the permission to publish any data marked in [redacted] that the Danish Medicine Council see fit. The name of the clinical expert must be kept confidential.

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1. Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	KIMMTRAK®[1]
Generic name	Tebentafusp[1]
Marketing authorization holder in Denmark	Immunocore[1]
ATC code	Not yet assigned[1]
Pharmacotherapeutic group	Antineoplastic agents; other antineoplastic agents[1]
Active substance(s)	Tebentafusp[1]
Pharmaceutical form(s)	Concentrate for solution for infusion (sterile concentrate)[1]
Mechanism of action	Tebentafusp is a bispecific fusion protein, comprised of a T cell receptor (TCR; targeting domain) fused to an antibody fragment targeting cluster of differentiation 3 (CD3; effector domain). The TCR end binds with high affinity to a gp100 peptide presented by human leukocyte antigen – A*02:01 (HLA-A*02:01) on the cell surface of uveal melanoma tumor cells, and the effector domain binds to the CD3 receptor on the polyclonal T cell.[1] An immune synapse is formed when the TCR targeting domain of tebentafusp binds to uveal melanoma cells and the CD3 effector domain binds to polyclonal T cells. This immune synapse results in redirection and activation of polyclonal T cells regardless of their native TCR specificity. Tebentafusp-activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of uveal melanoma tumor cells.[1]
Dosage regimen	The recommended dose of KIMMTRAK® is 20 micrograms on Day 1, 30 micrograms on Day 8, 68 micrograms on Day 15, and 68 micrograms once every week thereafter[1]

Overview of the pharmaceutical	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	KIMMTRAK® is indicated as monotherapy for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.[1]
Other approved therapeutic indications	None[1]
Will dispensing be restricted to hospitals?	Yes[1]
Combination therapy and/or co-medication	To minimize the risk of hypotension associated with cytokine release syndrome (CRS), administer intravenous fluids prior to starting KIMMTRAK® infusion based on clinical evaluation and the volume status of the patient.[1]
Packaging – types, sizes/number of units, and concentrations	1 vial with 0.5 ml containing 100 micrograms tebentafusp[1]
Orphan drug designation	Yes[2]

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2. Abbreviations

ADA	Anti-tebentafusp antibodies
AE	Adverse event
AIC	Akaike information criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BICR	Blinded Independent Central Review
BIC	Bayesian information criterion
BoR	Best overall response
BSA	Body surface area
BSC	Best supportive care
CD3	Cluster of differentiation 3
CE	Cost-effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CM	Cutaneous melanoma
COMS	Collaborative Ocular Melanoma Study
CR	Complete response
CRS	Cytokine release syndrome
CTLA-4	Cytotoxic T-lymphocyte antigen-4
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DMC	Danish Medicines Council
DoR	Duration of Response
DRG	Diagnosis-related group
DSU	Decision Support Unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Score
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
EQ-5D-5L	European Quality of Life – 5 dimensions – 5 levels
Gα	G-protein α-subunit
GEE	Generalized estimating equation
HLA	Human leukocyte antigen
HLA-A	Human leukocyte antigen class I
HR	Hazard ratio
HRQoL	Health-Related Quality of Life
HSUV	Health state utility values
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IgG4	Immunoglobulin G4
ImmTACs	Immune-mobilizing monoclonal T-cell receptors Against Cancer
Ipi/nivo	Ipilimumab in combination with nivolumab
ITT	Intention to treat
KM	Kaplan-Meier
KRIS	Koordinationsrådet for ibrugtagning af sygehusmedicin
LDH	Lactate dehydrogenase
LS	Least Squares
LY	Life year
MAE	Mean absolute error
MAIC	Match adjusted indirect comparison
mUM	Metastatic uveal melanoma
N/A	Not available
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small-cell lung carcinoma
NI	National Cancer Institute
OR	Overall response
ORR	Objective response rate
OS	Overall survival
PD	Progressed disease
PD-1	Programmed death receptor 1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-free survival
PH	Proportional hazard
PICO	Population, intervention, comparator, outcomes

PP	Post-progression state
PPP	Pharmacy purchase price
PR	Partial response
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
RECIST	Response Evaluation Criteria in Solid Tumours
RMSE	Root mean squared error
RR	Relative risk
RWE	Real-world evidence
SD	Stable disease
SE	Standard error
SEA	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology assessment
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TR-SAEs	Serious treatment related adverse event
TSD	Technical support document
TTD	Time to treatment discontinuation
UAIC	Unadjusted indirect comparison
ULN	Upper limit of normal
UM	Uveal melanoma
QALY	Quality-Adjusted Life Years
QoL	Quality of Life

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3. Tables and Figures

3.1 List of tables

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3.2 List of figures

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4. Summary

Uveal melanoma (UM) is a rare and aggressive cancer, distinctive from the more common cutaneous melanoma (CM) due to its different metastatic patterns, molecular drivers, and tumor-immune microenvironment [3–5]. The course of disease and prognosis are therefore also distinctive from CM as patients with UM have a poorer clinical response to systemic treatment resulting in a poor prognosis [4]. Fifty percent (50%) of all UM patients will develop metastasis, predominantly located in the liver due to the absence of lymphatic vessels in the eye, and less frequently located in lungs, skin, and bones [6,7].

Despite active treatment, the median overall survival (OS) of metastatic uveal melanoma (mUM) is expected to be below 12 months [8]. Within the first year of diagnosis, approximately 50% of patients die, with a relative 5-year survival of 15% [8–10]. There are currently no drugs approved that specifically targets mUM, leading to a lack of consensus on how mUM should be treated, both nationally and internationally. Clinical trials are therefore the first choice of treatment, whenever available. [11–15] Evidently, there is a high unmet need for an effective treatment developed specifically for mUM patients that can increase survival. When a clinical trial is not available, fit patients are offered a combination immunotherapy treatment consisting of ipilimumab and a programmed death receptor 1 (PD-1) inhibitor/programmed death-ligand 1 (PD-L1) inhibitor as first-line treatment. Unfit patients are offered chemotherapy with temozolomide as first-line treatment, which is also offered as second line treatment after combination immunotherapy for fit patients [16,17]. In Denmark the immunotherapy combination used for mUM patients is ipilimumab in combination with nivolumab (ipi/nivo). This has been confirmed by both the consulting clinical expert and the expert committee in the Danish Medicines Council (DMC).

Tebentafusp is part of a new class of T-cell receptor (TCR) therapeutics called immune-mobilizing monoclonal T-cell receptors against cancer (ImmTACs), and is indicated for the treatment of human leukocyte antigen-A*02:01 (HLA-A*02:01) positive adult patients with unresectable or metastatic UM [1]. Approximately 47% of patients with mUM are HLA-A*02:01 positive. Based on evidence from a Danish registry-based study and input from a consulting clinical expert, 7 - 10 patients are expected to be candidates for treatment with tebentafusp every year.

The efficacy and safety of tebentafusp has been investigated in the IMCgp100-202 study, an open-label phase III study, where tebentafusp was compared to investigators choice, which was either monotherapy with pembrolizumab, nivolumab, or dacarbazine. The primary endpoint was OS, secondary endpoints included progression-free survival (PFS), overall response (OR), duration of response (DoR), and disease control rate (DCR). Treatment with tebentafusp was associated with longer OS than investigators choice, with an OS of 21.7 months [95% CI; 18.6 – 28.6] and 16 [95% confidence interval (CI); 9.7 – 18.4] in the tebentafusp arm and control arm, respectively, and a hazard ratio (HR) for death of 0.51 [95% CI; 0.37 – 0.71] in favor of tebentafusp. The most common treatment-related adverse event (TRAE) of any grade in the tebentafusp arm were cytokine-related adverse events (AE), e.g., pyrexia (76%), chills (47%), and hypotension (38%). Cytokine release syndrome (CRS) occurred in 89% of the tebentafusp arm, with majority in the less severe grades: grade 1 (12%); grade 2 (76%); grade 3 (1 %); grade 4-5 (0%). Other common tebentafusp AEs included skin-related AEs, e.g., rash (83%), pruritus (69%), and erythema (23%). The discontinuation due to treatment-emergent adverse events (TEAE) was lower in the tebentafusp arm (2%) compared with the control arm (5%). No treatment related deaths were reported in either treatment arms. [4]

The efficacy and safety of ipi/nivo has been investigated in the GEM1402 study, a single-arm, non-randomized, open label phase II study that enrolled systemic treatment naive patients with mUM. The primary endpoint of GEM1402 was OS at 12 months, and the secondary endpoints were OS at 24 months, PFS, overall response rate (ORR), DCR, DoR, and safety. The median OS was 12.7 (95% CI, 7.1 to 18.3 months). The most common TRAEs were skin-related events (61.5%), followed by fatigue (57.7%) and liver-related events due to immunotherapy (36.5%). [18]

As no head-to-head comparison between tebentafusp and ipi/nivo exists a match adjusted indirect comparison (MAIC) was performed, where the data from IMCgp100-202 and GEM1402 studies was compared. The MAIC included

a comparison of OS and PFS between tebentafusp and ipi/nivo. In the MAIC, OS and PFS were analyzed for the total population, a population pooled according to hepatic disease, and a population pooled according to liver lesion size. In the MAIC, tebentafusp had a significant longer median OS ranging between 9.5 – 11.3 months, while the PFS was significantly increased with 0.3 – 1.7 months, depending on the compared population. A narrative comparison between tebentafusp and ipi/nivo via the Pelster et al. 2020 study was performed as per the DMC's request. However due to Pelster et al. 2020 including both previously treated and untreated mUM patients (whereas IMCgp100-202 only included previously untreated) the results from this analysis are not deemed to be scientifically valid.

The safety data from IMCgp100-202 and GEM1402 was analyzed in a narrative comparison. The comparison of the safety of tebentafusp and ipi/nivo, showed that ipi/nivo had a higher number of grade ≥ 3 (57.7% vs. 44%) and serious AEs (57.77% vs. 28.2%) compared with tebentafusp and a higher rate of discontinuation (23.1%) than tebentafusp (2.0%). No deaths due to TEAE's were reported in the tebentafusp arm while 2 deaths (3.8%) were reported in the ipi/nivo arm. [4,18]

The cost-effectiveness (CE) of tebentafusp vs ipi/nivo in HLA-A*02:01 positive adults with mUM was assessed using a three-state partitioned survival model structure from a limited societal perspective in accordance with the DMC's guidance. In the base case, the disease course of the target population was estimated over a lifetime horizon (i.e., 35 years with the target cohort's baseline age at 65 years old). All costs and health effects were discounted at 3.5% annually. The clinical parameters: OS, PFS, dosing, and grade ≥3 AEs for both treatment arms were estimated using data from the GEM1402 and the IMCgp100-202 study. The utilities were modelled based on time-to-death data from the literature. The OS extrapolation was performed by fitting a log-normal distribution to the OS data and generalized gamma distribution to the PFS data for both treatment arms.

In the base case analysis, it was estimated that over a lifetime horizon treatment with tebentafusp resulted in a gain of 1.04 quality-adjusted life years (QALYs) over ipi/nivo (total QALYs: 2.53 vs 1.48) per treated patient. Total costs per patient were estimated to be [redacted] and [redacted] for treatment with tebentafusp and ipi/nivo, respectively. The incremental cost-effectiveness ratio (ICER) was estimated to be [redacted] for tebentafusp compared to ipi/nivo. The key cost drivers were the tebentafusp drug cost and cost of subsequent treatment in the tebentafusp arm.

The budget impact assessment is based on the cost effectiveness analysis (CEA) and uses the key parameters (e.g., extrapolated OS and PFS curves, cost inputs, etc.). In the budget impact analysis, it is assumed that the population for whom tebentafusp is indicated will be approximately 10 patients per year. An assumed uptake of 80% among eligible patients in year 1, 90% uptake in year 2, and 100% uptake thereafter, were used in the budget impact analysis. The budgetary impact of introducing tebentafusp was estimated at approximately [redacted] in year 5.

5. The patient population, the intervention, and choice of comparator(s)

5.1 The medical condition and patient population

Uveal melanoma (UM) is a rare, life-threatening and aggressive cancer, distinctive from the more common cutaneous melanoma (CM), as it has different metastatic patterns, molecular drivers, and tumor-immune microenvironment [3–5]. The course of disease and prognosis are therefore also distinctive from CM, as patients with UM have a poorer clinical response to systemic treatment targeted to CM, resulting in a poor prognosis [4]. Among intraocular malignancies UM is the most common, accounting for approximately 85% of all cases. UM originates from melanocytes located in the anterior and posterior uveal tract that encompass the pigmented tissue of the choroid, ciliary body, and iris and is characterized by a driver mutation in the guanine nucleotide-binding protein subunit alpha family gene that encodes the G-protein α-subunit (Gα), leading to a constitutively active Gα pathway. [3,5,7] 90% of UM are confined to the choroid, whereas UM located in the ciliary body and iris appears in 6% and 4% of UM cases respectively. Symptoms of UM depend on the location and size of the tumor, and varies from asymptomatic to distorted vision, field of view defects, photopsia (flashes of light), pain, eye redness, and vision loss [3,13,19].

Fifty percent (50%) of all UM patients will develop metastasis. The metastases are predominantly located in the liver, due to hematogenous spread since the eye do not have a lymphatic system, followed by lungs, skin, and bone. [6,7,13] In a Danish register study, 41.5% of patients had isolated liver metastasis, 8.5% had isolated extrahepatic metastasis while 50% had both liver and extrahepatic metastasis, meaning 91.5% of the included patients experienced liver metastasis[16]. Meanwhile the Collaborative Ocular Melanoma Study (COMS) on metastatic disease status at death, found liver metastasis in 93% of patients[20]. Symptoms of metastatic uveal melanoma (mUM) corresponds to the placement of the metastasis. Common symptoms of liver metastasis (the most prevalent UM metastasis) includes loss of appetite, fatigue, fever, itchy skin, jaundice, bloated belly, leg swelling, pain in the upper right part of the abdomen, and hepatic encephalopathy [21]. Furthermore, studies show that mUM patients have a lower quality of life (QoL) and frequent mental health disorders, such as depression (<10% of patients) and anxiety (up to 30%) [22]. Due to the high risk of developing metastasis, patients with UM are initially monitored with imaging of the liver every three months. After a time, the frequency of the controls can be extended. [23]

mUM is treated via enrolment in clinical studies or with off-label chemotherapy and immunotherapy, but the treatments has showed negligible response rates. The survival rate for patients with mUM therefore remains low. [8,14,15] Within the first year of diagnosis, approximately 50% of patients die, with a relative 5-year survival of 15% [8–10]. In a Danish register study, the median overall survival (OS) of mUM patients treated with temozolomide prior to the introduction of immunotherapy was 7.8 months. Median OS was 10.0 months after the introduction of immunotherapy, where mUM patients were treated with pembrolizumab, and ipilimumab in combination with nivolumab (ipi/nivo). Similarly, the OS-rate at 12 months increased from 25.0% to 41.9%, respectively. [16]

According to the Danish Melanoma Group, approximately 75 people in Denmark develop UM every year, see Table 1 [13]. Fifty percent (50%) of patients with UM will progress to mUM, corresponding to 37-38 patients per year. Forty seven (47%) of mUM patients will be human leukocyte antigen class I (HLA-A) *02:01 positive, corresponding to 17 – 18 patients per year [24]. According to the Danish register study 126 patients with mUM were referred to systemic treatment during the years 2011–2018, corresponding to approximately 15-16 mUM patients per year corresponding to 7-8 patients with HLA-A*02:01 positive mUM per year. The consulting clinical expert associate professor Lars Ny, a Swedish oncologist specialized in UM from the University Hospital of Gothenburg, estimates that the Danish incidence rate is equal to the Swedish incidence rate, which would correspond to a Danish yearly incidence of HLA-A*02:01 positive mUM patients of approximately 9-10 [16,25]. Due to this it is there estimated that 7-10 patients will be candidates for tebentafusp treatment per year, as presented in Table 2 [16].

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Table 1. Incidence and prevalence in the past 5 years.

Year	2016	2017	2018	2019	2020
Incidence of UM [13]	75	75	75	75	75
Prevalence of UM in Denmark	Unknown	Unknown	Unknown	Unknown	Unknown
Global prevalence *	Unknown	Unknown	Unknown	Unknown	Unknown

*For small patient groups, also describe the worldwide prevalence
Abbreviations: UM, uveal melanoma

Table 2. Estimated number of patients eligible for treatment.

Year	2021	2022	2023	2024	2025
Number of patients in Denmark who are expected to use the tebentafusp [16,25]*	7-10	7-10	7-10	7-10	7-10

* Based on the assumption that 50% of patients present with UM will progress to metastatic UM, and 47% of these carry the HLA-A*02:01 allele

5.1.1 Patient populations relevant for this application

The patient population relevant for this assessment are patients with mUM who are HLA-A*02:01 positive[1]. In Denmark, the population indicated for the treatment with tebentafusp is estimated to include approximately 10–16 patients per year [16,25]. HLA-A*02:01 allele genotype can be determined by any validated human leukocyte antigen (HLA) genotyping assay, as mentioned by the Department of clinical Biochemistry at Rigshospitalet in an email correspondence (T.W. Thielsen, personal communication, November 30th, 2021). In Denmark, next generation sequencing is the applied genotyping assay.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Since tebentafusp is indicated for mUM patients this section will only describe the treatment of mUM. The treatment of UM is not described further. For patients with mUM, there is no established standard of care. Furthermore, there are currently no drugs approved that specifically targets mUM, leading to a lack of consensus on how mUM should be treated, both nationally and internationally. Due to the lack of targeted treatments, mUM is treated via enrolment in clinical studies or with off-label chemotherapy or off-label immunotherapy. The treatments has however showed negligible response rates and the survival rate for patients with metastatic UM remains low and has not improved in 40-plus years. [11–15] Due to these limitations, there is a need for targeted treatment, which can improve survival and the quality of life for mUM patients.

In 2020, a collaborative work between "Danske Multidisciplinære Cancer Grupper" and "Regionernes Kliniske Kvalitetsudviklingsprogram" developed a clinical guideline describing the current standard treatment for mUM. As there is no convincing data for survival for any treatment against mUM, the first choice should be enrolment in a clinical trial. When a clinical trial is not available, fit patients should be offered a combination of immunotherapy treatments consisting of ipilimumab and a programmed death receptor 1 (PD-1) inhibitor or a programmed death-ligand 1 (PD-L1) inhibitor. Unfit patient can be offered chemotherapy with temozolomide, which can also be offered as 2nd line treatment after immunotherapy for fit patients [16,17]. In Denmark, the combination treatment used is

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ipi/nivo, which has been confirmed by both the consulting clinical expert and the expert committee in the Danish Medicine Council (DMC). The treatment algorithm can be seen in **Figure 1**. Surgical resection of solitary liver metastasis should be considered in patients with a good general condition and with limited disease, where it is assessed, that radicalism is realistic. Other local treatment of liver metastasis should only be done under protocol [17].

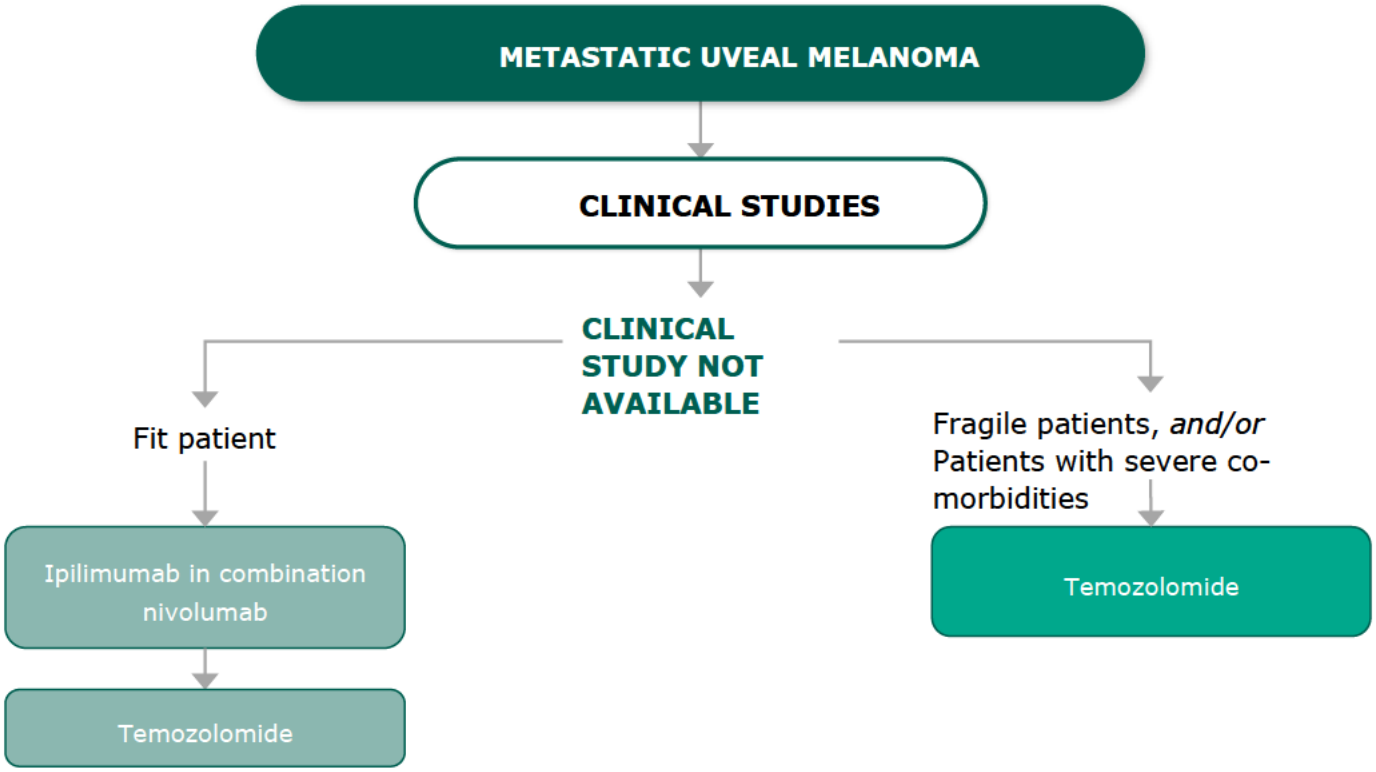

Figure 1. Current treatment algorithm of metastatic UM.

5.2.2 Choice of comparator(s)

According to clinical guidelines, the first choice (excluding clinical studies) is a combination of nivolumab and a PD-1/L1 inhibitor [17]. As agreed with the expert committee for Melanoma in the DMC, ipi/nivo has been chosen as the relevant comparator. Combination therapy with ipi/nivo is preferred over monotherapy because it has a higher response rate, however the response rates remain low. In the Danish registry study, no patients had a complete response (CR) rate, but patients on ipi/nivo had a partial response (PR) of 21.1% whereas monotherapy with ipilimumab had a PR of 0% [16]. Response rate is however not an optimal endpoint for tebentafusp, hence the primary endpoint was OS in the study chosen for this application [4]. In the Danish registry study an increase in OS could also be observed when treating with ipi/nivo, as the median OS increased from 9.9 months to 18.9 months and the 1-year OS rate from 50.0% to 57.7% when treating with ipi/nivo compared to ipilimumab monotherapy [16].

Eventhough the combination therapy with ipi/nivo has not previously been assessed by the DMC for mUM and the cost-effectiveness (CE) of this treatment has not been established it was decided to not conduct further comparative analyses of ipi/nivo and best supportive care (BSC). This is in line with the DMC guideline which states that treatments considered well established in Danish clinical practice can be exempted from such comparison. Ipi/nivo is based on the following reasonings considered a well-established treatment in Danish clinical practice of treatment of mUM:

1. Immunotherapies including ipi/nivo have been used for treatment of mUM since 2014 [16]
2. The Danish clinical treatment guideline "*Oncological treatment of Ocular melanoma*" describes that patients with metastatic ocular melanoma should be offered combination treatment with a cytotoxic T-lymphocyte antigen-4 (CTLA-4) (ipilimumab) and a PD-1 inhibitor (e.g. nivolumab) [17]
3. The combination treatment with ipi/nivo has a better effect compared to monotherapy with ipilimumab or pembrolizumab. Thus, supporting that ipi/nivo should be considered the best treatment available at this point in time (excluding clinical studies) [16]
4. According to the consulting clinical expert ipi/nivo is 1st line treatment in Sweden and is expected to be considered the standard treatment in Denmark [25].

A comparison with BSC is therefore not considered necessary since ipi/nivo is a well-established treatment in Danish clinical practice and has been since 2014[16]. Also, no placebo studies comparing tebentafusp nor ipi/nivo with placebo exists since UM is a serious life-threatening disease and a placebo study would be considered unethical.

Before ipi/nivo was introduced as standard treatment patients with mUM received treatment with temozolomide[16]. A comparison between ipi/nivo and the BSC at the time of the introduction of ipi/nivo, would therefore include a comparison between ipi/nivo and temozolomide. The cost-effectiveness of ipi/nivo has not previously been assessed by the DMC for mUM, however it was assessed for mesothelioma lung cancer where it was recommended when compared to platinum based chemotherapy [26]. Likewise 'Koordinationsrådet for ibrugtagning af sygehusmedicin' (KRIS) assessed and recommended the use of ipi/nivo for patients with CM in 2016 [27]. This indicates that the Danish Regions and the hospital departments deem the use and costs of ipi/nivo to be acceptable for CM. As the prognosis of mUM are worse than CM [4], it is reasonable to assume that ipi/nivo is cost-effective in patients with mUM. This is supported by the fact that ipi/nivo is currently used as standard treatment for patients with mUM and have been since 2014 [16]. Therefore, it follows that the regions view the cost of ipi/nivo for patients with mUM to be reasonable. As a result of the regions acceptance of the cost of ipi/nivo, it is not considered relevant to conduct another evaluation between ipi/nivo and temozolomide.

5.2.3 Description of the comparator(s)

The combination treatment with ipi/nivo is used for mUM patients in Danish clinical practice but is not recommended by the DMC or any other regulatory agencies for this indication. Further, the effects of ipi/nivo for treating mUM have only been investigated in single arm studies, and the evidence of effect is therefore not considered strong [18,28]. The options for the patients with mUM are thereby limited and outcomes remain poor. Ipilimumab and nivolumab will be described separately in Table 3 and Table 4 respectively.

Table 3. Description of ipilimumab.

Comparator: Ipilimumab	
Generic name and ATC-code	Ipilimumab (L01XC11)[29].
Mode of action	CTLA-4 is a key regulator of T-cell activity. Ipilimumab is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumor cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumor immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumor site, leading to an increase in the intratumorally T-effector/ T-regulatory cell ratio which drives tumor cell death. [29]
Pharmaceutical form	Concentrate for solution for infusion (sterile concentrate)[29].

Posology	The recommended induction regimen of YERVOY® is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses [29].
Method of administration	Intravenous infusion [29].
Dosing	3 mg/kg every 3 week [29].
Should the pharmaceutical be administered with other medicines?	Ipilimumab can be taken in combination with nivolumab as indicated for the treatment of adult patients with melanoma [29].
Treatment duration/criteria for end of treatment	Patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions [29].
Necessary monitoring, both during administration and during the treatment period	**Prior to the administration of ipilimumab** [29] - Hepatitis: Hepatic transaminase and bilirubin must be evaluated before each dose of ipilimumab, as early laboratory changes may be indicative of emerging immune-related hepatitis. Increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, tumor progression, or concomitant medication, and monitored until resolution. - Ipi/nivo: Before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumor characteristics, taking into consideration the observed benefits and the toxicity of the combination relative to nivolumab monotherapy. **During the treatment period - In combination with nivolumab** [29] - Cardiac and pulmonary adverse event: Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment. - Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with ipi/ may occur at any time during or after discontinuation of therapy. - Immune-related colitis: Patients should be monitored for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus or blood in the stool. - Immune-related pneumonitis: Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground-glass opacities, patchy filtrates), dyspnea, and hypoxia. - Immune-related hepatotoxicity: Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations - Immune-related nephritis and renal dysfunction: Patients should be monitored for signs and symptoms of nephritis or renal dysfunction. - Immune-related endocrinopathy: Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycemia and changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation).

- Adrenal insufficiency: Monitoring of adrenal function and hormone levels to ensure appropriate corticosteroid replacement is utilized.
- Hypophysis's: Monitoring of pituitary function and hormone levels to ensure appropriate hormone replacement is utilized.
- Symptomatic diabetes: Monitoring of blood sugar to ensure appropriate insulin replacement is utilized.
- Myotoxicity: If a patient develops signs and 17 symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay.
- Immune-related adverse reactions: For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes.

During the treatment period – Monotherapy [29]

- Immune-related reactions: For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes.
- Gastrointestinal reactions: Patients must be monitored for gastrointestinal signs and symptoms that may be indicative of immune-related colitis or gastrointestinal perforation.
- Mild to moderate diarrhea: close monitoring is advised.
- Severe diarrhea or colitis: Patients must be evaluated for evidence of gastrointestinal perforation or peritonitis.
- Immune-related hepatotoxicity: Increases in AST and ALT or total bilirubin should be monitored until resolution. For patients with Grade 2 transaminase or total bilirubin elevation, the scheduled dose of ipilimumab should be withheld, and liver function tests must be monitored until resolution. For patients with Grade 3 or 4 transaminase or total bilirubin elevation liver function tests must be monitored until normalization.
- Infusion reaction: Patients with mild or moderate infusion reaction may receive ipilimumab or ipi/nivowith close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.
- Drug-drug interactions: The use of anticoagulants is known to increase the risk of gastrointestinal hemorrhage. Since gastrointestinal hemorrhage is an adverse reaction with ipilimumab, patients who require concomitant anticoagulant therapy should be monitored closely.
- Motor neuropathy: Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting > 4 days must be evaluated, and non-inflammatory causes such as disease progression, infections, metabolic syndromes, and concomitant medication should be excluded.
- Adrenal crisis: If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, immediate administration of intravenous corticosteroids with mineralocorticoid activity is

	recommended, and the patient must be evaluated for presence of sepsis or infections.
Need for diagnostics or other tests (i.e. companion diagnostics)	No need [29].
Packaging	A vial of either 50 mg/10 ml or 200 mg/40 ml ipilimumab [29].

Table 4. Description of nivolumab.

Comparator: Nivolumab	
Generic name (ATC-code)	Nivolumab (L01XC17) [30].
Mode of action	Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody which binds to the PD-1 receptor and blocks its interaction with PD-L1 and programmed death-ligand 2 (PD-L2). The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are 39 expressed in antigen presenting cells and may be expressed by tumors or other cells in the tumor microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumor responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumor growth. [30]
Pharmaceutical form	Concentrate for solution for infusion (sterile concentrate) [30].
Posology	The recommended dose of OPDIVO® is either nivolumab 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes [30].
Method of administration	Intravenous infusion [30].
Dosing	240 mg every 2 weeks [30].
Should the pharmaceutical be administered with other medicines?	Nivolumab can be taken in combination with ipilimumab as indicated for the treatment of adult patients with melanoma [30].
Treatment duration/criteria for end of treatment	Treatment length is not described for melanoma, but for non-small-cell lung carcinoma (NSCLC) it is described as follows: Treatment with nivolumab, either as a monotherapy or in combination with ipilimumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient [30].
Necessary monitoring, both during administration and during the treatment period	Prior to the administration of ibrutinib treatment [30] - Severe endocrinopathies: Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycemia and changes in thyroid function. - Combination treatment with ipilimumab: Before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumor characteristics, taking into consideration the observed

benefits and the toxicity of the combination relative to nivolumab monotherapy.

During the treatment period [30]

- Cardiac and pulmonary adverse reactions: Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment.
- Adverse reaction: Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.
- Pneumonitis: Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy filtrates), dyspnea, and hypoxia.
- Severe diarrhea or colitis: Patients should be monitored for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool.
- Severe hepatitis: Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations.
- Severe nephritis and renal dysfunction: Patients should be monitored for signs and symptoms of nephritis or renal dysfunction.
- Severe endocrinopathies: Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycemia and changes in thyroid function.
- Hypothyroidism: Monitor thyroid function to ensure appropriate hormone replacement is utilized.
- Adrenal insufficiency: Monitor adrenal function and hormone levels to ensure appropriate corticosteroid replacement is utilized.
- Hypophysis's: Monitor pituitary function and hormone levels to ensure appropriate hormone replacement is utilized.
- Symptomatic diabetes: Monitor blood sugar to ensure appropriate insulin replacement is utilized.
- Myotoxicity: If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay.
- Infusion reaction: Patients with mild or moderate infusion reaction may receive nivolumab or ipi/nivo with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

Need for diagnostics or other tests (i.e. companion diagnostics)	No need [30].
Packaging	A vial of either 40 mg/4 mL, 100 mg/10 mL or 240 mg/24 mL nivolumab [30].

5.3 The intervention

Tebentafusp (KIMMTRAK®) is a new class of T-cell receptor (TCR) therapeutics called immune-mobilizing monoclonal T-cell receptors against cancer (ImmTACs), with high affinity and specificity for targeting UM cancer cells [4]. Tebentafusp is described in more detail in Table 5.

Table 5. Description of tebentafusp.

Intervention: tebentafusp	
Generic name (ATC-code)	Tebentafusp[1]
Mode of action	Tebentafusp is a bispecific fusion protein, comprised of a TCR targeting domain fused to an antibody fragment targeting cluster of differentiation 3 (CD3; effector domain). The TCR end binds with high affinity to a gp100 peptide presented by HLA – A*02:01 on the cell surface of UM tumor cells, and the effector domain binds to the CD3 receptor on the polyclonal T cell.[1] An immune synapse is formed when the TCR targeting domain of tebentafusp binds to UM cells and the CD3 effector domain binds to polyclonal T cells. This immune synapse results in redirection and activation of polyclonal T cells regardless of their native TCR specificity. Tebentafusp-activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of UM tumor cells. [1]
Pharmaceutical form	Concentrate for solution for infusion (sterile concentrate)[1].
Posology	The recommended dose of KIMMTRAK® is 20 micrograms on Day 1, 30 micrograms on Day 8, 68 micrograms on Day 15, and 68 micrograms once every week thereafter.[1] First three treatment doses First three doses of KIMMTRAK® should be administered in a hospital setting with overnight monitoring for signs and symptoms of cytokine release syndrome (CRS) for at least 16 hours. Vital signs should be monitored pre dose and at a minimum of every 4 hours until resolution of symptoms. If clinically indicated, more frequent monitoring or prolongation of hospitalization should be performed. If patients experience Grade 3 or 4 hypotension during any of the first three KIMMTRAK® infusions, patients should be monitored every hour for at least 4 hours in an outpatient setting for the next three infusions.[1] Subsequent treatment doses After 68 mcg dose level is tolerated (i.e., absence of Grade ≥ 2 hypotension requiring medical intervention), subsequent doses can be administered in appropriate outpatient ambulatory care setting. Patients should be observed for a minimum of 60 minutes following each infusion. For patients who have received outpatient treatment with KIMMTRAK® for at least 3 months and have not experienced any interruptions greater than 2 weeks, outpatient monitoring following infusion may be decreased to a minimum of 30 minutes for subsequent doses. [1]
Method of administration	Infusion [1].

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Dosing	The recommended dose of KIMMTRAK® is 20 micrograms on Day 1, 30 micrograms on Day 8, 68 micrograms on Day 15, and 68 micrograms once every week thereafter[1].
Should the pharmaceutical be administered with other medicines?	To minimize the risk of hypotension associated with CRS, administer intravenous fluids prior to starting KIMMTRAK® infusion based on clinical evaluation and the volume status of the patient [1].
Treatment duration/criteria for end of treatment	Patients should receive tebentafusp as long as the patient is deriving clinical benefit and in the absence of unacceptable toxicities [1].
Necessary monitoring, both during administration and during the treatment period	First three treatment doses: First three doses of KIMMTRAK® should be administered in a hospital setting with overnight monitoring for signs and symptoms of CRS for at least 16 hours. Vital signs should be monitored pre dose and at a minimum of every 4 hours until resolution of symptoms. If clinically indicated, more frequent monitoring or prolongation of hospitalization should be performed. If patients experience Grade 3 or 4 hypotension during any of the first three KIMMTRAK® infusions, patients should be monitored every hour for at least 4 hours in an outpatient setting for the next three infusions[1]. Subsequent treatment doses: After 68 mcg dose level is tolerated (i.e., absence of Grade ≥ 2 hypotension requiring medical intervention), subsequent doses can be administered in appropriate outpatient ambulatory care setting. Patients should be observed for a minimum of 60 minutes following each infusion. For patients who have received outpatient treatment with KIMMTRAK® for at least 3 months and have not experienced any interruptions greater than 2 weeks, outpatient monitoring following infusion may be decreased to a minimum of 30 minutes for subsequent doses[1].
Need for diagnostics or other tests (i.e. companion diagnostics)	The patients' needs to be tested for HLA-A*02:01 status before administering tebentafusp. This is done by next generation sequencing, as confirmed by the Department of Clinical Biochemistry at Rigshospitalet in an email correspondence
Packaging	0.5 ml x 1 vial containing 100 microgram in total[1].

Abbreviations: TCR: T-cell receptor; CDK3, Cluster of differentiation 3; CRS: Cytokine release syndrome; HLA-A: Human leukocyte antigen class 1

5.3.1 Treatment algorithm with the introduction of tebentafusp

Tebentafusp is indicated for patients with mUM who are HLA-A*02:01 positive, therefore the treatment algorithm is not expected to change for patients who are HLA-A*02:01 negative or for non-metastatic patients and therefore matches the description in section 5.2, Figure 1.

For patients who are HLA-A*02:01 positive the treatment algorithm is expected to be as follows, please see Figure 2 for details:

- 1st line treatment for all patients: Tebentafusp.
- 2nd line treatment for fit patients: Ipi/nivo
- 2nd line treatment for fragile patients/patients with severe comorbidities: Temozolomide
- 3rd line treatment for fit patients: Temozolomide

The new treatment algorithm has been estimated via inputs by a consulting clinical expert from Sweden, as it has not been possible to consult a Danish expert. The Swedish expert estimated that the treatment of mUM in Denmark and Sweden is similar. Therefore, the estimated treatment algorithm is expected to match a Danish setting, even though there is a slight uncertainty of not having consulted a Danish expert.

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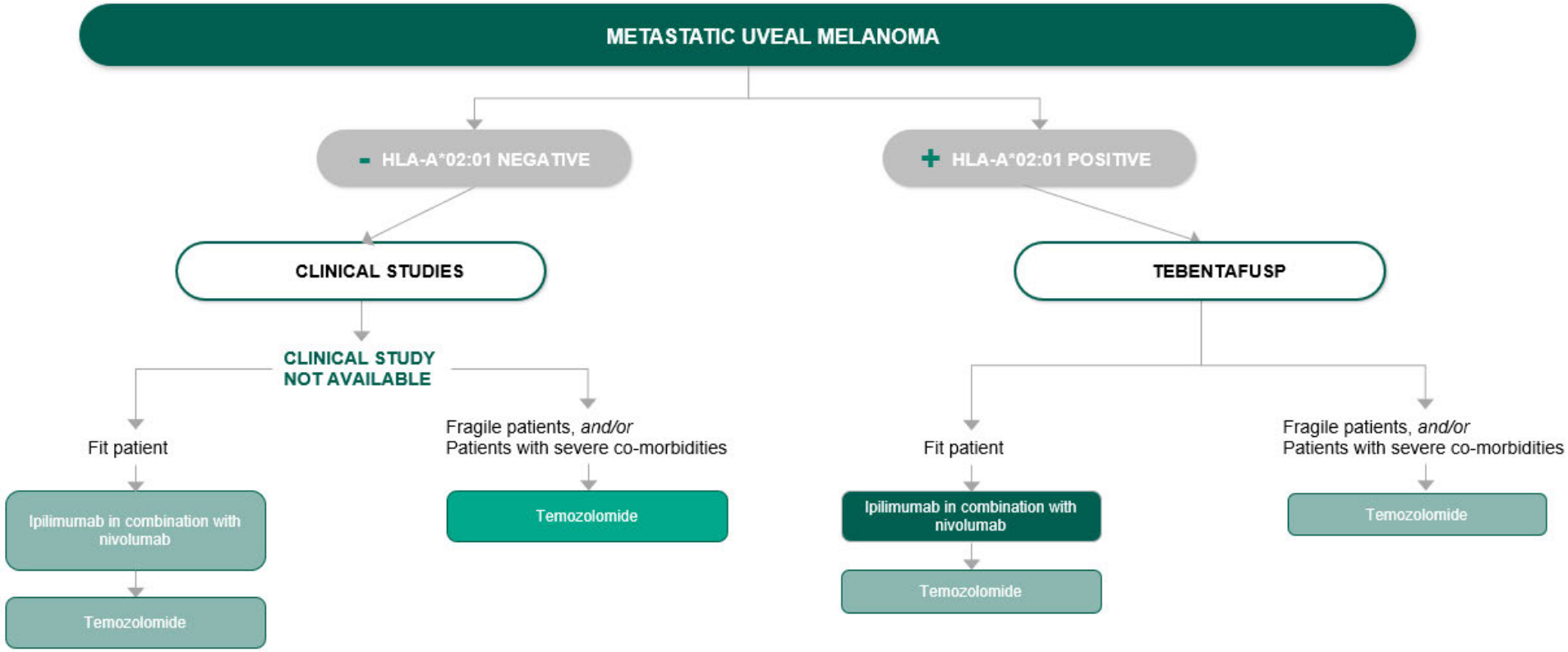


Figure 2. Expected treatment algorithm with the introduction of tebentafusp.[17,25]

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

Before conducting the systematic literature review (SLR) the IMCgp100-202 study was already identified. IMCgp100-202 is a head-to-head study comparing tebentafusp with pembrolizumab, nivolumab and dacarbazine monotherapy exists[4]. However, since the comparator in a Danish setting is ipi/nivo combination therapy, a SLR was conducted in order to identify studies that could be used for an indirect comparison.

The systemic literature searches were performed on the 17th to 18th of November 2021. The searches were performed on MEDLINE via Pubmed and CENTRAL via Cochrane Library. To identify ongoing trials, searches were also performed on clinicaltrials.gov (via https://clinicaltrials.gov/) and EU clinical trials registry (via https://www.clinicaltrialsregister.eu/). The latter searches were performed on the 19th of November 2021.

A primary screening based on title and abstract and a secondary screening was conducted based on full text for the references included in the primary screening. If there was uncertainty about the relevance of a record based on the abstract in the primary screening, it was included and taken forward to the secondary screening. The screening was conducted by one reviewer.

The systematic literature search identified 263 studies, which was reduced to 261 once duplicates were removed. Of these, 12 references were included via the primary screening, and 3 studies was identified as relevant for the assessment in the secondary screening, see Table 6. See Table 7 for ongoing tebentafusp UM studies excluded in the primary screening. For details, see Appendix A. The search on clinicaltrials.gov and the EU Clinical Trials Register for ongoing or completed studies did not identify any new records to be included, see Appendix A.

6.2 List of relevant studies

Table 6. Relevant studies included in the assessment.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Overall survival benefit with Tebentafusp in metastatic uveal melanoma - N Engl J Med 2021; 385:1196-1206[4].	IMCgp100-202[31]	NCT03070392[31]	Start date: October 16 2017 [31] Estimated completion date: March 2023[31]	Tebentafusp vs. investigators choice (pembrolizumab, ipilimumab or dacarbazine monotherapy) [4].
Nivolumab plus Ipilimumab for treatment-Näive metastatic Uveal melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary	(GEM1402) [32]	NCT02626962 [32]	Start date: April 2016 [32] Estimated completion date: December 2021 [32]	No comparator [18].

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Melanoma Group (GEM1402) - J Clin Oncol 2021; 39:586-598 [18].				
Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study. Journal of Clinical Oncology 39, no. 6. February 20, 2021. 599 -607. [28]	-	NCT01585194 [33]	Start date: November 2012 [33] Estimated completion date: December 2021[33]	No comparator[33].

Table 7. List of completed and ongoing tebentafusp UM studies not included in this application.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
A study of the intra-patient escalation dosing with IMCgp100-202 in Patients With Advanced Uveal Melanoma [34]	IMCgp100-102[34]	NCT02570308[34]	Start date: February 2016[34] Estimated completion date: March 202[34]	No comparator[34].

7. Efficacy and safety

7.1 Efficacy and safety of tebentafusp compared to ipi/nivo for HLA-A*02:01 positive adults with mUM

7.1.1 Relevant studies

In the SLR three possible studies were identified as relevant for the assessment of tebentafusp; IMCgp100-202, GEM1402, and Pelster et al. 2020. IMCgp100-202 is a head-to-head study between tebentafusp and pembrolizumab, ipilimumab and dacarbazine. GEM1402 and Pelster et al. 2020 are both studies that examine the effect of ipi/nivo in patients with mUM patients. A match adjusted indirect comparison (MAIC) was conducted to compare tebentafusp with ipi/nivo. During the development of the MAIC it was observed that GEM1402 was more suitable to use than Pelster et al. 2020, for a number of reasons, see section 7.1.2.4 for more detail. Pelster et al. 2020 was initially excluded for the assessment at this point. However, as per DMC's request, Pelster et al. 2020 was added as an extra analysis. In the following section IMCgp100-202, GEM1402 and Pelster et al. 2020 are described. [4,18,28]

7.1.1.1 IMCgp100-202

IMCgp100-202 is an ongoing phase III, randomized, open-label, active-comparator study that enrolled patients with HLA-A*02:01 positive advanced or mUM in a 1st line setting with no prior systemic or liver-directed chemo-, radio- or immunotherapy (prior surgical resection of liver metastases and adjuvant systemic therapy are acceptable). Patients in the intervention arm were treated intravenously with tebentafusp with a dose of 20 µg cycle 1 day 1, then 30 µg cycle 1 day 8 and 68 µg cycle 1 day 15 followed by 68 µg weekly. Treatment was continued until confirmed disease progression or unacceptable toxicity. Patients who were receiving tebentafusp, pembrolizumab, or ipilimumab could continue with treatment beyond the time of initial Response Evaluation Criteria in Solid Tumours (RECIST)-defined disease progression if they met all of the following prespecified criteria described in Appendix B. 252 patients were treated with tebentafusp. Patients in the comparator arm were treated with dacarbazine, ipilimumab, or pembrolizumab [4,35]:

- Dacarbazine: Administered at 1,000 mg/m^2 infusion every 3 weeks until disease progression or unacceptable toxicity. 7 Persons were treated with dacarbazine [4,35].
- Ipilimumab: Administered at 3 mg/kg infusion over 90 minutes every 3 weeks for a total of 4 treatments. 16 persons were treated with ipilimumab [4,35].
- Pembrolizumab: Administered at 2 mg/kg, up to a maximum of 200 mg, administered intravenously over 30 minutes every 3 weeks, or 200 mg fixed dose administered intravenously every 3 weeks, dependent on local guidelines, until confirmed disease progression or unacceptable toxicity. 103 persons were treated with pembrolizumab [4,35].

Crossover between treatment arms was not permitted during the trial, in accordance with the original design of the trial. However, based on the survival benefit observed at the first interim analysis, patients in the control arm were subsequently permitted to crossover to receive tebentafusp. The primary endpoint was OS, while the secondary endpoints was Progression-free Survival (PFS), Objective Response Rate (ORR), Duration of Response (DoR), and Disease Control Rate (DCR). The key safety endpoints are frequencies of treatment-emergent adverse events (TEAE), laboratory abnormalities, electrocardiogram (ECG) changes, and/or physical examination findings. A study schematic of IMCgp100-202 is presented in Figure 3 [4,35]. Please refer to Appendix B for detailed study description.

Figure 3. IMCgp100-202 study design [4,35].

7.1.1.2 GEM1402

GEM1402 is a single-arm, non-randomized, open label phase II study that enrolled systemic treatment naive patients with mUM. The patients received ipilimumab every 3 weeks for a total of four doses (Cycles 1 and 2) and nivolumab every 3 weeks for a total of four doses (Cycles 1 and 2) followed by nivolumab every 2 weeks until progression, intolerable toxicity, or withdrawal. The primary outcome was OS, and secondary outcomes were OS-rate at 24 months, PFS, ORR, DCR and DoR. A study schematic of GEM1402 is presented in Figure 4 [18]. An detailed study description is presented in Appendix B.

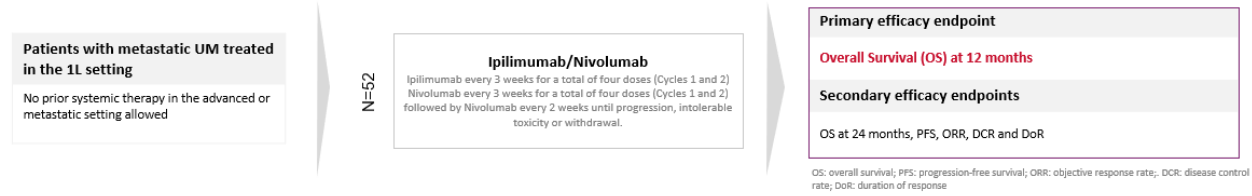


Figure 4. GEM1402 study design [18].

7.1.1.3 Pelster et al. 2020

Pelster et al. 2020 is a single-arm, open-label phase II study that enrolled patients with mUM with any number of prior treatments. The patients received ipilimumab and nivolumab every 3 weeks for a total of four doses followed by nivolumab up to 104 weeks or until disease progression, unacceptable toxicity, death, or withdrawal of consent. Nivolumab monotherapy was initially administered every 3 weeks at 3 mg/kg, but changed to 480 mg every 4 weeks. The primary endpoint was ORR and secondary outcomes were PFS, median OS, and 1-year OS. A study schematic of Pelster et al. 2020 is presented in Figure 5. [28,33] An detailed study description is presented in Appendix B.

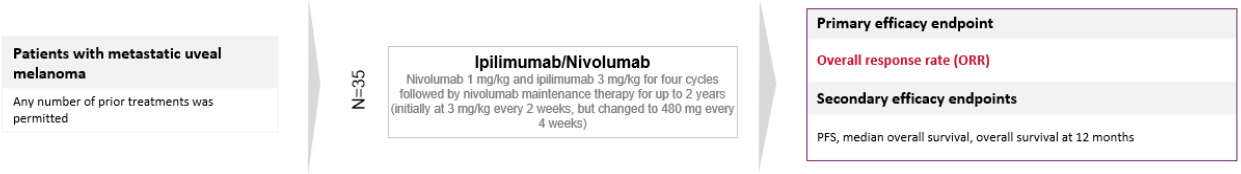


Figure 5. Pelster et al. 2020 study design [28,33].

7.1.1.4 Difference between IMCgp100-202 vs GEM1402 and Pelster et al. 2020

IMCgp100-202 is a phase III study, while both GEM1402 and Pelster et al. 2020 are phase II studies of patients with mUM. IMCgp100-202 is furthermore a randomized two-arm study with a comparator, whereas GEM1402 and Pelster et al. 2020 are single-arm studies with no comparators. The primary endpoints were OS, and secondary endpoints included PFS, ORR, DCR, and DoR in both IMCgp100-202 and GEM1402, whereas the primary endpoint in Pelster et al. 2020 was ORR and OS was a secondary endpoint [4,18,32,35].

Thus, the main differences between IMCgp100-202 and GEM1402 include being a two-arm vs. a single arm study, and the patient characteristics. The most clinically relevant difference in patient characteristics was the location of metastasis. In IMCgp100-202, only a small group of patients had only extrahepatic metastasis (5%) compared to a larger group in the GEM1402 study (23.5%) and the time from primary diagnosis was not available in the GEM1402 study. [4,18,28] These issues were addressed in the statistical indirect comparison analysis, see section 7.1.2.4. For a detailed description of baseline characteristics of patients included in each study, refer to Appendix C.

The main differences between Pelster et al. 2020 and IMCgp100-202 also include being a two-arm vs. a single-arm study and the patient population. The patient population in Pelster et al. 2020 was the inclusion of patients previously treated for mUM, whereas both IMCgp100-202 and GEM1402 only includes previously untreated patients. The patient populations in IMCgp100-202 and Pelster et al. 2020 are therefore not comparable in regards to the clinical efficacy. [4,18,28]

GEM1402 was therefore selected as the most appropriate study for the comparison with IMCgp100-202 as GEM1402 is currently the only available study examining ipi/nivo in a previously systemic untreated population, see Appendix B and F for more details. As the patient population in Pelster et al. 2020 does not reflect the patient population in clinical practice, it is not deemed appropriate for comparison with IMCgp100-202. However, as per DMC's request, a narrative comparison between IMCgp100-202 and Pelster et al. 2020 was conducted. The study populations in IMCgp100-202, GEM1402, and Pelster et al. 2020 are comparable with the Danish population regarding age and sex, while the clinical setting's performance score is expected to be worse due to the studies inclusion criteria of an Eastern Cooperative Oncology Group Performance Score (ECOG PS) 0-1, lower lactate dehydrogenase (LDH), and differences in metastatic location. Generally, the study population in the IMCgp100-202 study matched overall with the Danish mUM population, whereas the differences between the GEM1402 and Pelster et al. 2020 vs the Danish population was substantially higher, as the number of patients with only hepatic metastasis was substantially higher in GEM1402 and Pelster et al. 2020 than in the Danish population. [4,18,28] For a detailed description, refer to Appendix C.

7.1.2 Efficacy and safety – results per study

7.1.2.1 IMCgp100-202 efficacy and safety results

7.1.2.1.1 Overall Survival

The primary outcome, OS, is defined as the time from randomization to the date of death due to any cause. For patients without documentation of death, OS was censored at the last date of known 'alive' status. OS was followed continuously while patients were treated and every 3 months in the follow-up phase. The time of clinical cut-off for the first interim analysis was October 13, 2020, corresponding to a median follow-up of 14.1 months. [4]

OS curves, OS median with 95% confidence intervals (CI), and OS rate at 12 and 24 months have be estimated using Kaplan-Meier (KM) methodology. The arms were formally compared with the use of a 2-sided log-rank test, stratified according to LDH status. The hazard ratio (HR) and corresponding 2-sided CI was estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by LDH status (LDH above upper limit of normal (ULN) versus normal LDH) with the extent of liver metastases (largest hepatic metastatic lesion ≥ 44.5 mm) as an additional pre-specified co-variate. [4]

An ad hoc analysis was performed on the effect of stable vs. progressive disease on OS. A landmark approach was used to address the immortal time bias, meaning that OS was measured from day 100 and the patient's response was categorized on that day. This analysis was conducted using a Mantel-Haenszel 2-sided test statistic stratified by LDH status. The overall response (OR) and corresponding 2-sided CI was estimated using a logistic regression model, with the treatment arm as a single covariate, stratified by LDH status (LDH above ULN versus below ULN). [4]

The following result was observed at the first cutoff: 150 deaths had occurred in the intention to treat (ITT) population; 87 deaths were observed in the tebentafusp arm, while 63 deaths occurred in the control arm. The 1-year survival was 73% [95% CI; 66 – 79] in the tebentafusp arm and 59% [95% CI; 48 – 67%] in the control arm. The estimated OS was 21.7 months [95% CI; 18.6 – 28.6] and 16 [95% CI; 9.7 – 18.4] in the tebentafusp arm and control arm, respectively and the HR for death was 0.51 [95% CI; 0.37 – 0.71] in favor of tebentafusp, see Figure 6. [4]

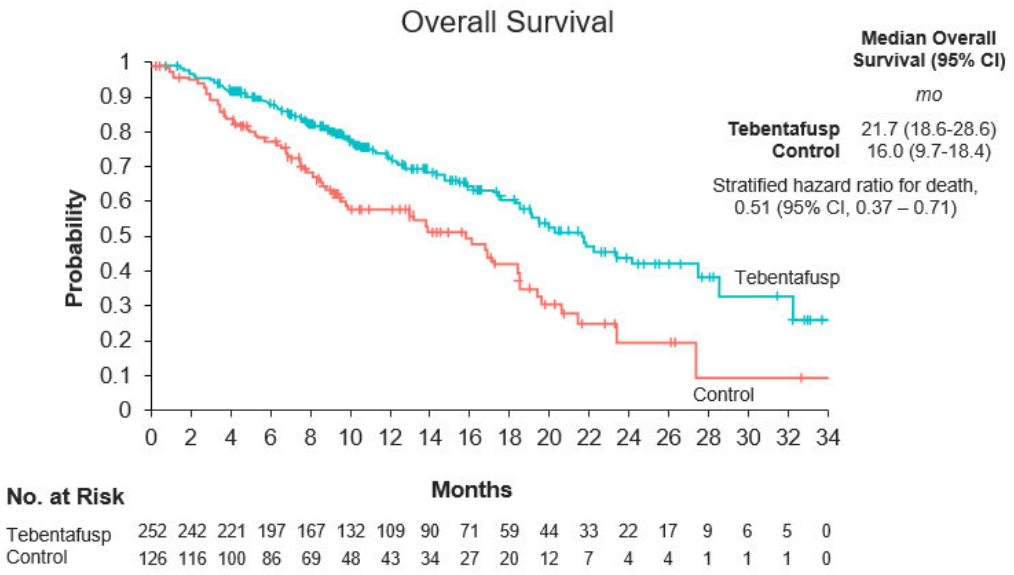
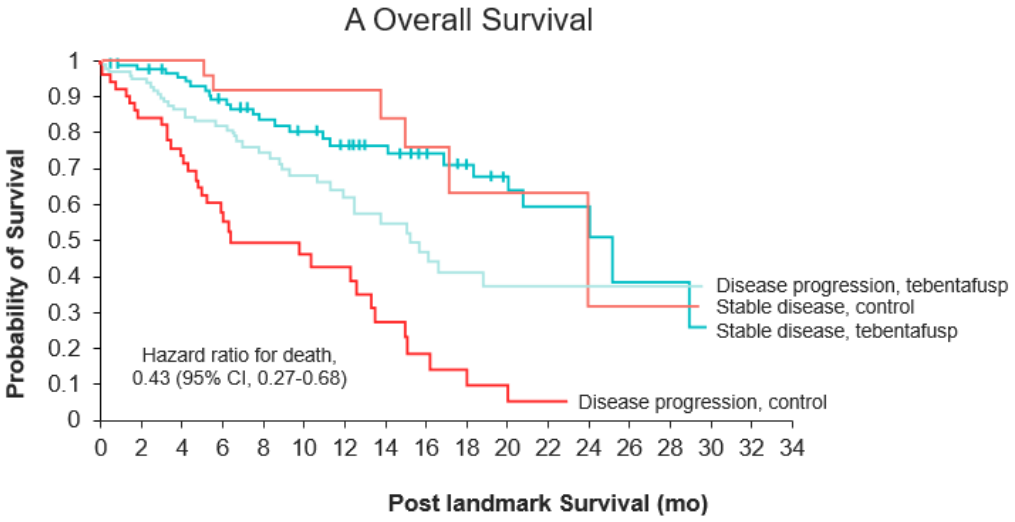


Figure 6. Kaplan-Meier estimates of OS according to treatment arm [4].

Abbreviation: No, numbers; OS, overall survival

In the landmark-based analysis, patients with disease progression as their best response at day 100 had an OS of 15.3 months [95% CI, 12.0 to not reached] compared to 6.5 months [95% CI, 4.9 to 13.4 months] in the control arm with a HR for death of 0.43 [95% CI, 0.27 to 0.68], see Figure 7.[4]



No. at Risk

Stable disease, tebentafusp	101	89	82	67	53	45	37	32	26	21	17	12	7	3	3	0
Stable disease, control	34	32	29	20	17	15	13	10	7	5	4	3	2	1	1	0
Disease progression, tebentafusp	105	92	78	62	47	38	29	22	17	11	6	4	3	2	2	0
Disease progression, control	53	42	35	23	16	13	11	6	4	3	2	1	0			

Figure 7. Landmark OS in patients with BoR of SD or disease progression [4].

Abbreviation: BoR, best overall response; CI, confidence interval; OS, overall survival; SD, stable disease

7.1.2.1.2 Overall survival subgroup analyses

Subgroup analyses for OS were conducted as pre-specified in trial protocol. Figure 8 shows a forest plot summarizing the key results of the OS subgroup analyses by treatment arm. The OS benefit provided by tebentafusp was observed across all prespecified major demographic and known prognostic subgroups, including a HR of 0.51 (95% CI 0.35-0.75) versus pembrolizumab, the most frequent investigator's choice agent.[4] It can be observed that survival is higher when the tumor size is smaller, as patients with UM are monitored continuously it can be expected that many patients with mUM will be diagnosed with a small tumor[4,23].

Subgroup	No. of Patients	No. (%) of Death	No. of Patients	No. (%) of Death	Hazard Ratio (95% CI)
Region					
North America	86	28 (33)	52	24 (46)	0.52 (0.30-0.91)
Non-North America	166	59 (36)	74	39 (53)	0.49 (0.33-0.74)
Investigator's Choice					
Pembrolizumab	199	65 (33)	103	49 (48)	0.51 (0.35-0.75)
Ipilimumab	40	16 (40)	16	7 (44)	0.89 (0.38-2.31)
Dacarbazine	13	6 (46)	7	7 (100)	0.29 (0.09-0.86)
Gender					
Male	128	48 (38)	62	35 (57)	0.48 (0.31-0.75)
Female	124	39 (32)	64	28 (44)	0.57 (0.35-0.94)
Age					
<65 yr	130	41 (32)	61	29 (48)	0.48 (0.30-0.79)
≥65 yr	122	46 (38)	65	34 (52)	0.58 (0.38-0.92)
EGOS status					
0	192	59 (31)	85	42 (49)	0.48 (0.33-0.72)
1	49	24 (49)	31	18 (58)	0.72 (0.39-1.36)
Baseline alkaline phosphatase					
≤ULN	198	49 (25)	102	43 (42)	0.44 (0.29-0.66)
>ULN	53	37 (70)	24	20 (83)	0.60 (0.35-1.05)
Lactate dehydrogenase					
≤ULN	162	28 (17)	80	29 (36)	0.35 (0.21-0.60)
>ULN	90	59 (66)	46	34 (74)	0.70 (0.46-1.09)
Largest metastatic lesion					
M1a (≤3.0 cm)	139	29 (21)	70	28 (40)	0.36 (0.21-0.61)
M1b (3.1-8.0 cm)	92	43 (47)	46	26 (57)	0.71 (0.44-1.17)
M1c (≥8.1 cm)	21	15 (71)	10	9 (90)	0.76 (0.34-1.82)
ITT population	**252**	**87 (35)**	**126**	**63 (50)**	**0.51 (0.37-0.71)**

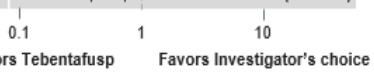


Figure 8. Forest plot of OS in subgroups [4].

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal.

7.1.2.1.3 Progression-free survival

PFS was defined as the time from randomization to the date of progression (RECIST v1.1) as determined by the Blinded Independent Central Review (BICR) or death due to any cause. Patients who had not progressed or died at the time of the analysis was censored at the time of the last evaluable tumor assessment. Patients who started a new anti-cancer therapy without a documented progression will be censored at the last time of a tumor assessment prior to the introduction of the new anticancer therapy. PFS is analyzed via the same statistical methods as OS. [4]

At 6 months, 31% of the tebentafusp arm were progression free and in the control arm 19% were progression free. The median PFS in the tebentafusp arms were 3.3 months (3.0 – 5.0) compared with 2.9 (2.8 – 3.0) in the control arm. The HR was 0.73 [95% CI, 0.58 – 0.95], see Figure 9.[4]

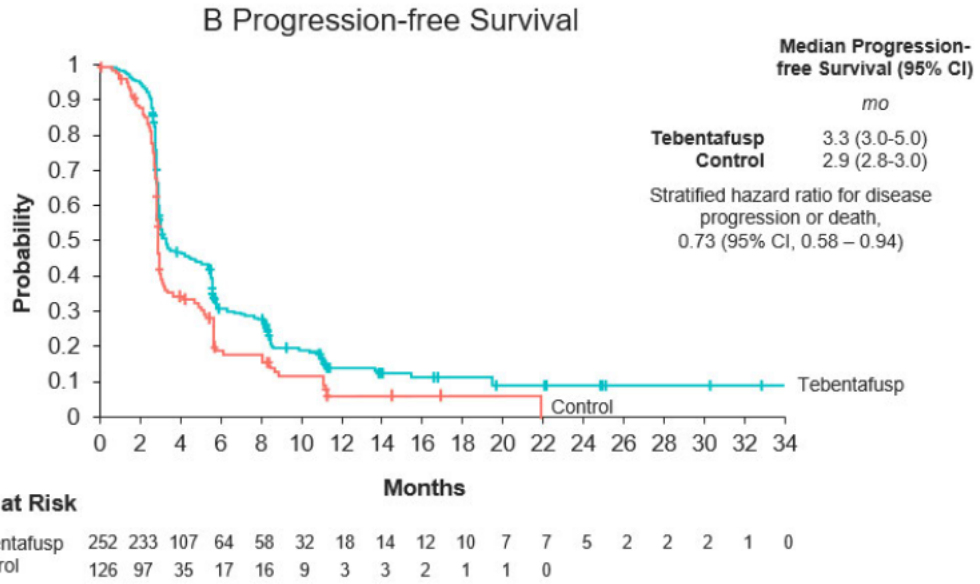


Figure 9. Kaplan-Meier estimates of PFS according to treatment arm [4].

Abbreviation: CI, confidence interval; No, numbers

7.1.2.1.4 Objective response rate and disease control

Objective response rate (ORR) is defined as the number of patients with a best overall response (BoR) of CR or PR divided by the number of patients for each treatment arm in the ITT population. [4] The BoR is defined as the best response designation up until progressed disease (PD) or last evaluable assessment in the absence of PD. Any CRs or PRs that occur after further anti-cancer therapy was received will not be included in the numerator for the ORR calculation by RECIST v1.1. The analysis of ORR will be conducted using a Mantel-Haenszel 2-sided test statistic stratified by LDH status using a logistic regression model, with the treatment arm as a single covariate, stratified by LDH status (LDH above ULN versus normal LDH). [4]

DCR is defined as the proportion of patients with a BoR of CR or PR, or stable disease (SD) recorded at least 24 weeks (± 1 week) after randomization of study drug and prior to any PD event. The estimated DCR and associated 90% CI for the true DCR was determined by the treatment arm. This analysis will then be repeated using the immune-related RECIST criteria for patients in the IMCgp100-202 Arm using an OR (immune-related PR or immune-related CR) and BoR of immune-related SD over 24 weeks. [4]

The ORR in the tebentafusp arm was 9% [95% CI, 6 – 13] and 5% [95% CI 2 -10] in the control arm, while the DCR was 46% [96% CI, 39 – 52] in the tebentafusp arm and 27% [95% CI, 20 – 36] in the control arm, see Table 8 [4].

Table 8. Best overall RECIST response rate [4].

	Tebentafusp (N=252), % (N)	Investigator's Choice (N=126), % (N)
ORR	9% (23)	5% (6)
CR	0.4% (1)	0
PR	9% (22)	5% (6)
SD	37% (92)	22% (28)

PD	52% (131)	62% (78)
Non-evaluable/Not applicable	2% (6)	11% (14)
DCR-12w (CR/PR/SD)	46% (115)	27% (34)
Stratified Odds Ratio for DCR, tebentafusp/investigator's choice (95% CI of odds ratio)	2.3 (1.5, 3.8)	

SD is ≥ 12 weeks
Stratified CMH test stratified by LDH status
Abbreviation: CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PR, partial response; PD, progressed disease; RECIST, Immune-related Response Evaluation Criteria In Solid Tumors; SD, stable disease

7.1.2.1.5 Safety

Adverse events (AE) were assessed by the investigator and were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, with the exception of CRS, which was evaluated and graded post hoc according to the 2019 recommendation of the American Society for Transplantation and Cellular Therapy for consensus grading for CRS, see Table 93 in Appendix E. The incidence of TEAE was summarized by system organ class and/or preferred term, severity (based on NCI CTCAE v4.03 grades), and type of AE.[4]

The following results were observed, see Table 9 and Appendix E for more details:

- 245 (100%) of patients experienced a TEAE in the tebentafusp arm, while 105 (95%) experienced a TEAE in the control arm [4].
- [redacted]
- 2% of patients in the tebentafusp arm discontinued treatment because of a TEAE while the number was 5% in the control arm [4].
- No treatment related death was reported in either arm [4].

Table 9. Summary of TEAEs in the ITT population [4,36].

	Tebentafusp (N = 245)	Investigator choice (N = 111)	Relative risk (RR)	95% CI
TEAE, n (%)	245 (100%)	105 (94.6%)	1.05	1.01 – 1.11
Treatment-related AEs (TRAE)	243 (99.2%)	91 (82.0%)	1.21	1.11 – 1.32
Serious TEAEs any grade	69 (28.2%)	26 (26.4%)	1.20	0.81 – 1.79
[redacted]				
[redacted]				
Related TEAE leading to discontinuation	5 (2.0%)	5 (4.5%)	0.45	0.13 – 1.53
[redacted]				
Any related TEAE Grade ≥3	109 (44.5%)	19 (17.1%)	2.60	1.69 – 4.01
[redacted]				

[redacted]	[redacted]	[redacted]	0.26	0.14 – 0.49
[redacted]	[redacted]	[redacted]	1.08	0.81 – 1.44
[redacted]	[redacted]	[redacted]	1.47	1.09 – 1.99
[redacted]	[redacted]	[redacted]	3.40	0.79 – 14.61
[redacted]	[redacted]	[redacted]	0.23	0.02 – 2.47
[redacted]	[redacted]	[redacted]	4.10	0.96 – 17.27
[redacted]				
[redacted]	[redacted]	[redacted]	-	-
[redacted]	[redacted]	[redacted]	-	-
[redacted]	[redacted]	[redacted]	1.04	0.70 – 1.54
[redacted]	[redacted]	[redacted]	0.87	0.55 – 1.36
[redacted]	[redacted]	[redacted]	0.23	0.02 – 2.47
Any related TEAE leading to death	0	0	-	-

Abbreviations: AE, adverse event; CTCAE, common terminology criteria for adverse events; ITT, intention-to-treat; RR, relative risk; SAE, serious adverse event; TEAE, treatment-emergent adverse events

*Some patients experience more than one dose reduction leading to the total number of reduction being 26 and 3 for tebentafusp and investigators choice, respectively.

The most common treatment-related AEs (TRAE) of any grade in the tebentafusp arm were cytokine-related AEs occurring, e.g pyrexia (76%), chills (47%), and hypotension (38%). CRS occurred in 89% of the tebentafusp arm. The majority of patients had CRS of grade 1 (12%) or grade 2(76%) while 1 % had grade 3 CRS, and no patients had grade 4 or 5 CRS. The other common tebentafusp AE were skin-related AEs, e.g., rash (83%), pruritus (69%), and erythema (23%). Rash was used as a composite term for a list of skin-related AEs of any grade. In the control arm, only expected AEs were observed. [4].

The safety profile of tebentafusp can therefore be categorized into two major types of AE: cytokine-mediated events and skin-related events. Cytokine-mediated AEs due to T-cell activation were reported in most of the patients, but most of the events were mild to moderate in severity and were managed with standard treatment interventions. Cytokine-mediated AEs occurred in the hours after the first few doses; therefore, overnight monitoring after the first three infusions is required. After the three first doses, cytokine-mediated AEs decreased in incidence and severity, and the extension of overnight monitoring beyond the three first doses was uncommon. The occurrence of skin-related AE, which were presumably due to the recognition of gp100-expressing melanocytes by tebentafusp, was also generally limited to the hours after administration of the first few doses.[4]

The incidence of AE was highest during the first 4 weeks of treatments, see Figure 10. After 3 weeks of treatment, most patients could therefore transition from receiving the treatment during admission to an outpatient setting. [4]

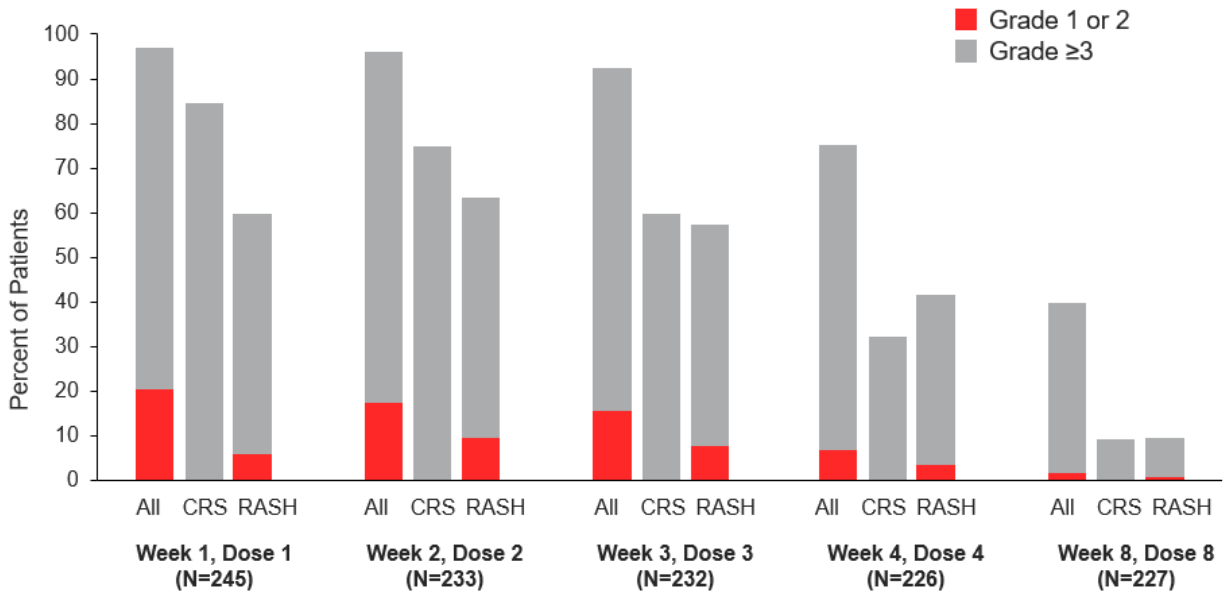


Figure 10. Incidence and Severity of TRAE's after Initial Doses of tebentafusp [4].

Abbreviations: CSR, Cytokine release syndrome; TRAE, treatment related adverse event

7.1.2.1.6 Anti-tebentafusp antibodies

The frequency of anti-drug (tebentafusp) antibodies (ADA) was 29% and 6% of patients had a decrease in tebentafusp serum concentration. The development of antibodies had no effect on OS, see Figure 11, and was not associated with an increased risk of hypersensitivity reactions. Table 10 displays the incidence of hypersensitivity AEs before and after the detection of ADA (directed to tebentafusp) among 61 tebentafusp-treated patients who developed ADA. Thirty-seven of the 61 patients who developed ADAs experienced a hypersensitivity AE. Thirty-six of these patients experienced a hypersensitivity AE before the detection of ADA compared to 5 patients who experienced a hypersensitivity AE after the detection of ADA. Four of these 5 patients experienced hypersensitivity AEs both before and after ADA detection. Only one patient experienced a hypersensitivity AE for the first time after the detection of ADA. These data confirm that there is no increased risk of hypersensitivity AEs after the onset of ADAs. [4]

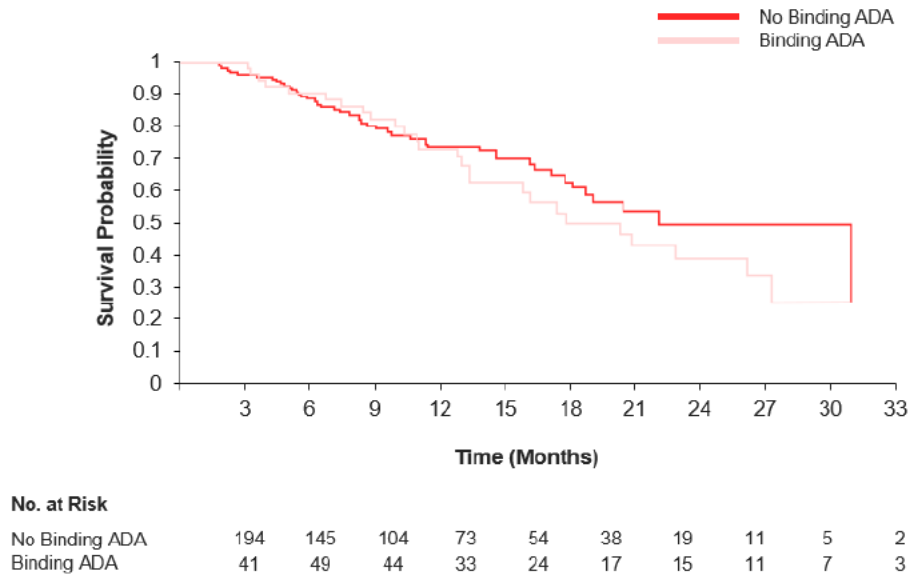


Figure 11. Simon-Makuch Estimates of OS by ADA Status [4].

Abbreviation: ADA, anti-drug (tebentafusp) antibodies; OS, overall survival

Table 10. Incidence of hypersensitivity adverse events before and after the detection and anti-drug antibodies.

Hypersensitivity AE Onset Before ADA	Hypersensitivity AE Onset After ADA n (%)		
	No	Yes	Total
No	24 (39)	1 (2)	25 (41)
Yes	32 (52)	4 (7)	36 (59)
Total	56 (82)	5 (8)	61 (100)

Abbreviations: ADA, anti-drug(tebentafusp) antibodies; AE, adverse event

7.1.2.1.7 Health-related quality of life data from the IMCgp100-202 trial

Health-related quality of life (HRQoL) data were collected in the IMCgp100-202 trial using two patient-reported outcome (PRO) instruments: the European Quality of Life -5 dimensions - 5 levels (EQ-5D-5L) questionnaire and European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30). Both questionnaires were completed at baseline, cycle 1 day 1, at day 1 of every other cycle through cycle 5 day 1, then every 4th cycle thereafter beginning with cycle 9 day 1, and at end of treatment. Patients entering the disease progression follow-up phase continued with both EORTC-QLQ-C30 and EQ-5D-5L assessments at 12-week intervals. During the survival follow-up phase, EQ-5D-5L assessments were continued every 3 months to inform post-progression health status. [36] A full description of the methodology is provided in appendix H.

EORTC-QLQ-C30

In both the tebentafusp and investigator's choice arms, patients were considered to be domain compliant (i.e., completion of at least 50% of the EORTC QLQ-C30 items) through cycle 17 day 1, with generally similar rates between the arms. Subsequently, patients in the tebentafusp arm remained domain compliant through cycle 29 Day 1, whereas compliance in the investigator's choice arm decreased to approximately 33% at cycle 29 day 1. [36]

At baseline, no differences in EORTC-QLQ-C30 scores were observed between the treatment arms for any of the domains. In general, throughout the study, the EORTC-QLC-C30 scores were similar between the treatment arms and remained stable for most domains. However, statistically significant and clinically meaningful least squares (LS) mean improvements from baseline were observed for fatigue at end of treatment (10.9 vs 20.1; p = 0.0445) and insomnia at cycle 5 day 1 (-9.3 vs 2.8; p = 0.0176), both favoring tebentafusp, and for constipation at end of treatment (3.2 vs -3.5; p = 0.0296), favoring investigator's choice. LS mean scores over time are illustrated in Figure 12,Figure 13 and Figure 14 for PRO symptoms of fatigue, insomnia, and constipation. Overall, there was no significant difference between the tebentafusp and investigator's choice arms for time to sustained deterioration across the different EORTC-QLQ-C30 domains. [36]

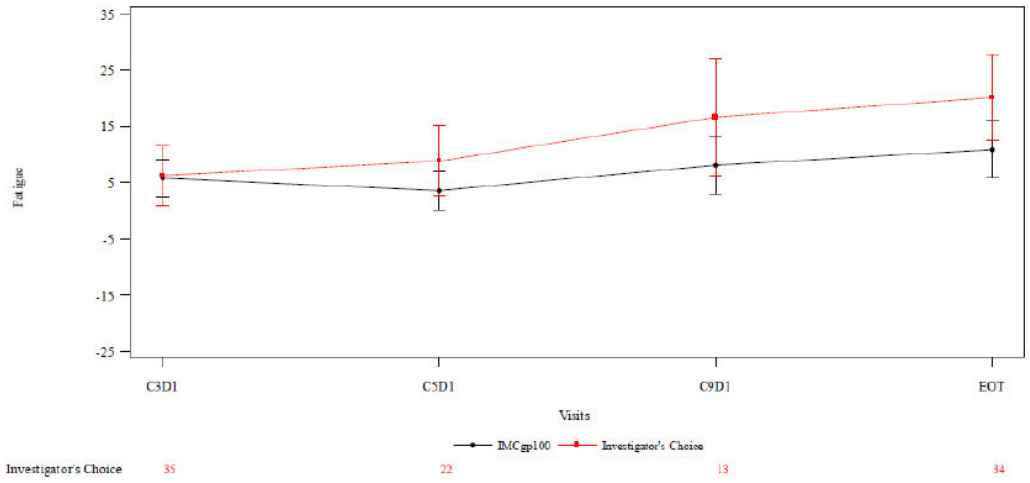


Figure 12. Least squares mean score over time for patient reported fatigue [36].

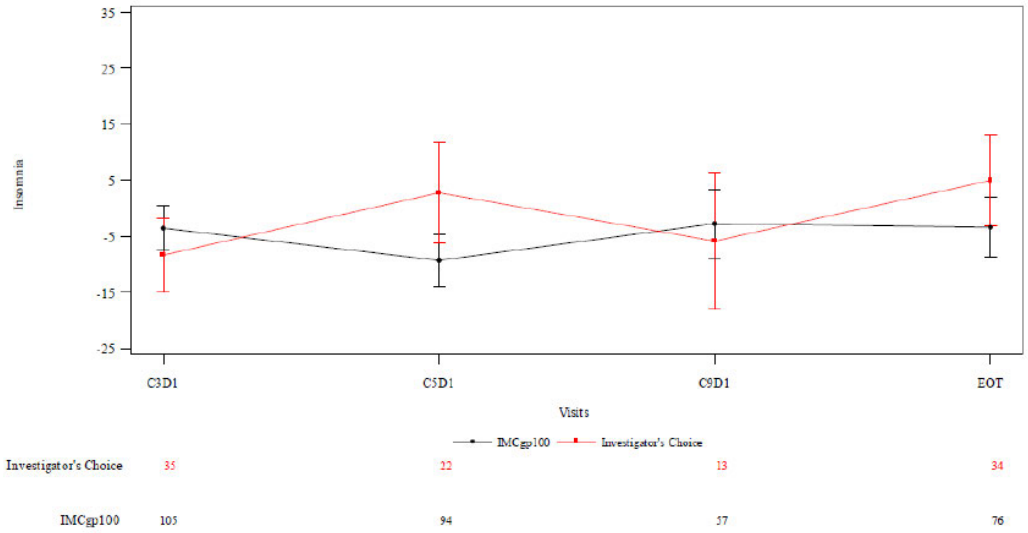


Figure 13. Least squares mean score over time for patient reported insomnia [36].

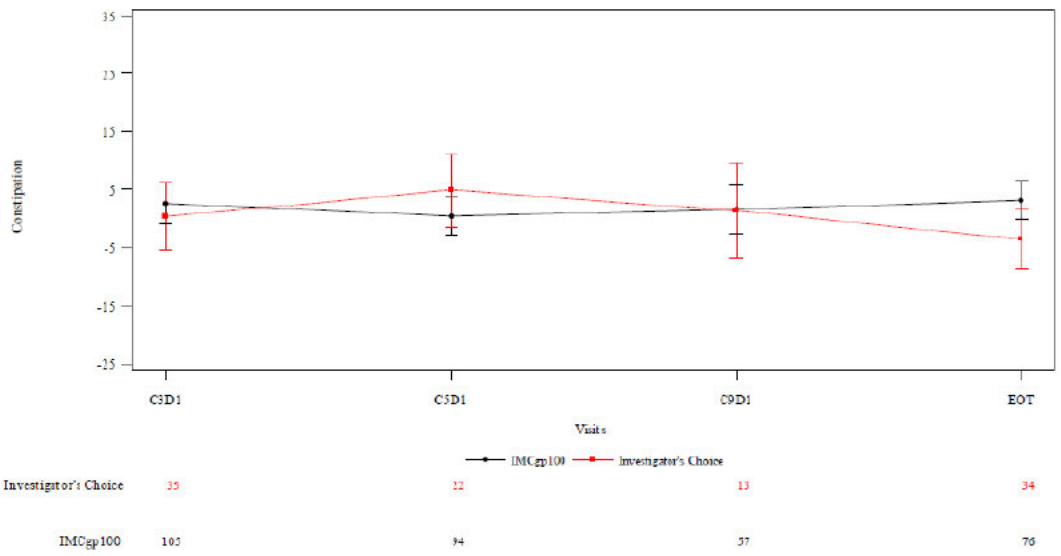


Figure 14. Least squares mean score over time for patient reported constipation [36].

The EORT QLQ-C30 is a condition specific measure and is one of the most commonly used in oncology trials [37]. However, it is not preference-based and thus cannot be used directly in economic evaluation.

EQ-5D data

Evaluation of HRQoL using EQ-5D directly from patients is the approach used in the CE model.

In both the tebentafusp and investigator's choice arms, patients were considered to be domain compliant through cycle 17 day 1, with generally similar rates between the arms. Subsequently, patients in the tebentafusp arm remained domain compliant through cycle 29 day 1, whereas compliance in the investigator's choice arm decreased to 40.0% at cycle 21 day 1 and 33.3% at each of cycle 25 day 1 and at end of treatment. [36] An overview of the compliance rates is provided in Table 114 in appendix H.

The descriptive analysis is based on the complete case data. At baseline a high proportion of patients report problems on the pain/discomfort (39%) and anxiety/depression dimensions (50%) was observed. Some patients report problems on the mobility (16%) and usual activities (20%) dimensions, and a small proportion of patients report problems onself-care (5%). [36] Summary statistics at baseline are presented in Table 11.

Table 11. EQ-5D summary statistics at baseline. [36]

	Mobility count (%)	Self-care count (%)	Usual activities count (%)	Pain/discomfort count (%)	Anxiety/depression count (%)
Level 1	229 (84.2%)	258 (94.9%)	219 (80.5%)	165 (60.7%)	135 (49.6%)
Level 2	32 (11.8%)	11 (4.0%)	41 (15.1%)	77 (28.3%)	85 (31.3%)
Level 3	7 (2.6%)	1 (0.4%)	11 (4.0%)	27 (9.9%)	40 (14.7%)
Level 4	2 (0.7%)	0 (0.0%)	1 (0.4%)	3 (1.1%)	7 (2.6%)
Level 5	2 (0.7%)	2 (0.7%)	0 (0.0%)	0 (0.0%)	5 (1.8%)
Reporting problems[a]	43 (15.8%)	14 (5.1%)	53 (19.5%)	107 (39.3%)	137 (50.4%)

[a]Level 2 to level 5

The EQ-5D-5L utility scores were initially analyzed and derived for the UK HTA by applying the van Hout et al. 2012 crosswalk algorithm [38] and using the UK EQ-5D-3L value set [39]. Thus, the following EQ-5D index scores presented in the following are based on the 3L value set. In the health economic analysis, the 5L value set have been applied in line with the DMC guideline, see section 8.4.

The mean EQ-5D index score at baseline was 0.835 (Table 12), and the mean age in the trial was 62 years old; this mean index baseline score is slightly higher than the UK EQ-5D norm for this age group, 0.799 [40], although similar.

At baseline, no differences in EQ-5D-5L scores were observed between the treatment arms for any of the domains. In general, throughout the study, mean change from baseline was similar between the treatment arms for all domains, although a slightly decreasing trend were noted. Summary statistics at each assessment time point are presented in Table 12. Mean EQ-5D scores, over time and by treatment arms, are also presented graphically in Figure 15. [36]

Table 12. EQ-5D utility summary statistics at each assessment time point.

Utility: UK value set	Count	Mean	25th percentile	Median	75th percentile	Minimum	Maximum
Baseline	272	0.835	0.765	0.848	1.000	-0.101	1
Cycle 3 day 1	218	0.864	0.768	0.879	1.000	0.363	1
Cycle 5 day 1	162	0.863	0.768	0.879	1.000	0.321	1
Cycle 9 day 1	99	0.838	0.768	0.837	1.000	0.161	1
Cycle 13 day 1	63	0.825	0.750	0.848	1.000	0.115	1
Cycle 17 day 1	33	0.834	0.778	0.837	1.000	0.249	1
Cycle 21 day 1	19	0.816	0.750	0.877	1.000	-0.025	1
Cycle 25 day 1	13	0.805	0.679	0.837	0.879	0.540	1
Cycle 29 day 1	16	0.808	0.738	0.837	0.879	0.408	1
End of treatment	170	0.774	0.689	0.778	0.883	-0.115	1
Survival follow-up day 90	56	0.762	0.693	0.778	0.881	-0.021	1
Survival follow-up day 180	35	0.803	0.758	0.837	1.000	-0.257	1
Survival follow-up day 270	25	0.820	0.768	0.879	1.000	0.275	1
Survival follow-up day 360	19	0.760	0.736	0.778	0.879	0.320	1

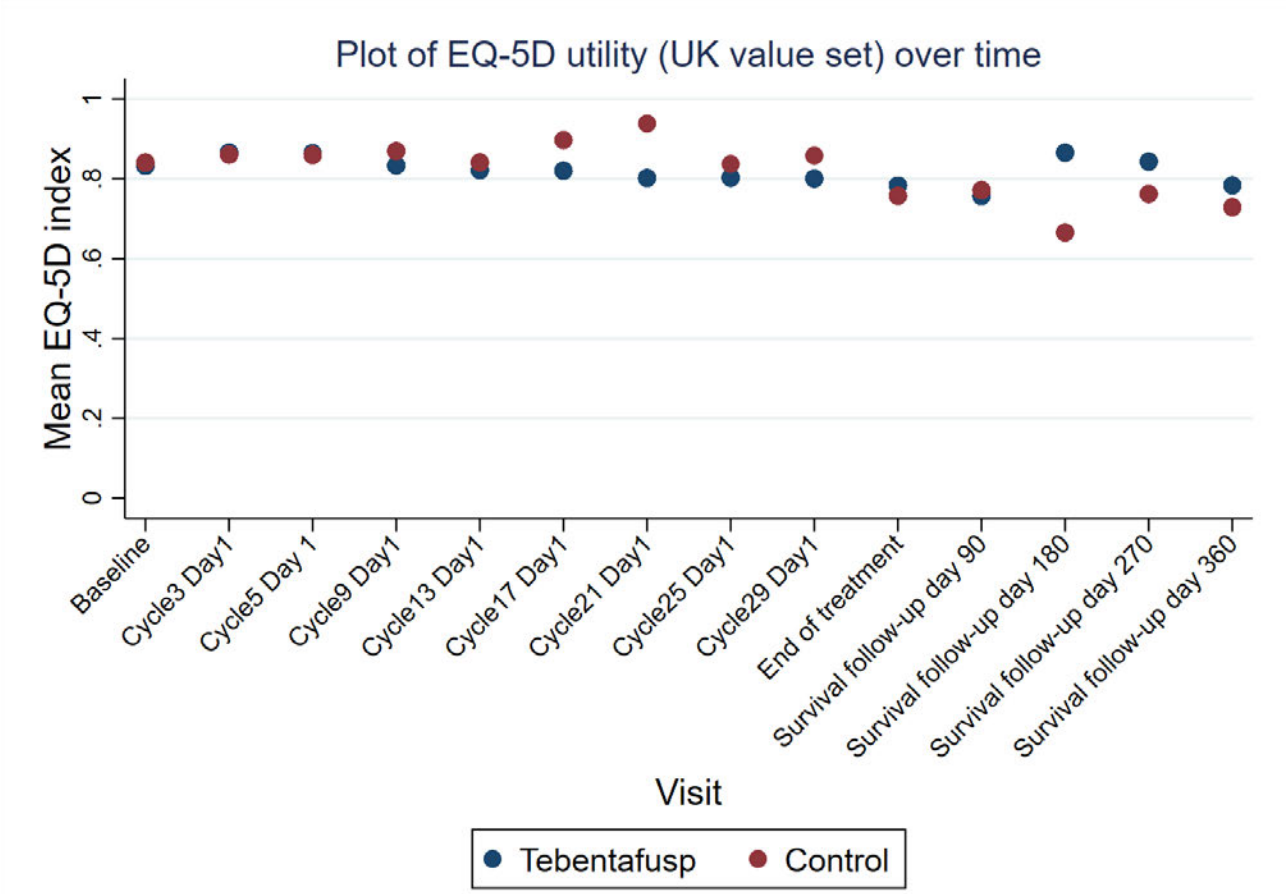


Figure 15. Plot of EQ-5D mean utility at each assessment time point and by treatment arm. [36]

7.1.2.2 GEM1402 overall survival and progression-free survival

The primary endpoint was 12-month OS, defined as the time from the first dose to death from any cause in the ITT population (n = 52). PFS was a secondary endpoint and defined as the time from the first nivolumab dose to progression of disease or death from any cause. The OS and PFS were calculated using the KM method with CIs at 95%. A logistic regression model and a Cox proportional hazard model comprising relevant clinical factors were used to evaluate the potential association with the response to treatment and survival variables. Subjects without PFS events were censored at the date of last clinical evaluation, and those alive had OS censored at the date of the last reported contact. Variables with P < 0.1 in the univariate analysis were included in the model. At the data collection cutoff (July 9, 2019), the median follow-up was 13.4 months (range, 0.8-35.2 months). [18]

The median OS was 12.7 (95% CI, 7.1 to 18.3 months), see Figure 16, with a 12- and 24-month OS rate of 51.9% (95% CI, 38.3 to 65.5) and 26.4% (95% CI, 14.2 to 38.6), respectively. OS in patients with only liver metastasis was shorter than that in patients with metastasis in other locations beyond the liver (9.2 months v 23.5 months) and in those with both liver and other metastasis (15.5 months), but the difference was not significant (P = 0.146), see Figure 17. [18]

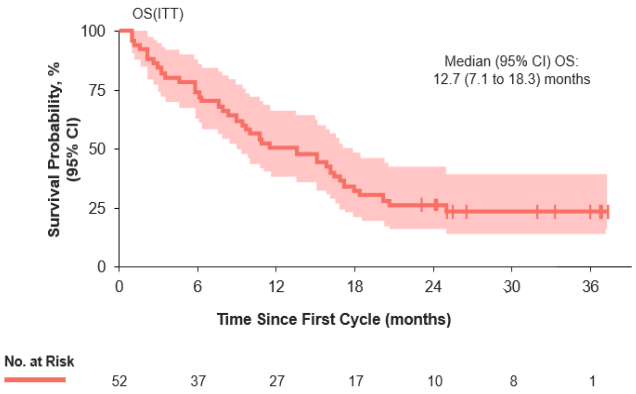


Figure 16. Median overall survival [18].

Abbreviation: CI, confidence interval; ITT, intention-to-treat; OS, overall survival

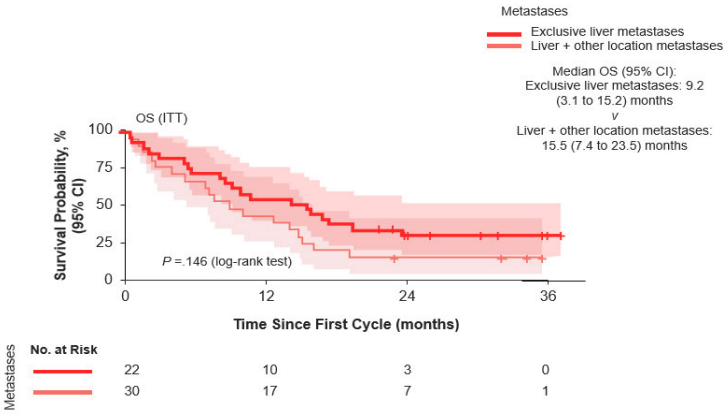


Figure 17. Overall survival by different metastasis patterns [18].

Abbreviation: CI, confidence interval; ITT, intention-to- treat; OS, overall survival

The median PFS was 3.0 (95% CI, 2.0 to 4.1) months, see Figure 18, with 28.8% (95% CI, 16.5 to 41.1) and 19.2% (95% CI, 8.5 to 29.9) of patients being progression free at 6 and 12 months, respectively. [18]

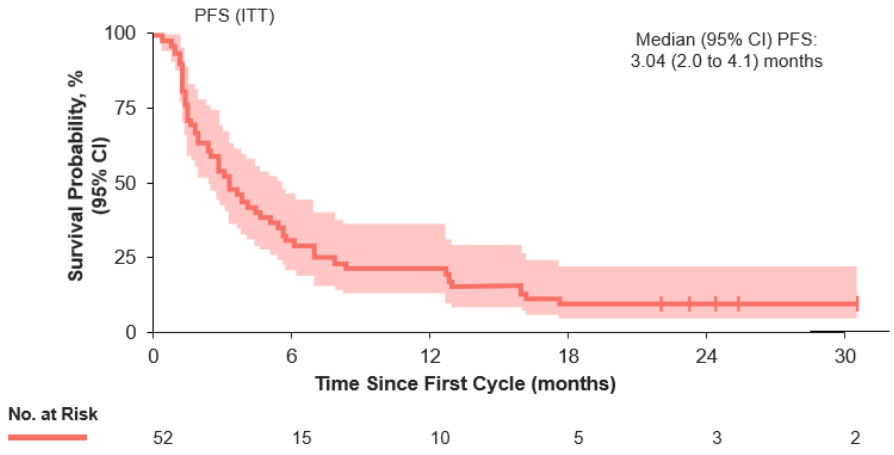


Figure 18. Median PFS in the GEM1402 study [18].

Abbreviation: CI, confidence interval; ITT, intention-to-treat; No, numbers; PFS, progression-free survival

7.1.2.3 GEM1402 Safety results

A medical history was obtained at baseline to capture relevant underlying conditions. Safety was evaluated for all patients receiving at least one dose of nivolumab and ipilimumab. Any occurrence of non-serious and serious AEs was reported from first dose up to and including follow-up visits. Safety was evaluated by using the NCI CTCAE, Version 4.0, and was based on medical review of AE reports, the results of vital sign measurements, physical examinations, and clinical laboratory tests.[18]

A total of 52 (100%) patients developed an AE, while 39 (75%) experienced a grade 3 or above AE. 49 (94.2%) experienced a TRAE, while 30 (57.7%) experienced a grade 3 or above TRAE. The most common TRAEs were skin-related events (61.5%), followed by fatigue (57.7%) and liver-related events (36.5%). 30 (57.7%) experienced a serious treatment-related adverse event (TR-SAEs), while 21 (40%) experienced a grade 3 or above TR-SAEs. The most

common TR-SAEs included fever (four events), liver-related events (three events) and diarrhea (three events). Two deaths (3.8%) were observed in patients who had experienced a TRAE. The TRAEs in question were Guillain-Barré syndrome and thyroiditis, respectively. See Table 13 and appendices D and E for further details. [18] Overall, the AE observed in the study did not differ greatly from the profile observed for ipi/nivo in CM. [18]

Table 13. GEM1402 safety results [18].

	Ipilimumab/Nivolumab (N = 52)
AEs, n (%)	52 (100)
TRAEs	49 (94.2)
TRAEs GRADE ≥ 3	30 (57.7)
TR-SAEs	30 (57.7)
TR-SAEs GRADE ≥ 3	21 (40.4)
Non-treatment related serious AEs	26 (50)
Non-treatment related serious event grade ≥ 3	14 (26.9)
Discontinuation due to clinically unacceptable toxicity	23.1% (12)
Treatment related deaths	2 (3.8)

Abbreviations: AE, adverse event; TRAE, treatment related adverse event; TR-SAE, treatment related serious adverse event

7.1.2.4 Pelster et al. 2020 efficacy and safety results

7.1.2.4.1 Overall Survival

Median overall survival and 1-year survival rate is a secondary endpoint in Pelster et al. 2020. OS is defined as the time from enrollment to death due to any cause, while 1-year overall survival rate was defined as the percentage of patients alive 1 year from enrollment. The median duration of follow-up was 13.0 months. [41]

The following results were observed for OS; the median OS was 19.1 months [95% CI, 9.6 months – not reached] and the 1-year OS rate was 56% [95% CI 38% to 71%]. [41]

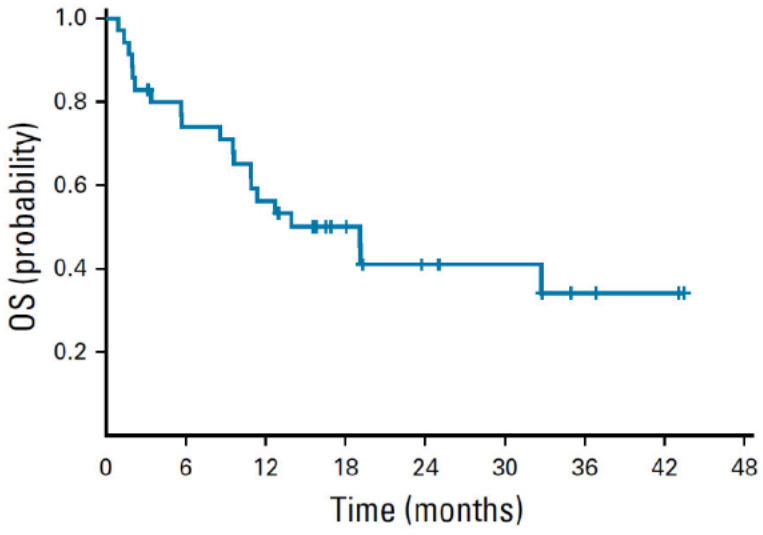


Figure 19: Kaplan-Meier estimate of overall survival (OS) [41].

7.1.2.4.2 Safety

Adverse events were assessed using the NCI CTCAE. Safety was monitored via adverse event assessments, common laboratory tests, and liver function tests. Monitoring where performed at each treatment during the induction treatment and every 4th week hereafter, until the patient was removed from the study. All patients were evaluable for toxicity from enrollment until day 100 after the last dose of the study drug. [41]

Thirty two (32) out of 35 patients (91%) experienced an AE while 29 (83%) experienced a TRAE. Grade 3-4 TRAEs occurred in 14 (40%). The most common AEs of any grade were diarrhea, abnormal liver enzymes, pruritis and hypothyroidism. Ten (10) patients corresponding to 29% discontinued treatment due to adverse events. No treatment related deaths occurred. [41]

Table 14. Pelster et al. 2020 safety data [41].

	Ipi/Nivo (N = 35)	
	Any	**Grade 3 or 4**
Any AEs, n (%)	32 (91)	20 (57)
TRAEs	29 (83)	14 (40)
Discontinuation due adverse events	10 (29)	-
Deaths due to adverse events	0 (0)	-

Abbreviations: AE, adverse event; TRAE, treatment related adverse event; TR-SAE, treatment related serious adverse event

7.1.3 Comparative analyses of efficacy and safety (IMCgp100-202 compared to GEM1402)

7.1.3.1 Methodology

In the Danish clinical setting, the relevant comparator to tebentafusp is a combination treatment with ipi/nivo. The IMCgp100-202 study does not include this comparator[4], meaning it is necessary to conduct an indirect comparison.

The method used was a MAIC. This methodology enables individual patient data (IPD) for tebentafusp from IMCgp100-202 to be compared to published summary level data from a study of ipi/nivo, while adjusting for differences in key patient characteristics between the two studies, in order to reduce the bias. As there is no common comparator linking tebentafusp and ipi/nivo, a so-called “unanchored” MAIC was performed.

No formal testing was conducted for the analyses, which are essentially exploratory in nature. Rather, HR and 95% CI were used to help make general conclusions about the comparisons being made. As well as the MAIC, a simple unadjusted indirect comparison (UAIC) was also performed, to evaluate the impact of the match-adjustment.

Two potential comparator studies were identified in the SLR described in section 6: GEM1402 [18] and Pelster et al. 2020 [28]. Both are single arm studies of ipi/nivo in UM. GEM1402 was selected as the most appropriate comparison because:

- GEM1402 is a purely untreated population like IMCgp100-202, while Pelster et al. 2020 is only 57% previously untreated [18,28].
- GEM1402 is larger than Pelster et al. 2020, n=52 vs. N=33 [18,28].

- GEM1402 is based on multi-institution data, while Pelster et al. 2020 is single institution [18,28].
- GEM1402 reports more of the key covariates used in matching the populations, see Covariates used in the MAIC under Appendix F [18,28].

As described above the population in Pelster et al. 2020 included both previously treated and untreated patients with mUM; 57% were previously untreated, 29% had received 1 prior treatment, 9% had received three prior treatment and 6% had received 4 prior treatment[41]. IMCgp100-202 however includes only previously untreated patients[4]. As the studies include two different patient population groups, it is not scientifically correct to compare IMCgp100-202 and Pelster et al. 2020 in a MAIC, but per request by the DMC the study IMCgp100-202 and Pelster et al. 2020 was compared using a narrative analysis.

Matching covariate can only be done on covariates that are reported in the summary level publication in GEM1402. The list of available variables is [18]:

- Age (years) – median
- Gender
- Baseline LDH – proportion in normal range (rather than log-transformed continuous variable)
- Baseline alkaline phosphatase – proportion in normal range (rather than log-transformed continuous variable)
- Disease location – hepatic only, extrahepatic only, hepatic and extrahepatic (rather than largest metastatic lesion continuous variable)
- ECOG PS at baseline, proportion 0 or ≥1

Time since primary diagnosis could not be used in the matching as it was not reported in GEM1402[18]. This is a potential unmeasured effect modifier and prognostic variable which should be considered when interpreting the results. No other important potential unmeasured effect modifier and prognostic values were identified.

As there are only a small number of patients with extrahepatic disease in IMCgp100-202 compared to GEM1402, this may impact the effective sample size and/or cause modelling issues. Therefore, two additional sensitivity analyses were planned to explore alternative ways of defining the disease location covariate applicable for matching:

1. Disease location pooled categories – Hepatic only, any extrahepatic (pooled extrahepatic only + hepatic and extrahepatic)
2. Largest metastatic liver lesion – proportion ≤3cm, >3cm, no liver lesions

Patients with missing values for any variables for the IMCgp100-202 study were excluded from the analysis. Proportions from the GEM1402 study used the number of subjects reporting data for that variable as a denominator (missing data was excluded from calculation of proportions for matching).

The endpoints investigated in the MAIC are OS, PFS and safety, for a complete description of the methodology please refer to Appendix F.

7.1.3.2 Results from the MAIC: Overall Survival (IMCgp100-202 study vs. GEM1402)

7.1.3.2.1 Overall survival analysis

Tebentafusp had an OS of 21.6 months and a 12-months survival rate of 78.6%, with the corresponding numbers for ipi/nivo being 12.1 months and 51.2%, see Figure 20. The median OS and 12-months OS rate for tebentafusp is therefore improved with 9.5 months and with 27.4%, respectively, compared with ipi/nivo. The robust standard error (SE) HR was 0.507 [95% CI, 0.324 -0.793] and the bootstrap HR was 0.507 [95% CI, 0.324 -0.761], see Table 15. [4,18]

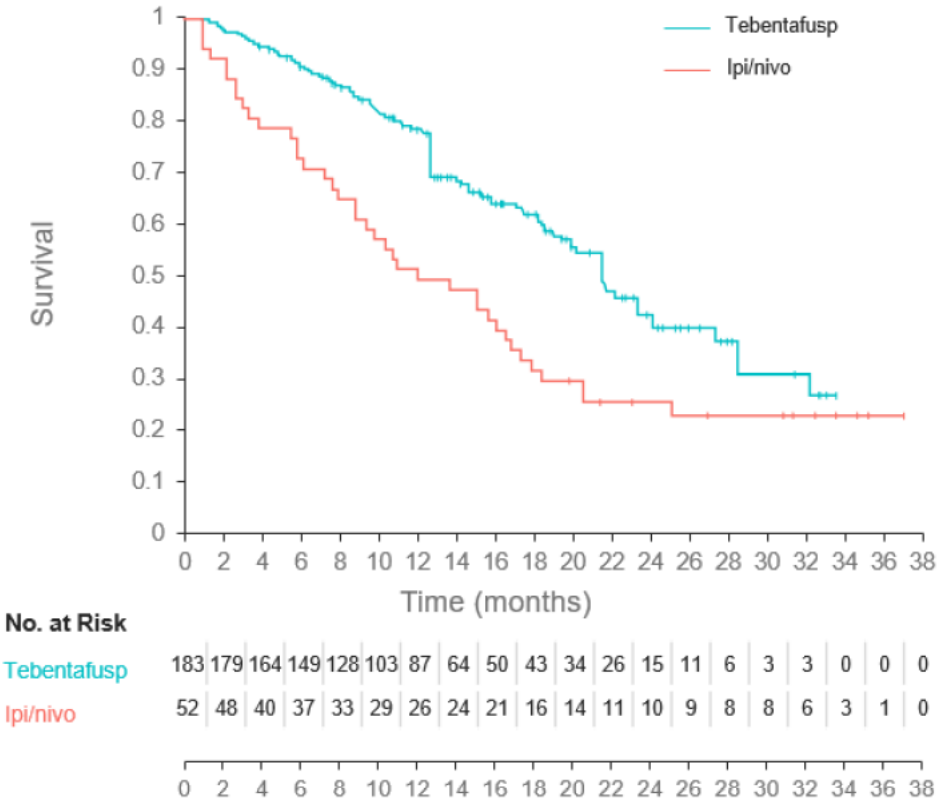


Figure 20. Kaplan-Meier plots of overall survival from the MAIC of tebentafusp versus ipi/nivo [4,18].

Abbreviations: ipi/nivo, ipilimumab in combination with nivolumab; MAIC, match adjusted indirect comparison; No, numbers

Table 15. Overall survival from the MAIC [4,18].

MAIC tebentafusp vs. ipi/nivo						
Treatment	**N**	**Events**	**Median OS (months)**	**12 months Survival (%)**	**HR [95% CI] robust SE**	**HR [95% CI] bootstrap**
Tebentafusp*	182.6	61.4	21.6	78.6	0.507 (0.324 – 0.793)	0.507 (0.324 – 0.761)
Ipi/nivo	52	39	12.1	51.2	-	-

* Data based on MAIC, see Appendix F.

Abbreviations: CI, confidence interval; HR, hazard ratio; Ipi/nivo, ipilimumab in combination with nivolumab; OS, overall survival; SE, standard error

7.1.3.2.2 Overall survival analysis on pooled extrahepatic patients

Tebentafusp had an OS of 23.4 months and a 12-months survival rate of 76.4%, with the corresponding numbers for ipi/nivo being 12.1 months and 51.2%, see Figure 21. The median OS and 12-months OS rate for tebentafusp is therefore improved with 11.3 months and with 25.2% percentage points, respectively, compared with ipi/nivo. The robust SE HR was 0.476 [95% CI, 0.313 -0.724], see Table 16. [4,18]

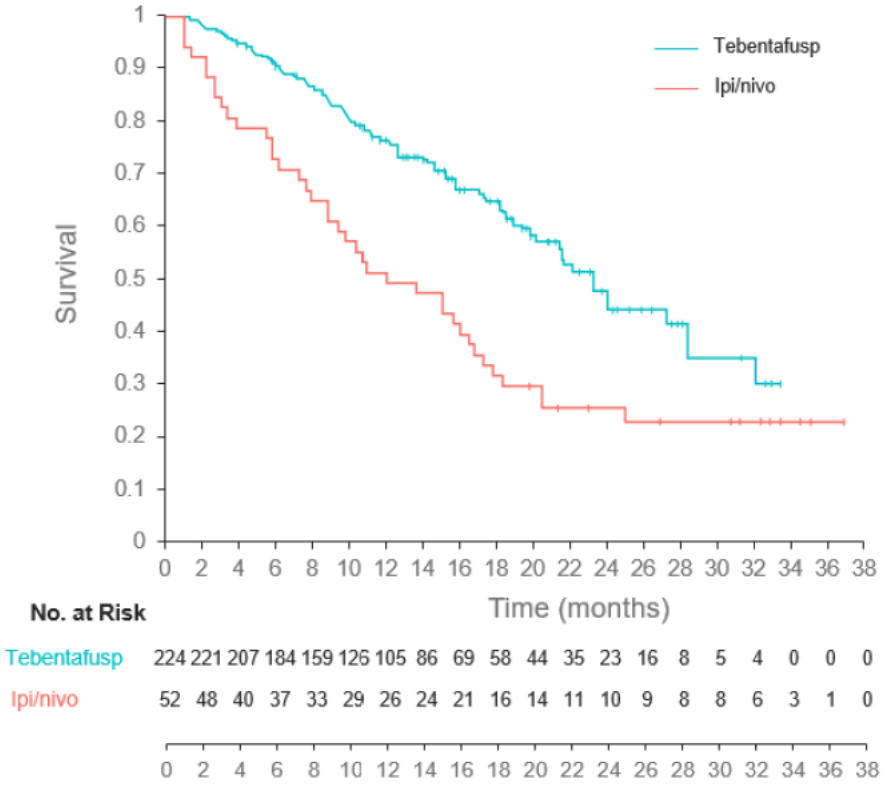


Figure 21. Kaplan-Meier plots of overall survival from the MAIC of tebentafusp for pooled extrahepatic categories versus ipi/nivo [4,18].

Abbreviations: ipi/nivo, ipilimumab in combination with nivolumab; MAIC, match adjusted indirect comparison; No, numbers

Table 16. Overall survival from the MAIC for pooled extrahepatic categories [4,18].

MAIC tebentafusp vs. ipi/nivo, extrahepatic only and hepatic+extrahepatic categories					
Treatment	**N**	**Events**	**Median OS**	**12 months Survival**	**HR [95% CI] robust SE**
Tebentafusp	224.5	73.4	23.4	76.4	0.476 (0.313 – 0.724)
Ipi/nivo	52	39	12.1	51.2	-

Abbreviations: CI, confidence interval; HR, hazard ratio; ipi/nivo, ipilimumab in combination with nivolumab; MAIC, match-adjusted indirect comparison; OS, overall survival; SE, standard error

7.1.3.2.3 Overall survival analysis on patients when using liver lesion size covariate

Tebentafusp had an OS of 21.6 months and a 12-months survival rate of 79.6%, with the corresponding numbers for ipi/nivo being 12.1 months and 51.2%, see Figure 22. The median OS and 12-months OS rate for tebentafusp is therefore improved with 9.5 months and 28.4% percentage points, respectively, compared to ipi/nivo. The robust SE HR was 0.495 [95% CI, 0.314 -0.781], see Table 17. [4,18]

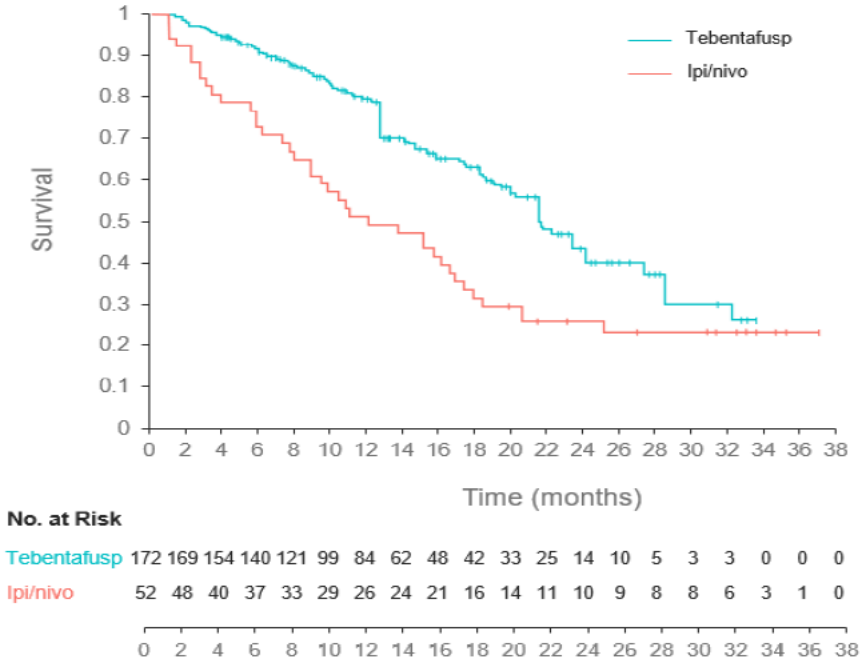


Figure 22. Kaplan-Meier plots of OS from MAIC of tebentafusp when using liver lesion size covariates versus ipi/nivo [4,18].

Abbreviations: MAIC, match-adjusted indirect comparison; No, numbers; OS, overall survival

Table 17. Overall survival from the MAIC when using liver lesion size covariates [4,18].

MAIC tebentafusp vs. Ipi/nivo, liver lesion covariate					
Treatment	**N**	**Events**	**Median OS**	**12 months Survival**	**HR [95% CI] robust SE**
Tebentafusp	172.4	57.1	21.6	79.6	0.495 (0.314 – 0.781)
Ipi/nivo	52	39	12.1	51.2	-

Abbreviations: CI, confidence interval; HR, hazard ratio; ipi/nivo, ipilimumab in combination with nivolumab; MAIC, match-adjusted indirect comparison; OS, overall survival; SE, standard error

7.1.3.2.4 Progression-free survival analysis

Tebentafusp had a PFS of 4.8 months and a 12-months PFS rate of 16.5%, with the corresponding numbers for ipi/nivo being 3.1 months and 15.4%, see Figure 23. The median PFS and 12-months PFS rate for tebentafusp is therefore improved with 1.7 months and with 1.1%, respectively, compared with ipi/nivo. The robust SE HR was 0.647 [95% CI, 0.445- 0.941), see Table 18. [4,18]

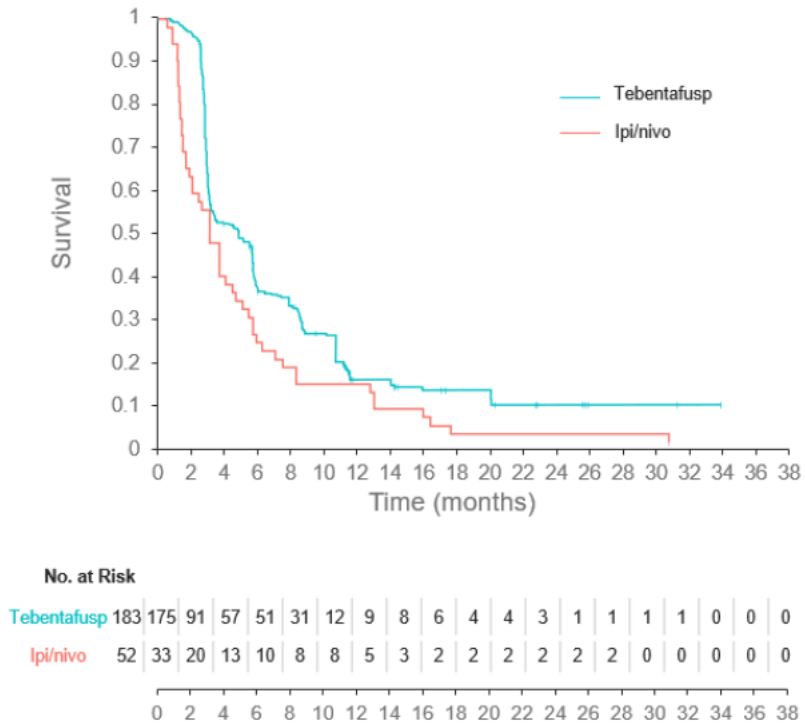


Figure 23. Kaplan-Meier plots of PFS from the MAIC of tebentafusp versus ipi/nivo [4,18].

Abbreviations: MAIC, match-adjusted indirect comparison; No, numbers; PFS, progression-free survival

Table 18. Progression-free survival from the MAIC [4,18].

MAIC tebentafusp vs. ipi/nivo					
Treatment	**N**	**Events**	**Median PFS (months)**	**12-months PFS**	**HR (95% CI), robust SE**
Tebentafusp	182.6	139.1	4.8	16.5%	0.647 (0.445, 0.941)
Ipi/nivo	52	51	3.1	15.4%	

Abbreviations: CI, confidence interval; HR, hazard ratio; ipi/nivo, ipilimumab in combination with nivolumab; MAIC, match-adjusted indirect comparison; PFS, progression-free survival; SE, standard error

7.1.3.2.5 Progression-free survival analysis on pooled extrahepatic patients

Tebentafusp had a PFS of 3.4 months and a 12-months PFS rate of 14.9%, with the corresponding numbers for ipi/nivo being 3.1 months and 15.4%, see Figure 24. The median PFS is therefore improved with 0.3 months, whereas the 12-months PFS rate for tebentafusp is reduced by 1.1%, compared with ipi/nivo. The robust SE HR was 0.702 [95% CI, 0.498 – 0.989), see Table 19. [4,18]

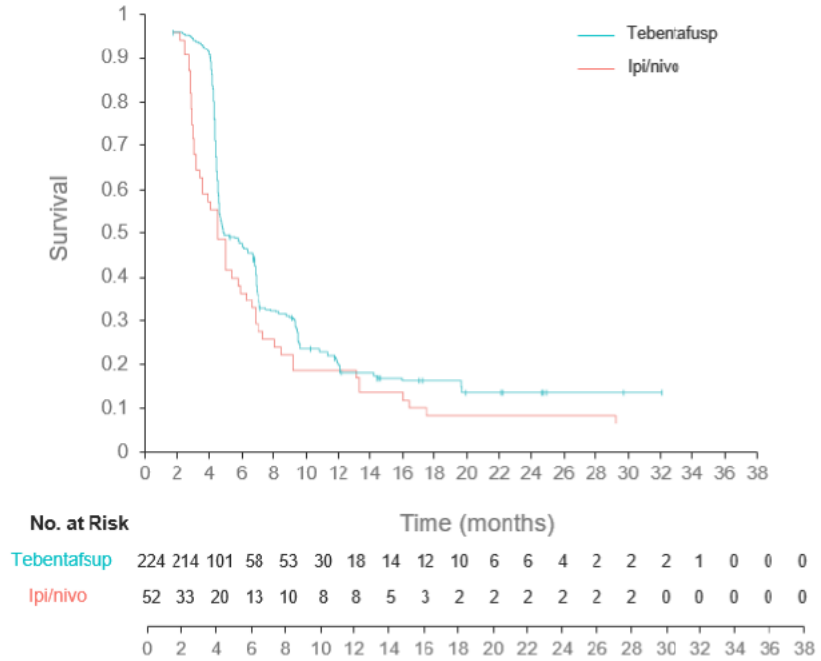


Figure 24. Kaplan-Meier plots of PFS from the MAIC of tebentafusp for pooled extrahepatic categories versus ipi/nivo [4,18].

Abbreviations: MAIC, match-adjusted indirect comparison; No, numbers; PFS, progression-free survival

Table 19. Progression-free survival from the MAIC for pooled extrahepatic categories [4,18].

MAIC tebentafusp vs. ipi/nivo, extrahepatic only and hepatic+extrahepatic categories					
Treatment	**N**	**Events**	**Median PFS (months)**	**12-month PFS rate**	**HR [95% CI], robust SE**
Tebentafusp	224.5	178.4	3.4	14.9%	0.702 (0.498, 0.989)
Ipi/nivo	52	51	3.1	15.4%	

Abbreviations: CI, confidence interval; HR, hazard ratio; ipi/nivo, ipilimumab in combination with nivolumab; MAIC, match-adjusted indirect comparison; PFS, progression-free survival; SE, standard error

7.1.3.2.6 Progression-free survival analysis on patients when using liver lesion size covariate

Tebentafusp had a PFS of 4.8 months and a 12-months PFS rate of 16.8%, with the corresponding numbers for ipi/nivo being 3.1 months and 15.4%, see Figure 25. The median PFS and 12-months PFS rate for tebentafusp is therefore improved with 1.7 months and with 1.4%, respectively, compared with ipi/nivo. The robust SE HR was 0.645 [95% CI, 0.441- 0.944), see Table 20. [4,18]

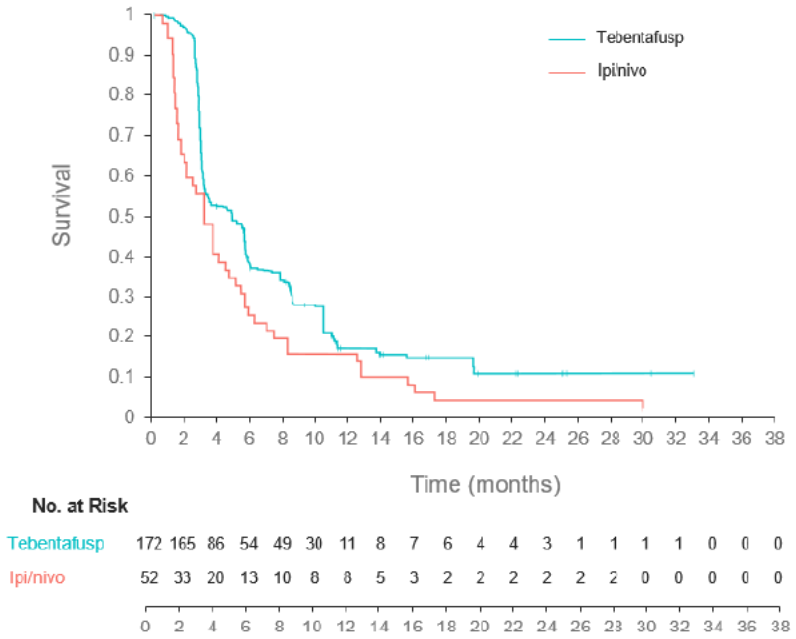


Figure 25. Kaplan-Meier plots of PFS from MAIC of tebentafusp when using liver lesion size covariates versus ipi/nivo [4,18].

Abbreviations: ipi/nivo, ipilimumab in combination with nivolumab; MAIC, match-adjusted indirect comparison; No, numbers; PFS, progression-free survival

Table 20. Progression-free survival from the MAIC when using liver lesion size covariates [4,18].

MAIC tebentafusp vs. ipi/nivo, liver lesion size covariate					
Treatment	**N**	**Events**	**Median PFS (months)**	**12-month PFS rate**	**HR (95% CI), robust SE**
Tebentafusp	172.4	130.7	4.8	16.8%	0.645 (0.441, 0.944)
Ipi/nivo	52	51	3.1	15.4%	-

Abbreviations: CI, confidence interval; HR, hazard ratio; ipi/nivo, ipilimumab in combination with nivolumab; MAIC, match-adjusted indirect comparison; PFS, progression-free survival; SE, standard error

7.1.3.2.7 Unadjusted indirect comparison results

Tebentafusp had an OS of 21.7 months and a 12-months survival rate of 74.7%, with the corresponding numbers for ipi/nivo being 12.1 months and 51.2%. The median OS and 12-months OS rate for tebentafusp is therefore improved with 9.6 months and 23.5% percentage points, respectively, compared to ipi/nivo. The robust SE HR was 0.514 [95% CI, 0.35 -0.756], see Table 21.

Table 21. Overall survival of tebentafusp and ipi/nivo in UAIC [4,18].

UAIC tebentafusp vs. Ipi/nivo, OS					
Treatment	**N**	**Events**	**Median OS**	**12 months Survival**	**HR [95% CI] robust SE**
Tebentafusp	240	82	21.7	74.7	0.514 (0.35 – 0.756)
Ipi/nivo	52	39	12.1	51.2	-

Abbreviations: CI, confidence interval; HR, hazard ratio; ipi/nivo, ipilimumab in combination with nivolumab; OS, overall survival; SE, standard error; UAIC, unadjusted indirect comparison

Tebentafusp had a PFS of 3.3 months and a 12-months PFS rate of 14.7%, with the corresponding numbers for ipi/nivo being 3.1 months and 15.4%. The median PFS is therefore improved with 0.2 months, whereas the 12-months PFS rate for tebentafusp is reduced by 0.7%, compared with ipi/nivo. The robust SE HR was 0.717 [95% CI, 0.525 – 0.978), see Table 22.

Table 22. Progression-free survival of tebentafusp and ipi/nivo in UAIC [4,18].

UAIC tebentafusp vs. Ip/nivo, PFS					
Treatment	**N**	**Events**	**Median PFS (months)**	**12 months PFS rate**	**HR [95% CI], robust SE**
Tebentafusp	240	190	3.3	14.7%	0.717 (0.525, 0.978)
Ipi/nivo	52	51	3.1	15.4%	

Abbreviations: CI, confidence interval; HR, hazard ratio; ipi/nivo, ipilimumab in combination with nivolumab; PFS, overall survival; SE, standard error; UAIC, unadjusted indirect comparison

7.1.3.2.8 Summary of indirect comparison result on overall survival

In all the MAIC analyses, the distribution of the adjusted patient characteristic for tebentafusp was closely matched to ipi/nivo, see Appendix F.

The effective sample size for tebentafusp was reduced considerably for the matchings, including the extrahepatic only or no liver lesions categories. This was because these populations were small in the IMCgp100-202 study. However, it remained larger than the observed sample size for ipi/nivo and was judged large enough for subsequent indirect comparisons to be performed.

In the MAIC, tebentafusp had a significant longer survival than ipi/nivo, between 9.5 – 11.3 months, regardless of covariates. The UAIC showed similar results to the MAIC with a significant median OS improvement of 9.6 months. PFS were significantly increased with 0.3 – 1.7 months when treating with tebentafusp compared to ipi/nivo in the MAIC, the UAIC showed a similar result to the MAIC with a significant median OS improvement of 0.2 months.

7.1.4 Narrative analyses of safety (IMCgp100-202 compared to GEM1402)

Given the number of patients in each treatment group, it is feasible to do a statistical comparison for around the top 5 most frequent AEs on all grades, however due to the difference in total population of each study a MAIC on safety would not provide any significant insights compared to a narrative analysis. The safety profiles were therefore compared using a narrative analysis. Over 90% of all patients on both Tebentafusp and ipi/nivo experiences a TRAE of any grade, when looking at grade ≥ 3 or above TRAES it can be observed that 44% of tebentafusp patients and 57.7% of ipi/nivo patients experiences this, for serious TREAS the number are [redacted] and 57.7% respectively, see Table 23. [4,18,42]

For tebentafusp the most common TRAE where cytokine-related AEs, such as pyrexia (76%), chills (47%), and hypotension (38%), and skin-related AEs, such as rash (83%), pruritus (69%), and erythema (23%). For ipi/nivo the most common adverse effects included, skin related events, fatigue and liver toxicity/liver-related evets. Liver injury due to immune checkpoint inhibitors accounted for 36% of all TRAEs in the current study, see Appendix E. [4,18,42]

According to the clinical expert, the most critical parameters to evaluate in regard to safety of tebentafusp and ipi/nivo are discontinuation due to AEs and death due to AEs. Discontinuation due to AEs and death due to AEs were

reported in 2.0% and 23.1% of patients treated with tebentafusp and ipi/nivo, respectively. Deaths due to AEs were reported in 0% and 2.8% in patients treated with tebentafusp and ipi/nivo respectively, see Table 23. The clinical expert supports that ipi/nivo is a treatment with a substantial AE profile, mainly due to immune-related side effects such as liver related AEs. In tebentafusp patients [redacted] patients experienced liver related AEs grade ≥ 3 while the number was 21.2% for ipi/nivo patients. Another relevant AE that inhibits patient are fatigue. Fatigue was experienced in 41% of tebentafusp patients and 57.7% of ipi/nivo patients. [4,18,42]

The overall safety data according to number of grade ≥ 3 and serious adverse events (SAEs) indicated that tebentafusp has a less toxic AE profile than ipi/nivo. This is further supported by the higher number of patient discontinuations ipi/nivo treatment than tebentafusp treatment and the number of deaths due to AE. The low number of patient discontinuations tebentafusp confirms that tebentafusp has a safe and manageable AE profile, and that CRS is not a major issue. [4,18,42]

Table 23. Adverse events for IMCgp100-202 and GEM1402 [4,18,42].

	Tebentafusp (N=245)	Ipi/Nivo (N = 52)
TRAEs any grade, n (%)	243 (99.2%)	49 (94.2%)
Grade ≥ 3 TRAE, n (%)	109 (44%)	30 (57.7%)
TR-SAE, n (%)	[redacted]	30 (57.7%)
Discontinuation due to TRAEs, n (%)	5 (2.0%)	12 (23.1%)*
Death due to TRAEs, n (%)	0	2 (3.8%)

Abbreviations: AE, adverse events; ipi/nivo, Ipilimumab in combination with nivolumab; TRAE, treatment related adverse events; TR-SAE, serious treatment related adverse event

*Unspecified whether the adverse events are treatment related or treatment emergent, GEM1402 uses the term clinically unacceptable toxicity

7.1.5 Results from the UAIC (IMCgp100-202 study vs. Pelster et al. 2020):

7.1.5.1 Overall Survival

Tebentafusp had an OS of 21.7 months, while ipi/nivo has an overall survival of 19.1 months, the 1-year survival rate was 74.4% vs. 56.2% respectively. The hazard ratio of survival was 0.767 [95% CI 0.464 – 1-269], Figure 26 and Table 24. [4,28]

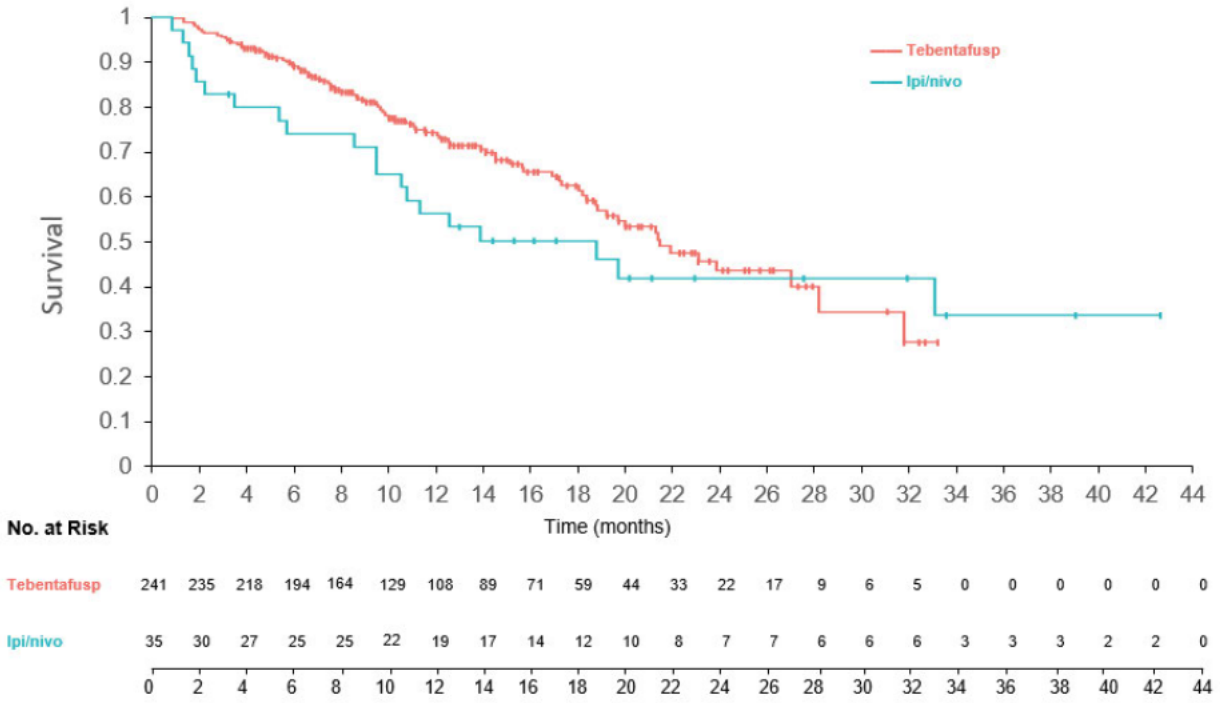


Figure 26. Kaplan-Meier plots of OS from IMCgp100-202 and Pelster et al. 2020 [4,28].

Abbreviations: ipi/nivo, Ipilimumab in combination with nivolumab; No, number.

Table 24. OS of IMGgp100-202 and Pelster et al. 2020 [4,28]..

Treatment	N	Events	Median (months)	12 months survival (%)	HR [95% CI]
Tebentafusp	241	83	21.7	74.4%	0.767 [0.464 – 1.269]
Ipi/nivo	35	20	19.1	56.2%	
Abbreviations: CI, confidence interval; HR, Hazard ratio; ipi/nivo, Ipilimumab in combination with nivolumab; N, number					

7.1.5.2 Safety

As stated in section 7.1.4, the most critical parameters to evaluate in regard to safety of tebentafusp and ipi/nivo according to the clinical expert are discontinuation due to AEs and death due to AEs. Discontinuation due to AEs and death due to AEs were reported in 2.0% and 29.0% of patients treated with tebentafusp and ipi/nivo, respectively. Deaths due to AEs were reported in 0% of patients in both patient groups.

The clinical expert supports that ipi/nivo is a treatment with a substantial AE profile, mainly due to immune-related side effects such as liver related AEs. In tebentafusp patients 6.1% patients experienced liver related AEs grade ≥ 3 was between 11 – 17 % for patients treated with ipi/nivo[4,28].

According to the safety data of tebentafusp and ipi/nivo, tebentafusp has less toxic AE profile than ipi/nivo. This can be observed by the higher number of patient discontinuations ipi/nivo treatment than tebentafusp (29% vs 2%). The low number of patient discontinuations tebentafusp confirms that tebentafusp has a safe and manageable AE profile, and that CRS is not a major issue.

Table 25. Adverse events for IMCgp100-202 and Pelster et al. 2020 [4,28].

	Tebentafusp (N=245)	Ipilimumab/Nivolumab (N = 35)
TRAEs any grade, n (%)	243 (99.2%)	32 (91)
Grade ≥ 3 TRAE, n (%)	109 (44%)	14 (40)
Discontinuation due to TRAEs, n (%)	5 (2.0%)	10 (29)
Death due to TRAEs, n (%)	0	0

Abbreviations: TRAE, treatment related adverse events

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8. Health economic analysis

8.1 Model

A systematic literature search was conducted to identify cost-effectiveness (CE) studies, which potentially could support the model developed for this application. However, since tebentafusp is a novel therapy and the first pharmaceutical to be assessed by the DMC for the treatment of mUM, no CE studies were identified. Hence, a de novo economic model was developed, in Microsoft Excel®, from the perspective of the National Health Service (NHS) in England and Wales in the first instance, in anticipation of submission to the National Institute for Health and Care Excellence (NICE) in 2021. However, the model was designed with a flexible architecture, allowing local adaptation to support health technology assessment (HTA) submissions in various markets. The model was adapted to Danish setting and model conceptualization was based on the clinical data available, a Danish real-world evidence (RWE) study, a target review of previous HTAs is metastatic melanoma, and insights from a clinical expert [16]. Features of the economic analysis are presented in Table 26.

Table 26. Features of the economic model.

Features	Description	Justification
Patient population	Adult patients with HLA-A*02:01 positive mUM, without prior treatment in the metastatic setting	Tebentafusp recognizes and thus targets HLA-A*02:01 positive melanoma cells.[4]
Perspective	Limited societal perspective	As per DMC guideline
Time horizon	Lifetime (35 years)	To capture health benefits and costs in line with DMC guideline. Based on the mean age in the RWE study, the starting age of the patient population is 65 years, this assumes a maximum patient age of 100 years [16].
Cycle length	One week	Consistent with the length of tebentafusp treatment cycles, and to reflect timing of transitions to disease progression and death
Half-cycle correction	Yes	Applied to account for the over or under estimation of transitions occurring at the beginning or end of the cycle [43]
Days per year	365.25	N/A
Discount rate	A discount rate of 3.5% was applied annually for both costs and health effects.	As per DMC guideline and in agreement with the Danish Ministry of Finance [44,45]
Model structure	Three-state (pre-progression, post-progression, and death) partitioned survival model	Partitioned survival models are commonly used to model cancer treatments [46].

Intervention	Tebentafusp	
Comparators	Ipi/nivo	Danish clinical practice according to the clinical expert
Clinical parameters	OS, PFS, dosing, and grade ≥3 Aes. Clinical inputs for all treatment arms were estimated using IPD from the GEM1402 [18] and the IMCgp100-202[4]	
Valuation of health effects	European Quality of Life – 5 dimensions – 5 levels (EQ-5D-5L) estimated utility values by treatment and health state	
Economic parameters	Treatment costs (drug and administration), patient time costs (patient time cost per hour, patient transportation costs to and from hospital), medical costs (outpatient visits, hospitalization, emergency room visits, and intensive care unit visits), AE management costs, and terminal care costs	As per DMC guideline [45]
Model outputs	Total costs and by category Total Lys and QALYs and by health states Incremental cost per QALY gained Budget impact analysis	

Abbreviations: AE, adverse event; DMC, Danish Medicines Council; EQ-5D-5L, European Quality of life – 5 dimensions – 5 levels; ipi/nivo, ipilimumab in combination with nivolumab; LY, life-years; mUM, metastatic uveal melanoma; N/A, not available; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life-years

8.1.1 Model structure

The model employs a partitioned survival method to determine the proportion of patients within each of the health states at every model cycle. The model is composed of three mutually exclusive health-state (pre-progression, post-progression, death) (Figure 27), which represent the stages of disease in mUM and are in line with the primary (OS) and secondary (PFS) efficacy endpoints in the IMCgp100-202 study. Patients enter the model in the pre-progression health state and stay in this state until disease progression is confirmed, upon which they move to the post-progression state (PD). Transition to the death state, which is an absorbing state, may occur from both the pre-progression and post-progression states, at any time point within the model. Patients cannot transition back from PD to PFS. The post-progression state is defined in accordance with the phase III IMCgp100-202 clinical trial secondary efficacy endpoint of PFS, as patients having confirmed disease progression per RECIST v1.1.

A one-week cycle length was used, to reflect patterns of treatment administration (weekly for tebentafusp) and transitions to disease progression. Half-cycle correction is applied to account for the over or under estimation of transitions occurring at the beginning or end of the cycle. The model base case uses a lifetime horizon, which is equivalent to 35 years based on the age of the cohort at the start of the model which is based on the median age reported in the RWE study (65 years old). The model time horizon was chosen to be sufficiently long to capture differences in all relevant costs and health benefits in line with the DMC guideline [45]. All costs and health effects are discounted at 3.5% from year 0-35 [44]. Background mortality was applied to reflect the Danish population's general mortality and to ensure that survival does not exceed that of the general population.

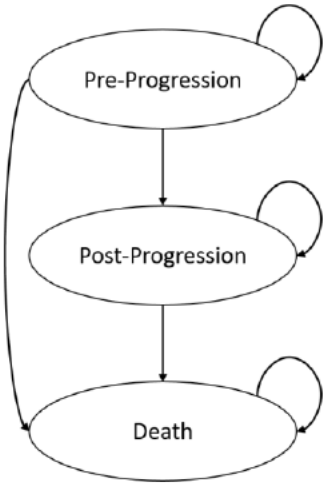

Figure 27. Schematic model structure.

8.1.2 Assumptions

A number of key assumptions were made in the base-case analysis and are summarized in Table 27.

Table 27. Key model assumptions.

Assumption	Rationale
Time to discontinuation was modelled based on a simple approach where a fraction of previously progressed patients was added to the current PFS population • The 'mean duration of treatment beyond progression' determined the number of previous cycles to include • The 'percent of patients treatment beyond progression' determined the fraction of progressed patient carried forward	As per the study protocol IMCgp-100-202, some patients continued to receive study drug beyond disease progression. Therefore, PFS may underestimate the proportions of patients on-treatment in a model cycle. Data from the IMCgp-100-202 trial and expert opinions were used to adjust the PFS curves to account for the additional treatment given. According to the clinical expert this assumption is not applicable to patients treated with ipi/nivo in clinical practice and it was therefore not assumed for the ipi/nivo arm in the model.
Cost	
Vial sharing is not allowed in either arm	This assumption was made in line with tebentafusp summary of product characteristics (SmPC) and given the very small patient population, implementing vial sharing would be challenging in clinical practice.
Post-progression health state costs (i.e. BSC) have been applied as a one-off cost	BSC is assumed to be provided for an average of four months in line with the study by and applied as a one-off cost upon progression for simplicity in the model.
The cost of AEs is applied as a one-off cost in the first model cycle, expected for endocrine disorders which was applied every six months.	In line with previous economic models. AEs with tebentafusp occurred mainly with the first three doses based on clinical experts' opinion. Endocrine disorders may be long-lasting, approach in line with TA319.

End-of-life costs of one year were applied to all patients in the model cycle in which patients die.	This assumption is in line with previous oncology models. It is expected that the majority of health care resource use required for palliative care in end-of-life patients is concentrated towards the last few months before their death.
Utilities	
Utilities modelled based on time-to-death	Based on clinical experts' opinion, this approach better reflect the changes in QoL of patients with metastatic UM, than disease status.
Disutility related to AEs are applied in the first model cycle.	In line with recent oncology models [47,48]. This assumption was made on the basis that AEs are expected to occur and be managed shortly after treatment during the monitoring period for tebentafusp. This approach is considered conservative for ipi/nivo where the level of toxicity is much higher as reported in section 7.1.4 and the AEs do necessarily occur shortly after treatment administration.

Abbreviations: AE, adverse event; BSC, best supportive care; ipi/nivo, ipilimumab in combination with nivolumab; PFS, progression-free survival; SmPC, summary of product characteristics; UM, uveal melanoma; QoL, quality of life

8.1.3 Model inputs

8.1.3.1 Clinical inputs

Ipi/nivo was not a comparator in the phase III IMCgp100-202 study. Hence, a MAIC was conducted to assess the clinical effectiveness of tebentafusp against ipi/nivo. The MAIC is based on the October 2020 data cut-off of the IMCgp100-202 trial and a single arm study of ipi/nivo in mUM [18]. Detailed results of the MAIC can be found in the supplementary report by Immunocore. AEs rates are taken from the IMCgp100-202 trial for tebentafusp and the study for ipi/nivo [18]. The state occupancy, i.e., the proportion of patients alive in the PFS and PD states, are derived from the PFS and OS curves fitted to the data and presented in section 8.3.

8.1.3.2 Drug costs

Clinical evidence suggests that some patients treated with immunotherapies, including tebentafusp, will derive clinical benefit after an initial assessment of PD. Therefore, as per the IMCgp100-202 study protocol, patients could continue treatment beyond disease progression. To estimate the total drug costs accrued within the model time horizon for the intervention and comparator, it was necessary to first determine the proportion of patients on treatment during each model cycle.

The IMCgp100-202 study reported the proportion of patients receiving the study treatments beyond disease progression and the mean duration of this extended treatment. In the study, 43.3% and 14.3% received treatment beyond progression in the intervention and comparator arm, respectively. However, the clinical expert stated that patients treated with ipi/nivo do not receive treatment beyond progression. Thus, in the base-case model, 43.3% and 0% for tebentafusp and ipi/nivo, respectively, was used in combination with the modelled PFS to estimate the proportion of patients on treatment in each model cycle. In the tebentafusp arm, the number of patients on treatment in a given cycle were estimated to be all those surviving and progression free, plus the proportion of patients progressing in all previous cycles up until the mean duration given in Table 28.

Table 28. Treatment beyond disease progression.

Treatment beyond progression	Tebentafusp	Ipi/nivo
Percentage of patients treated with study drug beyond progression	43.3%	0%
Mean duration of treatment beyond progression (weeks)	15.23	N/A

8.1.3.3 Costs associated with health states and adverse events

The pre-progression and post-progression states were associated with resource utilization for the management of the condition and Aes. Resource use have been derived from the literature and validated by the clinical expert and are comprised of consultations with clinicians, laboratory tests, radiographic scans, and hospital visits.

8.1.3.4 Subsequent therapies

In the IMCgp100-202, a proportion of patients received subsequent systemic therapies (chemotherapy or immunotherapies) following discontinuation of the study treatment. These costs were accounted for in the model, using data on treatment duration and proportion of usage derived from the trial data and clinical experts' opinion. The proportion of patients on-treatment during any given cycle was estimated as described above for drug costs.

8.1.3.5 Quality of life data

Utility values were derived from the EQ-5D-5L data collected in the IMCgp100-202 trial. Based on personal communications with clinicians, disease progression may not be a good proxy for measuring changes in the HRQoL of patients with mUM. Additionally, patients could stay on treatment beyond disease progression as per the study protocol, if they were still benefiting from treatment based on clinical assessment. Hence, the data was analyzed based on pre- (i.e., on treatment) and post-treatment discontinuation (i.e., off treatment). An approach based on time-to-death, based on the literature, was also implemented. The proportion of patients on-treatment during any given cycle was estimated as described above for drug costs.

8.1.4 Validation

The CE model was validated using two approaches. First, the internal validity of the model was assessed to verify whether the model performed the mathematical calculations according to its original specification. Secondly, the validity of the model outputs was tested by comparing the model's results against those reported in relevant clinical studies.

8.1.4.1 Internal validity

To ensure the internal validity of the model, a senior health economic modeler who was not previously involved in the submission, performed a thorough and systematic examination of multiple aspects of the model. First, the model was examined to ensure worksheets and formulas are programmed correctly. Subsequently, the model's behavior was examined by running verification checks to assess the consistency of the modelled outputs or indications of error in the results. The latter was achieved by using equal or extreme values in both treatment arms of the model and inspecting whether the results produced by the model matched the modeler's expectations.

8.1.4.2 External validity

To examine the external validity of the model results the predicted OS and PFS were compared with the 202 trial IC arm and three studies of treatments for mUM.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

A summary of the model inputs is presented in Table 29. Efficacy inputs were derived from the MAIC conducted based on data from IMCgp100-202 and GEM1402. The MAIC was the data source for the OS, PFS, time to treatment discontinuation (TTD), whereas rates of Aes, and quality of life (QoL) data, in both the tebentafusp and control arm of the model were derived directly from the clinical trials based on patient level data. TTD was modelled based on a simple approach where a fraction of previously progressed patients was added to the current PFS population. The 'mean duration of treatment beyond progression' determined the number of previous cycles to include. The 'percent of patients treated beyond progression' determined the fraction of progressed patient carried forward. This approach was adopted to better reflect clinical practice, where a fraction of patients is treated beyond treatment progression per RECIST. The costs associated with the treatments, disease management, and treatment of AEs were estimated using the Danish diagnosis-related group (DRG) tariff system. The resource use and frequencies reported for the intervention and comparator were validated by a clinical expert. HRQoL related to tebentafusp were estimated based on EQ-5D-5L data from the IMCgp100-202 converted using the Danish EQ-5D-5L preference weights. Patient costs were calculated in agreement with section 8.1.3 of the DMC guideline [45]. Patient costs include time-related costs based on the average salary in Denmark after taxes. The patient costs were estimated using the resource use and frequencies associated with the treatments, disease management, and treatment of AEs. Additionally, costs related to transportation were included assuming a total cost of DKK 101.54 going to and from the hospital.

Table 29. Clinical Input data used in model.

Name of estimates		Results from study (ITT)	Input value used in the model	How the input value is obtained/estimated
Clinical efficacy inputs				
Median OS	Tebentafusp, (95% CI) Tebentafusp (MAIC)	21.7 months, (18.6, 28.6) 21.6 months	21.6 months	The inputs are derived from the MAIC, the MAIC was conducted based on data from IMCgp100-202 and GEM1402. The full methodology is described in Appendix F.
	Ipi/nivo, (95% CI) Ipi/nivo (MAIC)	12.7 months, (7.1, 18.3) 12.1 months	12.1 months	
	Tebentafusp vs. Ipi/nivo (MAIC), HR (95% CI)	0.507, (0.324, 0.793)	0.507, (0.324, 0.793)	
Median PFS	Tebentafusp, (95% CI) Tebentafusp (MAIC)	3.3 months, (3.0, 5.0) 4.8 months	4.8 months	
	Ipi/nivo, 95% CI Ipi/nivo (MAIC)	3.0 months, (2.0, 4.1) 3.1 months	3.1 months	

Name of estimates		Results from study (ITT)	Input value used in the model	How the input value is obtained/estimated
	Tebentafusp vs. Ipi/nivo (MAIC), HR (95% CI)	0.647 (0.445, 0.941)	0.647 (0.445, 0.941)	
Cost input (DKK)				
Drug acquisition costs	Tebentafusp (Price per week)		DKK 92,449.88	See section 8.5.1
	Ipi/nivo (Price per treatment cycle (every 3 weeks)		Dose 1-4: DKK 135,420.46 Dose 5+: DKK 22,003.74	
Disease management	Pre-progression cost per cycle		DKK 1,674.87	Estimated based on disease management rates and cost of disease management activities derived from DRG tariffs 2022. See section 8.5.3
	At progression one-off		DKK 3,600.05	
	Post-progression one-off cost per 4 months		DKK 10,705.20	
	End-of life care one-off cost (one year)		DKK 71,612.00	
AE cost (tebentafusp)	Endocrine disorder		DKK 0.00	Estimated based on AE rates from IMCgp100-202, GEM1402, and cost of treatment of AEs derived from DRG tariffs 2022. See section 8.5.5.
	Other AEs		DKK 1,705.20	
AE cost (Ipi/nivo)	Endocrine disorder		DKK 461.25	
	Other AEs		DKK 8,006.52	
Patient costs	Pre-progression patient cost per cycle		DKK 393.91	Estimated based on disease management rates and the DMC unit costs guideline. See section 8.5.6
	At progression patient cost – one-off		DKK 1,485.13	
	Post-progression one-off cost per 4 months		DKK 10,741.09	

Name of estimates		Results from study (ITT)	Input value used in the model	How the input value is obtained/estimated
Utilities				
Health state utilities (time to death in days)	≥360 days		0.89	Utilities for time to death was based on the utility "on-treatment" derived from regression analysis from the IMCgp100-202 as the baseline and adjusted at each time to death category using the adjustment factor derived previously. See section 8.4.1.2
	270-360 days		0.77	
	180-270 days		0.71	
	90-180 days		0.71	
	30-90 days		0.62	
	<30 days		0.36	
AEs disutilities	Tebentafusp		0.0236	Using the approach to modelling utility values based on time to death, utility decrements were applied sourced from HTAs of nivolumab and ipilimumab in metastatic melanoma. See section 8.4.1.2.1
	Ipi/nivo		0.0337	

Abbreviations: AE, adverse event; CI, confidence interval; DMC, Danish Medicines Council; DRG, diagnosis-related group; HR, hazard ratio; HTA, health technology assessment; ipi/nivo, ipilimumab in combination with nivolumab; ITT, intention to treat; MAIC, match adjusted indirect comparison; OS, overall survival; PFS, progression-free survival

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The Danish patient population: The patient population relevant for this application is adult patients with HLA-A*02:01 positive mUM, without prior treatment in the metastatic setting. In Denmark, the population indicated for treatment with tebentafusp includes approximately 7-10 patients per year. See section 5.1.1. Data on patients with mUM in Denmark is sparse. Patient characteristics in Danish clinical practice are in this application derived from an RWE study based on registry data from patients with mUM with an initial oncological evaluation between January 2011 and December 2018.

Patient population in the clinical documentation submitted: The patients enrolled in IMCgp100-202 had local histologic or cytologic confirmation of mUM, were HLA-A*02:01 positive, and had received no prior systemic or liver directed therapy [4]. See patient characteristics in Table 86.

Patient population in the health economic analysis submitted: The patient characteristics from the MAIC were primarily applied in the model. The data was compared with a Danish RWE study. Where the data was comparable, data from the MAIC was used in the in model. In case of discrepancy patient characteristics from the RWE study were applied based on the assumption that the Danish RWE study is more transferable to the patient population in Danish clinical practice.

Table 30 provides an overview of relevant patient characteristics reported in the clinical documentation (IMCgp100-202, GEM1402, and MAIC), patient characteristics used in the model, and patient characteristics in Danish clinical practice based on a RWE study from 2019 on the real-world impact of immune checkpoint inhibitors in mUM in a Danish population [4,16,18,49].

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Table 30. Patient population.

Important baseline characteristics	Clinical documentation Source: [4,18] *MAIC			Used in the model		Danish clinical practice Source: [16]
	Tebentafusp	**Ipi/nivo**	**Tebentafusp Adjusted**	**Tebentafusp**	**Ipi/nivo**	**Post-ICI era**
N	240	52	182.6*			94
% Female (n/N)	49.2% (118/240)	44.2% (23/52)	44.2% (80.8/182.6)*		50%	50.0% (34/94)
% Extrahepatic disease (n/N)	3.8% (9/240)	21.2% (11/52)	21.2% (38.6/182.6)*			N/A
% Hepatic and Extrahepatic disease (n/N)	44.2% (106/240)	36.5% (19/52)	36.5 (66.7/ 182.6)*			N/A
% ECOG 0 (n/N)	79.6% (191/240)	84.6% (44/52)	84.6% (154.5/182.6)*			60.2% (53/88)
Mean weight, kg	78.86				78.86	
Mean body surface area (BSA)	1.90				1.90	
Median age, yrs	64 (23-92)	59 (26-84)	59.7*	65	65	65 (22-87)

* Data from the MAIC

**Patients with missing values for any variables were excluded from the analysis.

Abbreviations: BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; Ipi/nivo, ipilimumab in combination with nivolumab; MAIC, match adjusted indirect comparison; n=sample size; N=population size; N/A, Not available

Gender

The percentage of females was lower in IMCgp100-202 and GEM1402 compared with the percentage reported in the Danish RWE study. This discrepancy was assigned the inclusion and exclusion criteria in the clinical studies. The studies included male or female patients age ≥ 18 years at the time of informed consent and excluded women with childbearing potential as defined in Appendix B (Table 83 and Table 84). The studies thereby exclude a group of women that were not excluded in the RWE study. [4,16,18]

LDH-level

The percentage of normal LDH was similar in the clinical documentation and the MAIC. A higher percentage of normal LDH was reported in the Danish RWE study. The discrepancy in the percentage of patients with normal LDH at baseline has been reasoned with how the LDH levels were categorized in the studies. In the IMCgp100-202 study, the LDH levels were divided into ≤ ULN and ≥ ULN whereas the GEM1402 study categorized the LDH levels as *Normal*, *increased < 2.5 x ULN, Increased ≥ 2.5 x ULN,* and *Not available* [4,18]. The Danish RWE study categorized the *LDH levels as LDH ≤ ULN, LDH 1-2x ULN, LDH >2x ULN,* and *unknown* [16].

ECOG score

ECOG scores reported in the clinical documentation and MAIC are better compared to the RWE based on a Danish population with mUM. The discrepancy has been assigned the inclusion criteria for the studies IMCgp100-202 and GEM1402 where only patients with an ECOG performance status of 0 or 1 at screening were included.

Weight, height, and age

The mean weight across all patients in the IMCgp100-202 trial was used, 78.86 kg (N=377; SD=17.85; 95% CI: 77.06, 80.66), and a body surface area (BSA) of 1.90 m^2 was derived from the mean weight and height (169.86 cm) in the trial using the DuBois and DuBois formula. [50] No data on a population in Danish clinical practice was identified. Therefore, data from the clinical trial was applied in the model.

The adjusted median age in the MAIC (59.7 years) is lower compared to the median age in the IMCgp100-202 study (64 years). The discrepancy is due to the MAIC weights being influenced by the median age reported in GEM1402. The median age reported in the RWE (65 years) was similar to that reported in IMCgp100-202. The median age reported in the RWE was applied in the model as it was assumed to be more representative for the Danish population.

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice: In the current clinical guideline, the first choice is enrolment in a clinical trial. If a clinical trial is not an option, fit patients are offered a combination of immunotherapy treatments consisting of ipilimumab and a PD-1/L1 inhibitor, as described in section 5.2.1.

Intervention in the clinical documentation submitted: One clinical trial, IMCgp100-202, for tebentafusp assessing the relevant indication is included as clinical documentation. Patients were randomly assigned to treatment with tebentafusp (66.7%) or investigator's choice of treatment (33.3%), pembrolizumab, ipilimumab or dacarbazine. The clinical documentation submitted has previously been described in section 7.1.1.1.

Intervention in the health economic analysis submitted: Inputs regarding tebentafusp in the model are informed by the IMCgp100-202. The intervention is described below in the Table 31.

Table 31. Intervention.

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	20 µg on Day 1, 30 µg on Day 8 and 68 µg on Day 15	Same as clinical documentation	Expected to be similar in Danish clinical practice

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
	and at this dose once weekly thereafter. [1] (15-20 min infusion time)		
Length of treatment (time on treatment) (mean/median)	Patients should receive tebentafusp as long as the patient is deriving clinical benefit and in the absence of unacceptable toxicities [1]	Same as clinical documentation	Expected to be similar in Danish clinical practice
The pharmaceutical's position in Danish clinical practice	For patients who are HLA-A*02:01 positive it is expected that tebentafusp will replace clinical studies as 1st line treatment.	Same as clinical documentation	Expected to be similar in Danish clinical practice
Necessary monitoring, both during administration and during the treatment period	<u>First three treatment doses:</u> First three doses should be administered in a hospital setting with overnight monitoring for signs and symptoms of CRS for at least 16 hours. Vital signs should be monitored pre dose and at a minimum of every 4 hours until resolution of symptoms. If clinically indicated, more frequent monitoring or prolongation of hospitalization should be performed. [1] If patients experience Grade 3 or 4 hypotension during any of the first three KIMMTRAK® infusions, patients should be monitored every hour for at least 4 hours in an outpatient setting for the next three infusions. [1] <u>Subsequent doses:</u> After 68 mcg dose level is tolerated (i.e., absence of Grade ≥ 2 hypotension	<u>First three treatment doses:</u> First three doses of tebentafusp should be administered in a healthcare setting where providers have immediate access to medications and resuscitative equipment to manage CRS. Patients should be monitored for signs and symptoms of CRS during infusion and frequently monitored for at least for 16 hours after infusion is complete. [1] <u>Subsequent treatment doses:</u> Observe patients for a minimum of 30 minutes following each infusion. [1]	<u>First three treatment doses:</u> First three doses of tebentafusp should be administered in a healthcare setting where providers have immediate access to medications and resuscitative equipment to manage CRS. According to the clinical expert the treatment will be administered in the morning and patients will be monitored for signs and symptoms of CRS during infusion and frequently monitored throughout the day and discharged in the evening. <u>Subsequent treatment doses:</u> Observe patients for a minimum of 30 minutes following each infusion. [1]

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Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
	requiring medical intervention), subsequent doses can be administered in appropriate outpatient ambulatory care setting. Patients should be observed for a minimum of 60 minutes following each infusion. For patients who have received outpatient treatment with KIMMTRAK® for at least 3 months and have not experienced any interruptions greater than 2 weeks, outpatient monitoring following infusion may be decreased to a minimum of 30 minutes for subsequent doses. [1]		

Abbreviations: CRS, cytokine release syndrome; HLA-A, human leukocyte antigen class I

Discrepancy in the necessary monitoring during in the hours after administration of tebentafusp was identified and pointed out by the clinical expert. As per the summary of product characteristics (SmPC) for tebentafusp patients should be monitored for signs and symptoms of CRS during infusion and frequently monitored for at least 16 hours after infusion is complete for the first three doses, for subsequent doses a minimum of 30 minutes observation after infusion is required [1]. However, according to the clinical expert patients will be monitored for signs and symptoms of CRS during infusion, and frequently monitored throughout the day and discharged in the evening – within 12 hours. This expert opinion was reasoned with the scarcity of resources within the healthcare system. The monitoring was applied in the model based on the clinical documentation as the more conservative approach with a need for more healthcare resources. The impact of adjusting the necessary monitoring according to the expert opinion is tested in the scenario analysis.

8.2.2.3 Comparators

The current Danish clinical practice: The current relevant comparator according to Danish clinical practice is described in section 5.2.

Comparator(s) in the clinical documentation submitted: The comparator arm of the IMCgp100-202 trial does not reflect the comparator arm of the model submitted in the health economic analysis. In the clinical documentation patients were treated with investigator's choice of the immunotherapy drugs ipilimumab or pembrolizumab, or chemotherapy with dacarbazine.

As agreed with the expert committee for Melanoma in the DMC, ipi/nivo has been chosen as the relevant comparator. However, ipi/nivo was not a comparator in the phase III IMCgp100-202 study. Hence, a MAIC was conducted to assess the clinical effectiveness of tebentafusp against ipi/nivo. The MAIC is based on the October 2020 data cut-off of the IMCgp100-202 trial and a single arm study of ipi/nivo in mUM [18].

Comparator(s) in the health economic analysis submitted: The comparator included in the health economic analysis is ipi/nivo, which is in line with the Danish clinical practice described in section 5.2.3. Ipi/nivo is described in Table 32.

Table 32. Comparator – Ipi/nivo.

Comparator		Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Ipilimumab	Posology	Every 3 weeks for a total of 4 doses (90 min infusion time)	Same as clinical documentation	Expected to be similar in Danish clinical practice
	Length of treatment	As long as clinical benefit is observed or until unacceptable toxicity	Same as clinical documentation	Expected to be similar in Danish clinical practice
	The comparator's position in the Danish clinical practice	For fit patients ipi/nivo is recommended in 2nd line after clinical study in 1st if available	For HLA-A*02:01 positive patients who are fit it is expected that ipi/nivo will be used in 2nd line after tebentafusp in 1st line.	Expected to be similar in Danish clinical practice
Nivolumab	Posology	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks	Same as clinical documentation	Expected to be similar in Danish clinical practice
	Length of treatment	As long as clinical benefit is observed or until unacceptable toxicity	Same as clinical documentation	Expected to be similar in Danish clinical practice
	The comparator's position in the Danish clinical practice	For fit patients ipi/nivo is recommended in 2nd line after clinical study in 1st if available		For HLA-A*02:01 positive patients who are fit it is expected that ipi/nivo will be used as 2nd line after tebentafusp in 1st line.

Abbreviations: HLA-A, human leukocyte antigen class I; ipi/nivo, ipilimumab in combination with nivolumab

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation: The relative efficacy outcomes are summarized in section 7.1.2. The efficacy results for tebentafusp and ipi/nivo have been estimated via indirect comparisons. Efficacy results for the included trials were OS, PFS, and TTD.

Relevance of the documentation for Danish clinical practice:
OS and PFS are standard outcomes in oncology and are in several treatment guidelines for different types of cancers considered critical or important endpoints for assessment of the treatment effect. Based on recent descriptions from the DMC, these measurement methods are considered relevant in Danish clinical practice.

The relative efficacy outcomes in the submitted health economic analysis:
For tebentafusp and ipi/nivo OS and PFS curves were derived by fitting standard parametric models (exponential, Weibull, log normal, log logistic, Gompertz, generalized gamma and gamma) to IPD from the IMCgp100-202 study and GEM1402 study. The fitted curves were used to conduct the extrapolation analysis. The use of IPD enabled fitting the data separately to each treatment arm, negating the need to assume proportional hazard (PH). The efficacy outcomes used in the model and the relevance of these are presented in Table 33 and Table 34, respectively.

Table 33. Summary of text regarding value.

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Overall Survival	Time from patient inclusion to date of death due to any cause. Time Frame: Survival status will be assessed every 3 months from randomization until death, assessed up to 40 months. [51] OS were calculated by the KM method. The treatment arms were formally compared with the use of a 2-sided log-rank test, stratified according to LDH status.	OS based on MAIC Tebentafusp: 21.6 months Ipi/nivo: 12.1 months HR: 0.507, (0.324, 0.793)
Progression-Free Survival	The time from the randomized allocation to the date of tumor progression, or death due to any cause. Investigator assessed according to the RECIST, version 1.1. PFS were calculated by the KM method. The treatment arms were formally compared with the use of a 2-sided log-rank test.	PFS based on MAIC Tebentafusp: 4.8 months Ipi/nivo: 3.1 months HR: 0.647 (0.445, 0.941)

Abbreviations: HR, hazard ratio; ipi/nivo, ipilimumab in combination with nivolumab; KM, Kaplan-Meier; LDH, lactate dehydrogenase; MAIC, match adjusted indirect comparison; OS, overall survival; PFS, progression-free survival

Table 34. Summary of text regarding relevance.

Clinical efficacy outcome	Clinical documentation	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice

OS and PFS	OS KM survival analysis include median OS and OS rates at different time points.	OS and PFS are standard outcomes in oncology and are in several treatment guidelines for different types of cancers considered critical or important endpoints for assessment of the treatment effect	Based on recent descriptions from the DMC, these measurement methods are considered relevant in Danish clinical

Abbreviations: DMC, Danish Medicines Council; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the submitted clinical documentation: The clinical documentation for the AEs included in the model are IMCgp100-202 and GEM1402. An overview of AEs is presented in Appendix E.

Adverse reaction outcomes in the submitted health economic analysis:
AEs included in the health economic analysis are all grade 3 or higher AEs with a prevalence in more than 3% of patients, under treatment with tebentafusp in the IMCgp100-202 study or ipi/nivo in the GEM1402 study, as well as endocrine disorders of any grade, in line with submissions of ipilimumab and pembrolizumab in advanced melanoma [18,52,53]. This was because they are known to be related to the use of immune checkpoint inhibitors and are associated with high costs and/or long-term impacts.

In the tebentafusp arm, the AE rates are taken from the IMCgp100-202 study [4]. The AE rates in the ipi/nivo arm are taken from the GEM1402 study [18]. AE rates from both studies are presented in Table 35. The AEs and SAEs have been summed up to derive the rate of grade 3+ AEs, or any grade for endocrine disorders.

Table 35. Adverse event rates[4,18]

Adverse reaction outcome		Tebentafusp	Ipi/nivo
Category	**AEs**	**Used in the model (numerical value)**	**Used in the model (numerical value)**
Skin and subcutaneous tissue disorders	Rash	9.4%	9.6%
	Rash maculo-papular	8.6%	-
	Pruritus	4.5%	-
Investigations	AST increased	5.3%	-
	Lipase increased	4.1%	-
	ALT increased	3.3%	-
Vascular disorders	Hypertension	8.6%	-
	Hypotension	3.3%	-
General disorders and administration site conditions	Fatigue	5.3%	9.6%
	Pyrexia	3.7%	1.92%
Metabolism and nutrition disorders	Hypophosphataemia	4.1%	-
Hepatobiliary disorders	Hyperbilirubinaemia	3.3%	-
	Liver toxicity/liver-related events	-	26.9%

	Hepatitis	-	3.8%
Gastrointestinal disorders	Diarrhoea	1.2%	11.5%
Other	Guillain-Barré syndrome	-	3.8%
Endocrine disorders	Hypothyrodism	-	15.4%
	Thyroiditis	-	9.6%
Clinical documentation		IMCgp100-202	GEM1402
Used in model		Yes	Yes

Abbreviations: AE, adverse event; ipi/nivo, ipilimumab in combination with nivolumab

8.3 Extrapolation of relative efficacy

Extrapolation of OS and PFS was required as not all events were observed over the trial periods. The clinical data informing the model is based on the MAIC given that ipi/nivo was not a comparator in the IMCgp100-202 study. Both OS and PFS were analyzed to assess the clinical effectiveness of tebentafusp against ipi/nivo. However, TTD was not published in the GEM1402 and an analysis could not be conducted for this endpoint. Hence, TTD was not used in the extrapolation analysis in the model. In the absence of TTD data, an adjustment to PFS was made to best reflect the treatment duration based on IPD from the MAIC. For completeness, an assessment of the PH assumption was made and is presented in Appendix G. Although based on the data presented in Appendix G, the PH assumption does not seem violated, given the p value, which demonstrates statistical significance. Hence, the data were fitted separately to each treatment arm, as the IPD is available, negating the need to assume PH. This also gives additional flexibility in the model. Standard parametric models (exponential, Weibull, log-normal, log-logistic, Gompertz, generalized gamma, and gamma) were fitted, following NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance [54]. Hazard functions were used to assess the suitability of the parametric models. As the hazard functions increase before decreasing a non-monotonic hazard was considered more appropriate. Hence, exponential (constant hazard), Weibull, Gompertz and gamma (monotonic hazards which only increases or decreases) do not provide the most plausible options. Generalized gamma, log-logistic and log-normal (both of which are special cases of the generalized gamma) provide reasonable options. The graphs of the hazard functions did not allow to conclude on the choice of extrapolation. Thus, the final choice of the extrapolation model was made considering a range of evidence: Akaike information criterion (AIC), Bayesian information criterion (BIC), fit to the KM curve, clinical experts' opinion. The hazard functions for the parametric models are presented in Appendix G. Goodness-of-fit statistics, the AIC and BIC, are reported to assess the models' fit to the observed data, as well as visual inspection vs. the KM estimates. To identify the parametric model with the best fit, the AICs and BICs were initially ranked separately, followed by summation of both ranks for each parametric model. Based on the sum of ranks, the overall ranking was thus derived (the lower the value of sum of ranks, the better the fit).

8.3.1 Overall survival

Based on AIC and BIC presented in Table 36, the model with the best fit in the tebentafusp arm is gamma, although Weibull, log-normal, log-logistic, and generalized gamma are all a reasonable fit with the AIC and BIC being close, less than 2% change. In the ipi/nivo arm, the model with the best fit is the log-normal, although all models are reasonable with the AIC and BIC being within five points.

Table 36. Goodness-of-fit Akaike and Bayesian information criteria: overall survival standard parametric models.

	Tebentafusp			Ipi/nivo		
Model	**AIC**	**BIC**	**Ranking**	**AIC**	**BIC**	**Ranking**

Exponential	737.26	740.74	7	310.09	312.04	2
Weibull	721.97	728.94	2	312.08	315.98	7
Log-normal	722.82	729.78	4	308.72	312.63	1
Log-logistic	722.19	729.15	3	309.14	313.04	3
Gompertz	727.17	734.13	6	311.12	315.03	4
Generalized gamma	723.32	733.76	5	310.70	316.55	5
Gamma	721.45	728.41	1	311.96	315.87	5

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ipi/nivo, ipilimumab in combination with nivolumab

Plots of the extrapolation models overlayed with the KM curves and Rantala KM curves are presented in Figure 42 over the trial time horizon and in Figure 43 over a 15-year time horizon. Survival probabilities at various time-points are also presented in Table 104 and Table 105 in Appendix G.

Rantala and colleagues conducted a systematic review and meta-analysis of 78 studies (n=2494) in mUM [8]. They pooled data for 510 1st line patients. The KM curve constructed using data from these studies which only included patients (data reported in supplemental digital content 4, B. OS by percentage of 1st line treatments – 100%; green line) was digitized using WebPlotDigitizer [55], to reconstruct the patient-level data and plotted against the data from the IMCgp100-202 for comparison.

In the tebentafusp arm, the Weibull gives the most pessimistic extrapolation with a 5-year OS probability of 5% and the log-normal gives the most optimistic extrapolation with a 5-year OS probability of 20%. Based on clinical experts' opinion, a 5-year OS of 12-17% with tebentafusp is clinically plausible.

Rantala and colleagues found no clinically significant difference in OS by treatment modality [8], and that no therapy has demonstrated a significant improvement in OS in the last 40 years [24,56]. Hence it was considered that the data reported by Rantala et al. on first-line patients is the best benchmark available for comparison against the ipi/nivo data [8]. Additionally, the clinical experts consulted during the global model CEM development estimated that the OS under current treatment modalities is between 0% and 5% at 5 years. With this information in mind combined with the reasonable fits of most of the parametric models in both arms – log-normal and log-normal were applied as base case in both arms.

Applying the log-normal distribution to the ipi/nivo arm resulted in a 5-year OS of 9.64%. An estimate that is considered conservative give the expert input on the current treatment modalities being between 0-5% at year 5. Weibull and gamma are the two models with the statistically best fit for the tebentafusp arm, given the clinical expert expected the 5-year OS to be between 12-17%. Log-normal being the statistically fourth best fit was chosen to match the approach in the ipi/nivo arm, also the clinical expert did not find a 5-year OS of 20% for tebentafusp unrealistic, considering the mUM surveillance program, where patients are expected to be diagnosed earlier giving them a better chance of PFS.

8.3.2 Progression-free survival

Standard parametric models (exponential, Weibull, log-normal, log-logistic, Gompertz, generalized gamma and gamma) were fitted, following NICE DSU TSD 14 [54]. Based on AIC and BIC presented in Table 37, the model with the best fit in the tebentafusp arm is the generalized gamma. In the ipi/nivo arm, the model with the best fit is the generalized gamma, although log-normal and log-logistic are reasonable with the AIC and BIC being close, less than 2% difference.

Table 37. Goodness-of-fit Akaike and Bayesian information criteria: PFS standard parametric models.

	Tebentafusp			Ipi/nivo		
Model	AIC	BIC	Ranking	AIC	BIC	Ranking
Exponential	1137.17	1140.65	6	278.94	280.89	4
Weibull	1126.88	1133.84	5	280.92	284.82	7
Log-normal	1047.22	1054.18	3	267.10	271.00	2
Log-logistic	1044.84	1051.80	2	268.78	272.68	3
Gompertz	1136.65	1143.61	6	278.12	282.02	4
Generalized gamma	1000.48	1010.92	1	264.40	270.25	1
Gamma	1108.35	1115.31	4	280.49	284.39	6

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ipi/nivo, ipilimumab in combination with nivolumab

Plot of the extrapolation models overlayed with the KM curves are presented in Figure 46. Survival probabilities at various time-points are also presented in Table 107 and Table 108 in Appendix G.

8.4 Documentation of health-related quality of life

The EQ-5D-5L data collected in the IMCgp100-202 study are used in this health economic assessment of tebentafusp. Summary statistics of the collected data is presented in section 7.1.2.1.7. A description of data collection and management of missing data is provided in Appendix H.

8.4.1 Overview of health state utility values

Utility by health state/ disease progression was not considered relevant in this application since patients could stay on treatment beyond progression if a series of criteria were met and thus, TTD was deemed a better proxy for modelling utility data than disease progression [57]. This approach is referred to in the model as on/off treatment and is based on utilities derived from the IMCgp100-202 study. However, per request by the DMC, the modelling of utilities based on health state was included as an option in the model and is referred to as PFS/PD. Since EQ-5D were not assessed at progression, the on/off treatment utility values were applied as a proxy for PFS/PD utilities and were modelled based on PFS. Additionally, Hatswell et al. 2014 propose that quality of life of patients with metastatic melanoma may be less related to disease status (pre- or post-progression) than to time to death [57]. This approach of modelling utility based on time to death was also considered relevant for this assessment and was supported by the clinical expert consulting the UK HTA submission.

The number of responses to the EQ-5D questionnaire in the IMCgp100-202 trial was quite high during the treatment period. However, a high number of missing data was reported during the survival follow-up period, 60% to 70%. Additionally, it was observed that there was 6 months on average between the last EQ-5D assessment and death. Hence the EQ-5D data collected in the trial captured the QoL of patients on treatment, and shortly after progression but not near death. [36]

Given the high number of missing data following treatment discontinuation and the large gap between the last EQ-5D assessment and death (i.e., average of 6 months), it was not possible to use an approach based on time to death on the IMCgp100-202 data, as proposed by Hatswell et al. 2014, in a study of the QoL in patients with melanoma [57]. Thus, the utilities based on time to death are derived from the literature.

The two approaches of modeling utility, TTD and time to death that are applied in the model, are presented in the following sections. An overview of health state utility values (HSUVs) considered for this assessment are presented in Table 38. The Danish EQ-5D-5L preference weights were applied to the utilities derived from the IMCgp100-202 trial to achieve Danish specific utilities. Due to a lack of patient-level data, it was not possible to apply the Danish weights to the utilities derived from the literature.

Table 38. Overview of HSUV derived from the literature.

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
IMCgp100-202				
Baseline (On treatment)	0.875	EQ-5D-5L	DK	Mean estimate is based on mean of both trial arms in IMCgp100-202.
Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab – Committee paper TA366				
Time to death ≥360 days	0.82 [0.79, 0.84]	EQ-5D-3L	UK time trade-off value set [58].	Pooled mean values from the 10 mg/kg Q3W pembrolizumab and ipilimumab arms, as there was no significant difference in the QoL between the two arms. (Table 75 in the committee paper - TA366). It is based on statistical models fitted using EQ-5D collected in the KEYNOTE-006 trial [52,59].
Time to death 270-360 days	0.71 [0.63, 0.79]			
Time to death 180-270 days	0.66 [0.60, 0.72]			
Time to death 30-90 days	0.66 [0.60, 0.71]			
Time to death 30-90 days	0.57 [0.49, 0.65]			
Time to death <30 days	0.33 [0.11, 0.55]			
Nivolumab for treating advanced (unresectable or metastatic) melanoma				
AE disutility (tebentafusp)	-0.02360	EQ-5D-3L	UK time trade-off value set. [58]	Derived from the nivolumab arm in the single technology assessment (STA) of Nivolumab for treating advanced (unresectable or metastatic) melanoma. It is based on statistical models fitted using EQ-5D collected in Beausterien et al. (2009) and adjusted to frequency of AEs in CheckMate 066 trial [60,61].
Ipi/nivo for treating advanced melanoma				
AE disutility (ipi/nivo)	-0.03373	EQ-5D-3L	UK time trade-off value set. [58]	Derived from the ipi/nivo arm in the STA Nivolumab in combination with ipilimumab for treating advanced melanoma. It is based on statistical models fitted using EQ-5D collected in the CheckMate 067 trial [62].

	Results [95% CI]	Instrument	Tariff (value set) used	Comments

Abbreviations: AE, adverse event; CI, confidence interval; EQ-5D, European Quality of life – 5 dimensions; HSUV, health state utility values; NICE, National Institute for Health and Care Excellence; QoL, quality of life; STA, single technology assessment.

8.4.1.1 Utility values based on the IMCgp100-202 trial and time to treatment discontinuation

Based on the pattern of missing data, data imputation was conducted for baseline and the treatment phase, but not the survival follow-up period.

Mean imputation was used at baseline. Missing covariates and EQ-5D data were imputed with the mean value at baseline for continuous variables, or modal value for the categorical variables.

Multiple imputation was used for end of treatment given the high number of missing values. Multiple imputation was done using the 'mi impute' command in Stata, imputing missing EQ-5D utilities at end of treatment using chained equations with truncated regressions [63]. Forty-seven imputations were run, as this equaled the percentage of patients with missing EQ-5D records at the end of treatment. Multiple imputation was conducted using the following variables as covariates:

- Socio-demographic variables: age, sex, race, ethnicity, region, country (which were assumed to stay the same over the follow-up period)
- Clinical variables: ECOG (Eastern Cooperative Oncology Group) score at baseline, stage at initial diagnosis, presence of metastasis at initial diagnosis, LDH level at baseline, size of largest metastatic lesion at baseline, size of largest liver metastatic lesion at baseline (which are assumed to stay the same over the follow-up period)
- Other variables: treatment assignment, overall survival duration, time between baseline and the assessment timepoint, baseline score EQ-5D utility

For intermediate time points, linear interpolation was used as there was limited variation of the EQ-5D utility over time.

A generalized estimating equation (GEE) model was used to deal with the repeated measures of the same individuals, as it gives population average effects, which was appropriate for the purpose of a CEA. A range of model specifications was tested, including the covariates: age, sex, an indicator for whether the EQ-5D assessment was done before (i.e., on treatment), on or after treatment discontinuation (i.e., off treatment), and treatment arm.

The goodness of fit was modelled using mean absolute error (MAE) and root mean squared error (RMSE) for which a value closer to zero suggested a better fit to the data. All models provided similar results with a MAE between 0.103-0.089 and a RMSE of 0.147-0.146. The sex, age, and treatment arm covariates improved the model fit, hence the preferred model with the best fit included all covariates. The on/off treatment covariate was statistically significant at 1% level, and the age and sex covariates were statistically significant at the 5% level.

The utility estimates presented in Table 39 are adjusted to the Danish preference weights and were applied based on TTD, which in the model is based on the PFS curves and adjusted with treatment beyond progression.

Utility decrements associated with AEs were assumed to be captured by the health state utility of on/off treatment and was therefore not included in the TTD approach.

Table 39. Utility values based on the IMCgp100-202.

	Estimate	SE	P value

Male	0.026	0.012	0.028
> 65 years old	0.023	0.012	0.047
Investigator's choice	-0.012	0.014	0.360
Off treatment	-0.074	0.008	<0.001
_Cons (On treatment)	0.875	0.012	<0.001

8.4.1.2 Utility values from the literature based on time to death

A limited variation in the EQ-5D index over time was observed in the IMCgp100-202 study and led to the consideration of the approach of modelling utility based on time to death. However, running a regression analysis with time to death variables was not feasible given the low number of observations recorded at a time point close to patients' death. For patients who died during the observed period, the average time between the last EQ-5D assessment and death was 5.7 months. The number of observations by time to death categories would have been insufficient and did not allow estimation of the QoL of patients close to death.

Since modelling utility data based on time to death using EQ-5D data from IMCgp100-202 was not possible, a SLR was conducted to identify literature reporting utility based on time to death for patients with mUM. An overview of the SLR is provided in Appendix H and revealed no relevant studies. Thus, a hand searching approach of NICE appraisals was used to identify utility data modelled using a time to death approach for the immunotherapies commonly used in mUM (ipilimumab, pembrolizumab, nivolumab, ipi/nivo), and utility decrements associated with AEs for these therapies.

Based on clinicals experts' opinion (consulting on the UK HTA), the QoL of patients with mUM was assumed to be maintained until approximately 6 months to death, when symptoms start appearing heavily impacting on HRQoL. Hence, the clinical experts agreed that modelling based on time to death was appropriate in this setting as well.

Therefore, data from the base case in the HTA of pembrolizumab in advanced melanoma not previously treated with ipilimumab was used, with pembrolizumab being the main therapy used in the control arm of the IMCgp100-202 trial. Modelling utility based on pembrolizumab data in both treatment arms was considered relevant due to the minimal differences in EQ-5D scores observed between the treatment arms in the IMCgp100-202 study, see Figure 15. The primary source in which the EQ-5D data were collected was KEYNOTE-006 [59]. The data from the pembrolizumab appraisal was applied due to lack of appropriate data for ipi/nivo, ipilimumab and nivolumab monotherapy and to best reflect the decline in QoL over time experienced by patients with mUM based on clinical expert opinion. The data from the pembrolizumab appraisal was used to calculate the decline in QoL from the baseline utility value using a multiplicative approach. The baseline utility value was derived from IMCgp100-202, pooling data from both treatment arms.

The regression analysis described in 8.4.1.1 was conducted to estimate the utility value based on the covariates (sex, age, treatment arm, treatment status). The constant was estimated to be 0.875, and subsequently adjusted to each covariate associated with a coefficient. The adjusted baseline utility "on treatment" was thus estimated to be 0.89. Adjustment factors were calculated as the ratio of the utility at ≥360 days and the utility at subsequent time to death categories. The baseline utility was adjusted at each time to death category using the adjustment factor derived previously. The data is reported in Table 40.

Table 40. Utility data based on time to death.

Time to death in days	TA366	Multiplier	Adjusted
≥360 days	0.82	N/A	0.89

270-360 days	0.71	0.87	0.77
180-270 days	0.66	0.80	0.71
90-180 days	0.66	0.80	0.71
30-90 days	0.57	0.70	0.62
<30 days	0.33	0.40	0.36

Source: [52]

8.4.1.2.1 Adverse events disutilities

Based on insights from the clinical experts, the AEs in the tebentafusp arm happened mostly over the first 3 doses and were transient. Hence, these were not expected to significantly impact patients' HRQoL and the utility decrements were assumed to be captured by the health states utilities of on- and off-treatment. Therefore, no additional utility decrement was applied to the approach of modelling utility based on TTD.

Utility decrements were applied to the time to death approach and were sourced from two previous single technology assessment (STA) submissions: 'nivolumab for treating advanced (unresectable or metastatic) melanoma' [47] and 'nivolumab in combination with ipilimumab for treating advanced melanoma' [48]. The utility decrements applied for tebentafusp was based on statistical models fitted using EQ-5D data collected in Beausterien et al. (2009) and adjusted to frequency of AEs in CheckMate 066 trial [60,61]. The utility decrement applied for ipi/nivo is based on statistical models fitted using EQ-5D collected in the CheckMate 067 trial. [60,62] The utility decrements were applied in the first model cycle only. Patients treated with tebentafusp mostly experienced AEs with the first three doses, thus the utility decrements were applied in the first model cycle only. This approach is considered conservative since patients treated with ipi/nivo experienced AEs throughout the treatment according to the consulting clinical expert. The utility decrements applied in the model are reported in Table 41.

Table 41. Utility decrements for the interim model.

Intervention/Comparator	Utility decrement	Source
Treatment effect of tebentafusp	0.02360	TA384 [47]
Treatment effect of ipi/nivo	0.03373	TA400 [48]

8.4.2 Health state utility values used in the health economic model

Utility values were applied at each model cycle to the proportion of patients in the relevant state (on/off treatment based on TTD or based on the time to death tunnel states depending on the approach used) and adjusted for the length of the cycle. As per the DMC guidelines, utility values were discounted at an annual rate of 3.5% [45]. The base-case analysis is based on time to death, whereas the on-/off-treatment utility values derived from the trial data are used in a scenario analysis.

An overview of the utilities derived from the literature and the IMCgp100-202 trial is presented in Table 42. In the model the Danish EQ-5D-5L preference weights were applied to the utilities derived from the IMCgp100-202 trial to achieve Danish specific utilities [64]. Due to a lack of patient-level data, it was not possible to apply the Danish weights to the utilities derived from the literature.

An overview of the methodology of how the utilities were derived and adjusted is presented in section 7.1.2.1.7 and section 8.4.1.2.

Table 42. Summary of the HSUV used in the model.

	HSUV adjusted	Variation in PSA (assumption)	Source
Health state (Base case)			
≥360 days	0.89	+/-10%	Based on TA366/ KEYNOTE-006 trial – assumed that changes in QoL associated with time to death [59].
270-360 days	0.77	+/-10%	
180-270 days	0.71	+/-10%	
90-180 days	0.71	+/-10%	
30-90 days	0.62	+/-10%	
<30 days	0.36	+/-10%	
AE disutilities			
Treatment effect of tebentafusp	-0.0236	+/-10%	Based on TA384/ CheckMate 066 trial [47,60]
Treatment effect of ipi/nivo	-0.0337	+/-10%	Based on TA400/ CheckMate 067 trial [48,62]
Scenario analysis			
Male	0.026	+/-10%	Based on statistical models fitted using EQ-5D data collected in IMCgp100-202 trial and adjusted to the Danish preference weights [4].
> 65 yo	0.023	+/-10%	
Investigator's choice	-0.012	+/-10%	
Off treatment	-0.074	+/-10%	
_Cons	0.875	+/-10%	

Abbreviations: CI, confidence interval; EQ-5D, European Quality of life – 5 dimensions; HSUV, health state utility values; ipi/nivo, ipilimumab in combination with nivolumab

8.5 Resource use and costs

The costs in the model were estimated from a societal perspective. The following cost categories were included: drug acquisition and administration costs, routine management costs of the disease at pre- and post-progression (consultations with clinicians, lab test, scans, and hospital visits), end-of-life care, AE-related costs, and patient time and transportation costs. The costs in the model were discounted at a 3.5% annual rate. Where necessary, the unit costs were inflated to 2022 DKK using the appropriate price index.

The costs associated with the treatments, disease management, and treatment of AEs were estimated using the Danish DRG tariff system by combining diagnosis and procedure codes. The diagnosis code for the tebentafusp indication is "DC693M – Kræft I choroidea med metastaser". The diagnosis code seemed to be the primary driver when combining this diagnose code with different procedure codes, always resulting in the DRG tariff of DKK 1,095. As this was assumed to not reflect the actual cost of all the procedures included in the analysis, it was decided that the procedure codes should be the primary driver of the DRG tariff. Thus, the procedure/condition was chosen as both the diagnosis and procedure in the interactive DRG system to derive the appropriate DRG tariff. For an example, when assigning the DRG tariff for the AE "Diarrhea", the combination of diagnosis code "DC693M – Kræft i choroidea med metastaser" and procedure code "DK529B1 – Kemoterapi-induceret diaré" results in the DRG tariff of DKK 1,095, whereas choosing "DK529B1 – Kemoterapi-induceret diaré" as both the diagnosis and procedure code, leads to a DRG

tariff of DKK 6,756. However, one exception was made for the drug administration, as the DRG tariff of DKK 1,095 deemed appropriate.

8.5.1 Drug acquisition and administration costs

The drug costs were applied in the model based on treatment duration derived from the PFS curves and adjusted to the duration of treatment beyond PD. Additionally, a proportion of the patients received subsequent systemic treatment after discontinuation of the study drug in the IMCgp100-202 study. Based on the IMCgp100-202 study and the Danish treatment guideline, the cost of subsequent treatment is accounted for in the model and applied as a one-off cost upon treatment discontinuation.

8.5.1.1 Drug acquisition costs

The drug acquisition cost for comparator (ipi/nivo) is based on Pharmacy Purchase Price (PPP) and is presented in Table 43.

Table 43. Drug unit costs.

Drug	Vial size	PPP (per unit), DKK	Source
Tebentafusp	[redacted]	[redacted]	[redacted]
Ipilimumab	200 mg/40 ml vial (5 mg per 1 ml)	102,385.55	Medicinpriser.dk, Jan 2022 [65]
	50mg/10ml vial (5 mg per 1 ml)	25,653.53	Medicinpriser.dk, Jan 2022 [65]
Nivolumab	240 mg/24 ml vial (24 mg per 1 ml)	22,003.74	Medicinpriser.dk, Jan 2022 [65]
	100mg/10 ml vial (10 mg per 1 ml)	9,168.23	Medicinpriser.dk, Jan 2022 [65]
	40mg/4 ml vial (10 mg per 1 ml)	3,690.69	Medicinpriser.dk, Jan 2022 [65]

Abbreviations: PPP, Pharmacy Purchase Price

One vial of tebentafusp is used per administration as per the SmPC. In the comparator arm, the per cycle cost of drugs was calculated based on dosages in the GEM1402 study.

The mean weight across all patients in the IMCgp100-202 trial was used, which was 78.86 kg (n=377; SD=17.85; 95% CI 77.06 to 80.66), and a BSA of 1.90 m^2 was derived from the mean weight and height (169.86 cm) in the trial using the DuBois and DuBois formula [50]. Given the very low number of patients with mUM in Denmark, it was considered that vial sharing was not feasible. The drug quantities were therefore rounded-up to the nearest vial size. The drug dosage, treatment schedule, and administration times are presented in Table 44.

Table 44. Drug dosage regimen for tebentafusp and ipi/nivo.

Drug	Pharmaceutical form and route of administration	Dose	Frequency and administration time	Source
Tebentafusp	Concentrate for solution for infusion (single use vials)	20 mcg C1D1; 30 mcg C1D8; 68 mcg C1D15 and subsequent doses	Every week: Days 1, 8, and 15 of 21-day cycle (15-20 min infusion time)	IMCgp100-202 [4]
Ipilimumab/ Nivolumab	Concentrate for solution for infusion (single use vials)	Ipilimumab: 3 mg/kg (237 mg) administered intravenously	Ipilimumab: Every 3 weeks for a total of 4 doses (90 min infusion time)	GEM1402[18], SmPC[29,30]
		Nivolumab: 1 mg/kg (79 mg) administered intravenously at four doses and 3 mg/kg (237 mg) at subsequent doses	Nivolumab: Every 3 weeks for a total of 4 doses and subsequent doses every 2 weeks (60 min infusion time)	

8.5.1.2 Drug administration costs— Tebentafusp

Based on SmPC, the preparation of tebentafusp requires the use of 0.13 ml human albumin at 20% concentration for admixture [66]. Based on the SmPC for human albumin, once the container has been opened, the contents should be used immediately, and any unused product should be disposed of [67]. Hence, it was considered that vial sharing was not possible, and the full cost of a vial was included in the administration costs.

Tebentafusp is administered intravenously over a 15–20-minute period. Due to the possible cytokine release-associated toxicity, patients should according to the SmPC be monitored overnight for the first three doses, with vital signs monitoring prior to the dose administration and every 4 hours for at least 16 hours after dosing. Tebentafusp is therefore administered in the inpatient setting for the first 3 doses and in an outpatient setting thereafter. For the first three doses, the administration costs are based on the DRG tariff 02MA01 for the immunotherapy administration plus the long-term tariff as the cost for hospital stay. For the subsequent treatment doses, patients should be observed for 60 minutes, and if patients have been treated with tebentafusp for at least 3 months in an outpatient setting without experiencing interruptions >2 weeks, the observation can be decreased to 30 minutes. Therefore, for the fourth dose onward, the monitoring is assumed to be included in the administration cost, which is based on the DRG tariff 02MA01.

8.5.1.3 Drug administration costs – Ipilimumab/Nivolumab

Ipi/nivo is assumed to be given in an outpatient setting, based on the infusion time specified in the respective SmPC. Based on the SmPC, ipilimumab and nivolumab are administered intravenously over a 90-minute and 60-minute period, respectively. At baseline and before each dose of ipilimumab, liver function tests and thyroid function tests should be evaluated, hence the cost associated with these tests are added to the administration cost. The costs are presented in Table 45.

Table 45. Administration services unit costs.

Service	Unit cost, DKK	Source
Administration of ipi/nivo and tebentafusp	1,095.00	|02MA01|Øvrige indlæggelser eller besøg ved øjensygdomme| [68]
Inpatient stay	2,185.00	Long-term tariff
Human albumin 20%, 100 ml vial	448.80	[66]
Liver and thyroid function tests	357.00	[69]

In line with the licensed indication, patients are eligible to tebentafusp only if they are HLA-A*02:01 positive. Hence this test will be administered to patients to determine their eligibility to tebentafusp. The cost for the test was sourced "Rigshospitalets Labportal" and presented in Table 46. It is estimated that 47% of the mUM patients will test positive, which has been accounted for to adjust the cost. The cost is applied as a one-off cost upon treatment initiation in the tebentafusp arm.

Table 46. Cost of HLA-A*02:01 test in the tebentafusp arm.

Service	Value	Source
HLA-A*02:01 test	DKK 5,645.00	Rigshospitalets labportal [69], NPU26753 [70]
% of patients expected to test positive	47%	[71]
Adjusted cost of HLA-A*02:01 used in the model	DKK 12,010.64	Adjusted for proportion of patients testing negative

8.5.1.4 Drug acquisition and administration cost summary

The drug acquisition and administration costs for tebentafusp are summarized in Table 47 for the first four weekly doses, and consist of: Tebentafusp drug acquisition costs, costs of human albumin for admixture, administration costs, inpatient stay for monitoring for the first three doses, and HLA-A*02:01 test.

Table 47. Testing, administration, and drug acquisition costs for tebentafusp.

Weekly doses	Dose 1, DKK	Dose 2-3, DKK	Dose 4+, DKK
Drug acquisition	[redacted]	[redacted]	[redacted]
Human albumin	448.80	448.80	448.80
Drug administration	1,095.00	1,095.00	1,095.00
Inpatient stay	2,185.00	2,185.00	N/A
HLA-A*02:01 test	12,010.64	N/A	N/A
Total cost	[redacted]	[redacted]	[redacted]

The drug acquisition and administration costs for ipi/nivo are summarized in Table 48 for the first 5 doses and compose of: Ipi/nivo drug acquisition costs, immunotherapy administration costs, and liver and thyroid function tests.

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Table 48. Testing, administration, and drug acquisition costs for ipilimumab/nivolumab.

Ipilimumab	Dose 1-4, DKK Dose every three weeks	Dose 5+, DKK Dose every three weeks
Drug acquisition	128,039.08	N/A
Drug administration	1,095.00	N/A
Liver and thyroid function test	357.00	N/A
Nivolumab	**Dose 1-4, DKK** **Dose every three weeks**	**Dose 5+, DKK** **Dose every two weeks**
Drug acquisition	7,381.38	22,003.74
Drug administration	Drug administration cost is accounted for in the ipilimumab cost overview	1,095.00
Total cost	136,872.46	23,098.74

8.5.2 Cost of subsequent treatments

Following discontinuation of the active treatment with either tebentafusp or ipi/nivo, patients will receive some form of additional active treatment. According to the Danish treatment guidelines, these active treatments are either immunotherapy (ipi/nivo) or chemotherapy (temozolomide).

In line with IMCgp100-202 it is assumed that 43% and 46% of the patients who initially received tebentafusp and ipi/nivo, respectively, will receive subsequent treatment. Based on the consulting clinical expert, it is assumed that 2/3 of the patients will be fit for treatment with ipi/nivo, whereas the remaining 1/3 of the patients that receive subsequent treatment will be considered fragile or with severe comorbidities and be treated with temozolomide.

Temozolomide is administered at 200mg/m^2 once a day for 5 days every four weeks as presented in Table 49. Based on a BSA of 1.90 m^2, patients are given a dose of 380mg, at a cost of DKK 475.60 based on the PPP presented in Table 50 [72,73]. The cost for a four-week cycle is DKK 2,378. As temozolomide is administered perorally, there are no administration cost associated with the treatment.

The cost of subsequent therapies is applied in the model as a one-off cost upon treatment discontinuation.

Table 49. Drug dosage regimen for temozolomide.

Drug	Pharmaceutical form and route of administration	Dose	Frequency and administration time	Source
Temozolomide	Hard capsules	200 mg/m^2 (380 mg) administered orally	Once a day for 5 days every 4 weeks	[73]

Table 50. Drug unit cost for temozolomide.

Drug	Pack size	Pharmacy Purchase Price, DKK	Source
Temozolomide	180 mg/pcs, 5 pcs	1,960.00	Medicinpriser.dk, Jan 2022 [65]
	100 mg/pcs, 5 pcs	209.00	

Ipi/nivo was assumed to be given for 4 doses and nivolumab thereafter for either a maximum of 7 doses every two weeks, based on the study by Najjar et al. 2020 [74]. Based on the consulting clinical expert's opinion, temozolomide is given for an average of 6 months, which is applied in the model base case. The data on subsequent treatment derived from IMCgp100-202 study and consulting clinical expert's opinion is presented in Table 51.

Table 51. Cost of subsequent treatment.

Resource	Tebentafusp	Ipi/nivo
Subsequent treatment options		
% any subsequent treatment	43%	46%
% subsequent treatment with ipilimumab + nivolumab	66.7%	0%
% subsequent with temozolomide	33.3%	100%
Cost per therapy		
Ipi/nivo	DKK 709,181	
Temozolomide	DKK 14,268.00	
Subsequent treatment cost		
Weighted average cost	DKK 204,260.37	DKK 6,555.57

8.5.3 Health state costs

The costs associated with the PFS and PD health states have been calculated based on resource utilisation from literature and based on expert opinion, combined with DRG tariffs and "Rigshospitalets labportal". The health state costs are composed of consultations with clinicians, lab test, scans, and hospital visits.

No relevant studies on health-care resource utilization in patients with UM or mUM were identified in the literature. Therefore, literature on metastatic CM was used as a starting point for the estimation of resource utilisation. One relevant study conducted by McKendrick et al. (2016) was identified in which the resource utilization associated with the treatment of metastatic melanoma in 8 countries was estimated [75]. One of the countries included UK and due to the comparability between the Danish and UK healthcare setting, the resource utilization is assumed to be applicable for this model.

Based on the study, the resource use costs included in the PFS and PD health states were:

- Pre-progression: routine management during active treatment
- Post-progression:
  - Management at progression (one-off)
  - BSC

The resource utilization from the study by McKendrick et al., 2016 was presented to the consulting clinical expert with experience in the management of patients with mUM to determine which items were irrelevant in the context of mUM, and which resources for the treatment of mUM patients were not already captured and should be added [75]. The resource utilization was thus validated and changed by the clinical expert to reflect the Nordic setting.

Resource utilization related to brain and bone metastasises were deemed irrelevant, as was radiotherapy and consultation with general practitioner. Resource utilisation related to the management of liver metastases were added as well as consultations with an ophthalmic surgeon to provide follow-up care for the eye.

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The revised monthly resource utilisation and the unit cost associated with each resource in the routine management during the pre-progression phase, at disease progression, and post-progression with BSC for treatment with tebentafusp and ipi/nivo are presented in Table 52. It should be noted that the post-progression costs do not include the costs of subsequent therapies, as these have been accounted for separately, as presented in section 8.5.2.

Table 52. Resource utilization and unit costs for the disease management during the pre-progression phase, at progression, and post progression with best supportive care.

	Pre-progression*	At progression*	Post-progression*	Unit cost, DKK	Source
Medical consultations					
Hospital-based medical oncology consultation	1.00	1.00	0.67	1,515.00	|23MA04|Kontrolundersøgelse|[68]
Hospital-based oncology nurse visit	1.00		0.2	1,515.00	|23MA04|Kontrolundersøgelse|[68]
Psychology specialist consultation	0.03		0.05	1,971.00	Ambulant psykiatritakst, 2022 [68]
Surgeon consultation	0.01	0.03	0.01	1,515.00	|23MA04|Kontrolundersøgelse|[68]
Ophthalmic surgeon consultation	0.33	0.33	0.33	1,515.00	|23MA04|Kontrolundersøgelse|[68]
Hospitalizations					
Inpatient stay (oncology/general ward)		0.20	0.50	1,095.00	|02MA01|Øvrige indlæggelser eller besøg ved øjensygdomme|[68]
Emergency department visit			0.05	1,095.00	|02MA01|Øvrige indlæggelser eller besøg ved øjensygdomme|[68]
Day hospital visit (out-patient clinic)	0.25		0.13	1,095.00	|02MA01|Øvrige indlæggelser eller besøg ved øjensygdomme|[68]
Examinations					
Whole-body CT	0.33	0.05		2,411.00	|30PR06|CT scanning, kompliceret|[68]
PET-CT scan	0.33			2,411.00	|30PR06|CT scanning, kompliceret|[68]
Liver MRI	0.03			2,416.00	|30PR02|MR scanning, kompliceret|[68]
Complete blood count	1.00	1.00		427.00	Rigshospitalets labportal [69] Full overview of the included tests is provided in Appendix K
Complete metabolic panel	1.00	1.00		357.00	Rigshospitalets labportal [69] Full overview of the included tests is provided in Appendix K
Procedures					

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	Pre-progression*	At progression*	Post-progression*	Unit cost, DKK	Source
Surgical intervention (liver resection)	0.01			37,377.00	|07MA08|Ondartet sygdomme i lever, galeveje og bugspytkirtel, pat. mindst 18 år|[68]
Hepatic perfusion		0.20		7,318.00	|36PR04|Klinisk fysiologi/ nuklear medicin grp. D|[68]

*Monthly resource use

Resource utilization values and unit costs were multiplied to derive the health states costs, which are reported in Table 53. Based on the study by McKendrick, BSC is provided for an average of 4 months, thus it was assumed in the model that the entire cohort would receive BSC for an average of 4 months, and this value was added as a one-off cost at progression. The cost is applied to the patients leaving the PFS state at each cycle. [75]

Table 53. Health state costs.

Health state	Costs
Pre-progression (weekly cycle cost)	DKK 1,674.87
At progression (one-off cost)	DKK 3,600.05
Post-progression (BSC) (one-off)	DKK 10,705.20

Abbreviations: BSC, best supportive care

8.5.4 End-of-life care cost

To reflect the additional resources that are required to provide treatment to cancer patients towards the end of their life, an end-of-life cost was applied in the model. The cost was based on the DRG tariff 26MP48 "Specialiseret palliativ indsats, øvrig" of DKK 71,612.00, which was applied as a one-off cost to the new death at each cycle. For the proportion of patients living less than 1 year in the model, this cost was adjusted for the length of time alive in the model.

8.5.5 Adverse events cost

In the base case model, grade 3 or higher AEs, and colitis and endocrine disorders of any grade with a prevalence >3% are included. According to the clinical expert patients treated with ipi/nivo in clinical practice frequently experience other AEs, e.g., pneumonitis, not reported in GEM1402 study. However, in the base case model, only AEs reported in this study are included.

Cytokine-mediated AEs are commonly reported in patients treated with tebentafusp for the first 2-3 doses. For this reason, patients were monitored for every 4 hours for at least 16 hours after the first 3 doses during the dose-escalation period, to allow management of hypotension and other cytokine-related AEs. The cost of inpatient monitoring for the first three doses is captured within the administration costs for tebentafusp as this cost would already capture most of the costs associated with the management of CRS events and other AEs. Nevertheless, as a conservative measure AEs were costed in the tebentafusp arm, but it was assumed that the patients would not be admitted (on top of the three days of inpatients stay at administration). Therefore, only outpatient costs were included.

The cost of endocrine disorders was applied every 6 months based on NICE single technology appraisal assessment of ipilimumab [53]. For the other AEs, the weighted cost based on the rates of AEs was applied as a one-off cost in the first cycle in the model. As the AEs mainly occurs with the first 3 doses, this approach reflects clinical practice in the tebentafusp arm. Although this may not reflect clinical practice in the control arm, this approach was used as a conversative measure in the control arm. Additionally, in a scenario analysis, an assumption was made that the same proportion of inpatient vs. outpatient costs applied to the tebentafusp arm as did to the ipi/nivo arm.

The proportion of patients treated inpatient and outpatient for both treatment arms is validated by the clinical expert. The unit costs for each AE are derived from the DRG tariffs for 2022. The unit cost for AEs and the proportion of inpatient and outpatient treatment are presented in Table 54 and Table 55, respectively.

Table 54. Adverse event unit cost and proportion of AE treated in an inpatient setting.

Adverse events	Inpatient setting	Unit cost, DKK	Admission duration (days)	Source
Rash	5%	19,518.00	4	|09MA03|Lettere eller moderat hudsygdom, u. kompl. Bidiag. | [68]
Rash maculo-papular	5%	19,518.00	4	|09MA03|Lettere eller moderat hudsygdom, u. kompl. Bidiag. |[68]
Pruritus	5%	19,518.00	4	|09MA03|Lettere eller moderat hudsygdom, u. kompl. Bidiag. |[68]
Fatigue	10%	4,460.00	1	|23MA03|Symptomer og fund, u. kompl. bidiag. |[68]
Pyrexia	10%	30,549.00	6	|21MA03|Komplikationer ved behandling, u. kompl. bidiag. |[68]
Liver toxicity/liver-related events	30%	34,753.00	15	|07MA06|Akut infektiøs eller toksisk leversygdom|[68]
Hepatitis	30%	34,753.00	15*	|07MA06|Akut infektiøs eller toksisk leversygdom|[68]
Diarrhea	50%	6,756.00	1	|06MA11|Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. |[68]
Guillain-Barré syndrome	100%	67,383.00	22	|01MA03|Infektion i nervesystemet ekskl. virus meningit|[68]
Hypothyroidism	5%	1,845.00	1	|10MA01|Struma og stofskiftesygdomme|[68]
Thyroiditis	5%	1,845.00	1	|10MA01|Struma og stofskiftesygdomme|[68]

*According to the clinical expert treatment of these AEs requires admission beyond the trim point for ipi/nvio treatment. No Danish clinical guidelines supporting this expert statement were identified and thus no qualified estimate of the number of admissions could be made. The decision to use the trim points as the number of days admitted to hospital was therefore made.

Table 55. Adverse event unit cost and proportion of AE treated in an outpatient setting.

AEs	Outpatient setting	Unit cost, DKK	Source
Rash	95%	2,041.00	|09MA98|MDC09 1-dagsgruppe, pat. mindst 7 år |[68]
Rash maculo-papular	95%	2,041.00	|09MA98|MDC09 1-dagsgruppe, pat. mindst 7 år |[68]
Pruritus	95%	2,041.00	|09MA98|MDC09 1-dagsgruppe, pat. mindst 7 år |[68]
AST increased	100%	2,910.00	|07MA98|MDC07 1-dagsgruppe, pat. mindst 7 år |[68]
Lipase increased	100%	2,910.00	|07MA98|MDC07 1-dagsgruppe, pat. mindst 7 år |[68]
ALT increased	100%	2,910.00	|07MA98|MDC07 1-dagsgruppe, pat. mindst 7 år |[68]
Hypertension	100%	2,910.00	|07MA98|MDC07 1-dagsgruppe, pat. mindst 7 år |[68]
Hypotension	100%	1,901.00	|05MA08|Andre hjertesygdomme |[68]
Fatigue	90%	4,460.00	|23MA03| Symptomer og fund, u. kompl. bidiag. |[68]
Pyrexia	90%	1,887.00	|21MA98|MDC21 1-dagsgruppe, pat. mindst 7 år. |[68]
Hypophosphataemia	100%	1,954.00	|10MA98|MDC10 1-dagsgruppe, pat. mindst 7 år|[68]
Hyperbilirubinaemia	100%	2,910.00	|07MA98|MDC07 1-dagsgruppe, pat. mindst 7 år|[68]
Liver toxicity/liver-related events	70%	2,910.00	|07MA98|MDC07 1-dagsgruppe, pat. mindst 7 år|[68]
Hepatitis	70%	2,910.00	|07MA98|MDC07 1-dagsgruppe, pat. mindst 7 år|[68]
Diarrhea	50%	6,756.00	|06MA11|Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. |[68]
Hypothyroidism	95%	1,845.00	|10MA01|Struma og stofskiftesygdomme|[68]
Thyroiditis	95%	1,845.00	|10MA01|Struma og stofskiftesygdomme|[68]

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase

The weighted cost of AEs in each arm was calculated by factoring the incidence rate of each AE (Table 35) with the estimates of the cost per event and proportion of management in the inpatient and outpatient setting (Table 54 and Table 55). The weighted average costs of AEs by treatment arm in the model are reported in Table 56.

Table 56. Weighted average cost of adverse events by treatment arm.

	Tebentafusp	Ipi/nivo
Endocrine disorder	DKK 0.00	DKK 461.25
Other AEs	DKK 1,705.20	DKK 8,006.52

8.5.6 Patient costs

Patient costs are applied in the model to account for the time spent attending medical services at the rate of DKK 3.03 per minute. Transportation costs to and from the hospital for inpatient and outpatient treatment are also considered, representing 101.54 DKK.

8.5.6.1 Drug administration costs

Patient costs associated with receipt of treatment are transportation costs, cost of time spent on transportation, and cost of time spent for the administration of the drug and monitoring. The costs are applied to the proportion of patients on treatment at each model cycle, calculated based on the proportion of patients who are progression-free and those who have progressed but are still on treatment based on the IMCgp100-202 trial as described in section 8.1.1. In the tebentafusp arm, for the first administration, the costs of the time spent undergoing HLA status diagnosis test are also accounted for. In the ipi/nivo arm, the costs of the time spent undergoing liver and thyroid function before each administration of ipilimumab are also accounted for. The costs are detailed in Table 57.

Table 57. Patient costs at drug administration.

Costs	Unit cost (DKK)	Cost period	Total cost‡ (DKK)	Source
Patient time cost	3.03	1 minute	-	Medicinrådets værdisætning af enhedsomkostninger [76]
Transportation cost				
Patient transportation costs*	101.54	Per hospital visit (inpatient and outpatient)	-	Medicinrådets værdisætning af enhedsomkostninger [76]
Patient time consumption on transportation to and from hospital	90.88	30 minutes†	-	Medicinrådets værdisætning af enhedsomkostninger [76]
Diagnostic and test				
HLA-A*02:01 test (tebentafusp)	15.15	5 minutes	-	Assumption made by the applicant
Liver and thyroid function test (Ipilimumab)	15.15	5 minutes	-	Assumption made by the applicant
Treatment and monitoring				
Infusion with tebentafusp	53.01	15-20 min	245.43	IMC-gp100-202 [4]
Monitoring dose 1-3	4,362.22	1,440 min	-	SmPC, tebentafusp [1]

Costs	Unit cost (DKK)	Cost period	Total cost‡ (DKK)	Source
Monitoring dose 4-11	181.76	60 min	-	SmPC, tebentafusp [1]
Monitoring dose 12+	90.88	30 min	-	SmPC, tebentafusp [1]
Infusion with ipi/nivo, week 0-12	272.64	90 min	465.06	GEM1402 [18]
Infusion with ipi/nivo, week 12+	181.76	60 min	374.18	GEM1402 [18]
Temozolomide	-	-	-	-

* Costs for transportation to and from the hospital for treatment, based on the DMC assumption of 14 km distance to hospital.
† The average time spent on transportation to and from the hospital is based on an assumed average speed of 56 km/t.
‡ Includes the cost of transportation 101.54 DKK and the cost of time spent in transportation 90.88 DKK

Patient costs are also accounted for subsequent treatments. There are no patient costs associated with temozolomide as it is administered perorally. For treatment with ipi/nivo, the cost is the sum of the liver and thyroid function test, the transportation cost, patient cost for time spent on transportation, and the cost of the infusion time. For nivolumab monotherapy, the cost is the sum of the transportation costs, patient cost for time spent on transportation, and the cost of the infusion time. The costs are calculated and applied as described in section 8.5.2 and presented in Table 58.

Table 58. Patient cost for subsequent treatment.

	Tebentafusp	Ipi/nivo
Ipi/nivo	DKK 4,540.10	-
Temozolomide	DKK 0	DKK 0
Weighted average cost	DKK 3,026.88	DKK 0

8.5.6.2 Disease management costs

Patient costs are applied in the model to account for the time spent attending medical services at the rate of 3.03 DKK per minute. This rate is multiplied by the attendance duration to estimate the patient costs for each medical service. The costs of transportation and time spent on transportation are added to the costs of attendance to medical services. The patient cost for the medical services is presented in Table 59.

Table 59. Patient cost for the medical services.

Resource	Unit cost, DKK	Cost period	Total cost* (DKK)	Sources
Medical consultations				
Hospital-based medical oncology consultation	90.88	30 min	283.3	Assumption made by the applicant
Hospital-based oncology nurse visit	90.88	30 min	283.3	Assumption made by the applicant
Psychology specialist consultation	90.88	30 min	283.3	Assumption made by the applicant

Resource	Unit cost, DKK	Cost period	Total cost* (DKK)	Sources
Surgeon consultation	90.88	30 min	283.3	Assumption made by the applicant
Ophthalmic surgeon consultation	90.88	30 min	283.3	Assumption made by the applicant
Hospitalizations				
Inpatient stay (oncology/general ward)	4,362.22	1,440 min	4,554.64	Assumption made by the applicant
Emergency department visit	90.88	30 min	283.3	Assumption made by the applicant
Day hospital visit (out-patient clinic)	90.88	30 min	283.3	Assumption made by the applicant
Examinations				
Whole-body CT	181.76	60 min	374.18	Rigshospitalet [77]
PET-CT scan	363,60	120 min	556.02	Kræftens bekæmpelse [78]
Liver MRI	545.28	180 min	737.7	Hvidovrehospital [79]
Complete blood count	15.15	5 min	207.57	Rigshospitalets labportal [69]
Complete metabolic panel	15.15	5 min	207.57	Rigshospitalets labportal [69]
Procedures				
Surgical intervention (liver resection)	8,724.44	2,880 min	8,916.86	Patientinformation [80]
Hepatic perfusion	181.76	60 min	374.18	Reddy et al., 2014 [81]

*Includes the cost of transportation 101.54 DKK and the cost of time spent in transportation 90.88 DKK

Based on the patient unit costs and resource utilization associated with the routine management of the disease, the patient costs associated with the health states are derived and presented in Table 60.

Table 60. Patient health state costs.

Health state	Tebentafusp	Ipi/nivo
Pre-progression (weekly cycle cost)	DKK 393.91	DKK 393.91
At progression (one-off cost)	DKK 1,485.13	DKK 1,485.13
Post-progression (BSC) (one-off)	DKK 10,741.09	DKK 10,741.09

Abbreviations: BSC, best supportive care

8.5.6.3 Adverse events cost

For the estimation of patient costs related to the management of AEs, it is assumed that the duration of treatment in an outpatient and inpatient setting is 30 minutes per visit and 1440 minutes per admission day, respectively. The patient time costs related to AEs are based on the admission days presented in Table 54 and the unit costs presented in Table 61.

Table 61. Patient costs related to adverse events in both treatment arms.

Adverse events	Patient time cost, DKK	Total cost*, DKK
Outpatient costs†	90.88	283.3
Inpatient costs		
Rash	17,448.88	17,641.30
Rash maculo-papular	17,448.88	17,641.30
Pruritus	17,448.88	17,641.30
Fatigue	4,362.22	4,554.64
Pyrexia	26,173.32	26,365.74
Diarrhea	4,362.22	4,554.64
Liver toxicity/liver-related events	65,433.29	65,625.72
Hypothyrodism	4,362.22	4,554.64
Hepatitis	65,433.29	65,625.72
Thyroiditis	4,362.22	4,554.64
Guillain-Barré syndrome	95,968.86	96,161.28

*Includes the cost of transportation 101.54 DKK and the cost of time spent in transportation 90.88 DKK

†Applicable to all aEs

The weighted patient costs associated with aEs in each arm were calculated by factoring the incidence rate of each AE (Table 35) with the estimates of the patient cost per event (Table 61) and proportion of management in the inpatient and outpatient setting (Table 54 and Table 55). The weighted average costs of aEs by treatment arm in the model are reported in Table 62.

Table 62. Weighted average adverse events-related patient cost by treatment arm.

	Tebentafusp	Ipi/nivo
Endocrine disorder	DKK 0.00	DKK 124.22
Other aEs	DKK 183.29	DKK 10,330.95

Abbreviations: AE, adverse event

8.6 Results

8.6.1 Base case overview

In this section an overview of the base case model inputs is presented in Table 63.

Table 63. Base case overview

Model element		Input
Comparator		Ipilimumab in combination with nivolumab
Type of model		Partitioned survival model
Time horizon		35 years (lifetime)
Treatment line		1st line. Subsequent treatment lines included
Subsequent treatment	Tebentafusp	Treatment with tebentafusp is followed by ipi/nivo for fit patients and temozolomide for unfit patients.
	Ipi/nivo	Treatment with ipi/nivo is followed by temozolomide.
Measurement and valuation of health effects		The baseline utility value was adjusted to Danish preference weights. The utilities based on time-to-death were derived from the literature.
Included costs		Pharmaceutical costs Hospital costs Costs of aEs Patient costs
Dosage of pharmaceutical		Based on BSA, 1.90
Average time on treatment		Intervention: 10 months Comparator: 6.0 months
Parametric function for PFS	Tebentafusp	Generalized gamma
	Ipi/nivo	Generalized gamma
Parametric function for OS	Tebentafusp	Log-normal
	Ipi/nivo	Log-normal

Abbreviations: AEs, Adverse events: BSA, body surface area; ipi/nivo, ipilimumab in combination with nivolumab; OS, overall survival; PFS, progression-free survival

8.6.2 Base case results

Table 64 shows the results for the base case analysis. Patients treated with tebentafusp had improved OS compared with ipi/nivo, additionally the patients stayed longer in the progression-free state. The treatment with tebentafusp was associated with the highest LY and quality-adjusted life years (QALY), but also higher cost compared to ipi/nivo. Over a lifetime horizon, tebentafusp is estimated to be associated with a 1.19 increase in LYs (3.08 vs. 1.89), and a 1.04 increase in QALYs (2.53 vs 1.48) per treated patient. The improvement in outcomes for patients with mUM is mainly owed to a proportion of patients experiencing longer survival compared with the comparator. The base case incremental cost-effectiveness ratio (ICER) was [redacted] per QALY gained.

Table 64. Base case results

Per patient	Tebentafusp	Ipi/nivo	Difference
LYs gained			
Total LYs gained	3.08128	1.88942	1.19
LYs gained (PFS)	0.72925	0.57177	0.16

Per patient	Tebentafusp	Ipi/nivo	Difference
LYs gained (PPS)	2.35204	1.31765	1.03
QALYs			
Total QALYs	2.52620	1.48344	1.04
QALYs (PFS)	0.60393	0.45221	0.15
QALYs (PD)	1.94587	1.06497	0.88
QALYs (AE)	-0.02360	-0.03373	0.01
Costs			
Total costs	[redacted]	[redacted]	[redacted]
Drug costs	[redacted]	[redacted]	[redacted]
Administration costs	DKK 87,194.67	DKK 16,094.04	DKK 71,100.63
Subsequent treatment	DKK 201,468.76	DKK 6,492.35	DKK 194,976.41
Healthcare resources - PFS	DKK 63,730.54	DKK 49,968.73	DKK 13,761.81
Healthcare resources - PPS	DKK 14,132.88	DKK 14,167.30	DKK -34.42
Healthcare resources - Death	DKK 58,245.03	DKK 49,282.68	DKK 8,962.35
AE costs	DKK 1,705.20	DKK 8,803.61	DKK -7,098.41
Total patient costs	DKK 58,718.48	DKK 39,851.81	DKK 18,866.67
ICER (per QALY)			[redacted]
ICER (per LY)			[redacted]
Δ Costs			[redacted]
Δ QALYs			**1.04**
Δ LYs			**1.19**

Abbreviations: ICER, incremental cost-effectiveness ratio; ipi/nivo, ipilimumab in combination with nivolumab; LY, life year; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

8.7 Sensitivity analyses

8.7.1 Scenario analyses

To evaluate the impact of the model's structural assumption and choice of parameter values, multiple scenario analyses were conducted.

8.7.1.1 Choice of method of extrapolation of overall survival

The incremental LYs and QALYs were driven by the OS curve in the tebentafusp arm, hence it was important to test the impact of the chosen extrapolation method on the results. This section presents the results of a series of scenario analyses testing alternative combinations of standard parametric functions for extrapolating OS. Three parametric function combinations with reasonable fits were examined for the tebentafusp and ipi/nivo arm. The resulting ICERs and change from the base case are presented in [redacted]

[redacted]

8.7.1.2 Treatment beyond progression

According to the study protocol of IMCgp100-202, a proportion of the patients received the study drug beyond disease progression. Hence in the base case, data from the IMCgp100-202 trial were applied to adjust the PFS curves, and thus limiting the possibility of PFS underestimating the proportions of patients on-treatment in a model cycle. A scenario analysis was conducted to investigate the impact on the ICER when both treatment arms only followed the PFS curves, as in current clinical practice for ipi/nivo. The ICER was [redacted] representing a decrease of [redacted]

[redacted]

8.7.1.3 Source of utility data

In base case, the utility was applied based on time to death rather than disease status as detailed in section 8.4.2. A scenario analysis was conducted using the utility values derived from the EQ-5D data collected in the IMCgp100-202 trial. The ICER was [redacted], equal to an [redacted] increase from the base-case.

[redacted]

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[redacted]

8.7.1.4 Modelling of adverse events cost

In the model base case, the AEs were costed in the tebentafusp arm based on outpatient costs only, based on the assumption that the cost of overnight admission (already captured in the administration costs of tebentafusp) would already capture most of the management costs of AEs, as detailed in section 8.5.5. A scenario analysis was conducted where the costs of AEs are based on the same proportion of inpatient vs. outpatient costs applied to the tebentafusp arm as did to the ipi/nivo arm. The percentage change from base case ICER was very minimal. Furthermore, a second scenario was conducted to reflect a potential underestimation of the AE cost associated with ipi/nivo. A study by Geynisman et al. estimated the annual AE cost to be DKK 99,477 per patient [82]. This scenario analysis resulted in a decrease of [redacted] in the ICER.

[redacted]

8.7.1.5 Costs of subsequent treatment

Currently in clinical practice, patients receive subsequent treatment upon discontinuation. In the base case, the proportion of usage of subsequent treatment regimens were in line with IMCgp100-202, and the related costs were included. The length of the subsequent treatment for the tebentafusp arm in the model is equal to the 1st line treatment in the ipi/nivo arm, which may not reflect clinical practice. Thus, a scenario analysis was conducted excluding the cost of subsequent treatment in both treatment arms. The ICER was [redacted] representing a decrease of [redacted]

[redacted]

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8.7.2 Deterministic sensitivity analyses

A univariate sensitivity analysis was conducted to establish those parameters with the greatest impact on the model's results. To determine the parameters to which the model was most sensitive, the model was evaluated with each parameter set at a lower and upper value while other parameters remained constant. The parameters were varied with either 25%, 15% or 10% of its mean value, see Appendix J. Figure 28 presents a tornado diagram indicating the 15 parameters with the greatest influence on the ICER in a descending order. Table 70 presents the ICER as a result of using an upper and lower estimate for these parameters.

The parameter with the most impact on the results was the baseline utility value, as this was applied to patients until they are one year from death. The second parameter impacting the results was the age of a patient, as it determined the time frame over which patients may derive benefit. The third parameter with most impact on the results was mean weight, caused by the dosage of ipi/nivo being weight dependent. All other parameters have very limited impact on the results compared to the three aforementioned parameters.

[redacted]

In Table 71 and Figure 29, ICERs estimated with different values for the list price of the tebentafusp is presented. The list price is varied from 100% (full list price) to the percentage where the ICER becomes negative.

[redacted]

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[redacted]

8.7.3 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was conducted to describe how uncertainty around input parameters was translated into uncertainty around the estimated outputs of the model. Hence, suitable probability distributions were assigned to model parameters to characterize uncertainty around their mean values and have been reported in Appendix J. Values were sampled from the corresponding parameter distributions and were assigned to each parameter in an iterative process. The PSA was performed using 10,000 iterations, and the results of each of these iterations were used to determine the distribution of incremental costs and incremental QALYs, see Figure 30.

When available, the mean value and the SE of each parameter were used to parameterize the relevant probability distribution. When the latter was not available probability parameters were parameterized based on a 25% or 10% variation in the point estimate of the parameter.

The results of the PSA were presented within the CE plane in the form of a joint distribution of costs and QALYs, along with a mean value of the ICER and a 95% CI ellipse. Based on the scatter plot, it is apparent that the there is a larger spread across the Y axis of the scatter plot, indicating that costs were characterized by a higher degree of uncertainty than health benefits.
The mean incremental costs and QALYs as well as the ICER as estimated in the base-case PSA is presented in Table 72.

[redacted]

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The probability that each treatment was cost-effective, resulting in the highest net monetary benefit, is presented over different values of a CE threshold in the form of a cost-effectiveness acceptability curve (CEAC) in Figure 31.

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9. Budget impact analysis

9.1 Eligible population

Tebentafusp is indicated for the treatment of advanced (unresectable or metastatic) HLA-A*02:01-positive UM. The eligible population includes those patients diagnosed each year with mUM (incidence), as well as any patients with mUM who were diagnosed in previous years (prevalence). Patients diagnosed with mUM may only receive tebentafusp if they are HLA-A*02:01 positive.

As described in section 5.1, the number of eligible patients for treatment with tebentafusp in Denmark is estimated to be 7-10 per year. In the budget impact model, 10 is applied. When backtracking this calculation using the percentage of HLA-A*02:01 positive (47%), the annual mUM incidence is thus 21 patients. This is assumed to be the constant number of incident patients in all years.

As tebentafusp is only suitable for HLA-A*02:01-positive patients, 47% of patients with mUM would receive tebentafusp without considering the market share [71]. As no data on prevalence for mUM in Denmark was identified, the prevalence is calculated using survival data. Both incident and prevalent are presented in Table 73. It is assumed that all prevalent patients would be treated in the first year. The sequence of the development of the patient populations receiving either tebentafusp or ipi/nivo is presented in Figure 32.

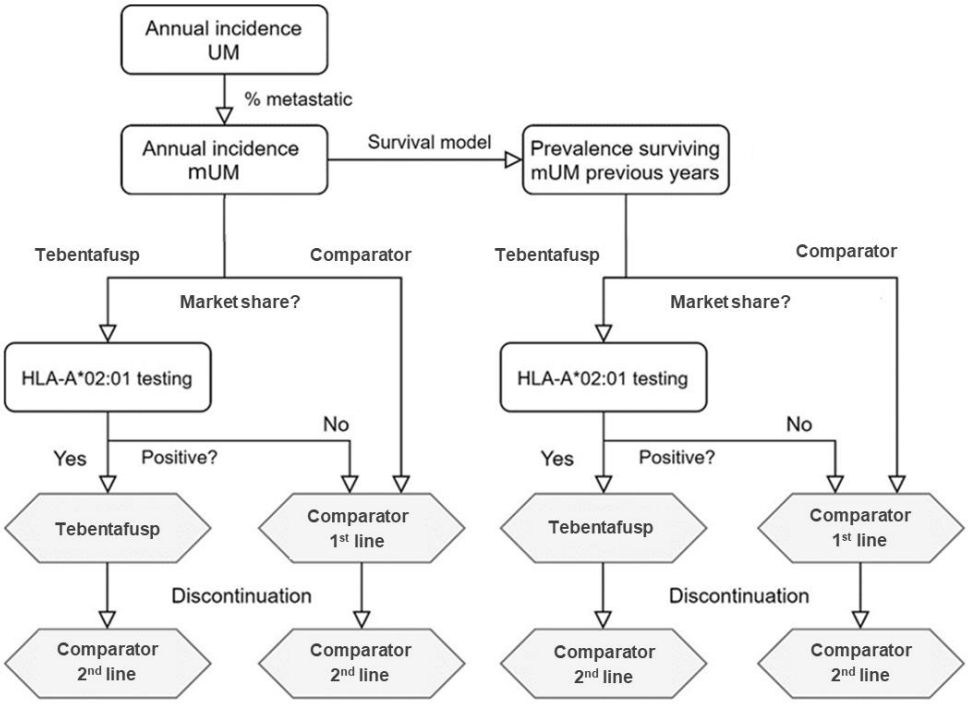

Figure 32. Sequence of the development of patients receiving tebentafusp or ipi/nivo.

9.2 Time on treatment

The number of patients considered to be on treatment each year was modelled based on time to treatment discontinuation for tebentafusp and based on survival data for ipi/nivo. The number of patients on treatment at the mid-point of each year was taken to represent the number of patients on treatment in that year, to which annual drug

costs were applied. The cost of subsequent therapies was only applied to the change in the number of patients off-treatment each year, since these were calculated based on average one-off costs.

9.3 Health state occupancy

The budget impact model implements a partitioned survival approach to the progression of the disease to account for differences in costs of managing different severity of health states. Survival functions for OS and PFS were used to model the numbers of patients in each state over time. These were sourced from the health economic analysis for tebentafusp and represent the base case approach.

The survival functions were used to calculate the expected proportions of patients in either PFS, PD or death each year. The midpoint of each year was used as the point estimate of the numbers in that state to which annual health state costs were applied. The costs of PFS and PD were applied to all patients in that state in a given year, whereas the end-of-life care costs were only applied to those patients dying in that year. The costs of PD are derived below as one-off costs on entry to this state, however, they are applied to all in this state each year.

9.4 Uptake and market share

The market share projections for tebentafusp and the numbers of patients on each treatment under each scenario are presented in Table 73. Under the current practice scenario, no patients receive tebentafusp and all are assigned to receive the composite comparator (ipi/nivo) treatment. In the scenario with tebentafusp, a gradual uptake is assumed with the following market shares; 80% in the first year, 90% in the second and reach a steady state of 100% from year three. Those not receiving tebentafusp due to market share in years 1 and 2 are assigned to ipi/nivo treatment. Those assigned to tebentafusp via market share who then test HLA-A*02:01 negative are also assigned to the composite ipi/nivo treatment.

Table 73. Number of patients expected to be treated over the next five-year period— if tebentafusp is recommended and not recommended.

	Year 1	Year 2	Year 3	Year 4	Year 5
mUM (incidence)	21	21	21	21	21
mUM (prevalence)	26	-	-	-	-
If tebentafusp is recommended					
Tebentafusp % market share	80%	90%	100%	100%	100%
% Patients testing HLA-A*02:01 positive	47%	47%	47%	47%	47%
Number of patients receiving tebentafusp*	18	9	10	10	10
Number of patients receiving ipi/nivo	29	12	11	11	11
If tebentafusp is not recommended					
Number of patients receiving ipi/nivo	47	21	21	21	21

* In year 1, metastatic UM (incidence + prevalence) = 47, multiplied by % patients testing HLA-A*02:01 positive and tebentafusp market share = 18.

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Table 74 shows the expected budget impact of tebentafusp for treating advanced (unresectable or metastatic) UM in Denmark.

Table 74. Expected budget impact of recommending tebentafusp for the current indication.

	Year 1	Year 2	Year 3	Year 4	Year 5
If tebentafusp is recommended					
Drug, administration, & monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health care costs	DKK 1,708,562.86	DKK 2,658,952.75	DKK 3,763,511.93	DKK 4,889,358.52	DKK 6,035,081.33
AE costs	DKK 288,714.88	DKK 123,977.41	DKK 116,834.02	DKK 116,834.02	DKK 116,834.02
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
If tebentafusp is not recommended					
Drug, administration, & monitoring costs	DKK 13,613,490.76	DKK 12,000,710.82	DKK 12,286,114.34	DKK 12,654,341.43	DKK 12,996,253.13
Health care costs	DKK 1,648,735.51	DKK 2,680,036.17	DKK 3,753,841.74	DKK 4,831,662.53	DKK 5,914,619.18
AE costs	DKK 414,547.09	DKK 188,267.90	DKK 188,267.90	DKK 188,267.90	DKK 188,267.90
Total cost	DKK 15,676,773.35	DKK 14,869,014.89	DKK 16,228,223.98	DKK 17,674,271.86	DKK 19,099,140.21

Table 75 presents the budget impact analysis for the introduction of tebentafusp. The analysis includes all treatment related costs relevant for the regions. According to the results presented in the table, the budget impact of tebentafusp ranges from approximately [redacted] the first 5 years following a positive recommendation.

Table 75. Expected incremental budget impact of recommending tebentafusp for the current indication.

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not recommended	DKK 15,676,773.35	DKK 14,869,014.89	DKK 16,228,223.98	DKK 17,674,271.86	DKK 19,099,140.21
Budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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10. Discussion on the submitted documentation

This assessment has shown that there is a statistically significant median OS benefit of treating HLA*02:01 positive mUM patients with tebentafusp compared to the current standard treatment of ipi/nivo. Furthermore, a narrative comparison of the safety data indicated that tebentafusp has a more manageable safety profile, this is specially highlighted with the difference in discontinuation rates between tebentafusp and ipi/nivo, 23.2% vs. 2.0%, respectively. The considerably higher discontinuation due to AEs in the ipi/nivo arm is also supported by the clinical expert's statement that treatment with ipi/nivo is very toxic for the patients and AEs are common.

This assessment contains certain limitations. Firstly, the comparison of tebentafusp and ipi/nivo are done via an indirect comparison, as no head-to-head comparison between the two treatment exists, while the comparison of safety profiles was done via a narrative description. The MAIC was conducted to account for as many uncertainties as possible, however it was only possible to match the populations via the covariates that were reported in the summary level publication of the GEM1402 study. Time since primary diagnosis could for example not be used in the matching as it was not reported in the GEM1402 study. This is a potential unmeasured EM/PV which should be considered when interpreting the results. . A narrative comparison between tebentafusp and ipi/nivo via Pelster et al. 2020 was performed as per the Danish Medicine Council's request. However due to Pelster et al. 2020 including both previously treated and untreated mUM patients (whereas IMCgp202 only included previously untreated) the result from this analysis are not deemed to be scientifically valid.

Secondly, there is a risk of bias in both the IMCgp100-202 and GEM1402 study; Both studies were unblinded studies and additionally, the population in both IMCgp100-202 and GEM1402 has a high performance score with 76% and 84.6% having an ECOG PS of 0 in IMCgp100-202 and GEM1402, respectively. Since the ECOG PS of 0 is higher in the GEM1402 study, this indicated that the population bias was highest in the GEM1402 study, which was supported by the clinical expert's evaluation of both studies. Both studies however reflect a population with a higher performance score than expected in the Danish clinical population, which is common when comparing trials with clinical practice.

Thirdly, when looking at the health economic analysis, the limitations include modelling of AE cost, QoL, and subsequent treatment costs. The clinical expert stated that patients in clinical practice experience other AEs that are not reported in the GEM1402 study, such as pneumonia. As the ipi/nivo AE costs in the model are only based on GEM1402 study, and does not include other AEs, the AE costs in clinical practice are probably higher than in this analysis. The possible higher AE cost associated with ipi/nivo is also supported by the literature. In the study by Geynisman et al., the grade 3/4 AE cost associated with ipi/nivo treatment in advanced cancer was assessed [82]. The annual AE costs per patient was estimated to be approximately DKK 99,477, which is considerably higher than the AE cost from the health economic analysis (DKK 8,803.61). Taking this into account, the cost of AE associated with ipi/nivo in the model is considerably underestimated [82]. Additionally, AE disutilities were only applied in the first cycle of the model. This approach quite accurately reflects the treatment with tebentafusp, where patients mostly experience AEs during the first 3 doses of tebentafusp. However, it is considered a conservative approach for ipi/nivo, where AEs, given the high toxicity and discontinuation due to AEs, occurs continuously throughout the model. By not applying the AE disutilities associated with ipi/nivo continuously throughout the model the QoL in the ipi/nivo arm is possibly higher compared to clinical practice. The underestimation of AE costs associated with ipi/nivo and the conservative approach used to apply the QoL is assumed to have a considerably impact in the model favoring ipi/nivo.

Lastly, there is an uncertainty in the health economic analysis around the cost calculation of subsequent treatment, which is one of the key cost drivers in the model. In the tebentafusp arm, it is assumed that the subsequent treatment length is equal to that of 1st line ipi/nivo treatment arm. However, as tebentafusp can be given continuously after disease progression, the duration of subsequent treatment with ipi/nivo is most likely shorter than when given as 1st

line treatment. Consequently, the cost of subsequent treatment in the tebentafusp arm is assumed to be lower in clinical practice.

Due to the fact that there are currently no effective treatments for mUM, the poor prognosis, and that tebentafusp is the only therapy that has shown a significant survival benefit in patients with mUM in a phase III study, it is considered an important and relevant treatment. Furthermore, subgroup analysis on OS in the IMCgp100-202 study indicated that the survival benefits were highest in patients with smaller tumors. Since patients with UM are monitored continuously in Denmark, there is a higher probability of diagnosing mUM when the tumors are small, leading to a better chance of achieving a higher OS. Due to the uncertainties in the health economic analysis, the cost difference between tebentafusp and ipi/nivo arms is potentially lower and the difference in QoL higher, which would result in a lower ICER and budget impact.

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12. References

1. EMA. Summary of Product: Tebentafusp. 2021.
2. EMA. Community Register of orphan medicinal products [Internet]. [cited 2021 Sep 14]. Available from: https://ec.europa.eu/health/documents/community-register/html/o2397.htm
3. Jager MJ, Shields CL, Cebulla CM, Abdel-Rahman MH, Grossniklaus HE, Stern MH, et al. Uveal melanoma. Nat Rev Dis Prim [Internet]. 2020;6(1):18–20. Available from: http://dx.doi.org/10.1038/s41572-020-0158-0
4. Nathan P, Hassel JC, Rutkowski P, Baurain JF, Butler MO, Schlaak M, et al. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med. 2021;385:1196–206.
5. Carvajal RD, Schwartz GK, Tezel T, Marr B, Francis JH, Nathan PD. Metastatic disease from uveal melanoma: Treatment options and future prospects. Br J Ophthalmol. 2016;101(1):38–44.
6. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Bastholt L, et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment – Update 2019. Eur J Cancer. 2020;126:159–77.
7. Krantz BA, Dave N, Komatsubara KM, Marr BP, Carvajal RD. Uveal melanoma: Epidemiology, etiology, and treatment of primary disease. Clin Ophthalmol. 2017;11:279–89.
8. Rantala ES, Hernberg M, Kivelä TT. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. Melanoma Res. 2019;29(6):561–8.
9. American Cancer Society. Eye cancer survival rates [Internet]. 2020 [cited 2022 Feb 10]. Available from: https://www.cancer.org/cancer/eye-cancer/detection-diagnosis-staging/survival-rates.html
10. American Cancer Society. Eye Cancer Early Detection, Diagnosis, and Staging. Am Cancer Soc [Internet]. 2020;1–24. Available from: https://www.cancer.org/content/dam/CRC/PDF/Public/8626.00.pdf
11. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika. 1993;80(3):557–72.
12. ClinicalTrials.gov. IMCgp100-102 study results [Internet]. [cited 2021 Nov 11]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT02570308?term=tebentafusp&draw=2&rank=2
13. Danske Multidisciplinære Cancer Grupper. Okulære melanomer. 2022;2019(december 2019):0–17.
14. Cleveland Clinic. Biopsy and Adjuvant Therapy May Help Improve Mortality Rate in Uveal Melanoma [Internet]. 2021 [cited 2022 Feb 7]. Available from: https://consultqd.clevelandclinic.org/uveal-melanoma-ocular-treatment-does-not-save-lives-of-patients-with-genetic-mutation/
15. Frenkel S, Rosenne H, Briscoe D, Hendler K, Bereket R, Molcho M, et al. Long-term uveal melanoma survivors: measuring their quality of life. Acta Ophthalmol. 2018;96(4):e421–6.
16. Bol KF, Ellebaek E, Hoejberg L, Bagger MM, Larsen MS, Klausen TW, et al. Real-world impact of immune checkpoint inhibitors in metastatic uveal melanoma. Cancers (Basel). 2019;11(10):11.
17. Danske Multidisciplinære Cancer Grupper. Onkologisk behandling af okulært melanom. 2020;0–15.
18. Piulats JM, Espinosa E, de la Cruz Merino L, Varela M, Alonso Carrión L, Martín-Algarra S, et al. Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402). J Clin Oncol. 2021;39(6):586–98.
19. Rodríguez A, Dueñas-Gonzalez A, Delgado-Pelayo S. Clinical presentation and management of uveal melanoma. Mol Clin Oncol. 2016;5(6):675–7.
20. Willson JKV, Albert DM, Diener-West M, McCaffrey L, Mo CS, Scully RE, et al. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the collaborative ocular melanoma study (coms) coms report no. 15. Arch Ophthalmol. 2001;119(5):670–6.
21. American Cancer Society. Liver Metastases [Internet]. 2020 [cited 2021 Oct 26]. Available from: https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/liver-metastases.html
22. Nshimiyimana R, Guzzetta CE, Brown M-M, Zhou Q, Johnson JM, Sato T, et al. Pilot study of anxiety, depression, and quality of life in patients with the diagnosis of metastatic uveal melanoma. Ann Oncol [Internet]. 2018;29(October):viii560. Available from: https://doi.org/10.1093/annonc/mdy296.011
23. Sundhedsstyrelsen. Pakkeforløb for kræft i øjne og orbita. 2016.
24. Yang J, Manson DK, Marr BP CR. Treatment of uveal melanoma: where are we now? Ther Adv Med Oncol. 2018;10:1–17.
25. Zealth, Clinical expert interviw.
26. Medicinrrådet. Medicinrådets anbefaling vedrørende nivolumab i kombinaiton med ipilimumab til behandling ad ikke-resektbale lungehindecancer. 20222.
27. KRIS. Anbefalinger - Modermærkekræft. 2016.

28. Pelster MS, Gruschkus SK, Bassett R, Gombos DS, Shephard M, Posada L, et al. Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study. J Clin Oncol. 2020;39(6):599–607.
29. EMA. Yervoy: EPAR - Product information [Internet]. 2021 [cited 2021 Oct 20]. p. 1–90. Available from: https://www.ema.europa.eu/en/documents/product-information/yervoy-epar-product-information_en.pdf
30. EMA. Opdivo: EPAR - product information [Internet]. 2021 [cited 2021 Oct 20]. p. 1–123. Available from: https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf
31. ClinicalTrials.gov. Tebentafusp 202 Study Results [Internet]. 2021 [cited 2021 Sep 16]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT03070392?term=tebentafusp&draw=2&rank=3
32. ClinicalTrials. Trial of Nivolumab in Combination With Ipilimumab in Subjects With Previously Untreated Metastatic Uveal Melanoma (GEM1402) [Internet]. 2021 [cited 2021 Oct 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT02626962
33. ClinicalTrials.gov. Nivolumab and Ipilimumab in Treating Patients With Metastatic Uveal Melanoma [Internet]. [cited 2021 Nov 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT01585194
34. ClinicalTrials.gov. A Study of the Intra-Patient Escalation Dosing Regimen With IMCgp100 in Patients With Advanced Uveal Melanoma [Internet]. [cited 2021 Nov 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT02570308
35. ClinicalTrials.gov. ClinicalTrials search and overview of trials including tebentafusp as intervention [Internet]. 2021 [cited 2021 Nov 11]. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=tebentafusp&cntry=&state=&city=&dist=
36. Immunocore. Clinical study report: IMCgp100-202.
37. Velikova G, Coens C, Efficace F, Greimel E, Groenvold M, Johnson C, et al. Health-Related Quality of Life in EORTC clinical trials - 30 years of progress from methodological developments to making a real impact on oncology practice. Eur J Cancer, Suppl. 2012;10(1):141–9.
38. Van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Heal. 2012;15(5):708–15.
39. Dolan P. Modeling Valuations for EuroQol Health States. Med Care. 1997;35(11):1095–108.
40. Szende A, Janssen B, Cabasés J. Self-reported population health: An international perspective based on EQ-5D. Self-Reported Population Health: An International Perspective Based on EQ-5D. 2014. 1–196 p.
41. Pelster MS, Gruschkus SK, Bassett R, Gombos DS, Shephard M, Posada L, et al. Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study. J Clin Oncol. 2021;39(6):599–607.
42. Nathan P, Hassel JC, Rutkowski P, Baurain J-F, Butler MO, Schlaak M, et al. Supplementary Appendix. N Engl J Med. 2021;385(13):1196–206.
43. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. 4th Revise. Oxford University Press; 2015.
44. Finansministeriet. Dokumentationsnotat - den samfundsokonomiske diskonteringsrente [Internet]. 2021. Available from: https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf
45. Medicinrådet. Medicinrådets metodevejledning for vurdering af nye lægemidler. 2021.
46. York Health Economics Consortium. Partitioned Survival Model [online] [Internet]. York. 2016 [cited 2022 Jan 19]. Available from: https://yhec.co.uk/glossary/partitioned-survival-model/
47. NICE. Nivolumab for treating advanced (unresectable or metastatic) melanoma (TA384). 2016;(February):1–33. Available from: http://www.nice.org.uk/guidance/TA384
48. NICE. Nivolumab in combination with ipilimumab for treating advanced melanoma. 2016;(July). Available from: https://www.nice.org.uk/guidance/ta400
49. Immunocore. Match-Adjusted Indirect Comparison of tebentafusp vs ipilimumab+nivolumab in patients with previously untreated uveal melanoma - Data on file. 2021.
50. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Clin Calorim. 1989;(10):111–35.
51. Clinical trial. Safety and Efficacy of IMCgp100 Versus Investigator Choice in Advanced Uveal Melanoma - Tabular view [Internet]. 2021 [cited 2021 Oct 26]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT03070392?term=tebentafusp&draw=2&rank=3
52. NICE. Pembrolizumab for advanced melanoma not previously treated with ipilimumab. Technol Apprais Guid [TA3666] [Internet]. 2015;(September 2017):33. Available from: www.nice.org.uk/guidance/ta366

53. NICE. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. 2014;(July). Available from: https://www.nice.org.uk/guidance/ta319
54. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. Sheff Rep by Decis Support Unit [Internet]. 2011;(0). Available from: https://www.ncbi.nlm.nih.gov/books/NBK395885/pdf/Bookshelf_NBK395885.pdf
55. Rohatgi A. WebPlotDigitizer [Internet]. 2021 [cited 2022 Feb 18]. Available from: https://automeris.io/WebPlotDigitizer/
56. Khoja L, Atenafu EG, Suciu S, Leyvraz S, Sato T, Marshall E, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks : an international rare cancers initiative (IRCI) ocular melanoma study Original article. 2019;(May):1370–80.
57. Hatswell AJ, Pennington B, Pericleous L, Rowen D, Lebmeier M, Lee D. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. Health Qual Life Outcomes. 2014;12(1):1–9.
58. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095–108.
59. Robert C, Schachter J, Long G V., Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372(26):2521–32.
60. Robert C, Long G V., Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in Previously Untreated Melanoma without BRAF Mutation . N Engl J Med. 2015;372(4):320–30.
61. Beusterien KM, Szabo SM, Kotapati S, Mukherjee J, Hoos A, Hersey P, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. 2009;101(3):387–9. Available from: http://dx.doi.org/10.1038/sj.bjc.6605187
62. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373(1):23–34.
63. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377–99.
64. Jensen CE, Sorensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Appl Heal Econ Heal Policy [Internet]. 2021/02/03. 2021;19(4):579–91. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33527304
65. Lægemiddelstyrelsen. Medicinpriser [Internet]. January. 2022. Available from: https://medicinpriser.dk/default.aspx
66. Lægemiddelstyrelsen. Medicinpriser - CSL Behring [Internet]. 2022 [cited 2022 Feb 11]. Available from: https://www.medicinpriser.dk/Default.aspx?VirksomtStof=Albumin
67. CSL Behring. Human albumin CSL Behring 20%. Available from: https://mri.cts-mrp.eu/human/downloads/DK_H_1508_003_FinalPI_1of3.pdf
68. Sundhedsdatastyrelsen. Takstsystem 2022. Datavarehus, Dokumentation og DRG [Internet]. 2022;1. Available from: https://sundhedsdatastyrelsen.dk/-/media/sds/filer/finansiering-og-afregning/takster/2022/takstsystem-2022.pdf
69. Rigshospitalet. Rigshospitalets Labportal [Internet]. 2022 [cited 2022 Feb 11]. Available from: https://labportal.rh.dk/Labportal.asp?ShowStart=Y
70. Rigshospitalet. Laboratorieundersøgelse- NPU26753 [Internet]. 2022 [cited 2022 Feb 11]. Available from: https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=4323
71. The Allele Frequency Net Database. Allele Frequency Net Database [Internet]. 2020 [cited 2022 Feb 18]. Available from: Allelefrequencies.net
72. Lægemiddelstyrelsen. Medicinpriser [Internet]. 2022 [cited 2022 Feb 11]. Available from: https://medicinpriser.dk/Default.aspx
73. pro.medicin.dk. Temozolomide “SUN” [Internet]. 2021 [cited 2022 Feb 11]. Available from: https://pro.medicin.dk/Medicin/Praeparater/7373
74. Najjar YG, Navrazhina K, Ding F, Bhatia R, Tsai K, Abbate K, et al. Ipilimumab plus nivolumab for patients with metastatic uveal melanoma: a multicenter, retrospective study. J Immunother cancer. 2020;8(1):1–9.
75. McKendrick J, Gijsen M, Quinn C, Barber B, Zhao Z. Estimating healthcare resource use associated with the treatment of metastatic melanoma in eight countries. J Med Econ. 2016;19(6):587–95.
76. Medicinradet. Værdisætning af enhedsomkostninger [Internet]. 2022. Available from: https://medicinraadet.dk/media/weslftgk/vaerdisaetning-af-enhedsomkostninger-vers-13_adlegacy.pdf

77. Rigshospitalet. CT-skanning [Internet]. [cited 2022 Feb 11]. Available from: https://www.rigshospitalet.dk/afdelinger-og-klinikker/diagnostisk/roentgen-og-skanning/undersoegelse-og-behandling/Sider/ct-skanning.aspx
78. Kræftens Bekæmpelse. PET/CT-scanning [Internet]. 2017 [cited 2022 Feb 11]. Available from: https://www.cancer.dk/hjaelp-viden/undersoegelser-for-kraeft/scanninger-billedundersoegelser/pet-ct-scanning/?gclid=EAIaIQobChMIlNuBu6P39QIVRYfVCh1p7ws9EAAYASAAEgJcl_D_BwE
79. Hvidovre Hospital. Leveren - MR-skanning [Internet]. [cited 2022 Feb 11]. Available from: https://www.hvidovrehospital.dk/undersoegelse-og-behandling/find-undersoegelse-og-behandling/Sider/Leveren---MR-skanning-25344.aspx
80. Aarhus Universitetshospital. Operation for svulst i leveren (åben leveroperation). 2020;1–6. Available from: https://e-dok.rm.dk/edok/media/media.nsf/vUpload/X72F2EAE5507DBFAAC1257F42003145B7/$file/Operation for svulst i leveren (åben leveroperation).pdf
81. Reddy SK, Kesmodel SB, Alexander HR. Isolated hepatic perfusion for patients with liver metastases. Ther Adv Med Oncol [Internet]. 2014;6(4):180–94. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4107710/pdf/10.1177_1758834014529175.pdf
82. Geynisman DM, Du EX, Yang X, Sendhil SR, Tejo V Del, Betts KA, et al. Temporal trends of adverse events and costs of nivolumab plus ipilimumab versus sunitinib in advanced renal cell carcinoma. Futur Oncol. 2021;1.
83. ClinicalTrials.gov. Study result of GEM 1402 [Internet]. 2021 [cited 2021 Oct 26]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT02626962?view=record
84. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant [Internet]. 2019;25(4):625–38. Available from: https://doi.org/10.1016/j.bbmt.2018.12.758
85. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for Population-Adjusted Indirect Comparisons in Submissions To Nice. Nice Dsu Tech Support Doc 18 [Internet]. 2016;(December):1–82. Available from: http://nicedsu.org.uk/wp-content/uploads/2017/05/Population-adjustment-TSD-FINAL.pdf
86. Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Kantor E, Bao Y, et al. Comparative Effectiveness Without Head-to-Head Trials -. Pharmacoeconomics [Internet]. 2010; Available from: https://link.springer.com/article/10.2165%2F11538370-000000000-00000
87. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-adjusted indirect comparisons: A new tool for timely comparative effectiveness research. Value Heal. 2012;15(6):940–7.
88. Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. Stat Med. 2016;35(30):5642–55.
89. Jackson C. A Platform for Parametric Survival Modeling in R. J Stat Softw. 2016;70(8):1–33.
90. Wickham H. Elegant Graphics for Data Analysis Second Edition [Internet]. Vol. 35. 2016. 10–1007 p. Available from: http://www.springer.com/series/6991

13. Appendix A: Literature search for efficacy and safety of intervention and comparator(s)

13.1 Objective, databases and registers

The objective of the literature search was to identify studies describing the efficacy and safety of tebentafusp, and the clinically relevant comparator ipi/nivo, in order to answer the following:

"What is the comparative efficacy and safety of tebentafusp versus ipi/nivo in the treatment of mUM?"

The systematic literature review was performed on 16 – 18 November 2021. The searches were performed on MEDLINE via Pubmed and CENTRAL via Cochrane Library, see Table 76. To identify ongoing trials in progress, searches were performed on clinicaltrials.gov (via https://clinicaltrials.gov/) and EU clinical trials register (via https://www.clinicaltrialsregister.eu/). These searches were performed on 19 November 2021, see Table 77 .

Table 76. Bibliographic databases included in the literature search.

Database	Platform	*Relevant period for the search*	Date of search *completion*
Embase	Cochrane Library	No filter on time period	16.11.2021
Medline	Pubmed	From 2020 week 46 and 10 years back	16.11.2021

Table 77. Registers included in the search.

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	See below	19.11.2021
EU Clinical Trials Register	EU Clinical Trials Register	See below	19.11.2021

13.2 Search strategies

The search strategy developed to meet the objective of the literature search was defined by the following inclusion and exclusion criteria described in Table 78.

Table 78. PICOs used in the systematic literature review

Elements	Inclusion Criteria	Exclusion Criteria
Population	- Adult patients with advanced or mUM/choroidal melanoma	- Previously treated patients (2nd line) - Patients with localized disease only (non-mUM/choroidal melanoma) - Pediatric patients
Intervention	- Tebentafusp	- Surgical interventions only
Comparator	- Ipilimumab/nivolumab	- N/A
Outcome	- OS - PFS - AEs and SAEs	- Outcome not listed in the "inclusion criteria" of PICOs

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Study design	- RCTs - Single arm trials - Conference abstracts	- Pharmacokinetic studies - Proof of concept studies - Case reports, case series, retrospective observational studies, editorials, and letters - Reviews/systematic reviews/pooled trial analyses - Non-human studies - Non-English abstracts and non-English full-text articles

Abbreviations: AEs, adverse events; PICOs, population, intervention, comparator, outcomes, study design; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; AEs: Adverse events; SAE, serious adverse events; UM, uveal melanoma

13.2.1 Search string

The following search string was used in Pubmed on the 17th of November, resulting in a total of 240 hits:

(((((((""Uveal melanom"" [Supplementary Concept]) OR (choroidal melanoma)) OR (choroidal melanoma)) OR (Iris melanoma)) OR (metastatic uveal melanoma)) OR (ocular melanoma)) AND ""Adul""[Mesh])) AND (tebentafusp)) OR (((((((Ipilimumab plus nivolumab) OR (Ipi/Nivo)) OR (Ipi-Nivo)) OR (nivolumab ipilimumab)) OR (ipilimumab nivolumab)) OR (yervoy plus opdivo)) OR (opdivo yervoy)) OR (yervoy opdivo)))

The following filters were applied in according to the PICOs: Clinical trial, randomized controlled trial, systematic review, 10 years, human. See Table 79 for the results of the search strategy on Pubmed.

Table 79. Search strategy applied on Pubmed*

No.	Query	Results
#1	**""Adul""[Mesh]**	744.173
#2	**""Uveal melanom"" [Supplementary Concept]**	67
#3	Choroidal Melanoma	129
#4	Iris melanoma	24
#5	Metastatic uveal melanoma	108
#6	Ocular melanoma	165
#7	#2 OR #3 OR #4 OR #5 OR #6	334
#8	Tebentafusp	3
#9	Ipilimumab plus nivolumab	129
#10	Ipi/Nivo	5
#11	Ipi-Nivo	5
#12	Nivolumab ipilimumab	299
#13	Ipilimumab nivolumab	299
#14	Yervoy plus opdivo	129
#15	Opdivo yervoy	299

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#16	Yervoy opdivo	299
#17	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	302
#18	#1 AND #7 AND #17	301

** Table 75 was realized 5 months after the SLR was originally done. Hence, the number of results represent available publications that fits the criteria as of the 19th of April. As the SLR from November has been conducted within 1 year, according to the DMCs guideline, the SLR will not be updated in regards to table 75..*

In Embase, the following search strategy was used, resulting in 22 hits, see Table 80.

Table 80. Search strategy in Embase.

No.	Query	Results
#1	Mesh descriptor [adult] explode all trees	481.600
#2	MeSh descriptor: [Uveal neoplasms] explode all trees	119
#3	Ipilimumab plus nivolumab	394
#4	Ipi-nivo	85
#5	Yervoy plus opdivo	19
#6	Ipilimumab nivolumab	934
#7	Yervoy opdivo	54
#8	Uveal melanoma	205
#9	Chroidal melanoma	113
#10	Iris melanoma	18
#11	Metastatic uveal melanoma	94
#12	Tebentafusp	8
#13	#1 AND #2 OR #8 OR #9 OR #10 OR #11	311
#14	#3 OR #4 OR #5 OR #6 OR #7 OR #12	945
#15	#13 AND #14	22

On clinicaltrials.gov and the EU Clinical Trials Register the following searches were conducted:

- (Uveal Melanoma OR choroidal melanoma OR iris melanoma OR metastatic uveal melanoma OR ocular melanoma) AND tebentafusp
    - Hits in clinicaltrials.gov: 2
    - Hits in Eu clinical trial register: 1

- (Uveal Melanoma OR choroidal melanoma OR iris melanoma OR metastatic uveal melanoma OR ocular melanoma) AND (Nivolumab AND Ipilimumab)
    - Hits in clinicaltrials.gov: 11
    - Hits in Eu clinical trial register: 5

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13.3 Results of literature review

On clinicaltrial.gov, the IMCgp100-202 study was identified while EU clinical trial register identified IMCgp100-202, GEM1402 and the Peltser et al. study. The remaining studies were excluded in accordance to the PICO and inclusion/exclusion criteria.

In the SLR, 263 studies were identified, which was reduced to 261 after a duplicate search. A primary screening based on title and abstract. If there was uncertainty about the relevance of a record based on the abstract in the primary screening, it was included and taken forward to secondary screening. The screening was performed by one reviewer. In the primary screening 12 studies were included for full text screening, with 3 being included as relevant for a potential indirect comparison, see Figure 33.

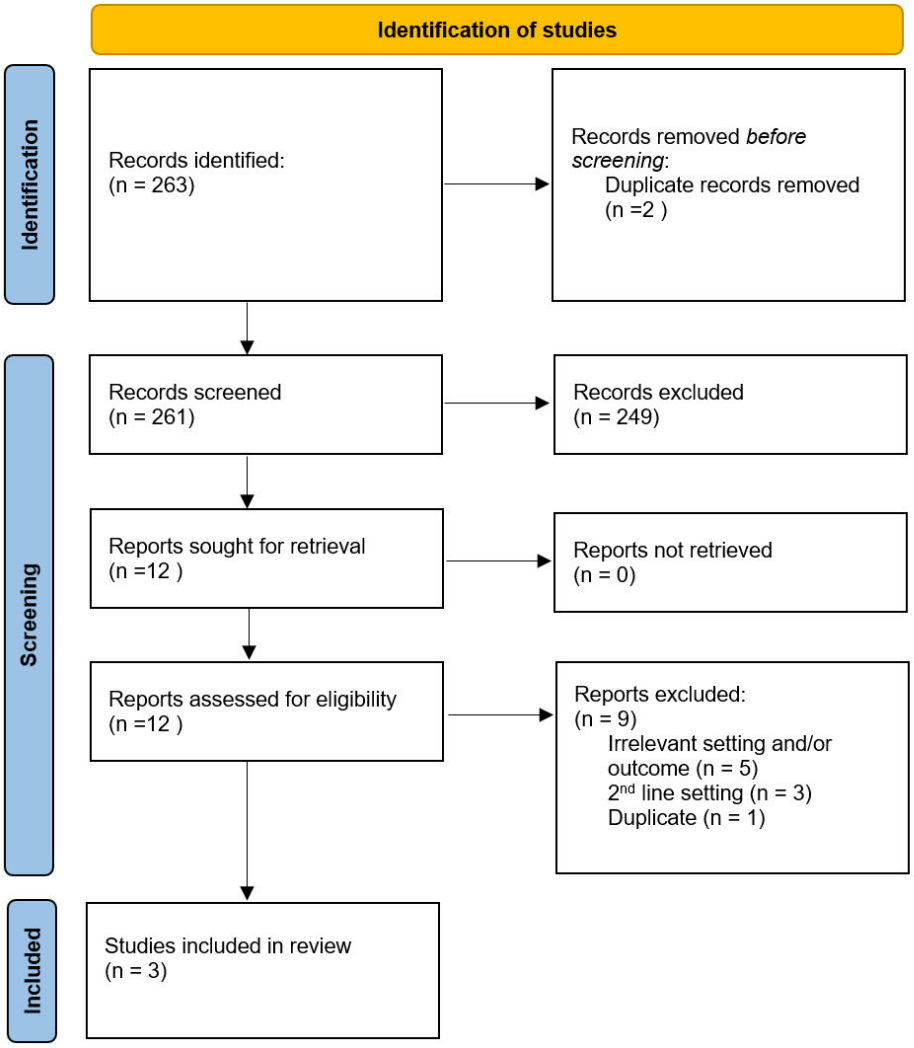

Figure 33. PRISMA flow chart of systematic literature review.

Below, a list of included studies based on the full text screening can be seen in Table 81, while a list of excluded studies based on full test screening can be seen in Table 82.

Table 81. Overview of study design for studies included in the technology assessment/analysis.

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
IMCgp100-202[4]	To evaluate the OS of HLA-A*02:01 positive adult patients with previously untreated advanced UM receiving tebentafusp (IMCgp100-202) compared to dacarbazine, ipilimumab, or pembrolizumab	It is an ongoing randomized, open-label, active-comparator study	Patients with HLA-A*02:01 positive advanced or metastatic uveal melanoma in the first line setting with no prior systemic or liver-directed chemo-,radio- or immunotherapy (prior surgical resection of liver metastases and adjuvant systemic therapy are acceptable)	Intervention: Tebentafusp, n = 252 Comparator: Pembrolizumba, ipililumab or dacarbazine, n = 126	OS Median follow-up period = 14.1 months	Safety, OFS, Quality of Life, Pharmacokinetics, ORR, DoR and DCR
GEM1402[18]	This study aimed to assess the efficacy of the combination of nivolumab (nivo) plus ipilimumab (ipi) as a 1st line therapy with respect to the 12-month OS in patients with metastatic uveal melanoma who are not eligible	It is a phase II multicenter, non-randomized, open label trial of ipi/nivo	Patients with previously untreated metastatic uveal melanoma	Ipi/Nivo, n = 52. No comparator	OS Median follow-up period = 13.4 months	OS rate, PFS, ORR, DCR, DoR

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Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	for liver resection.					
Pelster[28]	This phase II trial studies how well nivolumab and ipilimumab work in treating patients with uveal melanoma that has spread to other places in the body (metastatic)	Phase II, open label study	Patients with metastatic uveal melanoma	Ipi/Nivo, n = 35 No comparator	ORR Median follow-up period = 13.0 months	PFS, OS, OS rate

Table 82. Excluded studies from full text review.

Number	Reference	Reason for exclusion
1	Abstract CT002: Phase 3 randomized trial comparing tebentafusp with investigato''s choice in first line metastatic uveal melanoma. Proceedings of the American Association for Cancer Research Annual Meeting 2021; 2021 Apr 10-15 and May 17-21. Philadelphia (PA): AACR; Cancer Res 2021;81(13_Suppl): Abstract nr CT002.	Study results from the IMCgp100-202 study presented at a conference providing no new information relevant for the assessment.
2	64MO—- A phase (ph) II, multi-center study of the safety and efficacy of tebentafusp (tebe) (IMCgp100-202) in patients (pts) with metastatic uveal melanoma. Sato T et al. J. Clin. Oncol. 2018; 36(15_suppl): 9521	2nd line setting
3	Phase II multicenter, non-randomized, open label trial of nivolumab in combination with ipilimumab in subjects with previously untreated metastatic uveal melanoma. Abstract, immunotherapy of cancer; volume 27. supplement 6. October 1, 2016.	Trial description of GEM1402
4	Co-primary endpoint of overall survival for tebentafusp (tebe)-induced rash in a phase 3 randomized trial comparing tebe versus investigator's choice (IC) in first-line metastatic uveal melanoma. Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 9527-9527.	Abstract describing the association between rash and OS in the IMCgp100-202 study, which is described in the Nathan et al. publication and irrelevant for this assessment

Number	Reference	Reason for exclusion
5	Phase II multicenter, non-randomized, open label trial of nivolumab in combination with ipilimumab in subjects with previously untreated metastatic uveal melanoma. Abstract immunotherapy of cancer; volume 27. supplement 6. October 1, 2016.	Trial description of GEM1402 and duplicate of reference 3.
6	Phase II multicenter, single arm, open label study of nivolumab (NIVO) in combination with ipilimumab (IPI) as first line in adult patients (pts) with metastatic uveal melanoma: gEM1402 NCT02626962	GEM1402 study results less mature than the Piulats et al 2021 reference.
7	Characterization of cytokine release syndrome (CRS) following treatment with tebentafusp in patients (pts) with previously treated (2L+) metastatic uveal melanoma. Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 9531-9531.	2nd line setting.
8	1013P Similar overall survival in tebentafusp-treated 2L+ metastatic uveal melanoma regardless of prior immunotherapy	2nd line setting
9	Overall survival in patients who received checkpoint inhibitors after completing tebentafusp in a phase 3 randomized trial of first line metastatic uveal melanoma. Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 9526-9526.	An abstract describing the effect of treatment received after tebentafusp, which is an irrelevant endpoint for this assessment.

13.4 Quality assessment

This SLR followed the guidelines provided by the Danish Medicine council. The SLR is an update of an earlier SLR from 2020 which was used in the NICE application. The SLRs were carried out by two different companies, and ultimately included the same studies (IMCgp100-202, GEM1402 and Peltser et al.2020, which confirms the validity of the SLR. The SLR was able to identify studies of both the intervention and comparator with the relevant outcomes OS, PFS and safety.

The main limitation of this SLR includes, that it was carried out by a single person. However, since the result match with an earlier SLR used in the NICE application, this limitation is not assessed to have a major influence. Furthermore, since both GEM1402 and IMCgp100-202 are newer studies containing a relevant patient population and endpoints making an indirect comparison available, the result of the SLR are assessed as sufficient for this assessment.

13.5 Unpublished data

A limited amount of data has been provided via the CSR from the IMCgp100-202 and therefore has the same quality as in the study.

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14. Appendix B: Main characteristics of included studies

Table 83. Main characteristics of the IMCgp100-202 study.

Trial name: Safety and efficacy of IMCgp100 Versus Investigator Choice in Advanced Uveal Melanoma (IMCgp100-202) [31]	**NCT number: NCT03070392**[31]
Objective[4,31]	To evaluate the overall survival of HLA-A*02:01 positive adult patients with previously untreated advanced UM receiving tebentafusp compared to dacarbazine, ipilimumab, or pembrolizumab
Publications – title, author, journal, year[4]	Overall survival benefit with tebentafusp in metastatic uveal melanoma, Nathan P. et al–- N Engl J Med 2021; 385:1196-1206
Study type and design[4,31]	IMCgp100-202 is an ongoing randomized, open-label, active-comparator study, where patients with HLA-A*02:01 positive advanced or metastatic uveal melanoma in the first line setting with no prior systemic or liver-directed chemo-, radio- or immunotherapy (prior surgical resection of liver metastases and adjuvant systemic therapy are acceptable) are treated with either tebentafusp, dacarbazine, ipilimumab or pembrolizumab. Cross over is not permitted. A study schematic is presented in Figure 34.
Sample size (n) [4,31]	378

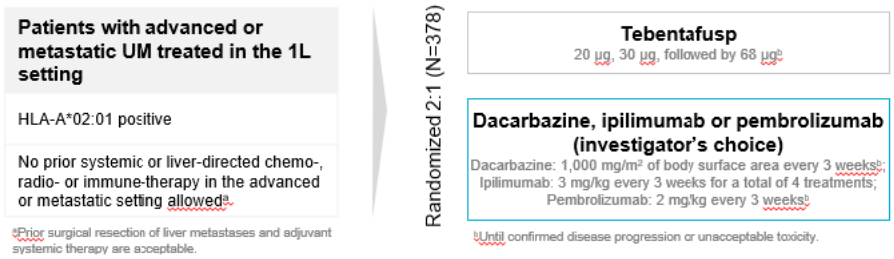


Figure 34. Study schematic of IMCgp100-202 study.

Main inclusion and exclusion criteria[31]	**Inclusion Criteria** - Male or female patients age ≥ 18 years of age at the time of informed consent - Ability to provide and understand written informed consent prior to any study procedures - Histologically or cytologically confirmed mUM - Must meet the following criteria related to prior treatment: • No prior systemic therapy in the metastatic or advanced setting including chemotherapy, immunotherapy, or targeted therapy • No prior regional, liver-directed therapy including chemotherapy, radiotherapy, or embolization • Prior surgical resection of oligometastatic disease is allowed • Prior neoadjuvant or adjuvant therapy is allowed provided administered in the curative setting in patients with localized disease. Patients may not be re-treated with an Investigato''s Choice therapy that was administered as adjuvant or neoadjuvant treatment. Additionally, patients who have received nivolumab as prior adjuvant/neoadjuvant treatment should not receive pembrolizumab as Investigato''s Choice therapy. - HLA A*02:01 positive by central assay - Life expectancy of > 3 months as estimated by the investigator - Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 at Screening - Patients have measurable disease or non-measurable disease according to RECIST v1.1 - All other relevant medical conditions must be well-managed and stable, in the opinion of the investigator, for at least 28 days prior to first administration of study drug **Exclusion Criteria** - Patient with any out-of-range laboratory values defined as: • Serum creatinine > 1.5 × ULN and/or creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 50 mL/minute • Total bilirubin > 1.5 × ULN, except for patients with Gilber''s syndrome who are excluded if total bilirubin > 3.0 × ULN or direct bilirubin > 1.5 × ULN • Alanine aminotransferase > 3 × ULN • Aspartate aminotransferase > 3 × ULN • Absolute neutrophil count < 1.0 × 10^9/L • Absolute lymphocyte count < 0.5 × 10^9/L • Platelet count < 75 × 10^9/L • Hemoglobin < 8 g/dL - History of severe hypersensitivity reactions (e.g., anaphylaxis) to other biologic drugs or monoclonal antibodies - Clinically significant cardiac disease or impaired cardiac function, including any of the following: • Clinically significant and/or uncontrolled heart disease such as congestive heart failure (New York Heart Association grade ≥ 2), uncontrolled

hypertension or clinically significant arrhythmia currently requiring medical treatment

- QT interval corrected by Friderici''s formula > 470 msec on screening ECG or congenital long QT syndrome
- Acute myocardial infarction or unstable angina pectoris < 6 months prior to Screening

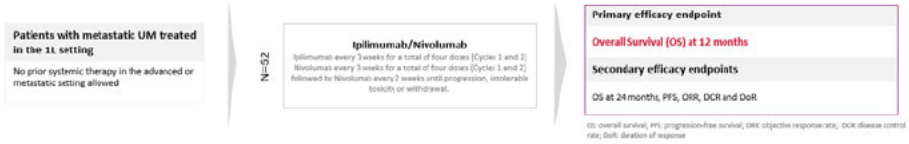
- Presence of symptomatic or untreated central nervous system (CNS) metastases, or CNS metastases that require doses of corticosteroids within the prior 3 weeks to study Day 1. Patients with brain metastases are eligible if lesions have been treated with localized therapy and there is no evidence of PD for at least 4 weeks by magnetic resonance imaging (MRI) prior to the first dose of study drug
- Active infection requiring systemic antibiotic therapy. Patients requiring systemic antibiotics for infection must have completed therapy at least 1 week prior to the first dose of study drug
- Known history of human immunodeficiency virus infection (HIV). Testing for HIV status is not necessary unless clinically indicated
- Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection per institutional protocol. Testing for HBV or HCV status is not necessary unless clinically indicated or the patient has a history of HBV or HCV infection
- Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type
- Any medical condition that would, in the investigato''s or sponso''s judgment, prevent the patien''s participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results
- Patients receiving systemic steroid therapy or any other systemic immunosuppressive medication at any dose level, as these may interfere with the mechanism of action of study treatment. Local steroid therapies (e.g., otic, ophthalmic, intra-articular, or inhaled medications) are acceptable
- History of adrenal insufficiency
- History of interstitial lung disease
- History of pneumonitis that required corticosteroid treatment or current pneumonitis
- History of colitis or inflammatory bowel disease
- Major surgery within 2 weeks of the first dose of study drug (minimally invasive procedures such as bronchoscopy, tumor biopsy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery and are not exclusionary)
- Radiotherapy within 2 weeks of the first dose of study drug, with the exception of palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass
- Use of hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF, M-CSF) ≤ 2 weeks prior to start of study drug. An erythroid-stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment and the patient is not red blood cell transfusion dependent

Trial name: Safety and efficacy of IMCgp100 Versus Investigator Choice in Advanced Uveal Melanoma (IMCgp100-202) [31]	NCT number: NCT03070392[31]
	- Pregnant, likely to become pregnant, or lactating women (where pregnancy is defined as the state of a female after conception and until the termination of gestation) - Women of childbearing potential who are sexually active with a non-sterilized male partner, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during study treatment, and must agree to continue using such precautions for 6 months after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician. - Male patients must be surgically sterile or use double barrier contraception methods from enrollment through treatment and for 6 months following administration of the last dose of study drug - Patients who are in an institution due to official or judicial order. - Patients who are the investigator or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in the conduct of the study. - Contraindication for treatment with Investigato''s choice alternatives (dacarbazine, ipilimumab and pembrolizumab) as per applicable labelling. Patient may have a contraindication to 1 or 2 of the choices if he/she is a candidate for dosing with at least 1 Investigato''s Choice and meets all other study eligibility criteria.
Intervention [31]	Treatment with tebentafusp with the dose of 20 µg cycle 1 day 1, then 30 µg cycle 1 day 8 and 68 µg cycle 1 day 15 followed by 68 µg weekly. All administrations are via infusion over 15 minutes. Treatment is continued until confirmed disease progression or unacceptable toxicity. 252 persons were treated with tebentafusp.
Comparator(s) [31]	- **Comparators, including dose, dose interval and number of patients:** Systemic dacarbazine, ipilimumab or pembrolizumab. In total 126 persons were treated with one of the three comparators: • **Dacarbazine:** Administered at 1,000 mg/m^2 of body surface area IV infusion every 3 weeks until disease progression or unacceptable toxicity. 7 Persons were treated with Dacarbazine. • **Ipilimumab:** Administered at 3 mg/kg IV infusion over 90 minutes every 3 weeks for a total of 4 treatments. 16 persons were treated with Ipilimumab. • **Pembrolizumab:** Administered at 2 mg/kg IV infusion up to a maximum of 200 mg administered intravenously over 30 minutes every 3 weeks or 200 mg fixed dose administered intravenously every 3 weeks were approved locally until confirmed disease progression or unacceptable toxicity. 103 persons were treated with pembrolizumab.
Follow-up time [4]	At the time of the clinical data cutoff for the first interim analysis (October 13, 2020), the median duration of follow-up was 14.1 months.
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints[31]	**Primary, secondary, and exploratory endpoints, including definition, method of measurement and if possible, time of measurement:** **Primary outcome**[31]**:** - Overall survival defined as the time from randomization to date of death due to any cause. The time frame was from randomization to the data cutoff date of 13th of October 2020; median follow-up duration was 14.1 months. **Secondary outcomes**[31]**:** - Safety: Number of participants with treatment-emergent adverse events. Defined as the number of participants with treatment-emergent adverse events, including laboratory abnormalities, ECG changes, and/or physical examination findings. Safety was assessed from informed consent through 90 days after end of treatment, up to 36 months. - Progression free survival defined as the time from randomization to the date of progression (RECIST v1.1) or death due to any cause. PFS was assessed every 3 months from randomization until disease progression or death, up to 36 months. - Quality of life defined as changes From Baseline in EQ-5D-5L Domain Scores. General health status was assessed using the EQ-5D-5L questionnaire, which includes five dimensions (5D): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 scoring levels, where 1 indicates a better health state (no problems) and 3 indicates a worse health state. A positive change indicates improvement. EQ-5D-5L was assessed at baseline (cycle 1 day 1) and on Day 1 of every other cycle to Cycle 5 Day 1, every fourth cycle thereafter, beginning with cycle 9 day 1 and end of treatment, up to 36 months. Each cycle is 28 days. - Quality of life defined as change from baseline in EQ-5D Visual Analogue Score (VAS). The EQ-5D VAS score records the participan''s self-rated health on a vertical visual analogue scale, with 0 being the worst imaginable health state and 100 being the best imaginable health state. A positive change indicates improvement. EQ-5D-5L VAS was assessed at baseline (cycle 1 day 1) and on day 1 of every other cycle to cycle 5 day 1, and every fourth cycle thereafter, beginning with cycle 9 day 1 and end of treatment, up to 36 months. Each cycle is 28 days. - Quality of life defined as change from baseline in EORTC QLQ-C30 Global Health Status. Global health status and quality of life was assessed using the EORTC QLQ-C30 questionnaire. The score range for the EORTC QLQ-C30 is from 0 to 100, with higher scores indicating better functioning and better global health status and health-related quality of life. A positive change indicates improvement. EORTC QLQ-C30 was assessed at baseline (cycle 1 day 1) and on day 1 of every other cycle to cycle 5 day 1, every fourth cycle thereafter, beginning with cycle 9 day 1 and end of treatment (EOT), up to 36 months. Each cycle is 28 days. - Pharmacokinetics: Tebentafusp concentration defines as serum pharmacokinetic concentrations of tebentafusp. Pharmacokinetic concentrations were assessed at pre-dose, end of infusion and after 12-24 hours in cycle 1 on days 1, 8 and 15. - Objective Response Rate (ORR) defined as the proportion of patients achieving an objective response (RECIST v1.1). ORR will be assessed after every participant has had at least 3 assessments, conducted every 3 months, up to 5.5 years. - Duration of response (DoR) defined as the time from first documented objective response (RECIST v1.1) until the date of documented disease progression. DOR will be assessed every 3 months from randomization until disease progression, assessed up to 5.5 years.

Trial name: Safety and efficacy of IMCgp100 Versus Investigator Choice in Advanced Uveal Melanoma (IMCgp100-202) [31]	NCT number: NCT03070392[31]
	- Disease control rate (DCR) defined as the proportion of patients with either an objective response or stable disease (RECIST v1.1). DCR will be assessed every 3 months from randomization until disease progression, up to 5.5 years. - Pharmacokinetics: Frequency of Anti-tebentafusp antibody formation. Approximately 5 assessments will be performed between first dose of tebentafusp and end of treatment, assessed up to 5.5 years.
Method of analysis[4]	With the exception of subgroup analyses, the proportional hazards (PH) assumption was tested via the method proposed by Lin et al. [11] for all results where a Cox proportional hazards model was used to provide a hazard ratio for the overall treatment effect[4].
Subgroup analyses[4]	A subgroup analysis was carried out on overall survival for patient with disease progression and stable disease and according to patient characteristics.
Other relevant information	N/A

Table 84. Main characteristics of the GEM1402 study.

Trial name: Trial of Nivolumab in Combination With Ipilimumab in Subject with Previously Untreated Metastatic Uveal Melanoma (GEM1402) [32]	**NCT number: NCT02626962** [32]
Objective [18,32]	This study aim was to assess the efficacy of the combination of nivolumab plus ipilimumab as a first-line therapy with respect to the 12-month overall survival (OS) in patients with mUM who were not eligible for liver resection.
Publications – title, author, journal, year[18]	Nivolumab Plus ipilimumab for treatment-näive metastatic uveal melanoma: An open-label, multicenter, phase II trial by the Spanish multidisciplinary melanoma group (GEM-1402) – Piulats JM et al, J Clin Oncol 2021; 39:586-598 [18].
Study type and design [18,32]	GEM1402 is a single-arm, non-randomized, open label phase II study that enrolled treatmentle patients with mUM. The patients received Ipilimumab every 3 weeks for a total of four doses (Cycles 1 and 2) and nivolumab every 3 weeks for a total of four doses (Cycles 1 and 2) followed by Nivolumab every 2 weeks until progression, intolerable toxicity, or withdrawal. The primary outcome was OS, and secondary outcomes were OS-rate at 24 months, PFS, ORR, DCR and DoR. A study schematic of GEM1402 is presented in Figure 35 [4,18,32,35]. **Figure 35. GEM1402 study design.** 
Sample size (n) [18,32]	52

Main inclusion and exclusion criteria [83]	**Inclusion Criteria**
	• Written informed consent must be provided
	• Patients must have a histological diagnosis of UM
	• Progressive metastatic disease at baseline. Progressive disease is defined as new or progressive lesions on cross-sectional imaging
	• Age>18 years
	• Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1
	• Measurable disease by CT or MRI per RECIST 1.1 criteria
	
	Exclusion Criteria
	• Prior systemic treatment for mUM
	• Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of cervix or breast, or incidental prostate cancer.
	• Autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and'Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., W'gener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis). Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
	• Any underlying medical or psychiatric condition, which in the opinion of the investigator will make the administration of nivolumab and ipilimumab hazardous or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea.
	• Any non-oncology vaccine therapy used for prevention of infectious diseases (for up to 1 month before or after any dose of nivolumab and ipilimumab).
	• A history of prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.
	• Concomitant therapy with any of the following: Interleukin (IL) -2, interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigation therapies; or chronic use of systemic corticosteroids, defined as >10mg daily prednisone equivalents. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
	• Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
	• Women of childbearing potential (WOCBP) as defined below, who:
	  ○ Are unwilling or unable to use an acceptable method of contraception to avoid pregnancy for their entire study period and for at least 8 weeks after cessation of study drug, or
	  ○ Have a positive pregnancy test at baseline, or
	  ○ Are pregnant or breastfeeding

Trial name: Trial of Nivolumab in Combination With Ipilimumab in Subject with Previously Untreated Metastatic Uveal Melanoma (GEM1402) [32]	NCT number: NCT02626962 [32]
Intervention [18,83]	Ipilimumab every 3 weeks for a total of four doses (Cycles 1 and 2) and nivolumab every 3 weeks for a total of four doses (Cycles 1 and 2, each cycle lasting 6 weeks) followed by Nivolumab every 2 weeks until progression, intolerable toxicity, or withdrawal.
Comparator(s) [18]	No comparator
Follow-up time [18]	At the data collection cutoff (July 9, 2019), the median follow-up was 13.4 months (range, 0.8-35.2 months).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints [83]	**Primary Outcome:** - Overall Survival at 12 months. Defined as percentage of patients alive at 1-year from first dose of treatment. **Secondary Outcome:** - Overall survival at 24 months. Defined as percentage of patients alive at 2-years from first dose of treatment. - Progression Free Survival (PFS). Defined as percentage of patients without progression of disease at month 3, according RECIST 1.1 criteria. - Global PFS according to RECIST 1.1 criteria. Defined as percentage of patients without progression of disease at month throughout follow-up, according RECIST 1.1 criteria. Time Frame: From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 48 months. - Objective Response Rate (ORR). Defined as response to treatment according to RECIST 1.1 criteria. Time Frame: 12 months. - Disease Control Rate. Defined as percentage of patients with disease control. Time Frame: From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 48 months. - Duration of response. Defined as Length of time between date of evidenced response and progression of disease or death. Time Frame: From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 48 months.
Method of analysis[18]	The OS and PFS were calculated using the Kaplan-Meier method with CIs at 95% (95% CI). A logistic regression model and a Cox proportional hazard model comprising relevant clinical factors were used to evaluate the potential association with the response to treatment and survival variables. Subjects without PFS events were censored at the date of last clinical evaluation, and those alive had OS censored at the date of the last reported contact. Variables with $P < 0.1$ in the univariate analysis were included in the model. Exclusive liver metastases versus liver and other location metastases were compared in the analysis of treatment response (Fisher's exact test) and OS and PFS (both with log-rank test). Safety analysis was performed in all patients who have received at least one dose of the study treatment.
Subgroup analyses [18]	N/A
Other relevant information	N/A

Table 85. Main characteristics of the Pelster et al. 2020.

Trial name: Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study	NCT number: NCT01585194
Objective	The aim of this phase II trial was to assess the efficacy of the combination of nivolumab plus ipilimumab in patients with metastatic uveal melanoma. [28]
Publications – title, author, journal, year	Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study – Pelster et al. 2020, J Clin Oncol 39:599-607. [28]
Study type and design	Pelster et al. 2020 is a single-institution, single-arm, open-label phase II study of nivolumab and ipilimumab in patients with metastatic uveal melanoma. During the induction phase of treatment, patients were administered nivolumab 1 mg/kg intravenously (IV)plus ipilimumab 3 mg/kg IV every 3 weeks, for a total of four doses. During the subsequent maintenance phase, treatment was continued with nivolumab. Nivolumab was dosed initially at 3 mg/kg IVevery 2 weeks, but during the time period of the study, the dosing was changed to 480 mg IV every 4 weeks because of a change in US Food and Drug Administration labeling. Treatment was continued for up to 104 weeks or until disease progression, unacceptable toxicity, death, or withdrawal. [28] **Figure 36. Pelster et al. 2020 study design** [28]. 
Sample size (n)	35 [28]
Main inclusion and exclusion criteria [28,33]	**Inclusion criteria:** • Willing and able to give written informed consent • History of uveal melanoma and documented metastatic disease with at least one measurable lesion is required; which is >= 1 cm x 1 cm (on spiral computed tomography [CT] or equivalent) • Any number of prior therapies is allowed • White blood cell (WBC) >= 2000/uL • Absolute neutrophil count (ANC) >= 1500/uL • Platelets >= 100 x 10^3/uL • Hemoglobin >= 9 g/dL • Creatinine =< 1.5 x upper limit of normal (ULN) or creatinine clearance (CrCl) > 40 mL/min (using the Cockcroft-Gault formula) • Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) =< 3 x ULN for patients without liver metastasis, =< 5 x ULN for liver metastases • Bilirubin =< 1.5 x ULN, (except patients with Gilbert's syndrome, who must have a total bilirubin less than 3.0 mg/dL) • In suspected patients no active or chronic infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C • Performance status Eastern Cooperative Oncology Group (ECOG) 0-1. • Baseline imaging in the form of CT chest, abdomen, pelvis with oral and intravenous contrast within 28 days of study entry; for patients with a contrast

allergy, choice of alternative body imaging will be at the discretion of the investigator or his designee; magnetic resonance imaging (MRI) of the brain is only needed if clinically indicated
- Prior to start of treatment must be more than 21 days elapsed from surgery, radiation therapy, or prior chemotherapy; more than 42 days elapsed from prior immune therapy including vaccines
- Women of childbearing potential (WOCBP) and fertile men with partners of childbearing potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 26 weeks after the last dose of investigational product, in such a manner that the risk of pregnancy is minimized

Exclusion criteria:

- Untreated primary uveal melanoma except in cases where metastatic disease is diagnosed at the time of primary disease
- Metastatic uveal melanoma patients with bone-only disease
- Any other malignancy from which the patient has been disease-free for less than 2 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix, breast, or prostate
- Autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis]; motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome and Myasthenia Gravis)
- Any underlying medical or psychiatric condition, which in the opinion of the investigator will make the administration of ipilimumab hazardous or obscure the interpretation of adverse events (AEs), such as a condition associated with frequent diarrhea
- Any non-oncology vaccine therapy used for prevention of infectious diseases (for up to 1 month before or after any dose of ipilimumab)
- Concomitant therapy with any of the following: tamoxifen, toremifene, IL 2, interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigation therapies; or chronic use of systemic corticosteroids greater than physiologic replacement doses; ocular steroid use is acceptable; (a) concomitant palliative radiation for the purposes of symptom management is allowed
- Women of childbearing potential (WOCBP) who: (a) are unwilling or unable to use an acceptable method of contraception to avoid pregnancy for their entire study period and for up to 26 weeks after cessation of study drug, or (b) have a positive pregnancy test at baseline, or (c) are pregnant or breastfeeding
- Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious) illness

Intervention [28]	**Induction phase:** Nivolumab 1 mg/kg IV plus ipilimumab 3 mg/kg IV every 3 weeks, for a total of four doses. **Maintenance phase:** Nivolumab was dosed initially at 3 mg/kg IV every 2 weeks, but during the time period of the study, the dosing was changed to 480 mg IV every 4 weeks because of a change in US Food and Drug Administration labeling. Treatment was continued for up to 104 weeks or until disease progression, unacceptable toxicity, death, or withdrawal of consent.
Comparator(s)	No comparator
Follow-up time	At the data collection cutoff (December 2, 2019), the median follow-up period was 13.0 months (range, 1.3- 43.5 months). [28]
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints [28,33]	Primary Outcome: - Overall response rate Secondary Outcome: - Progression-free survival - Median overall survival - One-year overall survival
Method of analysis	The target ORR was 20% with a null hypothesis of a 5% response rate. The ORR was presented with the corresponding 95% exact CI, and a one-sample test of proportions was used to test the null hypothesis. The Kaplan-Meier method was used to assess the distribution of time-to-event variables including OS and PFS. A landmark analysis was performed to compare PFS by incidence of toxicity while addressing the issue of immortal survival time among patients experiencing toxicities. Data analysis was performed using SAS version 9.4 (Cary, NC) and GraphPad Prism 7 Software (La Jolla, CA). [28]
Subgroup analyses	A subgroup analysis was carried out on progression-free survival for 1) patients with extrahepatic-only sites of metastases versus liver metastases, 2) patients with different American Joint Committee on Cancer M categories of disease, 3) patients removed from study for toxicities versus not removed from study. [28]
Other relevant information	N/A

15. Appendix C: Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 86. Baseline characteristics of patients in the IMCgp100-202, GEM1402 study and Danish Clinical Register Data.

	IMCgp100-202[4]		GEM1402[18]	Pelster et al. 2020[28]	Danish register data (post introduction of immunotherapy (2014 – 2018)[16]
	Tebentafusp (N=252)	Control arm (N=126)	Ipi/nivo (N=52)	Ipi/nivo (N = 35)	Temozolomide, ipilimumab, pembrolizumab or ipi/nivo N = 94
Median age (range) - year	64 (23-92)	66 (25-88)	59 (26-84)	62 (30 – 76)	65 (22-87)
Sex – no. (%)					
Male sex	128 (51)	62 (49)	29 (55.8)	12 (34)	47 (50.0)
Female sex	124 (49)	64 (51)	23 (44.2)	26 (66)	47 (50.0)
Median time since primary diagnosis (range) – year	3.0 (0.1 – 25)	2.4 (0.1 – 36)	N/A	N/A	N/A
ECOG performance status score – no. (%)					
0	192 (76)	85 (67)	44 (84.6)	25 (71)	53 (56.4)
1	49 (19)	31 (25)	8 (15.4)	10 (29)	25 (26.6)
2	0	1 (1)	0	0	9 (9.6)
3	N/A	N/A	N/A	0	1 (1.1)
Data missing	11 (4)	9 (7)	0	0	6 (6.4)
Lactate dehydrogenase					

Lactate dehydrogenase > ULN range – no. (%)	90 (36)	46 (37)	N/A	15 (43)	N/A
LDH: Median (range):	N/A	N/A	348.0 (155 - 6,200) IU/L	558 (359-6.145)	N/A
LDH: Median - no. (%)					
Normal	N/A	N/A	27 (51.9)	N/A	N/A
LDH ≤ ULN	N/A	N/A	N/A	20 (57)	34 (36.7)
LDH > ULN	90 (36)	46 (37)	N/A	15 (43)	N/A
LDH > 1 – 2 x ULN	N/A	N/A	N/A	N/A	33 (35.1)
LDH > 2 x ULN	N/A	N/A	N/A	N/A	22 (22.4)
Increased < 2.5 x ULN	N/A	N/A	9 (17.3)	N/A	N/A
Increased ≥ 2.5 x ULN	N/A	N/A	7 (13.5)	N/A	N/A
Not available	N/A	N/A	9 (17.3)	N/A	5 (5.3)
Metastatic disease at the time of UM diagnosis – no. (%)	N/A	N/A	4 (7.7)	N/A	N/A
Liver disease at the time of UM recurrence – no. (%)					
Liver disease	N/A	N/A	41 (78.8)	N/A	N/A
Unilobular	N/A	N/A	10 (19.2)	N/A	N/A
Multilobular	N/A	N/A	28 (53.8)	N/A	N/A
Largest metastatic lesions – no. (%)					
≤3.0 cm, stage M1a	139 (55)	70 (56)	23 (63.9)	17 (49)	N/A
3.1 to 8.0 cm, stage M1B	92 (37)	46 (37)	11 (30.6)	14 (40)	N/A
≥8.1 cm, stage M1c	21 (8)	10 (8)	2 (5.6)	4 (11)	N/A

Location of metastasis – no. (%)					
Hepatic only	131 (52)	59 (47)	22 (42.3)	11 (31)	39 (41.5)
Extrahepatic only	9 (4)	10 (8)	11 (23.5)	7 (20)	8 (8.5)
Hepatic and extrahepatic	111 (44)	55 (44)	19 (15.5)	17 (49)	47 (50.0)
Lungs	N/A	N/A	22 (42.3)	N/A	N/A
Bone	N/A	N/A	9 (17.3)	N/A	N/A
Nodal	N/A	N/A	5 (9.6)	N/A	N/A
Brain (not active)	N/A	N/A	2 (3.8)	N/A	N/A
Others	N/A	N/A	10 (19.2)	N/A	N/A
Data missing	1 (<1)	2 (2)	N/A	N/A	N/A
Prior local therapies of uveal melanoma - no. **(%)**					
Previous surgical therapy for metastatic disease	24 (10)	9 (7)	N/A	N/A	N/A
Enucleation	N/A	N/A	30 (57.7)	N/A	N/A
Brachytherapy	N/A	N/A	26 (50.0)	N/A	N/A
External radiotherapy	N/A	N/A	4 (7.7)	N/A	N/A
Conservative surgery	N/A	N/A	3 (5.8)	N/A	N/A
Any	N/A	N/A	2 (4)	N/A	N/A
Previous lines of treatment for mUM - no. **(%)**					
0	N/A	N/A	N/A	20 (57)	N/A
1	N/A	N/A	N/A	10 (29)	N/A
2	N/A	N/A	N/A	3 (9)	N/A

3	N/A	N/A	N/A	0 (0)	N/A
4	N/A	N/A	N/A	2 (6)	N/A
Types of prior therapy in metastatic setting – no. **(%)**					
Targeted therapy	N/A	N/A	N/A	6 (40)	N/A
Liver-directed therapy	N/A	N/A	N/A	3 (20)	N/A
Anti-PD-1 immunotherapy	N/A	N/A	N/A	2 (13)	N/A
Chemotherapy	N/A	N/A	N/A	1 (7)	N/A
Other	N/A	N/A	N/A	4 (27)	N/A
GGT: Median **(range)**	N/A	N/A	32.0 (12.0–803.0) IU/L	N/A	N/A
Normal	N/A	N/A	34 (65.4)	N/A	N/A
Increased < 2.5 x ULN	N/A	N/A	8 (15.4)	N/A	N/A
Increased ≥ 2.5 x ULN	N/A	N/A	6 (11.5)	N/A	N/A
Not available	N/A	N/A	4 (7.7)	N/A	N/A
Alkaline phosphatase: Median (range)	N/A	N/A	78 (43.2–826.0) IU/L	N/A	N/A
Normal	N/A	N/A	40 (76.9)	N/A	N/A
Increased (>ULN)	N/A	N/A	7 (13.5)	N/A	N/A
Not available	N/A	N/A	5 (9.6)	N/A	N/A
Gene alterations					
GNAQ – no. (%)					
Wild type	N/A	N/A	18 (72)	1 (3)	N/A
Mutant	N/A	N/A	7 (28)	16 (46)	N/A
GNA11- no. (%)					
Wild type	N/A	N/A	11 (44)	1 (3)	N/A

Mutant	N/A	N/A	14 (56)	5 (14)	N/A
SF3B1- no. (%)					
Wild type	N/A	N/A	22 (88)	N/A	N/A
Mutant	N/A	N/A	3 (12)	N/A	N/A
3p- no. (%)					
Wild type	N/A	N/A	7 (28)	N/A	N/A
Mutant	N/A	N/A	18 (72)	N/A	N/A
8q- no. (%)					
Wild type	N/A	N/A	6 (24)	N/A	N/A
Mutant	N/A	N/A	19 (76)		N/A
Gene expression profile					
Class 1A	N/A	N/A	N/A	2 (6)	N/A
Class 1B	N/A	N/A	N/A	3 (9)	N/A
Class 2	N/A	N/A	N/A	8 (23)	N/A

15.1 Comparability of patients across studies

The study populations of IMCgp202 are overall comparable, with the main differences being that time from diagnosis is not known in GEM1402 study and the number of patients with extrahepatic disease; In IMCgp100-202, 4% of the tebentafusp arm had extrahepatic only disease, while it was 23.5% in GEM1402. Time since primary diagnosis could therefore not be used for matching in the MAIC. This is a potential unmeasured EM/PV which should be considered when interpreting the results in the indirect analysis. Furthermore, two sensitivity analysis that explored alternative ways of defining the disease location covariate for matching, were carried out in the MAIC to overcome the differences in extrahepatic disease, see appendix F.

The study populations of IMCgp100-202 and Pelster et al. 2020 has some major differences. First of all, IMCgp100-202 only includes patients who have not yet received treatment for mUM, while Pelster et al. 2020 includes both previously treated and untreated patients. Approximately 44% of the Pelster et al. 2020 population has received one or more treatments for mUM. Secondly, 20% of the Pelster et al. 2020 population had extrahepatic disease only, while the number is 4% in the tebentafusp arm. The difference in the two studies, especially inclusion of previously treated patients in Pelster et al., 2020 makes the studies unsuitable for a MAIC. At the request from the DMC, a narrative comparison was, however, performed between IMCgp100-202 and Pelster et al. 2020.

15.2 Comparability of the study populations with Danish patients eligible for treatment

Since epidemiological data on the UV population in Denmark is limited, the comparison was based on a recently published study from Denmark on real-world treatment patterns and OS in patients with UM in the pre and post immunotherapy era. The post immunotherapy data was from 2014 -2018.[16]

The study populations in IMCgp100-202, GEM1402 and Pelster et al. 2020 are comparable with the Danish Population regarding age and sex. The performance score is worse for patients in the clinical setting, which is to be expected. The difference is caused by the inclusion criteria in the IMCgp100-202,GEM1402, and Pelster et al. 2020 of an ECOG PS 0-1. This means that the results are not transferable to patients with a PS ≥ 2. In the IMCgp100-202 study there were more patients with only extrahepatic or extrahepatic and hepatic metastasis and fewer with only hepatic metastasis compared to the Danish setting. In GEM1402 and Pelster et al. 2020 the number of patients with only extrahepatic metastasis was substantially higher than in the Danish patients, and the number of patient with hepatic and extrahepatic metastasis was substantially lower. [4,16,18] According to the Swedish expert the number of patients with a good performance score and extrahepatic metastasis in the GEM1402 study is unusually high, suggesting that there are some form of selection bias in the GEM1402 study. Likewise the number of patients with extrahepatic only disease in the Pelster et al. 2020 study matched the high number from GEM1402, which suggest that the patient population does not match a Danish clinical population as precisely as IMCgp100-202. This overall suggests that the results obtained in the GEM1402 and IMCgp100-202 studies may be better than what would be seen in a clinical setting.

Overall, the study population in the IMCgp100-202 study matched overall with the Danish patient population, whereas the differences between both GEM1402 and Pelster et al. 2020 vs the Danish population was substantially higher. The IMCgp100-202 results were used in the MAIC and compared to the GEM1402 results, where different patient characteristics were weighted, and two sensitivity analyses were carried out to accommodate the differences of metastasis. Therefore, the results in the assessment are deemed relevant for a Danish setting. [4,16,18]. Because of the population differences between IMCgp100-202 and Pelster et al. 2020, a MAIC could not be conducted. Thus a narrative analysis was carried out which makes the results from the IMCgp100-202 and Pelster et al. 2020 comparison less valid than the MAIC.

16. Appendix D: Efficacy and safety results per study

16.1 Definition, validity and clinical relevance of included outcome measures

Table 87. Definition, validity and clinical relevance of included outcome measures of IMCgp100-202.

IMCgp100-202 study[4]			
Outcome measure	**Definition** [51]	**Validity** [4,51]	**Clinical relevance**
Overall Survival	Time from patient inclusion to date of death due to any cause. Time Frame: Survival status will be assessed every 3 months from randomization until death, assessed up to 40 months[51]	N/A	OS were calculated by the Kaplan- Meyer method. The treatment arms were formally compared with the use of a 2-sided log-rank test, stratified according to LDH status. Minimal clinically important difference: The Danish medicine council has not previously assessed a drug for uveal melanoma, and the clinical expert did not provide an estimate. Due to the poor prognosis of mUM any OS benefits should be seen as clinically relevant.
Disease control	The proportion of patients with either complete response, partial response, or stable disease for at least 12 weeks	Investigator assessed Assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1	Response rates were calculated using a Mantel-Haenszel 2-sided test statistic stratified by LDH status. Minimal clinically important difference: The Danish medicine council has not previously assessed a drug for uveal melanoma, and the clinical expert did not provide an estimate.
Objective Response	The proportion of patients achieving either a partial or complete response.	Investigator assessed	The analysis of ORR was calculated using a Mantel-Haenszel 2-sided test statistic stratified by LDH status.

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IMCgp100-202 study[4]			
Outcome measure	**Definition** [51]	**Validity** [4,51]	**Clinical relevance**
		Assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1	Minimal clinically important difference: The Danish medicine council has not previously assessed a drug for uveal melanoma, and the clinical expert did not provide an estimate.
Progression-free survival	The time from the randomized allocation to the date of tumor progression, or death due to any cause.	Investigator assessed Assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1	PFS were calculated by the Kaplan- Meyer method. The treatment arms were formally compared with the use of a 2-sided log-rank test. Minimal clinically important difference: The Danish medicine council has not previously assessed a drug for uveal melanoma, and the clinical expert did not provide an estimate.
Duration of response	The time between first initial response, as assessed by investigator, and the date of documented tumor progression.	Investigator assessed Assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1	Descriptive statistics Minimal clinically important difference: The Danish medicine council has not previously assessed a drug for uveal melanoma, and the clinical expert did not provide an estimate.
Quality-of-Life	Defined via the scales: European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, European Quality of life – 5 dimensions (EQ-5D) Visual Analogue Score and EQ-5D-5L domain score.	Patient-reported outcome The assessment was done using EORTC QLQ-C30, EQ-5D Visual Analogue Score and, EQ-5D-5L domain score.	The health related quality of life (HRQOL) assessments will be measured in all patients at specified time points and changes from baseline assessments will be assessed between tebentafusp and investigators choice Minimal clinically important difference: The difference described as meaningful in the different scales

IMCgp100-202 study[4]			
Outcome measure	**Definition** [51]	**Validity** [4,51]	**Clinical relevance**
Safety	The number of participants that developed treatment-emergent adverse events. These events include laboratory abnormalities, ECG changes and/or physical examination findings.	Investigator assessed Assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03	Descriptive statistics Minimal clinically important difference: Narrative description
Pharmacokinetics	- AUC_{last}: The area under the curve (AUC) from time 0 to the last measurable concentration - Sampling time (t_{last}) - AUC_{inf}: The AUC from time 0 to infinity C_{max}: The maximum (peak) observed plasma, blood, serum, or other body fluid drug - Concentration after single dose administration - T_{max}: The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug - Concentration after single dose administration (time) - $t_{1/2}$: The elimination half-life associated with the	Investigator assessed Sparse pharmacokinetic (PK) and anti-drug antibody (ADA) blood samples were obtained in Arm 1 (tebentafusp) only. Blood samples for determination of tebentafusp concentration time profiles in serum and blood samples to assess the formation of any ADAs to tebentafusp were obtained throughout the study.	Descriptive statistics: including arithmetic and geometric mean, median, standard deviation, and coefficient of variation, geometric coefficient of variation, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation Minimal clinically important difference Not relevant

IMCgp100-202 study[4]			
Outcome measure	**Definition** [51]	**Validity** [4,51]	**Clinical relevance**
	terminal slope (λ_z) of a semi logarithmic - Concentration-time curve (time). Use qualifier for other half-lives - CL: The total body clearance of drug from the plasma V_z: The apparent volume of distribution during terminal phase (associated with λ_z) - (volume) - Accumulation Ratio = C_{max} (multiple Dose)/C_{max} (single dose)		

Table 88. Definition, validity and clinical relevance of included outcome measures of GEM1402.

GEM1402 study[18]			
Outcome measure	**Definition**	**Validity**	**Clinical relevance**
Overall Survival	OS is defined as the time from first nivolumab dose until death by any cause.[18]	N/A	OS were calculated using the Kaplan-Meier method with CIs at 95%. A logistic regression model and a Cox proportional hazard model comprising relevant clinical factors were used to evaluate the potential association with the response to treatment and survival variables

GEM1402 study[18]			
Outcome measure	**Definition**	**Validity**	**Clinical relevance**
			Minimal clinically important difference: The Danish medicine council has not previously assessed a drug for uveal melanoma, and the clinical expert did not provide an estimate.
PFS	PFS is defined as the time from first investigational product dose until objective tumor progression according to RECIST 1.1 or death by any cause, whatever occurs first. [18]	Investigator assessed Assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1	PFS were calculated using the Kaplan-Meier method with CIs at 95%. A logistic regression model and a Cox proportional hazard model comprising relevant clinical factors were used to evaluate the potential association with the response to treatment and survival variables Minimal clinically important difference: The Danish medicine council has not previously assessed a drug for uveal melanoma, and the clinical expert did not provide an estimate.

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GEM1402 study[18]			
Outcome measure	**Definition**	**Validity**	**Clinical relevance**
Safety	All patients who receive at least one dose of nivolumab and ipilimumab was evaluable for safety parameters. Any occurrence of non-serious or SAE from time of first dose forward, up to and including follow-up visits, was reported. An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment.	Investigator assessed Safety will be evaluated for all treated patients using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests.	Descriptive statistics Minimal clinically important difference Narrative description

16.2 Results per study

Table 89. Results of IMCgp100-202 (NCT03070392).

Results of IMCgp100-202 (NCT03070392)[4]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median overall survival	Tebentafusp	87/252	21.7 (18.6-28.6) months	5.7			HR: 0.51	0.37–0.71	<0.001	OS were calculated by the Kaplan- Meier method. The treatment arms were formally compared with the use of a 2-sided log-rank test, stratified according to LDH status.	[4]
	Control	63/126	16 (9.7–18.4) months								
Overall survival rate at 1 year	Tebentafusp	184/252	73% (66-79)	14.0**	3.96-24.11**	0.006**	RR: 1.24*	RR: 1.05 -1.47*	RR: 0.0095*		
	Control	74/126	59% (48-67)								
Median Progression-free survival	Tebentafusp	198/252	3.3 (3–5) months	0.4	N/A	N/A	HR: 0.73	0.58–0.94	0.01	PFS were calculated by the Kaplan- Meier method. The treatment arms were formally compared with the use of a 2-sided log-rank test,	[4]
	Control	97/126	2.9 (2.8–3) months								

Results of IMCgp100-202 (NCT03070392)[4]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Progression-free survival rate at 6 months	Tebentafusp	78/252	31%	12% points	2.58-20.38**	0.01**	RR: 1.63*	RR: 1.08-2.44*	RR: 0.02*	stratified according to LDH status.	
	Control	24/126	19%								
Disease control	Tebentafusp	115/252	46% (39-52)	19	8.69-28.32**	<0.001**	RR: 1.69*	RR: 1.23-2.32*	RR: 0.001*	Response rates were calculated using a Mantel-Haenszel 2-sided test statistic stratified by LDH status.	[4]
	Control	34/126	27% (20-36)								
Objective response rate	Tebentafusp	23/252	9% (6-13)	4% points	-2.07-8.94**	0.17**	RR: 1.84*	RR: 0.77-4.41*	RR: 0.17*	Response rates were calculated using a Mantel-Haenszel 2-sided test statistic stratified by LDH status.	[4]
	Control	6/126	5% (2-10)								
Treatment emergent adverse events	Tebentafusp	245/245	100%	5.4% points	2.11-11.27**	<0.001**	RR: 1.05	RR: 1.01*	RR: 0.01*	Descriptive statistics	[4]
	Control	105/111	94.6%								
Treatment-related adverse events	Tebentafusp	243/245	99.2%	17.2% points	10.81-25.40**	<0.001**	RR: 1.21	RR: 1.11-1.32*	RR: <0.001*	Descriptive statistics	[4]
	Control	91/111	82.0%								
	Tebentafusp	69/245	28.2%	1.8% points	-8.5 – 11.2**	0.72**	RR: 1.20	RR: 0.81 – 1.78*	RR: 0.36	Descriptive statistics	[4]

Results of IMCgp100-202 (NCT03070392)[4]												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Serious AEs of any grade	Control	26/111	26.4%								
[redacted]											
Related TEAEs leading to	Tebentafusp	5/245	2.0%	-2.5% points	-1.17-8.22**	0.18**	RR: 0.45	RR: 0.13-1.53*	RR: 0.20*	Descriptive statistics	[4]
	Control	5/111	4.5%								
[redacted]											
Related TEAE with CTCAE grade ≥3	Tebentafusp	109/245	44.5%	27.4% points	17.29-35.98**	<0.001**	RR: 2.60	RR: 1.69-4.01*	<0.001*	Descriptive statistics	[4]
	Control	19/111	17.1%								
[redacted]											

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Results of IMCgp100-202 (NCT03070392)[4]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
[redacted]											

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Results of IMCgp100-202 (NCT03070392)[4]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
[redacted]											
Related TEAE leading to death	Tebentafusp	0/245	0%	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[4]
	Control	0/111	0%								
Anti-tebentafusp antibodies	Tebentafusp	73/252	29%	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[4]
EORTC QLQ-C30 Fatigue, end of treatment (LS)	Tebentafusp	76/105	10.9	-9.2	N/A	0.0445	N/A	N/A	N/A	Least squares regression	[36]
	Control	34/35	20.1								
EORTC QLQ-C30 Insomnia at C5D1 (LS)	Tebentafusp	76/105	-9.3	-12.1	N/A	0.0176	N/A	N/A	N/A	Least squares regression	[36]
	Control	34/35	2.8								
EORTC QLQ-C30	Tebentafusp	76/105	3.2	-6.7	N/A	0.0296	N/A	N/A	N/A	Least squares regression	[36]

Results of IMCgp100-202 (NCT03070392)[4]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Constipation, end of treatment (LS)	Control	34/35	-3.5								
Mean utility, EQ-5D (Baseline)	Tebentafusp vs Control	272	0.835	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]
Mean utility, EQ-5D (Cycle 3 day 1)	Tebentafusp vs Control	218	0.864	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]
Mean utility, EQ-5D (Cycle 5 day 1)	Tebentafusp vs Control	162	0.863	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]
Mean utility, EQ-5D (Cycle 9 day 1)	Tebentafusp vs Control	99	0.838	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]
Mean utility, EQ-5D (Cycle 13 day 1)	Tebentafusp vs Control	63	0.825	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]
Mean utility, EQ-5D	Tebentafusp vs Control	33	0.834	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]

Results of IMCgp100-202 (NCT03070392)[4]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
(Cycle 17 day 1)											
Mean utility, EQ-5D (Cycle 21 day 1)	Tebentafusp vs Control	19	0.816	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]
Mean utility, EQ-5D (Cycle 25 day 1)	Tebentafusp vs Control	13	0.805	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]
Mean utility, EQ-5D (Cycle 29 day 1)	Tebentafusp vs Control	16	0.808	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]
Mean utility, EQ-5D (End of treatment)	Tebentafusp vs Control	170	0.774	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]
Mean utility, EQ-5D (Survival follow-up day 90)	Tebentafusp vs Control	56	0.762	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]
Mean utility, EQ-5D	Tebentafusp vs Control	35	0.803	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]

Results of IMCgp100-202 (NCT03070392)[4]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
(Survival follow-up day 180)											
Mean utility, EQ-5D (Survival follow-up day 270)	Tebentafusp vs Control	25	0.820	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]
Mean utility, EQ-5D (Survival follow-up day 360)	Tebentafusp vs Control	19	0.760	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[36]

* Relative risk (RR) calculated using: $RR = \frac{a/(a+b)}{c/(c+d)}$, with the SE of the log relative risk being: $SE\{\ln(RR)\} = \sqrt{\frac{1}{a} + \frac{1}{c} - \frac{1}{a+b} - \frac{1}{c+d}}$, and the 95% CI being:

$95\%\ CI = \exp(ln(RR) - 1.96 * SE\{ln(RR)\})\ to\ \exp(ln(RR) + 1.96 * SE\{ln(RR)\})$

** Absolute difference CI calculated using: $D - \sqrt{(\rho_1 - l_1)^2 + (u_2 - \rho_2)^2}$ to $D + \sqrt{(\rho_2 - l_2)^2 + (u_1 - \rho_1)^2}$ and p-value calculated using chi-squared test.

Table 90. Results of GEM1402 (NCT02626962).

Results of [GEM1402 (NCT02626962) [18]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival ITT	Ipi/nivo	-	12.7 months (95% CI, 7.1 to 18.3)	N/A	N/A	N/A	N/A	N/A	N/A		
Median OS in patients with exclusive liver metastasis	Ipi/nivo	-	9.2 months (95% CI, 3.1 to 15.2)	N/A	N/A	N/A	N/A	N/A	N/A		
Median OS in patients with liver + extrahepatic metastasis	Ipi/nivo	-	15.5 months (95% CI, 7.4 to 23.5)	N/A	N/A	N/A	N/A	N/A	N/A	OS were calculated using the Kaplan-Meier method with CIs at 95%.	[18]
OS-rates 12 month	Ipi/nivo	27/52	51.9% (95% CI, 38.3 to 65.5)	N/A	N/A	N/A	N/A	N/A	N/A		
OS-rates 24 month	Ipi/nivo	14/52	26.4% (14.2 to 38.6)	N/A	N/A	N/A	N/A	N/A	N/A		
Median Progression-free survival	Ipi/nivo	-	3.0 (95% CI, 2.0 to 4.1)	N/A	N/A	N/A	N/A	N/A	N/A	PFS were calculated using the Kaplan-Meier method with CIs at 95%.	[18]

Results of [GEM1402 (NCT02626962)] [18]											
Progression free survival rate at 6 months	Ipi/nivo	14/52	28.2% (95% CI, 16.5 to 41.1)	N/A	N/A	N/A	N/A	N/A	N/A		
Progression free survival rate at 12 months	Ipi/nivo	10/52	19.2% (95% CI, 8.5 to 29.9)	N/A	N/A	N/A	N/A	N/A	N/A		
Adverse events	Ipi/nivo	52/52	100%	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[18]
GRADE ≥ 3 adverse events	Ipi/nivo	30/52	57.7%	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[18]
Treatment related adverse events (TRAEs)	Ipi/nivo	49/52	94.2%	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[18]
Treatment related serious adverse events (TR-SAEs)	Ipi/nivo	30/52	57.7%	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[18]
TR-SAEs GRADE ≥ 3	Ipi/nivo	21/52	40.4%	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[18]
Non-treatment related serious adverse events	Ipi/nivo	26/52	50%	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[18]
Non-treatment related serious event grade ≥ 3	Ipi/nivo	14/52	26.9%	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[18]

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Results of [GEM1402 (NCT02626962)] [18]											
Treatment related deaths	Ipi/nivo	2/52	3.8%	N/A	N/A	N/A	N/A	N/A	N/A	Descriptive statistics	[18]

Table 91. Results of Pelster et al. 2020 (NCT01585194).

Results of Pelster et al. 2020 (NCT01585194) [28]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
OS	Ipi/nivo	-	19.1 months [95% CI, 9.6 – NR]	N/A	N/A		N/A	N/A	N/A	Kaplan-Meier method with CIs at 95%	
1 year survival rate		≈19/35	56% [95% CI, 38% – 71%]	N/A	N/A		N/A	N/A	N/A		
Adverse events any grade		32/35	91%	N/A	N/A		N/A	N/A	N/A	Descriptive statistics	[28]
Adverse event, grade ≥ 3		20/35	57%	N/A	N/A		N/A	N/A	N/A	Descriptive statistics	
Treatment related events, any grade		29/35	83%	N/A	N/A		N/A	N/A	N/A	Descriptive statistics	

Results of Pelster et al. 2020 (NCT01585194) [28]								
Treatment related events, grade ≥ 3	14/35	40%	N/A	N/A	N/A	N/A	N/A	Descriptive statistics
Discontinuation due adverse events	10/35	29%	N/A	N/A	N/A	N/A	N/A	Descriptive statistics
Death due to adverse event	0/35	0%	N/A	N/A	N/A	N/A	N/A	Descriptive statistics

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17. Appendix E: Safety data for intervention and comparator(s)

This appendix provides an overview of all adverse events observed in the IMCgp100-202 and GEM1402 study, furthermore safety specific data used in the assessment are described in appendix D, see Table 89 and Table 90.

17.1 IMCgp100-202 safety data

Table 92. Treatment related adverse events in IMCgp100-202 [4].

	Tebentafusp (N=245)		Investigator's Choice (N=111)	
Event term, n (%)	Any grade (≥20%)	Grade 3 (≥2%)	Any grade (≥20%)	Grade 3 (≥2%)
Any treatment-related adverse event	243 (99)	109 (44)	91 (82)	19 (17)
Cytokine release syndrome*	217 (89)	2 (1)	3 (3)	0
Rash**	203 (83)	45 (18)	27 (24)	0
Pyrexia	185 (76)	9 (4)	3 (3)	0
Pruritus	169 (69)	11 (4)	23 (21)	0
Chills	114 (47)	1 (<1)	3 (3)	0
Nausea	105 (43)	2 (1)	21 (19)	0
Fatigue	101 (41)	7 (3)	29 (26)	1 (1)
Hypotension	93 (38)	8 (3)	0	0
Dry skin	72 (29)	0	4 (4)	0

Vomiting	64 (26)	1 (<1)	7 (6)	0
Erythema	56 (23)	0	1 (1)	0
Headache	53 (22)	1 (<1)	3 (3)	1 (1)
Aspartate aminotransferase increased	47 (19)	11 (4)	9 (8)	0
Alanine aminotransferase increased	43 (18)	7 (3)	8 (7)	2 (2)
Lipase increased	32 (13)	9 (4)	7 (6)	6 (5)
Diarrhea	31 (13)	2 (1)	16 (14)	3 (3)
Lymphopenia	22 (9)	6 (2)	2 (2)	0
Hyperbilirubinemia	21 (9)	5 (2)	2 (2)	0
Hypophosphatemia	19 (8)	7 (3)	1 (1)	0
Hypertension	15 (6)	9 (4)	2 (2)	1 (1)

*Cytokine release syndrome was graded according to the 2019 recommendations of the American Society for Transplantation and Cellular Therapy for consensus grading for cytokine release syndrome. See Table 93

**Rash is a composite term for a list of skin-related adverse events of any grade

Table 93. ASTCT CRS Consensus Grading [84].

CRS Paramater	Grade 1	Grade 2	Grade 3	Grade 4

Fever*	Temperature ≥38 °C	Temperature ≥38 °C	Temperature ≥38 °C	Temperature ≥38 °C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

*Fever is defined as temperature ≥38°C not attributable to any other cause In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity In this case, CRS grading is driven by hypotension and/or hypoxia

†CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause For example, a patient with temperature of 39 5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS

‡Low-flow nasal cannula is defined as oxygen delivered at ≤6L/minute Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics High-flow nasal cannula is defined as oxygen delivered at >6L/minute

Table 94. Treatment-emergent adverse events in IMCgp100-202[42].

	Tebentafusp (N=245)	Investigator's Choice (N=111)
Event term, n (%)	Any grade (≥10%)	Any grade (≥10%)
Patients with any TEAE	245 (100)	105 (95)
Pyrexia	187 (76)	8 (7)
Pruritus	169 (69)	26 (23)
Rash	135 (55)	18 (16)
Fatigue	125 (51)	39 (35)

Nausea	120 (49)	29 (26)
Chills	117 (48)	4 (4)
Hypotension	95 (39)	3 (3)
Dry skin	77 (31)	4 (4)
Headache	75 (31)	11 (10)
Rash maculo-papular	75 (31)	9 (8)
Vomiting	73 (30)	10 (9)
Oedema peripheral	66 (27)	3 (3)
Diarrhea	61 (25)	22 (20)
Abdominal pain	60 (25)	17 (15)
Erythema	60 (25)	1 (1)
Aspartate aminotransferase increased	56 (23)	11 (10)
Arthralgia	53 (22)	18 (16)
Alanine aminotransferase increased	51 (21)	12 (11)
Cytokine release syndrome	51 (21)	0
Skin exfoliation	51 (21)	2 (2)
Abdominal pain upper	50 (20)	14 (13)

Hair color changes	48 (20)	0
Back pain	45 (18)	9 (8)
Decreased appetite	45 (18)	15 (14)
Constipation	44 (18)	13 (12)
Cough	44 (18)	11 (10)
Vitiligo	40 (16)	4 (4)
Asthenia	38 (16)	9 (8)
Hypertension	38 (16)	8 (7)
Lipase increased	35 (14)	7 (6)
Dyspnea	32 (13)	7 (6)
Hyperbilirubinemia	28 (11)	8 (7)
Dizziness	27 (11)	9 (8)
Hypophosphatasemia	27 (11)	2 (2)
Paranesthesia	27 (11)	1 (1)
Periorbital oedema	26 (11)	1 (1)
Anemia	25 (10)	4 (4)
Face oedema	25 (10)	2 (2)

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Flushing	25 (10)	1 (1)
Hypothyroidism	3 (1)	12 (11)
Hyperthyroidism	2 (1)	13 (12)

Table 95. Serious adverse events in IMCgp100-202[42].

	Tebentafusp	Investigator's Choice
System organ class/preferred term, n (%)	Any grade (≥10%)	Any grade (≥10%)
Patients with any serious TEAE	69 (28)	26 (23)
Infections and infestations	4 (2)	2 (2)
Anorectal infection	0	1 (1)
Appendicitis	1 (0.4)	0
COVID-19	1 (0.4)	0
Infections and infestations		
Erysipelas	1 (0.4)	0
Pneumonia	0	1 (1)
Pneumonia mycoplasmal	0	1 (1)
Salmonella sepsis	1 (0.4)	0
Neoplasms benign, malignant, and unspecified(incl cysts and polyps)	3 (1)	2 (2)

Meningioma	1 (0.4)	0
Metastases to abdominal cavity	0	1 (1)
Neoplasm progression	0	1 (1)
Tumour pain	2 (1)	0
Blood and lymphatic system disorders	1 (0.4)	0
Anaemia	1 (0.4)	0
Immune system disorders	25 (10)	0
Anaphylactic reaction	1 (0.4)	0
Cytokine release syndrome	24 (10)	0
Endocrine disorders	0	1 (1)
Hypopituitarism	0	1 (1)
Metabolism and nutrition disorders	1 (0.4)	3 (3)
Dehydration	0	2 (2)
Hyperglycaemia	0	1 (1)
Tumour lysis syndrome	1 (0.4)	0
Psychiatric disorders	1 (0.4)	0
Mental status changes	1 (0.4)	0

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Nervous system disorders	5 (2)	2 (2)
Brain oedema	1 (0.4)	0
Dizziness	1 (0.4)	0
Intracranial mass	0	1 (1)
Lethargy	0	1 (1)
Motor dysfunction	1 (0.4)	0
Presyncope	1 (0.4)	0
Seizure	0	1 (1)
Spinal cord compression	1 (0.4)	0
Eye disorders	2 (1)	1 (1)
Diplopia	1 (0.4)	0
Periorbital oedema	1 (0.4)	0
Uveitis	0	1 (1)
Cardiac disorders	0	1 (1)
Left ventricular dysfunction	0	1 (1)
Vascular disorders	5 (2)	0
Hypotension	5 (2)	0

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Respiratory, thoracic and mediastinal disorders	4 (2)	6 (5)
Cough	0	1 (1)
Dyspnoea	2 (1)	0
Pleurisy	0	1 (1)
Pneumonitis	0	1 (1)
Pulmonary embolism	1 (0.4)	3 (3)
Pulmonary oedema	1 (0.4)	0
Sleep apnoea syndrome	0	1 (1)
Gastrointestinal disorders	7 (3)	7 (6)
Abdominal pain	2 (1)	3 (3)
Abdominal pain upper	1 (0.4)	0
Colitis	0	1 (1)
Diarrhoea	0	1 (1)
Enteritis	0	1 (1)
Gastritis	0	1 (1)
Nausea	4 (2)	1 (1)
Vomiting	2 (1)	0

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Hepatobiliary disorders	8 (3)	3 (3)
Biliary obstruction	1 (0.4)	0
Hepatic failure	1 (0.4)	0
Hepatic necrosis	1 (0.4)	0
Hepatic pain	1 (0.4)	0
Hepatomegaly	0	1 (1)
Hepatotoxicity	2 (1)	0
Hyperbilirubinaemia	2 (1)	3 (3)
Hypertransaminasaemia	1 (0.4)	0
Skin and subcutaneous tissue disorders	14 (6)	0
Pruritus	1 (0.4)	0
Rash	6 (2)	0
Rash maculo-papular	4 (2)	0
Rash papular	1 (0.4)	0
Skin reaction	1 (0.4)	0
Urticaria	1 (0.4)	0
Musculoskeletal and connective tissue disorders	0	2 (2)

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Bone pain	0	1 (1)
Pathological fracture	0	1 (1)
Renal and urinary disorders	2 (1)	0
Acute kidney injury	1 (0.4)	0
Renal failure	1 (0.4)	0
Reproductive system and breast disorders	1 (0.4)	0
Scrotal inflammation	1 (0.4)	0
General disorders and administration siteconditions	7 (3)	3 (3)
Asthenia	1 (0.4)	0
Fatigue	1 (0.4)	0
Gait disturbance	0	1 (1)
General physical health deterioration	1 (0.4)	0
Pyrexia	6 (2)	2 (2)
Investigations	3 (1)	1 (1)
Alanine aminotransferase increased	1 (0.4)	0
Amylase increased	1 (0.4)	0
Aspartate aminotransferase increased	1 (0.4)	0

Blood creatinine increased	2 (1)	0
Lipase increased	0	1 (1)
Injury, poisoning and procedural complications	1 (0.4)	2 (2)
Fall	0	1 (1)
Procedural pain	1 (0.4)	1 (1)

17.2 GEM1402 safety data

Table 96. Summary of treatment related adverse events in GEM1402 [18].

GEM1402	Ipi/nivo			
Event term, n (%)[a]	All treatment related adverse events	Grade ≥ 3 treatment related adverse events	All treatment related serious adverse events	Grade ≥ 3 treatment related serious adverse events
Total	49 (94.2)	30 (57.7)	30 (57.7)	21 (40.4)
Skin-related events[b]	32 (61.5)	4 (7.7)	1 (1.9)	1 (1.9)
Fatigue	30 (57.7)	4 (7.7)	1 (1.9)	1 (1.9)
Liver toxicity/liver-related events[c]	19 (36.5)	11 (21.2)	3 (5.8)	3 (5.8)
Diarrhea	15 (28.8)	3 (5.8)	3 (5.8)	3 (5.8)
Fever	8 (15.4)	-	4 (7.7)	1 (1.9)
Nausea	7 (13.5)	-	-	-

Hypothyrodism	7 (13.5)	-	1 (1.9)	-
Edema	4 (7.7)	-	-	-
Hypophysitis	4 (7.7)	-	1 (1.9)	-
Hepatitis	4 (7.7)	-	2 (3.8)	2 (3.8)
Vomitting	3 (5.8)	-	-	-
Thyroiditis	3 (5.8)	-	2 (3.8)	2 (3.8)
Constipation	3 (5.8)	-	-	-
Arthralgia	3 (5.8)	-	-	-
Pericarditis	-	-	1 (1.9)	-
Jaundice	-	-	1 (1.9)	1 (1.9)
Intestinal perforation	-	-	1 (1.9)	1 (1.9)
Hyponatremia	-	-	1 (1.9)	1 (1.9)
Hyperthyroidism	-	-	1 (1.9)	1 (1.9)
Guillain-Barré syndrome	-	-	2 (3.8)	2 (3.8)
Drug administration incidences[d]	-	-	3 (5.8)	-
Colitis	-	-	1 (1.9)	1 (1.9)

Anemia	-	-	1 (1.9)	1 (1.9)

[a]Percentage calculated over the total number of patients included in in the safety analysis (N=52)
[b]Skin toxicity/skin symptoms: include rash and pruritus
[c]Liver toxicity includes all events reported by the investigators as both liver toxicity per se and laboratory abnormalities compatible
[d]Includes two drug administration or treatment reported incidences (quarantine) and 1 ipilimumab overdose

Table 97. Summary of adverse events in GEM1402 [18].

GEM1402	Ipi/nivo	
Event term, n (%)[a]	All adverse events	Grade 3 and 4 adverse events
Total	52 (100)	39 (75)
Skin toxicity/-related events[b]	30 (57.7)	5 (9.6)
Fatigue	35 (67.3)	6 (11.5)
Liver toxicity/liver-related events[c]	23 (44.2)	13 (25.0)
Diarrhea	19 (36.5)	4 (7.7)
Fever	15 (28.8)	2 (3.8)
Nausea	12 (23.1)	-
Hypothyrodism	10 (19.2)	-
Skin hypopigmentation	5 (9.6)	-
Abdominal pain	11 (21.2)	-

Anorexia	10 (19.2)	-
Cough	9 (17.3)	-
Headache	8 (15.4)	-
Vomiting	7 (13.5)	1 (1.9)
Clinical deterioration	7 (13.5)	4 (7.7)
Constipation	7 (13.5)	-
Arthralgia	7 (13.5)	-
Edema	6 (11.5)	-
Adrenal insufficiency	5 (9.6)	1 (1.9)
Upper respiratory infection	5 (9.6)	-
Back pain	5 (9.6)	-
Dyspnea	5 (9.6)	-
Hepatitis	4 (7.7)	2 (3.8)

[a]Percentage calculated over the total number of patients included in in the safety analysis (N=52)
[b]Skin toxicity/skin symptoms: include rash and pruritus
[c]Liver toxicity includes all events reported by the investigators as both liver toxicity per se and laboratory abnormalities compatible

Table 98. Summary of non-treatment related serious adverse events in GEM1402 [18].

GEM1402	Ipi/nivo

Event term, n (%)[a]	Non-treatment related serious adverse events	Non-treatment related serious adverse events with Grade ≥ 3
Total	26 (50.0)	14 (26.9)
Abdominal pain	1 (1.9)	-
Ascitis	1 (1.9)	1 (1.9)
Back pain	1 (1.9)	-
Clinical deterioration	5 (9.6)	4 (7.7)
Cholecystitis	1 (1.9)	1 (1.9)
Confusion	1 (1.9)	-
Spinal disc herniation	1 (1.9)	-
Epigastric pain	1 (1.9)	-
Fever	4 (7.7)	-
General discomfort	1 (1.9)	1 (1.9)
Hyponatremia	1 (1.9)	1 (1.9)
Myalgia	1 (1.9)	1 (1.9)
Pneumonia	1 (1.9)	-
Progression of disease	3 (5.8)	3 (5.8)

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Syncope	1 (1.9)	-
Sudden death	1 (1.9)	1 (1.9)
Vomiting	1 (1.9)	1 (1.9)

[a]Percentage calculated over the total number of patients included in in the safety analysis (N=52)

17.3 Pelster et al. 2020 safety data

Table 99. Summary of safety data from Pelster et al. 2020 [28]

Pelster et al. 2020[28]	Ipi/nivo	
Event term, n (%)[a]	Any grade	Garde 3 or 4
Diarrhea	21 (60)	3 (9)
Increased ALT	17 (49)	6 (17)
Increased AST	14 (40)	4 (11)
Pruritus	14 (40)	0(0)
Hypothyroidism	13 (37)	1 (3)
Rash	11 (31)	0 (0)
Pyrexia	8 (23)	0 (0)
Arthralgia	5 (14)	0 (0)

Adrenal Insufficiency	4 (11)	0 (0)
Eye disorder	3 (8)	0 (0)

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18. Appendix F: Comparative analysis of efficacy and safety

18.1 Methodology

In the Danish clinical setting, the relevant comparator to tebentafusp is a combination treatment with ipi/nivo. The IMCgp100-202 study does not include this comparator[4], meaning it is necessary to conduct an indirect comparison.

The method used was a MAIC. This methodology enables IPD for tebentafusp from IMCgp100-202 to be compared to published summary level data from a study of ipi/nivo, while adjusting for differences in key patient characteristics between the two studies, in order to reduce the bias.

Population-adjusted indirect comparisons such as a MAIC can overcome some of the limitations of simple unadjusted cross study-comparisons[85]. However, in cases such as this where there is not a common comparator between the trials, an unanchored indirect comparison is required. This loses the protection of randomization that is inherent in a network meta-analysis or anchored indirect comparison, requiring the strong assumption that all effect modifiers and prognostic variables are accounted for. Bias due to imbalanced effect modifiers or prognostic variables that are not collected and reported for both studies may still affect the result, and this should be considered in the interpretation.

The endpoints investigated in the MAIC are OS, PFS and safety.

18.2 Study design of MAIC

The general design of the MAIC is to:

1. Pre-specify the intended approach for deriving the weights for matching, including the baseline covariates to be considered for the weight calculation.
2. Evaluate the balance between comparison groups with respect to important baseline covariates, both before and after match-adjustment weighting, and to make a determination as to whether the balance and effective sample size after making adjustments is adequate enough to move forward with the analysis.
3. Conduct the intended indirect comparisons via the prescribed statistical methodology using the matching weights.

18.3 Comparable studies

Two potential comparator studies were identified in the SLR described in section 6 and appendix A: GEM1402 [18] and Pelster et al. 2020 [28]. Both are single arm studies of ipi/nivo in UM. GEM1402 was selected as the most appropriate comparison because:

- GEM1402 is a purely untreated population like IMCgp100-202, while Pelster et al. 2020 is only 57% previously untreated [18,28].
- GEM1402 is larger than Pelster et al. 2020, n=52 vs. n=33 [18,28].
- GEM1402 is based on multi-institution data, while Pelster et al. 2020 is single institution [18,28].
- GEM1402 reports more of the key covariates used in matching the populations, see below [18,28].

18.4 Covariates used in the MAIC

Matching covariate can only be done on covariates that are reported in the summary level publication in GEM1402. The list of available variables is [18]:

- Age (years) – median
- Gender
- Baseline LDH – proportion in normal range (rather than log-transformed continuous variable)
- Baseline alkaline phosphatase - proportion in normal range (rather than log-transformed continuous variable)
- Disease location – hepatic only, extrahepatic only, hepatic and extrahepatic (rather than largest metastatic lesion continuous variable)
- ECOG performance status at baseline, proportion 0 or ≥1

Time since primary diagnosis could not be used in the matching as it was not reported in GEM1402[18]. This is a potential unmeasured effect modifier and prognostic variable which should be considered when interpreting the results. No other important potential unmeasured effect modifier and prognostic values were identified.

As there are only a small number of patients with extrahepatic disease in IMCgp100-202 compared to GEM1402, this may impact the effective sample size and/or cause modelling issues. Therefore, two additional sensitivity analyses were planned to explore alternative ways of defining the disease location covariate applicable for matching:

- Disease location pooled categories - Hepatic only, any extrahepatic (pooled extrahepatic only + hepatic and extrahepatic)
- Largest metastatic liver lesion – proportion ≤3cm, >3cm, no liver lesions

Patients with missing values for any variables for the IMCgp100-202 study were excluded from the analysis. Proportions from the GEM1402 study used the number of subjects reporting data for that variable as a denominator (missing data was excluded from calculation of proportions for matching).

18.5 Statistical methodology

No formal testing was conducted for the analyses, which are essentially exploratory in nature. Rather, HR and 95% CI were used to help make general conclusions about the comparisons being made. As well as the MAIC, a simple UAIC was also performed, to evaluate the impact of the match-adjustment.

As there is no common comparator linking tebentafusp and ipi/nivo, a so-called “unanchored” MAIC was performed.

In an unanchored MAIC, it is assumed that we have a treatment k_I (in this case, tebentafusp) that has been studied in a population s_I for which we have IPD.

We have a comparator of interest k_A (in this case, ipi/nivo) that has been studied in a population s_A for which we only have aggregate data. The aim of the method is to re-weight the observed IPD results for k_I in population s_I to make it more similar to population s_A, thus enabling a comparison of k_I and k_A in a more comparable population.

The weights are calculated as follows [85–87]:

- Re-centre the IPD patient covariates X_{sI} by subtracting the aggregate data mean covariate value $\bar{X}_{sA}$ to create X'_{sI}
- The weights are then the values $\hat{\alpha}$ that minimize the following equation:

$$\sum_{j=1}^{n_I} \exp\left(\alpha^T \boldsymbol{X}'_{jsI}\right)$$

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Analysis can then be performed on the reweighted data using standard models, similar to in UAIC. Comparator patients are given a weight of 1.

Following the calculation of weights, it is necessary to determine whether the optimization procedure has worked correctly and whether the weights derived are sensible. It is easier to examine the distribution of the weights by scaling them, so that the rescaled weights are relative to the original unit weights of each individual. In other words, a rescaled weight > 1 means that an individual carries more weight in the re-weighted population than the original data. A rescaled weight < 1 means that an individual carries less weight in the re-weighted population than the original data.

A summary of the rescaled MAIC weights was produced, including the mean, standard deviation, median and range, and a histogram. The covariate distribution for the tebentafusp data pre-match and post-match was summarized and compared to the ipi/nivo study. The approximate effective sample size (ESS) was calculated using the methods in Phillippo et al., 2016 [85] – if this is small then it may indicate that the weights are highly variable due to a lack of population overlap, and so the MAIC estimate may be unstable.

18.6 Unadjusted indirect comparison (UAIC)

This methodology is described first, as the MAIC is an extension of the UAIC methodology. A UAIC assumes that all effect modifiers and prognostic variables (both measured and unmeasured) are balanced between trials. A Cox proportional hazards model was fit to the IPD or pseudo-IPD generated from the KM curves. The model included a covariate for treatment and used the Efron method for dealing with ties. The HR and 95% CI from the Cox model was presented. The number of patients and events on each arm was tabulated. KM curves were produced including numbers at risk, and median survival and 12-month survival rates were summarized.

18.7 Match-adjusted indirect comparison (MAIC)

A MAIC assumes that all effect modifiers and prognostic variables are accounted for (measured and correctly included as covariates in the matching, or unmeasured and balanced between trials). This is a very strong assumption, although less strong than that used for UAIC [85]. A weighted Cox proportional hazards model was fit similar to the UAIC but via applying the MAIC weights. CI and p-values were calculated using bootstrapping or robust variance estimators to account for the fact that the weights are estimated rather than known[88]. Results were presented in the same way as for UAIC, but the weighted tebentafusp/pembrolizumab data were used.

18.8 Results

Below a summary of the following can be found:

- Patient characteristics, observed and matched adjusted, see Table 93
- Histograms of absolute matching weights, see Figure 37
- Summary of matching weights, see Table 101.
- Results of the MAIC, see Table 102 and Figure 38

See the separate file Tebentafusp vs ipi-nivo MAIC stats report for a complete overview of the methodology and results.

Table 100. Observed and match-adjusted patient characteristics for tebentafusp (IMCgp100-202) and ipi/nivo (GEM1402) [4,18].

	Overall population			Patient characteristics pooling extrahepatic only and hepatic + extrahepatic categories			Patient characteristics when using liver lesion size covariates		
Characteristic	IMCgp100	IMCgp100 adjusted	Ipi/nivo	IMCgp100	IMCgp100 adjusted	Ipi/nivo	IMCgp100	IMCgp100 adjusted	Ipi/nivo
N	240.0	182.6	52.0	240.0	224.5	52.0	240.0	172.4	52.0
% female (n/N)	49.2% (118/240)	44.2% (80.8/182.6)	44.2% (23/52)	49.2% (118/240)	44.2% (99.3/224.5)	44.2% (23/52)	49.2% (118/240)	44.2% (76.3/172.4)	44.2% (23/52)
% normal LDH (n/N)	65% (156/240)	62.8% (114.6/182.6)	62.8% (27/43)	65% (156/240)	62.8% (140.9/224.5)	62.8% (27/43)	65% (156/240)	62.8% (108.3/172.4)	62.8% (27/43)
% normal ALP (n/N)	78.7% (189/240)	85.1% (155.4/182.6)	85.1% (40/47)	78.7% (189/240)	85.1% (191/224.5)	85.1% (40/47)	78.7% (189/240)	85.1% (146.8/172.4)	85.1% (40/47)
% Extrahepatic disease only (n/N)	3.8% (9/240)	21.2% (38.6/182.6)	21.2% (11/52)	47.9% (115/240)	57.7% (129.5/224.5)	57.7% (30/52)	N/A	N/A	N/A
% Hepatic and Extrahepatic disease (n/N)	44.2% (106/240)	36.5% (66.7/182.6)	36.5% (19/52)	N/A	N/A	N/A	N/A	N/A	N/A
% largest liver met <= 3cm (n/N)	N/A	N/A	N/A	N/A	N/A	N/A	55.8% (134/240)	48.9% (84.4/172.4)	48.9% (23/47)
% largest liver met > 3cm (n/N)	N/A	N/A	N/A	N/A	N/A	N/A	40.4% (97/240)	27.7% (47.7/172.4)	27.7% (13/47)
% ECOG 0 (n/N)	79.6% (191/240)	84.6% (154.5/182.6)	84.6% (44/52)	79.6% (191/240)	84.6% (189.9/224.5)	84.6% (44/52)	79.6% (191/240)	84.6% (145.9/172.4)	84.6% (44/52)
Median age, yrs	63.0	59.7	59.1	63.0	59.6	59.1	63.0	59.7	59.1
% with age > ipi/nivo median (n/N)	60.4% (145/240)	50% (91.3/182.6)	50% (26/52)	60.4% (145/240)	50% (112.2/224.5)	50% (26/52)	60.4% (145/240)	50% (86.2/172.4)	50% (26/52)

IMCgp100: Tebentafusp

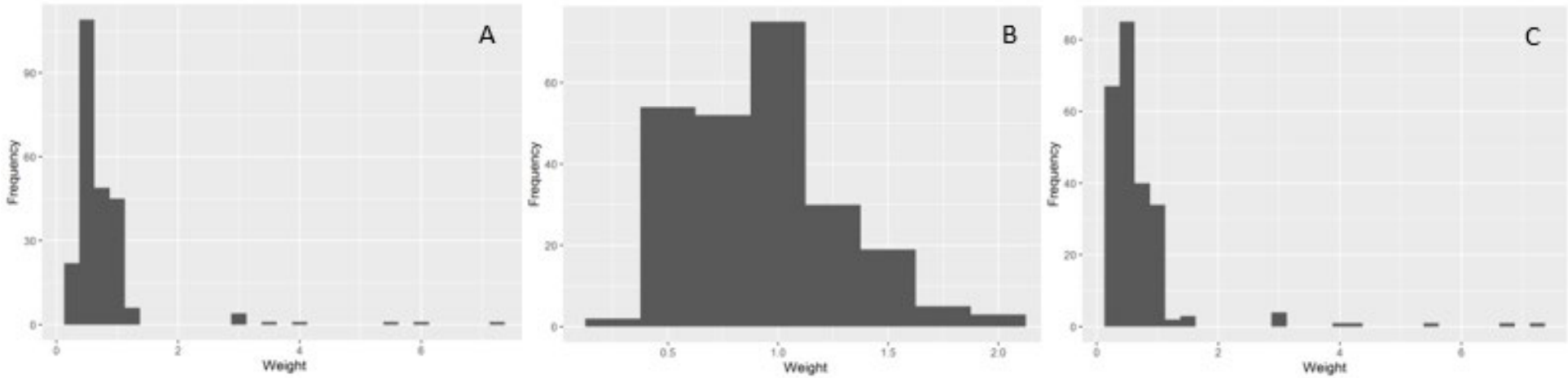

Figure 37. Histograms of absolute matching weights for tebentafusp matched with ipi/nivo for A) overall population, B) extrahepatic only and hepatic + extrahepatic categories and C) liver lesion size.

Table 101. Summary of matching weights; tebentafusp matched to ipi/nivo.

	Overall population		Patient characteristics pooling extrahepatic only and hepatic + extrahepatic categories		Patient characteristics when using liver lesion size covariates	
Statistic	Weights, rescaled	Weights, absolute	Weights, rescaled	Weights, absolute	Weights, rescaled	Weights, absolute
ESS (Effective sample size)	115.93	115.93	210.61	210.61	101.61	101.61
Sum	240	182.56	240	224.47	240	172.45
Mean	1	0.76	1	0.94	1	0.72
Min	0.34	0.26	0.32	0.29	0.27	0.19
Max	9.58	7.29	2.14	2	10.26	7.37
Number of zero observations	0	0	0	0	0	0
Number of near zero (<0.01) observations	0	0	0	0	0	0

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Table 102. Result from the matched adjusted Indirect comparison of tebentafusp and ipi/nivo via IMCgp100-202 and GEM1402.

Table A3a Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Unadjusted indirect comparison											
Median overall survival ‡	Tebentafusp	82/240	21.7 months	9.6	N/A	N/A	HR: 0.514	0.35, 0.756	N/A	The HR were calculated using a weighted Cox proportional hazards model that were fitted using UAIC weights. The model included a covariate for treatment and used the Efron method for dealing with ties	
	Ipi/nivo	39/52	12.1 months								
Overall survival rate – 12 months ‡	Tebentafusp	~179/240	74.7%	23.5*	9.21, 37.64*	<0.001*	RR: 0.46**	0.36, 0.58**	0.001**		
	Ipi/nivo	~26/52	51.2%								
Median Progression free survival ‡	Tebentafusp	190/240	3.3 months	0.2	N/A	N/A	HR: 0.717	0.525, 0.978		The HR were calculated using a weighted Cox proportional hazards model that were fitted	

Table A3a Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Ipi/nivo	51/52	3.1 months							using UAIC weights. The model included a covariate for treatment and used the Efron method for dealing with ties	
Progression free survival rates – 12‡	Tebentafusp	35/240	14.7%	-0.7*	-8.24, 13.46*	0.90*	RR: 0.95**	0.47, 1.92**	0.88**		
	Ipi/nivo	8/52	15.4%								
Match-adjusted indirect comparison* **											
Median overall survival (overall population)	Tebentafusp	61.4/182.6	21.6 months	9.5	N/A	N/A	HR: 0.507	0.324, 0.793	N/A	The HR were calculated using a weighted Cox proportional hazards model that were fitted using MAIC weights. Confidence intervals and p-values were calculated using bootstrapping or robust variance estimators to account for the fact that the weights are estimated rather than known	
	Ipi/nivo	39/52	12.1 months								

Table A3a Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Overall survival rate – 12 months (overall population)	Tebentafusp	143.5/182.6	78.6%	27.4*	12.84, 41.63*	<0.001*	RR: 1.52**	1.15, 1.99**	0.003**		
	Ipi/nivo	26.6/52	51.2%								
Median Progression free survival (overall population)	Tebentafusp	139.1/182.6	4.8 months	1.7	N/A	N/A	HR: 0.647	0.445, 0.941	N/A	The HR were calculated using a weighted Cox proportional hazards model that were fitted using MAIC weights. Confidence intervals and p-values were calculated using bootstrapping or robust variance estimators to account for the fact that the weights are estimated rather than known	
	Ipi/nivo	51/52	3.1 months								
Progression free survival	Tebentafusp	30.1/182.6	16.5%	1.1*	-11.91, 10.65*	0.85*	RR: 1.07**	0.52, 2.19**	0.85**		

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Table A3a Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
rates – 12 (overall population)	Ipi/nivo	8/52	15.4%								
Median overall survival (Pooled extrahepatic categories)	Tebentafusp	73.4/224.5	23.4 months	11.3	N/A	N/A	HR: 0.476	0.313, 0.724	N/A	The HR were calculated using a weighted Cox proportional hazards model that were fitted using MAIC weights. Confidence intervals and p-values were calculated using bootstrapping or robust variance estimators to account for the fact that the weights are estimated rather than known	
	Ipi/nivo	39/52	12.1 months								
Overall survival rate – 12 months	Tebentafusp	171.5/224.5	76.4%	25.2*	10.87, 39.34*	<0.001*	RR: 1.47**	1.12, 1.93**	0.005**		

Table A3a Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
(Pooled extrahepatic categories)	Ipi/nivo	26.6/52	51.2%								
Median Progression free survival (Pooled extrahepatic categories)	Tebentafusp	178.4/224.5	3.4	0.3	N/A	N/A	HR: 0.702	0.498, 0.989	N/A	The HR were calculated using a weighted Cox proportional hazards model that were fitted using MAIC weights. Confidence intervals and p-values were calculated using bootstrapping or robust variance estimators to account for the fact that the weights are estimated rather than known	
	Ipi/nivo	51/52	3.1								
Progression free survival – 12	Tebentafusp	33.4/224.5	14.9%	-0.5*	-8.55, 13.30*	0.93*	RR: 0.96**	0.47, 1.95**	0.90**		

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Table A3a Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
months (Pooled extrahepatic categories)	Ipi/nivo	8/52	15.4%								
Median overall survival (Liver lesion)	Tebentafusp	57.1/ 172.4	21.6 months				HR: 0.495	0.314, 0.781		The HR were calculated using a weighted Cox proportional hazards model that were fitted using MAIC weights. Confidence intervals and p-values were calculated using bootstrapping or robust variance estimators to account for the fact that the weights are estimated rather than known	
	Ipi/nivo	39/52	12.1 months								
Overall survival rate – 12 months (Liver lesion)	Tebentafusp	137.2/17 2.4	79.6%	28.4*	13.78, 42.63*	<0.001*	RR:1.53**	1.17, 2.01**	0.002**		
	Ipi/nivo	26.6/52	51.2%								

Table A3a Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median progression free survival (Liver lesion)	Tebentafusp	130.7/172.4	4.8 months	1.7			HR: 0.645	0.441, 0.944		The HR were calculated using a weighted Cox proportional hazards model that were fitted using MAIC weights. Confidence intervals and p-values were calculated using bootstrapping or robust variance estimators to account for the fact that the weights are estimated rather than known	
	Ipi/nivo	51/52	3.1 months								
Progression free survival rate – 12 months (Liver lesion)	Tebentafusp	29/172.4	16.8%	1.4*	-11.67, 11.10*	0.81*	RR: 1.10**	0.53, 2.25**	0.80**		
	Ipi/nivo	8/52	15.4%								

* Absolute difference CI calculated using: $D - \sqrt{(\rho_1 - l_1)^2 + (u_2 - \rho_2)^2}$ to $D + \sqrt{(\rho_2 - l_2)^2 + (u_1 - \rho_1)^2}$ and p-value calculated using chi-squared test.

** Relative risk (RR) calculated using: $RR = \frac{a/(a+b)}{c/(c+d)}$, with the SE of the log relative risk being: $SE\{\ln(RR)\} = \sqrt{\frac{1}{a} + \frac{1}{c} - \frac{1}{a+b} - \frac{1}{c+d}}$, and the 95% CI being:

95% $CI = \exp(ln(RR) - 1.96 * SE\{ln(RR)\})$ *to* $\exp(ln(RR) + 1.96 * SE\{ln(RR)\})$

*** Sample size and population size from the match-adjusted indirect comparison are rounded from decimal numbers.

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‡ The results from the UAIC are the same across all subgroups: overall population, pooled extrahepatic categories, and liver lesions.

CEA: Cost effectiveness analysis, HR: hazard ratio, Ipi/Nivo: Ipilimumab in combination with nivolumab, MAIC: match adjusted indirect comparison, RR: relative risk, UAIC: unadjusted indirect comparison

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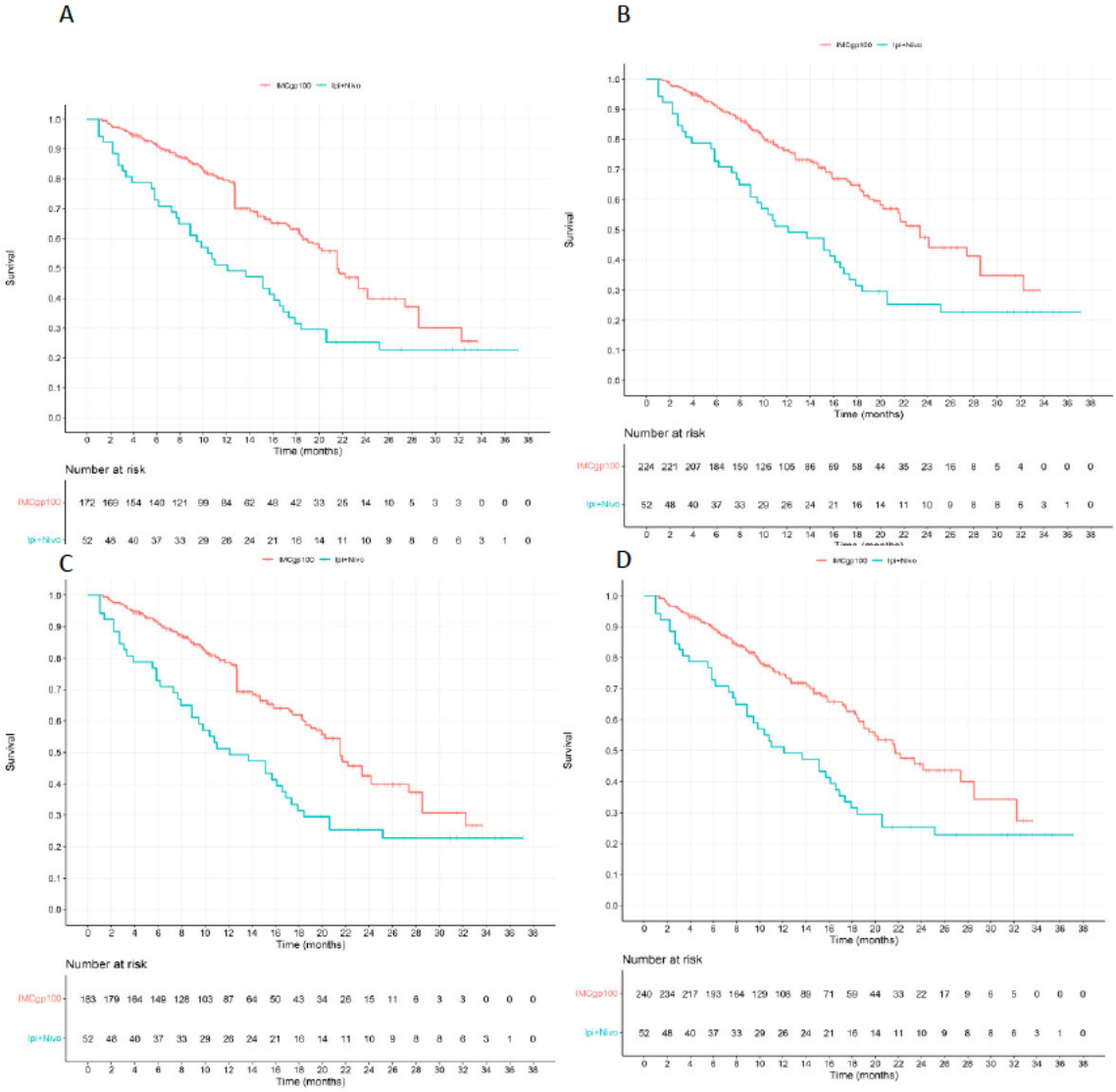

Figure 38. Kaplan Meier curves of overall survival for A) MAIC for overall population, B) MAIC for pooled extrahepatic categories C) MAIC for liver lesions size covariate and for D) UAIC

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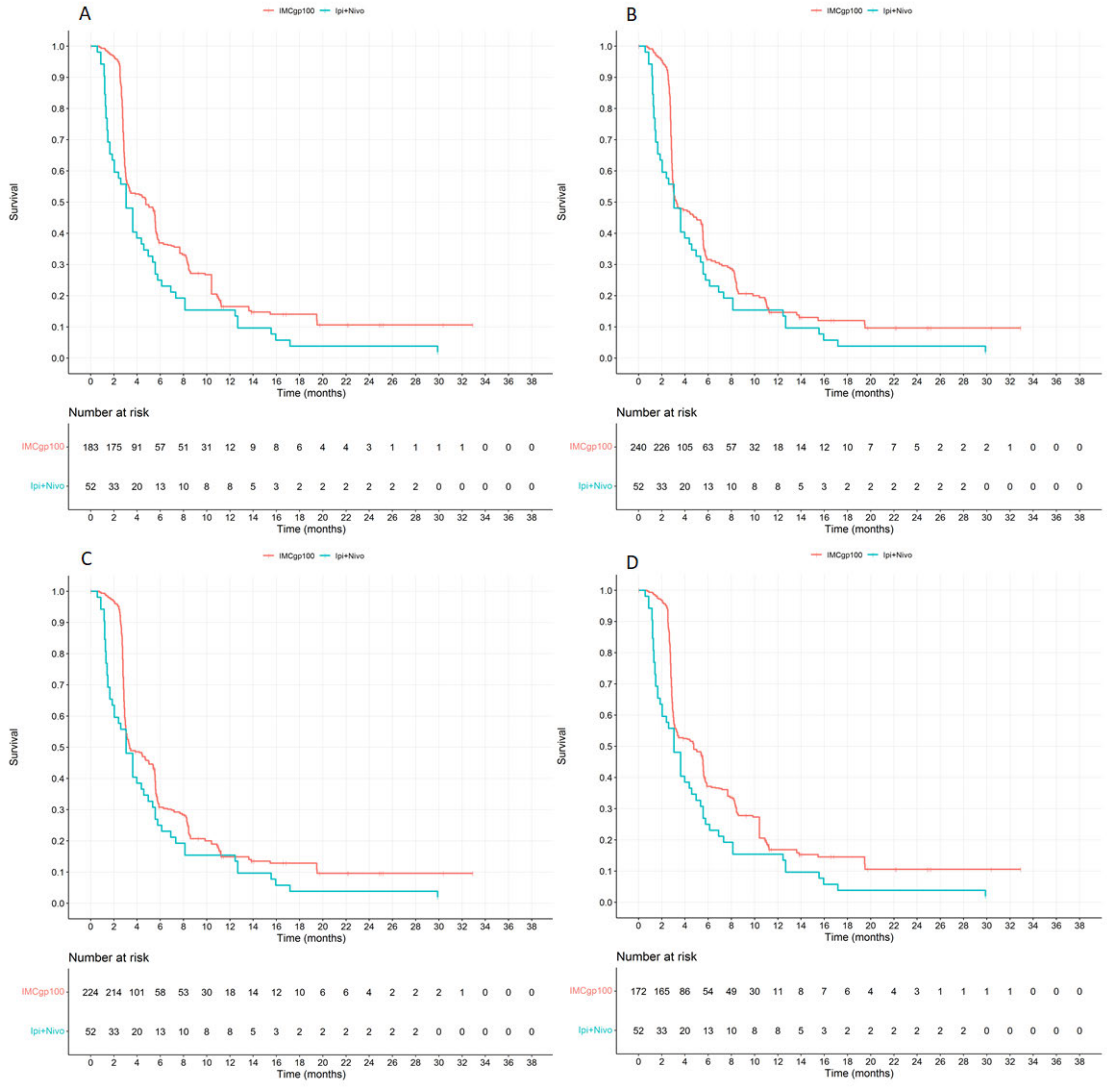

Figure 39. Kaplan Meier curves of progression-free survival A) MAIC for overall population, B) UAIC, C) MAIC for pooled extrahepatic categories and for D) MAIC for liver lesions size covariate

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19. Appendix G: Extrapolation

Extrapolation of OS and PFS was required as not all events were observed over the trial periods. IPD from the MAIC for both ipi/nivo and tebentafusp were used to conduct an extrapolation analysis. For completeness, an assessment of the PH assumption was made. Standard parametric models (exponential, Weibull, log-normal, log-logistic, Gompertz, generalized gamma, and gamma) were fitted, following NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance [54]. Hazard functions were used to assess the suitability of the parametric models. Goodness-of-fit statistics, the AIC and BIC, are reported to assess the models' fit to the observed data, as well as visual inspection vs. the KM estimates. To identify the parametric model with the best fit, the AICs and BICs were initially ranked separately, followed by summation of both ranks for each parametric model. Based on the sum of ranks, the overall ranking was thus derived (the lower the value of sum of ranks, the better the fit).

All analyses were conducted in the statistical software R version 3.5.1. The package "flexsurv" (v 2.1) [89] and ggplot2 [90] was used in addition to base R commands.

The TTD curves from IMCgp100-202 comparing tebentafusp and IC (pembrolizumab, ipilimumab and dacarbazine) are provided in section 19.3 per request by the DMC.

19.1 Overall survival

19.1.1 Assessment of the proportional hazard assumption

The PH assumption was assessed visually through log-log plots and Schoenfeld residual plots, plots of which are presented in Figure 40. The results of the statistical test give a *P* value of 0.015. Although based on the plots presented in, the proportional hazard assumption does not seem violated, given the p value, which demonstrates statistical significance, we fitted the data separately to each treatment arm, as the IPD is available, negating the need to assume PH. This also gives additional flexibility in the model.

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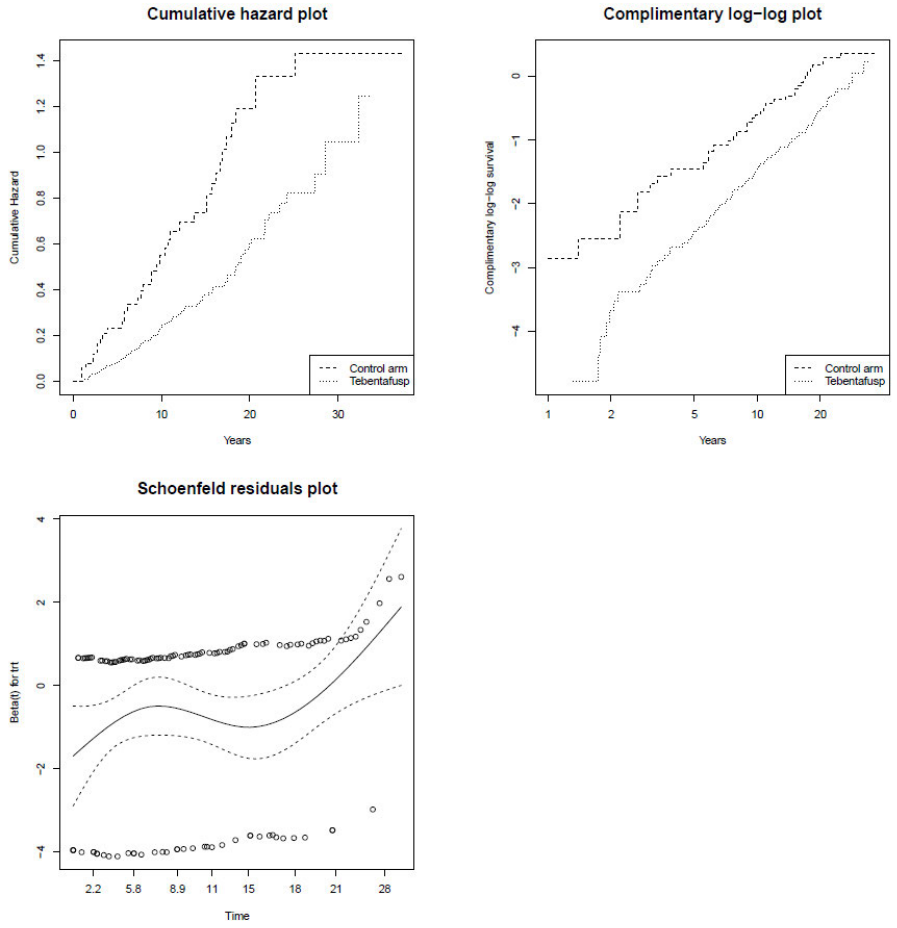

Figure 40. Visual assessment of the proportional hazard assumption for overall survival. (a) Cumulative hazard plot; (b) log-log plot; (c) Schoenfeld residuals plot.

19.1.2 Parametric models

19.1.2.1 Hazard functions

As the hazard functions increase before decreasing a non-monotonic hazard was considered more appropriate. Hence, exponential (constant hazard), Weibull, Gompertz and gamma (monotonic hazards which only increases or decreases) do not provide the most plausible options. Generalized gamma, log-logistic and log-normal (both of which are special cases of the generalized gamma) provide reasonable options. The graphs of the hazard functions did not allow to conclude on the choice of extrapolation. Thus, the final choice of the extrapolation model was made considering a range of evidence: Akaike information criterion (AIC), Bayesian information criterion (BIC), fit to the KM curve, clinical experts' opinion. The hazard functions for the OS parametric models are presented in Figure 41.

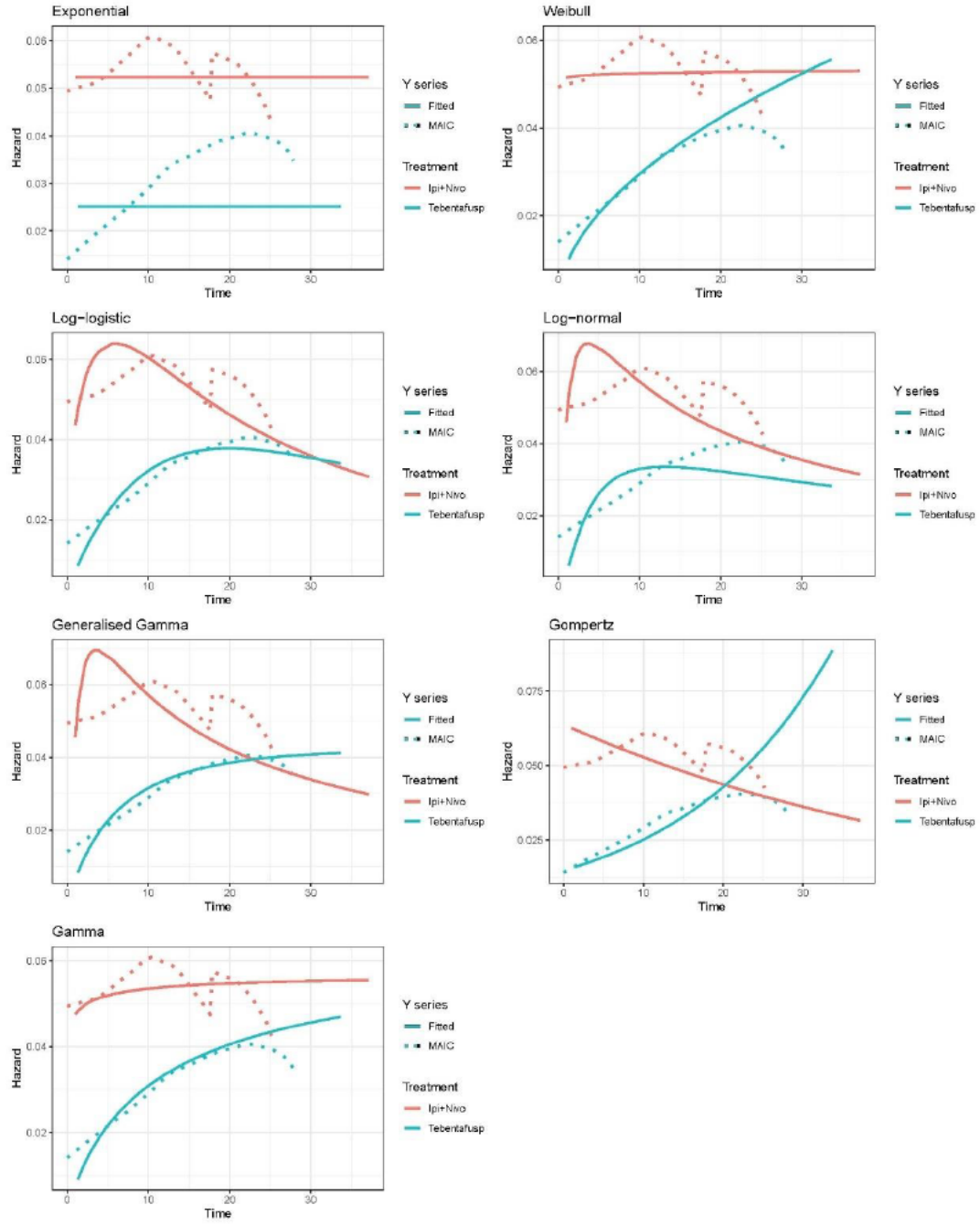

Figure 41. Hazard function of OS parametric models.

19.1.2.2 Statistical tests

Based on AIC and BIC presented in Table 103, the model with the best fit in the tebentafusp arm is the gamma, although Weibull, log-normal, log-logistic, and generalized gamma are all reasonable fit with the AIC and BIC being close, less than 2% change. In the ipi/nivo arm, the model with the best fit is the log-normal, although all models are reasonable with the AIC and BIC being within five points.

Table 103. Goodness-of-fit Akaike and Bayesian information criteria: overall survival standard parametric models.

	Tebentafusp			Ipi/nivo		
Model	**AIC**	**BIC**	**Ranking**	**AIC**	**BIC**	**Ranking**
Exponential	737.26	740.74	7	310.09	312.04	2
Weibull	721.97	728.94	2	312.08	315.98	7
Log-normal	722.82	729.78	4	308.72	312.63	1

Log-logistic	722.19	729.15	3	309.14	313.04	3
Gompertz	727.17	734.13	6	311.12	315.03	4
Generalized gamma	723.32	733.76	5	310.70	316.55	5
Gamma	721.45	728.41	1	311.96	315.87	5

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ipi/nivo, ipilimumab in combination with nivolumab

Plot of the extrapolation models overlayed with the KM curves and Rantala KM curves are presented in Figure 42 over the trial time horizon and in Figure 43 over a 15-year time horizon. Survival probabilities at various time-points are also presented in Table 104 and Table 105 in Appendix G.

Rantala and colleagues conducted a systematic review and meta-analysis of 78 studies (n=2494) in mUM. They pooled data for 510 first-line patients. The KM curve constructed using data from these studies which only included first-line patients (data reported in supplemental digital content 4, B. OS by percentage of first line treatments – 100%; green line) was digitized using WebPlotDigitizer [55], to reconstruct the patient-level data and plotted against the data from the IMCgp100-202 for comparison.

In the tebentafusp arm, the Weibull gives the most pessimistic extrapolation with a 5-year OS probability of 5% and the log-normal gives the most optimistic extrapolation with a 5-year OS probability of 20%. Based on clinical experts' opinion, a 5-year OS of 12-17% with tebentafusp is clinically plausible.

Rantala and colleagues found no clinically significant difference in OS by treatment modality[8], and that no therapy has demonstrated a significant improvement in OS in the last 40 years [24,56]. Hence it was considered that the data reported by Rantala et al. on first-line patients is the best benchmark available for comparison against the ipi/nivo data [8]. Additionally, the clinical experts consulted during the global model CEM development estimated that the OS under current treatment modalities is between 0% and 5% at 5 years. With this information in mind combined with the reasonable fits of most of the parametric models in both arms – log-normal and log-normal were applied as base case in both arms. Log-normal, gamma, generalized gamma and Weibull are tested in scenario analysis.

Applying the log-normal distribution to the ipi/nivo arm resulted in a 5-year OS of 9.64%. An estimated that is considered conservative give the expert input on the current treatment modalities being between 0-5% at year 5. Weibull and gamma are the two models with the statistically best fit for the tebentafusp arm, given the clinical expert expected the 5-year OS to be between 12-17%. Log-normal being the statistically fourth best fit was chosen to match the approach in the ipi/nivo arm, also the clinical expert did not find a 5-year OS of 20% for tebentafusp unrealistic, considering the mUM surveillance program, where patients are expected to be diagnosed earlier giving them a better chance of Progression-free survival. OS probabilities at various time-points are presented in Table 104 for ipi/nivo and Table 105 for tebentafusp.

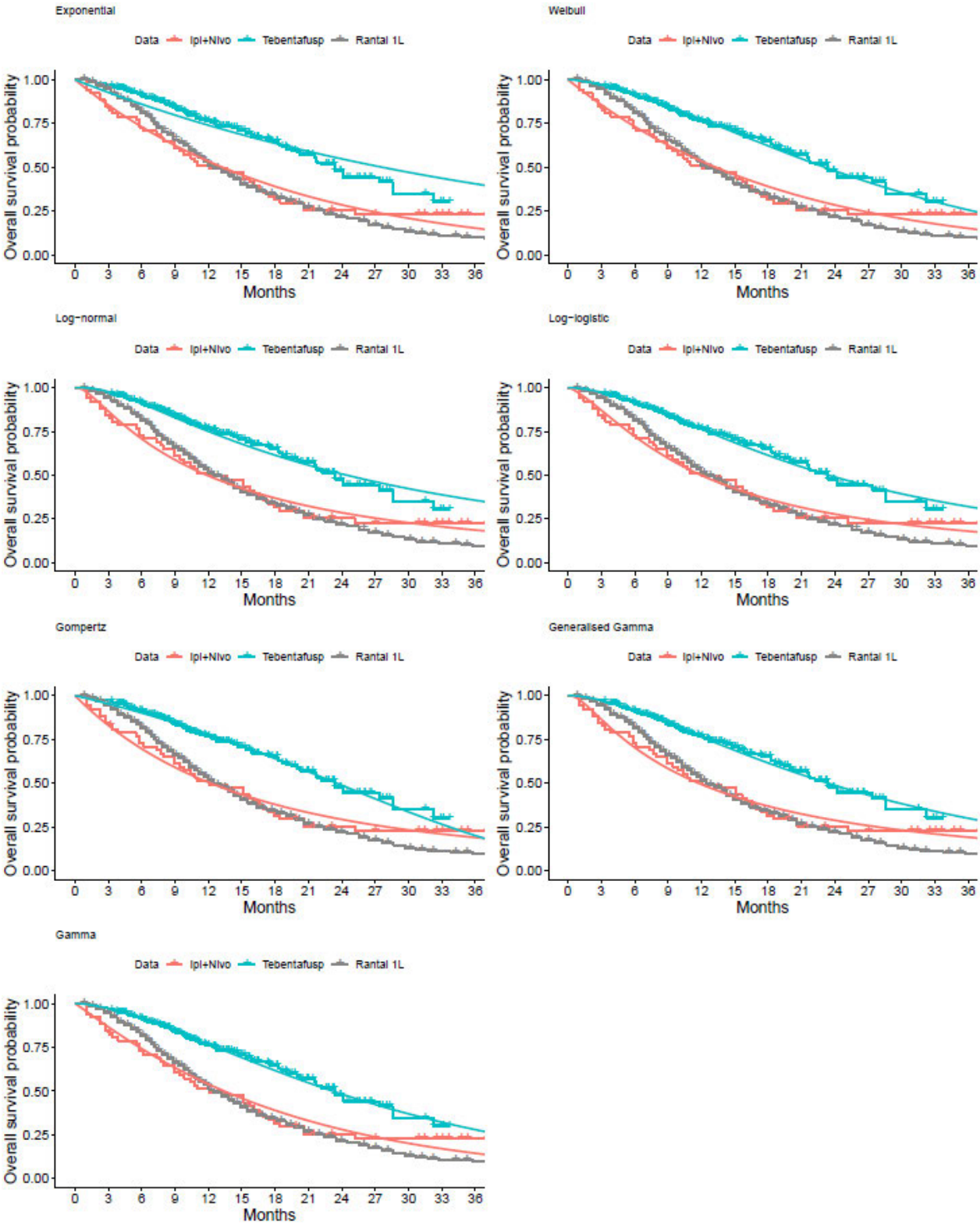

Figure 42. Overall survival standard parametric models - Trial time horizon.

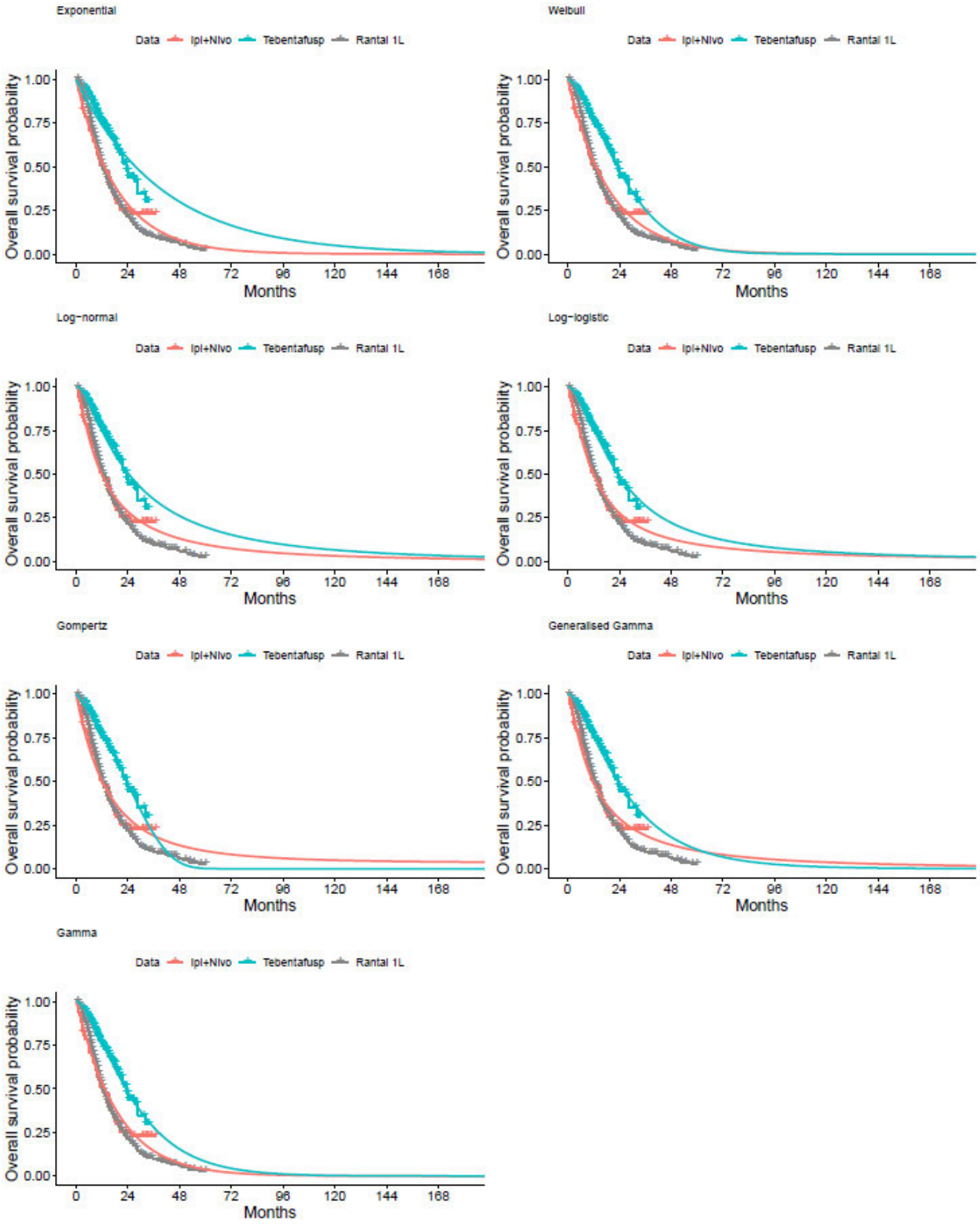

Figure 43. Overall survival standard parametric models -15-year time horizon.

Table 104. Overall survival parametric models versus Kaplan-Meier curve: ipi/nivo.

Months	Kaplan-Meier	Exponential	Weibull	Log normal	Log logistic	Gompertz	Generalized gamma	Gamma
Ranking based on AIC and BIC		2	7	1	3	4	5	5
6	72.8%	73.12%	73.34%	70.85%	72.27%	69.72%	70.47%	74.30%
9	61.0%	62.53%	62.71%	58.85%	59.84%	59.09%	58.44%	63.44%
12	51.2%	53.47%	53.60%	49.71%	50.05%	50.53%	49.39%	54.04%
18	31.5%	39.10%	39.12%	36.96%	36.42%	37.90%	36.90%	39.07%
24	25.3%	28.59%	28.53%	28.65%	27.80%	29.32%	28.81%	28.16%
30	22.8%	20.91%	20.79%	22.88%	22.06%	23.32%	23.21%	20.25%
36 (3 years)	22.8%	15.10%	14.96%	18.56%	17.91%	18.86%	19.01%	14.35%
48 (4 years)		8.08%	7.93%	13.05%	12.82%	13.36%	13.64%	7.38%
60 (5 years)		4.32%	4.19%	9.64%	9.77%	10.16%	10.28%	3.78%
120 (10 years)		0.19%	0.17%	3.15%	3.99%	4.88%	3.69%	0.13%

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

Table 105. Overall survival parametric models versus Kaplan-Meier curve: tebentafusp.

Months	Kaplan-Meier	Exponential	Weibull	Log normal	Log logistic	Gompertz	Generalized gamma	Gamma
Ranking based on AIC and BIC		7	2	4	3	6	5	1
6	91.3%	86.06%	91.52%	90.93%	91.63%	90.12%	91.45%	91.55%
9	83.7%	79.83%	84.85%	82.93%	84.32%	84.38%	84.16%	84.52%
12	76.4%	74.06%	77.52%	75.12%	76.46%	78.11%	76.46%	76.93%
18	64.9%	63.73%	62.36%	61.53%	61.48%	64.17%	61.67%	61.88%
24	47.6%	54.84%	48.10%	50.80%	49.09%	48.97%	48.89%	48.41%
30	34.8%	47.20%	35.77%	42.40%	39.47%	33.78%	38.41%	37.15%
36 (3 years)		40.38%	25.40%	35.53%	31.90%	19.81%	29.76%	27.80%
48 (4 years)		29.90%	12.02%	26.03%	22.10%	3.67%	18.10%	15.42%
60 (5 years)		22.15%	5.12%	19.67%	16.13%	0.15%	11.02%	8.31%
120 (10 years)		4.90%	0.02%	6.53%	5.40%	0.00%	0.99%	0.30%

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

19.2 Progression-free survival

19.2.1 Assessment of the proportional hazard assumption

The PH assumption was assessed visually through log-log plots and Schoenfeld residual plots, graphs of which are presented in Figure 44. The results of the statistical test give a *P* value of 0.022. Although based on the plots presented in Figure 44, the proportional hazard assumption does not seem violated, given the p value, which demonstrates statistical significance, we fitted the data separately to each treatment arm, as the IPD is available, negating the need to assume PH. This also gives additional flexibility in the model.

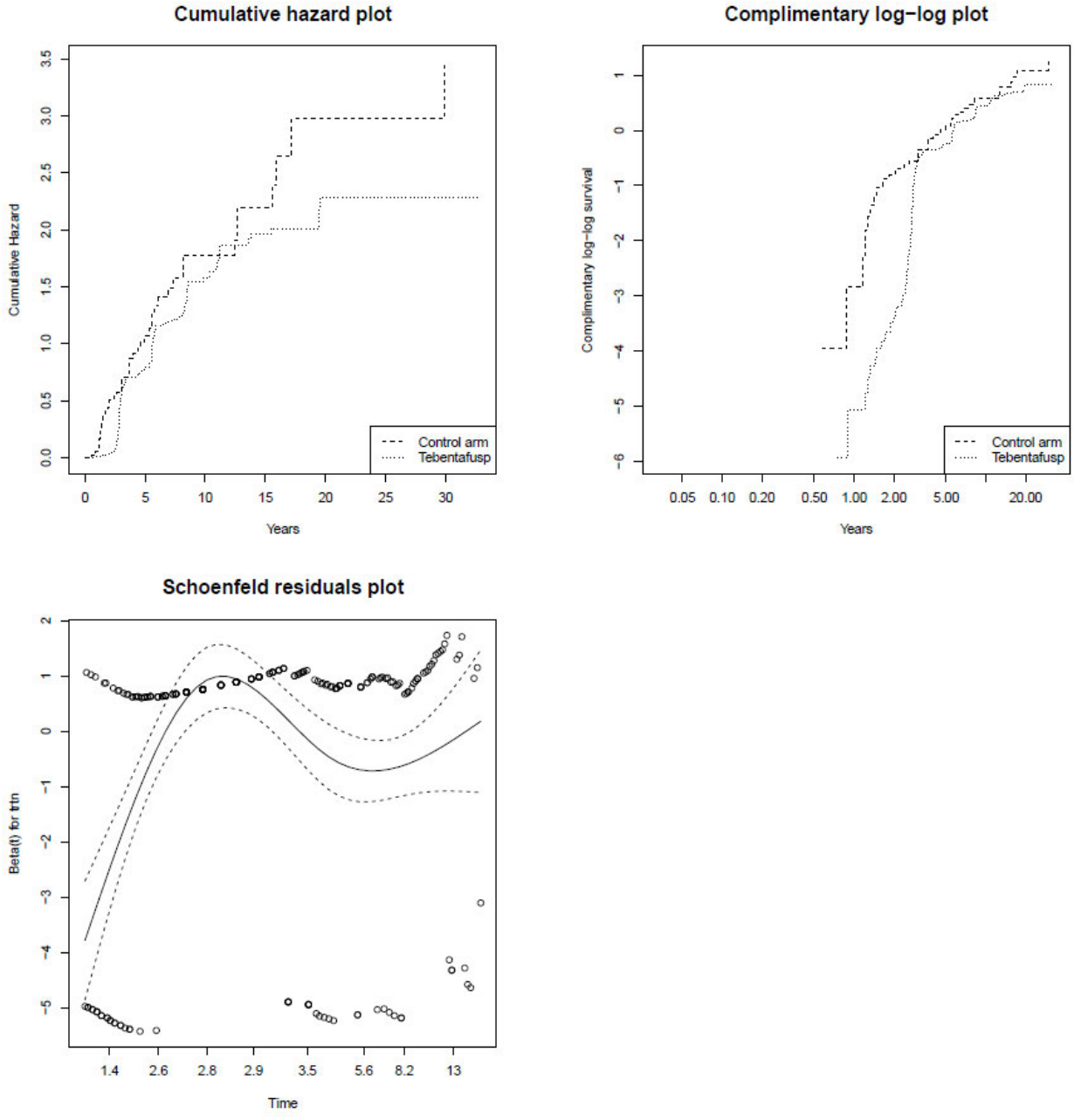

Figure 44. Visual assessment of the proportional hazard assumption for progression-free survival. (a) Cumulative hazard plot; (b) log-log plot; (c) Schoenfeld residuals plot.

19.2.2 Parametric models

19.2.2.1 Hazard functions.

As the hazard functions increase before decreasing a non-monotonic hazard was considered more appropriate. Hence, exponential (constant hazard), Weibull, Gompertz and gamma (monotonic hazards which only increases or decreases) do not provide the most plausible options. Generalized gamma, log-logistic and log-normal (both of which are special cases of the generalized gamma) provide reasonable options. The graphs of the hazard functions did not allow to conclude on the choice of extrapolation. Thus, the final choice of the extrapolation model was made considering a range of evidence: Akaike information criterion (AIC), Bayesian information criterion (BIC), fit to the KM curve, clinical experts' opinion. The hazard functions for the OS parametric models are presented in Figure 45.

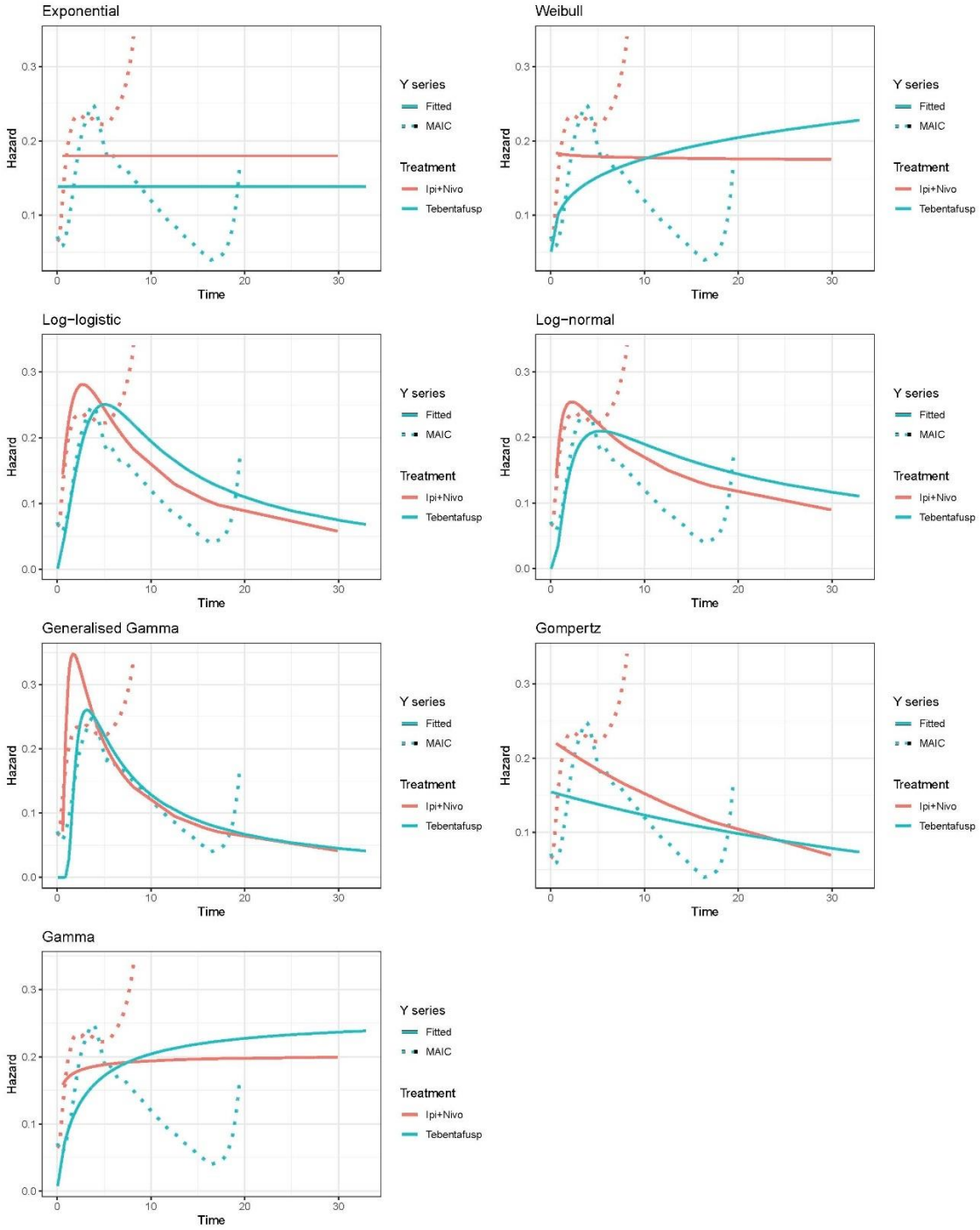

Figure 45. Hazard function of PFS parametric models.

19.2.2.2 Statistical tests

Standard parametric models (exponential, Weibull, log normal, log logistic, Gompertz, generalized gamma and gamma) were fitted, following NICE DSU TSD 14 guidance [54]. Based on AIC and BIC presented in Table 37, the model with the best fit in the tebentafusp arm is the generalized gamma. In the ipi/nivo arm, the model with the best fit is the generalized gamma, although log-normal and log-logistic are reasonable with the AIC and BIC being close, less than 2% difference.

Table 106. Goodness-of-fit Akaike and Bayesian information criteria: progression-free survival standard parametric models.

	Tebentafusp			Ipi/nivo		
Model	**AIC**	**BIC**	**Ranking**	**AIC**	**BIC**	**Ranking**
Exponential	1137.17	1140.65	6	278.94	280.89	4
Weibull	1126.88	1133.84	5	280.92	284.82	7
Log normal	1047.22	1054.18	3	267.10	271.00	2
Log logistic	1044.84	1051.80	2	268.78	272.68	3
Gompertz	1136.65	1143.61	6	278.12	282.02	4
Generalized gamma	1000.48	1010.92	1	264.40	270.25	1
Gamma	1108.35	1115.31	4	280.49	284.39	6

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ipi/nivo, ipilimumab in combination with nivolumab

Plot of the extrapolation models overlayed with the KM curves are presented in Figure 46. Survival probabilities at various time-points are also presented in Table 107 and Table 108 below.

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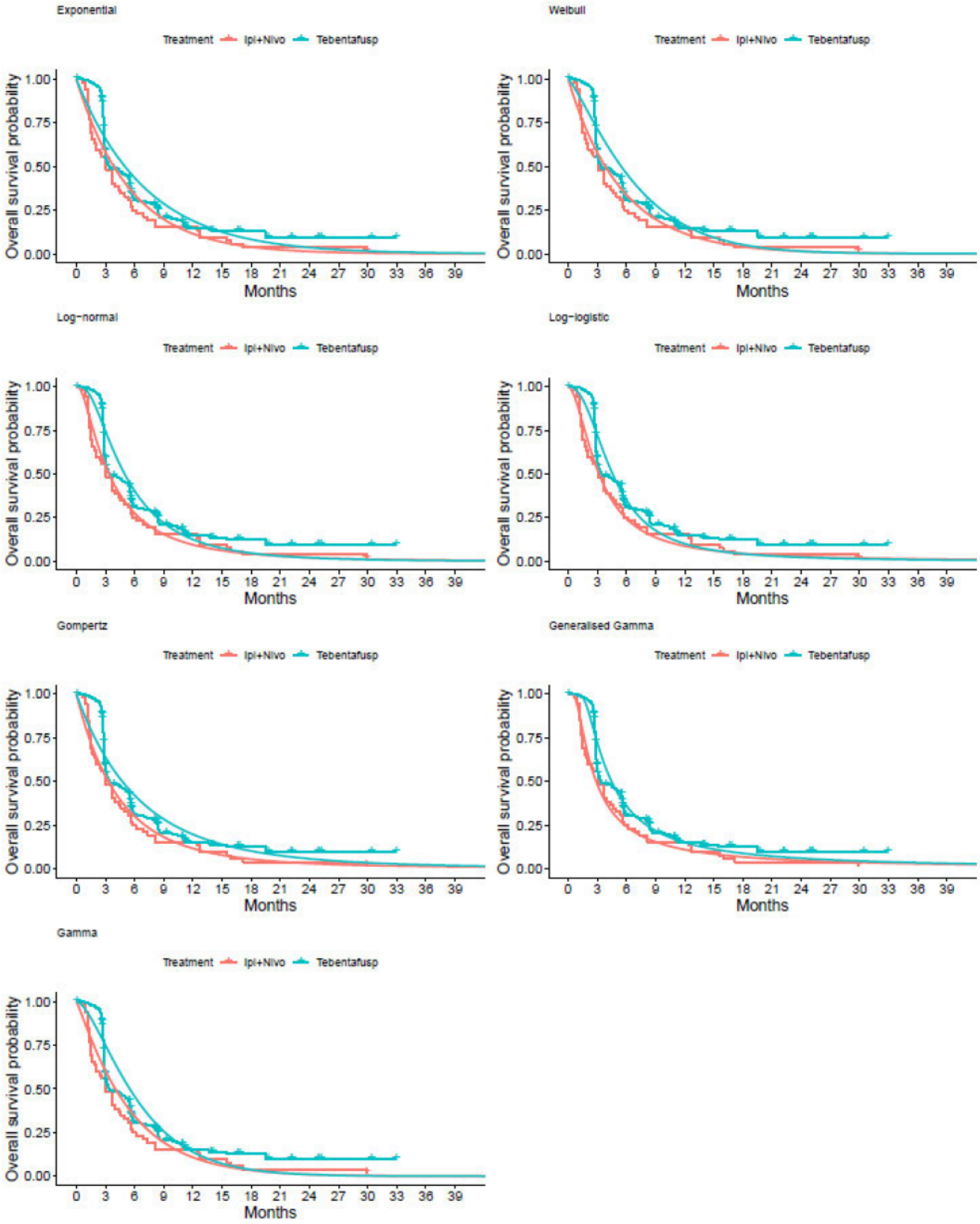

Figure 46. Progression-free survival standard parametric models.

Table 107. Progression-free survival parametric models versus Kaplan-Meier curve: ipilimumab + nivolumab.

Months	Kaplan-Meier	Exponential	Weibull	Log normal	Log logistic	Gompertz	Generalized gamma	Gamma

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Ranking based on AIC and BIC		**4**	**7**	**2**	**3**	**4**	**1**	**6**
6	25.0%	34.10%	33.92%	27.60%	24.56%	30.17%	24.27%	34.58%
9	15.38%	19.91%	19.91%	15.55%	13.73%	18.27%	15.40%	19.48%
12	15.38%	11.62%	11.72%	9.51%	8.75%	11.70%	11.00%	0.00%
18	3.9%	3.96%	4.08%	4.20%	4.48%	5.53%	6.75%	3.36%
24	3.9%	1.35%	1.42%	2.14%	2.74%	3.06%	4.75%	1.03%
30		0.46%	0.50%	1.21%	1.87%	1.91%	3.61%	0.31%
36 (3 years)		0.15%	0.17%	0.71%	1.35%	1.30%	2.85%	0.09%
48 (4 years)		0.02%	0.02%	0.30%	0.82%	0.78%	2.00%	0.01%
60 (5 years)		0.00%	0.00%	0.15%	0.55%	0.56%	1.51%	0.00%
120 (10 years)		0.00%	0.00%	0.15%	0.55%	0.56%	1.50%	0.00%

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

Table 108. Progression-free survival parametric models versus Kaplan-Meier curve: tebentafusp.

Months	Kaplan-Meier	Exponential	Weibull	Log normal	Log logistic	Gompertz	Generalized gamma	Gamma
Ranking based on AIC and BIC		**6**	**5**	**3**	**2**	**6**	**1**	**4**
6	30.8%	43.65%	46.11%	40.47%	35.15%	42.12%	35.98%	45.87%
9	20.7%	28.84%	28.15%	22.07%	17.76%	28.50%	21.87%	25.89%
12	14.9%	19.05%	16.55%	12.62%	10.10%	19.78%	15.09%	13.99%
18	12.9%	8.32%	5.25%	4.71%	4.28%	10.22%	8.83%	3.78%
24	9.6%	3.63%	1.53%	2.03%	2.27%	5.74%	6.01%	0.97%
30	9.6%	1.58%	0.41%	0.97%	1.38%	3.46%	4.45%	0.24%
36 (3 years)		0.67%	0.10%	0.49%	0.91%	2.19%	3.45%	0.05%
48 (4 years)		0.13%	0.01%	0.15%	0.47%	1.07%	2.34%	0.00%
60 (5 years)		0.02%	0.00%	0.06%	0.29%	0.62%	1.73%	0.00%
120 (10 years)		0.02%	0.00%	0.06%	0.28%	0.61%	1.73%	0.00%

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

19.3 Time to discontinuation

The clinical data informing the model is based on the MAIC given that ipi/nivo was not a comparator in the IMCgp100-202 study. Both OS and PFS were analyzed to assess the clinical effectiveness of tebentafusp against ipi/nivo. However, TTD was not published in the GEM1402 and an analysis could not be conducted for this endpoint. Hence, TTD was not used in the extrapolation analysis in the model. The TTD curves from

IMCgp100-202 comparing tebentafusp and IC (pembrolizumab, ipilimumab and dacarbazine) are provided in the following per request by the DMC.

In Figure 47 the KM curve for TTD is presented, and the median TTD is reported in Table 109.

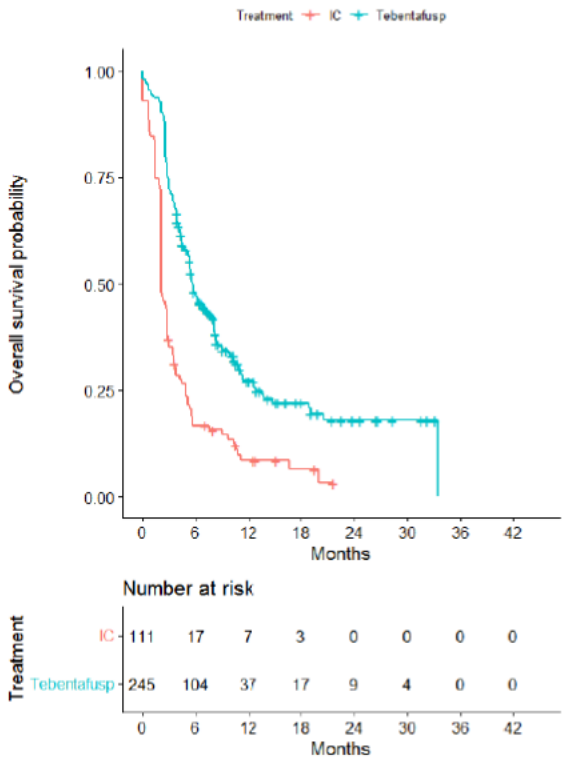

Figure 47. Kaplan-Maier curve TTD.

Table 109. Median TTD.

	Median TTD
Tebentafusp	5.6 (5.3, 7.6)
Investigator's choice	2.1 (2.1, 2.8)

19.3.1 Statistical tests

Standard parametric models (exponential, Weibull, log normal, log logistic, Gompertz, and generalized gamma) were fitted, following NICE DSU TSD 14 guidance [54]. The AIC and BIC are presented in Table 110 and provide information on the goodness of fit to the observed data. Based on the AIC and BIC the model with the best fit in the tebentafusp arm is the log-logistic. The model with the best fit in the IC arm was the Gompertz, although all but the log-normal distribution were reasonable as the AIC and BIC are all within five points.

Table 110. Goodness-of-fit Akaike and Bayesian information criteria: time to treatment discontinuation standard parametric models.

	Tebentafusp			IC		
Model	**AIC**	**BIC**	**Ranking**	**AIC**	**BIC**	**Ranking**

Exponential	1147.40	1150.90	3	495.39	498.10	3
Weibull	1149.40	1156.40	5	495.08	500.50	4
Log-normal	1162.08	1169.09	6	513.28	518.70	6
Log-logistic	1131.43	1138.43	1	492.98	498.40	2
Gompertz	1142.81	1149.81	2	490.06	495.48	1
Generalized Gamma	1145.80	1156.31	3	496.41	504.54	5

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; IC, investigator's choice

Plot of the extrapolation models overlayed with the KM curves are presented in Figure 48. Survival probabilities at various time-points for IC and tebentafusp are also presented in Table 111 and Table 112, respectively.

Table 111. Time to treatment discontinuation parametric models versus Kaplan-Meier curve: IC

Months	Kaplan-Meier	Exponential	Weibull	Log normal	Log logistic	Gompertz	Generalized gamma
Ranking based on AIC and BIC		**3**	**4**	**6**	**2**	**1**	**5**
6	16.7%	25.18%	25.26%	26.54%	23.91%	23.26%	24.82%
9	15.6%	12.64%	13.88%	18.53%	15.22%	13.73%	13.91%
12	8.6%	6.34%	7.80%	13.88%	10.76%	8.97%	8.10%
18	6.5%	1.60%	2.57%	8.78%	6.45%	4.82%	2.97%
24		0.40%	0.88%	6.12%	4.42%	3.21%	1.17%
30		0.10%	0.31%	4.52%	3.29%	2.46%	0.49%
36 (3 years)		0.02%	0.11%	3.45%	2.55%	2.06%	0.20%
48 (4 years)		0.00%	0.01%	2.24%	1.73%	1.72%	0.04%
60 (5 years)		0.00%	0.00%	1.56%	1.28%	1.59%	0.01%
120 (10 years)		0.00%	0.00%	0.45%	0.50%	1.50%	0.00%

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

Table 112. Time to treatment discontinuation parametric models versus Kaplan-Meier curve: tebentafusp.

Months	Kaplan-Meier	Exponential	Weibull	Log normal	Log logistic	Gompertz	Generalized gamma
Ranking based on AIC and BIC		**3**	**5**	**6**	**1**	**2**	**3**
6	47.6%	55.88%	55.85%	52.64%	52.44%	52.62%	54.54%
9	35.4%	41.77%	41.76%	40.96%	38.02%	40.02%	40.59%
12	27.2%	31.22%	31.24%	33.08%	28.81%	31.28%	30.69%
18	22.1%	17.45%	17.48%	23.19%	18.38%	20.52%	18.24%

24	18.0%	9.75%	9.79%	17.32%	12.94%	14.59%	11.28%
30	18.0%	5.45%	5.48%	13.48%	9.71%	11.06%	7.20%
36 (3 years)		2.98%	3.00%	10.73%	7.57%	8.78%	4.64%
48 (4 years)		0.93%	0.94%	7.37%	5.14%	6.34%	2.11%
60 (5 years)		0.29%	0.30%	5.36%	3.78%	5.12%	1.02%
120 (10 years)		0.00%	0.00%	1.72%	1.42%	3.57%	0.05%

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

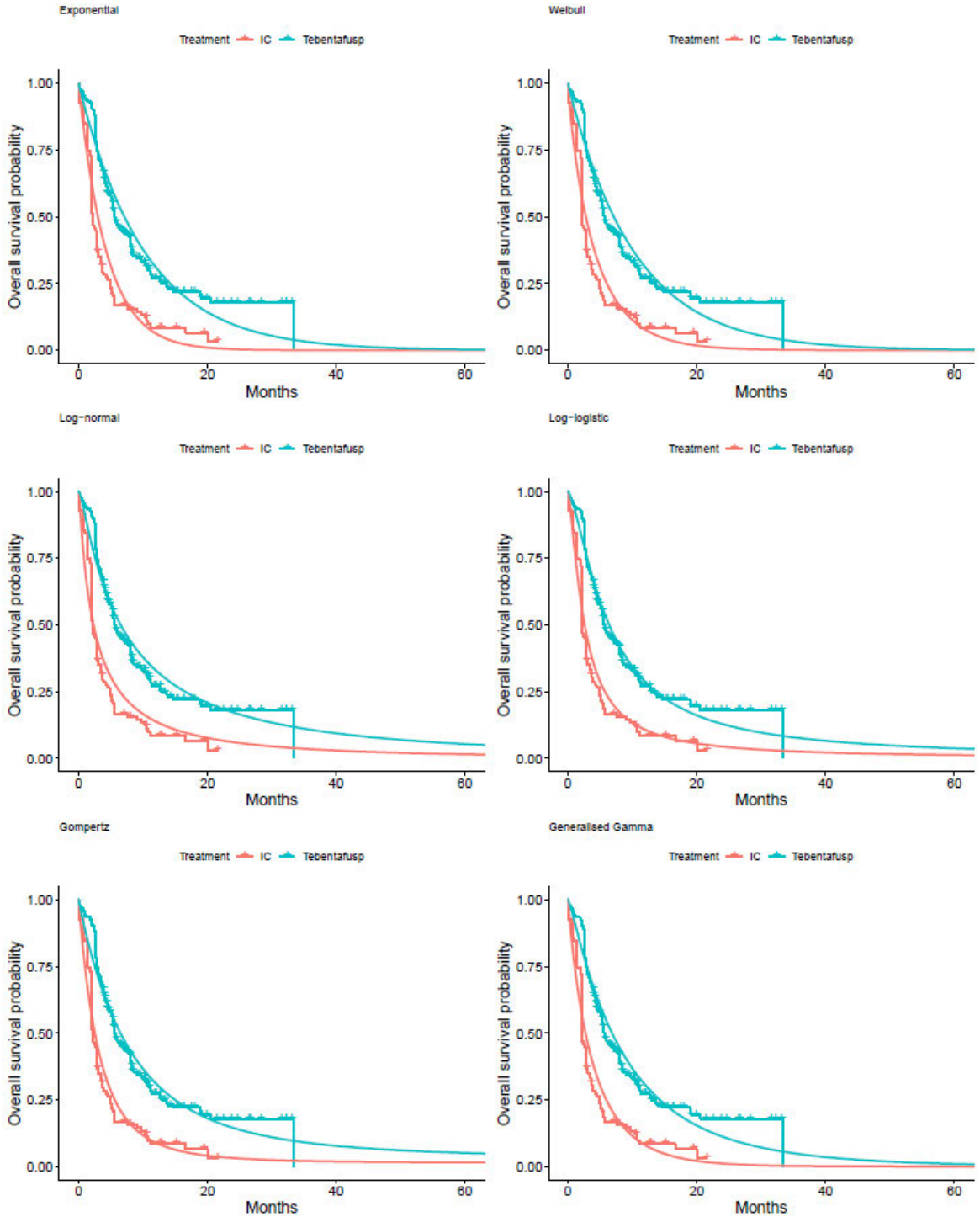

Figure 48. Time to treatment discontinuation standard parametric models.

20. Appendix H: Literature search for HRQoL data

20.1 EQ-5D-5L data from the IMCgp100-202 trial

20.1.1 Data collection

The EQ-5D-5L instrument were completed at baseline (i.e., prior to randomization). During the treatment phase, the PRO data were collected on the first day of each 3-week cycle for five cycles and every fourth cycle thereafter (i.e., every 12 weeks). The assessment was performed prior to study treatment when assessed at a visit during which treatment were administered. Patients entering the disease progression follow-up period continued with EQ-5D-5L assessments every 12 weeks. During the survival follow-up phase, EQ-5D assessments continued to be taken every 3 months. The schedule of the PRO data collection is detailed in Table 113. There were only two observations during the disease progression follow-up period; these were dropped from the analysis set.

Table 113. PRO data collection schedule IMCgp100-202 clinical trial.

		Screening phase	Treatment phase												Follow-up phase		
Procedure	**Protocol section**	**Screening**	**Cycle 1**						**Cycle 2**			**Cycle 3[a]**			**Later cycles**	**End of trial**	**90-day safety follow-up**	**Disease progression follow-up**	**Survival follow-up**
Day of cycle		-21 to -1	1	2	8	9	15	16	1	8	15	1	8	15	1-21				
Patient-reported outcomes	7.3.2		Patient-reported outcome assessments (EQ-5D,5L questionnaire and EORTC QLQ-C30) will be administered to all patients at C1D1, on D1 of every other cycle to C5D1, every fourth cycle, thereafter, beginning with C9D1, and end of treatment															Both EQ-5D,5L and EORTC QLQ-C30 every 12 weeks	EQ-5D,5L every 12 weeks

Abbreviation: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30

20.1.2 Missing data

There were 378 patients involved in the clinical trial: 252 in the tebentafusp arm and 126 in the investigator's choice arm. At baseline, 272 (72%) patients had completed the EQ-5D questionnaire, of whom 194 (77%) were patients in the tebentafusp arm and 78 (62%) in the investigator's choice arm. There were 319 patients who had completed the EQ-5D questionnaire at any time point in the trial.

Comparing the treatment duration for each patient with the schedule of assessment of the EQ-5D, it was determined the number of missing observations at each assessment time point up to the end of treatment. To assess the number of missing observations during the survival follow-up period, we compared the duration of OS for each patient with the schedule of assessment of the EQ-5D during the survival follow-up period shown in Table 113. The pattern of missing data is reported in Table 114.

Table 114. Pattern of missing EQ-5D-5L data, compliance rate

	Observed, n	Expected, n	Missing, n	Observation missing
Baseline	270	317	47	15%
Cycle 3 day 1	218	290	72	25%
Cycle 5 day 1	162	219	57	26%
Cycle 9 day 1	99	126	27	21%
Cycle 13 day 1	63	80	17	21%
Cycle 17 day 1	33	48	15	31%
Cycle 21 day 1	19	28	9	32%
Cycle 25 day 1	13	19	6	32%
Cycle 29 day 1	16	17	1	6%
End of treatment	170	317	147	46%
Survival follow-up day 90	56	130	94	72%
Survival follow-up day 180	35	92	57	62%
Survival follow-up day 270	25	70	45	64%
Survival follow-up day 360	19	49	30	61%

20.1.3 Data imputation

Based on the pattern of missing data, data imputation was conducted for baseline and the treatment phase, but not the survival follow-up period.

Mean imputation was used at baseline. Missing covariates and EQ-5D data were imputed with the mean value at baseline for continuous variables, or modal value for the categorical variables.

Multiple imputation was used for end of treatment given the high number of missing values. Multiple imputation was done using the 'mi impute' command in Stata, imputing missing EQ-5D utilities at end of treatment using chained equations with truncated regressions [63]. Forty-seven imputations were run, as this equaled the percentage of patients with missing EQ-5D records at the end of treatment. Multiple imputation was conducted using the following variables as covariates:

- Socio-demographic variables: age, sex, race, ethnicity, region, country (which were assumed to stay the same over the follow-up period).
- Clinical variables: ECOG score at baseline, stage at initial diagnosis, presence of metastasis at initial diagnosis, LDH level at baseline, size of largest metastatic lesion at baseline, size of largest liver metastatic lesion at baseline (which are assumed to stay the same over the follow-up period).
- Other variables: treatment assignment, OS duration, time between baseline and the assessment timepoint, baseline score EQ-5D utility.

For intermediate time points, linear interpolation was used as there was limited variation of the EQ-5D utility over time.

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20.2 Literature search

20.2.1 Objective of literature search

A literature review using systematic methodology was undertaken for European HTA submissions to identify and summarize the available HRQoL evidence for tebentafusp and relevant comparator therapies for the treatment of mUM.

20.2.2 Databases

The search plan included both electronic searching and hand-searching. In line with good practice guidelines, hand-searching was performed to identify further studies of interest. This included the searching of review articles, the reference lists of included full text publications and the searching of free text keywords in internet search engines.

The databases searched for this SLR were as follows:

- Embase (OvidSP)
- MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE<1946 to Present>, MEDLINE In-Process Citations & Daily Update (OvidSP)
- Health Technology Assessment Database (HTAD) (Wiley): https://www.cochranelibrary.com/
- Epistemonikos database: https://www.epistemonikos.org/en/
- Database of Abstracts of Reviews of Effects (DARE) (Wiley): https://www.cochranelibrary.com/
- The NHS economic evaluation database (NHSEED) https://www.crd.york.ac.uk/CRDWeb/

Table 115. Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	OvidSP interface	1974-2021	10.09.2021 (updated search)
MEDLINE	OvidSP interface	1946-2021	10.09. 2021 (updated search)
Cochrane Database of Systematic Reviews	Cochranelibrary.com	N/A	10.09.2021 (updated search)
CRD database (Includes DARE, HTAD, and NHSEED)	crd.york.ac.uk	N/A	11.05.2020 (initial search)
Epistemonikos	Epistemonikos.org	N/A	10.09.2021 (updated search)

Abbreviations: CRD, Centre for Reviews and Dissemination; DARE, Database of Abstracts of Reviews of Effects; HTAD, Health Technology Assessment Database; NHSEED, The NHS economic evaluation database; N/A, Not available

20.3 Search strategy

A search strategy for the review was developed and refined to recover relevant publications reporting health economic data for adult patients with advanced or mUM or CM. A SLR was conducted to identify health economic evidence for tebentafusp and any relevant comparator interventions for the treatment of advanced or metastatic UM. Thus, a single strategy was implemented to capture CE studies; cost and healthcare resource use studies; and studies reporting HRQoL outcomes relevant to the conditions. The search strategy

and searches were designed and run by an experienced Information Specialist. The search strategies had broadly two sets of terms:

- Terms to search for the health condition of interest
- Terms to search the subject area of interest

The search terms included a number of MeSH indexing and free-text terms to ensure that the highest proportion of relevant articles were captured. The key characteristics for the searches were the following:

- 1. Language: English
- 2. Scope countries: No limit
- 3. Publication type/status: No limit
- 4. Time frame: May 2020 and updated September 2021

20.3.1 PICOS

The eligibility of literature for inclusion in the literature review was based on the review question and areas of focus. The Population, Intervention, Comparator(s), Outcomes and Study design (PICOS) elements for this review are displayed in Table 116, Table 117, and Table 118. To be included, studies had to meet the PICOS elements listed in the PICOS table. Given that there is no standard treatment pathway for mUM, the inclusion criteria for comparators were kept broad; all potential comparators were included. The review excluded pharmacokinetic (PK) and proof of concept studies, studies indexed as case reports, case series, editorials and letters, reviews/systematic reviews and publications with non-English language title and abstracts.

Table 116. Economic evaluation

PICOS element	Inclusion criteria	Exclusion criteria
Population	Adult patients, aged ≥ 18 years, with advanced or metastatic UM/choroidal melanoma	Pediatric patients
Intervention /Comparator	- Tebentafusp, IMCgp100 - All other non-surgical therapeutic interventions used in the treatment of CM/UM	- Surgical interventions for CM/UM
Outcome	- ICER – cost per QALY - ICER – cost per measure of effect gained - Life years	- Any outcome not listed in the inclusion criteria
Study design	- Economic evaluations (including cost-minimization analysis studies, cost-consequence analysis studies, cost-benefit analysis studies, cost-effectiveness studies, cost utility studies, budget impact analyses or clinical trial-based economic evaluations) published 1999 onwards - Model-based economic evaluations and/or model (e.g. decision trees, Markov models etc.) 1999 onwards	- Non-human studies - PK and proof of concept studies - Studies not reporting empirical data - Studies reporting expert opinion only - Reviews/Systematic reviews - Studies indexed as case reports, cases series, editorials, and letters - Publications in non-English language

Abbreviations: CM, Choroidal melanoma; ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life; UM, uveal melanoma

Table 117. Healthcare related costs (HRC) and resource use

PICOS element	Inclusion criteria	Exclusion criteria
Population	Adult patients, aged ≥ 18 years, with advanced or metastatic UM/choroidal melanoma	Pediatric patients
Intervention /Comparator	- N/A	- N/A
Outcome	- Direct costs associated with UM or CM (e.g. medicines, healthcare labour costs, hospitalisations, surgery) - Indirect costs associated with UM or CM (e.g. absenteeism, work productivity, premature death) - Resource use (e.g. hospitalisations, GP visits, hospital length of stay) associated with UM or CM	- Any outcome not listed in the inclusion criteria
Study design	- All empirical studies reporting on costs and resource utilization for the specified patient population 1999-onwards	- Non-human studies - PK and proof of concept studies - Studies not reporting empirical data - Studies reporting expert opinion only - Reviews/Systematic reviews - Studies indexed as case reports, cases series, editorials, and letters - Publications in non-English language

Abbreviations: CM, Choroidal melanoma; UM, uveal melanoma

Table 118. HRQoL and utilities

PICOS element	Inclusion criteria	Exclusion criteria
Population	Adult patients, aged ≥ 18 years, with advanced or metastatic UM/choroidal melanoma	Pediatric patients
Intervention /Comparator	N/A	N/A
Outcome	- Utility estimates (EQ-5D, SF-6D) - HRQoL (other relevant instruments e.g. SF-36, disease specific instruments; FACT-G, FACT-M, EORTC-QLQC30, MFI))	- Any outcome not listed in the inclusion criteria
Study design	- Observational studies reporting utilities/HRQoL data 1999 onwards - RCTs reporting HRQoL data 1999 onwards	- Non-human studies - PK and proof of concept studies - Studies not reporting empirical data - Studies reporting expert opinion only - Reviews/Systematic reviews - Studies indexed as case reports, cases series, editorials, and letters - Publications in non-English language

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, Euroqol 5 dimensions; FACT, Functional Assessment of Cancer Therapy; HRQoL, Health-Related Quality of Life; MFI, multi-factorial fatigue inventory; PK, pharmacokinetics; QALY, quality-adjusted life; UM, uveal melanoma

20.3.2 Search strings

The search strings used to identify relevant health economic studies are shown below. Initial searches were performed on 11th May 2020, with a subsequent updated search on 10th September 2021. For the CRD Databases an update search was not required as no new records were added to CRD Databases since date of original searches.

Cochrane Library

Table 119. Cochrane Library search strategy

Search number, #	Search Algorithm	Search Yield (updated, September 2021)
1	MeSH descriptor: [Uveal Neoplasms] explode all trees	119
2	MeSH descriptor: [Choroid Neoplasms] explode all trees	50
3	#1 or #2	119
4	MeSH descriptor: [Melanoma] explode all trees	1887
5	#3 and #4	113
6	((uvea* or choroid* or ciliochoroid* or "ciliary body" or iridociliary or iris or ocular or intraocular or peripapillary or parapapillary) near/2 melanoma*):ti	247
7	aderhautmelanom*:ti	0
8	#6 or #7	247
9	#5 or #8 in Cochrane Reviews	0

CRD Database

Table 120. CRD Database search strategy

Search number, #	Search Algorithm	Search Yield (initial, May 2020)
1	MeSH DESCRIPTOR Uveal Neoplasms EXPLODE ALL TREES	7
2	MeSH DESCRIPTOR Choroid Neoplasms EXPLODE ALL TREES	1
3	#1 OR #2	7
4	MeSH DESCRIPTOR Melanoma EXPLODE ALL TREES	221
5	#3 AND #4	6
6	(((uvea* or choroid* or ciliochoroid* or "ciliary body" or iridociliary or iris or ocular or intraocular or peripapillary or parapapillary) AND melanoma*)):TI	6
7	(aderhautmelanom*):TI	0
8	#6 OR #7	6
9	#3 OR #8	8

Epistemonikos

Search number, #	Search Algorithm	Search Yield (updated)
1	title:(title:((((uveal OR choroid* OR ciliochoroid* OR "ciliary body" OR iridociliary OR iris OR ocular OR intraocular OR peripapillary OR parapapillary) AND melanoma*) OR aderhautmelanom*)))	57

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Table 121. Epistemonikos search strategy

MEDLINE (via OvidSP interface)

Table 122. MEDLINE search strategy

Search number, #	Search Algorithm	Search Yield (updated)
1	exp Uveal Neoplasms/	10160
2	exp Choroid Neoplasms/	5459
3	or/1-2	10160
4	exp Melanoma/	100264
5	3 and 4	7253
6	(((uvea$ or choroid$ or ciliochoroid$ or "ciliary body" or iridociliary or iris or ocular or intraocular or peripapillary or parapapillary) adj2 melanoma$) or aderhautmelanom$).ti,ab.	8164
7	5 or 6	9866
8	economics/	27365
9	exp "costs and cost analysis"/	248981
10	economics, dental/	1919
11	exp "economics, hospital"/	25293
12	economics, medical/	9152
13	economics, nursing/	4006
14	economics, pharmaceutical/	3016
15	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	887199
16	(expenditure$ not energy).ti,ab.	32557
17	(value adj1 money).ti,ab.	36
18	budget$.ti,ab.	31676
19	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1043999
20	((energy or oxygen) adj cost).ti,ab.	4363
21	(metabolic adj cost).ti,ab.	1538
22	((energy or oxygen) adj expenditure).ti,ab.	26681
23	20 or 21 or 22	31567
24	19 not 23	1036739
25	exp models, economic/ or ((economic$ or financ$ or cost$ or budget$ or expen$ or price or pricing or markov$) and model$).ti,ab.	216841
26	24 or 25	1083874
27	7 and 26	71
28	exp Health Care Costs/	68775
29	exp Employment/	92298
30	exp Work/	67052
31	Efficiency/	14348
32	Absenteeism/	9428

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Search number, #	Search Algorithm	Search Yield (updated)
33	"Cost of Illness"/	29464
34	"Length of Stay"/	95489
35	((employment or employed or employee$ or unemployment or unemployed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab.	2511
36	(productivity adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab.	3423
37	((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab.	11752
38	llsi.ti,ab.	16
39	(cost$ adj2 (illness or disease$ or sickness$ or care or healthcare)).ti,ab.	48557
40	(burden$ adj2 (illness or disease$ or sickness$ or care or healthcare)).ti,ab.	36604
41	((social or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$) adj3 (burden$ or consequenc$ or impact$ or problem$ or productivity or sickness or impairment$)).ti,ab.	108217
42	((allowance or status or long-term or pension$ or benefit$) adj2 disab$).ti,ab.	14281
43	((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab.	1971
44	budget$ impact$.ti,ab.	1798
45	budget$ implicat$.ti,ab.	72
46	resource$ use$.ti,ab.	11383
47	resource$ utili$.ti,ab.	12278
48	resource$ usage.ti,ab.	477
49	(length adj2 stay$).ti,ab.	65831
50	(hospital$ adj2 stay$).ti,ab.	99010
51	(duration adj2 stay$).ti,ab.	4012
52	extended stay$.ti,ab.	219
53	prolonged stay$.ti,ab.	1014
54	((hospitali?ation$ or hospitali?ed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab.	8677
55	economic consequenc$.ti,ab.	4052
56	or/28-55	634377
57	7 and 56	26
58	quality adjusted life year/	13717
59	(quality adjusted or adjusted life year$).ti,ab,kw.	19073
60	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kw.	12240
61	(illness state$1 or health state$1).ti,ab,kw.	7206

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Search number, #	Search Algorithm	Search Yield (updated)
62	(hui or hui1 or hui2 or hui3).ti,ab,kw.	1707
63	(multiattribute$ or multi attribute$).ti,ab,kw.	1023
64	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw.	16838
65	utilities.ti,ab,kw.	7946
66	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw.	13679
67	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw.	4738
68	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw.	23917
69	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	2058
70	"quality of life"/ and (health adj3 status).ti,ab,kw.	9887
71	(quality of life or qol).ti,ab,kw. and "cost-benefit analysis"/	14353
72	or/28-41	89470
73	7 and 42	15
74	quality-adjusted life years/ or quality of life/	231776
75	(sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.	27541
76	(sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.	2319
77	(sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.	6525
78	(sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab.	909
79	(sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.	425
80	(sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab.	658
81	(short form$ or shortform$).ti,ab.	37503
82	("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or EORTC-QLQ).ti,ab.	4550
83	"quality of life".ti,ab.	311567
84	(Quality adjusted life or Quality-adjusted-life).ti,ab.	14542
85	(euroqol or euro qol or euroqual or euro qual or eq5d or eq 5d or eq-5d or eq5-d or eq-sdq or eqsdq).ti,ab.	13141
86	(qol or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab.	63832
87	(hye or hyes).ti,ab.	75

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Search number, #	Search Algorithm	Search Yield (updated)
88	health$ year$ equivalent$.ti,ab.	40
89	(hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab.	1703
90	(quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab.	1001
91	(Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab.	4730
92	(QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab.	16729
93	(timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab.	9042
94	(15D or 15-D or "15 dimension").ti,ab.	5627
95	(HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab.	449
96	illness state$.ti,ab.	141
97	(utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$ or evaluat$ or scale$ or instrument$ or weight$ or information or data or unit or units or mean or cost$ or expenditure$ or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab.	39743
98	(utilities or disutili$).ti,ab.	8261
99	(Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab.	1030
100	((patient$ adj2 (attitude$ or compliance or "non compliance" or adheren$ or "non adherence" or participation or "non participation" or preference$ or satisf$ or dissatisf$ or toleran$ or intoleran$ or "reported outcome" or "reported outcomes")) or PROM or PROMS).ti,ab.	140648
101	or/74-100	573621
102	7 and 101	110
103	73 or 102	111
104	27 or 57 or 103	196
105	editorial/ or letter/ or case report/ or (editorial or letter or case reports).pt.	3719269
106	104 not 105	178

EMBASE (via OvidSP interface)

Table 123. EMBASE search strategy

Search number, #	Search Algorithm	Search Yield (updated)
1	exp uvea tumor/ or exp choroid tumor/	7841

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Search number, #	Search Algorithm	Search Yield (updated)
2	exp melanoma/	171852
3	1 and 2	5349
4	(((uvea$ or choroid$ or ciliochoroid$ or "ciliary body" or iridociliary or iris or ocular or intraocular or peripapillary or parapapillary) adj2 melanoma$) or aderhautmelanom$).ti,ab.	10689
5	3 or 4	12039
6	health-economics/	33644
7	exp economic-evaluation/	323219
8	exp health-care-cost/	307589
9	exp pharmacoeconomics/	212614
10	or/6-9	683399
11	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	1184350
12	(expenditure$ not energy).ti,ab.	44182
13	(value adj2 money).ti,ab.	2636
14	budget$.ti,ab.	41740
15	or/11-14	1223697
16	10 or 15	1562807
17	(metabolic adj cost).ti,ab.	1641
18	((energy or oxygen) adj cost).ti,ab.	4609
19	((energy or oxygen) adj expenditure).ti,ab.	33785
20	or/17-19	38892
21	16 not 20	1554801
22	economic model/ or ((economic$ or financ$ or cost$ or budget$ or expen$ or price or pricing or markov$) and model$).ti,ab.	279613
23	21 or 22	1611078
24	5 and 23	171
25	exp "health care cost"/	307589
26	exp employment/	105512
27	exp work/	382112
28	"cost of illness"/	20118
29	"length of stay"/	215935
30	((employment or employed or employee$ or unemployment or unemployed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab.	3159

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Search number, #	Search Algorithm	Search Yield (updated)
31	(productivity adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab.	4843
32	((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab.	16186
33	llsi.ti,ab.	18
34	(cost$ adj2 (illness or disease$ or sickness$ or care or healthcare)).ti,ab.	74743
35	(burden$ adj2 (illness or disease$ or sickness$ or care or healthcare)).ti,ab.	56409
36	((social or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$) adj3 (burden$ or consequenc$ or impact$ or problem$ or productivity or sickness or impairment$)).ti,ab.	144137
37	((allowance or status or long-term or pension$ or benefit$) adj2 disab$).ti,ab.	23013
38	((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab.	2878
39	budget$ impact$.ti,ab.	4955
40	budget$ implicat$.ti,ab.	103
41	resource$ use$.ti,ab.	17284
42	resource$ utili$.ti,ab.	22881
43	resource$ usage.ti,ab.	693
44	(length adj2 stay$).ti,ab.	123202
45	(hospital$ adj2 stay$).ti,ab.	163664
46	(duration adj2 stay$).ti,ab.	6267
47	extended stay$.ti,ab.	336
48	prolonged stay$.ti,ab.	1618
49	((hospitali?ation$ or hospitali?ed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab.	15637
50	economic consequenc$.ti,ab.	5252
51	or/25-50	1314507
52	5 and 51	100
53	quality adjusted life year/	29729
54	(quality adjusted or adjusted life year$).ti,ab,kw.	28260
55	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kw.	22924
56	(illness state$1 or health state$1).ti,ab,kw.	12606

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Search number, #	Search Algorithm	Search Yield (updated)
57	(hui or hui1 or hui2 or hui3).ti,ab,kw.	2633
58	(multiattribute$ or multi attribute$).ti,ab,kw.	1290
59	59 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw.	27249
60	utilities.ti,ab,kw.	13036
61	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw.	24987
62	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw.	7295
63	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw.	41154
64	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	3046
65	"quality of life"/ and (health adj3 status).ti,ab,kw.	17960
66	(quality of life or qol).ti,ab,kw. and "cost-benefit analysis"/	6015
67	or/53-66	146854
68	5 and 67	22
69	quality adjusted life year/ or quality of life index/	32587
70	Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/	40504
71	"International Classification of Functioning, Disability and Health"/ or "Ferrans and Powers Quality of Life Index"/	3167
72	(sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.	44715
73	(sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.	2601

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Search number, #	Search Algorithm	Search Yield (updated)
74	(sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.	10487
75	(sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab.	1656
76	(sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.	447
77	(sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab.	1061
78	(short form$ or shortform$).ti,ab.	51193
79	("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or EORTC-QLQ).ti,ab.	9389
80	"quality of life".ti,ab.	492601
81	(Quality adjusted life or Quality-adjusted-life).ti,ab.	22159
82	(euroqol or euro qol or euroqual or euro qual or eq5d or eq 5d or eq-5d or eq5-d or eq-sdq or eqsdq).ti,ab.	24206
83	(qol or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab.	114828
84	(hye or hyes).ti,ab.	146
85	health$ year$ equivalent$.ti,ab.	41
86	(hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab.	2611
87	(quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab.	1304
88	(Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab.	5640
89	(QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab.	28408
90	(timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab.	13697
91	15d.ti,ab.	2721

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92	(HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab.	679
93	illness state$.ti,ab.	213
94	(utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$ or evaluat$ or scale$ or instrument$ or weight$ or information or data or unit or units or mean or cost$ or expenditure$ or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab.	61380
95	(utilities or disutili$).ti,ab.	13481
96	(Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab.	1377
97	((patient$ adj2 (attitude$ or compliance or "non compliance" or adheren$ or "non adherence" or participation or "non participation" or preference$ or satisf$ or dissatisf$ or toleran$ or intoleran$ or "reported outcome" or "reported outcomes")) or PROM or PROMS).ti,ab.	222598
98	or/69-97	809714
99	5 and 98	169
100	68 or 99	170
101	24 or 52 or 100	380
102	editorial/ or letter/ or case report/ or (editorial or letter).pt.	4354330
103	101 not 102	342
104	(conference or "conference paper" or "conference proceeding" or "conference proceeding article" or "conference proceeding conference paper" or "conference proceeding editorial" or "conference proceeding note" or "conference proceeding review" or "journal conference abstract" or "journal conference paper" or "journal conference review").pt.	4950487
105	103 not 104	231
106	103 and 104	111
107	limit 106 to yr="2017 - 2021"	42
108	105 or 107	273

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20.4 Systematic selection of studies

In order to be selected, the publication had to fulfil all the inclusion criteria and none of the exclusion criteria in Table 116, Table 117, and Table 118. After de-duplication, every record retrieved in the search was independently reviewed by two reviewers and marked as include or exclude after review of the study title and abstract (where the latter was available). This is in line with NICE requirements for review of economic model inputs, which are accepted by HTA agencies across Europe. Where records appeared to satisfy the criteria for inclusion within this SLR based on the title and abstract, the full texts were retrieved for review. Each of these records were re-evaluated in a full-text review by two independent reviewers. Any indecisions were resolved through discussion until a consensus was reached. As well as pre-specified specific hand-searching, general hand-searching was also performed to identify further studies of interest; this included searching of review articles, the reference lists of included full text publications and free text searching. Texts identified via hand-searching were subjected to the same full text review process.

20.4.1 Results of the literature review

A PRISMA flow diagram of the studies identified in the economic literature review (CE, HRQoL, and cost and healthcare resource use studies) is shown in Figure 49. A total of six HRQoL studies were included for analysis and the list of the studies is presented in Table 125. None of the identified HRQoL studies involved patients receiving tebentafusp or reported generic HRQoL utility values. Therefore, the studies identified were assessed not to be relevant to the decision problem or the de novo model. The utility tools used in these studies are reported in Table 125. A total of four healthcare resource use and cost studies were included for analysis and the list of the studies is presented in Table 125. Three of the identified studies reported on costs of an in-hospital procedure not relevant to the decision problem and were not set in a European country. The fourth study was set in the UK and investigated the overall costs in patients with a diagnosis of UM. However, this study was an abstract; it omitted several significant costs associated with management of UM; and did not report disaggregated cost data. Because of these limitations, none of the studies were considered to be suitable to inform the decision problem or the *de novo* model. An overview of the excluded articles based on full-text review is presented in Table 124.

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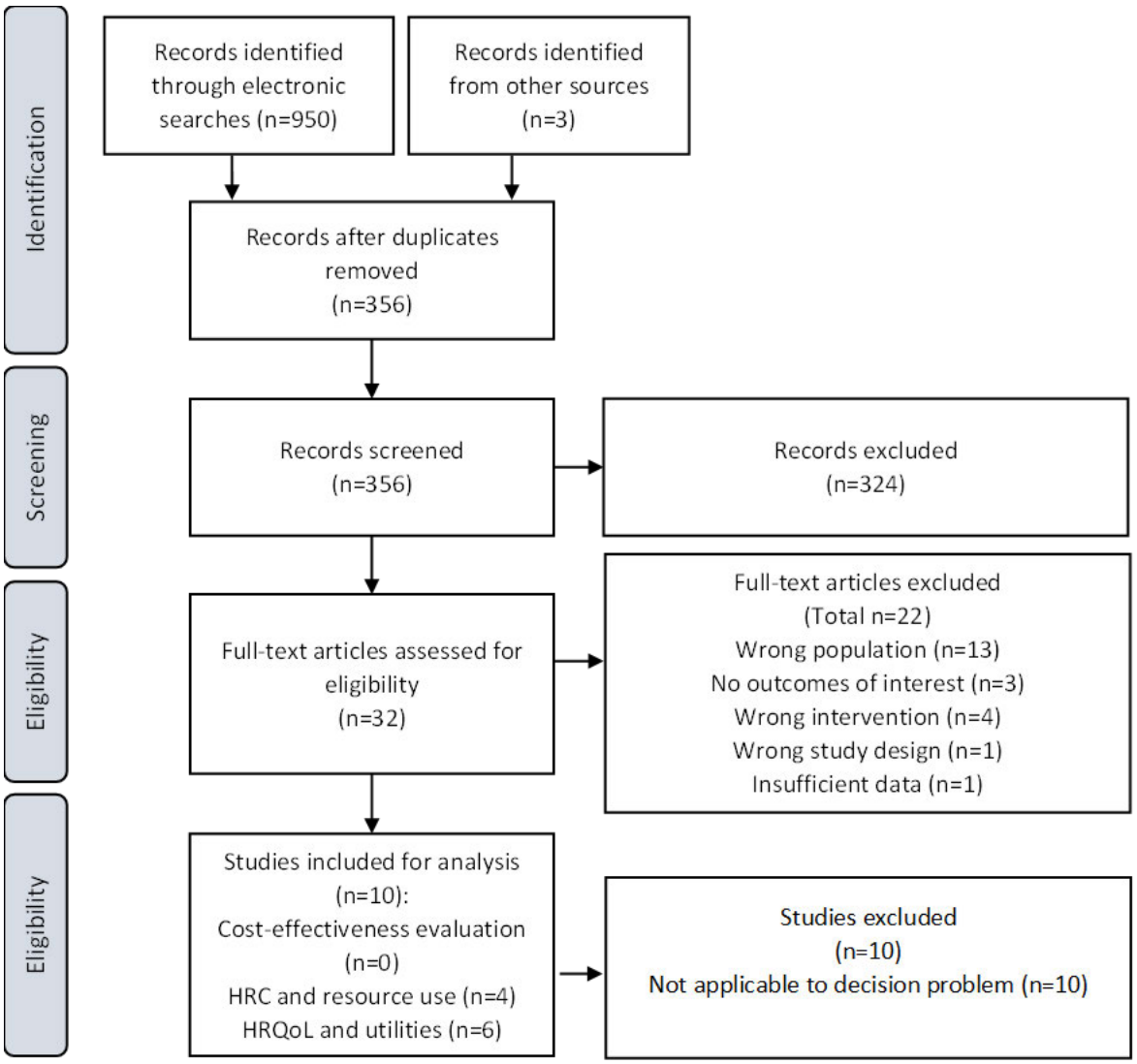

Figure 49. PRISMA Flow Chart (updated search, September 2021).

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Table 124. List of articles excluded based on a full-text review.

Author	Year	Title	Reason for exclusion
Adams	2017	Mapping the treatment pathway for metastatic uveal melanoma (mUM) patients in England: A qualitative pilot study	No outcome data of interest
Barsam	2019	Follow the nevus: the cost-utility of monitoring for growth of choroidal nevi	Wrong population
Barker	2020	Quality of Life Concerns in Patients with Uveal Melanoma after Initial Diagnosis	Wrong population
Blanco-RiveraMa	2008	Quality of life in patients with choroidal melanoma. [Spanish]	Wrong intervention
Brown	2021	Prediction of all-cause mortality from 24 month trajectories in patient-reported psychological, clinical and quality of life outcomes in uveal melanoma patients	Wrong population
Brown	2021	Is accurate routine cancer prognostication psychologically harmful? 5-year outcomes of life expectancy prognostication in uveal melanoma survivors	Wrong population
Bowers	2012	Feasibility study of two-stage hepatectomy for bilobar liver metastases	Wrong population
Chmielowska	2013	Translation and validation of the Polish version of the EORTC QLQ-OPT30 module for the assessment of health-related quality of life in patients with uveal melanoma	Wrong population

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Eleuteri	2021	Cost-utility analysis of a decade of liver screening for metastases using the Liverpool Uveal Melanoma Prognosticator Online (LUMPO)	Wrong intervention
Gollrad	2021	Quality of life and treatment-related burden during ocular proton therapy: a prospective trial of 131 patients with uveal melanoma	Wrong population
Klingenstein	2020	Screening for Predictive Parameters Requiring Psycho-Oncological Intervention via the National Comprehensive Cancer Network Distress Thermometer in the Follow-Up of Uveal Melanoma Patients	Wrong outcomes
Joh	2021	Outpatient ocular brachytherapy: The USC Experience	Wrong population
Lieb	2020	Psychosocial impact of prognostic genetic testing in uveal melanoma patients: a controlled prospective clinical observational study	Wrong population
Meijer	2019	Percutaneous hepatic perfusion with melphalan in patients with unresectable liver metastases from ocular melanoma using the Delcath System's second-generation hemofiltration system: A prospective phase II study	Insufficient data
Melia	2006	Quality of life after iodine 125 brachytherapy vs enucleation for choroidal melanoma - 5-Year results from the collaborative ocular melanoma study: COMS QOLS report no. 3	Wrong intervention

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Middlebrook	2016	Gene Expression Profile Testing in Uveal Melanoma: An Economic Model to Evaluate Resource use in the United States	Wrong population
Mouriaux	2012	Liver function testing is not helpful for early diagnosis of metastatic uveal melanoma	Wrong population
Nguyen	2020	External beam radiotherapy vs plaque brachytherapy in treatment of uveal melanoma: A cost analysis	Wrong intervention
Rostas	2017	Health-related quality of life during trans-arterial chemoembolization with drug-eluting beads loaded with doxorubicin (DEBDOX) for unresectable hepatic metastases from ocular melanoma	Wrong population
Walpole	2021	Microsimulation Model for Evaluating the Cost-Effectiveness of Surveillance in BAP1 Pathogenic Variant Carriers	Wrong intervention
Wright	2017	Liver Resection After Selective Internal Radiation Therapy with Yttrium-90 is Safe and Feasible: A Bi-institutional Analysis	Wrong population
Young	2021	CADTH Health Technology Review Yttrium-90 Microspheres for Intermediate or Advanced-Stage Hepatocellular Carcinoma	Wrong study design

Table 125. List of articles excluded after analysis.

Author, Year of publication	Title	
HRC and resource use		
Cheng, 2017	Quantifying standard of care (SOC) hospital-related resource utilisation for metastatic uveal melanoma (MUM) patients in NHS England (NHSE) using the hospital episodes statistics (HES) dataset	
Alexander, 2003	Hyperthermic isolated hepatic perfusion using melphalan for patients with ocular melanoma metastatic to liver	
De Leede, 2016	Isolated (hypoxic) hepatic perfusion with high-dose chemotherapy in patients with unresectable liver metastases of uveal melanoma: results from two experienced centres	
Van Etten, 2009	Isolated hypoxic hepatic perfusion with melphalan in patients with irresectable ocular melanoma metastases	
HRQoL and utilities		**Use of HRQoL/utilities tool**
Nshimiyimana, 2018	Pilot study of anxiety, depression, and quality of life in patients with the diagnosis of metastatic uveal melanoma	HADS, WHOQOL-BREF
Vogl, 2017	Percutaneous Isolated Hepatic Perfusion as a Treatment for Isolated Hepatic Metastases of Uveal Melanoma: Patient Outcome and Safety in a Multi-centre Study	Derived from short versions of the validated checklist EORTC QLQ-C30 v.3.0
Atkinson, 2017	Relationship between physician-adjudicated adverse events and patient-reported health-related quality of life in a phase II clinical trial (NCT01143402) of patients with metastatic uveal melanoma	FACT-M
Carvajal, 2018	Selumetinib in Combination With Dacarbazine in Patients With Metastatic Uveal Melanoma: A Phase III, Multicentre, Randomized Trial (SUMIT)	EORTC-QLQC30 v.3.0
Fiorentini, 2009	Intra-arterial hepatic chemoembolization (TACE) of liver metastases from ocular melanoma with slow-release irinotecan-eluting beads. Early results of a phase II	ESAS
Mouriaux, 2016	Sorafenib in metastatic uveal melanoma: efficacy, toxicity and health-related quality of life in a multicentre phase II study	FACT-G, MFI,

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21. Appendix I: Mapping of HRQoL data

HRQoL was assessed in the IMCgp100-202 study using EQ-5D-5L. The utilities applied in the model was adjusted to the Danish value set recommended by the DMC to derive Danish specific utilities.

21.1 Utility from IMCgp100-202

There were 378 patients involved in the clinical trial, 252 in the tebentafusp arm and 126 in the IC arm. At baseline, 272 (72%) patients had completed the EQ-5D questionnaire, of which there were 194 (77%) patients in the tebentafusp arm and 78 (62%) in the IC arm. There were 319 patients who have completed the EQ-5D questionnaire at any time point in the trial, of whom two who were not treated.

The numbers of missing observations were determined at each assessment time point up to the end of treatment, by comparing the treatment duration for each patient with the schedule of assessment of the EQ-5D. To assess the number of missing observations during the survival follow-up period, the duration of OS for each patient was compared with the schedule of assessment of the EQ-5D during the survival follow-up period (Table 126). The data is presented in Table 47. It was observed that during the treatment period, the number of responses to the EQ-5D questionnaire was relatively good, with only 15% of missing observations at baseline. This varied between 20% and 30% during the treatment phase, although it diminished by 46% at the end of treatment. However, this represented a high proportion of missing data during the survival follow-up period, of between 60% and 70%

Table 126. PRO data collection schedule IMCgp100-202 clinical trial.

	Screening Phase	Treatment Phase													Follow-up Phase		
Procedure	**Screening**	**Cycle 1**						**Cycle 2**			**Cycle 3**			**Later Cycles**	**EOT**	**90-day Safety Follow-up**	**Disease Progression Follow-up**	**Survival Follow-up**
Day of Cycle	-21 to -1	1	2	8	9	15	16	1	8	15	1	8	15	1–21				
Patient-reported outcomes		PRO assessments (EQ-5D,5L questionnaire and EORTC QLQ-C30) will be administered to all patients at C1D1, on D1 of every other cycle to C5D1, every fourth cycle thereafter, beginning with C9D1, and EOT															Both EQ-5D,5L and EORTC QLQ- C30 every 12 weeks	EQ-5D,5L every 12 weeks

Abbreviations: C, cycle; D, day; EORTC, European Organization for the Research and Treatment of Cancer; EOT, end of treatment

Table 127. Pattern of missingness of EQ-5D data, compliance rate.

	N obs.	N expected	N missing	% observation missing
Baseline	272	319	47	15%
Cycle 3 day 1	218	290	72	25%

Cycle 5 day 1	162	219	57	26%
Cycle 9 day 1	99	126	27	21%
Cycle 13 day 1	63	80	17	21%
Cycle 17 day 1	33	48	15	31%
Cycle 21 day 1	19	28	9	32%
Cycle 25 day 1	13	19	6	32%
Cycle 29 day 1	16	17	1	6%
End of treatment	170	317	147	46%
Survival follow-up day 90	56	130	94	72%
Survival follow-up day 180	35	92	57	62%
Survival follow-up day 270	25	70	45	64%
Survival follow-up day 360	19	49	30	61%

Abbreviations: N, number; Obs., Observation

Based on the pattern of missing data, data imputation was conducted for baseline and the treatment phase, but not the survival follow-up period.
Mean imputation was used at baseline. Missing covariates and EQ-5D data were imputed with the mean value at baseline for continuous variables, or modal value for the categorical variables.
Multiple imputation was used for end of treatment given the high number of missing values. Multiple imputation was done using the 'mi impute' command in Stata, imputing missing EQ-5D utilities at end of treatment using chained equations with truncated regressions [63]. Forty-seven imputations were run, as this equalled the percentage of patients with missing EQ-5D records at the end of treatment. Multiple imputation was conducted using the following variables as covariates:

- Socio-demographic variables: age, sex, race, ethnicity, region, country (which were assumed to stay the same over the follow-up period)
- Clinical variables: ECOG score at baseline, stage at initial diagnosis, presence of metastasis at initial diagnosis, LDH level at baseline, size of largest metastatic lesion at baseline, size of largest liver metastatic lesion at baseline (which are assumed to stay the same over the follow-up period)
- Other variables: treatment assignment, OS duration, time between baseline and the assessment timepoint, baseline score EQ-5D utility

For intermediate time points, linear interpolation was used as there was limited variation of the EQ-5D utility over time.

A generalised estimating equation (GEE) model was used to deal with the repeated measures of the same individuals, as it gives population average effects, which was appropriate for the purpose of a CE analysis.
A range of model specifications were tested, including the following covariates:

- Age
- Sex
- An indicator for whether the EQ-5D assessment was done before (i.e. on treatment) or, on or after treatment discontinuation (i.e. off treatment)
- Treatment arm

Based on the IMCgp100-202 study protocol (Immunocore 2018), patients could stay on treatment beyond disease progression if they met the criteria to continue treatment beyond confirmed PD based on RECIST v1.1. Hence, TTD was deemed a better proxy for modelling utility data than disease progression.

The goodness of fit was modelled using MAE and RMSE for which a value closer to zero suggested a better fit to the data. All models provided similar results with a MAE between 0.103-0.089 and a RMSE of 0.147-0.146. The model with the best fit included all covariates. The on/off treatment covariate was statistically significant at 1% level, and the age and sex covariates were statistically significant at the 5% level.

21.2 EQ-5D-5L Danish preference weights

EQ-5D norms by age groups are used in the model to apply an age adjustment factor to account for declining quality of life with age. The Danish EQ-5D norms for Denmark [40] are presented in Table 128.

Table 128. EQ-5D Danish preference weights.

Age group	Utility value
18-29	0.871
30-39	0.848
40-49	0.834
50-69	0.818
70-79	0.813
80+	0.721

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22. Appendix J: Probabilistic and deterministic sensitivity analyses

Table 129. Overview of probabilistic and deterministic sensitivity analysis

Variable	Value	PSA distribution	DSA parameter
General parameters			
Time horizon	Lifetime (35 years)	Fixed	Fixed
Discount rate – utilities	3.5%	Fixed	Fixed
Discount rate – costs	3.5%	Fixed	Fixed
Population parameters			
Age	65	Fixed	+/-15%
% female	50.0	Fixed	Fixed
Body weight	78.86 kg	Fixed	Fixed
Body surface area	1.90 m^2	Fixed	Fixed
Survival models			
OS – Tebentafusp	Log-normal	Fixed	Varied in a scenario analysis
OS – Control arm	Log-normal	Fixed	Varied in a scenario analysis
PFS – Tebentafusp	Generalized Gamma	Fixed	Fixed
PFS – Control arm	Generalized Gamma	Fixed	Fixed
Adverse event rates - tebentafusp			
Rash	9.4%	Fixed	Fixed
Rash maculo-papular	8.6%	Fixed	Fixed
Pruritus	4.5%	Fixed	Fixed
AST increased	5.3%	Fixed	Fixed
Lipase increased	4.1%	Fixed	Fixed
ALT increased	3.3%	Fixed	Fixed
Hypertension	8.6%	Fixed	Fixed
Hypotension	3.3%	Fixed	Fixed
Fatigue	5.3%	Fixed	Fixed
Pyrexia	3.7%	Fixed	Fixed
Hypophosphataemia	4.1%	Fixed	Fixed
Hyperbilirubinaemia	3.3%	Fixed	Fixed
Liver toxicity/liver-related events	0%	Fixed	Fixed
Hepatitis	0%	Fixed	Fixed
Diarrhoea (grade 3+)	1.2%	Fixed	Fixed
Guillain-Barré syndrome	0%	Fixed	Fixed
Hypothyroidism	0%	Fixed	Fixed
Thyroiditis	0%	Fixed	Fixed
Adverse event rates – control arm			

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Variable	Value	PSA distribution	DSA parameter
Rash	9.6%	Fixed	Fixed
Rash maculo-papular	0%	Fixed	Fixed
Pruritus	0%	Fixed	Fixed
AST increased	0%	Fixed	Fixed
Lipase increased	0%	Fixed	Fixed
ALT increased	0%	Fixed	Fixed
Hypertension	0%	Fixed	Fixed
Hypotension	0%	Fixed	Fixed
Fatigue	9.6%	Fixed	Fixed
Pyrexia	1.9%	Fixed	Fixed
Hypophosphataemia	0%	Fixed	Fixed
Hyperbilirubinaemia	0%	Fixed	Fixed
Liver toxicity/liver-related events	26.9%	Fixed	Fixed
Hepatitis	3.8%	Fixed	Fixed
Diarrhoea (grade 3+)	11.5%	Fixed	Fixed
Guillain-Barré syndrome	3.8%	Fixed	Fixed
Hypothyroidism	15.4%	Fixed	Fixed
Thyroiditis	9.6%	Fixed	Fixed
Health states utilities			
≥360 days	0.82	Beta	+/-10%
270-360 days	0.71	Beta	+/-10%
180-270 days	0.66	Beta	+/-10%
90-180 days	0.66	Beta	+/-10%
30-90 days	0.57	Beta	+/-10%
<30 days	0.33	Beta	+/-10%
On-treatment tebentafusp	0.888	Beta	+/-10%
Off-treatment tebentafusp	0.814	Beta	+/-10%
On-treatment ipi/nivo	0.876	Beta	+/-10%
Off-treatment ipi/nivo	0.801	Beta	+/-10%
AE disutilities			
Tebentafusp	-0.0236	Beta	+/-10%
Ipi/nivo	-0.0337	Beta	+/-10%
Drug unit costs (PPP)			
Tebentafusp 100 mcg/0.5 ml vial (200 mcg per 1ml)	[redacted]	Fixed	Fixed

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Variable	Value	PSA distribution	DSA parameter
Ipilimumab 50 mg/10 ml vial (5 mcg per 1 ml)	DKK 25,653.53	Fixed	Fixed
Nivolumab 240 mg/24 ml vial (24 mg per 1 ml)	DKK 22,003.74	Fixed	Fixed
Nivolumab 100 mg/10 ml vial (10 mg per 1 ml)	DKK 9,168.23	Fixed	Fixed
Nivolumab 40 mg/4 ml (10 mg per 1 ml)	DKK 3,690.69	Fixed	Fixed
Treatment administration-related costs			
Administration of immunotherapy	DKK 1,095	Gamma	+/-25%
Liver and thyroid function test	DKK 357	Gamma	+/-25%
Overnight hospital stay	DKK 2,185	Gamma	+/-25%
HLA-A*02:01 screen	DKK 5,645	Gamma	+/-25%
Human albumin 20%	DKK 448.8	Fixed	Fixed
% of patients expected to test positive	47%	Beta	+/-25%
Health state costs			
Pre-progression (per cycle)	DKK 1,674.87	Gamma	+/-25%
At progression (one-off)	DKK 3,600.05	Gamma	+/-25%
Post-progression (one-off cost per 4 months)	DKK 10,705.20	Gamma	+/-25%
End-of-life care (one-off cost) (one year)	DKK 71,612.00	Gamma	+/-25%
AE costs			
Rash/ Rash maculo-papular/ Pruritus (inpatient)	DKK 19,518	Gamma	+/-25%
Rash/ Rash maculo-papular/ Pruritus (outpatient)	DKK 2,041	Gamma	+/-25%
AST/ Lipase/ ALT increased (inpatient)	DKK 0	Fixed	Fixed
AST/ Lipase/ ALT increased (outpatient)	DKK 2,910	Gamma	+/-25%
Hypertension/ Hypotension (inpatient)	DKK 0	Fixed	Fixed
Hypertension (outpatient)	DKK 2,910	Gamma	+/-25%

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Variable	Value	PSA distribution	DSA parameter
Hypotension (outpatient)	DKK 1,901	Gamma	+/-25%
Fatigue (inpatient)/(outpatient)	DKK 4,460	Gamma	+/-25%
Pyrexia (inpatient)	DKK 30,549	Gamma	+/-25%
Pyrexia (outpatient)	DKK 1,887	Gamma	+/-25%
Hypophosphataemia/ Hyperbilirubinaemia (inpatient)	DKK 0	Fixed	Fixed
Hypophosphataemia (outpatient)	DKK 1,954	Gamma	+/-25%
Hyperbilirubinaemia (outpatient)	DKK 2,910	Gamma	+/-25%
Liver toxicity/liver-related events/ Hepatitis (inpatient)	DKK 34,753	Gamma	+/-25%
Liver toxicity/liver-related events/ Hepatitis (outpatient)	DKK 2,910	Gamma	+/-25%
Diarrhoea (grade 3+) (inpatient)/(outpatient)	DKK 6,756	Gamma	+/-25%
Guillain-Barré syndrome (inpatient)	DKK 67,383	Gamma	+/-25%
Guillain-Barré syndrome (outpatient)	DKK 0	Fixed	Fixed
Hypothyrodism (inpatient)/(outpatient)	DKK 1,845	Gamma	+/-25%
Thyroiditis (inpatient)	DKK 1,845	Gamma	+/-25%
Thyroiditis (outpatient)	DKK 1,845	Gamma	+/-25%
Patient AE cost			
Rash/ Rash maculo-papular/ Pruritus (inpatient)	DKK 17,641.3	Gamma	Fixed
Rash/ Rash maculo-papular/ Pruritus (outpatient)	DKK 283.3	Gamma	Fixed
AST increased (inpatient)	DKK 0	Gamma	Fixed
Lipase increased (inpatient)	DKK 0	Gamma	Fixed
ALT increased (inpatient)	DKK 0	Gamma	Fixed
AST/ Lipase/ ALT increased (outpatient)	DKK 283.3	Gamma	Fixed

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Variable	Value	PSA distribution	DSA parameter
Hypertension (inpatient)	DKK 0	Gamma	Fixed
Hypotension (inpatient)	DKK 0	Gamma	Fixed
Hypertension/ Hypotension (outpatient)	DKK 283.3	Gamma	Fixed
Fatigue (inpatient)	DKK 4,554.6	Gamma	Fixed
Pyrexia (inpatient)	DKK 26,365.7	Gamma	Fixed
Hypophosphataemia (inpatient)	DKK 0	Gamma	Fixed
Hyperbilirubinaemia (inpatient)	DKK 0	Gamma	Fixed
Fatigue/ Pyrexia/ Hypophosphataemia/ Hyperbilirubinaemia/ Liver toxicity/liver-related events/ Hepatitis/ Diarrhoea (grade 3+)/ Guillain-Barré syndrome/ Hypothyroidism/ Thyroiditis (outpatient)	DKK 283.3	Gamma	Fixed
Liver toxicity/liver-related events/ Hepatitis (inpatient)	DKK 65,625.7	Gamma	Fixed
Diarrhoea (grade 3+) (inpatient)	DKK 4,554.6	Gamma	Fixed
Guillain-Barré syndrome (inpatient)	DKK 96,161.3	Gamma	Fixed
Hypothyroidism/ Thyroiditis (inpatient)	DKK 4,554.6	Gamma	Fixed
Patient costs			
Pre-progression (per cycle)	DKK 393.9	Gamma	+/-25%
At progression (one-off)	DKK 1,485.13	Gamma	+/-25%
Post-progression (one-off cost per 4 months)	DKK 10,741.09	Gamma	+/-25%
Transportation costs	DKK 101.54	Gamma	+/-25%
Adverse events % management in inpatient and outpatient settings			
Rash/ Rash maculo-papular/ Pruritus (inpatient)	5%	Fixed	Fixed

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Variable	Value	PSA distribution	DSA parameter
Rash/ Rash maculo-papular/ Pruritus (outpatient)	95%	Fixed	Fixed
AST increased/ Lipase increased/ ALT increased (inpatient)	0%	Fixed	Fixed
AST increased/ Lipase increased/ ALT increased (outpatient)	100%	Fixed	Fixed
Hypertension/ Hypertension (inpatient)	0%	Fixed	Fixed
Hypertension/ Hypertension (outpatient)	100%	Fixed	Fixed
Fatigue (inpatient)	10%	Fixed	Fixed
Fatigue (outpatient)	90%	Fixed	Fixed
Pyrexia (inpatient)	10%	Fixed	Fixed
Pyrexia (outpatient)	90%	Fixed	Fixed
Hypophosphataemia/ Hyperbilirubinaemia (inpatient)	0%	Fixed	Fixed
Hypophosphataemia/ Hyperbilirubinaemia (outpatient)	100%	Fixed	Fixed
Liver toxicity/liver-related events (inpatient)	30%	Fixed	Fixed
Liver toxicity/liver-related events (outpatient)	70%	Fixed	Fixed
Hepatitis (inpatient)	30%	Fixed	Fixed
Hepatitis (outpatient)	70%	Fixed	Fixed
Diarrhoea (grade 3+) (inpatient)	50%	Fixed	Fixed
Diarrhoea (grade 3+) (outpatient)	50%	Fixed	Fixed
Guillain-Barré syndrome (inpatient)	100%	Fixed	Fixed
Guillain-Barré syndrome (outpatient)	0%	Fixed	Fixed
Hypothyroidism (inpatient)	5%	Fixed	Fixed

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Variable	Value	PSA distribution	DSA parameter
Hypothyroidism (outpatient)	95%	Fixed	Fixed
Thyroiditis (inpatient)	5%	Fixed	Fixed
Thyroiditis (outpatient)	95%	Fixed	Fixed
Subsequent treatment			
% of usage of subsequent therapies (tebentafusp arm)	43%	Beta	+/-10%
% of usage of ipi/nivo (tebentafusp arm)	67%	Beta	+/-10%
% of usage temozolomide (tebentafusp)	33%	Beta	+/-10%
% of usage of subsequent therapies (ipi/nivo arm)	46%	Beta	+/-10%
% of usage of ipi/nivo (ipi/nivo)	0%	Fixed	Fixed
% of usage temozolomide (ipi/nivo)	100%	Fixed	Fixed

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; ipi/nivo, ipilimumab+nivolumab

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Appendix K: Cost

The cost of DKK 427.00 for complete blood count is the total cost of the various laboratory tests included in the respective blood test and is presented in Table 130.

Table 130. Cost of complete blood count.

Resource	Unit cost, DKK	NPU code	Source
Hemoglobin;B	37.00	NPU02319	Rigshospitalets labportal [69]
Leukocytes	37.00	NPU02593	
Differential blood count (Basophilocytes;B, Eosinophilocytes;B, Lymphocytes;B, Metamyelocytes. +Myelocytes. +Promyelocytes;B, Monocytes;B, neutrophils;B)	108.00	NPU04100 (NPU01349, NPU01933, NPU02636, NPU026631, NPU02840, NPU02902)	
C-Reactive Protein [CRP];P	29.00	NPU19748	
Sodium;P	17.00	NPU03429	
Potassium;P	17.00	NPU03230	
Alanine transaminase [ALAT];P	29.00	NPU19651	
Aspartate transaminase [ASAT];P	29.00	NPU19654	
Bilirubin;P	29.00	NPU01370	
Basic phosphatase;P	29.00	NPU27783	
Creatinine;P	29.00	NPU04998	
Thrombocytes	37.00	NPU03568	
Total	427.00		

B: blood P: plasma

The cost of DKK 357.00 for complete metabolic panel is the total cost of the various laboratory tests included in the respective blood test and is presented in Table 131.

Table 131. Cost of complete metabolic panel.

Resource	Unit cost, DKK	NPU code	Source
Bicarbonate;P	31.00	NPU02410	Rigshospitalets labportal [69]
Albumin;P	29.00	NPU19673	
Chloride;P	31.00	NPU01536	
Glucose;P	29.00	NPU02192	
Sodium;P	17.00	NPU03429	
Potassium;P	17.00	NPU03230	
Alanine transaminase [ALAT];P	29.00	NPU19651	

Resource	Unit cost, DKK	NPU code	Source
Aspartate transaminase [ASAT];P	29.00	NPU19654	
Bilirubin;P	29.00	NPU01370	
Basic phosphatase;P	29.00	NPU27783	
Creatinine;P	29.00	NPU04998	
Protein;P	29.00	NPU03278	
Carbamide;P	29.00	NPU01459	
Total	357.00		

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