Medicinrådet

# Bilag til Medicinrådets vurdering af tebentafusp til behandling af metastatisk uvealt melanom

*Vers. 2.0*

# Bilagsoversigt

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

**Medicinrådets udkast til rapport om tebentafusp til behandling af metastatisk uvealt melanom**

Dokumentnummer 230518

Til Medicinrådet,

Immunocore vil imødekomme muligheden for at give kommentarer til Medicinrådets udkast til vurdering af KIMMTRAK® (tebentafusp) til behandling af metastatisk uvealt melanom (mUM). Vi anerkender rådets grundige evaluering og værdsætter deres anerkendelse af den dokumentation, der understøtter tebentafusp som en potentiel førstelinjebehandling for danske patienter.

Den opdaterede 3-års analyse af det fase III IMCgp100-202-studie har en median opfølgning på 43,3 måneder. Resultaterne bekræfter tebentafusp's overlevelsesfordel, med en median samlet overlevelse (OS) på 21,7 måneder og en 1-års OS-rate på 73%, sammenlignet med 12,6 måneder og 50 % for nivolumab + ipilimumab i det komparative GEM-1402-studie[1].

Det er værd at bemærke 3-års overlevelsesraten på 27% som afspejler en vedvarende og langsigtet effekt ud over den indledende behandling samt en øget robusthed af den 5-årige overlevelsesprognose med en klinisk plausibel 5-års OS på [redacted]. I gruppen med ipilimumab + nivolumab havde den model, der passede bedst, en generaliseret gammafordeling, hvilket resulterede i en 5-års OS på 4,36%.

Medicinrådet bemærker, at tebentafusp repræsenterer en ny behandlingsklasse for klinikere med hensyn til håndteringen af potentielle bivirkninger. Selvom dette kan være korrekt, er det værd at fremhæve, som rådet også gør, at færre patienter afbrød behandling med tebentafusp sammenlignet med ipilimumab + nivolumab (2,0% vs. 23,1%). GEM-1402 rapporterede 3,8% behandlingsrelaterede dødsfald mod ingen med tebentafusp. Derudover ses færre bivirkninger, som kræver langvarig immunsuppression ved behandling med tebentafusp; bivirkningsprofilen er mildere end ved ipilimumab + nivolumab.

Vi værdsætter Medicinrådets åbenhed over for anvendelsen af metoden "Average Treatment Effect on the Treated" (ATT) til justering af baselineforskelle via propensity score-analyse af patienter behandlet med tebentafusp fra IMCgp100-202-studiet og behandlet med nivolumab + ipilimumab fra GEM-1402-studiet. Selvom rådet undersøgte både ATT- og ATC-metoderne (Average Treatment Effect on the Comparator), blev ATT-metoden foretrukket i ansøgningen, da den bedst afspejler patientgruppen i klinisk praksis. Dette er også illustreret ved dens anvendelse som analysemetode i den peer-reviewed publikation af Piulats et al. (2024)[1]. Givet sjældenheden af mUM, skal det bemærkes, at ATT-gruppen havde et langt større datagrundlag (n=240) sammenlignet med ATC-gruppen (n=45). Derudover viste propensity score-analysen en tydelig OS-fordel for tebentafusp sammenlignet med ipilimumab + nivolumab på tværs af begge IPT-vægtede metoder; ATC 1-års OS 76% vs. 51% for ipilimumab + nivolumab; ATC HR = 0,61 (95% CI: 0,41; 0,92).

Som vist af Piulats et al. (2024) balancerede den inverse sandsynlighedsvægtede (IPTW) model centrale baselinevariabler, herunder alder, køn, LDH, alkalisk fosfatase, ECOG-performance status og sygdomsplacering, mellem IMCgp100-202 og GEM-1402, hvilket eliminerede målbar bias[1].

Den primære ATT-vægtede analyse viste en hazard ratio (HR) på 0,52 (95% CI: 0,35; 0,78) til fordel for tebentafusp, hvor alle følsomhedsanalyser bekræftede en konsistent OS-fordel af samme retning og størrelsesorden. Denne metodisk solide sammenligning styrker pålideligheden af den indirekte sammenligning og giver et solidt grundlag for Medicinrådets inddragelse af begge datasæt i den komparative vurdering.

Vi støtter fuldt ud Medicinrådets vurdering af, at populationerne i både IMCgp100-202 og GEM-1402 er relevante for dansk klinisk praksis[1].

Efter EMA-godkendelsen er tebentafusp blevet indarbejdet i nationale og europæiske retningslinjer for melanombehandling som standardbehandling for HLA-A*02:01–positive patienter med metastatisk uvealt melanom, hvilket afspejler en bred faglig konsensus om dets kliniske værdi[2].

For danske patienter giver disse data reelt håb om en behandling, der kan forlænge livet med en sygdom, hvor den historiske median overlevelse er under ét år. Efterhånden som tebentafusp bliver standard i hele Europa, vil en vurdering fra Medicinrådet, der er i overensstemmelse med denne konsensus, bidrage til at sikre lige adgang og forbedrede outcomes for danske patienter.

De nye 3-årige OS-data og den robuste ATT-vægtede sammenlignende analyse bekræfter den vedvarende og klinisk meningsfulde overlevelsesfordel ved tebentafusp. Den metodiske stringens i analysen og inddragelsen af både IMCgp100-202 og GEM-1402 som relevante datakilder udgør tilsammen et stærkt grundlag for en positiv endelig anbefaling.

Immunocore forbliver investeret i et fortsat samarbejde med Medicinrådet for at sikre, at danske patienter får adgang til denne transformative behandling, som leverer en klar og vedvarende overlevelsesfordel.

Med venlig hilsen

**Immunocore**

**Referencer**

1. Piulats JM, Watkins C, Costa-García M, Del Carpio L, Piperno-Neumann S, Rutkowski P, Hassel JC, Espinosa E, de la Cruz-Merino L, Ochsenreither S, Shoushtari AN, Orloff M, Salama AKS, Goodall HM, Baurain JF, Nathan P. *Overall survival from tebentafusp versus nivolumab plus ipilimumab in first-line metastatic uveal melanoma: a propensity score-weighted analysis. Ann Oncol.* 2024 Mar;35(3):317–326.
2. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, Bastholt L, m.fl. *European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment – Update 2024. Eur J Cancer.* 2025 Jan 17;215:115153.

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24.10.2025

MBA/LSC

# Forhandlingsnotat

| | |
|---|---|
| Dato for behandling i Medicinrådet | 19.11.2025 |
| Leverandør | Immunocore Ltd |
| Lægemiddel | KIMMTRAK (tebentafusp) |
| Ansøgt indikation | Behandling af human-leukocyt-antigen-(HLA) A*02:01-positive voksne patienter med ikke-resektabel eller metastatisk uvealt melanom |
| Nyt lægemiddel / indikationsudvidelse | Nyt lægemiddel (revurdering) |

## Prisinformation

Amgros har forhandlet følgende pris på KIMMTRAK (tebentafusp):

*Tabel 1: Forhandlingsresultat*

| Lægemiddel | Styrke (pakningsstørrelse) | AIP (DKK) | Nuværende SAIP, (DKK) | Nuværende rabat ift. AIP | Forhandlet SAIP (DKK) | Forhandlet rabat ift. AIP |
|---|---|---|---|---|---|---|
| KIMMTRAK | 100 µg/0,5 ml (1 stk.) | 98.684,16 | [redacted] | [redacted] | [redacted] | [redacted] |

Prisen er betinget af Medicinrådets anbefaling.

Det betyder at hvis Medicinrådet ikke anbefaler KIMMTRAK, indkøbes lægemidlet til nuværende SAIP.

## Aftaleforhold

[redacted]

Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

## Informationer fra forhandlingen

[redacted]

## Konkurrencesituationen

Der er ikke en anbefalet standardbehandling for metastatisk uvealt melanom i dansk klinisk praksis. Første behandlingsvalg vil ofte være indgang i et klinisk studie.

Tabel 2 viser den årlige lægemiddeludgift for KIMMTRAK og Opdivo (nivolumab) i kombination med Yervoy (ipilimumab), da det er denne behandling Medicinrådet har brugt som komparator i vurderingen. [redacted]

*Tabel 2: Sammenligning af lægemiddeludgifter pr. patient*

| Lægemiddel | Styrke (pakningsstørrelse) | Dosering | Pris pr. pakning (SAIP, DKK) | Lægemiddeludgift pr. år (SAIP, DKK) |
|---|---|---|---|---|
| KIMMTRAK | 100 µg/0,5 ml (1 stk.) | 20 µg på dag 1, 30 µg på dag 8, 68 µg på dag 15, og herefter 68 µg en gang om ugen, i.v. | [redacted] | [redacted] |
| Opdivo | 40 mg/4 ml (1 stk.) | 1 mg/kg* hver 3. uge i 12 uger, og herefter 6 mg/kg hver 4. uge, i.v. | [redacted] | [redacted] |
| Yervoy | 5 mg/ml, 10 ml | 3 mg/kg* hver 3. uge i 12 uger, i.v. | [redacted] | [redacted] |
| Total lægemiddeludgift for Opdivo + Yervoy | | | | [redacted] |

*Gennemsnitlig kropsvægt 78,9 kg, (IMCgp100-202-studiet) jævnfør Medicinrådets vurderingsrapport.

## Status fra andre lande

*Tabel 3: Status fra andre lande*

| Land | Status | Link |
|---|---|---|
| Norge | Ikke anbefalet | Link til anbefaling |
| England | Anbefalet | Link til anbefaling |
| Sverige | Anbefalet | Link til anbefaling |

## Opsummering

[redacted]

# Application for the reassessment of tebentafusp (KIMMTRAK®) for human leukocyte antigen (HLA)-A*02:01-positive adults with unresectable or metastatic uveal melanoma

| Color scheme for text highlighting | |
|---|---|
| Color of highlighted text | Definition of highlighted text |
| | Confidential information |

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# Abbreviations

| | |
|---|---|
| AE | Adverse event |
| AIC | Akaike information criterion |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| ATC | Average treatment effect of the control |
| ATE | Average treatment effect |
| ATT | Average treatment effect of the treated |
| BIC | Bayesian information criterion |
| BICR | Blinded Independent Central Review |
| BSA | Body surface area |
| BSC | Best supportive care |
| BoR | Best overall response |
| CE | Cost-effectiveness |
| CEAC | Cost-effectiveness acceptability curve |
| CI | Confidence interval |
| CM | Cutaneous melanoma |
| CR | Complete response |
| CRD | Centre for Reviews and Dissemination |
| CRS | Cytokine release syndrome |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTLA-4 | Cytotoxic T-lymphocyte antigen-4 |
| DARE | Database of Abstracts of Reviews of Effects |
| DCO | Data cut-off |
| DCR | Disease Control Rate |
| DET | Data extraction table |
| DMC | Danish Medicines Council |
| DRG | Diagnosis-related group |
| DSU | Decision Support Unit |
| DoR | Duration of Response |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |

| | |
|---|---|
| EMA | European Medicines Agency |
| EORTC QLQ-C30 | European Organization for Research and Treatment of Cancer quality of life questionnaire |
| EQ-5D-5L | EuroQol – 5 dimensions – 5 levels |
| FACT-G | Functional assessment of cancer therapy: general |
| FACT-M | Functional assessment of cancer therapy: melanoma |
| GEE | Generalized estimating equation |
| GP | General practitioner |
| HLA | Human leukocyte antigen |
| HLA-A | Human leukocyte antigen class I |
| HR | Hazard ratio |
| HRC | Healthcare related cost |
| HRQoL | Health-Related Quality of Life |
| HSA | Human albumin |
| HSUV | Health state utility values |
| HTA | Health technology assessment |
| HTAD | Health technology asses-sment database |
| IC | Investigators choice |
| ICER | Incremental cost-effectiveness ratio |
| IPD | Individual patient data |
| IPTW | Inverse probability of treatment weights |
| ITT | Intention to treat |
| IV | Intravenous |
| IgG4 | Immunoglobulin G4 |
| Ipi/nivo | Ipilimumab in combination with nivolumab |
| KM | Kaplan-Meier |
| KRIS | Koordinationsrådet for ibrugtagning af sygehusmedicin |
| Kg | Kilogram |
| LDH | Lactate dehydrogenase |
| LS | Least Squares |
| LY | Life year |
| MAE | Mean absolute error |
| MAIC | Match adjusted indirect comparison |
| MFI | Multidimensional Fatigue Inventory |
| Mg | Milligram |
| N/A | Not applicable |
| NCI | National Cancer Institute |
| NCT | National Clinical Trial |
| NHS | National Health Service |
| NHSEED | NHS economic evaluation database |
| NICE | National Institute for Health and Care Excellence |
| NSCLC | Non-small-cell lung carcinoma |
| 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 |
| PICOS | Population, intervention, comparator, outcomes, study design |
| PK | Pharmacokinetic |
| PPP | Pharmacy purchase price |
| PPS | Post-progression state |
| PR | Partial response |
| PRO | Patient-reported outcome |
| PS | Performance status |
| PSA | Probabilistic sensitivity analysis |
| Q3W | Every 3 weeks |
| QALY | Quality-adjusted life years |
| QoL | Quality of Life |
| RCT | Randomized controlled trial |

| | |
|---|---|
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RMSE | Root mean squared error |
| RR | Relative risk |
| RWE | Real-world evidence |
| SAP | Statistical analysis plan |
| SD | Stable disease |
| SE | Standard error |
| SEA | Serious adverse event |
| SF-36 | Short Form 36 items |
| SF-6D | Short Form 6 Dimension |
| SLR | Systematic literature review |
| SmPC | Summary of product characteristics |
| TEAE | Treatment-emergent adverse event |
| TR-SAEs | Serious treatment related adverse event |
| TRAE | Treatment-related adverse event |
| TSD | Technical support document |
| TTD | Time to treatment discontinuation |
| UK | United Kingdom |
| ULN | Upper limit of normal |
| UM | Uveal melanoma |
| mL | Milliliter |
| metUM | Metastatic uveal melanoma |
| µg/mcg | Micrograms |

# 1. Regulatory information on the medicine

| Overview of the medicine | |
|---|---|
| **Proprietary name** | KIMMTRAK® [1] |
| **Generic name** | Tebentafusp [1] |
| **Therapeutic indication as defined by EMA** | Tebentafusp 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] |
| **Marketing authorization holder in Denmark** | Immunocore Ltd [1] |
| **ATC code** | L01XX75 [2] |
| **Combination therapy and/or co-medication** | No [1] |
| **Date of EC approval** | 1st of April 2022 [3] |
| **Has the medicine received a conditional marketing authorization?** | No |
| **Accelerated assessment in the European Medicines Agency (EMA)** | Yes [4] |
| **Orphan drug designation (include date)** | Tebentafusp was designated as an orphan medicine for the treatment of uveal melanoma in the European Union on 19 February 2021 [5] |
| **Other therapeutic indications approved by EMA** | None [1] |
| **Other indications that have been evaluated by the DMC (yes/no)** | None |
| **Joint Nordic assessment (JNHB)** | Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No<br>Is the product suitable for a joint Nordic assessment? No<br>If no, why not? Not relevant due to unsimilar treatment practices |
| **Dispensing group** | BEGR [6] |
| **Packaging – types, sizes/number of units and concentrations** | One vial of 0.5 mL concentrate containing 100 micrograms (µg) of tebentafusp [1] |

# 2. Summary table

| Summary | |
|---|---|
| **Indication relevant for the assessment** | First-line treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma [1]. |
| **Dosage regiment and administration** | The recommended dose of tebentafusp is 20 µg on Day 1, 30 µg on Day 8, 68 µg on Day 15, and 68 µg once every week thereafter [1]. |

| Summary | |
|---|---|
| **Choice of comparator** | Ipilimumab in combination with nivolumab (ipi/nivo) |
| **Prognosis with current treatment (comparator)** | Metastatic uveal melanoma (metUM) is a life-threatening and aggressive type of cancer leading to decreased life expectancy and decreased health-related quality of life (HRQoL). There is no convincing data for prolonged survival in patients with metUM when treated with current treatment regimens (chemotherapy or check-point inhibitors). The treatments have shown negligible response rates and the survival rate for patients with metUM remains low and has not improved in over 40 years. Median overall survival (OS) is 12 months, and 5-year survival is less than 10% [7,8]. |
| **Type of evidence for the clinical evaluation** | Indirect comparison: Propensity score-based inverse probability of treatment weighting (IPTW). OS was assessed using IPT weighted Kaplan-Meier (KM) and Cox proportional hazard (PH) models. The analysis was based on individual patient data (IPD) from IMCgp100-202 (NCT03070392) and GEM-1402 (NCT02626962) [9]. |
| **Most important efficacy endpoints (Difference/gain compared to comparator)** | **OS:** In the average treatment effect of the treated (ATT) IPT weighted survival analysis, the IPTW-adjusted OS favored tebentafusp over ipi/nivo, with Hazard ratio (HR) of 0.52 [95% CI: 0.35, 0.78] [9]. |
| **Most important serious adverse events for the intervention and comparator** | **Tebentafusp:** the most common treatment related adverse events (TRAEs) were cytokine-related AEs, such as pyrexia (76%), chills (47%), and hypotension (38%), and skin-related AEs, such as rash (83%) and pruritus (70%). Twenty-eight (28%) experienced a serious adverse event (SAE) [10].<br>**Ipi/nivo:** The most common TRAEs were skin-related AEs (61.5%), fatigue (57.7%), and liver-related events (36.5%). Fifty-eight, 58% experienced serious TRAEs (TR-SAEs), while 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 [11]. |
| **Impact on health-related quality of life** | Clinical documentation: 0.875 using EuroQol – 5 dimensions – 5 levels (EQ-5D-5L) with Danish preference weights (95% CI is not reported).<br>Health economic model: Better than comparator. |
| **Type of economic analysis that is submitted** | The submitted economic analysis is a cost-utility analysis using a three-state (pre-progression, post-progression, and death) partitioned survival model approach.<br>The reassessment of tebentafusp will be based on a propensity score analysis using results from 3-year analysis from study IMCgp100-202 [10] and IPD from Study GEM-1402 [9]. |
| **Data sources used to model the clinical effects** | **Tebentafusp:** On the 21st of October 2023 the 3-year efficacy and safety results were published from the registrational randomized control trial IMCgp100-202. Study IMCgp100-202 is a phase III, randomized, open-label trial in which previously untreated HLA-A*02:01-positive patients with metUM were assigned in a 2:1 ratio to receive tebentafusp (tebentafusp group) or the investigator's choice of treatment with pembrolizumab, ipilimumab, or dacarbazine (control group). |

| Summary | |
|---|---|
| | **Ipi/nivo:** GEM-1402, a single-arm, non-randomized, open-label phase II study. |
| **Data sources used to model the health-related quality of life** | Two approaches of modeling utility:<br>• Time to treatment discontinuation (TTD): utilities (EQ-5D-5L) derived from the IMCgp100-202 study.<br>• Time to death based on literature (model base-case). |
| **Life years gained** | 1.30 years |
| **QALYs gained** | 1.12 Quality-adjusted life years (QALY) |
| **Incremental costs** | [redacted] |
| **ICER (DKK/QALY)** | [redacted] |
| **Uncertainty associated with the ICER estimate** | The three parameters with most impact on the incremental cost-effectiveness ratio (ICER): Baseline utility value for patients on treatment with tebentafusp, mean weight of the patients, and the percentage of patients in the tebentafusp group receiving subsequent treatment with ipi/nivo. |
| **Number of eligible patients in Denmark** | Incidence: 10 patients<br>Prevalence: 27 patients at launch |
| **Budget impact (in year 5)** | [redacted] |

# 3. The patient population, intervention, choice of comparator(s) and relevant outcomes

## 3.1 The medical condition

Uveal Melanoma (UM) is a rare and highly malignant disease that is biologically and genetically distinct from other melanomas, including cutaneous melanoma (CM). UM is distinguished from other melanomas by etiology and physiological, genetic, and epidemiological characteristics [7,12–14]. UM develops exclusively from melanocytes of the uveal tract that encompasses the choroid, ciliary body, and iris and is the most common primary intraocular malignancy in adults. However, it represents less than 5% of all melanoma cases [12]. The distinctiveness and rarity of uveal melanoma was recognized by the EMA and tebentafusp was designated with orphan status in the European Union (EU/3/21/2397) [5]. The primary disease is often detected during routine eye examinations. Symptoms may include blurred vision, vision loss, or other signs of visual disturbances (such as flashes of light or eye spots) [12,15,16]. Advances in detection and treatment of primary UM have been significant [17]. Despite treatments for the primary disease providing good local control in 90%-95% of cases, UM remains a life-threatening cancer. Up to 50% of patients develop metastatic disease. Tumor cells spread predominantly via the blood and metastases typically appear first in the liver (~90% of patients) [18]. Prior to the introduction of tebentafusp, prognosis was poor after diagnosis of metastatic disease with a historical median survival of ≤12 months

[12], with parenchymal liver failure the most common cause of death [19]. In UM, 90% of metastases occur in the liver [20,21] and less frequently in other visceral organs such as the lungs (24%), bones (16%) and skin (11%). The extent of metastasis to the liver is an important factor in the clinical course and survival [19]. MetUM is difficult to treat and there is no well-defined standard treatment. During the past 10 years, targeted treatments (e.g. BRAF-MEK inhibitor combinations) and immunotherapies (e.g. anti-Programmed death receptor 1 (PD-1) and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) biologics) have transformed the management and life expectancy of patients with CM. However, these treatments have not provided a significant improvement in survival for patients with metUM. Prior to the introduction of tebentafusp, there had been no improvement in survival for these patients in the past 40 years. This lack of progress in survival benefit appears linked to the distinct genetics of UM (e.g. absence of BRAF mutations) linked to immune biology (e.g. low tumor mutational burden) of UM compared with CM. Prior to the registrational study for tebentafusp, patients with UM were frequently excluded from metastatic melanoma immunotherapy trials because UM was generally considered to be an immunotherapy resistant subtype of melanoma [19]. Treatments have been studied for metUM, including liver-targeted therapies, conventional chemotherapy, protein kinase inhibitors, and checkpoint inhibitors, but none have demonstrated a proven survival benefit, and clinical trials were recommended, leaving patients without a proven effective treatment option [22]. Patients are currently offered treatment in clinical trials, if clinical trials are available or immunotherapy (checkpoint inhibitors) [7]. Survival for patients with metUM is median 12 months and 5-year survival is less than 10% [7,8]. Furthermore, studies show that metUM patients have a lower Quality of Life (QoL) and frequent mental health disorders, such as depression (up to 10% of patients) and anxiety (up to 30%) [23].

## 3.2 Patient population

According to the Danish Melanoma Group, approximately 75 people in Denmark develop UM every year, see Table 1 [24]. Approximately equal numbers of men and women are diagnosed, and the disease can occur in all age groups [7,25].

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

| Year | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|
| **Incidence of UM in Denmark** [7,24] | 75 | 75 | 75 | 75 | 75 |
| **Prevalence in Denmark** | Unknown | Unknown | Unknown | Unknown | Unknown |
| **Global prevalence *** | Unknown | Unknown | Unknown | Unknown | Unknown |

Up to 50% of patients with UM develop metastatic disease, corresponding to 37-38 Danish patients per year [12,26]. Treatment with tebentafusp is targeted at patients who are HLA-A*02:01 positive and have metastatic disease. Approximately half of patients with metUM in Denmark are estimated to be HLA-A*02:01 positive, corresponding to the distribution in the general population, with the HLA-A*02:01 positivity being determined through a blood test using next generation sequencing [7]. The patient population relevant for this assessment are patients with metUM who are HLA-A*02:01 positive [1]. In the assessment report of tebentafusp from March 2023, the Danish Medicines Council

(DMC) estimated the population eligible for the treatment with tebentafusp to include approximately 10 patients per year as presented in Table 2 [7].

**Table 2. Estimated number of patients eligible for treatment**

| Year | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Number of patients in Denmark who are eligible for treatment in the coming years** [7] | 10 | 10 | 10 | 10 | 10 |

## 3.3 Current treatment options

There is no current standard treatment for metUM in Danish clinical practice. In general, there is no convincing data for prolonged survival in patients with metUM when treated with current treatment regimens (chemotherapy or check-point inhibitors) [7,24]. With the current treatment regimens, patients with metUM have a median survival of 12 months, and the 5-year survival is less than 10% [7,8]. As illustrated in Figure 1, the first choice of treatment is therefore entry into a clinical trial, if possible. Based on the available studies, it is estimated that combination immunotherapy with a CTLA-4 + PD-1 inhibitor (ipi/nivo) should be offered to treatment-naïve patients with metUM. If the patient appears fragile, monotherapy with PD-1 antibodies (pembrolizumab or nivolumab) may be considered as an alternative [7,24]. Monotherapy with Anti-CTLA4 antibodies (ipilimumab) are not recommended due to its very limited clinical efficacy and toxicity [7]. According to Danish clinical guidelines, temozolomide can be used as 2$^{nd}$ line treatment for patients with good general condition [24]. However, in the previous assessment of tebentafusp the DMC did not consider the use of temozolomide as clinical practice [7]. Therefore, temozolomide is not included in the treatment algorithm illustrated in Figure 1. In addition to pharmaceutical treatments, local treatment (surgical resection, radiofrequency ablation, stereotactic body radiotherapy) of liver metastases should be considered in patients in good general condition and with limited disease without extra-hepatic spread, where radicality is considered realistic. Other localized treatment of liver metastases in patients with metUM should only be performed in clinical trials [7,24].

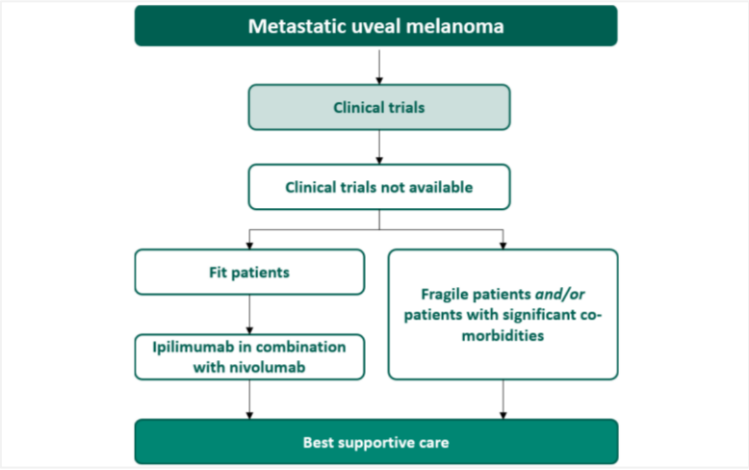


**Figure 1. Current treatment algorithm for Danish patients with metUM** [7,24]**.**

## 3.4 The intervention

Table 3 provides an overview of the intervention.

**Table 3. Description of tebentafusp**

| Overview of intervention | |
|---|---|
| **Indication relevant for the assessment** | First-line treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma [1]. |
| **ATMP** | Not applicable (N/A) |
| **Method of administration** | Infusion [1]. |
| **Dosing** | The recommended dose of tebentafusp is 20 µg on Day 1, 30 µg on Day 8, 68 µg on Day 15, and 68 µg once every week thereafter [1]. |
| **Dosing in the health economic model (including relative dose intensity)** | The modelled dosing corresponds to the recommended dose of tebentafusp 20 µg on Day 1, 30 µg on Day 8, 68 µg on Day 15, and 68 µg once every week thereafter [1].<br>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; 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 [27]. Adherence to treatment of 92% is included in the model. The relative dose intensity was 100%. |
| **Should the medicine be administered with other medicines?** | No. |
| **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:*<br>The first three doses of tebentafusp 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 four 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 after any of the first three infusions, patients should be monitored every hour for at least four hours in an outpatient setting for the next three infusions [1].<br>*Subsequent treatment doses:*<br>After the 68 µg 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 tebentafusp for at least 3 months and have not experienced any interruptions greater than two weeks, outpatient monitoring following infusion may be decreased to a minimum of 30 minutes for subsequent doses [1]. |

| Overview of intervention | |
|---|---|
| **Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?** | To receive treatment with tebentafusp, patients must be HLA-A*02:01 positive, which is determined through a blood test using next generation sequencing [1,7].<br>The costs of the HLA test are included in the model. |
| **Package size(s)** | One vial of 0.5 mL concentrate containing 100 µg of tebentafusp [1]. |

### 3.4.1 Description of ATMP (N/A)

### 3.4.2 The intervention in relation to Danish clinical practice

Tebentafusp is indicated for patients with metUM 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 and therefore matches the description in section 3.3, Figure 1.

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

- 1st line treatment for all patients: tebentafusp
- 2nd line treatment for fit patients: ipi/nivo
- 2nd line treatment for fragile patients and/or patients with significant comorbidities: best supportive care (BSC)
- 3rd line treatment for fit patients: BSC

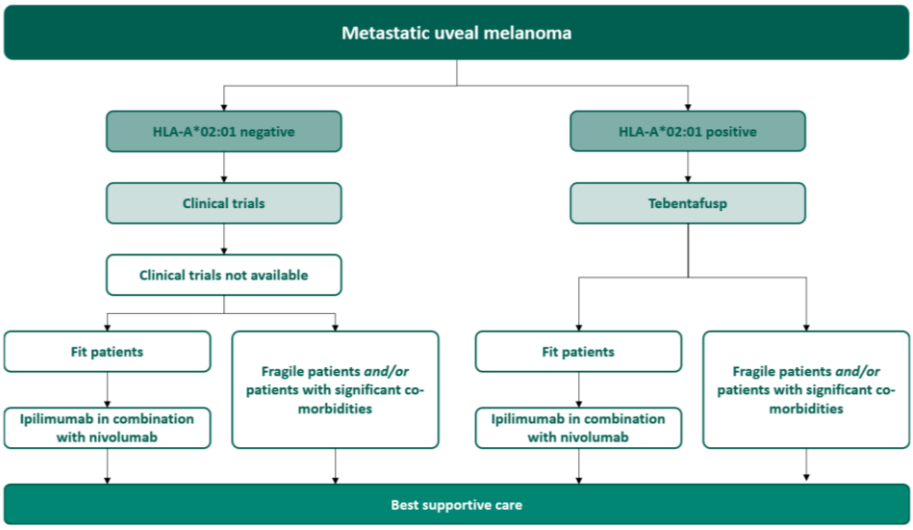


**Figure 2. Expected treatment algorithm with introduction of tebentafusp** [7,24]**.**
This algorithm is based on the current clinical treatment guidelines and the DMC assessment report of the initial submission of tebentafusp.

## 3.5 Choice of comparator

As mentioned in section 3.3, there is no established standard treatment for metUM in Danish clinical practice. According to Danish clinical guidelines and the DMC's assessment report of tebentafusp for treatment of metUM, the first choice of treatment (excluding clinical trials) is a combination of immunotherapy with a CLTLA-4 and a PD-1-inhibitor (ipi/nivo) [7,24]. In the DMC assessment report of tebentafusp, it is stated that

ipi/nivo as comparator reflects Danish clinical practice, why it remains the relevant comparator to tebentafusp for this reassessment [7].

### 3.5.1 Description of the comparator

The combination treatment with ipi/nivo is used for metUM patients in Danish clinical practice but is not recommended by the DMC or any other regulatory agencies specifically for HLA-A*02:01 positive adults with metUM. Furthermore, the effects of ipi/nivo for treating metUM have only been investigated in single-arm studies, and the evidence of effect is, therefore, not considered strong [11,28]. Consequently, the treatment options for patients with metUM are limited and outcomes remain poor. Ipilimumab and nivolumab are described separately in Table 4 and Table 5, respectively.

**Table 4. Description of ipilimumab**

| Overview of comparator: ipilimumab | |
|---|---|
| **Generic name** | Ipilimumab |
| **ATC code** | L01FX04 [29]. |
| **Mechanism 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 [30]. |
| **Method of administration** | Intravenous (IV) infusion [30]. |
| **Dosing** | Adults and adolescents 12 years of age and older and weighing at least 50 kg: 3 mg/kg Q3W for a total of 4 doses [30]. |
| **Dosing in the health economic model (including relative dose intensity)** | The dosing used in the health economic model corresponds to the recommended dose of 3 mg/kg Q3W for a total of 4 doses [7,30]. 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; 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 [27].<br>Adherence to treatment of 100% is included in the model. The relative dose intensity was 100%. |
| **Should the medicine be administered with other medicines?** | Ipilimumab can be taken in combination with 1 milligram/kilogram (mg/kg) nivolumab as indicated for the treatment of adult patients with melanoma [30]. |
| **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 [30]. |
| **Need for diagnostics or other tests (i.e. companion diagnostics)** | None [30]. |

| Overview of comparator: ipilimumab | |
|---|---|
| **Package size(s)** | A vial of either 50 mg/10 milliliter (mL) or 200 mg/40 mL ipilimumab [30]. |

**Table 5. Description of nivolumab**

| Overview of comparator: nivolumab | |
|---|---|
| **Generic name** | Nivolumab |
| **ATC code** | L01FF01 [31]. |
| **Mechanism 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 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 [32]. |
| **Method of administration** | IV infusion [32]. |
| **Dosing** | Adults and adolescents 12 years of age and older and weigh at least 50 kg: 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered IV Q3W for the first 4 doses [32]. |
| **Dosing in the health economic model (including relative dose intensity)** | The dosing used in the health economic model is 1 mg/kg Q3W for a total of 4 doses and subsequent doses of 6 mg/kg every 4 weeks [7]. 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; 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 [27]. Adherence to treatment of 100% is included in the model. The relative dose intensity was 100%. |
| **Should the medicine be administered with other medicines?** | Nivolumab can be taken in combination with ipilimumab as indicated for the treatment of adult patients with melanoma [32]. |
| **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 [32]. |
| **Need for diagnostics or other tests (i.e. companion diagnostics)** | None [32]. |
| **Package size(s)** | A vial of either 40 mg/4 mL, 100 mg/10 mL, 120 mg/12mL or 240 mg/24 mL nivolumab [32]. |

## 3.6 Cost-effectiveness of the comparator

The combination therapy with ipi/nivo has not previously been assessed by the DMC for metUM and the cost-effectiveness (CE) of this treatment has not been established. However, it was decided to not conduct further comparative analyses of ipi/nivo and BSC. This aligns with the DMC guideline stating that treatments considered well established in Danish clinical practice can be exempted from such comparison. Ipi/nivo as the relevant comparator is based on the following reasonings: immunotherapies including ipi/nivo have been used for treatment of metUM since 2014 [18], the Danish clinical treatment guideline "*Oncological treatment of Ocular melanoma"* describes that patients with metastatic ocular melanoma should be offered combination treatment with a CTLA-4 (ipilimumab) and a PD-1 inhibitor (e.g. nivolumab) [24], 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) [18], and lastly that according to the DMC, ipi/nivo as a comparator reflects Danish clinical practice and remains the relevant comparator to tebentafusp [7]. Considering the aforementioned reasons, comparison with BSC is deemed unnecessary. Furthermore, there is a lack of studies comparing either tebentafusp or ipi/nivo with placebo, given the severity of metUM as a life-threatening and aggressive disease, making the use of placebo in a study unethical. Although the CE of ipi/nivo has not previously been assessed by the DMC for metUM, it was assessed for mesothelioma lung cancer where it was recommended when compared to platinum-based chemotherapy [33]. Additionally, 'Koordinationsrådet for ibrugtagning af sygehusmedicin' (KRIS) assessed and recommended the use of ipi/nivo for patients with CM in 2016 [34]. 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 metUM are worse than CM [13], it is reasonable to assume that ipi/nivo is cost-effective in patients with metUM.

## 3.7 Relevant efficacy outcomes

### 3.7.1 Definition of efficacy outcomes included in the application

The relative efficacy outcomes included in this reassessment are OS and progression-free survival (PFS). Based on the prior assessment report of tebentafusp, the DMC stated that OS and PFS are considered as adequate efficacy outcomes for the assessment of tebentafusp and relevant in Danish clinical practice [7]. Furthermore, 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. OS is the gold standard primary end point to evaluate the outcome of any intervention that is assessed in oncologic clinical trials. OS is universally recognized as being unambiguous, unbiased, with a defined end point of paramount clinical relevance, and positive results provide confirmatory evidence that a given treatment extends the life of a patient [35].

**Study IMCgp100-202 (NCT03070392)**

The primary outcome in study IMCgp100-202 was OS, 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 [36]. OS was followed continuously while patients were treated and every 3 months in the follow-up phase [36,37]. PFS was a secondary outcome and defined as the time from randomization to the date of progression (Response Evaluation Criteria in Solid Tumors (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 [36]. Patients who had not progressed or died at the time of the analysis were censored at the time of the last evaluable tumor assessment. Patients who started a new anti-cancer therapy without a documented progression were censored at the last time of a tumor assessment prior to the introduction of the new anticancer therapy [37]. Methods of analysis of OS and PFS are described in detail in Appendix A in Table 63. The time of clinical cut-off for the primary analysis in IMCgp100-202 was October 13, 2020, corresponding to a median follow-up of 14.1 months [13,36]. The time of clinical cut-off for the 3-year analysis was July 3, 2023, corresponding to a median follow-up of 43.3 months [10]. Objective response rate (ORR) was another secondary outcome in the IMCgp100-202 trial and was included in the previous application for tebentafusp to the DMC. The DMC did not include data on response rates in the assessment, as PFS and OS were considered sufficient for evaluating efficacy [7]. However, as the latest data cutoff (DCO July 2023) also included updated ORR results these are presented in Appendix A. The definitions of efficacy outcomes from IMCgp100-202 are presented in Table 6.

**GEM-1402**

The primary endpoint of study GEM-1402 was 12-month OS, defined as the time from the first dose to death from any cause in the intention to treat (ITT) population, see Table 6. PFS was a secondary endpoint and defined as the time from the first nivolumab dose to progression of disease according RECIST 1.1 criteria or death from any cause [11,38]. 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. Methods of analysis of OS and PFS are described in detail in Appendix A in Table 64. At the DCO (July 9, 2019), the median follow-up was 13.4 months (range, 0.8-35.2 months). The definition of efficacy outcomes from GEM-1402 is presented in Table 6 [11].

**Table 6. Efficacy outcome measures relevant for the application**

| Outcome measure | Time point* | Definition | How was the measure investigated/method of data collection |
|---|---|---|---|
| **OS** | | | |
| ***Tebentafusp:*** IMCgp100-202 [36] | **Primary analysis/DCO October 2020†:** From randomization to the data cutoff date of October 13, 2020; median follow-up duration was 14.1 months [13,36]. **3-year analysis/DCO July 2023**: From | OS was defined as the time from randomization to date of death due to any cause [36].‡ | Evaluated as time-to-event analysis. OS was calculated by the KM method. The treatment groups were formally compared with the use of a 2-sided log-rank test, stratified according to lactase dehydrogenase (LDH) status. Treatment effects were characterized by the HR derived from a stratified Cox PH regression model, which was |

| Outcome measure | Time point* | Definition | How was the measure investigated/method of data collection |
|---|---|---|---|
| | randomization to the data cutoff date of July 3, 2023; median follow-up duration was 43.3 months [10]. | | stratified according to the LDH status - but only if the PH assumption was met [10,13]. |
| ***Ipi/nivo:*** GEM-1402 [38] | **Piulats et al., 2021**: 12 months after treatment start [38]. **Piulats et al., 2023:** duration of median follow-up was 35 months [9]. | OS was defined as the time from the first dose to death from any cause [38]. | OS was calculated by the KM method with CIs at 95% [11]. Logistic regression and Cox PH models were used to evaluate the potential association with response to treatment and survival [11]. |
| **PFS** | | | |
| ***Tebentafusp:*** IMCgp100-202 [36] | PFS was assessed every 3 months from randomization until disease progression or death, up to 36 months [36]. | PFS is defined as the time from randomization to the date of progression (RECIST v1.1) or death due to any cause [36]. | Investigator assessed. Evaluated as time-to-event analysis. PFS were calculated by the KM method. The treatment groups were formally compared with the use of a 2-sided log-rank test. Treatment effects were characterized by the HR derived from a stratified Cox PH regression model, which was stratified according to the LDH status - but only if the PH assumption was met [10,13]. |
| ***Ipi/nivo:*** GEM-1402 [38] | 3 months after treatment started [11,38]. | Percentage of patients without progression of disease at month 3, according RECIST 1.1 criteria [38]. | Investigator assessed [11]. OS was calculated by the KM method with CIs at 95%. Logistic regression and Cox PH models were used to evaluate the potential association with response to treatment and survival [11]. |

* Time point for data collection used in analysis (follow up time for time-to-event measures). †Interim analysis-1 according to the study protocol. ‡For study IMCgp100-202, the mean time from randomization to treatment was 2.649 days [39].

**Validity of outcomes**

The DMC stated in the assessment report of tebentafusp that the efficacy outcome measures were considered as adequate and relevant in Danish clinical practice [7]. Regarding the minimal clinically relevant difference, the DMC has not previously assessed a drug for metUM (aside from tebentafusp), and the clinical expert consulted in the initial application did not provide an estimate. Due to the poor prognosis of metUM, any OS benefits should be seen as clinically relevant.

# 4. Health economic analysis

## 4.1 Model structure

A systematic literature search was conducted to identify 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 metUM and the first pharmaceutical to demonstrate a proven survival benefit for metUM, no relevant CE studies were identified. Hence, a de novo global economic model was developed, in Microsoft Excel®, from the perspective of national healthcare provider organizations. The model was adapted to the Danish setting based on the clinical data from study IMCgp100-202 (DCO October 2020), a Danish real-world evidence (RWE) study, a target review of previous HTAs in metastatic melanoma, and insights collected from a clinical expert from the initial assessment of tebentafusp by DMC [40]. In 2023 the model was updated using data from the 3-year survival analysis of study IMCgp100-202 (DCO July 2023) [10]. The model employed 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-states (pre-progression, post-progression, and death) (Figure 3), which represent the stages of disease in metUM 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 (PFS) and stay in this state until disease progression is confirmed, upon which they move to the post-progression state (PPS). 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 PPS to PFS. The PPS is defined in accordance with phase III IMCgp100-202 clinical trial secondary efficacy endpoint of PFS, as patients having confirmed disease progression per RECIST v1.1.

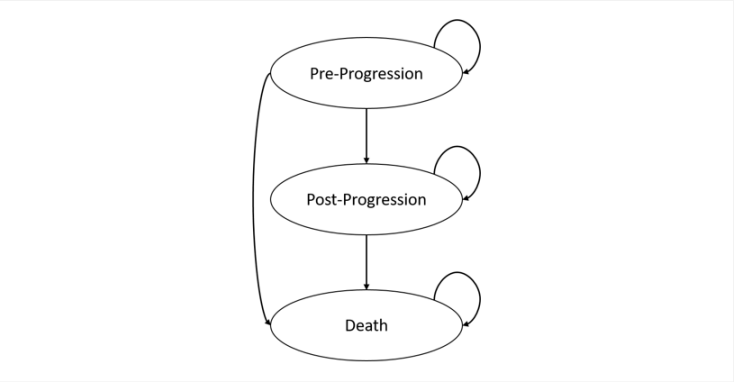


**Figure 3. Schematic model structure.**

## 4.2 Model features

Features of the economic analysis are presented in Table 7. 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 underestimation of transitions occurring at the beginning or end of the cycle. The model base case uses a lifetime horizon, which is equivalent to 34 years based on the data from the Danish Metastatic Melanoma Database in which the mean age in Danish patient population was 66 years old [7]. 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 [41]. All costs and health effects are discounted at 3.5% from year 1-34 [42]. 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.

**Table 7. Features of the economic model**

| Model features | Description | Justification |
|---|---|---|
| **Patient population** | Adult patients with HLA-A*02:01 positive metUM, without prior systemic or localized treatment in the metastatic setting | Tebentafusp recognizes and targets HLA-A*02:01 positive melanoma cells [10].<br>As per EMA indication [1]. |
| **Perspective** | Limited societal perspective | According to DMC guidelines [41]. |
| **Time horizon** | Lifetime (34 years) | To capture health benefits and costs in line with DMC guideline [41].<br>Based on the mean age from Danish Metastatic Melanoma Database, the starting age of the patient population is 66 years, this assumes a maximum patient age of 100 years [7]. |
| **Cycle length** | One week | Consistent with the length of tebentafusp treatment cycles, and to reflect timing of transitions to disease progression and death [13]. |
| **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]. |
| **Discount rate** | 3.5% | As per DMC guideline [41] and in agreement with the Danish Ministry of Finance [42]. |
| **Intervention** | Tebentafusp | |
| **Comparator(s)** | Ipi/nivo | Danish clinical practice according to DMC [7]. |
| **Outcomes** | OS, PFS, and grade ≥3 AEs. Clinical inputs for all treatment groups were estimated using IPD from GEM-1402 and IMCgp100-202. | 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 [10,11,13]. |

# 5. Overview of literature

## 5.1 Literature used for the clinical assessment

An updated systematic literature review (SLR) for the clinical assessment was conducted with PubMed on the 24th of February 2025. A detailed description of the updated SLR can be found in Appendix H while a detailed description of the original SLR is presented in the original submission to the DMC [40]. Clinical studies included based on the original and the updated SLR are presented in Table 8.

**Table 8. Relevant literature included in the assessment of efficacy and safety**

| Reference (Full citation incl. reference number)* | Trial name* | NCT identifier | Dates of study (Start and expected completion date, data cut-off and expected data cut-offs) | Used in comparison of* |
|---|---|---|---|---|
| Full paper Nathan P, Hassel J, Rutkowski P, et al. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med 2021;385:1196-1206. [13,36]. *Identified in original literature search [40]*<br>Full paper Hassel JC., Piperno-Neumann S, Rutkowski P, et al. Three-Year Overall Survival with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med 2023;389:2256-2266. [10] [36] *Identified in updated literature search* (Appendix H) | IMCgp100-202 | NCT03070392 | Start: 16/10/2017<br>Primary Completion: 13/10/2020<br>Completion (estimated): 06/2025<br>Data cut-off: 2020 [13,36]<br>Data cut-off: 2023 [10] [36] | Tebentafusp vs. Investigator's Choice (pembrolizumab, ipilimumab, or dacarbazine) for HLA-A*0201 positive adult patients with advanced UM treated in the first line setting with no prior systemic or liver-directed chemo-, radio- or immune-therapy administered in the advanced setting. |
| Full paper Piulats JM, Espinosa E, de la Cruz Merino L, 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):586-598. [11,35]<br>*Identified in original literature search [40]* | GEM-1402 | NCT02626962 | Start: 04/2016<br>Primary Completion: 05/2017<br>Completion: 22/07/2021 | Ipi/nivo as single arm in patients with previously untreated metUM. |
| Full paper Piulats JM, WatkinsC, Costa-García M, et al. Overall Survival From Tebentafusp Versus Nivolumab Plus Ipilimumab in First Line Metastatic Uveal Melanoma: A Propensity Score Weighted Analysis. Annals of Oncology 2024;35(3):317-326. [9]<br>*Identified in updated literature search* (Appendix H) | N/A | N/A | N/A | Tebentafusp vs. Ipi/nivo in untreated metUM population. |

## 5.2 Literature used for the assessment of health-related quality of life

Two updated SLRs (2021-2024 and 2024-2025) were undertaken for European Health technology assessment (HTA) submissions to identify and summarize the available HRQoL evidence for tebentafusp and relevant comparator therapies for the treatment of metUM. In the first updated review (2021-2024) a total of 140 deduplicated records were retrieved from the electronic search and 3 additional records were identified through other resources and were assessed for relevance. In the second updated review (2024-2025) a total of 178 electronic search records were assessed for relevance. A presentation of the original SLR is presented in the original submission to the DMC. Detailed descriptions of the updated SLRs are presented in Appendix J.

### 5.2.1 Updated reviews for HRQoL and utilities

**Updated review (2021-2024)**

At the title and abstract screening stage 15 records were identified as potentially relevant studies for HRQoL outcomes, and 4 records were included at the full-text screening stage. Two included publications reported the same study, and therefore the most up-to-date publication was used for data extraction. However, ultimately none of the three studies were considered suitable after adaptation to a Danish setting (Figure 29), see Appendix J for more details.

**Updated review (2024-2025)**

At the title and abstract screening stage, 9 records were identified as potentially relevant studies for HRQoL outcomes, and 2 records were included at the full-text screening stage (Figure 33). However, ultimately none of the 2 studies were considered suitable, see Appendix J for more details.

As no relevant studies was identified in the SLR, a hand searching approach of National Institute for Health and Care Excellence (NICE) appraisals was used to identify utility data modelled using a time to death approach for the immunotherapies commonly used in metUM. The literature used for HRQoL in the health economic model is listed in Table 9 and described further in section 1.

**Table 9. Relevant literature included for (documentation of) health-related quality of life (See section 10)**

| Reference (Full citation incl. reference number) | Health state/Disutility | Reference to where in the application the data is described/applied |
|---|---|---|
| Hatswell A, et al. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. Health and Quality of Life Outcomes. 2014;12:140 [44]<br>NICE. Tebentafusp for treating advanced uveal melanoma. Technology appraisal guidance [TA1027] [Internet]. 2025 [cited 2025 Apr 3]; Available from: | Advanced melanoma previously untreated with ipilimumab | The data is described in detail in section 10. |

| Reference (Full citation incl. reference number) | Health state/Disutility | Reference to where in the application the data is described/applied |
|---|---|---|
| https://www.nice.org.uk/guidance/ta102 [45] NICE. Pembrolizumab for advanced melanoma not previously treated with ipilimumab. Technol Apprais Guid [TA366] [Internet]. 2015;(September 2017):33. Available from: www.nice.org.uk/guidance/ta366 [46] | | |

## 5.3 Literature used for inputs for the health economic model

Two updated literature reviews (2021-2024 and 2024-2025) using systematic methodology were undertaken for European HTA submissions to identify CE studies, healthcare related costs (HRCs), and resource use. In the first updated review (2021-2024) a total of 140 deduplicated records were retrieved from the electronic search and 3 additional records were identified through other resources and were assessed for relevance. In the second updated review (2024-2025) a total of 178 electronic search records were assessed for relevance. A presentation of the original SLR is presented in the original submission to the DMC. Detailed descriptions of the updated SLRs are presented in Appendix J.

### 5.3.1 Updated reviews for cost-effectiveness

**Updated review (2021-2024)**

At the title and abstract screening stage 3 records were identified as potentially relevant studies for CE outcomes, but only 1 record was included at the full-text screening stage for data extraction. Ultimately, the one identified record was excluded due to not being relevant for the health economic model specifically adapted to a Danish setting (Figure 30 in Appendix J).

**Updated review (2024-2025)**

At title and abstract and full-text screening stages, a single record (HTA report) met the inclusion criteria and was included for data extraction (Figure 34). Ultimately, the one identified record was excluded due to not being relevant for the health economic model specifically adapted to a Danish setting.

### 5.3.2 Updated reviews for HRCs and resource use

**Updated review (2021-2024)**

At the title and abstract screening stage 5 records were identified as potentially relevant studies for HRC and resource use outcomes, but no records was included at the full-text screening stage for data extraction (Figure 31 in Appendix J).

**Updated review (2024-2025)**

At the title and abstract screening stage, 8 records were identified as potentially relevant publication. After full-text screening, 1 study was identified as relevant for resource use

outcomes (Figure 35). Ultimately, the one identified record was excluded due to not being relevant for the health economic model specifically adapted to a Danish setting. The literature used for the health economic model is listed in Table 10 and described further in Section 11.4.

**Table 10. Relevant literature used for input to the health economic model**

| Reference (Full citation incl. reference number) | Input/estimate | Method of identification | Reference to where in the application the data is described/applied |
|---|---|---|---|
| McKendrick J, et al. Estimating healthcare resource use associated with the treatment of metastatic melanoma in eight countries. J Med Econ. 2016;19(6):587–95 [47] | Resource use | Hand search | The data is described in detail in section 11.4. |

# 6. Efficacy

## 6.1 Efficacy of tebentafusp compared to ipi/nivo for previously untreated patients with metUM

### 6.1.1 Relevant studies

The included studies in this resubmission are based on the initial submission of tebentafusp for metUM [7]. The included studies are IMCgp100-202 [36] and GEM-1402 [38]. IMCgp100-202 is a head-to-head study between tebentafusp and Investigator's Choice from pembrolizumab, ipilimumab, and dacarbazine [36]. GEM-1402 is a single-arm trial to examine the OS of ipi/nivo in patients with metUM patients [38]. In the following sections IMCgp100-202 and GEM-1402 are described. The study by Piulats et al. (2023) in this application provides an indirect comparison based on individual patient-level data from the IMCgp100-202 and GEM-1402 studies [9]. The Pelster et al. (2020) study is not included in this submission, as the DMC in the previous assessment of tebentafusp for metUM, have stated that the study is not considered relevant as it includes previously treated patients [7]. Table 11 provides an overview of the study designs of the studies included in the comparison.

**Table 11. Overview of study design for studies included in the comparison.**

| Trial name (NCT-number) [reference] | Study design | Study duration | Patient population | Intervention | Comparator | Outcomes and follow-up period |
|---|---|---|---|---|---|---|
| IMCgp100-202 (NCT03070392) [36]<br>*Nathan et al., 2021* [48]<br>*Hassel et al., 2023* [49] | Phase III, randomized, open-label, active-comparator study | October 2017 to June 2025 | HLA-A*0201 positive adult patients with previously untreated advanced UM | Tebentafusp administered at 20 mcg cycle 1 day1, then 30 mcg cycle 1 day 8, then 68 mcg cycle 1 day 15 and weekly thereafter by IV infusion over 15 minutes until confirmed disease progression or unacceptable toxicity | Dacarbazine administered at 1,000 mg/m$^2$ of BSA IV infusion every 3 weeks (Q3W) until disease progression or unacceptable toxicity OR Ipilimumab administered at 3 mg/kg IV infusion over 90 minutes Q3W for a total of 4 treatments OR pembrolizumab administered at 2 mg/kg IV infusion up to a maximum of 200 mg over 30 minutes Q3W or 200 mg fixed dose administered IV Q3W where approved locally until confirmed disease progression or unacceptable toxicity | The primary endpoint was OS, while the secondary endpoints were PFS, ORR, DoR and DCR [36].<br>**OS**: assessed from randomization to the data cut-off date of for the primary analysis (13-Oct-2020; median follow-up duration was 14.1 months) and for the 3-year analysis (3-Jul-2023; median follow-up duration was 43.3 months) [10,36]<br>**PFS:** assessed every 3 months from randomization until disease progression or death, up to 36 months [36].<br>**ORR**: assessed after every participant has had at least 3 assessments, conducted every 3 months, up to 5.5 years [36].<br>**DoR**: assessed every 3 months from randomization until disease progression, assessed up to 5.5 years [36].<br>**DCR**: assessed every 3 months from randomization until disease progression, up to 5.5 years [36]. |
| GEM-1402 (NCT02626962) [38]<br>*Piulats et al., 2021* [11] | Single-arm, non-randomized open label phase II study | April 2016 to July 2021 | Patients with previously untreated, unresectable or metUM | Ipilimumab Q3W for a total of four doses (Cycles 1 and 2) and nivolumab Q3W for a total of four doses (Cycles 1 and 2) followed by nivolumab every 2 weeks until progression, | No comparator, single-arm | The primary outcome was OS, and secondary outcomes were OS-rate at 24 months, PFS, ORR, DCR and DoR [38].<br>**OS:** 12 months after treatment start [38]<br>**PFS:** 3 months [38]<br>**ORR:** 12 months [38]<br>**DoR:** assessed from date of randomization until the date of first documented progression or date |

| Trial name (NCT-number) [reference] | Study design | Study duration | Patient population | Intervention | Comparator | Outcomes and follow-up period |
|---|---|---|---|---|---|---|
| | | | | intolerable toxicity, or withdrawal.) | | of death from any cause, whichever came first, assessed up to 48 months [38]<br>**DCR:** 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 [38] |
| *Piulats et al., 2023* [9] | Indirect comparison. A propensity score-weighted analysis | IMCgp100-202: median duration of follow up of 43.3 months.<br>GEM-1402: median duration of follow up of 35 months. | Previously untreated patients with metUM | Tebentafusp | Ipi/nivo<br>Pembrolizumab | The primary endpoint was OS [9–11] |

### 6.1.2 Comparability of studies

IMCgp100-202 [36] is a prospective phase III randomized-controlled trial, while GEM-1402 [38] is a prospective phase II single-arm trial of treatment naïve patients with metUM. The primary endpoint in both trials was OS, and secondary endpoints included PFS, ORR, Disease Control Rate (DCR), and Duration of Response (DoR) in both IMCgp100-202 and GEM-1402 studies [11,13] [36,37]. Given the lack of a randomized comparison, the adjusted indirect treatment comparison by Piulats et al. (2023) analyzed the OS benefit of tebentafusp over ipi/nivo. While differences in patient characteristics may introduce bias when comparing treatments across studies, this limitation can be addressed through the application of propensity score modeling where individual patient-level data is available, as was the case here [9].

#### 6.1.2.1 Comparability of patients across studies

According to the DMC, the study populations in IMCgp100-202 and GEM-1402 are overall assessed to be comparable [7]. The most clinically relevant difference in patient characteristics between IMCgp100-202 and GEM-1402 was the location of metastasis [36,37]. In IMCgp100-202, only a small group of patients (5%) had only extrahepatic metastasis compared to a larger group in the GEM-1402 study (21.2%) and the time from primary diagnosis was not available in the GEM-1402 study [13,48]. These issues were addressed in the indirect comparison by Piulats et al. (2023) and are described in section 7.1.2 [9]. The baseline characteristics of patients in study IMCgp100-202 and GEM-1402 are presented in Table 12.

**Table 12. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety**

| | **IMCgp100-202** [13] [49] | | **GEM-1402** [11] |
|---|---|---|---|
| | **Tebentafusp (n = 252)** | **Control (n = 126)** | **Ipi/nivo (n = 52)** |
| **Median age, year (range)** | 64 (23-92) | 66 (25-88) | 59 (26-84) |
| **Gender, n (%)** | | | |
| Male | 128 (51) | 62 (49) | 29 (55.8) |
| Female | 124 (49) | 64 (51) | 23 (44.2) |
| **Median time since primary diagnosis (range, year)** | 3.0 (0.1-25) | 2.4 (0.1-36) | N/A |
| **ECOG PS, n (%)** | | | |
| 0 | 193 (77) | 85 (67) | 44 (84.6) |
| 1 | 49 (19) | 31 (25) | 8 (15.4) |
| 2 | 0 | 1 (1) | 0 |
| 3 | 0 | 0 | 0 |
| *Data missing* | 11 (4) | 9 (7) | *0* |

| | IMCgp100-202 [13] [49] | | GEM-1402 [11] |
|---|---|---|---|
| | Tebentafusp (n = 252) | Control (n = 126) | Ipi/nivo (n = 52) |
| **LDH >Upper limit of normal (ULN) (105-205), n (%)** | 90 (36) | 46 (37) | 27 (51.9) |
| *Data missing* | N/A | N/A | N/A |
| **Liver disease by UM recurrence, n (%)** | | | |
| Live disease | N/A | N/A | 41 (78.8) |
| Unilobular | N/A | N/A | 10 (19.2) |
| Multilobular | N/A | N/A | 2 (5.6) |
| **Largest metastatic lesion, n (%)** | | | |
| ≤3.0 cm, stage M1a | 139 (55) | 70 (56) | 23 (63.9) |
| 3.1 to 8.0 cm, stage M1b | 92 (37) | 46 (37) | 11 (30.6) |
| ≥8.1 cm, stage M1c | 21 (8) | 10 (8) | 2 (5.6) |
| **Location of metastasis, n (%)** | | | |
| Hepatic only | 131 (52) | 59 (47) | 22 (42.3) |
| Extrahepatic only | 9 (4) | 10 (8) | 11 (21.2) |
| Hepatic and extrahepatic | 113 (45) | 55 (44) | 19 (36.5) |
| Lungs | N/A | N/A | 22 (42.3) |
| Bone | N/A | N/A | 9 (17.3) |
| Nodal | N/A | N/A | 5 (9.6) |
| Brain (not active) | N/A | N/A | 2 (3.8) |
| Others** | N/A | N/A | 10 (19.2) |
| Data missing | 1 (0.4) | 2 (2) | N/A |
| **Prior local therapies, n (%)** | | | |
| Previous surgical therapy for metastatic disease | 24 (10) | 9(7) | N/A |
| Enucleation | N/A | N/A | 30 (57.7) |
| Brachytherapy | N/A | N/A | 26 (50.0) |
| External radiotherapy | N/A | N/A | 4 (7.7) |
| Conservative surgery | N/A | N/A | 3 (5.8) |
| Any | N/A | N/A | 2 (4) |

| | IMCgp100-202 [13] [49] | | GEM-1402 [11] |
|---|---|---|---|
| | Tebentafusp (n = 252) | Control (n = 126) | Ipi/nivo (n = 52) |
| **Previous treatment lines of metUM, n (%)** | | | |
| 0 | 252 (100) | 126 (100) | 52 100) |
| 1-4 | 0 (0) | 0 (0) | 0 (0) |
| **Other locations include lumbar (n = 2), perihepatic (n = 2), peritoneum (n = 2), skin (n = 1), pleura (n = 1), kidney (n = 1), and adrenal (n = 1) | | | |

### 6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The study populations in IMCgp100-202 and GEM-1402 are comparable with the Danish population regarding age and sex, while the performance score in the clinical setting is expected to be worse due to the studies inclusion criteria of an Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1, lower LDH, and differences in metastatic location [9–11,13,48,49]. In section 2.3.1 in the DMC's assessment report of tebentafusp it is stated that the study population in IMCgp100-202 is a selected patient population with better general health compared to the Danish patient population. However, in section 3.3.2 in the DMC's assessment report of tebentafusp, it is also stated that the patients are generally in good health, when they are diagnosed (often with an ECOG PS of 0-1), why it is assumed that the study population is comparable with Danish patients eligible for treatment. Relevant baseline characteristics for the Danish patient population and the corresponding values used in the health economic model are presented in Table 13. The reported values for the Danish patient population are based on 87 patients treated with ipi/nivo in the period July 2017 until November 2021 [7].

**Table 13. Characteristics in the relevant Danish population and in the health economic model**

| | Value in Danish population (n=87) [7] | Value used in health economic model [7] [13][49] |
|---|---|---|
| **Median age, year (range)** | 66 (20 - 80) | 66 |
| **Gender, n (%)** | | |
| Female | 39 (44.8) | 44.8% |
| **Median time since primary diagnosis, years** | N/A | 3.0 (0.1-25) |
| **ECOG PS, n (%)** | | |
| 0 | 63 (72.4) | 193 (77) |
| 1 | 22 (25.3) | 49 (19) |
| 2 | 2 (2.3) | 0 |
| **LDH >ULN (105-205), n (%)** | 42 (48.3) | N/A |
| **Largest metastatic lesion, n (%)** | | |
| ≤3.0 cm, stage M1a | N/A | N/A |
| 3.1 to 8.0 cm, stage M1b | N/A | N/A |

| | | |
|---|---|---|
| ≥8.1 cm, stage M1c | N/A | N/A |
| **Location of metastasis, n (%)** | | |
| Hepatic only | 44 (50.5) | N/A |
| Extrahepatic only | 5 (5.7) | N/A |
| Hepatic and extrahepatic | 38 (46.3) | N/A |
| Lungs | 25 (28.7) | N/A |
| Bone | 29 (33.3) | N/A |
| Nodal | 15 (17.2) | N/A |
| Brain (not active) | 4 (4.6) | N/A |
| **Prior local therapies, n (%)** | | |
| Previous surgical therapy for metastatic disease | N/A | N/A |
| **Previous treatment lines of metUM, n (%)** | | |
| 0 | 82 (94,2) | N/A |
| 1 | 3 (3,4) | N/A |
| 2 | 1 (1.1) | N/A |
| 3 | 0 (0) | N/A |
| 4 | 1 (1.1) | N/A |
| **Mean weight, kg** | N/A | 78.86 |
| **Mean BSA, $m^2$** | N/A | 1.90 |

### 6.1.4 Efficacy – results per IMCgp100-202

In the following section, the results for the endpoints, OS (including subgroup analyses), and PFS for DCO July 2023 are presented. Results for DCO October 2020 (primary analysis) and ORR for both DCOs are presented in Appendix A and described in detail in Appendix L.

#### 6.1.4.1 Overall survival – DCO October 2020

OS results from DCO October 2020 were presented in the previous application to the DMC. The results are also presented in Appendix A and described in detail in Appendix L.3.1.

#### 6.1.4.2 Overall survival – DCO July 2023

The time of clinical cut-off for the 3-year analysis of survival was July 3, 2023, corresponding to a median follow-up of 43.3 months [10]. The 3-year analysis showed a continued survival benefit favoring tebentafusp. The estimated median OS was 21.6 months [95% CI, 19.0; 24.3] in the tebentafusp group and 16.9 months [95% CI, 12.9; 19.5] in control group, with a HR for death of 0.68 [95% CI, 0.54; 0.87], see Figure 39 [10]. The survival rate at 12, 24, and 36 months in the tebentafusp treatment group was 72%, 45%, and 27%, respectively. This is compared to the control group in which the respective survival rates was 60%, 30%, and 18%, see Figure 39 in Appendix L.3 [10]. An

analysis conducted to include the patients who crossed over to the tebentafusp group censored at the start of treatment with tebentafusp, resulted in a HR for death of 0.70 [95% CI, 0.54; 0.90]. The 100-day landmark analysis involved the patients with the best OR of progressive disease at day 100 after randomization and resulted in a longer post-landmark OS in the tebentafusp treatment group compared to the control group, with a HR for death of 0.62 [95% CI, 0.44; 0.89] in favor of tebentafusp, see Figure 40 in Appendix L.3 [10].

#### 6.1.4.3 Overall survival subgroup analyses – DCO October 2020

OS subgroup analyses results from DCO October 2020 were presented in the previous application to the DMC. The results are also presented in Appendix A and described in detail in Appendix L.4.1.

#### 6.1.4.4 Overall survival subgroup analyses – DCO July 2023

Subgroup analyses for OS were conducted as pre-specified in trial protocol. Figure 42 in Appendix A.1 shows a forest plot summarizing the key results of the OS subgroup analyses by treatment group. The OS benefit of tebentafusp was observed across almost all prespecified major demographic and known prognostic subgroups, including a HR of 0.73 [95% CI, 0.56; 0.96] versus pembrolizumab [49].

#### 6.1.4.5 Progression-free survival – DCO October 2020

PFS results from DCO October 2020 were presented in the previous application to the DMC. The results are also presented in Appendix A and described in detail in Appendix L.5.1.

#### 6.1.4.6 Progression-free survival – DCO July 2023

PFS was 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 [36]. Patients who had not progressed or died at the time of the analysis were censored at the time of the last evaluable tumor assessment [37]. As presented in Figure 44 in Appendix L.5., the percentage of patients who were progression free at 12, 24, and 36 months among those treated with tebentafusp was 17%, 8%, and 4%, respectively, as compared with 9%,3%, and 0% among the patients in the control group [49]. Median PFS was 3.4 months [95% CI, 3.0; 5.4] in the tebentafusp group and 2.9 months [95% CI, 2.8; 3.0] in the control group. The stratified HR for progression or death was 0.76 [95% CI, 0.60; 0.97], see Figure 44 in Appendix L.5.

#### 6.1.4.7 Summary of primary efficacy results from IMCgp100-202

In DCO October 2020, the estimated OS was 21.7 months [95% CI; 18.6; 28.6] and 16.0 months [95% CI; 9.7;18.4] in the tebentafusp group and control group, respectively and the HR for death was 0.51 [95% CI; 0.37; 0.71] in favor of tebentafusp. In DCO July 2023, the estimated OS was 21.6 months [95% CI; 19.0; 24.3] in the tebentafusp group and

16.9 months [95% CI, 12.9; 19.5] in control group, with a HR for death of 0.68 [95% CI, 0.54; 0.87]. Results of the 3-year analysis of OS from study IMCgp100-202 supported a continued long-term survival benefit with tebentafusp among previously untreated HLA-A*02:01-positive patients with metUM.

### 6.1.5 Efficacy – results per GEM-1402

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 median OS was 12.7 months (95% CI, 7.1; 18.3), see Figure 48 in Appendix M.3, with a 12- and 24-month OS rate of 51.9% (95% CI, 38.3; 65.5) and 26.4% (95% CI, 14.2; 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 vs 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 49 in Appendix M.3. The median PFS was 3.0 [95% CI, 2.0; 4.1] months, see Figure 50 in Appendix M.3, 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 [11].

# 7. Comparative analyses of efficacy

The comparative analysis performed in this resubmission applies the above mentioned two most recent DCOs for IMCgp100-202 (July 3, 2023; median follow-up 43.3 months) and GEM-1402 (August 2023; median follow-up 35 months). The framework for this comparative analysis is the adjusted indirect analysis presented by Piulats et al. (2023) and colleagues. The primary objective of the analysis performed by Piulats et al. (2023) was to compare, using propensity score-based methods, OS of tebentafusp (IMCgp100-202) to OS of ipi/nivo (GEM-1402) in metUM patients in the 1$^{st}$ line setting. A secondary objective was to compare OS of pembrolizumab (IMCgp100-202) to OS of ipi/nivo (GEM-1402). The results from the secondary objective are not reported in this resubmission [9]. For a more detailed description of propensity score analysis, refer to Appendix C. Propensity score methods have been widely used in epidemiological settings for treatment comparisons involving nonrandomized studies. The approach mimics the effect of randomization by creating a balance between groups of patients with respect to important covariates of baseline demographic and disease characteristics, which enables adjustment for difference between two groups and valid statistical comparisons. Propensity score methods can be used in any setting involving the comparison of nonrandomized groups provided there is access to individual patient-level data with adequate information on known important prognostic factors. The authors reported a propensity score-weighted analysis using patient-level data from two metUM clinical trials to compare OS in patients treated with tebentafusp or pembrolizumab (IMCgp100-202) with OS in patients treated with the combination of ipi/nivo (GEM-1402) [9].

### 7.1.1 Differences in definitions of outcomes between studies

There are no discrepancies in the definition of the primary endpoint, OS, in study IMCgp100-202 and GEM-1402 [11,13].

### 7.1.2 Method of synthesis

Analyses were performed using SAS software version 9.4 in a validated statistical computing environment running Windows Server 2012. The prospective analyses were conducted using retrospective data sources according to a pre-specified statistical analysis plan (SAP) outlining the details of the propensity score-based methodology and covariates for adjustment prior to initiating the analyses. The covariates considered for the propensity score model were age, gender, baseline LDH (≤ or > ULN), baseline alkaline phosphatase (ALP) (≤ or > ULN), disease location (hepatic only, extrahepatic only, hepatic, and extrahepatic), ECOG PS (0 or ≥1), and time from primary diagnosis to metastasis. Due to the limited proportion of patients with extrahepatic disease only in IMCgp100 compared to GEM-1402, potential impacts on effective sample size and/or modelling issues were acknowledged. Consequently, two alternative approaches to defining the disease location covariate were explored: disease location pooled categories (hepatic only, any extrahepatic [pooled extrahepatic only plus hepatic and extrahepatic]) and largest metastatic liver lesion (≤3 cm, >3 cm, no liver lesions). Propensity scores were estimated using the identified covariates as main effects in a logistic regression model. Separate models were fitted for comparing tebentafusp vs ipi/nivo aiming to predict the probability of a patient in the analysis population being treated with tebentafusp (i.e., being from IMCgp100-202 rather than GEM-1402) with the propensity score representing the probability of being treated with tebentafusp. The decision on the final set of covariates in the primary propensity score generating model was based on several factors such as model fit statistics, distribution of propensity scores/weights (minimizing extreme weights, etc.), and amount of missing data. These decisions were made without knowledge and independent of the impact on the survival analysis outcomes [9]. The final propensity score analysis incorporated all planned covariates. The three-level disease location covariate was used in the final model for the following reasons: it demonstrated no model fitting issues with a good balance between treatments after weighting with no extreme weights; it provided more information than two-level disease location pooled categories; it was more strongly associated with patients in IMCgp100-202 vs GEM-1402 compared to the two-level (extrahepatic only is one of the more imbalanced factors between the studies); and resulted in less missing data compared to the largest metastatic liver lesion covariate, while maintaining slightly better balance for other covariates such as age. The propensity scores were converted to inverse probability of treatment weights (IPTWs), assigning a weight of 1 to patients treated with tebentafusp. Subsequently, these IPTWs were applied in a weighted survival analysis to adjust for differences in patient characteristics across treatments. Schematic of IPT-weighting is presented in Figure 10 [9]. The primary endpoint, OS, was assessed through weighted KM curves including medians and 95% CIs as well as 1-year estimates. Additionally, an IPT-weighted HR and 95% CI were derived from a weighted Cox regression model, utilizing robust sandwich estimation for variance calculation. To provide context, groups were also compared using an unadjusted Cox regression model

and unweighted KM curves to evaluate the impact and direction of IPT weighting on the naive unadjusted treatment effect (see Figure 15). In Piulats et al., 2023, the primary survival analysis was a complete case, excluding patients with missing data for at least one relevant covariate using the ATT IPT weights. Sensitivity analyses included alternative missing data methods (multiple imputation) and weights (stabilized and unstabilized average treatment effect of the control (ATC), average treatment effect (ATE)) and a multivariate Cox regression analysis adjusted for the same effects as in the primary propensity score model [9]. In the model base-case, the ATT approach is applied. In the ATT approach, the reference population is the patients who received tebentafusp in the study IMCgp100-202, and the ipi/nivo patients are weighted to match the tebentafusp patients. The ATT approach was considered most appropriate as it better reflects the trial population and overall estimates for tebentafusp. A schematic of ATT IPT-weighting for a single confounder (disease location) is presented in Figure 10 in Appendix C.6.4. In addition, the model also allows for the ATC approach, where the reference population is that of the Piulats et al. study who received ipi/nivo, and patients in the tebentafusp group are weighted to match patients in the ipi/nivo group. In the primary complete case analysis, 12 out of 252 patients (4.8%) who received tebentafusp in IMCgp100-202, and 7 out of 52 patients (13.5%) who received ipi/nivo in GEM-1402 were excluded due to missing baseline covariates. The IPTW analysis included a total of 240 patients in the tebentafusp group and 45 patients in the ipi/nivo group. Key baseline covariates such as LDH, ALP, and ECOG PS were generally well-balanced across the two treatments. More patients in GEM-1402 have extrahepatic disease only, however, following IPT weighting, all key baseline characteristics were well balanced. The observed and IPT-weighted (ATT) patient characteristics for tebentafusp and ipi/nivo are presented in Table 14, and Figure 12 and Figure 13 in Appendix C.7.1.

**Table 14. Patient characteristics observed and IPT weighted (ATT) by treatment** [9].

| Characteristic | Tebentafusp observed (n=240) | Ipi/nivo observed (n=45) | Tebentafusp weighted (n=240[a]) | Ipi/nivo weighted (n=241.9[a]) |
|---|---|---|---|---|
| Age (years) mean (SD) | 61.2 (12.02) | 59.3 (13.3) | 61.2 (12.0) | 61.7 (30.2) |
| Male | 122 (50.8%) | 23 (51.1%) | 122 (50.8%) | 112.6 (46.6%) |
| Baseline LDH > ULN | 84 (35.0%) | 19 (42.2%) | 84 (35.0%) | 81.8 (33.8%) |
| Baseline ALP > ULN | 51 (21.3%) | 7 (15.6%) | 51 (21.3%) | 50.6 (20.9%) |
| Disease location extrahepatic only | 9 (3.8%) | 10 (22.2%) | 9 (3.8%) | 8.5 (3.5%) |
| Disease location hepatic only | 123 (51.3%) | 20 (44.4%) | 123 (51.3%) | 124.0 (51.3%) |
| Disease location both | 108 (45.0%) | 15 (33.3%) | 108 (45.0%) | 109.4 (45.2%) |
| ECOG PS 0 | 191 (79.6%) | 38 (84.4%) | 191 (79.6%) | 199.3 (82.4%) |
| Time from diagnosis to metastasis (years) mean (SD) | 4.0 (4.4) | 4.7 (4.6) | 4.0 (4.4) | 4.1 (9.6) |

[a]Weighted N is the sum of the weights.

### 7.1.3 Results from the comparative analysis

This patient-level propensity score-weighted analysis, which was well balanced for key baseline covariates, demonstrated that tebentafusp resulted in significantly superior OS (HR=0.52 [95% CI: 0.35; 0.78]) compared with ipi/nivo in patients with previously

untreated metUM. Based on the IPTW analysis, the calculated 1-year OS rates of 73% for tebentafusp and 50% for ipi/nivo were very similar to those observed in each of the original trials (73% and 52%, respectively). The results from the comparative analysis are presented in Figure 14 in Appendix C.7.2 and Table 15 [9].

**Table 15. Results from the comparative analysis of tebentafusp vs. ipi/nivo for patients with untreated metUM** [9].

| Outcome measure | Tebentafusp (n=240) | Ipi/nivo (n=45) | Result |
|---|---|---|---|
| **Median OS** [9] | Median: 21.7 months | Median: 12.6 months | HR = 0.52 [95 % CI: 0.35; 0.78] |
| **OS 1-year rate** [9] | 73% | 50% | - |

The sensitivity analyses for tebentafusp vs ipi/nivo showed consistent superior OS with all IPTW HRs of ≤ 0.61. The results are presented in Figure 15 in Appendix A.1.1.

#### 7.1.4 Efficacy – results per [outcome measure] (N/A)

# 8. Modelling of efficacy in the health economic analysis

## 8.1 Presentation of efficacy data from the clinical documentation used in the model

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 IMCgp100-202 for tebentafusp and GEM-1402 for ipi/nivo. The clinical inputs for OS for tebentafusp and ipi/nivo are based on IPD from the latest DCO for both studies (July 2023 and August 2023, respectively). However, IPD for PFS was not available for the latest DCOs of the two studies and therefore PFS for tebentafusp is based on the match adjusted indirect comparison (MAIC) using DCO October 2020 from study IMCgp100-202 and DCO July 2019 from GEM-1402. No modifications have been made to the MAIC since the initial DMC assessment of tebentafusp; hence, it is not included in this section. The MAIC, however, is comprehensively detailed in the initial submission to the DMC [40].

### 8.1.1 Extrapolation of efficacy data

For completeness, an assessment of the PH assumption was made and is presented in Appendix D. Based on the data presented in Appendix D, the results overall indicate that the PH assumption holds. However, given the availability of the IPD, the data were fitted separately to each treatment group, negating the need to assume PH. This also allows for 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 [50]. Hazard functions were used to assess the suitability of the parametric models and are presented in Appendix D. 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 increase or decrease) 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 the following: Akaike information criterion (AIC), Bayesian information criterion (BIC), visual inspection of fit to the KM curve, and clinical experts' opinion. 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 (see Appendix D). To identify the parametric model with the best fit, the AICs and BICs were initially ranked separately, followed by a 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 the sum of ranks, the better the fit).

#### 8.1.1.1 Extrapolation of overall survival

Based on AIC and BIC for ATT-weights presented in Appendix D, the model with the best fit in the tebentafusp group is the log-logistic distribution. According to the published 3-year analysis of OS for tebentafusp, which provided a more robust prediction of long-term survival indicating a 5-year OS of >15%, the application of the log-logistic distribution to the tebentafusp group resulted in a clinically plausible 5-year OS of [redacted] In the ipi/nivo group, the model with the best fit is generalized gamma, which resulted in a 5-year OS of 4.36%. Based on the clinical expert consulted in the initial assessment of tebentafusp, external evidence and DMC assessment report, generalized gamma distribution was assessed to be clinically plausible, and thus chosen in the base case [7,8]. A summary of assumptions associated with extrapolation of OS is presented in Table 16, and the observed OS for tebentafusp and ipi/nivo is illustrated in Figure 4.

**Table 16. Summary of assumptions associated with extrapolation of overall survival**

| Method/approach | Description/assumption |
|---|---|
| **Data input** | Tebentafusp: NCT03070392, IMCgp100-202 (DCO July 2023) [10]<br>Ipi/nivo: NCT02626962, GEM-1402 (DCO August 2023) [11] |
| **Model** | Full parametrization |
| **Assumption of proportional hazards between intervention and comparator** | No |
| **Function with best AIC fit** | Tebentafusp: Log-logistic<br>Ipi/nivo: Generalized Gamma |
| **Function with best BIC fit** | Tebentafusp: Log-logistic<br>Ipi/nivo: Generalized Gamma |
| **Function with best visual fit** | Tebentafusp: Log-logistic<br>Ipi/nivo: Exponential/Generalized Gamma |
| **Function with best fit according to evaluation of smoothed hazard assumptions** | Tebentafusp: log-logistic/log-normal/generalized gamma<br>Ipi/nivo: None |

| Method/approach | Description/assumption |
|---|---|
| **Validation of selected extrapolated curves (external evidence)** | Clinical expert opinion on clinical plausibility consulted in initial application of tebentafusp, and DMC assessment report of tebentafusp |
| **Function with the best fit according to external evidence** | Tebentafusp: N/A<br>Ipi/nivo: Exponential |
| **Selected parametric function in base case analysis** | Tebentafusp: Log-logistics<br>Ipi/nivo: Generalized Gamma |
| **Adjustment of background mortality with data from Statistics Denmark** | Yes |
| **Adjustment for treatment switching/cross-over** | No |
| **Assumptions of waning effect** | No |
| **Assumptions of cure point** | No |

**Figure 4. Observed time-to-event data (OS) for tebentafusp and ipi/nivo.**

#### 8.1.1.2 Extrapolation of progression-free survival

The description for extrapolation of PFS has not changed since the initial assessment for tebentafusp. For description of the extrapolation of PFS, refer to the previous application [40] or Appendix D.2. A summary of assumptions associated with extrapolation of PFS is presented in Table 17, and the observed PFS for tebentafusp and ipi/nivo is illustrated in Figure 5.

**Table 17. Summary of assumptions associated with extrapolation of progression-free survival.**

| Method/approach | Description/assumption |
|---|---|
| **Data input** | Tebentafusp: NCT03070392, IMCgp100-202 (DCO October 2020) [13]<br>Ipi/nivo: NCT02626962, GEM-1402 (DCO July 2019) [11] |
| **Model** | Full parametrization |

| Method/approach | Description/assumption |
|---|---|
| **Assumption of proportional hazards between intervention and comparator** | No |
| **Function with best AIC fit** | Tebentafusp: Generalized Gamma<br>Ipi/nivo: Generalized Gamma |
| **Function with best BIC fit** | Tebentafusp: Generalized Gamma<br>Ipi/nivo: Generalized Gamma |
| **Function with best visual fit** | Tebentafusp: Generalized Gamma<br>Ipi/nivo: Generalized Gamma |
| **Function with best fit according to evaluation of smoothed hazard assumptions** | Tebentafusp: Generalized Gamma<br>Ipi/nivo: Generalized Gamma |
| **Validation of selected extrapolated curves (external evidence)** | Clinical expert opinion on clinical plausibility consulted in initial application of tebentafusp, and DMC assessment report of tebentafusp [40] |
| **Function with the best fit according to external evidence** | N/A |
| **Selected parametric function in base case analysis** | Tebentafusp: Generalized Gamma<br>Ipi/nivo: Generalized Gamma |
| **Adjustment of background mortality with data from Statistics Denmark** | Yes |
| **Adjustment for treatment switching/cross-over** | No |
| **Assumptions of waning effect** | No |
| **Assumptions of cure point** | No |

**Figure 5. Observed time-to-event data (PFS) for tebentafusp and ipi/nivo.**

### 8.1.2 Calculation of transition probabilities (N/A)

**Table 18. Transitions in the health economic model**

| Health state (from) | Health state (to) | Description of method | Reference |
|---|---|---|---|
| Disease-free survival | Recurrence | N/A | N/A |
| | Death | N/A | N/A |
| Recurrence | Death | N/A | N/A |

| | | | |
|---|---|---|---|
| Health state/Transition | N/A | N/A | N/A |

## 8.2 Presentation of efficacy data from additional documentation (N/A)

## 8.3 Modelling effects of subsequent treatments

Clinical evidence suggests that some patients treated with immunotherapies, including tebentafusp, will derive clinical benefit after an initial assessment of Progressed disease (PD) [51–53]. Therefore, as per the IMCgp100-202 study protocol, patients could continue treatment beyond disease progression. 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 group, respectively [39]. However, the clinical expert consulted for the initial application stated that patients treated with ipi/nivo do not receive treatment beyond progression. Thus, 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 group, the number of patients on treatment in a given cycle was 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 19.

**Table 19. Treatment beyond disease progression.**

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

## 8.4 Other assumptions regarding efficacy in the model

### 8.4.1 Treatment adherence

#### 8.4.1.1 Clinical data

In study IMCgp100-202 (DCO October 2020), 42.4% of the patients treated with tebentafusp had an interruption at any time, with a mean duration of 22.2 days, and 18 patients (7.3%) had a reduction from protocol dose level. Based on an analysis of dose interruption on the safety and efficacy of tebentafusp, after reaching 68 mcg, patients receiving tebentafusp can have one or two omissions of less than 2 weeks duration with minimal impact on safety and efficacy. That means up to four weeks a year or a compliance of 92% (48/52). The majority of treatment interruptions in the trial were less than two weeks (72%). Treatment restart was typically in the outpatient setting (95%), without dose modification from the most recent dose (98%) or steroid premedication (98%). Grade 2 CRS was uncommon at restart and occurred mostly in patients with preceding grade 2 CRS. As observed in Table 20, treatment interruption in the investigators choice (IC) group was limited (16.5%) and most patients did not have an

interruption or a dose reduction (83.5%). Therefore, an adherence of ipi/nivo was not applied to the model [54].

#### 8.4.1.2 Modelling approach

Duration of treatment based on the date of first dose to date of discontinuation (i.e., TTD) does not account for missed doses or interruptions. A compliance of 92% for tebentafusp reflects up to four doses missed in a year (two interruptions of up to two weeks, 48/52 weeks). The total combined costs of tebentafusp plus administration are weighted to account for the number of interruptions/missed doses for a compliance of 92%. An adjustment for adherence was not applied to the ipi/nivo group because the interval between infusions is 3 weeks for the combination therapy and two weeks for nivolumab monotherapy. The burden on patients is significantly less as demonstrated by the limited treatment interruptions in the trial (Table 20) with similar therapies (pembrolizumab, ipilimumab) and treatment intervals. Patients discontinuing treatment permanently are accounted for in the time to treatment discontinuation (TTD) [39,55].

**Table 20. Summary of dose interruptions and reductions (safety analysis set) - IMCgp100-202.**

| | IMCgp100-202 (N=245) | Investigator's Choice (N=111) |
|---|---|---|
| **Received intrapatient dose escalation as planned** | | |
| Yes | 215 (87.8) | 0 |
| No | 30 (12.2%) | 0 |
| **No interruption and no reduction at any time** | 137 (55.9%) | 94 (84.7%) |
| **At least one interruption or reduction** | 108 (44.1%) | 17 (15.3%) |
| **No interruption at any time** | 141 (57.6%) | 96 (86.5%) |
| **Number of patients with an interruption[1]** | | |
| Any | 104 (42.4%) | 15 (13.5%) |
| 1 interruption | 63 (25.7%) | 15 (13.5%) |
| 2 interruptions | 17 (6.9%) | 0 |
| 3 interruptions | 10 (4.1%) | 0 |
| 4 interruptions | 3 (1.2%) | 0 |
| 5 interruptions | 3 (1.2%) | 0 |
| 6 interruptions | 2 (0.8%) | 0 |
| 7 interruptions | 1 (0.4%) | 0 |
| 8 interruptions | 1 (0.4%) | 0 |
| 9 interruptions | 1 (0.4%) | 0 |
| 10 interruptions | 2 (0.8%) | 0 |
| 12 interruptions | 1 (0.4%) | 0 |
| Total number of interruptions | 222 | 15 |
| **Reason for interruption at any time** | | |
| Missed Visit | 89 (40.1%) | 2 (13.3%) |
| Adverse Event | 50 (22.5%) | 12 (80.0%) |

| | IMCgp100-202 (N=245) | Investigator's Choice (N=111) |
|---|---|---|
| Delayed Administration | 36 (16.2%) | 0 |
| Other | 34 (15.3%) | 0 |
| Scheduled visit not done | 10 (4.5%) | 1 (6.7) |
| Unknown | 2 (0.9%) | 0 |
| Missing | 1 (0.5%) | 0 |
| **Duration of interruption (days)** | | |
| n | 104 | 15 |
| Mean (SD) | 22.2 (27.05) | 24.0 (11.19) |
| Median | 14.0 | 21.0 |
| Min, Max | 0, 146 | 14, 49 |
| **No reduction at any time** | 227 (92.7%) | 109 (98.2%) |

Interruptions are only counted if study drug administration restarts following interruption.

[1]The total number of interruptions is the sum of all patients' interruptions. It is the denominator of the reason for interruption at any time. Source: [54]

## 8.5 Overview of modelled average treatment length and time in model health state

Estimates for the modelled average and modelled median of OS predicted by the extrapolation model are presented in Table 21. In Table 22 an overview of the modelled average treatment length and time in model health state is provided.

**Table 21. Estimates in the model**

| | Modelled average Overall survival (Tebentafusp sheet, cell AA4 and Ipi+Nivo sheet, cell AA4) | Modelled median Overall survival (Tebentafusp sheet, cell AA6 and Ipi+Nivo sheet, cell AA6) | Observed median from Piulats et al., 2023 [9] |
|---|---|---|---|
| **Tebentafusp** | 35.7 months | 21.4 months | 21.7 months |
| **Ipi/nivo** | 17.4 months | 10.3 months | 12.6 months |

**Table 22. Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction.**

| Treatment | Treatment length [months] | PFS health state [months] | OS [months] |
|---|---|---|---|
| **Tebentafusp** | 10.8 | 9.4 | 35.7 |
| **Ipi/nivo** | 8.4 | 6.9 | 17.4 |

# 9. Safety

## 9.1 Safety data from the clinical documentation

In the following sections, the safety data for tebentafusp from IMCgp100-202 (DCO October 2020 and July DCO 2023) and safety data for ipi/nivo from GEM-1402 are presented.

### 9.1.1 Safety data from IMCgp100-202 – DCO October 2020

The safety data from the DCO October 2020 was described in the previous application to the DMC and is thus presented in Appendix L.6.1.

### 9.1.2 Safety data from IMCgp100-202 – DCO July 2023

The safety profile of the 3-year analysis of survival (DCO July 2023) remained consistent with the primary analysis (DCO October 2020), with no new types of AEs with long-term administration [10,49]. The most common TRAE of any grade in the tebentafusp group were rash (83%), pyrexia (76%), pruritus (70%), and hypotension (38%) [10,49]. Grade 3 or 4 TRAEs occurred in 116 (47%); the most common being rash (19%), and an elevation in the aspartate aminotransferase (AST) level (6%), see Table 23 [10,49].

**Table 23. Summary of TRAEs in the Safety Analysis Set – DCO July 2023** [10,49].

| | IMCgp100-202 DCO July 2023 | | | |
|---|---|---|---|---|
| | Tebentafusp (n = 245) | | Investigator choice (n = 111) | |
| | Any grade (≥20%)* | Grade 3-4 (≥2%)* | Any grade (≥20%)* | Grade 3-4 (≥2%)* |
| Any TRAE, n (%) | 244 (100) | 116 (47) | 91 (82) | 20 (18) |
| *CRS†* | *217 (89)* | *2 (1)* | - | - |
| Rash‡ | 204 (83) | 46 (19) | 30 (27) | 0 |
| Pyrexia | 187 (76) | 11 (5) | - | - |
| Pruritus | 171 (70) | 11 (5) | 25 (23) | 0 |
| Chills | 120 (49) | 2 (1) | - | - |
| Nausea | 110 (45) | 3 (1) | - | - |
| Fatigue | 103 (42) | 7 (3) | 28 (25) | 1 (1) |
| Hypotension | 93 (38) | 9 (4) | - | - |
| Dry skin | 72 (29) | 0 | - | - |
| Vomiting | 66 (27) | 1 (0) | - | - |
| Erythema | 59 (24) | 0 | - | - |
| Headache | 53 (22) | 1 (0) | - | - |
| AST increased | 52 (21) | 14 (6) | - | - |
| Hair color changes | 50 (20) | 0 | - | - |

| | IMCgp100-202 DCO July 2023 | | | |
|---|---|---|---|---|
| | Tebentafusp (n = 245) | | Investigator choice (n = 111) | |
| | Any grade (≥20%)* | Grade 3-4 (≥2%)* | Any grade (≥20%)* | Grade 3-4 (≥2%)* |
| Alanine aminotransferase (ALT) increased | 49 (20) | 9 (4) | - | - |
| Lipase increased | 36 (15) | 9 (4) | - | - |
| Lymphopenia | 23 (9) | 7 (3) | - | - |
| Hyperbilirubinemia | 22 (9) | 5 (2) | | |
| Hypophosphatemia | 20 (8) | 8 (3) | - | - |
| Hypertension | 17 (7) | 10 (4) | - | - |

*Related AEs reported in ≥20% incidence for events at any grade or ≥2% of grade 3-4. †CRS was graded according to 2019 American Society for Transplantation and Cellular Therapy consensus grading. ‡ Rash is a composite term for a list of skin-related AEs.

CRS occurred in 89% of the patients in the tebentafusp group and was most frequent in the first 4 weeks of treatment, see Table 23 [10,49]. The majority of the patients who had CRS (88%) had grade 1 (12%) or 2 (76%) as the maximum grade. 2 (1%) patients had a grade 3 event. The grade 3 or 4 TRAEs that occurred after the initial 6 months of treatment were primarily laboratory abnormalities (e.g., increases in the AST level) that were temporally associated with disease progression. No new treatment-related discontinuations were reported: during the trial, 2% of the patients in the tebentafusp group and 5% of those in the control group discontinued treatment because of AEs that were related to treatment. No new treatment-related deaths occurred during the trial. Selected tebentafusp-related AEs over time is presented in Figure 46 in Appendix L.6. Most tebentafusp-related AEs occurred within the first 4 weeks of treatment during administration of step-up doses and decreased in frequency and severity with subsequent doses, see Figure 46 in Appendix L.6 [10].

### 9.1.3 Safety data from GEM-1402

A medical history was obtained at baseline to capture relevant underlying conditions. Safety was evaluated for all patients receiving at least one dose of ipi/nivo. Any occurrence of non-serious and serious AEs was reported from the first dose up to and including follow-up visits. Safety was evaluated by using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, and was based on the medical review of AE reports, the results of vital sign measurements, physical examinations, and clinical laboratory tests. See Table 24, Appendix B and Appendix D for further details. Overall, the AEs observed in the study did not differ greatly from the profile observed for ipi/nivo in CM [11].

**Table 24. GEM-1402 safety results** [11]

| | Ipi/nivo (n = 52) |
|---|---|
| **AEs, n (%)** | 52 (100) |
| **TRAEs, n (%)** | 49 (94) |

| | |
|---|---|
| **TRAEs GRADE ≥ 3 , n (%)** | 30 (58) |
| **TR-SAEs, n (%)** | 30 (58) |
| **TR-SAEs GRADE ≥ 3, n (%)** | 21 (40) |
| **Non-treatment related SAEs, n (%)** | 26 (50) |
| **Non-treatment related serious event grade ≥ 3, n (%)** | 14 (27) |
| **Discontinuation due to clinically unacceptable toxicity, n (%)** | 23.1% (12) |
| **Treatment related deaths, n (%)** | 2 (4) |

**Table 25. Overview of safety events.**

| | IMCgp100-202 | | | | GEM-1402 [11] | |
|---|---|---|---|---|---|---|
| | DCO October 2020 [13,48,54] | | DCO July 2023 [10,49] | | | |
| | Tebentafusp (n=245) | Investigator's Choice (n=111) | Tebentafusp, (n=245) | Investigator's Choice (n=111) | Ipi/nivo (n=52) | Difference, % [95 % CI] |
| **Number of adverse events, n** | N/A | N/A | N/A | N/A | N/A | N/A |
| **Number and proportion of patients with ≥1 adverse events, n (%)** | TRAE: 243 (99%) | TRAE: 91 (82%) | TRAE: 244 (100%) | TRAE: 91 (82%) | AE: 52 (100%)<br>TRAE: 49 (94%) | N/A |
| **Number of serious adverse events, n** | N/A | N/A | N/A | N/A | N/A | N/A |
| **Number and proportion of patients with ≥ 1 serious adverse events, n (%)** | 69 (28%) | 26 (23%) | 79 (32%) | 24 (22%) | TR-SAE: 30 (58%) | N/A |
| **Number of CTCAE grade ≥ 3 events, n** | N/A | N/A | N/A | N/A | N/A | N/A |
| **Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)** | Related TEAE: 109 (45) | Related TEAE: 19 (17) | TRAE: 116 (47) | TRAE: 20 (18%) | TRAE: 30 (58%) | N/A |
| **Number of adverse reactions, n** | N/A | N/A | N/A | N/A | N/A | N/A |
| **Number and proportion of patients with ≥ 1 adverse reactions, n (%)** | N/A | N/A | N/A | N/A | N/A | N/A |
| **Number and proportion of patients who had a dose reduction, n (%)** | 18 (7.3) | 2 (1.8) | N/A | N/A | N/A | N/A |
| **Number and proportion of patients who discontinue treatment regardless of reason, n (%)** | N/A | N/A | N/A | N/A | 48 (92%) | N/A |

| | IMCgp100-202 | | | | GEM-1402 [11] | |
|---|---|---|---|---|---|---|
| | DCO October 2020 [13,48,54] | | DCO July 2023 [10,49] | | | |
| | Tebentafusp (n=245) | Investigator's Choice (n=111) | Tebentafusp, (n=245) | Investigator's Choice (n=111) | Ipi/nivo (n=52) | Difference, % [95 % CI] |
| **Number and proportion of patients who discontinue treatment due to adverse events, n (%)** | AE: 8 (3.3%)<br>TRAE: 5 (2%) | AE: 7 (6.3%)<br>TRAE: 5 (5%) | TRAE: 5 (2%) | TRAE: 5 (5%) | 12 (23.1%)* | N/A |

Time period for DCO 2020: The median duration of treatment was 163.0 days for tebentafusp and 65.0 days for investigator's choice (CSR) [54].
*Discontinuation due to clinically unacceptable toxicity.

**Table 26. Serious adverse events (≥ 5%).**

| | IMCgp100-202 | | | | | | | | GEM-1402 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | DCO October 2020 [48] | | | | DCO July 2023 [49] | | | | [11] | |
| **Adverse events** | **Tebentafusp (n=245)** | | **Investigator's Choice (n=111)** | | **Tebentafusp (n=245)** | | **Investigator's Choice (n=111)** | | **Ipi/nivo (n=52)** | |
| | Number of patients with adverse events | Number of adverse events | Number of patients with adverse events | Number of adverse events | Number of patients with adverse events | Number of adverse events | Number of patients with adverse events | Number of adverse events | Number of patients with adverse events | Number of adverse events |
| **Serious adverse event, n (%)** | 69 (28%) | N/A | 26 (23%) | N/A | 79 (32%) | N/A | 24 (22%) | N/A | 30 (58%) | N/A |
| **Immune system disorders** | 25 (10%) | N/A | 0 | N/A | 25 (10%) | N/A | 0 | N/A | N/A | N/A |
| CRS | 24 (10%) | N/A | 0 | N/A | 24 (10%) | N/A | 0 | N/A | N/A | N/A |
| **Respiratory, thoracic and mediastinal disorders** | 4 (2%) | N/A | 6 (5%) | N/A | 5 (2%) | N/A | 6 (5%) | N/A | N/A | N/A |

| | IMCgp100-202 | | | | | | | | GEM-1402 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | DCO October 2020 [48] | | | | DCO July 2023 [49] | | | | [11] | |
| **Adverse events** | **Tebentafusp (n=245)** | | **Investigator's Choice (n=111)** | | **Tebentafusp (n=245)** | | **Investigator's Choice (n=111)** | | **Ipi/nivo (n=52)** | |
| **Gastrointestinal disorders** | 7 (3%) | N/A | 7 (6%) | N/A | 8 (3%) | N/A | 7 (6%) | N/A | N/A | N/A |
| Diarrhea | 0 | N/A | 1 (1%) | N/A | 0 | N/A | 1 (1%) | N/A | 3 (6%) | N/A |
| **Hepatobiliary disorders /Liver toxicity/liver-related events**** | 8 (3%) | N/A | 3 (3%) | N/A | 7 (3%) | N/A | 3 (3%) | N/A | 3 (6%) | N/A |
| **Skin and subcutaneous tissue disorders** | 14 (6%) | N/A | 0 | N/A | 15 (6%) | N/A | 0 | N/A | 1 (2%) | N/A |
| Fever | 6 (2%) | N/A | 2 (2%) | N/A | 7 (3%) | N/A | 2 (2%) | N/A | 4 (8%) | N/A |
| Drug administration incidences^ | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | 3 (6%) | N/A |

^Includes two drug administrations or treatment reported with incidences (quarantine) and 1 ipilimumab overdose. ** Liver toxicity includes all events reported by the investigators as both liver toxicity per se and laboratory abnormalities compatible.

### 9.1.4 Narrative analysis of safety (IMCgp100-202 vs GEM-1402)

This section includes a narrative analysis of safety comparing treatment with tebentafusp from IMCgp100-202 (DCO July 2023) to treatment with ipi/nivo GEM-1402 [11,48]. Aggregated results for safety data only were available for the GEM-1402 study [11] however, due to the differences in the patient characteristics of each study, a MAIC for safety analyses was not deemed feasible to provide significant additional insights compared to a simple narrative analysis. The safety profiles for the two studies were therefore compared using a narrative analysis. Over 90% of all patients treated with either tebentafusp or ipi/nivo experienced a TRAE of any grade, while grade ≥3 or above TRAEs were reported in 47% of patients in the tebentafusp group and 58% of patients in the ipi/nivo group. For serious TRAEs, the numbers were 32% and 58% respectively, see Table 27 [10,11,49]. For tebentafusp the most common TRAE were cytokine-related AEs, such as pyrexia 76%, chills 49%, and hypotension 38%, together with skin-related AEs, such as rash 83%, pruritus 70%, and erythema 24% [10,49]. For ipi/nivo the most common adverse effects included, skin-related events (62%), fatigue (58%), and liver toxicity/liver-related events (37%) [11]. According to the clinical expert consulted in the initial assessment, 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 [56]. Discontinuation due to AEs were reported in 2% and 23% of patients treated with tebentafusp and ipi/nivo, respectively. Deaths due to AEs were reported in 0% and 4% of patients treated with tebentafusp and ipi/nivo respectively, see Table 27 [11,13,48]. According to the clinical expert consulted in the initial assessment and based on DMC assessment of tebentafusp, ipi/nivo is described as a well-known treatment with a heavy safety profile, mainly due to immune-related side effects such as liver related AEs [7,56]. Another relevant AE that patients developed is fatigue, which occurred in 42% of patients treated with tebentafusp and 58% of patients treated with ipi/nivo [11,48]. The overall safety data according to the number of grades ≥3 and SAEs indicated that tebentafusp had a less toxic safety profile than ipi/nivo [10,11,13,48,49]. This is supported by the DMC's previous assessment of tebentafusp, which states that tebentafusp has numerically fewer grades ≥ 3 and less serious adverse reactions than ipi/nivo [7]. Tebentafusp having a less toxic safety profile is further supported by the higher number of patient discontinuations with ipi/nivo than tebentafusp and the number of treatment-related deaths [10,11,49]. 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 [10,11,13,48,49]. The safety results from the 3-year analysis remained consistent with the primary analysis of tebentafusp [10,49].

**Table 27. Adverse events for IMCgp100-202 and GEM-1402.**

| | IMCgp100-202 | | GEM-1402 |
|---|---|---|---|
| | Tebentafusp, DCO October 2020 [13,48] (n=245) | Tebentafusp, DCO July 2023 [10,49] (n=245) | Ipi/nivo [11] (n = 52) |
| **TRAEs any grade, n (%)** | 243 (99) | 244 (100) | 49 (94) |
| **Grade ≥ 3 TRAE, n (%)** | 109 (44) | 116 (47) | 30 (58) |

| | | | |
|---|---|---|---|
| **TR-SAE, n (%)** | 69 (28) | 79 (32) | 30 (58) |
| **Discontinuation due to TRAEs, n (%)** | 5 (2) | 5 (2) | 12 (23)* |
| **Death due to TRAEs, n (%)** | 0 | 0 | 2 (4) |

*Unspecified whether the AEs are treatment related or treatment emergent, GEM-1402 uses the term clinically unacceptable toxicity

### 9.1.5 Adverse events used in the health economic model

The clinical documentation for the AEs included in the model are IMCgp100-202 (DCO October 2020) and GEM-1402 (DCO July 2019) due to the comparable median follow-up. AEs included in the health economic analysis are all grade ≥3 AEs with a prevalence in more than 3% of patients, under treatment with tebentafusp in the IMCgp100-202 study or ipi/nivo in the GEM-1402 study, as well as endocrine disorders of any grade, in line with NICE appraisals of ipilimumab and pembrolizumab in advanced melanoma [11,46,57]. This is justified by the knowledge of being related to the use of immune checkpoint inhibitors and are associated with high costs and/or long-term impacts. AE rates from both studies are presented in Table 28. The AEs and SAEs have been summed up to derive the rate of grade ≥3 AEs, or any grade for endocrine disorders.

**Table 28. Adverse events used in the health economic model (≥3%).**

| Adverse events, n (%) | Tebentafusp | Ipi/nivo | | |
|---|---|---|---|---|
| | **Frequency used in economic model for intervention** | **Frequency used in economic model for comparator** | **Source** | **Justification** |
| Rash | 9.4% | 9.6% | [54] | The AEs reported in this table is related to the use of immune checkpoint inhibitors and are associated with high cost and/or long-term impacts. |
| Rash maculo-papular | 8.6% | - | [54] | |
| Pruritus | 4.5% | - | [54] | |
| AST increased | 5.3% | - | [54] | |
| Lipase increased | 4.1% | - | [54] | |
| ALT increased | 3.3% | - | [54] | |
| Hypertension | 8.6% | - | [54] | |
| Hypotension | 3.3% | - | [54] | |
| Fatigue | 5.3% | 9.6% | [54] | |
| Pyrexia | 3.7% | 1.92% | [54] | |
| Hypophosphataemia | 4.1% | - | [54] | |
| Hyperbilirubinaemia | 3.3% | - | [54] | |
| Liver toxicity/liver-related events | - | 26.9% | [54] | |
| Hepatitis | - | 3.8% | [54] | |
| Diarrhoea | 1.2% | 11.5% | [54] | |
| Guillain-Barré syndrome | - | 3.8% | [54] | |
| Hypothyrodism | - | 15.4% | [54] | |
| Thyroiditis | - | 9.6% | [54] | |

## 9.2 Safety data from external literature applied in the health economic model (N/A)

**Table 29 Adverse events that appear in more than X % of patients**

| Adverse events | Intervention (N=x) | | | Comparator (N=x) | | | Difference, % (95 % CI) | |
|---|---|---|---|---|---|---|---|---|
| | Number of patients with adverse events | Number of adverse events | Frequency used in economic model for intervention | Number of patients with adverse events | Number of adverse events | Frequency used in economic model for comparator | Number of patients with adverse events | Number of adverse events |
| **Adverse event, n** | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

# 10. Documentation of health-related quality of life (HRQoL)

HRQoL data was collected in the IMCgp100-202 trial using two patient-reported outcome (PRO) instruments: the EQ-5D-5L questionnaire, and the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) (see Table 30) [54].

**Table 30. Overview of included HRQoL instruments.**

| Measuring instrument | Source | Utilization |
|---|---|---|
| EQ-5D-5L | IMCgp100-202 | Utilities in the health economic model – scenario analysis. |
| EORTC QLQ-C30 | IMCgp100-202 | Clinical effect. |
| EQ-5D | KEYNOTE-006 | Utilities in the health economic model – base case. |

## 10.1 Presentation of the health-related quality of life

The presentation of HRQoL data has not been updated since the last assessment by the DMC, as no new data has been available. This approach has been verified by the DMC.

### 10.1.1 Study design and measuring instrument

The EQ-5D is one of the most commonly used generic preference-based measure of HRQoL. Evaluation of HRQoL using EQ-5D directly from patients is consistent with DMC guidelines and is the approach used in the CE model. The EORT QLQ-C30 is a condition specific measure and is one of the most commonly used in oncology trials [76]. However, it is not preference-based and thus not preferred for economic evaluations. Data collection and results for EORTC-QLQ-C30 is presented in Appendix F.

### 10.1.2 Data collection for EQ-5D-5L

The EQ-5D-5L questionnaire was completed at baseline (i.e. prior to randomization), at 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 completion of the EQ-5D-5L at 12-week intervals. During the survival follow-up phase, the EQ-5D-5L was complete every 3 months to inform post-progression health status [54]. An overview of the collection of PRO data throughout the IMCgp100-202 trial is presented in Table 80 in Appendix F.

#### 10.1.2.1 Missing data

There were 378 patients involved in the clinical trial, 252 in the tebentafusp group, and 126 in the IC group. At baseline, 272 (72%) patients had completed the EQ-5D-5L questionnaire, 194 (77%) patients in the tebentafusp group and 78 (62%) in the IC group. 319 patients completed the EQ-5D-5L at any time point in the trial, of whom two were

not treated. The numbers of missing observations were determined at each 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-5L. 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 for the EQ-5D-5L during the survival follow-up period (Table 80 in Appendix F). The data are presented in Table 31. During the treatment period, the number of responses to the EQ-5D-5L questionnaire was relatively high, 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%. Based on the pattern of missing data, data imputation was conducted and is detailed in section 10.2.2 [39].

**Table 31. Pattern of missingness of EQ-5D data, compliance rate** [39].

| | 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% |

### 10.1.3 HRQoL results - EQ-5D-5L

Based on the overview of the compliance rates provided in Table 31, patients in both the tebentafusp and IC groups were considered to be domain compliant through cycle 17 day 1, with generally similar rates between the groups. Subsequently, patients in the tebentafusp group remained domain compliant through cycle 29 day 1, whereas compliance in the IC group decreased to 40.0% at cycle 21 day 1 and 33.3% at each of cycle 25 day 1 and at end of treatment. The descriptive analyses are based on the complete case data. At baseline, a high proportion of patients reported problems regarding the pain/discomfort (39%) and anxiety/depression dimensions (50%) was observed. Some patients reported problems regarding the mobility (16%) and usual activities (20%) dimensions, and a small proportion of patients reported problems regarding the self-care (5%) dimension [54]. A summary of statistics at baseline are presented in Table 81 in Appendix F. The EQ-5D-5L utility scores were initially analyzed

and derived for the United Kingdom (UK) HTA by applying the van Hout et al. 2012 crosswalk algorithm [58] and using the UK EQ-5D-3L value set [59]. Thus, the following EQ-5D-5L utility scores presented in the following are based on the 3L value set. In the health economic analysis, the EQ-5D-5L value set has been applied in line with the DMC guideline, see section 10.2. The mean EQ-5D utility score at baseline was 0.835 (Table 32), and the mean age in the trial was 62 years old; this mean utility baseline score is slightly higher than the UK EQ-5D population norm for this age group, 0.799 [60], although similar. At baseline, no differences in EQ-5D utilities were observed between the treatment groups for any of the domains. In general, throughout the study, mean change from baseline was similar between the treatment groups for all domains, although a slightly decreasing trend was noted. A summary of statistics at each assessment time point are presented in Table 32. Mean EQ-5D utilities, over time and by treatment groups, are also presented graphically in Figure 6, Figure 22, and Figure 23.

**Table 32. HRQoL EQ-5D utility summary statistics at each assessment time point** [39].

| 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 |

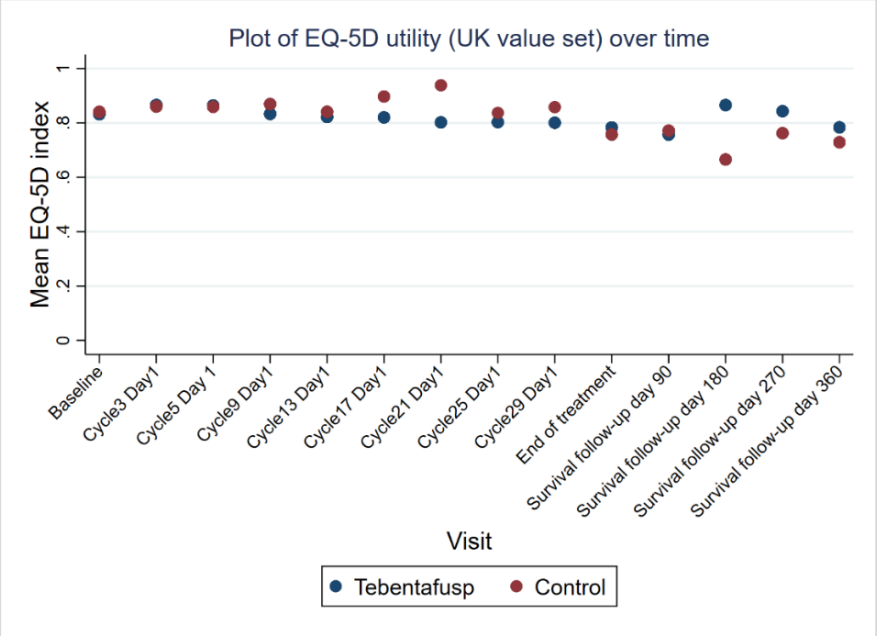


**Figure 6. Plot of EQ-5D mean utility at each assessment time point and by treatment group** [39].

## 10.2 Health state utility values (HSUVs) used in the health economic model

### 10.2.1 Overview of HSUVs

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 [44]. This approach is referred to in the model as on/off treatment and is based on utilities derived from study IMCgp100-202. 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 utilities 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 QoL of patients with metastatic melanoma may be less related to disease status (pre- or post-progression) than to time to death [44]. 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-5L in IMCgp100-202 was quite high (observations missing from 6% to 32%) during the treatment period. However, a high number of missing data was reported during the post-treatment survival follow-up period, 61% to 72%, for all patients (Table 31). Additionally, it was observed that there were 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 [54]. Given the high number of missing data following treatment discontinuation and the large gap between the last EQ-5D assessment and death (i.e., an 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 [44]. Thus, the utilities based on time to death are derived from the literature. An overview of health state utility values (HSUVs) considered for this assessment is presented in Table 33.

**Table 33. Overview of health state utility values.**

| | 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 groups 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 [59]. | Pooled mean values from the 10 mg/kg Q3W pembrolizumab and ipilimumab groups, as there was no significant difference in the QoL between the two groups. (Table 75 in the committee paper - TA366). It is based on statistical models fitted using EQ-5D collected in the KEYNOTE-006 trial [46] [61]. |
| 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] | | | |

### 10.2.2 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 [62]. 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.

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 CE analysis. 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 group. 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 group covariates improved the model fit, hence the preferred model with the best fit included all covariates. The age and sex covariates were statistically significant at the 5% level. The on/off treatment covariate was statistically significant at a 1% level, and the utility declined by 0.074 points after treatment discontinuation. The utility estimates presented in Table 34 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.

**Table 34. 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 |

### 10.2.3 Utility values from the literature based on time to death

A limited variation in the EQ-5D utility during the treatment period (mean: 0.834 [95%CI: 0.824, 0.844], Table 82) 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 metUM. An overview of the SLR is provided in Appendix J 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 metUM (ipilimumab,

pembrolizumab, nivolumab, ipi/nivo). Based on clinical experts' opinion (consulting on the UK HTA), the QoL of patients with metUM was assumed to be maintained until approximately 6 months to death, when symptoms start appearing heavily impacting 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 group of the IMCgp100-202 trial. Modelling utility based on pembrolizumab data in both treatment groups was considered relevant due to the minimal differences in EQ-5D scores observed between the treatment groups in the IMCgp100-202 study, see Figure 6. The primary source in which the EQ-5D data was collected was study KEYNOTE-006 (NCT01866319) [63]. 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 metUM 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 groups. The regression analysis described in section 10.2.2 was conducted to estimate the utility value based on the covariates (sex, age, treatment group, 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 35.

**Table 35. Utility data based on time to death** [46]**.**

| 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 |

### 10.2.4 Health state utility 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% [41]. 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 (section 12.2.1.1). An overview of the utilities derived from the literature and the IMCgp100-202 trial is presented in Table 36. 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.

**Table 36. Summary of health state utility values 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 [61]. |
| 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% | |
| **Scenario analysis** | | | |
| Male | 0.026 | +/-10% | Based on statistical models fitted using EQ-5D-5L data collected in IMCgp100-202 trial and adjusted to the Danish preference weights [13]. |
| > 65 yo | 0.023 | +/-10% | |
| Investigator's choice | -0.012 | +/-10% | |
| Off treatment | -0.074 | +/-10% | |
| _Cons | 0.875 | +/-10% | |

### 10.2.5 HSUV calculation

EQ-5D population norms by age groups were used in the model to apply an age adjustment factor to account for declining QoL with age. The utility estimates based on IMCgp100-202 were adjusted to the Danish preference weights. It was not possible to apply the Danish weights to the utility estimates derived from the literature due to a lack of patient-level data.

#### 10.2.5.1 Mapping (N/A)

### 10.2.6 Disutility calculation

The disutilities associated with AEs from the literature that were initially included in DMC's assessment report of tebentafusp have been omitted from the current analysis. This exclusion is justified as these disutilities are already accounted for in the applied utility values.

### 10.2.7 HSUV results

Refer to sections 10.2.1 and 10.2.4.

## 10.3 Health state utility values (HSUV) measured in other trials than the clinical trials forming the basis for relative efficacy

The HSUV used as base case in the health economic model was based on time to death derived from the literature. Please refer to section 10.2 and Appendix J for a detailed description.

# 11. Resource use and associated costs

The costs in the model were estimated from a limited 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), AE-related costs, and patient time and transportation costs. The costs in the model were discounted at a 3.5% annual rate. The costs associated with the treatments, disease management, and treatment of AEs were estimated using the Danish diagnosis-related group (DRG) tariff system according to DMC guideline [41].

## 11.1 Medicines - intervention and comparator

The medicine costs were applied in the model based on treatment duration derived from the PFS curves and adjusted to the duration of treatment beyond PD. The drug acquisition cost for comparator (ipi/nivo) was based on Pharmacy Purchase Price (PPP), presented in Table 37. A discount of [redacted] was applied to the PPP of tebentafusp to reflect the new price of [redacted].

**Table 37. Medicine unit costs.**

| Drug | Vial size | PPP (per unit), DKK | Source |
|---|---|---|---|
| **Tebentafusp** | 100 mcg/0.5 ml vial (200 µg per 1ml) | 98,684.16 | Medicinpriser.dk, Feb 2025 [2] |
| **Ipilimumab** | 200 mg/40 ml vial (5 mg per 1 ml) | 95,188.99 | Medicinpriser.dk, Feb 2025 [29] |
| | 50mg/10ml vial (5 mg per 1 ml) | 23,850.38 | Medicinpriser.dk, Feb 2025 [65] |
| **Nivolumab** | 240 mg/24 ml vial (24 mg per 1 ml) | 20,457.13 | Medicinpriser.dk, Feb 2025 [31] |
| | 100mg/10 ml vial (10 mg per 1 ml) | 8,523.80 | Medicinpriser.dk, Feb 2025 [66] |
| | 40mg/4 ml vial (10 mg per 1 ml) | 3,431.27 | Medicinpriser.dk, Feb 2025 [67] |

One vial of tebentafusp was used per administration as per the summary of product characteristics (SmPC). In the comparator group, the per cycle cost of drugs was calculated as per the SmPC. Given the very low number of patients with metUM in Denmark, it was considered that vial sharing was not feasible. The drug quantities were therefore rounded-up to the nearest vial size. Hereby it was assumed that patients only

received whole vials, accounting for medicine waste and can be considered a conservative approach to estimating the cost of tebentafusp. The drug dosage regimen used in the model is presented in Table 38.

**Table 38. Drug dosage regimen used in the model.**

| Medicine | Dose | Relative dose intensity | Frequency | Vial sharing |
|---|---|---|---|---|
| **Tebentafusp** | 20 µg C1D1;<br>30 µg C1D8;<br>68 µg C1D15 and subsequent doses | 100% | Every week: Days 1, 8, and 15 of 21-day cycle (15-20 min infusion time) | No |
| **Ipi/nivo** | Ipilimumab: 3 mg/kg administered IV | 100% | Ipilimumab: Q3W for a total of 4 doses (90 min infusion time) | No |
| | Nivolumab: 1 mg/kg administered intravenously at four doses and 6 mg/kg at subsequent doses | | Nivolumab: Q3W for a total of 4 doses and subsequent doses every 4 weeks (60 min infusion time) | No |

## 11.2 Medicines– co-administration (N/A)

## 11.3 Administration costs

### 11.3.1 Administration costs - Tebentafusp

Based on the SmPC, the preparation of tebentafusp requires the use of 0.13 ml human albumin at 20% concentration for admixture [68]. Based on the SmPC for human albumin (HSA), once the container has been opened, the contents should be used immediately, and any unused product disposed of [69]. Hence, it was considered that vial sharing was not possible, and the full cost of a vial for HSA was included in the administration costs. Tebentafusp is administered IV over a 15–20-minute period. Due to the risk of cytokine release-associated toxicity, according to the SmPC, patients should 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.

### 11.3.2 Administration costs – ipi/nivo

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 IV 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. Based on the DMC's assessment report of tebentafusp, the cost associated with these tests are captured in the DRG tariff for drug administration [7]. The costs are presented in Table 39.

**Table 39. Administration costs used in the model.**

| Administration type | Frequency | Unit cost [DKK] | DRG code | Reference |
|---|---|---|---|---|
| **Administration (IV) of tebentafusp and ipi/nivo** | Refer to Table 38. | 1,085 | \|02MA01\| Øvrige kontakter ved øjensygdomme \| | DRG 2025 [70] |
| **Inpatient stay** | The first three doses | 2,404 | Long-term tariff | DRG 2025 [70] |
| **Human albumin 20%, 100 ml vial** | Every week: Days 1, 8, and 15 of 21-day cycle | 448.80 | - | Tebentafusp SmPC [1] |

## 11.4 Disease management costs

The costs associated with the PFS and PD health states have been calculated based on resource utilization from literature and based on expert opinion, combined with DRG tariffs and "Rigshospitalets labportal" [70,71]. The health state costs are composed of consultations with clinicians, lab tests, scans, and hospital visits. In the initial application of tebentafusp, no relevant studies on health-care resource utilization in patients with UM or metUM were identified in the literature. In the two updated SLRs conducted in January 2024 and March 2025 (Appendix J), no additional relevant studies were identified. Therefore, literature on metastatic CM was used as a starting point for the estimation of resource utilization. One relevant study conducted by McKendrick et al. (2016) was identified in which the resource utilization associated with the treatment of metastatic melanoma in eight countries was estimated [47]. One of the countries included was the UK. Due to the comparability between the Danish and UK healthcare setting, the resource utilization was assumed to be applicable for the initial assessment by the DMC [40]. Based on the study, the resource use costs included in the PFS and PD health states were routine management during active treatment for pre-progression and management at progressions and BSC for post-progression.

In the initial assessment of tebentafusp by DMC, 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 metUM to determine which items were irrelevant in the context of metUM, and which resources for the treatment of metUM patients were not already captured and should be added [47]. 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 (GP). 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.

In this re-assessment of tebentafusp, the resource utilization was further adjusted to DMC assessment report of tebentafusp from 2023 [47]. The adjustments included the following:

- Pre-progression: exclusion of psychology specialist consultation, surgeon consultation, ophthalmic surgeon consultation, emergency department visit, complete blood count, and liver resection. Frequency of blood tests (complete metabolic panel) is adjusted from 1 to 2 per month.
- At progression: exclusion of surgeon consultation, ophthalmic surgeon consultation, and hepatic perfusion.
- Post-progression: inclusion of psychology specialist consultation, surgeon consultation, ophthalmic surgeon consultation, and emergency department visit.

The adjusted monthly resource utilization 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 40, Table 41, and Table 42, respectively.

**Table 40. Disease management costs (pre-progression) used in the model.**

| Activity | Frequency* | Unit cost [DKK] | DRG code | Reference |
|---|---|---|---|---|
| **Medical consultations** | | | | |
| Hospital-based medical oncology consultation | 1 | 1,494.00 | \|23MA04\|Kontrolundersøgelse\| | DRG 2025 [70] |
| Hospital-based oncology nurse visit | 1 | 1,494.00 | \|23MA04\|Kontrolundersøgelse\| | DRG 2025 [70] |
| **Examinations** | | | | |
| Whole-body CT | 0.33 | 2,701.00 | \|30PR06\|CT scanning, kompliceret\| | DRG 2025 [70] |
| PET-CT scan | 0.33 | 2,701.00 | \|30PR06\|CT scanning, kompliceret\| | DRG 2025 [70] |
| Liver MRI | 0.03 | 2,603.00 | \|30PR02\|MR scanning, kompliceret\| | DRG 2025 [70] |
| Complete metabolic panel | 2 | 247.00 | Rigshospitalets labportal. Full overview of the included tests is provided in Appendix K | Rigshospitalets labportal [71] |

*monthly resource use

**Table 41. Disease management costs (at progression) used in the model.**

| Activity | Frequency* | Unit cost [DKK] | DRG code | Reference |
|---|---|---|---|---|
| **Medical consultations** | | | | |
| Hospital-based medical oncology consultation | 1 | 1,494.00 | \|23MA04\|Kontrolundersøgelse\| | DRG 2025 [70] |
| **Hospitalizations** | | | | |

| Activity | Frequency* | Unit cost [DKK] | DRG code | Reference |
|---|---|---|---|---|
| Inpatient stay (oncology/general ward) | 0.2 | 1,085.00 | \|02MA01\|Øvrige kontakter ved øjensygdomme\| | DRG 2025 [70] |
| **Examinations** | | | | |
| Whole-body CT | 0.05 | 2,701.00 | \|30PR06\|CT scanning, kompliceret\| | DRG 2025 [70] |
| Complete blood count | 1 | 191.00 | Rigshospitalets labportal. Full overview of the included tests is provided in Appendix K | Rigshospitalets labportal [71] |
| Complete metabolic panel | 1 | 247.00 | Rigshospitalets labportal. Full overview of the included tests is provided in Appendix K | Rigshospitalets labportal [71] |
| *monthly resource use | | | | |

**Table 42. Disease management costs (post-progression) used in the model.**

| Activity | Frequency* | Unit cost [DKK] | DRG code | Reference |
|---|---|---|---|---|
| **Medical consultations** | | | | |
| Hospital-based medical oncology consultation | 0.67 | 1,494.00 | \|23MA04\|Kontrolundersøgelse\| | DRG 2025 [70] |
| Hospital-based oncology nurse visit | 0.2 | 1,494.00 | \|23MA04\|Kontrolundersøgelse\| | DRG 2025 [70] |
| Psycology specialist consultation | 0.05 | 2,168.00 | Ambulant psykiatritakst 2025 | Psykiatritakst 2025 [70] |
| Surgeon consultation | 0.01 | 1,494.00 | \|23MA04\|Kontrolundersøgelse\| | DRG 2025 [70] |
| Ophthalmic surgeon consultation | 0.33 | 1,494.00 | \|23MA04\|Kontrolundersøgelse\| | DRG 2025 [70] |
| **Hospitalizations** | | | | |
| Inpatient stay (oncology/general ward) | 0.5 | 1,085.00 | \|02MA01\|Øvrige kontakter ved øjensygdomme\| | DRG 2025 [70] |
| Emergency department visit | 0.05 | 1,085.00 | \|02MA01\|Øvrige kontakter ved øjensygdomme\| | DRG 2025 [70] |
| Day hospital visit (out-patient clinic) | 0.13 | 1,085.00 | \|02MA01\|Øvrige kontakter ved øjensygdomme\| | DRG 2025 [70] |
| *monthly resource use | | | | |

Resource utilization values and unit costs were multiplied to derive the health states costs, which are reported in Table 43. 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.

Table 43. Health state costs for both treatment groups.

| Health state | Costs |
|---|---|
| Pre-progression (weekly cycle cost) | DKK 1,335.69 |
| At progression (one-off cost) | DKK 1,958.00 |
| Post-progression (BSC) (one-off) | DKK 10,615.76 |

## 11.5 Costs associated with management of adverse events

In the base case model, grade 3 or higher AEs, and colitis and endocrine disorders of any grade with a prevalence >3% were included. According to the clinical expert, patients treated with ipi/nivo in clinical practice frequently experience other AEs, e.g., pneumonitis, not reported in GEM-1402 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 [1]. 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 group, 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 six months based on NICE single technology appraisal assessment of ipilimumab [57]. 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 three doses, this approach reflects clinical practice in the tebentafusp group. Although this may not reflect clinical practice in the control group, this approach was used as a conversative measure in the control group. Additionally, in a scenario analysis, an assumption was made that the same proportion of inpatient vs. outpatient costs applied to the tebentafusp group as did to the ipi/nivo group. The proportion of patients treated inpatient and outpatient for both treatment groups was validated by the clinical expert in the initial assessment of tebentafusp. In this re-assessment of tebentafusp the inclusion of AEs and proportion of patients treated inpatient and outpatient has been further adjusted based on the DMC assessment report of tebentafusp [7]. The unit costs for each AE are derived from the DRG tariffs for 2025. The unit cost for AEs and the proportion of inpatient and outpatient treatment are presented in Table 44 and Table 45, respectively.

Table 44. Cost associated with management of adverse events (inpatient).

| | Inpatient setting | DRG code | Unit cost/DRG tariff (DKK) [70] |
|---|---|---|---|
| Rash | 5% | \|09MA03\|Lettere eller moderat hudsygdom, u. kompl. Bidiag. \| | 21,118.00 |
| Rash maculo-papular | 5% | \|09MA03\|Lettere eller moderat hudsygdom, u. kompl. Bidiag. \| | 21,118.00 |

| | Inpatient setting | DRG code | Unit cost/DRG tariff (DKK) [70] |
|---|---|---|---|
| **Pruritus** | 5% | \|09MA03\|Lettere eller moderat hudsygdom, u. kompl. Bidiag. \| | 21,118.00 |
| **Hypotension** | 50% | \|05MA08\| Andre hjertesygdomme \| | 2,240.00 |
| **Fatigue** | 10% | \|23MA03\|Symptomer og fund, u. kompl. bidiag. \| | 5,271.00 |
| **Pyrexia** | 10% | \|21MA03\|Komplikationer ved behandling, u. kompl. bidiag.\| | 31,708.00 |
| **Liver toxicity/liver-related events** | 10% | \|07MA06\|Akut infektiøs eller toksisk leversygdom\| | 46,506.00 |
| **Hepatitis** | 30% | \|07MA06\|Akut infektiøs eller toksisk leversygdom\| | 46,506.00 |
| **Diarrhea** | 50% | \|06MA11\|Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. \| | 4,977.00 |
| **Guillain-Barré syndrome** | 100% | \|01MA03\|Infektion i nervesystemet ekskl. virus meningitis\| | 75,620.00 |

**Table 45. Cost associated with management of adverse events (outpatient).**

| | Outpatient setting | DRG code | Unit cost/DRG tariff (DKK) [70] |
|---|---|---|---|
| **Rash** | 95% | \|09MA98\|MDC09 1-dagsgruppe, pat. mindst 7 år \| | 1,578.00 |
| **Rash maculo-papular** | 95% | \|09MA98\|MDC09 1-dagsgruppe, pat. mindst 7 år \| | 1,578.00 |
| **Pruritus** | 95% | \|09MA98\|MDC09 1-dagsgruppe, pat. mindst 7 år \| | 1,578.00 |
| **Hypertension** | 100% | \|07MA98\|MDC07 1-dagsgruppe, pat. mindst 7 år \| | 2,072.00 |
| **Hypotension** | 50% | \|07MA98\|MDC07 1-dagsgruppe, pat. mindst 7 år \| | 2,072.00 |
| **Fatigue** | 90% | \|23MA03\| Symptomer og fund, u. kompl. bidiag. \| | 5,271.00 |
| **Pyrexia** | 90% | \|21MA98\|MDC21 1-dagsgruppe, pat. mindst 7 år\| | 1,753.00 |
| **Hyperbilirubinaemia** | 100% | \|07MA98\|MDC07 1-dagsgruppe, pat. mindst 7 år \| | 2,072.00 |
| **Liver toxicity/liver-related events** | 90% | \|07MA98\|MDC07 1-dagsgruppe, pat. mindst 7 år \| | 2,072.00 |
| **Hepatitis** | 70% | \|07MA98\|MDC07 1-dagsgruppe, pat. mindst 7 år \| | 2,072.00 |
| **Diarrhea** | 50% | \|06MA11\|Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. \| | 4,977.00 |
| **Hypothyroidism** | 100% | \|10MA01\|Struma og stofskiftesygdomme\| | 1,790.00 |

| | Outpatient setting | DRG code | Unit cost/DRG tariff (DKK) [70] |
|---|---|---|---|
| **Thyroiditis** | 100% | \|10MA01\|Struma og stofskiftesygdomme\| | 1,790.00 |

The weighted costs of AEs in each group were calculated by factoring the incidence rate of each AE (Table 28) with the estimates of the cost per event and proportion of management in the inpatient and outpatient setting (Table 44 and Table 45). The weighted average costs of AEs by treatment group in the model are reported in Table 46.

**Table 46. Weighted average cost of adverse events by treatment group.**

| | Tebentafusp | Ipi/nivo |
|---|---|---|
| **Endocrine disorder** | DKK 0 | DKK 447.50 |
| **Other AEs** | DKK 1,404.80 | DKK 6,668.51 |

## 11.6 Subsequent treatment costs

A proportion of the patients received subsequent systemic treatment after discontinuation of the study drug in the IMCgp100-202 study. Based on study IMCgp100-202 [13] and the Danish treatment guideline [7,24], the cost of subsequent treatment was accounted for in the model and applied as a one-off cost upon treatment discontinuation. In line with IMCgp100-202 it was assumed that 43% and 46% of the patients who initially received tebentafusp and ipi/nivo, respectively, received subsequent treatment. Based on the clinical expert consulted in the previous submission, it was assumed that 2/3 of the patients were fit for treatment with ipi/nivo, whereas the remaining 1/3 of the patients that received subsequent treatment were considered fragile or with severe comorbidities and received BSC [56]. The costs associated with BSC were assumed to be captured as one-off costs in the hospital costs related to post-progression health state [7]. Ipi/nivo was assumed to be given for four doses and nivolumab thereafter for a maximum of seven doses every two weeks, corresponding to a treatment duration of six months. Assumptions regarding vial sharing and medicine waste are described in Section 11.1. The medicines of subsequent treatment are presented in Table 49. The cost of subsequent therapies is presented in Table 48 and was applied in the model as a one-off cost upon treatment discontinuation.

**Table 47. Medicine costs of subsequent treatments.**

| Medicine | Strength | Package size | PPP [DKK] | Relative dose intensity | Average duration of treatment |
|---|---|---|---|---|---|
| **Ipi/nivo** | Refer to Table 37. | Refer to Table 37. | Refer to Table 37. | Refer to Table 38. | 6 months based on the dosages reported in Table 38. |

**Table 48. Cost of subsequent treatment.**

| Resource | Tebentafusp | Ipi/nivo |
|---|---|---|
| **Subsequent treatment options** | | |
| % any subsequent treatment | 43% | 46% |

| Resource | Tebentafusp | Ipi/nivo |
|---|---|---|
| % subsequent treatment with ipi/nivo | 67% | 0% |
| % on BSC | 33% | 100% |
| **Cost per therapy** | | |
| Ipi/nivo | DKK 633,826 | |
| **Subsequent treatment cost** | | |
| Weighted average cost | DKK 180,739 | DKK 0 |

**Table 49. Medicines of subsequent treatments**

| Medicine | Dose | Relative dose intensity | Frequency | Vial sharing |
|---|---|---|---|---|
| **Ipi/nivo** | Refer to Table 38. | Refer to Table 38. | Ipilimumab: Q3W for a total of 4 doses<br>Nivolumab: Q3W for a total of 4 doses and subsequent doses every 2 weeks for a total of maximum 7 doses | Refer to Table 38. |

## 11.7 Patient costs

Patient costs are applied in the model to account for the time spent attending medical services at the rate of DKK 3.13 per minute. Transportation costs to and from the hospital for inpatient and outpatient treatment are also considered, representing DKK 140. Patient costs are calculated in accordance with the DMCs catalogue for valuing unit costs version 1.8 [72].

### 11.7.1 Drug administration costs

Patient costs associated with receiving 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 4.1. In the tebentafusp group, for the first administration, the costs of the time spent undergoing HLA status diagnosis test are also accounted for. In the ipi/nivo group, 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 50.

**Table 50. Patient cost used in the model: Drug administration.**

| Activity | Unit cost, DKK | Time spent | Total cost‡ | Source |
|---|---|---|---|---|
| Patient time cost | 3.13 | 1 min | - | DMC's catalogue of unit costs [72]. |

| Activity | Unit cost, DKK | Time spent | Total cost‡ | Source |
|---|---|---|---|---|
| **Transportation cost** | | | | |
| Patient transportation costs* | 140.00 | Per hospital visit (in- and outpatient) | - | DMC's catalogue of unit costs [72]. |
| Patient time spent on transportation to and from hospital | 134.29 | 43 min† | - | DMC's catalogue of unit costs. [72] |
| **Diagnostic and test** | | | | |
| HLA-A*02:01 test (tebentafusp) | 16.92 | 5 min | - | Assumption |
| **Treatment and monitoring** | | | | |
| Infusion with tebentafusp | 59.21 | 15-20 min | 344.21 | IMCgp100-202 [13] |
| Monitoring dose 1-3 | 4,872.00 | 1,440 min | - | SmPC, tebentafusp [1] |
| Monitoring dose 4-11 | 203.00 | 60 min | - | SmPC, tebentafusp [1] |
| Monitoring dose 12+ | 101.50 | 30 min | - | SmPC, tebentafusp [1] |
| Infusion with ipi/nivo, week 0-12 | 609.00 | 90 min | 894.00 | GEM-1402 [11] |
| Infusion with ipi/nivo, week 12+ | 304.50 | 60 min | 589.50 | GEM-1402 [11] |

*Costs for transportation to and from the hospital for treatment, based on the DMC assumption of 40 km distance to and from 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 DKK 140 and the cost of time spent in transportation DKK 134.29.

Patient costs related to subsequent treatments are also accounted for. 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 11.6 and presented in Table 51.

**Table 51. Weighted average for subsequent treatment.**

| | Tebentafusp | Ipi/nivo |
|---|---|---|
| **Ipi/nivo** | DKK 5,269.50 | DKK 0 |
| **Weighted average cost** | DKK 3,513.18 | DKK 0 |

### 11.7.2 Disease management costs

Patient costs are applied in the model to account for the time spent attending medical services at the rate of 3.13 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. This approach is in accordance with the DMCs catalogue for valuing unit costs version 1.8 [72]. The patient cost for the medical services is presented in Table 52.

Table 52. Patient cost used in the model: Medical services.

| Activity | Unit cost, DKK | Time spent | Total cost* | Source |
|---|---|---|---|---|
| **Medial consultations** | | | | |
| Hospital-based medical oncology consultation | 94.00 | 30 min | 368.29 | Assumption† |
| Hospital-based oncology nurse visit | 94.00 | 30 min | 368.29 | Assumption† |
| Psychology specialist consultation | 94.00 | 30 min | 368.29 | Assumption† |
| Surgeon consultation | 94.00 | 30 min | 368.29 | Assumption† |
| Ophthalmic surgeon consultation | 94.00 | 30 min | 368.29 | Assumption† |
| **Hospitalizations** | | | | |
| Inpatient stay (oncology/general ward) | 4,512.00 | 1440 min | 4,786.29 | Assumption† |
| Emergency department visit | 94.00 | 30 min | 368.29 | Assumption† |
| Day hospital visit (out-patient clinic) | 94.00 | 30 min | 368.29 | Assumption† |
| **Examinations** | | | | |
| Whole-body CT | 188.00 | 60 min | 462.29 | Rigshospitalet [73] |
| PET-CT scan | 376.00 | 120 min | 650.29 | Kræftens bekæmpelse [74] |
| Liver MRI | 470.00 | 150 min | 744.29 | Hvidovre Hospital [75] |
| Complete blood count | 15.67 | 5 min | 289.95 | Assumption† |
| Complete metabolic panel | 15.67 | 5 min | 289.95 | Assumption† |

*It also includes the cost of transportation DKK 140 and the cost of time spent in transportation DKK 134.29.
†These assumptions were previously accepted by the DMC in the initial assessment of tebentafusp [7].

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 53.

Table 53. Patient cost used in the model: Medical services in the health states for both treatments.

| Health state | Costs |
|---|---|
| **Pre-progression (weekly cycle cost)** | DKK 426.49 |
| **At progression (one-off cost)** | DKK 1,905.45 |
| **Post-progression (BSC) (one-off)** | DKK 11,693.90 |

### 11.7.3 Adverse events costs

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 unit costs presented in Table 50 and the admission days presented in Table 54.

Table 54. Patient cost used in the model: Adverse events.

| Adverse events | Admission days | Patient time cost, DKK | Total cost*, DKK |
|---|---|---|---|
| **Outpatient costs†** | - | 94.00 | 386.29 |
| **Inpatient costs** | | | |
| Rash | 4 | 18,048.00 | 18,322.29 |
| Rash maculo-papular | 4 | 18,048.00 | 18,322.29 |
| Pruritus | 4 | 18,048.00 | 18,322.29 |
| Fatigue | 1 | 4,512.00 | 4,786.29 |
| Pyrexia | 6 | 27,072.00 | 27,346.29 |
| Hypotension | 1 | 4,512.00 | 4,786.29 |
| Liver toxicity/liver-related events | 12 | 54,144.00 | 54,410.29 |
| Hepatitis | 12 | 54,144.00 | 54,410.29 |
| Diarrhea | 1 | 4,512.00 | 4,786.29 |
| Guillain-Barré syndrome | 20 | 90,240.00 | 90,514.29 |
| Hypothyrodism | 1 | 4,512.00 | 4,786.29 |
| Thyroiditis | 1 | 4,512.00 | 4,786.29 |

*It also includes the cost of transportation DKK 140 and the cost of time spent in transportation DKK 134.29
†Applicable to all AEs

The weighted patient costs associated with AEs in each group were calculated by factoring the incidence rate of each AE (Table 28) with the estimates of the patient cost per event (Table 54) and proportion of management in the inpatient and outpatient setting (Table 44 and Table 45). The weighted average costs of AEs by treatment group in the model are reported in Table 55.

Table 55. Weighted adverse events-related patient costs by treatment group.

| | Tebentafusp | Ipi/nivo |
|---|---|---|
| **Endocrine disorder** | DKK 0 | DKK 92.07 |
| **Other AEs** | DKK 601.03 | DKK 6,229.39 |

## 11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost) (N/A)

# 12. Results

## 12.1 Base case overview

An overview of the base case including the central aspects is provided in Table 56.

Table 56. Base case overview

| Feature | Description |
|---|---|
| Comparator | Ipi/nivo |
| Type of model | Three-state (pre-progression, post-progression, and death) partitioned survival model |
| Time horizon | 34 years (lifetime) |
| Treatment line | 1st line. Subsequent treatment is included. |
| Measurement and valuation of health effects | The utilities are based on time-to-death derived from the literature. The Danish EQ-5D-5L population weights were applied to the baseline utility value derived from study IMCgp100-202. |
| Costs included | Medicine costs<br>Hospital costs<br>Costs of adverse events<br>Patient costs |
| Dosage of medicine | Based on BSA, 1.90 |
| Average time on treatment | Tebentafusp: 10.84 months<br>Ipi/nivo: 8.40 months |
| Parametric function for PFS | Tebentafusp: Generalized Gamma<br>Ipi/nivo: Generalized Gamma |
| Parametric function for OS | Tebentafusp: Log-logistic<br>Ipi/nivo: Generalized Gamma |
| Inclusion of waste | Yes |
| Average time in model health state (tebentafusp)<br>PFS<br>OS<br>Death | <br>Approx. 9.4 months<br>Approx. 35.7 months<br>Absorbing state, once patients enter this state, they remain there. |

### 12.1.1 Base case results

Table 57 shows the results of 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 life years (LYs) and quality-adjusted life years (QALYs), but also higher cost compared to ipi/nivo. Over a lifetime horizon, tebentafusp was estimated to be associated with a 1.30 increase in LYs (2.69 vs 1.39), and a 1.12 increase in QALYs (2.20 vs 1.08) per treated patient. The improvement in outcomes for patients with metUM was mainly owed to a proportion of patients experiencing longer survival compared with the comparator. The base case ICER was [redacted] per QALY gained.

Table 57. Base case results, discounted estimates

| | Tebentafusp | Ipi/nivo | Difference |
|---|---|---|---|
| Medicine costs | [redacted] | [redacted] | [redacted] |
| Medicine costs – co-administration | N/A | N/A | N/A |
| Administration | [redacted] | [redacted] | [redacted] |

| | Tebentafusp | Ipi/nivo | Difference |
|---|---|---|---|
| Disease management costs | [redacted] | [redacted] | [redacted] |
| Costs associated with management of adverse events | [redacted] | [redacted] | [redacted] |
| Subsequent treatment costs | [redacted] | [redacted] | [redacted] |
| Patient costs | [redacted] | [redacted] | [redacted] |
| Palliative care costs | N/A | N/A | N/A |
| **Total costs** | [redacted] | [redacted] | [redacted] |
| Life years gained (PFS) | 0.72841 | 0.54991 | 0.17850 |
| Life years gained (PPS) | 1.96335 | 0.83745 | 1.12590 |
| **Total life years** | **2.69176** | **1.38736** | **1.30440** |
| QALYs (PFS) | 0.59833 | 0.42585 | 0.17249 |
| QALYs (PD) | 1.60286 | 0.65151 | 0.95135 |
| QALYs (adverse reactions) | 0 | 0 | 0 |
| **Total QALYs** | **2.20120** | **1.07735** | **1.12384** |
| **Incremental costs per life year gained** | | [redacted] | |
| **Incremental cost per QALY gained (ICER)** | | [redacted] | |

## 12.2 Sensitivity analyses

### 12.2.1 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 G. Figure 7 presents a tornado diagram indicating the 15 parameters with the greatest influence on the ICER in descending order. Table 58 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 adjusted baseline utility "on treatment" for patients treated with tebentafusp. The second parameter with the most impact was the mean weight of a patient, as both ipilimumab and nivolumab are dosed based on weight increasing the mean dose per patient when the mean weight is increased. The third and fourth parameter with the most impact on the results was the percentage of patients in the tebentafusp group receiving ipi/nivo as subsequent treatment and subsequent therapies in general, respectively. All other parameters have a limited impact on the results compared to the four aforementioned parameters.

**Figure 7. Tornado diagram.**

Table 58. ICER at lower and upper value of parameter from univariate sensitivity analysis.

| Parameter | ICER at lower value of parameter | ICER at upper value of parameter |
|---|---|---|
| On treatment Tebentafusp (0.80, 0.98) | [redacted] | [redacted] |
| Mean weight (70.97, 86.75) | [redacted] | [redacted] |
| Subsequent treatment% of usage of ipilimumab + nivolumabTebentafusp (0.60; 0.73) | [redacted] | [redacted] |
| Subsequent treatment% of usage of subsequent therapies Tebentafusp (0.38; 0.47) | [redacted] | [redacted] |
| Health states costs Pre-progression - cost per cycle Tebentafusp (1001.77; 1669.61) | [redacted] | [redacted] |
| Health states costs Pre-progression - cost per cycle Ipi+Nivo (1001.77; 1669.61) | [redacted] | [redacted] |
| Age (64.52; 87.29) | [redacted] | [redacted] |
| Administration of Immunotherapy (801.00; 1335.00) | [redacted] | [redacted] |
| Time to death in days (≥360 days) (0.74; 0.90) | [redacted] | [redacted] |
| Patient costs Pre-progression - cost per cycle (319.87; 533.11) | [redacted] | [redacted] |
| Patient costs Tebentafusp monitoring - dose 1-3 (3654.00; 6090.00) | [redacted] | [redacted] |
| Patient costs Pre-progression - cost per cycle (319.87; 533.11) | [redacted] | [redacted] |
| % HLA positive (0.38; 0.63) | [redacted] | [redacted] |
| Patient costs Post-progression - one off (4 months) (8770.42; 14617.37) | [redacted] | [redacted] |
| Patient costs Post-progression - one off (4 months) (8770.42; 14617.37) | [redacted] | [redacted] |

#### 12.2.1.1 Scenario analyses

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

##### 12.2.1.1.1 Choice of OS extrapolation

The incremental LYs and QALYs were driven by the OS curve in the tebentafusp group, hence it was important to test the impact of the chosen extrapolation method on the results. Table 59 presents the results of a series of scenario analyses testing alternative combinations of standard parametric functions for extrapolating OS. Four parametric function combinations with reasonable fits were examined for the tebentafusp and ipi/nivo group.

##### 12.2.1.1.2 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 was in line with study IMCgp100-202, and the related costs were included. The

length of the subsequent treatment for the tebentafusp group in the model is equal to the 1st line treatment in the ipi/nivo group, which may not reflect clinical practice. Thus, a scenario analysis was conducted excluding the cost of subsequent treatment in both treatment groups. The ICER was [redacted], representing a decrease of [redacted]

#### 12.2.1.1.3 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, 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 groups only followed the PFS curves, as in current clinical practice for ipi/nivo. The ICER was [redacted], representing a decrease of [redacted].

#### 12.2.1.1.4 Source of utility data

In base case, the utility was applied based on time to death rather than disease status as detailed in section 10.2. One scenario analysis was conducted using the utility values derived from the EQ-5D data collected in the IMCgp100-202 trial, and as per DMC request in initial assessment of tebentafusp a scenario analysis was conducted using utility based on health states, specifically progression-free disease (PFS) and PD. The results are presented in Table 59.

**Table 59. Scenario analyses results.**

| | Change | Reason / Rational / Source | Incremental cost (DKK) | Incremental benefit (QALYs) | ICER (DKK/QALY) |
|---|---|---|---|---|---|
| **Base case** | - | - | [redacted] | 1.12 | [redacted] |
| **Tebentafusp: log-logistic Ipi/nivo: Gomperz** | [redacted] | Refer to section 12.2.1.1.1 and Appendix D | [redacted] | 1.13 | [redacted] |
| **Tebentafusp: log-normal Ipi/nivo: Gomperz** | [redacted] | | [redacted] | 1.08 | [redacted] |
| **Tebentafusp: log-logistic Ipi/nivo: Exponential** | [redacted] | | [redacted] | 1.17 | [redacted] |
| **Tebentafusp: Log-normal Ipi/nivo: Generalized Gamma** | [redacted] | | [redacted] | 1.07 | [redacted] |
| **Tebentafusp: without subsequent treatment Ipi/nivo: without subsequent treatment** | [redacted] | Refer to section 12.2.1.1.2 | [redacted] | 1.12 | [redacted] |

| | Change | Reason / Rational / Source | Incremental cost (DKK) | Incremental benefit (QALYs) | ICER (DKK/QALY) |
|---|---|---|---|---|---|
| **Tebentafusp: PFS only Ipi/nivo: PFS only** | [redacted] | Refer to section 12.2.1.1.3 | [redacted] | 1.12 | [redacted] |
| **Utility using IMCgp100-202 trial (on/off treatment)** | [redacted] | Refer to section 12.2.1.1.4 | [redacted] | 1.08 | [redacted] |
| **Utility using health states (PFS/PD)** | [redacted] | | [redacted] | 1.06 | [redacted] |

### 12.2.2 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 G. 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 8. 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 there is a larger spread across the X axis of the scatter plot, indicating that health benefits were characterized by a higher degree of uncertainty than costs. The mean incremental costs and QALYs as well as the ICER as estimated in the base case PSA is presented in Table 60. 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 9.

**Table 60. Results from the base-case PSA.**

| | Incremental cost (DKK) | Incremental benefit (QALYs) | ICER (DKK/QALY) |
|---|---|---|---|
| Tebentafusp | [redacted] | 1.11 | [redacted] |

**Figure 8. Scatter plot.**

**Figure 9. Cost-effectiveness acceptability curve for willingness-to-pay threshold.**

# 13. Budget impact analysis

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. 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. As per DMC assessment report of tebentafusp, the end-of-life care costs were not applied [7].

## 13.1 Number of patients (including assumptions of market share)

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 61 presents the number of new patients expected to be treated over the next 5 years if the medicine is recommended and not recommended.

**Table 61. Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share).**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| | | | **Recommendation** | | |
| **Tebentafusp*** | 19 | 9 | 10 | 10 | 10 |
| **Ipi/nivo** | 28 | 11 | 10 | 10 | 10 |
| | | | **Non-recommendation** | | |
| **Tebentafusp** | 0 | 0 | 0 | 0 | 0 |
| **Ipi/nivo** | 47 | 20 | 20 | 20 | 20 |

* In year 1, metastatic UM (incidence + prevalence) = 47, multiplied by % patients testing HLA-A*02:01 positive and tebentafusp market share = 19.

## 13.2 Budget impact

Table 62 shows the expected budget impact for the introduction of tebentafusp for treating advanced (unresectable or metastatic) UM in Denmark based on the published list price for tebentafusp. The analysis includes all treatment-related costs relevant for the regional hospital budgets. According to the results presented in Table 62, the budget

impact of tebentafusp ranges from [redacted] to [redacted] in the first 5 years following a positive recommendation.

**Table 62. Expected budget impact of recommending the medicine for the indication.**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| The medicine under consideration is recommended | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| The medicine under consideration is NOT recommended | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Budget impact of the recommendation** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

# 14. List of experts

UM is a rare disease, and the number of experts is limited with most of the experts being a part of the expert committee supporting the DMC. Hence, it was necessary to consult a clinical expert from a different country to validate the initial assessment submitted in 2022 [40]. The clinical expert used in the initial assessment was from Sweden. Sweden has a patient population and a treatment algorithm similar to the Danish setting, and therefore the clinical expert's inputs are considered relevant.

[redacted]

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# Appendix A. Main characteristics of studies included

**Table 63. Main characteristics of studies included**

| **Trial name: A Phase III Randomized, Open-label, Multi-center Study of the Safety and Efficacy of IMCgp100 Compared With Investigator Choice in HLA-A*0201 Positive Patients With Previously Untreated Advanced Uveal Melanoma** | **NCT number: NCT03070392** |
|---|---|
| **Objective** | 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 [13,36]. |
| **Publications – title, author, journal, year** | Overall survival benefit with tebentafusp in metastatic uveal melanoma, Nathan P. et al - N Engl J Med 2021; 385:1196-1206 DOI: 10.1056/NEJMoa2103485 [13]<br>Three-Year Overall Survival with Tebentafusp in Metastatic Uveal Melanoma, Hassel C. et al., - N Engl J Med 2023; 389:2256-2266. DOI: 10.1056/NEJMoa2304753 [10]<br>Overall survival from tebentafusp versus nivolumab plus ipilimumab in first-line metastatic uveal melanoma: a propensity score-weighted analysis, Piulats J.M. et al., - Ann Oncol 2023. DOI: 10.1016/j.annonc.2023.11.013 [9] |
| **Study type and design** | IMCgp100-202 is a randomized, open-label, active-comparator phase 2 study closed in 2023, where patients with HLA-A*02:01 positive advanced or metUM 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 36 [13,36]. |
| **Sample size (n)** | 378 [15,33] |
| **Main inclusion criteria** | **Inclusion Criteria** [36]<br>• Male or female patients age ≥18 years of age at the time of informed consent<br>• Ability to provide and understand written informed consent prior to any study procedures<br>• Histologically or cytologically confirmed metUM<br>• Must meet the following criteria related to prior treatment:<br>- No prior systemic therapy in the metastatic or advanced setting including chemotherapy, immunotherapy, or targeted therapy<br>- No prior regional, liver-directed therapy including chemotherapy, radiotherapy, or embolization<br>- Prior surgical resection of oligometastatic disease is allowed<br>- 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 Investigator's choice therapy that was administered as adjuvant or neoadjuvant treatment. Additionally, patients who have |

| Trial name: A Phase III Randomized, Open-label, Multi-center Study of the Safety and Efficacy of IMCgp100 Compared With Investigator Choice in HLA-A*0201 Positive Patients With Previously Untreated Advanced Uveal Melanoma | NCT number: NCT03070392 |
|---|---|
| | received nivolumab as prior adjuvant/neoadjuvant treatment should not receive pembrolizumab as Investigator's Choice therapy.<br>• HLA A*02:01 positive by central assay<br>• Life expectancy of >3 months as estimated by the investigator<br>• ECOG PS of 0 or 1 at Screening<br>• Patients have measurable disease or non-measurable disease according to RECIST v1.1<br>- 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 |
| **Main exclusion criteria** | **Exclusion Criteria** [36]<br>• Patient with any out-of-range laboratory values defined as:<br>- Serum creatinine >1.5 × ULN and/or creatinine clearance (calculated using Cockcroft-Gault formula, or measured) <50 mL/minute.<br>- Total bilirubin >1.5 × ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin >3.0 × ULN or direct bilirubin >1.5 × ULN<br>- ALT >3 × ULN<br>- AST >3 × ULN<br>- Absolute neutrophil count <1.0 × 109/L<br>- Absolute lymphocyte count <0.5 × 109/L<br>- Platelet count <75 × 109/L<br>- Hemoglobin <8 g/dL<br>• History of severe hypersensitivity reactions (e.g., anaphylaxis) to other biologic drugs or monoclonal antibodies<br>• Clinically significant cardiac disease or impaired cardiac function, including any of the following:<br>- 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<br>- QT interval corrected by Fridericia's formula >470 msec on screening electrocardiogram (ECG) or congenital long QT syndrome<br>- Acute myocardial infarction or unstable angina pectoris <6 months prior to Screening<br>• 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<br>• 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<br>• Known history of human immunodeficiency virus infection (HIV). Testing for HIV status is not necessary unless clinically indicated |

| Trial name: A Phase III Randomized, Open-label, Multi-center Study of the Safety and Efficacy of IMCgp100 Compared With Investigator Choice in HLA-A*0201 Positive Patients With Previously Untreated Advanced Uveal Melanoma | NCT number: NCT03070392 |
|---|---|

- 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 investigator's or sponsor's judgment, prevent the patient'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., optic, 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
- 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

| Trial name: A Phase III Randomized, Open-label, Multi-center Study of the Safety and Efficacy of IMCgp100 Compared With Investigator Choice in HLA-A*0201 Positive Patients With Previously Untreated Advanced Uveal Melanoma | NCT number: NCT03070392 |
|---|---|
| | for 6 months following administration of the last dose of study drug<br>• Patients who are in an institution due to official or judicial order.<br>• 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.<br>Contraindication for treatment with Investigator'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 Investigator's Choice and meets all other study eligibility criteria. |
| **Intervention** | 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 [36]. |
| **Comparator(s)** | **Comparators, including dose, dose interval, and number of patients:** Systemic dacarbazine, ipilimumab, or pembrolizumab. In total 126 people were treated with one of the three comparators:<br>• **Dacarbazine:** Administered at 1,000 mg/m$^2$ of BSA IV infusion Q3W until disease progression or unacceptable toxicity. 7 Persons were treated with dacarbazine.<br>• **Ipilimumab:** Administered at 3 mg/kg IV infusion over 90 minutes Q3W for a total of 4 treatments. 16 persons were treated with ipilimumab.<br>**Pembrolizumab:** Administered at 2 mg/kg IV infusion up to a maximum of 200 mg administered IV over 30 minutes Q3W or 200 mg fixed dose administered intravenously Q3W were approved locally until confirmed disease progression or unacceptable toxicity. 103 persons were treated with pembrolizumab. |
| **Follow-up time** | At the time of the clinical DCO for the primary analysis (October 13, 2020), the median duration of follow-up was 14.1 months [13].<br>At the time of the clinical DCO for the 3-year analysis (July 3, 2023), the median duration of follow-up was 43.3 months [10]. |
| **Is the study used in the health economic model?** | Yes |
| **Primary, secondary and exploratory endpoints** | **Primary, secondary, and exploratory endpoints, including definition, method of measurement and if possible, time of measurement:**<br>**Primary outcome** [10][36]:<br>• OS defined as the time from randomization to date of death due to any cause. For the first interim analysis the time frame was from randomization to the DCO date of 13$^{th}$ of October 2020; median follow-up duration was 14.1 months. For the 3-year analysis the time frame was from randomization to the DCO date of July 3$^{rd}$ 2023; median follow-up duration was 43.3 months.<br>**Secondary outcomes** [36]:<br>• Safety: Number of participants with TEAEs. Defined as the number of participants with TEAEs, 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.

- PFS 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 participant'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 HRQoL. 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 (PK): Tebentafusp concentration defines as serum PK concentrations of tebentafusp. PK concentrations were assessed at pre-dose, end of infusion and after 12-24 hours in cycle 1 on days 1, 8 and 15.
- 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.
- 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.
- Disease control rate (DCR) defined as the proportion of patients with either an objective response or stable disease (RECIST v1.1).

| Trial name: A Phase III Randomized, Open-label, Multi-center Study of the Safety and Efficacy of IMCgp100 Compared With Investigator Choice in HLA-A*0201 Positive Patients With Previously Untreated Advanced Uveal Melanoma | NCT number: NCT03070392 |
|---|---|
| | DCR will be assessed every 3 months from randomization until disease progression, up to 5.5 years.<br>PK: 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** | With the exception of subgroup analyses, the PH assumption was tested via the method proposed by Lin et al. [76] for all results where a Cox PH model was used to provide a HR for the overall treatment effect [13].<br>Time-to-event estimates of OS and PFS were calculated using KM methodology. The groups were formally compared with the use of a 2-sided log-rank test, stratified according to LDH status. The HR and corresponding 2-sided CI was estimated using a Cox PH model, with treatment group as a single covariate, stratified by LDH status (LDH above ULN versus normal LDH) with the extent of liver metastases (largest hepatic metastatic lesion ≥ 44.5 mm) as an additional pre-specified co-variate [13,54].<br>An ad hoc analysis was performed on the effect of stable versus 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 [13]. 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 group as a single covariate, stratified by LDH status (LDH above ULN versus below ULN) [13,54]. |
| **Subgroup analyses** | A subgroup analysis was carried out on OS for patient with disease progression and stable disease (SD) and according to patient characteristics [13] |
| **Other relevant information** | N/A |

**Table 64. Main characteristic of GEM-1402**

| Trial name: Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402) | NCT number: NCT02626962 |
|---|---|
| **Objective** | The study aimed to assess the efficacy of the combination of nivolumab (nivo) plus ipilimumab (ipi) as first-line therapy with respect to 12-month OS in patients with metUM who are not eligible for live resection [11]. |
| **Publications – title, author, journal, year** | Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402), Piulats J.M. et al. *J Clin Oncol* 2021; 39:586-598 DOI: 10.1200/JCO.20.00550 [11]. |
| **Study type and design** | GEM-1402 was a completed, open-label, multicenter, single-arm phase II trial investigating the efficacy of nivolumab plus ipilimumab as a first-line treatment for patients with metUM who were not eligible for liver |

| Trial name: Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402) | NCT number: NCT02626962 |
|---|---|
| | resection. As a single-arm study, no randomization or blinding was allowed. Crossover was not permitted [11]. |
| **Sample size (n)** | 52 [11] |
| **Main inclusion criteria** | **Inclusion criteria** [11,38]<br>• Written informed consent must be provided;<br>• Patients must have a histological diagnosis of uveal melanoma;<br>• Progressive metastatic disease at baseline. Progressive disease is defined as new or progressive lesions on cross-sectional imaging;<br>• Age>18 years;<br>• ECOG PS 0 to 1;<br>• Measurable disease by CT or MRI per RECIST 1.1 criteria; |
| **Main exclusion criteria** | **Exclusion Criteria** [11,38]<br>• Prior systemic treatment for metUM.<br>• 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.<br>• 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 (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [eg, Wegener'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.<br>• 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.<br>• 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).<br>• 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 costimulation or immune checkpoint pathways.<br>• 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 |

| Trial name: Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402) | NCT number: NCT02626962 |
|---|---|
| | 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.<br>• Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (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.<br>• Women of childbearing potential (WOCBP) as defined below, who:<br>○ 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<br>○ have a positive pregnancy test at baseline, or<br>○ are pregnant or breastfeeding. |
| **Intervention** | Patients received nivolumab (1 mg/kg IV over 60 minutes) in combination with ipilimumab (3 mg/kg IV over 90 minutes) Q3W for a total of four doses (cycles 1 and 2, each cycle = 6 weeks). Following the induction phase, patients received nivolumab (3 mg/kg IV over 60 minutes) every 2 weeks (cycle 3 and beyond, each cycle = 6 weeks).<br>A total of 52 patients received the intervention [11,38]. |
| **Comparator(s)** | N/A |
| **Follow-up time** | At the data collection cutoff (July 9, 2019), the median follow-up was 13.4 months (range, 0.8-35.2 months) [11,38]. |
| **Is the study used in the health economic model?** | Yes |
| **Primary, secondary and exploratory endpoints** | Primary endpoint [11,38]:<br>• The primary endpoint was the 12-month OS, defined as the time from the first dose to death from any cause in the intention-to-treat (ITT) population<br>Secondary endpoints [11,38]<br>• OS at 24 months, defined as the percentage of patients alive at 2-years from first dose of treatment<br>• Progression Free Survival (PFS), defined as a percentage of patients without progression of disease at month 3, according to RECIST 1.1 criteria<br>• Global PFS according to RECIST 1.1 criteria, defined as percentage of patients without progression of disease at month throughout follow-up, according to RECIST 1.1 criteria<br>• ORR at 12 months, defined as response to treatment according to RECIST 1.1 criteria<br>• Disease Control Rate, defined as percentage of patients with disease control |

| Trial name: Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402) | NCT number: NCT02626962 |
|---|---|
| | • DoR, defined as length of time between date of evidenced response and progression of disease or death<br>AEs and treatment-related AE's were monitored throughout the study period and graded according to the NCI CTCAE, v4.0. |
| **Method of analysis** | The OS and PFS were calculated using the KM method with CIs at 95%. A logistic regression model and a Cox PH 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) [11,38]. |
| **Subgroup analyses** | N/A |
| **Other relevant information** | N/A |

# Appendix B. Efficacy results per study

**Results per study**

**Table 65. Results of IMCgp100-202 (NCT03070392) – DCO October 2020.**

| Results of IMCgp100-202 (NCT03070392) – DCO October 2020 [13] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 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 OS | Tebentafusp | 87/252 | 21.7 [18.6; 28.6] months | 5.7 | N/A | N/A | HR = 0.51 | [0.37; 0.71] | <0.001 | OS was calculated by the KM method. The treatment groupss were formally compared with the use of a 2-sided log-rank test, stratified according to LDH status. | [13] |
| | Control | 63/126 | 63 (16) [9.7; 18.4] months | | | | | | | | |
| OS rate at 1 year | Tebentafusp | 184/252 | 73% [66; 79] | 14.0% | [3.96; 24.11]** | 0.006** | RR = 1.24* | [1.05; 1.47]* | 0.0095* | | [13] |
| | Control | 74/126 | 59% [48; 67] | | | | | | | | |
| 100-day landmark OS | Tebentafusp | 105 | 15.3 months [12.0; NR] | 8.8 months | N/A | N/A | HR = 0.43 | [0.27; 0.68] | N/A | Estimated using KM methodology. | [13] |
| | Control | 53 | 6.5 months [4.9; 13.4] | | | | | | | | |
| Median PFS | Tebentafusp | 198/252 | 3.3 [3; 5] months | 0.4 | N/A | N/A | HR = 0.73 | [0.58; 0.94] | 0.01 | PFS was calculated by the KM method. The treatment groups were formally compared with the use of a 2-sided log-rank test, stratified according to LDH status. | [13] |
| | Control | 97/126 | 2.9 [2.8; 3] months | | | | | | | | |
| PFS rate at 6 months | Tebentafusp | 252 | 78 (31%) | 12% | [2.58; 20.38]** | 0.01** | RR = 1.63* | [1.08; 2.44]* | 0.02* | | |
| | Control | 126 | 24 (19%) | | | | | | | | |

| Results of IMCgp100-202 (NCT03070392) – DCO October 2020 [13] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 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** | | |
| Disease control | Tebentafusp | 252 | 115 (46%) [39; 52] | 19% | [8.69; 28.32]** | <0.001** | RR = 1.69* | [1.23; 2.32]* | 0.001* | Response rates were calculated using a Mantel-Haenszel 2-sided test stratified by LDH status. | [13] |
| | Control | 126 | 34 (27%) [20; 36] | | | | | | | | |
| ORR | Tebentafusp | 252 | 23 (9%) [6; 13] | 4% | [-2.07; 8.94]** | 0.17** | RR = 1.92* | [0.80; 4.59]* | 0.144* | Response rates were calculated using a Mantel-Haenszel 2-sided test stratified by LDH status. | [13] |
| | Control | 126 | 6 (5%) [2; 10] | | | | | | | | |
| TEAEs | Tebentafusp | 245 | 245 (100%) | 5.4% | [2.11; 11.29]** | <0.001** | RR = 1.05* | [1.01; 1.11]* | 0.014* | Descriptive statistics | [13] |
| | Control | 111 | 105 (94.6%) | | | | | | | | |
| TRAEs | Tebentafusp | 245 | 243 (99.2%) | 17.2% | [10.81; 25.40]** | <0.001** | RR = 1.21* | [1.11-1.32]* | <0.001* | Descriptive statistics | [13] |
| | Control | 111 | 91 (82.0%) | | | | | | | | |
| Serious AEs of any grade | Tebentafusp | 245 | 69 (28.2%) | 1.8% | [-8.5; 11.2]** | 0.73** | RR = 1.20* | [0.81; 1.78]* | 0.36* | Descriptive statistics | [13] |
| | Control | 111 | 26 (26.4%) | | | | | | | | |
| Treatment emergent SAEs | Tebentafusp | 245 | 54 (22.0%) | 14.8% | [6.86; 21.41]** | <0.001** | RR = 3.06 | [1.51; 6.21]* | 0.002* | Descriptive statistics | [13] |
| | Control | 111 | 8 (7.2%) | | | | | | | | |
| TEAEs leading to discontinuation | Tebentafusp | 245 | 8 (3.3%) | 3.0% | [-1.44; 9.35]** | 0.19** | RR = 0.52* | [0.19; 1.39]* | 0.19* | Descriptive statistics | [13] |
| | Control | 111 | 7 (6.3%) | | | | | | | | |
| Related TEAEs leading to discontinuation | Tebentafusp | 245 | 5 (2.0%) | 2.5% | [-1.17-8.22]** | 0.18** | RR = 0.45* | [0.13-1.53]* | 0.20* | Descriptive statistics | [13] |
| | Control | 111 | 5 (4.5%) | | | | | | | | |

| Results of IMCgp100-202 (NCT03070392) – DCO October 2020 [13] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 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** | | |
| TEAE with CTCAE grade ≥3 | Tebentafusp | 245 | 133 (54.3%) | 18.3% | [7.13; 28.63]** | 0.0014** | RR = 1.51* | [1.15; 1.98]* | 0.0033* | Descriptive statistics | [13] |
| | Control | 111 | 40 (36.0%) | | | | | | | | |
| Related TEAE with CTCAE grade ≥3 | Tebentafusp | 245 | 109 (44.5%) | 28.4% | [18.27; 36.98]** | <0.001** | RR = 2.60* | [1.69; 4.01]* | <0.001* | Descriptive statistics | [13] |
| | Control | 111 | 19 (17.1%) | | | | | | | | |
| TEAE with CTCAE grade 1 | Tebentafusp | 245 | 14 (5.7%) | 15.8% | [8.24; 24.63]** | <0.001** | RR = 0.26* | [0.14; 0.49]* | <0.001* | Descriptive statistics | [13] |
| | Control | 111 | 24 (21.5%) | | | | | | | | |
| TEAE with CTCAE grade 2 | Tebentafusp | 245 | 98 (40.0%) | 3.2% | [-7.81; 13.66]** | 0.5669** | RR = 1.08* | [0.81; 1.44]* | 0.5869* | Descriptive statistics | [13] |
| | Control | 111 | 41 (36.8%) | | | | | | | | |
| TEAE with CTCAE grade 3 | Tebentafusp | 245 | 117 (47.8%) | 15.4.% | [4.35; 25.54]** | 0.007** | RR = 1.47* | [1.09; 1.99]* | 0.0111* | Descriptive statistics | [13] |
| | Control | 111 | 36 (32.4%) | | | | | | | | |
| TEAE with CTCAE grade 4 | Tebentafusp | 245 | 15 (6.1%) | 4.3% | [-0.81; 8.25]** | 0.078** | RR = 3.40* | [0.79; 14.61]* | 0.1002* | Descriptive statistics | [13] |
| | Control | 111 | 2 (1.8%) | | | | | | | | |
| TEAE with CTCAE grade 5 | Tebentafusp | 245 | 1 (0.4%) | 1.4% | [-0.87; 5.94]** | 0.180** | RR = 0.23* | [0.021; 2.47]* | 0.2233* | Descriptive statistics | [13] |
| | Control | 111 | 2 (1.8%) | | | | | | | | |
| Any dose reductions | Tebentafusp | 245 | 18 (7.3%) | 5.5% | [0.26; 9.67]** | 0.037** | RR = 4.08* | [0.96; 17.27]* | 0.0564* | Descriptive statistics | [13] |
| | Control | 111 | 2 (1.8%) | | | | | | | | |
| Dose reductions due to AEs | Tebentafusp | 26 | 22 (84.6%) | 15.4% | [-41.51; 33.55]** | 0.4719** | RR = 0.85* | [0.72; 0.10]* | 0.0458* | Descriptive statistics | [13] |
| | Control | 3 | 3 (100%) | | | | | | | | |
| Dose reduction due to other reasons | Tebentafusp | 26 | 4 (15.4%) | 15.4% | [-41.51; 33.55]** | 0.4719** | RR = 1.33* | [0.087; 20.37]* | 0.8362* | Descriptive statistics | [13] |
| | Control | 3 | 0 (0%) | | | | | | | | |

| Results of IMCgp100-202 (NCT03070392) – DCO October 2020 [13] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 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** | | |
| TEAR leading to dose or infusion interruptions | Tebentafusp | 245 | 62 (25.3%) | 1.0% | [-9.10; 10.11]** | 0.8402** | RR = 1.04* | [0.70; 1.54]* | 0.8433* | Descriptive statistics | [13] |
| | Control | 111 | 27 (24.3%) | | | | | | | | |
| Any related TEAE leading to dose or infusion interruption | Tebentafusp | 245 | 44 (18.0%) | 2.7% | [-5.68; 12.19]** | 0.5468** | RR = 0.87* | [0.55; 1.36]* | 0.5348* | Descriptive statistics | [13] |
| | Control | 111 | 23 (20.7%) | | | | | | | | |
| Any TEAE leading to death | Tebentafusp | 245 | 1 (0.4%) | 1.4% | [-0.87; 5.94]** | 0.1797** | RR = 0.23* | [0.02; 2.47]* | 0.2233* | Descriptive statistics | [13] |
| | Control | 111 | 2 (1.8%) | | | | | | | | |
| Related TEAE leading to death | Tebentafusp | 245 | 0 (0%) | N/A | N/A | N/A | N/A | N/A | N/A | Descriptive statistics | [13] |
| | Control | 111 | 0 (0%) | | | | | | | | |
| Anti-tebentafusp antibodies | Tebentafusp | 220 | 63 (29%) | N/A | N/A | N/A | N/A | N/A | N/A | Descriptive statistics | [13] |
| 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 (LS) regression | [54] |
| | 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 | LS regression | [54] |
| | 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 | LS regression | [54] |

| Results of IMCgp100-202 (NCT03070392) – DCO October 2020 [13] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 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 | [54] |
| 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 | [54] |
| 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 | [54] |
| 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 | [54] |
| 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 | [54] |
| Mean utility, EQ-5D (Cycle 17 day 1) | Tebentafusp vs Control | 33 | 0.834 | N/A | N/A | N/A | N/A | N/A | N/A | Descriptive statistics | [54] |
| 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 | [54] |
| 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 | [54] |

| Results of IMCgp100-202 (NCT03070392) – DCO October 2020 [13] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 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** | | |
| 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 | [54] |
| 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 | [54] |
| 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 | [54] |
| Mean utility, EQ-5D (Survival follow-up day 180) | Tebentafusp vs Control | 35 | 0.803 | N/A | N/A | N/A | N/A | N/A | N/A | Descriptive statistics | [54] |
| 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 | [54] |
| 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 | [54] |

* Relative risk (RR) calculated using: $RR = \frac{a/(a+b)}{c/(c+d)}$, with the SE of the log RR 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 66. Results of IMCgp100-202 (NCT03070392) - DCO July 2023.**

| Results of IMCgp100-202 (NCT03070392) – DCO July 2023 [10] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 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 OS | Tebentafusp | 252 | 21.6 months [19.0; 24.3] | 4.7 months | N/A | N/A | HR = 0.68 | [0.54; 0.87] | N/A | OS was evaluated as time-to-event analysis and was calculated by the KM method. The treatment groups were formally compared with the use of a 2-sided log-rank test. Treatment effects were characterized by the HR derived from a stratified Cox PH regression model, which was stratified according to the LDH status - but only if the PH assumption was met. [10,13] | [10] |
| | Control | 126 | 16.9 months [12.9; 19.5] | | | | | | | | |
| OS rate at 1 year | Tebentafusp | 252 | 175 (72%) | 12% | [1.98; 22.15]** | 0.019** | RR = 1.22* | [1.02; 1.44]* | 0.026* | OS rate for 1 year has been estimated using KM methodology. | [10] |
| | Control | 126 | 72 (60%) | | | | | | | | |
| OS rate at 2 years | Tebentafusp | 252 | 106 (45%) | 15% | [4.59; 24.57]** | 0.005** | RR = 1.47* | [1.08; 2.01]* | 0.015* | OS rate for 2 years has been estimated using KM methodology. | [10] |
| | Control | 126 | 36 (30%) | | | | | | | | |
| OS rate at 3 years | Tebentafusp | 252 | 53 (27%) | 9% | [-0.17; 17.15]** | 0.054** | RR = 1.56* | [0.94; 2.58]* | 0.084* | OS rate for 3 years has been estimated using KM methodology. | [10] |
| | Control | 126 | 17 (18%) | | | | | | | | |
| 100-day landmark OS | Tebentafusp | 104 | 15.1 months [11.5; 17.4] | 4 months | N/A | N/A | HR = 0.62 | [0.44; 0.89] | N/A | Estimated using KM methodology. | [10] |
| | Control | 53 | 10.1 months [5.4; 13.6] | | | | | | | | |

| Results of IMCgp100-202 (NCT03070392) – DCO July 2023 [10] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 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 | Tebentafusp | 252 | 3.4 months [3.0; 5.4] | 0.5 months | N/A | N/A | HR = 0.76 | [0.60; 0.97] | N/A | PFS was investigator assessed and evaluated as time-to-event analysis [10,13]<br>PFS were calculated by the KM method. The treatment groups were formally compared with the use of a 2-sided log-rank test. [10,13]<br>Treatment effects were characterized by the HR derived from a stratified Cox PH regression model, which was stratified according to the LDH status - but only if the PH assumption was met. [10,13] | [10] |
| | Control | 126 | 2.9 months [2.8; 3.0] | | | | | | | | |
| Progression free survival, rate 1 year | Tebentafusp | 252 | 41 (17%) | 8% | [0.48; 14.41]** | 0.037** | RR = 2.93* | [1.35; 6.34]* | 0.006* | PFS rate for 1 year has been estimated using KM methodology. | [10] |
| | Control | 126 | 7 (9%) | | | | | | | | |
| Progression free survival, rate 2 years | Tebentafusp | 252 | 16 (8%) | 5% | [-0.39; 9.42]** | 0.060** | RR = 4.00* | [0.93; 17.13]* | 0.062* | PFS rate for 2 years has been estimated using KM methodology. | [10] |
| | Control | 126 | 2 (3%) | | | | | | | | |
| Progression free survival, | Tebentafusp | 252 | 6 (4%) | 4% | [0.53; 7.19]** | 0.023** | RR = 6.53* | [0.37; 114.93]* | 0.200* | PFS rate for 3 years has been estimated using KM methodology. | [10] |
| | Control | 126 | 0 (0%) | | | | | | | | |

| Results of IMCgp100-202 (NCT03070392) – DCO July 2023 [10] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 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 | | |
| rate 3 years | | | | | | | | | | | |
| ORR | Tebentafusp | 252 | 28 (11%) | 6% | [-0.25; 11.19]** | 0.055** | OR = 2.46 | [1.00; 6,06] | N/A | Response rates were calculated using a Mantel-Haenszel 2-sided test statistic stratified by LDH status [13]. The 95% CIs were calculated with the use of the exact Clopper–Pearson method [10]. | [10] |
| | Control | 126 | 6 (5%) | | | | | | | | |
| CR | Tebentafusp | 252 | 1 (0.4%) | 0.4% | [-2.58; 2.22]** | 0.478** | RR=1.51* | [0.06; 36.71]* | 0.8016* | Descriptive statistics | [10] |
| | Control | 126 | 0 (0%) | | | | | | | | |
| PR | Tebentafusp | 252 | 27 (11%) | 6% | [-0.25; 11.19]** | 0.055** | RR = 2.25* | [0.95; 5.31]* | 0.064* | Descriptive statistics | [10] |
| | Control | 126 | 6 (5%) | | | | | | | | |
| SD | Tebentafusp | 252 | 87 (35%) | 13% | [3.22; 21.78]** | 0.010** | RR = 1.55* | [1.08; 2.25]* | 0.019* | Descriptive statistics | [10] |
| | Control | 126 | 28 (22%) | | | | | | | | |
| PD | Tebentafusp | 252 | 132 (52%) | 13% | [2.41; 22.91]** | 0.016** | RR = 0.80* | [0.68; 0.96]* | 0.014* | Descriptive statistics | [10] |
| | Control | 126 | 82 (65%) | | | | | | | | |
| NE | Tebentafusp | 252 | 5 (2%) | 6% | [1.58; 12.18]** | 0.005** | RR = 0.25* | [0.09; 0.72]* | 0.010* | Descriptive statistics | [10] |
| | Control | 126 | 10 (8%) | | | | | | | | |
| | Tebentafusp | 252 | 115 (46%) | 19% | | <0.001** | OR = 2.34 | [1.45; 3.76] | N/A | | [10] |

| Results of IMCgp100-202 (NCT03070392) – DCO July 2023 [10] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 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** | | |
| Disease control at 12 weeks | Control | 126 | 34 (27%) | | [8.69; 23.32]** | | | | | The odds ratio and 95% CI were calculated with a Stratified Cochran–Mantel–Haenszel test, with stratification according to LDH status (i.e., LDH level higher than the upper limit of the normal range or less than or equal to the upper limit of the normal range). [10] | |
| TRAEs any grade | Tebentafusp | 245 | 244 (100%) | 18% | [11.77; 26.18]** | <0.0001** | RR = 1.21* | [1.11; 1.33]* | <0.0001* | Descriptive statistics | [10] |
| | Control | 111 | 91 (82%) | | | | | | | | |
| Grade ≥ 3 TRAE | Tebentafusp | 245 | 116 (47%) | 29% | [18.76; 37.69]** | <0.0001** | RR = 2.63* | [1.73; 3.99]* | <0.0001* | Descriptive statistics | [10] |
| | Control | 111 | 20 (18%) | | | | | | | | |
| TR-SAE | Tebentafusp | 245 | 79 (32%) | 10% | [-0.20; 19.05]** | 0.054** | RR = 1.63* | [1.70; 2.47]* | 0.0218* | Descriptive statistics | [10] |
| | Control | 111 | 24 (22%) | | | | | | | | |
| Discontinuation due to TRAEs | Tebentafusp | 245 | 5 (2%) | 3% | [-0.81; 8.88]** | 0.121** | RR = 0.45* | [0.13; 1.53]* | 0.2031* | Descriptive statistics | [10] |
| | Control | 111 | 5 (5%) | | | | | | | | |
| Death due to TRAEs | Tebentafusp | 245 | 0 (0%) | 0% | [-1.54; 3.35]** | N/A | RR = 0.46* | [0.01; 22.80]* | 0.0694* | Descriptive statistics | [10] |
| | Control | 111 | 0 (0%) | | | | | | | | |

* RR calculated using: $RR = \frac{a/(a+b)}{c/(c+d)}$, with the SE of the log RR 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 67. Results of GEM1402 (NCT02626962).**

| Results of GEM-1402 (NCT02626962) [11] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 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 OS ITT | Ipi/nivo | - | 12.7 months [7.1; 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 [3.1; 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 [7.4; 23.5] | N/A | N/A | N/A | N/A | N/A | N/A | OS were calculated using the KM method with CIs at 95%. | [11] |
| OS-rates 12 month | Ipi/nivo | 27/52 | 51.9% [38.3; 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; 38.6] | N/A | N/A | N/A | N/A | N/A | N/A | | |
| Median PFS | Ipi/nivo | - | 3.0 [2.0; 4.1] | N/A | N/A | N/A | N/A | N/A | N/A | PFS were calculated using the KM method with CIs at 95%. | [11] |
| Progression free survival rate at 6 months | Ipi/nivo | 14/52 | 28.2% [16.5; 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% [8.5; 29.9) | N/A | N/A | N/A | N/A | N/A | N/A | | |
| AEs | Ipi/nivo | 52 | 52 (100%) | N/A | N/A | N/A | N/A | N/A | N/A | Descriptive statistics | [11] |

| Results of GEM-1402 (NCT02626962) [11] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 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 | | |
| GRADE ≥ 3 AEs | Ipi/nivo | 52 | 30 (57.7%) | N/A | N/A | N/A | N/A | N/A | N/A | Descriptive statistics | [11] |
| TRAEs | Ipi/nivo | 52 | 49 (94.2%) | N/A | N/A | N/A | N/A | N/A | N/A | Descriptive statistics | [11] |
| TR-SAEs | Ipi/nivo | 52 | 30 (57.7%) | N/A | N/A | N/A | N/A | N/A | N/A | Descriptive statistics | [11] |
| TR-SAEs GRADE ≥ 3 | Ipi/nivo | 52 | 21 (40.4%) | N/A | N/A | N/A | N/A | N/A | N/A | Descriptive statistics | [11] |
| Non-TR-SAEs | Ipi/nivo | 52 | 26 (50%) | N/A | N/A | N/A | N/A | N/A | N/A | Descriptive statistics | [11] |
| Non-treatment related serious event grade ≥ 3 | Ipi/nivo | 52 | 14 (26.9%) | N/A | N/A | N/A | N/A | N/A | N/A | Descriptive statistics | [11] |
| Treatment related deaths | Ipi/nivo | 52 | 2 (3.8%) | N/A | N/A | N/A | N/A | N/A | N/A | Descriptive statistics | [11] |

# Appendix C. Comparative analysis of efficacy

## C.1 Objective

The framework for this comparative analysis is the indirect analysis presented by Piulats et al. (2023) and colleagues [9]. The primary objective of the analysis performed by Piulats et al. (2023) was to compare, using propensity score-based methods, OS of tebentafusp (IMCgp100-202) to OS on ipi/nivo (GEM-1402) in metUM patients in the 1st line setting.

The comparative analysis performed in this resubmission applies to the two most recent DCOs for IMCgp100-202 (July 3, 2023; median follow-up 43.3 months) and GEM-1402 (August 2023; median follow-up 35 months) [9].

## C.2 Study design and plan

The general design of this analysis and any propensity score analysis is to:

1. Pre-specify the intended approach for deriving propensity scores, including the baseline covariates to be considered for the propensity score model.
2. Evaluate the balance between comparison groups with respect to important baseline covariates both before and after adjusting for the propensity score and to decide as to whether the balance after making adjustments is adequate enough to move forward with the analysis.
3. Conduct the intended comparisons via the prescribed propensity score methodology.

HRs and 95% CIs were used to help draw general conclusions about the comparisons being made.

## C.3 Study population

The tebentafusp group of the ITT population from study IMCgp100-202 (n=252) and the ITT population of study GEM-1402 (n=52) were used.

## C.4 Endpoints and covariates

### C.4.1 Endpoints

The primary endpoint for this analysis is OS.

For study IMCgp100-202, this was OS as defined in the study's primary SAP.

For study GEM-1402, this was derived from the supplied variables as 'Date end of follow-up' – 'Date treatment started' + 1. patients with 'Status at end of follow-up' of "Alive" were censored at the end of follow-up.

### C.4.2 Covariates

The covariates to be considered for the propensity score model and for the baseline covariates to be compared both before and after making propensity score adjustments included the same list of variables adjusted for in the previous MAIC (described in initial assessment of tebentafusp [7]).

Modelling can only be done on covariates as supplied for GEM-1402 and therefore the list of variables included are:

- Age (years)
- Gender
- Baseline LDH – ≤/> ULN (rather than log-transformed continuous variable)
- Baseline ALP – ≤/> ULN (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 from primary diagnosis to metastasis (months) (rather than time from primary diagnosis to treatment, since this is not available for GEM-1402)

No important potential unmeasured confounders were identified.

As there are only a small number of patients with extrahepatic disease only in study IMCgp100-202 compared to GEM-1402, this may impact the effective sample size and/or cause modelling issues. Therefore, two alternative ways of defining the disease location covariate were also investigated:

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

The primary analysis used the definition that provided the best overall model in terms of balancing model fit statistics, distribution of propensity scores/weights (minimizing extreme weights etc.), and amount of missing data. The decision on the set of covariates to include in the primary analysis was made without knowledge of the impact of the covariates on the outcome of the survival analyses.

## C.5 Missing data

There are no missing data for the OS outcome. However, some patients have missing data for one or more baseline covariates in the propensity score model.

The primary analysis was a "complete case" analysis - excluding patients with missing data for at least one relevant covariate from both groups (resulting in n=240 tebentafusp group and 45 in ipi/nivo group).

A sensitivity analysis using multiple imputation of missing baseline covariate values was performed. The imputation model included terms for baseline age, gender, LDH, ALP, disease location, largest metastatic liver lesion, ECOG, and time from primary diagnosis to metastasis. Separate models were used for each treatment group. 20 imputed datasets were generated using Markov Chain Monte Carlo methods in the SAS procedure PROC MI. Each imputed dataset was analyzed using the propensity score generating model and subsequent survival analyses per the primary analysis. Results were combined using Rubin's rules via SAS PROC MIANALYZE.

## C.6 Statistical methodology

### C.6.1 General considerations

For sensitivity analyses, multivariate Cox regression models were also used. Analyses were performed using SAS software version 9.4 in a validated statistical computing environment running Windows Server 2012.

### C.6.2 Descriptive statistics

The covariates described in section C.4.2 were summarized using standard descriptive statistics (n, mean, standard deviation, median, minimum, and maximum for continuous factors; n and percent for categorical data) both unweighted and weighted as described in section C.6.4. Adjusted and unadjusted standardized differences between comparison groups were calculated.

The OS endpoint was summarized via KM estimates for the median (including 95% CIs) and the 1-year estimates. HRs and 95% CIs came from Cox PH models as described in section C.6.7.

### C.6.3 Propensity score model

The covariates described in section C.4.2 were used as main effects in a logistic regression model. This modelled the probability of a patient in the analysis population being treated with tebentafusp (i.e. being from study IMCgp100-202 rather than GEM-1402). This model was used to compare patients receiving tebentafusp to patients receiving ipi/nivo. The propensity score was the probability of being treated with tebentafusp. The decision on the final set of covariates to include in the primary propensity score generating model was based on several factors such as model fit statistics, distribution of propensity scores/weights (minimizing extreme weights etc.), and amount of missing data. The decision was made without knowledge of the impact on the outcome of the survival analyses.

### C.6.4 Inverse probability of treatment weights (IPTW)

IPTW is the common nomenclature for the propensity score method that involves weighting of groups by the propensity score. ATT weights [77] were used as primary:

$$w_i = T_i + \frac{p_i(1 - T_i)}{(1 - p_i)}$$

Where:

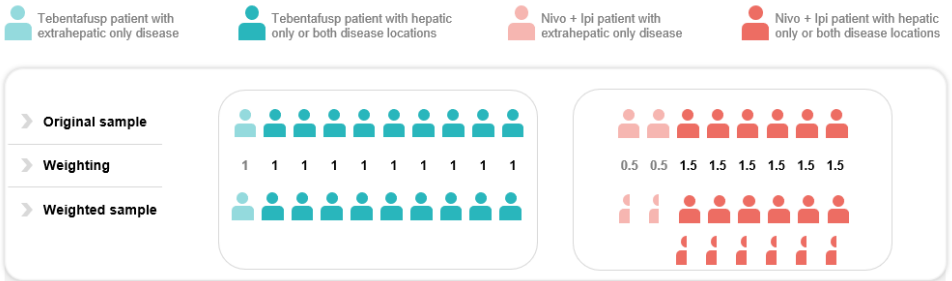
*i* = subscript for the i-th patient

*w* = the weight

*p* = the propensity score as derived from the appropriate logistic regression model

T =1 for patients with tebentafusp and 0 for patients with ipi/nivo

With these ATT weights, tebentafusp patients receive a weight of 1 and ipi+nivo patients receive a weight of $p_i/(1- p_i)$. With this weighting, the reference population is the population of tebentafusp treated patients (i.e. study 202) and ipi/nivo patients are weighted so that they are generally more similar to this reference population. A schematic of ATT IPT-weighting for a single confounder (disease location) is presented in Figure 10.




| | Tebentafusp | | Nivolumab + Ipilimumab | |
|---|---|---|---|---|
| | Extrahepatic only | Hepatic only or both disease location | Extrahepatic only | Hepatic only or both disease location |
| Original sample | 1 (10%) | 9 (90%) | 2 (25%) | 6 (75%) |
| Weighting | 1 | 1 | 0 | 1.5 |
| Weighted sample | 1 (10%) | 9 (90%) | 1 (10%) | 9 (90%) |

**Figure 10. Schematic of ATT IPT-weighting for a single confounder, disease location** [9].

The analyses were repeated using ATC weights, where the roles of tebentafusp and ipi/nivo are reversed in the above equation. The analyses were also repeated using ATE of the combined population weights, ATTi/pi (tebentafusp patients receive a weight of 1/pi and ipi/nivo patients receive a weight of 1/(1-pi).

Analyses using ATC and ATE weights were only conducted for the complete case approach, as there were no marked differences in ATT weight-based results observed with other missing data handling methods. Weights were evaluated visually for outliers using plots of the propensity score on the x-axis and weight on the y-axis with separate colors/symbols for the two comparison groups. If there are clear outlying weights, especially if outliers are more common in one group vs. the other, then stabilized weights [78] and/or trimmed weights could be considered. Stabilized weights were calculated as:

$$sw_{i,k} = w_i \frac{n_k}{\sum_{k=1}^{2} n_k}$$

Where:

*i* = subscript for the i-th patient on treatment group *k*

*k* = subscript for the k-th comparison group

*n* = the number of patients in the respective group

Trimmed weights would have been applied by assigning outlier weights to the highest non-outlying value in the respective group, if applicable.

#### C.6.4.1 Justification for IPTW over other propensity score approaches

Other common propensity score model approaches include matching, stratification, and covariate adjustment. A limitation of matching is the need for a large pool of data to find appropriately matched patients to those for whom the propensity score was modelled. Given the relatively small number of patients in the comparison groups, this is likely to be prohibitive in the current analysis.

When applied to time-to-event endpoints such as OS, matching, stratification, and covariate adjustment all have the potential to produce biased estimates of KM estimates and marginal HRs [79].

Considering these limitations, the IPTW approach with the appropriate weighting strategies is best suited for the current analysis considering the available sample size, the time-to-event endpoint, and the desired measurements for the objective.

### C.6.5 Assessing propensity score overlap

Before moving forward with the planned sets of analyses, the overlap of the propensity scores between the two comparison groups was assessed visually via box plots. If the boxes (i.e. the interquartile ranges) between the groups do not overlap, then the differences between the two groups may not be adequate for comparison**.** If this occurs, then remaining comparisons between the groups described in this appendix must be interpreted cautiously.

### C.6.6 Comparison of baseline characteristics before and after weighting

The baseline covariates described in section C.4.2 were compared between patients treated with tebentafusp and patients treated with ipi/nivo using standard descriptive statistics.

The same sets of comparisons were made after applying the IPTW weights as described in section C.6.4.

### C.6.7 Comparing IPTW adjusted survival between comparison groups

The adjusted survival for each comparison group was evaluated visually using weighted KM curves and associated medians and 1-year survival estimates along with 95% CIs. An IPTW-weighted HR and 95% CI was also produced from a weighted Cox regression model. Variance was calculated via robust sandwich estimation. This was applied by using the `COVS` option and a `WEIGHTS` statement in PROC PHREG.

For context, groups were also compared using an unadjusted Cox regression model and unweighted KM curves, to evaluate the impact and direction that the IPTW weighting had on the naive unadjusted treatment effect.

#### C.6.7.1 Sensitivity analysis

As a sensitivity analysis, a multivariate Cox regression model was used to evaluate the effect of tebentafusp vs ipi/nivo on OS relative to other baseline prognostic factors. The model included all effects in the primary propensity score model.

### C.6.8 Clarifications and changes to planned analyses

All planned covariates were included in the propensity score model. The three-level disease location covariate (hepatic only, extrahepatic only, hepatic and extrahepatic) was used, for the following reasons:

- No model fitting issues, good balance between treatments after weighting, no extreme weights
- More information than 2-level disease location
- More strongly associated with which being in IMCgp100-202 vs GEM-1402 than 2-level (extrahepatic only is one of the more imbalanced factors between the studies)
- Less missing data than largest metastatic liver lesion and slightly better balance for e.g. age
- Used as primary in the previous MAIC vs GEM-1402

The decision on the covariates to use in the propensity score model was made without knowledge of the impact of this on the subsequent analyses.

## C.7 Results

Results are presented for the primary analysis (complete case, ATT weights). In the primary complete case analysis 12/252 (4.8%) tebentafusp patients and 7/52 (13.5%) ipi/nivo patients were excluded due to missing baseline covariates. No patients are excluded due to missing data in the sensitivity analysis using multiple imputation.

### C.7.1 Propensity score modelling and IPTWs

In the propensity score model, the strongest covariate influencing the propensity for receiving tebentafusp vs ipi/nivo was disease location (Table 68).

**Table 68. Propensity score model covariate effects (tebentausp vs ipi/nivo).**

| Covariate | Comparison | Odds ratio (95% CI) for receiving tebentafusp | p-value |
|---|---|---|---|
| Age (years) | Continuous | 1.016 (0.988, 1.044) | 0.2661 |
| Gender | F vs M | 0.988 (0.505, 1.936) | 0.9730 |
| Baseline LDH | <=ULN vs >ULN | 1.571 (0.743, 3.320) | 0.2366 |
| Baseline ALP | <=ULN vs >ULN | 0.904 (0.341, 2.395) | 0.8385 |
| Disease location | Extrahepatic vs both | 0.121 (0.040, 0.367) | 0.0006 |
| | Hepatic vs both | 0.831 (0.398, 1.737) | |
| ECOG | 0 vs 1 | 0.650 (0.248, 1.705) | 0.3817 |

| Covariate | Comparison | Odds ratio (95% CI) for receiving tebentafusp | p-value |
|---|---|---|---|
| Time from diagnosis to metastasis (years) | Continuous | 0.989 (0.917, 1.066) | 0.7647 |

As seen in Table 69 and Figure 11, there was reasonable overlap of propensity scores distributions between treatment groups.

**Table 69. Summary of propensity scores distribution by treatment.**

| Planned treatment | N Obs | Mean | Std Dev | Median | Minimum | Maximum | Sum |
|---|---|---|---|---|---|---|---|
| Tebentafusp | 252 | 0.8559570 | 0.0793090 | 0.8736525 | 0.3952486 | 0.9429993 | 205.4296777 |
| Ipi/nivo | 52 | 0.7682293 | 0.1831512 | 0.8568020 | 0.3023705 | 0.9292147 | 34.5703203 |

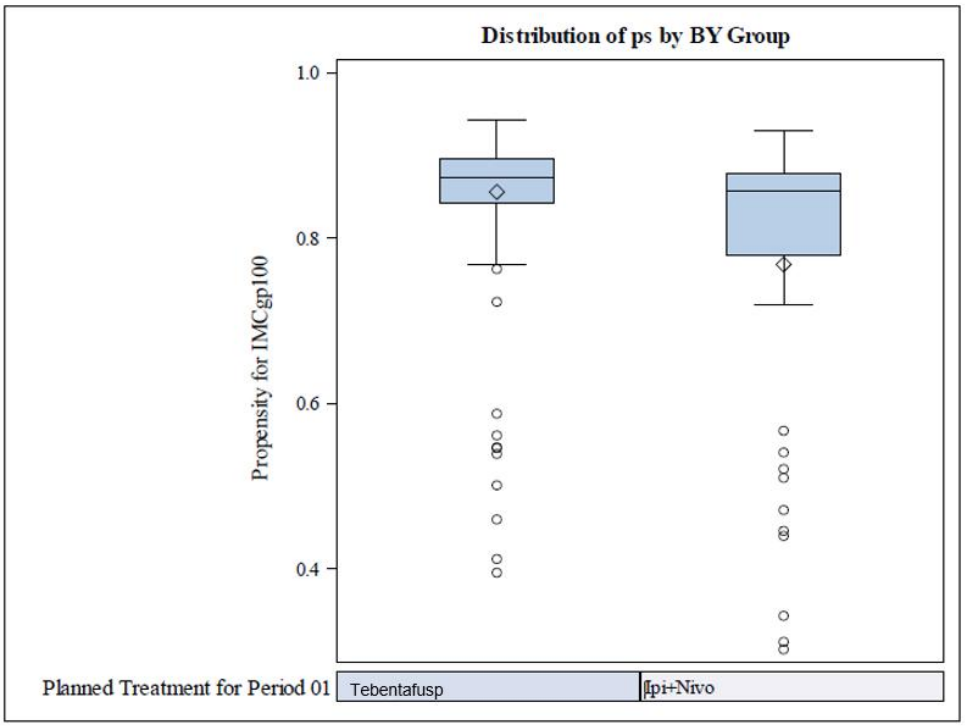



**Figure 11. Boxplot of propensity scores distribution by treatment.**

There were no clear weight outliers and no extreme weights observed, see Table 70.

**Table 70. Summary of IPTWs (ATT) distribution by treatment.**

| | | IPT weights (ATT) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Planned treatment | N Obs | N | Mean | Std Dev | Median | Minimum | Maximum | Sum |
| Tebentafusp | 252 | 240 | 1.0000000 | 0 | 1.0000000 | 1.0000000 | 1.0000000 | 240.0000000 |
| Ipi/nivo | 52 | 45 | 5.3762412 | 3.0441183 | 5.9833358 | 0.4334257 | 13.1272307 | 241.9308562 |

| IPT weights (ATT stabilized) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Planned treatment | N Obs | Mean | Std Dev | Median | Minimum | Maximum | Sum |
| Tebentafusp | 252 | 0.8421053 | 0 | 0.8421053 | 0.8421053 | 0.8421053 | 202.1052632 |
| Ipi/nivo | 52 | 0.8488802 | 0.4806503 | 0.9447372 | 0.0684356 | 2.0727206 | 38.1996089 |

Good balance in patient characteristics between treatments was achieved after weighting, see Table 71.

**Table 71. Patient characteristics. Observed and IPT weighted (ATT) by treatment.**

| Characteristic | Tebentafusp observed (n=240) | Ipi/nivo observed (n=45) | Tebentafusp weighted (n=240[a]) | Ipi/nivo weighted (n=241.9[a]) |
|---|---|---|---|---|
| Age (years) mean (SD) | 61.2 (12.02) | 59.3 (13.3) | 61.2 (12.0) | 61.7 (30.2) |
| Male | 122 (50.8%) | 23 (51.1%) | 122 (50.8%) | 112.6 (46.6%) |
| Baseline LDH > ULN | 84 (35.0%) | 19 (42.2%) | 84 (35.0%) | 81.8 (33.8%) |
| Baseline ALP > ULN | 51 (21.3%) | 7 (15.6%) | 51 (21.3%) | 50.6 (20.9%) |
| Disease location extrahepatic only | 9 (3.8%) | 10 (22.2%) | 9 (3.8%) | 8.5 (3.5%) |
| Disease location hepatic only | 123 (51.3%) | 20 (44.4%) | 123 (51.3%) | 124.0 (51.3%) |
| Disease location both | 108 (45.0%) | 15 (33.3%) | 108 (45.0%) | 109.4 (45.2%) |
| ECOG PS 0 | 191 (79.6%) | 38 (84.4%) | 191 (79.6%) | 199.3 (82.4%) |
| Time from diagnosis to metastasis (years) mean (SD) | 4.0 (4.4) | 4.7 (4.6) | 4.0 (4.4) | 4.1 (9.6) |

[a]Weighted N is the sum of the weights.

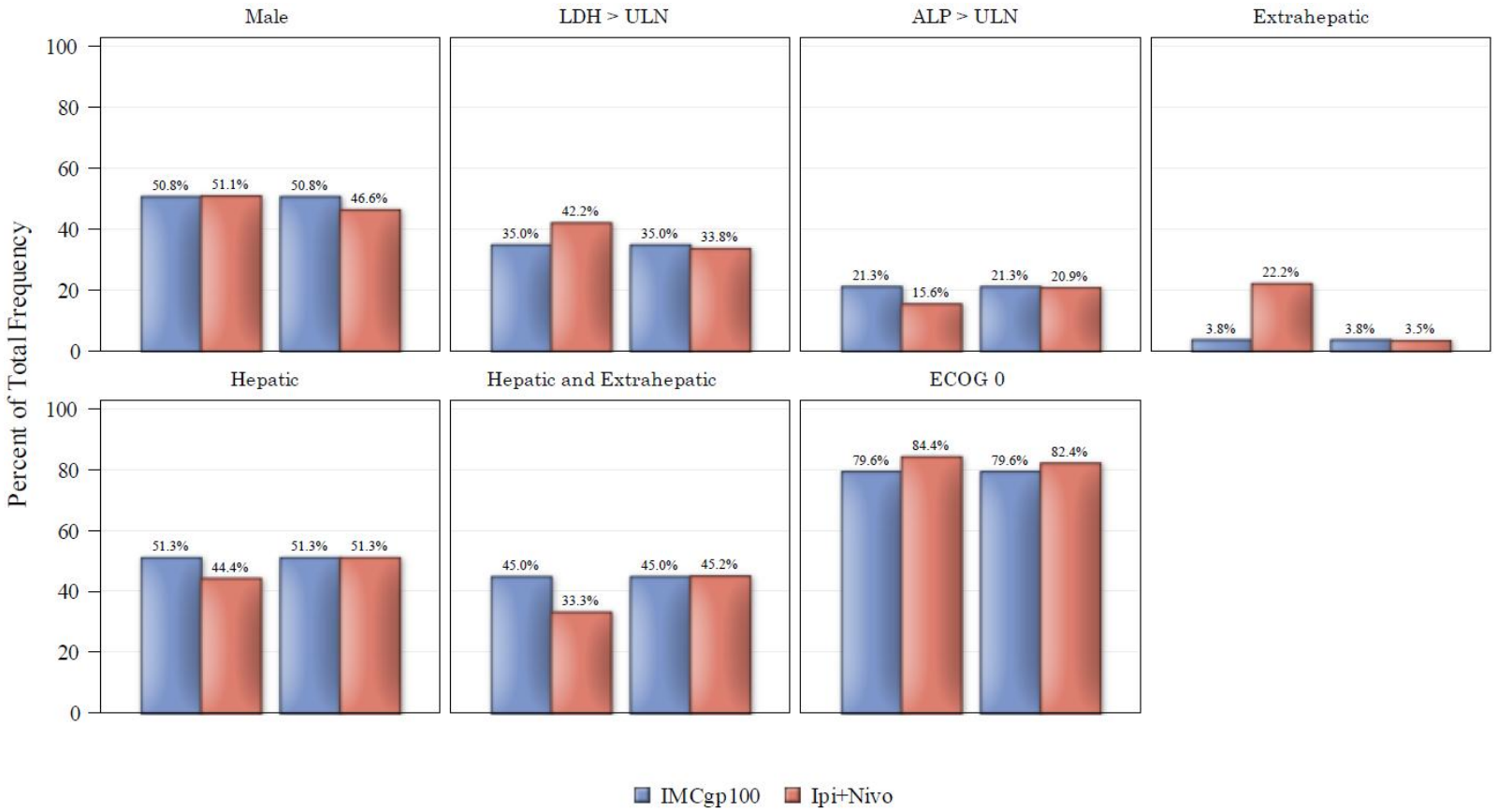



**Figure 12. Bar plots of categorial patient characteristics, observed [first two bars] and IPT-weighted (ATT) [second two bars] by treatment.**

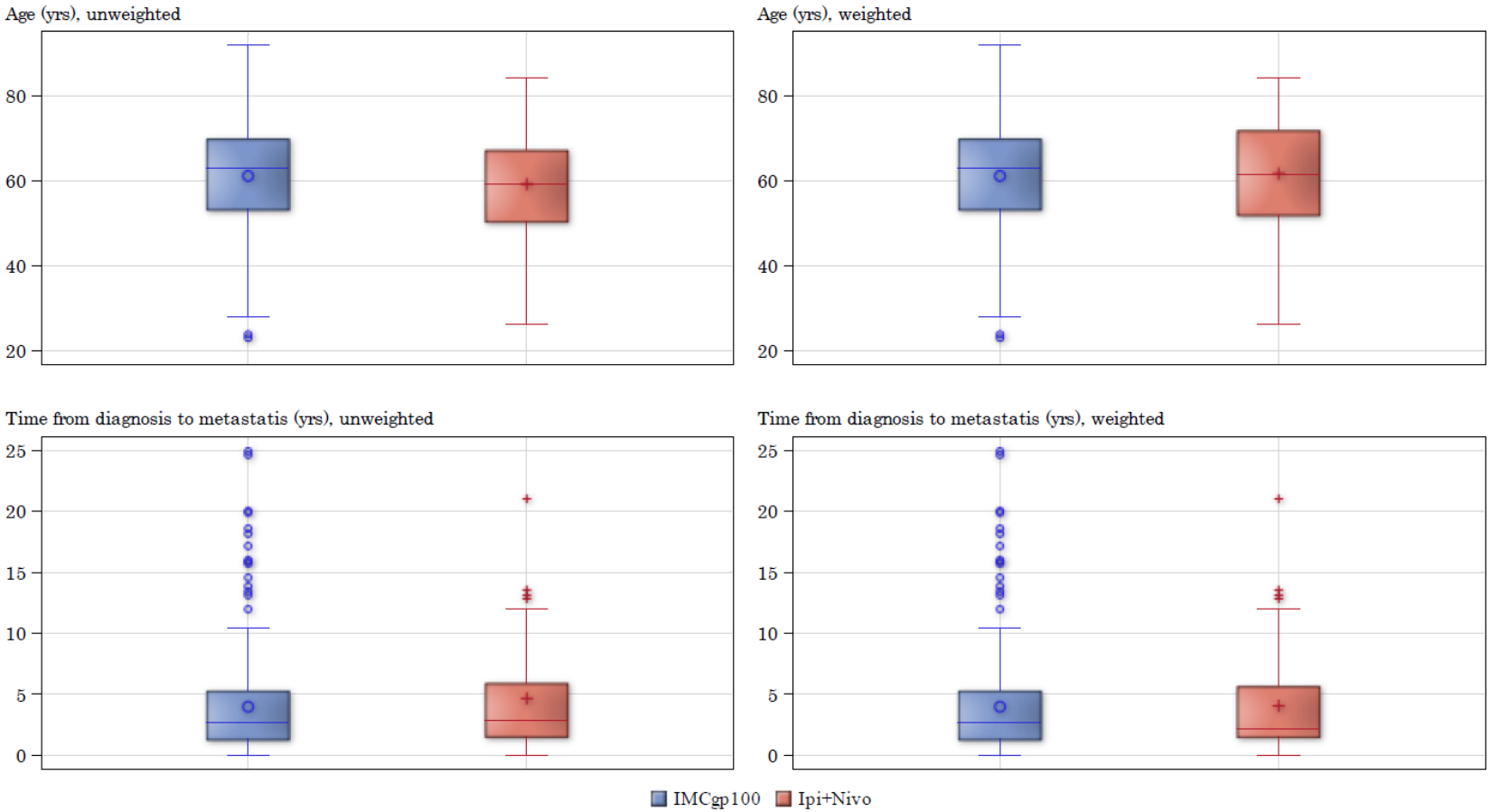



**Figure 13. Box plots of continuous patient characteristics, observed and IPT-weighted (ATT) by treatment**

Therefore, there were no major concerns about the generated weights, and IPT weighted survival analyses were then conducted.

### C.7.2 IPTW adjusted survival

In all analyses, regardless of the method for handling missing data or the type of IPT weights used, OS was longer for tebentafusp than for ipi/nivo. This was also the case for the unadjusted analysis.

The IPT weighting numerically increased the relative OS benefit for tebentafusp, suggesting that patients in the GEM-1402 study had slightly better prognosis than those in the tebentafusp group of the IMCgp100-202 study.

Results were also consistent with the previously conducted match-adjusted indirect comparison using the primary DCO (October 2020) for study IMCgp100-202 and summary-level data rather than IPD for study GEM-1402 (DCO July 2019) [7]. The results are presented in Table 72.

**Table 72. Overall survival analyses comparing tebentafusp and ipi/nivo, IPT weighted and unadjusted.**

| | N (ESS) | | Median / 12 month OS | | |
|---|---|---|---|---|---|
| **Model** | **Tebentafusp** | **Ipi/nivo** | **Tebentafusp** | **Ipi/nivo** | **HR (95% CI)** |
| Complete case, IPT ATT weights (primary) | 240 (240) | 241.9 (34.3) | 21.7m/73.4% | 12.6m/50.3% | 0.525 (0.352, 0.781) |
| Multiple imputation, IPT ATT weights (sensitivity) | 252 | 255 | 21.6m/72.3% | 12.6-14.1m/ 52.9-54.1%* | 0.550 (0.383, 0.791) |
| Complete case, IPT ATT stabilized weights (sensitivity) | 202.1 (240) | 38.2 (34.3) | 21.7m/73.4% | 12.6m/50.3% | 0.496 (0.324, 0.759) |
| Complete case, multivariate Cox analysis (sensitivity) | 240 | 45 | - | - | 0.411 (0.275, 0.615) |
| Complete case, IPT ATE weights | 284.3 (234.6) | 286.9 (36.8) | 21.7m/73.8% | 12.6m/50.5% | 0.540 (0.367, 0.794) |
| Complete case, IPT ATC weights | 44.3 (123.1) | 45 (45) | 22.2m/76.2% | 12.6m/51.1% | 0.612 (0.406, 0.923) |
| Match-adjusted indirect comparison (Oct 2020 DCO) | 183 | 52 | 21.6m/78.6% | 12.1m/51.2% | 0.507 (0.324, 0.793) |
| Unadjusted complete case | 240 | 45 | 21.7m/73.4% | 12.6m/51.1% | 0.634 (0.444, 0.904) |

| | N (ESS) | | Median / 12 month OS | | |
|---|---|---|---|---|---|
| **Model** | **Tebentafusp** | **Ipi/nivo** | **Tebentafusp** | **Ipi/nivo** | **HR (95% CI)** |
| (no IPT weighting) | | | | | |
| Unadjusted multiple imputation (no IPT weighting) | 252 | 52 | 21.6m/72.3% | 13.4m/53.8% | 0.664 (0.474, 0.929) |

*range across 20 imputations. ESS=Effective Sample Size, included for IPT complete case analyses

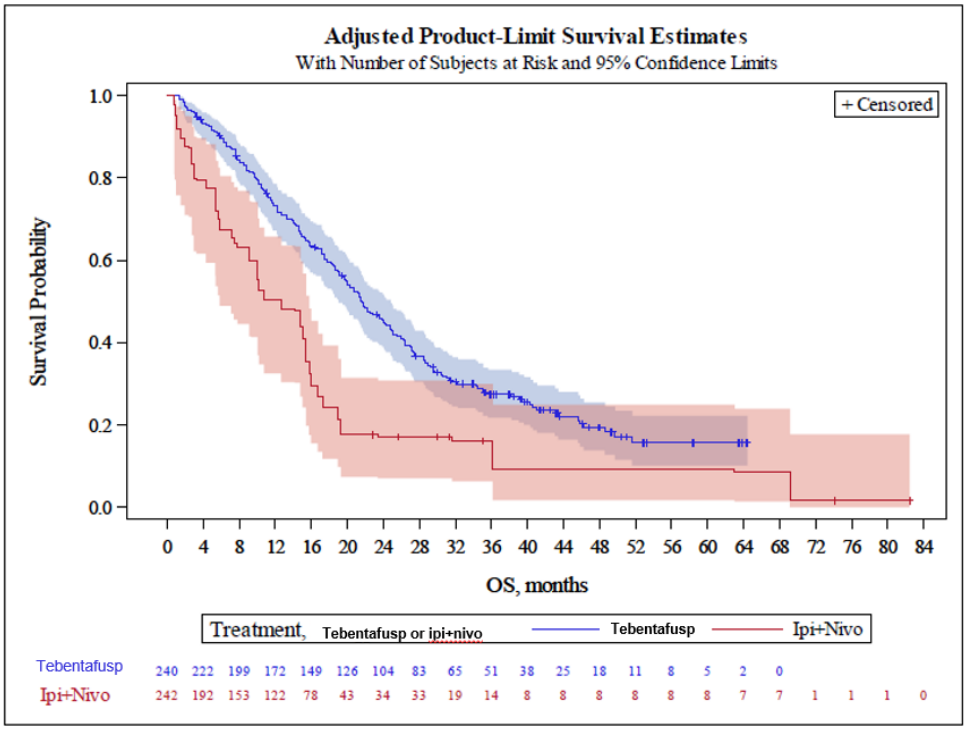



**Figure 14. Kaplan-Meier plot of IPT weighted survival (complete case, ATT weights) [including 95% confidence limits].**

### C.7.3 Sensitivity analyses

The sensitivity analyses for tebentafusp vs ipi/nivo showed consistent superior OS with all IPTW HRs of ≤ 0.61. The results are presented in Figure 15.

| Model | Tebe *N* | Nivo + Ipi *N* | HR (95% CI) |
|---|---|---|---|
| **PS-based IPTW analyses** | | | |
| Complete case, IPT ATT weights (primary) | 240 | 242 | 0.52 (0.35-0.78) |
| Multiple imputation, IPT ATT weights | 252 | 255 | 0.55 (0.38-0.79) |
| Complete case, IPT ATT stabilized weights | 202 | 38 | 0.50 (0.32-0.76) |
| Complete case, IPT ATE weights | 284 | 287 | 0.54 (0.37-0.79) |
| Complete case, IPT ATC weights | 44 | 45 | 0.61 (0.41-0.92) |
| **Other models** | | | |
| Complete case, multivariate Cox analysis | 240 | 45 | 0.41 (0.28-0.62) |
| **Unadjusted analyses** | | | |
| Unadjusted complete case | 240 | 45 | 0.63 (0.44-0.90) |
| Unadjusted multiple imputation | 252 | 52 | 0.66 (0.47-0.93) |


**Figure 15. Forest plot of adjusted HRs for primary and sensitivity analysis** [9].

The base case results are presented in Table 73.

**Table 73. Comparative analysis of studies comparing tebentafusp to ipi/nivo for patients with metUM in the 1st line setting.**

| Outcome | | Absolute difference in effect | | | Relative difference in effect | | | Method used for quantitative synthesis | Result used in the health economic analysis? |
|---|---|---|---|---|---|---|---|---|---|
| | Studies included in the analysis | Difference | CI | P value | Difference | CI | P value | | |
| Median OS (ATT) | IMCgp100-202 (DCO July 2023) and GEM-1402 (DCO August 2023) | 9.1 months | N/A | N/A | HR: 0.52 | 0.35–0.78 | N/A | Assessed through weighted KM curves, including medians and 95% Cis, as well as 1-year estimates. Additionally, an IPT-weighted HR and 95% CI were derived from a weighted Cox regression model, utilizing robust sandwich estimation for variance calculation. | Yes |
| 1-year OS rate | IMCgp100-202 (DCO July 2023) and GEM-1402 (DCO August 2023) | 13% | N/A | N/A | N/A | N/A | N/A | Assessed through weighted KM curves, including medians and 95% Cis, as well as 1-year estimates. Additionally, an IPT-weighted HR and 95% CI were derived from a weighted Cox regression model, utilizing robust sandwich estimation for variance calculation. | Yes |

# Appendix D. Extrapolation

## D.1 Extrapolation of overall survival

### D.1.1 Data input

Extrapolation of OS was required as not all events were observed over the trial periods. The clinical data informing the model is based on IMCgp100-202 for tebentafusp and GEM-1402 for ipi/nivo. The clinical inputs for OS for tebentafusp and ipi/nivo are based on the latest data for both studies, July 2023 for IMCgp100-202 and <month> 2023 for GEM-1402.

### D.1.2 Model

Full parametrization.

### D.1.3 Proportional hazards

The PH assumption was assessed visually through cumulative hazard plots, log-log plots, and Schoenfeld residual plots.

The cumulative hazard plot, log(-log(S)) versus log(time) plot, and Schoenfeld residual plot for the base-case ATT analysis are presented in Figure 16. The results of the statistical test produced a p-value <0.001. Based on the p-value, the PH assumption may be rejected. However, the cumulative hazard plot and the Schoenfeld residual plot do not show a violation of the PH assumption. The log-log survival plot shows potential convergence of the control and the tebentafusp groups which does not strongly support the assumption of PH; however, this may be due to low numbers at risk at this time point. Overall, the results indicate that the PH assumption holds.

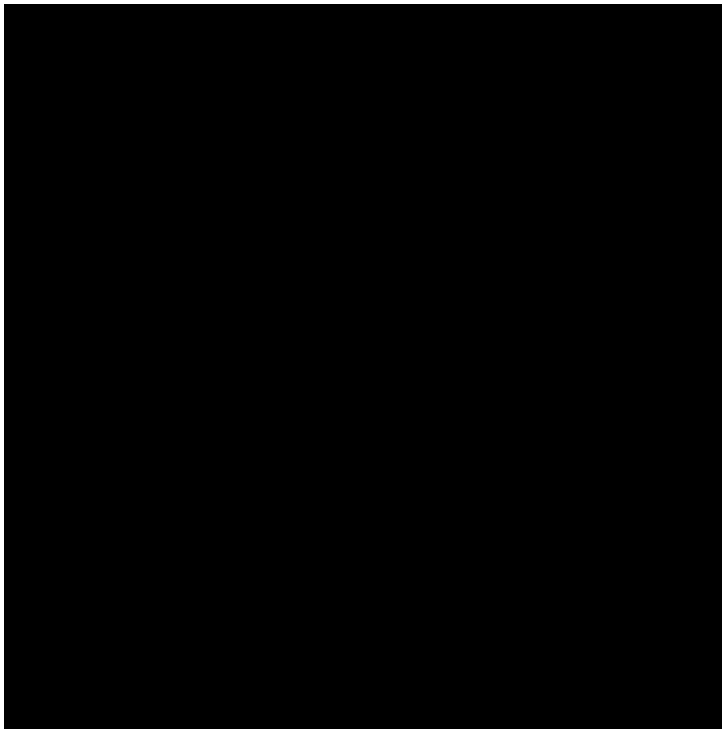


**Figure 16. Visual assessment of the proportional hazard assumption for overall survival. Cumulative hazard plot (upper left), Complimentary log-log plot (upper right), Schoenfeld residuals plot (lower left).**

Given the availability of the IPD, the data were fitted separately to each treatment group, negating the need to assume PH. This also allows for additional flexibility in the model.

### D.1.4 Evaluation of statistical fit (AIC and BIC)

Based on AIC and BIC for ATT-weights presented in Table 69, the model with the best fit in the tebentafusp group is the log-logistic. In the ipi/nivo group, the model with the best fit is generalized gamma, which based on the clinical expert consulted in initial assessment of tebentafusp and DMC assessment report was assessed to be clinically plausible and thus chosen in the base case.

**Table 74. Goodness-of-fit Akaike and Bayesian information criteria: overall survival standard parametric models.**

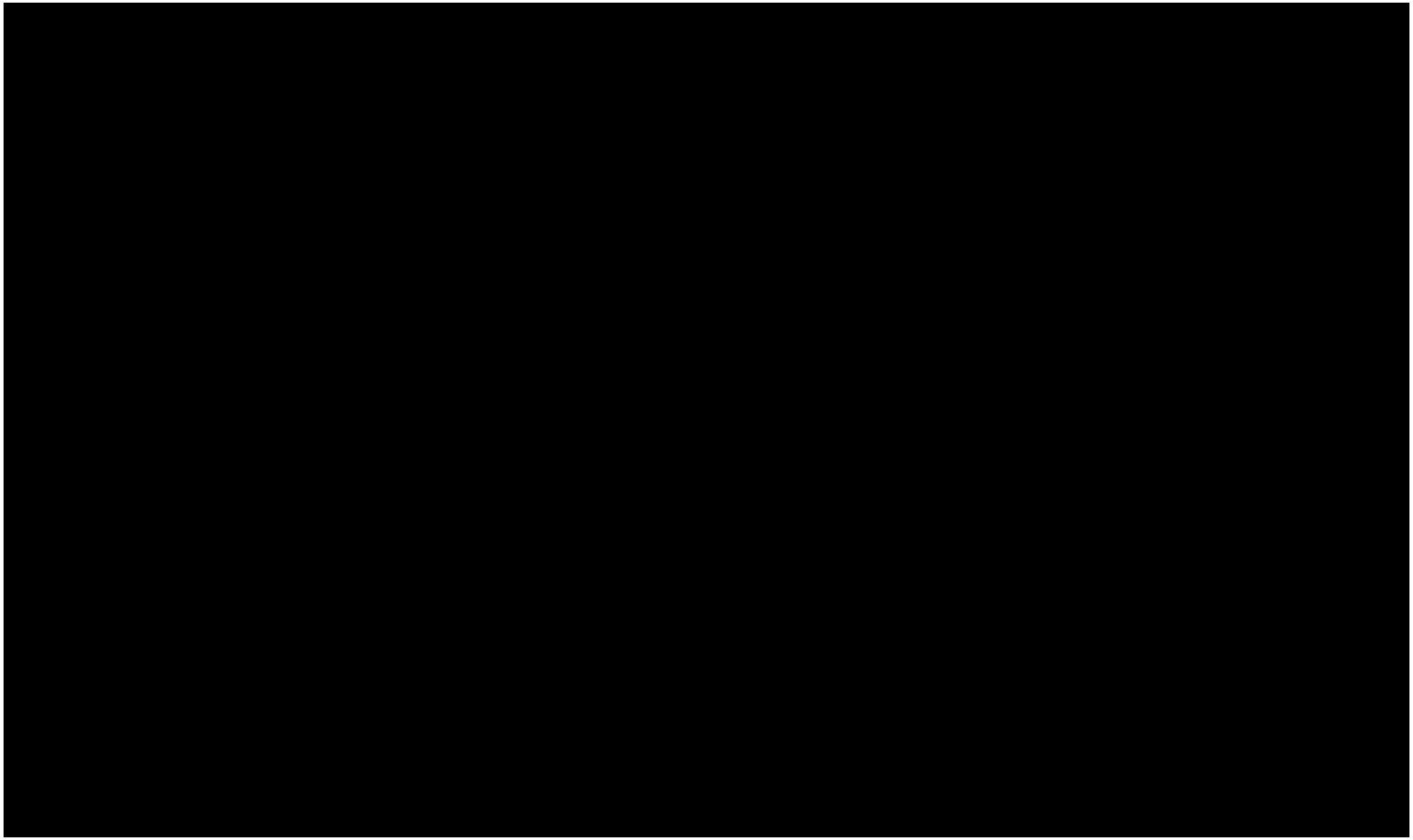
| | Tebentafusp | | | Ipi/nivo | | |
|---|---|---|---|---|---|---|
| **Model** | **AIC** | **BIC** | **Ranking** | **AIC** | **BIC** | **Ranking** |
| **Exponential** | 1615.6 | 1619.1 | 6 | 1631.8 | 1633.7 | 4 |
| **Weibull** | 1604.0 | 1610.9 | 5 | 1633.8 | 1637.4 | 6 |
| **Log-normal** | 1598.8 | 1605.8 | 2 | 1628.5 | 1632.1 | 2 |
| **Log-logistic** | 1595.5 | 1602.5 | 1 | 1628.5 | 1632.1 | 3 |
| **Gompertz** | 1614.4 | 1621.4 | 6 | 1631.2 | 1634.8 | 4 |
| **Generalized gamma** | 1598.5 | 1609.0 | 3 | 1626.6 | 1632.0 | 1 |
| **Gamma** | 1600.6 | 1607.5 | 4 | 1633.3 | 1636.9 | 5 |

### D.1.5 Evaluation of visual fit

Plot of the extrapolation models overlayed with the KM curves are presented in Figure 17.

### D.1.6 Evaluation of 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. The plots of the hazard functions for OS (ATT) are presented in Figure 18



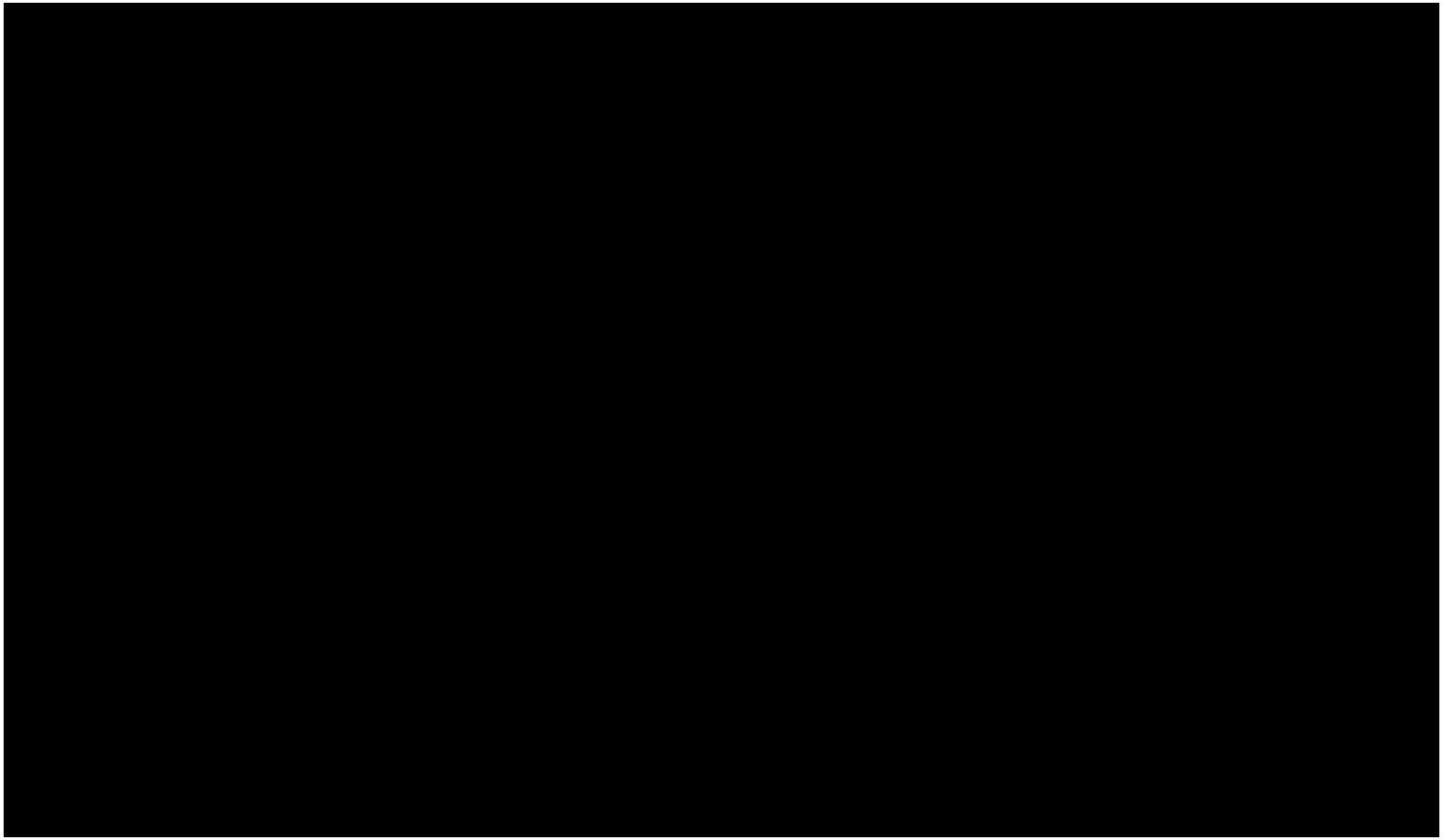
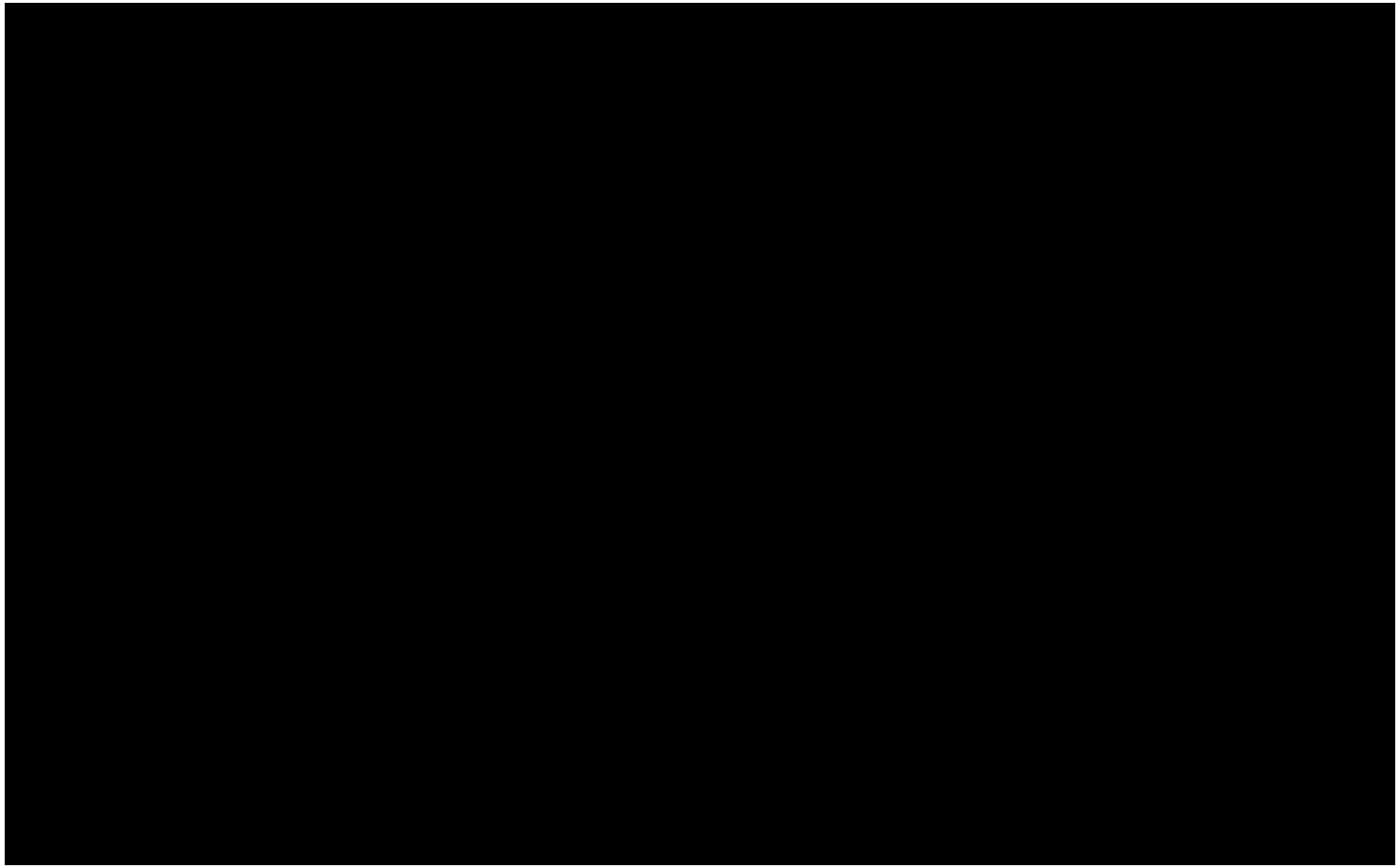


**Figure 17. Overall survival standard parametric model**



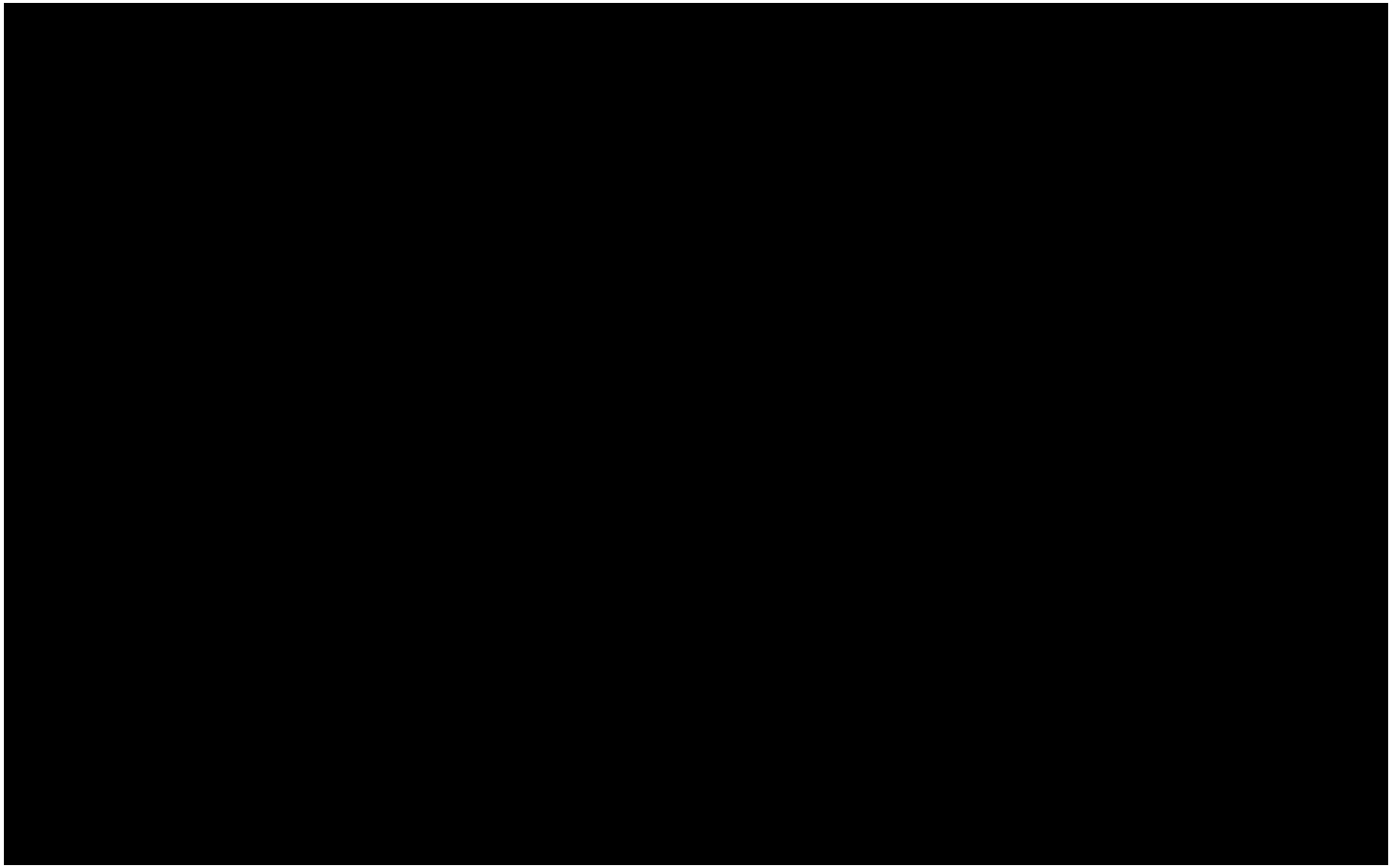


**Figure 18. Hazard function of OS (ATT) parametric models**

### D.1.7 Validation and discussion of extrapolated curves

**Tebentafusp**

Based on AIC and BIC for ATT-weights, the model with the best fit (i.e. ranked highest, Table 74) in the tebentafusp group was the log-logistic distribution. According to the published 3-year analysis of OS for tebentafusp, which provided a more robust prediction of long-term survival indicating a 5-year OS of >15%, the application of the log-logistic distribution to the tebentafusp group resulted in a clinically plausible 5-year OS of [redacted].

**Ipi/nivo**

Rantala and colleagues conducted a systematic review and meta-analysis of 78 studies (n=2494) in metUM. They pooled data for 510 1st line patients. Rantala and colleagues found no clinically significant difference in OS by treatment modality, and that no therapy has demonstrated a significant improvement in OS in the last 40 years [8,18,55]. 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. 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. This was furthermore supported by the DMC, as the parametric distribution chosen by the DMC in the assessment report of tebentafusp resulted in a 5-year OS for ipi/nivo of 4.32%. Given this information, the parametric distribution with the best fit (i.e. ranked highest, Table 72) for ipi/nivo (Generalized Gamma) was chosen in the base case model, providing a 5-year OS of 4.36%.

### D.1.8 Adjustment of background mortality

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.

### D.1.9 Adjustment for treatment switching/cross-over

None.

### D.1.10 Waning effect (N/A)

### D.1.11 Cure-point (N/A)

## D.2 Extrapolation of progression-free survival

### D.2.1 Data input

Extrapolation of PFS was required as not all events were observed over the trial periods. The clinical data informing the model is based on MAIC using IMCgp100-202 for tebentafusp and GEM-1402 for ipi/nivo. The clinical inputs for PFS for tebentafusp are based on the MAIC (described in the initial submission for tebentafusp [40]) using DCO October 2020 from IMCgp100-202 and DCO July 2019 from GEM-1402. For this reason,

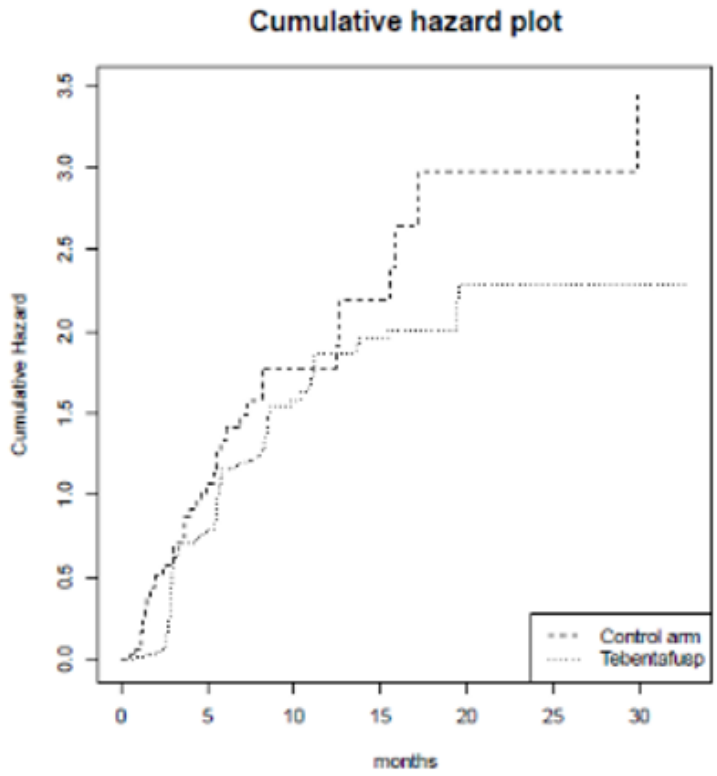
the extrapolation of PFS described in the current section does not differ from the initial submission.

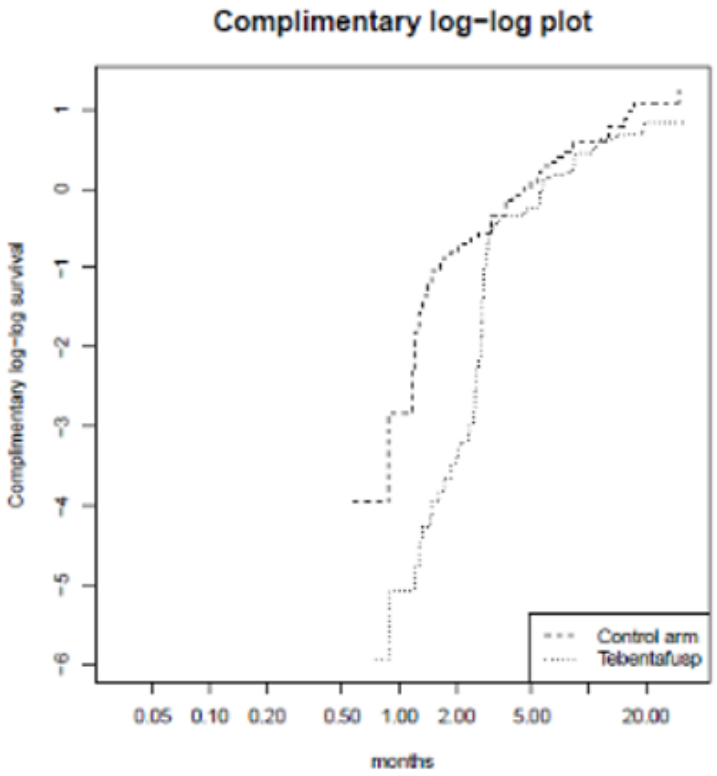
### D.2.2 Model

Full parametrization.

### D.2.3 Proportional hazards

The PH assumption was assessed visually through log-log plots and Schoenfeld residual plots, graphs of which are presented in Figure 19. The results of the statistical test give a p-value of 0.022. Although based on the plots presented in Figure 19, the PH assumption does not seem violated, given the p-value, which demonstrates statistical significance, we fitted the data separately to each treatment group, as the IPD is available, negating the need to assume PH. This also gives additional flexibility in the model.


Cumulative hazard plot
Cumulative Hazard
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
0
5
10
15
20
25
30
months
Control arm
Tebentafusp


Complimentary log−log plot
Complimentary log−log survival
1
0
−1
−2
−3
−4
−5
−6
0.05
0.10
0.20
0.50
1.00
2.00
5.00
20.00
months
Control arm
Tebentafusp

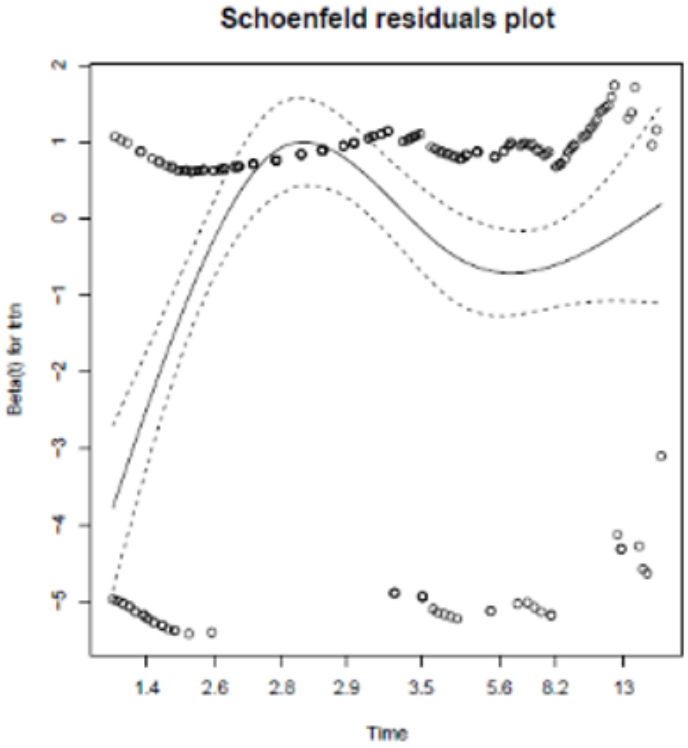



**Figure 19. Visual assessment of the proportional hazard assumption for progression-free survival. (upper left) Cumulative hazard plot; (upper right) log-log plot; (lower left) Schoenfeld residuals plot.**

### D.2.4 Evaluation of statistical fit (AIC and BIC)

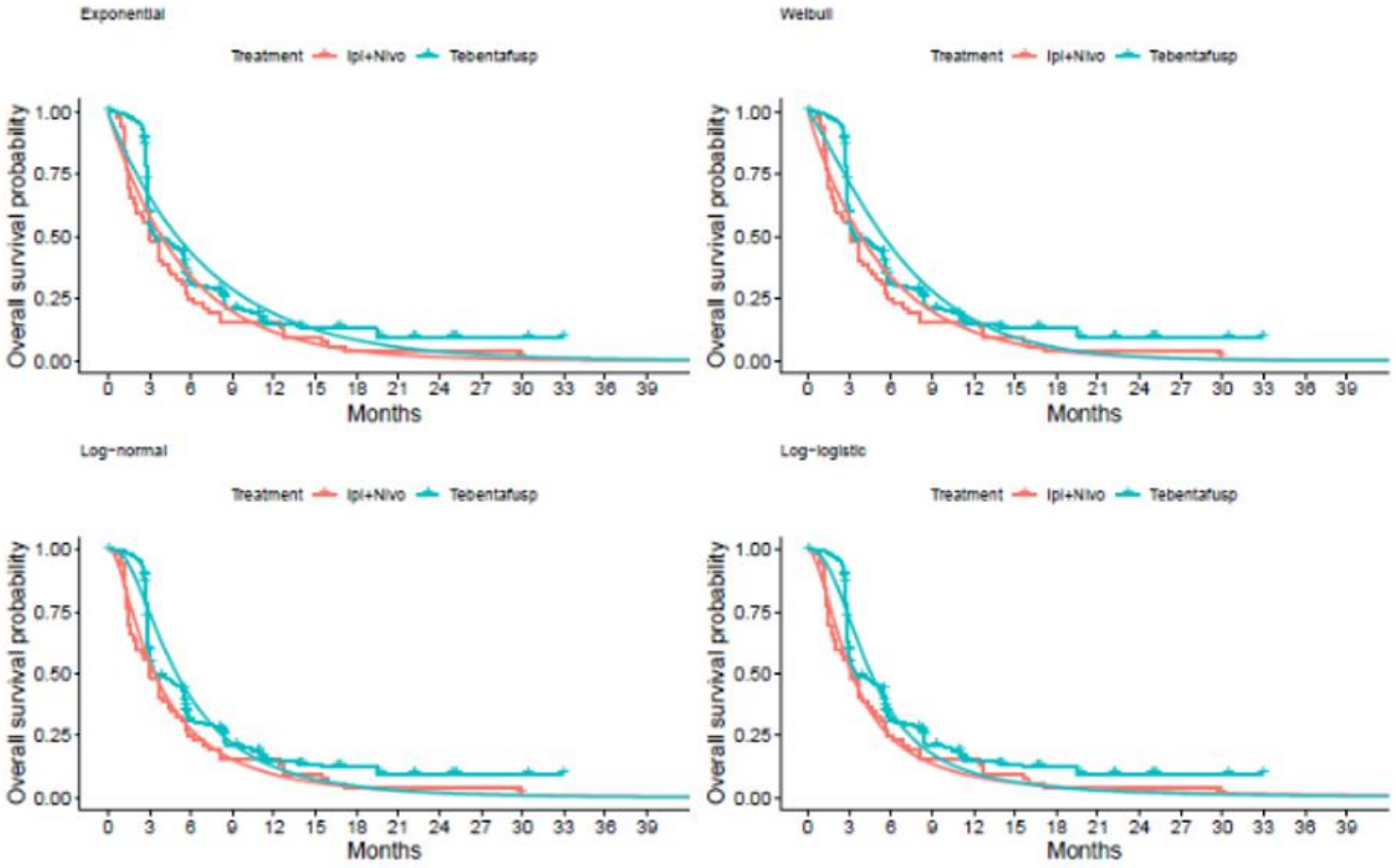
Standard parametric models (exponential, Weibull, log normal, log logistic, Gompertz, generalized gamma, and gamma) were fitted, following NICE DSU TSD 14 guidance [50]. Based on AIC and BIC presented in Table 75, the model with the best fit in the tebentafusp group was the generalized gamma. In the ipi/nivo group, 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 75. 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 |

### D.2.5 Evaluation of visual fit

Plot of the extrapolation models overlayed with the KM curves are presented I Figure 20. Survival probabilities at various time-points for tebentafusp and ipi/nivo are also presented in Table 76 and Table 77, respectively.


Exponential
Weibull
Log-normal
Log-logistic
Treatment Ipi+Nivo Tebentafusp
Overall survival probability
1.00
0.75
0.50
0.25
0.00
0 3 6 9 12 15 18 21 24 27 30 33 36 39
Months

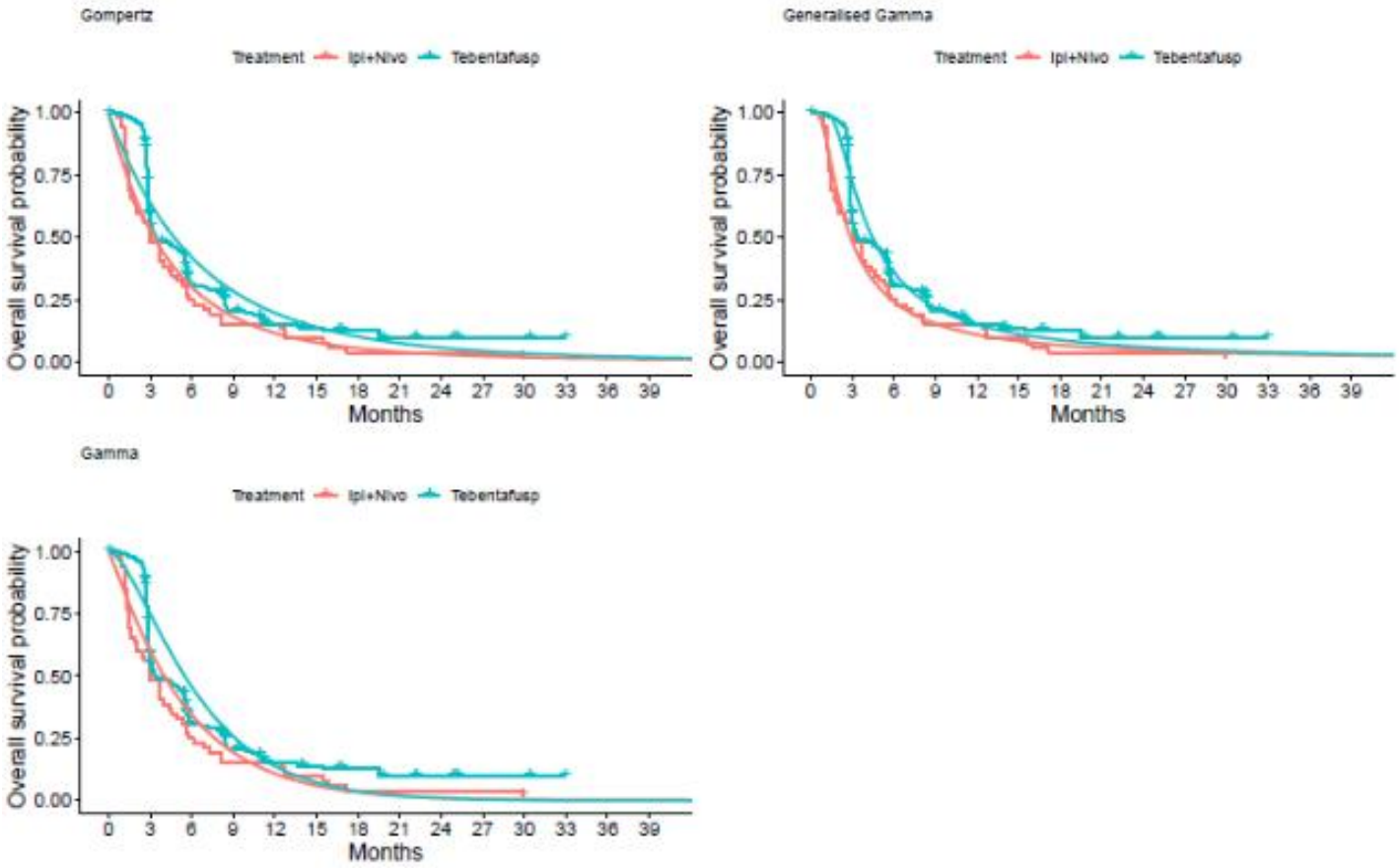



**Figure 20. Progression-free survival standard parametric models.**

Table 76. 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% |

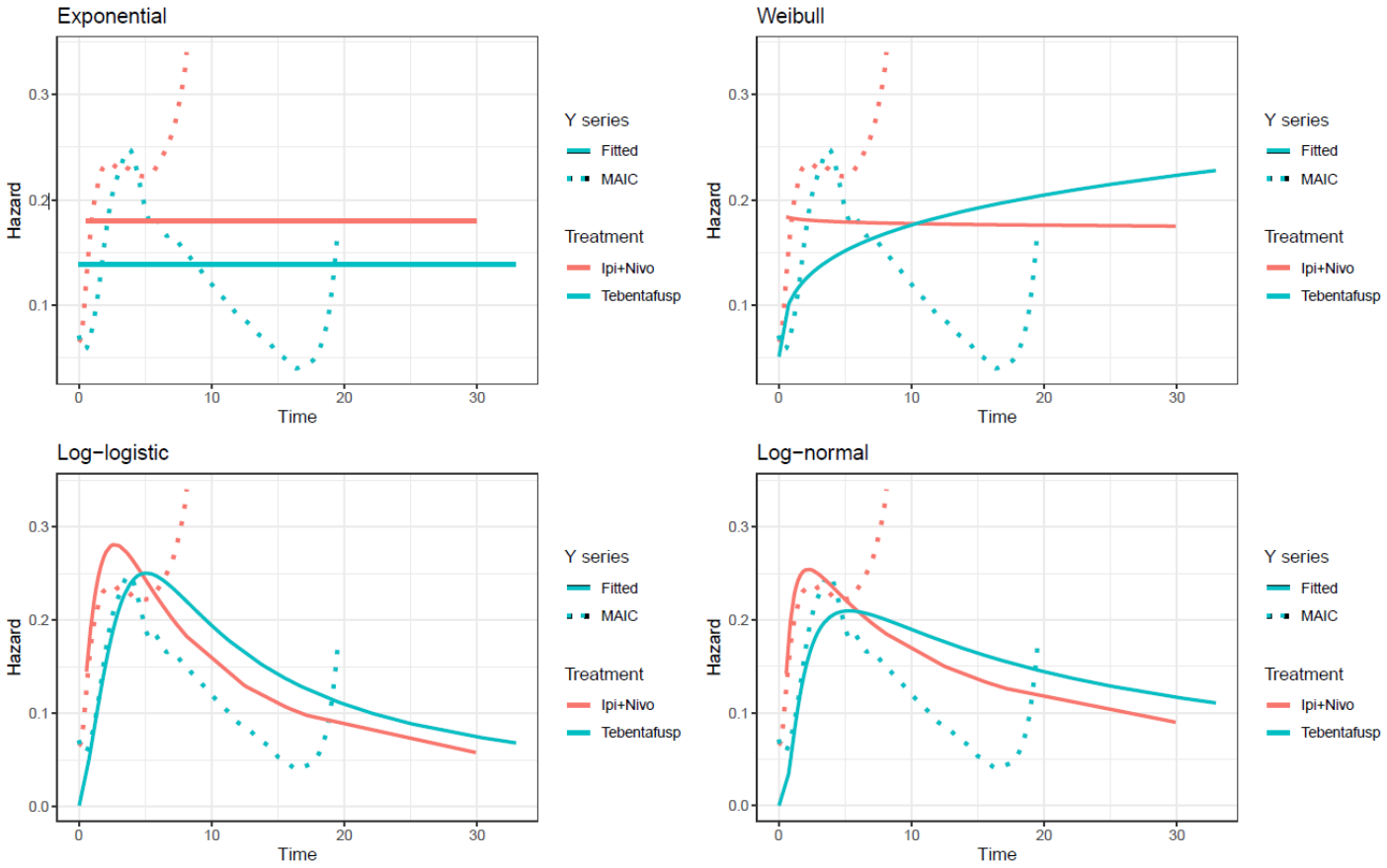
Table 77. Progression-free survival parametric models versus Kaplan-Meier curve: ipi/nivo.

| Months | Kaplan-Meier | Exponential | Weibull | Log normal | Log logistic | Gompertz | Generalized gamma | Gamma |
|---|---|---|---|---|---|---|---|---|
| Ranking based on AIC and BIC | | 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% |

### D.2.6 Evaluation of 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. The hazard functions for the PFS parametric models are presented in Figure 21.


Exponential
Weibull
Log−logistic
Log−normal
Hazard
Time
0
10
20
30
0.0
0.1
0.2
0.3
Y series
Fitted
MAIC
Treatment
Ipi+Nivo
Tebentafusp

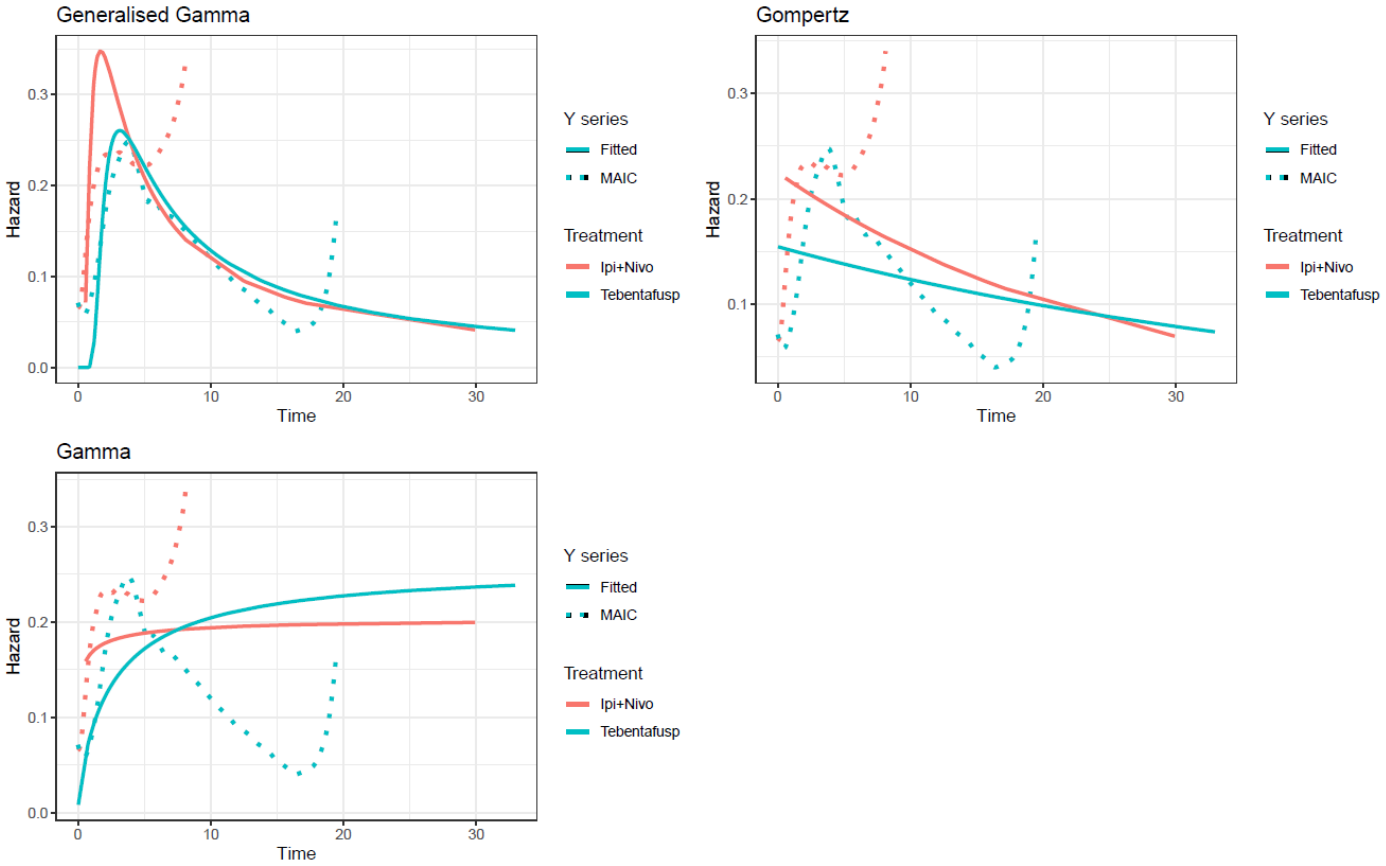



**Figure 21. Hazard function of PFS parametric models.**

### D.2.7 Validation and discussion of extrapolated curves

The validation and discussion of the extrapolated curves can be found in section D.2.4, D.2.5 and D.2.6.

### D.2.8 Adjustment of background mortality

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.

### D.2.9 Adjustment for treatment switching/cross-over

None.

### D.2.10 Waning effect (N/A)

### D.2.11 Cure-point (N/A)

# Appendix E. Serious adverse events

The SAEs reported in study IMCgp100-202 are listed in Table 78 and the TR-SAEs reported in study GEM-1402 are listed in Table 79.

## E.1 IMCgp100-202 safety data

**Table 78. Summary of serious adverse events reported in IMCgp100-202.**

| | DCO October 2020 [48] | | DCO July 2023 [49] | |
|---|---|---|---|---|
| | Tebentafusp | Investigator's Choice | Tebentafusp | Investigator's Choice |
| System organ class/preferred term, n (%) | Any grade (≥10%) | Any grade (≥10%) | Any grade (≥10%) | Any grade (≥10%) |
| Patients with any serious TEAE | 69 (28) | 26 (23) | 79 (32) | 24 (22) |
| Infections and infestations | 4 (2) | 2 (2) | 6 (2) | 2 (2) |
| Anorectal infection | 0 | 1 (1) | 0 | 1 (1) |
| Appendicitis | 1 (0.4) | 0 | 1 (0.4) | 0 |
| COVID-19 | 1 (0.4) | 0 | 1 (0.4) | 0 |
| COVID-19 pneumonia | N/A | N/A | 1 (0.4) | 0 |
| Diverticulitis | N/A | N/A | 1 (0.4) | 0 |
| Erysipelas | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Pneumonia | 0 | 1 (1) | 0 | 1 (1) |
| Pneumonia mycoplasmal | 0 | 1 (1) | 0 | 1 (1) |
| Salmonella sepsis | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Neoplasms benign, malignant, and unspecified (incl. cysts and polyps) | 3 (1) | 2 (2) | 4 (2) | 1 (1) |
| Meningioma | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Metastases to abdominal cavity | 0 | 1 (1) | 0 | 1 (1) |
| Neoplasm progression | 0 | 1 (1) | 1 (0.4) | 0 |
| Tumor pain | 2 (1) | 0 | 2 (1) | 0 |
| Blood and lymphatic system disorders | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Anemia | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Immune system disorders | 25 (10) | 0 | 25 (10) | 0 |
| Anaphylactic reaction | 1 (0.4) | 0 | 1 (0.4) | 0 |
| CRS | 24 (10) | 0 | 24 (10) | 0 |
| Endocrine disorders | 0 | 1 (1) | 0 | 1 (1) |
| Hypopituitarism | 0 | 1 (1) | 0 | 1 (1) |

| | DCO October 2020 [48] | | DCO July 2023 [49] | |
|---|---|---|---|---|
| | Tebentafusp | Investigator's Choice | Tebentafusp | Investigator's Choice |
| System organ class/preferred term, n (%) | Any grade (≥10%) | Any grade (≥10%) | Any grade (≥10%) | Any grade (≥10%) |
| Metabolism and nutrition disorders | 1 (0.4) | 3 (3) | 2 (1) | 3 (3) |
| Dehydration | 0 | 2 (2) | 0 | 2 (2) |
| Failure to thrive | N/A | N/A | 1 (0.4) | 0 |
| Hyperglycemia | 0 | 1 (1) | 0 | 1 (1) |
| Tumor lysis syndrome | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Psychiatric disorders | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Mental status changes | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Nervous system disorders | 5 (2) | 2 (2) | 6 (2) | 2 (2) |
| Brain oedema | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Dizziness | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Intracranial mass | 0 | 1 (1) | 0 | 1 (1) |
| Lethargy | 0 | 1 (1) | N/A | N/A |
| Motor dysfunction | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Presyncope | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Seizure | 0 | 1 (1) | 0 | 1 (1) |
| Spinal cord compression | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Transient ischemic attack | N/A | N/A | 1 (0.4) | 0 |
| Eye disorders | 2 (1) | 1 (1) | 3 (1) | 1 (1) |
| Diplopia | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Periorbital oedema | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Uveitis | 0 | 1 (1) | 0 | 1 (1) |
| Vitreous hemorrhage | N/A | N/A | 1 (0.4) | 0 |
| Cardiac disorders | 0 | 1 (1) | 4 (2) | 1 (1) |
| Acute myocardial infarction | N/A | N/A | 1 (0.4) | 0 |
| Angina pectoris | N/A | N/A | 1 (0.4) | 0 |
| Cardiac failure congestive | N/A | N/A | 1 (0.4) | 0 |
| Left ventricular dysfunction | 0 | 1 (1) | 0 | 1 (1) |
| Myocardial infarction | N/A | N/A | 1 (0.4) | 0 |
| Vascular disorders | 5 (2) | 0 | 6 (2) | 0 |
| Hypotension | 5 (2) | 0 | 6 (2) | 0 |
| Respiratory, thoracic, and mediastinal disorders | 4 (2) | 6 (5) | 5 (2) | 6 (5) |
| Cough | 0 | 1 (1) | 0 | 1 (1) |
| Dyspnea | 2 (1) | 0 | 1 (0.4) | 0 |
| Pleurisy | 0 | 1 (1) | 0 | 1 (1) |
| Pneumonitis | 0 | 1 (1) | 1 (0.4) | 1 (1) |

| | DCO October 2020 [48] | | DCO July 2023 [49] | |
|---|---|---|---|---|
| | Tebentafusp | Investigator's Choice | Tebentafusp | Investigator's Choice |
| System organ class/preferred term, n (%) | Any grade (≥10%) | Any grade (≥10%) | Any grade (≥10%) | Any grade (≥10%) |
| Pulmonary embolism | 1 (0.4) | 3 (3) | 2 (1) | 3 (3) |
| Pulmonary oedema | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Sleep apnea syndrome | 0 | 1 (1) | 0 | 1 (1) |
| Gastrointestinal disorders | 7 (3) | 7 (6) | 8 (3) | 7 (6) |
| Abdominal pain | 2 (1) | 3 (3) | 3 (1) | 3 (3) |
| Abdominal pain upper | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Colitis | 0 | 1 (1) | 0 | 1 (1) |
| Diarrhea | 0 | 1 (1) | 0 | 1 (1) |
| Enteritis | 0 | 1 (1) | 0 | 1 (1) |
| Gastritis | 0 | 1 (1) | 0 | 1 (1) |
| Nausea | 4 (2) | 1 (1) | 5 (2) | 1 (1) |
| Vomiting | 2 (1) | 0 | 2 (1) | 0 |
| Hepatobiliary disorders | 8 (3) | 3 (3) | 7 (3) | 3 (3) |
| Biliary obstruction | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Hepatic failure | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Hepatic necrosis | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Hepatic pain | 1 (0.4) | 0 | 1 (0.4) | 1 (1) |
| Hepatomegaly | 0 | 1 (1) | 0 | 1 (1) |
| Hepatotoxicity | 2 (1) | 0 | 2 (1) | 0 |
| Hyperbilirubinemia | 2 (1) | 3 (3) | 1 (0.4) | 3 (3) |
| Hypertransaminasemia | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Skin and subcutaneous tissue disorders | 14 (6) | 0 | 15 (6) | 0 |
| Dermatitis | N/A | N/A | 1 (0.4) | 0 |
| Pruritus | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Rash | 6 (2) | 0 | 5 (2) | 0 |
| Rash maculo-papular | 4 (2) | 0 | 4 (2) | 0 |
| Rash papular | 1 (0.4) | 0 | 2 (1) | 0 |
| Skin reaction | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Urticaria | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Musculoskeletal and connective tissue disorders | 0 | 2 (2) | 0 | 2 (2) |
| Bone pain | 0 | 1 (1) | 0 | 1 (1) |
| Pathological fracture | 0 | 1 (1) | 0 | 1 (1) |
| Renal and urinary disorders | 2 (1) | 0 | 2 (1) | 0 |
| Acute kidney injury | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Renal failure | 1 (0.4) | 0 | 1 (0.4) | 0 |

| | DCO October 2020 [48] | | DCO July 2023 [49] | |
|---|---|---|---|---|
| | Tebentafusp | Investigator's Choice | Tebentafusp | Investigator's Choice |
| System organ class/preferred term, n (%) | Any grade (≥10%) | Any grade (≥10%) | Any grade (≥10%) | Any grade (≥10%) |
| Reproductive system and breast disorders | 1 (0.4) | 0 | N/A | N/A |
| Scrotal inflammation | 1 (0.4) | 0 | N/A | N/A |
| General disorders and administration site conditions | 7 (3) | 3 (3) | 8 (3) | 2 (2) |
| Asthenia | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Chills | N/A | N/A | 1 (0.4) | 0 |
| Fatigue | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Gait disturbance | 0 | 1 (1) | N/A | N/A |
| General physical health deterioration | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Pain | N/A | N/A | 1 (0.4) | 0 |
| Pyrexia | 6 (2) | 2 (2) | 7 (3) | 2 (2) |
| Investigations | 3 (1) | 1 (1) | 2 (1) | 1 (1) |
| ALT increased | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Amylase increased | 1 (0.4) | 0 | 1 (0.4) | 0 |
| AST increased | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Blood creatinine increased | 2 (1) | 0 | N/A | N/A |
| Lipase increased | 0 | 1 (1) | 0 | 1 (1) |
| Injury, poisoning and procedural complications | 1 (0.4) | 2 (2) | 3 (1) | 1 (1) |
| Fall | 0 | 1 (1) | 0 | 1 (1) |
| Multiple fractures | N/A | N/A | 1 (0.4) | 0 |
| Patella fractures | N/A | N/A | 1 (0.4) | 0 |
| Procedural pain | 1 (0.4) | 1 (1) | 1 (0.4) | 0 |

## E.2 GEM-1402 safety data

**Table 79. Summary of treatment-related serious adverse events reported in GEM-1402.**

| | GEM-1402 [11] Ipi/nivo | |
|---|---|---|
| Event term, n (%)[a] | All treatment-related serious adverse events | Grade ≥3 treatment-related serious adverse events |
| Total TR-SAEs | 30 (58) | 21 (40) |
| Skin-related events[b] | 1 (2) | 1 (2) |
| Fatigue | 1 (2) | 1 (2) |

| | GEM-1402 [11] Ipi/nivo | |
|---|---|---|
| Event term, n (%)[a] | **All treatment-related serious adverse events** | **Grade ≥3 treatment-related serious adverse events** |
| Liver toxicity/liver-related events[c] | 3 (6) | 3 (6) |
| Diarrhea | 3 (6) | 3 (6) |
| Fever | 4 (8) | 1 (2) |
| Nausea | - | - |
| Hypothyroidism | 1 (2) | - |
| Edema | - | - |
| Hypophysitis | 1 (2) | - |
| Hepatitis | 2 (4) | 2 (4) |
| Vomiting | - | - |
| Thyroiditis | 2 (4) | 2 (4) |
| Constipation | - | - |
| Arthralgia | - | - |
| Pericarditis | 1 (2) | - |
| Jaundice | 1 (2) | 1 (2) |
| Intestinal perforation | 1 (2) | 1 (2) |
| Hyponatremia | 1 (2) | 1 (2) |
| Hyperthyroidism | 1 (2) | 1 (2) |
| Guillain-Barré syndrome | 2 (4) | 2 (4) |
| Drug administration incidences[d] | 3 (6) | - |
| Colitis | 1 (2) | 1 (2) |

[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 administrations or treatment reported with incidences (quarantine) and 1 ipilimumab overdose.

# Appendix F. Health-related quality of life

## F.1 Data collection for EORTC-QLQ-C30

EORTC QLQ-C30 questionnaires were completed at baseline (i.e. prior to randomization), at 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 assessments at 12-week intervals. An overview of the collection of PRO data throughout the IMCgp100-202 trial is presented in Appendix F.

**Table 80. PRO data collection schedule IMCgp100-202 clinical trial** [54].

| | **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 | | | | |
| **PROs** | | 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 |

## F.2 HRQoL results – EQ-5D

**Table 81. EQ-5D summary statistics at baseline** [54].

| | 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

**Table 82. Mean EQ-5D utility over the treatment period**[39]

| | N | Mean | Standard error | 95% CI lower bound | 95% CI upper bound |
|---|---|---|---|---|---|
| **ITT set** | 1065 | 0.834 | 0.005 | 0.824 | 0.844 |
| **Tebentafusp** | 803 | 0.835 | 0.006 | 0.823 | 0.846 |
| **Control** | 262 | 0.832 | 0.010 | 0.812 | 0.853 |

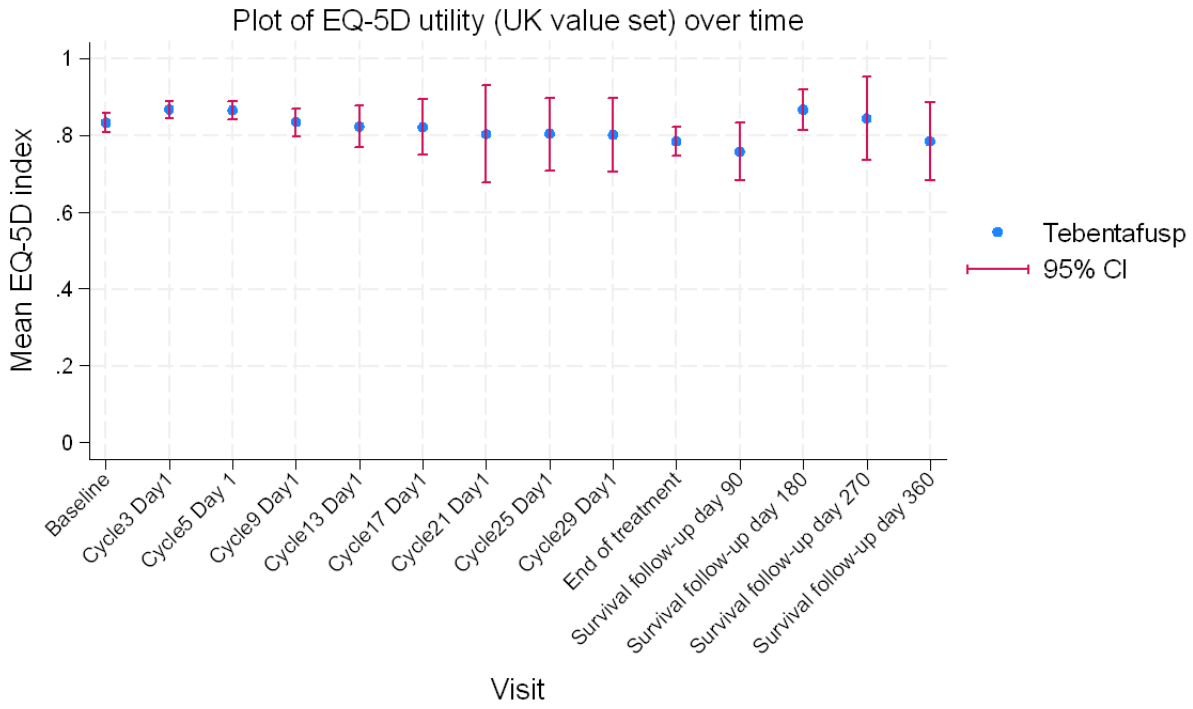



**Figure 22. Plot of EQ-5D mean utility at each assessment time point - tebentafusp group**[39]

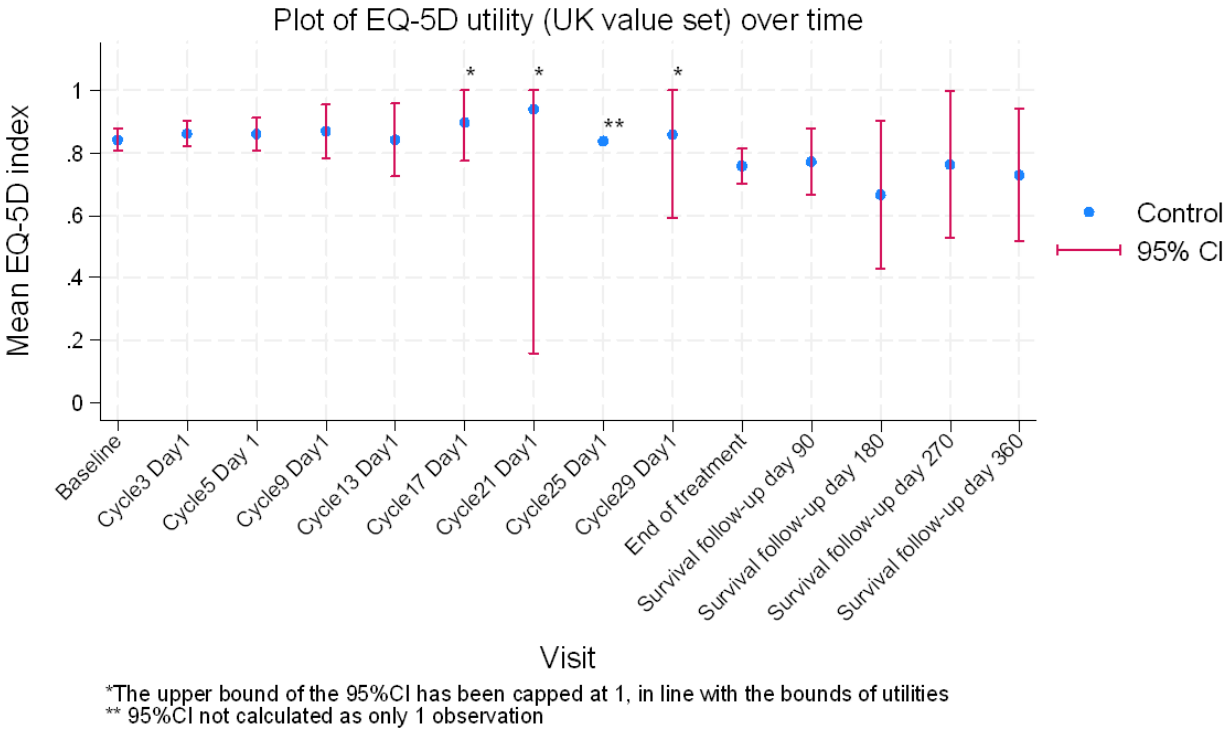



**Figure 23. Plot of EQ-5D mean utility at each assessment time point - control group** [39]

## F.3 HRQoL results – EORTC-QLQ-C30

In both the tebentafusp and IC groups, 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 groups consistent with EQ-5D-5L results. Subsequently, patients in the tebentafusp group remained domain compliant through cycle 29 Day 1, whereas compliance in the IC group decreased to approximately 33% at cycle 29 day 1. At baseline, no differences in EORTC-QLQ-C30 scores were observed between the treatment groups for any of the domains. In general, throughout the study, the EORTC-QLC-C30 scores were similar between the treatment groups and remained stable for most domains, supporting the EQ-5D-results. However, statistically significant and clinically meaningful LS mean improvements from baseline were observed for fatigue at the 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 IC. LS mean scores over time are illustrated in Figure 24, Figure 25 and in Figure 26 for PRO symptoms of fatigue, insomnia, and constipation. Overall, there was no significant difference between the tebentafusp and IC groups for time to sustained deterioration across the different EORTC-QLQ-C30 domains [54].

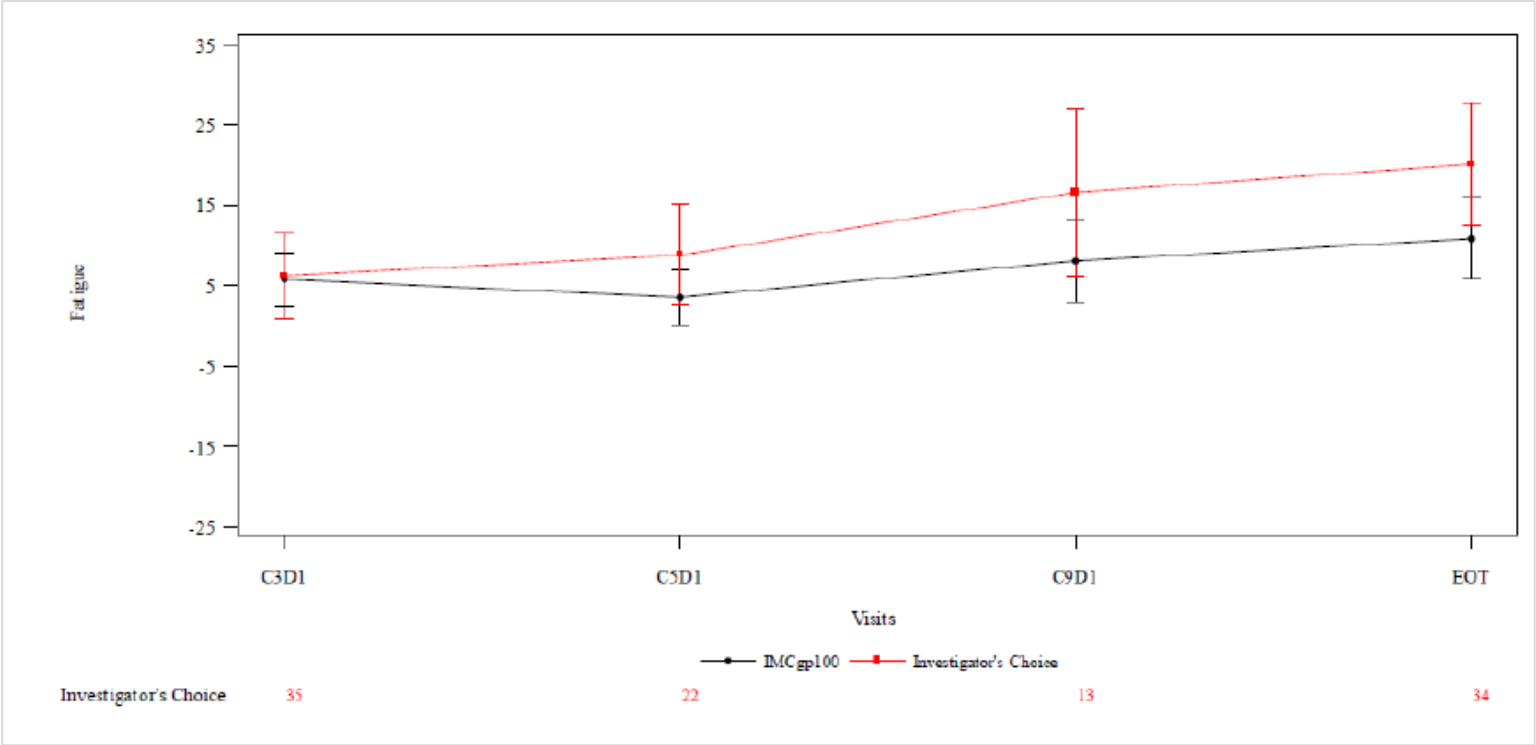



**Figure 24. Least squares mean score over time for patient-reported fatigue.**

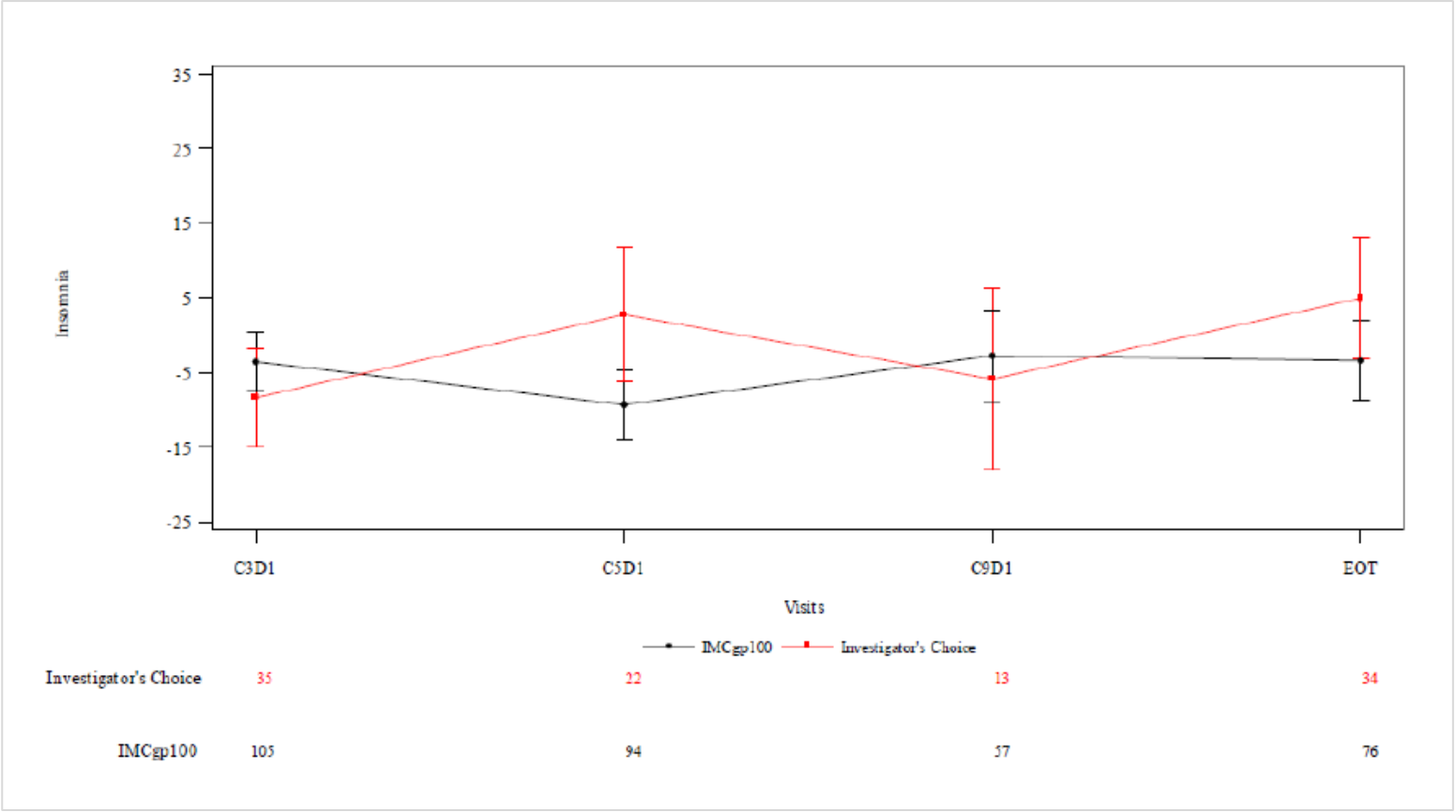



**Figure 25. Least squares mean score over time for patient-reported insomnia.**

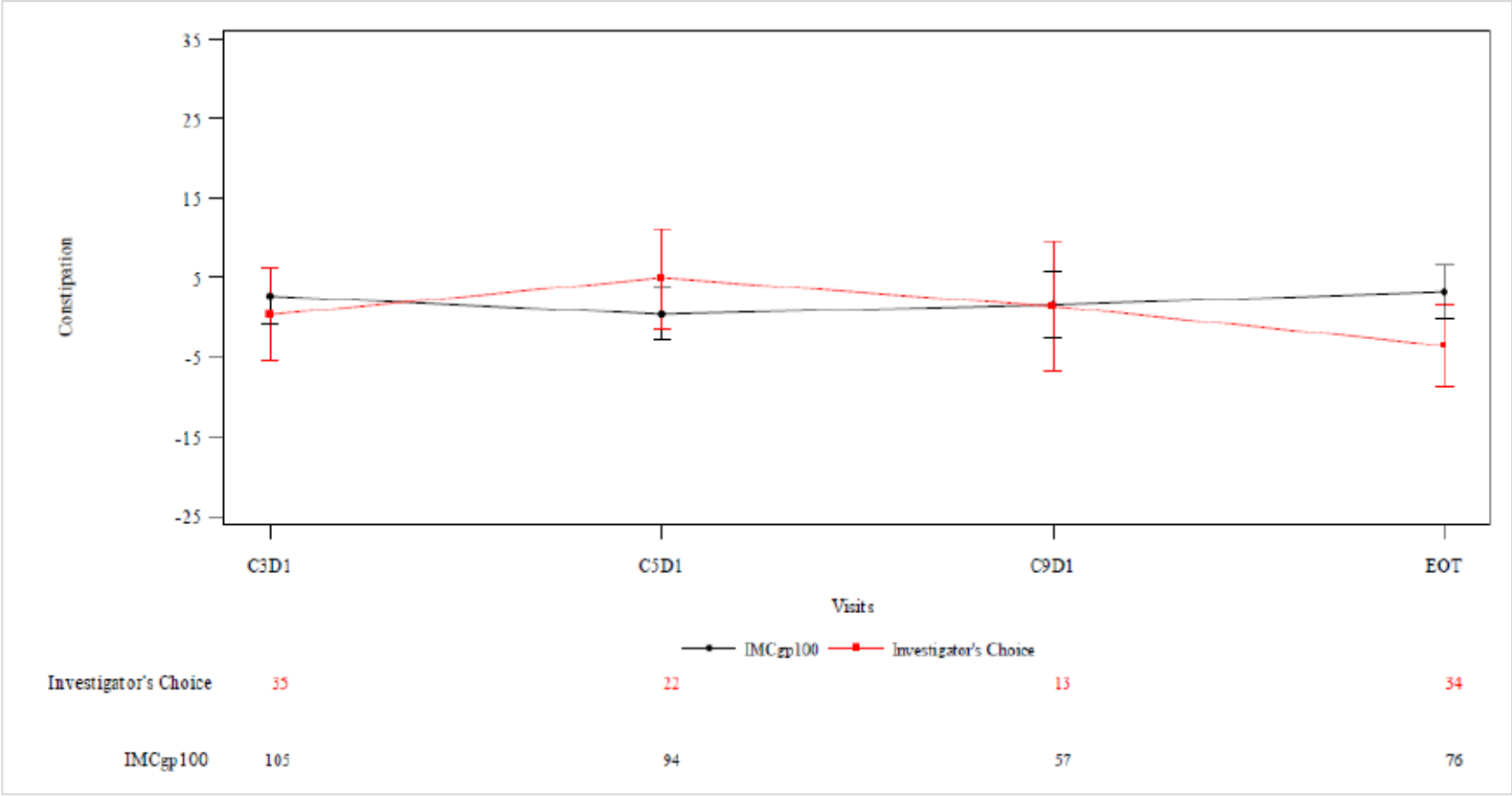



**Figure 26. Least squares mean score over time for patient-reported constipation.**

# Appendix G. Probabilistic sensitivity analyses

**Table 83. Overview of parameters in the PSA.**

| Input parameter | Point estimate | Lower bound | Upper bound | Probability distribution |
|---|---|---|---|---|
| **General parameters** | | | | |
| Time horizon | Lifetime (34 years) | Not varied | | Fixed |
| Discount rate – costs 0-35 years | 3.5% | Not varied | | Fixed |
| Discount rate – health benefits 0-35 years | 3.5% | Not varied | | Fixed |
| Discount rate – costs 35+ years | 2.5% | Not varied | | Fixed |
| Discount rate – health benefits 35+ years | 2.5% | Not varied | | Fixed |
| **Populations parameters** | | | | |
| Age | 66 | -15% | +15% | Fixed |
| % female | 44.8 | -25% | +25% | Fixed |
| Body weight | 78.86 kg | -10% | +10% | Fixed |
| BSA | 1.90 $m^2$ | -10% | +10% | Fixed |
| **Starting points*** | | | | |
| Starting point, % at risk (tebentafusp) | 15% | Not varied | | Fixed |
| Starting point, % at risk (ipi/nivo) | 15% | Not varied | | Fixed |
| Starting point, timepoint (tebentafusp) | 15 | Not varied | | Fixed |
| Starting point, timepoint (ipi/nivo) | 5 | Not varied | | Fixed |
| **Survival models** | | | | |
| OS – Tebentafusp | Log-logistics | Not varied | | Fixed |
| OS – Control group | Generalized Gamma | Not varied | | Fixed |
| PFS – Tebentafusp | Generalized Gamma | Not varied | | Fixed |
| PFS – Control group | Generalized Gamma | Not varied | | Fixed |
| **AE rates - tebentafusp** | | | | |
| Rash | 9.4% | Not varied | | Fixed |
| Rash maculo-papular | 8.6% | Not varied | | Fixed |
| Pruritus | 4.5% | Not varied | | Fixed |
| AST increased | 5.3% | Not varied | | Fixed |
| Lipase increased | 4.1% | Not varied | | Fixed |
| ALT increased | 3.3% | Not varied | | Fixed |
| Hypertension | 8.6% | Not varied | | Fixed |
| Hypotension | 3.3% | Not varied | | Fixed |

| Input parameter | Point estimate | Lower bound | Upper bound | Probability distribution |
|---|---|---|---|---|
| Fatigue | 5.3% | Not varied | | Fixed |
| Pyrexia | 3.7% | Not varied | | Fixed |
| Hypophosphataemia | 4.1% | Not varied | | Fixed |
| Hyperbilirubinaemia | 3.3% | Not varied | | Fixed |
| Liver toxicity/liver-related events | 0% | Not varied | | Fixed |
| Hepatitis | 0% | Not varied | | Fixed |
| Diarrhoea (grade 3+) | 1.2% | Not varied | | Fixed |
| Guillain-Barré syndrome | 0% | Not varied | | Fixed |
| Hypothyroidism | 0% | Not varied | | Fixed |
| Thyroiditis | 0% | Not varied | | Fixed |
| **AE rates – control group** | | | | |
| Rash | 9.6% | Not varied | | Fixed |
| Rash maculo-papular | 0% | Not varied | | Fixed |
| Pruritus | 0% | Not varied | | Fixed |
| AST increased | 0% | Not varied | | Fixed |
| Lipase increased | 0% | Not varied | | Fixed |
| ALT increased | 0% | Not varied | | Fixed |
| Hypertension | 0% | Not varied | | Fixed |
| Hypotension | 0% | Not varied | | Fixed |
| Fatigue | 9.6% | Not varied | | Fixed |
| Pyrexia | 1.9% | Not varied | | Fixed |
| Hypophosphataemia | 0% | Not varied | | Fixed |
| Hyperbilirubinaemia | 0% | Not varied | | Fixed |
| Liver toxicity/liver-related events | 26.9% | Not varied | | Fixed |
| Hepatitis | 3.8% | Not varied | | Fixed |
| Diarrhoea (grade 3+) | 11.5% | Not varied | | Fixed |
| Guillain-Barré syndrome | 3.8% | Not varied | | Fixed |
| Hypothyroidism | 15.4% | Not varied | | Fixed |
| Thyroiditis | 9.6% | Not varied | | Fixed |
| **Health states utilities** | | | | |
| ≥360 days | 0.82 | -10% | +10% | Beta |
| 270-360 days | 0.71 | -10% | +10% | Beta |
| 180-270 days | 0.66 | -10% | +10% | Beta |
| 90-180 days | 0.66 | -10% | +10% | Beta |
| 30-90 days | 0.57 | -10% | +10% | Beta |
| <30 days | 0.33 | -10% | +10% | Beta |
| On-treatment tebentafusp | 0.89 | -10% | +10% | Beta |
| Off-treatment tebentafusp | 0.81 | -10% | +10% | Beta |
| On-treatment ipi/nivo | 0.88 | -10% | +10% | Beta |

| Input parameter | Point estimate | Lower bound | Upper bound | Probability distribution |
|---|---|---|---|---|
| Off-treatment ipi/nivo | 0.80 | -10% | +10% | Beta |
| **Drug unit costs (PPP)** | | | | |
| Tebentafusp 100 mcg/0.5 ml vial (200 mcg per 1ml) | DKK 98,684.16 | Not varied | | Fixed |
| Ipilimumab 50 mg/10 ml vial (5 mcg per 1 ml) | DKK 23,850.38 | Not varied | | Fixed |
| Nivolumab 240 mg/24 ml vial (24 mg per 1 ml) | DKK 20,457.13 | Not varied | | Fixed |
| Nivolumab 100 mg/10 ml vial (10 mg per 1 ml) | DKK 8,523.8 | Not varied | | Fixed |
| Nivolumab 40 mg/4 ml (10 mg per 1 ml) | DKK 3,431.27 | Not varied | | Fixed |
| **Treatment administration-related costs** | | | | |
| Administration of immunotherapy | DKK 1,068.00 | -25% | +25% | Gamma |
| Overnight hospital stay | DKK 2,316.00 | -25% | +25% | Gamma |
| HLA-A*02:01 screen | DKK 6,070.00 | -25% | +25% | Gamma |
| Human albumin 20% | DKK 448.8 | Not varied | | Fixed |
| % of patients expected to test positive | 50% | -25% | +25% | Beta |
| **Health state costs – tebentafusp and control group** | | | | |
| Pre-progression (per cycle) | DKK 1335.68 | -25% | +25% | Gamma |
| At progression (one-off) | DKK 1958.00 | -25% | +25% | Gamma |
| Post-progression (one-off cost per 4 months) | DKK 10,615.76 | -25% | +25% | Gamma |
| **AE costs** | | | | |
| Rash (inpatient) | DKK 21,118.00 | -25% | +25% | Gamma |
| Rash (outpatient) | DKK 1,578.00 | -25% | +25% | Gamma |
| Rash maculo-papular (inpatient) | DKK 21,118.00 | -25% | +25% | Gamma |
| Rash maculo-papular (outpatient) | DKK 1,578.00 | -25% | +25% | Gamma |
| Pruritus (inpatient) | DKK 21,118.00 | -25% | +25% | Gamma |
| Pruritus (outpatient) | DKK 1,578.00 | -25% | +25% | Gamma |
| Hypertension (inpatient) | DKK 0.00 | Not varied | | Fixed |
| Hypertension (outpatient) | DKK 2,072.00 | -25% | +25% | Gamma |
| Hypotension (inpatient) | DKK 2,240.00 | -25% | +25% | Gamma |
| Hypotension (outpatient) | DKK 2,072.00 | -25% | +25% | Gamma |
| Fatigue (inpatient) | DKK 5,271.00 | -25% | +25% | Gamma |
| Fatigue (outpatient) | DKK 5,217.00 | -25% | +25% | Gamma |
| Pyrexia (inpatient) | DKK 31,708.00 | -25% | +25% | Gamma |
| Pyrexia (outpatient) | DKK 1,753.00 | -25% | +25% | Gamma |
| Hyperbilirubinaemia (inpatient) | DKK 0.00 | Not varied | | Fixed |
| Hyperbilirubinaemia (outpatient) | DKK 2,072.00 | -25% | +25% | Gamma |
| Liver toxicity/liver-related events (inpatient) | DKK 46,506.00 | -25% | +25% | Gamma |

| Input parameter | Point estimate | Lower bound | Upper bound | Probability distribution |
|---|---|---|---|---|
| Liver toxicity/liver-related events (outpatient) | DKK 2,072.00 | -25% | +25% | Gamma |
| Hepatitis (inpatient) | DKK 46,506.00 | -25% | +25% | Gamma |
| Hepatitis (outpatient) | DKK 2,072.00 | -25% | +25% | Gamma |
| Diarrhoea (grade 3+) (inpatient) | DKK 4,977.00 | -25% | +25% | Gamma |
| Diarrhoea (grade 3+) (outpatient) | DKK 4,977.00 | -25% | +25% | Gamma |
| Guillain-Barré syndrome (inpatient) | DKK 75,620.00 | -25% | +25% | Gamma |
| Guillain-Barré syndrome (outpatient) | DKK 0.00 | Not varied | | Fixed |
| Hypothyrodism (inpatient) | DKK 1,790.00 | -25% | +25% | Gamma |
| Hypothyrodism outpatient) | DKK 1,790.00 | -25% | +25% | Gamma |
| Thyroiditis (inpatient) | DKK 1,790.00 | -25% | +25% | Gamma |
| Thyroiditis (outpatient) | DKK 1,790.00 | -25% | +25% | Gamma |
| **Patient AE costs** | | | | |
| Rash (inpatient) | DKK 18,322.28 | -25% | +25% | Gamma |
| Rash (outpatient) | DKK 368.28 | -25% | +25% | Gamma |
| Rash maculo-papular (inpatient) | DKK 18,322.28 | -25% | +25% | Gamma |
| Rash maculo-papular (outpatient) | DKK 368.28 | -25% | +25% | Gamma |
| Pruritus (inpatient) | DKK 18,322.28 | -25% | +25% | Gamma |
| Pruritus (outpatient) | DKK 368.28 | -25% | +25% | Gamma |
| Hypertension (inpatient) | DKK 0.00 | Not varied | | Fixed |
| Hypertension (outpatient) | DKK 368.28 | -25% | +25% | Gamma |
| Hypotension (inpatient) | DKK 4,786.28 | -25% | +25% | Gamma |
| Hypotension (outpatient) | DKK 368.28 | -25% | +25% | Gamma |
| Fatigue (inpatient) | DKK 4,786.28 | -25% | +25% | Gamma |
| Fatigue (outpatient) | DKK 368.28 | -25% | +25% | Gamma |
| Pyrexia (inpatient) | DKK 27,346.28 | -25% | +25% | Gamma |
| Pyrexia (outpatient) | DKK 368.28 | -25% | +25% | Gamma |
| Hyperbilirubinaemia (inpatient) | DKK 0.00 | Not varied | | Fixed |
| Hyperbilirubinaemia (outpatient) | DKK 368.28 | -25% | +25% | Gamma |
| Liver toxicity/liver-related events (inpatient) | DKK 58,749.00 | -25% | +25% | Gamma |
| Liver toxicity/liver-related events (outpatient) | DKK 386.50 | -25% | +25% | Gamma |
| Hepatitis (inpatient) | DKK 54,418.28 | -25% | +25% | Gamma |
| Hepatitis (outpatient) | DKK 368.28 | -25% | +25% | Gamma |
| Diarrhoea (grade 3+) (inpatient) | DKK 4,786.28 | -25% | +25% | Gamma |
| Diarrhoea (grade 3+) (outpatient) | DKK 368.28 | -25% | +25% | Gamma |
| Hypothyroidism (inpatient) | DKK 4,786.28 | -25% | +25% | Gamma |
| Hypothyroidism (outpatient) | DKK 368.28 | -25% | +25% | Gamma |
| Thyroiditis (inpatient) | DKK 4,786.28 | -25% | +25% | Gamma |

| Input parameter | Point estimate | Lower bound | Upper bound | Probability distribution |
|---|---|---|---|---|
| Thyroiditis (outpatient) | DKK 368.28 | -25% | +25% | Gamma |
| Guillain-Barré syndrome (inpatient) | DKK 90,514.28 | -25% | +25% | Gamma |
| Guillain-Barré syndrome (outpatient) | DKK 0.00 | Not varied | | Fixed |
| **Patient costs** | | | | |
| Pre-progression (per cycle) | DKK 426.48 | -25% | +25% | Gamma |
| At progression (one-off) | DKK 1,905.44 | -25% | +25% | Gamma |
| Post-progression (one-off cost per 4 months) | DKK 11,693.89 | -25% | +25% | Gamma |
| Transportation costs | DKK 140.00 | -25% | +25% | Gamma |
| **AEs % management in inpatient and outpatient settings** | | | | |
| Rash (inpatient) | 5% | Not varied | | Fixed |
| Rash (outpatient) | 95% | Not varied | | Fixed |
| Rash maculo-papular (inpatient) | 5% | Not varied | | Fixed |
| Rash maculo-papular (outpatient) | 95% | Not varied | | Fixed |
| Pruritus (inpatient) | 5% | Not varied | | Fixed |
| Pruritus (outpatient) | 95% | Not varied | | Fixed |
| Hypertension (inpatient) | 0% | Not varied | | Fixed |
| Hypertension (outpatient) | 100% | Not varied | | Fixed |
| Hypotension (inpatient) | 50% | Not varied | | Fixed |
| Hypotension (outpatient) | 50% | Not varied | | Fixed |
| Fatigue (inpatient) | 10% | Not varied | | Fixed |
| Fatigue (outpatient) | 90% | Not varied | | Fixed |
| Pyrexia (inpatient) | 10% | Not varied | | Fixed |
| Pyrexia (outpatient) | 90% | Not varied | | Fixed |
| Hyperbilirubinaemia (inpatient) | 0% | Not varied | | Fixed |
| Hyperbilirubinaemia (outpatient) | 100% | Not varied | | Fixed |
| Liver toxicity/liver-related events (inpatient) | 10% | Not varied | | Fixed |
| Liver toxicity/liver-related events (outpatient) | 90% | Not varied | | Fixed |
| Hepatitis (inpatient) | 30% | Not varied | | Fixed |
| Hepatitis (outpatient) | 70% | Not varied | | Fixed |
| Diarrhoea (grade 3+) (inpatient) | 50% | Not varied | | Fixed |
| Diarrhoea (grade 3+) (outpatient) | 50% | Not varied | | Fixed |
| Guillain-Barré syndrome (inpatient) | 100% | Not varied | | Fixed |
| Guillain-Barré syndrome (outpatient) | 0% | Not varied | | Fixed |
| Hypothyroidism (inpatient) | 0% | Not varied | | Fixed |
| Hypothyroidism (outpatient) | 100% | Not varied | | Fixed |
| Thyroiditis (inpatient) | 0% | Not varied | | Fixed |
| Thyroiditis (outpatient) | 100% | Not varied | | Fixed |

| Input parameter | Point estimate | Lower bound | Upper bound | Probability distribution |
|---|---|---|---|---|
| **Subsequent treatment** | | | | |
| % of usage of subsequent therapies (tebentafusp group) | 43% | -10% | +10% | Beta |
| % of usage of ipi/nivo (tebentafusp group) | 67% | -10% | +10% | Beta |
| % of usage of subsequent therapies (ipi/nivo group) | 46% | -10% | +10% | Beta |
| % of usage of ipi/nivo (ipi/nivo) | 0% | -10% | +10% | Fixed |

*Starting point is where the parametric fit is applied to the KM data where a flexible model used for PFS and DoT

# Appendix H. Literature searches for the clinical assessment

## H.1 Efficacy and safety of the intervention and comparator(s)

The objective of the literature search was to update the literature search from the previous application, identifying studies describing the efficacy and safety of tebentafusp and the clinically relevant comparator ipi/nivo, to answer the following:

“What is the comparative efficacy and safety of tebentafusp versus ipi/nivo in the treatment of metUM?” [7]

The updated literature search for the clinical efficacy and safety was performed on February 24, 2025. The search was performed on MEDLINE via PubMed, see Table 84.

**Table 84. Bibliographic databases included in the literature search.**

| Database | Platform/source | Relevant period for the search | Date of search completion |
|---|---|---|---|
| **PubMed** | https://pubmed.ncbi.nlm.nih.gov/ | 18 November 2021 to 24 February 2025 | 24.02.2025 |

### H.1.1 Search strategies

The search was performed in PubMed on February 24, 2025. The search strategy is almost identical to the original literature search with minor adjustments to the search string as “Uveal melanoma” is a MeSH Term and no longer categorized as Supplementary Concept. Moreover, KIMMTRAK has been added to ensure inclusion of generic and proprietary names of both intervention and comparator. The search string is presented in Table 85. The search included terms for free text and keywords (Medical Subject Heading (MeSH)) combined using Boolean combination techniques.

**Table 85. Search strategy table for PubMed.**

| No. | Query | Results |
|---|---|---|
| **#1** | "Uveal melanoma" [MeSH Terms] | 2,232 |
| **#2** | ((((("Uveal melanom*") OR (choroidal melanoma)) OR (iris melanoma)) OR (metastatic uveal melanoma)) OR (ocular melanoma) | 12,508 |
| **#3** | #1 OR #2<br>("Uveal melanoma"[MeSH Terms]) OR (((((("Uveal melanom*") OR (choroidal melanoma)) OR (iris melanoma)) OR (metastatic uveal melanoma)) OR (ocular melanoma)) | 12,508 |
| **#4** | (KIMMTRAK) OR (tebentafusp) OR ("tebentafusp" [Supplementary Concept]) | 116 |
| **#5** | ((((((((("Ipilimumab plus nivolumab") OR (ipilimumab)) OR (nivolumab)) OR (ipi/nivo)) OR (ipi-nivo)) OR ("ipi nivo")) OR | 14,319 |

| No. | Query | Results |
|---|---|---|
| | ("nivolumab ipilimumab")) OR ("ipilimumab nivolumab")) OR (yervoy plus opdivo)) OR (opdivo yervoy)) OR (yervoy opdivo) | |
| **#6** | #4 OR #5<br>((KIMMTRAK) OR (tebentafusp) OR ("tebentafusp" [Supplementary Concept])) OR ((((((((((("Ipilimumab plus nivolumab") OR (ipilimumab)) OR (nivolumab)) OR (ipi/nivo)) OR (ipi-nivo)) OR ("ipi nivo")) OR ("nivolumab ipilimumab")) OR ("ipilimumab nivolumab")) OR (yervoy plus opdivo)) OR (opdivo yervoy)) OR (yervoy opdivo)) | 12,375 |
| **#7** | #3 AND #6<br>((KIMMTRAK) OR (tebentafusp) OR ("tebentafusp" [Supplementary Concept])) OR ((((((((((("Ipilimumab plus nivolumab") OR (ipilimumab)) OR (nivolumab)) OR (ipi/nivo)) OR (ipi-nivo)) OR ("ipi nivo")) OR ("nivolumab ipilimumab")) OR ("ipilimumab nivolumab")) OR (yervoy plus opdivo)) OR (opdivo yervoy)) OR (yervoy opdivo)) | 316 |
| **#8** | (("Uveal melanoma"[MeSH Terms]) OR (((((("Uveal melanom*") OR (choroidal melanoma)) OR (iris melanoma)) OR (metastatic uveal melanoma)) OR (ocular melanoma))) AND (((KIMMTRAK) OR (tebentafusp) OR ("tebentafusp" [Supplementary Concept])) OR ((((((((((("Ipilimumab plus nivolumab") OR (ipilimumab)) OR (nivolumab)) OR (ipi/nivo)) OR (ipi-nivo)) OR ("ipi nivo")) OR ("nivolumab ipilimumab")) OR ("ipilimumab nivolumab")) OR (yervoy plus opdivo)) OR (opdivo yervoy)) OR (yervoy opdivo))) Filters: from 2021/11/18 - 2025/2/24 | 152 |

### H.1.2 Systematic selection of studies

The database search conducted on February 24, 2025 identified 152 records which were screened (Figure 27). Two reviewers assessed the relevance of identified studies based on title and abstract (first pass) for inclusion using the selection criteria Table 86. The selection criteria have not been changed since the original SLR to an extent that is expected to impact the result of the literature search. In full-text copies of all potentially relevant records were obtained and evaluated in more detail (second pass) against the selection criteria.

Based on the selection criteria defined for the Danish submission in Table 86, 152 clinical references were screened based on title and abstract and 18 articles were full-text screened. This resulted in the inclusion of the following 2 clinical references including 1 clinical study, and 1 comparative analysis of the IMCgp100-202 [44][49] and GEM-1402 [11] clinical studies.

A list of included studies based on the full-text screening for efficacy and safety based on the selection criteria defined for the Danish submission is presented in Table 86 and excluded studies based on the full-text review is presented in Table 88.

**Table 86. Inclusion and exclusion criteria used for assessment of studies.**

| Clinical effectiveness | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | • Adult patients with metUM | • Studies that do not include patients of interest to the SLR |

| | | |
|---|---|---|
| | | • Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest<br>• Studies conducted in a setting not relevant to the Danish submission |
| **Intervention** | • Tebentafusp | • No intervention of interest |
| **Comparators** | • Ipilimumab<br>• Nivolumab | • No comparators of interest |
| **Outcomes** | • Efficacy (e.g. OS, PFS, ORR, DoR, HRQoL)<br>• Safety (e.g. AEs) | • No reported outcomes of interest, i.e., only reporting pharmacodynamics, PKs, genetic, cellular, or molecular outcomes |
| **Study design/publication type** | • Randomized control trials (RCTs)<br>• Phase II, single-arm trials<br>• Article, abstract<br>• | • Cross-sectional studies<br>• Animal studies<br>• In vitro/ex vivo studies<br>• Individual case study reports<br>• Non-RCTs<br>• Observational studies (including patient registries)<br>• Phase 1 studies<br>• Short survey<br>• Reviews<br>• Letters<br>• Comment articles<br>• Article in press |
| **Language restrictions** | • English | • Non-English |

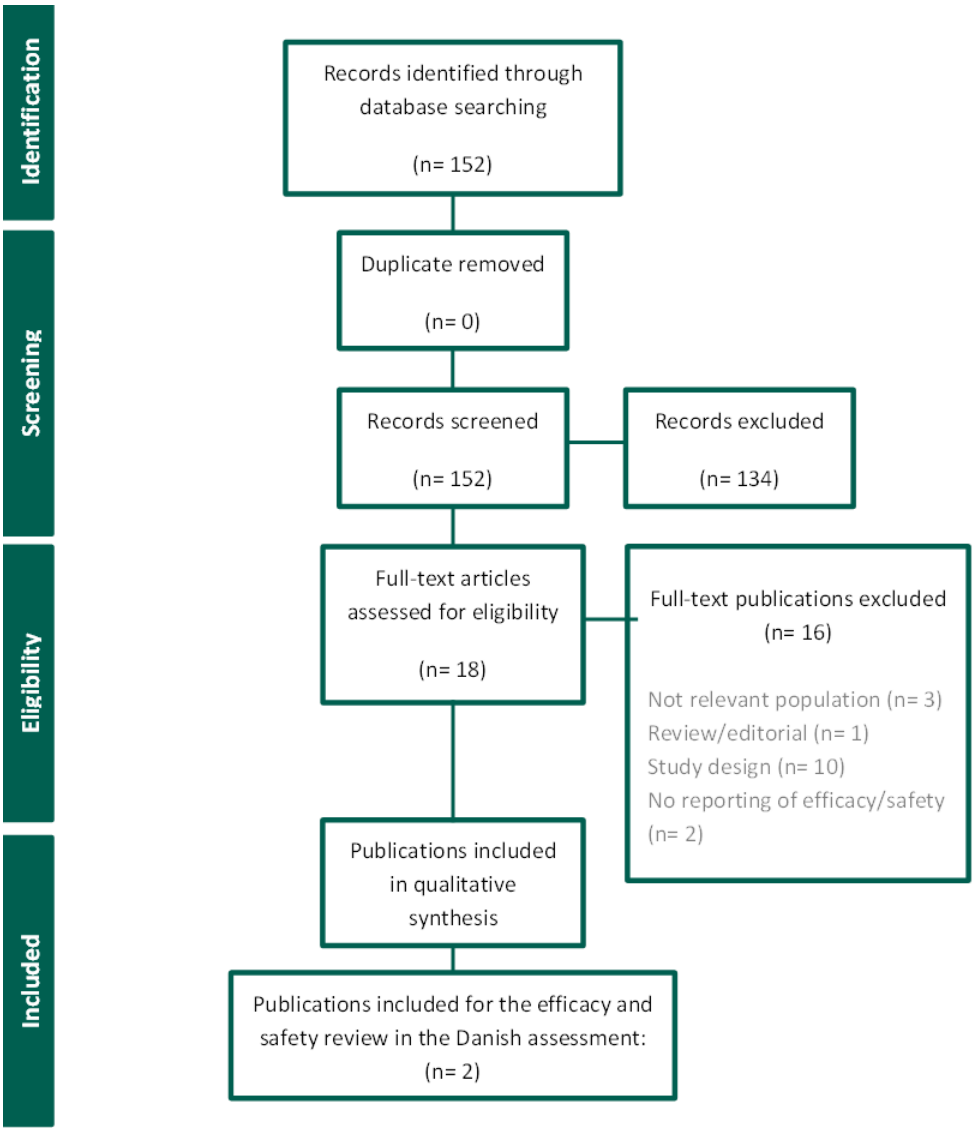



**Figure 27. PRISMA flow chart for clinical literature search.**

**Table 87. Overview of study design for studies included in the analysis based on the SLR.**

| 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 [36]<br>*Hassel et al., 2023* [49] | 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 | Ongoing randomized, open-label, active-comparator study | Patients with HLA-A*02:01 positive advanced or metUM 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:**<br>Tebentafusp, n = 252<br><br>**Comparator:**<br>Pembrolizumab, ipilimumab or dacarbazine, n = 126 | The primary outcome was OS.<br><br>**Study duration**:<br>October 2017 to June 2025<br><br>**DCO October 2020**:<br>Median follow-up period = 14.1 months [48]<br><br>**DCO July 2023:**<br>Median follow-up period = 43.3 months [49] | Safety, PFS, Quality of Life, PKs, ORR, DoR and DCR |
| *Piulats et al. 2023* [9] | To compare OS of tebentafusp (IMCgp100-202) to OS of ipi/nivo (GEM-1402) in metUM patients in the 1st line setting. A secondary objective was to compare OS of pembrolizumab (IMCgp100-202) to OS of ipi/nivo (GEM-1402). | Comparative indirect analysis using propensity score-based methods | Patients with previously untreated metUM | **Intervention**:<br>Tebentafusp, n = 240<br><br>**Comparator:**<br>Ipi/nivo, n = 45 | The primary outcome was OS.<br><br>**Study duration:**<br>IMCgp100-202: DCO July 2023<br>GEM-1402:<br>DCO August 2023 | N/A |

### H.1.3 Excluded fulltext references

**Table 88. Excluded studies from full-text review.**

| | Reference | Reason for exclusion |
|---|---|---|
| 1 | Tomsitz, D., Ruf, T., Heppt, M., Staeger, R., Ramelyte, E., Dummer, R., Garzarolli, M., Meier, F., Meier, E., Richly, H., Gromke, T., Siveke, J. T., Franklin, C., Klespe, K. C., Mauch, C., Kilian, T., Seegräber, M., Schilling, B., French, L. E., Berking, C., … Heinzerling, L. (2023). Tebentafusp in Patients with Metastatic Uveal Melanoma: A Real-Life Retrospective Multicenter Study. *Cancers*, *15*(13), 3430. https://doi.org/10.3390/cancers15133430 | Not relevant study design |
| 2 | Dian, Y., Liu, Y., Zeng, F., Sun, Y., & Deng, G. (2024). Efficacy and safety of tebentafusp in patients with metastatic uveal melanoma: A systematic review and meta-analysis. *Human Vaccines & Immunotherapeutics*, *20*(1). https://doi.org/10.1080/21645515.2024.2374647 | Not relevant study design |
| 3 | Fahmy, L. M, Schreidah, C. M, McDonnell, D. E, Carvajal, R. D, Magro, C. M, & Geskin, L. J. (2023). Cutaneous type IV hypersensitivity reaction following tebentafusp treatment for uveal melanoma. *Dermatology Online Journal*, 29(6). http://dx.doi.org/10.5070/D329662993 Retrieved from https://escholarship.org/uc/item/277908hf | Case report |
| 4 | Petzold, A., Steeb, T., Wessely, A., Koch, E. A. T., Vera, J., Berking, C., & Heppt, M. V. (2023). Is tebentafusp superior to combined immune checkpoint blockade and other systemic treatments in metastatic uveal melanoma? A comparative efficacy analysis with population adjustment. *Cancer treatment reviews*, *115*, 102543. https://doi.org/10.1016/j.ctrv.2023.102543 | Not relevant study design |
| 5 | Sacco JJ, Carvajal RD, Butler MO, et al. Long-term survival follow-up for tebentafusp in previously treated metastatic uveal melanoma. *Journal for ImmunoTherapy of Cancer* 2024;12:e009028. doi:10.1136/jitc-2024-009028 | Not relevant population |
| 6 | Pham, J. P., On, L., Ardolino, L., Hurwitz, J., Salaun, H., Sim, H. W., & Joshua, A. M. (2023). Efficacy of immune checkpoint inhibition in metastatic uveal melanoma: a systematic review and meta-analysis. *Melanoma research*, *33*(4), 316–325. https://doi.org/10.1097/CMR.0000000000000900 | Not relevant study design |
| 7 | Luo, S., Xie, C., Lin, N., Lin, D., Gu, D., Lin, S., Huang, X., Xu, X., & Weng, X. (2023). Cost-effectiveness analysis of an orphan drug tebentafusp in patients with metastatic uveal melanoma and a call for value-based pricing. *Melanoma research, 33*(6), 525–531. https://doi.org/10.1097/CMR.0000000000000919 | No reporting of efficacy/safety |
| 8 | Salaün, H., de Koning, L., Saint-Ghislain, M., Servois, V., Ramtohul, T., Garcia, A., Matet, A., Cassoux, N., Mariani, P., Piperno-Neumann, S., & Rodrigues, M. (2022). Nivolumab plus | Not relevant study design |

| | Reference | Reason for exclusion |
|---|---|---|
| | ipilimumab in metastatic uveal melanoma: a real-life, retrospective cohort of 47 patients. *Oncoimmunology*, *11*(1), 2116845. https://doi.org/10.1080/2162402X.2022.2116845 | |
| 9 | Dummer, R., Corrie, P., Gutzmer, R., Meniawy, T. M., Del Vecchio, M., Lebbé, C., Guida, M., Dutriaux, C., Dreno, B., Meyer, N., Ferrucci, P. F., Dalle, S., Khattak, M. A., Grob, J. J., Briscoe, K., Larkin, J., Mansard, S., Lesimple, T., Guidoboni, M., Sabatini, S., … Maio, M. (2023). First-Line, Fixed-Duration Nivolumab Plus Ipilimumab Followed by Nivolumab in Clinically Diverse Patient Populations With Unresectable Stage III or IV Melanoma: CheckMate 401. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, *41*(23), 3917–3929. https://doi.org/10.1200/JCO.22.02199 | Not relevant patient population |
| 10 | Hua, G., Carlson, D., & Starr, J. R. (2022). Tebentafusp-tebn: A Novel Bispecific T-Cell Engager for Metastatic Uveal Melanoma. *Journal of the advanced practitioner in oncology*, *13*(7), 717–723. https://doi.org/10.6004/jadpro.2022.13.7.8 | Review/editorial |
| 11 | Rodrigues, M., Ramtohul, T., Rampanou, A. *et al.* Prospective assessment of circulating tumor DNA in patients with metastatic uveal melanoma treated with tebentafusp. *Nat Commun* **15**, 8851 (2024). https://doi.org/10.1038/s41467-024-53145-0 | Not relevant study design |
| 12 | Eteghadi, A., Ebrahimi, M., & Heidari keshel, S. (2024). New immunotherapy approaches as the most effective treatment for uveal melanoma. *Critical Reviews in Oncology/Hematology 194, 104260.* https://doi.org/10.1016/j.critrevonc.2024.104260 | Not relevant patient population |
| 13 | Vitek, L., Goronflot, T., Dutriaux, C., Deleuze, A., Le Corre, Y., Duval-Modeste, A. B., Fresnard, C., Jeudy, G., Lamoureux, A., Gaudy-Marqueste, C., Legoupil, D., Baroudjian, B., L'Orphelin, J. M., Peuvrel, L., Khammari, A., Mortier, L., & Quereux, G. (2024). Efficacy and Tolerability of Tebentafusp in Metastatic Uveal Melanoma: A Real-life Retrospective Multicentre Study. *Acta dermato-venereologica*, *104*, adv41297. https://doi.org/10.2340/actadv.v104.41297 | Not relevant study design |
| 14 | Maurer, A., Clerici, G., Schaab, J.A. *et al.* Immunotherapy response and resistance in patients with advanced uveal melanoma: a retrospective cohort study. *Clin Exp Med* **24**, 234 (2024). https://doi.org/10.1007/s10238-024-01497-8 | Not relevant study design |
| 15 | Vounckx, M., Tijtgat, J., Stevens, L. *et al.* A randomized phase II clinical trial of stereotactic body radiation therapy (SBRT) and systemic pembrolizumab with or without intratumoral avelumab/ipilimumab plus CD1c (BDCA-1)$^{+}$/CD141 (BDCA-3)$^{+}$ myeloid dendritic cells in solid tumors. *Cancer Immunol Immunother* **73**, 167 (2024). https://doi.org/10.1007/s00262-024-03751-0 | Not relevant patient population |

| | Reference | Reason for exclusion |
|---|---|---|
| 16 | Andreia Cristina de Melo, Evandro Lucena, Danielli Cristina Muniz de Oliveira, João P B Viola, Frequency of HLA-A*02:01 in the Brazilian population and its impact on uveal melanoma systemic treatment, *The Oncologist*, Volume 29, Issue 8, August 2024, Pages e1098–e1099, https://doi.org/10.1093/oncolo/oyae112 | No reporting of efficacy/safety |

### H.1.4 Quality assessment

This SLR followed the guidelines provided by the DMC. The SLR is an update of an earlier SLR from 2021 which was used in the previous DMC application.

The conducted SLR had several strengths, adhering to the best practices for conducting and reporting systematic reviews. The search was performed in a relevant database, and the PICO and the inclusion and exclusion criteria were defined before the literature searched. Relevant search terms for the intervention, comparator, and outcomes of interest were applied.

The original literature search had one limitation in that a single researcher screened the records based on title/abstract and subsequently carried out the full-text assessment. Nevertheless, in cases where the researcher faced uncertainty regarding a particular article, consultation with the project manager was consulted prior to making the decision to include or exclude the article. The records identified in the updated literature search were, however, screened for title/abstract and full text assessed by two independent researchers, strengthening the updated literature search.

### H.1.5 Unpublished data

No new unpublished data has been included in this application. The unpublished data included in this application is from the previous DMC application in which a very limited amount of data was provided via the CSR from study IMCgp100-202 and therefore has the same quality as in the study. Additionally, unpublished clinical data was not included in the health economic model.

# Appendix I. Literature searches for health-related quality of life

## I.1 Health-related quality-of-life search

The updated literature search for HRQoL is described in detail in Appendix J as part of SLR for inputs to the health economic model.

# Appendix J. Literature searches for input to the health economic model

## J.1 External literature for input to the health economic model

In May 2020, a SLR was conducted to identify publications reporting economic data (including economic evaluations, healthcare resource use and costs, and utilities and HRQoL data) regarding treatment of adult patients with advanced or metastatic UM or choroidal melanoma. The purpose of the review was to inform an evidence package to support HTA submissions and subsequently updates of the SLR were conducted in September 2021, January 2024 and March 2025 to fulfil the requirements set out by national health authority bodies. The original SLR from 2020 and the updated review from 2021 are previously described in detail in the original application to the DMC [40].

### J.1.1 Objective of literature search

**Updated review (2021-2024)**

The aim of this SLR was to update the evidence in the current economic SLR (September 2021), for tebentafusp and relevant comparator interventions for the treatment of adult patients with advanced or metastatic UM or choroidal melanoma, by identifying all relevant studies between October 2021 and January 2024, and in accordance to a priori specified eligibility criteria. The highest quality and most relevant evidence identified by the literature reviews was considered for inclusion to inform an evidence package to support European HTA submissions.

**Updated review (2024-2025)**

The aim of this SLR is to update the evidence in the current economic SLR (January 2024), for tebentafusp and relevant comparator interventions for the treatment of adult patients with advanced or metastatic UM or choroidal melanoma, by identifying all relevant studies between January 2024 and March 2025, and in accordance to a priori specified eligibility

criteria. The highest quality and most relevant evidence identified by the literature reviews was considered for inclusion to inform an evidence package to support European HTA submissions.

### J.1.2 Research questions

To meet the study objectives, the following research question will be addressed using evidence from relevant publications:

- What is the economic evidence for tebentafusp and its comparators in the treatment advanced or metastatic UM?

This will include reviewing literature reporting on the following:

- CEof tebentafusp and its comparators in the treatment of metastatic UM or choroidal melanoma
- HRQoL and utilities in metastatic UM or choroidal melanoma
- HRC and resource use resulting from metastatic UM or choroidal melanoma

The research questions remain unchanged through all updates of the economic SLR.

### J.1.3 Search methodology

A search strategy for the review was developed and refined to recover relevant publications reporting economic data for adult patients with advanced or metastatic UM or choroidal melanoma. 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

Key characteristics for searches are listed below:

- Language: no limit
- Countries: no limit
- Publication type/status: no limit
- Time frame:
  **Original:** 1999 – May 2020
  **1st Update:** June 2020 – September 2021
  **2nd Update:** October 2021 – January 2024
  **3rd Update:** January 2024 – March 2025

#### J.1.3.1 Electronic databases

**Updated review (2021-2024)**

The search plan included both electronic searching and hand-searching. Databases searched for this systematic literature review included:

- 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): http://www.thecochranelibrary.com
- Epistemonikos database: https://www.epistemonikos.org/en/
- Database of Abstracts of Reviews of Effects (DARE) (Wiley): https://www.cochranelibrary.com/
- The National health service (NHS) economic evaluation database (NHSEED) https://www.crd.york.ac.uk/CRDWeb/
- The German collaborative database: https://www.pharmnet-bund.de/

Searches included controlled vocabulary terms (MeSH terms in Medline and EMTREE terms in Embase) and free text terms to ensure that the highest proportion of relevant articles were captured. The date on which the searches were performed, and the search strategies used in each database searched, has been provided in section J.1.6 so that the search strategy can be replicated and the searches re-run at a later date if necessary. An overview of the sources included in the search is provided in Table 89.

**Table 89. Sources included in the updated search 2021-2024.**

| Database | Platform/source | Relevant period for the search | Date of search completion |
|---|---|---|---|
| **Embase** | OvidSP | October 2021 – January 2024 | 15.01.2024 |
| **Medline** | OvidSP | October 2021 – January 2024 | 15.01.2024 |
| **Centre for Reviews and Dissemination (CRD) database (Includes DARE, HTAD, and NHSEED)** | Cochranelibrary.com | October 2021 – January 2024 | 15.01.2024 |
| **Epistemonikos** | Epistemonikos.org | October 2021 – January 2024 | 15.01.2024 |
| **German database** | Pharmnet-bund.dk | October 2021 – January 2024 | 15.01.2024 |

**Updated review (2024-2025)**

The search plan included both electronic searching and hand-searching. Databases searched for this systematic literature review included:

- 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): http://www.thecochranelibrary.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/
- The German collaborative database: https://www.pharmnet-bund.de/

Searches included controlled vocabulary terms (MeSH terms in Medline and EMTREE terms in Embase) and free text terms to ensure that the highest proportion of relevant articles were captured. The date on which the searches were performed, and the search strategies used in each database searched, has been provided in section J.1.6 so that the search strategy can be replicated and the searches re-run at a later date if necessary. For this review update (March 2025), the search strategies will be translated as necessary for each of the resources searched. An overview of the sources included in the search is provided in Table 90.

**Table 90. Sources included in the updated search 2024-2025**

| Database | Platform/source | Relevant period for the search | Date of search completion |
|---|---|---|---|
| **Embase** | OvidSP | January 2024 – March 2025 | 06.03.2025 |
| **Medline** | OvidSP | January 2024 – March 2025 | 06.03.2025 |
| **CRD database (Includes DARE, HTAD, and NHSEED)** | Cochranelibrary.com | January 2024 – March 2025 | 06.03.2025 |
| **Epistemonikos** | Epistemonikos.org | January 2024 – March 2025 | 06.03.2025 |
| **German database** | Pharmnet-bund.dk | January 2024 – March 2025 | 06.03.2025 |

### J.1.3.2 Supplemental searching

**Updated review (2021-2024) and updated review (2024-2025)**

In line with good practice guidelines, 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 keyword searching in internet search engines. This approach was applied in both updated reviews from 2021-2024 and 2024-2025.

### J.1.4 Eligibility criteria – PICOS

**Updated review (2021-2024) and updated review (2024-2025)**

The Population, Intervention, Comparator(s), Outcomes, and Study design (PICOS) elements for this review are displayed in Table 91, Table 92, and Table 93. To be included, studies had to meet the PICOS elements listed in the PICOS tables. Given that there is no standard treatment pathway for metastatic uveal melanoma, the inclusion criteria for comparators were kept broad; all potential comparators were included. The review excluded 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 abstract.

**Table 91. Economic evaluation.**

| PICOS element | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Adult patients, aged ≥ 18 years, with advanced or metUM/choroidal melanoma | Paediatric patients (<18 years) |
| **Intervention/Comparator** | - Tebentafusp, IMCgp100<br>- All other non-surgical therapeutic interventions used in the treatment of choroidal melanoma /metUM | - Surgical interventions for choroidal melanoma /metUM |
| **Outcome** | - ICER – cost per QALY<br>- ICER – cost per measure of effect gained<br>- LYs | - Any outcome not listed in the inclusion criteria |
| **Study design** | - Economic evaluations (including cost-minimisation 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<br>- Model-based economic evaluations and/or model (e.g. decision trees, Markov models etc.) 1999 onwards | - Non-human studies<br>- PK and proof of concept studies<br>- Studies not reporting empirical data<br>- Studies reporting expert opinion only<br>- Reviews/Systematic reviews<br>- Studies indexed as case reports, case series, editorials and letters<br>- Publications in non-English language |
| **Publication year** | **Original:** 1999 – May 2020<br>**1st Update:** June 2020 – September 2021<br>**2nd Update:** October 2021 – January 2024<br>**3rd Update:** January 2024 – March 2025 | Publications prior to 1999 |

**Table 92. Healthcare related costs (HRC) and resource use.**

| PICOS element | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Adult patients, aged ≥18 years, with advanced or metUM/ choroidal melanoma | Paediatric patients (<18 years) |
| **Intervention/Comparator** | N/A | N/A |
| **Outcome** | - Direct costs associated with metUM or choroidal melanoma (e.g. medicines, healthcare labour costs, hospitalisations, surgery)<br>- Indirect costs associated with metUM or choroidal melanoma (e.g. absenteeism, | - Any outcome not listed in the inclusion criteria |

| PICOS element | Inclusion criteria | Exclusion criteria |
|---|---|---|
| | work productivity, premature death)<br>- Resource use (e.g. hospitalisations, GP visits, hospital length of stay) associated with metUM or choroidal melanoma | |
| **Study design** | - All empirical studies reporting on costs and resource utilisation for the specified patient population 1999-onwards | - Non-human studies<br>- PK and proof of concept studies<br>- Studies not reporting empirical data<br>- Studies reporting expert opinion only<br>- Reviews/Systematic reviews<br>- Studies indexed as case reports, case series, editorials and letters<br>- Publications in non-English language |
| **Publication year** | **Original:** 1999 – May 2020<br>**1st Update:** June 2020 – September 2021<br>**2nd Update:** October 2021 – January 2024<br>**3rd Update:** January 2024 – March 2025 | Publications prior to 1999 |

**Table 93. HRQoL and utilities.**

| PICOS element | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Adult patients, aged ≥ 18 years, with advanced or metUM/choroidal melanoma | Paediatric patients (<18 years) |
| **Intervention/Comparator** | N/A | N/A |
| **Outcome** | - Utility estimates (EQ-5D, Short Form 6 Dimension (SF-6D))<br>- HRQoL (other relevant instruments e.g. Short Form 36 items (SF-36), disease specific instruments; Functional assessment of cancer therapy: general (FACT-G), functional assessment of cancer therapy: melanoma (FACT-M), EORTC-QLQC30, MFI)) | - Any outcome not listed in the inclusion criteria |
| **Study design** | - Observational studies reporting utilities/HRQoL data 1999 onwards<br>- RCTs reporting HRQoL data 1999 onwards | - Non-human studies<br>- PK and proof of concept studies<br>- Studies not reporting empirical data |

| PICOS element | Inclusion criteria | Exclusion criteria |
|---|---|---|
| | | - Studies reporting expert opinion only<br>- Reviews/Systematic reviews<br>- Studies indexed as case reports, case series, editorials, and letters<br>- Publications in non-English language |
| **Publication year** | **Original:** 1999 – May 2020<br>**1st Update:** June 2020 – September 2021<br>**2nd Update:** October 2021 – January 2024<br>**3rd Update:** January 2024 – March 2025 | Publications prior to 1999 |

### J.1.5 Data extraction strategy

**Updated review (2021-2024) and updated review (2024-2025)**

Data from the relevant publications was extracted by a reviewer into a bespoke data extraction table (DET), designed to collect information relevant to the review and developed in consultation with Immunocore Ltd. This included, but was not limited to:

- Study characteristics: Author(s), year of publication, title study design and objectives, intervention (if applicable), key time points, setting, country, follow-up duration and total study duration.
- Baseline characteristics: Age, sample size, gender, disease duration, disease stage, details of metastasis.
- CE outcomes:
  - ICER – cost per QALY,
  - ICER – cost per measure of effect gained,
  - LYs.
- HRC and resource use outcomes:
  - Direct costs: medicines, healthcare labour costs, hospitalisations, surgery,
  - Indirect costs: measures of absenteeism, work productivity, premature death,
  - Resource use: hospitalisations, GP visits, hospital length of stay.
- HRQoL and utilities use:
  - Utilities estimates: EQ-5D, SF-6D,
  - HRQoL and any other relevant instruments e.g. 36-Item Short Form Survey (SF-36), disease specific instruments; Functional Assessment of Cancer Therapy - General (FACT-G), Functional Assessment of Cancer Therapy - melanoma (FACT-M), European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQC30), and/or Multidimensional Fatigue Inventory (MFI).

To avoid double counting of patients, where multiple publications relate to the same patient cohort or where pooled analysis was identified, the references selected for inclusion were those which provided the most complete follow up or the most useful outcomes.

### J.1.6 Search strings

The search strings used to identify relevant health economic studies are shown below. The literature review was conducted over the 4 separate time periods to ensure the most relevant and up-to-date studies had been captured. The first search strategies were designed and run in May 2020 and subsequent update literature searches were performed in September 2021, January 2024, and March 2025.

**Updated review (2021-2024)**

**Table 94. Cochrane Library search strategy (2021-2024).**

| Search number, # | Search Algorithm | Search Yield (updated, January 2024) |
|---|---|---|
| 1 | MeSH descriptor: [Uveal Neoplasms] explode all trees | 142 |
| 2 | MeSH descriptor: [Choroid Neoplasms] explode all trees | 61 |
| 3 | #1 or #2 | 142 |
| 4 | MeSH descriptor: [Melanoma] explode all trees | 2767 |
| 5 | #3 and #4 | 136 |
| 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 | 292 |
| 7 | aderhautmelanom*:ti | 0 |
| 8 | #6 or #7 | 292 |
| 9 | #5 or #8 in Cochrane Reviews | 0 |

**Table 95. Epistemonikos search strategy (2021-2024).**

| Search number, # | Search Algorithm | Search Yield (updated January 2024) |
|---|---|---|
| 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*))) | 80 |

**Table 96. MEDLINE (via OvidSP interface) search strategy (2021-2024).**

| Search number, # | Search Algorithm | Search Yield (updated January 2024) |
|---|---|---|
| 1 | exp Uveal Neoplasms/ | 10892 |
| 2 | exp Choroid Neoplasms/ | 5653 |
| 3 | or/1-2 | 10892 |

| | | |
|---|---|---|
| 4 | exp Melanoma/ | 110586 |
| 5 | 3 and 4 | 7813 |
| 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. | 9334 |
| 7 | 5 or 6 | 11063 |
| 8 | economics/ | 27522 |
| 9 | exp "costs and cost analysis"/ | 268141 |
| 10 | economics, dental/ | 1921 |
| 11 | exp "economics, hospital"/ | 25786 |
| 12 | economics, medical/ | 9262 |
| 13 | economics, nursing/ | 4013 |
| 14 | economics, pharmaceutical/ | 3123 |
| 15 | (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. | 1086904 |
| 16 | (expenditure$ not energy).ti,ab. | 38043 |
| 17 | (value adj1 money).ti,ab. | 41 |
| 18 | budget$.ti,ab. | 36644 |
| 19 | 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 | 1253016 |
| 20 | ((energy or oxygen) adj cost).ti,ab. | 4865 |
| 21 | (metabolic adj cost).ti,ab. | 1759 |
| 22 | ((energy or oxygen) adj expenditure).ti,ab. | 29698 |
| 23 | 20 or 21 or 22 | 35239 |
| 24 | 19 not 23 | 1244868 |
| 25 | exp models, economic/ or ((economic$ or financ$ or cost$ or budget$ or expen$ or price or pricing or markov$) and model$).ti,ab. | 280525 |
| 26 | 24 or 25 | 1303482 |
| 27 | 7 and 26 | 95 |
| 28 | exp Health Care Costs/ | 72521 |
| 29 | exp Employment/ | 101301 |
| 30 | exp Work/ | 70853 |
| 31 | Efficiency/ | 15735 |
| 32 | Absenteeism/ | 9816 |
| 33 | "Cost of Illness"/ | 31919 |
| 34 | "Length of Stay"/ | 103668 |
| 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. | 30594190 |

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|---|---|---|
| 36 | (productivity adj2 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. | 4190 |
| 37 | ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab. | 13659 |
| 38 | llsi.ti,ab. | 16 |
| 39 | (cost$ adj2 (illness or disease$ or sickness$ or care or healthcare)).ti,ab. | 57266 |
| 40 | (burden$ adj2 (illness or disease$ or sickness$ or care or healthcare)).ti,ab. | 49573 |
| 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$)).ti,ab. | 135568 |
| 42 | ((allowance or status or long-term or pension$ or benefit$) adj2 disab$).ti,ab. | 17097 |
| 43 | ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab. | 2239 |
| 44 | budget$ impact$.ti,ab. | 2300 |
| 45 | budget$ implicat$.ti,ab. | 85 |
| 46 | resource$ use$.ti,ab. | 13606 |
| 47 | resource$ utili$.ti,ab. | 16028 |
| 48 | resource$ usage.ti,ab. | 657 |
| 49 | (length adj2 stay$).ti,ab. | 82621 |
| 50 | (hospital$ adj2 stay$).ti,ab. | 119371 |
| 51 | (duration adj2 stay$).ti,ab. | 4869 |
| 52 | extended stay$.ti,ab. | 267 |
| 53 | prolonged stay$.ti,ab. | 1192 |
| 54 | ((hospitali?ation$ or hospitali?ed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. | 10857 |
| 55 | economic consequenc$.ti,ab. | 4874 |
| 56 | or/28-55 | 740053 |
| 57 | 7 and 56 | 32 |
| 58 | quality adjusted life year/ | 16058 |
| 59 | (quality adjusted or adjusted life year$).ti,ab,kw. | 24221 |
| 60 | (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. | 15161 |
| 61 | (illness state$1 or health state$1).ti,ab,kw. | 8611 |
| 62 | (hui or hui1 or hui2 or hui3).ti,ab,kw. | 2032 |
| 63 | (multiattribute$ or multi attribute$).ti,ab,kw. | 1389 |
| 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. | 20533 |
| 65 | utilities.ti,ab,kw. | 9675 |

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|---|---|---|
| 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. | 18178 |
| 67 | (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. | 6212 |
| 68 | (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. | 27217 |
| 69 | (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw. | 2430 |
| 70 | "quality of life"/ and (health adj3 status).ti,ab,kw. | 11919 |
| 71 | (quality of life or qol).ti,ab,kw. and "cost-benefit analysis"/ | 17316 |
| 72 | or/58-71 | 108742 |
| 73 | 7 and 72 | 17 |
| 74 | quality-adjusted life years/ or quality of life/ | 293287 |
| 75 | (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. | 31176 |
| 76 | (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. | 2696 |
| 77 | (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. | 7848 |
| 78 | (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab. | 1022 |
| 79 | (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. | 466 |
| 80 | (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab. | 771 |
| 81 | (short form$ or shortform$).ti,ab. | 45463 |
| 82 | ("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or EORTC-QLQ).ti,ab. | 5678 |
| 83 | "quality of life".ti,ab. | 387707 |
| 84 | (Quality adjusted life or Quality-adjusted-life).ti,ab. | 17883 |
| 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. | 17469 |
| 86 | (qol or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. | 79567 |

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|---|---|---|
| 87 | (hye or hyes).ti,ab. | 76 |
| 88 | health$ year$ equivalent$.ti,ab. | 40 |
| 89 | (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. | 2026 |
| 90 | (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab. | 1210 |
| 91 | (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab. | 6547 |
| 92 | (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab. | 21379 |
| 93 | (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab. | 11685 |
| 94 | (15D or 15-D or "15 dimension").ti,ab. | 6224 |
| 95 | (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab. | 518 |
| 96 | illness state$.ti,ab. | 176 |
| 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. | 47895 |
| 98 | (utilities or disutili$).ti,ab. | 10075 |
| 99 | (Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab. | 1405 |
| 100 | ((patient$ 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. | 173820 |
| 101 | or/74-100 | 697668 |
| 102 | 7 and 101 | 133 |
| 103 | 73 or 102 | 134 |
| 104 | 27 or 57 or 103 | 246 |
| 105 | editorial/ or letter/ or case report/ or (editorial or letter or case reports).pt. | 4069845 |
| 106 | 104 not 105 | 224 |

**Table 97. EMBASE (via OvidSP interface) search strategy (2021-2024)**

| Search number, # | Search Algorithm | Search Yield (updated January 2024) |
|---|---|---|
| 1 | exp uvea tumor/ or exp choroid tumor/ | 11253 |
| 2 | exp melanoma/ | 201983 |
| 3 | 1 and 2 | 5959 |
| 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. | 12534 |
| 5 | 3 or 4 | 14042 |
| 6 | health-economics/ | 36197 |
| 7 | exp economic-evaluation/ | 362090 |
| 8 | exp health-care-cost/ | 347518 |
| 9 | exp pharmacoeconomics/ | 237072 |
| 10 | or/6-9 | 769272 |
| 11 | (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. | 1431046 |
| 12 | (expenditure$ not energy).ti,ab. | 51590 |
| 13 | (value adj2 money).ti,ab. | 3074 |
| 14 | budget$.ti,ab. | 48373 |
| 15 | or/11-14 | 1476733 |
| 16 | 10 or 15 | 1849491 |
| 17 | (metabolic adj cost).ti,ab. | 1912 |
| 18 | ((energy or oxygen) adj cost).ti,ab. | 5149 |
| 19 | ((energy or oxygen) adj expenditure).ti,ab. | 38104 |
| 20 | or/17-19 | 43928 |
| 21 | 16 not 20 | 1840479 |
| 22 | economic model/ or ((economic$ or financ$ or cost$ or budget$ or expen$ or price or pricing or markov$) and model$).ti,ab. | 356283 |
| 23 | 21 or 22 | 1911785 |
| 24 | 5 and 23 | 222 |
| 25 | exp "health care cost"/ | 347518 |
| 26 | exp employment/ | 130042 |
| 27 | exp work/ | 442722 |
| 28 | "cost of illness"/ | 21540 |
| 29 | "length of stay"/ | 280259 |
| 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. | 3813 |
| 31 | (productivity adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. | 5924 |

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| 32 | ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab. | 19056 |
| 33 | llsi.ti,ab. | 18 |
| 34 | (cost$ adj2 (illness or disease$ or sickness$ or care or healthcare)).ti,ab. | 89256 |
| 35 | (burden$ adj2 (illness or disease$ or sickness$ or care or healthcare)).ti,ab. | 76142 |
| 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$)).ti,ab. | 178630 |
| 37 | ((allowance or status or long-term or pension$ or benefit$) adj2 disab$).ti,ab. | 27871 |
| 38 | ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab. | 3344 |
| 39 | budget$ impact$.ti,ab. | 6128 |
| 40 | budget$ implicat$.ti,ab. | 126 |
| 41 | resource$ use$.ti,ab. | 20660 |
| 42 | resource$ utili$.ti,ab. | 29387 |
| 43 | resource$ usage.ti,ab. | 918 |
| 44 | (length adj2 stay$).ti,ab. | 156027 |
| 45 | (hospital$ adj2 stay$).ti,ab. | 198812 |
| 46 | (duration adj2 stay$).ti,ab. | 7689 |
| 47 | extended stay$.ti,ab. | 425 |
| 48 | prolonged stay$.ti,ab. | 1976 |
| 49 | ((hospitali?ation$ or hospitali?ed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. | 19367 |
| 50 | economic consequenc$.ti,ab. | 6219 |
| 51 | or/25-50 | 1574107 |
| 52 | 5 and 51 | 143 |
| 53 | quality adjusted life year/ | 36406 |
| 54 | (quality adjusted or adjusted life year$).ti,ab,kw. | 35175 |
| 55 | (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. | 27994 |
| 56 | (illness state$1 or health state$1).ti,ab,kw. | 15042 |
| 57 | (hui or hui1 or hui2 or hui3).ti,ab,kw. | 3232 |
| 58 | (multiattribute$ or multi attribute$).ti,ab,kw. | 1609 |
| 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. | 32434 |
| 60 | utilities.ti,ab,kw. | 15492 |
| 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 | 32415 |

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|---|---|---|
| | 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. | |
| 62 | (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. | 9276 |
| 63 | (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. | 46753 |
| 64 | (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw. | 3631 |
| 65 | "quality of life"/ and (health adj3 status).ti,ab,kw. | 20686 |
| 66 | (quality of life or qol).ti,ab,kw. and "cost-benefit analysis"/ | 6984 |
| 67 | or/53-66 | 176378 |
| 68 | 5 and 67 | 28 |
| 69 | quality adjusted life year/ or quality of life index/ | 39577 |
| 70 | Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ | 50822 |
| 71 | "International Classification of Functioning, Disability and Health"/ or "Ferrans and Powers Quality of Life Index"/ | 3707 |
| 72 | (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. | 50732 |
| 73 | (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. | 3015 |
| 74 | (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. | 12477 |
| 75 | (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab. | 1867 |
| 76 | (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. | 534 |
| 77 | (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab. | 1220 |
| 78 | (short form$ or shortform$).ti,ab. | 61753 |
| 79 | ("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or EORTC-QLQ).ti,ab. | 11828 |
| 80 | "quality of life".ti,ab. | 608388 |
| 81 | (Quality adjusted life or Quality-adjusted-life).ti,ab. | 27186 |
| 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. | 31473 |

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|---|---|---|
| 83 | (qol or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. | 141431 |
| 84 | (hye or hyes).ti,ab. | 185 |
| 85 | health$ year$ equivalent$.ti,ab. | 41 |
| 86 | (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. | 3221 |
| 87 | (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab. | 1565 |
| 88 | (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab. | 7846 |
| 89 | (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab. | 35702 |
| 90 | (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab. | 17475 |
| 91 | 15d.ti,ab. | 2965 |
| 92 | (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab. | 798 |
| 93 | illness state$.ti,ab. | 261 |
| 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. | 74002 |
| 95 | (utilities or disutili$).ti,ab. | 16200 |
| 96 | (Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab. | 1840 |
| 97 | ((patient$ 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. | 276048 |
| 98 | or/69-97 | 995236 |
| 99 | 5 and 98 | 211 |
| 100 | 68 or 99 | 213 |
| 101 | 24 or 52 or 100 | 499 |
| 102 | editorial/ or letter/ or case report/ or (editorial or letter).pt. | 4850517 |
| 103 | 101 not 102 | 452 |
| 104 | (conference or "conference paper" or "conference proceeding" or "conference proceeding article" or | 5806595 |

| | | |
|---|---|---|
| | "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. | |
| 105 | 103 not 104 | 288 |
| 106 | 103 and 104 | 164 |
| 107 | limit 106 to yr="2017 - 2024" | 95 |
| 108 | 105 or 107 | 383 |

### Updated review (2024-2025)

**Table 98. Cochrane Library (CDSR) search strategy (2024-2025).**

| Search number, # | Search Algorithm | Search Yield |
|---|---|---|
| 1 | MeSH descriptor: [Uveal Neoplasms] explode all trees | 168 |
| 2 | MeSH descriptor: [Choroid Neoplasms] explode all trees | 66 |
| 3 | #1 or #2 | 168 |
| 4 | MeSH descriptor: [Melanoma] explode all trees | 2761 |
| 5 | #3 and #4 | 161 |
| 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 | 314 |
| 7 | aderhautmelanom*:ti | 0 |
| 8 | #6 or #7 | 314 |
| 9 | #5 or #8 in Cochrane Reviews | 0 |

**Table 99. Epistemonikos search strategy (2024-2025).**

| Search number, # | Search Algorithm | Search Yield |
|---|---|---|
| 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*))) | 94 |

**Table 100. MEDLINE (via OvidSP interface) search strategy (2024-2025).**

| Search number, # | Search Algorithm | Search Yield |
|---|---|---|
| 1 | exp Uveal Neoplasms/ | 11286 |
| 2 | exp Choroid Neoplasms/ | 5752 |
| 3 | or/1-2 | 11286 |
| 4 | exp Melanoma/ | 114651 |

| | | |
|---|---|---|
| 5 | 3 and 4 | 8138 |
| 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. | 9880 |
| 7 | 5 or 6 | 11626 |
| 8 | economics/ | 27545 |
| 9 | exp "costs and cost analysis"/ | 276888 |
| 10 | economics, dental/ | 1922 |
| 11 | exp "economics, hospital"/ | 26130 |
| 12 | economics, medical/ | 9302 |
| 13 | economics, nursing/ | 4013 |
| 14 | economics, pharmaceutical/ | 3156 |
| 15 | (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. | 1191242 |
| 16 | (expenditure$ not energy).ti,ab. | 40678 |
| 17 | (value adj1 money).ti,ab. | 42 |
| 18 | budget$.ti,ab. | 39203 |
| 19 | 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 | 1361928 |
| 20 | ((energy or oxygen) adj cost).ti,ab. | 5100 |
| 21 | (metabolic adj cost).ti,ab. | 1863 |
| 22 | ((energy or oxygen) adj expenditure).ti,ab. | 31120 |
| 23 | 20 or 21 or 22 | 36972 |
| 24 | 19 not 23 | 1353340 |
| 25 | exp models, economic/ or ((economic$ or financ$ or cost$ or budget$ or expen$ or price or pricing or markov$) and model$).ti,ab. | 313897 |
| 26 | 24 or 25 | 1417594 |
| 27 | 7 and 26 | 109 |
| 28 | exp Health Care Costs/ | 74654 |
| 29 | exp Employment/ | 105279 |
| 30 | exp Work/ | 73032 |
| 31 | Efficiency/ | 16098 |
| 32 | Absenteeism/ | 10054 |
| 33 | "Cost of Illness"/ | 33886 |
| 34 | "Length of Stay"/ | 109365 |
| 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. | 3300 |
| 36 | (productivity adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. | 4619 |

| | | |
|---|---|---|
| 37 | ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab. | 14617 |
| 38 | llsi.ti,ab. | 19 |
| 39 | (cost$ adj2 (illness or disease$ or sickness$ or care or healthcare)).ti,ab. | 62282 |
| 40 | (burden$ adj2 (illness or disease$ or sickness$ or care or healthcare)).ti,ab. | 57351 |
| 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$)).ti,ab. | 150104 |
| 42 | ((allowance or status or long-term or pension$ or benefit$) adj2 disab$).ti,ab. | 18605 |
| 43 | ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab. | 2364 |
| 44 | budget$ impact$.ti,ab. | 2640 |
| 45 | budget$ implicat$.ti,ab. | 95 |
| 46 | resource$ use$.ti,ab. | 14785 |
| 47 | resource$ utili$.ti,ab. | 18656 |
| 48 | resource$ usage.ti,ab. | 771 |
| 49 | (length adj2 stay$).ti,ab. | 90713 |
| 50 | (hospital$ adj2 stay$).ti,ab. | 130210 |
| 51 | (duration adj2 stay$).ti,ab. | 5518 |
| 52 | extended stay$.ti,ab. | 315 |
| 53 | prolonged stay$.ti,ab. | 1285 |
| 54 | ((hospitali?ation$ or hospitali?ed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. | 12009 |
| 55 | economic consequenc$.ti,ab. | 5211 |
| 56 | or/28-55 | 795951 |
| 57 | 7 and 56 | 39 |
| 58 | quality adjusted life year/ | 17518 |
| 59 | (quality adjusted or adjusted life year$).ti,ab,kw. | 27358 |
| 60 | (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. | 16589 |
| 61 | (illness state$1 or health state$1).ti,ab,kw. | 9226 |
| 62 | (hui or hui1 or hui2 or hui3).ti,ab,kw. | 2183 |
| 63 | (multiattribute$ or multi attribute$).ti,ab,kw. | 1559 |
| 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. | 22556 |
| 65 | utilities.ti,ab,kw. | 10430 |
| 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 | 20465 |

| | | |
|---|---|---|
| | 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. | |
| 67 | (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. | 6938 |
| 68 | (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. | 28847 |
| 69 | (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw. | 2624 |
| 70 | "quality of life"/ and (health adj3 status).ti,ab,kw. | 12740 |
| 71 | (quality of life or qol).ti,ab,kw. and "cost-benefit analysis"/ | 18602 |
| 72 | or/58-71 | 118814 |
| 73 | 7 and 72 | 19 |
| 74 | quality-adjusted life years/ or quality of life/ | 315965 |
| 75 | (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. | 32946 |
| 76 | (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. | 2907 |
| 77 | (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. | 8499 |
| 78 | (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab. | 1080 |
| 79 | (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. | 478 |
| 80 | (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab. | 814 |
| 81 | (short form$ or shortform$).ti,ab. | 49611 |
| 82 | ("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or EORTC-QLQ).ti,ab. | 6280 |
| 83 | "quality of life".ti,ab. | 432503 |
| 84 | (Quality adjusted life or Quality-adjusted-life).ti,ab. | 19523 |
| 85 | (euroqol or euro qol or euroqual or euro qual or eq5d or eq 5d or eq-5d or eq5-d or eq-sdq or eqsdq).ti,ab. | 19673 |
| 86 | (qol or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. | 87882 |
| 87 | (hye or hyes).ti,ab. | 78 |
| 88 | health$ 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. | 2177 |
| 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. | 1331 |
| 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. | 8044 |
| 92 | (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab. | 24166 |
| 93 | (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab. | 13032 |
| 94 | (15D or 15-D or "15 dimension").ti,ab. | 6529 |
| 95 | (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab. | 553 |
| 96 | illness state$.ti,ab. | 188 |
| 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. | 52544 |
| 98 | (utilities or disutili$).ti,ab. | 10869 |
| 99 | (Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab. | 1627 |
| 100 | ((patient$ 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. | 192913 |
| 101 | or/74-100 | 768664 |
| 102 | 7 and 101 | 146 |
| 103 | 73 or 102 | 147 |
| 104 | 27 or 57 or 103 | 278 |
| 105 | editorial/ or letter/ or case report/ or (editorial or letter or case reports).pt. | 4241197 |
| 106 | 104 not 105 | 253 |

**Table 101. EMBASE (via OvidSP interface) search strategy (2024-2025)**

| Search number, # | Search Algorithm | Search Yield (updated January 2024) |
|---|---|---|
| 1 | exp uvea tumor/ or exp choroid tumor/ | 19827 |

| | | |
|---|---|---|
| 2 | exp melanoma/ | 216826 |
| 3 | 1 and 2 | 14099 |
| 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. | 13287 |
| 5 | 3 or 4 | 16466 |
| 6 | health-economics/ | 37098 |
| 7 | exp economic-evaluation/ | 381885 |
| 8 | exp health-care-cost/ | 364705 |
| 9 | exp pharmacoeconomics/ | 250503 |
| 10 | or/6-9 | 810794 |
| 11 | (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. | 1548858 |
| 12 | (expenditure$ not energy).ti,ab. | 54701 |
| 13 | (value adj2 money).ti,ab. | 3219 |
| 14 | budget$.ti,ab. | 51434 |
| 15 | or/11-14 | 1597353 |
| 16 | 10 or 15 | 1985708 |
| 17 | (metabolic adj cost).ti,ab. | 2013 |
| 18 | ((energy or oxygen) adj cost).ti,ab. | 5377 |
| 19 | ((energy or oxygen) adj expenditure).ti,ab. | 39755 |
| 20 | or/17-19 | 45865 |
| 21 | 16 not 20 | 1976269 |
| 22 | economic model/ or ((economic$ or financ$ or cost$ or budget$ or expen$ or price or pricing or markov$) and model$).ti,ab. | 394187 |
| 23 | 21 or 22 | 2055150 |
| 24 | 5 and 23 | 330 |
| 25 | exp "health care cost"/ | 364705 |
| 26 | exp employment/ | 140933 |
| 27 | exp work/ | 472489 |
| 28 | "cost of illness"/ | 22107 |
| 29 | "length of stay"/ | 309003 |
| 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. | 4093 |
| 31 | (productivity adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. | 6426 |
| 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. | 20235 |

| | | |
|---|---|---|
| 33 | llsi.ti,ab. | 20 |
| 34 | (cost$ adj2 (illness or disease$ or sickness$ or care or healthcare)).ti,ab. | 96140 |
| 35 | (burden$ adj2 (illness or disease$ or sickness$ or care or healthcare)).ti,ab. | 86565 |
| 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$)).ti,ab. | 195214 |
| 37 | ((allowance or status or long-term or pension$ or benefit$) adj2 disab$).ti,ab. | 29601 |
| 38 | ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab. | 3531 |
| 39 | budget$ impact$.ti,ab. | 6748 |
| 40 | budget$ implicat$.ti,ab. | 142 |
| 41 | resource$ use$.ti,ab. | 22199 |
| 42 | resource$ utili$.ti,ab. | 33211 |
| 43 | resource$ usage.ti,ab. | 1037 |
| 44 | (length adj2 stay$).ti,ab. | 169229 |
| 45 | (hospital$ adj2 stay$).ti,ab. | 215822 |
| 46 | (duration adj2 stay$).ti,ab. | 8670 |
| 47 | extended stay$.ti,ab. | 482 |
| 48 | prolonged stay$.ti,ab. | 2126 |
| 49 | ((hospitali?ation$ or hospitali?ed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. | 21132 |
| 50 | economic consequenc$.ti,ab. | 6582 |
| 51 | or/25-50 | 1694804 |
| 52 | 5 and 51 | 194 |
| 53 | quality adjusted life year/ | 39637 |
| 54 | (quality adjusted or adjusted life year$).ti,ab,kw. | 39182 |
| 55 | (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. | 30286 |
| 56 | (illness state$1 or health state$1).ti,ab,kw. | 16077 |
| 57 | (hui or hui1 or hui2 or hui3).ti,ab,kw. | 3496 |
| 58 | (multiattribute$ or multi attribute$).ti,ab,kw. | 1738 |
| 59 | (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. | 35157 |
| 60 | utilities.ti,ab,kw. | 16528 |
| 61 | (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. | 35730 |

| | | |
|---|---|---|
| 62 | (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. | 10152 |
| 63 | (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. | 48853 |
| 64 | (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw. | 3866 |
| 65 | "quality of life"/ and (health adj3 status).ti,ab,kw. | 22477 |
| 66 | (quality of life or qol).ti,ab,kw. and "cost-benefit analysis"/ | 7246 |
| 67 | or/53-66 | 190700 |
| 68 | 5 and 67 | 33 |
| 69 | quality adjusted life year/ or quality of life index/ | 42974 |
| 70 | Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ | 55826 |
| 71 | "International Classification of Functioning, Disability and Health"/ or "Ferrans and Powers Quality of Life Index"/ | 3987 |
| 72 | (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix).ti,ab. | 52984 |
| 73 | (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. | 3236 |
| 74 | (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. | 13257 |
| 75 | (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab. | 1925 |
| 76 | (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. | 561 |
| 77 | (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab. | 1283 |
| 78 | (short form$ or shortform$).ti,ab. | 66398 |
| 79 | ("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or EORTC-QLQ).ti,ab. | 13087 |
| 80 | "quality of life".ti,ab. | 668165 |
| 81 | (Quality adjusted life or Quality-adjusted-life).ti,ab. | 29458 |
| 82 | (euroqol or euro qol or euroqual or euro qual or eq5d or eq 5d or eq-5d or eq5-d or eq-sdq or eqsdq).ti,ab. | 34691 |
| 83 | (qol or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. | 153407 |
| 84 | (hye or hyes).ti,ab. | 202 |
| 85 | health$ year$ equivalent$.ti,ab. | 41 |

| | | |
|---|---|---|
| 86 | health$ year$ equivalent$.ti,ab. | 41 |
| 87 | (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. | 3485 |
| 88 | (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab. | 1683 |
| 89 | (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab. | 9540 |
| 90 | (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab. | 39602 |
| 91 | (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab. | 19136 |
| 92 | 15d.ti,ab. | 3071 |
| 93 | (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab. | 854 |
| 94 | illness state$.ti,ab. | 275 |
| 95 | (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. | 80234 |
| 96 | (utilities or disutili$).ti,ab. | 17321 |
| 97 | (Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab. | 2091 |
| 98 | ((patient$ 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. | 302534 |
| 99 | or/69-97 | 1089453 |
| 100 | 5 and 98 | 248 |
| 101 | 68 or 99 | 250 |
| 102 | 24 or 52 or 100 | 660 |
| 103 | editorial/ or letter/ or case report/ or (editorial or letter).pt. | 5062908 |
| 104 | 101 not 102 | 603 |
| 105 | (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 | 6172183 |

| | | |
|---|---|---|
| | review" or "journal conference abstract" or "journal conference paper" or "journal conference review").pt. | |
| 106 | 103 not 104 | 411 |
| 107 | 103 and 104 | 192 |
| 108 | limit 106 to yr="2017 - 2025" | 120 |

### J.1.7 Results of the literature search

#### J.1.7.1 Study selection

**Updated review (2021-2024)**

An overview of the flow of articles through the screening and selection process during this SLR (CE, HRQoL, and cost and healthcare resource use) are depicted in the PRISMA flow diagram shown in Figure 28. In this current update 687 records were identified from the electronic database searches. After deduplication, 140 electronic search records (Table 102) and 3 additional records found via handsearching were assessed for relevance. After title and abstract screening by 2 independent reviewers, a total of 20 citations were included for full-text screening. The full list of records excluded at the full-text screening phase is presented in Table 103. As in the existing review, the main reason for exclusion was the wrong population such as patients with non-metastatic UM. This resulted in 5 records (5 publications and 4 studies) being identified that matched the inclusion criteria; 1 CE study (Figure 30) and 3 HRQoL and utility studies (Figure 29). The only identified CE study in this review update utilizing clinical trial data (Figure 31), was from the US payer perspective and therefore cannot be applied to other countries. Furthermore, inconsistencies in use of HRQoL tools in the three studies limit the ability to review patient impact of the various treatments that have been trialed for metastatic UM. Because of these limitations, none of the studies were considered to be suitable to inform the decision problem or the health economic model (Table 104).

**Table 102. Electronic database search results.**

| Source | Records found | After deduplications |
|---|---|---|
| **CDSR** | 0 | 0 |
| **Epistemonikos** | 80 | 23 |
| **MEDLINE** | 224 | 49 |
| **Embase** | 383 | 68 |
| **Total** | **687** | **140** |

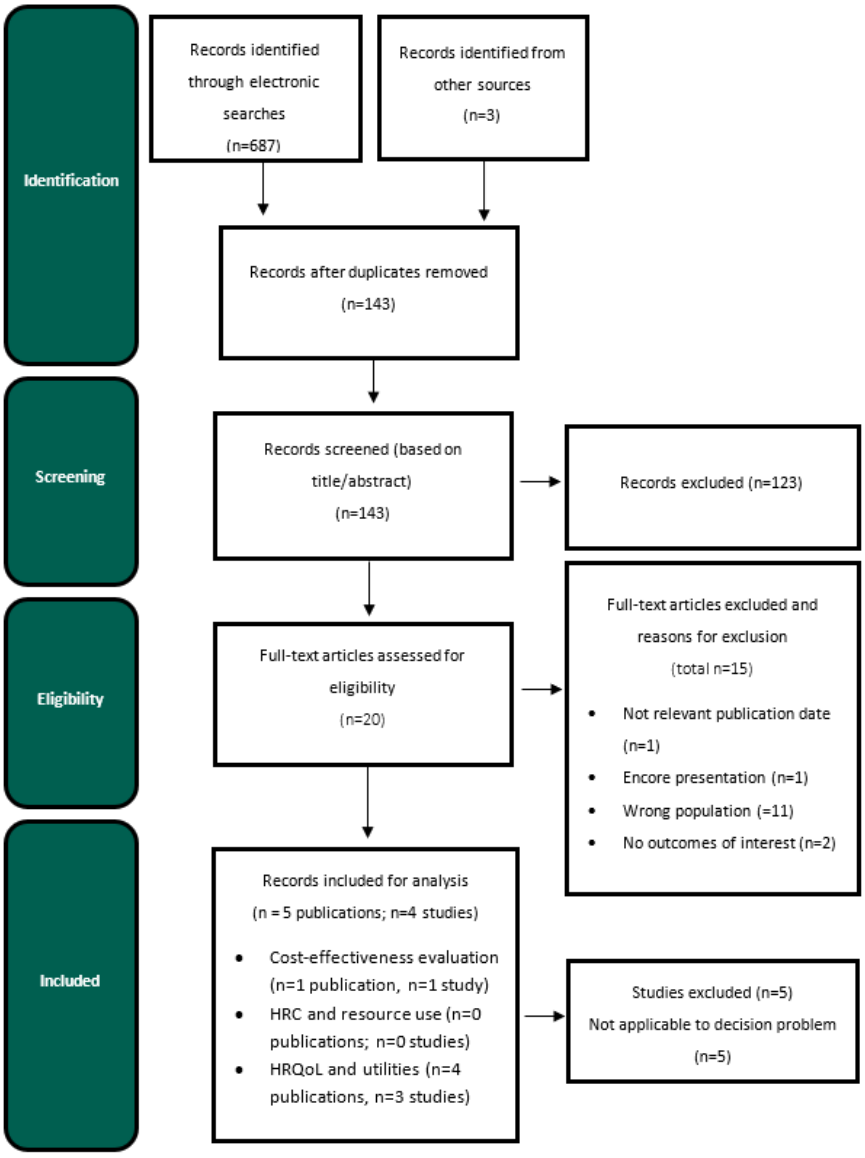


**Figure 28. PRISMA flow diagram for 2021-2024 review update**


**Figure 29. HRQoL and utilities literature review flow diagram: 2021-2024 review update.**


**Figure 30. Cost-effectiveness systematic literature review flow diagram: 2021-2024 review update.**


**Figure 31. Healthcare related costs and resource use systematic literature review flow diagram: 2021-2024 review update.**

**Table 103. List of records excluded from this study based on a full-text review and the reason for each exclusion: 2021-2024 review update.**

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| **Brown** | 2022 | Prediction of all-cause mortality from 24 month trajectories in patient-reported psychological, clinical and quality of life outcomes in uveal melanoma patients | Not relevant publication date |
| **Brown** | 2023 | Prevalence, temporal course and risk factors for phantom eye symptoms in uveal melanoma | Not relevant population |
| **Cappelli** | 2023 | PP05 Presentation Time: 5:06 PM: I-125 Eye-Plaque Seed Economics: To Re-Use or to Not Re-Use? | Not relevant population |
| **Dupere** | 2021 | Intensity modulated high dose rate ocular brachytherapy using Se-75 | Not relevant population |
| **Fusetti** | 2023 | Experiences of a Multidisciplinary Approach in a European Comprehensive Cancer Center | Not relevant population |
| **Gollrad** | 2021 | Quality of life and treatment-related burden during ocular proton therapy: a prospective trial of 131 patients with uveal melanoma | Not relevant population |
| **Gollard** | 2022 | Impact of Adjuvant Ocular Interventions on the Quality of Life of Patients with Uveal Melanoma after Proton Beam Therapy | Not relevant population |
| **Heudobler** | 2023 | A prospective phase I and consecutive phase II, two-arm, randomized multi-center trial of temsirolimus in combination with pioglitazone, etoricoxib and metronomic low-dose trofosfamide versus dacarbazine (DTIC) in patients with advanced melanoma (MEL001) | Not relevant population |
| **Maniraho** | 2023 | Quality-of-life measurement in high-risk patients with uveal melanoma receiving adjuvant sunitinib or valproic acid | Not relevant population |
| **Maniraho** | 2023 | Quality-of-life measurement in high-risk patients with uveal melanoma receiving adjuvant sunitinib or valproic acid | Not relevant population |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| **Piperno-Neumann** | 2022 | Early together: A randomized phase III study of early palliative care in metastatic uveal melanoma (MUM) | No relevant outcome |
| **Vigneswaran** | 2022 | Temporal evolution in quality of life following melphalan percutaneous hepatic perfusion for patients with metastatic uveal melanoma | Encore presentation |
| **Westley** | 2023 | Outcomes of Tolerability, Acute Toxicity and Quality of Life from MR-Guided Radiation Therapy (1.5T MR-Linac) for Liver Metastases in the MOMENTUM Study | Not relevant population |
| **Mc Glacken-Byrne** | 2023 | Ocular oncology service during the COVID-19 outbreak: uveal melanoma characteristics presenting in 2019 compared to 2020. | Not relevant population |
| **Ribeiro** | 2023 | 1131P Management of metastatic uveal melanoma (MUM) patients on tebentafusp in a real-world setting. | Not relevant outcome |

**Table 104. List of studies excluded after analysis: 2021-2024 review update.**

| Author, Year of publication | Title | |
|---|---|---|
| **CE** | | |
| **Luo, 2023** | CE analysis of an orphan drug tebentafusp in patients with metastatic uveal melanoma and a call for value-based pricing | |
| **HRQoL and utilities** | | **Use of HRQoL/utilities tool** |
| **Rabsahl et al. 2023** | Depression and anxiety in patients with uveal melanoma undergoing curative proton treatment-A prospective study | PHQ-9/ GAD-7 |
| **Vigneswaran 2023** | Temporal evolution in quality of life following melphalan percutaneous hepatic perfusion for patients with metastatic uveal melanoma | FACT-G |
| **Tong 2023** | Quality of life analysis of patients treated with percutaneous hepatic perfusion for uveal melanoma liver metastases. | EORTC-QLQ C30 |

### Updated review (2024-2025)

An overview of the flow of articles through the screening and selection process during this SLR (CE, HRQoL, and cost and healthcare resource use) are depicted in the PRISMA flow diagram shown in Figure 32. In this current update, 878 records were identified from the electronic searches. After deduplication, 178 electronic search records were assessed for relevance. After title and abstract screening by 2 independent reviewers, a total of 162 citations were excluded. Subsequently, 16 citations were included for full-text screening. Twelve citations failed to meet the inclusion criteria at the full-text screening stage. A

detailed list of records excluded at this stage are outlined in Table 106. The most frequent reasons for exclusion at the full-text screening stage was non-relevant population (n=10). This resulted in 4 records (2 full-text articles, 1 conference abstract, and 1 HTA report) being identified that matched the inclusion criteria. The only identified CE study in this review was the HTA report (Figure 34), adopting the Canadian publicly funded healthcare payer perspective and can thus not be applied to a Danish setting. One study identified in this review reported resource use outcomes in patients with metastatic UM (Figure 35). However, the study evaluated clinical outcomes from a tebentafusp UK expanded access program and is therefore not applicable to a Danish setting. The two studies reporting HRQoL and utilities (Figure 33) included populations that did not match that of the Danish population. Because of these limitations, none of the studies were considered to be suitable to inform the decision problem or the health economic model.

**Table 105. Electronic database search results.**

| Source | Records found | After deduplications |
|---|---|---|
| **CDSR** | 0 | N/A |
| **Epistemonikos** | 94 | 13 |
| **MEDLINE** | 253 | 35 |
| **Embase** | 531 | 130 |
| **Total** | **878** | **178** |

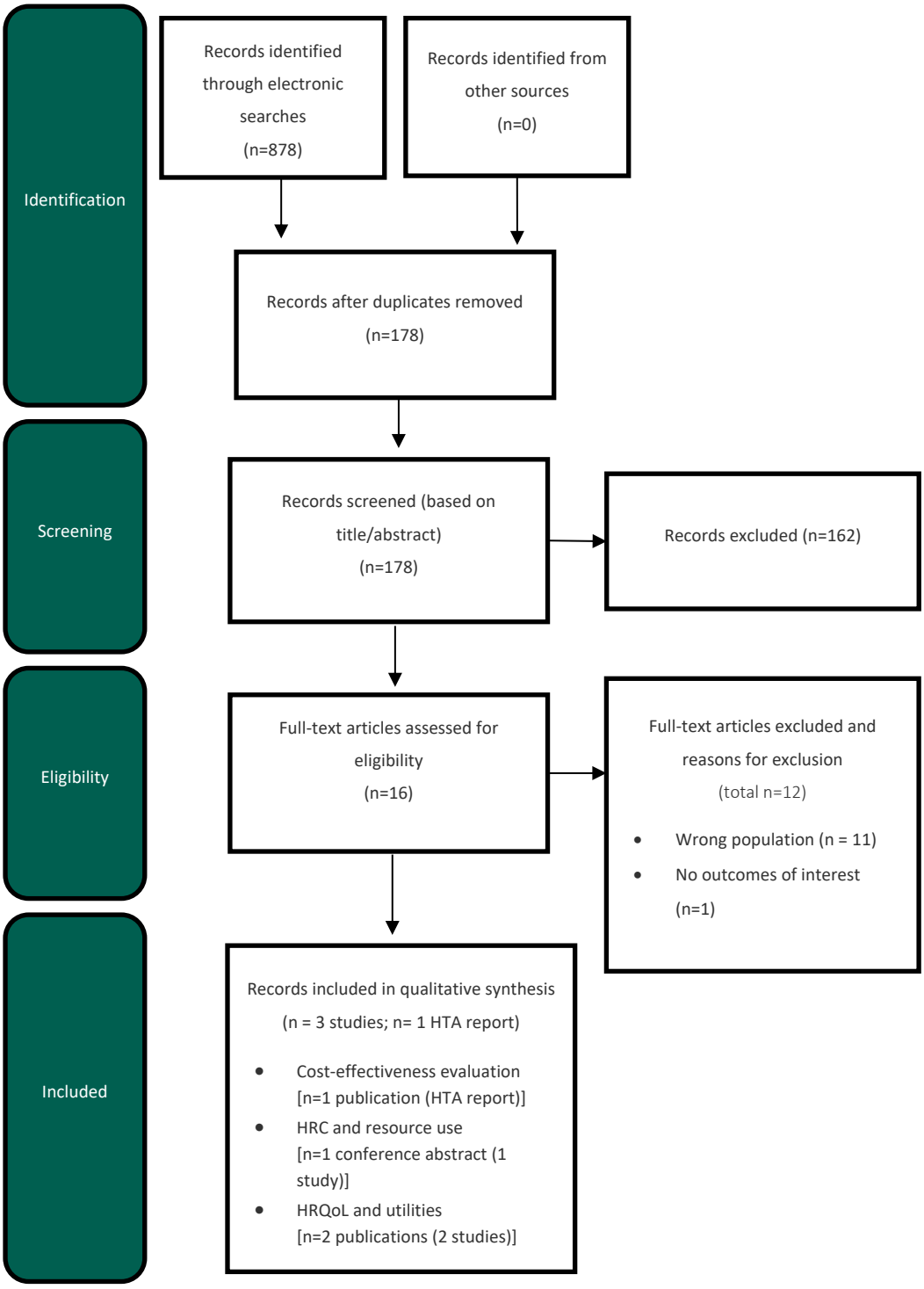


**Figure 32. PRISMA flow diagram for 2024-2025 review update**


**Figure 33. HRQoL and utilities literature review flow diagram: 2024-2025 review update**

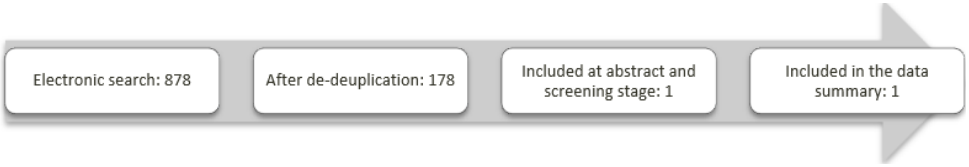


**Figure 34. Cost-effectiveness systematic literature review flow diagram: 2024-2025 review update**


**Figure 35. Healthcare related costs and resource use literature review flow diagram: 2024-2025 review update**

**Table 106. List of records excluded from this study based on a full-text review and the reason for each exclusion: 2024-2025 review update.**

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| Cappelli | 2024 | I-125 eye-plaque seed economics: To re-use or to not re-use? A single institutional cost savings analysis of re-using I-125 radioactive seeds for eye-Plaque brachytherapy | Not relevant population |
| Mensah | 2024 | Assessment of Social Vulnerabilities of Care and Prognosis in Adult Ocular Melanomas in the US | Not relevant population |
| Dennis | 2025 | Surgical Costs of Enucleation Versus Plaque Brachytherapy for Intraocular Malignancy: A Time-Driven Activity-Based Costing Approach | Not relevant population |
| Beneke | 2024 | Clinical outcomes of uveal melanoma patients in the emergency department | Not relevant population |
| Kolbe | 2024 | Development of a multimodal therapy concept for the rehabilitation of people with uveal melanoma | Not relevant population |
| Rault | 2024 | Facilitating patient-oncologist communication in advanced treatment-resistant cancer: development and feasibility testing of a question prompt list | Not relevant population |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| Ng | 2024 | What matters most to people with metastatic uveal melanoma? A qualitative study to inform future measurement of health-related quality of life | Not relevant outcomes |
| Brown | 2024 | Prevalence, temporal course and risk factors for phantom eye symptoms in uveal melanoma | Not relevant population |
| Tong | 2024 | Correction to: Quality of Life Analysis of Patients Treated with Percutaneous Hepatic Perfusion for Uveal Melanoma Liver Metastases | Not relevant outcome |
| Davidson | 2024 | Local anaesthesia under sedation versus general anaesthesia for brachytherapy-treated patients with uveal melanoma: A patient-reported outcome study | Not relevant population |
| Mangana[a] | 2017 | Multicenter, real-life experience with checkpoint inhibitors and targeted therapy agents in advanced melanoma patients in Switzerland | Not relevant population |
| Scherz[a] | 2017 | Case management to increase quality of life after cancer treatment: A randomized controlled trial | Not relevant population |

[a] Publications with relevant indexing or some updates in Ovid made after the 2024

**Table 107. List of studies excluded after analysis: 2024-2025 review update.**

| Author, Year of publication | Title | |
|---|---|---|
| **CE** | | |
| CADTH, 2023 | CADTH Reimbursement Recommendation: Tebentafusp (Kimmtrak) | |
| **HRQoL and utilities** | | **Population** |
| Olofsson Bagge et al., 2024 | Survival and Quality of Life after Iolated Hepatic Perfusion with Melphalan as a Treatment for Uveal Melanoma Liver Metastases – Final Results from the Phase III Randomized Controlled Trial SCANDIUM | Patients with liver metastases from uveal melanoma |
| Tong et al., 2024 | Quality of Life Analysis of Patients Treated with Percutaneous Hepatic Perfusion for Uveal Melanoma Liver Metastases | Patients with liver metastases from uveal melanoma treated with percutaneous hepatic perfusion with melphalan |
| **HRCs and resource use** | | |
| Nathan et al., 2024 | Clinical outcomes from a tebentafusp UK expanded access program in patients with metastatic uveal melanoma | |

# Appendix K. Costs

The cost of DKK 191.00 for complete blood count is the total cost of the various laboratory tests included in the respective blood test and is presented in Table 108.

**Table 108. Cost of complete blood count.**

| Resource | Unit cost, DKK | NPU code | Source |
|---|---|---|---|
| Hemoglobin;B | 18 | NPU02319 | Rigshospitalets labportal [71] |
| Leukocytes | 18 | NPU02593 | |
| Differential blood count (Basophilocytes;B, Eosinophilocytes;B, Lymphocytes;B, Metamyelocytes. +Myelocytes. +Promyelocytes;B, Monocytes;B, neutrophils;B) | 18 | NPU04100 (NPU01349, NPU01933, NPU02636, NPU026631, NPU02840, NPU02902) | |
| C-Reactive Protein [CRP];P | 20 | NPU19748 | |
| Sodium;P | 14 | NPU03429 | |
| Potassium;P | 14 | NPU03230 | |
| Alanine transaminase [ALAT];P | 14 | NPU19651 | |
| Aspartate transaminase [ASAT];P | 16 | NPU19654 | |
| Bilirubin;P | 14 | NPU01370 | |
| Basic phosphatase;P | 13 | NPU27783 | |
| Creatinine;P | 14 | NPU04998 | |
| Thrombocytes | 18 | NPU03568 | |
| **Total** | **191.00** | | |

The cost of DKK 247.00 for complete metabolic panel is the total cost of the various laboratory tests included in the respective blood test and is presented in Table 109.

**Table 109. Cost of complete metabolic panel.**

| Resource | Unit cost, DKK | NPU code | Source |
|---|---|---|---|
| Bicarbonate;P | 20 | NPU02410 | Rigshospitalets labportal [71] |
| Albumin;P | 14 | NPU19673 | |
| Chloride;P | 72 | NPU01536 | |
| Glucose;P | 14 | NPU02192 | |
| Sodium;P | 14 | NPU03429 | |
| Potassium;P | 14 | NPU03230 | |
| Alanine transaminase [ALAT];P | 14 | NPU19651 | |
| Aspartate transaminase [ASAT];P | 16 | NPU19654 | |
| Bilirubin;P | 14 | NPU01370 | |
| Basic phosphatase;P | 13 | NPU27783 | |
| Creatinine;P | 14 | NPU04998 | |

| Resource | Unit cost, DKK | NPU code | Source |
|---|---|---|---|
| Protein;P | 14 | NPU03278 | |
| Carbamide;P | 14 | NPU01459 | |
| **Total** | **247.00** | | |

# Appendix L. IMCgp100-202 results and figures

## L.1 Study design

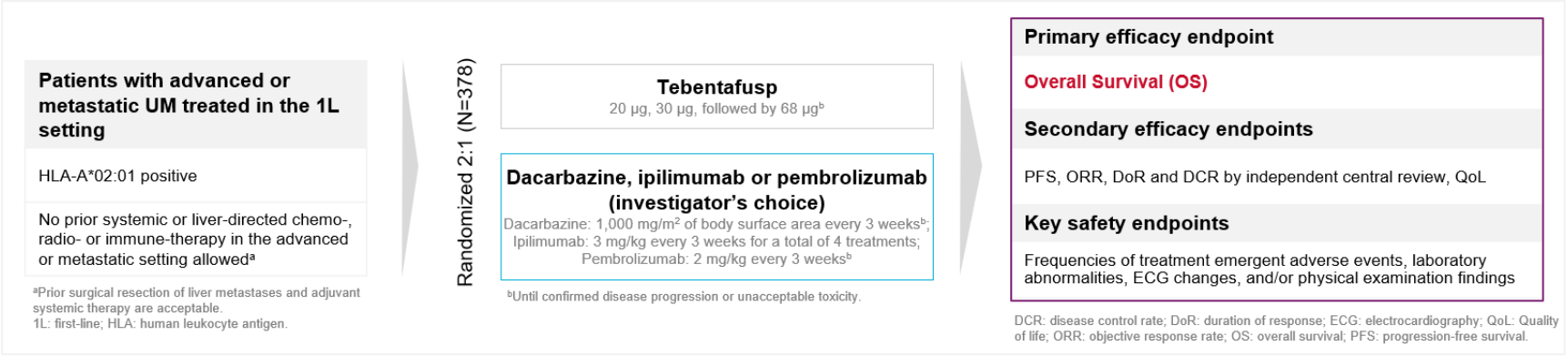


**Figure 36. IMCgp100-202 study design** [10,13,80].

## L.2 Objective response rate results

### L.2.1 Objective response rate and disease control – DCO October 2020

ORR is defined as the number of patients with a best overall response (BoR) of Complete response (CR) or Partial response (PR) divided by the number of patients for each treatment group in the ITT population [13]. The BoR is defined as the best response designation up until 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 was conducted using a Mantel-Haenszel 2-sided test statistic stratified by LDH status using a logistic regression model, with the treatment group as a single covariate, stratified by LDH status (LDH above ULN versus normal LDH) [13].

DCR is defined as the proportion of patients with a BoR of CR or PR, or 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 group. This analysis will then be repeated using the immune-related RECIST criteria for patients in the IMCgp100-202 group using an OR (immune-related PR or immune-related CR) and BoR of immune-related SD over 24 weeks [13].

The ORR in the tebentafusp group was 9% [95% CI, 6; 13] and 5% [95% CI 2; 10] in the control group, while the DCR was 46% [96% CI, 39; 52] in the tebentafusp group and 27% [95% CI, 20; 36] in the control group, see [13].

**Table 110. Best overall RECIST response rate – DCO October 2020** [13].

| | Tebentafusp (n=252), n, (%) | Investigator's Choice (n=126), n, (%) |
|---|---|---|
| **ORR** | 23 (9%) | 6 (5%) |
| **CR** | 1 (0.4%) | 0 |
| **PR** | 22 (9%) | 6 (5%) |
| **SD** | 92 (37%) | 28 (22%) |
| **PD** | 131 (52%) | 78 (62%) |
| **Non-evaluable/Not applicable** | 6 (2%) | 14 (11%) |
| **DCR-12w (CR/PR/SD)** | 115 (46%) | 34 (27%) |
| **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
Source: [13]

### L.2.2 Objective response rate and disease control – DCO July 2023

In the 3-year analysis, the ORR in the tebentafusp group was 11% and 5% in the control group, while the PD was 52% the tebentafusp group and 65% in the control group, see Table 111 [10].

**Table 111. Best overall RECIST response rate – DCO July 2023.**

| | Tebentafusp (n=252), n (%) | Investigator's Choice (n=126), n (%) |
|---|---|---|
| **Best Overall Reponse** | | |
| CR | 1 (<1%) | 0 |
| PR | 27 (11%) | 6 (5%) |
| SD | 87 (35%) | 28 (22%) |
| PD | 132 (52%) | 82 (65%) |
| NE | 5 (2%) | 10 (8%) |
| **Objective response** | 28 (11%) | 6 (5%) |
| Stratified OR for objective response | 2.46 [1.00; 6,06] | Reference |
| **Disease control at 12 weeks** | 115 (46%) | 34 (27%) |
| Stratified OR for disease control | 2.34 [1.45; 3.76] | Reference |

Disease control was defined as CR, PR or SD for ≥ 12 weeks
Stratified CMH test stratified by LDH status
Source: [10]

## L.3 Overall survival results

### L.3.1 DCO October 2020

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 [36,37]. OS was followed continuously while patients were treated and every 3 months in the follow-up phase [54]. The date of clinical cut-off for the primary analysis was October 13, 2020, corresponding to a median follow-up of 14.1 months [13].

The following result was observed at the first data cutoff: 150 deaths had occurred in the ITT population; 87 deaths were observed in the tebentafusp group, while 63 deaths occurred in the control group. The 1-year OS was 73% [95% CI, 66; 79] in the tebentafusp group and 59% [95% CI, 48; 67] in the control group. The estimated OS was 21.7 months [95% CI, 18.6; 28.6] and 16.0 months [95% CI, 9.7; 18.4] in the tebentafusp group and control group, respectively and the HR for death was 0.51 [95% CI, 0.37; 0.71] in favor of tebentafusp, see Figure 37 [13].

In the landmark-based analysis, patients with disease progression as the best response before day 100, an OS of 15.3 months [95% CI, 12.0; not reached] in the tebentafusp group was observed compared to 6.5 months [95% CI, 4.9; 13.4 months] in the control group with a HR for death of 0.43 [95% CI, 0.27; 0.68], see Figure 38 [13].

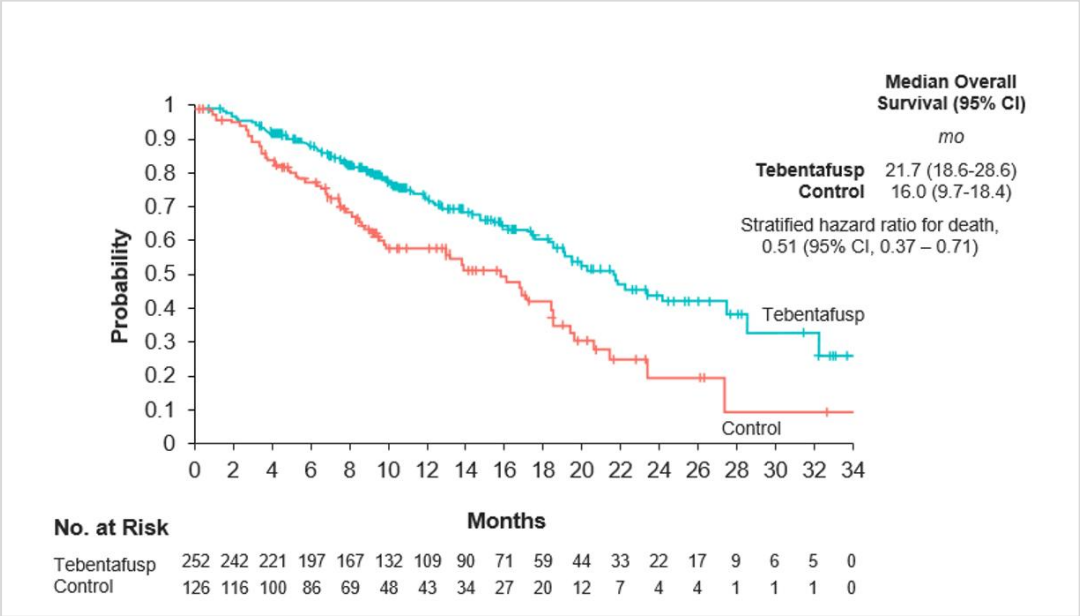


**Figure 37. Kaplan-Meier estimates of OS according to treatment group, DCO October 2020** [13].

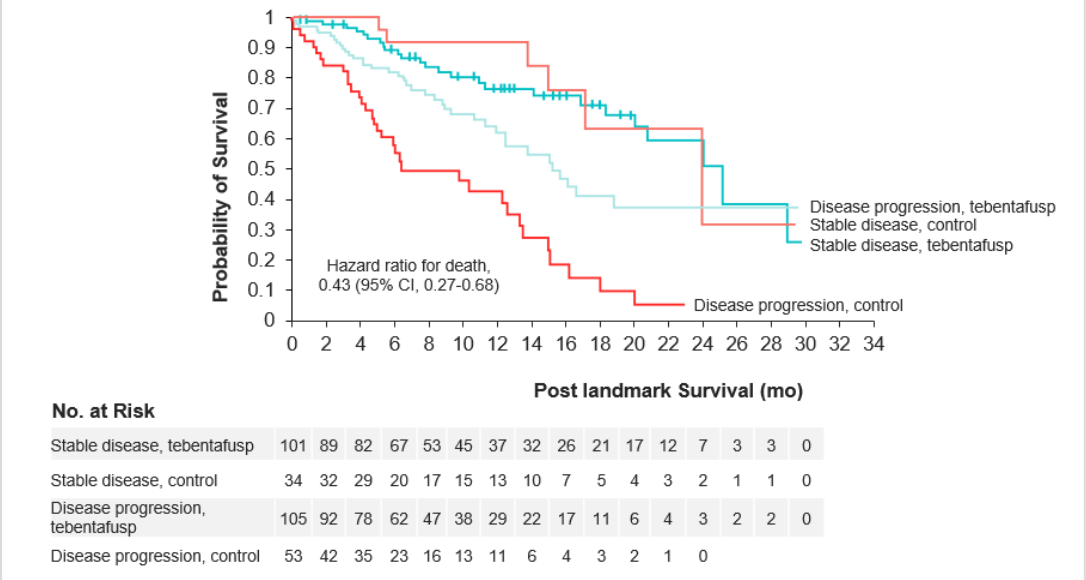


**Figure 38. Landmark OS in patients with BoR of SD or disease progression, DCO October 2020** [13].

### L.3.2 DCO July 2023

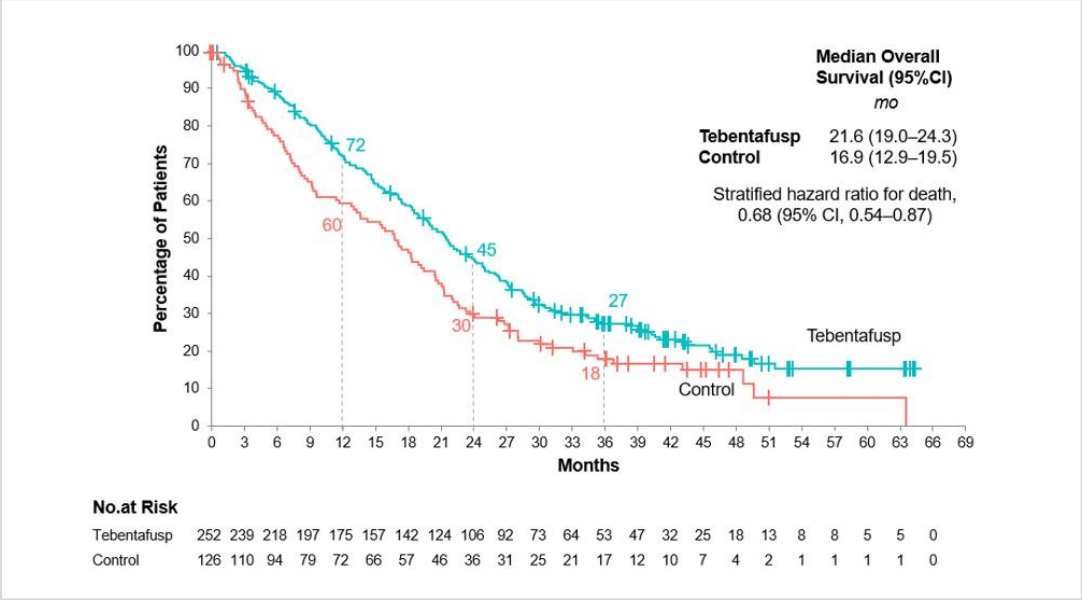


**Figure 39. Kaplan-Meier estimates of OS according to treatment group, DCO July 2023.**

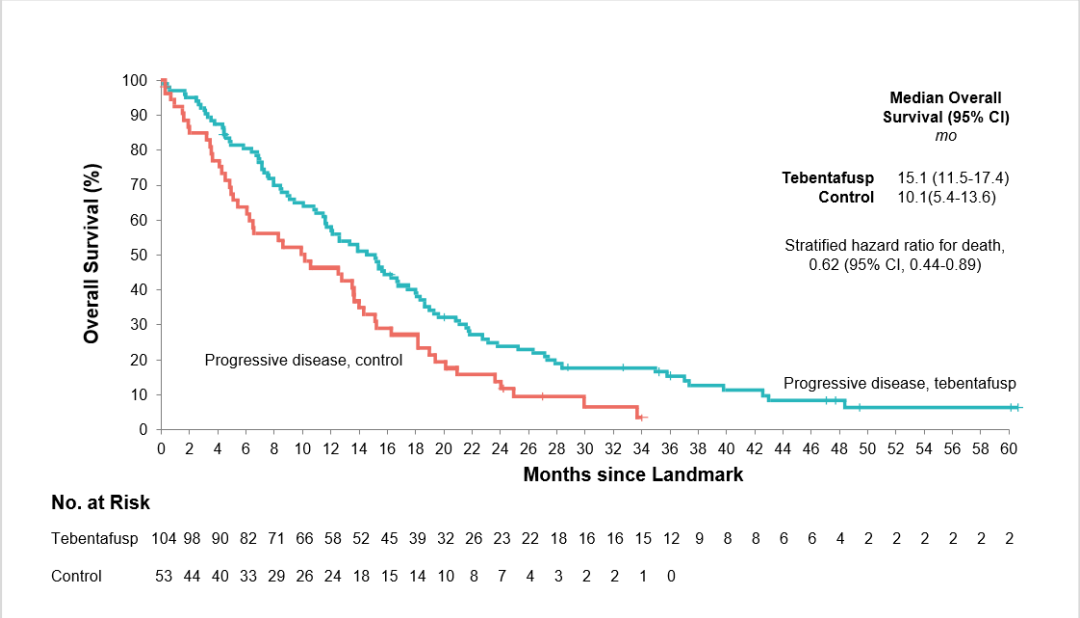


**Figure 40. Landmark OS in patients with BoR of SD or disease progression, DCO July 2023** [10].

## L.4 Overall survival subgroup analyses results

### L.4.1 DCO October 2020

Subgroup analyses for OS were conducted as pre-specified in trial protocol. Figure 41 shows a forest plot summarizing the key results of the OS subgroup analyses by treatment group. The OS benefit of 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 [13]. 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 metUM will be diagnosed with a small tumor [13,81].

| 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 41. Forest plot of OS in subgroups – DCO October 2020** [13]

### L.4.2 DCO July 2023

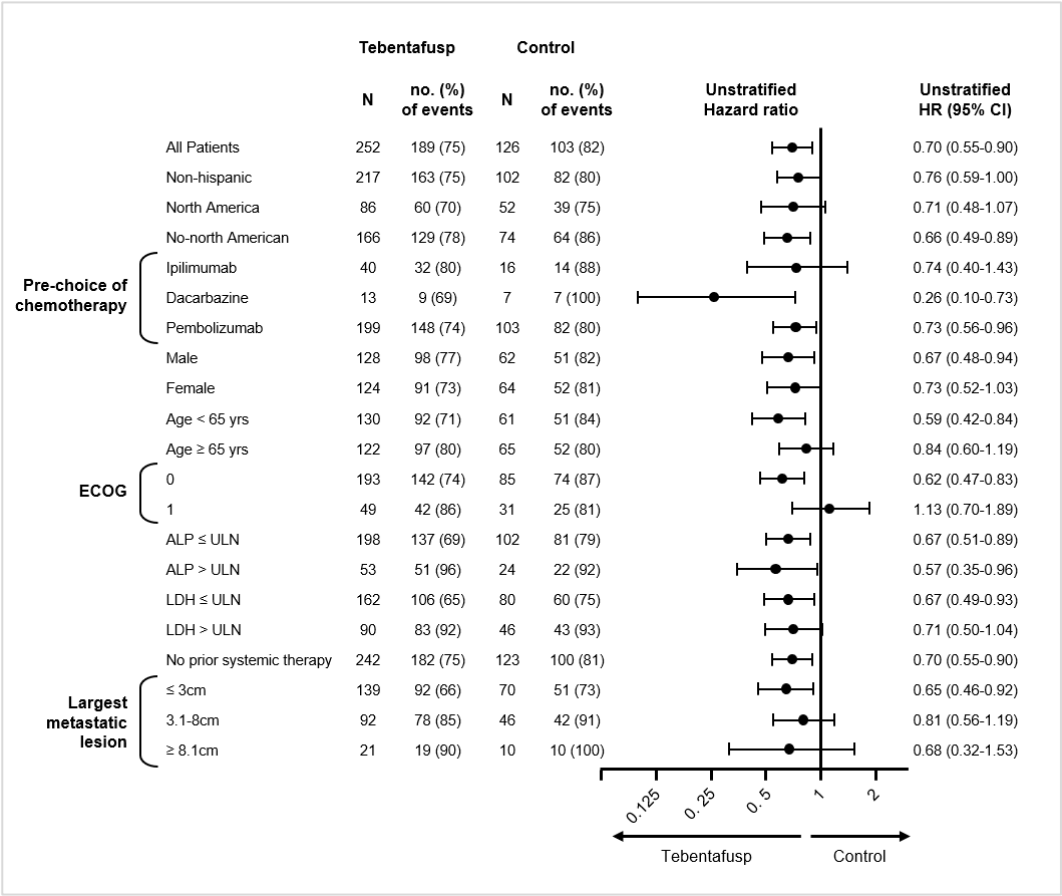


**Figure 42. Prespecified subgroup analysis of overall survival in the ITT population – DCO July 2023** [49]

## L.5 Progression-free survival results

### L.5.1 DCO October 2020

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 [13].

At 6 months, 31% of the tebentafusp group were progression free and in the control group 19% were progression free. The median PFS in the tebentafusp groups were 3.3 months (3.0 – 5.0) compared with 2.9 (2.8 – 3.0) in the control group. The HR was 0.73 [95% CI, 0.58;  0.95], see Figure 43 [13].

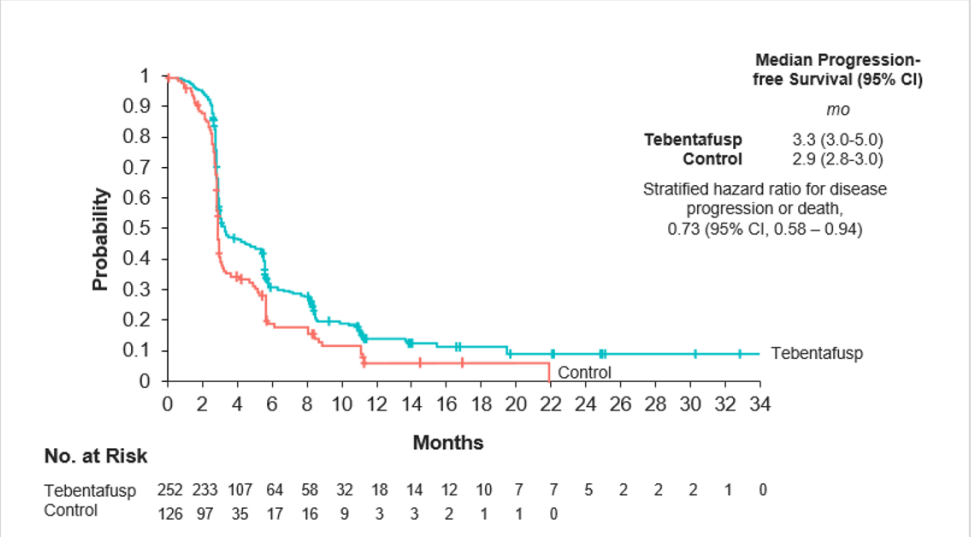


**Figure 43. Kaplan-Meier estimates of PFS according to treatment group – DCO October 2020** [13].

### L.5.2 DCO July 2023

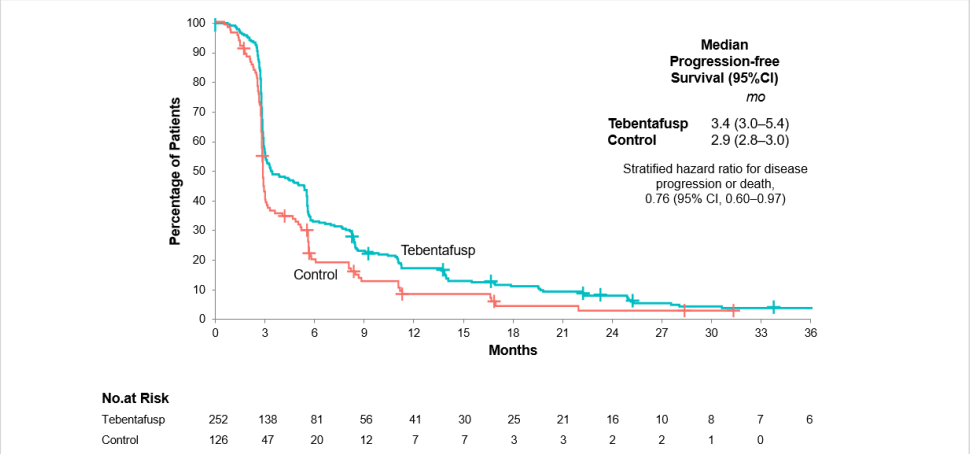


**Figure 44. Kaplan-Meier estimates of PFS according to treatment group - DCO July 2023** [49]

## L.6 Safety data

### L.6.1 DCO October 2020

AEs were assessed in the Safety Analysis Set, which included all randomized patients who received at least one full or partial dose of tebentafusp or investigator's choice. AEs were assessed by the investigator and were graded according to the NCI 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. 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 [13].

The following results were observed, see Table 112 for more details:

- 245 (100%) of patients experienced a TEAE in the tebentafusp group, while 105 (95%) experienced a TEAE in the control group [13].
- 69 (28%) experienced a serious adverse event (SAE) in the tebentafusp group, while 26 (23%) experienced a SAE in the control group [13]. For more details see Appendix E.
- 133 (54.3%) in the tebentafusp group and 40 (36%) in the control group experienced a TEAE with a CTCAE grade 3 or above [13,54].
- 8 (3.35%) and 7 (6.3%) in the tebentafusp and control group withdrew from treatment due to a TEAE, while 18 (7.3%) and 2 (1.8%) experienced a dose reduction [13,54].
- 5 (2%) of patients in the tebentafusp group discontinued treatment because of a TEAE while the number was 5 (5%) in the control group [13].
- No treatment related death was reported in either group [13].

**Table 112. Summary of TEAEs in the Safety Analysis Set – DCO October 2020** [13,54].

| | Tebentafusp (N = 245) | Investigator choice (N = 111) | RR | 95% CI |
|---|---|---|---|---|
| **TEAE, n (%)** | 245 (100) | 105 (94.6) | 1.05 | 1.01; 1.11 |
| **TRAE, n (%)** | 243 (99.2) | 91 (82.0) | 1.21 | 1.11; 1.32 |
| **Serious TEAEs any grade, n (%)** | 69 (28.2) | 26 (26.4) | 1.20 | 0.81; 1.79 |
| **Related serious TEAEs, n (%)** | 54 (22.0) | 8 (7.2) | 3.05 | 1.51; 6.21 |
| **TEAE leading to discontinuation, n (%)** | 8 (3.3) | 7 (6.3) | 0.45 | 0.19; 1.39 |
| **Related TEAE leading to discontinuation, n (%)** | 5 (2.0) | 5 (4.5) | 0.45 | 0.13; 1.53 |
| **CTCAE Grade ≥3 TEAE, n (%)** | 133 (54.3) | 40 (36.0) | 1.51 | 1.15; 1.98 |
| **Any related TEAE Grade ≥3** | 109 (44.5) | 19 (17.1) | 2.60 | 1.69; 4.01 |
| **TEAE by CTCAE grade, n (%)** | | | | |
| 1 | 14 (5.7) | 24 (21.5) | 0.26 | 0.14; 0.49 |
| 2 | 98 (40.0) | 41 (36.9) | 1.08 | 0.81; 1.44 |
| 3 | 117 (47.8) | 36 (32.4) | 1.47 | 1.09; 1.99 |
| 4 | 15 (6.1) | 2 (1.8) | 3.40 | 0.79; 14.61 |
| 5 | 1 (0.4) | 2 (1.8) | 0.23 | 0.02; 2.47 |
| **Any dose reduction, n (%)** | 18 (7.3) | 2 (1.8) | 4.10 | 0.96; 17.27 |
| **Reasons for reduction, n (%)** | | | | |
| AE*, n (%) | 22 (84.6) | 3 (100.0) | - | - |
| Other*, , n (%) | 4 (15.4) | 0 | - | - |
| TEAE leading to dose or infusion interruption, n (%) | 62 (25.3) | 27 (24.3) | 1.04 | 0.70; 1.54 |
| Any related TEAE leading to dose or infusion interruption, n (%) | 44 (18.0%) | 23 (20.7) | 0.87 | 0.55; 1.36 |
| Any TEAE leading to death, n (%) | 1 (0.4%) | 2 (1.8) | 0.23 | 0.02; 2.47 |
| Any related TEAE leading to death, n (%) | 0 | 0 | - | - |

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

The most common treatment-related AEs (TRAE) of any grade in the tebentafusp group were cytokine-related AEs occurring, e.g. pyrexia (76%), chills (47%), and hypotension (38%). CRS occurred in 89% of the tebentafusp group. 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 group, only expected AEs were observed [13].

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 AEs, 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. [13]

The incidence of AE was highest during the first 4 weeks of treatments, see Figure 45. After 3 weeks of treatment, most patients could therefore transition from receiving the treatment during admission to an outpatient setting [13].

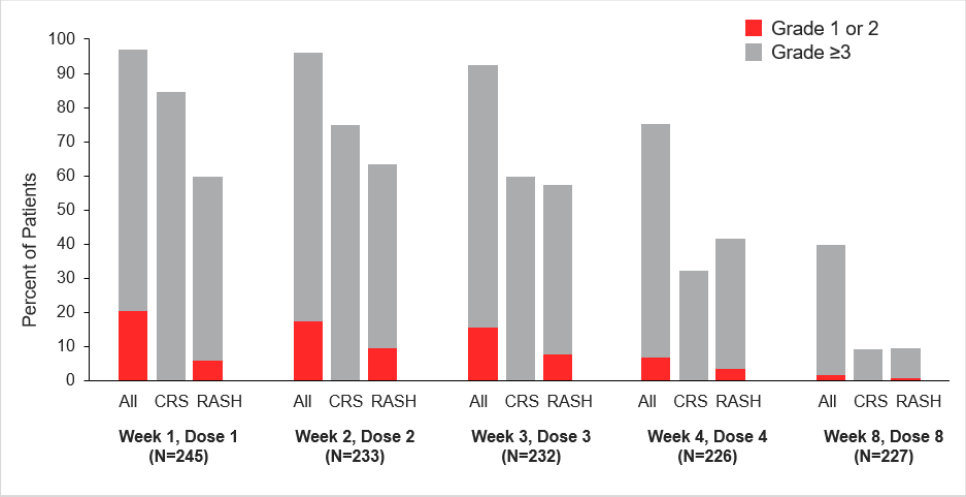


**Figure 45. Incidence and severity of TRAE's after initial doses of tebentafusp – DCO October 2020** [13].

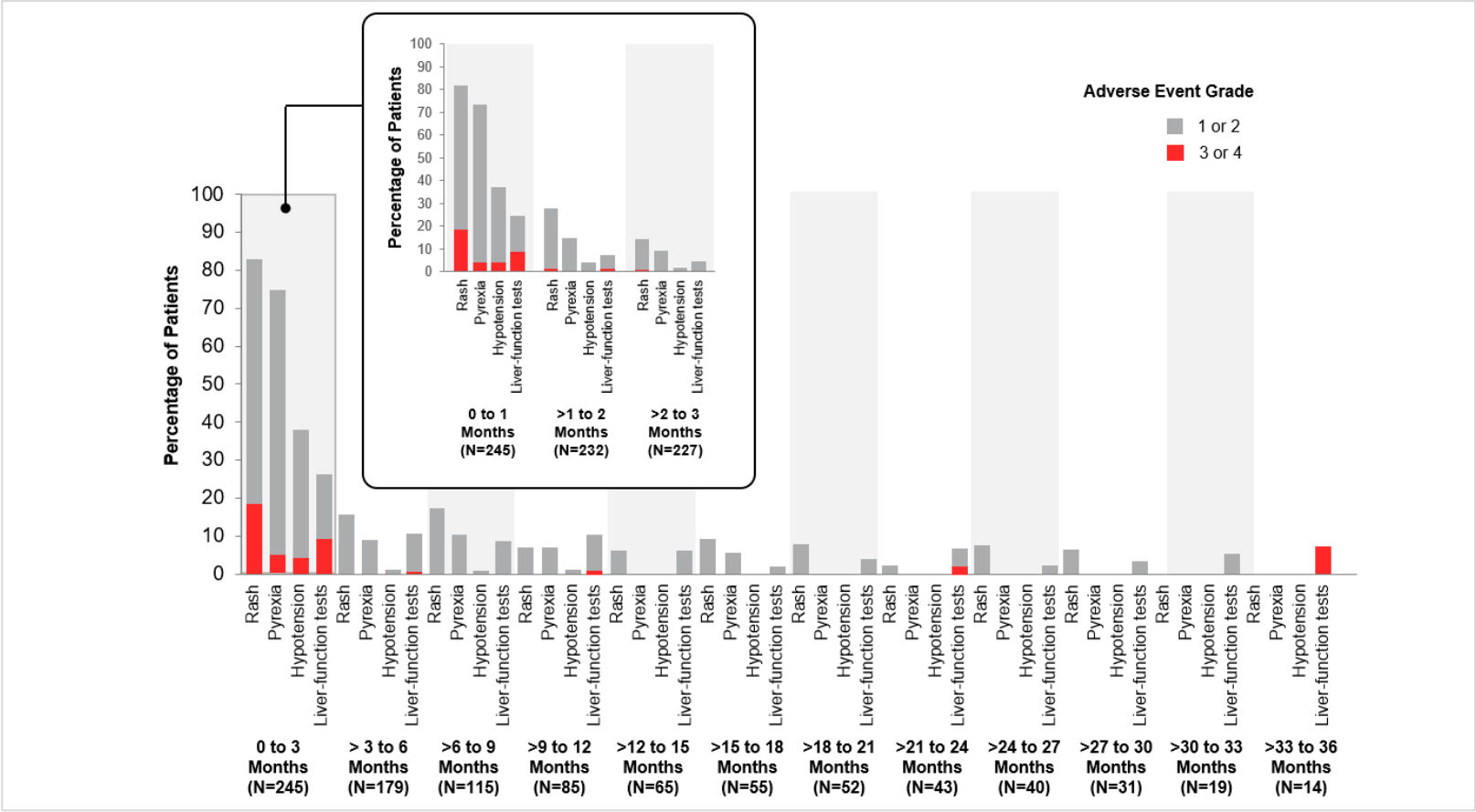


**Figure 46. Selected tebentafusp-related AEs over time – DCO July 2023** [10].

# Appendix M. GEM-1402 figures

## M.1 Study design

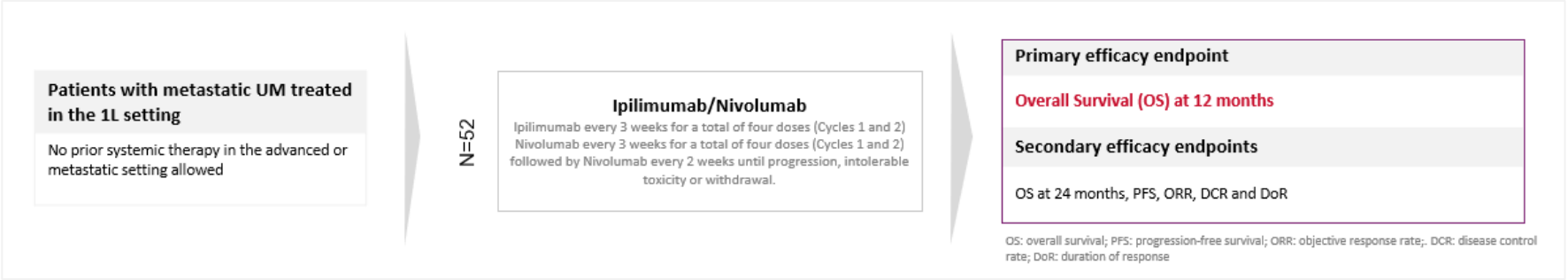


**Figure 47. GEM-1402 study design** [11] [38].

## M.2 Kaplan-Meier plots of OS

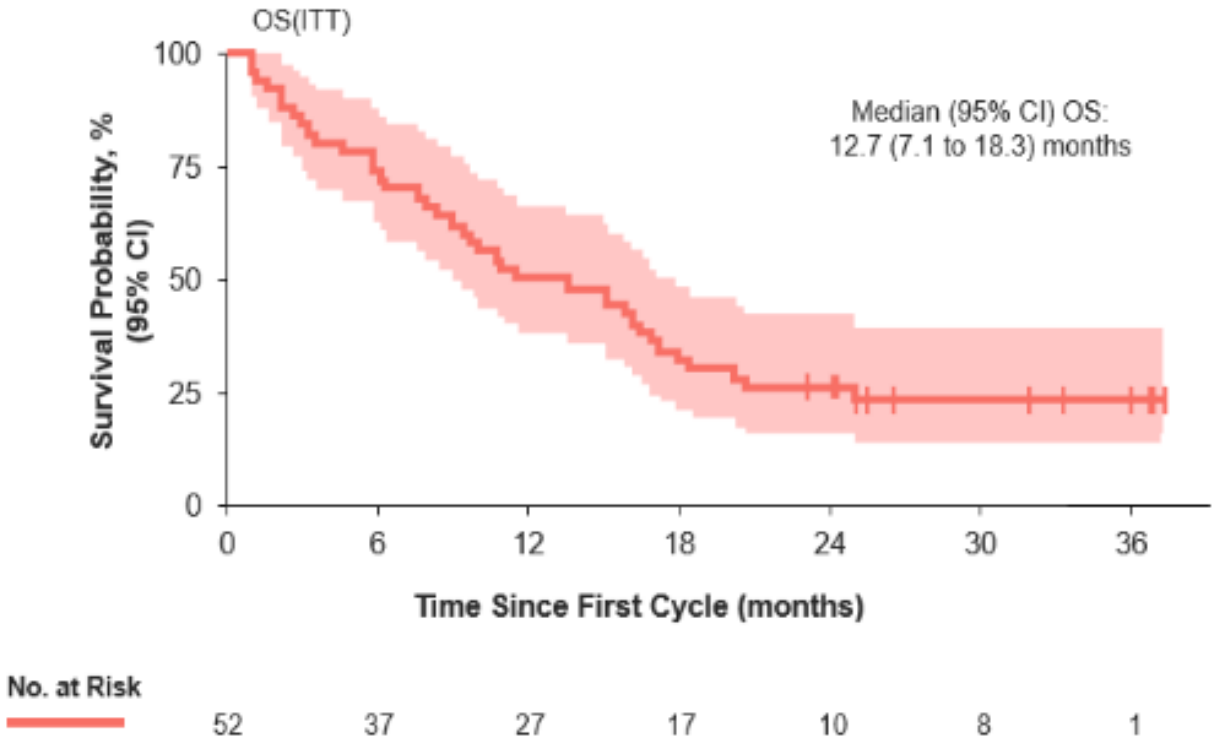


**Figure 48. Median overall survival** [11].

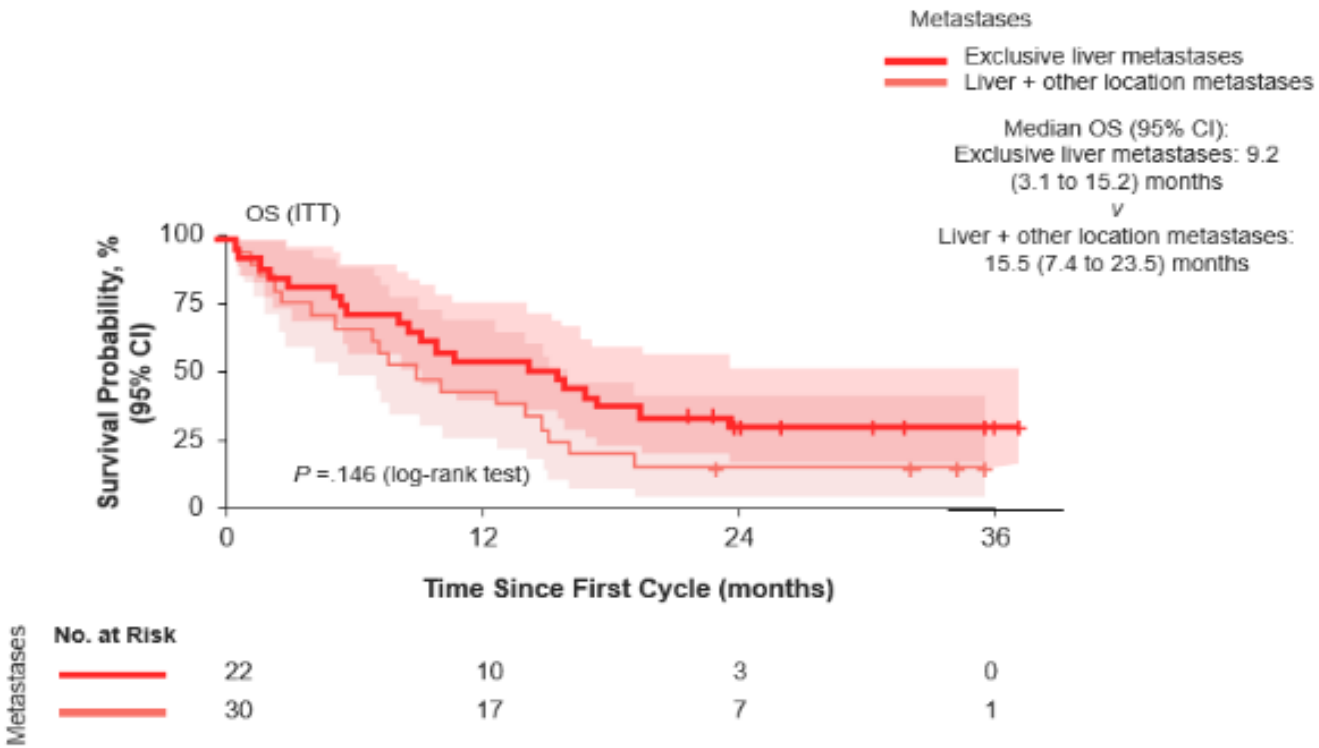


**Figure 49. Overall survival by different metastasis patterns** [11].

## M.3 Kaplan-Meier plot of PFS

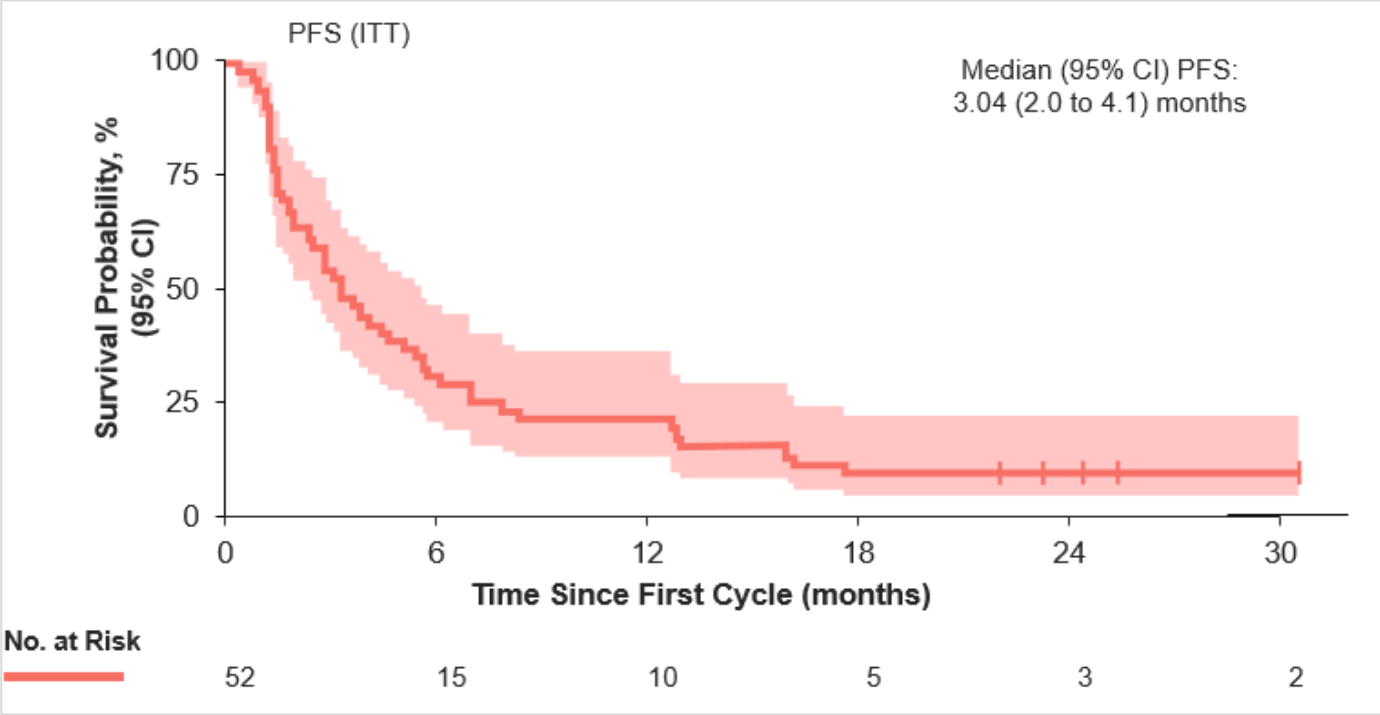


**Figure 50. Median PFS in the GEM-1402 study** [11].

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