NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Immunocore

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Melanoma Focus
   b. OcuMel
   c. Royal College of Pathologists

4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

5. **Evidence Review Group report – factual accuracy check**

6. **Technical engagement response from company Immunocore**
   a. Addendum 1 to TE response
   b. Addendum 2 – clarification to addendum 1

7. **Technical engagement responses and statements from experts:**
   a. Rumana Hussain, Consultant Ocular Oncologist - clinical expert nominated by the Royal College of Pathologists
   b. Jo Gumbs - patient expert, nominated by OcuMel UK
   c. Patient expert, nominated by OcuMel UK
   d. Paul Nathan, Consultant in Medical Oncology - clinical expert, nominated by Melanoma Focus and Immunocore *(*see item 8a)*

8. **Technical engagement responses from consultees and commentators:**
   a. Melanoma Focus

9. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews
   a. ERG addendum to TE response

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Document B

Company evidence submission

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Contents

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE....1
Contents....2
Tables and figures....4
Abbreviations....9
B.1 Decision problem, description of the technology and clinical care pathway....12
B.1.1 Decision problem....12
B.1.2 Description of the technology being appraised....16
B.1.3 Health condition and position of the technology in the treatment pathway....21
Summary....21
B.1.3.1 Clinical manifestation and diagnosis....21
B.1.3.2 Epidemiology and risk factors....23
B.1.3.3 Pathophysiology....23
B.1.3.4. Quality of life....24
B.1.3.4 Patient treatment pathways....25
B.1.3.5 Tebentafusp....27
B.1.3.6 Unmet need....30
B.1.4 Equality considerations....31
B.2 Clinical effectiveness....32
B.2.1 Identification and selection of relevant studies....32
B.2.1.1 Search strategy....32
B.2.1.2 Study selection....32
B.2.2 List of relevant clinical effectiveness evidence....32
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence....36
B.2.3.1 IMCgp100-202 study....36
B.2.3.2 IMCgp100-102 study....44
B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence....49
B.2.4.1 IMCgp100-202 study....49
B.2.4.2 IMCgp100-102 study....53
B.2.5 Quality assessment of the relevant clinical effectiveness evidence....54
B.2.6 Clinical effectiveness results of the relevant trials....55
B.2.6.1 Overall survival....56
B.2.6.2 Overall survival in tebentafusp-induced rash....61
B.2.6.3 Progression-free survival....65
B.2.6.4 Objective response rate, best overall response and disease control rate....67
B.2.6.5 Duration of response....70
B.2.6.6 Time to response....72
B.2.7 Overall survival subgroup analyses....73
B.2.8 Meta-analysis....74
B.2.9 Indirect and mixed treatment comparisons....75

B.2.10 Adverse reactions 82
B.2.10.1 Treatment-emergent adverse events 82
B.2.10.1 Cytokine release syndrome 84
B.2.10.2 Acute skin reactions 85
B.2.10.3 Liver function abnormalities 87
B.2.10.4 Summary of treatment-related AEs 88
B.2.11 Ongoing studies 89
B.2.12 Innovation 89
B.2.13 Interpretation of clinical effectiveness and safety evidence 90
B.3 Cost effectiveness 93
B.3.1 Published cost-effectiveness studies 93
B.3.2 Economic analysis 94
B.3.2.1 Patient population 95
B.3.2.2 Model structure 95
B.3.2.4 Intervention technology and comparators 98
B.3.3 Clinical parameters and variables 99
B.3.3.1 ITT analysis set 100
B.3.3.2 Subgroup tumour ≤30mm 134
B.3.3.3 Adverse events 163
B.3.4 Measurement and valuation of health effects 164
B.3.4.1 Health-related quality-of-life data from clinical trials 165
B.3.4.2 Mapping 170
B.3.4.3 Health-related quality-of-life studies 170
B.3.4.4 Adverse reactions 171
B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis 172
B.3.5 Cost and healthcare resource use identification, measurement and valuation 174
B.3.5.1 Intervention and comparators' costs and resource use 174
B.3.5.2 Cost of subsequent therapies 182
B.3.5.3 Health-state unit costs and resource use 183
B.3.5.4 Adverse reaction unit costs and resource use 188
B.3.5.5 Miscellaneous unit costs and resource use 192
B.3.6 Summary of base-case analysis inputs and assumptions 192
B.3.6.1 Summary of base-case analysis inputs 192
B.3.6.2 Assumptions 196
B.3.7 Base-case results 198
B.3.7.1 Base-case incremental cost-effectiveness analysis results 198
B.3.8 Sensitivity analyses 200
B.3.8.1 Probabilistic sensitivity analysis 200
B.3.8.2 Deterministic sensitivity analysis 202
B.3.8.3 Scenario analysis 204

B.3.8.5 Summary of sensitivity analyses results....207
B.3.9 Subgroup analysis - Patients with tumour < 30mm....208
B.3.10 Validation....209
B.3.11 Interpretation and conclusions of economic evidence....212
References....214

Tables and figures

Table 1. The decision problem....13
Table 2. Technology being appraised....19
Table 3. Patient numbers eligible for tebentafusp treatment in England and Wales....28
Table 4. Clinical effectiveness evidence....34
Table 5. Detailed characteristics of IMCgp100-202 study....39
Table 6. Detailed characteristics of IMCgp100-102 study....46
Table 7. Summary of statistical analyses of the IMCgp100-202 study (NCT03070392)....50
Table 8. Effect of tebentafusp on objective response rate, best overall response, and disease control rate, study IMCgp100-202....68
Table 9. Effect of tebentafusp on objective response rate, best overall response, and disease control rate, study IMCgp100-102....69
Table 10. Effect of tebentafusp on duration of response, study IMCgp100-202....70
Table 11. Effect of tebentafusp on duration of response, study IMCgp100-102....71
Table 12. Potential comparator studies....75
Table 13. Variables used for matching in the MAIC....76
Table 14. Results from the main and sensitivity analyses for the MAICs and UAIC....77
Table 15. Treatment-emergent adverse events occurring in ≥20% patients in study IMCgp100-202....83
Table 16. Select post-baseline laboratory abnormalities occurring in ≥20% or Grade 3-4 (≥5%) in UM patients in study IMCgp100-202 (Immunocore 2021a)....88
Table 17. Features of the economic analysis....94
Table 18. Median OS ITT set both data cut-offs....101
Table 19. Goodness-of-fit criterions AIC and BIC – OS ITT set IC arm DCO October 2020 and August 2021....102
Table 20. OS parametric models IC arm ITT set DCO October 2020 vs KM curve and Rantala et al first-line....104
Table 21. OS parametric models IC arm ITT set DCO August 2021 vs KM curve and Rantala et al first-line....105
Table 22. Goodness of fit criteria AIC and BIC....110
Table 23. Median PFS ITT set both data cut-offs....112
Table 24. Goodness-of-fit criterions AIC and BIC – PFS ITT set IC arm DCO October 2020 and August 2021....113
Table 25. PFS parametric models vs. KM curve IC ITT set arm DCO October 2020....115
Table 26. PFS parametric models vs. KM curve IC arm ITT set DCO August 2021....116
Table 27. Goodness-of-fit criterions AIC and BIC – PFS ITT set Tebentafusp arm DCO October 2020 and August 2021....117
Table 28. PFS parametric models vs. KM curve Tebentafusp ITT set arm DCO October 2020....117

Table 29. PFS parametric models vs. KM curve Tebentafusp arm ITT set DCO August 2021 118
Table 30.PFS state occupancy hybrid model using KM curve + parametric tail from 15% of patient at risk 121
Table 31. Median TTD ITT set both data cut-offs 123
Table 32. Goodness-of-fit criterions AIC and BIC – TTD ITT set IC arm DCO October 2020 and August 2021 125
Table 33. TTD parametric models vs. KM curve IC arm ITT set DCO October 2020 126
Table 34. TTD parametric models vs. KM curve IC arm ITT set DCO August 2021 127
Table 35. Goodness-of-fit criterions AIC and BIC – TTD ITT set Tebentafusp arm DCO October 2020 and August 2021 128
Table 36. TTD parametric models vs. KM curve Tebentafusp arm ITT set DCO October 2020 129
Table 37. TTD parametric models vs. KM curve Tebentafusp arm ITT set DCO August 2021 130
Table 38. TTD state occupancy hybrid model using KM curve + parametric tail (from 15% of patient at risk) 134
Table 39. Median OS subgroup tumour ≤30mm both data cut-offs 135
Table 40. Goodness-of-fit criterions AIC and BIC – OS subgroup tumour ≤30mm IC arm DCO October 2020 and August 2021 136
Table 41. OS parametric models vs. KM curve IC arm subgroup tumour ≤30mm DCO October 2020 137
Table 42. OS parametric models vs. KM curve IC arm subgroup tumour ≤30mm DCO August 2021 138
Table 43. Goodness-of-fit criterions AIC and BIC – OS subgroup tumour ≤30mm tebentafusp arm DCO October 2020 and August 2021 139
Table 44. OS parametric models vs. KM curve Tebentafusp arm subgroup tumour ≤30mm DCO October 2020 140
Table 45. OS parametric models vs. KM curve Tebentafusp arm subgroup tumour ≤30mm DCO August 2021 141
Table 46. Median PFS subgroup tumour ≤30mm both data cut-offs 147
Table 47. Goodness-of-fit criterions AIC and BIC – PFS subgroup tumour ≤30mm IC arm DCO October 2020 and August 2021 147
Table 48. PFS parametric models vs. KM curve IC arm subgroup tumour ≤ 30mm DCO October 2020 148
Table 49. PFS parametric models vs. KM curve IC arm subgroup tumour ≤30mm DCO August 2021 149
Table 50. Goodness-of-fit criterions AIC and BIC – PFS subgroup tumur≤30mm IC arm DCO October 2020 and August 2021 150
Table 51. PFS parametric models vs. KM curve Tebentafusp arm subgroup tumour ≤ 30mm DCO October 2020 151
Table 52. PFS parametric models vs. KM curve Tebentafusp arm subgroup tumour ≤30mm DCO August 2021 152
Table 53. Median TTD subgroup tumour ≤30mm both data cut-offs 154
Table 54. Goodness-of-fit criterions AIC and BIC – TTD subgroup tumour ≤30mm IC arm DCO October 2020 and August 2021 154
Table 55. TTD parametric models vs. KM curve IC arm subgroup tumour ≤30mm DCO October 2020 156

Table 56. TTD parametric models vs. KM curve IC arm subgroup tumour ≤30mm DCO August 2021 157
Table 57. Goodness-of-fit criterions AIC and BIC – TTD subgroup tumour ≤30mm Tebentafusp arm DCO October 2020 and August 2021 158
Table 58. TTD parametric models vs. KM curve Tebentafusp arm subgroup tumour ≤30mm DCO October 2020 159
Table 59. TTD parametric models vs. KM curve Tebentafusp arm subgroup tumour ≤30mm DCO August 2021 160
Table 60. Rates of adverse events included in the model 163
Table 61. PRO data collection schedule IMGhg100-202 clinical trial 167
Table 62. Pattern of missingness of EQ-5D data 168
Table 63. Utility values based on the IMCgp100-202 trial data 170
Table 64. Utility data based on time to death 171
Table 65. Utility decrements for the interim model 172
Table 66. Summary of utility values for cost-effectiveness analysis 172
Table 67. Drug unit costs 175
Table 68. Drug dosage regimen in the IMCgp100-202 trial 176
Table 69. Administration services unit costs 178
Table 70. Cost of HLA-A*02:01 test in the tebentafusp arm 179
Table 71. Testing, administration, and drug acquisition costs for Tebentafusp (weekly dose) 179
Table 72. Testing, administration, and drug acquisition costs for the Investigator's choice arm (one dose every three weeks) 181
Table 73. Costs of subsequent therapies 183
Table 74. Resource utilisation for the management of the disease during the pre-progression phase, at progression and post-progression with best supportive care 185
Table 75. Unit cost of resource use 186
Table 76. Health state costs 188
Table 77. Proportion of patients managed for AEs in the inpatient and outpatients settings 189
Table 78. Unit costs of adverse events 190
Table 79. Weighted average cost of AEs by treatment arm 191
Table 80. Summary of variables applied in the economic model 192
Table 81. Key model assumptions 197
Table 82. Base-case results 199
Table 83. Results of the base-case PSA 201
Table 84. Results of the univariate sensitivity analysis 203
Table 85 Results of scenario analyses of alternative methods of extrapolating PFS 204
Table 86. Results of scenario analyses of alternative methods of extrapolating PFS 205
Table 87. Results of scenario analyses using alternative parametric survival models 206
Table 88. Results of scenario analyses using patients cure proportions for survival 207
Table 89. Scenario analysis subgroup tumour ≤30mm 209
Table 90. Summary of model results compared with clinical data 211

Figure 1. Structure of tebentafusp (Damato et al. 2019) 16
Figure 2. Schematic representation of proposed tebentafusp mode of action 18
Figure 3. Location of uveal melanoma within the eye (iris, ciliary body, choroid). Adapted from Milam and Daniels (2018) 24
Figure 4. Patient flow of patients diagnosed with primary UM (adapted from Nathan et al. 2015) 29

Figure 5. IMCgp100-202 consort diagram: Study design, participant enrolment and disposition in the ITT population at the first interim analysis 38
Figure 6. IMCgp100-102 study schema 44
Figure 7. Kaplan-Meier estimate of overall survival, study IMCgp100-202 for both data cut-offs (A) October 2020; (B) August 2021 57
Figure 8. Kaplan-Meier estimate of overall survival in study IMCgp100-202 in comparison to historical data by Rantala et al. (2019a) 58
Figure 9. Post-landmark (day 100) overall survival in patients with best overall response of stable disease or disease progression (Nathan et al. 2021) 59
Figure 10. Kaplan-Meier plot of overall survival in Phase 2 dose expansion of study IMCgp100-102 (N=127) 60
Figure 11. Kaplan-Meier plot of overall survival in Phase 2 dose expansion of study IMCgp100-102 in comparison to historical data published by Rantala et al. (2019a) 61
Figure 12. Kaplan-Meier IPTW analysis (A) IPTW adjusted OS by rash status in tebentafusp treated patients (B) IPTW adjusted OS in tebentafusp-treated patients who do not experience rash compared to investigator's choice patients 64
Figure 13. Kaplan-Meier estimate of PFS, study IMCgp100-202 for both data cut-offs (A) October 2020; (B) August 2021 66
Figure 14. Kaplan-Meier plot of PFS (RECIST v1.1) by ICR in Phase 2 dose expansion of study IMCgp100-102 67
Figure 15. Swimmer plot for time to response, study IMCgp100-202 73
Figure 16. Forest plot of overall survival trends by subgroup (ITT) 74
Figure 17. Kaplan-Meier plots of overall survival from match-adjusted indirect comparison (MAIC) of tebentafusp versus ipilimumab + nivolumab 78
Figure 18. Kaplan-Meier plots of overall survival from match-adjusted indirect comparison (MAIC) of pembrolizumab versus ipilimumab + nivolumab 79
Figure 19. Percentage of treated patients experiencing any grade or grade ≥3 treatment related rash after each does of tebentafusp. 86
Figure 20. Incidence and severity of treatment-related adverse events after initial doses of tebentafusp in study IMCgp100-202 (Nathan et al. 2021) 89
Figure 21. Schematic model structure 96
Figure 22. Kaplan-Meier curve OS ITT set for both data cut-offs (a) October 2020; (b) August 2021 101
Figure 23. Kaplan Meier curves OS IMCgp100-202 for Tebentafusp and IC vs. Rantala et al.; (a) October 2020 DCO (b) August 2021 DCO 104
Figure 24. OS standard parametric models IC arm ITT set October 2020 DCO - (a) Trial time horizon; (b) 15-year time horizon 106
Figure 25. OS standard parametric models IC arm ITT set August 2021 DCO - (a) trial time horizon; (b) 15-year time horizon 108
Figure 26. OS spline model tebentafusp arm ITT set August 2021 DCO - (a) Trial time horizon; (b) 15-year time horizon 111
Figure 27. Kaplan-Meier curve PFS ITT set for both cut-offs (a) October 2020; (b) August 2021 113
Figure 28. PFS standard parametric models ITT set; (a) October 2020 DCO; (b) August 2021 DCO 119
Figure 29. PFS Kaplan-Meier + parametric tail (generalised gamma); (a) October 2020 DCO; (b) August 2021 DCO 121
Figure 30. Kaplan-Meier curve TTD ITT set for both data cut-offs (a) October 2020; (b) August 2021 122

Figure 31. PFS and TTD ITT set; (a) IC October 2020 DCO; (b) Tebentafusp October 2020 DCO; (c) IC August 2021 DCO; (d) Tebentafusp August 2021 DCO 124
Figure 32. TTD standard parametric models ITT set; (a) October 2020 DCO; (b) August 2021 DCO 131
Figure 33. TTD Kaplan-Meier + parametric tail; (a) October 2020 DCO; (b) August 2021 DCO 133
Figure 34. Kaplan-Meier curve OS subgroup tumour ≤30mm for both data cut-offs (a) October 2020; (b) August 2021 135
Figure 35. OS Standard parametric models subgroup tumour ≤ 30mm DCO October 2020 - (a) Individual fit trial time horizon; (b) Individual fit 15-year time horizon 142
Figure 36. OS Standard parametric models subgroup tumour ≤30mm DCO August 2021- (a) Individual fit trial time horizon; (b) Individual fit 15-year time horizon 143
Figure 37. Kaplan-Meier curve PFS subgroup tumour ≤30mm for both data cut-offs (a) October 2020; (b) August 2021 146
Figure 38. Kaplan-Meier curve TTD subgroup tumour ≤30mm for both data cut-offs (a) October 2020; (b) August 2021 153
Figure 39. TTD standard parametric models subgroup tumour ≤30mm; (a) October 2020 DCO; (b) August 2021 DCO 161
Figure 40. Cost-effectiveness plane – incremental costs vs. incremental QALYs 201
Figure 41. Cost-effectiveness acceptability curve for willingness-to-pay threshold 202
Figure 42. Tornado diagram 203

Abbreviations

AE	Adverse event
AIC	Akaike's Information Criterion
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
BIC	Bayesian Information Criterion
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CM	Cutaneous melanoma
CR	Complete response
CRS	Cytokine release syndrome
CT	Computerized tomography
DCO	Data cut-off
DCR	Disease control rate
DSU	Decision support unit
ECOG	Eastern Cooperative Oncology Group
EM	Effect modifier
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	The 5-level EQ-5D version
GEP	Gene expression profiling
HADS	Hospital Anxiety and Depression Scale
HLA	Human leukocyte antigen
HR	Hazard ratio
HRQoL	Health-related quality of life

HSS	Highly specialised services
IC	Investigator’s choice
ICER	Incremental cost-effectiveness ration
ICR	Independent central review
ImmTAC	Immune-mobilizing monoclonal T-cell receptors against cancer
IPD	Individual patient data
IPTW	Inverse Probability of Treatment Weighting
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumours
ITT	Intention-to-treat
KM	Kaplan Meier
LDH	Lactate dehydrogenase
LINAC	Linear particle accelerator
LUMPO	Liverpool Uveal Melanoma Prognosticator Online
LY	Life-year
MAIC	Matched adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency
NHSE&I	NHS England and NHS improvement
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
ONS	Office for national statistics
OS	Overall survival
OWSA	One-way sensitivity analyses
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PLD	Patient-level data
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis

PV	Prognostic variable
QoL	Quality of life
ROBINS-I	Risk of bias in non-randomized studies of interventions
RCT	Randomised control trial
RECIST	Response Evaluation Criteria in Solid Tumours
SD	Stable disease
SD	Standard deviation
SoC	Standard of Care
SIGN	Scottish intercollegiate network
SPC	Summary of product characteristics
TCR	T-cell receptor
TEAEs	Treatment-emergent adverse events
TNM	Tumour-node-metastasis
TSD	Technical support document
TTD	Time to treatment discontinuation
UAIC	Unadjusted indirect comparison
UM	Uveal melanoma
WHOQOL-BREF	World Health Organisation Quality of Life-BREF instrument

B.1 Decision problem, description of the technology and clinical care pathway

Summary
Tebentafusp is indicated for the treatment of advanced (metastatic or unresectable) uveal melanoma (UM) in HLA-A*02:01 positive adults

B.1.1 Decision problem

The objective of this submission is to appraise the clinical and cost-effectiveness of tebentafusp covering its full marketing authorisation for treating advanced (unresectable or metastatic) HLA-A*02:01-positive uveal melanoma (UM).

Further details of the decision problem are shown in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from NICE scope
Population	Adults with advanced (unresectable or metastatic) HLA-A*0201-positive uveal melanoma	Adults with advanced (unresectable or metastatic) HLA-A*02:01-positive uveal melanoma	NA
Intervention	Tebentafusp	Tebentafusp (KIMMTRAK®)	NA
Comparator(s)	• Immunotherapies (pembrolizumab, ipilimumab, nivolumab [alone or in combination with ipilimumab]) • Chemotherapy (dacarbazine) • Best supportive care may be an additional comparator for people who have had previous treatment	Established clinical management without tebentafusp; currently there is no approved therapy for advanced uveal melanoma and the UK treatment guidelines recommend patients are enrolled in clinical trials. The investigators choice comparator therapies in the randomised controlled trial (RCT) on tebentafusp were therapies frequently used in clinical practice in metastatic uveal melanoma patients: pembrolizumab, ipilimumab, or dacarbazine, therefore we consider these to be the most relevant comparator treatments. Data from comparing tebentafusp and ipilimumab plus nivolumab combination therapy will be presented from a matching and adjusted indirect comparison analysis.	NA

Outcomes	The outcome measures to be considered include the following: • Mortality • Morbidity, including damage to organs • Remission rate and duration of remission • Change in renal function • Use of immunosuppressants and corticosteroids • Adverse effects of treatment (including infection rates) • HRQoL	• Overall survival (OS) • Progression free survival (PFS) • Objective Response Rate (ORR) • Duration of response (DOR) • Adverse effects of treatment • Health-related quality of life (HRQoL)	The outcomes reflect the clinical endpoints of the Phase 3 RCT on tebentafusp
Economic analysis	The economic analysis is consistent with the NICE reference case which stipulates: • The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	The cost-effectiveness of treatments will be expressed in terms of incremental cost per QALY. The time horizon for estimating clinical and cost effectiveness will be a lifetime horizon, which is long enough to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per NICE scope

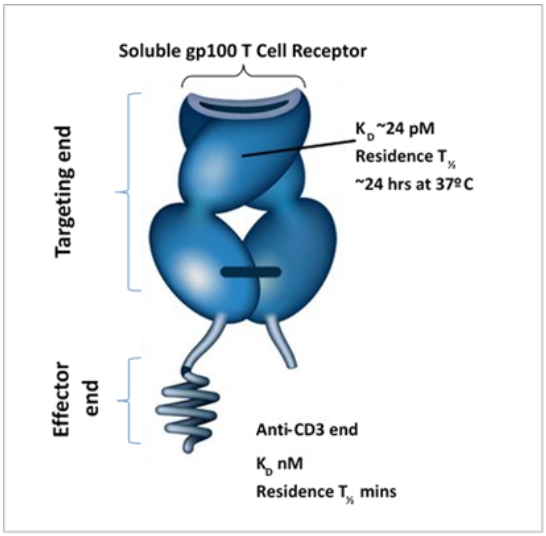
	The use of tebentafusp is conditional on the presence of HLA-A*0201. The economic modelling includes the costs associated with diagnostic testing for HLA-A*0201 in people with uveal melanoma who would not otherwise have been tested. A sensitivity analysis is provided without the cost of the diagnostic test.		
Subgroups to be considered	NA	For this rare cancer there are no subgroups that need to be considered in the context of a NICE submission. Immunocore have conducted subgroup analyses according to the study protocol that show benefit across all groups.	
Special considerations including issues related to equity or equality	No equity or equality issues have been identified.	No equity or equality issues have been identified.	
Abbreviations: DOR, duration of response; HLA-A, human leukocyte antigen (A locus); HRQoL, health-related quality of life; NA, not applicable; NICE, National institute for Health and Care Excellence; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised control trial			

B.1.2 Description of the technology being appraised

- Tebentafusp is an ImmTAC® (Immune mobilising monoclonal T cell receptor Against Cancer) molecule: a new class of T cell redirecting bispecific fusion proteins with a novel mechanism of action
- ImmTAC® molecules use an engineered high affinity T cell receptor (TCR) to target a specific protein, including intracellular proteins that are processed and presented as peptide-HLA complexes on target cell surfaces
- Tebentafusp is the first and only proven effective systemic treatment for metastatic UM
- Tebentafusp is a highly innovative treatment that offers a convenient mode of administration to allow patients with limited life expectancy to receive care close to home following the first 3-weeks of treatment

Tebentafusp (KIMMTRAK®) is one of a new class of T-cell receptor therapeutics called immune-mobilizing monoclonal T-cell receptors against cancer (ImmTACs®). Tebentafusp is a targeted treatment for advanced (unresectable or metastatic) HLA-A*02:01-positive UM.

Figure 1. Structure of tebentafusp (Damato et al. 2019)



Tebentafusp is a bispecific fusion protein, comprised of a T cell receptor (TCR; targeting domain) fused to an antibody fragment targeting CD3 (cluster of differentiation 3; effector domain) (Figure 1). The TCR end binds with high affinity to a glycoprotein 100 (gp100) peptide presented by human leukocyte antigen-A*02:01

(HLA-A*02:01) on the cell surface of UM tumour cells, and the effector domain binds to the CD3 receptor on polyclonal T cells (Figure 2A).

Tebentafusp targets a specific peptide fragment of gp100 presented at the cell surface complexed with HLA-A*02:01. The mechanism constitutes part of the natural cell processing of all proteins and presentation at the cell surface for recognition by the adaptive immune system. For tebentafusp to bind and exert its therapeutic effect, gp100 must be correctly processed to the 9-residue peptide (YLEPGPVTA) and presented at the surface as the HLA-A*02:01-peptide complex. Therefore, the antitumour activity of tebentafusp is restricted to patients with the HLA-A*02:01 allele, which is present in ~47% of the white population (Lowe et al. 2019; The Allele Frequencies Database 2021).

An immune synapse is formed when the TCR targeting domain of tebentafusp binds to UM cells and the CD3 effector domain binds to polyclonal T cells (Figure 2B). This immune synapse results in redirection and activation of polyclonal T cells regardless of their native TCR specificity. Tebentafusp-activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of UM tumour cells.

The mode of action of tebentafusp is illustrated in Figure 2B. Following binding to the tumour cell surface, the anti-CD3 domain of tebentafusp activates a T-cell–mediated antitumour response via T cells resident in the tumour and stimulation of T-cell migration from peripheral blood. Activation of both CD4+ and CD8+ T cells triggers tumour-specific cytolytic activity, elaboration of inflammatory cytokines, and T-cell proliferation (Martinez-Lostao et al. 2015).

Figure 2. Schematic representation of proposed tebentafusp mode of action

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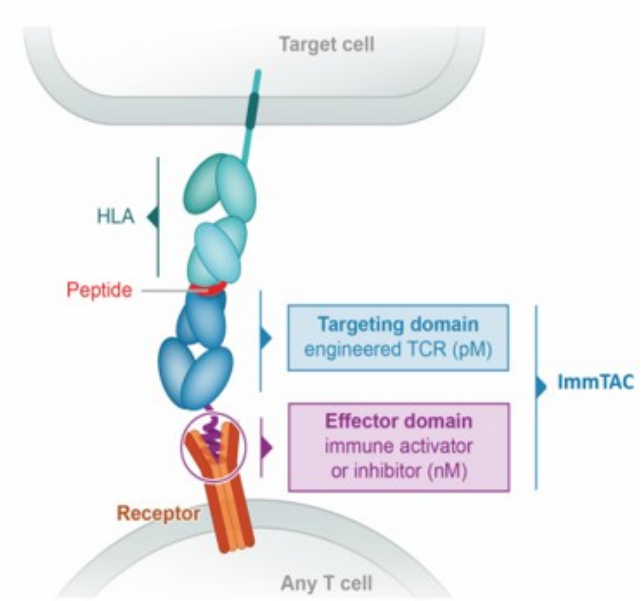
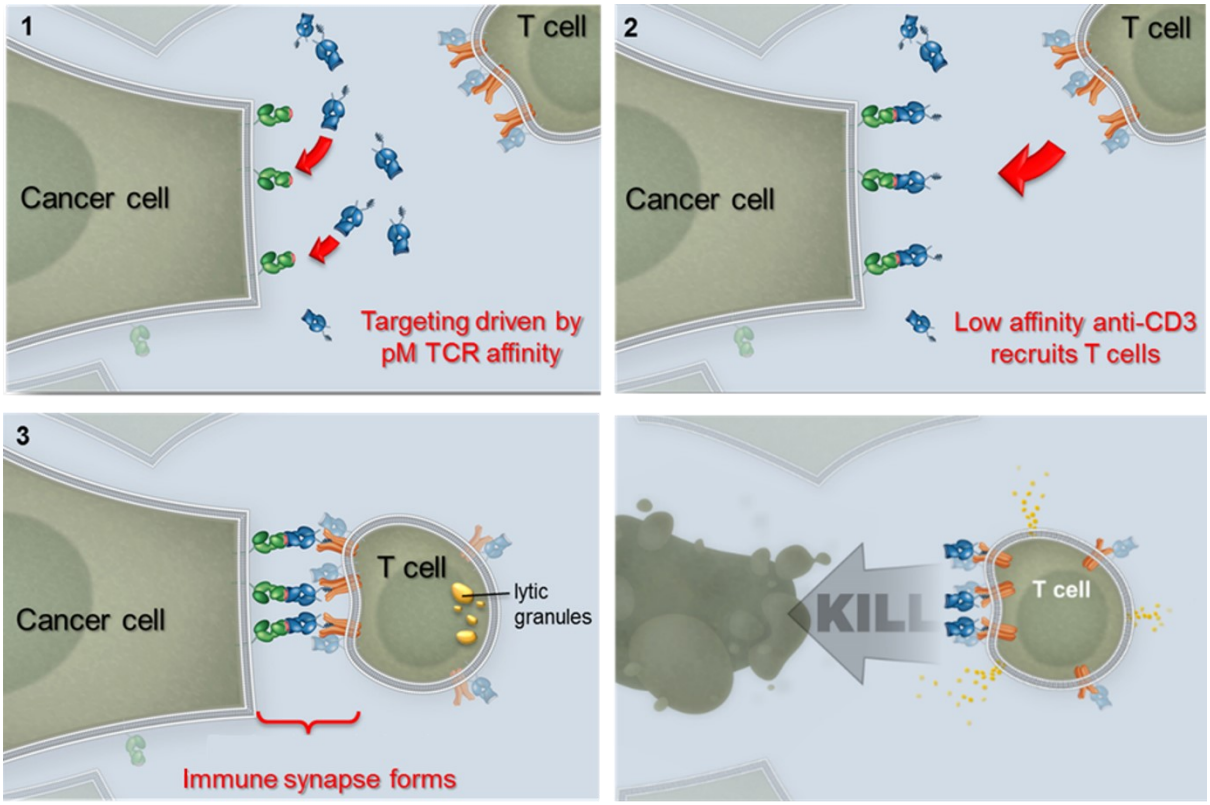
A



B



[A] The ImmTAC® (e.g., tebentafusp) is bispecific, connecting to the target cell (via the targeting domain) and recruiting T cells (via the effector domain). **[B]** Formation of an immune synapse happens when tebentafusp connects to a receptor with the CD3 effector function and to target cells presenting the specific HLA complex it is designed for. Tebentafusp activates a T-cell–mediated antitumor response via T cells resident in the tumour or stimulation of T-cell migration from peripheral blood resulting in an inflammatory response that kills the cancer cells.

Tebentafusp is supplied as a solution in single dose vials of 100 mcg/0.5 mL to be diluted with sodium chloride (0.9%) solution containing human albumin prior to intravenous infusion. It is administered at a dose of 20 µg on day 1, 30 µg on day 8, and 68 µg weekly thereafter. Treatment with tebentafusp is recommended to continue until the treating clinician deems it is no longer clinically beneficial to the patient, considering the full clinical status of the patient. The median treatment duration with tebentafusp for patients in the pivotal RCT (study IMCgp100-202) was 7.3 months. The first three doses of tebentafusp require administration in a hospital setting to allow for monitoring for signs and symptoms of cytokine release syndrome (CRS) during infusion and for 16 hours after infusion is complete. After the third infusion, and once the patient tolerates the most recent infusion without Grade ≥ 2 hypotension, subsequent doses can be administered in appropriate out-patient ambulatory care settings with 30 minutes monitoring following each infusion.

More details of the technology are presented in Table 2. The draft summary of product characteristics (SmPC) is available in Appendix C. The European public assessment report is not yet available.

Table 2. Technology being appraised

UK approved name and brand name	Tebentafusp/IMCgp100 (Brand name: KIMMTRAK®)
Mechanism of action	Immune mobilising monoclonal T cell receptor Against Cancer (ImmTAC®) drug. Tebentafusp targets HLA-A*02:01-positive uveal melanoma cells, then via its anti-CD3+ domain recruits T-cells and other immune system cells to destroy cancerous cells.
Marketing authorisation/CE mark status	Marketing authorisation for tebentafusp is being reviewed in the UK under the Project Orbis initiative (Type A). Marketing authorisation is not yet approved anywhere in the world. [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Tebentafusp is indicated as monotherapy for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic UM.
Method of administration and dosage	Tebentafusp is supplied as a solution in single dose vials to be diluted with sodium chloride (0.9%)

	solution containing human albumin prior to intravenous infusion. The recommended dose of tebentafusp is 20 µg on day 1, 30 µg on day 8, 68 mcg on day 15, and 68 µg once every week thereafter.
Additional tests or investigations	Patients treated with tebentafusp must have HLA-A*02:01 genotype determined by any validated HLA genotyping assay.
List price and average cost of a course of treatment	The UK list price for tebentafusp is [redacted] per vial. The average cost for a course of treatment would be [redacted] at list price.
Patient access scheme (if applicable)	[redacted]

B.1.3 Health condition and position of the technology in the treatment pathway

Summary

- UM is a rare, highly malignant, and life-threatening disease that initially affects the vascular layers of the eye
- Approximately half of all patients go on to develop metastatic disease. In 90% of patients, the first metastatic site is the liver and eventual liver failure is the predominant cause of death from the disease
- Patients with metastatic UM have a median survival time of around 12 months
- No proven effective systemic treatments specifically for metastatic UM are available and the UK NICE-approved clinical guidelines recommend patients are referred to clinical trial programmes
- There is major unmet need for novel and effective treatment options for this rare life-limiting disease
- The estimated incidence of metastatic UM patients who will be clinically eligible to receive tebentafusp is ~100 per year

B.1.3.1 Clinical manifestation and diagnosis

Clinical presentation

Diagnosing UM can be challenging, depending on the size, location, and appearance of the tumour. Many patients are asymptomatic (30.2%) and are diagnosed during a routine eye examination (Krantz et al. 2017). The most common presenting symptom in those with primary UM is blurred vision (37.8%), but patients may also present with metamorphopsia (shapes of objects are visually distorted) or photopsia (flashing visual disturbances) (Damato and Damato 2012). Fine needle aspiration biopsy can be used at the time of diagnosis to assess the prognosis and metastatic potential of the primary tumour (Sellam et al. 2016).

Staging for primary UM follows the American Joint Committee on Cancer (AJCC) Tumour-Node-Metastasis (TNM) staging system for eye cancer (Kujala et al. 2013). In addition, an online tool, the Liverpool Uveal Melanoma Prognosticator Online (LUMPO), is available to generate an all-cause mortality curve according to recognised survival factors (Coupland et al. 2013; Testa et al. 2017).

Current UK clinical guidelines recommend the primary disease is treated using radiotherapy such as brachytherapy or proton beam therapy. Brachytherapy plaque treatment is preferred, but it is not suitable for all patients (such as those with large tumours). Other radiotherapy options include proton beam radiotherapy or stereotactic radiotherapy, using a Leksell Gamma Knife or linear particle accelerator (LINAC) (NHS England, 2014). For some patients, enucleation is necessary, but physicians aim to use treatments that can preserve vision when feasible (Coupland et al. 2013). Surgical approaches using local resection techniques, such as transretinal endoresection are technically challenging and not recommended for UM arising from the choroid or ciliary body (Bechrakis et al. 2010; Yang et al. 2018).

Surveillance for metastatic disease

Following treatment of primary disease, prognostication and risk prediction for stratification is undertaken on the best available evidence, taking into account clinical, morphological, and genetic factors (Nathan et al. 2015a). This can include using primary tumour gene expression profiling (GEP), which has been shown to accurately determine whether they are at low or high risk of developing metastases (Plasseraud et al. 2016; Aaberg et al. 2020). Specific genetic alterations can also be assessed, e.g., loss of BAP1 expression which is associated with worse survival (Szalai et al. 2018). Other methods used by clinicians to determine risk stratification include clinical factors such as TNM staging (Shields et al. 2009), IGF-1 levels (Economou et al. 2005), and cytogenetics (status of chromosomes 3, 5, and 8) (Damato et al. 2007). The genetic features of UM have strong associations to the clinical prognosis; however, for accurate monitoring, a combination of clinical tests and imaging studies is required (Damato et al. 2011).

Patients determined to be at low risk for metastasis undergo liver function tests and/or imaging studies such as ultrasound, computed tomography scan, or magnetic resonance imaging once a year. Those determined to be high risk require similar tests at least 2-4 times per year; approximately 65% of high-risk patients will go on to relapse with metastatic disease within five years of their primary disease treatment (Damato et al. 2011; Plasseraud et al. 2016; Carvajal et al. 2017). The life expectancy of patients with metastatic UM is currently dismal and has not changed

in the last 40-years (when accurate records began) and more effective therapies are urgently needed (Khoja et al. 2019).

B.1.3.2 Epidemiology and risk factors

In the UK, UM is a rare disease, the total incidence population for UM based on ONS diagnostic codes C69.3 and C69.4 is 540 patients per year (ONS 2019), of whom around half will go on to develop metastatic UM (Kolandjian et al. 2013).

Some epidemiologic studies have reported a higher incidence of UM in males; however, a large cohort study has demonstrated that there is no incidence difference between males and females, with previously reported differences being associated with age (Shields et al. 2009; Singh et al. 2011). UM can occur rarely in children and young adults but is much more common in older age groups (Al-Jamal et al. 2016). The median patient age at diagnosis is 62 years; however, the peak age range for diagnosis is between 70 and 79 years (Andreoli et al. 2015; Amaro et al. 2017). In addition, a meta-analysis on associated risk factors for UM found cutaneous and iris nevi, light-coloured irises, fair skin colour, propensity to sunburn, cutaneous freckles and ocular/oculodermal melanocytosis constituted risk factors for developing UM (Singh et al. 1998; Nayman et al. 2017).

Metastatic UM develops in 40-50% of cases (Kolandjian et al. 2013; Singh et al. 2018b; Yang et al. 2018) with hematogenous spread (via the circulatory system) to the liver first, occurring in 90% of individuals who develop metastatic disease. The most common metastatic localisations in the remaining 10% of patients are in the lungs and bones (Bedikian 2006; Tsantoulis et al. 2019). The extent of metastatic disease in the liver is an important determinant of clinical progression and survival (Nathan et al. 2015a). Liver failure is the most common cause of death in metastatic UM; patients have a median survival time of 12 months, with about half dying within 1 year (Carvajal et al. 2017; Rantala et al. 2019a).

B.1.3.3 Pathophysiology

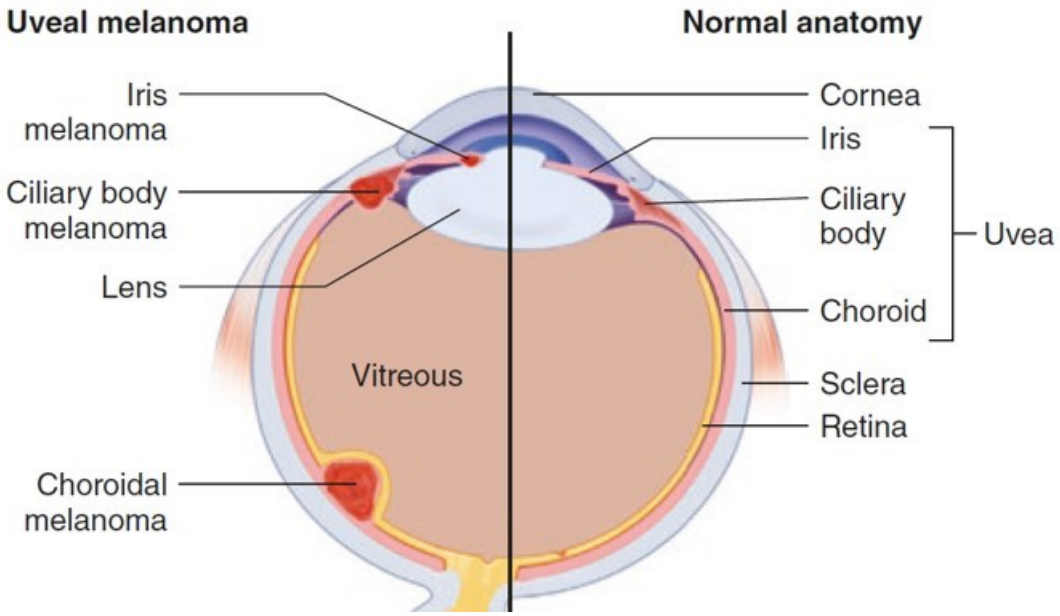
UM is distinct from other types of melanoma in its molecular pathology and pathophysiology. It arises from pigmented melanocyte cells in the choroid of the eye, iris, or ciliary body (Figure 3). Primary UM localised to the choroid occurs in 85% to

90% of cases; more rarely, it arises from cells in the ciliary body (5-8%) or the iris (3%-5%) (Nathan et al. 2015a; Krantz et al. 2017).

UM refers strictly to intraocular melanoma and is fundamentally different to melanoma of the eyelid and conjunctiva. Eyelid and conjunctival melanoma are external to the eye and have similar pathogenesis, genetics, risk factors, routes of metastasis, and response to treatment as cutaneous melanoma (CM).

UM and CM are both derived from melanocyte cells, but they are pathologically very distinct cancers with differing clinical and molecular features, as well as different risk factors, genetics, and modes of metastatic spread (van der Kooij et al. 2019). As a result, UM and CM have very different responses to treatments and while there are numerous effective therapies for CM there are still no proven effective therapies for UM.

Figure 3. Location of uveal melanoma within the eye (iris, ciliary body, choroid). Adapted from Milam and Daniels (2018)



B.1.3.4. Quality of life

Evidence, although sparse, suggests that patients with metastatic UM have a lower quality of life (QoL) and a greater frequency of mental-health disorders, including anxiety and depression. A study by Nshimiyimana et al. (2018) demonstrated that,

among 65 metastatic UM patients completing the Hospital Anxiety and Depression Scale (HADS) and the World Health Organization Quality of Life-BREF (WHOQOL-BREF) instruments, 30.8% (n=20) had at least borderline anxiety, 13.8% (n=9) had at least borderline depression, and 32.3% (n=21) had a decrease in QoL. Patients aged 18 to 60 years had a significantly higher anxiety score (7.52±3.65; P=0.003) and lower QoL in environmental health (32.48±5.23; P=0.006) than patients aged >60 years. Moreover, those with a shorter duration of illness since metastasis had higher anxiety scores (<1 year [7.79 ±3.72], 1 to 5 years [5.75 ±3.45], >5 years [3.70 ±2.79]; P=0.01) (Nshimiyimana 2018).

A study in Israel assessed the QoL of UM patients utilising the European organisation for research and treatment of cancer quality of life questionnaire (EORTC QLQ), comprised of the EORTC QLQ-C30 (a general cancer module) and the EORTC QLQ-OPT30 (a module specific to ophthalmic cancer) (Frenkel et al. 2018). Despite the small cohort size (n=13) rendering the statistical analysis invalid, the study demonstrated a trend towards lower QoL in the general QoL variable, more mental health symptoms, and more worries about the future among patients with metastatic UM compared to patients with primary UM.

B.1.3.4 Patient treatment pathways

UM is a rare disease and for metastatic UM there are currently no NICE clinical guidelines, patient pathways, or technical assessments on the condition. The following NICE guidance is available for CM on the use of checkpoint inhibitors, several of which cover advanced melanoma generically:

- Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma [TA268] (NICE 2012)
- Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma [TA319] (NICE 2014)
- Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab [TA357] (NICE 2015c)
- Pembrolizumab for advanced melanoma not previously treated with ipilimumab [TA366] (NICE 2015b)

- Nivolumab for treating advanced (unresectable or metastatic) melanoma [TA384] (NICE 2016a)
- Nivolumab in combination with ipilimumab for treating advanced melanoma [TA400] (NICE 2016b)

There are NICE clinical guidelines on *Melanoma: assessment and management* [NG14] (NICE 2015a) and accompanying patient pathways on this condition (NICE 2021a). However, guidance on cutaneous malignant melanoma is of limited relevance to primary UM and metastatic UM because they are pathologically very distinct cancers (Singh et al. 2018a). In addition, patients with metastatic UM were excluded from the registration trials for checkpoint inhibitors further demonstrating the NICE clinical guidelines on *Melanoma are* inappropriate for metastatic UM.

A single UK NICE accredited guideline was published for UM (Nathan et al. 2015a). This guideline used methodology consistent with the Scottish Intercollegiate Network (SIGN). A summary of the guidelines is illustrated in Figure 4. Additionally, there is an NHS service contract published for the condition which is in the remit of the Highly Specialised Service (HSS) for ocular oncology (NHS England 2014).

Treatment of primary UM is generally effective. However, up to 50% of patients are of high risk of developing metastatic disease, predominantly (~90%) in the liver. Active surveillance for metastatic UM is recommended (Nathan et al. 2015). Prognosis is poor following diagnosis of metastases with survival typically less than 12 months.

There is no nationally accepted standard of care (SoC) for metastatic UM. Current guidelines recommend clinical trial participation when clinically appropriate (Nathan et al. 2015a). Prior to the development of tebentafusp, there were no treatments that have demonstrated a significant clinical or survival benefit. Studies show fewer than 10% of patients with metastatic UM achieve an overall response to treatments tested (Carvajal et al. 2017).

Two large comprehensive meta-analyses have recently been published on clinical trials for metastatic UM. The clinical trials had tested a wide range of therapeutic approaches including liver-directed therapies, systemic chemotherapies,

immunotherapies, and targeted agents. The first examined individual patient data from 29 clinical trials conducted between 2000-2016 on a total of 912 patients examining a range of therapeutic approaches. This meta-analysis demonstrated a median OS of 10.2 months (95% CI: 9.5 to 11.0) and a 12-month OS rate of 43% (95% CI: 40 to 47) (Khoja et al. 2019). The second meta-analysis examined 2494 patient outcomes from 37 prospective studies and 41 retrospective studies conducted between 1980 and 2017. The median OS was 12.8 months (95% CI: 12 to 13.6) and a 12-month OS rate of 52% (95% CI: 50 to 54) (Rantala et al. 2019a).

B.1.3.5 Tebentafusp

Tebentafusp will be indicated for treatment of HLA-A*02:01-positive adults with unresectable or metastatic UM.

Current NICE treatment guidelines for the treatment of melanoma, i.e., guidelines NG14 and CSG8, refer specifically to skin cancer (CM) and do not include unresectable or metastatic UM. Consequently, tebentafusp, the first licensed treatment for this rare disease, does not fit within the present NICE guidelines for melanoma. Tebentafusp will set a new SoC offering the first effective treatment option for HLA-A*02:01-positive patients with unresectable or metastatic UM (Figure 4).

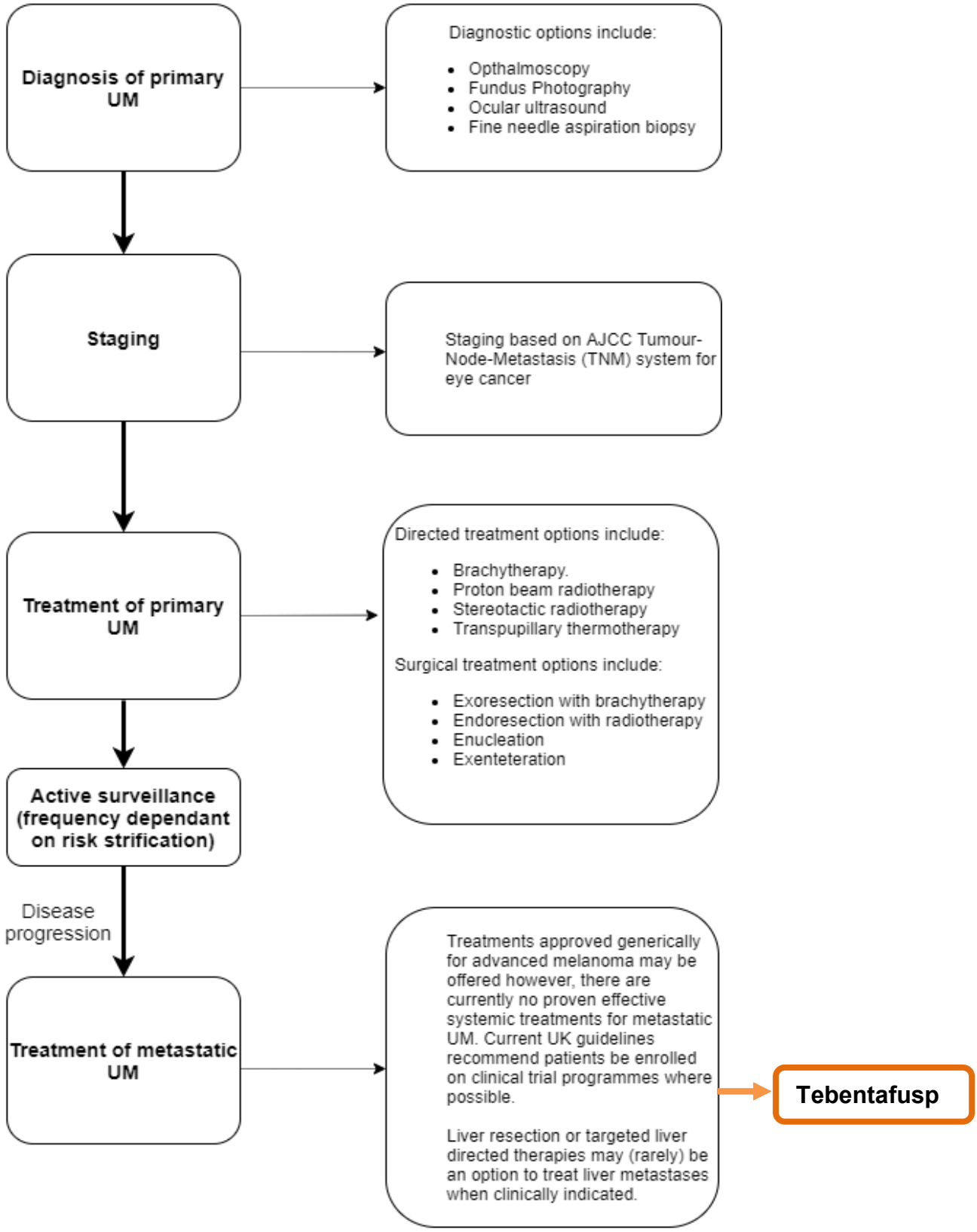
Patient population for tebentafusp

UM is a rare disease, the total patient population for UM based on ONS codes C69.3 and C69.4 is 540 patients (ONS 2019), of whom 40-50% will develop metastatic disease (Kolandjian et al. 2013). Just less than half of these patients will be HLA-A*02:01-positive, and not all will be clinically eligible for treatment. Clinical experts have advised that some patients with metastatic UM do not wish to pursue treatment options due old age and/or fragility. The total patient population eligible for tebentafusp is, therefore, estimated to be less than 100 patients per year. Table 3 outlines the calculations for incidence and prevalence of metastatic UM in England and Wales, based on source data from the Office of National Statistics.

Table 3. Patient numbers eligible for tebentafusp treatment in England and Wales

Input	Patient number	Reference
Incidence of UM	540	ONS (2019)
Incidence of metastatic UM (50%)	270	Kolandjian et al. (2013)
HLA-A*02:01-positive patients (47%)	127	The Allele Frequencies Database (2021)
Final incidence (clinically eligible patients)	102	Clinical expert opinion
Estimated prevalence based on current survival data (one-year survival 12-15%)	~115	(Nathan et al. 2015a)

Figure 4. Patient flow of patients diagnosed with primary UM (adapted from Nathan et al. 2015)



Abbreviations: UM, uveal melanoma; OCT, ocular coherence tomography

B.1.3.6 Unmet need

Currently, there is no nationally accepted SoC for patients who have been diagnosed with metastatic UM. The NICE accredited guidelines recommend clinical trial participation when clinically appropriate (Nathan et al. 2015a).

A wide range of treatment modalities have been studied in the treatment of metastatic UM in trials, including liver-directed therapies (e.g., hepatic resection, hepatic intra-arterial chemotherapy, hepatic arterial chemoembolization, isolated hepatic perfusion), systemic chemotherapy, immunotherapy (e.g., anti-CTLA-4 monoclonal antibody or PD-L1 blocking antibody), and targeted agents (e.g., MEK inhibitors) (Carvajal et al. 2017; Rantala et al. 2019a). No therapy has demonstrated a substantial benefit specifically for patients with metastatic UM (Yang et al. 2018; Khoja et al. 2019). Fewer than 10% of patients achieve an overall response to these treatments (Carvajal et al. 2017).

As a result of limited treatment options, the prognosis and outcomes of patients with metastatic UM have not improved in nearly 40 years. The median survival time of patients with metastatic UM is 6 to 12 months after a distant metastasis has been detected (Schefler and Kim 2018) and the 5-year relative survival is ~15% (statistics 2020).

Tebentafusp is the first therapy to have shown significant clinical benefit, particularly a survival benefit.

B.1.4 Equality considerations

The use of tebentafusp for UM is not likely to raise any equality issues.

B.2 Clinical effectiveness

Summary
The clinical development programme for tebentafusp in the treatment of metastatic UM included two major clinical trials following a first in human study: 1. **A randomised controlled trial (RCT), study IMCgp100-202, in previously untreated patients** (NCT03070392) initiated in October 2017 with a primary completion date in October 2021, and a final study completion date estimated to be March 2023 2. **A single-arm dose-ranging trial, study IMCgp100-102, in patients treated with one or more prior lines of therapy, including chemotherapy, immunotherapy, or local therapy** (NCT02570308) initiated in February 2016 with primary completion in June 2020

B.2.1 Identification and selection of relevant studies

Full details of the identification and selection of the relevant studies are provided in Appendix D.

B.2.1.1 Search strategy

A systematic literature review (SLR) was conducted to identify all relevant clinical evidence from the published literature reporting the clinical efficacy, safety, and tolerability of relevant comparator therapies to tebentafusp for adult patients with advanced UM.

The searches were designed to meet the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. Initial searches were performed in March 2020 and an updated search was performed in September 2021.

Full details of the searches are provided in Appendix D.

B.2.1.2 Study selection

Details of the methods of study selection are provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

In total, three studies with tebentafusp were included which informed the decision problem. These were a first-in-human Phase 1 study (NCT01211262), known as the

IMCgp100-01 study (Middleton et al. 2020), a Phase 1/2 study, known as the IMCgp100-102 study (NCT02570308) (Sacco et al. 2020) and a Phase 3 randomised control trial (RCT), known as the IMCgp100-202 study (NCT03070392) (Nathan et al. 2021). The characteristics of these studies are summarised in Table 4.

Table 4. Clinical effectiveness evidence

Study	IMCgp100-202 (NCT03070392)	IMCgp100-102 (NCT02570308)	IMCgp100-01 (NCT01211262)
Study design	Multicentre, parallel, open label, randomised, Phase 3 trial	Phase 1 study was standard dose escalation design; Phase 2 was an expansion cohort study with patients receiving prior systemic treatment or liver-directed treatment	Multicentre, Phase 1, open-label, dose-finding study
Population	Patients with local histologically or cytologically confirmed metastatic UM, who were HLA-A*02:01–positive. Patients had no previous systemic or liver-directed therapy for metastatic disease; had an ECOG score of 0 or 1; and had at least one measurable lesion, according to RECIST (version 1.1.20)	Patients with a histologically or cytologically confirmed diagnosis of metastatic UM with a life expectancy of >3 months and who tested positive for HLA-A*02:01. Patients who experienced disease progression while on 1 or 2 prior lines of therapy, including chemotherapy, immunotherapy, or targeted therapy, in the metastatic or advanced setting were included in the Phase 2 dose expansion cohort.	Patients with advanced melanoma who were HLA-A*02:01–positive. Patients had predominantly CM (N=61), although UM (N=19) and other origin (acral, lentiginous, mucosal, and unknown primary) were included (N=4)
Intervention(s)	Tebentafusp at a dose of 20 µg on day 1, 30 µg on day 8, and 68 µg weekly thereafter	Tebentafusp administered as an escalation regimen consisting of fixed doses at 20 µg, 30 µ µg then incrementally increased to explore the optimum therapeutic dose. The Phase 1 part of the study identified 20 µg, 30 µg then 68 µg weekly thereafter as the appropriate dose for the Phase 2 dose expansion phase.	Tebentafusp administered at a weekly (arm 1) and a daily (arm 2) basis. Dose escalation from 5 to 900 ng/kg; dose expansion to 600 ng/kg converted to a 50 µg flat dose and once daily (4 days every 3 weeks, dose ranges from 10 to 50 µg). In this study intra-patient escalation was tested with 20, 30, 50 µg regimen. 50 µg was identified as MTD.
Comparator(s)	Investigator's choice of treatment: • pembrolizumab • ipilimumab	N/A	N/A

Study	IMCgp100-202 (NCT03070392)	IMCgp100-102 (NCT02570308)	IMCgp100-01 (NCT01211262)
	• dacarbazine		
Indicate if trial supports application for marketing authorisation	Yes	Yes	Yes
Indicate if trial used in the economic model	Yes	No	No
Rationale for use/non-use in the model	Pivotal Phase 3 trial providing comparative evidence on the efficacy and safety of tebentafusp with standard care	Single-armed trial did not report comparative data	Single-armed trial did not report comparative data
Reported outcomes specified in the decision problem	• OS (primary outcome) • PFS • ORR • DOR • Adverse effects of treatment • HRQoL (EQ-5D,5L and EORTC QLQ-C30 instrument)	• ORR (primary outcome) • PFS • OS • DOR • Adverse effects of treatment	• MTD of daily administration • MTD of weekly administration • Treatment-related adverse events • BOR per Response Evaluation Criteria In Solid Tumors (RECIST)
All other reported outcomes	• PK profile • Anti-tebentafusp antibody formation • Peripheral cytokine levels • Health- and treatment-related medical resource utilisation associated with the advanced UM disease pathway	• Identification of MTD • Anti-tebentafusp antibody formation • MinR	• PK profile • Anti-tebentafusp antibody formation • Peripheral cytokine levels • Analysis of biomarkers

Abbreviations: BOR, best overall response; CM, cutaneous melanoma; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; FIH, first in human; HRQoL, health-related quality of life; KM, Kaplan-Meier; MinR, minor response rate; MTD, maximum tolerated dose; metastatic UM, metastatic uveal melanoma; NA, not applicable; OOR, objective response rate; OS, overall survival; PFS, progression free survival; PKs, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumours

Study IMCgp100-102 (NCT02570308) was not used to populate the economic model but is included in sections 2.2 to 2.6. The results of this study are relevant to advanced UM patients previously treated with one or two lines of therapy. This study was not included in the economic model because it is a single arm study with a smaller sample size. Study IMCgp100-01

is not considered further in this dossier because it does not inform the decision-problem.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

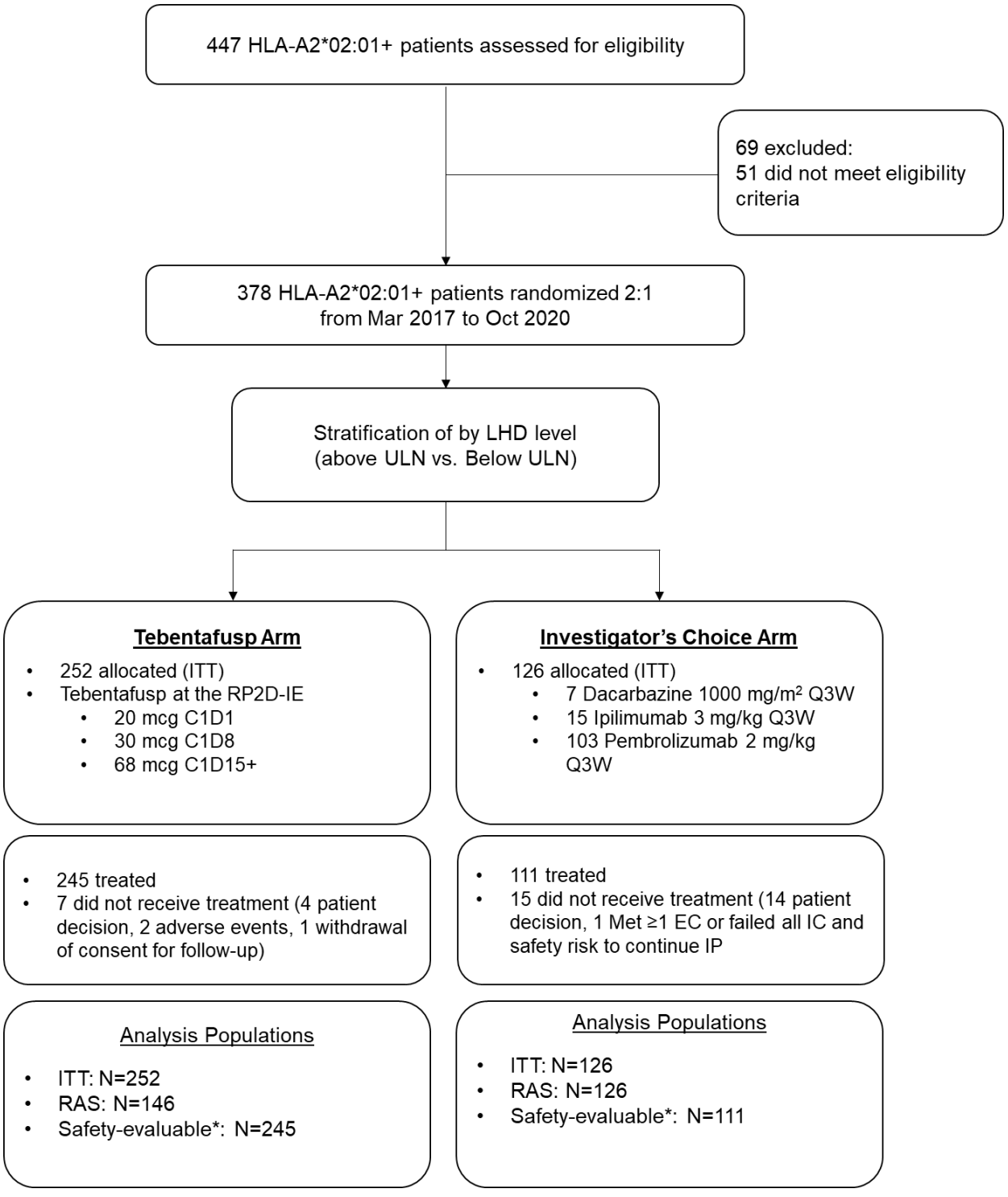
B.2.3.1 IMCgp100-202 study

Study IMCgp100-202 is an ongoing, multicentre, parallel, open-label, Phase 3 trial, which randomised previously untreated patients with metastatic UM who were HLA-A* 02:01–positive to receive tebentafusp (intervention group) or the investigator's choice of therapy with single-agent pembrolizumab, ipilimumab, or dacarbazine (control group) in a 2:1 ratio. Prior to this study, no therapy had demonstrated a survival benefit in patients with metastatic UM (Khoja et al. 2019; Rantala et al. 2019a). In the absence of standard care guidelines, clinicians have used checkpoint inhibitor treatments (e.g., ipilimumab or pembrolizumab) based on their approval for advanced melanoma generically (Nathan et al. 2015b). Thus, two options of checkpoint inhibitor treatments (pembrolizumab or ipilimumab) or an option of chemotherapy (dacarbazine) using the approved doses and regimens for treatment of metastatic melanoma were selected for the investigator's choice comparators. When the study was designed, combination immunotherapies (e.g., ipilimumab + nivolumab) were not regarded as standard care by clinical experts.

Patients were stratified according to their lactate dehydrogenase (LDH) level, because LDH level at the time of diagnosis has been identified as having a significant impact on prognosis in metastatic UM, being associated with shortened OS (Khoja et al. 2019). A schematic illustration of the trial design is reported in Figure 5.

The primary aim of the study was to compare the overall survival (OS) in the tebentafusp group with the investigator's choice of "standard care". On the basis of earlier data from the Phase 2 study IMCgp100-102 (Sacco et al. 2020), a second primary aim was to assess if rash is associated with survival in tebentafusp-treated patients. The randomisation of this study is intended to prevent bias in the choice of treatment assignment. Given the frequency of rash or pruritis following the first infusion, an open-label design was chosen because the treatment assignment could not be blinded. Patients (N=378) were enrolled into the IMCgp100-202 study between March 2017 through to June 2020. Two interim analyses were planned after the occurrence of approximately 150 events and 200 events (60% and 80% of the anticipated events). Results are also presented from a data cut-off performed in August 2021. Following the first interim analysis (October 2020), patients in the control arm were permitted to cross over to receive tebentafusp, results from the August 2021 data cut include these patients. Analysis of the primary interim data (October 2020) has been published, with a median duration of follow-up of 14.1 months (Nathan et al. 2021). Details of the IMCgp100-202 study are reported in Table 5.

Figure 5. IMCgp100-202 consort diagram: Study design, participant enrolment and disposition in the ITT population at the first interim analysis



Abbreviations: C, cycle; D, Day; HLA, human leukocyte antigen; ITT, intention-to-treat, LDH, lactate dehydrogenase; RAS, rash analysis dataset; RP2D, recommended phase 2 dose; ULN, upper limit of normal
*Includes all patients who received ≥1 dose of study treatment. †Defined as the time from randomization to the date of death or database cut-off date of October 13, 2020, if the patient was alive.

Table 5. Detailed characteristics of IMCgp100-202 study

Trial number	Study IMCgp100-202 (NCT03070392) (data on file)
Trial design	Phase 3 multi-centre, open-label, parallel, randomised controlled trial
Eligibility criteria for participants	Inclusion criteria 1. Male or female patients aged ≥18 years of age at the time of informed consent 2. Ability to provide and understand written informed consent prior to any study procedures 3. Histologically or cytologically confirmed metastatic UM 4. Had to meet the following criteria related to prior treatment: • No prior systemic therapy in the metastatic or advanced setting including chemotherapy, immunotherapy, or targeted therapy • No prior regional liver-directed therapy, including chemotherapy, radiotherapy, or embolisation • Prior surgical resection of oligometastatic disease was allowed • Prior neoadjuvant or adjuvant therapy was allowed provided administered in the curative setting in patients with localised disease. Patients must not have been retreated with an investigator's choice therapy that was administered as adjuvant or neoadjuvant treatment. Additionally, patients who received nivolumab as prior adjuvant/neoadjuvant treatment should not have received pembrolizumab as investigator's choice therapy 5. HLA-A*02:01 positive by central assay 6. Life expectancy of > 3 months as estimated by the investigator 7. ECOG performance status score of 0 or 1 at screening 8. Patients had measurable or non-measurable disease according to RECIST v1.1 9. All other relevant medical conditions had to be well-managed and stable, in the opinion of the investigator, for at least 28 days prior to first administration of study drug Key Exclusion criteria Patient with any out-of-range laboratory values defined as: 1. Serum creatinine >1.5 × ULN and/or creatinine clearance <50 mL/minute 2. Total bilirubin >1.5 × ULN, except for patients with Gilbert's syndrome, who were excluded if total bilirubin >3.0 × ULN or direct bilirubin >1.5 × ULN 3. Alanine aminotransferase >3 × ULN 4. Aspartate aminotransferase >3 × ULN 5. Absolute neutrophil count <1.0 × 109/L 6. Absolute lymphocyte count <0.5 × 109/L 7. Platelet count <75 × 109/L 8. Hemoglobin <8 g/dL

<table>
<tr><td></td><td>9. History of severe hypersensitivity reactions (e.g., anaphylaxis) to other biologic drugs or monoclonal antibodies
10. Clinically significant cardiac disease or impaired cardiac function</td></tr>
<tr><td>Settings and locations where the data were collected</td><td>
<table>
<tr><th>United States and Canada</th><th>Australia</th></tr>
<tr><td>• UCLA Medical Center
• The Angeles Clinic and Research Institute
• Byers Eye Institute, Stanford University
• California Pacific Medical Center
• University of Colorado
• Mount Sinai Medical Center
• Winship Cancer Institute of Emory University
• Northwestern University
• The University of Chicago Medicine
• University of Iowa
• Massachusetts General Hospital
• Dana Farber Cancer Institute
• Washington University School of Medicine
• Roswell Park Cancer Institute
• Columbia University Medical Center
• Memorial Sloan Kettering Cancer Center
• Duke University Health System
• The Ohio State University
• University of Oklahoma
• Portland Providence Medical Center
• Thomas Jefferson University Hospital
• University of Pittsburgh Medical Center
• Houston Methodist Cancer Center</td><td>• Saint Vincent’s Hospital
• Melanoma Institute of Australia
• Central Adelaide Local Health Network, Royal Adelaide Hospital Cancer Center
• Peter MacCallum Cancer Center
Belgium
• Institut Roi Albert II Cliniques Universitaires St-Luc
France
• Centre Antoine Lacassagne
• Institut Curie
Germany
• Universitaetsklinikum Koeln Dermatologie und Venerologie
• Charite - Campus Benjamin Franklin
• Universitätsklinikum Carl Gustav Carus
• University Hospital Essen
• University of Hamburg
• Nationales Centrum für Tumorerkrankungen
• Klinik und Poliklinik für Dermatologie und Allergolog
Italy
• Fondazione ICCRS
• Istituto Nazionale Tumori - IRCCS Fondazione "G. Pascale" - UOC Melanoma, Immunoterapia Oncologica e Terapie Innovative</td></tr>
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	• Cross Cancer Institute • Princess Margaret Cancer Centre	
	Netherlands	**Switzerland**
	• LUMC Medical Oncology	• University of Zurich Hospital
	Poland	**United Kingdom**
	• Centrum Onkologii - Instytut im. Marii Sklodowskiej-C	• Mount Vernon Cancer Centre • The Clatterbridge Cancer Centre • Beatson West of Scotland Cancer Centre
	Russian Federation	**Ukraine**
	• Federal State Budgetary Institution N.N. Blokhin National Medical Research Center of Oncology • Federal State Budget Institution National Medical Research Center of Oncology • State Budgetary Healthcare Institution Volgograd Regional Clinical Oncology Dispensary	• Dnipropetrovsk State Medical Academy • Kyiv Munitipal Hospital • Uzhhorod Central City Clinical Hospital • Zaporizhzhia Regional Clinical Oncology Center
	Spain	
	• Institut Catala d'Oncologia (ICO) - L'Hospitalet • Hospital Universitario La Paz • Hospital Clínico Universitario de Santiago de Compostela • Hospital Universitario General de Valencia • Hospital Universitario Virgen Macarena	
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered)	From March 2017 to June 2020, a total of 442 HLA-A*02:01–positive patients were screened, with 378 patients being eligible for inclusion. Patients were randomised in a 2:1 ratio to either of two treatment groups (arms 1 and 2): <u>Arm 1: tebentafusp (n=252)</u> All patients randomised to arm 1 received tebentafusp by IV infusion following the intra-patient escalation regimen. Patients received 20 µg on C1D1, 30 µg on C1D8, and an escalated dose of 68 µg on C1D15 and weekly thereafter. Due to the anticipated cytokine release-associated toxicity with tebentafusp following the first three doses, patients were monitored for at least 16 hours after dosing as an inpatient following the weekly doses on C1D1, C1D8, and C1D15. Use of prophylactic steroids was not mandated.	

Intervention(s) (n=[x]) and comparator(s) (n=[x]) **Permitted and disallowed concomitant medication**	Arm 2: Investigator's choice (n=126) All patients randomised to arm 2 received investigator's choice of one of the following three options: • Dacarbazine at the standard dosing regimen in UM of 1000 mg/m^2 given on Day 1 of each 21-day cycle (n=7) • Ipilimumab at the dosing regimen for unresectable or metastatic melanoma of 3 mg/kg given on Day 1 of each 21-day cycle for a maximum of 4 doses (n=16) • Pembrolizumab at the dosing regimen of 2 mg/kg up to a maximum of 200 mg or 200 mg administered IV were approved locally given on Day 1 of each 21-day cycle. The preferred investigator's choice agent was selected prior to randomization. No extended monitoring after dosing was required in Arm 2 (n=103) Concomitant medications (e.g., anti-diarrhoeal drugs, antiemetics, or electrolyte supplementation) deemed necessary to provide adequate prophylactic or supportive care were allowed, except for medications identified as prohibited. There was no difference in drug restrictions between arms.
Primary outcomes (including scoring methods and timings of assessments)	The predefined, dual primary objectives were: • To compare the OS in all patients randomised to tebentafusp monotherapy versus all patients randomised to investigator's choice monotherapy • To compare the OS in all patients randomised to tebentafusp monotherapy who develop a rash within the first week of treatment versus all patients randomised to investigator's choice monotherapy Both objectives relate to HLA-A*02:01-positive patients with advanced UM with no prior treatment in the metastatic setting. The OS endpoint, which is used in the model, is defined as the time from randomisation until death by any cause.
	An additional primary objective was to compare the OS in all patients randomised to tebentafusp monotherapy who develop a rash within the first week of treatment versus all patients randomised to investigator's choice monotherapy. The rationale for this was related to the analysis of study IMCgp100-102, which reported that rash appeared to be associated with a clinical benefit across all efficacy endpoints including tumour shrinkage and PFS (both per an independent radiology committee) and OS. Therefore, this shared primary objective aimed to confirm these analyses by comparing OS in patients randomised to tebentafusp monotherapy who developed a rash within the first week of treatment, with those who did not.
Other outcomes used in the economic model/specified in the scope	The secondary outcome used in the study is PFS (comparison of arms 1 and 2). PFS was defined as the time from randomisation to the date of first documented progression (per RECIST v1.1.) as determined by investigator assessment or death due to any cause, whichever occurred first, regardless. Radiological assessments for PFS were performed as scheduled every 12 weeks, using a reference to C1D1 and were not to follow delays incurred during the treatment period. Other outcomes reported that were specified in the scope were: • ORR (using RECIST v1.1)

	• DOR (using RECIST v1.1) • Adverse effects of treatment • HRQoL (using the EQ-5D-5L for generic HRQoL and the EORTC QLQ-C30 for disease-specific HRQoL)
Co-primary endpoints	The following co-primary endpoint subgroup analyses were analysed for OS and PFS: ethnicity; gender; age; ECOG status; alkaline phosphatase status; LDH status; prior systemic therapy; largest metastatic lesion recorded at baseline; region; investigator's choice of chemotherapy (ipilimumab, dacarbazine and pembrolizumab)
Abbreviations: C, cycle; D, day; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; IV, intravenous; HLA, human leukocyte antigen; LDH, lactic dehydrogenase; metastatic UM, metastatic uveal melanoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PFS2, time to second disease progression; RECIST, Response Evaluation Criteria in Solid Tumours	

B.2.3.2 IMCgp100-102 study

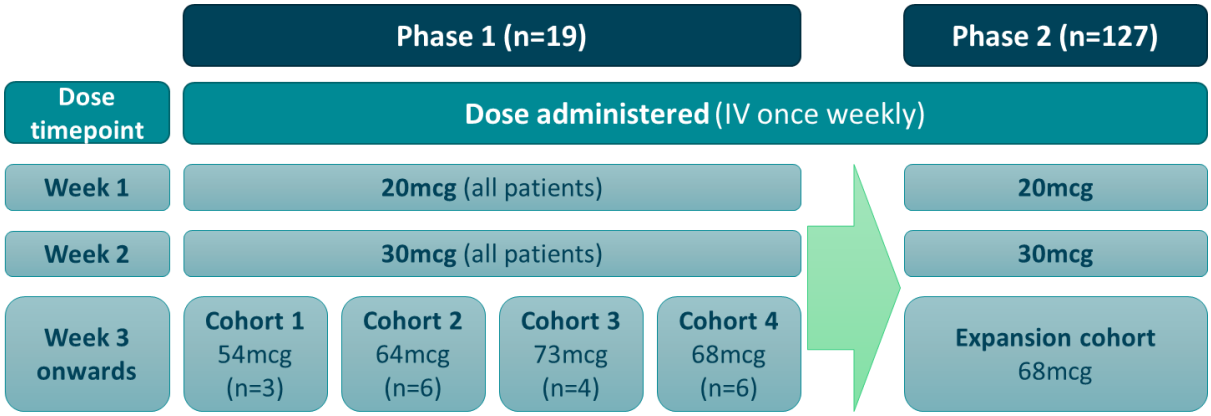
The IMCgp100-102 study (NCT02570308) was a Phase 1/2, single-arm, open label multicentre study. The results were presented at the European Society for Medical Oncology conference (ESMO, 2020) (Sacco et al. 2020). It followed a first in human safety study (Middleton et al. 2020). Study IMCgp100-102 was designed with two phases:

1. Phase 1 (dose-finding) aimed to identify the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) and/or the recommended Phase 2 dose (RP2D) of tebentafusp using a process of dose escalation

2. Phase 2 (expansion) aimed to estimate the objective response rate (ORR) based on the Response Evaluation Criteria in Solid Tumours (RECIST v1.1) in patients with metastatic UM who were treated with the recommended RP2D

The study had a number of secondary objectives, including: assessment of the antitumour effect of tebentafusp through measurement of OS, progression free survival (PFS), disease control rate (DCR), time to response, and duration of response (DOR); assessment of safety and tolerability; characterisation of pharmacokinetics; and evaluation of anti-tebentafusp antibody formation. Exploratory analyses were also performed to identify prognostic predictors of good or poor clinical outcomes. A summary of the study schema is illustrated in Figure 6.

Figure 6. IMCgp100-102 study schema



The population enrolled in Phase 1 (n=19) had a histologically or cytologically confirmed diagnosis of metastatic UM and had tested positive for HLA-A*02:01, as assessed by a central assay. Patients in Phase 1 were not excluded on the basis of previous therapies. For the Phase 2 (expansion) study (n=127), patients were initially categorised into cohorts depending on the previous treatments they had received (cohort A being second-line to checkpoint inhibitors, cohort B being second or third-line to a range of therapies). However, it was found there was significant overlap between the cohorts, so analysis was conducted on the combined cohort. Details of the IMCgp100-102 study are reported in Table 6. Study IMCgp100-102 (NCT02570308) was not used to populate the economic model but is included in sections 2.2 to 2.6. Although relevant to the decision problem, this study was not included in the economic model because it is a single arm study with a smaller sample size.

Table 6. Detailed characteristics of IMCgp100-102 study

Trial number	Study IMCgp100-102 (NCT02570308) (data on file)
Trial design	Phase 1/2 open-label, multicentre study using an intra-patient escalation dosing regimen.
Eligibility criteria for participants	Inclusion criteria 1. Male or female patients aged ≥18 years at the time of informed consent 2. Ability to provide and understand written informed consent prior to any study procedures 3. Histologically or cytologically confirmed diagnosis of metastatic UM 4. Surgically sterile patients or patients of childbearing potential who agree to use highly effective methods of contraception during study dosing and for 6 months after last dose of study drug 5. HLA-A*0201 positive 6. ECOG performance status of 0 or 1 at screening 7. Patients in Phase 2 will include patients with previously treated uveal melanoma in the metastatic setting Exclusion criteria 1. Presence of symptomatic or untreated CNS metastases, or CNS metastases that require doses of corticosteroids 2. History of severe hypersensitivity reactions to other biologic drugs or monoclonal antibodies 3. Patient with any out-of-range laboratory values 4. Clinically significant cardiac disease or impaired cardiac function 5. Active infection requiring systemic antibiotic therapy 6. Known history of HIV infection 7. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection per institutional protocol 8. Patients receiving systemic treatment with systemic steroid therapy or any other immunosuppressive medication at any dose level that would interfere with the action of the study drugs, in the opinion of the investigator 9. Malignant disease, other than that being treated in this study 10. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study because of safety concerns, compliance with clinical study procedures, or interpretation of study results 11. Presence of National Cancer Institute–Common Terminology Criteria for Adverse Events grade ≥2 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if grade ≥3) because of prior cancer therapy 12. Pregnant, likely to become pregnant, or lactating women

Settings and locations where the data were collected	The study was set up in 18 centres in the United States, 2 centres in Germany, 4 centres in Spain, and 2 centres in the United Kingdom (The Clatterbridge Cancer Centre and Mount Vernon Cancer Centre).
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	Phase 1 study (dose escalation) Patients (n=19) received tebentafusp at 20 µg in week 1, and at 30 µg in week 2. At week 3 onwards, patients received tebentafusp at 54 µg (n=3), 64 µg (n=6), 73 µg (n=4), and 68 µg (n=6). Phase 2 (expansion cohort) Patients (n=127) received tebentafusp at 20 µg in week 1, and at 30 µg in week 2. At week 3 onwards, all patients received tebentafusp at 68 µg. During the course of the study, patients were not permitted to receive other additional investigational drugs, agents, devices, chemotherapy, or any other therapies that may have been active against cancer. Additionally, no other systemic therapeutic monoclonal antibodies, except for denosumab and tocilizumab if required for patient care, and no immunosuppressive medication, were administered while on this study, unless prescribed to manage toxicity. While systemic corticosteroid therapy may have interfered with the mechanism of action of the study medications, its use was recommended in some settings.
Primary outcomes (including scoring methods and timings of assessments)	For the Phase 1 dose escalation study, efficacy was not the primary endpoint. For the Phase 2 the primary outcome was the ORR. This was measured using RECIST criteria (v. 1.1) according to an independent central review.
Other outcomes used in the economic model/specified in the scope	Two additional outcomes were used in the economic model: • OS, defined as the time from the first day of the first cycle until death by any cause. • PFS, defined as the time from randomization to the date of first documented progression (per RECIST v1.1.) as determined by investigator assessment or death due to any cause, whichever occurred first, regardless. Modified irRECIST for patients who continue treatment beyond RECIST v1.1 disease progression Radiologic assessments were performed every 8 or 12 weeks. Other outcomes reported that were specified in the scope were: • ORR (using RECIST v1.1) • DOR (using RECIST v1.1) • Adverse effects of treatment • HRQoL, assessed using the EQ-5D-5L for generic HRQoL and the EORTC QLQ-C30 for disease specific HRQoL
Pre-planned subgroups	Initially it was intended that two separate expansion cohorts in metastatic UM would be enrolled: • Cohort A was to enrol patients with metastatic UM in the second-line setting after disease progression following systemic treatment with a checkpoint inhibitor and to recruit approximately 20 patients • Cohort B was to enrol patients with metastatic UM in the second or third line setting with up to one prior line of liver-directed therapy and to recruit approximately 130 patients

	However, in practice, there was significant overlap between the Cohort A and Cohort B populations, and it was not clear that patients belonged distinctly in either cohort. Therefore, this dossier will present data for the single combined phase 2 dose expansion cohort. No analysis of predefined subgroups was undertaken. However, exploratory ad hoc analysis was undertaken to understand factors associated with good or poor outcomes.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; IV, intravenous; irRECIST, immune related Response Evaluation Criteria in Solid Tumours; HLA, human leukocyte antigen; MTD, maximum tolerated dose; metastatic UM; metastatic uveal melanoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumours	

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 IMCgp100-202 study

The IMCgp100-202 study is an ongoing parallel registration RCT. Results were published in a peer reviewed journal in 2021 (Nathan et al. 2021). The primary endpoint was OS as evaluated in a time-to-event analysis. On the basis of a Phase 2 study that showed an association between rash and survival (Sacco et al. 2020), a co-primary endpoint was included of a prespecified analysis of OS in patients in the tebentafusp group in whom a rash had developed within 1 week after initiation of tebentafusp treatment, compared with all patients in the control group. However, as reported in a presentation at the American Society of Clinical Oncology (ASCO) 2021 (Hassel et al. 2021), further analysis of study IMCgp100-202 found that rash did not independently predict survival following adjustment for differences in baseline prognostic factors. Further details are provided in Section B.2.6.2.

The study analysis was performed on the intention-to-treat (ITT) population using appropriate hierarchal ranking of outcomes. Data is presented from the interim analysis October 2020 data cut-off and from a data cut-off in August 2021. On the basis of the survival benefit observed at the first interim analysis, patients in the control group were subsequently permitted to cross over to receive tebentafusp and data presented for the August 2021 cut-off includes this subset of patients.

The primary and secondary efficacy outcomes were analysed using time-to-event analysis using a landmarking approach to avoid immortal time bias (Gleiss et al. 2018).

The patient flow of the study is reported in Appendix D. Patients who discontinued drug treatment, because of progressive disease (PD) or for other reasons, were not considered withdrawn from the study and were included in analysis. A more detailed description of the statistical analysis undertaken is reported in Table 7.

Table 7. Summary of statistical analyses of the IMCgp100-202 study (NCT03070392)

Analysis domain	**IMCgp100-202 (NCT03070392)** **Primary interim analysis***
Hypothesis and aims	
Hypothesis objective	The dual primary objectives are to compare the OS in all patients randomised to tebentafusp monotherapy: • Compared with all patients randomised to investigator's choice monotherapy • Who develop a rash within the first week of treatment versus all patients randomised to investigator's choice monotherapy Both objectives relate to HLA-A*02:01-positive patients with advanced UM with no prior treatment in the metastatic setting
Statistical analysis of outcomes	
Descriptive statistics	Continuous variables were summarised using descriptive statistics (number of observations, mean, standard deviation, median, 25th and 75th percentiles, minimum, maximum). CIs were 95% and all tests were 2-sided, unless otherwise specified in the description of the analyses. For binomial variables, the normal approximation methods were employed unless otherwise specified.
Analysis of primary efficacy	There were two analyses of the primary endpoint of OS, relating to the two study objectives. The overall study 2-sided α-level of 5% was split between these objectives. For the first primary analysis of OS in the RAS, 10% of the study's overall Type I error rate was allocated to this analysis (α=0.5%). For the second primary analysis of OS in all randomised patients, 90% of the study's overall Type I error rate was allocated to this analysis (α=4.5%). However, if the first interim OS analysis in the RAS crossed the prespecified stopping boundary, then the α from that analysis was carried over to this ITT analysis and the overall α-level for that analysis would therefore be 5%. Otherwise, an overall α-level of 4.5% was applied to the ITT OS analyses. Both the first and second primary analyses used a 2-sided log-rank test stratified by LDH status. OS was compared between treatment arms using the Kaplan-Meier method and a stratified log-rank test.
Analysis of secondary efficacy endpoints	Secondary efficacy endpoints included PFS, ORR, BOR, DOR, and DCR. PFS and BOR were to be tested in a hierarchical manner. If the ITT analysis of OS was significant, then the ITT analysis of PFS was to follow next. If the ITT analysis of PFS was significant, then the ITT analysis of BOR was to be tested last.

	PFS was compared between treatment arms using a stratified log-rank test and were estimated using the Kaplan-Meier method. ORR and DCR were compared between treatment arms using a stratified Cochran Mantel-Haenszel test adjusting for baseline LDH status. Descriptive statistics for DOR were based on Kaplan-Meier estimates. CIs for secondary outcomes were not adjusted for multiplicity and therefore should not be used to infer cause-effect relationships.
Analysis of safety endpoints	All safety analyses were performed on the Safety Analysis Set. Safety data presented by treatment arm were summarized on an 'as treated' basis. Safety and tolerability variables included TEAEs, deaths, clinical laboratory parameters, vital signs, 12-lead ECG results, physical examinations, and extent of exposure. The type and severity of AE was based on NCI CTCAE (v4.03) grades) in relation to study treatment by treatment arm.
Patient flow	
Sample size, power calculation	OS was the primary endpoint for this study. Assuming a 2:1 randomisation ratio of tebentafusp versus investigator's choice, 250 events (deaths) were needed in the randomised trial to provide 89% power to detect a difference of survival distribution that could be characterised by a 0.645 HR for OS with a 2-sided significance level of 0.045. Assuming OS was exponentially distributed, this may have translated to a median OS of 18.6 months in the tebentafusp arm and 12 months in the investigator's choice arm. Considering a non-uniform recruitment of about 33 months and 10% annual drop-out rate, 369 patients needed to be randomised in a 2:1 ratio to the 2 arms in order to observe 250 events after 51 months as follows: • 246 patients to Arm 1 (tebentafusp) • 123 patients to Arm 2 (investigator's choice)
Data management, patient withdrawals and continuation	Study treatment was discontinued once PD was identified based on RECIST v1.1 unless criteria for treatment beyond initial PD was met. Other reasons for discontinuation included completion of investigator's' choice treatment regimen, initiation of alternative anticancer treatment, unacceptable toxicity, withdrawal of consent, and pregnancy. Patients assigned to tebentafusp, ipilimumab, or pembrolizumab who are treated beyond initial RECIST v1.1 PD had to permanently discontinue study treatment if they experience further progression warranting treatment discontinuation. Further progression warranting treatment discontinuation is defined as **ANY** one of the following observed at least 4 weeks after the initial PD assessment per RECIST v1.1: **1)** an additional ≥ 20% increase in tumour burden (sum of diameters of both target and new measurable lesions) accompanied by an absolute increase of ≥ 5 mm; **2)** unequivocal PD of non-target lesions; or **3)** new non-measurable lesions.

	Patients who discontinued study treatment were not to be considered withdrawn from the study and were included in ITT analysis.
Missing data and censoring	Patients who had not progressed or died at the time of the analysis were censored at the time of the last evaluable tumour assessment. Patients who progressed or died following at least 2 missed tumour assessments or not evaluable assessments were censored at the time of the last evaluable tumour assessment prior to the missed/not evaluable assessments.

Abbreviations: AE, adverse event; BOR, best overall response; DCR, disease control rate; DOR, duration response rate; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention to treat; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; RAS, rash analysis set; TEAE, treatment-emergent adverse events; UM, uveal melanoma.

* The primary interim analysis was triggered by the Independent Data Monitoring Committee's recommendation to unblind the study following the first prespecified interim analysis that was to occur when approximately 60% of the death events (150 events) had been observed

B.2.4.2 IMCgp100-102 study

The IMCgp100-102 study is a single arm study and did not include comparative analyses. Hence, there was no formal statistical testing of data. Statistical analysis was descriptive according to specified populations sets: ITT and safety analysis set. The results described in section B.2.6 are from the dose expansion Phase 2 part of the study on 127 metastatic UM patients.

The primary efficacy variable was ORR, defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) based on blinded independent central review (ICR), according to RECIST v1.1. Results from both investigators assessment and ICR assessment are presented in section B.2.6. Some patients who experienced PD per RECIST v1.1 consented to continue to be treated according to irRECIST guidelines until confirmed, unequivocal progression (immune-related progressive disease) was documented via modified irRECIST. Progression based on modified irRECIST was assessed as an exploratory endpoint. The denominator in the calculation of ORR was the number of patients in the full analysis set. ORR was estimated according to the number and percentage of patients with an objective response. The associated 95% two-sided CI for the true ORR using the exact Clopper-Pearson method was also reported. Secondary efficacy variables that were also reported based on RECIST v1.1 criteria. Event rates were estimated at 3, 6, 9, and 12 months using the Kaplan-Meier method. The corresponding 95% CIs were reported as well as the median time to event, with corresponding 95% CIs. Tumour size was presented graphically using a waterfall plot, to present each patient's best percent change in tumour size and BOR as a separate bar. In addition, spider plots were produced to display the percent change in tumour size across time for all patients.

The patient flow of the study is reported in Appendix D. Patients who discontinued drug treatment, because of PD or for other reasons, were not considered withdrawn from the study and were included in analysis.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality of the IMCgp100-202 RCT was assessed using the RoB2 tool (Sterne et al. 2019) and was found to be at low overall risk of bias (Appendix D). The quality of the IMCgp100-102 single arm study was assessed using the ROBINS-I tool and was found to be at low overall risk of bias (Appendix D). Full details of the quality assessment are provided in Appendix D.

B.2.6 Clinical effectiveness results of the relevant trials

Summary

A Phase 3 trial (study IMCgp100-202) in previously untreated metastatic UM patients (N=378) randomised 2:1 to tebentafusp (N=252) versus investigator's choice (N=126) therapy, demonstrated:

- Overall survival at 1 year was 73% in the tebentafusp arm and 59% in the control arm (HR of death, 0.51; 95% confidence interval [CI], 0.37-0.71; P<0.001) in the ITT population
- Progression-free survival was also significantly higher in the tebentafusp arm than in the control arm (31% vs. 19% at 6 months; HR of disease progression or death, 0.73; 95% CI, 0.58-0.94; P = 0.01)
- Analysis of patients with best overall response (BOR) of progressive disease (PD) before day 10, demonstrated tebentafusp was associated with an estimated median duration of OS of 15.3 months (95% CI: 12.0-NC) compared to 6.5 months (95% CI: 4.9-13.4) with investigators choice (HR of death: 0.43, 95% CI: 0.27-0.68)

A Phase 2 trial in metastatic UM patients previously treated with one or more prior lines of therapy (expansion Phase 2 study IMCgp100-102) in 127 patients demonstrated:

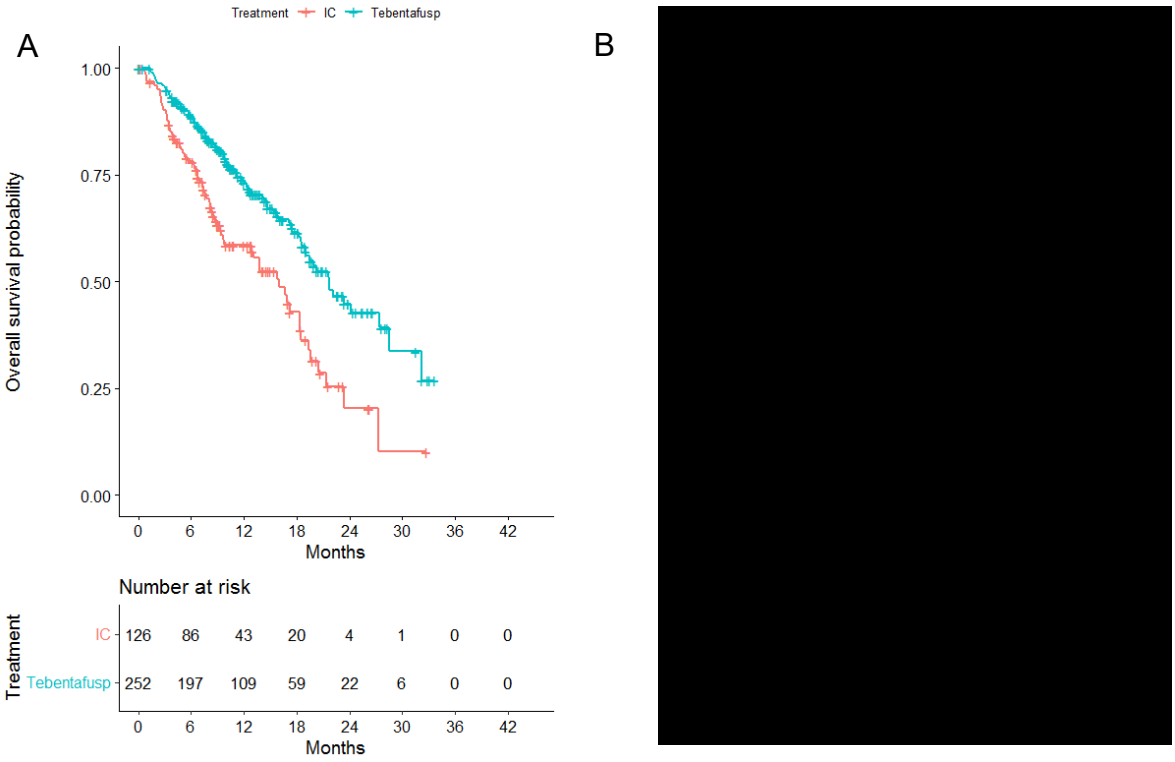
- When assessed by ICR, the primary endpoint of ORR per RECIST v1.1 was 4.7% (95% CI: 1.8-10.0%), with 6 patients, all of whom had received prior immuno-oncology treatment, achieving PR
- At a median follow-up of 19.6 months, the median OS of patients was 16.8 months (95% CI: 12.9-21.3)
- OS rates were 61.8% at 12 months and 37.0% at 24 months

B.2.6.1 Overall survival

IMCgp100-202 study

Based on the first interim analysis from the October 2020 data cut (150 events median follow-up duration of 14.1 months), the primary endpoint of OS favoured tebentafusp with a HR of 0.51 (95% confidence interval [CI]: 0.37-0.71; P<0.0001). The Kaplan-Meier estimates demonstrate median OS was prolonged in the tebentafusp arm compared with the investigator's choice arm: 21.7 months (95% CI: 18.6-28.6) for tebentafusp vs 16.0 months (95% CI: 9.7-18.4) for investigator's choice (Figure 7A). OS rates at 12 months and 24 months for tebentafusp were 73.2% and 44.8%, respectively, and for investigator's choice were 58.5% and 20.3%, respectively. The most recent data cut-off, from August 2021, with a median follow-up time [redacted]; OS [redacted] Figure 7B demonstrates [redacted]

Figure 7. Kaplan-Meier estimate of overall survival, study IMCgp100-202 for both data cut-offs (A) October 2020; (B) August 2021



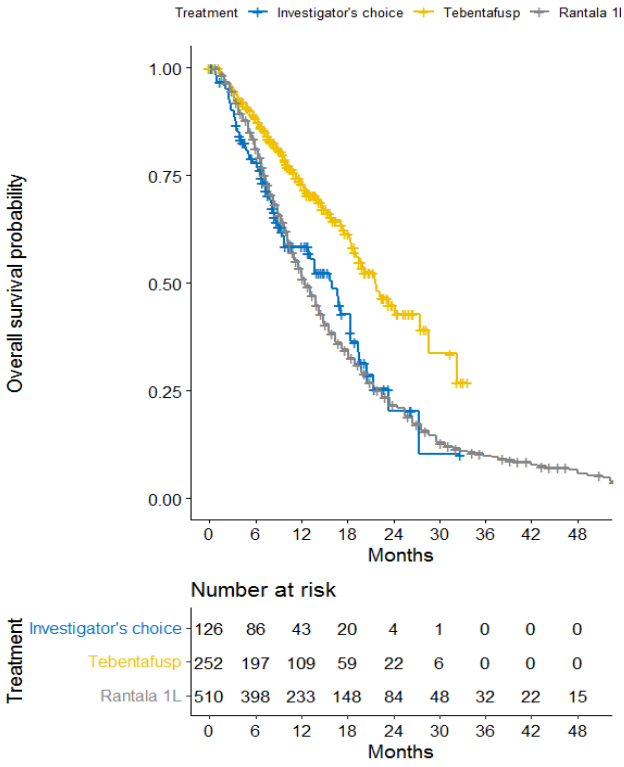
	Median (Months)(95% CI)	
	October 2020	**August 2021**
Tebentafusp (N=252)	21.7 (18.6, 28.6)	[redacted]
Investigator's choice (N=126)	16.0 (9.7, 18.4)	[redacted]

**The data includes cross-overs from the IC to tebentafusp arm between October 2020 and August 2021*

Abbreviations: CI, confidence interval; IC Investigators choice; ITT, intent-to-treat

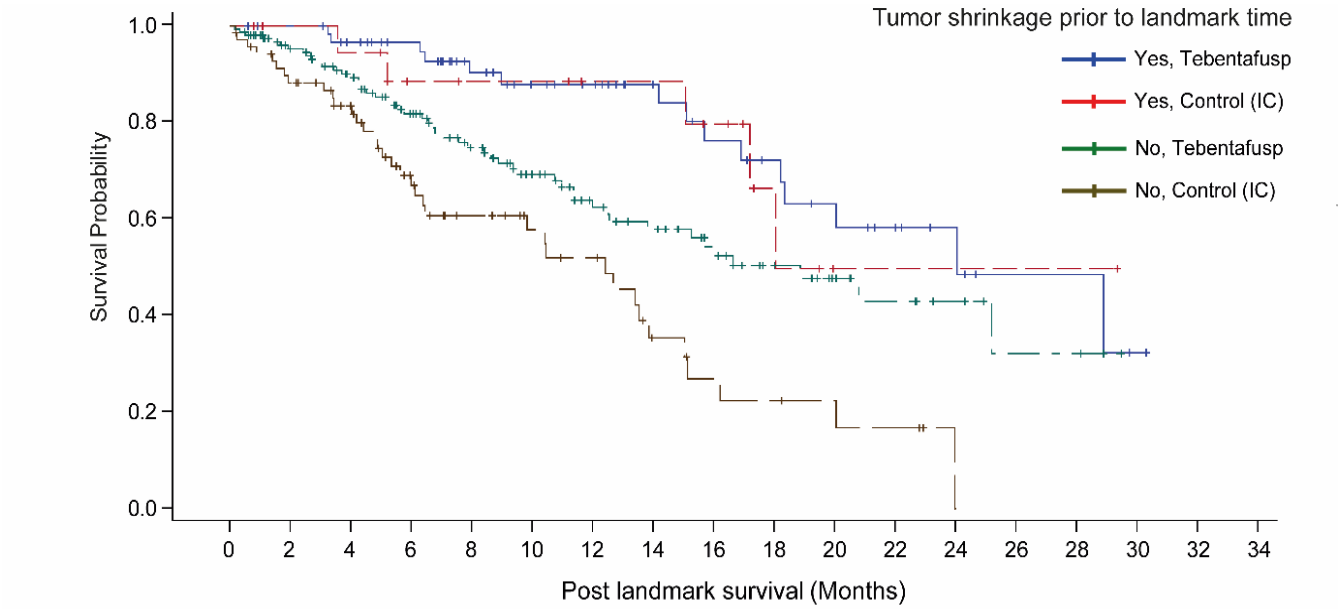
To contextualise the results of study IMCgp100-202, Figure 8 provides an overlay of the results from a meta-analysis performed on a wide range of treatment modalities for metastatic UM. This study pooled data for 510 first-line (1L) patients treated with conventional chemotherapy, chemoimmunotherapy, hepatic intra-arterial chemotherapy and transarterial chemoembolization. The Kaplan-Meier curves for OS in the tebentafusp arm, investigator's choice arm, and 1L patients reported in Rantala et al are reported in Figure 8. The Kapan-Meier curve in the control arm of study IMCgp100-202 is similar to the data from Rantala et al, with the same trajectory. A median OS across all treatment modalities of 1.07 years (≈13 months) (range: 0.59-2.50 years) was reported, and no clinically significant difference in OS by treatment modality (Rantala et al. 2019a).

Figure 8. Kaplan-Meier estimate of overall survival in study IMCgp100-202 in comparison to historical data by Rantala et al. (2019a)



In a post-hoc exploratory analysis of patients with best overall response (BOR) of progressive disease (PD) before day 100, tebentafusp was associated with an estimated median duration of OS of 15.3 months (95% CI: 12.0-NC) compared to 6.5 months (95% CI: 4.9-13.4) with investigators choice (HR of death: 0.43, 95% CI: 0.27-0.68) (Figure 9). This benefit appeared to be independent of prognostic variables at baseline prior to the study starting. Some patients had regression of some target lesions despite having a BOR of PD; however, the OS benefit was also observed among patients who had no tumour shrinkage and only tumour growth as their best change while they were receiving treatment (Figure 9). In addition, more patients in the tebentafusp arm than in the control arm had tumour regression that did not meet the RECIST criteria for partial response. In both groups, tumour regression was associated with longer OS. This finding implies a clinically meaningful effect on OS for metastatic UM patients, even if a patient had no RECIST-based radiographically significant decrease in tumour size (Nathan et al. 2021).

Figure 9. Post-landmark (day 100) overall survival in patients with best overall response of stable disease or disease progression (Nathan et al. 2021)



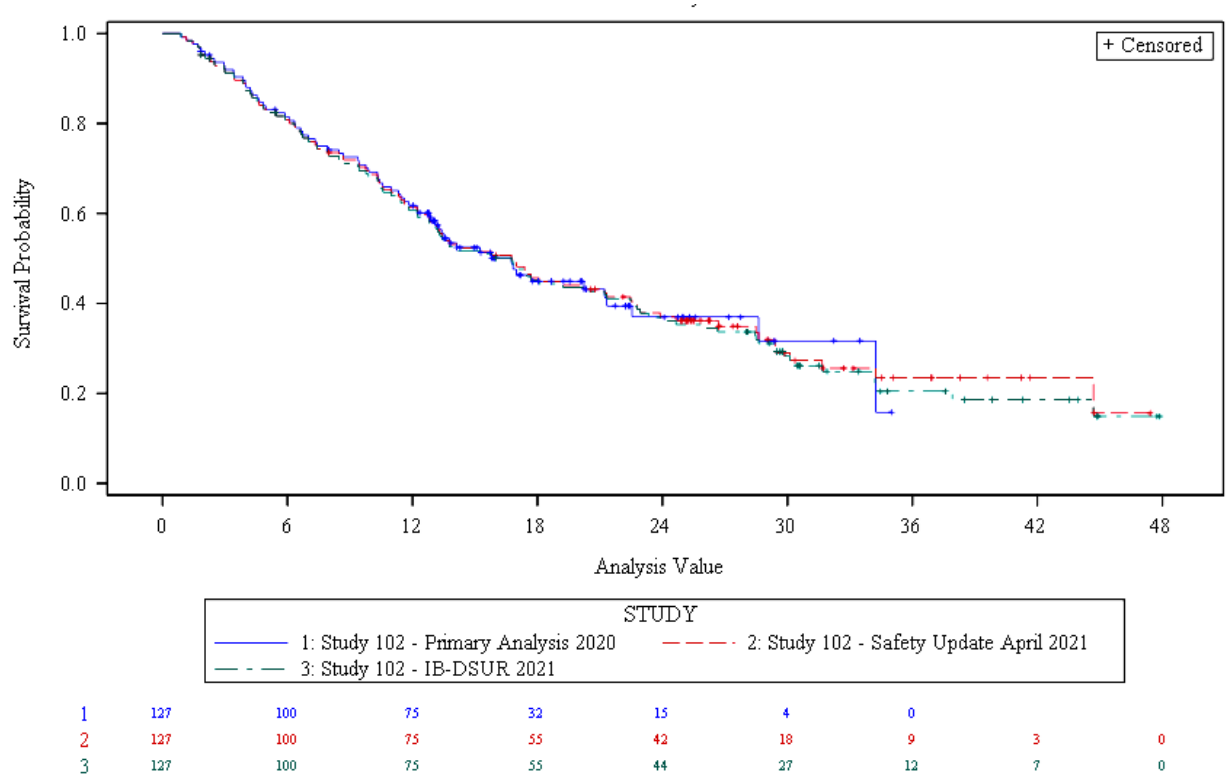
No. at Risk

Yes, Tebentafusp	64	60	55	49	39	33	30	24	19	16	13	10	6	3	3	1	0
Yes, Control (IC)	20	18	17	13	12	12	10	10	8	4	2	1	1	1	1	0	
No, Tebentafusp	155	133	114	90	71	58	44	37	29	21	13	9	6	3	3	0	
No, Control (IC)	70	59	50	34	25	20	17	9	6	5	4	3	1	0			

IMCgp100-102 study

In the IMCgp100-102 study Phase 2 dose expansion cohort, the median OS was 16.8 months (95% CI: 12.9-21.3), for a median follow-up of 19.6 months (95% CI: 16.0-22.2). Of the 127 patients in the dose expansion cohort, the OS rates were 61.8% (95% CI: 52.6-69.8%) at 12 months and 37.0% (95% CI: 26.5-47.5%) at 24 months. A Kaplan-Meier estimate of OS by RECIST v1.1 assessed by the investigator is depicted in Figure 10.

Figure 10. Kaplan-Meier plot of overall survival in Phase 2 dose expansion of study IMCgp100-102 (N=127)

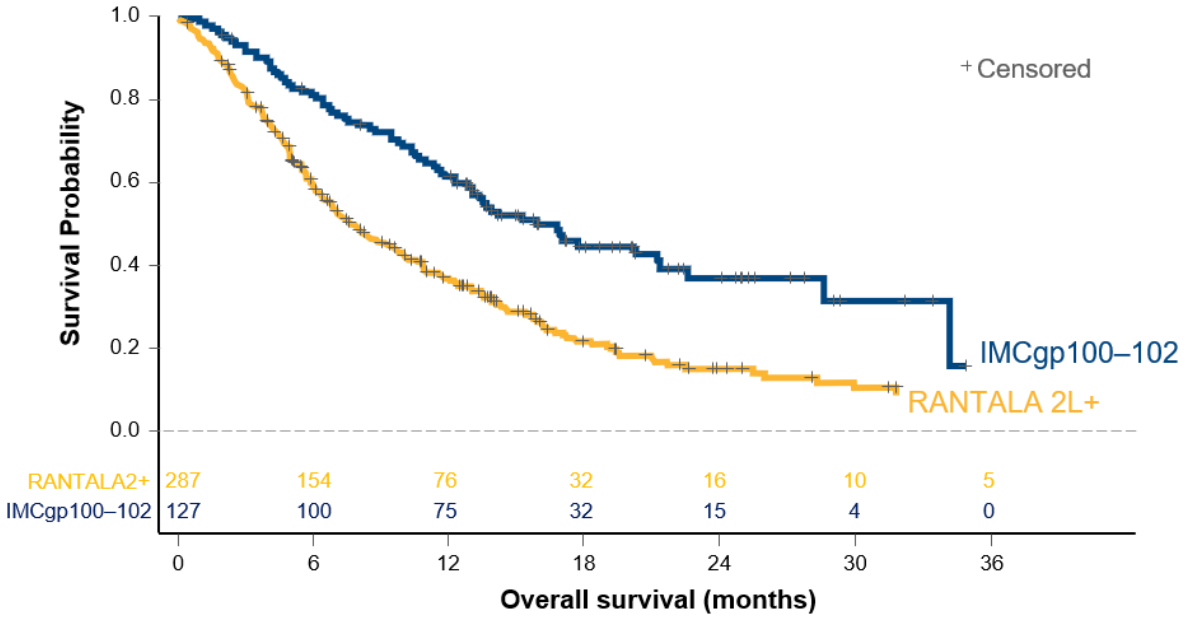


Abbreviations: CI, confidence interval

Events were deaths due to any cause. Patients not known to have died at the time of analysis are censored.

Figure 11 shows a Kaplan-Meier plot of the OS in Phase 2 dose expansion of study IMCgp100-102 in an unadjusted comparison to historical published data (Rantala et al. 2019a).

Figure 11. Kaplan-Meier plot of overall survival in Phase 2 dose expansion of study IMCgp100-102 in comparison to historical data published by Rantala et al. (2019a)



Study	Uveal population	Median (95%CI)	1-yr OS (95%CI)
IMCgp100-102 N=127	**100% 2L+**	**16.8 (12.9, 21.3)**	**62% (53, 70)**
Rantala et al. N=287	100% 2L+	7.8 (6.5, 9.7)	37% (31, 43)

Abbreviations: CI, confidence interval; OS, overall survival

B.2.6.2 Overall survival in tebentafusp-induced rash

In study IMCgp100-202, OS in tebentafusp-induced rash patients was examined as a pre-specified analysis. This was part of the co-primary objective to compare the OS in all patients randomised to tebentafusp who develop a rash within the first week of treatment versus all patients randomised to investigator's choice. The rationale was based on results from study IMCgp100-102, reporting that rash appeared to be associated with a clinical benefit across all efficacy endpoints including tumour shrinkage and PFS (both investigator assessment and per Independent Central Review (ICR)) and OS. Therefore, this shared primary objective aimed to confirm these analyses by comparing OS in patients randomised to tebentafusp who developed a rash within the first week of treatment, with those who did not.

Rash was defined as composite of preferred AE terms including rash, dermatitis, eczema and other select skin AE terms. Hypo/hyperpigmentation AEs were defined as pigment change AEs in the skin or hair (ephelides, eyelash discoloration, eyelash hypopigmentation, hair colour changes, skin hyperpigmentation, skin hypopigmentation, solar lentigo, vitiligo).

Tebentafusp patients with week 1 rash had significantly longer OS compared to the investigator's choice arm (HR: 0.35 [95% CI 0.23-0.53], P<0.0001). The estimated 1-year OS rates were 83% vs 59%, respectively. The 50 (20%) tebentafusp patients who did not experience rash by week 3 had a 1-year OS rate of 55%.

Baseline prognostic factors were balanced in the tebentafusp and investigator choice arms at trial outset however the baseline characteristics between the no rash (1-year OS, 58.6%), rash (1-year OS=82.9%) and investigators choice arm (1-year OS, 58.5%) were not balanced (since rash occurs after randomisation). Tebentafusp treated patients experiencing rash in Week 1 had a lower frequency of baseline negative prognostic factors (e.g., smaller tumour size, lower LDH) compared to tebentafusp treated patients without rash and the investigator control arm. Likewise, tebentafusp patients without a rash in Week 1 tended to have higher frequency of known baseline negative prognostic factors (e.g., larger tumour size and higher LDH) than investigator's choice control arm.

To understand the impact of this, a propensity score analysis (inverse probability weighting approach, IPTW), which corrects for confounding and allows for OS comparison between non-randomised patient groups, was used to construct weighted Kaplan-Meier curves to compare patients who did and did not experience a week 1 rash after starting tebentafusp treatment.

Statistical Methods

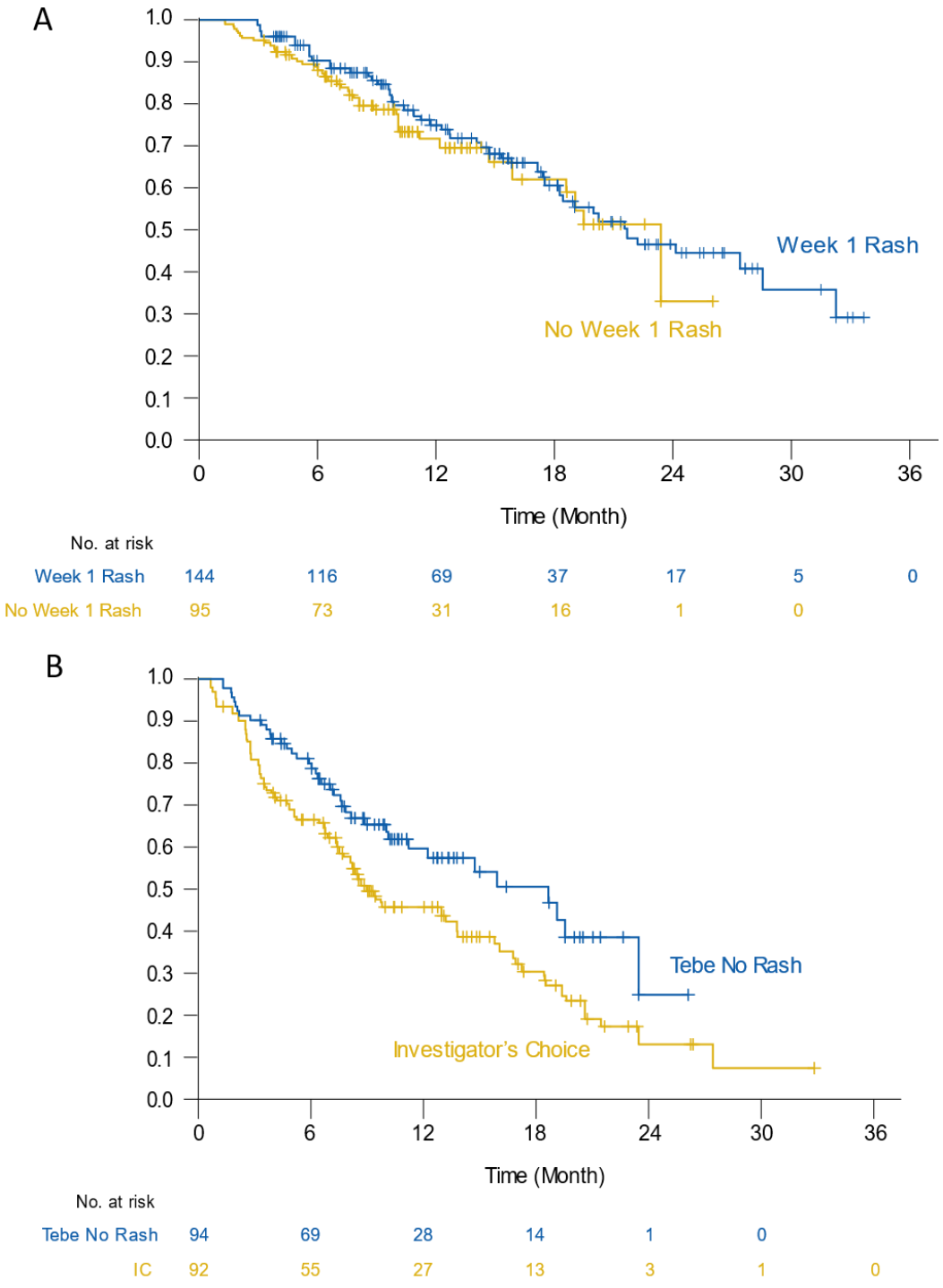
Overall study-wide alpha was controlled at 0.05, with 90% assigned to ITT and 10% to rash. The analysis was conducted on the primary interim analysis (data cut-off October 2020). Treatment groups were formally compared via a stratified log-rank test. Multivariate Cox model of patients randomised to tebentafusp was used to assess impact of week 1 rash and known baseline prognostic factors on overall

survival. A propensity score analysis using an inverse probability weighting approach (IPTW) was used to construct weighted Kaplan-Meier curves to compare patients who did and did not experience a week 1 rash after starting tebentafusp treatment.

Results

In this analysis, there was no difference in OS between tebentafusp treated patients who did or did not experience a Week 1 rash; therefore, rash did not independently impact survival after adjusting for known prognostic factors (Figure 12). IPTW analysis was also used to compare tebentafusp-treated patients without rash in week 1 vs the investigator's choice arm. In this analysis, patients who received tebentafusp who did not experience rash appeared to have better survival compared to patients in the investigator's choice arm (HR=0.62; 95% CI: 0.41-0.92) (Figure 12). Therefore, accounting for baseline prognostic factors, tebentafusp patients without rash still appeared to derive benefit compared to investigator's choice treated patients.

Figure 12. Kaplan-Meier IPTW analysis (A) IPTW adjusted OS by rash status in tebentafusp treated patients (B) IPTW adjusted OS in tebentafusp-treated patients who do not experience rash compared to investigator's choice patients



Summary of OS in tebentafusp induced rash

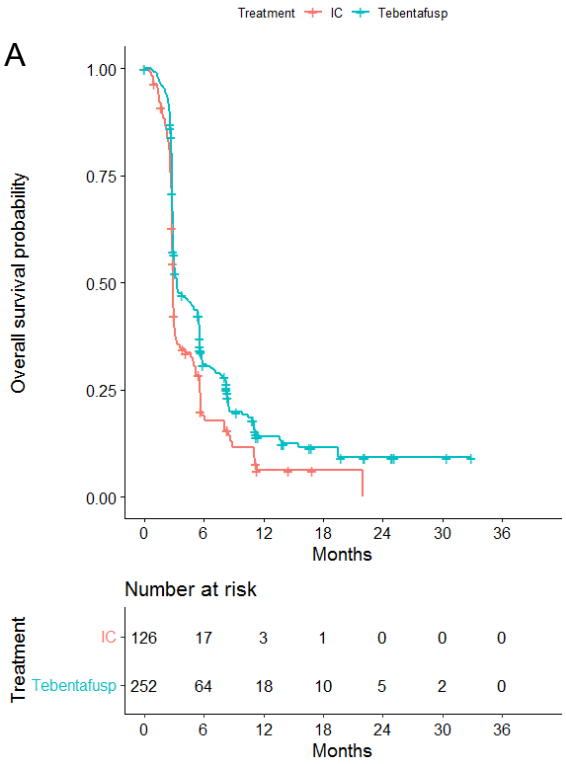
- Skin-related AEs were common in tebentafusp-treated patients.
- Rash decreased in incidence and severity after the first 3-4 doses, was generally manageable with simple interventions such as oral antihistamines and topical corticosteroids, rarely resulted in drug interruption and resulted in no patient discontinuations of tebentafusp due to rash.
- The strong association between rash in week 1 and OS benefit from tebentafusp suggests that rash may be a marker that the immune system can be mobilised by tebentafusp to target gp100+ cells.
- The use of rash for clinical management decisions is not appropriate because rash was associated with better baseline prognostic factors and was not an independent predictor of OS.

B.2.6.3 Progression-free survival

IMCgp100-202 study

At a median follow-up duration of 11.4 months, median PFS, assessed by investigator, was 3.3 months (95% CI: 3.0-5.0) in the tebentafusp arm and 2.9 months (95% CI: 2.9-3.0) in the investigator's choice arm (HR=0.73; 95% CI: 0.58-0.94; P=0.0139) (Figure 13A). Kaplan-Meier estimates of PFS rates at 6 months were 30.9% (95% CI: 25.0-37.0) and 18.9% (95% CI: 12.0-27.2), respectively. Figure 13B presents the data from the August 2021 data cut, showing the results [redacted]

Figure 13. Kaplan-Meier estimate of PFS, study IMCgp100-202 for both data cut-offs (A) October 2020; (B) August 2021



B [redacted]

	Median (Months) (95% CI)	
	October 2020	**August 2021**
Tebentafusp (N=252)	3.3 (3.0-5.0)	[redacted]
Investigator's choice (N=126)	2.9 (2.8-3.0)	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; IC, investigator's choice; ITT, intent-to-treat

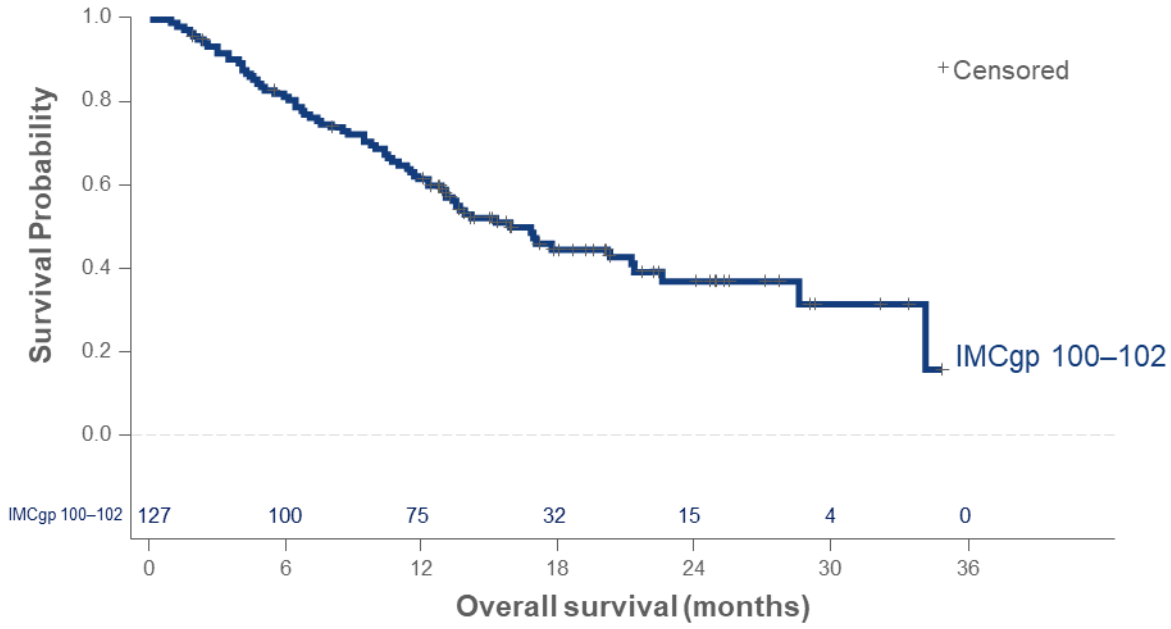
IMCgp100-102 study

In the Phase 2 dose expansion cohort (N=127) of study IMCgp100-102, the median PFS (assessed by RECIST v1.1 by the investigator) was 2.3 months (95% CI 1.90-3.70). A total of 114 (89.8%) patients had the event of PD (105 [82.7%] patients) or death in the absence of PD (9 [7.1%] patients). The estimated PFS rates were 25.8% (95% CI 18.5-33.7%) at 6 months and 12.8% (95% CI 7.6-19.4%) at 12 months.

IMCgp100-102 results were also assessed by ICR; the median PFS was 2.8 months (95% CI 2.0-3.7%). The estimated PFS rates were 25% (95% CI: 17.8%-32.9%) at 6 months and 11% (95% CI: 6.2-17.2%) at 12 months. A total of 90 patients (71%)

were treated beyond disease progression, with the median duration of treatment post RECIST-PD 87.5 days (range: 1-703 days). A Kaplan-Meier estimate of PFS by RECIST v1.1 assessed by ICR is depicted in Figure 14.

Figure 14. Kaplan-Meier plot of PFS (RECIST v1.1) by ICR in Phase 2 dose expansion of study IMCgp100-102



Abbreviations: CI, confidence interval

Events were either disease progression or death in the absence of disease progression, which occurred within 2 tumour assessment visits of the last evaluable assessment. Events that did not occur within 2 tumour assessment visits were censored.

Tumour assessment was based on RECIST v1.1 by investigator opinion.

B.2.6.4 Objective response rate, best overall response and disease control rate

IMCgp100-202 study

The effect of tebentafusp on ORR, BOR, and DCR in study IMCgp100-202 per investigator assessment is shown in Table 8.

ORR per investigator assessment in study IMCgp100-202 was 9.1% (95% CI 5.9-13.4) for tebentafusp and 4.8% (95% CI 1.8-10.1) for investigator's choice.

In the tebentafusp arm, BORs were 1 CR (0.4%) and 22 PRs (8.7%); 92 patients (36.5%) had stable disease (SD), and 131 (52.0%) had PD. In the investigator's

choice arm, there were no CRs; 6 patients (4.8%) had PRs, 28 (22.2%) had SD, and 78 (61.9%) had PD.

DCR (defined as CR + PR + SD ≥12 weeks) favoured the tebentafusp arm compared with investigator's choice, with rates of 45.6% (95% CI: 39.4-52.0) and 27.0% (95% CI 19.5-35.6), respectively.

Notably however, as mentioned in section B.2.6.1, response by RECIST appears to underestimate OS benefit from tebentafusp; long OS (≥12 months) was observed across all categories of RECIST response, even PD (Figure 9).

Table 8. Effect of tebentafusp on objective response rate, best overall response, and disease control rate, study IMCgp100-202

Trial	**IMCgp100-202**	
Treatment arm	Tebentafusp	Investigator's choice
Population (N)	252	126
Objective response rate (CR or PR)		
n (%)	23 (9.1%)	6 (4.8%)
95% CI	5.9-13.4	1.8-10.1
Stratified odds ratio (tebentafusp/investigator's choice) (95% CI of odds ratio)	1.98 (0.79-4.97)	NA
Best overall response		
CR, n (%)	1 (0.4%)	0 (0.0%)
PR, n (%)	22 (8.7%)	6 (4.8%)
PD, n (%)	131 (52.0%)	78 (61.9%)
SD ≥12 weeks, n (%)	92 (36.5%)	28 (22.2%)
Not evaluable	6 (2.4%)	14 (11.1%)
Disease control rate (CR or PR or SD ≥12 weeks)		
n (%)	115 (45.6%)	34 (27.0%)
95% CI	39.4-52.0	19.5-35.6
Stratified odds ratio (tebentafusp/investigator's choice) (95% CI of odds ratio)	2.33 (1.45-3.75)	NA
Abbreviations: CI, confidence interval; CR, complete response; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease		

IMCgp100-102 study

The effect of tebentafusp on ORR, BOR, and DCR in study IMCgp100-102 per investigator assessment or ICR is shown in Table 9.ORR assessed by ICR was the primary endpoint of this study.

Of the 127 patients who received tebentafusp in the Phase 2 dose expansion cohort of study IMCgp100-102, an OR of PR was observed in 9 (7.1%) patients (95% CI 3.3%-13.0%), per investigator assessment. The rate of minimum response (MinR) or better (per investigator assessment) was 15.0% (19 of 127 patients; 95% CI 9.3-22.4%).

The DCR per investigator assessment was 33.1% (42 patients; 95% CI 25.0- 42.0%) at ≥16 weeks and 23.6% (30 patients; 95% CI 16.5-32.0%) at ≥24 weeks.

Table 9. Effect of tebentafusp on objective response rate, best overall response, and disease control rate, study IMCgp100-102

Trial	**IMCgp100-102 (Phase 2 dose expansion)**	
	Investigator assessment	**ICR assessment**
Treatment arm	Tebentafusp	
Population (N)	127	
Objective response rate (CR or PR)		
n (%)	9 (7.1%)	6 (4.9%)
95% CI	1.8-10.1	1.8-10.3
Best overall response		
CR, n (%)	0 (0.0%)	0 (0.0%)
PR, n (%)	9 (7.1%)	6 (4.9%)
PD, n (%)	63 (49.6%)	59 (48.0%)
SD ≥8 weeks, n (%)	51 (40.2%)	55 (44.7%)
SD ≥16 weeks, n (%)	33 (26.0%)	33 (26.8%)
SD ≥24 weeks, n (%)	21 (16.5%)	22 (17.9%)
MinR, n (%)	10 (7.9%)	8 (6.5%)
Unconfirmed CR or PR	0 (0.0%)	1 (0.8%)
Not evaluable	4 (3.1%)	3 (2.4%)
Disease control rate (CR or PR or SD ≥16 weeks)		
n (%)	42 (33.1%)	39 (31.7%)
95% CI	25.0- 42.0	23.6-40.7
Disease control rate (CR or PR or SD ≥24 weeks)		
n (%)	30 (23.6%)	28 (22.8%)

95% CI	16.5-32.0	15.7-31.2
Abbreviations: CI, confidence interval; CR, complete response; ICR, independent central review; MinR, minimum response; PD, progressive disease; PR, partial response; SD, stable disease		

When assessed by ICR, the primary endpoint of ORR per RECIST v1.1 was 4.7% (95% CI 1.8-10.0%) (Table 9), with 6 patients, all of whom had received prior immuno-oncology treatment, achieving PR. The median DOR was 8.7 months (95% CI 5.6-24.5), and the estimated percentage of ongoing responders was 60% (95% CI 12.6-88.2%) at 6 months, and 20% (95% CI 0.8-58.2%) at 12 months.

Of the 127 patients, 57 patients (45%) had SD at ≥8 weeks. The DCR was 32% (40 patients; 95% CI 23.5-40.3%) at ≥16 weeks and 23% (29 patients; 95% CI 15.9-31.1%) at ≥24 weeks. Any tumour shrinkage was seen in 44% of patients.

B.2.6.5 Duration of response

IMCgp100-202 study

The median duration of response was 9.9 months (95% CI 5.4-NC) for tebentafusp (23 patients) and 9.7 months (95% CI 2.7-NC) for investigator's choice (9 patients). The KM estimates for duration of response at 6 months were 60.6% (95% CI 34.2-7.2%) and 50.0% (95% CI11.1-80.4%), respectively (Table 10). Due to the low number of patients achieving ORR there is high uncertainty in this analysis.

Table 10. Effect of tebentafusp on duration of response, study IMCgp100-202

Trial	**IMCgp100-202**	
Treatment arm	**Tebentafusp**	**Investigator's choice**
Population (N)	252	126
Patients achieving OR (N')	23	6
Median follow-up, months (95% CI)	10.8 (2.8-13.8)	9.3 (2.8-NC)
DOR, months		
PFS events, n (%)	9 (39.1%)	4 (66.7%)
PD	9 (39.1%)	4 (66.7%)
Death	0 (0.0%)	0 (0.0%)
Median (95% CI), months	9.9 (5.4-NC)	9.7 (2.7-NC)
Kaplan-Meier estimates for DOR (95% CI) [No. at risk]		
3 months	84.8 (59.5-94.9) [n=14]	50.0 (11.1-80.4) [n=2]
6 months	60.6 (34.2-7.2) [n=10]	50.0 (11.1-80.4) [n=2]
9 months	54.5 (28.9-74.4) [n=7]	50.0 (11.1-80.4) [n=2]

Trial	IMCgp100-202	
Treatment arm	**Tebentafusp**	**Investigator's choice**
12 months	46.8 (21.8-68.4) [n=4]	50.0 (11.1-80.4) [n=2]
Abbreviations: CI, confidence interval; DOR, duration of response; NC, not calculable; OR, objective response; PD, progressive disease; PFS, progression-free survival		

IMCgp100-102 study

The effect of tebentafusp on the duration of response in the Phase 2 dose expansion cohort of IMCgp100-102 study per investigator assessment or ICR is shown in Table 11.

The median duration of objective response per investigator assessment was not calculable (NC; 95% CI 3.1-NC). The landmark analysis of duration of response was 75.0% (95% CI 31.5-93.1%) at 6 months and 56.3% (95% CI 14.7-84.2%) at 12 months.

The median duration of MinR or better per investigator assessment was 17.3 months (95% CI: 7.4-NC). The estimated percentage of responders (including those with a MinR) was 84.2% (95% CI: 58.7-94.6%) at 6 months and 51% (95% CI: 26.7-71.0%) at 12 months.

Table 11. Effect of tebentafusp on duration of response, study IMCgp100-102

Trial	IMCgp100-102 (Phase 2 dose expansion)	
	Investigator's assessment	**ICR assessment**
Treatment arm	**Tebentafusp**	
Population (N)	127	
Median follow-up, months (95% CI)	10.42 (3.61-21.42)	23.26 (10.38-NC)
Number of patients with an OR (N')	9	6
Total number of events [a]	3	5
Total censored for any reason	6	1
Kaplan-Meier analysis		
Median (95% CI) duration of objective response, months	NC (3.713-NC)	8.706 (5.552-24.542)
Estimated % of patients in response at [b]		
3 months (95% CI)	100.0% (NC-NC)	100.0% (NC-NC)
6 months (95% CI)	75.0% (31.5-93.1)	60.0% (12.6-88.2)
9 months (95% CI)	56.3% (14.7-84.2)	40.0% (5.2-75.3)
12 months (95% CI)	56.3% (14.7-84.2)	20.0% (0.8-58.2)

Median (95% CI) duration of MinR or better, months	17.3 (7.4-NC)	10.3 (5.8-23.2)
Estimated % of patients in response at		
6 months (95% CI)	84.2% (58.7-94.6)	78.6% (47.2-92.5)
12 months (95% CI)	51% (26.7-71.0)	33.3% (10.9-58.0)

[a] Events were patients with a date of disease progression or death in the absence of disease progression, following the first documented objective response (CR or PR). Patients without disease progression or death, were censored at the last evaluable tumour assessment. Response confirmation was required ≥4 weeks later following initial evaluation for complete and partial response.

[b] Percentage of patients in response were estimated using the Kaplan-Meier method

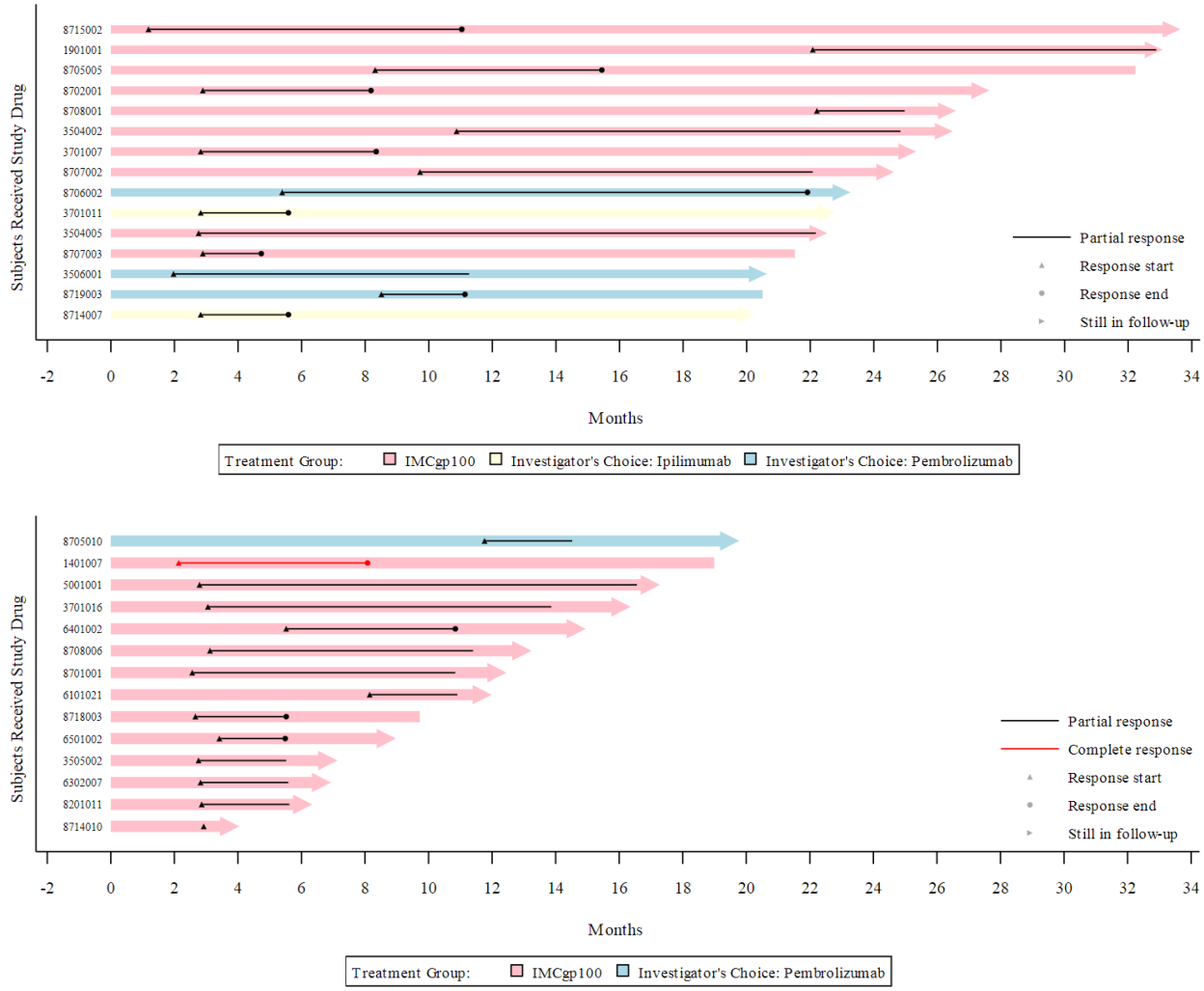
Abbreviations: CI, confidence interval; CR, complete response; ICR, independent central review; MinR, minimum response; NC, not calculable; OR, objective response; PR, partial response

B.2.6.6 Time to response

IMCgp100-202 study

In the subset of responders (23 in the tebentafusp arm and 6 in the investigator's choice arm), time to response occurred earlier in the tebentafusp arm than the investigator's choice arm, at a median of 2.9 months (range: 1.2-22.2) and 4.1 months (range: 2.0-11.8), respectively. The swimmer plot for time to response is shown in Figure 15.

Figure 15. Swimmer plot for time to response, study IMCgp100-202



IMCgp100-102 study

The mean time to objective response, by investigator assessment, was 9.5 months (standard deviation (SD) 7.6), with response times ranging from 1.6 to 25.8 months.

The mean (SD) time to OR, by ICR assessment, was 7.0 months (±6.9), with response times ranging from 1.6 to 20.5 months.

B.2.7 Overall survival subgroup analyses

Subgroup analyses for OS and PFS were conducted for study IMCgp100-202 as pre-specified in trial protocol. Details of the analysis are described in Appendix E. Figure 16 shows a forest plot summarising the key results of the OS subgroup analyses by treatment group. The OS benefit provided by tebentafusp was observed

across all prespecified major demographic and known prognostic subgroups, including a HR of 0.51 (95% CI 0.35-0.75) versus pembrolizumab, the most frequent investigator's choice agent. Similarly, consistent benefit of tebentafusp was observed for PFS across most subgroups, with the exception of the Hispanic and prior systemic therapy subgroups for which the sample sizes were too small to draw any conclusion (Appendix E).

Figure 16. Forest plot of overall survival trends by subgroup (ITT)

	Tebentafusp		Investigator's choice		
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)
ECOG 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)**

Tebentafusp ← → Investigator's choice

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

B.2.8 Meta-analysis

No meta-analyses have been conducted.

B.2.9 Indirect and mixed treatment comparisons

In clinical practice, the approval of checkpoint inhibitors generically for advanced melanoma has, in recent years, led to some UM patients being treated with ipilimumab + nivolumab combination therapy. Since this was not included as a comparator in the registration trial for tebentafusp, the IMCgp100-202 study, it was necessary to subsequently understand the relative efficacy of both tebentafusp and pembrolizumab versus ipilimumab + nivolumab. In the absence of head-to-head trials between tebentafusp versus ipilimumab + nivolumab and pembrolizumab versus ipilimumab + nivolumab, an indirect treatment comparison (ITC) was required to synthesise the relative differences in OS in for patients with untreated metastatic UM.

An SLR was conducted of which, two studies were identified as potential comparator studies, namely Piulats et al. (2021b) and Pelster et al. (2021b) (Table 12). Both are single arm studies of ipilimumab + nivolumab in UM. Piulats et al. (2021b) was selected as the most appropriate comparison for several reasons including it is a purely untreated population like the IMCgp100 study 202 (Pelster et al. (2021b) is only 57% previously untreated) and it reports more of the key covariates.

Table 12. Potential comparator studies

Author	Year	Title
Pelster et al.	2021	Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study [NCT01585194]
Piulats et al.	2021	Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402) [NCT02626962]

Given the lack of a common comparator between tebentafusp and pembrolizumab with ipilimumab + nivolumab, a matching adjusted indirect comparison (MAIC) was selected as the most appropriate analysis approach. In this case and for the Piulats study, the OS Kaplan-Meier curves were digitised and the Guyot algorithm (Guyot et al. 2012) was applied to generate pseudo-IPD for use in the analysis.

The MAIC methodology followed is described in Phillippo et al. (2016) using the method of moments approach described in Signorovitch et al. (2010). A weighted

Cox proportional hazards model was fit applying the MAIC weights. Confidence intervals and p-values were calculated using bootstrapping or robust variance estimators to account for the fact that the weights are estimated rather than known (Austin 2016). An unadjusted indirect comparison (UAIC) was also conducted for comparison. Matching was conducted based on the variables listed in Table 13. Two sensitivity analyses were also conducted to explore alternative ways of defining the disease location covariate for matching and are also given in Table 13.

Table 13. Variables used for matching in the MAIC

Variable	Description
Primary analysis	
Age	Years, median
Gender	Male, Female
Baseline LDH	Proportion in normal range (rather than log-transformed continuous variable)
Baseline ALP	Proportion in normal range (rather than log-transformed continuous variable)
Disease location	Hepatic only, extrahepatic only, hepatic and extrahepatic (rather than largest metastatic lesion continuous variable)
ECOG performance status at baseline	Proportion 0 or ≥1
Sensitivity analysis 1	
Disease location pooled categories	Hepatic only, any extrahepatic (pooled extrahepatic only + hepatic and extrahepatic)
Sensitivity analysis 2	
Largest metastatic liver lesion	Proportion ≤3cm, >3cm, no liver lesions
Abbreviations: ALP, alkaline phosphatase; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group	

Results of the main analysis and sensitivity analyses comparing tebentafusp versus ipilimumab + nivolumab and pembrolizumab versus ipilimumab + nivolumab using the MAIC and UAIC methodology is given in

Table 14. Patient characteristics, both observed and matched as well as respective effective sample sizes, is given in Appendix D for all analyses. KM curves are also given for the MAIC analyses. The resulting KM curves for the tebentafusp versus ipilimumab + nivolumab comparison from the MAICs are given in Figure 17 for the main analysis and both sensitivity analyses along with their respective numbers at

risk. Similarly, Figure 18 provides the resulting KM curves for the pembrolizumab versus ipilimumab + nivolumab comparison from the MAICs.

Table 14. Results from the main and sensitivity analyses for the MAICs and UAIC

Analysis	MAIC		UAIC
	Robust SE	Bootstrap	Robust SE
	HR (95% CI)	HR (95% CI)	HR (95% CI)
IMCgp100 versus ipilimumab + nivolumab			
Main analysis	[redacted]	[redacted]	[redacted]
Sensitivity analysis 1	[redacted]	[redacted]	[redacted]
Sensitivity analysis 2	[redacted]	[redacted]	[redacted]
Pembrolizumab versus ipilimumab + nivolumab			
Main analysis	[redacted]	[redacted]	[redacted]
Sensitivity analysis 1	[redacted]	[redacted]	[redacted]
Sensitivity analysis 2	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; MAIC, matching-adjusted indirect comparison; NA, not applicable; SE, standard error, UAIC, unadjusted indirect comparison

Figure 17. Kaplan-Meier plots of overall survival from match-adjusted indirect comparison (MAIC) of tebentafusp versus ipilimumab + nivolumab

(A) main analysis, (B) sensitivity analysis 1 - pooled extrahepatic categories and (C) sensitivity analysis 2 - liver lesion size covariate.

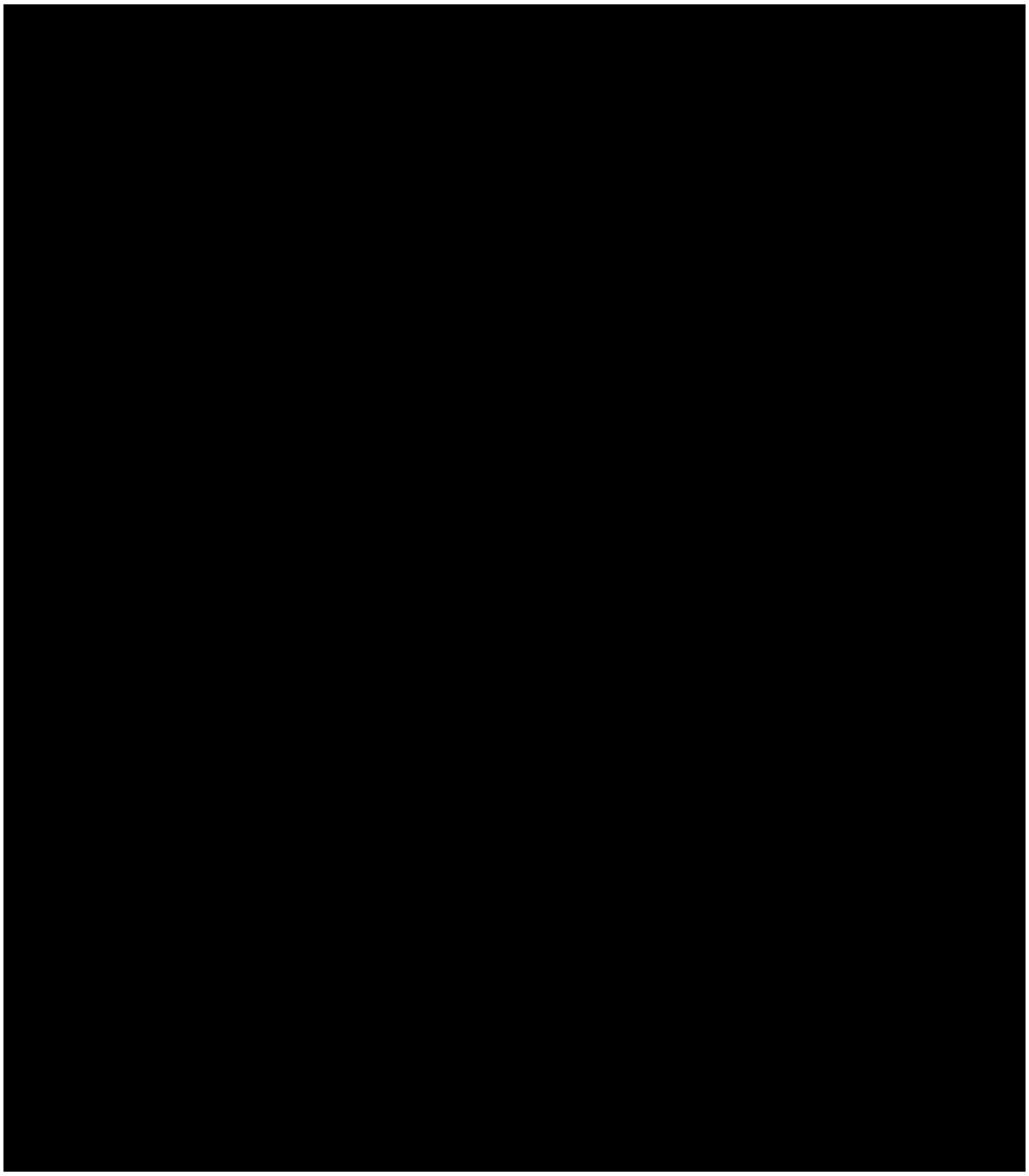
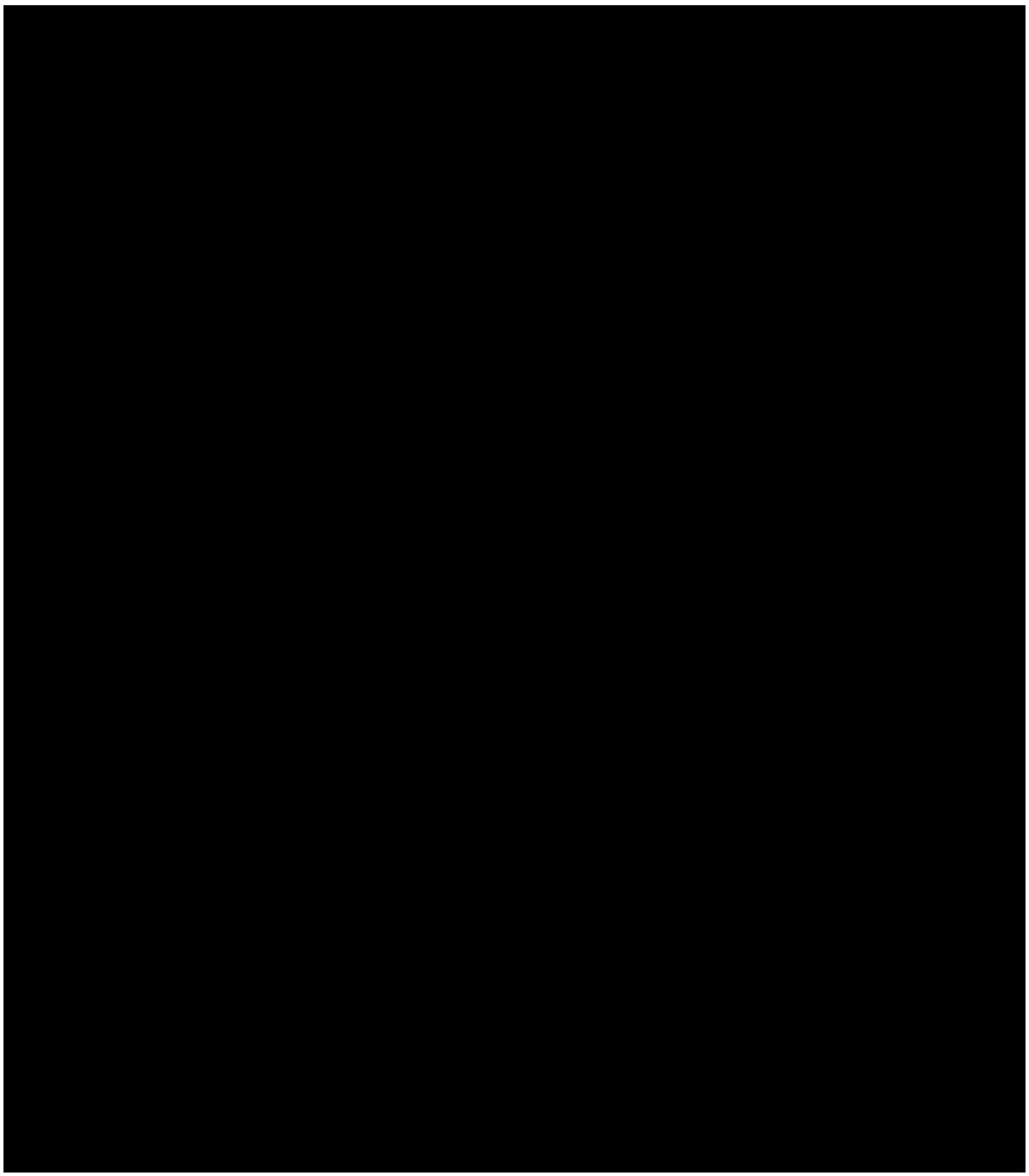


Figure 18. Kaplan-Meier plots of overall survival from match-adjusted indirect comparison (MAIC) of pembrolizumab versus ipilimumab + nivolumab

(A) main analysis, (B) sensitivity analysis 1 - pooled extrahepatic categories and (C) sensitivity analysis 2 - liver lesion size covariate



All analysis results comparing tebentafusp against ipilimumab + nivolumab show a statistically significant [redacted] in those patients receiving tebentafusp compared with those receiving ipilimumab + nivolumab. This supports the case that [redacted] For the MAIC, the alternative approaches to defining disease location [redacted] of those patients receiving tebentafusp compared with those receiving ipilimumab + nivolumab, although results were [redacted] there was little sensitivity to the definition of disease location in the population. Results from [redacted]

None of the results comparing patients receiving pembrolizumab versus those receiving ipilimumab + nivolumab were [redacted] There was a difference in the results between the main analysis and sensitivity analysis 1 for the MAIC indicating that there is some sensitivity [redacted] indicate less of a reduction in the hazard for patients receiving [redacted]

Effective sample sizes across all comparisons for tebentafusp and pembrolizumab was reduced considerably after matching but deemed sufficient for interpretation given the initial unmatched population sizes.

The MAICs presented represent the most robust source of efficacy available for the given populations of interest. The approach accounts for cross-trial differences in patient characteristics and adjusted patient characteristics closely matched those of the comparator populations. Time since primary diagnosis could not be used in the matching as it was not reported for the Piulats et al. (2021b) study. This is a potential unmeasured effect modifier/prognostic variable which should be considered when interpreting the results. No other important potential unmeasured effect modifiers/prognostic variables were identified. A limitation of the MAIC methodology is that it is not possible to adjust for differences in outcome definitions. There was a small difference in the definition in OS between studies; in the IMCgp100-202 study

OS was defined as time from randomisation to death from any cause, with those still alive censored at last date of known 'alive' status, whereas for Piulats et al. (2021b), OS was reported in the primary publication as time from first dose to death from any cause, with those still alive censored at date of last reported contact. Any bias introduced by differences in the outcome definition is thought to be minimal.

Summary

- In all analyses, the matching performed well and the distribution of the adjusted patient characteristics for tebentafusp/pembrolizumab was closely matched to ipilimumab + nivolumab.

- The effective sample size for tebentafusp (and pembrolizumab, to a lesser extent) was reduced considerably for the matchings including the extrahepatic only or no liver lesions categories. This was due to the imbalance of these categories between the studies.

- For the match-adjusted indirect comparison of tebentafusp versus ipilimumab + nivolumab, [redacted] regardless of the covariate used for matching. Similar results were observed in the unadjusted indirect comparison.

- For the match-adjusted indirect comparison of pembrolizumab versus ipilimumab + nivolumab, there was [redacted] regardless of the covariate used for matching, although results numerically favoured [redacted]. Similar results were observed in the unadjusted indirect comparison.

B.2.10 Adverse reactions

Summary
• The adverse event profile of tebentafusp was predictable, manageable and transient • The most common treatment-related AEs in the tebentafusp group were cytokine-mediated events (due to T-cell activation) and skin-related events (due to glycoprotein 100–positive melanocytes), including rash (83%), pyrexia (76%), and pruritus (69%) • These AEs decreased in incidence and severity after the first three or four doses and infrequently led to discontinuation of the trial treatment (2%) • No treatment-related deaths were reported

B.2.10.1 Treatment-emergent adverse events

Study IMCgp100-202

In study IMCgp100-202, the frequency of TEAEs from any cause was 100% in the tebentafusp arm and 94.6% in the investigator's choice arm. Grade ≥3 AEs occurred in 54.3% and 36.0% of patients, respectively. Grade ≥3 AEs that were considered related to study drug by the investigator occurred in 44.5% and 17.1% of patients in the tebentafusp and investigator's choice arms, respectively. The incidence of serious TEAEs was 28.2% in the tebentafusp arm and 23.4% in the investigator's choice arm. None of the deaths in either arm was considered to be treatment related.

The most common treatment-related TEAEs for tebentafusp (occurring in >30% of patients) were pyrexia (76.3%), pruritus (69.0%), rash (55.1%), fatigue (51.0%), nausea (49.0%), chills (47.8%), hypotension (38.8%), dry skin (31.4%), headache (30.6%), and rash maculo-papular (30.6%). TEAEs occurring in ≥20% patients are presented in Table 15.

Discontinuation of treatment because of TEAEs occurred in 8 patients (3.3%) in the tebentafusp arm and 7 patients (6.3%) in the investigator's choice arm; 5 of the 8 patients (2%) in the tebentafusp arm had events that were considered treatment related.

Table 15. Treatment-emergent adverse events occurring in ≥20% patients in study IMCgp100-202

Adverse Reactions	Study IMCgp100-202			
	Tebentafusp (N=245)		Investigator's choice (N=111)	
	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
Cytokine release syndrome[1]	89	0.8	3	0.0
Rash[3]	83	18.4	28	0.0
Pyrexia[2]	76	3.7	7	0.9
Pruritus	69	4.5	23	0.0
Fatigue[4]	64	5.7	42	0.9
Nausea[2]	49	2.0	26	0.9
Chills[2]	48	0.4	4	0.0
Hypo/hyper-pigmentation[5]	47	0.4	6	0.0
Abdominal pain[6]	45	2.9	33	3.6
Oedema[7]	45	0.0	10	0.0
Hypotension[2]	39	3.3	3	0.0
Dry skin	31	0.0	4	0.0
Headache[2]	31	0.4	10	0.9
Vomiting[2]	30	1.2	9	0.0
Diarrhoea	25	1.2	20	2.7
Erythema	25	0.0	1	0.0
Arthralgia	22	0.8	16	0.0

[1] CRS was adjudicated using the ASTCT consensus grading of CRS criteria.(Lee et al. 2019) Adjudicated CRS is provided in lieu of investigator reported CRS

[2] Some of the events may be associated with CRS or may be isolated reported events

[3] Includes blister, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatosis, drug eruption, eczema, eczema eyelids, erythema multiforme, exfoliative rash, interstitial granulomatous dermatitis, lichenification, lichenoid keratosis, palmar-plantar erythrodysaesthesia syndrome, papule, psoriasis, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, seborrhoea, seborrhoeic dermatitis, skin abrasion, skin erosion, skin exfoliation, skin irritation, skin plaque, solar dermatitis, toxic skin eruption, urticaria

[4] Includes fatigue and asthenia

[5] Includes achromotrichia acquired, ephelides, eyelash discolouration, eyelash hypopigmentation, hair colour changes, lentigo, pigmentation disorder, retinal depigmentation, skin depigmentation, skin discolouration, skin hyperpigmentation, skin hypopigmentation, solar lentigo, vitiligo

[6] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, flank pain, gastrointestinal pain and hepatic pain

[7] Includes eye oedema, eye swelling, eyelid oedema, periorbital swelling, periorbital oedema, swelling of eyelid, pharyngeal oedema, lip oedema, lip swelling, face oedema, generalized oedema, localized oedema, oedema, oedema peripheral, peripheral swelling, swelling, swelling face

Study IMCgp100-102

Treatment related adverse events (TRAE) were generally cutaneous or cytokine mediated (T cell activation) and included pyrexia (80%), pruritus (67%), and chills (64%). Grade ≥3 TRAEs that occurred were rash maculo-papular (13%), hypotension (8%), increased aspartate aminotransferase (AST), and hypophosphatemia (5% each). TRAEs decreased in frequency and severity after the first 3 doses of tebentafusp. Cytokine release syndrome (CRS) occurred at 3% Grade 3 and 1% Grade 4. There were no grade 5 TRAEs or treatment related deaths.

B.2.10.1 Cytokine release syndrome

CRS (based on retrospective sponsor adjudication using ASTCT consensus grading 2019) has occurred following tebentafusp infusion. It is a systemic inflammatory response that has been described after infusion of several antibody-based therapies and is identified on the basis of the presence of pyrexia, hypotension, and hypoxia. CRS events following tebentafusp infusion were mostly mild to moderate in severity and were generally reversible within 2 days using standard management strategies such as antipyretics and IV fluids.

In study IMCgp100-202, 89% of patients experienced any grade CRS. Most patients had Grade 1 (12%) or Grade 2 (76%) CRS; the incidence of Grade 3 CRS was 0.8%. There were no Grade 4 CRS or death due to CRS. Diagnosis of CRS following tebentafusp infusion was based most frequently on pyrexia followed by hypotension and infrequently hypoxia. Pyrexia and hypotension were reported in 76% and 38% of patients, respectively. Other commonly observed symptoms with CRS included chills (47%), nausea (43%), vomiting (26%), fatigue (41%) and headache (22%). These events occurred at a >10% point higher frequency in the tebentafusp treatment arm than the investigator’s choice arm; and are consistent with the mechanism of action of tebentafusp (Salama et al. 2021).

Most patients experienced CRS following each of the first three tebentafusp infusions, with decreasing severity and frequency. In majority of cases CRS started the day of infusion. Pyrexia was noted in nearly all cases of CRS, and in these patients, an increase in body temperature generally occurred within the first 8 hours

after tebentafusp infusion. CRS rarely (1.2%) led to treatment discontinuation. All CRS symptoms were reversible and were mostly managed with intravenous fluids, antihistamines, non-steroidal anti-inflammatory drugs, or a single dose of corticosteroid. Two patients (0.8%) with Grade 3 CRS received tocilizumab.

In the Phase 2 dose expansion cohort of study IMCgp100-102, 86% of patients presented with the AE CRS; most frequently the CRS classified events were pyrexia (80%) and hypotension (50%). CRS was a serious AE in 3.15% of patients.

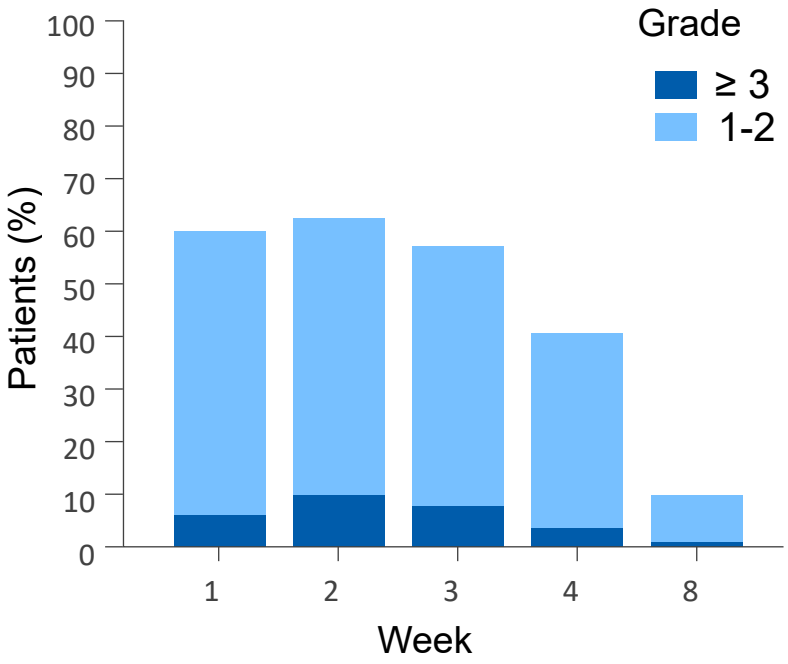
B.2.10.2 Acute skin reactions

Acute skin reactions have been reported with tebentafusp infusion, which may be due to the recognition of gp100-expressing melanocytes in the skin by tebentafusp, i.e., on-target AE.

In study IMCgp100-202, acute skin reactions occurred in 91% of patients treated with tebentafusp including any grade rash[1] (grouped term, 83.0%), pruritus (69.0%), erythema (25.0%) and cutaneous oedema (grouped term, 27.0%). Most skin reactions were Grade 1 (27.0%) or 2 (38.0%) and some tebentafusp treated patients experienced Grade 3 (18.4%). Grade 3 reactions with the highest incidence were rash and rash maculo-papular. No Grade 4 or 5 events or deaths relating to skin reactions were observed.

[[1]Rash was defined as composite of preferred AE terms including rash, dermatitis, eczema and other select skin AE terms]

Figure 19. Percentage of treated patients experiencing any grade or grade ≥3 treatment related rash after each does of tebentafusp.



Acute skin reactions typically occurred following each of the first three tebentafusp infusions, with decreasing severity and frequency (Figure 19). The median time to onset of acute skin reactions was 1 day in the tebentafusp treated patients and median time to improvement to Grade ≤1 was 6 days. Rash was generally manageable with simple interventions such as oral antihistamines and topical corticosteroids. Systemic corticosteroids were used infrequently to treat rash (10% of patients experiencing rash) and majority of symptoms resolved without any systemic corticosteroid or any long term sequalae. Only 2.4% of patients had treatment interrupted due to a skin-related AE. There were no discontinuations of tebentafusp due to acute skin reactions. No cases of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported.

In study IMCgp100-102, acute skin reactions occurred in patients in Phase 1 dose escalation cohorts and patients in the Phase 2 dose expansion cohort (Immunocore 2015). Rash occurred in 16.7%, 50.0%, 33.3%, and 33.1% of patients in Phase 1 dose escalation cohorts 2, 3 and 4, and the Phase 2 expansion cohort, respectively. Pruritus occurred in all cohorts; 100.0%, 66.7%, 100.0%, 100.0% and 68.5% in Phase 1 dose escalation cohorts 1, 2, 3 and 4, and Phase 2 expansion cohort,

respectively. Erythema was also reported in the Phase 1 dose escalation cohorts 1 (33.3%), 2 (66.7%), 3 (75.0%) and 4 (33.3%), and Phase 2 expansion cohort (17.3%). Generalised rash and maculo-papular were severe adverse events in 0.8% and 2.4% of patients in the Phase 2 dose expansion cohort. There were no events of Grade 4 or 5 severity. None of the TEAEs in the rash category were serious and none resulted in dose interruption or discontinuation of tebentafusp.

In the Phase 2 dose expansion cohort in study IMCgp100-102, 88.2% of patients experienced AEs for rash; 15.7% of which were of Grade 3 severity. No events of Grade 4 or 5 were reported. The most common Grade 3 rash events were rash maculo-papular (11.0%) and rash (2.7%). 3.1% of patients had serious AEs in the rash category that included rash maculo-papular and rash generalized. None of the TEAEs in the rash category resulted in discontinuation of tebentafusp. Tebentafusp-related rash was most common in the initial weeks of treatment across the Phase 1 dose escalation and Phase 2 dose expansion cohorts, becoming less frequent by the second month of treatment. Less than 1% of patients reported events of Grade ≥3 severity after Day 35 of treatment. No cases of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported.

B.2.10.3 Liver function abnormalities

Post-baseline laboratory abnormalities (haematology, chemistry, and liver function tests) occurring in ≥20% or Grade 3-4 (≥5%) following treatment with tebentafusp or investigator's choice in Study IMCgp100-202, compared to baseline, are summarised in Table 16.

Ninety-five percent of patients had pre-existing liver metastasis, and ALT/AST increases to Grade ≥1 were observed in 64.5% of patients treated with tebentafusp. No deaths due to ALT/AST elevations were observed and more than 90% of patients were able to continue treatment beyond worst grade ALT/AST elevation. Most (71%) ALT/AST elevations generally occurred within the first three tebentafusp infusions. Most patients experiencing Grade 3 or 4 ALT/AST elevations had improvement to Grade ≤1 within 7 days. Elevations in bilirubin have been reported in 27% of patients and these were primarily associated with increased size of liver metastasis (Immunocore 2021a).

Table 16. Select post-baseline laboratory abnormalities occurring in ≥20% or Grade 3-4 (≥5%) in UM patients in study IMCgp100-202 (Immunocore 2021a)

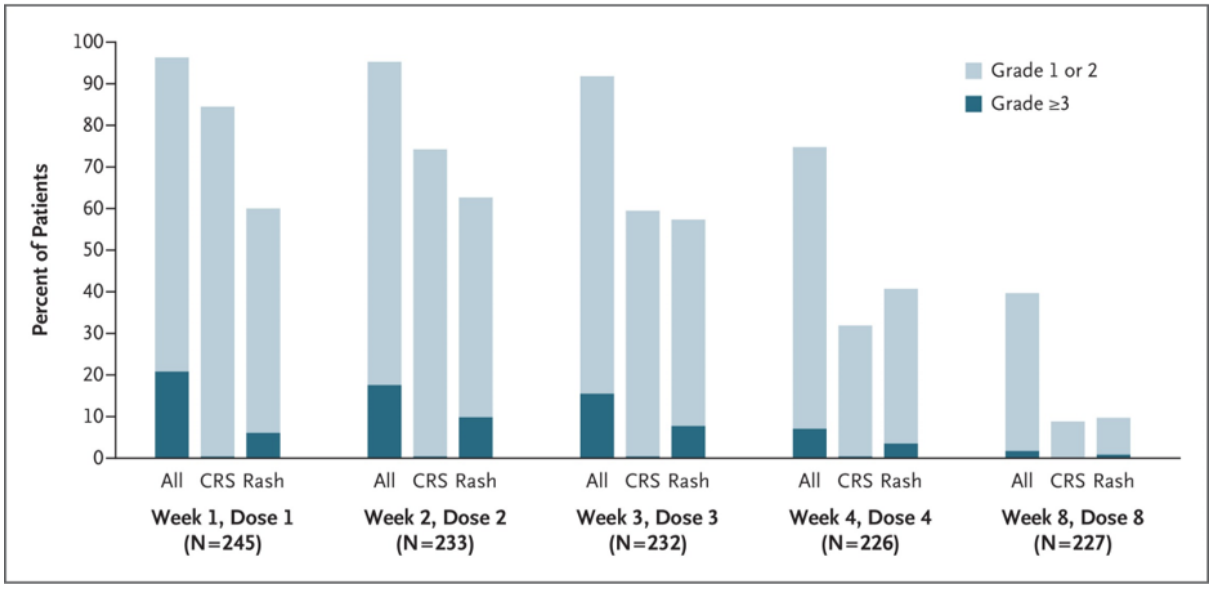
	Study IMCgp100-202			
	Tebentafusp (N=245)		Investigator Choice Therapy (N=111)	
Lab Parameter	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
Haematology				
Lymphocyte count decreased	222 (90.6)	136 (55.5)	29 (26.6)	2 (1.8)
Chemistry				
Phosphate decreased	124 (51.5)	29 (12.0)	20 (19.6)	2 (2.0)
Lipase increased	91 (37.8)	36 (14.9)	29 (28.2)	6 (5.8)
Amylase increased	56 (23.0)	10 (4.1)	19 (18.1)	1 (1.0)
Liver Function Tests				
AST increased	132 (54.8)	30 (12.4)	43 (39.8)	3 (2.8)
ALT increased	126 (52.3)	22 (9.1)	32 (29.4)	2 (1.8)
Bilirubin increased	65 (26.5)	11 (4.5)	16 (14.5)	8 (7.3)
Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase				

B.2.10.4 Summary of treatment-related AEs

The safety profile of tebentafusp was consistent across the two studies and appears to be independent of prior therapies. It can be categorised into two major types of AEs: cytokine-mediated events and skin-related events. Both types of AEs decreased in frequency and severity with repeated dosing over the first weeks of treatment (Figure 20). Cytokine-mediated AEs due to T-cell activation were reported in most of the patients, but the majority of events were mild to moderate in severity and were managed symptomatically with standard treatment interventions. These events occurred in the hours after the first few doses; therefore, overnight monitoring of all patients after the first three infusions was required. After this induction period, cytokine mediated AEs decreased in incidence and severity, and the extension of overnight monitoring beyond that required by the protocol was uncommon.

The occurrence of skin-related AEs was also generally limited to the hours after administration of the first few doses. Overall, few patients discontinued treatment with tebentafusp owing to TRAEs, and no tebentafusp-related deaths were reported during the trials.

Figure 20. Incidence and severity of treatment-related adverse events after initial doses of tebentafusp in study IMCgp100-202 (Nathan et al. 2021)



B.2.11 Ongoing studies

There are no additional ongoing studies of tebentafusp in advanced UM. Study IMCgp100-202 is estimated to complete in March 2023.

B.2.12 Innovation

Tebentafusp is a new pioneering medical technology invented in the UK and is a first-in-class novel biologic, termed ImmTAC®. Tebentafusp is the first treatment to demonstrate a survival benefit for metastatic or advanced UM, it is the first bispecific biologic to show activity with solid tumours and is the first TCR-based medicine to demonstrate a survival benefit. This new approach to treating disease has the potential for broad utility beyond the treatment of cancer to improve patients' lives.

Tebentafusp is a bispecific fusion protein, comprised of a TCR (targeting domain) fused to an antibody fragment targeting CD3 (cluster of differentiation 3; effector domain). The TCR end binds with high affinity to a gp100 peptide presented by human leukocyte antigen – A*02:01 (HLA-A*02:01) on the cell surface of UM tumour cells, and the effector domain binds to the CD3 receptor on the polyclonal T cell.

An immune synapse is formed when the TCR targeting domain of tebentafusp binds to UM cells and the CD3 effector domain binds to polyclonal T cells. This immune

synapse results in redirection and activation of polyclonal T cells regardless of their native TCR specificity. Tebentafusp-activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of UM tumour cells.

Tebentafusp has demonstrated significant clinical efficacy and a predictable and manageable safety profile, therefore providing a valuable new treatment option for HLA-A*02:01 positive metastatic UM patients, an orphan disease with a high mortality rate and no current specifically approved systemic treatment options.

B.2.13 Interpretation of clinical effectiveness and safety evidence

UM is a rare, highly malignant, and life-threatening disease that affects the vascular layers of the eye; up to half of all patients go on to develop metastatic disease. UM has a 1-year OS of ~50% after diagnosis of metastatic disease.

Current treatment options for metastatic UM are limited and no therapy has demonstrated a survival benefit specifically for patients with metastatic UM. There is currently no specific NICE-approved SoC for patients who develop metastatic UM, and the current UK clinical guidelines recommend clinical trial participation (Nathan et al. 2015a). Checkpoint inhibitors are available as a treatment because they are recommended for advanced melanoma generically; however, these were approved based on cutaneous melanoma studies and are of limited relevance to metastatic UM because they are pathologically very distinct cancers (Singh et al. 2018a). In addition, patients with metastatic UM were excluded from the registration trials for checkpoint inhibitors further demonstrating the NICE clinical guidelines on *Melanoma* are not currently appropriate for metastatic UM.

The Phase 3 RCT, study IMCgp-100-202, has demonstrated that patients randomised to tebentafusp as first-line therapy had almost half the risk of death compared with those treated with investigator's choice therapies (i.e., pembrolizumab, ipilimumab or chemotherapeutic dacarbazine) after a median follow-up of 14.1 months. The estimated one-year OS rate was 73.2% among patients in the tebentafusp arm, compared with 58.5% in the investigator's choice arm. The ORR was 9.1% (95% CI: 5.9-13.4) for tebentafusp vs 4.8% (95% CI: 1.8-10.1) for investigator's choice. Notably, response by RECIST was shown to underestimate OS

benefit from tebentafusp; long OS (≥12 months) was observed across all categories of RECIST response, even PD (Figure 5). OS benefit was also observed among patients who had no tumour shrinkage and only tumour growth as their best change while they were receiving treatment. In addition, more patients in the tebentafusp group than in the control group had tumour regression that did not meet the RECIST criteria for PR, and tumour regression was associated with longer OS. RECIST was therefore determined not to be an appropriate measure of disease progression as there was a clinically meaningful effect on outcomes for patients in the absence of radiologically significant effect on tumour size. This observation may be accounted for by the mode of action of tebentafusp in the induction of an inflammatory response at the metastatic site and could be more broadly applicable to T-cell receptor bispecifics in solid-tumours.

Recent single-group, Phase 2 studies involving patients with UM who were treated with ipilimumab plus nivolumab showed a 1-year survival of 52% and 56% (Piulats et al. 2021b; Pelster et al. 2021b), as examined in section B.2.9. The 1-year OS with tebentafusp was 73% — a result that was higher than that reported for the combination of ipilimumab and nivolumab. The OS result observed in the control arm of study IMCgp100-202 (58%) was slightly higher than those reported in recent meta-analyses (52-56%) (Khoja et al. 2019; Rantala et al. 2019a).

In addition, study IMCgp100-102 demonstrated the potential clinical benefit of tebentafusp in treating metastatic UM who have previously received one or more prior lines of therapy, including chemotherapy, immunotherapy, or local therapy. The median OS in tebentafusp-treated patients was 16.8 months 16.8 months (95% CI: 12.9-21.3), and the OS rates were 61.8% (95% CI: 52.6-69.8%) at 12 months and 37.0% (95% CI: 26.5-47.5%) at 24 months. This is higher than the OS experienced with previously tested treatments (OS: 7.8 months [95% CI: 6.5-9.7], 1-year survival rate: 37% [95% CI: 31-43]), reported by a meta-analysis published by Rantala et al. (2019).

The safety profile of tebentafusp is consistent with its MoA, predictable and clinically manageable with appropriate surveillance and intervention. The rate of treatment

discontinuation was lower in the tebentafusp arm compared with the investigator's choice arm (3.3% versus 6.3%, respectively).

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

De novo cost-effectiveness model

- A de novo cohort partitioned survival model with an NHS and PSS perspective was developed to evaluate the cost-effectiveness of tebentafusp over a lifetime horizon for the treatment of patients with HLA-A*02:01 positive advanced metastatic UM. The population is in line with the NICE scope.

- Clinical outcomes used to inform this economic analysis include PFS, OS, time to treatment discontinuation (TTD) and occurrence of adverse events from the IMCgp100-202 phase III trial. Utility data was derived from both the EQ-5D data collected in the trial and the literature. Costs inputs were taken from the NHS reference costs, BNF, PSSRU, the literature and clinical experts' opinion.

Survival analysis

- OS is modelled using standard parametric models in the control arm. A spline model has been used in the tebentafusp arm [redacted]. Alternative methods, including standard parametric models, and a cure fraction are also explored.

- A hybrid modelling approach was used for PFS and TTD, using the KM curves plus parametric extrapolation.

Base-case results

- The base-case ICER is [redacted]. The QALY gains are driven by the longer OS in the tebentafusp arm, with a proportion of the patients experiencing long-term survival. The incremental costs are mainly driven by the acquisition cost of tebentafusp.

Sensitivity analysis

- Parameter uncertainty was explored through probabilistic sensitivity analysis with structural uncertainty and key assumptions explored through scenario analyses and deterministic one-way sensitivity analyses.

- The sensitivity analysis demonstrates that the ICER is very sensitive to the choice of model for the extrapolation of the OS in the tebentafusp arm, as this drives the size of the incremental QALYs. Results from the PSA show that there is a significant level of uncertainty associated with the model

chosen in the base-case for the extrapolation of the OS in the tebentafusp arm.

- The incremental costs are driven by the acquisition cost of tebentafusp, and associated with less uncertainty [redacted] and this is modelled using the TTD KM curve and parametric models for the extrapolation of the tail.

An SLR was undertaken with the aim of identifying all published economic evidence relating to tebentafusp and any relevant comparator interventions for the treatment of advanced or metastatic UM. Searches were undertaken in May 2020 in relevant libraries and databases reporting on economic studies. Full details of the methodology used is reported in Appendix G. No relevant cost-effectiveness or cost-utility analyses were identified.

B.3.2 Economic analysis

No cost-effectiveness studies in metastatic UM or UM were identified in the systematic literature review. Additionally, tebentafusp is a novel therapy and the first one to be assessed for use within the NHS specifically for the treatment of metastatic UM. Hence, a de novo economic model was developed, in Microsoft Excel®, to inform the decision making. The model conceptualisation was based on the clinical data available, a target review of previous HTAs is metastatic melanoma and insights from clinical experts. Features of the economic analysis are presented in Table 17.

Table 17. Features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Time horizon	Lifetime (38 years)	To capture of health benefits and costs in line with NICE reference case
Cycle length	One week	Consistent with the length of tebentafusp treatment cycles, and to reflect timing of transitions to disease progression and death
Half-cycle correction	Yes	As per NICE reference case
Perspective	NHS and PSS	As per NICE reference case

Treatment waning effect?	Yes	Treatment effect is captured implicitly by survival data and corresponding models
Days per year	365.25	NA
Discount rate for utilities and costs	3.5%	As per NICE reference case
Source of clinical data	IMCgp100-202 clinical trial	Phase III trial assessing the efficacy of tebentafusp, in line with NICE method guide
Source of utilities	IMCgp100-202 and literature review	In line with NICE method guide
Source of costs	Published databases, literature review and clinical experts opinion	In line with NICE method guide

B.3.2.1 Patient population

The patient population in the model reflects the patient population of the Phase III trial IMCgp100-202, i.e., adult patients with HLA-A*02:01 positive metastatic uveal melanoma, without prior treatment in the metastatic setting. This population is also consistent with the population defined in the final scope.

Patient's starting age in the model is 62 years, based on the mean age in the IMCgp100-202 trial and it was assumed that 49.7% of patients entering the model were women in line with the trial data.

B.3.2.2 Model structure

The model employs a partitioned survival method to determine the proportion of patients within each of the health states at every model cycle. The model is composed of three mutually exclusive health-state (pre-progression, post-progression, death) (Figure 21), with represent the stages of disease in metastatic UM 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 (progression-free survival (PFS)) health state and stay in this state until disease progression is confirmed, upon which they move to the post-progression state (progressed disease (PD)). Transition to the death state, which is an absorbing state, may occur from both the pre-progression and post-progression states, at any time point within the model. Patients cannot transition back from PD to PFS.

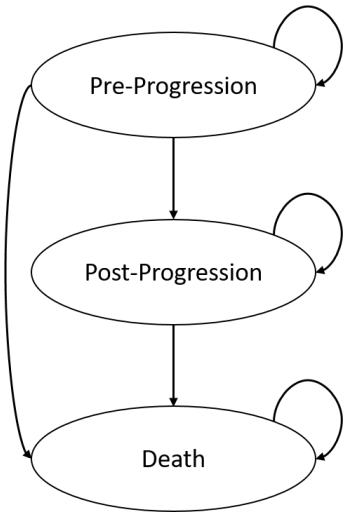
The post-progression state is defined in accordance with the Phase III IMCgp100-202 clinical trial secondary efficacy endpoint of progression-free survival, as patients having confirmed disease progression per RECIST v1.1.

A one-week cycle length was used, to be able to reflect patterns of treatment administration (weekly for tebentafusp) and transitions to disease progression and death. This is also consistent with cycle length used in previous economic evaluation of immunotherapies in advanced melanoma. Half-cycle correction is applied to account for the over or under estimation of transitions occurring at the beginning or end of the cycle.

The model base case uses a lifetime horizon, which is equivalent to 38 years based on the age of the cohort at the start of the model which is based on the mean age at baseline in the trial (62 years old). The model time horizon was chosen to be sufficiently long to capture differences in all relevant costs and health benefits in line with the NICE reference case.

All costs and health outcomes are discounted at 3.5%.

Figure 21. Schematic model structure



Clinical inputs

The model inputs on the clinical efficacy and safety are derived from the IMCgp100-202 for both arms of the model. The state occupancy, proportion of patients alive in the PFS and PD states, are derived from the PFS and OS curves from the trial.

Drug costs

Drug acquisition and administration costs were based on time to treatment discontinuation (TTD) in the IMCgp100-202 clinical trial rather than based on disease progression, as per the study protocol, patients could stay on treatment beyond progression. Clinical evidence suggests that some patients treated with immunotherapies, including tebentafusp, will derive clinical benefit after an initial assessment of PD.

Health states and AEs costs

The pre-progression and post-progression states were associated with resource utilisation for the management of the condition and AEs. Resource use have been derived from the literature and clinical experts' opinion and are comprised consultations with clinicians, lab test, scans and hospital visits.

Subsequent therapies

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

Quality of life

Utility values were derived from the EQ-5D-5L data collected in the IMCgp100-202 trial. Based on personal communications with clinicians, disease progression may not be a good proxy for measuring changes in the QoL of patients with metastatic UM. Additionally, patients could stay on treatment beyond disease progression as per the study protocol, benefiting still from treatment based on clinical opinion. Hence, the data was analysed based on pre- (i.e., on treatment) and post-treatment discontinuation (i.e., off treatment). An approach based on time-to death, based on the literature, is also implemented.

Model outputs

Results are reported in terms of cost per life years (LY) gained and costs per quality adjusted life years (QALY) gained. Incremental cost-effectiveness ratios (ICER) are also reported in line with NICE requirements.

B.3.2.4 Intervention technology and comparators

The intervention is tebentafusp (IMCgp100). Tebentafusp is a concentrate for solution for infusion available in 0.10 mg/mL vials. Each vial is intended for use as single-dose only. Tebentafusp is administered weekly following a dose escalation regimen, starting with 20mcg on Day 1, 30mcg on Day 8 and 68mcg on Day 15 and once weekly thereafter (Immunocore 2021a). Tebentafusp is administered as an IV infusion over 15-20 minutes (Immunocore 2021b).

The comparator arm in the model reflects the control arm of the IMCgp100-202 trial, in which patients were treated with investigator's choice of immunotherapies, ipilimumab or pembrolizumab, or chemotherapy, dacarbazine. Out of the 126 patients randomized to the control arm, 103 (81.7%) were treated with pembrolizumab, 16 (12.7%) with ipilimumab, and seven (5.6%) with dacarbazine. Given that is no treatment approved specifically for the treatment of metastatic UM, there is no standard of care and patients are offered immunotherapy, although the evidence for these is based on cutaneous melanoma (NICE 2021b). People for whom immunotherapy is not suitable may have dacarbazine chemotherapy or best supportive care. The comparator arm in the IMCgp100-202 study was considered by clinical experts as reflective of current practice in the UK.

Pembrolizumab was administered as per the licensed dosing regimen in patients with advanced melanoma, that is 2 mg/kg, to a maximum dose of 200mg, as an IV infusion over 30 minutes every three weeks.

Ipilimumab was administered as per the licensed dosing regimen in patients with advanced melanoma, that is 3 mg/kg as an IV infusion over 90 minutes every three weeks for a maximum of four doses.

Dacarbazine was administered at the standard dosing regimen in UM, that is 1000 mg/m^2 every three weeks, with an infusion time of 60 minutes.

B.3.3 Clinical parameters and variables

The clinical inputs in the model are derived from the IMCgp100-202 clinical trial, which was an open-label, randomized, Phase III study of tebentafusp versus Investigator's Choice (dacarbazine, ipilimumab, or pembrolizumab). The clinical trial is the data source for the overall survival, progression-free survival, time to treatment discontinuation, rates of adverse events and quality of life data, in both the tebentafusp and control arm in the model.

Extrapolation of the OS, PFS and TTD data was required as not all events were observed over the trial period. Two cuts of the data are used in the economic model, October 2020 and August 2021. It is important to note that up until the first interim analysis of October 2020, patients in the investigator's choice arm were not allowed to cross-over to receive tebentafusp. Beyond this time point, as the primary endpoint was met which showed superiority of tebentafusp and given the prognosis of the disease under currently treatment options, cross-over was allowed for ethical reasons. Between the data-cut-off (DCO) of October 2020 and September 2021, [redacted] patients had crossed over from the IC arm to tebentafusp arm (Immunocore 2018). The most recent DCO, from August 2021, with a median follow-up time of [redacted] months is used in the base-case at it provides the most information on the effectiveness of tebentafusp, however it has not been adjusted for cross-over from the IC arm to tebentafusp. The data cut off (DCO) of the primary analysis, October 2020, with a median duration of follow-up for all patients of 14.1 months, is used in scenario analysis.

Parametric models (exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma) were fitted, following NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance (Latimer 2011) and TSD 21 (NICE-DSU 2020) for flexible approaches (NICE-DSU 2013). The different models fitted were assessed to determine whether they provided a good fit to the observed data and that the extrapolated portion of the curve was clinically plausible. This assessment was based on goodness of fit statistics, including the Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) for which lower values indicate a better fit, as well as visual comparison with the Kaplan-Meier

curves. The extrapolated portion of the curves were compared to historical data, where available, in the control arm. When no data was available in the literature for comparison, e.g., in the tebentafusp arm, clinical experts' opinion was sought to determine what was clinically plausible.

For completeness, the PH assumption was assessed statistically and visually through log-log plots and Schoenfeld residual plots. However, given the availability of the patient-level data (PLD), models were fitted separately to each arm of the trial, negating the need to assume PH. The results of the PH assumption tests are not reported.

B.3.3.1 ITT analysis set

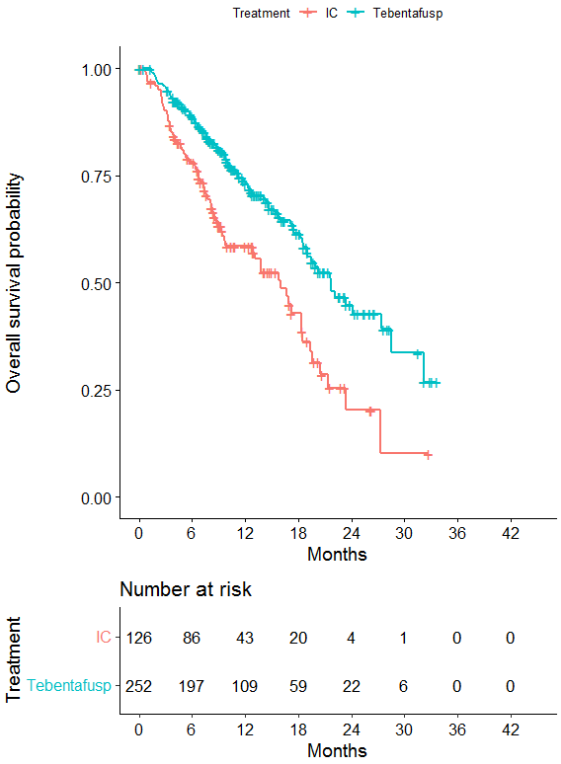
Overall survival

Kaplan-Meier curves

We present in Figure 22, the Kaplan Meier curve for the OS at both data cut-offs for comparison, as well as the median OS in Table 18. We note that the KM curves are very similar with both DCO, the August 2021 DCO confirming the OS trajectory. Additionally, we observe [redacted] with the August 2021 DCO, although this section of the curve is based on a small number of patients remaining at risk. The [redacted] as has been observed with immune checkpoint inhibitors (Chen 2013; Gibson et al. 2017). Long term follow up on studies of ipilimumab and nivolumab in advanced melanoma, following primary cancers that were biologically distinct to UM, have set a precedence for the expected outcomes of targeted biologics that mobilise the immune system against cancer (Hodi et al. 2018). We acknowledge that there is uncertainty which will be resolved by following up the patients which Immunocore Ltd is committed to, and the next data cut is anticipated to be available [redacted]. Although we also observe [redacted] as such a pattern for the OS KM curve has not been reported with historical data (Rantala et al. 2019a), which is presented for comparison in the next section.

Figure 22. Kaplan-Meier curve OS ITT set for both data cut-offs (a) October 2020; (b) August 2021

(a)



(b)

[redacted]

Table 18. Median OS ITT set both data cut-offs

	October 2020	**August 2021**
Tebentafusp (N=252)	21.7 (18.6, 28.6)	[redacted]
Investigator's choice (N=126)	16.0 (9.7, 18.4)	[redacted]
*The data includes cross-overs from the IC to tebentafusp arm between October 2020 and August 2021		

Extrapolation analysis - Investigator's Choice

The six-standard parametric distributions were fitted to the data. Based on the AIC and BIC, presented in Table 19 for both the October 2020 and August 2021 DCO, which provide information on the goodness of fit to the observed data, the model with the best fit in the control arm is the Weibull, although all models are reasonable based on statistical fit, as all the AIC and BIC are within five points.

Table 19. Goodness-of-fit criterions AIC and BIC – OS ITT set IC arm DCO October 2020 and August 2021

	October 2020			August 2021		
Model	AIC	BIC	Ranking	AIC	BIC	Ranking
Exponential	505.46	508.29	4	640.26	643.10	3
Weibull	502.21	507.88	1	638.83	644.51	1
Log-normal	503.77	509.44	3	639.59	645.26	2
Log-logistic	503.63	509.31	2	639.73	645.40	4
Gompertz	503.81	509.48	5	640.49	646.16	6
Generalised Gamma	503.86	512.37	6	639.97	648.48	5
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion						

Based on the Kaplan-Meier curve for the control arm, investigator's choice of pembrolizumab, ipilimumab and dacarbazine, the probability of patients being alive at [redacted]% (Table 20 and Table 21), with a [redacted]. This data is comparable to data published in the literature: Rantala and colleagues conducted a systematic review and meta-analysis of 78 studies (n=2494) in metastatic uveal melanoma and reported a median OS across all treatment modalities of 1.07 years (≈13 months) (range: 0.59–2.50 years), and no clinically significant difference in OS by treatment modality (Rantala et al. 2019). Similarly, Khoja and colleagues conducted a meta-analysis in metastatic UM and reported a median OS of 10.2 months and 1-year OS of 43% (Khoja et al. 2019). In both studies, KM plots reported show a survival probability of approximately zero by year 5 regardless of treatment modalities. Hence, it is reasonable to expect that the OS extrapolated curve in the control arm reaches close 0 by year 5, in line with historical data. Additionally, based on clinical experts' opinion, the OS under current treatment modalities is between 0% and 5% at 5 years. Based on this assumption, the tail of the log-normal and log-logistic are unrealistic, with a probability of being alive at year 5 of 10% (Table 20 and Table 21), and these models were ruled out.

Rantala and colleagues investigated the impact of line of treatment on overall survival. They pooled data for 510 first-line patients and reported Kaplan Meier graphs. These patients were treated with conventional chemotherapy, chemoimmunotherapy, hepatic intra-arterial chemotherapy and transarterial chemoembolization. We appreciate that these interventions differ from the investigator's choice arm of the IMCgp100-202 trial. However, given that Rantala and colleagues found no clinically significant difference in OS by treatment modality, and that no therapy demonstrated a significant improvement in OS in the last 40 years (Yang et al. 2018; Khoja et al. 2019), we believe that the data reported by Rantala and colleagues on first-line patients is the best benchmark available for comparison against the trial control arm.

The Kaplan Meier curve reported in Rantala et al, constructed using data from studies which only included first-line patients (Supplemental digital content 4, B.Overall survival by percentage of first line treatments – 100%; green line) was digitised using WebPlotDigitizer, to reconstruct the PLD and plot against the data from the IMCgp100-202 for comparison. The Kaplan Meier curves for OS in the tebentafusp arm, IC arm, and first first-line patients reported in Rantala et al are reported in Figure 23. We observe that the Kapan Meier curve in the control arm is similar to the data from Rantala et al, with the same trajectory. As noted previously, up-until the first interim analysis of October 2020, patients in the investigator's choice arm were not allowed to cross-over to receive tebentafusp. After October 2020, and as the primary endpoint was met, patients were allowed to cross over for ethical reasons. Hence, the [redacted].

Figure 23. Kaplan Meier curves OS IMCgp100-202 for Tebentafusp and IC vs. Rantala et al.; (a) October 2020 DCO (b) August 2021 DCO

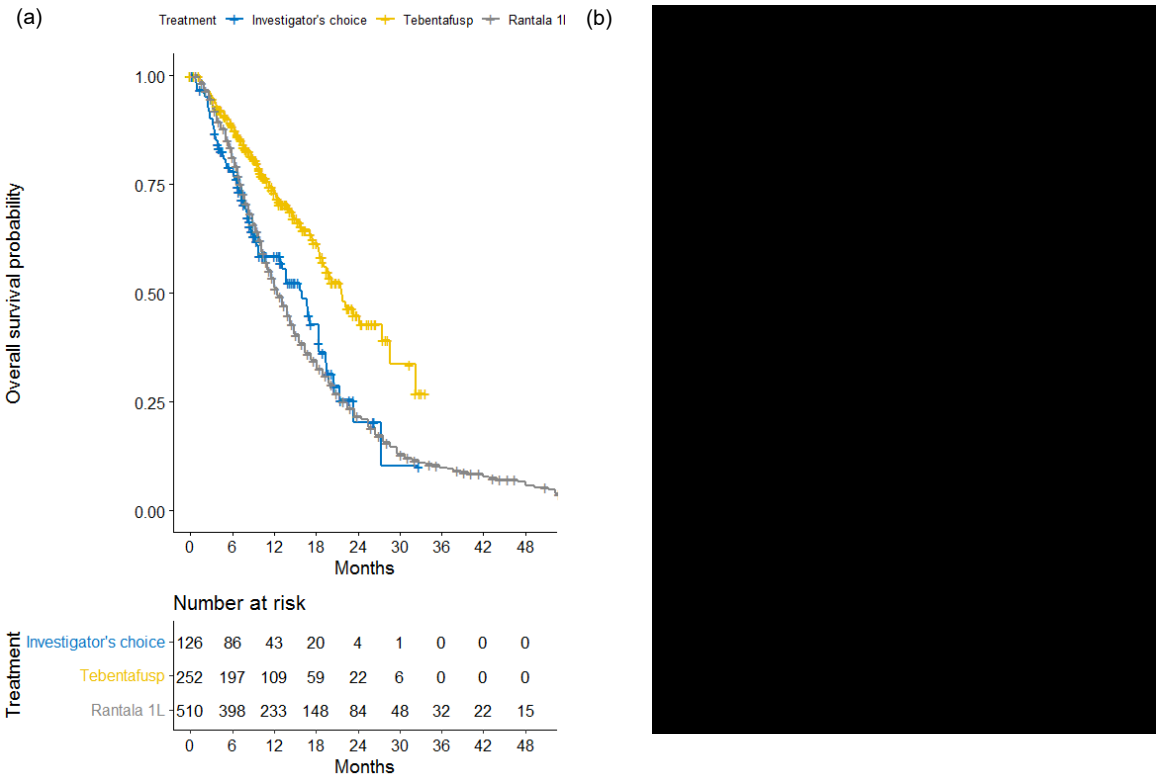


Table 20. OS parametric models IC arm ITT set DCO October 2020 vs KM curve and Rantala et al first-line

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**4**	**1**	**3**	**2**	**5**	**6**
6	**78.1%**	74.2%	78.8%	75.9%	77.8%	78.1%	78.1%
9	**63.2%**	63.9%	67.0%	63.5%	65.0%	67.5%	65.8%
12	**58.5%**	55.0%	56.0%	53.7%	54.3%	57.3%	54.9%
18	**42.9%**	40.8%	37.7%	39.5%	38.6%	38.8%	37.8%
24	**20.3%**	30.2%	24.3%	30.2%	28.6%	23.8%	25.9%
30	**10.2%**	22.4%	15.2%	23.7%	22.1%	12.9%	17.8%
36 (3 years)		16.4%	9.1%	18.9%	17.4%	5.8%	12.1%
48 (4 years)		9.0%	3.1%	12.8%	11.9%	0.6%	5.8%
60 (5 years)		5.0%	1.0%	9.2%	8.7%	0.0%	2.8%
120 (10 years)		0.2%	0.0%	2.6%	3.1%	0.0%	0.1%

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

Table 21. OS parametric models IC arm ITT set DCO August 2021 vs KM curve and Rantala et al first-line

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**3**	**1**	**2**	**4**	**5**	**6**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

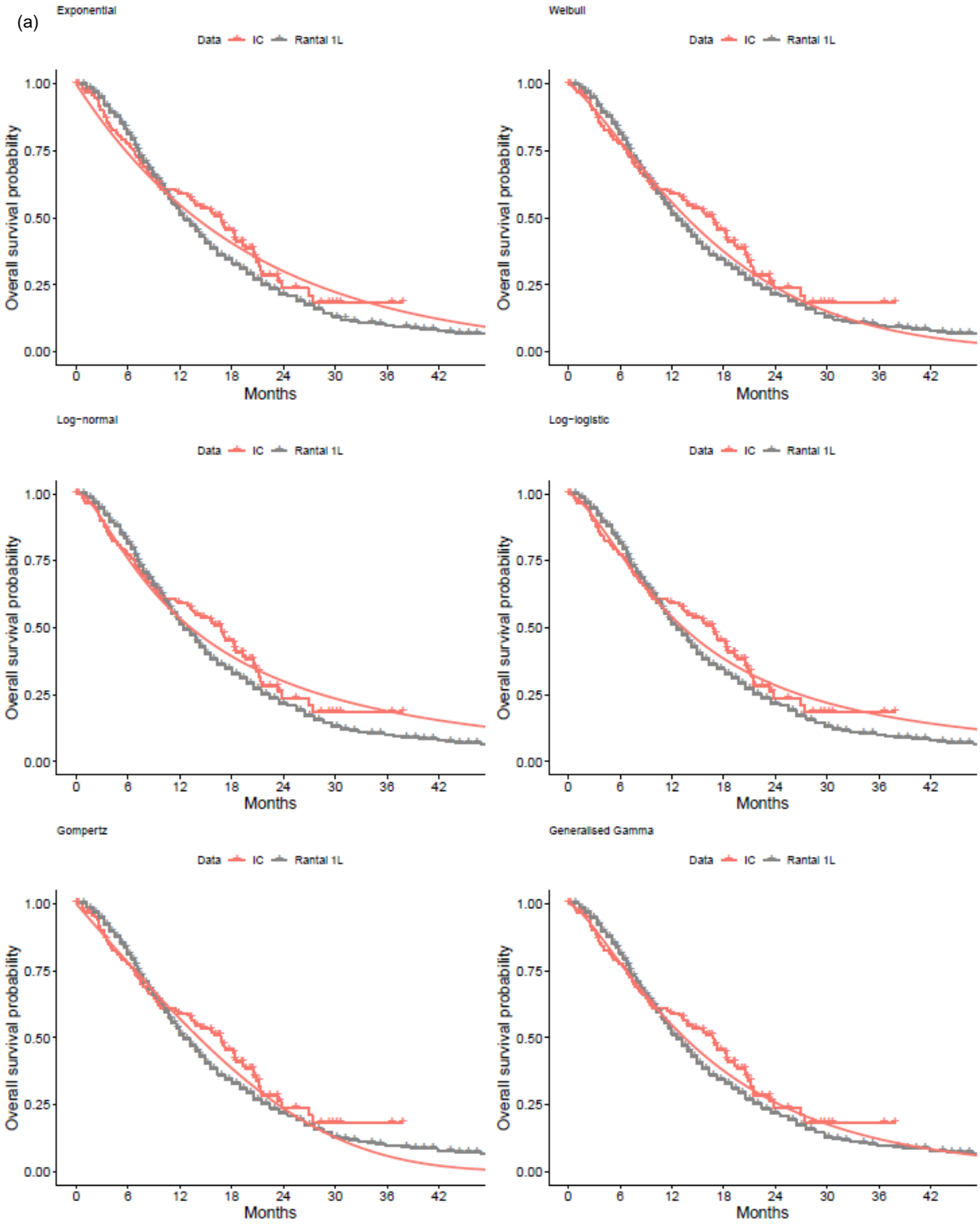
From visual inspection and comparison of the probabilities of being alive at different time points (Table 20 and Table 21), we note that the exponential provides an unrealistic fit, with the extrapolated portion of the curves giving survival probabilities larger than historical data. Based on AIC and BIC, the Weibull model is the best fit and it provides a good long-term fit compared to historical data,

Figure 24 and

Figure 25, and based on clinical expert's opinion. The Gompertz and generalised gamma also provide a good fit over the trial period based on statistical fit and visual inspection. We note however that the Gompertz diverges from the historical data at the tail. The extrapolation with the generalised gamma also fits the observed data quite well and matches historical data and is, therefore, used in scenario analysis.

Figure 24. OS standard parametric models IC arm ITT set October 2020 DCO - (a) Trial time horizon; (b) 15-year time horizon

(a)



(b)

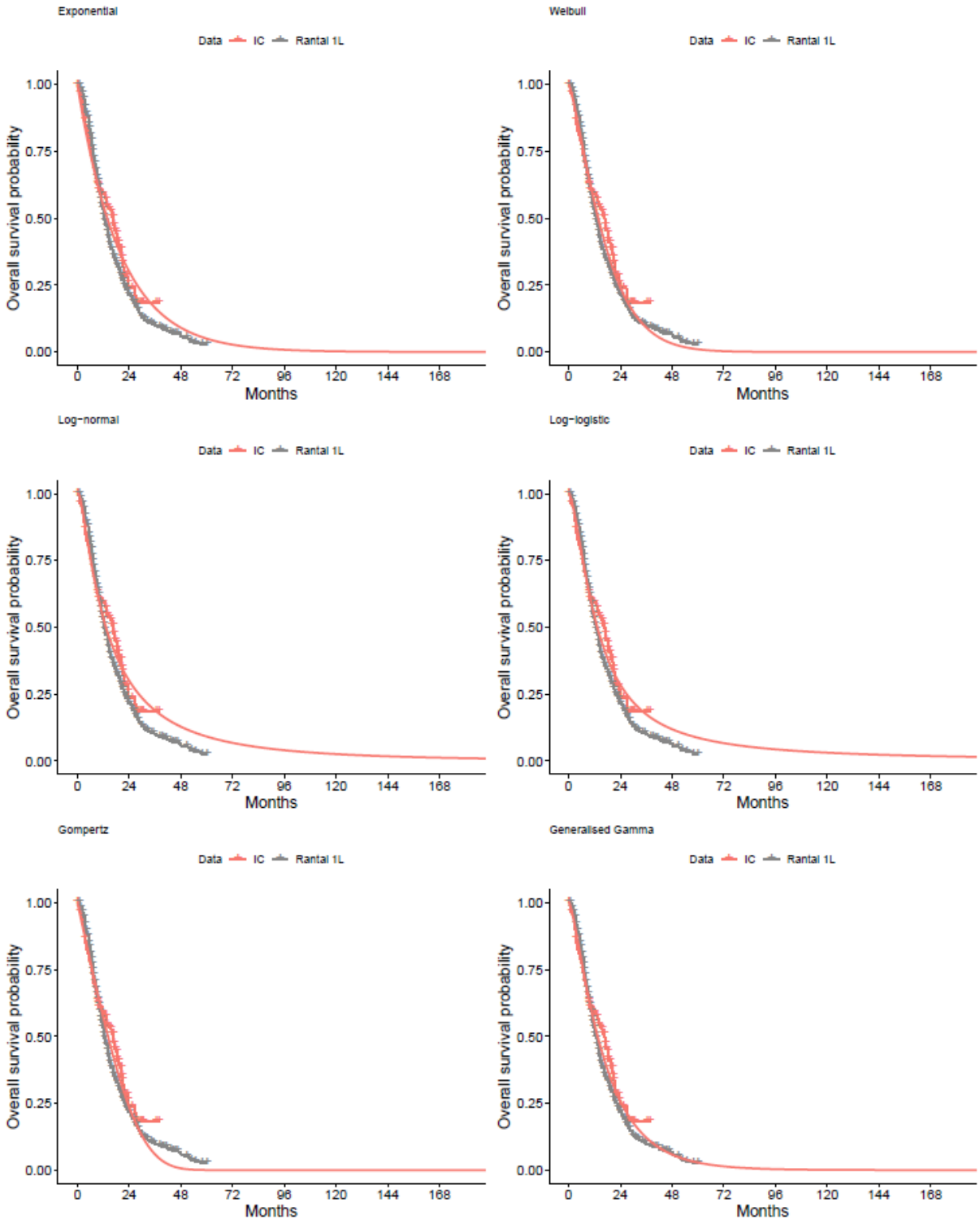
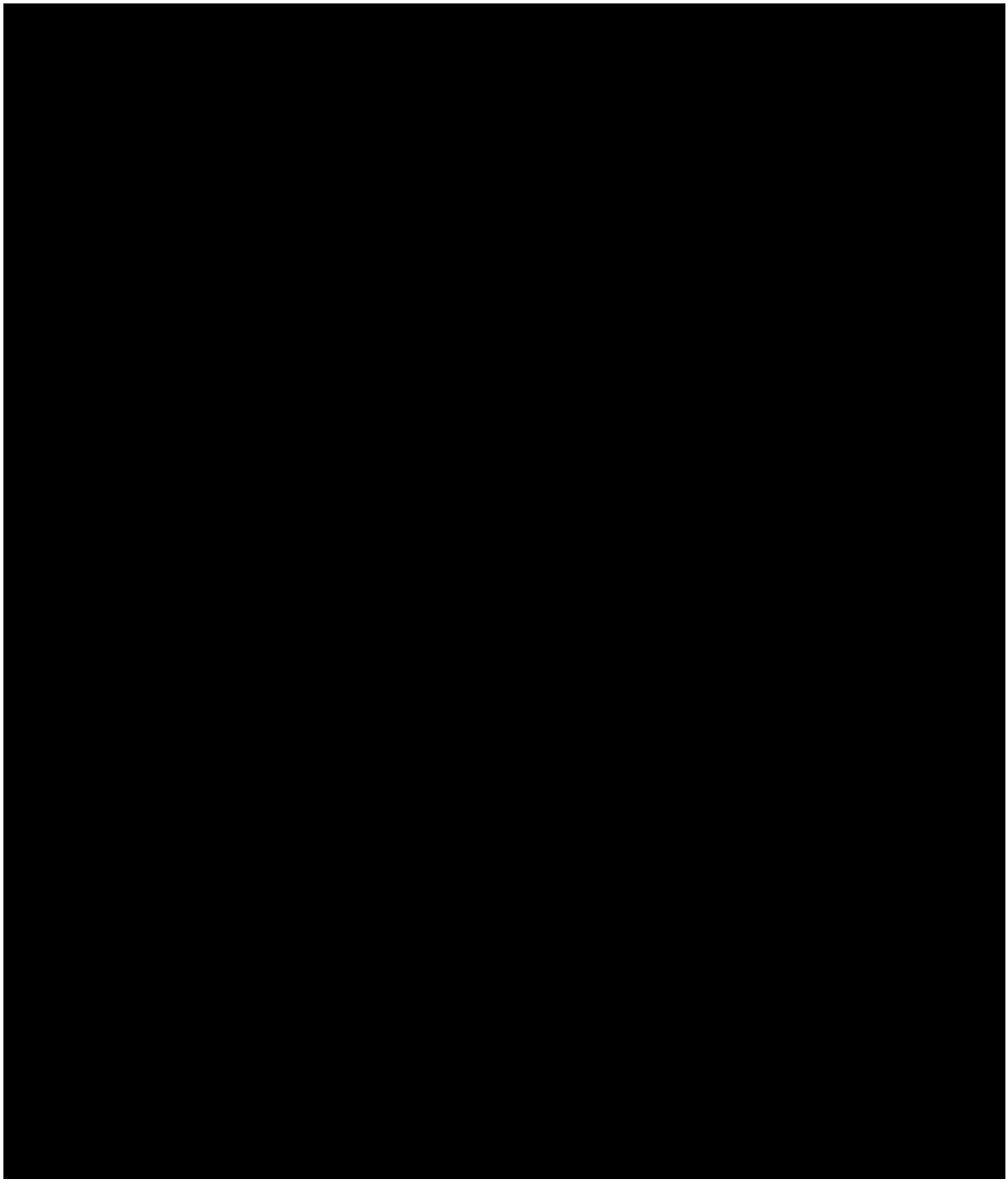
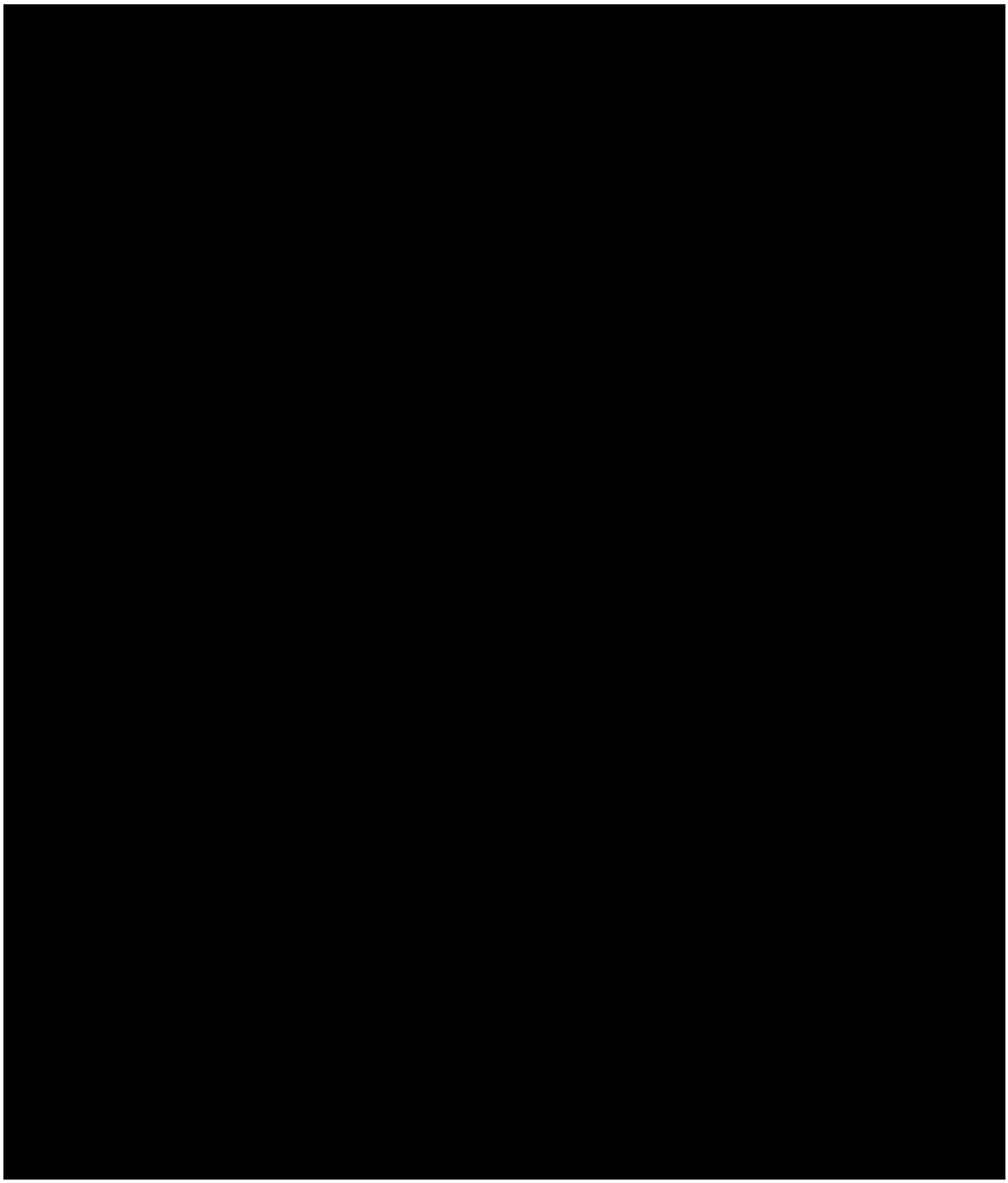


Figure 25. OS standard parametric models IC arm ITT set August 2021 DCO - (a) trial time horizon; (b) 15-year time horizon

(a)



(b)



Extrapolation analysis - Tebentafusp

Standard parametric models were fitted in the tebentafusp arm. Although, some models provided a good fit over the observed period, none allowed to properly model the change in the survival profile around [redacted] follow-up in the August 2021 DCO, as observed on the KM curve, Figure 22. Hence, we fitted flexible parametric models (cubic spline models) following NICE DSU TSD 21 on flexible methods for survival analysis. This approach has been used to model the survival function of immune checkpoint inhibitors (Gibson et al. 2017). Three potential functional forms of model types were considered: proportional hazards model, proportional odds and probit. These have been defined as “hazard”, “odds” and “normal” scale models respectively, as with no knots, these reduce to Weibull, log-logistic and lognormal models respectively. We tested a range of approaches with one, two and three knots. The model chosen for the base-case is a three knots [redacted] We chose a knot at [redacted] and chose the position of the other knots to be evenly spread. We also tested fitting the model without specifying the location of the knots on the time scale, which are then evenly spread on the time scale. The AIC and BIC are reported on

Table 22, and show that the model with [redacted]. The weekly mortality rate that is generated from the modelled OS is adjusted so that it can never fall below the mortality rate for the general population for that age group. The mortality rate for the general population, in single years of age, was sourced from the latest life tables (2018-2020) published by the Office for National Statistics (ONS).

Table 22. Goodness of fit criteria AIC and BIC

	3 knots (25%, 50%, 75%)	**3 knots** [redacted]
AIC	1137.44	1134.96
BIC	1155.09	1152.61

Figure 26. OS spline model tebentafusp arm ITT set August 2021 DCO - (a) Trial time horizon; (b) 15-year time horizon

Alternatively, standard parametric models are also implemented in the model, and can also be combined with background mortality when the survival curve reaches a certain percentage (e.g., [redacted]). For this approach, the user additionally needs to specify the proportion of patients (from those alive at the specified time point) to whom to apply background mortality, named the “long-term survivors”, while the rest of the patients are applied the mortality rate from the parametric curve. Background mortality has been taken from the latest life tables published by the ONS (2018-2020). This approach has been implemented to reflect that a proportion of the patients may have durable responses and survive in the long-term as has been observed with immune checkpoint inhibitors for the treatment of metastatic melanoma.

Progression-free survival

Kaplan-Meier curves

We present in Figure 27, the Kaplan Meier curve for the PFS at both data cut-offs for comparison, as well as the median PFS in Table 23. [redacted] with the KM curves reaching below [redacted] survival probability in the control arm and below [redacted] survival probability in the tebentafusp arm. Hence, there is limited need for extrapolation.

Radiologic assessment for tumour response determined according to RECIST v1.1 were performed every 12 weeks as per the protocol schedule. This resulted in a protocol-driven drop of PFS at week 12 corresponding to the first assessment, which limited the fit of the parametric distributions. Hence, the model base-case is based on a hybrid approach using the KM curves (non-parametric) and the parametric curves only for extrapolation of the tail. To derive the extrapolated portion of the curve (beyond the time point at which there is a switch from the KM curve to the parametric data), the rate of progression was derived from the parametric curve and applied to the state occupancy at time t-1 to derive the state occupancy at time t.

$$r(t) = \ln \frac{s(t-1)}{s(t)}$$

$$S(t) = \mathrm{S(t-1)} * (1 - (1 - \exp(-\mathrm{r(t)})$$

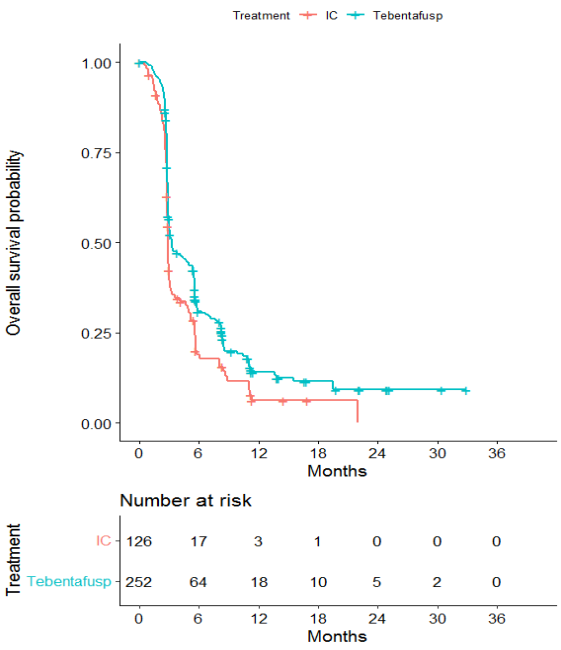
s(t) is the survival probability from the parametric model at time t, *S(t)* is the survival probability of the hybrid model for the extrapolated portion of the curve.

For additional flexibility, the model was set-up to also provide the option of only using the parametric curves. The results based on the parametric curves are also reported for comparison.

Table 23. Median PFS ITT set both data cut-offs

	October 2020	**August 2021**
Tebentafusp (N=252)	3.3 (3.0, 5.0)	[redacted]
Investigator's choice (N=126)	2.9 (2.8, 3.0)	[redacted]

Figure 27. Kaplan-Meier curve PFS ITT set for both cut-offs (a) October 2020; (b) August 2021



[redacted]

Extrapolation analysis

Based on the AIC and BIC, presented in Table 24 for both the October 2020 and August 2021 DCO, which provide information on the goodness of fit to the observed data, the model with the best fit in the control arm is the log-logistic, although the generalised gamma and log-normal also provide a reasonable fit to the observed data based on statistical fit.

Table 24. Goodness-of-fit criterions AIC and BIC – PFS ITT set IC arm DCO October 2020 and August 2021

	October 2020			**August 2021**		
Model	AIC	BIC	Ranking	[redacted]	[redacted]	[redacted]
Exponential	504.35	507.19	5	[redacted]	[redacted]	[redacted]
Weibull	489.50	495.18	4	[redacted]	[redacted]	[redacted]
Log-normal	457.55	463.22	2	[redacted]	[redacted]	[redacted]
Log-logistic	452.92	458.59	1	[redacted]	[redacted]	[redacted]
Gompertz	505.30	510.98	6	[redacted]	[redacted]	[redacted]
Generalised Gamma	454.95	463.46	2	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion						

Comparing the probability of patients being progression-free in the control arm, derived from the fitted models with the PFS data from the trial, presented in Table 25 and

Table 26, and from visual inspection, Figure 28, the generalised gamma is the model chosen for the base-case. It is a more conservative approach with the probability of being progression free reaching below 1% by 24 months. The log-logistic and lognormal also have a reasonable fit to the data and tail and will be tested in scenario analysis.

Table 25. PFS parametric models vs. KM curve IC ITT set arm DCO October 2020

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**5**	**4**	**2**	**1**	**6**	**2**
6	**18.9%**	29.5%	29.4%	23.5%	18.7%	30.1%	23.0%
9	**11.7%**	16.0%	11.7%	9.4%	7.3%	15.3%	10.7%
12	**6.2%**	8.7%	4.1%	4.2%	3.5%	7.3%	5.8%
18	**6.2%**	2.6%	0.4%	1.0%	1.2%	1.4%	2.2%
24		0.8%	0.0%	0.3%	0.6%	0.2%	1.1%
30		0.2%	0.0%	0.1%	0.3%	0.0%	0.6%
36 (3 years)		0.1%	0.0%	0.0%	0.2%	0.0%	0.4%
48 (4 years)		0.0%	0.0%	0.0%	0.1%	0.0%	0.2%
60 (5 years)		0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
120 (10 years)		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

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

Table 26. PFS parametric models vs. KM curve IC arm ITT set DCO August 2021

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**5**	**4**	**3**	**1**	**6**	**1**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

Based on the AIC and BIC, presented in Table 27 for both the October 2020 and August 2021 DCO, which provide information on the goodness of fit to the observed data, the model with the best fit in the tebentafusp arm is the generalised gamma.

Table 27. Goodness-of-fit criterions AIC and BIC – PFS ITT set Tebentafusp arm DCO October 2020 and August 2021

	October 2020			**August 2021**		
Model	AIC	BIC	Ranking	AIC	BIC	Ranking
Exponential	1168.06	1171.59	5	1336.44	1339.97	5
Weibull	1157.64	1164.70	4	1335.66	1342.72	5
Log-normal	1077.85	1084.91	3	1251.41	1258.47	3
Log-logistic	1075.42	1082.48	2	1248.51	1255.57	2
Gompertz	1167.51	1174.57	5	1327.02	1334.07	4
Generalised Gamma	1037.02	1047.61	1	1202.36	1212.95	1
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion						

Table 28. PFS parametric models vs. KM curve Tebentafusp ITT set arm DCO October 2020

Months	**KM**	**Exponential**	**Weibull**	**Lognormal**	**Log-logistic**	**Gompertz**	**Generalised gamma**
Ranking based on AIC and BIC		**5**	**4**	**3**	**2**	**5**	**1**
6	**30.9%**	42.5%	44.8%	39.0%	33.9%	41.0%	35.0%
9	**19.8%**	27.7%	26.9%	21.1%	17.1%	27.5%	21.2%
12	**14.1%**	18.1%	15.5%	12.0%	9.7%	18.9%	14.6%
18	**11.5%**	7.7%	4.8%	4.5%	4.2%	9.6%	8.5%
24	**9.2%**	3.3%	1.3%	1.9%	2.2%	5.3%	5.8%
30	**9.2%**	1.4%	0.3%	0.9%	1.4%	3.1%	4.2%
36 (3 years)		0.6%	0.1%	0.5%	0.9%	2.0%	3.3%
48 (4 years)		0.1%	0.0%	0.1%	0.5%	0.9%	2.2%
60 (5 years)		0.0%	0.0%	0.1%	0.3%	0.5%	1.6%
120 (10 years)		0.0%	0.0%	0.0%	0.1%	0.1%	0.6%
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

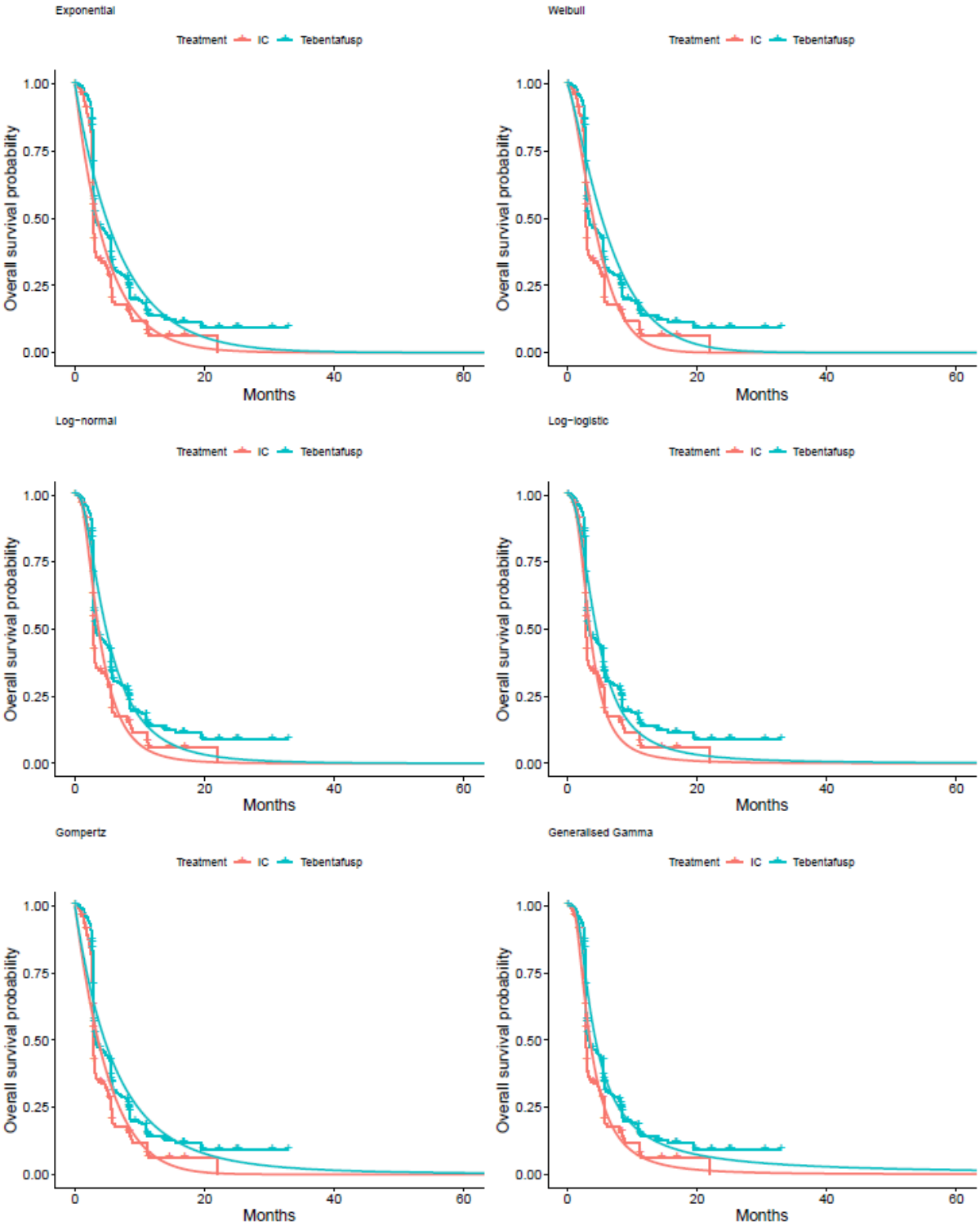
Table 29. PFS parametric models vs. KM curve Tebentafusp arm ITT set DCO August 2021

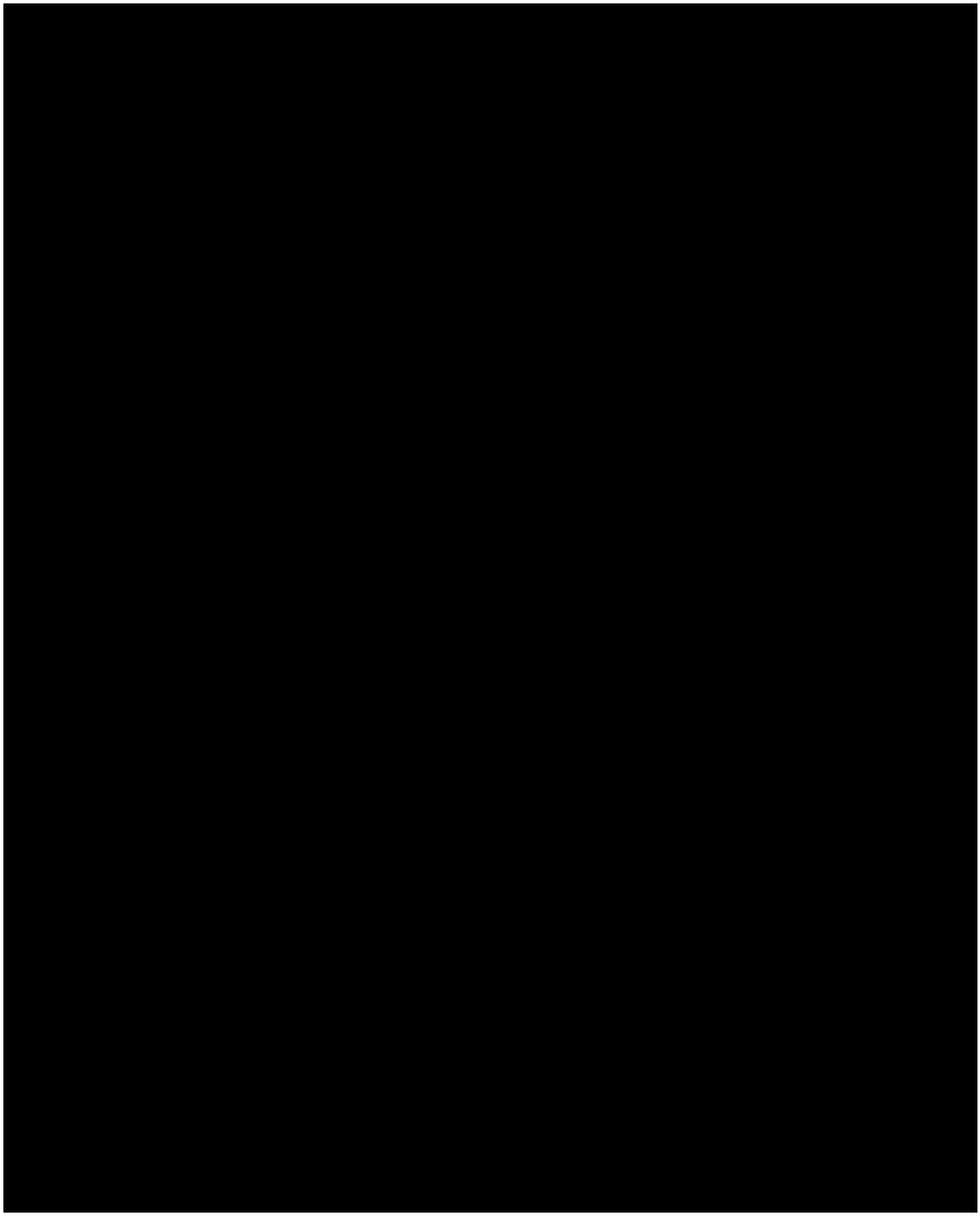
Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		5	5	3	2	4	1
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

Comparing the probability of patients being progression-free in the tebentafusp arm, derived from the fitted models with the PFS data from the trial, presented in Table 28 and Table 29, and from visual inspection, Figure 28, the generalised gamma is the best fitting model and used in the base-case. It is a close fit to the observed data [redacted] with the probability of being progression free reaching [redacted] We note however that the curves [redacted] The log-logistic and lognormal also have a reasonable fit to the data and tail and will be tested in scenario analysis.

Figure 28. PFS standard parametric models ITT set; (a) October 2020 DCO; (b) August 2021 DCO

(a)



(b) 

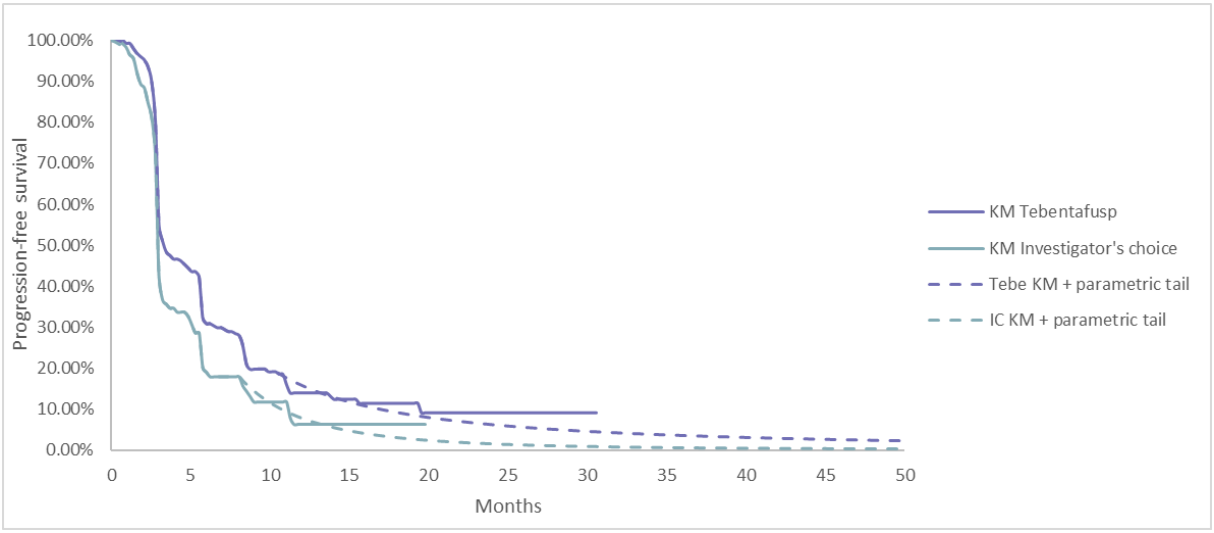
The Kaplan-Meier data is used until the time point at which only 15% of the patients remain at risk, which is derived from the Kaplan-Meier estimates. A scenario will be conducted where this is set at 15% of the patients remaining at risk.

The PFS data in the model is adjusted to ensure that it is never higher than the OS.

The hybrid approach is presented graphically in Figure 29, and the state occupancy in Table 30.

Figure 29. PFS Kaplan-Meier + parametric tail (generalised gamma); (a) October 2020 DCO; (b) August 2021 DCO

(a)



(b)

Table 30. PFS state occupancy hybrid model using KM curve + parametric tail from 15% of patient at risk

	October 2020		August 2021	
	Tebentafusp (generalised gamma)	**Investigator's choice (generalised gamma)**	**Tebentafusp (generalised gamma)**	**Investigator's choice (generalised gamma)**
6	30.9%	23.31%	[redacted]	[redacted]
9	24.4%	10.90%	[redacted]	[redacted]

12	16.8%	5.90%	[redacted]	[redacted]
18	9.8%	2.27%	[redacted]	[redacted]
24	6.6%	1.10%	[redacted]	[redacted]
30	4.9%	0.61%	[redacted]	[redacted]
36 (3 years)	3.8%	0.37%	[redacted]	[redacted]
48 (4 years)	2.5%	0.17%	[redacted]	[redacted]
60 (5 years)	1.9%	0.09%	[redacted]	[redacted]
120 (10 years)	0.7%	0.01%	[redacted]	[redacted]

Time to treatment discontinuation

We present in Figure 30, the Kaplan Meier curves for the TTD at both data cut-offs for comparison, as well as the median TTD in Table 31. A high proportion of events have been observed during the trial follow-up, with the KM curves reaching below [redacted] probability of being on treatment in the control arm and below [redacted] in the tebentafusp arm.

Figure 30. Kaplan-Meier curve TTD ITT set for both data cut-offs (a) October 2020; (b) August 2021

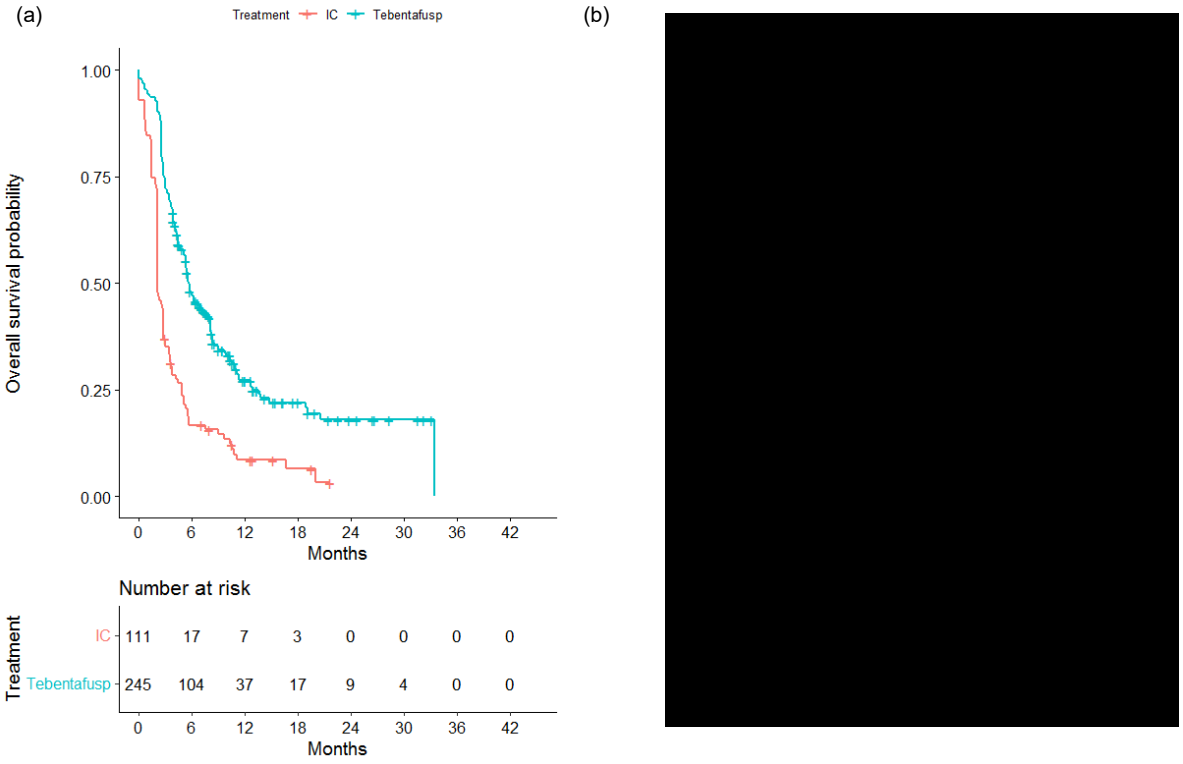


Table 31. Median TTD ITT set both data cut-offs

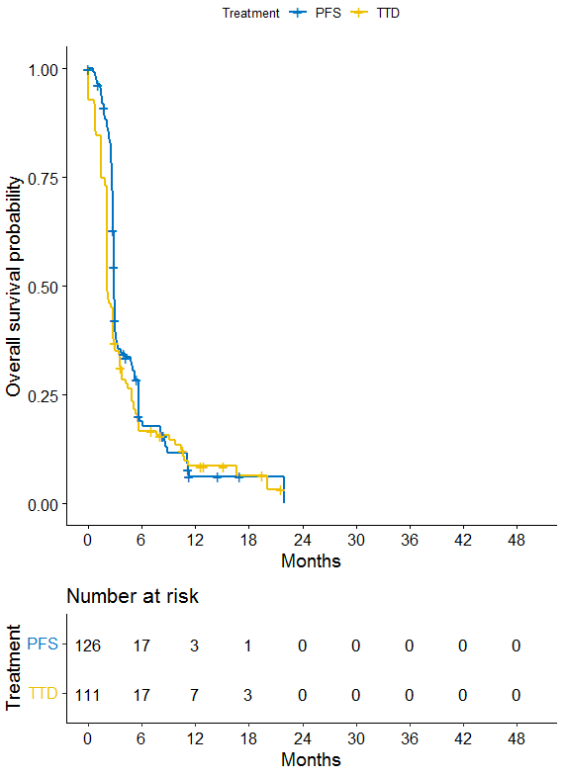
	October 2020	August 2021
Tebentafusp (N=245)	5.6 (5.3, 7.6)	[redacted]
Investigator's choice (N=111)	2.1 (2.1, 2.8)	[redacted]

Treatment discontinuation was contingent on confirmed disease progression based on RECIST v1.1. We note that the KM curve has a similar shape to the PFS curve, driven by the radiological assessment for tumour response every 12 weeks. This limited the fit of the parametric distributions. Given this and that a high proportion of events were observed during the trial follow-up, the model base-case uses a hybrid approach using the KM curves and the parametric curves only for extrapolation of the tail. This is implemented in the same way as described for the PFS. For additional flexibility, the model was set-up to also provide the option of only using the parametric curves. The results based on the parametric curves are also be reported for comparison.

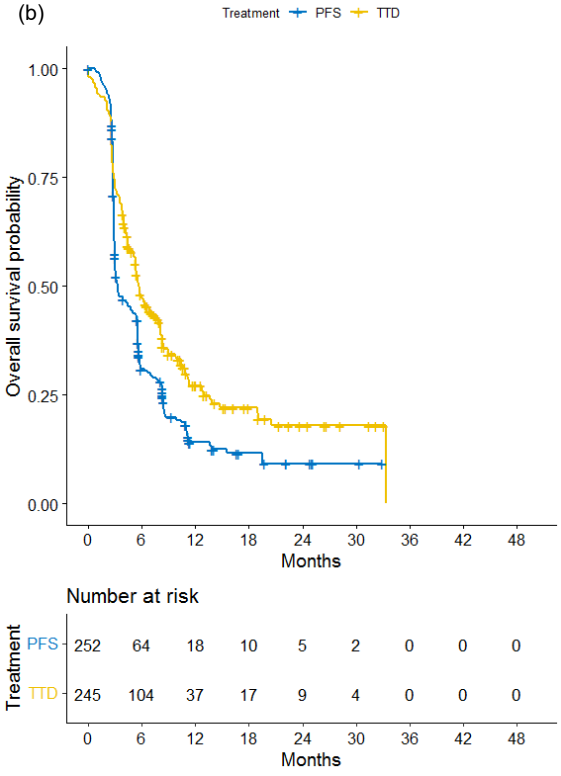
Although treatment discontinuation was based on disease progression, patients could stay on treatment beyond confirmed PD based on RECIST v1.1 unless criteria for treatment beyond initial PD was met. As can be observed in Figure 31, the PFS and TTD are almost identical in the IC arm, patients indeed discontinued based on confirmed disease progression. In the tebentafusp arm however, patients stayed on treatment beyond disease progression. This is the reason why we choose to estimate drug costs based on TTD rather than PFS.

Figure 31. PFS and TTD ITT set; (a) IC October 2020 DCO; (b) Tebentafusp October 2020 DCO; (c) IC August 2021 DCO; (d) Tebentafusp August 2021 DCO

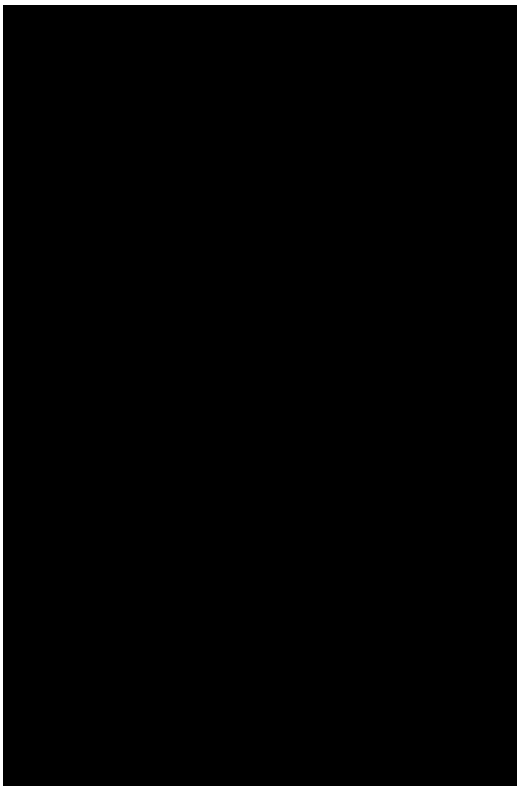
(a)



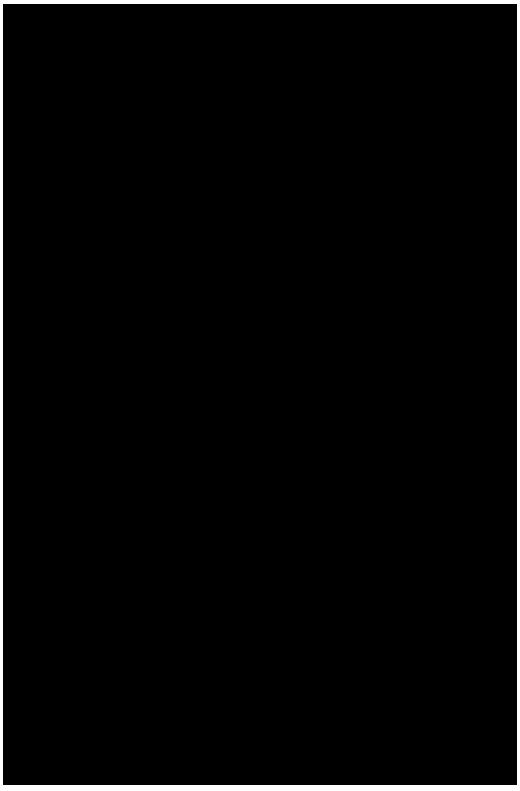
(b)



(c)



(d)



Extrapolation analysis

The AIC and BIC are presented in Table 32 for both the October 2020 and August 2021 DCO and provide information on the goodness of fit to the observed data. With the October 2020 DCO, the model with the best fit in the control arm is the Gompertz, although all but the log-normal are reasonable as the AIC and BIC are all within five points. With the August 2021 DCO, the Gompertz and log-logistic provide the best fit with the lowest AIC and BIC, although the Weibull may also be acceptable.

Table 32. Goodness-of-fit criterions AIC and BIC – TTD ITT set IC arm DCO October 2020 and August 2021

	October 2020			**August 2021**		
Model	AIC	BIC	Ranking	AIC	BIC	Ranking
Exponential	495.39	498.10	3	[redacted]	[redacted]	[redacted]
Weibull	495.08	500.50	4	[redacted]	[redacted]	[redacted]
Log-normal	513.28	518.70	6	[redacted]	[redacted]	[redacted]
Log-logistic	492.98	498.40	2	[redacted]	[redacted]	[redacted]
Gompertz	490.06	495.48	1	[redacted]	[redacted]	[redacted]
Generalised Gamma	496.41	504.54	5	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion						

Comparing the probability of patients being on treatment in the control arm, derived from the fitted models with the TTD data from the trial, presented in Table 33 and

Table 34, and from visual inspection, Figure 32, we note that the [redacted] which is likely unrealistic. Given that the PFS and TTD are very similar in the control arm, we would expect that the extrapolation would follow the same trajectory with less than 5% of the patients remaining on treatment beyond 2 years and about 0% at 5 years. Based on this, the generalised gamma is used in the model base-case and the log-logistic and Weibull are tested in a scenario analysis.

Table 33. TTD parametric models vs. KM curve IC arm ITT set DCO October 2020

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

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

Table 34. TTD parametric models vs. KM curve IC arm ITT set DCO August 2021

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**4**	**3**	**6**	**2**	**1**	**4**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

Based on the AIC and BIC, presented in Table 62 for both the October 2020 and August 2021 DCO, which provide information on the goodness of fit to the observed data, the models with the best fit in the tebentafusp arm is the log-logistic.

Table 35. Goodness-of-fit criterions AIC and BIC – TTD ITT set Tebentafusp arm DCO October 2020 and August 2021

	October 2020			August 2021		
Model	AIC	BIC	Ranking	AIC	BIC	Ranking
Exponential	1147.40	1150.90	3	1404.70	1408.21	3
Weibull	1149.40	1156.40	5	1405.15	1412.15	5
Log-normal	1162.08	1169.09	6	1412.19	1419.19	6
Log-logistic	1131.43	1138.43	1	1381.81	1388.82	1
Gompertz	1142.81	1149.81	2	1393.05	1400.05	2
Generalised Gamma	1145.80	1156.31	3	1398.12	1408.62	3
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion						

Comparing the probabilities of being on treatment with the data from the KM curves, Table 36 and Table 37, the log-logistic provides a good fit over the trial period. Based on clinical experts' opinion and current data, the proportion of patients expected to still be on treatment with tebentafusp at 5 and 10 years is expected to be low. Given this, the Gompertz may not be realistic. Hence, the generalised gamma is used in the model base-case. The log-logistic and exponential are tested in scenario analysis. [redacted] Given this and the hybrid approach used where the KM curve is used directly, the choice of curve for the extrapolation of the tail in the tebentafusp arm has a little impact on the model results.

Table 36. TTD parametric models vs. KM curve Tebentafusp arm ITT set DCO October 2020

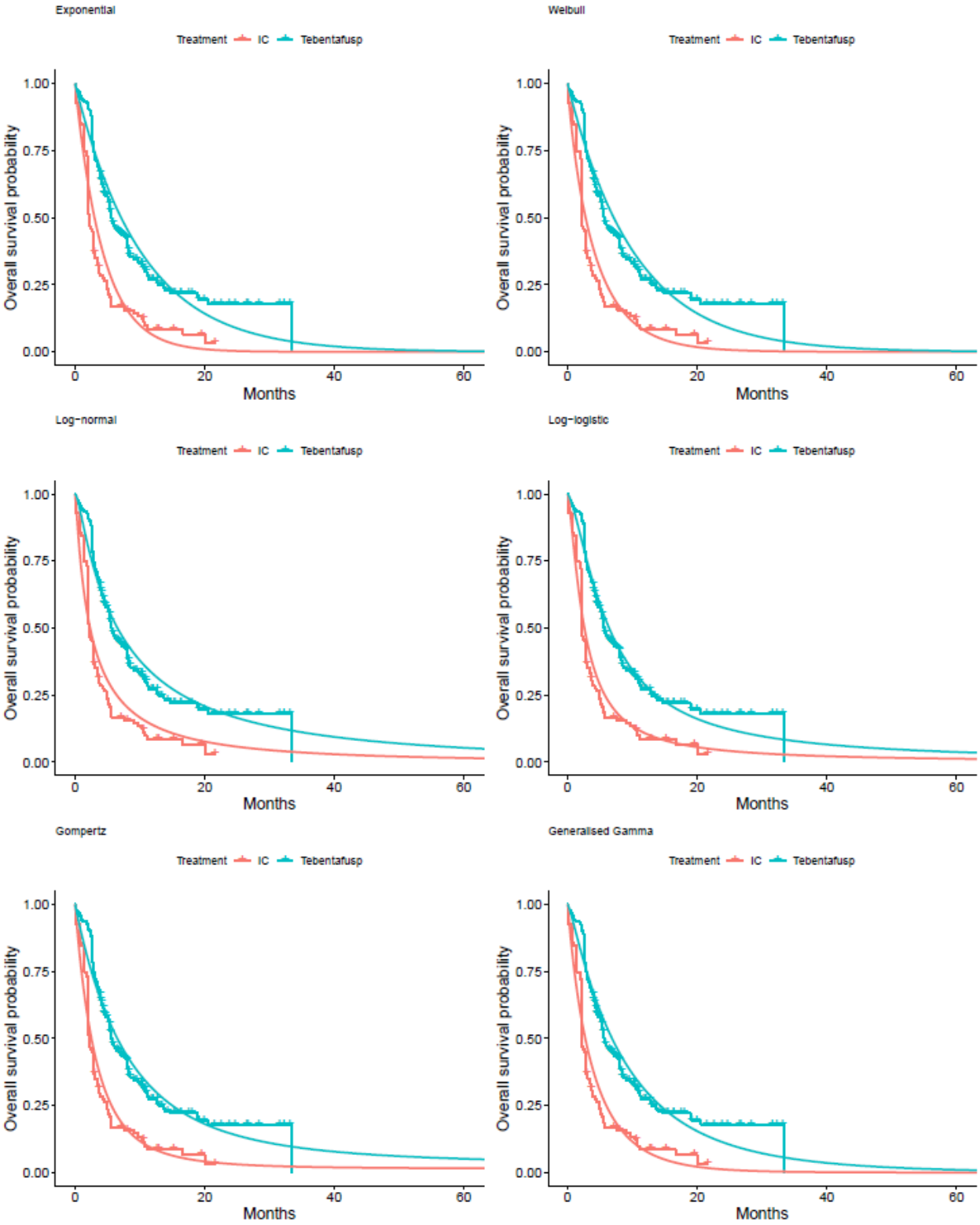
Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**3**	**5**	**6**	**1**	**2**	**3**
6	47.6%	55.88%	55.85%	52.64%	52.44%	52.62%	54.54%
9	35.4%	41.77%	41.76%	40.96%	38.02%	40.02%	40.59%
12	27.2%	31.22%	31.24%	33.08%	28.81%	31.28%	30.69%
18	22.1%	17.45%	17.48%	23.19%	18.38%	20.52%	18.24%
24	18.0%	9.75%	9.79%	17.32%	12.94%	14.59%	11.28%
30	18.0%	5.45%	5.48%	13.48%	9.71%	11.06%	7.20%
36 (3 years)		2.98%	3.00%	10.73%	7.57%	8.78%	4.64%
48 (4 years)		0.93%	0.94%	7.37%	5.14%	6.34%	2.11%
60 (5 years)		0.29%	0.30%	5.36%	3.78%	5.12%	1.02%
120 (10 years)		0.00%	0.00%	1.72%	1.42%	3.57%	0.05%
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

Table 37. TTD parametric models vs. KM curve Tebentafusp arm ITT set DCO August 2021

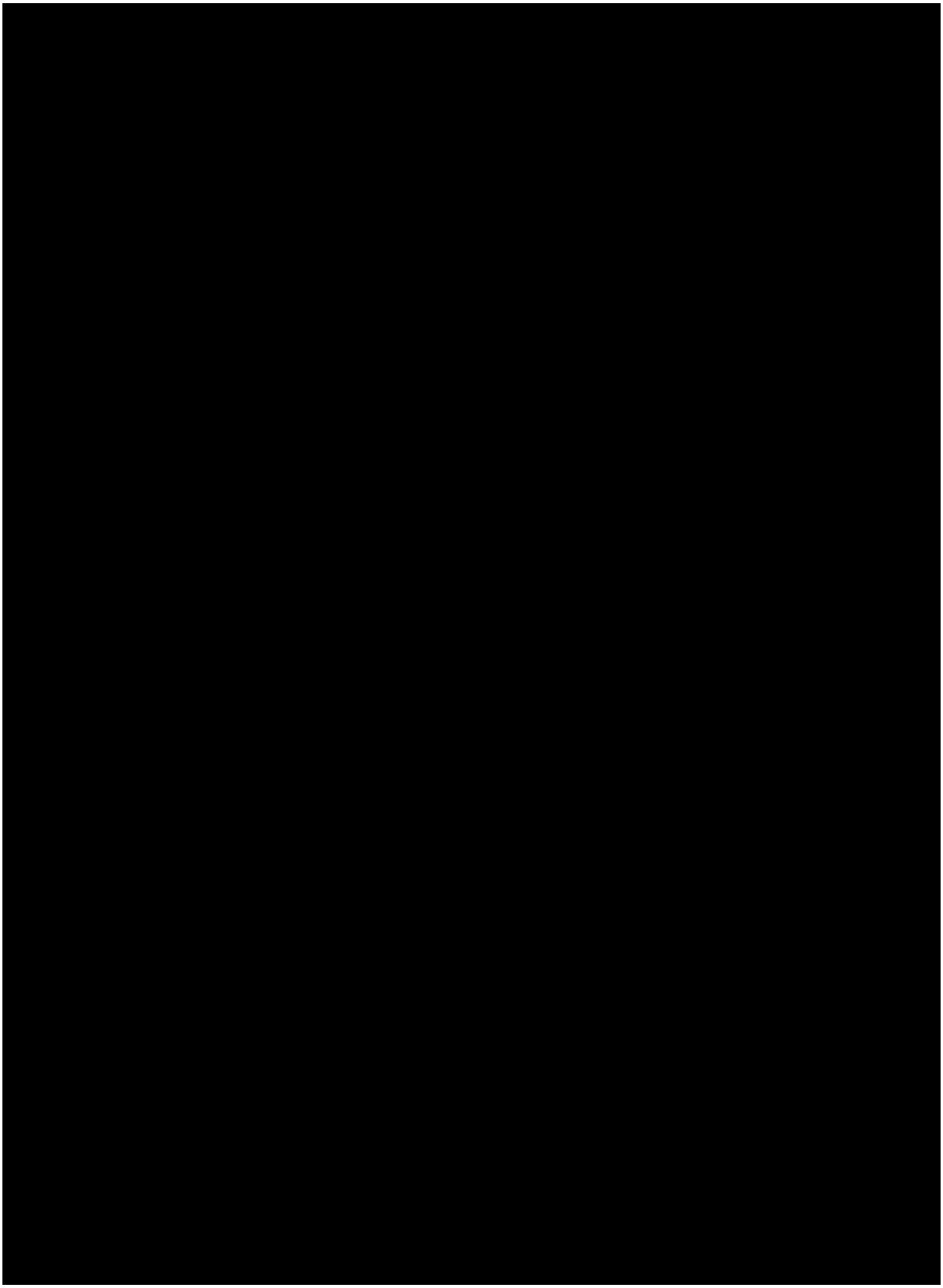
Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**3**	**5**	**6**	**1**	**2**	**3**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

Figure 32. TTD standard parametric models ITT set; (a) October 2020 DCO; (b) August 2021 DCO

(a)



(b)



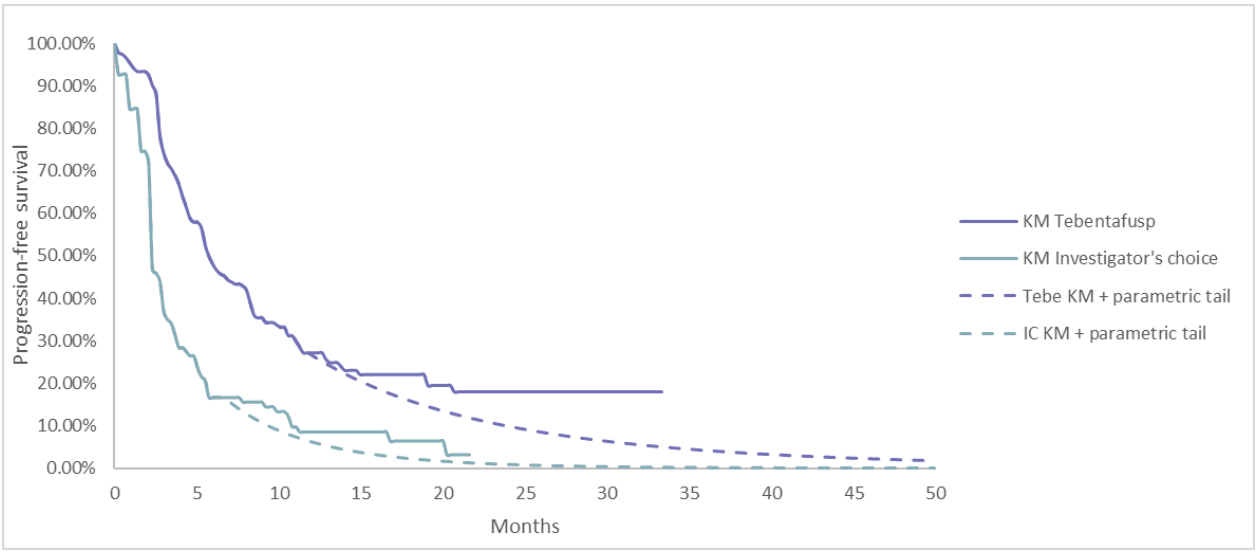
The Kaplan-Meier data is used until the time point at which only [redacted] of the patients remain at risk, which is derived from the Kaplan-Meier estimates. A scenario will be conducted where this is set at [redacted] of the patients remaining at risk.

The TTD data in the model is adjusted so that it is never higher than the OS, i.e., only patients who are alive can receive treatment.

The hybrid approach is presented graphically in Figure 33, and the state occupancy in Table 38.

Figure 33. TTD Kaplan-Meier + parametric tail; (a) October 2020 DCO; (b) August 2021 DCO

(a)



(b)

[redacted]

Table 38. TTD state occupancy hybrid model using KM curve + parametric tail (from 15% of patient at risk)

	October 2020		August 2021	
	Tebentafusp (generalised gamma)	**Investigator's choice (generalised gamma)**	**Tebentafusp (generalised gamma)**	**Investigator's choice (generalised gamma)**
6	48.0%	16.68%	[redacted]	[redacted]
9	35.4%	10.73%	[redacted]	[redacted]
12	26.6%	6.24%	[redacted]	[redacted]
18	15.8%	2.29%	[redacted]	[redacted]
24	9.8%	0.90%	[redacted]	[redacted]
30	6.2%	0.37%	[redacted]	[redacted]
36 (3 years)	4.0%	0.16%	[redacted]	[redacted]
48 (4 years)	1.8%	0.03%	[redacted]	[redacted]
60 (5 years)	0.9%	0.01%	[redacted]	[redacted]
120 (10 years)	0.0%	0.00%	[redacted]	[redacted]

B.3.3.2 Subgroup tumour ≤30mm

Overall survival

Kaplan-Meier curve

There is a growing body of evidence documenting the associating between tumour burden and response to immunotherapies, thus the particular interest in this population subgroup (Dall'Olio et al. 2021).

Hence, we investigate the health outcomes of patients with baseline largest metastatic tumour with a diameter of less than 30mm, thereafter called "tumour30".

We present in Figure 22, the Kaplan Meier curve for the OS at both data cut-offs for comparison, as well as the median OS in Table 18. We note that the overall survival in this subgroup is [redacted], and in particular [redacted]

Figure 34. Kaplan-Meier curve OS subgroup tumour ≤30mm for both data cut-offs (a) October 2020; (b) August 2021

(a) (b)

Table 39. Median OS subgroup tumour ≤30mm both data cut-offs

	October 2020	August 2021
Tebentafusp (N=139)	[redacted]	[redacted]
Investigator's choice (N=70)	[redacted]	[redacted]

Extrapolation analysis

The six-standard parametric distributions were fitted to the data. Based on the AIC and BIC, presented in Table 61 for both the October 2020 and August 2021 DCO, which provide information on the goodness of fit to the observed data, the model with the best fit in the control arm is the Gompertz, although the generalised gamma and Weibull are reasonable.

Table 40. Goodness-of-fit criterions AIC and BIC – OS subgroup tumour ≤30mm IC arm DCO October 2020 and August 2021

	October 2020			August 2021		
Model	**AIC**	**BIC**	**Ranking**	**AIC**	**BIC**	**Ranking**
Exponential	242.80	245.05	5	[redacted]	[redacted]	[redacted]
Weibull	236.69	241.18	2	[redacted]	[redacted]	[redacted]
Log-normal	241.31	245.81	5	[redacted]	[redacted]	[redacted]
Log-logistic	239.43	243.93	4	[redacted]	[redacted]	[redacted]
Gompertz	235.36	239.86	1	[redacted]	[redacted]	[redacted]
Generalised Gamma	236.22	242.97	2	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion						

The OS in this subgroup is [redacted] as the expectation is that a small tumour burden is associated with better outcomes. Hence, the Gompertz and generalised gamma have [redacted] based on clinical opinion. [redacted] is more closely aligned with the results of the ITT set, and historical data. This is also more conservative. The parametric curves are presented in for the October 2020 DCO Figure 35 and

Figure 36 for the August 2021 DCO.

Table 41. OS parametric models vs. KM curve IC arm subgroup tumour ≤30mm DCO October 2020

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**5**	**2**	**5**	**4**	**1**	**2**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

Table 42. OS parametric models vs. KM curve IC arm subgroup tumour ≤30mm DCO August 2021

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**5**	**2**	**5**	**4**	**1**	**3**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The six-standard parametric distributions were fitted to the data. Based on the AIC and BIC, presented in Table 43 for both the October 2020 and August 2021 DCO, which provide information on the goodness of fit to the observed data, the model with the best fit in the tebentafusp arm is the Gompertz, although the generalised gamma, Weibull and log-logistic are reasonable.

Table 43. Goodness-of-fit criterions AIC and BIC – OS subgroup tumour ≤30mm tebentafusp arm DCO October 2020 and August 2021

	October 2020			August 2021		
Model	AIC	BIC	Ranking	AIC	BIC	Ranking
Exponential	304.42	307.36	6	518.91	521.85	6
Weibull	290.88	296.75	2	495.34	501.21	1
Log-normal	297.47	303.34	5	504.99	510.86	5
Log-logistic	292.77	298.64	3	497.23	503.10	3
Gompertz	288.86	294.73	1	496.66	502.53	2
Generalised Gamma	291.28	300.09	3	496.94	505.75	3
Abbreviatons: AIC, Akaike's information criterion; BIC, Bayesian information criterion						

In the tebentafusp arm, the Gompertz model provides a very good fit over the observed period comparing the survival probability for the observed data Table 44, with the data derived from the parametric model. The tail of the curve is however [redacted] with a survival probability [redacted] (Table 44). The same is observed with the generalised gamma. Based on clinical experts' opinion that the OS would be between 12-17%, and given that outcomes in this subgroup are expected to be better than for the ITT, [redacted] is chosen for the subgroup analysis.

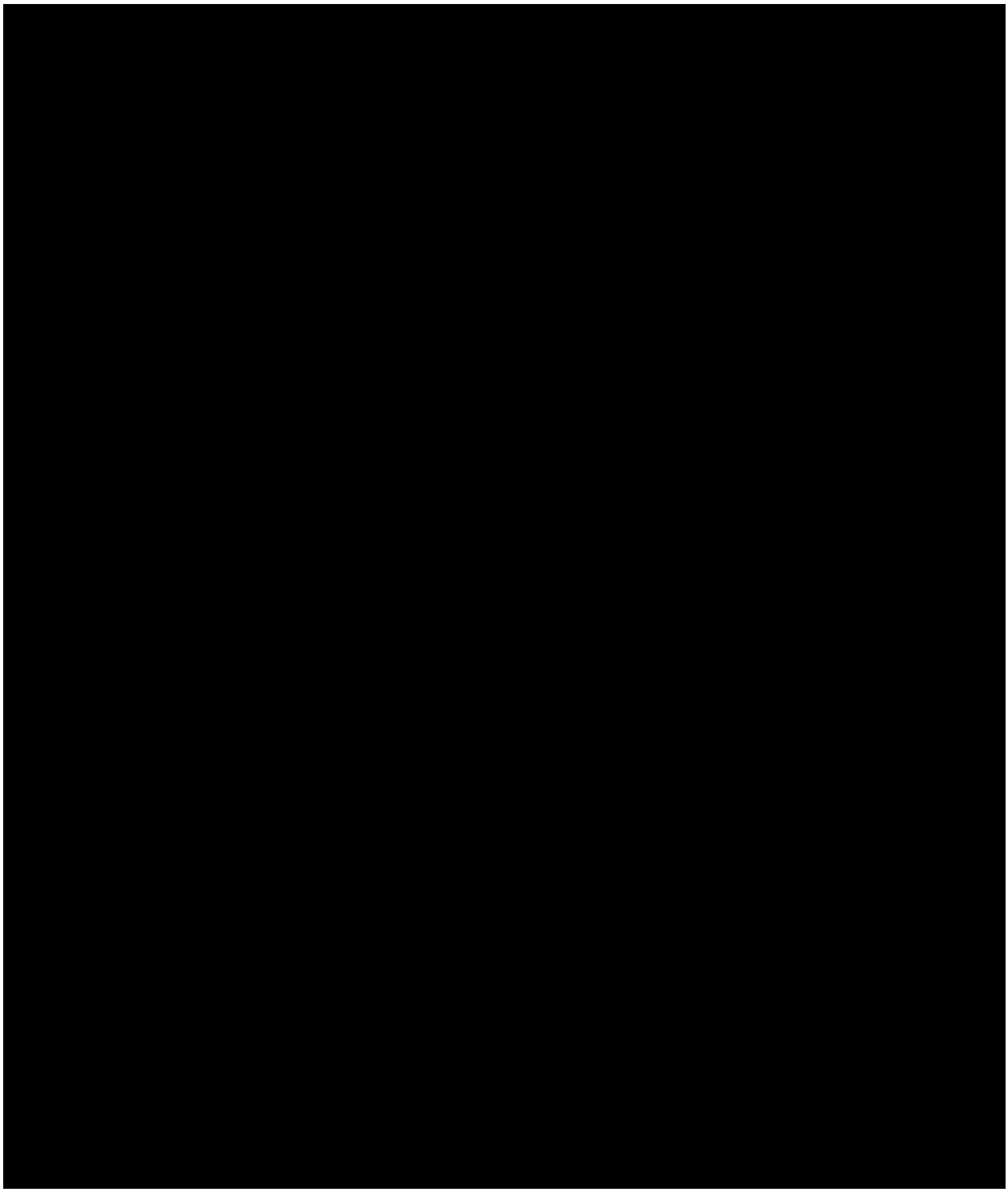
Table 44. OS parametric models vs. KM curve Tebentafusp arm subgroup tumour ≤30mm DCO October 2020

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**6**	**2**	**5**	**3**	**1**	**3**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

Table 45. OS parametric models vs. KM curve Tebentafusp arm subgroup tumour ≤30mm DCO August 2021

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**6**	**1**	**5**	**3**	**2**	**3**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 35. OS Standard parametric models subgroup tumour ≤ 30mm DCO October 2020 - (a) Individual fit trial time horizon; (b) Individual fit 15-year time horizon



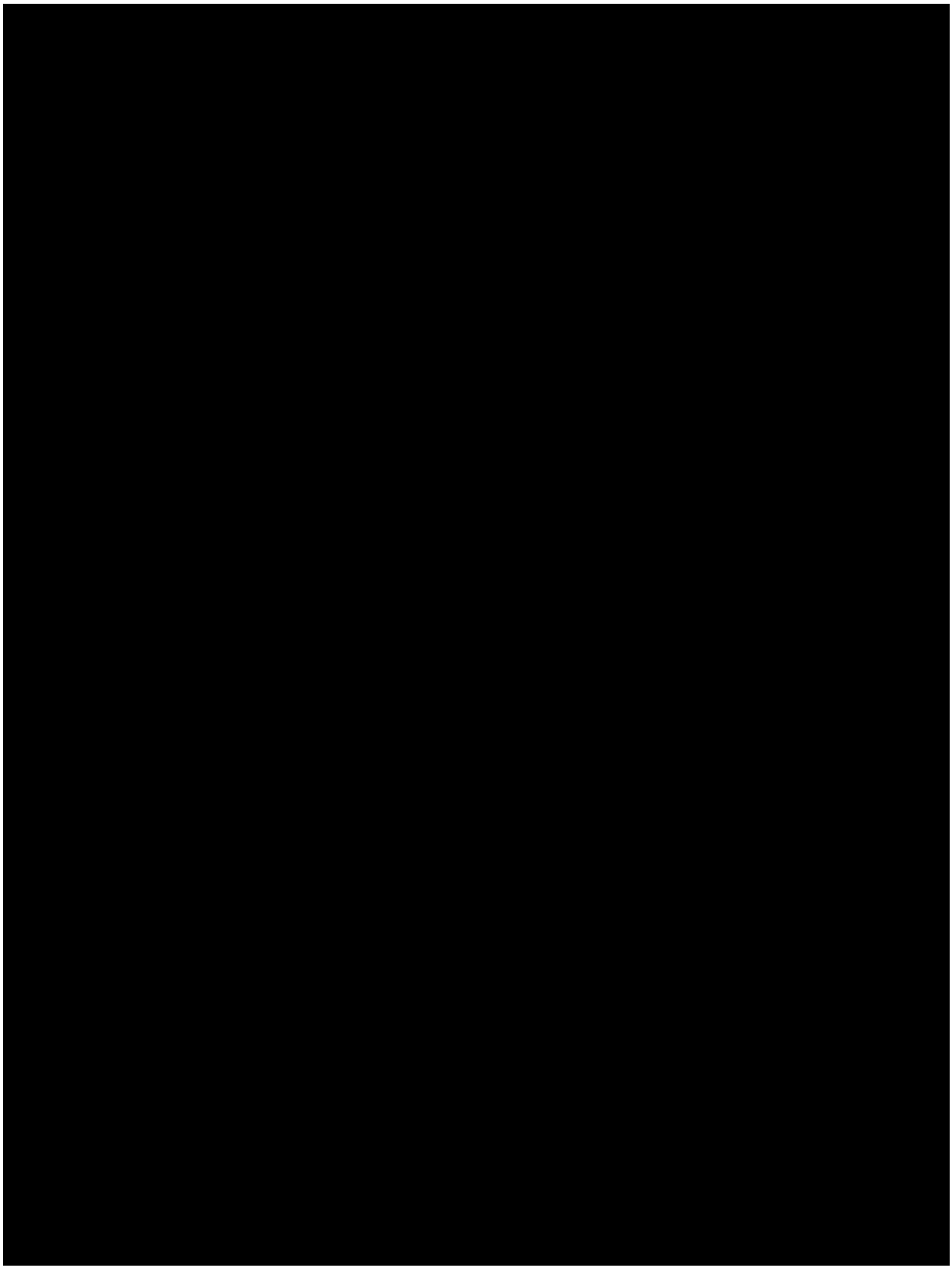
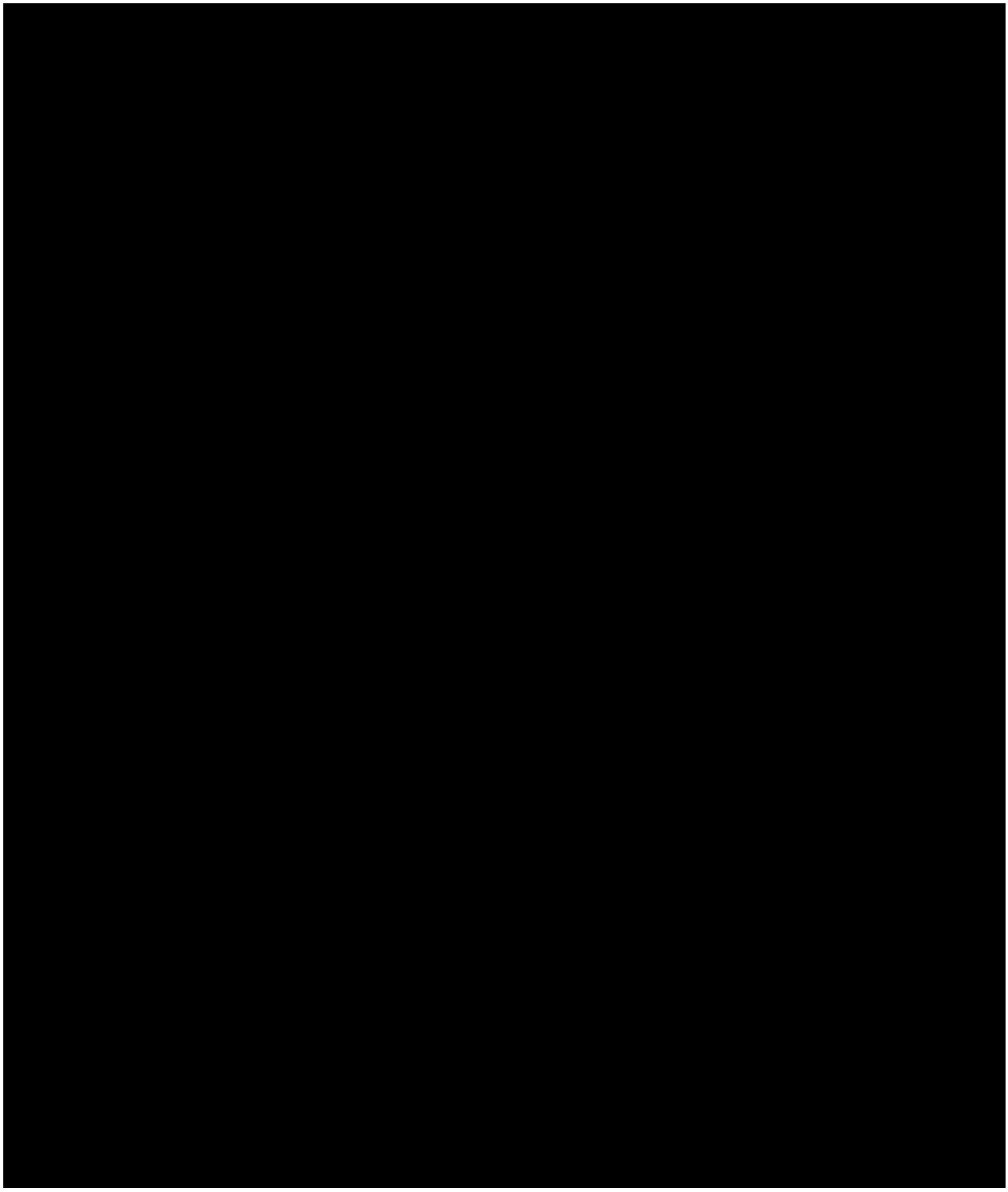
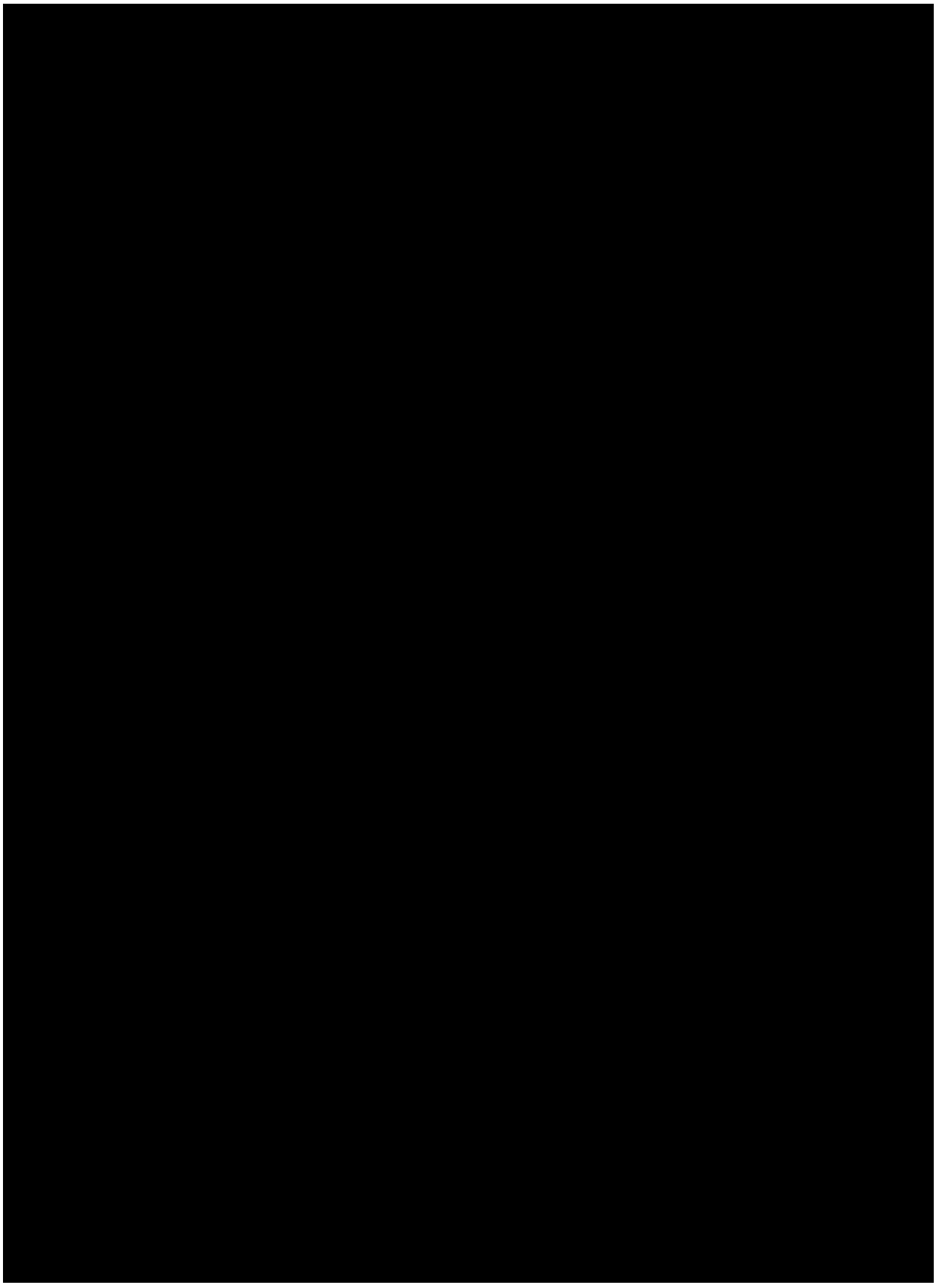


Figure 36. OS Standard parametric models subgroup tumour ≤30mm DCO August 2021- (a) Individual fit trial time horizon; (b) Individual fit 15-year time horizon





Progression-free survival

Kaplan Meier curve

In Figure 37 the Kaplan Meier curve for the PFS at both data cut-offs is presented for comparison, as well as the median PFS in Table 18. The median PFS in this subgroup is longer in the tebentafusp arm compared to the ITT set (3.4 months in the ITT vs. [redacted] in this subgroup) but not in the control arm (2.9 months in the ITT set vs. [redacted] in this subgroup). This supports the association between tumour burden and response to treatment with immunotherapies.

Similarly to the ITT set, because of the shape of the curve limits the fit of the parametric model, a hybrid approach using non-parametric estimates (KM curves) and parametric curves for the extrapolation of the tail, is used.

Figure 37. Kaplan-Meier curve PFS subgroup tumour ≤30mm for both data cut-offs (a) October 2020; (b) August 2021

Table 46. Median PFS subgroup tumour ≤30mm both data cut-offs

	October 2020	August 2021
Tebentafusp (N=149/150)	[redacted]	[redacted]
Investigator's choice (N=126)	[redacted]	[redacted]

Survival analysis

The six-standard parametric distributions were fitted to the data. Based on the AIC and BIC, presented in Table 47 for both the October 2020 and August 2021 DCO, which provide information on the goodness of fit to the observed data, the model with the best fit in the control arm is the log-logistic, although generalised gamma and log-normal are also reasonable.

Table 47. Goodness-of-fit criterions AIC and BIC – PFS subgroup tumour ≤30mm IC arm DCO October 2020 and August 2021

	October 2020			**August 2021**		
Model	AIC	BIC	Ranking	AIC	BIC	Ranking
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion						

Comparing the probability of patients being progression-free in the control arm, derived from the fitted models with the PFS data from the trial, presented in Table 48 and Table 49, it was observed that the [redacted] provides a reasonable fit over the observed period but has however quite a short tail. The [redacted] with the probability of being progression free reaching below [redacted]. It is the preferred model for the subgroup analysis, being more conservative. [redacted] are tested in scenario analysis.

Table 48. PFS parametric models vs. KM curve IC arm subgroup tumour ≤ 30mm DCO October 2020

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**6**	**4**	**2**	**1**	**5**	**2**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

Table 49. PFS parametric models vs. KM curve IC arm subgroup tumour ≤30mm DCO August 2021

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**4**	**4**	**3**	**2**	**6**	**1**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

The six-standard parametric distributions were fitted to the data. Based on the AIC and BIC, presented in Table 50 for both the October 2020 and August 2021 DCO, which provide information on the goodness of fit to the observed data, the model with the best fit in the tebentafusp arm is the generalised gamma.

Table 50. Goodness-of-fit criterions AIC and BIC – PFS subgroup tumur≤30mm IC arm DCO October 2020 and August 2021

	October 2020			**August 2021**		
Model	AIC	BIC	Ranking	AIC	BIC	Ranking
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion						

In the tebentafusp arm, comparing the PFS derived from the fitted models, with the data from the trial, presented in Table 51 and Table 52, [redacted] fits the data best over the observed period, [redacted] models also provide a reasonable fit over the observed period and have a more realistic tail with PFS reaching [redacted]

Table 51. PFS parametric models vs. KM curve Tebentafusp arm subgroup tumour ≤ 30mm DCO October 2020

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**5**	**4**	**2**	**3**	**6**	**1**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

Table 52. PFS parametric models vs. KM curve Tebentafusp arm subgroup tumour ≤30mm DCO August 2021

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**5**	**6**	**2**	**3**	**4**	**1**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC, Akaike's information criterion; BIC, Bayesian information criterion							

Time to treatment discontinuation

Kaplan-Meier curve

In Figure 38, the Kaplan Meier curve for the TTD at both data cut-offs is presented for comparison, as well as the median TTD in Table 53. We note that the median TTD in this subgroup is longer in the tebentafusp arm compared to the ITT set (5.7 months in the ITT vs. [redacted] in this subgroup) but not in the control arm (2.1 months in the ITT set vs. [redacted] in this subgroup). This supports the association between tumour burden and response to treatment with immunotherapies.

Similar to the ITT set, because the shape of the curve limits the fit of the parametric model, a hybrid approach using non-parametric estimates (KM curves) and parametric curves for the extrapolation of the tail, is used.

Figure 38. Kaplan-Meier curve TTD subgroup tumour ≤30mm for both data cut-offs (a) October 2020; (b) August 2021

Table 53. Median TTD subgroup tumour ≤30mm both data cut-offs

	October 2020	August 2021
Tebentafusp (N=136)	[redacted]	[redacted]
Investigator's choice (N=62)	[redacted]	[redacted]

Extrapolation analysis

The six-standard parametric distributions were fitted to the data. Based on the AIC and BIC, presented in Table 54 for both the October 2020 and August 2021 DCO, which provide information on the goodness of fit to the observed data, the model with the best fit in the control arm is the Gompertz, although log-logistic, exponential and Weibull are also reasonable.

Table 54. Goodness-of-fit criterions AIC and BIC – TTD subgroup tumour ≤30mm IC arm DCO October 2020 and August 2021

	October 2020			August 2021		
Model	AIC	BIC	Ranking	AIC	BIC	Ranking
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion						

Comparing the probability of patients being on treatment in the control arm, derived from the fitted models with the TTD data from the trial, presented in Table 55, the [redacted] provides a reasonable fit over the observed period. However, we note that the [redacted] where there are a very low number of patients at risk. This is likely unreasonable, as seen previously [redacted] and the expectation is that most patients [redacted] We note that [redacted]

[redacted], has a very similar fit and a more reasonable long-term extrapolation and is therefore preferred for the subgroup analysis.

Table 55. TTD parametric models vs. KM curve IC arm subgroup tumour ≤30mm DCO October 2020

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**3**	**4**	**6**	**2**	**1**	**5**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 56. TTD parametric models vs. KM curve IC arm subgroup tumour ≤30mm DCO August 2021

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**5**	**3**	**6**	**2**	**1**	**4**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

The six-standard parametric distributions were fitted to the data. Based on the AIC and BIC, presented in Table 57 for both the October 2020 and August 2021 DCO, which provide information on the goodness of fit to the observed data, the models with the best fit in the tebentafusp arm is [redacted] although the [redacted] also provide good fits.

Table 57. Goodness-of-fit criterions AIC and BIC – TTD subgroup tumour ≤30mm Tebentafusp arm DCO October 2020 and August 2021

	October 2020			**August 2021**		
Model	AIC	BIC	Ranking	AIC	BIC	Ranking
Exponential	620.93	623.84	4	304.33	306.58	4
Weibull	619.45	625.28	4	302.29	306.79	4
Log-normal	606.09	611.92	1	280.42	284.91	3
Log-logistic	607.33	613.16	2	277.86	282.36	2
Gompertz	622.89	628.72	6	305.84	310.34	6
Generalised Gamma	607.78	616.52	3	274.47	281.21	1
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion						

Comparing the probability of being on treatment derived from the survival curves with the TTD data from the trial, presented in Table 58 and Table 59, [redacted] and therefore will be used in the base case for tebentafusp. The [redacted] gamma are used in sensitivity analysis.

Table 58. TTD parametric models vs. KM curve Tebentafusp arm subgroup tumour ≤30mm DCO October 2020

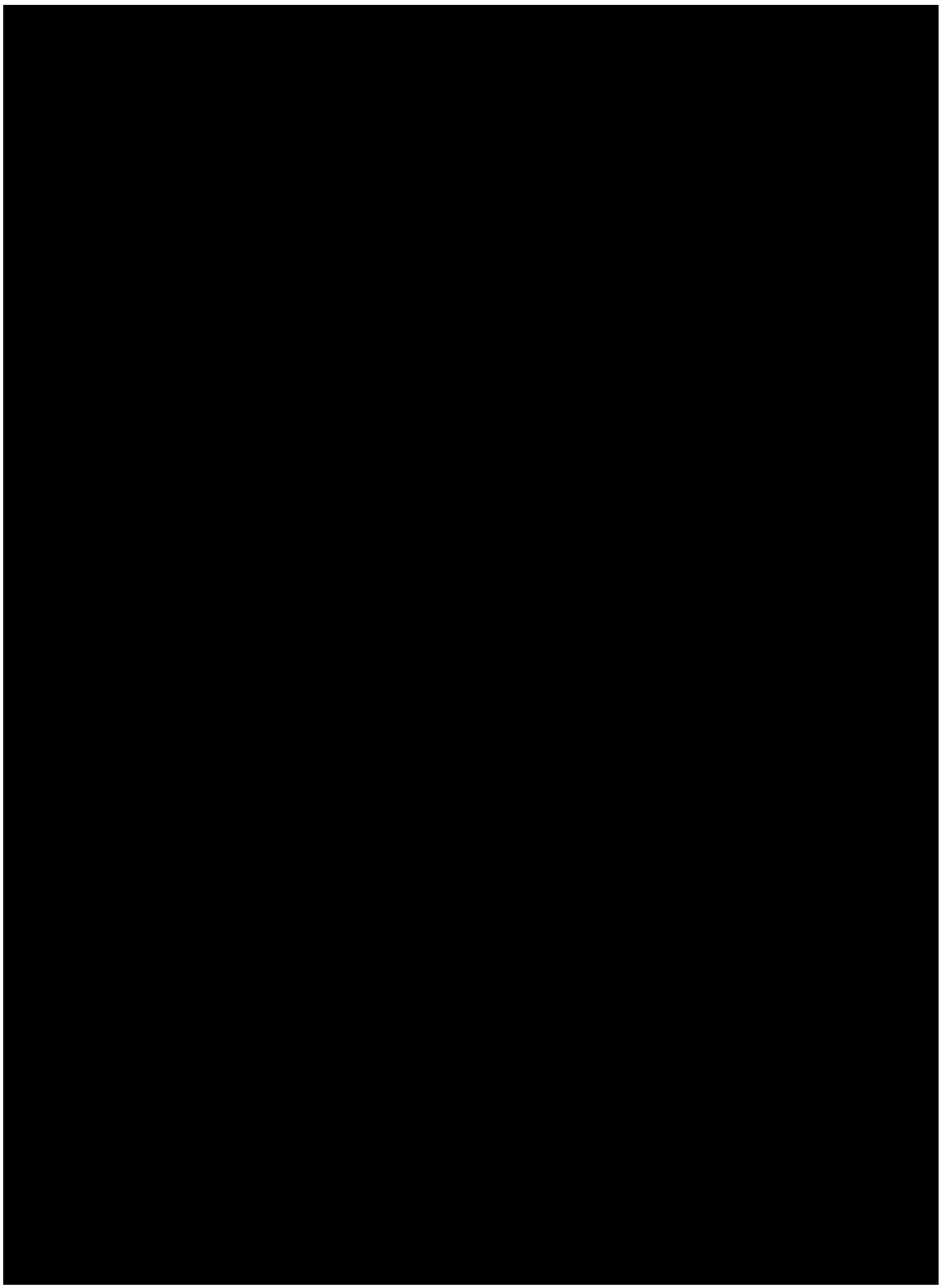
Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**4**	**4**	**1**	**2**	**6**	**3**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

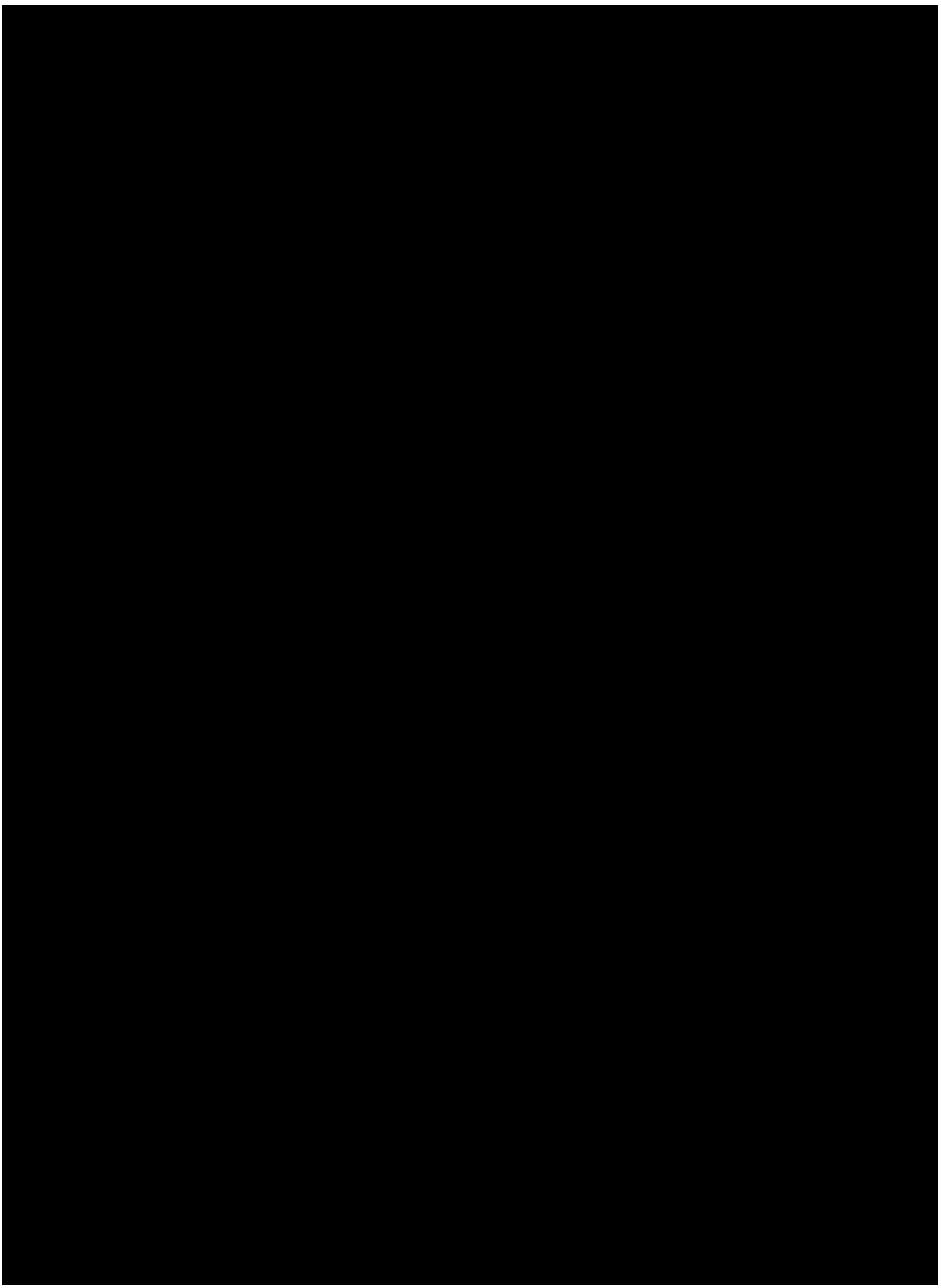
Table 59. TTD parametric models vs. KM curve Tebentafusp arm subgroup tumour ≤30mm DCO August 2021

Months	KM	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC		**4**	**6**	**1**	**2**	**5**	**2**
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

Figure 39. TTD standard parametric models subgroup tumour ≤30mm; (a) October 2020 DCO; (b) August 2021 DCO

(a)



(b) 

B.3.3.3 Adverse events

Adverse events (AE) rates have been derived from the IMCgp100-202 clinical trial (Immunocore 2021a). The AEs that are expected to have a significant impact on costs or HRQoL have been included in the model. These include all grade 3 or higher AEs with a prevalence in more than 3% of all patients plus endocrine disorders and colitis any grade in line with submission of ipilimumab and pembrolizumab in advanced melanoma (NICE 2013b, 2015d) as these are associated with high costs even at lower grade.

Cytokine-mediated AEs are commonly reported in patients treated with tebentafusp. For this reason, patients were monitored overnight after the first 3 doses during the dose escalation period to allow management of hypotension and other cytokine-related AEs. Immunocore conducted a post-hoc analysis of AEs and concomitant medications reported by investigators to comprehensively identify all potential episodes of cytokine release syndrome (CRS) based on ASTCT consensus criteria (Lee et al. 2019; Salama 2021). The most common cytokine-mediated AEs were pyrexia, chills, nausea, hypotension and hypoxia. Out of the 805 distinct CRS episodes which occurred in 217 of 245 tebentafusp-treated patients, 99.6% were mild to moderate (grade 1 and 2). Out of the 60% of the patients who had grade 2+ CS, only 49% required IV fluid. The number of patients requiring escalation of care (e.g., tocilizumab, vasopressor) is extremely small (4 patients out of 217 who had at least one CSR episode). This explains why CSR is not captured given the AEs selection criteria for the model stated above. The cost of inpatient monitoring for the first three doses is captured within the administration costs for tebentafusp. Based on clinical experts' opinion, this cost would already capture most of the costs associated with the management of CRS events and other AEs.

Table 60. Rates of adverse events included in the model

Category	AE	Tebentafusp	Control
Skin and subcutaneous tissue disorders	Rash	9.4%	0.0%
	Rash maculo-papular	8.6%	0.0%
	Pruritus	4.5%	0.0%

Investigations	AST increased	5.3%	0.9%
	Lipase increased	4.1%	5.4%
	ALT increased	3.3%	1.8%
Vascular disorders	Hypertension	8.6%	2.7%
	Hypotension	3.3%	0.0%
General disorders and administration site conditions	Fatigue	5.3%	0.9%
	Pyrexia	3.7%	0.9%
Metabolism and nutrition disorders	Hypophosphataemia	4.1%	0.9%
Hepatobiliary disorders	Hyperbilirubinaemia	3.3%	4.5%
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	0.8%	3.6%
Gastrointestinal disorders	Colitis (any grade)	0.0%	2.7%
	Diarrhoea (grade 3+)	1.2%	2.7%
Endocrine disorders	Hyperthyroidism (any grade)	0.4%	11.7%

B.3.4 Measurement and valuation of health effects

Summary
The EQ-5D-5L was collected in the IMCgp100-202 trial and utility values were derived applying the Van Hout et al algorithm. Based on clinical experts' opinion, disease status may not appropriately reflect changes in the QoL of patients and that modelling utilities based on time to death would be more appropriate. This approach has been applied in previous NICE HTAs of immune checkpoint inhibitors in metastatic melanoma. Utility values were derived from a previous assessment of pembrolizumab in metastatic melanoma. Utility decrements for AEs are applied. A scenario analysis is conducted using utility values derived from a statistical model fitted using EQ-5D data collected in the IMCgp100-202.

B.3.4.1 Health-related quality-of-life data from clinical trials

Health related quality of lie (HRQoL) was assessed in the IMCgp100-202 study using both the EQ-5D-5L and the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life-Core 30 (QLQ-C30) questionnaires.

The EORTC QLQ-C30 and EQ-5D-5L instruments were completed at baseline (i.e., prior to randomization of treatment). During the treatment phase, the PRO data was collected on the first day of each 3-week cycle for five cycles and every fourth cycle thereafter (i.e., every 12 weeks). The assessment was performed prior to study treatment when assessed at a visit when treatment was planned. Patients entering the disease progression follow-up period continued with both EORTC QLQ-C30 and EQ-5D-5L assessments every 12 weeks. During the survival follow-up phase, EQ-5D assessments only were continued every 3 months (Immunocore 2018). The schedule of the PRO data collection is detailed in Table 61. Please note that there were only 2 observations during the disease progression follow-up period, hence these have been dropped from the analysis set. The analysis of the PRO data was based on the ITT analysis set.

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 NICE reference case and is the approach used in the cost-effectiveness model. The UK EQ-5D-5L tariff has not been adopted by NICE, hence the EQ-5D-5L was mapped to the EQ-5D-3L using the Van-Hout et al. crosswalk algorithm and the Dolan EQ-5D-3L value set in line with NICE reference case (van Hout et al. 2012; Dolan 1997; NICE 2013a).

There were 378 patients involved in the clinical trial, 252 in the tebentafusp arm and 126 in the IC arm. At baseline, [redacted] patients have completed the EQ-5D questionnaire, of which [redacted] patients in the tebentafusp arm and [redacted] in the IC arm. There are [redacted] patients who have completed the EQ-5D questionnaire at any time point in the trial.

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

We determined the number of missing observations at each assessment time point up to the end of treatment, by comparing the treatment duration for each patient with the schedule of assessment of the EQ-5D. To assess the number of missing observations during the survival follow-up period, we compared the duration of overall survival for each patient with the schedule of assessment of the EQ-5D during the survival follow-up period (Table 61). The data is presented in Table 62. We observe that during the treatment period, the number of responses to the EQ-5D questionnaire is quite good. There are only [redacted] of missing observations at baseline. This varies between [redacted] and [redacted] during the treatment phase, although it reaches [redacted] at the end of treatment. There is however a high proportion of missing data during the survival follow-up period, [redacted].

Table 61. PRO data collection schedule IMGhg100-202 clinical trial

	Screening Phase	Treatment Phase														Follow-up Phase		
Procedure	**Screening**	**Cycle 1**						**Cycle 2**			**Cycle 3[a]**			**Later Cycles[a]**	**EOT**	**90-day Safety Follow-up**	**Disease Progression Follow-up**	**Survival Follow-up**
Day of Cycle	**-21 to -1**	**1**	**2**	**8**	**9**	**15**	**16**	**1**	**8**	**15**	**1**	**8**	**15**	**1–21**				
Patient-reported outcomes[r]		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

Table 62. Pattern of missingness of EQ-5D data

	N obs.	N expected	N missing	% observation missing
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 21 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 25 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 29 day 1	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up day 90	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up day 180	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up day 270	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up day 360	[redacted]	[redacted]	[redacted]	[redacted]
N, number; Obs., Observation				

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

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

Multiple imputation is 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 (White et al. 2011). We ran 47 imputations, as this equalled the percentage of patients with missing EQ-5D records at end of treatment. Multiple imputation is conducted using the following variables as covariates:

- Socio-demographic variables: age, sex, race, ethnicity, region, country (which are 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, overall survival duration, time between baseline and the assessment timepoint, baseline score EQ-5D utility

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

We used a generalised estimating equation (GEE) model to deal with the repeated measures of the same individuals and as it gives population average effects, which is suitable given the requirements for health technology assessment and economic evaluation.

We tested a range of model specifications, including the following covariates:

- Age
- Sex
- An indicator for whether the EQ-5D assessment was done before (i.e., on treatment) or, on or after treatment discontinuation (i.e., off treatment)
- Treatment arm

As detailed in section B.3.3.1.3, patients could stay on treatment beyond disease progression if they still derived benefit from the treatment based on the clinicians' assessment. Hence, TTD was deemed a better proxy for modelling utility data than disease progression.

We measured goodness of fit using mean absolute error and root mean squared error for which a value closer to zero suggest a better fit to the data. [redacted]

[redacted]. The sex, age and treatment arm covariates were not statistically significant and did not improve the model fit, hence the preferred model was the one with only the on/off treatment covariate. The on/off treatment covariate is statistically significant at 1% level, and the utility declines by [redacted] points after treatment discontinuation.

The utility estimates are applied based on the TTD curves in the model. This data is used in a scenario analysis.

Table 63. Utility values based on the IMCgp100-202 trial data

	Estimate	SE
On-treatment (reference)	NA	NA
Off-treatment	[redacted]	[redacted]
Constant	[redacted]	[redacted]

B.3.4.2 Mapping

Utility mapping was not required as the EQ-5D was collected directly from patients in the IMCgp100-202 trial, which is consistent with the NICE reference case.

B.3.4.3 Health-related quality-of-life studies

No studies were identified in the literature providing utility values in patients with metastatic UM.

Based on a study by Hatswell and colleagues (Hatswell et al. 2014), the quality of life of patients with metastatic melanoma may be less related to disease status (pre- or post-progression) than to time to death. Modelling utility data based on time to death has been used in multiple HTAs of immune checkpoint inhibitors in metastatic melanoma. Based on clinicals experts' opinion, the quality of life of patients with metastatic UM is maintained until approximately 6 months to death when symptoms start appearing heavily impacting on QoL. Hence, they agreed that modelling based on time to death was appropriate in this setting as well.

Analysing the EQ-5D data from the trial based on time to death was not possible. For the patients who died during the observed period, the average time between the last EQ-5D assessment and death was [redacted] months, hence the number of observations

by time to death categories would have been insufficient. Therefore, we used the data from the company base case in the HTA of pembrolizumab in advanced melanoma not previously treated with ipilimumab, pembrolizumab being the main therapy used in the control arm of the INCgp100-202 trial (NICE 2015d). We calculated adjustment factors as the ratio of the utility at ≥360 days and the utility at subsequent time to death categorises. We used the utility "on-treatment" derived from the regression analysis Table 63 as the baseline and adjusted at each time to death category using the adjustment factor derived previously. The data is presented in Table 64. To apply this approach to modelling utilities, we implemented tunnel states in the model to calculate the proportion of patients alive more than 360 days from the relevant cycle, alive between 270-360 days from the relevant cycle, etc. This approach is used in the base-case.

Table 64. Utility data based on time to death

Time to death in days	TA366	Multiplier	Adjusted
≥360 days	0.82	NA	[redacted]
270-360 days	0.71	0.87	[redacted]
180-270 days	0.66	0.80	[redacted]
90-180 days	0.66	0.80	[redacted]
30-90 days	0.57	0.70	[redacted]
<30 days	0.33	0.40	[redacted]

B.3.4.4 Adverse reactions

Based on insights from clinical experts, the AEs in the tebentafusp arm happened mostly over the first three doses and were transient. Hence, these were no expected to significantly impact on patients' HRQoL. Using the EQ-5D data from the IMCgp100-202 trial, we assume that the impact of AEs is already captured in the estimates and no additional utility decrement were applied in the model.

Using the approach to modelling utility values based on time to death, we have applied utility decrements sourced from HTAs of nivolumab and ipilimumab in metastatic melanoma and presented in Table 65. A weighted average utility decrement is calculated for the control arm, based on the proportion of patients on the different regimens in the trial. The utility decrements are applied in the first model cycle only, which is likely conservative as although patients experienced AEs mostly

with the first three doses of tebentafusp, this is not the case with pembrolizumab and ipilimumab based on clinical experts' opinion.

Table 65. Utility decrements for the interim model

Intervention/Comparator	Utility decrement	Source
Treatment effect of ipilimumab	-0.0210	TA319 (NICE 2013b)
Treatment effect of pembrolizumab	-0.0210	Assumption – same as ipilimumab
Treatment effect of dacarbazine	-0.0236	TA384 (NICE 2015e)
Treatment effect of tebentafusp	-0.0236	Assumption – same as ipilimumab

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Utility values are 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), adjusted for the length of the cycle. As per the NICE reference case, utility values were discounted on an annual rate of 3.5%.

The base-case analysis is based on time to death and the on-/off-treatment utilities values derived from the trial data are used in a scenario analysis.

Table 66. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Base-case				
≥360 days	0.82	+/-10%	Section B.3.4.3	Based on TA366 – assumed that changes in QoL associated with time to death
270-360 days	0.71	+/-10%	Section B.3.4.3	Based on TA366 – assumed that changes in QoL associated with time to death

180-270 days	0.66	+/-10%	Section B.3.4.3	Based on TA366 – assumed that changes in QoL associated with time to death
90-180 days	0.66	+/-10%	Section B.3.4.3	Based on TA366 – assumed that changes in QoL associated with time to death
30-90 days	0.57	+/-10%	Section B.3.4.3	Based on TA366 – assumed that changes in QoL associated with time to death
<30 days	0.33	+/-10%	Section B.3.4.4	Based on TA366 – assumed that changes in QoL associated with time to death
Treatment effect of ipilimumab	-0.0210	+/-10%	Section B.3.4.4	TA319 (NICE 2013b)
Treatment effect of pembrolizumab	-0.0210	+/-10%	Section B.3.4.4	Assumption – same as ipilimumab
Treatment effect of dacarbazine	-0.0236	+/-10%	Section B.3.4.4	TA384 (NICE 2015e)
Treatment effect of tebentafusp	-0.0236	+/-10%	Section B.3.4.4	Assumption – same as ipilimumab
Scenario analysis				
On-treatment	[redacted]	+/-10%	Section B.3.4.1	Based on statistical models fitted using EQ-5D data collected in IMCgp100-202 trial
Off-treatment	[redacted]	+/-10%	Section B.3.4.1	Based on statistical models fitted using EQ-5D data collected in IMCgp100-202 trial
Abbreviations: HS, health state; AR, adverse reaction				

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Summary
The following costs have been included in the model: • Drug acquisition and administration costs • A one-off cost for HLA-A*02:01 testing, to determine eligibility to tebentafusp, as this is not part of current routine in metastatic UM. • Inpatient monitoring after the first three doses of tebentafusp in line with the SPC • Drug and administration costs of subsequent therapies • Costs related to the routine management of the disease at pre- and post-progression (consultations with clinicians, lab test, scans and hospital visits) • End-of life care • AE-related costs The unit costs were sourced from the NHS reference costs, the BNF, PSSRU and the literature.

Costs in the model were estimated from the NHS and PSS perspective. The following cost categories were included: treatment acquisition and administration costs, routine management costs (consultations with clinicians, lab test, scans and hospital visits), end-of-life care and AE-related costs. All costs in the model were discounted at a 3.5% annual rate. Where necessary, the unit costs were inflated to 2019/2020 pounds using the PSSRU pay and price index.

B.3.5.1 Intervention and comparators' costs and resource use

Unit costs for the drug acquisition and resource utilisation related to the administration of the drugs are presented in this section. A summary of all the costs in the tebentafusp and control arm is presented at the end of the section. The drug costs are applied in the model based on the TTD curves. Additionally, a proportion of the patients received subsequent systemic therapy after discontinuation of the study

drug in the IMCgp100-202 study. The cost of subsequent therapies is account for in the model and applied as a one-off cost upon treatment discontinuation.

Drug acquisition costs

The drug acquisition costs are presented in Table 67. List prices are used for ipilimumab and pembrolizumab as the associated patient access schemes (PAS) are not known to Immunocore Ltd. [redacted] This does not apply to the control arm.

Table 67. Drug unit costs

Drug	Vial size	List price (per unit)	Source
Tebentafusp	100 mcg/0.5 mL vial (200 mcg per 1mL)	[redacted]	Immunocore Ltd
Ipilimumab	200 mg/40 ml vial (5 mg per 1 ml)	£ 15,000.00	BNF online (October 2021)
	50mg/10ml vial (5 mg per 1 ml)	£ 3,750.00	BNF online (October 2021)
Pembrolizumab	100 mg/4 mL vial (25 mg per 1 mL0	£ 2,630.00	BNF online (October 2021)
Dacarbazine	500 mg per vial	£ 37.50	BNF online (October 2021)
	1000 mg per vial	£ 70.00	BNF online (October 2021)
Abbreviations: BNF, British National Formulary			

The drug dosage, treatment schedule and administration times are presented in Table 68. One vial of tebentafusp is used per administration as per the SPC. In the comparator arm, the per cycle cost of drugs was calculated based on dosages in the IMCgp100-202 study, which for pembrolizumab and ipilimumab are in line with the licensed dosing regimen in patients with advanced melanoma, and with the standard dosing regimen in UM for dacarbazine. The mean weight across all patients in the IMCgp100-202 trial is used, 78.86kg (N=377; SD=17.85; 95% CI: 77.06, 80.66), and a body surface area (BSA) of 1.90m^2 was derived from the mean weight and height

(169.86 cm) in the trial and the DuBois and DuBois formula (Du Bois and Du Bois 1989). Given the very low number of patients with metastatic UM, we considered that vial sharing is not feasible. The drug quantities were therefore rounded-up to the nearest vial size. We note that a BSA of 1.79m^2 for cancer patients in the UK has been previously reported in the literature (Sacco et al. 2010). Based on the assumption of no vial sharing, the drug acquisition costs for dacarbazine would be the same for a BSA between 1.01m^2 and 2m^2, and this parameter is therefore not varied in sensitivity analysis. Similarly, the drug acquisition costs of pembrolizumab and ipilimumab would be the same for a mean patient weight of 67kg to 83kg. Given that the 95% CI for the mean weight falls within this range, this parameter was not be varied in sensitivity analysis.

Table 68. Drug dosage regimen in the IMCgp100-202 trial

Treatment	Pharmaceutical form and route of administration	Dose	Frequency and administration time
Tebentafusp	Concentrate for solution for infusion (single use vials)[1]	20 mcg C1D1; 30 mcg C1D8; 68 mcg C1D15 and subsequent doses[1]	Every week: Days 1, 8, and 15 of 21-day cycle 15-20 min infusion time[1]
Ipilimumab	Concentrate for solution for infusion[1]	3 mg/kg administered intravenous[1]	Every 3 weeks for a total of 4 doses: Day 1 of every 21-day cycle[1] 90 min infusion time[2]
Pembrolizumab	Lyophilized powder[1]	2 mg/kg up to a maximum of 200 mg administered intravenously[1]	Every 3 weeks: Day 1 of every 21-day cycle[1] 30 min infusion time[3]
Dacarbazine	Powder for intravenous[1] infusion	1000 mg/m2 administered intravenous[1]	Every 3 weeks: Day 1 of every 21-day cycle[1] 60 min infusion time[4]
C- cycle; D - day, mcg – microgram 1. (Immunocore 2018); 2. (EMA 2020b); 3. (EMA 2020a); 4. (Wright 2015), 5. (EMA 2015)			

Drug administration costs – Investigator's choice

Administration and monitoring costs are taken from the latest published National Cost Collection for the NHS 2019/2020 version 2 (formerly called NHS Reference

costs) and presented in Table 69. Ipilimumab, pembrolizumab and dacarbazine are assumed to be given in a day case setting, based on the infusion time specified in the respective SPC and presented in Table 69.

Based on SPC (EMA 2020b), ipilimumab is administered intravenously over a 90-minute period, therefore the unit cost related to code SB13Z (Deliver more Complex Parenteral Chemotherapy at First Attendance) is used for the first attendance and the unit cost related to code SB15Z (Deliver Subsequent Elements of a Chemotherapy Cycle) for subsequent administrations. Additionally, liver function tests and thyroid function tests should be evaluated at baseline and before each dose of Ipilimumab, hence the unit costs related to code DAPS04 (Clinical Biochemistry) is added to the administration costs.

Based on the SmPC (EMA 2020a), Pembrolizumab is administered intravenously over a 30-minute period, therefore the unit cost related to code SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance) is used for the first attendance and the unit cost related to code SB15Z for subsequent administration.

Based on an NHS trust chemotherapy protocol for dacarbazine(Wright 2015), the infusion time is 60 minutes and therefore administration costs will be based on SB13Z for the first dose and SB15Z for subsequent doses.

*Testing and drug a*dministration costs – Tebentafusp

Based on SPC, the preparation of tebentafusp requires the use of 0.13 mL human albumin at 20% concentration for admixture. Based on the SPC for human albumin (EMA 2018), once the container has been opened, the contents should be used immediately and any unused product should be disposed of. Hence, we considered that vial sharing is not possible, and the full cost of a vial is included in the administration costs.

Tebentafusp is administered intravenously over a 15-20-minute period. Due to the possible cytokine release-associated toxicity, patients are monitored overnight for the first 3 doses, with vital signs monitoring prior to the dose administration and every four hours for at least 16 hours after dosing. Tebentafusp is therefore administered in the inpatient setting for the first three doses and in a day case setting

thereafter. For the first three doses, the administration costs are based on the unit cost for code SB12Z for the chemotherapy administration plus the cost of a hospital stay based on a weighted average cost of elective inpatient excess bed days. For the fourth dose onward, the administration costs are based on the unit cost for the code SB15Z. The costs are presented in Table 69.

Table 69. Administration services unit costs

Service	Unit cost	Source
SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance	£295.92	CHEM (day case and Reg day/night) – 2019/202 National Cost Collection
SB13Z - Deliver more Complex Parenteral Chemotherapy at First Attendance	£329.75	CHEM (day case and Reg day/night) - 2019/202 National Cost Collection
SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle	£363.37	CHEM (day case and Reg day/night) - 2019/202 National Cost Collection
DAPS04 – Clinical Biochemistry	£1.20	DAPS – 2019/202 National Cost Collection
Human albumin 20%	£27.00	BNF October 2021
Elective inpatient excess bed days (weighted average across all areas)	£450.81	EL-XS - National schedule of NHS costs 2017/2018 (inflated to 2019/2020)
Abbreviations: BNF, British National Formulary		

In line with the licensed indication, patients are eligible to tebentafusp only if they are HLA-A*02:01 positive. Hence this test will be administered to patients to determine their eligibility to tebentafusp. Given that this test is not part of routine practice, the costs if accounted for. The cost for the test was sourced from an economic evaluation of HLA-A*31:01 testing from the perspective of the National Health Service (NHS) in the United Kingdom (Plumpton et al. 2015). We assumed that the cost of the HLA-A*31:01 test is applicable to the HLA-A*02:01 test. In this study, the cost of genotyping was based on personal communication with the NHS Blood and

Transplant service, and based on a two-stage process: an initial screen for HLA-A*31 and, in patients who test positive, a second high-resolution test for the specific HLA-A*31:01 allele. We assumed that the total cost for the test is the sum of the two tests, although the second test would only be conducted in a sub-set of patients. As this cost is only applied in the tebentafusp arm, we consider that is a conservative assumption. The costs of the HLA test are presented in Table 70. It is estimated that 47% of the metastatic UM patients would test positive, which has been accounted for to adjust the cost. The cost is applied as a one-off cost upon treatment initiation in the tebentafusp arm.

Table 70. Cost of HLA-A*02:01 test in the tebentafusp arm

	Item	Value	Source
A	Cost of HLA-A*31 screen + HLA-A*31:01 high resolution test	£163.18	(Plumpton et al. 2015) inflated to 2019/2020
B	% of patients expected to test positive	47%	Estimation from Immunocore (allelefrequencies.net)
C	Adjust costs of HLA-A*02:01 used in the model	£347.19	C=A*(1/B)

Drug costs and administration summary

The drug and administration costs in the Tebentafusp arm are summarised in Table 71 for the first four weekly doses and composed of:

- Tebentafusp drug acquisition costs
- Chemotherapy administration costs
- Cost of human albumin for admixture
- Inpatient stay for monitoring for the first three doses
- HLA-A*02:01 test

Table 71. Testing, administration, and drug acquisition costs for Tebentafusp (weekly dose)

Weekly doses	Dose 1	Dose 2-3	Dose 4+
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration	£295.92	£363.37	£363.37

Human albumin	£27.00	£27.00	£27.00
Inpatient stay	£450.81	£450.81	NA
HLA-A*02:01	£347.19	NA	NA
Total cost	[redacted]	[redacted]	[redacted]
Abbreviations: NA, not applicable			

The drug acquisition and administration costs for pembrolizumab, ipilimumab and pembrolizumab are summarised in Table 72 for the first two to four doses. The cost in the control arm is calculated as a weighted average to reflect the control arm in the IMCgp100-202 trial, i.e., investigator's choice of ipilimumab (12.7%), pembrolizumab (81.7%) and dacarbazine (5.6%). As ipilimumab may be administer for a maximum of four doses, ipilimumab is only accounted for in the weighted costs, for the first four doses. The total costs are a sum of:

- Drug acquisition cost
- Drug administration costs
- Liver and thyroid function tests for ipilimumab

Table 72. Testing, administration, and drug acquisition costs for the Investigator's choice arm (one dose every three weeks)

Dose every three weeks	Pembrolizumab		Ipilimumab		Dacarbazine		
	Dose 1	**Dose 2+**	**Dose 1**	**Dose 2-4**	**Dose 1**	**Dose 2+**	
Drug acquisition	£5,260.00	£5,260.00	£18,750.00	£18,750.00	£150.00	£150.00	
Drug administration	£295.92	£363.37	£329.75	£363.37	£295.92	£363.37	
Liver and thyroid function test	NA	NA	£1.20	£1.20	NA	NA	
Total cost	£5,555.92	£5,623.37	£19,080.95	£19,114.57	£445.92	£513.37	
Weighted costs – 1st dose	81.7%		12.7%		5.6%		**£6,989.50**
Weighted costs – dose 2-4		81.7%		12.7%		5.6%	**£7,052.65**
Weighted costs – Dose 5+		81.7%				5.6%	**£4,625.40**
Abbreviations: NA, not applicable							

B.3.5.2 Cost of subsequent therapies

Following discontinuation of the active treatment assigned in the IMCgp100-202 trial, many patients went on to receive some form of additional active treatment. These active treatments can be grouped into chemotherapy (assumed to be dacarbazine for costing in the model) and immunotherapies (pembrolizumab, ipilimumab, nivolumab and ipi+nivo combination therapy). Data on subsequent treatments derived from IMCgp100-202 study data for the UK is presented in Table 73. The costs per therapy were calculated in the same way as described in the previous section, including drug acquisition and administration costs to cover a period given by the mean subsequent treatment duration. The cost of nivolumab is taken from the BNF (October 2021) (40mg/4mL vial £439, 100mg/10mL vial £1,097, 240mg/24mL vial £2,633). The combination therapy ipilimumab and nivolumab is assumed to be given for three cycles and nivolumab thereafter for either a maximum of 7 doses every two weeks, based on the study by (Najjar et al. 2020) and colleagues, or the remainder of the treatment duration, whichever was shortest.

The weighted average cost for each of tebentafusp and the control arm was obtained by first calculating the average cost for immunotherapy, using the immunotherapy proportions and costs in Table 73. This was multiplied by the proportion of patients receiving immunotherapy and then combined with the expected cost of dacarbazine (cost multiplied by subsequent treatment with dacarbazine). Finally, this cost was multiplied by the proportion of patients receiving any subsequent treatment.

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

Table 73. Costs of subsequent therapies

Resource	Tebentafusp	SoC
Subsequent treatment options		
% any subsequent treatment	[redacted]	[redacted]
% subsequent treatment with dacarbazine	[redacted]	[redacted]
% subsequent with immunotherapy	[redacted]	[redacted]
Subsequent treatment duration (days)	[redacted]	[redacted]
Subsequent use of immunotherapy		
% ipilimumab + nivolumab	[redacted]	[redacted]
% ipilimumab monotherapy	[redacted]	[redacted]
% pembrolizumab	[redacted]	[redacted]
% nivolumab	[redacted]	[redacted]
Cost per therapy*		
Dacarbazine	£4,553	£3,013
Ipilimumab + nivolumab	£94,919	£85,929
Ipilimumab monotherapy	£76,425	£76,425
Pembrolizumab	£50,543	£33,673
Nivolumab	£38,885	£23,904
Subsequent treatment cost		
Weighted average cost	[redacted]	[redacted]
*Per therapy costs calculated as described in section B.3.5.1		

B.3.5.3 Health-state unit costs and resource use

The costs associated with the PFS and PD health states have been calculated based on resource utilisation sourced from the literature and based on clinical experts' opinion, combined with unit costs from the National Cost Collection for the NHS 2019/2020 version 2. The health state costs are composed of consultations with clinicians, lab test, scans and hospital visits.

No study on health-care resource utilisation in patients with UM or metastatic UM, providing the necessary data, were identified in the literature. Hence, we used metastatic melanoma as a starting point for the estimation of resource utilisation, which was considered an acceptable proxy by clinical experts. We identified a study conducted by McKendrick et al. (2016) and colleagues who estimated the resource utilisation associated with the treatment of metastatic melanoma in routine clinical

practice in eight countries, including the United Kingdom. The study was based on a Delphi consensus panel (country-specific). The panellists recruited had a least five years of experience after completion of training and experience in the treatment of patients with metastatic melanoma. The majority of the panellists in the study were oncologists (83%). The UK panel was comprised of seven specialists. This study has been used in TA562, encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma (NICE 2019).

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

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

The resource utilisation from the study were presented to two UK clinicians experienced in the management of patients with metastatic UM to determine which items were irrelevant in the context of metastatic UM and which resources for the treatment of metastatic UM patients were not already captured and should be added, and frequency of use. It is important to note that as there is no standard of care for the management of metastatic UM, patients may receive a broad range of treatment options depending on the treatment centres where care is provided. Including such a level of complexity into the costing would not have added benefits in the context of the current decision problem. Hence, we asked the clinicians to focus on mainstay activities for the management of this patient population. Resource utilisation related to brain and bone metastasises were deemed irrelevant as well as radiotherapy. 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 following for example enucleation or radiotherapy at the primary disease stage. The revised (monthly) resource utilisation for the routine management during the

pre-progression phase, at disease progression and post-progression with BSC are presented in Table 74.

Table 74. Resource utilisation for the management of the disease during the pre-progression phase, at progression and post-progression with best supportive care

	Pre-progression*	At progression (one off)	Post-progression*
Medical consultations			
Medical oncologist consultation	1	1	0.67
Oncology nurse visit	0.6		0.2
GP consultation	0.33		0.53
Psychology specialist consultation	0.03		0.05
Surgeon consultation	0.01	0.025	0.01
Ophthalmic surgeon consultation	0.25		0.25
Hospital visits			
Inpatient stay (oncology/general ward)	0.25	0.20	0.33
Emergency department visit	0.03		0.05
Day hospital visit	0.25		0.13
Examinations			
Whole-body CT	0.33		
Liver CT		0.05	
Liver MRI	0.03	0.05	
Complete blood count	1		
Complete metabolic panel	1		
Procedures			
Surgical intervention	0.01	0.025	0.01
Hepatic perfusion		0.20	

* Monthly resource use

Abbreviations: CT, Computerised Tomography Scan; GP, general practitioner; MRI, Magnetic Resonance Imaging Scan;

The unit costs associated with each resource are presented in Table 75. As liver failure is the primary cause of death in this patient population, we assumed that the inpatient stays in the post-progression phase are related to liver failure problems (Nathan et al. 2015a). In line with TA562, an extra medical oncologist consultation per month was added in the pre-progression phase. Please note that the post-progression costs do not include the costs of subsequent therapies which have been accounted for separately, as presented in section B.3.5.2.

Table 75. Unit cost of resource use

	Unit cost	Source
Medical consultations		
Medical oncologist consultation	£192.85	Outpatient attendance, code 370 Medical oncologist (Total) – 2019/202 National Cost Collection
Oncology nurse visit	£99.30	Community Health Services; Specialist Nursing, Cancer Related, Adult, Face to face – 2019/202 National Cost Collection
GP consultation	£39.23	10.3b General practitioner — unit costs, including direct care staff costs, with qualification – PSSRU Unit Costs of Health and Social Care2020
Psychology specialist consultation	£200.97	Outpatient attendance, code 656 Clinical Psychology (Total) – 2019/202 National Cost Collection
Surgeon consultation	£192.28	Outpatient attendance, code 105 Hepatobiliary & Pancreatic Surgery (Total) – 2019/202 National Cost Collection
Ophthalmic surgeon	£112.52	Outpatient attendance, code 460 Medical ophthalmology (Total) – 2019/202 National Cost Collection
Hospital visits		
Inpatient stay (oncology/general ward)	£361.56	Weighted average of excess bed days for elective (E-XS) and non-elective (NE-XS) inpatients stays for all HRGs - National schedule of NHS costs 2017/2018 (inflated to 2019/2020)
Inpatient stay (oncology/general ward) – post-progression	£2477.97	Weighted average non-elective long stay (NEL) and short stay (NES), GC01, Liver Failure Disorders – 2019/202 National Cost Collection
Emergency department visit	£375.84	A&E VB03Z Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment, Type 01 admitted – 2019/202 National Cost Collection

Day hospital visit	£192.85	Outpatient attendance, code 370 Medical oncologist (Total) – 2019/202 National Cost Collection
Examinations		
Whole-body CT	£147.45	RD26Z, Computerised Tomography Scan of more than three areas, Outpatient – 2019/202 National Cost Collection
Liver MRI	£145.33	Diagnostic Imaging RD01A/RD02A/RD03Z (weighted average), Magnetic Resonance Imaging Scan of One Area Outpatient – 2019/202 National Cost Collection
Liver CT s		
Complete blood count	£2.56	Clinical biochemistry
Complete metabolic panel	£1.20	Haematology
Procedures		
Surgical intervention	£1931.15	Total HRGs, GC12 Malignant, Hepatobiliary or Pancreatic Disorders – 2019/202 National Cost Collection
Hepatic perfusion	£428.26	SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance, CHEM (day case and Reg day/night) - 2019/202 National Cost Collection

Resource utilisation, presented in Table 74, and unit costs, presented in Table 75, were multiplied to derive the health states costs, presented in Table 76. Based on the study by McKendrick, BSC is provided for an average of four months (McKendrick et al. 2016). Based on this, we are assuming in the model that the entire cohort would receive BSC for an average of four months and the monthly cost was multiplied by four and applied as a one-off cost at progression. The cost is applied to the patients leaving the PFS state at each cycle. We acknowledge that this is a limitation, as some patients would be classified as progressed because they died rather than due to disease progression. [redacted] Hence the over-estimation of the costs if likely limited. Calculating the number of new PD cases at each model cycle is not possible, leading to some counter-intuitive results, which is a limitation of partitioned-survival models.

Table 76. Health state costs

Health state	
Pre-progression (weekly cycle cost)	£129.02
At progression (one-off cost)	£389.70
Post-progression (BSC) (one-off)	£4,318.06
Abbreviations: BSC, best supportive care	

End-of-life care

To reflect that additional resources are required to provide treatment to cancer patients towards the end of their life, an end-of-life cost was used in the model. The cost of hospital and social care in the final year of life for cancer patients is estimated to be £12,540 (PSSRU 2020). Given that this cost captures the last year of life, no costs for palliative care were included in the post-progression health state. It is applied as a one-off cost to the new death at each cycle. For the proportion of patients living less than one year in the model, this cost is adjusted for the length of time alive in the model.

B.3.5.4 Adverse reaction unit costs and resource use

Grade 3 or higher AEs with a prevalence in more than 3% of all patients plus endocrine disorders and colitis any grade are included in the model. The costs of the different AEs have been calculated based on the proportion of patients who would be treated in the inpatient and outpatient settings, respectively, combined with unit costs derived from the literature and the National Cost Collection for the NHS 2019/2020 version 2.

Based on clinical experts' opinion, the AEs associated with tebentafusp are concentrated over the first three doses, and there are very few AEs at later doses. Additionally, for the first three doses, patients are admitted overnight for monitoring, and the cost of an inpatient stay is already accounted for in the administration costs. Based on clinical experts' opinion, this cost would already capture the majority of the costs related to AEs. We have nevertheless costed the grade 3+ AEs in the tebentafusp arm to be conservative but assumed that the patients would not be admitted (on top of the three days of inpatients stay at administration) and used

outpatient costs only. In a scenario analysis, we are assuming the same proportion of inpatient vs. outpatient costs as in the control arm.

The cost of endocrine disorders is applied every 6 months based on the ipilimumab TA319 (NICE 2013b). For the other AEs, the weighted cost based on the rates of AEs is applied as a one-off cost in the first cycle in the model. This approach reflects clinical practice in the tebentafusp arm, based on clinical experts' opinion, as the AEs are mainly occurring with the first three doses. Although this may not reflect clinical practice in the control arm, this approach was used and accepted in previous submissions of checkpoint inhibitors for the treatment of metastatic melanoma. This approach is likely to be conservative as based on clinical experts' opinion, patients experience AEs with tebentafusp only with the first couple of doses, which is not the case with pembrolizumab and ipilimumab.

The proportions of management of AEs in the inpatient and outpatient settings are based on the pembrolizumab submission for advanced melanoma not previously treated with ipilimumab (TA366), where possible and clinical experts' opinion otherwise (NICE 2015d). The data is presented in Table 77.

Table 77. Proportion of patients managed for AEs in the inpatient and outpatient settings

	Inpatient setting	Outpatient setting	Source
Rash	5%	95%	TA366
Rash maculo-papular	5%	95%	TA366
Pruritus	5%	95%	TA366
AST increased		100%	Assumption validated by clinical experts
Lipase increased		100%	Assumption validated by clinical experts
ALT increased		100%	Assumption validated by clinical experts
Hypertension		100%	Assumption validated by clinical experts
Hypotension		100%	Assumption validated by clinical experts
Fatigue	10%	90%	TA366
Pyrexia	100%		TA366

Hypophosphataemia		100%	Assumption validated by clinical experts
Hyperbilirubinaemia		100%	Assumption validated by clinical experts
Pulmonary embolism	100%		Assumption validated by clinical experts
Colitis (any grade)	100%		TA366
Diarrhoea (grade 3+)	50%	50%	TA366
Hyperthyroidism (any grade)	10%	90%	Assumption validated by clinical experts

The unit costs of AEs are taken from a study by Wehler and colleagues, who estimated the economic burden of toxicities associated with treating metastatic melanoma in eight countries, including the United Kingdom (Wehler et al. 2017). This study was used in TA562 (NICE 2020). The unit costs are presented in Table 78. For other AEs, unit costs were derived from the National Cost Collection for the NHS 2019/2020 version 2. Where needed, the costs were inflated to 2019/2020 pounds.

Table 78. Unit costs of adverse events

	Inpatient setting	Outpatient setting	Source
Rash	£1834.21	£272.10	Wehler et al 2017 inflated to 2019/2020
Rash maculo-papular	£1834.21	£272.10	Wehler et al 2017 inflated to 2019/2020
Pruritus	£1834.21	£272.10	Wehler et al 2017 inflated to 2019/2020
AST increased	NA	£272.10	Wehler et al 2017 inflated to 2019/2020
Lipase increased	NA	£272.10	Wehler et al 2017 inflated to 2019/2020
ALT increased	NA	£272.10	Wehler et al 2017 inflated to 2019/2020
Hypertension	NA	£272.10	Wehler et al 2017 inflated to 2019/2020
Hypotension	NA	£272.10	Assumption same as hypertension
Fatigue	£1456.44	£272.10	Weighted average cost non-elective long (NLS) and short (NES) stay, KC05 Fluid or Electrolyte Disorders- -

			National schedule of NHS costs 2017/2018 (inflated to 2019/2020) Assumed same cost as the other AEs based Wehler et al 2017
Pyrexia	£1732.31	NA	Wehler et al 2017 inflated to 2019/2020
Hypophosphataemia	NA	£272.10	Assumed same cost as the other AEs
Hyperbilirubinaemia	NA	£272.10	Assumed same cost as the other AEs
Pulmonary embolism	£1,525.01	NA	Weighted average cost non-elective long (NLS) and short (NES) stay, DZ09 Pulmonary embolus - National schedule of NHS costs 2017/2018 (inflated to 2019/2020)
Colitis (any grade)	£4644.06	NA	Assumed same as diarrhoea
Diarrhoea (grade 3+)	£4644.06	£272.10	Wehler et al 2017 inflated to 2019/2020
Hyperthyroidism (any grade)	£1,257	£272.10	Weighted average cost non-elective long (NLS) and short (NES) stay, KA07 Non-Surgical Thyroid Disorders - National schedule of NHS costs 2017/2018 (inflated to 2019/2020)

The cost of AEs in each arm is calculated by factoring the incidence rate of each AE (Table 60) with the estimates of the cost per event (Table 78) and proportion of management in the inpatient and outpatient setting (Table 77). The weighted average costs of AEs by treatment arm in the model is presented in Table 79.

Table 79. Weighted average cost of AEs by treatment arm

	Tebentafusp	Investigator's choice
Endocrine disorder	£1.09	£82.99
Other adverse events	£165.98	£309.97

B.3.5.5 Miscellaneous unit costs and resource use

No other resource use is considered in the model.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

The variables applied in the economic model are summarised in Table 80. Point estimates and uncertainty around each parameter was informed by data and assumptions described in previous sections. Parameters were explored through both probabilistic and one-way sensitivity analyses (OWSA).

Table 80. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General parameters			
Time horizon	Lifetime (38 years)	Fixed	B.3.2.2
Cycle length	7 days	Fixed	B.3.2.2
Discount rate - utilities	3.5%	Fixed	B.3.2
Discount rate - costs	3.5%	Fixed	B.3.2
Population parameters			
Age	62	Fixed	B.3.2
% female	48.7%	Fixed	B.3.2
Body weight	78.86kg		B.3.5.1
Body surface area	1.90 m^2		B.3.5.1
Proportion of usage of the drug regimens in the investigator's choice arm			
Pembrolizumab	81.7%	Dirichlet	B.3.2.4
Ipilimumab	12.7%	Dirichlet	B.3.2.4
Dacarbazine	5.6%	Dirichlet	B.3.2.4
Survival models			
OS - Tebentafusp	Thee knots proportional hazard spline model	parameter estimates simulated from the asymptotic normal distribution	B.3.3.1
OS - Control arm	Weibull	Cholesky decomposition	B.3.3.1
PFS - Tebentafusp	KM + generalised gamma	KM: Greenwood exponential	B.3.3.1

		Parametric model: Cholesky decomposition	
PFS – Control arm	KM + generalised gamma	KM; Greenwood exponential Parametric model: Cholesky decomposition	B.3.3.1
TTD - Tebentafusp	KM + generalised gamma	KM; Greenwood exponential Parametric model: Cholesky decomposition	B.3.3.1
TTD - Tebentafusp	KM + generalised gamma	KM; Greenwood exponential Parametric model: Cholesky decomposition	B.3.3.1
Adverse event rates – tebentafusp			
Rash	9.4%	Fixed	B.3.3.3
Rash maculo-papular	8.6%	Fixed	B.3.3.3
Pruritus	4.5%	Fixed	B.3.3.3
AST increased	5.3%	Fixed	B.3.3.3
Lipase increased	4.1%	Fixed	B.3.3.3
ALT increased	3.3%	Fixed	B.3.3.3
Hypertension	8.6%	Fixed	B.3.3.3
Hypotension	3.3%	Fixed	B.3.3.3
Fatigue	5.3%	Fixed	B.3.3.3
Pyrexia	3.7%	Fixed	B.3.3.3
Hypophosphataemia	4.1%	Fixed	B.3.3.3
Hyperbilirubinaemia	3.3%	Fixed	B.3.3.3
Pulmonary embolism	0.8%	Fixed	B.3.3.3
Colitis (any grade)	0.0%	Fixed	B.3.3.3
Diarrhoea (grade 3+)	1.2%	Fixed	B.3.3.3
Hyperthyroidism	0.4%	Fixed	B.3.3.3
Adverse event rates – control arm			
Rash	0.0%	Fixed	B.3.3.3
Rash maculo-papular	0.0%	Fixed	B.3.3.3
Pruritus	0.0%	Fixed	B.3.3.3
AST increased	0.9%	Fixed	B.3.3.3

Lipase increased	5.4%	Fixed	B.3.3.3
ALT increased	1.8%	Fixed	B.3.3.3
Hypertension	2.7%	Fixed	B.3.3.3
Hypotension	0.0%	Fixed	B.3.3.3
Fatigue	0.9%	Fixed	B.3.3.3
Pyrexia	0.9%	Fixed	B.3.3.3
Hypophosphataemia	0.9%	Fixed	B.3.3.3
Hyperbilirubinaemia	4.5%	Fixed	B.3.3.3
Pulmonary embolism	3.6%	Fixed	B.3.3.3
Colitis (any grade)	2.7%	Fixed	B.3.3.3
Diarrhoea (grade 3+)	2.7%	Fixed	B.3.3.3
Hyperthyroidism	11.7%	Fixed	B.3.3.3
Health states utilities			
≥360 days	0.84	Beta	B.3.4.5
270-360 days	0.73	Beta	B.3.4.5
180-270 days	0.68	Beta	B.3.4.5
90-180 days	0.68	Beta	B.3.4.5
30-90 days	0.59	Beta	B.3.4.5
<30 days	0.34	Beta	B.3.4.5
On-treatment	[redacted]	Beta	B.3.4.5
Off-treatment	[redacted]	Beta	B.3.4.5
Treatment effect of ipilimumab	-0.0210	Beta	B.3.4.5
Treatment effect of pembrolizumab	-0.0210	Beta	B.3.4.5
Treatment effect of dacarbazine	-0.0236	Beta	B.3.4.5
Treatment effect of tebentafusp	-0.0236	Beta	B.3.4.5
Treatment acquisition costs per pack (unit costs at list price)			
Tebentafusp 100/0.5mL	[redacted]	Fixed	B.3.5.1
Ipilimumab 50mg/10ml vial	£ 3,750.00	Fixed	B.3.5.1
Pembrolizumab 100 mg/4mL vial	£ 2,630.00	Fixed	B.3.5.1
Dacarbazine 500 mg per vial	£ 37.50	Fixed	B.3.5.1
Treatment eligibility and administration-related costs			
SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance	£295.92	Gamma	B3.5.1
SB13Z - Deliver more Complex	£329.75	Gamma	B3.5.1

Parenteral Chemotherapy at First Attendance			
SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle	£363.37	Gamma	B3.5.1
DAPS04 – Clinical Biochemistry	£1.20	Gamma	B3.5.1
Human albumin 20%	£27.00	Fixed	B3.5.1
Cost of HLA-A*02:01	£163.18	Gamma	B3.5.1
% of patients expected to test positive	47%	Fixed	B3.5.1
Health state costs			
Pre-progression (per cycle)	£129	Gamma	B.3.5.2
At progression (one-off)	£390	Gamma	B.3.5.2
Post-progression (one-off)	£4,318	Gamma	B.3.5.2
End-of-life care (one-off)	£12,540	Fixed	B.3.5.2
Adverse events % management in inpatient and outpatient settings			
Rash/ Rash maculo-papular/ Pruritus (inpatient)	5%	Fixed	B.3.5.3
Rash/ Rash maculo-papular/ Pruritus (outpatient)	95%	Fixed	B.3.5.3
AST increased/ Lipase increased/ ALT increased (outpatient)	100%	Fixed	B.3.5.3
Hypertension/ Hypertension (outpatient)	100%	Fixed	B.3.5.3
Fatigue (inpatient)	10%	Fixed	B.3.5.3
Fatigue (outpatient)	90%	Fixed	B.3.5.3
Pyrexia (inpatient)	100%	Fixed	B.3.5.3
Hypophosphataemia/ Hyperbilirubinaemia (outpatient)	100%	Fixed	B.3.5.3
Pulmonary embolism (inpatient)	100%	Fixed	B.3.5.3
Colitis (inpatient)	100%	Fixed	B.3.5.3

Diarrhoea (outpatient)	50%	Fixed	B.3.5.3
Diarrhoea (inpatient)	50%	Fixed	B.3.5.3
Hyperthyroidism (inpatient)	10%	Fixed	B.3.5.3
Hyperthyroidism (outpatient)	90%	Fixed	B.3.5.3
Adverse events costs			
Rash/ Rash maculo-papular/ Pruritus (inpatient)	£1834.21	Gamma	B.3.5.3
Rash/ Rash maculo-papular/ Pruritus (outpatient)	£272.10	Gamma	B.3.5.3
AST increased/ Lipase increased/ ALT increased (outpatient)	£272.10	Gamma	B.3.5.3
Hypertension/ Hypertension (outpatient)	£272.10	Gamma	B.3.5.3
Fatigue (inpatient)	£1456.44	Gamma	B.3.5.3
Fatigue (outpatient)	£272.10	Gamma	B.3.5.3
Pyrexia (inpatient)	£1732.31	Gamma	B.3.5.3
Hypophosphataemia/ Hyperbilirubinaemia (outpatient)	£272.10	Gamma	B.3.5.3
Pulmonary embolism (inpatient)	£1,525.01	Gamma	B.3.5.3
Colitis (inpatient)	£4644.06	Gamma	B.3.5.3
Diarrhoea (outpatient)	£4644.06	Gamma	B.3.5.3
Diarrhoea (inpatient)	£272.10	Gamma	B.3.5.3
Hyperthyroidism (inpatient)	£1,257	Gamma	B.3.5.3
Hyperthyroidism (outpatient)	£272.10	Gamma	B.3.5.3
Abbreviations: CI, confidence interval			

B.3.6.2 Assumptions

A number of key assumptions were made in the base-case analysis. These key assumptions have been previously described throughout Sections B.3.3, B.3.4 and B.3.5., and are summarised in Table 81.

Table 81. Key model assumptions

Assumption	Rationale	Reference to section in submission
Survival analysis		
Overall survival was model in the tebentafusp arm, using a three-knot spline model assuming that a proportion of the patients would be long-term survivors	This assumption is in line with the early evidence suggesting that a proportion of patients will derive long-term benefits with tebentafusp, as has been observed with immune checkpoint inhibitors for the treatment of metastatic melanoma	B.3.2
Drug acquisition costs		
Vial sharing is not allowed in either arms	This assumption was made in line with tebentafusp SPC and given the very small patient population, implementing vial sharing would be challenging in clinical practice.	B.3.5.1
Other costs		
Post-progression health state costs (best-supportive care) have been applied as a one-off cost	BSC is assumed to be provided for an average of four months in line with the study by McKendrick et al. (2016) and applied as a one-off cost upon progression for simplicity in the model	B.3.5.3
The cost of adverse events is applied as a one-off cost in the first model cycle, expected for endocrine disorders which was applied every six months.	In line with previous economic models. AEs with tebentafusp occurred mainly with the first three doses based on clinical experts opinion. Endocrine disorders may be long-lasting, approach in line with TA319 (NICE 2013b)	B.3.5.4
The costs of AEs in the tebentafusp arm are based on outpatient costs only	Based on clinical experts' opinion, patients experienced AEs with the first couple of doses of tebentafusp and very few at later doses. Additionally, patients are admitted overnight for the first three doses and clinical experts believed that this would already account for the costs of management of AEs.	B.3.5.3
End of life costs of one year were applied to all patients in the model cycle in which patients die.	This assumption is in line with previous oncology models. It is expected that the majority of HRCU required for palliative care in end of life patients is concentrated towards the last few months before their death.	B.3.5.3

Utilities		
Utilities modelled based on time-to-death	Based on clinical experts' opinion, this approach better reflect the changes in QoL of patients with metastatic UM, than disease status	B.3.4
Disutilities related to adverse events are applied in the first model cycle.	In line with recent oncology models. This assumption was made on the basis that AEs are expected to occur and be managed shortly after treatment.	B.3.4

B.3.7 Base-case results

Base-case results of the economic analysis for a 38-year time horizon and with a discount rate of 3.5% for both costs and outcomes, are presented in Table 82.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Using the [redacted] per tebentafusp vial, it was estimated that over a lifetime horizon tebentafusp was associated with a [redacted] increase in life years ([redacted] vs. [redacted]), and a [redacted] increase in QALYs ([redacted]) per treated patient. Both the improvement in life expectancy and in HRQoL of patients with metastatic UM is considered substantial. This improvement in outcomes of patients with metastatic UM is mainly owed to a proportion of patients experiencing longer survival compared with the comparator. The base-case deterministic ICER was [redacted] per QALY gained.

Table 82. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Tebentafusp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to describe how uncertainty around input parameters is translated into uncertainty around the estimated outputs of the model. Hence, suitable probability distributions were assigned to model parameters to characterise uncertainty around their mean values and have been presented in Table 80. Values were sampled from the corresponding parameter distributions and were assigned to each parameter in an iterative process. This process was repeated for 10,000 times, and the results of each of these iterations were used to determine the distribution of incremental costs and incremental QALYs.

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

The results of the PSA were presented within the cost-effectiveness plane in the form of a joint distribution of costs and QALYs, along with a mean value of the ICER and a 95% confidence interval ellipse (Figure 40). It is apparent from that the largest spread is across the X axis of the scatter plot showing that health benefits are characterised by a high degree of uncertainty. The probability that each treatment is cost-effective, resulting in the highest net monetary benefit, is presented over different values of a cost-effectiveness threshold in the form of a cost-effectiveness acceptability curve (CEAC) in Figure 41.

Table 83 presents the mean incremental costs and QALYs as well as the ICER as estimated in the base-case PSA.

Table 83. Results of the base-case PSA

Technologies	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)
Tebentafusp	[redacted]	[redacted]	[redacted]
Control	-	-	-
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years			

Figure 40. Cost-effectiveness plane – incremental costs vs. incremental QALYs

[redacted]

Figure 41. Cost-effectiveness acceptability curve for willingness-to-pay threshold

B.3.8.2 Deterministic sensitivity analysis

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.

Upper and lower values of model parameters were determined by their 95% CIs or ±1.96 standard errors, depending on format of source data reporting. When no information was available regarding a parameter's uncertainty then the variation around the mean value was modelled by varying the parameter by 25% or 10% of its mean value.

Figure 42 presents a tornado diagram indicating the 10 parameters with the greatest influence on the ICER in a descending order. Table 84 presents the ICER as a result of using an upper and lower estimate for these parameters.

We note that the parameter that has the most impact on the results is the age of a patient as it determines the time frame over which patients may derive benefit. The second parameter impacting the results is the baseline utility value as this is applied

to patients until they are one year from death. The third parameter is the cost of administration of chemotherapy at subsequent attendance, related to the duration of treatment of Tebentafusp which is administered on a weekly basis. All other parameters have very limited impact on the results.

Figure 42. Tornado diagram

Table 84. Results of the univariate sensitivity analysis

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Mean patient age (46.5, 77.5)	[redacted]	[redacted]
On-treatment health state utility [IMCgp100-202] (0.76, 0.93)	[redacted]	[redacted]
Cost of subsequent chemotherapy attendance (272.5, 454.2)	[redacted]	[redacted]
Pre-progression health state cost - per cycle (96.8, 161.3)	[redacted]	[redacted]
Proportion female patients (0.37, 0.62)	[redacted]	[redacted]
Disutility of tebentafusp adverse events (0.019, 0.023)	[redacted]	[redacted]
Cost of overnight hospital stay (338.1, 563.5)	[redacted]	[redacted]
Disutility of dacarbazine adverse events (0.021, 0.026)	[redacted]	[redacted]
Health state utility, time to death 270-360 days (0.64, 0.78)	[redacted]	[redacted]
Health state utility, time to death 30-90 days (0.51, 0.63)	[redacted]	[redacted]

B.3.8.3 Scenario analysis

The impact of both structural assumptions and choice of parameter values were further explored through a number of scenario analyses. The scenarios that were evaluated are outlined below.

***Choice of method of extrapolation** of PFS*

We explored the choice of the method for the extrapolation of the PFS. We tested the log-logistic and lognormal curves, which were second best choice for the PFS curve as detailed in section B.3.3.1.2. We also tested the impact of the time-point at which there is a switch from the KM curves to the parametric curve, testing 10% of patients at risk in place of 15% of patients at risk in the base-case. We note that the impact on the results is very limited due to the difference in the costs between the two arms being driven by the TTD curves, and the difference in LY/QALYs being driven by the OS curve.

Table 85 Results of scenario analyses of alternative methods of extrapolating PFS

Scenario	ICER (£/QALY)	% change
Base-case KM + Generalised gamma	[redacted]	NA
KM + log-logistic	[redacted]	-0.37%
KM + log-normal	[redacted]	-0.43%
Generalised gamma	[redacted]	-0.06%
Log-logistic	[redacted]	-0.41%
Log-normal	[redacted]	-0.41%
Base-case (KM + generalised gamma; 10% at risk)	[redacted]	0.00%

Choice of method of extrapolation of TTD

We explored the choice of the method for the extrapolation of the TTD. We tested the log-logistic and lognormal curves, which were second best choice for the PFS curve as detailed in section B.3.3.1.2. We also tested the impact of the time-point at which there is a switch from the KM curves to the parametric curve, testing 10% of patients at risk in place of 15% of patients at risk in the base-case.

We note that when using the hybrid approach, the choice of curve has a very limited impact on the ICER as most patients have discontinued by the time-point when there is a switch from the KM to the parametric curve and as there is a [redacted]. When using solely the parametric curves, the ICER is increased by about 5% depending on the distribution chosen. However, the parametric curves did not provide such a good fit to the data, thus the hybrid approach chosen for the base-case.

Table 86. Results of scenario analyses of alternative methods of extrapolating PFS

Scenario	ICER (£/QALY)	% change
Base-case KM + Generalised gamma	[redacted]	NA
KM + log-logistic	[redacted]	-0.24%
KM + exponential	[redacted]	0.22%
KM + Weibull	[redacted]	-0.14%
Generalised gamma	[redacted]	4.11%
Log-logistic	[redacted]	0.24%
Exponential	[redacted]	7.53%
Weibull	[redacted]	5.80%
Base-case (KM + generalised gamma; 10% at risk)	[redacted]	0.16%

Source of utility data

We conducted a scenario analysis using the utility values derived from the EQ-5D data collected in the IMCgp100-202 trial. The data is applied based on TTD rather than disease status as detailed in section B.3.4. The ICER is [redacted] which is equivalent to an 8.34% increase compared to the base-case.

Choice of method of extrapolation of overall survival and data-cut-off

The incremental LYs and QALYs are driven by the OS curve in the tebentafusp arm, hence the importance of testing the impact of the chosen method on the results. This section presents the results of a series of scenario analyses testing alternative combinations of standard parametric functions for extrapolating overall survival. A

total of nine parametric function combinations have been examined for the tebentafusp and control arm.

The August 2021 DCO was used in the base-case providing the longest follow-up and therefore the most information on the clinical effectiveness of tebentafusp. However, the control arm was not adjusted for treatment cross-over, [redacted] as presented in section B.3.3. Therefore, the series of scenarios based on standard parametric curves are presented for both DCO, for comparison. The preferred model is the Weibull for the control arm, which is well aligned with the data on first-line patients reported in the meta-analysis conducted by Rantala and colleagues (Rantala et al. 2019). We also tested generalised gamma and Gompertz which were second best but also reasonable fits. In the tebentafusp arm, the log-logistic distribution for OS is used providing the best fit and a clinically plausible long-term extrapolation based on clinical experts' opinion. Generalised gamma and log-normal are also reasonable fits and tested. All other parameters are as per the base-case analysis. The resulting ICERs and change from the base case are presented Table 87.

Table 87. Results of scenario analyses using alternative parametric survival models

Scenario (Parametric models)	August 2021 DCO		October 2020 DCO	
	ICER (£/QALY)	% change	ICER (£/QALY)	% change
Base-case (August 2021 DCO) Spline (tebentafusp) Weibull (comparator)	[redacted]	NA	[redacted]	NA
Log-logistic (tebentafusp) Weibull (comparator)	[redacted]	76.2%	[redacted]	48.9%
Log-logistic (tebentafusp) Gompertz (comparator)	[redacted]	70.0%	[redacted]	42.9%
Log-logistic (tebentafusp) Generalised Gamma (comparator)	[redacted]	97.0%	[redacted]	58.8%
Lognormal (tebentafusp) Weibull (comparator)	[redacted]	70.1%	[redacted]	48.9%
Lognormal (tebentafusp) Gompertz (comparator)	[redacted]	64.7%	[redacted]	43.1%
Lognormal (tebentafusp) Generalised gamma (comparator)	[redacted]	90.0%	[redacted]	35.1%

Generalised Gamma (tebentafusp) Weibull (comparator)	[redacted]	176.4%	[redacted]	114.6%
Generalised Gamma (tebentafusp) Gompertz (comparator)	[redacted]	161.3%	[redacted]	152.6%
Generalised Gamma (tebentafusp) Generalised Gamma (comparator)	[redacted]	231.0%	[redacted]	152.6%

There is evidence to suggest a trend towards long-term survival for a fraction of patients treated with tebentafusp. This effect has been incorporated in the model by applying the mortality rates for the general population to a fraction of the patients treated with tebentafusp after a certain time point (e.g., survival probability of [redacted] with the August 2021 DCO). The results of varying this cure fraction [redacted] are presented in Table 88. The initial survival phase was modelled using parametric models assuming a Weibull hazard function in both arms since this provided a good fit in the early phase.

Table 88. Results of scenario analyses using patients cure proportions for survival

Scenario (cure fraction)	August 2021 DCO		October 2020 DCO	
	ICER (£/QALY)	% change	ICER (£/QALY)	% change
50%	[redacted]	2.7%	[redacted]	-3.7%
60%	[redacted]	-10.5%	[redacted]	-15.7%
70%	[redacted]	-20.6%	[redacted]	-25.0%
80%	[redacted]	-28.7%	[redacted]	-32.5%
90%	[redacted]	-35.3%	[redacted]	-38.6%

B.3.8.5 Summary of sensitivity analyses results

Extensive sensitivity and scenario analyses were conducted to explore the robustness of model results subject to changes in parameter values, and to consider the impact of structural uncertainties and choice of parameter values.

The results of the sensitivity analyses focussing on the methods of extrapolating PFS and TTD indicate that the model results are not sensitive to the choice of modelling

approach. This is not surprising, since, up to the end of the clinical trial study period, PFS and TTD are modelled based on the KM curves. It is only beyond the study period that parametric survival models are applied in order to extrapolate for the remainder of the time horizon. The number of patients progression-free or on-treatment at the beginning of the extrapolation phase, however, is relatively small and there are then only a small number of possible events that can be impacted by the choice of modelling approach.

In a DSA, the parameters with the most significant impact on the results are the baseline utility value as this is applied to patients until one year from death, and the cost of administration of subsequent attendance, related to the treatment duration of tebentafusp.

The ICER is most sensitive to the choice of model for the extrapolation of the OS in the tebentafusp arm, as this drives the size of the incremental QALYs, with ICERs varying between [redacted] and [redacted] depending on the extrapolation method and DCO chosen. Results from the PSA show that there is a significant level of uncertainty associated with the model chosen in the base-case for the extrapolation of the OS in the tebentafusp arm. The uncertainty is likely driven by the low number of patients at risk at the tail of the KM curves. The incremental costs are driven by the acquisition cost of tebentafusp. [redacted].

B.3.9 Subgroup analysis - Patients with tumour < 30mm.

There is a growing body of evidence documenting the associating between tumour burden and response to immunotherapies, thus the particular interest in this population subgroup (Dall'Olio et al. 2021).

The subgroup analysis examines the impact of implementing survival models based on restricted subpopulations of patients with baseline largest metastatic tumour with a diameter of less than 30mm.

PFS and TTD are modelled using KM curves and generalised gamma for the extrapolation of the tail in both arms. Given that the choice of curve for the extrapolation of the tail of the PFS and TTD have little impact on the model results as seen in previous scenario analysis, these are kept fixed. We model the OS in the control arm using Weibull which provided the best fit and present results for the log-logistic and log-normal in the tebentafusp arm. The results for both DCO are presented in Table 89, along with the ICER for the ITT set (using the same distributions) for comparison.

Table 89. Scenario analysis subgroup tumour ≤30mm

Scenario: Parametric model for OS	August 2021 DCO ICER (£/QALY)			October 2020 DCO ICER (£/QALY)		
	ITT	Subgroup	% change	ITT	Subgroup	% change
Log-normal (tebentafusp)	[redacted]	[redacted]	-22.3%	[redacted]	[redacted]	-35.0%
Log-logistic (tebentafusp)	[redacted]	[redacted]	-3.0%	[redacted]	[redacted]	-15.6%

B.3.10 Validation

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

Internal validity

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

and inspecting whether the results produced by the model matched the modeller's expectations.

External validity

To examine the external validity of the model results we compared the predicted overall survival and progression free survival with the 202 trial IC arm, and three studies of treatments for metastatic UM.

Table 90. Summary of model results compared with clinical data

Comparison	Model IC arm	Trial 202 (IC arm – Oct 2020)	(Rantala et al. 2019b)	(Piulats et al. 2021a)	(Pelster et al. 2021a)
Description	Control arm predicted by the model	Investigator's choice arm of 202 study	Meta-analysis of published data	Open label, single arm study of IV nivolumab (1 mg/kg) in combination with IV ipilimumab (3 mg/kg) in patients with systemic treatment-naive, histologically confirmed metastatic UM	Open-label, single-arm phase II study of nivolumab (1 mg/kg) in combination with IV ipilimumab (3 mg/kg) in patients with metastatic UM
Median OS	[redacted]	16.0 (95% CI, 9.7 to 18.4) months	1.07 years (95% CI, 1.0 to 1.13) years	12.7 (95% CI, 7.1 to 18.3) months	19.1 months (95% CI, 9.6 months to not reached [NR])
Median PFS	[redacted]	2.9 months (95% CI: 2.9-3.0)	NR	3.0 (95% CI, 2.0 to 4.1 months)	5.5 months (95% CI, 3.4 to 9.5 months)
12-month OS rate	[redacted]	62% (95% CI, 53 to 70%)	52% (95% CI, 47 to 55%)	51.9% (95% CI, 38.3 to 65.5)	56% (95% CI, 38% to 71
24-month OS rate	[redacted]		21% (95% CI, 18-25%)	26.4% (95% CI, 14.2 to 38.6)	NR

Abbreviations: OS, overall survival; PFS, progression-free survival

B.3.11 Interpretation and conclusions of economic evidence

A systematic review of the economic literature did not identify any published economic evaluations of tebentafusp for the treatment of patients with metastatic UM (Section B.3.1), and it was therefore necessary to develop a de novo cost-effectiveness model.

The three-state (pre-progression, post-progression and death) partitioned survival model structure used is aligned with disease pathway, the endpoints from the clinical trial and previous models in metastatic melanoma and oncology more broadly. The core assumptions, including the extrapolation of the OS, PFS and TTD endpoints were discussed with UK-based clinical experts. Unit costs and resource use were sourced from UK sources. The patient population and investigator's choice of the IMCgp100-202 clinical trial were deemed relevant to UK practice by the clinical experts. Hence, this economic evaluation of tebentafusp is considered to be relevant to patients with metastatic UM in England and Wales.

The key clinical inputs, PFS, OS, and TTD were modelled with KM curves and parametric models to extrapolation beyond the trial time horizon. Extrapolation methods were chosen and applied in line with NICE TSD on survival analysis, and the choice of model was informed by the fit to the observed period, comparison to historical data for the control arm and clinical plausibility.

Based on the base-case analysis [redacted], the ICER is [redacted]. The QALY gains are driven by the longer OS in the tebentafusp arm, with a proportion of the patients experiencing long-term survival. The incremental costs are mainly driven by the acquisition cost of tebentafusp.

Extensive sensitivity and scenario analyses were also conducted to explore the robustness of model results subject to changes in parameter values, and to consider the impact of structural uncertainties and choice of parameter values.

The ICER is most sensitive to the choice of model for the extrapolation of the OS in the tebentafusp arm, as this drives the size of the incremental QALYs, with ICERs varying between [redacted] and [redacted] depending on the extrapolation method and DCO chosen. Results from the PSA show that there is a significant level of

uncertainty associated with the model chosen in the base-case for the extrapolation of the OS in the tebentafusp arm. The uncertainty is likely driven by the low number of patients at risk at the tail of the KM curves. The incremental costs are driven by the acquisition cost of tebentafusp. Given that there is an [redacted], which are modelled based on the KM curves, and parametric model only for the extrapolation of the tail, there is less uncertainty on the incremental costs. Later data cut-offs of the IMCgp100-202 study will allow to resolve the uncertainty around the extrapolation of the survival curve in the tebentafusp arm and thus around the incremental cost per QALY gained per patient treated with tebentafusp compared to currently offered treatments.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]

Clarification questions

November 2021

File name	Version	Contains confidential information	Date
ID1441 clarification questions v2.0_080322 updated CiCAiC	2.0	Yes	08.03.22

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Literature Searches

A1. Given the low number of results retrieved for each search, please explain the rationale behind not searching more broadly in regard to study design.

The only study design limit applied in the searches was the trials filter used in the clinical SLR. We did not limit to RCTs only but used a broader trials filter designed to retrieve trials of any design.

A2. Were any additional searches run to identify papers on adverse events (AEs)? If not, please explain what impact this may have had.

No additional searches were run to specifically identify papers on adverse events. If a clinical trial did report only AEs then it would still have been included in accordance with the PICOs criteria of the clinical SLR.

A3. Please elaborate on the justification for searching only Embase for conference abstracts within the past three years.

As recommended in the NICE Guideline Manual for reviews of health care interventions, MEDLINE and EMBASE were the two main bibliographic databases searched for this review. MEDLINE does not contain conference abstracts, so only EMBASE was searched for conference abstracts. A three-year search limit applied because where clinical trial results are reported in abstracts, this is typically prior to publication of the full clinical trial

results upon final study reporting, three years was considered to be a sufficient time frame to capture any early reports of studies that were not yet fully published.

A4. The Emtree term “uvea melanoma/” did not appear in any of the Embase search strategies, both in the clinical effectiveness and economics systematic literature reviews (SLRs).

Please rerun these searches to include this term and ensure that no relevant records have been missed.

Clinical SLR

Searches were rerun in Embase to include the Emtree term ‘uvea melanoma’.

Search results:

Eighty-nine additional records were identified for the clinical SLR. On deduplication of these records against all results found in other databases, six duplicate records were identified and removed. The title and abstracts of the remaining 83 records were screened independently by two reviewers. Seventy-three records were excluded after title and abstract screening. Full texts of 10 records were screened and two new studies met the eligibility criteria for inclusion. Studies excluded after full text screening and the updated PRISMA for the clinical SLR has been provided in **Appendix 1** (**Figure 33**). Studies that were excluded following full text screening and the reason for exclusion is detailed in **Appendix 2**

Table 43.

Summary of the trials:

A phase II RCT conducted in US (McWilliams et al., 2018) and a phase II single arm trial conducted in Japan (Namikawa et al., 2018) were identified by the updated Embase search. An overview of the two new included studies is provided in Table 1 and Table 2. Studies included patients with advanced/metastatic melanoma. Hence, patients with uveal melanoma (UM) formed a subgroup of the total population. Total population size and number of patients with uveal melanoma were 148 (total) and 26 (UM) for the RCT and 30 (total) and 2 (UM) for the single arm trial, respectively. Baseline characteristics for patients with

uveal melanoma was reported only in the RCT (McWilliams et al., 2018) and is presented in **Table 1**.

Both studies assessed the efficacy and safety of systemic treatments (RCT: chemotherapy (McWilliams et al., 2018); single arm trial: immunotherapy (Namikawa et al., 2018)). The RCT compared the combination of carboplatin, paclitaxel, and bevacizumab with or without everolimus (CPBE or CPB). The single arm trial assessed efficacy and safety of treatment with a combination of ipilimumab and nivolumab in patients with advanced melanoma. The studies reported a number of outcomes for the total study population. However, limited outcomes (PFS and PR) were reported for the uveal melanoma subgroup, results of which are presented in **Table 2**. The study by Namikawa et al. (2018) with two UM patients in the trial was testing ipilimumab plus nivolumab, two studies identified in the SLR also used this combination of immunotherapy in a larger population of European metastatic UM patients and therefore the data from these studies provides more transferable evidence for the UK patient population on a much greater number of patients.

Overall survival for both studies was reported on a mixed population, for McWilliams et al. (2018) a median OS of 14.5 months for CPB versus 10.8 months for CPBE (HR, 1.16; 95% CI, 0.84-1.84) was reported. For Namikawa et al. (2018) At the median follow-up period of 14.1 months, median OS and centrally assessed PFS were not reached. However, since both of these only reported results for the mixed population of patients with different types of metastatic melanoma, no meaningful comparisons can be made.

Table 1: Study and patient characteristics

Study Reference/ Trial no.	Study design /Location	Study population	Intervention/ Comparator(s)	Type of therapy	Sample size	Patient characteristics	Outcome reported
(McWilliams et al., 2018) **NCT00976573**	Phase II randomised open label trial United States	• Patients aged ≥18 years with histologically confirmed stage IV malignant melanoma not amenable to surgery. • Patients were required to have a, measurable disease, a life expectancy of ≥4 months, ECOG score of 0 to 1, and ≤1 prior chemotherapy-based regimen (no prior taxane-based regimens). • Prior adjuvant non-taxane-based chemotherapy and/or adjuvant immunotherapy were allowed and there was no limit on the number of prior biologics, immunologic, or targeted therapies.	**Intervention (CPB): Carboplatin** (AUC 5 IV on day 1 and repeated every 28 days); **paclitaxel** (80 mg/m^2 IV on days 1, 8, and 15); and **bevacizumab** (10 mg/kg IV on days 1 and 15) **Comparator (CPBE):** CPB regimen and **everolimus** (5 mg three times weekly all 4 weeks and repeated every 28 days). Treatment was continued until disease progression or unacceptable toxicity.	Systemic: Chemotherapy	Total population: 148 Patients with UM: n=26 (CPB arm: 16; CPBE arm: 10)	**For patients with UM** **Age** (years, median): CPB arm: 59.5; CPBE arm: 60.2 **Male** (n, %): CPB arm: 12 (75%); CPBE arm: 6 (60%) **Received Prior chemotherapy** (n, %): CPB arm: 3 (18.8%); CPBE arm: 2(20%) **Received prior immunotherapy** (n, %): CPB arm: 3 (18.8%); CPBE arm: 4(40%) **BRAF mutation wildtype** (n, %): CPB arm: 8 (100%); CPBE arm: 4(100%)	**Total population:** PFS, OS, tumour response rate, and AEs. **UM:** PFS and tumour response
(Namikawa et al., 2018) **JapicCTI-152869**	Open label single arm multicentre phase II trial Japan	• Treatment-naïve patients aged ≥20 years with confirmed unresectable stage III/IV or recurrent melanoma and ECOG performance status of 0-1.	**Nivolumab** (1 mg/kg IV) plus **ipilimumab** (3 mg/kg IV) per cycle for two 3-week cycles, followed by 6-week cycles with biweekly **nivolumab** (3 mg/kg). Treatment continued until establishment of CR or PD or development of unacceptable toxicity or withdrawal of consent.	Systemic: immunotherapy	Total population: 30 Patients with UM: 2	Not reported specifically for patients with UM.	**Total population:** ORR, DCR, OS, PFS, DoR, TtR, BOR, AEs and TRAEs **UM**: ORR (CR+PR)

BRAF mutation was analysed for 12 patients with UM. Abbreviations: AEs: adverse events; BOR: best overall response; CPB: carboplatin + paclitaxel +bevacizumab; CBPE: carboplatin + paclitaxel +bevacizumab + everolimus; CR: complete response; DCR: disease control rate; DoR: duration of response; ECOG: Eastern Cooperative Oncology

Group; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression free survival; PR: partial response; SD: stable disease ; ToT: time to response; TRAEs: treatment related adverse events; UM: uveal melanoma.

Table 2: Summary of outcome results in each study

Study Reference/ Trial no.	Treatment arm	Population	Population (i.e., CE, ITT etc.)	Evaluable population (n)	Outcome reported	Result	P value between group difference
Randomised control trial							
(McWilliams et al., 2018) **NCT00976573**	Carboplatin + paclitaxel +bevacizumab	Uveal melanoma (n=16) and mucosal melanoma (n=1)	Modified ITT (1 patient was later determined to be ineligible)	Total 27 (UM:25 and MM: 2)	PFS: defined as the number of days between randomization until documentation of disease progression or death.	PFS (median): 5.6 months	NR
	Carboplatin + paclitaxel +bevacizumab + everolimus	Uveal melanoma (n=10) and mucosal melanoma (n=1)	Modified ITT (1 patient was later determined to be ineligible)			PFS (median): 4.5 months	NR
	Carboplatin + paclitaxel +bevacizumab	Uveal melanoma (n=16)	ITT	16	Tumour response rate	PR (n, %): 1(6%)	NA
	Carboplatin + paclitaxel +bevacizumab + everolimus	Uveal melanoma (n=10)	ITT	10		No response reported	NA
Single arm trial							
(Namikawa et al., 2018) **JapicCTI-152869**	Nivolumab + ipilimumab for two 3-week cycles, followed by 6-week cycles with biweekly nivolumab.	Uveal melanoma (n=2)	Modified ITT (patients who received nivolumab or ipilimumab at least once)	2	ORR (CR+PR) as per the RECIST guidelines, version 1.1	ORR (CR+PR), (n% [95% CI]): 0/2 (0.0) [0.0, 84.2]	NA

Abbreviations: CR: complete response; ITT: intention to treat; ORR: objective response rate; PFS: progression free survival; PR: partial response; UM: uveal melanoma; RECIST: Response Evaluation Criteria in Solid Tumours.

Economic SLR

Search results

Fifty-four additional records were identified for the economic SLR and one record was removed after deduplication. Forty-five records were excluded at title and abstract screening and full texts of eight records were screened. No new study was identified for the economic SLR. The updated PRISMA for economic SLR is presented in **Appendix 1 ,**

Figure 34. Studies excluded after full text screening along with their reason of exclusion are listed in **Appendix 2, Table 44.**

A5. The German database PharmNet-Bund is included in Section G.1.1.1 of Appendix G of the company submission (CS) as part of the list of resources searched. However, the corresponding strategy appears to be missing.

Please provide this in full along with the search date and date of any update searches.

The inclusion of PharmNet-Bund in Section G.1.1.1 was an error and it was not part of the final literature searches. It was initially searched in the context of searching for additional European studies however we have since confirmed that PharmNet-Bund is a portal for German clinical trials that are included in the EU clinical trials register, which is included in the WHO ICTRP register and was included in the overall search strategy.

Section B: Clarification on clinical effectiveness data

Decision Problem

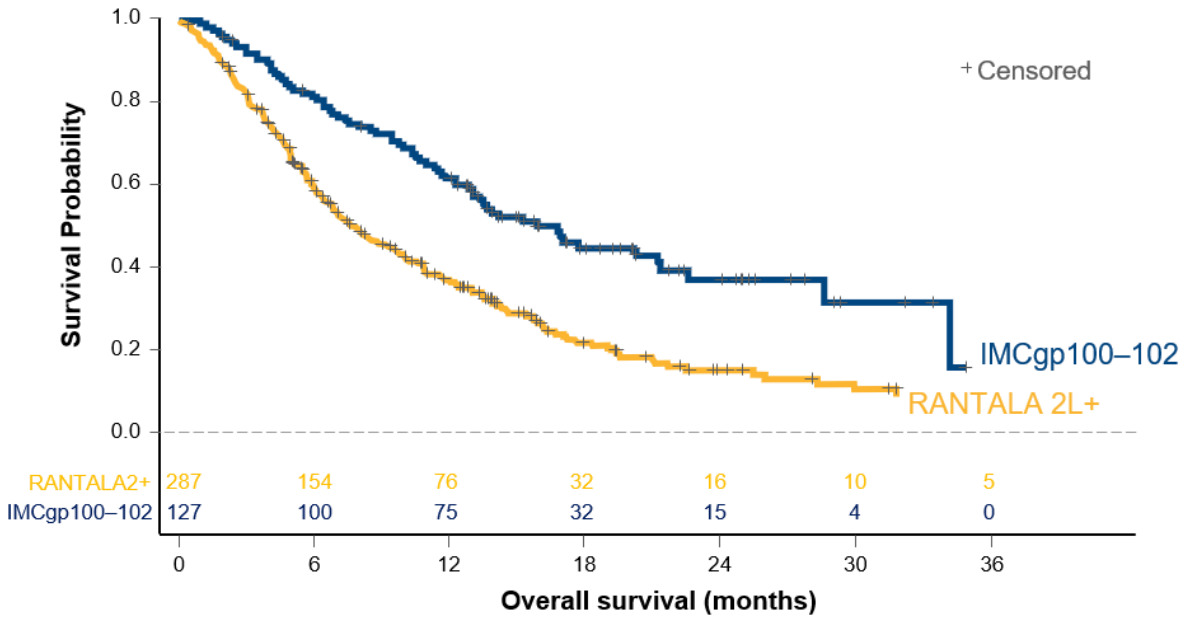
B1. Priority question. Neither the scope nor the decision problem specifies that advanced (unresectable or metastatic) uveal melanoma patients need to be treatment naïve. However, the population description for the economic analysis includes "…without prior treatment in the metastatic setting".

a. **Please confirm that the decision problem should be amended to include that patients need to be treatment naïve.**

b. **If this is not the case, please provide both clinical and economic analyses in the population of those who are treatment experienced.**

Evidence for the effectiveness of tebentafusp as a second line therapy is provided in the CS Document B section B.2.6.1. Study IMCgp100-102 demonstrated the potential clinical benefit of tebentafusp in treating metastatic UM who have previously received one or more prior lines of therapy, including chemotherapy, immunotherapy, or local therapy. The median OS in tebentafusp-treated patients was 16.8 months (95% CI: 12.9-21.3), and the OS rates were 61.8% (95% CI: 52.6-69.8%) at 12 months and 37.0% (95% CI: 26.5-47.5%) at 24 months. This is higher than the OS experienced with previously tested treatments (OS: 7.8 months [95% CI: 6.5-9.7], 1-year survival rate: 37% [95% CI: 31-43]), reported by a meta-analysis published by Rantala et al. (2019), Figure 1.

Figure 1. Kaplan-Meier plot of overall survival in Phase 2 dose expansion of study IMCgp100-102 (tebentafusp as second-line treatment) in comparison to historical data of second line treatments published by Rantala et al. (2019)



The decision problem should not be amended to include treatment naïve patients. The most robust evidence available because it based on an RCT which demonstrates the efficacy of tebentafusp in metastatic UM. A survey of UK clinicians has demonstrated 83% of UK clinicians (31 clinicians surveyed) would already choose tebentafusp as a first-line therapy for metastatic UM. It is therefore anticipated that within the first 2-years of being available, all HLA-A*02:01 positive metastatic UM patients who are clinically eligible for tebentafusp would receive it as first line therapy. Only patients who are already on treatment once tebentafusp comes becomes available are likely to receive it as a second line therapy, it would therefore be unethical to not make tebentafusp available to those patients who had not yet had the opportunity to receive it.

Systematic literature review (SLR)

B2. Priority question. Table in Appendix D of the company submission (CS) shows that 11 randomised controlled trials (RCTs) and 49 single arm trials were identified in the clinical effectiveness SLR.

a. **Please justify why each of the identified studies were not included as clinical effectiveness evidence in the CS.**

Appendix 3 (see separate document) contains the full summary reference table of included studies in the clinical SLR, the studies were selected based on the PICOS criteria and each of these studies were included in the SLR.

Please perform quality assessments of all studies included in the clinical effectiveness SLR.

Quality assessments have been performed on all studies included in the clinical SLR and summarised in: Appendix 3: Quality assessment of clinical SLR included studies.

B3. Please state how the data extraction and risk of bias assessment processes were carried out, i.e. how many reviewers were involved at each stage, how discrepancies were solved, and if a third reviewer was involved in resolving disagreements.

In order to be selected for data extraction, the publication had to fulfil all the inclusion criteria and none of the exclusion criteria shown in the PICOS. After de-duplication, every record retrieved in the search was independently reviewed by two reviewers and marked as include or exclude following a review of the study title and abstract (where the latter is available). Full-text articles were obtained for records that meet the criteria for inclusion. Each record was then re-evaluated in a full-text review by two independent reviewers. Any disagreements in decision were resolved through discussion until a consensus was reached, or else a third reviewer was involved to resolve the discrepancy.

Clinical effectiveness evidence

B4. Priority question. Regarding the choice of comparator treatment Table 5 of the CS states that "the preferred investigator's choice agent was selected prior to randomization".

Please provide separate analyses of all outcomes comparing tebentafusp with each comparator (dacarbazine, ipilimumab, pembrolizumab) according to investigator's choice.

Table 3 Subgroup Analysis of OS by Pre-choice of chemotherapy (ipilimumab, dacarbazine and pembrolizumab) and treatment

	Median OS (95% CI), months		12-month OS rate, %		HR (95% CI)	P-value
	Tebentafusp	Investigator's Choice	Tebentafusp	Investigator's Choice		
Investigators choice of chemotherapy						
Dacarbazine (n=13, 7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab (n=199, 103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (n=40, 16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4 Subgroup Analysis of PFS by Pre-choice of chemotherapy (ipilimumab, dacarbazine and pembrolizumab) and treatment

	PFS events, n (%) Progressive disease	Median PFS (95% CI), months	Kaplan-Meier estimates for PFS (95% CI) [No.at risk]	HR (95% CI)

	Tebentafusp	Investigator's Choice	Tebentafusp	Investigator's Choice	Tebentafusp	Investigator's Choice	
Investigator's choice of chemotherapy							
Dacarbazine (n=13, 7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab(n=199, 103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (n=40, 16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B5. Priority question. Although the IMCgp100-202 Phase III clinical trial is ongoing, patient enrolment was between March 2017 through to June 2020 with three United Kingdom (UK) study sites being reported in Table 5 of the CS.

a. **Please summarise, tabulate, and discuss the baseline and demographic characteristics of enrolled patients.**

Demographics and baseline characteristics were generally well balanced between the two treatment arms (Table 5). Overall, the majority of patients were white (87.0%) and approximately half were female (49.2%), with a median age of 64.0 years (range, 23 to 92 years). Approximately half of the patients were ≥ 65 years of age. Nearly two-thirds of patients were from the non-North American region (63.5%). By country, most patients were enrolled in the US (31.7%) and Germany (15.6%). The vast majority of patients (94.5%) had an ECOG performance status score of 0 or 1 at baseline.

Table 5 Demographics and baseline characteristics study IMC100gp-202

Characteristic	Tebentafusp(N=252)	Investigator'sChoice (N=126)	Overall (N=378)
Age, years			
n	252	126	378
Mean (Std)	61.3 (11.9)	63.6 (10.7)	62.1 (11.6)
Median (Min, Max)	63.5 (23, 92)	65.5 (25, 88)	64.0 (23, 92)
Age group, n (%)			
<65	130 (51.6)	61 (48.4)	191 (50.5)
≥65	122 (48.4)	65 (51.6)	187 (49.5)
Gender, n (%)			
Female	124 (49.2)	64 (50.8)	188 (49.7)
Male	128 (50.8)	62 (49.2)	190 (50.3)
Race, n (%)			

American Indian/Alaska Native	0	1 (0.8)	1 (0.3)
White	222 (88.1)	107 (84.9)	329 (87.0)
Not reported	23 (9.1)	14 (11.1)	37 (9.8)
Not allowed as per local regulatory	5 (2.0)	3 (2.4)	8 (2.1)
Unknown	1 (0.4)	1 (0.8)	2 (0.5)
Other	1 (0.4)	0	1 (0.3)
Ethnicity, n (%)			
Hispanic or Latino	3 (1.2)	6 (4.8)	9 (2.4)
Not Hispanic or Latino	217 (86.1)	102 (81.0)	319 (84.4)
Not reported	29 (11.5)	16 (12.7)	45 (11.9)
Unknown	3 (1.2)	2 (1.6)	5 (1.3)
ECOG performance status, n (%)			
0	192 (76.2)	85 (67.5)	277 (73.3)
1	49 (19.4)	31 (24.6)	80 (21.2)
2	0	1 (0.8)	1 (0.3)
Missing	11 (4.4)	9 (7.1)	20 (5.3)

(Adapted from Clinical study report, Table 12 (Immunocore, 2021)

Baseline Disease Characteristics

Baseline disease characteristics were generally well balanced between the 2 treatment arms and representative of a first-line metastatic UM population Table 6. For most patients, the choroid was the initial UM site (75.7%) and metastasis was not observed at initial diagnosis (92.3%).Approximately one-third of patients had LDH > ULN 250 U/L (36.0%), a poor prognostic factor for advanced UM, and more than half of the patients' largest metastatic lesion recorded at baseline was ≤ 3 cm (55.3%). For the majority of patients (79.9%), the pre- randomization choice of therapy was pembrolizumab. Most patients did not receive prior surgery for metastatic disease (91.3%).

Table 6 Baseline Disease Characteristics IMC100gp-202 (ITT Analysis Set)

Characteristic	Tebentafusp(N=252)	Investigator 'sChoice (N=126)	Overall (N=378)
Site of initial uveal melanoma, n (%)			
Iris	3 (1.2)	5 (4.0)	8 (2.1)
Ciliary body	25 (9.9)	13 (10.3)	38 (10.1)
Choroid	193 (76.6)	93 (73.8)	286 (75.7)
Unknown	30 (11.9)	14 (11.1)	44 (11.6)
Missing	1 (0.4)	1 (0.8)	2 (0.5)

Stage of initial diagnosis, n (%)			
I	48 (19.0)	14 (11.1)	62 (16.4)
II	89 (35.3)	40 (31.7)	129 (34.1)
III	56 (22.2)	34 (27.0)	90 (23.8)
IV	23 (9.1)	7 (5.6)	30 (7.9)
Missing	36 (14.3)	31 (24.6)	67 (17.7)
Was metastasis observed at initialdiagnosis, n (%)			
Yes	17 (6.7)	10 (7.9)	27 (7.1)
No	234 (92.9)	115 (91.3)	349 (92.3)
Missing	1 (0.4)	1 (0.8)	2 (0.5)
Baseline LDH, U/L [a]			
n	234	117	351
Mean (Std)	361.9 (476.2)	281.2 (187.5)	335.0 (405.1)
Median (Min, Max)	207.0 (119, 5572)	204.0 (133, 1199)	207.0 (119, 5572)
Randomization stratum, n (%)			
LDH ≤ULN 250 U/L	162 (64.3)	80 (63.5)	242 (64.0)
LDH >ULN 250 U/L	90 (35.7)	46 (36.5)	136 (36.0)
Largest metastatic lesion at baseline, n(%)			
≤3 cm	139 (55.2)	70 (55.6)	209 (55.3)
3.1-8.0 cm	92 (36.5)	46 (36.5)	138 (36.5)
≥8.1 cm	21 (8.3)	10 (7.9)	31 (8.2)
Pre-randomization choice of treatment,n (%)			
Pembrolizumab	199 (79.0)	103 (81.7)	302 (79.9)
Ipilimumab	40 (15.9)	16 (12.7)	56 (14.8)
Dacarbazine	13 (5.2)	7 (5.6)	20 (5.3)
Prior surgery for metastatic disease [b]			
Yes	24 (9.5)	9 (7.1)	33 (8.7)
No	228 (90.5)	117 (92.9)	345 (91.3)

ITT = Intent-to-treat; LDH = lactate dehydrogenase; Max = maximum; Min = minimum; Std = standard deviation; ULN = upper limit of normal.

[a] LDH value is based on central laboratory.

[b] Prior surgery for metastatic disease is based on a medical review.

a. Please provide the number of UK patients randomised and provide the baseline characteristics of these patients by study arm.

In total 33 patients were enrolled in the RCT study IMC100gp-202, 26 patients were randomised to tebentafusp and seven patients were randomised to investigators choice. For comparison Table 7 and Table 8 provide the demographics and baseline disease characteristics of the UK patients by study arm.

Table 7 Demographics and baseline characteristics study IMC100gp-202 (UK patients)

Patients in United Kingdom	Tebentafusp (N=26)	Investigator's Choice (N=7)	Overall (N=33)
Age, years			
n	26	7	33
Mean (Std)	70.0 (12.7)	62.9 (6.8)	61.4 ()
Median (Min, Max)	66.5 (24, 76)	64 (56, 72)	65 (24, 76)
Age group, n (%)			
<65	11 (42.3)	5 (71.4)	16 (48.5
≥65	15 (57.7)	2 (28.6)	17 (52.5)
Gender, n (%)			
Female	14 (53.9)	3(42.9)	17 (52.5)
Male	12 (46.1)	4 (57.1)	16 (48.5)
Race, n (%)			
White	24 (92.3)	7 (100)	31 (93.9)
Unknown/Not reported	2 (7.7)	0	2 (6.1)
Ethnicity, n (%)			
Not Hispanic or Latino	24 (92.3)	7 (100)	31 (93.9)
Unknown	2 (7.7)	0	2 (6.1)
ECOG performance status, n (%)			
0	19 (73)	7 (100)	26 (78.8)
1	7 (26.9)	0	7 (21.1)

Table 8 Baseline Disease Characteristics IMC100gp-202 (UK patients)

Characteristic	Tebentafusp (N=26)	Investigator's Choice (N=7)	Overall (N=33)
Site of initial uveal melanoma, n (%)			
Iris	0	1 (14.3)	1 (3.0)
Ciliary body	5 (19.2)	3 (42.9)	8 (24.2)
Choroid	21 (80.8)	3 (42.9)	24 (72.7)
Stage of initial diagnosis, n (%)			
I	2 (7.7)	0	2 (6.1)
II	9 (34.6)	0	9 (27.3)
III	13 (50.0)	4 (57.1)	17 (51.5)
IV	1 (3.9)	1 (14.3)	2 (6.1)
Missing	1 (3.9)	2 (28.6)	3 (9.1)
Was metastasis observed at initial diagnosis, n (%)			
Yes	1 (3.85)	1 (14.3)	2 (6.1)
No	25 (96.2)	6 (85.7)	31 (93.9)
Baseline LDH, U/L[a]			
n	23	7	30
Mean (Std)	270.0 (113.6)	242.7 (88.0)	263.7 (107.3)
Median (Min, Max)	224 (125, 552)	214 (158, 405)	219 (125, 552)
Randomization stratum, n (%)			
LDH ≤ULN 250 U/L	14 (53.9)	5 (71.4)	19 (57.6)
LDH >ULN 250 U/L	12 (46.2)	2 (28.6)	14 (42.4)
Largest metastatic lesion at baseline, n (%)			
≤3 cm	15 (57.7)	4 (57.1)	19 (57.6)
3.1-8.0 cm	10 (34.5)	3 (42.9)	13 (39.4)
≥8.1 cm	1 (3.8)	0	1 (3.0)
Pre-randomization choice of treatment, n (%)			
Pembrolizumab	11 (42.3)	4 (57.1)	15 (45.5)
Ipilimumab	15 (57.7)	3 (42.9)	18 (54.6)
Dacarbazine	0	0	
Prior surgery for metastatic disease[b]			
Yes	18 (69.2)	5 (71.4)	23 (69.7)
No	8 (30.8)	2 (28.6)	10 (30.3)

ITT = Intent-to-treat; LDH = lactate dehydrogenase; Max = maximum; Min = minimum; Std = standard deviation;ULN = upper limit of normal.

[a] LDH value is based on central laboratory.

[b] Prior surgery for metastatic disease is based on a medical review.

b. Please elaborate on the generalisability of the study baseline characteristics (age, gender, bodyweight, clinical characteristics etc) to the general UK population and also whether these are consistent with UK clinical practice. If possible, supporting evidence should be provided.

The study baseline characteristics were considered to be broadly reflective of the UK metastatic UM patient population following an advisory board consultation with three UK clinical specialists in metastatic UM. Small differences were noted that were felt to be typical of clinical trial populations such as patients with slightly better overall health and a younger mean age range.

c. Is the trial comparator (investigator choice) consistent with UK clinical practice and is chemotherapy only (dacarbazine) a potential comparator (in UK clinical practice) as per scope? Please provide supporting evidence.

The trial comparator of investigators choice was similar to UK practise; 73% of patients are treated with an immunotherapy as the first line treatment (based on a survey of six clinicians treating a total of 43 patients). This is most commonly pembrolizumab or ipilimumab plus nivolumab combination therapy (which has become more common in recent years, subsequent to the start of the tebentafusp clinical trial). An advisory board with UK metastatic UM clinical specialists noted that there was no evidence that ipilimumab plus nivolumab combination therapy is more efficacious than either as a single agent or pembrolizumab alone. However, due to the absence of any alternative and the approval of these treatments for metastatic melanoma generically, there are no other options for these patients who have dismal prospective survival outcomes. Chemotherapy alone is rarely employed in metastatic UM, and amongst six UM specialised clinicians consulted, chemotherapy was not reported as a treatment they use in metastatic UM.

d. Are the subsequent treatments provided in the trial as well as the case mix consistent with UK clinical practice (see CS Table 73)?

The subsequent treatments in the trial are mostly immunotherapies, which is broadly reflective of UK clinical practise and this is due to the NICE guidelines on checkpoint inhibitors for Stage III and Stage IV melanoma, despite the lack of evidence of survival benefit in metastatic UM. However unlike the trial, combination immunotherapies (e.g., ipilimumab plus nivolumab) seems to be less common than

single agent (clinician opinion). Chemotherapy is not frequently used in the UK for metastatic UM.

e. Please provide full details on the processes used to implement randomisation and allocation concealment.

A randomization ratio of 2:1 was implemented in the study design. The randomization in this study was intended to prevent bias in the choice of treatment assignment. Given the distinct toxicity patterns at the first infusion of the agents being studied (tebentafusp versus Investigator's Choice), the open-label design was chosen because the treatment assignment cannot be blinded. The Independent Data Monitoring Committee (IDMC) also recommended to unblind the study, necessary because of the distinct toxicity patterns of the therapies. The preferred Investigator's Choice agent was selected prior to randomisation. During the conduct of the study, a trial integrity document dictated that study personnel within Immunocore were not permitted to look at the data by treatment group in aggregate. The acceptance of that recommendation by the sponsor allowed Immunocore to produce the unblinded outputs and conduct additional analyses.

f. While it is understood that the study primary completion date was October 2021, with a final study completion date estimated to be March 2023, please provide (if available) the full data and details of the analysis completed to date. Alternatively, please give an indication on when more data will be available.

Full data and details of the analysis completed to date was provided in the CS. The completion of the study is event driven, the next data cut will be upon 80 events and it is not possible to determine precisely when this will be. Our best estimate is the next planned data cut (Interim Analysis 2) will be during second half of 2022.

B6. Table 15 of the CS provides an overview of treatment- emergent adverse events occurring in ≥20% patients in study IMCgp100-202. There are clear differences between the arms in multiple listed adverse reactions. Please provide the following:

a. Justification for the initial application of a 20% threshold for reporting of this data rather than a lower threshold of 5 or 10%.

The additional data provided in the Clinical Study Report attachment to the CS reports TRAEs at a threshold of ≥10%:

Table 9 Treatment-emergent Adverse Events by System Organ Class and Preferred Term Occurring in ≥10% of Patients in Either Treatment Arm (Safety Analysis Set)

System Organ Class Preferred Term	Tebentafus p(N=245)		Investigator's Choice (N=111)	
	n (%)	EAIR (per 100 PY) [a]	n (%)	EAIR (per 100 PY) [a]
Respiratory, thoracic and mediastinal disorders	**93 (38.0)**	**76.5**	**23 (20.7)**	**49.2**
Cough	44 (18.0)	28.5	11 (9.9)	22.1
Dyspnoea	32 (13.1)	19.4	7 (6.3)	13.2
Gastrointestinal disorders	**194 (79.2)**	**333.3**	**66 (59.5)**	**244.6**
Nausea	120 (49.0)	114.2	29 (26.1)	68.6
Vomiting	73 (29.8)	54.6	10 (9.0)	19.2
Diarrhoea	61 (24.9)	42.7	22 (19.8)	49.7
Abdominal pain	60 (24.5)	40.0	17 (15.3)	34.0
Abdominal pain upper	50 (20.4)	31.5	14 (12.6)	28.1
Constipation	44 (18.0)	26.8	13 (11.7)	26.7
Hepatobiliary disorders	**51 (20.8)**	**32.1**	**17 (15.3)**	**32.9**
Hyperbilirubinaemia	28 (11.4)	16.4	8 (7.2)	15.0
Skin and subcutaneous tissue disorders	**229 (93.5)**	**2141.9**	**51 (45.9)**	**160.4**
Pruritus	169 (69.0)	323.8	26 (23.4)	60.9
Rash	135 (55.1)	176.6	18 (16.2)	37.1
Dry skin	77 (31.4)	59.1	4 (3.6)	7.8
Rash maculo-papular	75 (30.6)	59.9	9 (8.1)	17.6
Erythema	60 (24.5)	42.4	1 (0.9)	1.8
Skin exfoliation	51 (20.8)	34.0	2 (1.8)	3.7
Hair colour changes	48 (19.6)	31.5	0	0
Vitiligo	40 (16.3)	25.8	4 (3.6)	7.7
Musculoskeletal and connective tissue disorders	**116 (47.3)**	**108.2**	**35 (31.5)**	**98.3**
Arthralgia	53 (21.6)	34.8	18 (16.2)	41.1
Back pain	45 (18.4)	28.8	9 (8.1)	18.0
General disorders and administration site conditions	**231 (94.3)**	**1939.6**	**56 (50.5)**	**172.3**
Pyrexia	187 (76.3)	387.7	8 (7.2)	15.2
Fatigue	125 (51.0)	124.4	39 (35.1)	101.4
Chills	117 (47.8)	113.3	4 (3.6)	7.6
Oedema peripheral	66 (26.9)	45.6	3 (2.7)	5.6
Asthenia	38 (15.5)	23.2	9 (8.1)	17.7
Face oedema	25 (10.2)	15.1	2 (1.8)	3.7
Investigations [c]	**132 (53.9)**	**137.9**	**37 (33.3)**	**87.2**

AST increased	56 (22.9)	36.6	11 (9.9)	21.4
ALT increased	51 (20.8)	33.4	12 (10.8)	23.5
Lipase increased	35 (14.3)	21.7	7 (6.3)	13.4

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ASTCT = American Society for Transplantation andCellular Therapy; CRS = cytokine release syndrome; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-years; SOC = system organ class; TEAE = treatment-emergent adverse event.
Patients with multiple TEAEs are counted once for each system organ class/preferred term.
Includes TEAEs with an onset date on or after the date of first dose or pre-treatment TEAEs that increase in severity on or after the date of first dose up to an including 90 days following the date of last dose of study drug or up to an includingthe date of initiation of the first subsequent therapy (whichever occurs first).
MedDRA v23.1.

[a] EAIR is defined as the number of patients with the event divided by the total exposure time of all patients who are at risk of the event. For patients with no reported event, the exposure is the time from the date of first dose of study druguntil 90 days after the last dose of stud drug or until the start of subsequent anticancer therapy, whichever occurs first.For patients who experience the event, the exposure time is the time from the date of first dose of study drug to the start date of the first event.

[b] As reported by the investigator based on Lee, 2014 criteria. Refer to Section 12.2.3.4.1 (CSR) for Sponsor-adjudicated CRSbased on the more comprehensive 2019 ASTCT consensus grading for CRS (Lee, 2019).

[c] This SOC includes laboratory abnormalities reported as adverse events by the investigator and does not reflect alllaboratory abnormalities reported in the study. Refer to Section 12.4.2 (CSR) for a detailed presented of laboratory abnormalities, including liver enzyme abnormalities (Section 12.4.2.2.1- CSR).

Source: Table 14.3.1.2. (Tables CSR- attachment to CS))

a. The reproduced table containing this data adjusted for occurrences in ≥5% patients.

Table 10 Adverse reactions reported in ≥5% of patients treated with IMCgp100 or IC at any grade in study IMCgp100-202 Safety Population

	IMCgp100-202 Number (%) of Patients (N=245)		Investigators Choice Number (%) of Patients (N=111)	
System Organ Class Preferred Term	**Any Grade**	**>=Grade 3**	**Any Grade**	**>=Grade 3**
Number of patients with any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated Cytokine Release Syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Rash[1]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue[4]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]
Melanocyte-related AE[2]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain[3]	[redacted]	[redacted]	[redacted]	[redacted]
Edema[5]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine release syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]

Constipation				
Cough				
Hypertension				
Dyspnoea				
Hyperbilirubinaemia				
Dizziness				
Hypophosphataemia				
Paraesthesia				
Anaemia				
Flushing				
Lymphopenia				
Myalgia				
Pain in extremity				
Tachycardia				
Insomnia				
Alopecia				
Dyspepsia				
Nasopharyngitis				
Hypomagnesaemia				
Hypokalaemia				
Influenza like illness				
Oropharyngeal pain				
Muscle spasms				
Urinary tract infection				
Anxiety				
Night sweats				

1 Blister, Dermatitis, Dermatitis acneiform, Dermatitis allergic, Dermatitis bullous, Dermatitis contact, Dermatosis, Drug eruption, Eczema, Eczema eyelids, Erythema multiforme, Exfoliative rash, Interstitial granulomatous dermatitis, Lichenification, Lichenoid keratosis, Palmar-plantar erythrodysaesthesia syndrome, Papule, Psoriasis, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash vesicular, Seborrhoea, Seborrhoeic dermatitis, Skin abrasion, Skin erosion, Skin exfoliation, Skin irritation, Skin plaque, Solar dermatitis, Toxic skin eruption, Urticaria

2 Achromotrichia acquired, Ephelides, Eyelash discolouration, Eyelash hypopigmentation, Hair colour changes, Lentigo, Pigmentation disorder, Retinal depigmentation, Skin depigmentation, Skin discolouration, Skin hyperpigmentation, Skin hypopigmentation, Solar lentigo, Vitiligo

3 Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, Flank pain, Gastrointestinal pain, Hepatic pain

4 Asthenia, Fatigue

5 Eye oedema, Eye swelling, Eyelid oedema, Face oedema, Generalised oedema, Lip oedema, Lip swelling, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema, Periorbital swelling, Peripheral swelling, Pharyngeal oedema, Swelling, Swelling face, Swelling of eyelid

B7. Is there post-progression treatment with immunotherapy (pembrolizumab or Ipilimumab) in the trial?

There was post-progression treatment for patients on immunotherapies (pembrolizumab or ipilimumab) and tebentafusp, which is also an immunotherapy.

Criteria for Treatment Beyond Initial RECIST v1.1 Disease Progression as detailed in the clinical trial protocol, (Immunocore, 2018):

Clinical evidence suggests that a minority of patients treated with immunotherapies, including tebentafusp, will derive clinical benefit after an initial assessment of PD. For patients in arm 1 (tebentafusp) and arm 2 (receiving pembrolizumab or ipilimumab), if initial PD based on RECIST v1.1 occurs, treatment may continue according to the protocol-specified regimen provided ALL of the following criteria continue to be met:

• Absence of signs or symptoms indicating clinically significant PD

• No decline in ECOG performance status

• No impending threat to vital organs/critical anatomical sites (eg, spinal cord compression, liver function decline) requiring urgent alternative medical intervention or where continuation of study therapy would prevent institution of such intervention

• Absence of any of the investigational product discontinuation criteria

In accordance with the clinical trial protocol patients assigned to tebentafusp, ipilimumab, or pembrolizumab who are treated beyond initial RECIST v1.1 PD must permanently discontinue study treatment if they experience further progression warranting treatment discontinuation. Further progression warranting treatment discontinuation is defined as ANY one of the following observed at least 4 weeks after the initial PD assessment per RECIST v1.1: 1) an additional ≥ 20% increase in tumour burden (sum of diameters of both target and new measurable lesions) accompanied by an absolute increase of ≥ 5 mm; 2) unequivocal PD of non-target lesions; or 3) new non-measurable lesions.

B8. In the trial progression-free survival is measured using RECIST; does this account for pseudo progression given the comparator includes immunotherapy?

The use of PFS assessment per RECIST v1.1 was applied to both treatment arms. As detailed above, patients were allowed to continue on treatment beyond initial RECIST v1.1 disease progression. Tebentafusp is also an immunotherapy and data on file indicates it is subject to a similar likelihood of demonstrating pseudo progression as the immunotherapies in the comparator arm. Equal application of this measure across both treatment arms was considered an optimal approach for a commonly recognised subjective comparative measure of what is effectively a surrogate endpoint prior to OS outcomes being available. The Clinical Trial Protocol amendment 4 (March 2020) details the updated criteria for measurement of disease progression beyond RECIST v1.1 to determine continued disease progression and ensure patient safety.

Indirect comparisons

B9. Priority question. Please summarise and tabulate the details of the indirect treatment comparison (ITC) feasibility assessment for heterogeneity performed on the studies included in the clinical effectiveness SLR. Please include columns comparing the study designs, patient characteristics, dosing, interventions, comparators, and outcomes.

The systematic literature review identified two clinical trials reporting ipilimumab plus nivolumab (ipi+nivo) combination therapy on a population of metastatic UM patients only. The two potential comparator studies identified were: Piulats et al. (2021b) and Pelster et al. (2021a). Both are single arm studies of ipi+nivo in metastatic UM. A summary of key characteristics of these studies and study 202 (tebentafusp versus investigators choice) is provided in **Table 11**. Piulats was selected as the most appropriate comparison because:

- It comprises treatment-naive patients only, similar to the RCT for tebentafusp study IMCgp100-202. The study by Pelster et al. comprised a mixture of patients who had received prior-treatment or were treatment naïve patients (57%) and reported results for the mixed group.
- It has a larger population than Pelster
- It is based on multi-institution data (Pelster is single institution)
- It reports more of the key covariates to use in matching

Table 11: Study characteristics for ITC feasibility assessment

	Study 202, tebentafusp	Study 202, investigator's choice	Piulats 2021, ipi+nivo	Pelster 2021, ipi+nivo
N	252	126	52	35
% previously untreated	100%	100%	100%	57.1% (20/35)
Age, mean	61.3 yrs	63.6 yrs	Not reported	Not reported
Age, median	63.5 yrs	65.5 yrs	59.1 yrs	62 yrs
% female (n/N)	49.2% (124/252)	50.8% (64/126)	44.2% (23/52)	65.7% (23/35)
% normal LDH	64.3% (162/252)	63.5% (80/252)	62.8% (27/43)	57.1% (20/35)
% normal ALP	78.9% (198/251)	81.0% (102/126)	85.1% (40/47)	Not reported
% largest liver met ≤3cm	54.8% (138/252)	53.2% (67/126)	48.9% (23/47)	Not reported
% largest liver met >3cm	41.3% (104/252)	37.3% (47/126)	27.7% (13/47)	Not reported

% no liver metastases	4.0% (10/252)	9.5% (12/126)	23.4% (11/47)	Not reported
% Hepatic disease only	52.2% (131/251)	47.6% (59/124)	42.3% (22/52)	31.4% (11/35)
% Extrahepatic disease only	3.6% (9/251)	8.1% (10/124)	21.2% (11/52)	20.0% (7/35)
% Hepatic + extrahepatic disease	44.2% (111/251)	44.4% (55/124)	36.5% (19/52)	48.6% (17/35)
% ECOG 0	79.7% (192/241)	72.6% (85/117)	84.6% (44/52)	71.4% (25/35)
OS outcomes ipi+nivo			Median (95% CI) 12.7m (7.1-18.3) 12m rate 51.9% 24m rate 26.4%	Median (95% CI) 19.1m (9.6-NR) 12m rate 56.0%

B10. Priority question. Please provide a full technical report for the matching adjusted indirect comparison (MAIC) with justification for methods chosen and tests for validity in accordance with technical support document (TSD) 18.

As per B9, the Piulats et al. (2021) study was considered as the most appropriate comparator study. Since the Piulats study was a single-arm study, no anchored comparison was feasible and therefore only unanchored approaches were considered. Given that only aggregate data was available for the Piulats study, it was determined that an unanchored matching adjusted indirect comparison (MAIC) was the most appropriate approach to compare outcomes between Piulats and study 202. Using a MAIC allows a comparison of outcomes between the studies while adjusting for differences in key patient characteristics to reduce the bias of a naïve or unadjusted comparison. This is in accordance with the flow chart for selecting methods for indirect comparisons given in Appendix A of TSD 18.

To ensure the robustness of the analyses, populations were compared to ensure overlap, the intended approach for deriving the weights for matching, including the baseline covariates to be considered for the weight calculation were all prespecified and the balance between comparison groups with respect to important baseline covariates both before and after match-adjustment weighting, to determine whether the balance and effective sample size after making adjustments is adequate enough to move forward with the analyses were evaluated. All effect modifiers/prognostic variables were adjusted for in the analyses where possible in line with the assumptions of the MAIC approach and the recommendation in TSD 18. Time since

primary diagnosis could not be used in the matching since this was not reported in the Piulats study. No other important potential unmeasured effect modifiers/prognostic variables were identified. In addition, a simple unadjusted indirect comparison (UAIC) was also performed, to evaluate the impact of the match-adjustment.

B11. Priority question. The Piulats study was preferred to the Pelster study arbitrarily on the basis of four criteria (treatment experience, size, location, number of covariates for matching).

The criteria for study selection is not 'arbitrary'. Several of these factors are prognostic to OS in metastatic UM and important for the MAIC produced to provide a robust analysis.

- Treatment experience i.e. receiving prior treatment has two impacts (a) patients are at a later stage of disease progression if they are already on a second line of treatment which is especially important for disease with very short overall survival (12-15 months, Nathan et al. (2015)) (b) Published meta-analysis data clearly demonstrates a large difference in OS outcomes on a range of treatments employed for first line (1.07 years (≈13 months) (range: 0.59-2.50 years)) versus second line therapy (7.8 (range: 6.5, 9.7)) (Rantala et al., 2019).

- In accordance with clinical practise of monitoring tumour size and categorising by TNM staging, the size and location of liver metastases is a clinical prognostic factor which can impact OS outcomes therefore an important covariate for population matching in a MAIC.

Given the high risk of bias of any single MAIC, please conduct a MAIC using the Pelster study as well as MAICs of any other studies of nivolumab plus ipilimumab in metastatic uveal melanoma, including Heppt 2019 (J Immunother Cancer. 2019; 7: 299) and Najjar 2020 (J Immunother Cancer. 2020; 8(1): e000331).

As outlined above a MAIC on Pelster was not considered feasible due to the confounding factor of prior treatment. Najjar 2020 was a multicentre retrospective study that comprised a mixed group (43% of patients had received various prior

treatments). In contrast to the prospective study design of Piulats et al. (2021), the study by Heppt et al. (2019) was also a multicentre retrospective, observational study with comprise a mixed group of patients who were treatment naïve (78%) or received prior treatment. A MAIC analysis between Study IMC100gp-202 and either Pelster et al. or Heppt et al. was not considered to be feasible.

B12. Priority question. Please provide a MAIC where the investigator's choice as well as the tebentafusp data from the IMCgp100-102 trial are adjusted to match the nivolumab plus ipilimumab data.

*Update following clarification call on 2nd December, this question should have read: Please provide a MAIC where the investigator's choice as well as the tebentafusp data from the IMCgp100-**202** trial are adjusted to match the nivolumab plus ipilimumab data.*

A MAIC analysis is currently underway to provide the above request of a comparison on the investigator choice arm (pembrolizumab, ipilimumab or dacarbazine) of the IMCgp100-202 study versus the Piulats (2021) single arm study of ipilimumab plus nivolumab and will be provided on 16th December as agreed following consultation with NICE.

B13. Please discuss rationale for choice of outcome measure in the ITC.

Overall survival is the primary efficacy endpoint of the tebentafusp clinical trial and the most substantiated measure of efficacy for immunotherapeutic treatments in oncology, it is also the key driver of clinical effectiveness in the model. An alternative outcome commonly used in oncology is PFS, however many studies have shown that it is an ineffective efficacy measurement for immunotherapies – concurrent with the reference to pseudo progression issues for immunotherapies in an earlier question in this document. PFS is also a challenging outcome to compare across studies due to the semi-subjective nature of imaging analysis, difference in definition (e.g. RESIST v.1.1 and irRESIST), and also differences in timing of scans performed on patients. Furthermore, PFS is particularly problematic measure for combination treatments, as outlined in the publication by Gyawali and Prasad (2017) which uses ipilimumab plus nivolumab combination as as a specific example. In summary OS is the most consistent outcome measure across different studies on oncology therapies.

Section C: Clarification on cost-effectiveness data

Model structure

C1. The National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) TSD 19 recommended the use of state transition models (STMs) alongside partitioned survival models (PSMs) to verify the plausibility of PSM extrapolations and explore key clinical uncertainties in the extrapolation period.

a. Please justify the use of a PSM given the issues highlighted in NICE DSU TSD 19, particularly regarding the extrapolation of progression-free survival (PFS) and overall survival (OS) while assuming structural independence between these endpoints.

We acknowledge that the structural independence of endpoints is a limitation of partitioned survival models. However, as noted in TSD 19, “in the context of a within-trial analysis or a case in which data have been fully observed, PSM and state transition modelling approaches are expected to produce similar results if modelling and fitting have been done appropriately, as relationships between endpoints are reflected within the data.”

In the investigator’s choice arm, based on the October 2020 data cut-off, the Kaplan-Meier curve shows that only 6.2% of the patients are still progression-free and 10.2% alive at the end of the follow-up. Hence, most of the events have been observed, and there is limited uncertainty regarding the extrapolation. Regarding the OS, we have compared the results of the extrapolation analysis to data from the literature and validated the choice of model with clinical experts, and the results are well aligned with published clinical data, sections B.3.3.1 and B.3.10 of the submission dossier and question 4.e of the clarification questions. Hence, we consider that using a PSM or state-transition model would produce very similar results in the control arm.

In the tebentafusp arm, based on the October 2020 data cut-off, the Kaplan-Meier curve shows that 9.2% of the patients are still progression-free and 33.6% alive at the end of the survival follow-up. Based on the August 2021 data cut-off, the Kaplan-Meier curve shows that [redacted] of the patients are progression-free and [redacted] alive at the end of the survival follow-up. Most of the PFS events have been observed and there

is limited uncertainty regarding the extrapolation of the PFS endpoint. We note that the treatment effect size is larger for OS than for PFS, suggesting that PFS, defined as disease progression per RECIST v1.1 criteria, may be poorly correlated with OS. This has been documented for other types of immunotherapies like the checkpoint inhibitors, nivolumab and pembrolizumab (Gyawali and Prasad, 2017). Hence, the assumption of structural independence is likely to be less of a concern in this context. We consider appropriate to use a PSM for this decision problem.

b. Please use state transition modelling to assist in verifying the plausibility of the PSM extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11).

For the reasons outlined in C1.a, we consider that PSM is an appropriate model structure and that as the data are mature there would be very little difference between the two modelling approaches. Therefore, we considered that building a STM was not necessary.

Intervention and comparator

C2. Priority question. The final scope mentions the following treatments as comparators: pembrolizumab, ipilimumab, nivolumab alone or in combination with ipilimumab, dacarbazine, and best supportive care for people who have had previous treatments. In the CS the comparator reflects the control arm of the IMCgp100-202 trial, in which patients were treated with investigator's choice of immunotherapies (ipilimumab or pembrolizumab), or chemotherapy (dacarbazine).

a. Please provide a justification for not including nivolumab alone or in combination with ipilimumab, based on ITC, as a comparator in the economic model.

A MAIC was conducted to compare the efficacy of pembrolizumab, the main therapy in the investigator's choice arm, and ipilimumab in combination with nivolumab. The results are presented in section B2.9 of the CS and showed that there was no statistically significant difference in overall survival between pembrolizumab and ipilimumab + nivolumab. Additionally, based on clinical expert's opinion and as stated at the decision problem meeting, ipilimumab + nivolumab is less frequently

used in clinical practice in the UK, use of this combination therapy is employed in the absence of any available specific treatment options for patients with dismal life expectancy. The IC arm was considered appropriately representative of clinical practice in the UK. Therefore, we considered that the IC arm was the most relevant comparator for the decision problem and ipilimumab and nivolumab was not included as a comparator in the CEM. Nivolumab and pembrolizumab are PD-1 inhibitors, i.e., same class of drug, therefore nivolumab monotherapy is equivalent to pembrolizumab and therefore we considered unnecessary to include nivolumab as a comparator in the CEM.

b. **Please provide an updated economic model and scenario analyses including nivolumab alone or in combination with ipilimumab, based on indirect comparison, as a comparator in the economic model (also considering the response to clarification questions B9 to B13).**

The response to this question is related to B12 - A MAIC analysis is currently underway to provide the requested of a comparison on the investigator choice arm (pembrolizumab, ipilimumab or dacarbazine) of the IMCgp100-202 study versus the Piulats (2021) single arm study of ipilimumab plus nivolumab and will be provided on 16th December as agreed following consultation with NICE.

When the new MAIC analysis is available we will generate KM overlays to provide a comparison of tebentafusp, investigators choice and ipilimumab plus nivolumab. There is great similarity between the pembrolizumab arm (representing 82% of the control arm) and ipilimumab plus nivolumab demonstrated by the MAIC provided in CS. The overlay will enable inference of ipilimumab plus nivolumab on the CEM.

c. **Please provide a justification for using the treatment mix as observed in the IMCgp100-202 trial as comparator, instead of using the results of this trial stratified for investigator's choice of treatment enabling a fully incremental evaluation of the intervention, pembrolizumab, ipilimumab and dacarbazine.**

Using the treatment mix as the comparator in the model is aligned with the IMCgp100-202 study design (Immunocore, 2018). There are 126 patients enrolled in the control arm of the IMCgp100-202 trial of whom 103 (81.7%) were treated with pembrolizumab, 16 (12.7%) with ipilimumab, and seven (5.6%) with dacarbazine.

The sample size for ipilimumab and dacarbazine are very small, analysing the data separately would have been associated with high uncertainty. Rantala et al. (2019) and colleagues conducted a systematic review and meta-analysis of 78 studies (n=2494) in metastatic uveal melanoma. They reported hazard ratios for overall survival, based on Cox regression, for a range of treatment modalities compared to conventional chemotherapy. The hazard ratios ranged from 0.92 to 1.13 with confidence intervals overlapping, and p-value being significant for a very limited number of therapies. Based on these findings, they concluded that there was no clinically significant difference in OS by treatment modalities. Hence, we deem appropriate to use the treatment mix as the comparator in the model.

d. Please provide the results of a fully incremental analysis (and updated economic model used for this analysis) with all comparators listed in the scope (pembrolizumab, ipilimumab, nivolumab alone or in combination with ipilimumab, dacarbazine, and best supportive care for people who have had previous treatments) as comparators modelled separately.

As discussed in question 2.d, it was not possible to analyse the data separately by treatment modality in the investigator's choice arm. However, for illustration purposes, we present here the results of an incremental analysis where the drug acquisition costs in the IC arm are modelled only based on the costs of pembrolizumab, ipilimumab or dacarbazine. The results are presented in Table 12.

Pembrolizumab is dominated by dacarbazine. By extended dominance, Ipilimumab and investigator's choice are ruled out, as tebentafusp can provide additional QALYs at lower costs. After dominance rules have been applied, the ICER for adopting tebentafusp, compared to dacarbazine is [redacted]. However, as noted in the NICE scope, people with advanced (unresectable or metastatic) uveal melanoma are usually offered immunotherapy and people for whom immunotherapy is not suitable may have dacarbazine chemotherapy or best supportive care. Hence, we consider that dacarbazine is not the most relevant comparator for this decision problem. If deviating from the comparison against the investigator's choice, which based on clinical expert's opinion is representative of UK clinical practice, we believe that a comparison against pembrolizumab or ipilimumab would be more aligned with the

"true" ICER. We present in Table 13 the ICER for tebentafusp versus each of the individual comparators.

Table 12. Full incremental analysis results

Comparators	Costs	QALYs	ICER
Dominance			
Tebentafusp	[redacted]	[redacted]	
Investigator's choice	[redacted]	[redacted]	
Pembrolizumab	[redacted]	[redacted]	
Ipilimumab	[redacted]	[redacted]	
Dacarbazine	[redacted]	[redacted]	
Extended-dominance			
Tebentafusp	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]
Investigator's choice	[redacted]	[redacted]	[redacted]
Dacarbazine	[redacted]	[redacted]	NA
Results after dominance rules applied			
Tebentafusp	[redacted]	[redacted]	£[redacted]
Dacarbazine	[redacted]	[redacted]	NA
Note: These results are based on the base-case. Ipilimumab + nivolumab post-tebentafusp was received by ~55% of patients. However, use of Ipilimumab + nivolumab in UK is less common as explained by clinical experts at the decision problem meeting.			

Table 13. ICER Tebentafusp vs. each comparator

	Tebentafusp vs. 202 control arm	Tebentafusp vs. Pembrolizumab	Tebentafusp vs. Ipilimumab	Tebentafusp vs. Dacarbazine
ICER (QALYs)	**£**[redacted]	**£**[redacted]	**£**[redacted]	**£**[redacted]
ICER (LYs)	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Δ Costs	[redacted]	[redacted]	[redacted]	[redacted]
Δ QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Δ LYs	[redacted]	[redacted]	[redacted]	[redacted]

Figure 2. Cost-effectiveness plane

[redacted]

C3. It is stated that the mix of treatments that constitutes the control arm of the IMCgp100-202 trial as well as the subsequent treatments used in the model reflect UK clinical practice according to consulted experts.

Please provide a full description of the methods and results of the expert consultation conducted to inform these model assumption and inputs.

An advisory board was conducted and three clinical experts on metastatic uveal melanoma provided feedback on current UK clinical practise. In the absence of approved systemic treatment options specifically for metastatic UM, treatments can vary, but the experts agreed that the control arm in the trial was broadly reflective of UK clinical practice. Chemotherapy alone is rarely employed in metastatic UM in the UK.

Effectiveness

C4. Priority question. The estimation of parametric survival models seems inconsistent with reported guidance from NICE DSU TSD 14 and 21 on (flexible methods for) survival analyses. Please provide, for OS, PFS and time to treatment discontinuation (TTD) separately for the intervention and comparator:

a. **Tables with the numbers of patients at risk, per 3 months.**

The requested figures are presented below.

Figure 3. Kaplan-Meier curve OS ITT set for both data cut-offs (a) October 2020; (b) August 2021

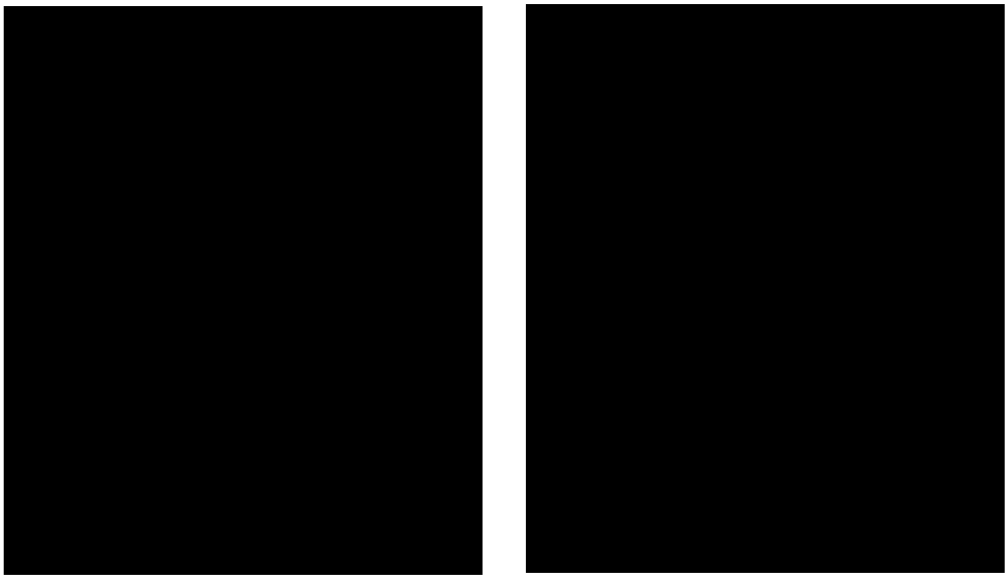


Figure 4. Kaplan-Meier curve PFS ITT set for both cut-offs (a) October 2020; (b) August 2021

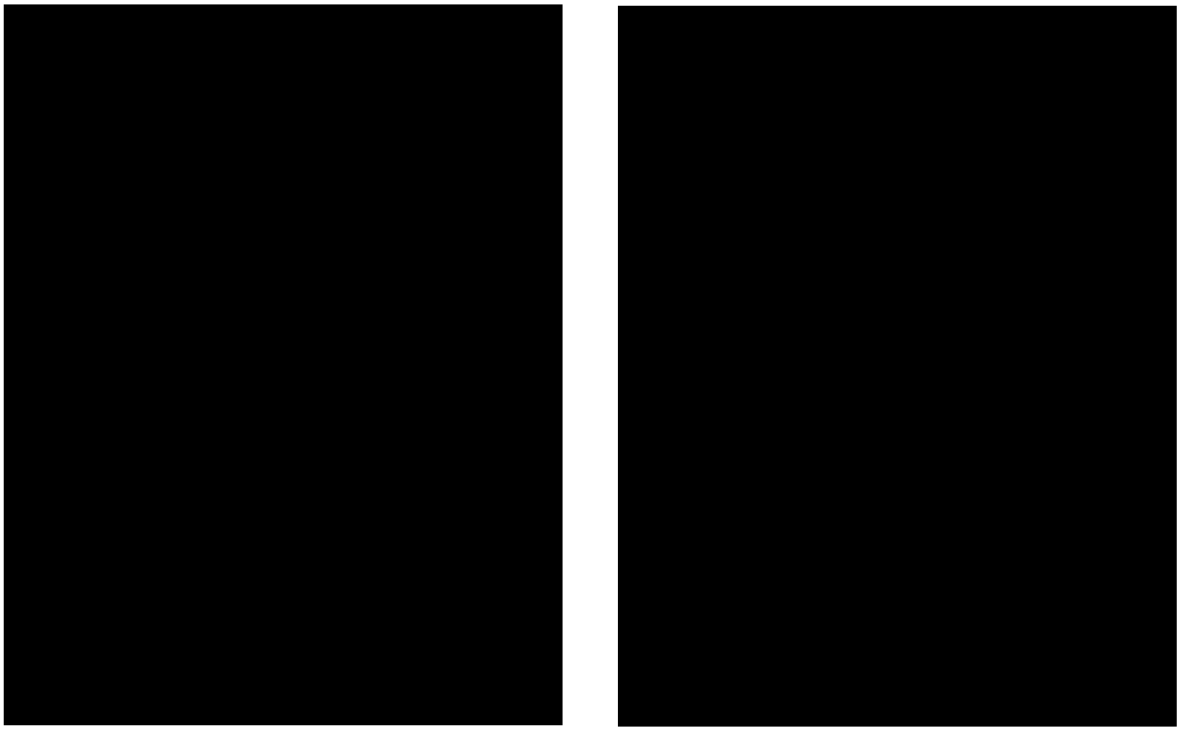


Figure 5. Kaplan-Meier curve TTD ITT set for both data cut-offs (a) October 2020; (b) August 2021

Figure 6. Kaplan-Meier curve OS subgroup tumour ≤30mm for both data cut-offs (a) October 2020; (b) August 2021

Figure 7. Kaplan-Meier curve PFS subgroup tumour ≤30mm for both data cut-offs (a) October 2020; (b) August 2021

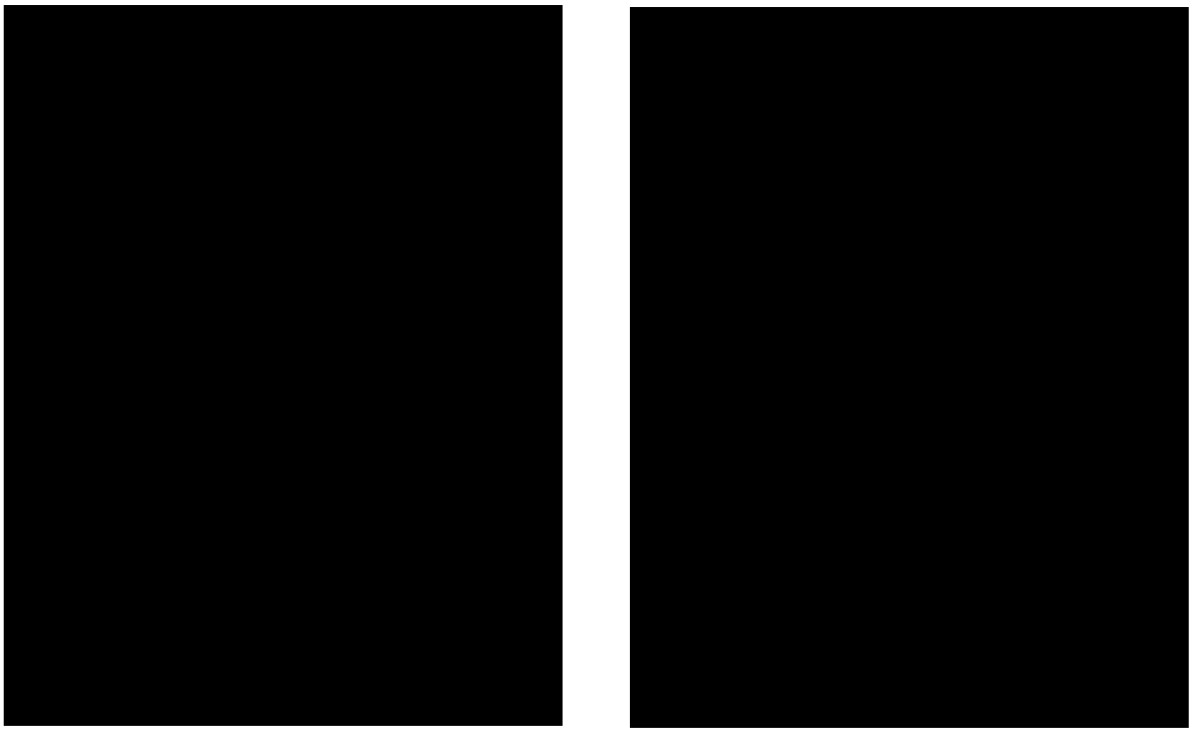


Figure 8. Kaplan-Meier curve TTD subgroup tumour ≤30mm for both data cut-offs (a) October 2020; (b) August 2021

b. To examine the proportional hazard assumption:

a. Plot the scaled Schoenfeld residuals versus time (all survival curves)

b. Plot the log cumulative hazard versus log time

Figure 9. Visual assessment of the proportional hazard assumption for overall survival: intent-to-treat set, data cut-off October 2020. (a) log-log plot; (b) Schoenfeld residuals plot

Figure 10. Visual assessment of the proportional hazard assumption for overall survival intent-to-treat set, data cut-off August 2021. (a) log-log plot; (b) Schoenfeld residuals plot

Figure 11. Visual assessment of the proportional hazard assumption for progression-free survival intent-to-treat set, data cut-off October 2020. (a) log-log plot; (b) Schoenfeld residuals plot

Figure 12. Visual assessment of the proportional hazard assumption for progression-free survival intent-to-treat set, data cut-off August 2021. (a) log-log plot; (b) Schoenfeld residuals plot

Figure 13. Visual assessment of the proportional hazard assumption for time to treatment discontinuation intent-to-treat set, data cut-off October 2020. (a) log-log plot; (b) Schoenfeld residuals plot

Figure 14. Visual assessment of the proportional hazard assumption for time to treatment discontinuation intent-to-treat set, data cut-off August 2021. (a) log-log plot; (b) Schoenfeld residuals plot

c. **To examine the heuristics of the hazard function over time:**

    a. **Plot the smoothed hazards over time**

Figure 15. Smoothed hazard overall survival ITT set. (a) October 2020 DCO; (b) August 2021 DCO

Figure 16. Smoothed hazard progression-free survival ITT set. (a) October 2020 DCO; (b) August 2021 DCO

Figure 17. Smoothed hazard time-to-treatment discontinuation ITT set. (a) October 2020 DCO; (b) August 2021 DCO

d. To examine diagnostics of parametric survival models (using the observed data):

a. Plot the cumulative hazard versus time

Figure 18. Cumulative hazard overall survival ITT set. (a) October 2020 DCO; (b) August 2021 DCO

Figure 19. Cumulative hazard progression-free survival ITT set. (a) October 2020 DCO; (b) August 2021 DCO

Figure 20. Cumulative hazard time-to-treatment discontinuation ITT set. (a) October 2020 DCO; (b) August 2021 DCO

b. Plot the log smoothed hazard versus time

Figure 21. Log smoothed hazard overall survival ITT set. (a) October 2020 DCO; (b) August 2021 DCO

Figure 22. Log smoothed hazard progressin-free survival ITT set. (a) October 2020 DCO; (b) August 2021 DCO

Figure 23. Log smoothed hazard time-to-treatment discontinuation ITT set. (a) October 2020 DCO; (b) August 2021 DCO

c. Plot the standard normal quartiles versus log time

Figure 24. Standard normal quartiles overall survival ITT set. (a) October 2020 DCO; (b) August 2021 DCO

Figure 25. Standard normal quartiles progression-free survival ITT set. (a) October 2020 DCO; (b) August 2021 DCO

Figure 26. Standard normal quartiles time-to-treatment discontinuation ITT set. (a) October 2020 DCO; (b) August 2021 DCO

d. Plot the log survival odds versus log time

Figure 27. Log survival odds overall survival ITT set. (a) October 2020 DCO; (b) August 2021 DCO

Figure 28. Log survival odds progression-free survival ITT set. (a) October 2020 DCO; (b) August 2021 DCO

Figure 29. Log survival odds time-to-treatment discontinuation ITT set. (a) October 2020 DCO; (b) August 2021 DCO

e. **To examine the validity of the extrapolation beyond the data, please provide supporting evidence that the extrapolations are consistent with relevant external data and/or expert opinion. In case of expert opinion, please provide a full description of the methods and results of the expert consultation conducted.**

Results of the extrapolation analysis for the investigator's choice arm were compared to data from the literature in sections B.3.3.1 and B.3.10 of the submission and also validated by clinical experts.

Rantala and colleagues conducted a systematic review and meta-analysis of 78 studies (n=2494) in metastatic uveal melanoma. They pooled data for 510 first-line patients and reported Kaplan Meier graphs. These patients were treated with conventional chemotherapy, chemoimmunotherapy, hepatic intra-arterial chemotherapy and transarterial chemoembolization. We appreciate that these interventions differ from the investigator's choice arm of the IMCgp100-202 trial. However, given that Rantala and colleagues found no clinically significant difference in OS by treatment modality, and that no therapy demonstrated a significant improvement in OS in the last 40 years (Yang et al., 2018, Khoja et al., 2019), we believe that the data reported by Rantala and colleagues on first-line patients is the most appropriate benchmark available for comparison against the IC arm of study IMCgp100-202.

The Kaplan Meier curve reported in Rantala et al., constructed using data from studies which only included first-line patients (Supplemental digital content 4, B. Overall survival by percentage of first line treatments – 100%; green line) was digitised using WebPlotDigitizer, to reconstruct the patient-level data and plot against the data from the IMCgp100-202 for comparison. Figure 30 presents the data reported by Rantala and colleagues (Rantala et al., 2019) against the Kaplan Meier curve for the IC arm and standard parametric models based on the October 2020 data cut-off. The Weibull and generalised gamma models provide very good fits to both the trial data and the data from Rantala.

Additionally, we presented in Table 14 overall survival data at 12 months and 24 months from the IMCgp100-202 trial, extrapolation analysis results for the Weibull and generalised gamma models compared to data from three published study, including the meta-analysis conducted by Rantala and colleagues. We observed that the results of the extrapolation analysis are aligned with the study IMCgp100-202 data and the data from the literature.

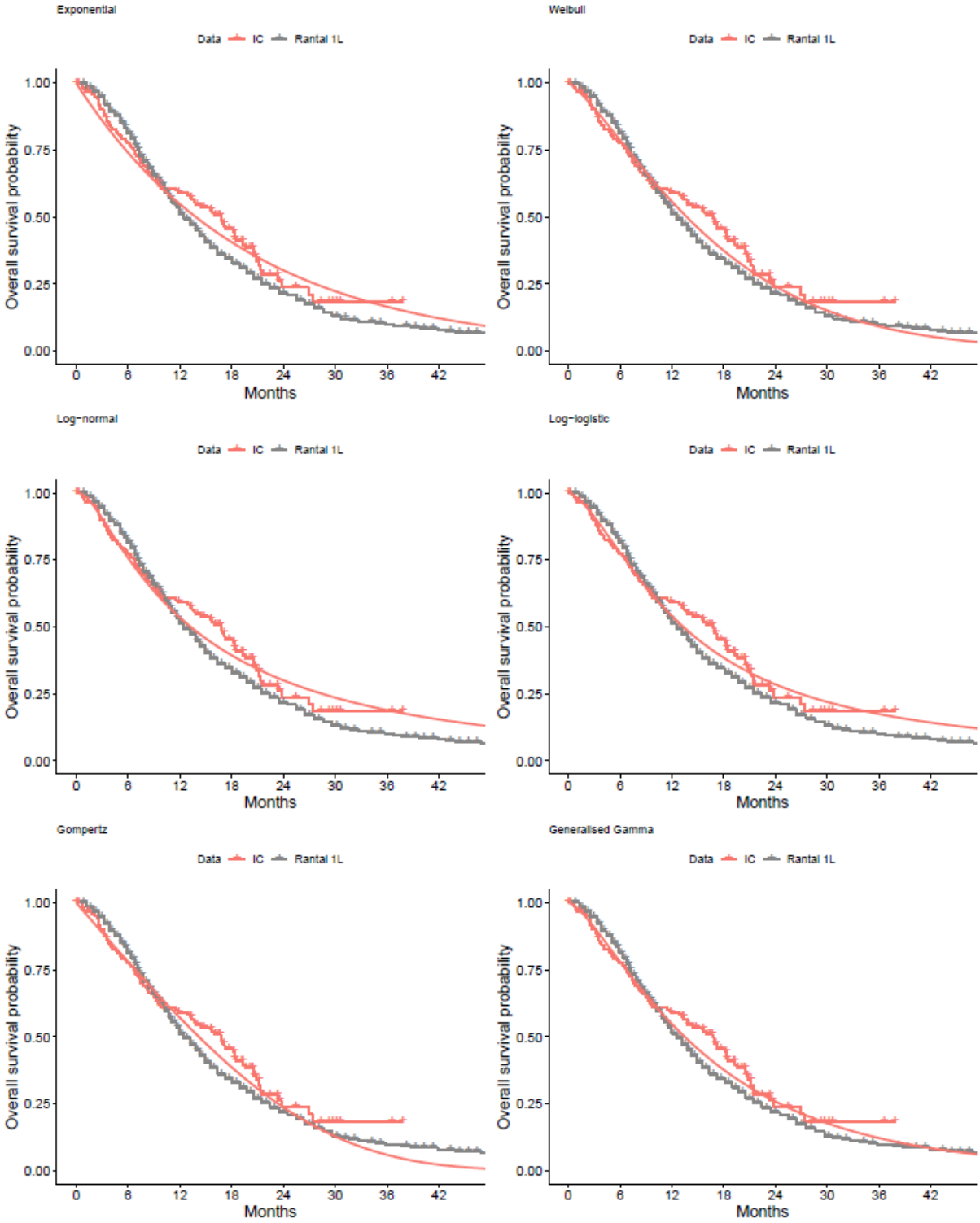
Based on historical data, the 5-year OS is expected to be close to zero (Khoja et al., 2019, Rantala et al., 2019). The extrapolation models were also presented to clinical expert for validation. Based on clinical expert's opinion, OS is expected to be between 0%-5% at year five. Both the Weibull and generalised gamma were aligned with this expectation, with a 5-year OS of 1% and 2.8% respectively.

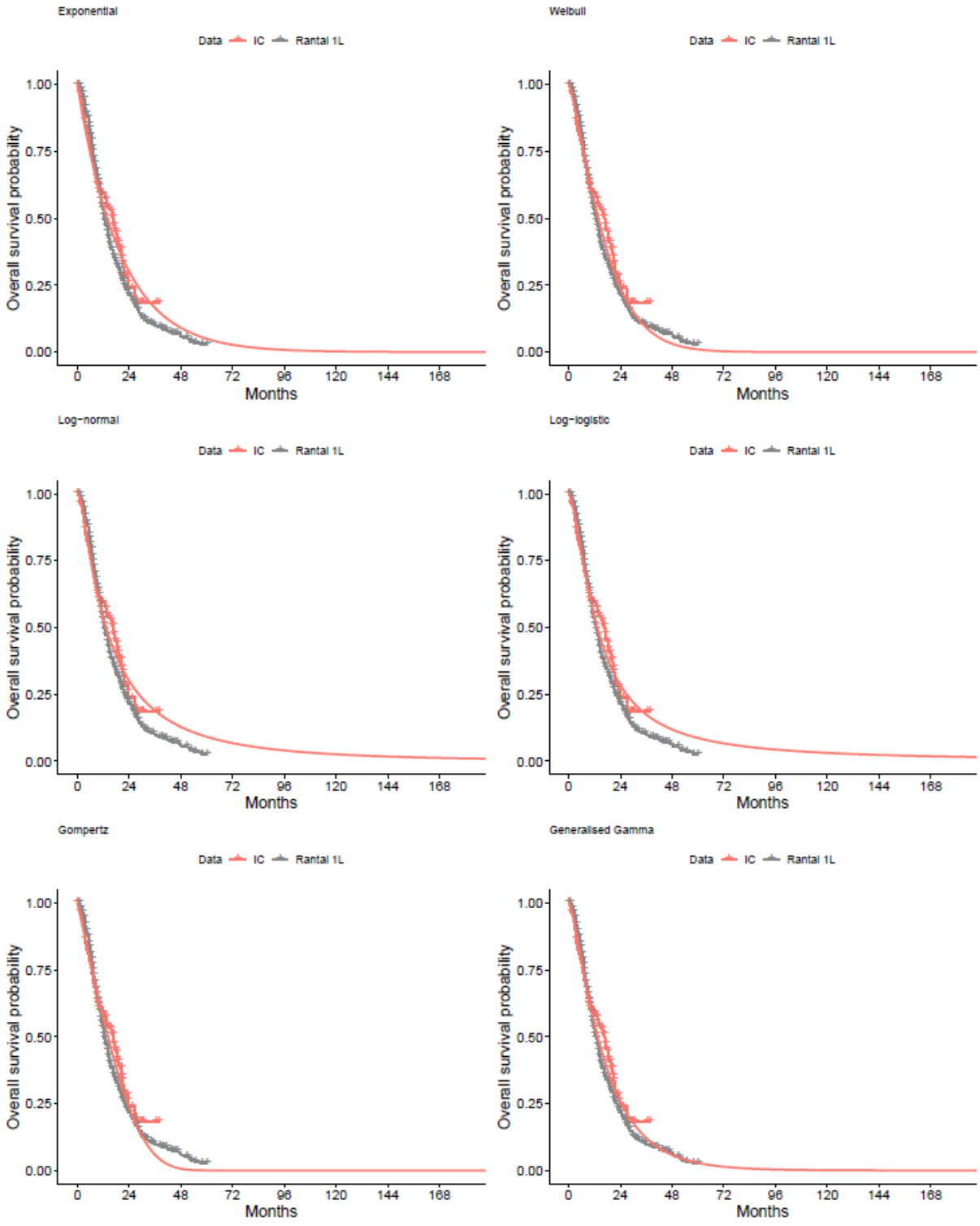
We also compared the median PFS reported in the trial, with the prediction for the preferred parametric model, generalised gamma, with data from the literature. The results are presented in Table 14 and show that the extrapolation is aligned with data from the literature.

Table 14. Comparison of trial data and extrapolation analysis data cut-off October 2020 with clinical data from the literature

	IMCgp100-202 investigator's choice arm (Oct 2020)	Weibull	Generalised gamma	Rantala et al. (2019)	Piulats et al. (2021a)	Pelster et al. (2021b)
Description	Kaplan-Meier estimates of the control arm in the trial	Predictions of the fitted model	Predictions of the fitted model	Meta-analysis of published data	Open label, single arm study of IV nivolumab (1 mg/kg) in combination with IV ipilimumab (3 mg/kg) in patients with systemic treatment-naive, histologically confirmed metastatic UM	Open-label, single-arm phase II study of nivolumab (1 mg/kg) in combination with IV ipilimumab (3 mg/kg) in patients with metastatic UM
1-year OS	58.5% (95% CI, 48.3%-67.3%)	[redacted]	[redacted]	52% (95% CI, 47%-55%)	51.9% (95% CI, 38.3%-65.5%)	56% (95% CI, 38%-71%
Median OS	16.0 (9.7, 18.4)	[redacted]	[redacted]	1.07 years (~12.8 months) (95% CI, 1.0 to 1.13) years	12.7 (95% CI, 7.1 to 18.3) months	19.1 months (95% CI, 9.6 months to not reached [NR])
24-month OS rate	20.3% (95% Ci, 9.1%-34.7%)	[redacted]	[redacted]	21% (95% CI, 18-25%)	26.4% (95% CI, 14.2 to 38.6)	NR
Median PFS	2.9 months (95% CI: 2.9-3.0)	[redacted]	[redacted]	NR	3.0 (95% CI, 2.0 to 4.1 months)	5.5 months (95% CI, 3.4 to 9.5 months)
CI, confidence interval; NR, not reported; OS, overall survival						

Figure 30. OS standard parametric models IC arm ITT set October 2020 DCO - (a) Trial time horizon; (b) 15-year time horizon





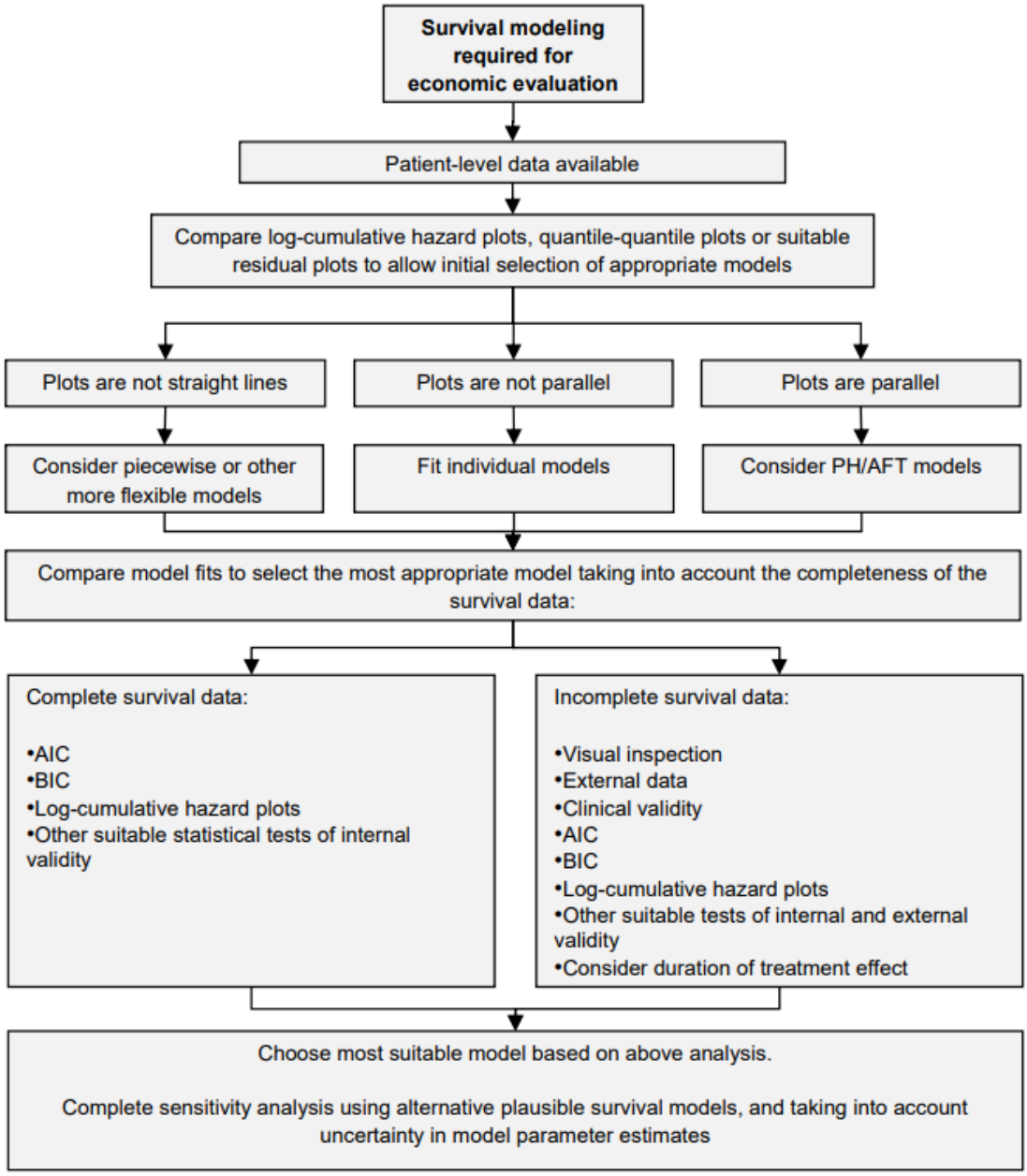
f. Please justify the selection of the approaches to estimate and extrapolate OS, PFS, and TTD, taking into account the responses to the preceding questions as well as the "Survival Model Selection Process Algorithm" provided in NICE DSU TSD 14.

The approach that was adopted to the selection of methods for modelling and extrapolating OS, PFS and TTD are consistent with “Survival Model Selection Process Algorithm” provided in NICE DSU TSD 14.

From the response to question C4, part b, log cumulative hazard plots exhibit non-linearity and non-proportionality while Schoenfeld residuals do not appear constant over time. These features are most apparent in the case of the PFS data, but also exist to a lesser extent in the TTD and OS results.

We considered a wide range of individual parametric models as well as more flexible approaches (in the form of cubic splines) and constructed the economic model with functionality to switch between these alternative approaches.

Model selection was based on the recommended goodness of fit statistics, including AIC and BIC, visual inspection of log-cumulative hazards plots as well as with consideration of theoretical and clinical plausibility through the use expert opinion (C4 part e).



g. As suggested in NICE DSU TSD 14, please provide "substantial justification" in case different types of parametric models are used for different treatment arms.

PFS and TTD are modelled using a hybrid modelling approach, using the KM curve up to a cut-point when extrapolation is based on standard parametric model. This approach was adopted as the data is mature, i.e., most of the events have been observed. The same distributions were chosen for the PFS and TTD in the base-case for the extrapolation of the tail. For the OS, we chose to use different modelling

approaches for the two arms to provide a more accurate clinical picture of overall survival in the tebentafusp arm. We used a spline-model to model [redacted]. This may reflect durable response of a sub-group of patients as has been observed with immune checkpoint inhibitors (Chen, 2013, Gibson et al., 2017), although we acknowledge that this section of the curve is based on a small number of patients remaining at risk. The uncertainty will be reduced during future planned data readouts (interim analysis 2 and final analysis) according to the protocol of study IMCgp100-202. The interim analysis 2 is expected to be available during the second half of 2022.

C5. A three knots proportional hazard spline model is used to estimate and extrapolate OS for tebentafusp.

a. **Please justify, that standard parametric survival models are not appropriate to estimate and extrapolate OS for tebentafusp, e.g. why is it inappropriate to use the generalized Gamma?**

Standard parametric models were fitted in the tebentafusp arm. Although, some models provided a good fit over the observed period, none allowed to appropriately model [redacted] follow-up in the August 2021 DCO, as observed on the KM curve.

[redacted]. The uncertainty will be reduced during future planned data readouts (interim analysis 2 and final analysis) according to the protocol of study IMCgp100-202, the second interim analysis is expected to be available during the second half of 2022. We chose to use a spline model to provide a more representative clinical picture of overall survival with tebentafusp that reflects a durable survival benefit observed with other immunotherapies.

b. **Please clarify for the estimated spline-based models how many patients were at risk (per treatment) after the specified knot locations (both using the default knot locations (i.e. 25%, 50%, 75%) as well as the knot locations selected for the CS base-case).**

The number of patients at risk at the different knot locations are detailed in Table 15.

Table 15. Spline models – patients at risk at the different knot locations

Knot location	N at risk
Manually specified knots location	
11	184
22	67
33	15
Default knots location	
25% ~ 6.7 months	213
50% ~ 11.7 months	173
75% ~ 18.6 months	98

c. **Please justify, also based on the responses to the previous question, the use of the three knots proportional hazard spline model, i.e. why specifically 3 knots and why specifically the hazards scale were used?**

Three potential functional forms of model types were considered: proportional hazards model, proportional odds and probit. These have been defined as “hazard”, “odds” and “normal” scale models respectively, as with no knots, these reduce to Weibull, log-logistic and lognormal models respectively. We tested a range of approaches with one, two and three knots. AIC and BIC as well as visual inspection were used to assess model goodness of fit. The three knots hazard model was chosen, providing the best fit to the observed data [redacted].

d. **When extrapolating based on spline-based models, this is based completely on the linearity assumption (on a transformed scale of the survival function), which may result in implausible projections. Please justify that the linearity assumption is plausible for extra-polating (technically beyond the last placed knot).**

The weekly mortality rate that is generated from the modelled OS is adjusted so that it can never fall below the mortality rate for the general population for that age group and avoid implausible projections in the model. The mortality rate for the general population, in single years of age, was sourced from the latest life tables (2018-2020) published by the Office for National Statistics (ONS).

e. **Please justify the use of the spline-based models given the responses to the preceding (sub-) questions.**

Although, some models provided a good fit over the observed period, none allowed to properly model [redacted] follow-up in the August 2021 DCO, as observed on the KM curve.

[redacted] as has been observed with immunotherapies (Chen, 2013, Gibson et al., 2017). We chose to use a spline model to provide a more representative clinical picture of overall survival with tebentafusp that reflects a durable survival benefit observed with other immunotherapies.

f. **Regarding the model implementation of the spline models, please provide the parameters of the spline models used. Please justify the implementation of the spline based models in the probabilistic sensitivity analysis (PSA) using "parameter estimates simulated from the asymptotic normal distribution" presumably copied in the "Spline_3k_PSA" worksheet (instead of a similar implementation as the standard parametric models using the "PSA inputs parametric" worksheet) and elaborate on the implications.**

The model parameters for the spline models are presented in Table 16. For simplicity, alternative parameter estimates under sampling uncertainty were generated in R, and used to estimate state occupancy in R. This approach is equivalent to how the parameters for the standard parametric models are varied in a PSA in Excel.

Table 16 Model parameters for spline models

	Estimate	SE
Gamma 0	-5.113	0.585
Gamma 1	1.738	0.346
Gamma 2	0.496	0.363
Gamma 3	-4.310	2.253
Gamma 4	-54.421	26.311

C6. Based on the CS, it appears that the hybrid models (Kaplan Meier (KM) + generalised gamma) used for PFS and TTD, are implemented using parametric

survival models that are estimated from baseline (time = 0) instead of being estimated specifically from the cut-point, i.e. point when switching from KM data to the parametric survival models.

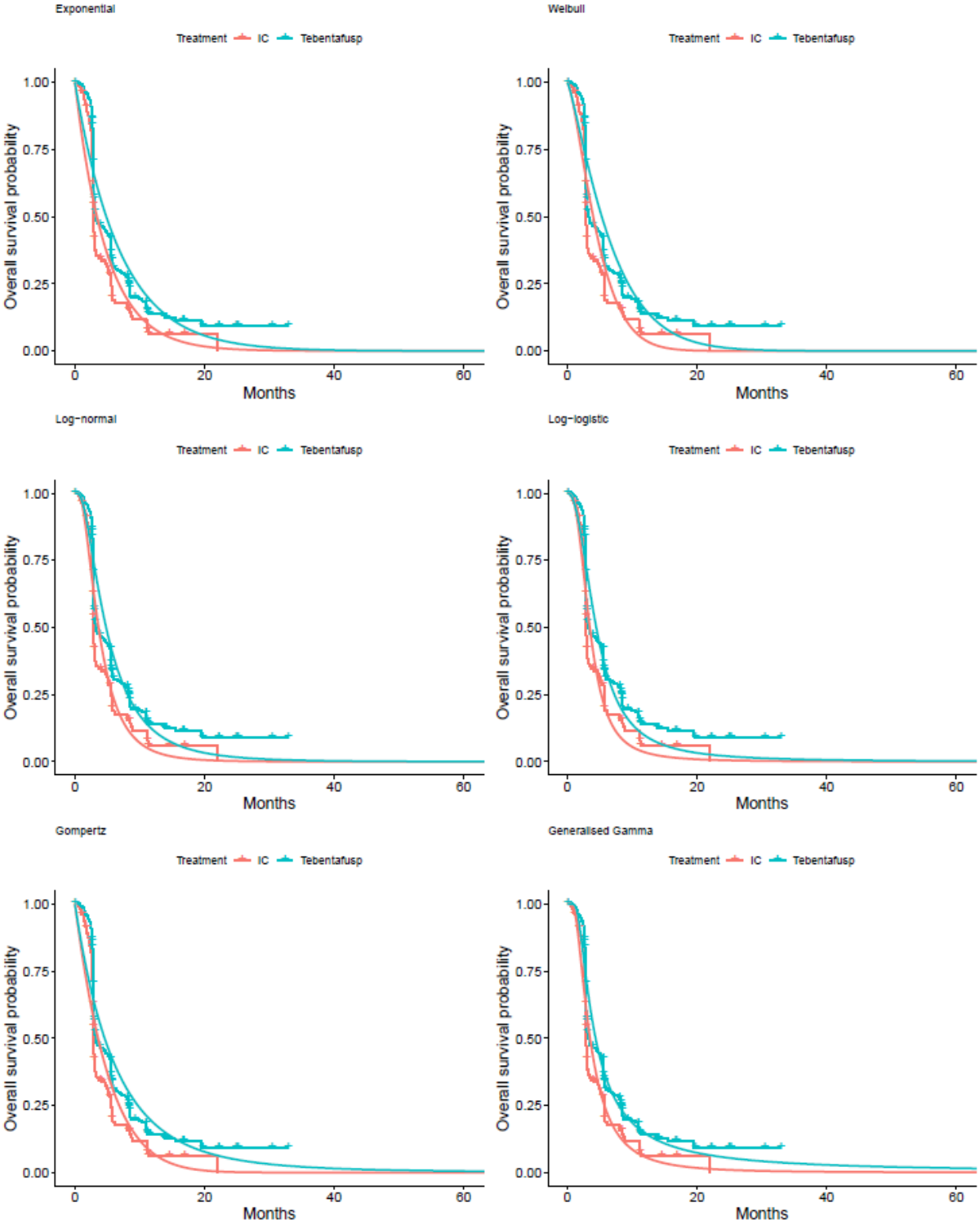
a. Please justify the hybrid approach used and provide an updated economic model as well as scenario analyses using parametric survival models estimated from the cut-point (instead of from baseline; i.e. time = 0) to inform the hybrid model.

Standard parametric models have been fitted to PFS and are presented in Figure 31 for the October DCO overlayed with the KM curves of the trial data. We note that only 7% of the patents remain progression-free at the end of the follow-up in the control arm and 10% in the tebentafusp arm. Hence, although extrapolation was required, this was to generate a small proportion of the data and there is limited uncertainty regarding the extrapolation as most of the data have been observed. The parametric models provided reasonable fits, replicating the shape of PFS KM curves, however, they under-estimate the proportion of patients being progression-free in the early months of the trial. Given the maturity of the data, the hybrid model was deemed the best approach; modelling the state of occupancy as closely aligned as possible to the observed data.

Fitting the models from the cut-point would have led to higher uncertainty in the extrapolations given the low number of patients at risk beyond this time-point. Whereas there is little uncertainty in the extrapolations when using the whole dataset given that most of the PFS events have been observed. Additionally, fitting the data from baseline allowed incorporation of the parametric models and comparison of the CEM results using the hybrid model or the parametric models alone. These results are presented in Table 85 of the CS and show that the approach used makes no difference to the results (less than 1% change in the ICER).

The same rationale is applied for TTD. Additionally, [redacted], the need for extrapolation was further limited and the KM estimates give the most accurate picture to date of the treatment duration for patients treated with tebentafusp.

Figure 31. PFS standard parametric models ITT set October 2020 DCO



b. Please clarify how many events occurred before and after the cut-point.

In the base-case, the cut-point is defined as the time-point when 15% of the patients remain at risk. In the control arm, this is equivalent to approximately [redacted]

There are [redacted] beyond this time-point. In the tebentafusp arm, this is equivalent to approximately [redacted] and there are [redacted] beyond this time point.

c. Please clarify how many patients were at risk at the cut-point.

The model is flexible allowing the user to define the cut-point either based on the proportion of patients remaining at risk, based on which the cut-point is derived, or directly defining the cut-points (in months). The base-case is based on the first approach, with the cut-point defined as 15% of the patients remain at risk, which is equivalent to approximately [redacted] in the control arm and [redacted] in the tebentafusp arm.

d. As stated in NICE DSU TSD 21 on flexible methods for survival analysis (wherein the 'hybrid' models are defined as piecewise models): *"Where a piecewise model is fitted to a single dataset, splitting the data into sections according to time means that sample sizes are reduced in later segments of the curve. This is a particular issue in later sections of the curve, where patient numbers at risk may be very small and the number of observed events may be low, leading to large standard errors and uncertainty when fitting survival models. A key point is that it is the model fitted to the latest section of the curve that is used for extrapolation"*. Please justify the plausibility of the (extrapolation) approach used for the estimated piecewise models, given the number of patients at risk and observed events (both per treatment) to estimate the tail.

As detailed in question 6.a, most of the PFS and TTD have been observed, hence, there is limited uncertainty in the extrapolation models fitted. Additionally, the standard models provided a reasonable fit to the data, although they underestimate the proportion of patients being progression-free or on-treatment in the early months of the trials. Hence, we chose to directly use the KM curve and the parametric models only for the extrapolation of the tail to be as closely aligned with the observed data as possible. Fitting the data from the cut-point would have increased the uncertainty in the fitted models given the limitations described in the NICE DSU TSD 21 and highlighted in the question. We fitted the models from baseline to make use of the whole dataset given the maturity of the data and to avoid these limitations.

e. As stated in NICE DSU TSD 21 on flexible methods for survival analysis: *"the cut-points for the various intervals may be arbitrary and may importantly influence the results of an analysis"*. Please justify the selected cut-point given the responses above and provide an updated economic model as well as scenario analyses assuming different cut-points (with the parametric survival models estimated from the specific cut-point).

We acknowledge that the cut-point may be arbitrary, however it has very limited impact on the results of the analysis. We demonstrated this in the CS by presenting a scenario analysis where the cut-point is defined based on 10% of the patients remaining at risk compared to 15% in the base-case (Table 86). We present additional scenarios below where the proportion of patients remaining at risk is varied between 5% and 20% in Table 17 and Table 18. The choice of the cut-point has a very limited impact on the results.

Table 17. Scenario analysis PFS cut-point

	Inc. Costs	Inc. QALYs	ICER	% change
Base-case 15%	[redacted]	[redacted]	[redacted]	NA
5%	[redacted]	[redacted]	[redacted]	0.04%
10%	[redacted]	[redacted]	[redacted]	0.00%
20%	[redacted]	[redacted]	[redacted]	-0.05%

Table 18. Scenario analysis TTD cut-point

	Inc. Costs	Inc. QALYs	ICER	% change
Base-case 15%	[redacted]	[redacted]	[redacted]	NA
5%	[redacted]	[redacted]	[redacted]	-0.92%
10%	[redacted]	[redacted]	[redacted]	0.16%
20%	[redacted]	[redacted]	[redacted]	-0.45

f. As stated in NICE DSU TSD 21 on flexible methods for survival analysis: *"piecewise models may appear clinically unjustifiable and implausible, if sudden changes in hazards are modelled"*. Please justify that the piecewise models are clinically justifiable and plausible in this respect.

The hybrid model approach is used in this context to model the state occupancy as closely aligned as possible to the observed data, given that most of the PFS and TTD events have been observed, the data is mature. The approach was not used to model changes in hazards; hence we consider the approach used appropriate.

g. Please justify the use of the 'hybrid' models given the responses to the preceding (sub-) questions.

The PFS and TTD KM estimates reach below 10%, demonstrating that most of the events have been observed over the trial follow-up period. Hence, we believe that there is limited uncertainty in the fitted models. Although the standard parametric models provided reasonable fit to the data, they underestimate the proportion of patients being progression-free or on-treatment in the early month of the trial. Hence, we adopted this hybrid approach, using the KM estimates to a cut-point when the parametric models were applied for extrapolation, to model the state occupancy as closely aligned to the observed data as possible.

C7. Cross-over was allowed for the September 2021 data-cut-off point for IMCgp100-202 from the investigator choice arm to tebentafusp. However, the analyses were not adjusted for cross-over.

a. Please provide clinical effectiveness analyses of PFS and OS wherein treatment effectiveness is corrected for cross-over (consistent with the recommendations provided in NICE DSU TSD 16).

b. Please provide an updated economic model and scenario analyses wherein treatment effectiveness is corrected for cross-over.

RESPONSE

Given the time constraints for responding to these clarifications, and the high number of questions marked as priority by the ERG, we have focussed on those questions and deprioritised this question.

Adverse events

C8. According to CS section B.3.3.3, "*the cost of inpatient monitoring for the first three doses is captured within the administration costs for tebentafusp. Based on clinical experts' opinion, this cost would already capture most of the costs associated with the management of CRS events and other AEs.*" Please provide an updated economic

model and scenario analyses wherein episodes of cytokine release syndrome (CRS) and other AEs are explicitly incorporated.

The costs of AEs are already explicitly incorporated into the model. The costs of the different AEs have been calculated based on the proportion of patients who would be treated in the inpatient and outpatient settings, respectively, combined with unit costs derived from the literature and the National Cost Collection for the NHS 2019/2020 version 2.

Based on clinical expert's opinion, patients treated with tebentafusp experience AEs mainly with the first three doses, and very few with subsequent doses. Patients are admitted overnight for the first three doses, this cost is incorporated in the administration costs of tebentafusp. Clinical experts considered that these costs would already capture the costs of managing the AEs. We have nevertheless costed the AEs (grade 3+ and colitis and endocrine disorders any grade) in the tebentafusp arm to be conservative in the total anticipated cost. It is assumed that the patients would not be admitted to hospital (on top of the three days of inpatients stay at administration) for subsequent administrations which are costed as outpatient treatment. This is aligned with the SmPC guidance for tebentafusp treatment.

We present in Table 19 the results of a scenario analysis, assuming the same proportion of inpatient vs. outpatient costs as in the control arm. The impact on the ICER is negligible.

Table 19. Scenario analysis adverse events costs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremen-tal QALYs	ICER (£/LYG)	ICER (£/QALY)	% change
Base-case									
Tebentafusp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
Comparator	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Scenario									
Tebentafusp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+0%
Comparator	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years									

Immunocore conducted a post-hoc analysis of AEs reported by investigators to comprehensively identify all potential episodes of cytokine release syndrome (CRS) based on ASTCT consensus criteria (Lee et al., 2019, Salama 2021). The results demonstrated the most common cytokine-mediated treatment-related AEs observed in the study are pyrexia, chills, nausea, hypotension and hypoxia. The AEs included in the model are all grade 3 or higher AEs with a prevalence in more than 3% of all patients. Based on these criteria, AEs which were classified as CRS events are not included in the model. However, pyrexia and hypotension met the criteria and are included in the model. Therefore, we consider that the cytokine-mediated treatment-related AEs relevant from a modelling perspective that may impact on costs and/or quality of life, are captured in the model.

C9. CS Table 60 lists the AE included in the model. Diarrhoea is defined as grade 3+, colitis and hyperthyroidism are defined as any grade while no explicit grade is provided (in CS Table 60) for the other AE.

a. Please provide, for all AE listed in CS Table 60, the grade used to define the AE.

All the adverse events included are grade 3+ except colitis and endocrine disorders which are included at any grade because of requirements for long-term management. The approach is described in section B.3.3.3 and B.3.5.4. The list of adverse events included in the model and the grade and prevalence thresholds applied are provided in Table 20.

Table 20. Adverse events included in the economic model

Adverse event	Grade	Prevalence
Rash	3+	>3%
Rash maculo-papular	3+	>3%
Pruritus	3+	>3%
AST increased	3+	>3%
Lipase increased	3+	>3%
ALT increased	3+	>3%
Hypertension	3+	>3%
Hypotension	3+	>3%
Fatigue	3+	>3%
Pyrexia	3+	>3%
Hypophosphataemia	3+	>3%

Hyperbilirubinaemia	3+	>3%
Pulmonary embolism	3+	>3%
Colitis (any grade)	Any	Any
Diarrhoea (grade 3+)	3+	>3%
Hyperthyroidism	Any	Any

b. Please justify the definition of AE (as provided in the response to the previous sub question).

The AEs included are all grade 3 or higher with a prevalence in more than 3% of all patients, plus endocrine disorders and colitis at any grade. Hyperthyroidism (endocrine disorders) and colitis were events of particular interest since these are known to be related to the use of immune checkpoint inhibitors and are associated with high costs and/or long-term management. Grade 3+ AEs have been included as these are expected to have a significant impact on costs and/or HRQoL. These criteria for inclusion were broadly in line with those implemented in technology appraisals of immune checkpoint inhibitors (in metastatic melanoma) relevant to the investigator's choice therapies.

- Ipilimumab (TA319): any grade 3+ event, or grade 2+ for diarrhoea, with an incidence greater than or equal to 3%
- Pembrolizumab (TA557): included adverse events for endocrine disorder (any grade), diarrhoea (grade 2+) and other adverse events (grade 3+)

Quality of life

C10. Priority question. In the IMCgp100-202 trial, EQ-5D-5L data were used in a scenario analysis (using the Van-Hout crosswalk algorithm). Due to the missing data from the EQ-5D-5L questionnaires, data imputation was performed for baseline (mean imputation) and treatment phase (multiple imputation) but not for the survival follow-up period (i.e. assuming missingness is completely at random).

i. **Mean imputation and assuming missingness is completely at random is suboptimal and potentially biases the results. Please justify the approach used (potentially illustrating the pattern of missing data).**

Based on a study by White and Thompson (2005), imputation of missing baseline data of a randomised trial is recommended, analysis of complete cases being inefficient. Mean imputation is used for baseline only. The assumption for mean imputation is that the randomisation process should have accounted for any imbalances between arms and therefore imputing missing baseline covariates with mean baseline values should not introduce any bias.

ii. **Please adopt the same multiple imputation approach for all data and provide an updated economic model and scenario analyses wherein these data are used.**

Multiple imputation of missing baseline covariates is inappropriate and would bias the baseline mean, hence this analysis was not implemented.

iii. **Please justify why no distinction between PFS and PD is made in the analyses presented in CS Table 63.**

PFS and PD are equivalent. In the trial, disease progression is assessed based on RECIST v1.1 criteria, and patients are not progression free for a long period, equivalently have disease progression if they met these criteria.

iv. **Please include PFS and PD as covariate and provide an updated economic model and scenario analyses wherein these data are used.**

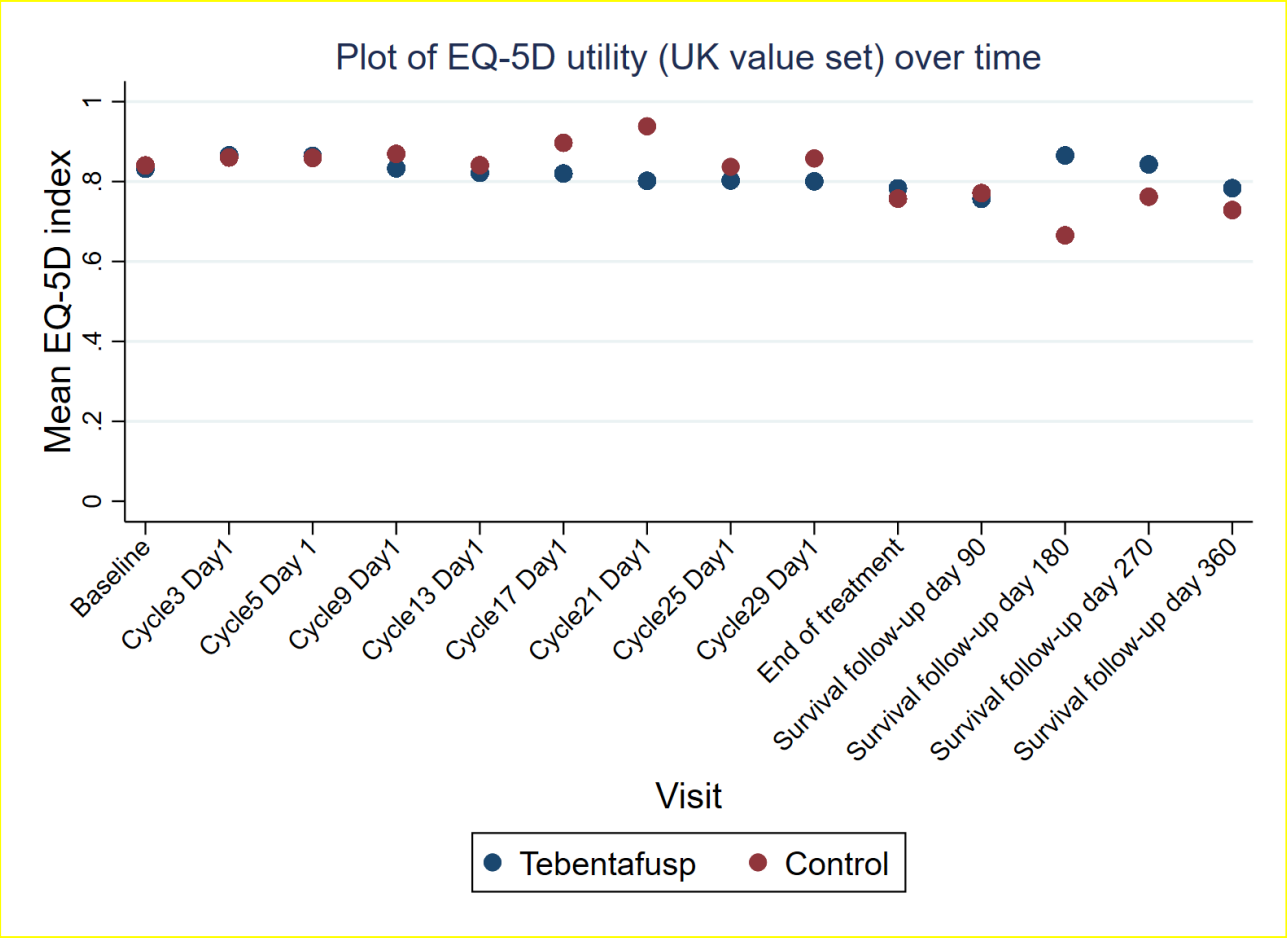
PFS and PD are equivalent, dependant, and perfectly colinear. Including both outcomes as explanatory variables in an analysis would lead to one being dropped due to perfect correlation/colinearity.

v. **The utilities presented in CS Table 63 are applied based on the TTD curves in the model. Please justify that the on/off treatment covariate is assumed treatment independent. Please justify not incorporating waning of treatment utility benefit for being on treatment and elaborate on the implications.**

In the trial, patients discontinued treatment upon confirmed disease progression per RECIST v1.1 criteria. Hence, the on/off treatment covariate is independent of treatment assignment. As can be observed in Figure 32, there is limited variation in the utility values over time or between treatment arm during the treatment phase. Therefore, we did not include a treatment waning effect while on treatment. The

decline in QoL is capture by proximity to death in the base case, or treatment status in the scenario analysis based on the trial data.

Figure 32. Plot of EQ-5D mean utility at each assessment time point and by treatment arm: intent-to-treat set



vi. Please justify the choice of the data imputation approach instead of the use of a generalized linear mixed model that includes the covariates that are mentioned in the data imputation.

Data imputation and GLM are different types of method to achieve different objectives and are not comparable. Data imputation is a method used prior to analysing data to reduce bias in the estimates. GLM's are used for data analysis. However, they do not account for the correlation between repeated observations for each participant as occurs in a longitudinal data set, which is why we opted for a generalized estimating equations model.

vii. **Please use the original EQ-5D data from the IMCgp 100-202 trial (using the Van-Hout crosswalk algorithm) without imputation and apply a generalized linear mixed model (taking into account the nested data) that includes the covariates that are mentioned in the data imputation, as well as the covariates for the on/off treatment, and for being PFS or PD. Please also provide an updated economic model and scenario analyses wherein these data are used (without applying the time-to-death utility values), and please include scenario analyses considering waning of treatment utility benefit for being on treatment.**

Multiple imputation is only looking at one separate outcome, i.e., one observation of EQ-5D, without considering the overall trend described by the repeated observations for each participant in the longitudinal data. Therefore, the covariates used for multiple imputation would not necessarily be statistically significant predictors for the trend in EQ-5D over time (based on the multiple observations per respondent). Therefore, we have conducted the complete case analysis using the same approach as described in the CS.

We used a generalised estimating equation (GEE) model to deal with the repeated measures of the same individuals and as it gives population average effects, which is suitable given the requirements for health technology assessment and economic evaluation.

We tested a range of model specifications, including the following covariates:

- Age
- Sex
- An indicator for whether the EQ-5D assessment was done before (i.e., on treatment) or, on or after treatment discontinuation (i.e., off treatment)
- Treatment arm

We measured goodness of fit using mean absolute error and root mean squared error for which a value closer to zero suggest a better fit to the data. All models provided similar results with a RMSE of 0.174 and a MAE of 0.128. The treatment arm, age and gender variables were not statistically significant, although they improved the model fit as measured by the lower MAE and RMSE compared with the

other models. The preferred model included all the aforementioned variables, and the regression outputs are presented in Table 21. The on/off treatment covariate is statistically significant at 1% level.

Table 21. Utility values based on the IMCgp100-202 trial data

	Estimate	SE
Female (reference)	NA	NA
Male	0.027	0.015
Age	0.000	
Tebentafusp (reference)	NA	NA
Control arm	-0.018	0.017
On-treatment (reference)	NA	NA
Off-treatment	-0.065	0.021
Constant	0.799	0.015

As detailed in response to question 10.e, there is little variation in the utility values over time and by treatment arm, hence waning of treatment utility benefit for being on treatment is not considered. The utility model based on the complete case analysis, presented in Table 21, was implemented in the CEM and the results are presented in Table 22. However, we believe that the complete case analysis is not appropriate (White and Thompson, 2005) and the utilities modelled based on the imputed dataset is more appropriate. We note that whether we use the imputed dataset or the compete-case analysis there is little difference in changes to the ICER.

Table 22. Scenario utility based on complete case analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)	% change
Base-case (utilities based on time to death)									
Tebentafusp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
Comparator	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Scenario (utilities based on treatment status – imputed data set)									
Tebentafusp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+8%
Comparator	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Scenario (utilities based on treatment status – Complete-case analysis)									
Tebentafusp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+6%
Comparator	[redacted]	[redacted]	[redacted]	NA	NA		NA		NA
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years									

C11. Utility data were collected in the IMCgp100-202 trial with the EQ-5D-5L questionnaire. However, these trial data were not (directly) used in the base-case analysis of the economic model. Rather data from technology appraisal (TA) 366 (pembrolizumab for advanced melanoma not previously treated with ipilimumab) were used.

a. Please justify not using EQ-5D data, based on the IMCgp100-202 trial, as the primary source for estimating utility values in the CS base-case analysis, and elaborate on the suitability of the data used from TA366 in terms of the different populations and treatments used. Please also elaborate on the suitability of the data used from TA319 and TA384 (as well as related assumptions highlighted in CS Table 65) in terms of comparability of the population and treatments considered in these assessments.

Based on clinical expert's opinion, decline in QoL of patients with metastatic uveal melanoma is more related to proximity to death, when symptoms start appearing that impact QoL, rather than on disease progression or treatment status. This has previously been reported for patients treated with metastatic melanoma (Hatswell et al., 2014). Hence, applying utility data based on time to death was the preferred approach. However, analysing the trial data using this approach was not feasible.

For the patients who died during the observed period, the average time between the last EQ-5D assessment and death was [redacted] months, hence the number of observations by time to death categories would have been insufficient.

The analysis of the trial data showed that there was no statistically significant differences in utility values between the tebentafusp and the control arm. Additionally, based clinical experts' opinion, metastatic melanoma is an acceptable proxy for uveal melanoma. Hence, we consider appropriate to use the data from TA366 which is an evaluation of pembrolizumab for the treatment of advanced melanoma, because was the predominant therapy of the trial control arm.

Utility decrements for the impact of adverse events for ipilimumab and dacarbazine were obtained from TA319 and TA366, respectively, evaluating these therapies for the treatment of metastatic melanoma. The safety profile of these therapies is expected to be independent of the indications the drugs are used for. Therefore, we consider it is appropriate to use the utility decrements derived from these TAs in the CEM.

b. Please 1) justify the inclusion of utility data based on time to death and 2) explain how time to death utilities are combined with on and off treatment utilities, and; 3) explain how the multipliers (CS Table 64) are calculated and used.

Based on clinical expert's opinion, decline in QoL of patients with metastatic uveal melanoma is more related to proximity to death, when symptoms start appearing, impacting on QoL, rather than on disease progression or treatment status. This has previously been reported for patients treated with metastatic melanoma (Hatswell et al., 2014).

Time to death utilities and on/off utilities are separate approaches to modelling QoL in the model. The two are not combined. Time to death utilities are used in the model base-case. A scenario analysis was presented where utilities are modelled based on treatment status.

We calculated multiplier to derive the utility decrement of progressing towards death, to apply these to the baseline utility from the trial data. The multipliers are calculated as a ratio, using >360 days as a reference. This is detailed in Table 23.

Table 23. Utility data based on time to death

Time to death in days	TA366	Multiplier
≥360 days	0.82	NA
270-360 days	0.71	0.87 (0.71/0.82)
180-270 days	0.66	0.80 (0.66/0.82)
90-180 days	0.66	0.80 (0.66/0.82)
30-90 days	0.57	0.70 (0.57/0.82)
<30 days	0.33	0.40 (0.40/0.33)

c. As highlighted in CS section B.3.5, *"Calculating the number of new PD* [progressive disease] *cases at each model cycle is not possible … which is a limitation of partitioned-survival models"*. Therefore, it is not possible to 'track patients' through the health states. Given this limitation, how are the time to death utilities implemented? Please elaborate on the limitations and implications of this implementation.

The utility values based on time to death are applied to patients based on how close to death they are. This approach assumes that QoL is unrelated to disease progression and instead that QoL declines as patients near death. Indeed, studies have shown that the QoL of patients with metastatic melanoma deteriorated closer to death rather than at progression (Hatswell et al., 2014). Clinical experts' confirmed that the same is observed for patients with metastatic UM.

Although not explicitly modelled, the approach used is equivalent to using tunnel states (≥360 days, 270-360 days, 180-270 days, 90-180 days, 30-90 days, <30 days) to stratify the patient cohort based on time to death and apply the relevant utility values. The tunnel states have been implemented in the updated CEM for clarity.

C12. Table 62 of the CS summarises the number of patients in both arms that completed the EQ-5D-5L questionnaire during the trial. Please provide the pattern of missingness of EQ-5D data per arm.

The pattern of missingness of data by treatment arm is presented in Table 24.

Table 24. Pattern of missingness of EQ-5D data

	N obs.	N expected	N missing	% observation missing
Tebentafusp				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 21 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 25 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 29 day 1	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up day 90	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up day 180	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up day 270	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up day 360	[redacted]	[redacted]	[redacted]	[redacted]
Investigator's choice arm				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 21 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 25 day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 29 day 1	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up day 90	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up day 180	[redacted]	[redacted]	[redacted]	[redacted]

Survival follow-up day 270	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up day 360	[redacted]	[redacted]	[redacted]	[redacted]
N, number; Obs., Observation				

C13. Please compare the estimated utilities (reported in the CS and based on the responses provided above) with UK general population utilities (matched based on age and gender) and elaborate on the implications for the results. Please provide an updated economic model and scenario analyses capping the maximum utility value based on these UK general population utility values.

The mean EQ-5D index score at baseline is [redacted]. The mean age in the trial (used as the cohort starting age in the model) was 62 years old; this mean index baseline score is slightly higher than the UK EQ-5D norm for this age group, 0.819 (Szende et al. 2014), although similar. We acknowledge that using utility values which are higher than the UK norm for the same age group presents a limitation. However, as the same utility is applied in the two study arms, and we are interested in the incremental QALYs gained, this has a limited impact on the results.

We implemented a scenario to cap the baseline utility value at the norm for this age group. The results are presented in Table 25. This demonstrates that there is little impact on the overall results.

Table 25. Scenario analysis utilities capped at the UK norm

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)	% change
Base-case									
Tebentafusp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
Comparator	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Scenario									
Tebentafusp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+3%
Comparator	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years									

Costs and resource use

C14. Priority question. As per section "Drug acquisition costs" of the CS, after 18 months, the cost of tebentafusp is assumed to be zero, and only the drug administration costs are included.

a. **Please elaborate and justify assuming no drug acquisition costs after 18 months.**

b. **Please elaborate whether this assumption is in line with the effectiveness data obtained from the IMCgp 100-202 trial.**

c. **Please provide an updated economic model and scenario analyses relaxing this assumption, i.e. estimating drug acquisition costs based on the TTD without assuming no costs after 18 months.**

RESPONSE

a. From B.3.5 Drug acquisition costs, "Additionally, there is [redacted] of tebentafusp by the NHS in the model. [redacted]". This is not an assumption but is the proposed pricing approach, in order reduce the uncertainty in the budget impact and overall treatment cost. It has no impact on the duration of treatment provided nor any other clinical aspects of the model.

b. As described in part a, the [redacted] has no impact on any clinical aspects of the model and in no way does it impact on treatment effectiveness data from the IMCgp100-202 trial.

c. In the current model, drug costs are based on TTD in the usual way with those patients discontinuing treatment no longer incurring any treatment costs. [redacted]. [redacted] can both by modified in the Model Settings.

C15. Given the trial's short survival and the addition of the subsequent therapies cost on the model, please justify the inclusion of end-of-life costs and consider to what degree this constitutes double counting of costs. Please provide an updated economic model and scenario analyses, excluding end-of-life costs.

RESPONSE

The health state costs are composed of consultations with clinicians, lab tests, scans and hospital visits relating to either the routine management of metastatic UM or following particular events such as disease progression. The costs for end-of-life care were sourced from the PSSRU report [PSSRU (2020) Unit Costs of Health and Social Care 2020] on costs of health and social care. This provides the mean total cost of care services received by cancer patients in the last twelve months of life. This includes hospital care (66% of total cost) and social care (34% of total cost). It is possible that a fraction of pre-progression and progressed disease health state costs, such as medical consultation and hospital visits, would in fact be accounted for in the overall end-of-life costing.

In the cost-effectiveness model it is straightforward for the user to input alternative cost values for end-of life-care. One alternative approach would be to use only the social care component of the end-of-life care costs. However, the cost of end-of-life care does not have a significant impact on the results. For example, setting the end-of-life care costs to zero has a negligible impact on the resulting ICER (ICER changes from [redacted] to [redacted]). A further breakdown of these results is provided in Table 26.

Table 26. Scenario analysis end-of-life costs

Result	Intervention	SoC
Cost (with EoL costs)	[redacted]	[redacted]
Cost (without EoL costs)	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
ICER (with EoL costs)	[redacted]	
ICER (without EoL costs)	[redacted]	

ICER: Incremental cost-effectiveness ratio;
EoL: End of life;
SoC: Standard of care

C16. In CS section B.3.5.3 it is stated that *"calculating the number of new PD cases at each model cycle is not possible, leading to some counter-intuitive results, which is a limitation of partitioned-survival models"*. Therefore it was assumed *"that the entire cohort would receive BSC for an average of four months and the monthly cost was multiplied by four and applied as a one-off cost at progression"*.

a. Please justify this assumption and elaborate why, given the limitations of partitioned-survival models, the monthly BSC (best supportive care) costs were not applied per cycle in the PD health state (which is a possibility, also in partitioned-survival models).

b. Please provide an updated economic model and scenario analyses applying the monthly BSC costs per cycle in the PD health state (excluding the one-off cost at progression).

RESPONSE

a. The cost of managing disease post-progression was obtained from a study of the healthcare resource use associated with the treatment of metastatic melanoma (McKendrick et al. 2016). No study on health-care resource utilisation in patients with UM or metastatic UM, providing the necessary data, was identified in the literature. Hence, we used metastatic melanoma as a starting point for the estimation of resource utilisation, which was considered an acceptable proxy by clinical experts. The resource utilisation from the study were presented to two UK clinicians experienced in the management of patients with metastatic UM to determine which items were irrelevant in the context of metastatic UM and which resources for the treatment of metastatic UM patients were not already captured and should be added, as well as frequency of use.

   The study by McKendrick et al. provided monthly resource use data and pointed to an average of four months in post-progression before patients would receive palliative/terminal care. Given the relatively short life expectancy for patients with metastatic UM, we assumed that the assumption holds and applied the four months costs as one-off cost in the model. Patients

subsequently incurred end-of-life care costs at the point of death. Applying the post-progression cost for the whole duration a patient in the PD state would lead to double-counting of the end-of-life costs.

b. We consider that applying the monthly BSC costs per cycle in the PD health state, for the whole duration a patient is in the PD state is not appropriate as is would lead to double-counting with the end-of-life costs and so this scenario was not implemented.

C17. Some patients were modelled to receive subsequent treatment after the discontinuation of the active treatment.

a. Please provide justification for the subsequent treatment duration and clarify the calculations used to obtain the estimated subsequent treatment duration (reported in CS Table 73).

b. Please provide scenario analyses wherein duration of subsequent treatment is maximized to continue until death.

RESPONSE

a. The duration of subsequent treatment was extracted from the results of the IMCgp100-202 study. This reported the duration of anti-neoplastic therapies since discontinuation of the study drug by treatment arm. For systemic therapy, the mean durations were [redacted] We derived the number of three weeks cycles, rounded up to the nearest integer, giving [redacted] cycles in the control arm and [redacted] in the tebentafusp arm.

b. Based on clinical expert's opinion, it is not clinically plausible that patients will receive active treatment all the way up to death. Patients will switch to 'end-of-life' or best supportive care close to death, costs of which are accounted for in the 'end-of-life' costs. We believe the proposed scenario is not clinically relevant and was not implemented.

C18. Table 73 of the CS summarises the costs of subsequent therapies. However, the percentages of subsequent treatment options do not add to 100%.

a. Please provide information on the denominators and calculations used to obtain these values.

We derive the proportion of usage of the different treatment options for non-North American patients in the trial. About [redacted] of the patients received subsequent systemic therapy (chemotherapy or immunotherapies). Patients may have had multiple records (multiple subsequent therapies); hence the proportions of usage of chemotherapy and immunotherapies do not add up to 100%. The results by treatment arm are presented in Table 27

Table 27. Proportion of usage of the different therapy options

	Tebentafusp	IC	Total	Tebentafusp	IC
Systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b. Please justify if the use of the subsequent therapies presented in the CS reflects the UK practice for the population of interest.

A survey was conducted with UK clinical experts to understand current treatment practices in the treatment of patients with metastatic uveal melanoma. Based on these responses, only 7% of patients received subsequent systemic treatment, 50% receiving pembrolizumab and 50% ipilimumab + nivolumab. The results of the scenario analysis are presented in Table 28.

Table 28. Scenario subsequent therapies

Scenario	Δ Costs	Δ QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	[redacted]	NA
Subsequent therapies - UK clinical practice	[redacted]	[redacted]	[redacted]	-3%

Results and uncertainty analyses

C19. Priority question. According to CS Appendix E, sites were asked to record for all patients the intended investigator choice treatment prior to randomisation. Considering the responses to question B4, please provide an updated economic model and subgroup analyses based on pre-choice of chemotherapy (ipilimumab, dacarbazine and pembrolizumab).

RESPONSE

Pre-choice of therapy (ipilimumab, dacarbazine, pembrolizumab) prior to randomisation, and planned and actual treatment received are identical for all patients in the investigator's choice arm, i.e. if investigator chose pembrolizumab for IC prior to randomisation and patient was allocated to the IC arm, the patient received pembrolizumab.

C20. Considering the CS base-case results.

a. Please provide a comparison of the observed survival as well as progression free survival (e.g. using restricted mean survival time; RMST) and the undiscounted life years (LYs) as well as undiscounted progression free LYs (estimated in the model) by filling out the Table below using different periods/truncation points (with justification) to calculate the RMST.

Restricted mean survival time (RMST) is equivalent to the area under the KM curve from the beginning of the study through that time point. RMST were calculated for different cut-points: (1) median OS in the control arm; (2) time-point when at least 15% of the patients are still on treatment, (3) maximum follow-up in the control arm. Undiscounted life-years were estimated from the model for the same time-point. The data is presented in Table 29.

Table 29. Comparison of observed and modelled outcomes August 2021 DCO

	Observed	Modelled
	Restricted mean survival time (RMST)	Estimated undiscounted life-years
OS - RMST period / truncation point: 16.7 months (selected based on median in OS in control arm)		
Tebentafusp	[redacted]	[redacted]
Comparator	[redacted]	[redacted]
Increment	[redacted]	[redacted]
OS - RMST period / truncation point: 21.2 months (selected based on at least 15% of patients at risk)		
Tebentafusp	[redacted]	[redacted]
Comparator	[redacted]	[redacted]
Increment	[redacted]	[redacted]
OS - RMST period / truncation point: 27.3 months (selected based on maximum follow-up time in the control arm)		
Tebentafusp	[redacted]	[redacted]
Comparator	[redacted]	[redacted]
Increment	[redacted]	[redacted]
PFS - RMST period / truncation point: 2.9 months (selected based on median PFS in control arm)		
Tebentafusp	[redacted]	[redacted]
Comparator	[redacted]	[redacted]
Increment	[redacted]	[redacted]
PFS - RMST period / truncation point: 8.1 months (selected based on at least 15% of patients at risk)		
Tebentafusp	[redacted]	[redacted]
Comparator	[redacted]	[redacted]
Increment	[redacted]	[redacted]
PFS - RMST period / truncation point: 21.9 months (selected based on maximum follow-up time in the control arm)		
Tebentafusp	[redacted]	[redacted]
Comparator	[redacted]	[redacted]
Increment	[redacted]	[redacted]

b. Please elaborate on the plausibility of the differences between observed and modelled outcomes (proportion accumulated beyond observed data) for:

    a. tebentafusp

b. the comparator (investigator's choice of immunotherapies, ipilimumab or pembrolizumab, or chemotherapy, dacarbazine)

c. the increment

The differences between the observed and modelled outcomes are very similar, showing that the extrapolations are well aligned with the data from study IMCgp100-202.

c. Regarding the model estimated differences between the intervention and the comparator (in terms of PFS, LYs and quality-adjusted life years (QALYs)); please provide an explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence (NICE DSU TSD 19 recommendation 13).

Table 29 shows that the observed and modelled OS and PFS are well aligned. The differences in the outcomes, reflect the differences observed within the IMCgp100-202 study. The LYs and QALYs gains are driven by the longer OS in the tebentafusp arm, with durable response experienced by a sub-group of patients as has been observed with immune checkpoint inhibitors (Chen, 2013, Gibson et al., 2017).

C21. CS section B.3.8 provides the incremental cost effectiveness ratio (ICER) estimates of different sensitivity and scenario analyses.

a. Please also provide the incremental costs and incremental QALYs for all sensitivity and scenario analyses.

b. In CS section B.3.8.2 it is noted (based on CS Figure 42 and CS Table 84) that patient age has the most impact on the results, i.e. ICER estimate. Please explain the mechanism by which this parameter is impacting the result and elaborate on the plausibility that this parameter is most impactful.

RESPONSE

a. The incremental costs and QALYs for the 10 parameters with the greatest influence on the ICER (in a descending order) are presented in **Table 30**. These are the incremental results when each parameter is set to the lower value of the specified range.

Table 30. Results of the univariate sensitivity analysis using lower value

Parameter	Inc. Costs	Inc. QALYs
Mean patient age (46.5, 77.5)	[redacted]	[redacted]
On-treatment health state utility [IMCgp100-202] (0.76, 0.93)	[redacted]	[redacted]
Cost of subsequent chemotherapy attendance (272.5, 454.2)	[redacted]	[redacted]
Pre-progression health state cost-per cycle (96.8, 161.3)	[redacted]	[redacted]
Proportion female patients (0.37, 0.62)	[redacted]	[redacted]
Disutility of tebentafusp adverse events (0.019, 0.023)	[redacted]	[redacted]
Cost of overnight hospital stay (338.1, 563.5)	[redacted]	[redacted]
Disutility of dacarbazine adverse events (0.021, 0.026)	[redacted]	[redacted]
Health state utility, time to death 270-360 days (0.64, 0.78)	[redacted]	[redacted]
Health state utility, time to death 30-90 days (0.51, 0.63)	[redacted]	[redacted]

The incremental costs and QALYs for the 10 parameters with the greatest influence on the ICER (in a descending order) are presented in **Table 31**. These are the incremental results when each parameter is set to the upper value of the specified range.

Table 31. Incremental results of the univariate sensitivity analysis using upper value

Parameter	Inc. Costs	Inc. QALYs
Mean patient age (46.5, 77.5)	[redacted]	[redacted]
On-treatment health state utility [IMCgp100-202] (0.76, 0.93)	[redacted]	[redacted]
Cost of subsequent chemotherapy attendance (272.5, 454.2)	[redacted]	[redacted]
Pre-progression health state cost-per cycle (96.8, 161.3)	[redacted]	[redacted]
Proportion female patients (0.37, 0.62)	[redacted]	[redacted]
Disutility of tebentafusp adverse events (0.019, 0.023)	[redacted]	[redacted]
Cost of overnight hospital stay (338.1, 563.5)	[redacted]	[redacted]
Disutility of dacarbazine adverse events (0.021, 0.026)	[redacted]	[redacted]
Health state utility, time to death 270-360 days (0.64, 0.78)	[redacted]	[redacted]
Health state utility, time to death 30-90 days (0.51, 0.63)	[redacted]	[redacted]

b. The extrapolation of patient survival is based on the IMCgp100-202 trial data. For the tebentafusp arm this uses the spline model to reflect the [redacted]. This predicts a decline in the mortality rate for surviving patients. The predicted mortality rate, in later years, can fall below the background rate of mortality – in which case the background mortality rate is applied.

   If an older cohort is specified, then the background mortality rate is considerably higher. This means that the background rate exceeds the spline modelled mortality rate much sooner than for a younger cohort. This only impacts the tebentafusp arm since the IC arm does not use a spline model. Therefore, the potential benefits of tebentafusp appear to be less in an older cohort as the spline-based survival is rapidly replaced by the relatively higher background mortality.

This represents a limitation of the model's ability to further extrapolate treatment benefits into the future for a patient cohort with differing characteristics to that assessed in the clinical study.

C22. CS section B.3.9 provides subgroup analyses based on tumour ≤30 mm

a. Please provide a detailed description of this subgroup, including whether this ≤30 mm refers to the largest metastatic lesion recorded at baseline (as specified in CS Appendix E).

The subgroup analysis for patients with tumour ≤30 mm is based on the subgroup of patients in the trial, with largest metastatic lesion recorded at baseline ≤30 mm.

b. Please clarify whether this subgroup analyses were prespecified a priori for the cost effectiveness analyses.

It was a pre-specified subgroup of the clinical trial and thus was deemed relevant for the cost-effectiveness analysis.

c. Please provide extensive justification why this subgroup is selected for the cost effectiveness analyses.

There is a growing body of evidence documenting the associating between tumour burden and response to immunotherapies, thus the particular interest in this population subgroup (Dall'Olio et al. 2021). Based on data from the literature, it is expected that a smaller tumour burden at baseline is associated with better response to immunotherapies and thus better health outcomes, as evidenced in the tebentafusp RCT Study-IMCgp100-202.

d. Please clarify whether there is statistical interaction between this subgroup and the treatment effect and elaborate on the mechanism (biological rational) that might potentially cause the interaction effect.

We fitted a cox proportional hazard model with the following as covariates: treatment assignment, tumour size and an interaction term between the two variables. Treatment assignment is defined a dummy variable, taking the value 0 for the control arm and 1 for tebentafusp. Tumour size is defined as a dummy variable, taking the value 0 for tumour size ≤30 mm and 1 for >30mm. The results are presented below

for overall survival and show that the interaction term is statistically significant at the 5% level.

Table 32. Cox proportional hazard model overall survival with interaction term

	Coef	Exp(coef)	SE(coef)	Z	P
Trt	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tumour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trt [redacted]tumour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

e. Please clarify whether the interaction (if observed) is consistent across closely related outcomes within the study.

The same model was run for progression-free survival, the interaction term is not statistically significant.

Table 33. Cox proportional hazard model progression-free survival with interaction term

	Coef	Exp(coef)	SE(coef)	Z	P
Trt	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tumour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trt [redacted]tumour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

f. Please provide all sensitivity and scenario analyses presented in CS section B.3.8 for this subgroup, including the incremental costs and incremental QALYs as well as the estimated ICERs.

CS B.3.9 presents various results for the subgroup of patients with tumour size ≤30mm. These include alternative parametric survival models and data cut-offs. Rather than give the full breakdown of sensitivity analysis results for all of these options examined, we have focused on the scenario for tumour size ≤30mm using log-normal OS parametric model for tebentafusp with the August 2021 DCO.

The incremental costs and QALYs for the 10 parameters with the greatest influence on the ICER (in a descending order) are presented in **Table 34** and **Table 35**. **Table 34** is using the parameter at its lower value while **Table 35** is using its upper value. **Table 35** gives the results for the scenarios examined.

Table 34. Results of the univariate sensitivity analyses for tumour ≤30mm using lower parameter value

Parameter	Inc. Costs	Inc. QALYs	ICER
Pre-progression IMCgp100-202 (0.76, 0.93)	[redacted]	[redacted]	[redacted]
Chemo subsequent attendance (272.53, 454.21)	[redacted]	[redacted]	[redacted]
Age (46.50, 77.50)	[redacted]	[redacted]	[redacted]
Health states costs Pre-progression - cost per cycle (96.77, 161.28)	[redacted]	[redacted]	[redacted]
Adverse events disutility Treatment effect of tebentafusp (0.02, 0.02)	[redacted]	[redacted]	[redacted]
Adverse events disutility Treatment effect of dacarbazine (0.02, 0.03)	[redacted]	[redacted]	[redacted]
Overnight hospital stay (338.11, 563.51)	[redacted]	[redacted]	[redacted]
Data from the literature Time to death in days 270-360 days (0.64, 0.78)	[redacted]	[redacted]	[redacted]
Data from the literature Time to death in days 30-90 days (0.51, 0.63)	[redacted]	[redacted]	[redacted]
Data from the literature Time to death in days ≥360 days (0.74, 0.90)	[redacted]	[redacted]	[redacted]

Table 35. Results of the univariate sensitivity analyses for tumour ≤30mm using upper parameter value

Parameter	Inc. Costs	Inc. QALYs	ICER
Pre-progression IMCgp100-202 (0.76, 0.93)	[redacted]	[redacted]	[redacted]
Chemo subsequent attendance (272.53, 454.21)	[redacted]	[redacted]	[redacted]
Age (46.50, 77.50)	[redacted]	[redacted]	[redacted]
Health states costs Pre-progression - cost per cycle (96.77, 161.28)	[redacted]	[redacted]	[redacted]
Adverse events disutility Treatment effect of tebentafusp (0.02, 0.02)	[redacted]	[redacted]	[redacted]
Adverse events disutility Treatment effect of dacarbazine (0.02, 0.03)	[redacted]	[redacted]	[redacted]
Overnight hospital stay (338.11, 563.51)	[redacted]	[redacted]	[redacted]
Data from the literature Time to death in days 270-360 days (0.64, 0.78)	[redacted]	[redacted]	[redacted]
Data from the literature Time to death in days 30-90 days (0.51, 0.63)	[redacted]	[redacted]	[redacted]
Data from the literature Time to death in days ≥360 days (0.74, 0.90)	[redacted]	[redacted]	[redacted]

Table 36. Results of the scenario analyses for tumour ≤30mm subgroup

Scenario	Δ Costs	Δ QALYs	ICER	Δ% from base-case ICER
Base-case	[redacted]	[redacted]	[redacted]	0.000%
Utility based on treatment status	[redacted]	[redacted]	[redacted]	6.288%
PFS switch 10% at risk	[redacted]	[redacted]	[redacted]	-0.096%
TTD switch 10% at risk	[redacted]	[redacted]	[redacted]	0.310%

Validation and transparency

C23. The internal validation described in section B.3.10 appears extensive. However, the results of the validity assessments are not described nor are detailed validation exercises (i.e. specific black-box tests) described.

a. Please provide a detailed description of the validity assessment performed as well as the results.

To ensure the internal validity of the model, a senior health economic modeller who was not previously involved in the model development, performed a thorough and systematic examination of multiple aspects of the model. First, the model was examined to ensure worksheets and formulas are programmed correctly. Subsequently, the model's behaviour was examined by running verification checks to assess the consistency of the modelled outputs, or indications of error in the results. The latter was achieved by using equal or extreme values in both treatment arms of the model and inspecting whether the results produced by the model matched the modeller's expectations. The procedures conducted, as well as expected model outputs are presented in **Table 37**. Finally, functionalities (restore defaults, DSA, PSA) where run to verify that they work appropriately

Table 37. Procedures for model validation

Procedure	Implementation	Expectation	Check
Utilities			
All utilities set to 0	Set all health state utility values to 0	QALYS=0	✓
All utilities set to 1	• Set all health state utilities to 1	LY = QALYs	✓

	• Set adverse event utilities to 0 • Set utility norms (used for age adjustment) to 1		
Increase adverse event disutility values	Increase AE disutility to -0.05	QALYs decrease	✓
Discount rate for outcomes	Set discount rate for outcomes to 0	discounted QALYs = undiscounted QALYs	✓
Increase/reduce the model time horizon accordingly	• Set time horizon to 20 years • Increase time horizon to 25 years • Decrease time horizon to 15 years	• QALYs gained increase • QALYs gained decrease	✓
Increase age of patients	Increase age from 62 to 70	LY and QALYs lower than in the base-case	✓
Costs			
Lower treatment cost in the intervention arm	Half the treatment costs in the intervention arm	ICER decreases	✓
All costs set to 0	Set all cost parameters to zero	No costs	✓
Discount rate for costs	Set discount rate for costs to 0	discounted costs = undiscounted costs	✓
Increase intervention treatment effects	• Set to Weibull in the intervention arm, all other parameters equal • Set to log-normal for comparison	ICER decreases	✓
General checks			
Swap key inputs across engines that are exact replicates (e.g. parametric survival functions inputs)	• Set OS, PFS and TTD parameters in the intervention arm equal to the parameters in the control arm	• Curves for the same distributions overlap • LYs and QALYs equal between the arms	✓

b. Please provide complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results.

Table 38. TECH-VER black box checklist

Test description (please also document how the test is conducted)	Result
Pre-analysis calculations	
Does the technology (drug/device, etc.) acquisition cost increase with higher prices?	Yes
Does the drug acquisition cost increase for higher weight or body surface area?	Yes
Does the probability of an event, derived from an OR/RR/HR and baseline probability, increase with higher OR/RR/HR?	NA
In a partitioned survival model, does the progression-free survival curve or the time on treatment curve cross the overall survival curve?	No
If survival parametric distributions are used in the extrapolations or time-to-event calculations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (Weibull or Gamma) distribution(s) after replacing/transforming some of the parameters?	Yes
Is the HR calculated from Cox proportional hazards model applied on top of the parametric distribution extrapolation found from the survival regression?	NA
For the treatment effect inputs, if the model uses outputs from WINBUGS, are the OR, HR, and RR values all within plausible ranges? (Should all be non-negative and the average of these WINBUGS outputs should give the mean treatment effect)	NA
Event-state calculations	
Calculate the sum of the number of patients at each health state	The model implements this check
Check if all probabilities and number of patients in a state are greater than or equal to 0	Number of new PD can be below zero due to assumptions made regarding possible transitions, acknowledged as a limitation
Check if all probabilities are smaller than or equal to 1	Yes
Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	They are larger
In case of lifetime horizon, check if all patients are dead at the end of the time horizon	% alive = 0.22
Discrete event simulation specific: Sample one of the 'time to event' types used in the simulation from the specified distribution. Plot the samples and compare the mean and the variance from the sample	NA
Set all utilities to 1	Yes
Set all utilities to 0	Yes

Test description (please also document how the test is conducted)	Result
Decrease all state utilities simultaneously (but keep event-based utility decrements constant)	Yes
Set all costs to 0	Yes
Put mortality rates to 0	Yes
Put mortality rate at extremely high	Yes
Set the effectiveness-, utility-, and safety-related model inputs for all treatment options equal	Yes
In addition to the inputs above, set cost-related model inputs for all treatment options equal	Yes
Change around the effectiveness-, utility- and safety-related model inputs between two treatment options	
Check if the number of alive patients estimated at any cycle is in line with general population life-table statistics	NA
Check if the QALY estimate at any cycle is in line with general population utility estimates	Yes
Set the inflation rate for the previous year higher	NA - cost inflation adjustment implemented outside the model
Calculate the sum of all ingoing and outgoing transition probabilities of a state in a given cycle	NA - Partitioned survival model
Calculate the number of patients entering and leaving a tunnel state throughout the time horizon	NA - Partitioned survival model
Check if the time conversions for probabilities were conducted correctly.	NA - Partitioned survival model
Decision tree specific: Calculate the sum of the expected probabilities of the terminal nodes	NA
Patient-level model specific: Check if common random numbers are maintained for sampling for the treatment arms	NA
Patient-level model specific: Check if correlation in patient characteristics is taken into account when determining starting population	NA
Increase the treatment acquisition cost	Yes
Population model specific: Set the mortality and incidence rates to 0	NA
Result calculations	
Check the incremental life-years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	Yes
Check the incremental cost results. Are they in line with the treatment costs?	Yes
Total life years greater than the total QALYs	Yes
Undiscounted results greater than the discounted results	Yes
Divide undiscounted total QALYs by undiscounted life years	Yes
Subgroup analysis results: How do the outcomes change if the characteristics of the baseline change?	Yes

Test description (please also document how the test is conducted)	Result
Could you generate all the results in the report from the model (including the uncertainty analysis results)?	Yes
Do the total life-years, QALYs, and costs decrease if a shorter time horizon is selected?	Yes
Is the reporting and contextualization of the incremental results correct?	Yes
Are the reported ICERs in the fully incremental analysis non-decreasing?	Yes
If disentangled results are presented, do they sum up to the total results (e.g. different cost types sum up to the total costs estimate)?	Yes
Check if half-cycle correction is implemented correctly (total life-years with half-cycle correction should be lower than without)	Yes
Check the discounted value of costs/QALYs after 2 years	NA - discounting is implemented weekly and on each cost component
Set discount rates to 0	Yes
Set mortality rate to 0	Yes
Put the consequence of adverse event/discontinuation to 0 (0 costs and 0 mortality/utility decrements)	Yes
Divide total undiscounted treatment acquisition costs by the average duration on treatment	Yes
Set discount rates to a higher value	Yes
Set discount rates of costs/effects to an extremely high value	Yes
Put adverse event/discontinuation rates to 0 and then to an extremely high level	Yes
Double the difference in efficacy and safety between the new intervention and comparator, and report the incremental results	NA - not readily implemented in this PSA
Do the same for a scenario in which the difference in efficacy and safety is halved	
Uncertainty analysis calculations	
Are all necessary parameters subject to uncertainty included in the OWSA?	Yes
Check if the OWSA includes any parameters associated with joint uncertainty (e.g. parts of a utility regression equation, survival curves with multiple parameters)	No
Are the upper and lower bounds used in the one-way sensitivity analysis using confidence intervals based on the statistical distribution assumed for that parameter?	Where applicable
Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations?	Yes
Check that all parameters used in the sensitivity analysis have appropriate associated distributions – upper and lower bounds	Yes

Test description (please also document how the test is conducted)	Result
should surround the deterministic value (i.e. upper bound ≥ mean ≥ lower bound)	
Standard error and not standard deviation used in sampling	Yes
Lognormal/gamma distribution for HRs and costs/resource use	Yes
Beta for utilities and proportions/probabilities	Yes
Dirichlet for multinomial	Yes
Multivariate normal for correlated inputs (e.g. survival curve or regression parameters)	Yes
Normal for other variables as long as samples do not violate the requirement to remain positive when appropriate	Yes
Check PSA output mean costs, QALYs, and ICER compared with the deterministic results. Is there a large discrepancy?	No
If you take new PSA runs from the Microsoft Excel model do you get similar results?	Yes
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes
Does the PSA cloud demonstrate an unexpected behavior or have an unusual shape?	No
Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes
Do the explored scenario analyses provide a balanced view on the structural uncertainty (i.e. not always looking at more optimistic scenarios)?	Yes
Are the scenario analysis results plausible and in line with a priori expectations?	Yes
Check the correlation between two PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	OK
If a certain seed is used for random number generation (or previously generated random numbers are used), check if they are scattered evenly between 0 and 1 when they are plotted	NA
Compare the mean of the parameter samples generated by the model against the point estimate for that parameter; use graphical methods to examine distributions, functions	NA - this check is not readily implemented
Check if sensitivity analyses include any parameters associated with methodological/structural uncertainty (e.g. annual discount rates, time horizon)	Yes - to a limited extent
Value of information analysis if applicable: Was this implemented correctly?	NA
Which types of analysis? Were aggregated parameters used? Which parameters are grouped together? Does it match the write-up's suggestions?	NA
Is EVPI larger than all individual EVPPIs?	NA
Is EVPPI for a (group of) parameters larger than the EVSI of that (group) of parameter(s)?	NA
Are the results from EVPPI in line with OWSA or other parameter importance analysis (e.g. ANCOVA)?	NA

Test description (please also document how the test is conducted)	Result
Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings? (Additional macro can be embedded to the PSA code, which stops the PSA when an error such as negative transition probability is detected)	Yes
Check if all sampled input parameters in the PSA are correctly linked to the corresponding event/state calculations	Yes

C24. Please provide cross validations, i.e. comparisons with other relevant NICE TAs focussed on similar, potentially relevant, diseases (e.g. related NICE recommendations and NICE Pathways listed in the final scope) and elaborate on the identified differences regarding:

a. Model structure and assumptions

b. Input parameters related to:

    a. Clinical effectiveness

    b. Health state utility values

    c. Resource use and costs

c. Estimated (disaggregated) outcomes per comparator/ intervention

    a. Life years

    b. QALYs

    c. Costs

There are no NICE TAs relevant to this decision problem. Tebentafusp is the first treatment under evaluation by NICE for the treatment of metastatic uveal melanoma. Tebentafusp is the first proven effective treatment for metastatic uveal melanoma supported by a registrational study. Uveal melanoma is biologically distinct from skin melanoma with different physiological, genetic, and epidemiologic characteristics.

C25. CS Table 90 provides a helpful comparison of modelled results and clinical data. Please extend this overview by adding 12 and 24 month PFS.

We presented in Table 39 the modelled results versus clinical trial data and data from the literature. We have added 6-month and 12-month PFS rather than 12-month and 24-month PFS as this is more in line with data reported in the literature (PFS being close to 0% by 24 month).

Table 39. Summary of model results compared with clinical data

Comparison	Model IC arm (Oct 2020)	Trial 202 (IC arm – Oct 2020)	Rantala et al. (2019)	(Piulats et al., 2021b)	Pelster et al. (2021b)
Description	Control arm predicted by the model	Investigator's choice arm of 202 study	Meta-analysis of published data	Open label, single arm study of IV nivolumab (1 mg/kg) in combination with IV ipilimumab (3 mg/kg) in patients with systemic treatment-naive, histologically confirmed metastatic UM	Open-label, single-arm phase II study of nivolumab (1 mg/kg) in combination with IV ipilimumab (3 mg/kg) in patients with metastatic UM
Median OS	[redacted]	16.0 (95% CI, 9.7-18.4) months	1.07 (95% CI, 1.0 to 1.13) years	12.7 (95% CI, 7.1 to 18.3) months	19.1 months (95% CI, 9.6 months to not reached [NR])
Median PFS	[redacted]	2.9 months (95% CI, 2.9-3.0)	NR	3.0 (95% CI, 2.0 to 4.1 months)	5.5 months (95% CI, 3.4 to 9.5 months)
12-month OS rate	[redacted]	58.5% (95% CI, 48.3%-67.3%)	52% (95% CI, 47 to 55%)	51.9% (95% CI, 38.3 to 65.5)	56% (95% CI, 38% to 71
24-month OS rate	[redacted]	20.3% (95% CI, 9.1%-34.7%)	21% (95% CI, 18-25%)	26.4% (95% CI, 14.2 to 38.6)	NR (~40% from graphic reading)
6-month PFS	[redacted]	18.9% (95% CI, 12.0%-27.2%)	NR	28.8% (95% CI, 16.5 to 41.1)	NR (~45% from graphic reading)
12-month PFS	[redacted]	11.7% (95% CI, 6.1%-19.2%)	NR	19.2% (95% CI, 8.5 to 29.9)	NR (~15% from graphic reading)

Abbreviations: OS, overall survival; PFS, progression-free survival; NR, not reported

C26. CS Tables 20 and 21 provide a helpful comparison of modelled results and clinical data.

a. Please extend these Tables by including the KM data from Rantala et al. (as indicated in the Table header).

The data from Rantala et al., presented in

Table 40 and **Table 41** has been added as requested. Please note that this data was not reported in the paper and was derived by Rantala et al. by digitisation of the KM curves to create pseudo-PLD.

Table 40. OS parametric models IC arm ITT set DCO October 2020 vs KM curve and Rantala et al first-line (digitised)

Months	KM	Rantala (digitised)	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC			**4**	**1**	**3**	**2**	**5**	**6**
6	**78.1%**	81.3%	74.2%	78.8%	75.9%	77.8%	78.1%	78.1%
9	**63.2%**	66.0%	63.9%	67.0%	63.5%	65.0%	67.5%	65.8%
12	**58.5%**	51.1%	55.0%	56.0%	53.7%	54.3%	57.3%	54.9%
18	**42.9%**	34.5%	40.8%	37.7%	39.5%	38.6%	38.8%	37.8%
24	**20.3%**	21.7%	30.2%	24.3%	30.2%	28.6%	23.8%	25.9%
30	**10.2%**	13.0%	22.4%	15.2%	23.7%	22.1%	12.9%	17.8%
36 (3 years)		9.8%	16.4%	9.1%	18.9%	17.4%	5.8%	12.1%
48 (4 years)		6.7%	9.0%	3.1%	12.8%	11.9%	0.6%	5.8%
60 (5 years)		2.7%	5.0%	1.0%	9.2%	8.7%	0.0%	2.8%
120 (10 years)			0.2%	0.0%	2.6%	3.1%	0.0%	0.1%
	Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

Table 41. OS parametric models IC arm ITT set DCO August 2021 vs KM curve and Rantala et al first-line

Months	KM	Rantala (digitised)	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
Ranking based on AIC and BIC			**3**	**1**	**2**	**4**	**5**	**6**
6	[redacted]	81.3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	66.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	51.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	34.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	21.7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	13.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3 years)		9.8%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4 years)	[redacted]	6.7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5 years)	[redacted]	2.7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10 years)	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion							

b. Please elaborate on the plausibility of using data from Rantala et al. to compare the modelled results given the differences in treatments, e.g. Rantala et al. is based on chemotherapy only, without the immunotherapy options included in the control arm of the IMCgp 100-202 trial.

Rantala et al. conducted a meta-analysis of studies in metastatic uveal melanoma, including a range of treatment modalities, not just chemotherapy. In particular, they have included nine studies on checkpoint inhibitors (anti-PD-1, anti-CTLA4 antibody), which included studies on the immunotherapies included in the control arm. Rantala et al. reported no clinically significant difference in OS by treatment modality, and no therapy demonstrated a significant improvement in OS in the last 40 years (Yang et al., 2018, Khoja et al., 2019). Therefore, we believe that the data reported by Rantala et al. on first-line patients is the most appropriate benchmark available for comparison with the trial IC arm of study IMCgp100-202.

C27. The investigator's choice clinical trial OS reported in CS Appendix J Table (12 months) seems incorrect.

Please provide a corrected version of this Table if applicable.

RESPONSE

The corrected table is provided in Table 42.

Table 42. Comparison of modelled overall survival with results of the IMCgp100-202 study

Technology	Clinical trial OS		Modelled OS	
	Tebentafusp	IC	Tebentafusp	IC
Median survival (months)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
6 months	[redacted]	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]	[redacted]

Section D: Textual clarification and additional points

D1. Priority question. Considering Table 82, end of life criteria might apply.

Please clarify whether end of life criteria should be considered for this CS. If so, please provide the relevant details.

End of life criteria should apply for this company submission; further details are provided below:

i. *The treatment is indicated for patients with a short life expectancy, normally less than 24 months*

The current life expectancy for patients with metastatic uveal melanoma is very short. The median survival from the time of development of metastatic disease is 12-15 months and 1-year survival is around 50% (Nathan et al., 2015, Kuk et al., 2016, Damato et al., 2019).

ii. *There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment*

The Phase 3 RCT, study IMCgp-100-202, has demonstrated that patients randomised to tebentafusp as first-line therapy had a significant reduction of risk of death compared with those treated with investigator's choice therapies (i.e., pembrolizumab, ipilimumab or chemotherapeutic dacarbazine) after a median follow-up of 14.1 months. The estimated one-year OS rate was 73.2% among patients in the tebentafusp arm, compared with 58.5% in the investigator's choice arm. Historical data from two large meta-analyses examining a range of treatment options that have been tested in metastatic UM demonstrate 1-year overall survival for previously tested treatments is reported to be 52-56% (Khoja et al., 2019, Rantala et al., 2019). Current NICE approved clinical guidelines for metastatic UM suggest patients should be enrolled on clinical trials (Nathan et al., 2015). In the absence of specific approved systemic treatments clinicians can employ treatments that are recommend for any type of metastatic melanoma such as ipilimumab, nivolumab or pembrolizumab. None of these treatments have shown demonstratable survival benefit, as single agents or in combination, that is comparable to tebentafusp for metastatic UM. Based on the cost-effectiveness model, the life-year gain is [redacted] years in

the base-case. The incremental LYs range between [redacted], depending on the approach used to modelling OS.

iii. The treatment is licensed or otherwise indicated, for small patient populations.

Uveal melanoma is a rare disease as recognised by the orphan designation for tebentafusp from the Committee for Orphan Medicinal Products (EMA, 2021) and the anticipated orphan designation of tebentafusp from the MHRA. The incidence of primary UM is 540 patients annually in the UK (ONS 2019), half these patients go on develop metastatic disease (Yang et al., 2018). The estimated incidence of metastatic UM patients who will be clinically eligible to receive tebentafusp, the indication for the technology being appraised is ~100 per year.

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Appendices

Appendix 1

Clinical and economic SLR updated PRSIMA diagrams

Figure 33: PRISMA flow diagram for clinical SLR, adapted from Moher et al. (2009).

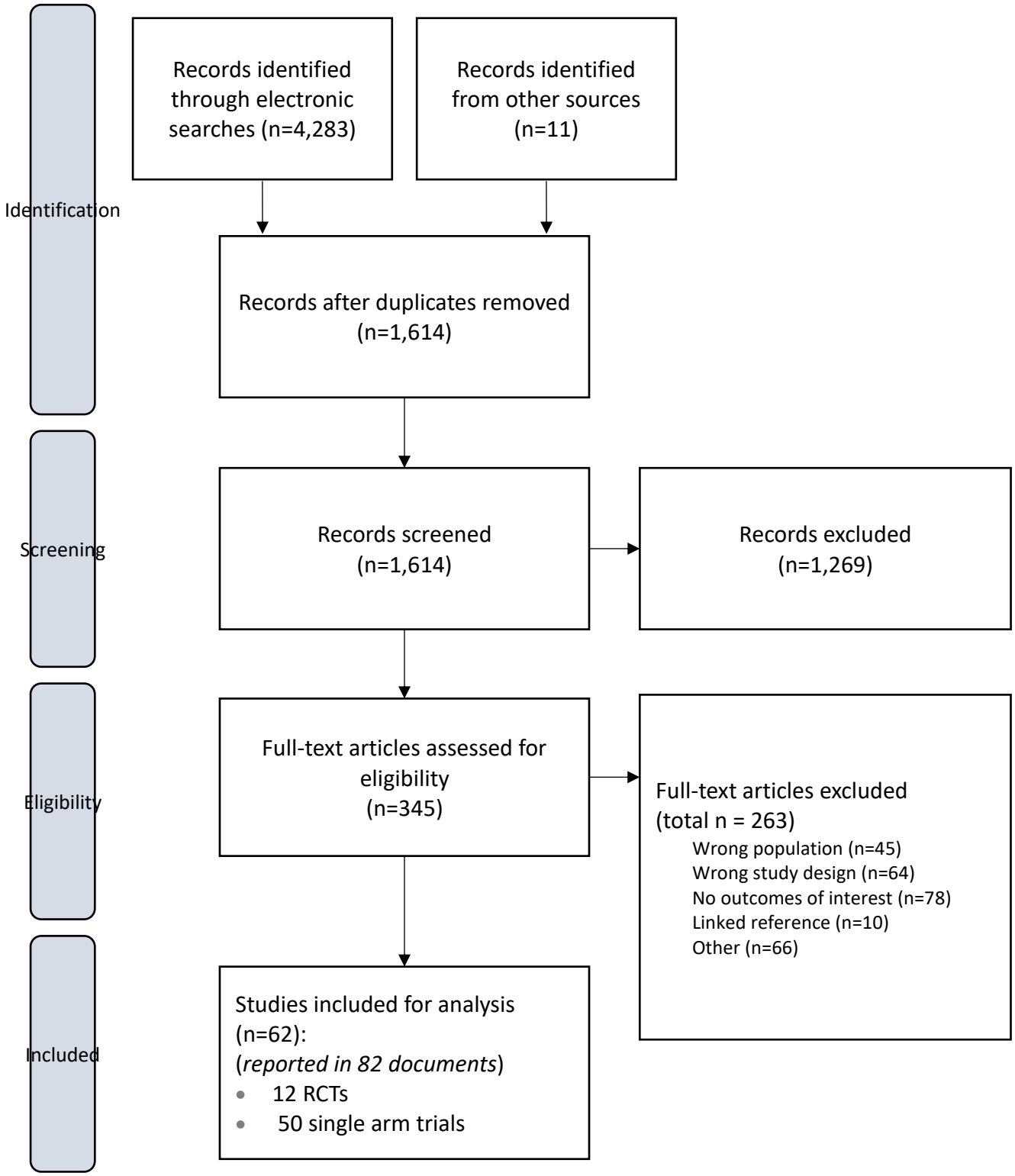
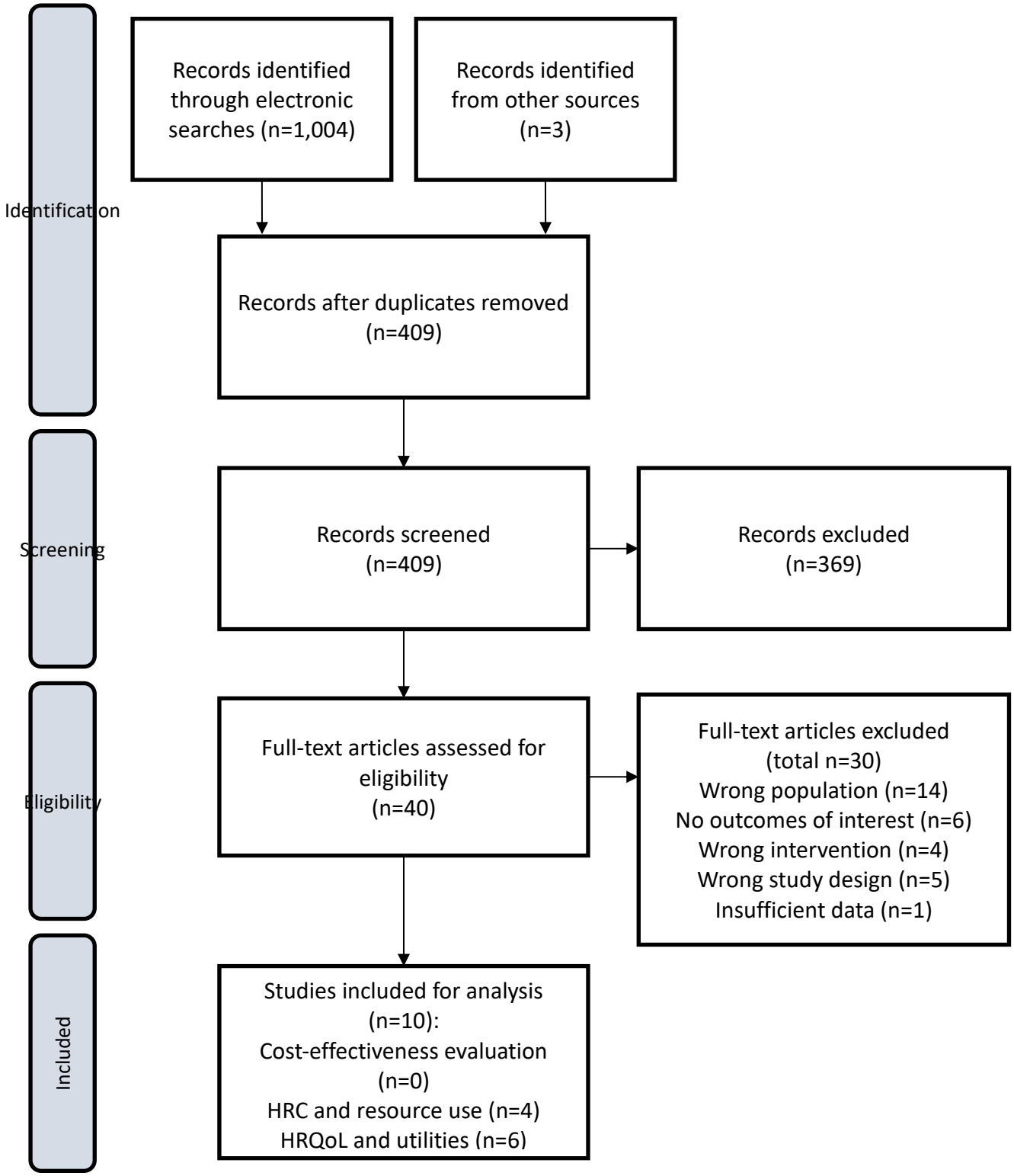


Figure 34: PRISMA flow diagram for economic SLR, adapted from Moher et al. (2009).



Appendix 2

Table 43: List of records excluded from clinical SLR based on a full-text review and the reason for each exclusion.

Author	Year	Title	Reason for exclusion
Glitza, I. C	2020	Phase Ib study to evaluate the safety of selinexor (SEL) in combination with pembrolizumab (PEM) in patients with advanced malignancies- the: The melanoma experience	Outcomes not specific to UM or choroidal melanoma
Gonsalves, C. F.	2009	Chemoembolization of hepatic malignancy	Wrong study design
Jung, M.	2017	Ipilimumab real-world efficacy and safety in Korean melanoma patients from the Korean named-patient program cohort	Outcomes not specific to UM or choroidal melanoma
Kelleher, F. C	2012	Molecular therapeutic advances in personalized therapy of melanoma and non-small cell lung cancer	Wrong study design
Khattak, M.	2013	Targeted therapy and immunotherapy in advanced melanoma: An evolving paradigm	Wrong study design
Khushalani, N. I.	2019	CA045-001: A phase III, randomized, open label study of bempegaldesleukin (NKTR-214) plus nivolumab (NIVO) versus NIVO monotherapy in patients (pts) with previously untreated, unresectable or metastatic melanoma (MEL)	Wrong population
Lawson,D.H	2015	Randomized, placebo-controlled, phase III trial of yeast-derIVed granulocyte-macrophage colony-stimulating factor (GM-CSF) versus peptide vaccination versus GM-CSF plus peptide vaccination versus placebo in patients with no evidence of disease after comp	Outcomes not specific to UM or choroidal melanoma
Tjulandin, S	2021	Novel PD-1 inhibitor prolgolimab: expanding non-resectable/metastatic melanoma therapy choice	Outcomes not specific to UM or choroidal melanoma

Table 44: List of records excluded from economic SLR based on a full-text review and the reason for each exclusion.

Author	Year	Title	Reason for exclusion
Buffery, D.	2015	The 2015 oncology drug pipeline: Innovation drives the race to cure cancer	Wrong study design
Khushalan, N. I.	2019	CA045-001: A phase III, randomized, open label study of bempegaldesleukin (NKTR-214) plus nivolumab (NIVO) versus NIVO monotherapy in patients (pts) with previously untreated, unresectable or metastatic melanoma (MEL)	Wrong population
Mangana, J.	2017	Multicenter, real-life experience with checkpoint inhibitors and targeted therapy agents in advanced melanoma patients in Switzerland	Outcomes not specific to UM or choroidal melanoma
Russi, A.	2017	Case study on an ipilimumab cost-containment strategy in an Italian hospital	Outcomes not specific to UM or choroidal melanoma
Savoia, P.	2016	Ipilimumab (Anti-Ctla-4 Mab) in the treatment of metastatic melanoma: Effectiveness and toxicity management	Wrong study design
Scherz, N.	2017	Case management to increase quality of life after cancer treatment: A randomized controlled trial	Outcomes not specific to UM or choroidal melanoma
Wang, D.	2015	A critical appraisal of the clinical utility of proton therapy in oncology	Wrong study design

Wouters, M. W.	2018	ECCO essential requirements for quality cancer care: Melanoma	Wrong study design

Appendix 3

Clinical SLR outcomes and quality assessment

See attached document

NICE National Institute for Health and Care Excellence

Professional organisation submission

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Melanoma Focus**

3. Job title or position	**Trustee of Melanoma Focus**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	Melanoma Focus, a national UK charity is unique in its field, combining the functions of professional education, patient support and advocacy with the role of providing representation and up-to-date scientific information for UK healthcare professionals involved in melanoma. Melanoma Focus organises two professional meetings a year, creates guidelines on rare melanomas using NICE-accredited methodology and produces other consensus guidelines. **Funding is from personal donations and fundraising activities, professional membership and sponsorship for various activities**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Melanoma Focus has received funding from multiple Pharma in the field of melanoma as sponsorship for meetings and a project; **Funding has always been multiple Pharma supporting meetings/projects**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**no**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve survival
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Improvement of Overall Survival vs standard of care with a Hazard Ration of < 0.7

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	With immune checkpoint inhibitors, chemotherapy, surgery, hepatic chemosaturation / embolisation
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. UK Uveal Melanoma Guidelines (nathan et al, EJC, 2015 – currently under revision). NICE approved.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Yes

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	A change in standard of care
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Will be at expert specialist cancer centres (as is current treatment)
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients must be HLA A2.01
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Treating clinicians will need to be trained in AE management
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No formal starting/stopping rules
15. Do you consider that the use of the technology will result in any substantial health-	Yes. QALY insensitive to QOL improvement

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Very innovative
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Disease control improves QOL
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – many UK patients on this study
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	OS
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	No
21. How do data on real-world experience compare with the trial data?	Major improvement in comparison to historical outcomes with previous standard treatments
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Only an option for the 50% ofpatients who are HLA A2.01
22b. Consider whether these issues are different from issues with current care and why.	As above

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Uveal Melanoma entirely different from cutaneous melanoma (EMA have accepted it as a distinct entity).
- Rare tumour with poor survival for metastatic disease and major clinical need.
- No survival advantage proven with current therapy
- This is the first agent to improve survival for metastatic UM. HR of 0.51 for OS is a profound benefit.
- This is highly innovative – first drug of this class to show survival benefit in solid cancer. Reflected by acceptance in NEJM.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

NICE National Institute for Health and Care Excellence

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Patient organisation submission

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]

About you	
1.Your name	[redacted]
2. Name of organisation	OcuMel UK
3. Job title or position	National Director
4a. Brief description of the organisation (including who funds it). How many members does it have?	OcuMel UK is a registered charity supporting people affected by ocular melanoma. Our vision is a world where ocular melanoma patients are given the information, support and treatment they need. We run a helpline and enable peer support through our online community and events. We provide psychological, emotional and bereavement support to members at no cost. We have approx. 700 members, and most of our income comes from the community we support through donations and fundraising efforts. Immunocore has been one of three companies that we have received funds from over the past three years. See below:

09/11/2018	Immunocore	Sponsorship of conference	6,000
05/06/2019	Medac	Sponsorship of conference	10,000
11/06/2019	Immunocore	Sponsorship of conference	10,000
24/07/2019	Aura Bioscience	Sponsorship of conference	4,013
29/08/2019	Immunocore	Fundraising T-shirts	53
12/12/2019	Immunocore	Sponsorship of nurse	10,000
12/02/2021	Medac	Patient Grant Funding	110,000

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? No

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry? No	
5. How did you gather information about the experiences of patients and carers to include in your submission?	We created and shared a survey in our monthly bulletin, on social media and in our online forums. It is being circulated to clinicians so that more patients can have an input into this review. We expect to share the results of this survey ahead of the committee meeting in May 2022. We were part of a group with Public Health England to better partition the data around Eye Cancer, and a more breakdown of ages will be available in November 2021. The following papers were used in this submission: Hussain RN, Coupland SE, Kalirai H, et al. Small High-Risk Uveal Melanomas Have a Lower Mortality Rate. *Cancers (Basel)*. 2021;13(9):2267. Published 2021 May 8. doi:10.3390/cancers13092267 Sacco JJ, Kalirai H, Kenyani J, Figueiredo CR, Coulson JM, Coupland SE. Recent breakthroughs in metastatic uveal melanoma: A cause for optimism? Futur Oncol [Internet]. 2018;14(14):1335–8 Yang J, Manson DK, Marr BP, Carvajal RD. Treatment of uveal melanoma: where are we now? Ther Adv Med Oncol [Internet]. 2018 Jan 1 [cited 2021 Jul 13];10:1758834018757175 Carvajal RD, Schwartz GK, Tezel T, Marr B, Francis JH, Nathan PD. Metastatic disease from uveal melanoma: treatment options and future prospects. Br J Ophthalmol [Internet]. 2017;101(1):38–44
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	<u>6A. What is it like to live with the condition?</u> Ocular Melanoma (OM) is a rare cancer. There are two types of ocular melanoma: Uveal Melanoma (UM) and Conjunctival Melanoma (CM). UM affects the structures in the middle layer of the eye. The causes of this disease are not really understood, and unfortunately there is nothing that can be done to prevent it. The average age of UM patients is thought to be 60, but OcuMel UK have a significant proportion of younger people in our forums, including people in their 20s and 30s with stage 4 disease. Around 600-700 people a year in the UK will be diagnosed with OM, and about 95% of these patients will have UM. 50% of patients will become stage 4, usually in years 1-3 after primary diagnosis, but it is known to recur after 25 years and still be aggressive in nature.

	Ocular melanoma is not just about the eye. Patients are unaware whether their cancer will return but they are aware that if it does, it is terminal and aggressive in nature. There are techniques to calculate risks of metastatic disease, but this involves a biopsy which is not routinely available at every specialist centre. Patients might need to travel to a specialist centre. Treatments for the primary tumour have largely remained the same over the years but benefits from prognostic biopsies are increasing. Vision loss is common. Enucleated patients report difficulties with depth perception, pouring drinks, using stairs, whereas patients treated with proton beam or plaque initially retain their vision, but this tends to deteriorate with time. Long-term fatigue is often reported in our forums although there has been little data published on this topic. Treatment of the cancer in the eye is usually successful. However 50% of patients will eventually develop metastatic tumours. This can happen at any time after the first diagnosis, though typically within 3-4 years. The common sites of metastasis include liver (89%), lung (29%), bone (17%), skin and subcutaneous tissue (12%), and lymph node (11%). In a study of long-term prognosis of patients with uveal melanoma who were observed for a median of 28 years, the Kaplan–Meier estimates of metastasis were 32% by 5 years, 50% by 15 years, 56% by 25 years, and 62% by 35 years. There is currently no cure for metastatic UM. Patients are scanned every 6 months and live their lives in 6 monthly blocks. If metastatic disease is detected, they may only have a life expectancy of 6-9 months, perhaps 12, depending on how early it was detected. Approximately 10% of people can have a liver resection. The overall median survival for patients treated with surgery/ablation was 27 (14–90) months. When the cancer returns, it may be possible to repeat the resection. This is not always possible as tumours may be peppered throughout the liver. Cancer can also occur in other sites including bones, lungs, pancreas and brain. Patients live with the knowledge that metastatic UM is terminal, so they live in fear. A patient described this disease as having a loaded gun just behind them every day that clicks every so often to remind you that your life could change instantly. The psychological burden is immense and psychological support is not available on the NHS to the majority of UK patients. *"I know too many people who didn't get the treatment they needed. I naively felt reassured when they told me I was at 'low risk' of my cancer returning. I only had ultrasounds, but I thankfully heard some patients were being offered MRI scans and so I asked my team for this to be arranged. It wasn't easy but thankfully I did, as after a few scans, they found 3 tumours in my liver."* UM patient **Impact on patients**

	Some stage 4 patients have few symptoms, and are either working or have taken early retirement because of their vision loss, but may live active lives raising young children, helping with grandchildren, volunteering and enjoying other activities. Others can experience severe symptoms. Physical considerations Many patients report severe fatigue. Some stage 4 UM patients may experience symptoms associated with liver cancer, including fatigue, feeling generally unwell, pain, loss of appetite, nausea and/or vomiting, massive weight loss, generalised itching, fluid in the abdomen, jaundice, liver enlargement and spleen enlargement. Tumours may develop outside of the liver, including in the lungs, bones, pancreas and brain. These tumours may not always be diagnosed or treated due to the aggressive nature of the liver cancer in most stage 4 patients. Bone metastases are typically very painful. The long-term physical impact on the eye can include loss of vision, cataracts, diplopia, glaucoma, and visual disturbances such as flashing lights and phantom images. The chances of a patient developing issues will depend on many factors such as the type, location and size of the tumour, and the treatment that they have had. This vision loss can have practical implications for patients with advanced UM. Practical considerations Vision loss following treatment for UM can create an additional burden in dealing with the effects of stage 4 cancer. Patients are initially treated in one of 4 national centres for eye cancer and have to travel for appointments. Travelling long distances continues for patients with metastatic disease, as liver-directed treatments can only be performed at specialist liver centres. Psychological and social considerations Patients are highly aware of the risk of metastatic spread, and that there is no cure for stage 4 UM. Knowing this, is terrifying and many patients struggle with this. *"We need some hope to reduce the despair of knowing we have no effective treatments available."* UM patient Patients have to live with the very real risk of untreatable stage 4 cancer throughout their lives. Metastatic cancers can be aggressive and the disease may well be very advanced before it is identified, meaning patients may not have long to live once they become aware of their diagnosis with stage 4 cancer. Knowing that a treatment existed

	that could extend and improve the lives of stage 4 patients would, in fact, have a benefit to all UM patients at risk of stage 4 UM – the prospect of hope would doubtless improve the quality of life of all those living with UM. *"My life changed in the 'Blink of an eye'. I dreaded hearing that my eye would need to come out. I didn't hear it at first, but after Plaque Brachytherapy and Proton Beam Therapy 6 years later, losing my eye is what I wish for...I'm not afraid...I am tired of pain, and the 6 monthly bouts of traumatic fear of my MRI scans and my liver saying, "sorry I'm growing in here too". Christmas this year is ruined as fear and anxiety consumes all. When I hear I am clear, I can breathe, love, live and laugh until the next date. Fear has changed my personality."* UM patient. 6B What do carers experience when caring for someone with the condition? Some stage 4 UM patients will require care to support them with needs arising from vision loss and the psychological pressures of 6 monthly scans and the physical, practical and psychological challenges of stage 4 UM. This can put a strain on relationships within a family. *"When we learnt my father had stage 4 disease, we all felt totally helpless and immediately blamed ourselves for assuming a treatment plan would follow. We had no idea there was so little available. We wasted so much time heading from one hospital to the next trying to find something. By the time he was looked after by a specialist, his disease was very advanced. We have no doubts that had it come sooner, we would have had longer together… It's left us with little trust in the system."* Daughter of UM patient.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Treatments for stage 4 UM are limited and, ultimately, have a limited impact on the terminal disease. Patients speak of the impact lack of hope has on their lives. As one UM patient said, *"What do I think of treatments for stage 4 disease? Scared, as they are hardly in existence."* Around 10% of patients can have a liver resection, but the cancer will eventually return: *"I really was one of the lucky ones as I was able to have liver surgery to take them out. I have been able to see my children through school, I still work full-time and help my mum who is 92 years old. I can't even describe how little treatment options we have. They have told me it will come back and, I hope I can have another liver resection and if I can't, I really hope Tebentafusp is available as it's terrifying otherwise. Next week is scan week and this really doesn't get any easier."* UM patient

	Patients who cannot have a liver resection are offered immunotherapy if they are well enough to undergo treatment. Some patients receive immunotherapy, Ipilimumab/Nivolumab, which has severe side effects in most patients. Warning signs and admissions into hospital are often shared on our online forums: *"I was advised there was no standard of care. The treatment offered was immunotherapy at less than 8% success rate, this was devastating news to myself and my family. Where do you go from here? I was broken. I was told I had 3-6 months of life if no treatment was taken up. I started on Keytruda in December 2020 and had 3 treatments with no success. I had the mindset I had to be in that 8%. The next immunotherapy was Ipilimumab. I had 3 treatments and had mild progression of the liver disease. I also had side effects, of fatigue, nausea, loss of appetite, brain fog, 3 emergency visits to hospital, 2 over nights stays, colitis, liver levels extremely high which meant eventually I had to stop ipi. I suffered for 4 months losing weight (8kg), having diarrhoea, vomiting and the side effects above. I had no energy. I was cycling, doing yoga and walking prior to February 2021. I was researching the world for treatments to help my disease and my liver was peppered with 25+ lesions across both lobes."* UM patient Finally, patients may be offered chemotherapy. This may be offered locally but has typical side effects and poor outcomes. We know extremely poor responses have been seen with both chemo. Liver targeted treatments can sometimes control liver disease, but it has no effect on systemic disease, from which the patient inevitably dies. Navigating the limited treatment options, with little hope of a successful therapy takes a toll on patients and families: *"I found myself having to support my dad and answer questions that I didn't have the answers to. At every corner we received conflicting advice, as there is so little known. I had the responsibility for helping him decide what to do. Deep down I knew we were running out of time and the pressure was immense. I couldn't take the backseat and just support him, he needed hope, we all did."* UM daughter Tebentafusp has changed the direction of care for HLA-0201 positive patients and we are finally seeing patients able to live with this condition. It's incredible to speak to people who would certainly have lost their life without it and simply amazing they feel so well.
8. Is there an unmet need for patients with this condition?	There is no cure for stage 4 UM and treatments such as liver resection aim to prolong life and manage the cancer for as long as possible. Unfortunately, the cancer is usually very aggressive, and these treatments may not be effective. The condition is terminal and there is a need for a systemic treatment that can prolong and improve the lives of those with UM. In April 2021 NICE published Interventional Procedure guidance on Chemosaturation. See https://www.nice.org.uk/guidance/ipg691/chapter/1-Recommendations. There is no current funding in place.

	Some patients have privately raised £240,000 for private treatment. This treatment aims to control liver metastases only. It is not a systemic treatment and patients still have no treatment to address their underlying condition.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Tebentafusp will be used for HLA-0201 positive patients, which is around 50% of the UM population. The main advantage is the effectiveness of the treatment – it works! This treatment is spoken of favourably in our community forums, with people experiencing few side effects unlike other systemic treatment options which are usually considerable and lifelong. Approval of this treatment will bring a change for the physical and psychological impact of uveal melanoma. When someone developed metastatic disease historically, there was a short window where they lived with the condition. We now hear people saying, '*when I was first on treatment'*, and then they go onto say that 2 years later, their side effects have settled. We haven't had people living with systemic treatments before. It is truly incredible. *"I came across this trial drug, which had just finished its 2 year trial period and the results paper released was very exciting for me and gave hope. I quickly got in touch with my oncologist and she put me in touch with another oncologist who was running the trial at their cancer centre, but it was difficult as the drug has to go through a process before it could be offered to patients like myself. I was advised maybe 18 months. I was devastated as time was not on my side, the mental state this process left me in was appalling. I chased this drug with intention and emailed Immunocore direct with a plea to get this drug through my oncologist. My brother and close friend also contacted Immunocore on my behalf, they kindly responded and directed me to my oncologist to contact them and advised family/friend they could only speak to patient or oncologist. I chased this drug hard and eventually, in May, I received my first treatment of Tebentafusp. I was nervous, excited and relieved I'd finally got there."* UM patient We would expect severe side effects to be shared on our forums, but there have been very few discussions about Tebentafusp. People report only rashes and weekly hospital visits. Our biggest issue is that the clinical trial closed as COVID began and only a few people have managed to get access through an Early Access Programme. A key expectation for Tebentafusp is that it will prevent metastasis and progression of cancer in all parts of the body, not just the liver. This will offer hope to stage 4 patients as well as those living with the real risk of developing metastatic disease and the stress of 6 monthly monitoring checks. *"My family are overjoyed to have their wife, momma, nannie & daughter successfully treated and able to live life better under this black cloud of this terrible rare disease."* UM Patient

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Tebentafusp will require a weekly infusion in a hospital-based specialist centre. This will involve a lot of travel which may not be easy for some patients, especially those with problems following vision loss. We understand that no break in treatment will be possible, and there will be uncertainty as to the duration of treatment. We expect Tebentafusp to be generally well tolerated after initial side effects but that patients may lose pigment in skin, find their eyebrows turn white and lose their eyelashes. Some patients have reported harsh side effects at the start of treatment: *"In May, I received my first treatment of Tebentafusp. I was nervous, excited and relieved I'd finally got there. I had to fly to the appointment and relocate for the first 4 weeks, then I proceeded to fly in and fly out. It was a stressful time, and had side effects of severe rash, hypotension and high temperature during the first 3 treatments. The first 1-10 weeks left me with blisters, rashes, swollen eye, face & neck, hives. It was intense on the first 3 treatments during the overnight stays*." UM Patient For some patients the biggest challenge has been travelling to treatment centres twice a week: *"Although the initial side effects are harsh for some, not all, this does settle down and consequent side effects are minimal and can be lived with. This is not the case for other immunotherapy drugs that can have very severe side effects. The initial harsh side effects can be off putting for some. Not everyone has easy access to the treatment. We had a 5 hr return journey twice a week which was very tiring. If the treatment can get NICE approval, hopefully it will be more accessible to more people.* UM Patient People with this condition typically have reduced vision and therefore travelling to appointments can be challenging, with many needing assistance from family or friends. Approval of this drug will enable more sites to offer the treatment and reduce travelling times for patients.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why. No.	

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are aware of geographical variation in access to treatment including scans to identify metastatic disease. We do not know if this results in variations in survival rates for UM.
Other issues	
13. Are there any other issues that you would like the committee to consider?	OcuMel UK is undertaking a survey of OM patients and would like to share this output ahead of the committee meeting in 2022.
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Stage 4 UM is a terminal disease with no effective treatment.
- All UM patients live at risk of developing metastatic disease and face 6 monthly monitoring throughout their life.
- The risk of developing stage 4 cancer, which currently has no satisfactory treatment, is a devastating psychological burden for all patients and their families.
- Tebentafusp is well tolerated and expected to significantly prolong and improve life in stage 4 UM patients. It will have an impact on all secondary tumours, not just liver tumours.
- The prospect of an effective treatment will not only benefit patients with advanced UM, it will also relieve some of the fear and anxiety all UM patients and their families face as they watch and wait to see if they will be in the 50% of patients who develop metastatic UM.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Opthalmologists/Royal College of Pathologists**

3. Job title or position	**Consultant Ocular Oncologist, Royal Liverpool Hospital**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Professional membership organisation**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**no**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**no**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Local tumour control Reduce the risk of vision/eye threatening complications
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Reduction in tumour size on ultrasound Continued tumour stability long term

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Local tumour control is well established; prognostic markers are also well understood. However treatment of metastatic disease is limited and generally unsuccessful.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Poor control of metastatic disease currently. This newer drug may change the long term outcomes of a subset of these patients
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	None established yet, although it seems that a certain subset of patients with specific HLA characteristics are more likely to respond. We may create guidelines which incorporate the indentification of such patients at the time of treatment of their local disease
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	This drug is still in its early phases of use, and as such the experience is limited

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Long term control and treatment of metastatic disease would be ground breaking in this area of medicine
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This drug will be used by medical oncologists in a similar manner to other treatments for metastatic uveal melanoma
• How does healthcare resource use differ between the technology and current care?	The success of current care to control metastatic disease is lower; this drug has shown more promise than any before
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Directly under medical oncologists with some experience and interest in metastatic disease from uveal melanoma in the hospital setting
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Absolutely. The current treatment outcomes are poor
• Do you expect the technology to increase length of life more than current care?	For the correctly identified subgroup of patient in whom this treatment works, this will certainly give an increased life expectancy
• Do you expect the technology to increase health-related quality of life more than current care?	I would expect the treatment to not only prolong life but to prolong the period of life with minimal medical intervention due to better tumour control
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This treatment is for patients with metastatic uveal melanoma, and works best in those with certain HLA characteristics.
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The treatment regime and administration will be similar to current chemotherapeutic agents for this disease. There is unlikely to be an increase in burden of patient time or healthcare professionals input. However, it is likely that these treatments would be undertaken or supervised by specilists with experience in this field, which may require patients to travel further than their local hospital for advice and treatment planning at least
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not sure
15. Do you consider that the use of the technology will result in any substantial health-	no

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	As mentioned above, the current treatment outcomes are poor, and as such this drug is likely to have a significant impact on patient survival and long term control of metastatic illness related to uveal melanoma.
• Is the technology a 'step-change' in the management of the condition?	no
• Does the use of the technology address any particular unmet need of the patient population?	Successful treatment of metastatic disease

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects are limited to those similar to other chemotherapeutic agents
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	no
• If not, how could the results be extrapolated to the UK setting?	Experiences medical oncologists would oversee and direct treatment protocols
• What, in your view, are the most important outcomes, and were they measured in the trials?	Control of metastatic disease and prolongation of life, both of which were measured in trials
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not in my area of expertise
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	no
21. How do data on real-world experience compare with the trial data?	Not my area of expertise
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	If patients are to travel long distances to centres with higher levels of experience and expertise, this may produce a geographical inequality.
22b. Consider whether these issues are different from issues with current care and why.	most metastatic uveal melanoma is best treated in specialist centres, but this is currebtly not the case

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Local tumour control of uveal melanoma is good.
- Current treatment of metastatic uveal melanoma is poor with poor outcomes
- Mortality of uveal melanoma patients is apporx 50%
- There are well established prognostic markers but as yet these have not aided in prevention/treatment of metastatic disease
- Tebentafusp has proven to be the most successful treatment so far for metastatic uveal melanoma

Thank you for your time.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Tebentafusp for the treatment of advanced (metastatic or unresectable) uveal melanoma in HLA-A*02:01 positive adults [ID1441]

Produced by Kleijnen Systematic Reviews (KSR) Ltd, United Kingdom (UK) in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University, the Netherlands

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Declared competing interests of the authors

None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Andrea Fernández Coves and Willem Witlox acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Charlotte Ahmadu and Nigel Armstrong critiqued the clinical effectiveness methods and evidence as well as the company's economic evaluation and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report, and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

Abbreviations

AE	Adverse event
AIC	Akaike information criterion
AiC	Academic in confidence
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CiC	Commercial in confidence
CNS	Central nervous system
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRS	Cytokine release syndrome
CS	Company submission
DARE	Database of Abstracts of Reviews of Effects
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	European Quality of Life-5 Dimensions-5 levels
EORTC-QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
FE	Fixing errors
FV	Fixing violations
GP	General practitioner
HLA-A	Human leukocyte antigen (A locus)
HR	Hazard ratio
HRQoL	Health-related quality of life
HTAD	Health Technology Assessment Database
IC	Investigator's choice
ICER	Incremental cost effectiveness ratio
ICR	Independent central review
ICTRP	International Clinical Trials Registry Platform
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LDH	Lactate dehydrogenase
LY	Life year
MAIC	Matching-adjusted indirect comparison

MCAR	Missing completely at random
mcg	Microgram
MHRA	Medicines and Healthcare Products Regulatory Agency
MinR	Minor response rate
MTD	Maximum tolerated dose
N	Number of participants
N/A	Not applicable
NC	Not calculable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PF	Progression-free
PFLY	Progression-free life year
PFS	Progression-free survival
PICOS	Population, intervention, comparator(s), outcome(s), study design(s)
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PSA	Probabilistic sensitivity analysis
PSM	Partioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
RAS	Rash analysis dataset
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RMST	Restricted mean survival time
RP2D	Recommended phase 2 dose
RR	Response rate
SAE	Serious adverse event
SE	Standard error
SLR	Systematic literature review
STA	Single technology appraisal
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UAIC	Unadjusted indirect comparison
UK	United Kingdom
ULN	Upper limit of normal
UM	Uveal melanoma
UMC+	University Medical Centre+
WHO	World Health Organization

Table of Contents

Abbreviations **3**

Table of Tables **7**

Table of Figures **9**

1. EXECUTIVE SUMMARY **10**

1.1 Overview of the ERG's key issues 10
1.2 Overview of key model outcomes 10
1.3 The decision problem: summary of the ERG's key issues 11
1.4 The clinical effectiveness evidence: summary of the ERG's key issues 12
1.5 The cost effectiveness evidence : summary of the ERG's key issues 12
1.6 Other key issues: summary of the ERG's view 17
1.7 Summary of the ERG's view 18

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM **20**

2.1 Population 24
2.2 Intervention 24
2.3 Comparators 24
2.4 Outcomes 25
2.5 Other relevant factors 25

3. CLINICAL EFFECTIVENESS **26**

3.1 Critique of the methods of review(s) 26
3.1.1 Searches 26
3.1.2 Inclusion criteria 27
3.1.3 Critique of data extraction 28
3.1.4 Quality assessment 28
3.1.5 Evidence synthesis 29
3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these) 29
3.2.1 IMCgp100-102 32
3.2.2 IMCgp100-202 32
3.2.3 Efficacy results 38
3.2.4 Safety results 48
3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison 54
3.4 Critique of the indirect comparison and/or multiple treatment comparison 55
3.5 Additional work on clinical effectiveness undertaken by the ERG 56
3.6 Conclusions of the clinical effectiveness section 56

4. COST EFFECTIVENESS **58**

4.1 ERG comment on company's review of cost effectiveness evidence 58
4.1.1 Searches performed for cost effectiveness section. 58
4.1.2 Inclusion/exclusion criteria 59
4.1.3 Conclusions of the cost effectiveness review 60
4.2 Summary and critique of company's submitted economic evaluation by the ERG 60
4.2.1 NICE reference case checklist 60

4.2.2 Model structure 61
4.2.3 Population 62
4.2.4 Interventions and comparators 62
4.2.5 Perspective, time horizon and discounting 64
4.2.6 Treatment effectiveness and extrapolation 64
4.2.7 Adverse events 74
4.2.8 Health-related quality of life 75
4.2.9 Resources and costs 79

5. COST EFFECTIVENESS RESULTS 84

5.1 Company's cost effectiveness results 84
5.2 Company's sensitivity analyses 86
5.3 Model validation and face validity check 86
5.3.1 Face validity assessment 86
5.3.2 Technical verification 86
5.3.3 Comparisons with other technology appraisals 86
5.3.4 Comparison with external data 86

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES 88

6.1 Exploratory and sensitivity analyses undertaken by the ERG 88
6.1.1 ERG base-case 88
6.1.2 ERG exploratory scenario analyses 89
6.1.3 ERG subgroup analyses 89
6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG 92
6.3 ERG's preferred assumptions 94
6.4 Conclusions of the cost effectiveness section 95

7. END OF LIFE 97

8. REFERENCES 99

Table of Tables

Table 1.1: Summary of key issues 10

Table 1.2: Key issue 1: Mixed therapy (investigator's choice) as comparator precludes separate evaluation of tebentafusp versus each comparator 11

Table 1.3: Key issue 2: Lack of comparison to nivolumab monotherapy 12

Table 1.4: Key issue 3: Frequency of adverse events in tebentafusp 12

Table 1.5: Key issue 4: Model structure – Use of a partitioned survival model 13

Table 1.6: Key issue 5: Interventions and comparators –The use of the treatment mix in the IC arm of the IMCgp100-202 study as single comparator and not including nivolumab as comparator 13

Table 1.7: Key issue 6: Treatment effectiveness and extrapolation – Long-term PFS and OS extrapolations 14

Table 1.8: Key issue 7: Health-related quality of life – Not primarily using IMCgp100-202 trial EQ-5D data and time-to-death HRQoL approach being inconsistent with common modelling practices 14

Table 1.9: Key issue 8: Resource use and costs – One-off application of BSC costs 15

Table 1.10: Key issue 9: Resource use and costs – Percentage of patients using each IC treatment 16

Table 1.11: Key issue 10: Company's cost effectiveness results - proportion of (PF)LY accumulated beyond the observed data 16

Table 1.12: Key issue 11: Model validation and face validity check – Probabilistic analyses for alternative OS, PFS and TTD assumptions 17

Table 1.13: Summary of ERG's preferred assumptions and ICER 18

Table 2.1: Statement of the decision problem (not as presented by the company) 20

Table 3.1: Resources searched for clinical efficacy and safety. March 2020 & Sept 2021 26

Table 3.2: Eligibility criteria used in study selection for RCT and non-RCT evidence 27

Table 3.3: Clinical effectiveness evidence presented in the CS 30

Table 3.4: Detailed characteristics of IMCgp100-202 study 34

Table 3.5: Effect of tebentafusp on objective response rate (CR or PR) 42

Table 3.6: Effect of tebentafusp on objective response rate, best overall response, and disease control rate, study IMCgp100-102 (CR or PR) 43

Table 3.7: Effect of tebentafusp on duration of response, study IMCgp100-202 43

Table 3.8: Effect of tebentafusp on duration of response, study IMCgp100-102 44

Table 3.9: Subgroup analysis of OS by pre-choice of chemotherapy (ipilimumab, dacarbazine and pembrolizumab) and treatment 46

Table 3.10: Subgroup analysis of PFS by pre-choice of chemotherapy (ipilimumab, dacarbazine and pembrolizumab) and treatment 46

Table 3.11: Adverse reactions reported in ≥5% of patients at any grade in study IMCgp100-202 Safety Population 49

Table 3.12: Treatment-emergent adverse events occurring in ≥20% patients in study IMCgp100-202 51

Table 3.13: Panel of post-baseline laboratory abnormalities occurring in ≥20% or Grade 3-4 (≥5%) in UM patients in study IMCgp100-202 52

Table 3.14: Results from the main and sensitivity analyses for the MAICs and UAIC 55

Table 4.1: Resources searched for cost effectiveness studies, HRQoL and healthcare cost and resource use studies. May 2020 and Sept 2021 58

Table 4.2: Eligibility criteria for the systematic literature reviews 59

Table 4.3: NICE reference case checklist 60

Table 4.4: Selection of approach to estimate and extrapolate OS, PFS and TTD for ITT population (based on August 2021 data cut-off) 64

Table 4.5: Selection of approach to estimate and extrapolate OS, PFS and TTD for ≤30 mm subgroup (based on August 2021 data cut-off) 69

Table 4.6: Health state utility values 76

Table 4.7: Total treatment costs 80

Table 4.8: Health state costs 81

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1) 90

Table 6.2: Deterministic ERG base-case 92

Table 6.3: Deterministic scenario analyses (conditional on ERG base-case 1) 93

Table of Figures

Figure 3.1: Trial design IMCgp100-102 study 32

Figure 3.2: IMCgp100-202 consort diagram of the ITT population at the first interim analysis 37

Figure 3.3: Kaplan-Meier estimate of overall survival, study IMCgp100-202 for both data cut-offs (A) October 2020; (B) August 2021 39

Figure 3.4: Kaplan-Meier plot of overall survival in Phase 2 dose expansion 40

Figure 3.5: Kaplan-Meier estimate of Progression Free Survival, (A) October 2020; (B) August 2021 41

Figure 3.6: Kaplan-Meier plot of PFS (RECIST v1.1) by ICR in Phase 2 dose expansion of study IMCgp100-102 42

Figure 3.7: Overall survival trends by subgroup (ITT) 45

Figure 3.8: Percentage of treated patients experiencing any grade or grade ≥3 treatment related rash after each does of tebentafusp 52

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues relate to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary in presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see Sections 3 (decision problem), 4 (clinical effectiveness) and 5 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1 provides a summary of key issues.

Table 1.1: Summary of key issues

ID1441	Summary of issue	Report Section
1	Mixed therapy (IC) as comparator precludes separate evaluation of tebentafusp versus each comparator	2.3, 3.2
2	Lack of comparison to nivolumab monotherapy	2.3
3	Frequency of adverse events in tebentafusp	3.2.4
4	Model structure – Use of a partitioned survival model	4.2.2
5	The use of the treatment mix in the IC arm of the IMCgp100-202 study as single comparator and not including nivolumab as comparator	4.2.4
6	Long-term PFS and OS extrapolations	4.2.6
7	Not primarily using the IMCgp100-202 trial EQ-5D data and time-to-death HRQoL approach being inconsistent with common modelling practices	4.2.8
8	One-off application of BSC costs	4.2.9
9	Percentage of patients using each IC treatment	4.2.9
10	Proportion of (PF)LYs accumulated beyond the observed data	5.1
11	Probabilistic analyses for alternative OS, PFS and TTD assumptions	5.3

BSC = best supportive care; EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; IC = investigator's choice; LY = life year; OS = overall survival; PFLY = progression-free life years; PFS = progression-free survival; TTD = time to treatment discontinuation

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost per QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased progression-free survival (PFS; time in the progression-free (PF) health state increased by [redacted] years; i.e. [redacted] years) and overall survival (OS; survival increased by [redacted] years; i.e. [redacted] years) compared with the comparator. This resulted in [redacted] post-progression benefits of [redacted] (estimates retrieved from the company submission (CS), Appendix J).
- Treatment benefits (in terms of OS, PFS and utility benefits) are maintained for the whole duration of the time horizon i.e., no waning of these treatment benefits.

Overall, the technology is modelled to affect costs by:

- The higher drug costs (additional costs of [redacted]) compared with the comparator, higher administration costs (additional costs of £[redacted]) as well as higher subsequent treatment costs (additional costs of £[redacted]; estimates retrieved from the CS, Appendix J).
- The higher drug costs are driven by the higher unit costs and the time to treatment discontinuation (TTD, combined with the [redacted] assumption).
- Notably, despite the increased post-progression survival, the post-progression costs are lower for tebentafusp compared with the comparator.

The company performed and presented the results of probabilistic sensitivity analyses (PSAs), deterministic sensitivity analyses (DSAs) as well as scenario analyses. The parameters that have the greatest effect on the ICER (based on the company's sensitivity analyses) were:

- Age
- The baseline utility value
- Subsequent chemotherapy attendance

The following CS scenarios had a substantial impact on the ICER:

- Approach to estimate OS
- Source of utility data
- Choice of method of extrapolation of TTD

1.3 The decision problem: summary of the ERG's key issues

The ERG identified two issues related to the comparators used in the CS, detailed in Tables 1.2 and 1.3.

Table 1.2: Key issue 1: Mixed therapy (investigator's choice) as comparator precludes separate evaluation of tebentafusp versus each comparator

Report Section	**2.3, 3.2**
Description of issue and why the ERG has identified it as important	The comparison with IC prevents a separate assessment of tebentafusp versus dacarzabine, ipilimumab and pembrolizumab, which are included in the scope and which seem to vary in terms of relative effectiveness and are therefore likely to vary in whether tebentafusp is cost effective in comparison to them.
What alternative approach has the ERG suggested?	Given that patients were stratified by IC, an unbiased estimate of effectiveness of tebentafusp versus each individual comparator is possible.

Report Section	2.3, 3.2
What is the expected effect on the cost effectiveness estimates?	The effect on cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	Separate effectiveness and safety analyses of tebentafusp versus each of the comparators, dacarzabine, ipilimumab and pembrolizumab. The results of these analyses could then be input into separate cost effectiveness analyses.
ERG = Evidence Review Group; IC = investigator's choice	

Table 1.3: Key issue 2: Lack of comparison to nivolumab monotherapy

Report Section	2.3, 3.2
Description of issue and why the ERG has identified it as important	There is no comparison between tebentafusp and nivolumab monotherapy, which is included in the scope.
What alternative approach has the ERG suggested?	The feasibility of an indirect comparison needs to be assessed. If feasible, this needs to be carried out.
What is the expected effect on the cost effectiveness estimates?	The effect on cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	An indirect comparison with nivolumab monotherapy employing the best feasible method.
ERG = Evidence Review Group	

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Key issues 1 and 2, detailed in Section 1.3 apply to this Section as well. Key issue 3 concerns the frequency of adverse events, see Table 1.4.

Table 1.4: Key issue 3: Frequency of adverse events in tebentafusp

Report Section	3.2.4
Description of issue and why the ERG has identified it as important	The frequency of grade ≥3 TEAEs in study IMCgp100-202 was reported to be [redacted] in the tebentafusp arm ([redacted]) than in the investigator choice arm ([redacted]).
What alternative approach has the ERG suggested?	No alternative approach is suggested by the ERG who wanted to bring this to the attention of the committee.
What is the expected effect on the cost effectiveness estimates?	Adverse events have been included in the economic model, see Section 4.2.7 for details.
What additional evidence or analyses might help to resolve this key issue?	N/A
ERG = Evidence Review Group; N/A = not applicable; TEAE = treatment-emergent adverse event	

1.5 The cost effectiveness evidence: summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the ERG's summary and detailed critique in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in Tables 1.5

to 1.12. The most prominent issues highlighted by the ERG were the estimation of OS, PFS and TTD; the comparators considered; the approach to incorporate health-related quality of life (HRQoL) and the approach to incorporate costs related to the post-progression health state.

Table 1.5: Key issue 4: Model structure – Use of a partitioned survival model

Report Section	**4.2.2**
Description of issue and why the ERG has identified it as important	NICE DSU TSD 19 recommends the use of state transition modelling to assist in verifying the plausibility of partitioned survival model extrapolations and to address uncertainties in the extrapolation period.
What alternative approach has the ERG suggested?	Compare the results of the partitioned survival model to the outcomes of a state transition model.
What is the expected effect on the cost effectiveness estimates?	According to the ERG there is considerable uncertainty related to the extrapolation of the OS endpoint in the tebentafusp arm. This uncertainty has a potentially substantial impact on the ICER as the [redacted] of gains in the economic model are accumulated beyond the observed data period.
What additional evidence or analyses might help to resolve this key issue?	Use of state transition modelling to assist in verifying the plausibility of partitioned survival model extrapolations
DSU = Decision Support Unit; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; NICE = National Institute for Health and Care Excellence; OS = overall survival; TSD = Technical Support Document	

Table 1.6: Key issue 5: Interventions and comparators –The use of the treatment mix in the IC arm of the IMCgp100-202 study as single comparator and not including nivolumab as comparator

Report Section	**4.2.4**
Description of issue and why the ERG has identified it as important	The company used the treatment mix in the IC arm of the IMCgp100-202 study as the single comparator in their analyses. This is justified by the absence of a standard of care and clinical expert opinion. As a consequence, in the company's analyses equal effectiveness of pembrolizumab, ipilimumab and dacarbazine is assumed. This assumption does not seem to be supported by trial data. Furthermore, nivolumab, alone or in combination with ipilimumab, is not included as a comparator in the economic model.
What alternative approach has the ERG suggested?	The ERG considers it good modelling practice to include all comparators listed in the final scope as separate comparators in the economic model as costs and effectiveness may differ. Furthermore, the methods of clinical expert elicitation to justify the company's approach are not transparent.
What is the expected effect on the cost effectiveness estimates?	The comparators listed in the final scope differ in costs and possible effectiveness. The magnitude and direction of impact on the ICER is difficult to determine.
What additional evidence or analyses might help to resolve this key issue?	The results of a separate analysis of each IC treatment in the IMCgp100-202 study could be used as inputs in CEAs of tebentafusp versus each of these treatments. Also, the results of an indirect treatment comparison with nivolumab monotherapy could be incorporated in the model to further inform the incremental costs and

Report Section	4.2.4
	QALYs of tebentafusp and the comparators listed in the final scope. This includes considering analyses stratified by IC treatment, incorporating treatment specific OS, PFS, and TTD (not only treatment specific acquisition costs as done in clarification response C2).
CEA = cost effectiveness analysis; ERG = Evidence Review Group; IC = investigator's choice; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation	

Table 1.7: Key issue 6: Treatment effectiveness and extrapolation – Long-term PFS and OS extrapolations

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	The long-term extrapolations were uncertain (only [redacted] patients were at risk at 36 months for tebentafusp and IC respectively, when considering OS) and the [redacted] of gains are accumulated beyond the observed data period. Moreover, the plausibility of assuming a continued treatment effect over the lifetime horizon of the model is unclear.
What alternative approach has the ERG suggested?	Alternative assumptions related to extrapolation of PFS and OS, including treatment waning assumptions, should be explored by the company.
What is the expected effect on the cost effectiveness estimates?	Depending on the scenario, the impact can be substantial. This is also illustrated by the [redacted] of (PF)LYs gains that are accumulated beyond the observed data period.
What additional evidence or analyses might help to resolve this key issue?	Exploring alternative assumptions and using IMCgp100-202 trial data with additional follow-up.
ERG = Evidence Review Group; IC = investigator's choice; OS = overall survival; PFS = progression-free survival; PFLY = progression-free life year	

Table 1.8: Key issue 7: Health-related quality of life – Not primarily using IMCgp100-202 trial EQ-5D data and time-to-death HRQoL approach being inconsistent with common modelling practices

Report Section	4.2.8
Description of issue and why the ERG has identified it as important	The CS base-case predominantly used utility values from TA366 instead of EQ-5D data from the IMCgp100-202 trial, due to missing data. The ERG believes this approach was not appropriately justified, given that UM, as argued by the company, is biologically distinct from skin melanoma with different physiological, genetic, and epidemiologic characteristics, and the different population and treatment options used in each case. In addition, the data imputation approach used by the company to deal with the missing data was suboptimal and likely to introduce bias. Moreover, the ERG considers that the use of utility values based on time-to-death rather than disease status was not appropriately justified. This approach is flawed from multiple perspectives: i) it is inconsistent with the model structure and common modelling practices (criticised previously, e.g., in TA366) and does not reflect

Report Section	4.2.8
	the decline in HRQoL after progression; ii) the implementation is not transparent; and iii) lacks face validity.
What alternative approach has the ERG suggested?	As requested in clarification question C10, the company could use the original EQ-5D data from the IMCgp100-202 trial (using the Van-Hout crosswalk algorithm) without imputation and apply a generalised linear mixed model that includes the covariates that are considered in the data imputation, and the covariates for the on/off treatment, and for being PFS or PD. Moreover, it would be informative if the company would provide an updated economic model and scenario analyses using utility values based on disease status rather than time-to-death.
What is the expected effect on the cost effectiveness estimates?	The ERG is unable to determine the effect and magnitude on the ICER. Nevertheless, given the increased post-progression survival with tebentafusp, the use of time-to-death utilities is most likely not conservative. Additionally, the incomplete clarification responses from the company were not helpful to explore the expected effect on the cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	As requested in clarification question C10, the company could use the original EQ-5D data from the IMCgp100-202 trial (using the Van-Hout crosswalk algorithm) without imputation and apply a generalised linear mixed model that includes the covariates that are considered in the data imputation, and the covariates for the on/off treatment, and for being PFS or PD. Moreover, it would be informative if the company would provide an updated economic model and scenario analyses using utility values based on disease status rather than time-to-death.
CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; PD = progressive disease; PFS = progression-free survival; TA = technology appraisal; UM = uveal melanoma	

Table 1.9: Key issue 8: Resource use and costs – One-off application of BSC costs

Report Section	4.2.9
Description of issue and why the ERG has identified it as important	BSC costs were applied independently of how long a patient stayed in the PD state in the model. BSC costs were applied in the model as a one-off costs that accounted for four months of BSC; however, patients treated with tebentafusp stayed in the PD state for longer than IC. The justification why the BSC costs were not applied per cycle in the PD health state was not considered appropriate by the ERG, and the company did not provide a scenario analysis (or updated economic model) following this approach.
What alternative approach has the ERG suggested?	The company could present an updated economic model and scenario analyses applying the monthly BSC costs per cycle in the PD health state and excluding the one-off costs at progression.
What is the expected effect on the cost effectiveness estimates?	By calculating the healthcare costs of BSC per cycle in the PD health state, the health state costs of tebentafusp will increase for the base-case. Therefore, this would increase the ICER, as shown in the ERG analyses.
What additional evidence or analyses	The ERG have developed an updated economic model and scenario analyses applying the monthly BSC (instead of one-off) costs per

Report Section	4.2.9
might help to resolve this key issue?	cycle in the PD health state (as requested in clarification question C16).
BSC = best supportive care; ERG = Evidence Review Group; IC = investigator's choice; ICER = incremental cost effectiveness ratio; PD = progressive disease	

Table 1.10: Key issue 9: Resource use and costs – Percentage of patients using each IC treatment

Report Section	4.2.9
Description of issue and why the ERG has identified it as important	One of the main factors influencing IC acquisition costs was the percentage of patients using each treatment. Although the standard of care is not yet agreed for UM treatment, the company did not provide detailed analyses on the effect of varying this parameter in scenario analyses.
What alternative approach has the ERG suggested?	The company could present an updated economic model and scenario analyses exploring the effects of the percentage of patients using each IC.
What is the expected effect on the cost effectiveness estimates?	See ERG scenario analyses. Notably these analyses do not incorporate treatment specific OS, PFS and TTD which should ideally be incorporated when adjusting these proportions. Hence, the ERG is unable to determine the effect and magnitude on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Scenario analyses exploring the effects on the ICER of each treatment option separately, also including treatment specific OS, PFS and TTD. This connects to the key issue related to Section 4.2.4.
ERG = Evidence Review Group; IC = investigator's choice; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation; UM = uveal melanoma	

Table 1.11: Key issue 10: Company's cost effectiveness results - proportion of (PF)LY accumulated beyond the observed data

Report Section	5.1
Description of issue and why the ERG has identified it as important	The proportion of (PF)LY accumulated beyond the observed data is substantially larger for tebentafusp than for IC. Moreover, considering the increments, approximately [redacted] (or more depending on the truncation point) of the LYs are gained beyond the observed data period for tebentafusp compared with IC while this is approximately [redacted] (or more depending on the truncation point) for PFLY. This indicates that the [redacted] of gains are accumulated beyond the observed data period and hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted (as requested but not provided in the company's response to clarification question C20). This includes verifying the plausibility of the partitioned survival model extrapolations (see Section 4.2.2).
What alternative approach has the ERG suggested?	Providing additional explanation of the mechanism by which the model generated the differences as well as a justification for why they are plausible based upon available evidence is warranted. This includes verifying the plausibility of the partitioned survival model extrapolations.

Report Section	5.1
What is the expected effect on the cost effectiveness estimates?	The expected impact is unclear but is potentially substantial. Although the anticipated direction is unclear, the extrapolation in terms of proportion of (PF)LY accumulated beyond observed data is substantially larger for tebentafusp than for IC and thus alternative assumptions with less extrapolation would likely increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	See suggestions above, as well as using IMCgp100-202 trial data with additional follow-up.
ERG = Evidence Review Group; IC = investigator's choice; ICER = incremental cost effectiveness ratio; LY = life year; PFLY = progression-free life year	

Table 1.12: Key issue 11: Model validation and face validity check – Probabilistic analyses for alternative OS, PFS and TTD assumptions

Report Section	5.3
Description of issue and why the ERG has identified it as important	The model submitted by the company did not allow the ERG to run probabilistic analyses for the ERG base-case with alternative assumptions for estimating OS, PFS and TTD. Probabilistic analysis is in line with the NICE reference case and good modelling practices.
What alternative approach has the ERG suggested?	Fix the functionality "*Click to update default values with current values"* so this works for all input parameters.
What is the expected effect on the cost effectiveness estimates?	Unclear but for the CS base-case the probabilistic ICER is lower (ICER of £[redacted] per QALY gained) than the deterministic ICER (ICER of £[redacted] per QALY gained)
What additional evidence or analyses might help to resolve this key issue?	A revised economic model submitted by the company, which includes the ERG preferred options and allows these analyses to be run probabilistically.
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; OS = overall survival; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life year; PFS = progression-free survival; TTD = time to treatment discontinuation	

1.6 Other key issues: summary of the ERG's view

The original CS did not include any details on whether end of life criteria might apply to this CS and the ERG requested clarification on this point.

The ERG reviewed the arguments presented in the response to the request for clarification.

i. Based on the evidence provided by the company, it is likely that patients with metastatic uveal melanoma (UM) meet the criterion *"The treatment is indicated for patients with a short life expectancy, normally less than 24 months"*. However, it should be noted that the population defined in the NICE final scope is *"adults with advanced (unresectable or metastatic) HLA-A*0201-positive UM"*. While the main study identified in the CS, IMCgp100-202, included participants with *"histologically or cytologically confirmed diagnosis of metastatic UM"*, it is unclear whether this criterion would be met for patients with advanced but non-metastatic UM.

ii. As summarised in Section 3.2.3.1.1, results of IMCgp100-202 indicate that *"the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment"*. However, is should be noted that the comparison was to investigator's choice,

and, as highlighted in Section 3.2.3.5.1, treatment effects differ by drug used, i.e. the committee should consider this issue in light of the drugs usually used in the NHS setting. In particular, there appears to be little if any difference in median OS between tebentafusp and ipilimumab.

1.7 Summary of the ERG's view

The CS base-case probabilistic and deterministic ICERs were £[redacted] and £[redacted] per QALY gained, respectively. This was increased in the subgroup with the largest metastatic lesion recorded at baseline ≤30mm (deterministic CS base-case ICER of £[redacted] per QALY gained). The estimated ERG base-case ICER range (deterministic), based on the ERG preferred assumptions, was £[redacted] to £[redacted] per QALY gained. The ERG was unable to produce probabilistic base-case analyses (as highlighted in the model validation section). The most influential adjustments were related to the estimation of OS, post-progression health state costs and the TTD. The ICER increased most in the scenario analysis with alternative assumptions regarding different proportions for IC treatments.

There is large remaining uncertainty about the effectiveness and relative effectiveness of tebentafusp, which can be at least partly resolved by the company by conducting further analyses. According to the ERG the current approach (both in the CS and ERG base-case) to incorporate health-related quality of life is flawed and this could conceivably change, most likely increase, the ICER. Moreover, the current assessment does not provide an appropriate estimation of the comparators listed in the scope. Therefore, the ERG believes that the CS nor the ERG report contains an unbiased ICER of tebentafusp compared with relevant comparators.

Table 1.13: Summary of ERG's preferred assumptions and ICER

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixing violation (1- Post progression health state costs)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixing violation (2- Extrapolation of PFS)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixing violation (3- Extrapolation of TTD)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Matter of judgement (4a- Extrapolation of OS – generalised gamma)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Matter of judgement (4a- Extrapolation of OS – log logistic)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base-case 1 (Extrapolation of OS – generalised gamma)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case 2 (Extrapolation of OS – log logistic)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG = Evidence Review Group, IC = investigator's choice; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (not as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from NICE scope	ERG comment
Population	Adults with advanced (unresectable or metastatic) HLA-A*0201-positive UM	Adults with advanced (unresectable or metastatic) HLA-A*02:01-positive UM	N/A	The population addressed in the decision problem is in line with the final scope, however, the population in the identified trial is narrower, as detailed in Section 2.1.
Intervention	Tebentafusp	Tebentafusp (KIMMTRAK®)	N/A	The intervention is in line with the NICE scope.
Comparator(s)	• Immunotherapies (pembrolizumab, ipilimumab, nivolumab [alone or in combination with ipilimumab]) • Chemotherapy (dacarbazine) • Best supportive care may be an additional comparator for people who have had previous treatment	Established clinical management without tebentafusp; currently there is no approved therapy for advanced uveal melanoma and the UK treatment guidelines recommend patients are enrolled in clinical trials. The investigator's choice comparator therapies in the RCT on tebentafusp were therapies frequently used in clinical practice in metastatic uveal melanoma patients: pembrolizumab, ipilimumab, or dacarbazine, therefore we consider these to be the most relevant comparator treatments.	N/A	The comparators are in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from NICE scope	ERG comment
		Data from comparing tebentafusp and ipilimumab plus nivolumab combination therapy will be presented from a matching and adjusted indirect comparison analysis.		
Outcomes	The outcome measures to be considered include the following*: • Progression-free survival (PFS) • Overall survival (OS) • Response rate • Duration of response (DOR) • Adverse effects of treatment • Health-related quality of life (HRQoL)	• OS • PFS • Objective Response Rate (ORR) • DOR • Adverse effects of treatment • Health-related quality of life (HRQoL)	The outcomes reflect the clinical endpoints of the phase 3 RCT on tebentafusp	The outcomes are in line with the NICE final scope.
Economic analysis	The economic analysis is consistent with the NICE reference case which stipulates: The cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	The cost effectiveness of treatments will be expressed in terms of incremental cost per QALY. The time horizon for estimating clinical and cost effectiveness will be a lifetime horizon, which is long enough to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	As per NICE scope	Economic analysis is partly in line with the reference case and the NICE scope, see Section 4

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from NICE scope	ERG comment
	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of tebentafusp is conditional on the presence of HLA-A*0201. The economic modelling includes the costs associated with diagnostic testing for HLA-A*0201 in people with UM who would not otherwise have been tested. A sensitivity analysis is provided without the cost of the diagnostic test.			
Subgroups to be considered	If evidence allows, consideration will be given to the clinical and cost effectiveness of tebentafusp at different lines of therapy**.	For this rare cancer there are no subgroups that need to be considered in the context of a NICE submission. Immunocore have conducted subgroup analyses according to the study protocol that show benefit across all groups.		Subgroup analyses for region, investigator's choice, gender, age, ECOG status, baseline alkaline phosphatase, lactase dehydrogenase and largest metastatic lesion were explored, see Section 3.2.3.5.
Special considerations including issues related to equity or equality	No equity or equality issues have been identified.	No equity or equality issues have been identified.		In line with the NICE final scope.

Based on Table 1 of the CS[1] and NICE Final Scope[2]

* The NICE final scope outcomes listed in the CS were incorrectly listed and have been rectified to accurately reflect the NICE final scope outcomes.

** Recommendation for subgroups to be considered published in NICE final scope have replaced the 'NA' stated in the CS.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from NICE scope	ERG comment
CS = company submission; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; ERG = Evidence Review Group; HLA-A = human leukocyte antigen (A locus); HRQoL = health-related quality of life; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PSS = Personal Social Services; QALY = quality-adjusted life year; RCT = randomised control trial; UK = United Kingdom; UM = uveal melanoma				

2.1 Population

The population defined in the National Institute for Health and Care Excellence (NICE) **final scope** is:

- Adults with advanced (unresectable or metastatic) HLA-A (human leukocyte antigen (A locus))*0201-positive uveal melanoma (UM).[2]

The population in the **decision problem** of the company submission (CS) is:

- Adults with advanced (unresectable or metastatic) HLA-A*02:01-positive UM.[1]

The population included in the **identified trial evidence**, the IMCgp-100-202 study, is:

- Previously untreated patients with metastatic UM who were HLA-A* 02:01–positive to receive tebentafusp (intervention) or one of three investigator's choice comparators: dacarbazine, ipilimumab, or pembrolizumab.

The proposed indication for tebentafusp is as follows: tebentafusp is indicated as monotherapy for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic UM.[1]

Marketing authorisation for tebentafusp is currently being reviewed in the United Kingdom (UK) under the Project Orbis initiative (Type A).[1] The marketing authorisation application was submitted to [redacted].[1] Marketing authorisation for tebentafusp has not been approved anywhere in the world.[1]

ERG comment: The ERG notes that although the company alluded to the submission population being in line with the NICE final scope, evidence from the identified included trial is notably for a narrower population i.e., treatment naïve HLA-A* 02:01–positive metastatic UM patients.

2.2 Intervention

The intervention, tebentafusp (KIMMTRAK®), is in line with the NICE final scope.[2]

The recommended dosing regimen for tebentafusp is: 20 µg on day 1, 30 µg on day 8, and 68 µg weekly thereafter until the attending physician deems the intervention to no longer be of clinical benefit to the patient.[1] No additional tests or investigations required prior to the administration of tebentafusp were indicated by the company. However, the first three doses of tebentafusp will require administration in a hospital setting to allow for monitoring of any signs or symptoms of cytokine release syndrome (CRS) during infusion, and for 16 hours after infusion has been completed.[1]

2.3 Comparators

The description of the comparators in the NICE final scope is as follows:[2]

- Immunotherapies (pembrolizumab, ipilimumab, nivolumab [alone or in combination with ipilimumab])
- Chemotherapy (dacarbazine)
- Best supportive care (BSC) may be an additional comparator for people who have had previous treatment

The company considered the immunotherapies, pembrolizumab and ipilimumab, and the chemotherapy, dacarbazine, as the most relevant comparator treatments, as they were the investigator's choice comparator therapies in the randomised controlled trial (RCT) for a head-to-head comparison with tebentafusp.[1]

The company also presented a matching-adjusted indirect comparison (MAIC) analysis comparing tebentafusp and ipilimumab plus nivolumab.[1]

ERG comment: Comparison with investigator's choice (IC) prevents an evaluation of tebentafusp in relations to each of the comparators separately: there is likely to be variation in effectiveness and safety and thus which treatment is cost effective. Because randomisation was stratified by IC, an unbiased estimate of treatment effect of tebentafusp versus each individual comparator is possible. The company did provide a subgroup analysis estimating the hazard ratio for overall survival, but no other such subgroup data were reported in the CS.[1] In response to the request for clarification, subgroup results were provided, see Section 3.2.3.5.[3]

The feasibility of conducting indirect comparisons with nivolumab combination therapy with ipilimumab (recommended for treating advanced melanoma)[4] are discussed in Sections 3.3 and 3.4 of this report. Nivolumab alone had been recommended for treating advanced [unresectable or metastatic] melanoma by NICE.[5] However, no comparison was made with nivolumab monotherapy nor was there any feasibility assessment of an indirect comparison.

2.4 Outcomes

The NICE final scope lists the following outcome measures:[2]

- Progression-free survival (PFS)
- Overall survival (OS)
- Response rate (RR)
- Duration of response (DOR)
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

These were all well assessed in the IMCgp-100-202 study.

ERG comment: Results for all outcomes have been summarised in Section 3.2 of this report.

2.5 Other relevant factors

According to the company, tebentafusp is innovative because it *"offers a convenient mode of administration to allow patients with limited life expectancy to receive care close to home following the first 3-weeks of treatment"* (CS, Section B.1.2).[1] The company also highlights tebentafusp as a pioneering drug that will set a new standard of care for HLA-A*02:01-positive patients with unresectable or metastatic UM as tebentafusp is *"the first and only proven effective systemic treatment for metastatic UM"* (CS, Sections B.1.2, B.1.3.5).[1]

According to the company, no equality issues relating to the use of tebentafusp in patients with UM are likely to arise (CS, Section B.1.4)[1]

ERG comment: The company did not claim that tebentafusp fulfils the NICE end of life criteria and the ERG requested clarification on this point, see Section 7.[6]

As the first three doses of tebentafusp will require administration and monitoring for 16 hours post-administration in a hospital setting, and weekly out-patient ambulatory care drug administration followed by 30 minutes of monitoring will only become appropriate once the patient tolerates the most recent infusion without grade ≥2 hypotension, in the context of short life expectancies among UM patients, tebentafusp does not appear to be very innovative.

The economic analysis is partly in line with the reference case and the NICE scope, see Section 4.

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

3.1.1 Searches

Appendix D of the CS provided details of the systematic literature searches used to identify clinical efficacy and safety evidence.[7] Searches were developed by an information specialist and were conducted in March 2021 and updated September 2021. The ERG has presented only the major limitations of each search strategy in the report. A summary of the resources searched are provided in Table 3.1.

Table 3.1: Resources searched for clinical efficacy and safety. March 2020 & Sept 2021

Resource	Host/Source	Date Range of most recent search	Date searched
Databases			
Embase	Ovid	1974-2021/wk38	10.3.20 Updated 29.9.21
MEDLINE & MEDLINE In-Process	Ovid	1946-2021/09/27	10.3.20 Updated 29.9.21
CENTRAL	Wiley	All years	10.3.20 Updated 29.9.21
CDSR	Wiley	All years	10.3.20 Updated 29.9.21
DARE	CRD	All years	10.3.20*
HTAD	CRD	All years	10.3.20*
Epistemonikos	Internet	All years	10.3.20 Updated 29.9.21
Trials registries			
ClinicalTrials.gov	Internet	All years	10.3.20 Updated 29.9.21
WHO ICTRP	Internet	All years	10.3.20 Updated 29.9.21
Additional searches			
Hand-searching of reference lists of key included articles.			
Free text keyword search in internet search engines.			

* No updates required as no new records have been added to DARE/HTAD since the original searches were run

CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CRD = Centre for Reviews and Dissemination; DARE = Database of Abstracts of Reviews of Effects; HTAD = Health Technology Assessment Database; ICTRP = International Clinical Trials Registry Platform; WHO = World Health Organization

ERG comment:

- Searches were reported for a good range of resources, including two trials databases. Strategies for both the original and update searches were provided and were clearly structured and well documented.
- Additional internet searches and reference checking to identify relevant material not retrieved by the main searches were undertaken.
- The company reported using relevant systematic literature reviews (SLRs) on this topic to identify search terms and to compare included studies, as well as the use of the PRESS (Peer Review of Electronic Search Strategies) checklist to ensure the quality of search strategies.[8, 9]
- Searches were structured to combine terms for the condition (advanced or metastatic UM or choroidal melanoma) with a broad trials filter designed to retrieve trials of any design . Searches were not limited by date or language, apart from the conference proceedings in Embase which were limited to the last three years, although it is not clear if all relevant conferences are indexed by this database.
- The ERG queried whether any separate adverse events (AEs) searches were performed.[6] The company responded that no additional searches had been run other than those stated in the clinical SLR (Appendix D of the CS).[3, 7] Guidance by the Centre for Reviews and Dissemination (CRD)[10] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. This loss of recall may have been mitigated by the range of resources searched, the additional internet searches and checking of reference lists.
- The ERG noted that the Emtree term 'uvea melanoma' was missing from the clinical effectiveness and economics Embase searches. In their response to the request for clarification the company reran the searches and provided an examination of the additional 89 records returned. Although two additional relevant papers were identified, the mixed population of patients with different types of metastatic melanoma within the studies ultimately meant that no meaningful comparisons could be made and this did not affect the overall outcome of the results.

3.1.2 Inclusion criteria

The eligibility criteria used in screening for eligible RCTs and non-RCTs has been summarised in Table 3.2. The company indicated that two reviewers were involved in independently screening articles for inclusion both at the abstract, and full-text screening stage, and disagreements were resolved through discussion or by the involvement of a third reviewer to resolve the discrepancy if a consensus could not be reached.

Table 3.2: Eligibility criteria used in study selection for RCT and non-RCT evidence

Category	Inclusion criteria	Exclusion criteria
Population	Adult patients with advanced or metastatic UM/choroidal melanoma	Patients with localised disease only (non-metastasised UM/choroidal melanoma), paediatric patients
Interventions	Tebentafusp, IMCgp100	Surgical interventions only
Comparators	All other therapeutic interventions used in the treatment of UM/choroidal melanoma	N/A

Category	Inclusion criteria	Exclusion criteria
Outcomes	• Efficacy: OS, PFS, ORR, DCR, QoL • Safety: AEs and SAEs	Outcome not listed in the "inclusion criteria" of PICOS
Study design	• RCTs • Single arm trials • Conference abstracts • Studies comparing the intervention with a comparator or studies comparing two comparators	• Pharmacokinetic studies • Proof of concept studies • Case reports, case series, retrospective observational studies, editorials, and letters • Reviews/systematic reviews/pooled trial analyses • Non-human studies
Language	English language abstracts and English language full-text articles	Non-English abstracts and non-English full-text articles
Time limit	N/A	N/A

Based on Table 1 of Appendix D of the CS[7]
AE = adverse event; CS = company submission; DCR = disease control rate; N/A = not applicable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PICOS = population, intervention, comparator(s), outcome(s), study design(s); QoL = quality of life; RCT = randomised controlled trial; SAE = serious adverse event; UM = uveal melanoma

ERG comment: Given the final scope issued by NICE, the PICOS (population, intervention, comparator(s), outcome(s), study design(s)) for inclusion were appropriate, and the study selection process was expedient for reducing bias. However, the ERG notes that the company did not specify which interventions consisted of the *"all other therapeutic interventions used in the treatment of UM/choroidal melanoma"*.[7]

3.1.3 Critique of data extraction

As the CS did not outline the data extraction process, in its clarification letter, the ERG asked the company to give clarification on its data extraction process.[6] In its response to the request for clarification, the company stated that, "*In order to be selected for data extraction, the publication had to fulfil all the inclusion criteria and none of the exclusion criteria shown in the PICOS… Any disagreements in decision were resolved through discussion until a consensus was reached, or else a third reviewer was involved to resolve the discrepancy."*[3]

ERG comment: As the company did not clarify how many reviewers were involved in the data extraction process, the ERG cannot confirm if errors in data extraction were minimised.

3.1.4 Quality assessment

As it was unclear whether the quality assessment was carried out independently by two reviewers, in its clarification letter, the ERG asked the company to give clarification on how many reviewers were involved in the risk of bias assessments using the Cochrane RoB2 tool.[6, 11] In its response to the request for clarification, the company stated that, *"Any disagreements in decision were resolved through discussion until a consensus was reached, or else a third reviewer was involved to resolve the discrepancy"*.[3]

ERG comment: As the company did not clarify how many reviewers were involved in the quality assessment process, the ERG cannot confirm if errors in risk of bias assessments were minimised.

3.1.5 Evidence synthesis

As stated in Section B 2.8 of the CS, no meta-analyses were conducted.[1]

The company provided an indirect treatment comparison (ITC) to synthesise the relative differences in OS for patients with untreated metastatic UM on tebentafusp versus ipilimumab plus nivolumab, and pembrolizumab versus ipilimumab plus nivolumab. This has been expounded on in Sections 3.3 and 3.4 of this report.

ERG comment: Although the company did not offer a justification for why a meta-analysis was not conducted, it can be inferred that as efficacy data supporting the use of tebentafusp for the treatment of UM was primarily provided by the ongoing Phase III RCT, IMCgp100-202 and the Phase I/II single-arm study, IMCgp-100-102, a meta-analysis would be inessential.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS provided an overview of three studies related to the clinical evidence:[1]

1. A first-in-human phase 1 study (NCT01211262), known as the IMCgp100-01 study[12];
2. A phase I/II single arm study, known as the IMCgp100-102 study (NCT02570308);[13] and
3. An ongoing phase III RCT, known as the IMCgp100-202 study (NCT03070392)[14].

The characteristics of each of these studies have been provided in Table 4 of the CS.[1]

The CS clarified that the IMCgp100-01 study did not receive any further attention in the submission as it does not inform the decision-problem. Therefore, the clinical development programme for tebentafusp in the treatment of metastatic UM included two major clinical trials:

- The first, the IMCgp100-102 study consisted of two phases with phase 1 being a dose escalation design to determine the optimal dosing regimen, while phase 2 was an expansion cohort design where the optimal dosing was administered.
- The second study, IMCgp100-202, is an ongoing multicentre, parallel, open label, randomised, phase 3 trial where Tebentafusp is administered at a dose of 20 μg on day 1, 30 μg on day 8, and 68 μg weekly thereafter and compared against investigator's choice of treatment.

The characteristics of the IMCgp100-102 and IMCgp100-202 trials are summarised in Table 3.3 below.

Table 3.3: Clinical effectiveness evidence presented in the CS

	IMCgp100-102 (NCT02570308)	IMCgp100-202 (NCT03070392)
Study design	Phase 1 study was standard dose escalation design; Phase 2 was an expansion cohort study with patients receiving prior systemic treatment or liver-directed treatment	Multicentre, parallel, open label, randomised, Phase 3 trial
Population	Patients with a histologically or cytologically confirmed diagnosis of metastatic UM with a life expectancy of >3 months and who tested positive for HLA-A*02:01. Patients who experienced disease progression while on 1 or 2 prior lines of therapy, including chemotherapy, immunotherapy, or targeted therapy, in the metastatic or advanced setting were included in the Phase 2 dose expansion cohort.	Patients with local histologically or cytologically confirmed metastatic UM, who were HLA-A*02:01–positive. Patients had no previous systemic or liver-directed therapy for metastatic disease; had an ECOG score of 0 or 1; and had at least one measurable lesion, according to RECIST (version 1.1.20)
Intervention(s)	Tebentafusp administered as an escalation regimen consisting of fixed doses at 20 µg, 30 µg then incrementally increased to explore the optimum therapeutic dose. The Phase 1 part of the study identified 20 µg, 30 µg then 68 µg weekly thereafter as the appropriate dose for the Phase 2 dose expansion phase.	Tebentafusp at a dose of 20 µg on day 1, 30 µg on day 8, and 68 µg weekly thereafter
Comparator(s)	N/A	Investigator's choice of treatment: • pembrolizumab • ipilimumab • dacarbazine
Indicate if trial supports application for marketing authorisation	Yes	Yes
Indicate if trial used in the economic model	No	Yes
Rationale for use/non-use in the model	Single-armed trial did not report comparative data	Pivotal Phase 3 trial providing comparative evidence on the efficacy and safety of tebentafusp with standard care

	IMCgp100-102 (NCT02570308)	IMCgp100-202 (NCT03070392)
Reported outcomes specified in the decision problem	• ORR (primary outcome) • PFS • OS • DOR • Adverse effects of treatment	• OS (primary outcome) • PFS • ORR • DOR • Adverse effects of treatment • HRQoL (EQ-5D-5L and EORTC QLQ-C30 instrument)
All other reported outcomes	• Identification of maximum tolerated dose • Anti-tebentafusp antibody formation • MinR	• Pharmacokinetic profile • Anti-tebentafusp antibody formation • Peripheral cytokine levels • Health- and treatment-related medical resource utilisation associated with the advanced UM disease pathway

Based on Table 4 of the CS[1]
CS = company submission; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life-5 Dimensions-5 levels; EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HLA-A = human leukocyte antigen (A locus); HRQoL = health-related quality of life; N/A = not applicable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; UM = uveal melanoma

3.2.1 IMCgp100-102

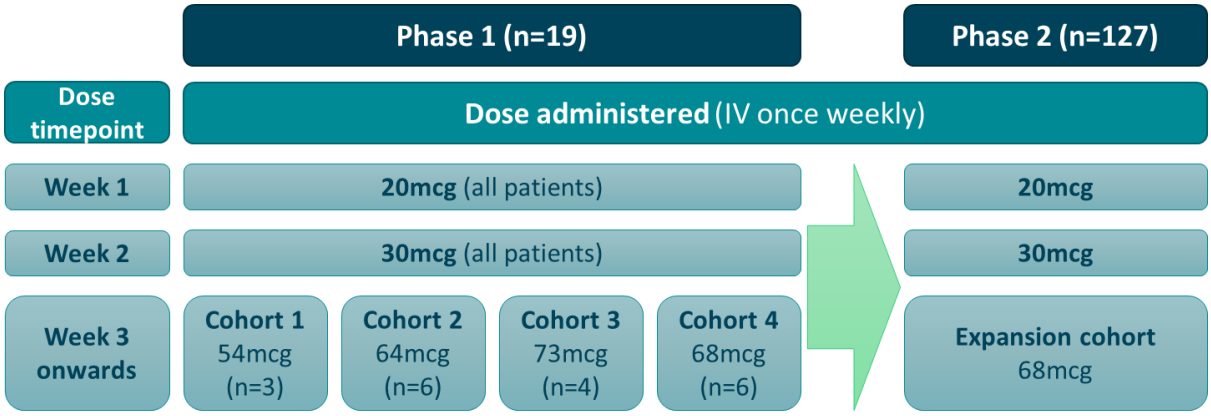
The IMCgp100-102 study (NCT02570308) was designed with two phases:

1. Phase 1 (dose-finding) aimed to identify the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) and/or the recommended phase 2 dose (RP2D) of tebentafusp using a process of dose escalation

2. Phase 2 (expansion) aimed to estimate the objective response rate (ORR) based on the Response Evaluation Criteria in Solid Tumours (RECIST v1.1) in patients with metastatic UM who were treated with the recommended RP2D.

The trial design is summarised in Figure 3.1 below.

Figure 3.1: Trial design IMCgp100-102 study



Based on Figure 6 of the CS[1]
CS = company submission; IV = intravenous; mcg = microgram

The primary objective of phase 1 was to evaluate the optimal dosing by administration of tebentafusp at 20 µg in week 1, and at 30 µg in week 2. From week 3 onwards, patients received tebentafusp at a dosage of either 54 µg (n=3), 64 µg (n=6), 73 µg (n=4), or 68 µg (n=6). At phase 2, initial intentions had initially been to have two separate expansion cohorts. The first cohort was to enrol patients with metastatic UM in the second line setting after disease progression following systemic treatment with a checkpoint inhibitor, while the second cohort was to enrol patients with metastatic UM in the second or third line setting with up to one prior line of liver-directed therapy. However, the CS states that because there was significant overlap between the populations earmarked for each cohort, data are presented for the single combined phase 2 dose expansion cohort.[1] Details of the methodology relevant to study are provided in Table 3.4 below.

Study IMCgp100-102 was not used to populate the economic model as it is a single arm study with a smaller sample size (n=127). The results of this study are relevant to advanced UM patients previously treated with one or two lines of therapy. The IMCgp100-102 study did not include comparative analyses as it was a single arm study. The results described in Section B.2.6 of the CS are from the dose expansion phase 2 part of the study.[1]

3.2.2 IMCgp100-202

The IMCgp100-202 study is a multicentre, parallel, open-label, phase III trial, which randomised previously untreated patients with metastatic UM who were HLA-A* 02:01–positive to receive

tebentafusp or the investigator's choice of therapy. The CS states that as there are no current approved therapies for the treatment of advanced UM in the UK guidelines, checkpoint inhibitor treatments (pembrolizumab or ipilimumab) or an option of chemotherapy (dacarbazine) using the approved doses and regimens for treatment of metastatic melanoma were selected for the investigator's choice comparators.[1] Patients enrolled were stratified based on lactate dehydrogenase (LDH) level and the primary aim of the study was to compare overall survival in the tebentafusp group with the investigator's choice treatments, a second primary aim was to assess if rash is associated with survival in tebentafusp-treated patients.

The CS confirms that an open label design was selected as treatment allocation could not be blinded due to the frequency of rash and puritis after the first infusion. Patient enrolment was conducted between March 2017 and June 2020. The CS describes planned interim analyses at 60% and 80% of anticipated events and confirms that results are presented from a data cut-off performed in August 2021 are presented. The CS clarifies that following the first interim analysis at 60% of anticipated events in October 2020, patients in the control arm were permitted to cross over to receive tebentafusp, results from the August 2021 data cut include these patients while the data from the primary interim analysis has been published.[14]

Please see Table 3.4 below for details of the IMCgp100-202 study and Figure 3.2 for a summary of the study design, participant enrolment and disposition in the intention-to-treat (ITT) population at the first interim analysis in October 2020.

Table 3.4: Detailed characteristics of IMCgp100-202 study

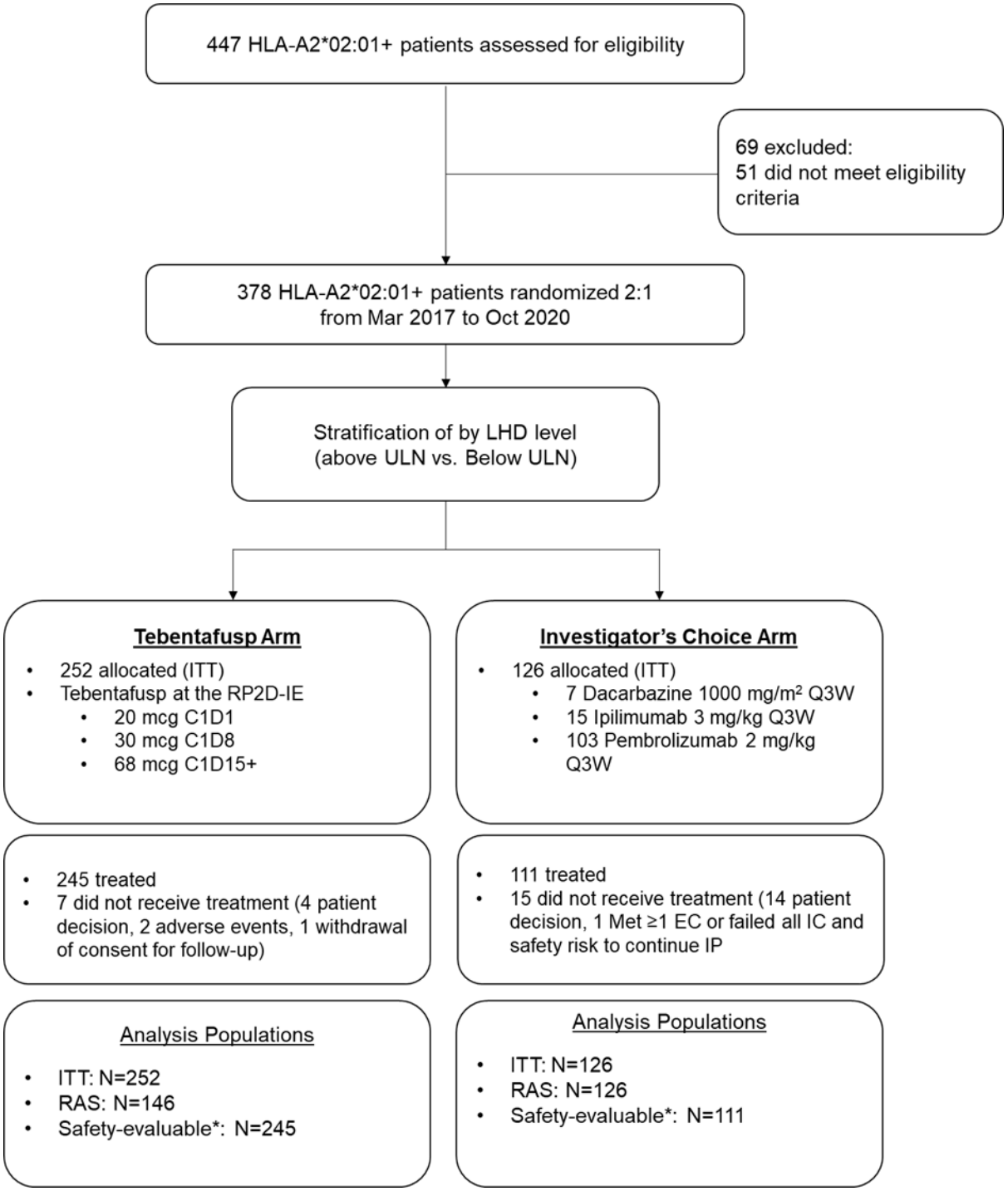
Trial number	Study IMCgp100-202 (NCT03070392) (data on file)
Trial design	Phase 3 multi-centre, open-label, parallel, randomised controlled trial
Eligibility criteria for participants	**Inclusion criteria** 1. Male or female patients aged ≥18 years of age at the time of informed consent 2. Ability to provide and understand written informed consent prior to any study procedures 3. Histologically or cytologically confirmed metastatic UM 4. Had to meet the following criteria related to prior treatment: • No prior systemic therapy in the metastatic or advanced setting including chemotherapy, immunotherapy, or targeted therapy • No prior regional liver-directed therapy, including chemotherapy, radiotherapy, or embolisation • Prior surgical resection of oligometastatic disease was allowed • Prior neoadjuvant or adjuvant therapy was allowed provided administered in the curative setting in patients with localised disease. Patients must not have been retreated with an investigator's choice therapy that was administered as adjuvant or neoadjuvant treatment. Additionally, patients who received nivolumab as prior adjuvant/neoadjuvant treatment should not have received pembrolizumab as investigator's choice therapy 5. HLA-A*02:01 positive by central assay 6. Life expectancy of > 3 months as estimated by the investigator 7. ECOG performance status score of 0 or 1 at screening 8. Patients had measurable or non-measurable disease according to RECIST v1.1 9. All other relevant medical conditions had to be well-managed and stable, in the opinion of the investigator, for at least 28 days prior to first administration of study drug **Key Exclusion criteria** Patient with any out-of-range laboratory values defined as: 1. Serum creatinine >1.5 × ULN and/or creatinine clearance <50 ml/minute 2. Total bilirubin >1.5 × ULN, except for patients with Gilbert's syndrome, who were excluded if total bilirubin >3.0 × ULN or direct bilirubin >1.5 × ULN 3. Alanine aminotransferase >3 × ULN 4. Aspartate aminotransferase >3 × ULN 5. Absolute neutrophil count <1.0 × 109/l 6. Absolute lymphocyte count <0.5 × 109/l

	7. Platelet count <75 × 109/l 8. Hemoglobin <8 g/dl 9. History of severe hypersensitivity reactions (e.g., anaphylaxis) to other biologic drugs or monoclonal antibodies 10. Clinically significant cardiac disease or impaired cardiac function
Settings and locations where the data were collected	The study was set up in 25 centres in the United States and Canada, 1 centre in the Netherlands, 1 centre in Poland, 3 centres in the Russian Federation, 5 centres in Spain, 4 centres in Australia, 1 centre in Belgium, 2 centres in France, 7 centres in Germany, 2 centres in Italy, 1 centre in Switzerland, 4 centres in the Ukraine, and 3 centres in the UK (Mount Vernon Cancer Centre, The Clatterbridge Cancer Centre, and Beatson West of Scotland Cancer Centre).
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	From March 2017 to June 2020, a total of 442 HLA-A*02:01–positive patients were screened, with 378 patients being eligible for inclusion. Patients were randomised in a 2:1 ratio to either of two treatment groups (arms 1 and 2): **Arm 1: tebentafusp (n=252)** All patients randomised to arm 1 received tebentafusp by IV infusion following the intra-patient escalation regimen. Patients received 20 µg on C1D1, 30 µg on C1D8, and an escalated dose of 68 µg on C1D15 and weekly thereafter. Due to the anticipated cytokine release-associated toxicity with tebentafusp following the first three doses, patients were monitored for at least 16 hours after dosing as an inpatient following the weekly doses on C1D1, C1D8, and C1D15. Use of prophylactic steroids was not mandated. **Arm 2: Investigator's choice (n=126)** All patients randomised to arm 2 received investigator's choice of one of the following three options: • Dacarbazine at the standard dosing regimen in UM of 1000 mg/m2 given on Day 1 of each 21-day cycle (n=7) • Ipilimumab at the dosing regimen for unresectable or metastatic melanoma of 3 mg/kg given on Day 1 of each 21-day cycle for a maximum of 4 doses (n=16) • Pembrolizumab at the dosing regimen of 2 mg/kg up to a maximum of 200 mg or 200 mg administered IV were approved locally given on Day 1 of each 21-day cycle. The preferred investigator's choice agent was selected prior to randomization. No extended monitoring after dosing was required in Arm 2 (n=103) Concomitant medications (e.g., anti-diarrhoeal drugs, antiemetics, or electrolyte supplementation) deemed necessary to provide adequate prophylactic or supportive care were allowed, except for medications identified as prohibited. There was no difference in drug restrictions between arms.
Primary outcomes (including scoring methods and timings of assessments)	The predefined, dual primary objectives were: • To compare the OS in all patients randomised to tebentafusp monotherapy versus all patients randomised to investigator's choice monotherapy • To compare the OS in all patients randomised to tebentafusp monotherapy who develop a rash within the first week of treatment versus all patients randomised to investigator's choice monotherapy

	Both objectives relate to HLA-A*02:01-positive patients with advanced UM with no prior treatment in the metastatic setting. The OS endpoint, which is used in the model, is defined as the time from randomisation until death by any cause. An additional primary objective was to compare the OS in all patients randomised to tebentafusp monotherapy who develop a rash within the first week of treatment versus all patients randomised to investigator's choice monotherapy. The rationale for this was related to the analysis of study IMCgp100-102, which reported that rash appeared to be associated with a clinical benefit across all efficacy endpoints including tumour shrinkage and PFS (both per an independent radiology committee) and OS. Therefore, this shared primary objective aimed to confirm these analyses by comparing OS in patients randomised to tebentafusp monotherapy who developed a rash within the first week of treatment, with those who did not.
Other outcomes used in the economic model/specified in the scope	The secondary outcome used in the study is PFS (comparison of arms 1 and 2). PFS was defined as the time from randomisation to the date of first documented progression (per RECIST v1.1.) as determined by investigator assessment or death due to any cause, whichever occurred first, regardless. Radiological assessments for PFS were performed as scheduled every 12 weeks, using a reference to C1D1 and were not to follow delays incurred during the treatment period. Other outcomes reported that were specified in the scope were: • ORR (using RECIST v1.1) • DOR (using RECIST v1.1) • Adverse effects of treatment HRQoL (using the EQ-5D-5L for generic HRQoL and the EORTC QLQ-C30 for disease-specific HRQoL)
Co-primary endpoints	The following co-primary endpoint subgroup analyses were analysed for OS and PFS: ethnicity; gender; age; ECOG status; alkaline phosphatase status; LDH status; prior systemic therapy; largest metastatic lesion recorded at baseline; region; investigator's choice of chemotherapy (ipilimumab, dacarbazine and pembrolizumab)

Based on Table 5 of the CS[1]
CS = company submission; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = European Quality of Life-5 Dimensions-5 levels; HLA-A = human leukocyte antigen (A locus); HRQoL = health-related quality of life; IV = intraveneous; LDH = lactate dehydrogenase; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; UK = United Kingdom; ULN = upper limit of normal; UM = uveal melanoma

Figure 3.2: IMCgp100-202 consort diagram of the ITT population at the first interim analysis



Based on Figure 5 of the CS[1]

Note: "LHD" in the Figure should read "LDH", as indicated in the footer of that Figure in the CS.

CS = company submission; HLA-A = human leukocyte antigen (A locus); ITT = intention-to-treat; LDH = lactate dehydrogenase; RAS = rash analysis dataset; RP2D = recommended phase 2 dose; ULN = upper limit of normal

Statistical analysis of the IMCgp100-102 study did not include a comparative analyses. Hence, there was no formal statistical testing of data. Statistical analysis was descriptive according to specified populations sets: ITT and safety analysis set, see Sections 3.2.3 and 3.2.4..

3.2.3 Efficacy results

According to Table 1 of the CS, the following outcomes were addressed: OS, PFS, ORR, DOR and HRQoL.[1]

Data are presented in the CS for both the IMCgp100-202 and IMCgp100-102 trials and is reproduced below.

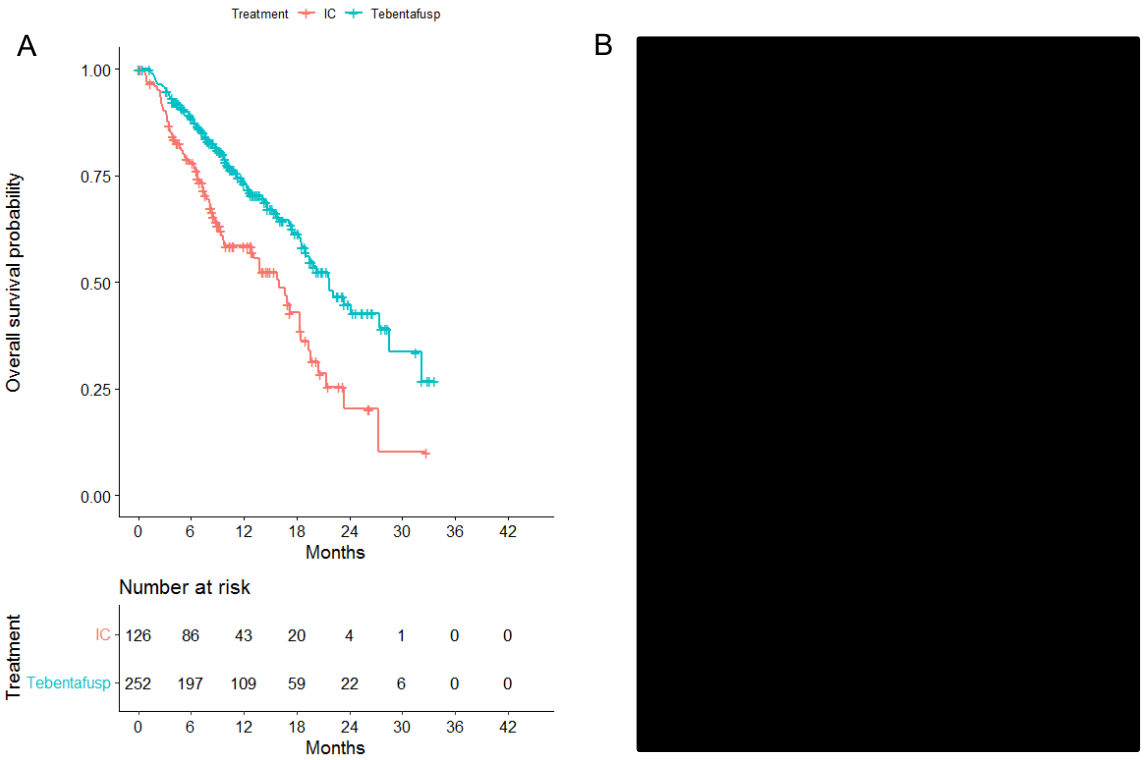
It should be noted that the CS states that *"Study IMCgp100-102 (NCT02570308) was not used to populate the economic model but is included in sections 2.2 to 2.6* [of the CS]. *Although relevant to the decision problem, this study was not included in the economic model because it is a single arm study with a smaller sample size"*.[1] While IMCgp100-102 is not included in economic modelling, it is presented here for clarity and transparency.

3.2.3.1 Overall Survival

3.2.3.1.1 IMCgp100-202

At the October 2020 data cut off, OS favoured tebentafusp with a hazard ratio (HR) of 0.51 (95% confidence interval (CI) 0.37 to 0.71; P<0.0001). The CS reports that Kaplan-Meier estimates demonstrate median OS as prolonged in the tebentafusp arm compared with the investigator's choice (IC) arm: 21.7 months (95% CI 18.6 to 28.6) for tebentafusp vs. 16.0 months (95% CI 9.7 to 18.4) for IC (Figure 3.3A). OS rates at 12 months and 24 months for tebentafusp were 73.2% and 44.8%, respectively, and for investigator's choice were 58.5% and 20.3%, respectively. The August 2021 cut-off had a median follow-up time of [redacted]. Figure 3.3B shows [redacted]

Figure 3.3: Kaplan-Meier estimate of overall survival, study IMCgp100-202 for both data cut-offs (A) October 2020; (B) August 2021



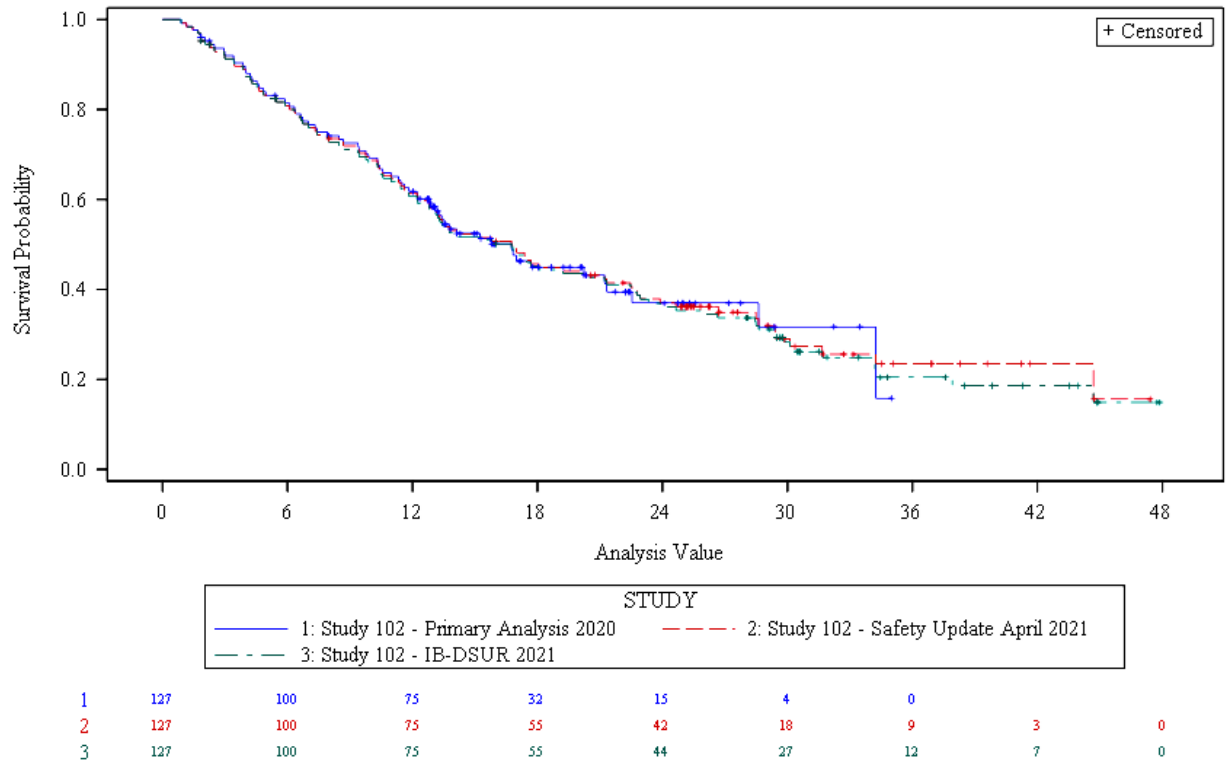
	Median (Months)(95% CI)	
	October 2020	**August 2021**
Tebentafusp (N=252)	21.7 (18.6 to 28.6)	[redacted]
Investigator's choice (N=126)	16.0 (9.7 to 18.4)	[redacted]

* The data include cross-overs from the IC to tebentafusp arm between October 2020 and August 2021
Based on Figure 7 of the CS[1]
CI = confidence interval; CS = company submission; IC = investigator's choice; N = number of participants

3.2.3.1.2 IMCgp100-102

Median OS was 16.8 months (95% CI 12.9 to 21.3), for a median follow-up of 19.6 months (95% CI 16.0 to 22.2). The OS rates from 127 patients in the dose expansion phase were 61.8% (95% CI 52.6 to 69.8%) at 12 months and 37.0% (95% CI 26.5 to 47.5%) at 24 months. Kaplan-Meier estimate of OS by RECIST v1.1 performed by the investigator is depicted in Figure 3.4.

Figure 3.4: Kaplan-Meier plot of overall survival in Phase 2 dose expansion



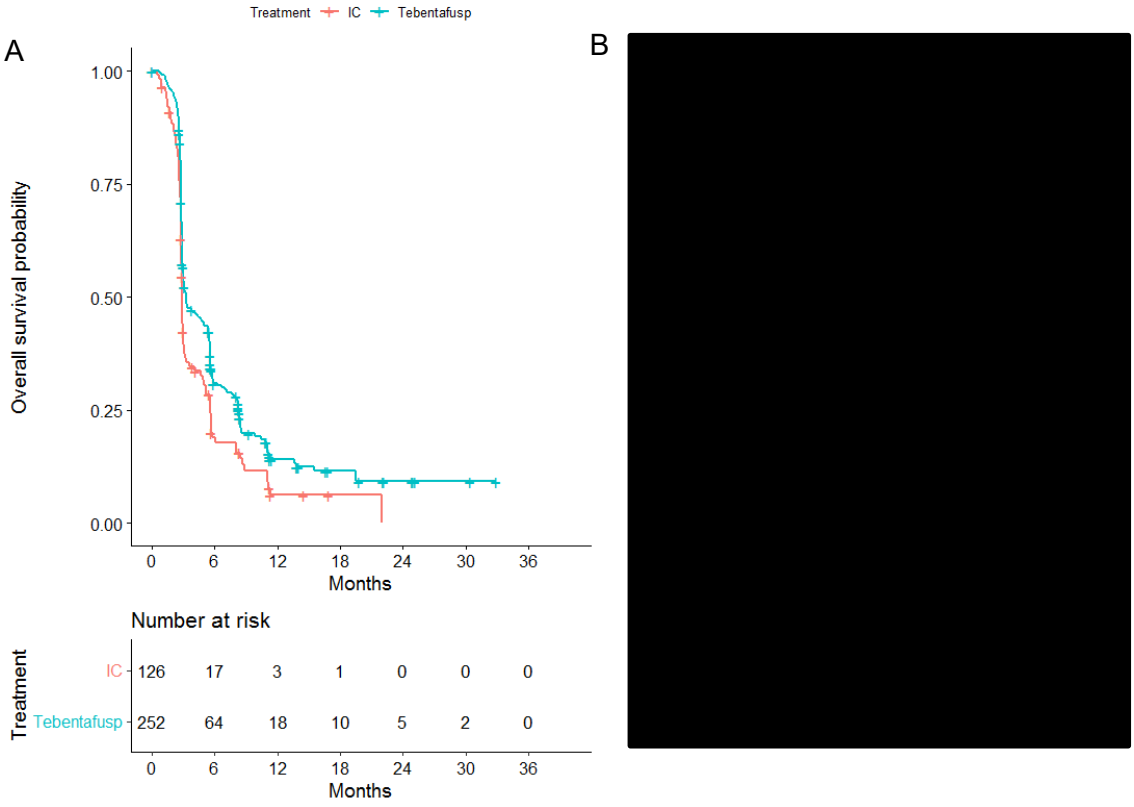
Based on Figure 10 of the CS[1]
Events were deaths due to any cause. Patients not known to have died at the time of analysis are censored.
CI = confidence interval; CS = company submission

3.2.3.2 Progression free Survival (PFS)

3.2.3.2.1 IMCgp100-202

At a median follow-up duration of 11.4 months, median PFS, assessed by investigator, was 3.3 months (95% CI 3.0 to 5.0) in the tebentafusp arm and 2.9 months (95% CI 2.9 to 3.0) in the IC arm (HR 0.73; 95% CI 0.58 to 0.94; P=0.0139; Figure 3.5A). KM estimates of PFS rates at 6 months were 30.9% (95% CI 25.0 to 37.0) and 18.9% (95% CI 12.0 to 27.2), respectively. Figure 3.5B presents the data from the August 2021 data cut, showing the results [redacted].

Figure 3.5: Kaplan-Meier estimate of Progression Free Survival, (A) October 2020; (B) August 2021



	Median (Months)(95% CI)	
	October 2020	**August 2021**
Tebentafusp (N=252)	3.3 (3.0 to 5.0)	[redacted]
Investigator's choice (N=126)	2.9 (2.8 to 3.0)	[redacted]

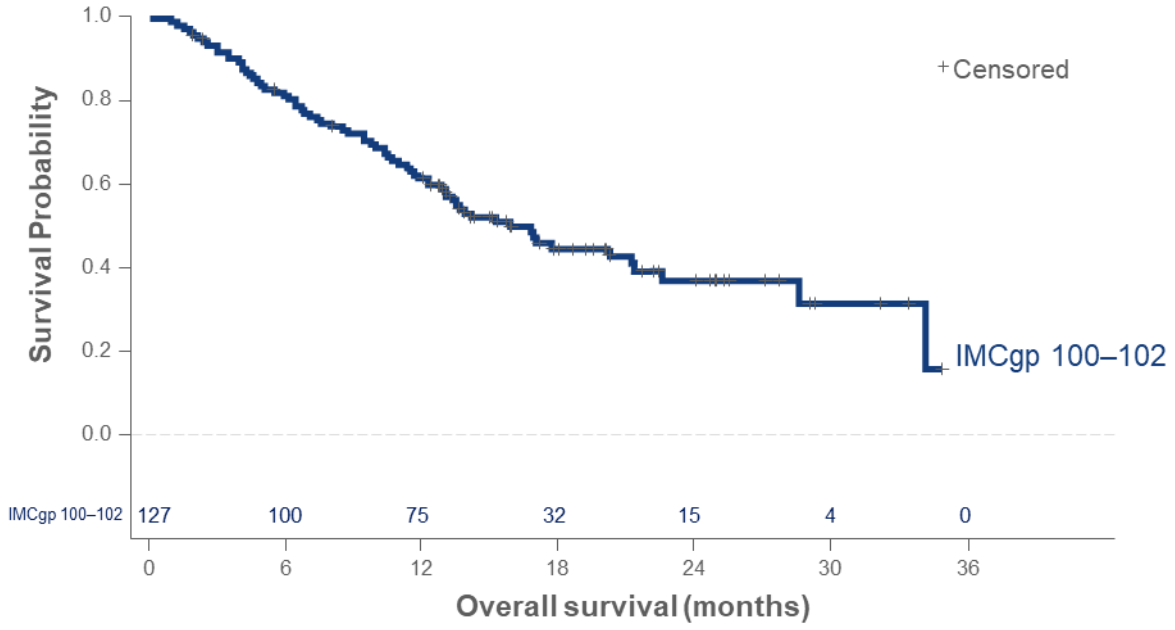
Based on Figure 13 of the CS[1]
CI = confidence interval; CS = company submission; N = number of participants

3.2.3.2.2 IMCgp100-102

Median PFS was 2.3 months (95% CI 1.90 to 3.70) and 114 (89.8%) patients had the event of progressive disease (PD; 105 [82.7%] patients) or death in the absence of PD (9 [7.1%] patients). The estimated PFS rates were 25.8% (95% CI 18.5 to 33.7%) at 6 months and 12.8% (95% CI 7.6 to 19.4%) at 12 months.

When results were assessed by independent central review (ICR); the median PFS was 2.8 months (95% CI 2.0 to 3.7%). The estimated PFS rates were 25% (95% CI 17.8% to 32.9%) at 6 months and 11% (95% CI 6.2 to 17.2%) at 12 months. Ninety patients (71%) were treated beyond disease progression, with the median duration of treatment post RECIST-PD 87.5 days (range 1 to 703 days). A Kaplan-Meier (KM) estimate of PFS by RECIST v1.1 assessed by ICR is depicted in Figure 3.6.

Figure 3.6: Kaplan-Meier plot of PFS (RECIST v1.1) by ICR in Phase 2 dose expansion of study IMCgp100-102



Based on Figure 14 of the CS[1]
Events were either disease progression or death in the absence of disease progression, which occurred within 2 tumour assessment visits of the last evaluable assessment. Events that did not occur within 2 tumour assessment visits were censored. Tumour assessment was based on RECIST v1.1 by investigator opinion.
CS = company submission; ICR = independent central review; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours

3.2.3.3 Objective Response Rate

3.2.3.3.1 IMCgp100-202

ORR determined by investigator assessment, presented in Table 3.5, was 9.1% (95% CI 5.9 to 13.4) for tebentafusp and 4.8% (95% CI 1.8 to 10.1) for investigator's choice.

Table 3.5: Effect of tebentafusp on objective response rate (CR or PR)

Treatment arm	Tebentafusp	Investigator's choice
	N=252	N=126
n (%)	23 (9.1%)	6 (4.8%)
95% CI	5.9-13.4	1.8-10.1
Stratified odds ratio (tebentafusp/ investigator's choice) (95% CI of odds ratio)	1.98 (0.79-4.97)	N/A
Based on Table 8 of the CS[1] Data from best overall response and disease control rate included in Table 8 of the CS but not presented here. CI =confidence interval; CR =complete response; CS = company submission; N = number of partcipants; N/A = not applicable; PR = partial response		

3.2.3.3.2 IMCgp100-102

The effect of tebentafusp on ORR, per investigator assessment or ICR is shown in Table 3.6. ORR assessed by ICR was the primary endpoint of this study and was stated to be 4.9% (95% CI 1.8 to

10.0%) although the accompanying text in the CS stated that the ORR assessed by ICR was 4.7% (95% CI 1.8 to 10.0%).[1]

Table 3.6: Effect of tebentafusp on objective response rate, best overall response, and disease control rate, study IMCgp100-102 (CR or PR)

Trial	IMCgp100-102 (Phase 2 dose expansion)	
	Investigator assessment	ICR assessment
	N=127	
n (%)	9 (7.1%)	6 (4.9%)
95% CI	1.8-10.1	1.8-10.3

Based on Table 9 of the CS.[1]
Data from best overall response and disease control rate included in Table 9 of CS but not presented here.
CI =confidence interval; CR =complete response; CS = company submission; ICR = independent central review; N = number of participants treated; N/A = not applicable; PR = partial response

3.2.3.4 Duration of Response

3.2.3.4.1 IMCgp100-202

Median duration of response was 9.9 months (95% CI 5.4 to not calculable (NC)) for tebentafusp and 9.7 months (95% CI 2.7 to NC) for IC. KM estimates for duration of response were 60.6% (95% CI 34.2 to 7.2%) and 50.0% (95% CI 11.1 to 80.4%) at 6 months, respectively (Table 3.7). According to the CS, there is high uncertainty due to the low number of patients achieving ORR.[1] It should be noted that in the CS, the text accompanying Table 10 stated that nine IC patients were considered in the analysis, however, the table states that six patients achieved OR.

Table 3.7: Effect of tebentafusp on duration of response, study IMCgp100-202

	Tebentafusp	Investigator's choice
	N=252	N=126
Patients achieving OR (N)	23	6
Median follow-up, months (95% CI)	10.8 (2.8 to 13.8)	9.3 (2.8 to NC)
DOR, months		
PFS events, n (%)	9 (39.1%)	4 (66.7%)
PD	9 (39.1%)	4 (66.7%)
Death	0 (0.0%)	0 (0.0%)
Median (95% CI), months	9.9 (5.4 to NC)	9.7 (2.7 to NC)
Kaplan-Meier estimates for DOR (95% CI) [No. at risk]		
3 months	84.8 (59.5-94.9) [n=14]	50.0 (11.1-80.4) [n=2]
6 months	60.6 (34.2-7.2) [n=10]	50.0 (11.1-80.4) [n=2]
9 months	54.5 (28.9-74.4) [n=7]	50.0 (11.1-80.4) [n=2]
12 months	46.8 (21.8-68.4) [n=4]	50.0 (11.1-80.4) [n=2]

Based on Table 10 of the CS[1]
CI = confidence interval; CS = company submission; N = number of participants; NC = not calculable; OR = objective response; PD = progressive disease; PFS = progression-free survival

3.2.3.4.2 IMCgp100-102

The effect of tebentafusp on the duration of response in the phase 2 dose expansion cohort of IMCgp100-102 study per investigator assessment or ICR is shown in Table 3.8. Median duration of objective response per investigator assessment was not calculable (NC; 95% CI 3.1 to NC). The analysis of duration of response at 6 months was 75.0% (95% CI 31.5 to 93.1%) and at 12 months was 56.3% (95% CI 14.7 to 84.2%). The median duration of minor response rate (MinR) or better per investigator assessment was 17.3 months (95% CI 7.4 to NC). The estimated percentage of responders (including those with a MinR) at 6 months was 84.2% (95% CI 58.7 to 94.6%) and at 12 months was 51% (95% CI 26.7 to 71.0%).

Table 3.8: Effect of tebentafusp on duration of response, study IMCgp100-102

	IMCgp100-102 (Phase 2 dose expansion)	
	Investigator's assessment	**ICR assessment**
	N=127	
Median follow-up, months (95% CI)	10.42 (3.61 to 21.42)	23.26 (10.38 to NC)
Number of patients with an OR (N)	9	6
Total number of events[a]	3	5
Total censored for any reason	6	1
Kaplan-Meier analysis		
Median (95% CI) duration of objective response, months	NC (3.713 to NC)	8.706 (5.552 to 24.542)
Estimated % of patients in response at[b]		
3 months (95% CI)	100.0% (NC to NC)	100.0% (NC to NC)
6 months (95% CI)	75.0% (31.5 to 93.1)	60.0% (12.6 to 88.2)
9 months (95% CI)	56.3% (14.7 to 84.2)	40.0% (5.2 to 75.3)
12 months (95% CI)	56.3% (14.7 to 84.2)	20.0% (0.8 to 58.2)
Median (95% CI) duration of MinR or better, months	17.3 (7.4 to NC)	10.3 (5.8 to 23.2)
Estimated % of patients in response at		
6 months (95% CI)	84.2% (58.7 to 94.6)	78.6% (47.2 to 92.5)
12 months (95% CI)	51% (26.7 to 71.0)	33.3% (10.9 to 58.0)

Based on Table 11 of the CS[1]
[a] Events were patients with a date of disease progression or death in the absence of disease progression, following the first documented objective response (CR or PR). Patients without disease progression or death, were censored at the last evaluable tumour assessment. Response confirmation was required ≥4 weeks later following initial evaluation for complete and partial response.
[b] Percentage of patients in response were estimated using the Kaplan-Meier method
CI = confidence interval; CR = complete response; CS = company submission; MinR = minor response rate; N = number of participants; NC = not calculable; OR = objective response; PR = partial response

3.2.3.5 Survival subgroup analysis

The CS included data on various subgroup analyses for overall survival for trial IMCgp100-202 which are summarised below.[1] No information was provided on any subgroup analysis for trial IMCgp100-102.

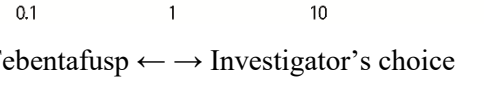
3.2.3.5.1 IMCgp100-202

Subgroup analyses for OS and PFS were conducted by region, investigator's choice treatments, gender, age, ECOG status, baseline alkaline phosphatase, lactate dehydrogenase, and largest metastatic lesion. Figure 3.7 summarises the key results of the analyses by treatment group. The OS benefit provided by tebentafusp was observed across all prespecified major demographic and known prognostic subgroups, including a HR of 0.51 (95% CI 0.35 to 0.75) compared to pembrolizumab, which is the most frequent IC medication.

Tables 3.9 and 3.10 present results for OS and PFS by pre-choice of chemotherapy, respectively.

Figure 3.7: Overall survival trends by subgroup (ITT)

	Tebentafusp		Investigator's choice		
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)
ECOG 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)**



Based on Figure 16 of the CS[1]

CI = confidence interval; CS = company submission; ECOG = Eastern Cooperative Oncology Group; ITT = intention-to-treat; ULN = upper limit of normal

Table 3.9: Subgroup analysis of OS by pre-choice of chemotherapy (ipilimumab, dacarbazine and pembrolizumab) and treatment

	Median OS (95% CI), months		12-month OS rate, %		HR (95% CI)	P-value
	Tebentafusp	IC	Tebentafusp	IC		
IC of chemotherapy						
Dacarbazine (n=13, 7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab (n=199, 103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (n=40, 16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 3 of the response to the request for clarification[3]
CI = confidence interval; HR = hazard ratio; IC = investigator's choice; OS = overall survival

Table 3.10: Subgroup analysis of PFS by pre-choice of chemotherapy (ipilimumab, dacarbazine and pembrolizumab) and treatment

	PFS events, n (%) Progressive disease		Median PFS (95% CI), months		Kaplan-Meier estimates for PFS (95% CI) [No. at risk]		HR (95% CI)
	Tebentafusp	IC	Tebentafusp	IC	Tebentafusp	IC	
IC of chemotherapy							
Dacarbazine (n=13, 7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab(n=199, 103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab (n=40, 16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 4 of the response to the request for clarification[3]
CI = confidence interval; HR = hazard ratio; IC = investigator's choice; PFS = progression-free survival

ERG comment: As detailed in Section 2.3, comparison with IC prevents an evaluation of tebentafusp in relations to each of the comparators separately: there is likely to be variation in effectiveness and safety and thus which treatment is cost effective. In response to the request for clarification, the company provided subgroup analyses (Tables 3.9 and 3.10).[3] These Tables confirm that relative effectiveness of treatments differ, e.g. [redacted] of OS for ipilimumab (Table 3.9) as well as of PFS for pembrolizumab and ipilimumab (Table 3.10).

3.2.4 Safety results

3.2.4.1 Adverse events

3.2.4.1.1 Study IMCgp100-202

The frequency of treatment-emergent adverse events (TEAEs) from any cause was 100% in the tebentafusp arm and 94.6% in the investigator's choice arm (see Table 3.11). Grade ≥3 AEs occurred in 54.3% and 36.0% of patients, respectively. Grade ≥3 AEs that were considered related to study drug by the investigator occurred in 44.5% and 17.1% of patients in the tebentafusp and investigator's choice arms, respectively. The incidence of serious TEAEs was 28.2% in the tebentafusp arm and 23.4% in the investigator's choice arm. None of the deaths in either arm was considered to be treatment related.

The CS does state that 89% of patients experienced any grade CRS. Most patients had grade 1 (12%) or grade 2 (76%) CRS; the incidence of grade 3 CRS was 0.8%. There were no grade 4 CRS or death due to CRS.[1] Diagnosis of CRS following tebentafusp infusion was based most frequently on pyrexia followed by hypotension and infrequently hypoxia. Pyrexia and hypotension were reported in 76% and 38% of patients, respectively. Other commonly observed symptoms with CRS included chills (47%), nausea (43%), vomiting (26%), fatigue (41%) and headache (22%), although these symptoms may also be isolated and not necessarily associated with CRS. These events occurred at a >10% point higher frequency in the tebentafusp treatment arm than the IC arm; and are consistent with the mechanism of action of tebentafusp.[15] However, the ERG notes that these values are again not fully consistent between Table(s) and text.

The CS reports that most patients experienced CRS following each of the first three tebentafusp infusions, with decreasing severity and frequency. In the majority of cases, CRS started on the day of infusion. Pyrexia was noted in nearly all cases of CRS, and in these patients, an increase in body temperature generally occurred within the first 8 hours after tebentafusp infusion. CRS rarely (1.2%) led to treatment discontinuation. All CRS symptoms were reversible and were mostly managed with intravenous fluids, antihistamines, non-steroidal anti-inflammatory drugs, or a single dose of corticosteroid. Two patients (0.8%) with grade 3 CRS received tocilizumab.

The CS reported that acute skin reactions occurred in 91% of patients treated with tebentafusp including any grade rash (grouped term, 83.0%), pruritus (69.0%), erythema (25.0%) and cutaneous oedema (grouped term, 27.0%).[1] Grade 1 and 2 skin reactions accounted for 27.0% and 38.0%, respectively, of all reactions, with 18.4% of reactions at grade 3. Grade 3 reactions with the highest incidence were rash and rash maculo-papular. No grade 4 or 5 events or deaths relating to skin reactions were observed.

According to the CS, acute skin reactions typically occurred following each of the first three tebentafusp infusions, with decreasing severity and frequency (Figure 3.8).[1] The median time to onset was one day in the tebentafusp treated patients and median time to improvement to Grade ≤1 was six days. Rash was manageable with interventions such as oral antihistamines and topical corticosteroids. Systemic corticosteroids were used infrequently to treat rash (10% of patients with rash) and majority of symptoms resolved without any systemic corticosteroid or any long term sequalae. However, 2.4% of patients had the treatment interrupted due to a skin-related AE. There were no discontinuations of tebentafusp due to acute skin reactions. No cases of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported.

Ninety-five percent of patients had pre-existing liver metastasis, and alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) increases to grade ≥1 were observed in 64.5% of patients treated with tebentafusp. No deaths due to ALT/AST elevations were observed and more than 90% of patients were able to continue treatment beyond worst grade ALT/AST elevation. Most (71%) ALT/AST elevations generally occurred within the first three tebentafusp infusions. Most patients experiencing grade 3 or 4 ALT/AST elevations had improvement to Grade ≤1 within 7 days. Elevations in bilirubin have been reported in 27% of patients and these were primarily associated with increased size of liver metastasis (Table 3.13).[16]

The CS stated that discontinuation of treatment because of TEAEs occurred in eight patients (3.3%) in the tebentafusp arm and seven patients (6.3%) in the IC arm; five of the eight patients (2%) in the tebentafusp arm had events that were considered treatment related although this data are not tabulated in the Table.

Table 3.11: Adverse reactions reported in ≥5% of patients at any grade in study IMCgp100-202 Safety Population

	IMCgp100-202 Number (%) of Patients (N=245)		Investigator's Choice Number (%) of Patients (N=111)	
System Organ Class Preferred Term	**Any Grade**	**≥Grade 3**	**Any Grade**	**≥Grade 3**
Number of patients with any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated Cytokine Release Syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Rash[1]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue[2]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]
Melanocyte-related AE[3]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain[4]	[redacted]	[redacted]	[redacted]	[redacted]
Edema[5]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine release syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]

	IMCgp100-202 Number (%) of Patients (N=245)		Investigator's Choice Number (%) of Patients (N=111)	
System Organ Class Preferred Term	**Any Grade**	**≥Grade 3**	**Any Grade**	**≥Grade 3**
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Hyperbilirubinaemia	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Flushing	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]
Night sweats	[redacted]	[redacted]	[redacted]	[redacted]

Based on response to the request for clarification[3]

[1] Blister, Dermatitis, Dermatitis acneiform, Dermatitis allergic, Dermatitis bullous, Dermatitis contact, Dermatosis, Drug eruption, Eczema, Eczema eyelids, Erythema multiforme, Exfoliative rash, Interstitial granulomatous dermatitis, Lichenification, Lichenoid keratosis, Palmar-plantar erythrodysaesthesia syndrome, Papule, Psoriasis, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash vesicular, Seborrhoea, Seborrhoeic dermatitis, Skin abrasion, Skin erosion, Skin exfoliation, Skin irritation, Skin plaque, Solar dermatitis, Toxic skin eruption, Urticaria

[2] Asthenia, Fatigue

[3] Achromotrichia acquired, Ephelides, Eyelash discolouration, Eyelash hypopigmentation, Hair colour changes, Lentigo, Pigmentation disorder, Retinal depigmentation, Skin depigmentation, Skin discolouration, Skin hyperpigmentation, Skin hypopigmentation, Solar lentigo, Vitiligo

[4] Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, Flank pain, Gastrointestinal pain, Hepatic pain

	IMCgp100-202 Number (%) of Patients (N=245)		Investigator's Choice Number (%) of Patients (N=111)	
System Organ Class Preferred Term	**Any Grade**	**≥Grade 3**	**Any Grade**	**≥Grade 3**

[5] Eye oedema, Eye swelling, Eyelid oedema, Face oedema, Generalised oedema, Lip oedema, Lip swelling, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema, Periorbital swelling, Peripheral swelling, Pharyngeal oedema, Swelling, Swelling face, Swelling of eyelid
TEAE = treatment-emergent adverse event

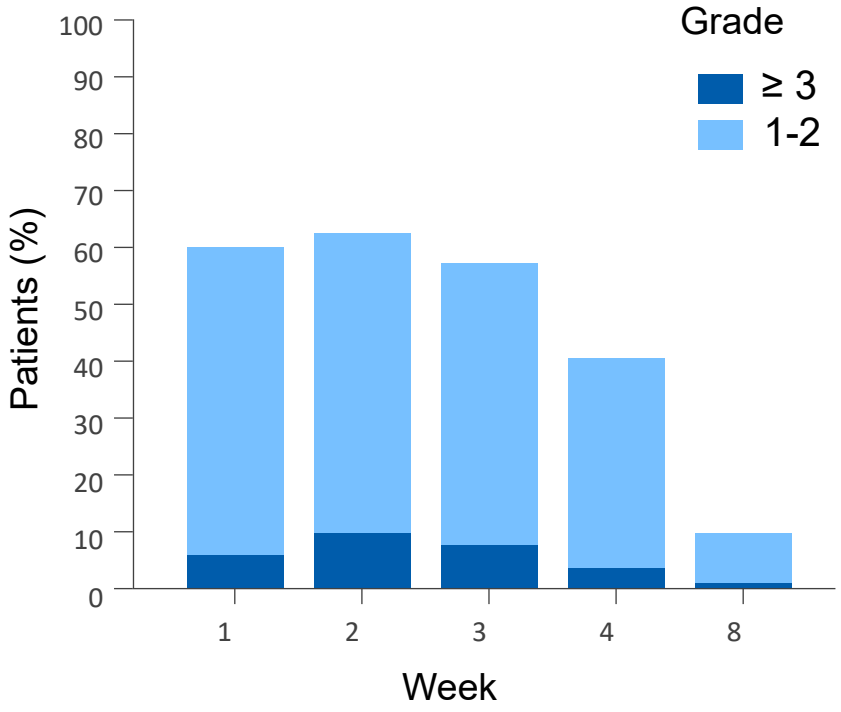
Table 3.12: Treatment-emergent adverse events occurring in ≥20% patients in study IMCgp100-202

	Tebentafusp (N=245)		Investigator's choice (N=111)	
Adverse reaction	**Any Grade (%)**	**Grade ≥3 (%)**	**Any Grade (%)**	**Grade ≥3 (%)**
Cytokine release syndrome[a]	89	0.8	3	0.0
Rash[b]	83	18.4	28	0.0
Pyrexia[c]	76	3.7	7	0.9
Pruritus	69	4.5	23	0.0
Fatigue[d]	64	5.7	42	0.9
Nausea[c]	49	2.0	26	0.9
Chills[c]	48	0.4	4	0.0
Hypo/hyper-pigmentation[e]	47	0.4	6	0.0
Abdominal pain[f]	45	2.9	33	3.6
Oedema[g]	45	0.0	10	0.0
Hypotension[c]	39	3.3	3	0.0
Dry skin	31	0.0	4	0.0
Headache[c]	31	0.4	10	0.9
Vomiting[c]	30	1.2	9	0.0
Diarrhoea	25	1.2	20	2.7
Erythema	25	0.0	1	0.0
Arthralgia	22	0.8	16	0.0

Based on Table 15 of the CS[1]
[a] CRS was adjudicated using the ASTCT consensus grading of CRS criteria.[17] Adjudicated CRS is provided in lieu of investigator reported CRS
[b] Includes blister, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatosis, drug eruption, eczema, eczema eyelids, erythema multiforme, exfoliative rash, interstitial granulomatous dermatitis, lichenification, lichenoid keratosis, palmar-plantar erythrodysaesthesia syndrome, papule, psoriasis, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, seborrhoea, seborrhoeic dermatitis, skin abrasion, skin erosion, skin exfoliation, skin irritation, skin plaque, solar dermatitis, toxic skin eruption, urticaria
[c] Some of the events may be associated with CRS or may be isolated reported events
[d] Includes fatigue and asthenia
[e] Includes achromotrichia acquired, ephelides, eyelash discolouration, eyelash hypopigmentation, hair colour changes, lentigo, pigmentation disorder, retinal depigmentation, skin depigmentation, skin discolouration, skin hyperpigmentation, skin hypopigmentation, solar lentigo, vitiligo

	Tebentafusp (N=245)		Investigator's choice (N=111)	
Adverse reaction	**Any Grade (%)**	**Grade ≥3 (%)**	**Any Grade (%)**	**Grade ≥3 (%)**
[f] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, flank pain, gastrointestinal pain, and hepatic pain [g] Includes eye oedema, eye swelling, eyelid oedema, periorbital swelling, periorbital oedema, swelling of eyelid, pharyngeal oedema, lip oedema, lip swelling, face oedema, generalised oedema, localized oedema, oedema, oedema peripheral, peripheral swelling, swelling, swelling face ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; CS = company submission; N = number of participants				

Figure 3.8: Percentage of treated patients experiencing any grade or grade ≥3 treatment related rash after each does of tebentafusp



Based on Figure 19 of the CS[1]
CS = company submission

Table 3.13: Panel of post-baseline laboratory abnormalities occurring in ≥20% or Grade 3-4 (≥5%) in UM patients in study IMCgp100-202

	Tebentafusp (N=245)		Investigator Choice Therapy (N=111)	
Lab Parameter	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
Haematology				
Lymphocyte count decreased	222 (90.6)	136 (55.5)	29 (26.6)	2 (1.8)
Chemistry				
Phosphate decreased	124 (51.5)	29 (12.0)	20 (19.6)	2 (2.0)
Lipase increased	91 (37.8)	36 (14.9)	29 (28.2)	6 (5.8)

	Tebentafusp (N=245)		Investigator Choice Therapy (N=111)	
Lab Parameter	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
Amylase increased	56 (23.0)	10 (4.1)	19 (18.1)	1 (1.0)
Liver Function Tests				
AST increased	132 (54.8)	30 (12.4)	43 (39.8)	3 (2.8)
ALT increased	126 (52.3)	22 (9.1)	32 (29.4)	2 (1.8)
Bilirubin increased	65 (26.5)	11 (4.5)	16 (14.5)	8 (7.3)

Based on Table 16 of the CS[1]
ALT = alanine aminotransferase; AST = aspartate transaminase; CS = company submission; UM = uveal melanoma

3.2.4.1.2 Study IMCgp100-102

According to the CS, treatment-related adverse events (TRAEs) were generally cutaneous or cytokine mediated (T cell activation) and included pyrexia (80%), pruritus (67%), and chills (64%).[1] Grade ≥3 TRAEs that occurred were rash maculo-papular (13%), hypotension (8%), increased AST, and hypophosphatemia (5% each). TRAEs decreased in frequency and severity after the first 3 doses of tebentafusp. CRS occurred at 3% grade 3 and 1% grade 4. There were no grade 5 TRAEs or treatment related deaths.

The CS reports that 86% of patients presented with the CRS and the most frequently classified CRS events were pyrexia (80%) and hypotension (50%). CRS was a serious AE in 3.15% of patients.[1]

The CS reports that acute skin reactions occurred in both phases of the trial. Rash occurred in 16.7%, 50.0%, 33.3%, and 33.1% of patients in phase 1 dose escalation cohorts 2, 3 and 4, and the phase 2 expansion cohort, respectively. Pruritus occurred in all cohorts; 100%, 66.7%, 100%, 100% and 68.5% in phase 1 dose escalation cohorts 1, 2, 3 and 4, and phase 2 expansion cohort, respectively. Erythema was also reported in the phase 1 dose escalation cohorts 1 (33.3%), 2 (66.7%), 3 (75.0%) and 4 (33.3%), and phase 2 expansion cohort (17.3%). Generalised rash and maculo-papular, respectively, were serious adverse events (SAEs) in 0.8% and 2.4% of patients in the phase 2 dose expansion cohort. There were no events of grade 4 or 5 severity. None of the TEAEs in the rash category were serious and none resulted in dose interruption or discontinuation of tebentafusp.

According to the CS, in the phase 2 dose expansion cohort, 88.2% of patients experienced AEs for rash; 15.7% of which were of grade 3 severity.[1] No events of grade 4 or 5 were reported. The most common grade 3 rash events were rash maculo-papular (11.0%) and rash (2.7%). A few patients (3.1%) had serious AEs in the rash category that included rash maculo-papular and rash generalised. None of the TEAEs in the rash category resulted in discontinuation of tebentafusp. Tebentafusp-related rash was most common in the initial weeks of treatment across the phase 1 dose escalation and phase 2 dose expansion cohorts, becoming less frequent by the second month of treatment. Less than 1% of patients reported events of grade ≥3 severity after day 35 of treatment. No cases of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported.

ERG comment: The ERG has several observations regarding the AEs:

- The ERG notes that, according to the CS, the frequency of grade ≥3 TEAEs in study IMCgp100-202 was reported to be [redacted] in the tebentafusp arm ([redacted]) than in the investigator choice arm ([redacted]). Grade ≥3 AEs that were deemed to be related to

study drug by the investigator also occurred more often in the tebentafusp arm (44.5%) than in the investigator's choice arm (17.1%). However it is noted that limited information is provided on AEs experienced in study IMCgp100-102 and while it is accepted this trial is not considered in the economic modelling, access to this data would have been of interest to inform a fuller understanding.

- A further point of note is the use of terminologies in describing AEs. While TEAEs were reported for study IMCgp100-202, there appears to be unclear categorisation and reporting of AE's for trial IMCgp100-102 with treatment-*related* adverse events (TRAE) and treatment-*emergent* adverse events (TEAEs) seemingly used interchangeably.
- Furthermore, the ERG sought clarification on the reporting of adverse events by requesting data on AEs that occurred in ≥5% of patients at any grade in study IMCgp100-202.[6] The response to request for clarification included relevant data, see Table 3.11.[3] The most frequently AEs reported in ≥5% of patients at any grade were broadly consistent with those reported in ≥20% of patients at any grade (Table 3.12).

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS states that, in the absence of a direct head-to-head trial, an SLR was conducted to identify studies by which an indirect comparison with nivolumab + ipilimumab combination therapy.[1] Two studies were identified, both single arm and in metastatic UM.[18, 19] Only one study, by Pilulats et al. 2021, was chosen for the indirect comparison on the following basis: purely untreated population like the IMCgp100 study 202 (Pelster et al. 2021) was only 57% previously untreated) and it reports more of the key covariates used for the adjustment in the indirect comparison (see Section 3.4).[19]

ERG comment: It was unclear to the ERG whether no other studies might have been suitable for a comparison with nivolumab + ipilimumab. The ERG in a pragmatic citation search also located two other studies of this comparator in a metastatic UM population, albeit of mixed treatment experience.[20, 21] Therefore, the ERG asked for further clarification regarding the application of eligibility criteria for study choice. The company responded by reiterating the eligibility criteria, including larger study size.[3] The company also emphasised the importance of treatment experience, citing a meta-analysis to show that OS was higher for first-line.[22]

The ERG could not locate the figures reported in the clarification letter, but the meta-analysis did appear to show a clear advantage in survival for studies where 100% first line compared to 0% first line.[22] Given that the three studies not included for the indirect comparison mixed first-line and treatment experienced one would therefore have expected that OS would be lower in those studies than in the study used for the indirect comparison, Pilulats et al. 2021, which was the only one that was pure first-line. However, this is not the case: median OS (95% CI) in months were as follows:

- Pilulats et al. 2021: 12.7 (7.1 to 18.3)
- Pelster et al. 2021: 19.1 (9.6 to NR)
- Najjar et al. 2020: 15 (10.9 to 21.6)
- Heppt et al. 2019: 16.1 (12.9 to 19.3)

This suggests that there is a large amount of variation in outcome that cannot be explained solely by treatment experience. On that basis and because of the high risk of bias of the method of indirect comparison (discussed in Section 3.4), the ERG still considers that there is validity in comparing the results of a comparison with nivolumab + ipilimumab using all four studies. Indeed, the median OS

with tebentafusp in study IMCgp100-102 of 16.8 months (95% CI: 12.9-21.3) would be lower than in one of the comparator studies. This therefore constitutes a key issue.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Given the lack of a common comparator the company performed a matching-adjusted indirect comparison (MAIC) to estimate OS using a Cox proportional hazards model, citing Phillippo et al. 2016, which is NICE Technical Support Document (TSD) 18.[23] The covariates chosen for matching were:[7]

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

The company did not state how it was determined that these covariates could be confounding (were either treatment effect modifying or prognostic), as required to reduce the bias via a MAIC.[23] The company did, however, state that time since diagnosis was missing from the Pilulats et al. 2021 study and was a potential confounder and that *"no other important potential [confounders] were identified"* (p. 46, Appendices).[7] The company stated that the small number of patients with extrahepatic disease only in IMCgp100-202 study, compared with the study by Piulats et al. 2021 had the *"...potential to impact the effective sample size and/or cause modelling issues"* (p. 46, Appendices).[7] Therefore, two sensitivity analyses were conducted as ways of defining the disease location covariate for matching:

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

Results of the MAIC were presented as summary hazard ratios (HRs, see Table 3.14) and KM plots for each of the main analysis and the two sensitivity analyses.

Table 3.14: Results from the main and sensitivity analyses for the MAICs and UAIC

Analysis	MAIC		UAIC
	Robust SE	Bootstrap	Robust SE
	HR (95% CI)	HR (95% CI)	HR (95% CI)
IMCgp100 versus ipilimumab + nivolumab			
Main analysis	[redacted]	[redacted]	[redacted]
Sensitivity analysis 1	[redacted]	[redacted]	[redacted]
Sensitivity analysis 2	[redacted]	[redacted]	[redacted]

Based on Table 14 of the CS[1]
CI = confidence interval; CS = company submission; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; N/A = not applicable; SE = standard error; UAIC = unadjusted indirect comparison

ERG comment: Important information recommended in TSD 18 was not presented by the company.[1, 23] In particular:

- No evidence was presented for effect modifier prognostic status.
- Covariate distributions were not presented to check for degree of overlap in covariates between the IMCgp100 and ipilimumab + nivolumab trials.
- Weight distributions were not reported including the number of individuals receiving zero weight. Effective sample size was also not reported.

Therefore, the ERG requested that a full technical report be included in line with TSD 18, but the company did not provide this in their response to the request for clarification.[3]

The results showed that the adjustment appeared to have little effect on the HR in comparison to the unadjusted estimate. This does raise the question as to the degree to which any bias had been addressed, as TSD 18 states that *"Hoaglin, in a series of letters critiquing an unanchored comparison by Di Lorenzo et al. based upon a matching approach similar to MAIC, remarked that, without providing evidence that the adjustment compensates for the missing common comparator arms and the resulting systematic error, the ensuing results 'are not worthy of consideration'"* (p. 57).[23]

Given the large risk of bias, the ERG also requested in the clarification letter that MAICs be conducted using the three studies referred to in Section 3.3,[19-21] but the company did not provide these analyses, citing prior treatment as a confounding factor.[3] However, as alluded to in Section 3.3, the ERG would argue that there appears to be confounding beyond treatment experience that is required to explain the variation in OS between the four studies and, more specifically the fact that OS is lowest for the study that according to treatment experience or lack thereof that was used for the MAIC. Therefore, it would still seem reasonable to include indirect comparisons using the other three studies, thus implying that this remains a key issue.

3.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work was undertaken by the ERG.

3.6 Conclusions of the clinical effectiveness section

The CS and response to the request for clarification provided sufficient details for the ERG to appraise the literature searches.[1, 24] Overall, searches were well presented and reproducible. Searches were carried out on a good range of resources, including two trials registries. A supplementary internet search and the checking of references of included articles was undertaken to identify additional studies not retrieved by the main searches.

The CS presented the results of two studies:

1. The IMCgp100-102 study is a phase I/II clinical study of IMCgp100 in participants with advanced UM. Study IMCgp100-102 was not used to populate the economic model as it is a single arm study with a smaller sample size (n=127).
2. The IMCgp100-202 study is a multicentre, parallel, open-label, phase III trial, which randomised previously untreated patients with metastatic UM who were HLA-A* 02:01–positive to receive tebentafusp or the investigator's choice of therapy.

Detailed efficacy results are presented in Section 3.2.3 while detailed safety results are presented in Section 3.2.4:

- **OS** rates at 12 months and 24 months for tebentafusp were 73.2% and 44.8%, respectively, and for investigator's choice were 58.5% and 20.3%, respectively. The August 2021 cut-off had a median follow-up time of [redacted].
- KM estimates of **PFS** rates at 6 months were 30.9% (95% CI 25.0 to 37.0) and 18.9% (95% CI 12.0 to 27.2), respectively. Results from the August 2021 data cut showed that [redacted].
- **ORR** determined by investigator assessmentwas 9.1% (95% CI 5.9 to 13.4) for tebentafusp and 4.8% (95% CI 1.8 to 10.1) for investigator's choice.
- Median **duration of response** was 9.9 months (95% CI 5.4 to NC) for tebentafusp and 9.7 months (95% CI 2.7 to NC) for IC. KM estimates for duration of response were 60.6% (95% CI 34.2 to 7.2%) and 50.0% (95% CI 11.1 to 80.4%) at 6 months, respectively
- Regarding **HRQoL**, As detailed in Section 4.2.8, the EQ-5D-5L data that were collected in the IMCgp100-202 trial (see CS Tables 61 and 62) were not used directly in the CS base-case analysis.
- **Subgroup analyses** pilimumab confirm that relative effectiveness of treatments differ, e.g. [redacted] of OS for ipilimumab (Table 3.9) as well as of PFS for pembrolizumab and ipilimumab, this has been highlighted as key issue.
- Regarding **safety results**, the frequency of grade ≥3 TEAEs in study IMCgp100-202 was reported to be [redacted] in the tebentafusp arm ([redacted]) than in the investigator choice arm ([redacted]). Grade ≥3 AEs that were deemed to be related to study drug by the investigator also occurred more often in the tebentafusp arm (44.5%) than in the investigator's choice arm (17.1%). The frequency of AEs has been highlighted as another key issue.

As detailed in Sections 3.3 and 3.4, the CS described the results of a MAIC. The ERG identified some additional studies that could have been relevant for the indirect treatment comparison of tebentafusp with nivolumab + ipilimumab. However, these studies were not considered by the company. Furthermore, the ERG feels that important information recommended in TSD 18 was not presented by the company. The ERG is also concerned about the lack of comparison to nivolumab monotherapy which has been identified as another key issue.

4. COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis (CEA) studies. However, the search Section 4.1.1 also contains summaries and critiques of other searches related to cost effectiveness presented in the CS. Therefore, the following section includes searches for the CEA review, measurement, and evaluation of health effects as well as for cost and healthcare resource identification, measurement, and valuation.

4.1.1 Searches performed for cost effectiveness section.

One set of systematic literature searches was performed to identify cost effectiveness analyses, HRQoL and healthcare cost and resource use studies (CS Appendix G).[7]

Appendix G of the CS reported a single set of literature searches used to identify cost effectiveness studies; cost and healthcare resource use studies; and studies reporting HRQoL outcomes relevant to the conditions of interest.[7] Searches were developed by an information specialist and conducted in May 2020 and updated in September 2021. A summary of the resources searched are provided in Table 4.1. The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

Table 4.1: Resources searched for cost effectiveness studies, HRQoL and healthcare cost and resource use studies. May 2020 and Sept 2021

Resource	Host/Source	Date Range of most recent search	Date searched
Databases			
Embase	Ovid	1974-2021/wk36	12.5.20 Updated 10.9.21
MEDLINE & MEDLINE In-Process	Ovid	1946-2021/09/10	12.5.20 Updated 10.9.21
CDSR	Wiley	All years	11.5.20 Updated 10.9.21
HTAD	CRD	All years	11.5.20*
NHS EED	CRD	All years	11.5.20*
DARE	CRD	All years	11.5.20*
Epistemonikos	Internet	All years	11.5.20 Updated 10.9.21
Additional searches			
Handsearching of reference lists of key included articles.			

* No updates required as no new records have been added to DARE/HTAD/NHS EED since the original searches were run
CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; EED = Economic Evaluation Database; HRQoL = health-related quality of life; HTAD = Health Technology Assessment Database; NHS = National Health Service

ERG comment:

- A good range of resources were searched for the economic SLR and searches were clearly structured and documented. Strategies made good use of both free text and subject headings.

- Section G.1.1.1 of the CS appendices included the German database PharmNet.Bund in a list of resources searched, but no corresponding strategy appeared in the appendices.[7] The company clarified that this had been included in error and that its contents were searched as part of the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) register search reported in Appendix D.[3, 7]
- As with the clinical effectiveness searches, the company reported using relevant SLRs and key articles to ensure that the strategy retrieved the most relevant records, a supplementary search of the reference lists of key articles for additional relevant material was undertaken.
- As reported in the clinical effectiveness section (see Section 3.1.1), the ERG noted that the Emtree term 'uvea melanoma' was missing from both the clinical effectiveness and economics Embase searches. In response to the request for clarification, the company reran the searches.[3] Of the additional 54 records returned for the economics SLR, no new relevant records were identified.

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies, HRQoL studies and costs and resource use studies are presented in Table 4.2.

Table 4.2: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	Adult patients, aged ≥ 18 years, with advanced or metastatic uveal melanoma/choroidal melanoma	Paediatric patients
Intervention[a]	Tebentafusp, IMCgp100	Surgical interventions for UM/choroidal melanoma
Comparator[a]	All other non-surgical therapeutic interventions used in the treatment of UM/choroidal melanoma	Surgical interventions for UM/choroidal melanoma
Outcomes(s) 1 (Published economic evaluations)	ICER – cost per QALY ICER – cost per measure of effect gained Life years	Any outcome not listed in the inclusion criteria
Outcomes(s) 2 (HRQoL studies)	Utility estimates (EQ-5D, SF-6D) HRQoL (other relevant instruments e.g. SF-36, disease specific instruments; FACT-G, FACT-M, EORTC-QLQC30, MFI))	
Outcomes(s) 3 (Cost/resource use studies)	Direct costs associated with UM or choroidal melanoma (e.g., medicines, healthcare labour costs, hospitalisations, surgery) Indirect costs associated with UM or choroidal melanoma (e.g. absenteeism, work productivity, premature death) Resource use (e.g., hospitalisations, GP visits, hospital length of stay) associated with UM or choroidal melanoma	
Study design 1 (Cost effectiveness analysis studies)	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	Non-human studies PK and proof of concept studies Studies not reporting empirical data

	Inclusion criteria	Exclusion criteria
	Model-based economic evaluations and/or model (e.g. decision trees, Markov models etc.) 1999 onwards	Studies reporting expert opinion only Reviews/Systematic reviews Studies indexed as case reports, cases series, editorials, and letters Publications in non-English language
Study design 2 (HRQoL studies)	Observational studies reporting utilities/HRQoL data 1999 onwards RCTs reporting HRQoL data 1999 onwards	
Study design 3 (Cost/resource use studies)	All empirical studies reporting on costs and resource utilisation for the specified patient population 1999-onwards	
Based on Appendix Tables 7 to 9 of the CS[7] [a] No restriction was used for the HRQoL and costs and resource use searches CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GP = general practitioner; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; UM = uveal melanoma		

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. The rationales for excluding studies after full paper reviewing (CS Appendix Figure 4) are considered appropriate given the defined in- and exclusion criteria.[7]

4.1.3 Conclusions of the cost effectiveness review

The CS provides an overview of the included cost effectiveness, HRQoL and resource use and costs studies, but no specific conclusion was formulated.

ERG comment: The CS and the response to request for clarification provided sufficient details for the ERG to appraise the literature searches. Overall, searches were well presented and reproducible. Searches were carried out on a good range of resources, including two trials registries. A supplementary internet search and the checking of references of included articles was undertaken to identify additional studies not retrieved by the main searches.

Eligibility criteria were suitable for the SLR performed.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.3: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	In line with reference case
Perspective on costs	NHS and PSS	In line with reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	In line with reference case
Time horizon	Long enough to reflect all important differences in costs	In line with reference case

Element of health technology assessment	Reference case	ERG comment on company's submission
	or outcomes between the technologies being compared	
Synthesis of evidence on health effects	Based on systematic review	Partly in line with reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	In line with reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Partly in line with reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	In line with reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	In line with reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	In line with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	In line with reference case

ERG = Evidence Review Group; EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; NHS = National Health Service; PSS = Personal Social Services; QALY = quality adjusted life year; UK = United Kingdom

4.2.2 Model structure

The company developed a de novo partitioned survival model (PSM) with three health states (pre-progression, post-progression, and death) and a one-week cycle length, programmed in Microsoft® Excel. All patients started in the pre-progression health state. The post-progression health state was defined in accordance with the Phase III IMCgp100-202 clinical trial secondary efficacy endpoint of progression-free survival, as patients having confirmed disease progression per RECIST v1.1. A half-cycle correction was applied.

ERG comment: The main concern of the ERG relates to the use of a partitioned survival model. The NICE Decision Support Unit (DSU) TSD 19 recommends the use of state transition modelling to assist in verifying the plausibility of partitioned survival model extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11).[25]

Moreover, the assumption of structural independence between endpoints is highlighted as an important limitation of a PSM. For this model structure, this means that the probability of dying would be independent of the time at which progression took place (i.e. independent modelling of PFS and OS). In their response to clarification question C1 the company argued that a PSM is appropriate in this case for the following reasons.[3] First, they state the PFS and OS data in the IC arm are mature (based on the

October 2020 data cut-off, the KM curve shows that only 6.2% of the patients are still progression-free and 10.2% alive at the end of the follow-up). In the tebentafusp arm, based on the October 2020 data cut-off, the Kaplan-Meier curve shows that [redacted]% of the patients are still progression-free (hence there is limited uncertainty regarding the extrapolation of this endpoint) and [redacted]% of the patients is still alive at the end of the follow-up. Based on the August 2021 data cut-off these numbers are [redacted]% and [redacted]%, respectively. Based on this the company argued there is limited uncertainty regarding the extrapolation of the PFS endpoint. They further stated that the treatment effect size is larger for OS than for PFS, which may indicate that PFS is poorly correlated with OS. The ERG agrees data for the IC arm and for the PFS endpoint in the tebentafusp arm seem mature, but this is not the case for the OS endpoint in the tebentafusp arm. According to the ERG there is considerable uncertainty related to the extrapolation of the OS endpoint in the tebentafusp arm (see Section 4.2.6). This uncertainty has a potentially substantial impact on the ICER as the [redacted] of gains in the economic model are accumulated beyond the observed data period (Table 5.1). One way to assist in verifying the plausibility of the partitioned survival model extrapolation would have been to compare the results to the outcomes of a state transition model.

4.2.3 Population

The patient population in the model reflects the patient population of the Phase III trial IMCgp100-202: adult patients with HLA-A*02:01 positive metastatic UM, without prior treatment in the metastatic setting. In the final scope the population is not restricted to treatment naïve patients. The starting age in the model is 62 years and 49.7% are women (based on the IMCgp100-202 trial).

ERG comment: The main concern of the ERG relates to the restriction to treatment naïve patients. In response to clarification question B1, the company argued that the population should not be restricted to treatment naïve patients.[3] This issue has been discussed in Section 2.1.

4.2.4 Interventions and comparators

The intervention is tebentafusp; a concentrate for solution for IV infusion available in 0.10 mg/ml vials. Tebentafusp is administered following a dose escalation regimen, starting with 20 mcg on day 1, 30 mcg on day 8, and 68 mcg on day 15 and once weekly thereafter (see Section 2.2).

The comparator in the economic evaluation reflects the control arm of the IMCgp100-202 trial, in which patients were treated with IC of immunotherapies (ipilimumab or pembrolizumab), or chemotherapy (dacarbazine). Out of the 126 patients randomised to the IC arm of the IMCgp100-202 trial, 103 (81.7%) were treated with pembrolizumab, 16 (12.7%) with ipilimumab, and seven (5.6%) with dacarbazine There is currently no standard of care and patients may receive a broad range of treatment options. Clinical experts consulted by the company, considered the comparator arm in the IMCgp100-202 study as reflective of current practice in the UK.[1] The treatments used in this study were all mentioned as comparator in the NICE final scope.[2] Nivolumab (alone or in combination with ipilimumab) was also included as a relevant comparator in the final scope by NICE, but was not considered as comparator in the cost effectiveness analyses of the CS, see Section 2.3.

Pembrolizumab was administered as per the licensed dosing regimen in patients with advanced melanoma, that is 2 mg/kg, to a maximum dose of 200 mg, as an IV infusion over 30 minutes every three weeks. Ipilimumab was administered as per the licensed dosing regimen in patients with advanced melanoma, that is 3 mg/kg as an IV infusion over 90 minutes every 3 weeks for a maximum of four doses. Dacarbazine was administered at the standard dosing regimen in UM, that is 1000 mg/m^2 every 3 weeks, with an infusion time of 60 minutes.

ERG comment: The main concerns of the ERG relate to: a) not including nivolumab (alone and/or in combination with ipilimumab) as a comparator, and b) using a treatment mix as observed in the IMCgp100-202 study as comparator.

a) The ERG asked a justification for not including nivolumab alone or in combination with ipilimumab, based on ITC, as a comparator in the economic model.[6] In response to clarification question C2 the company stated that it was unnecessary to include nivolumab alone or in combination with ipilimumab as a comparator for the following reasons.[3] First, a MAIC (CS section B2.9) had shown no statistically significant difference between in OS between pembrolizumab and nivolumab with ipilimumab.[1] In addition, the three clinical experts they consulted stated that nivolumab with ipilimumab is less frequently used in clinical practice in the UK. The company further argued that nivolumab monotherapy and pembrolizumab are to be considered equivalent as they are the same class of drug. The company provided a MAIC to compare the IC arm of the IMCgp100-202 study versus the Piulats et al. 2021 single arm study of ipilimumab plus nivolumab.[18] The results of this analysis showed similar or even somewhat better OS and PFS in the IC arm of the IMCgp100-202 study. Based on this, and together with the higher costs of ipilimumab plus nivolumab, the company argued that the ICER of tebentafusp versus nivolumap with ipilimimab would be similar or lower than versus the IC arm of the IMCgp100-202 study. The ERG considers the approach suboptimal, as it would have been good modelling practice to include nivolumab alone or in combination with ipilimumab as a comparator in the economic analysis based on the available evidence (see also comment b). It should also be noted that details on the clinical expert consultation were not provided, apart from the information that an advisory board was conducted and three clinical experts on metastatic UM provided feedback on current UK clinical practise.

b) The ERG asked a justification for using the treatment mix as observed in the IC arm of the IMCgp100-202 study as a single comparator, and asked for an amended economic model enabling a fully incremental evaluation of tebentafusp, pembrolizumab, ipilimumab and dacarbazine.[6] In response, the company argued that it was not possible to analyse the data for ipilimumab and dacarbazine separately because of the small number of patients that received these treatments.[3] The response further stated that, based on the meta-analysis of Rantala et al. 2019,[22] it could be concluded that there was no clinically significant difference in OS by treatment modalities, and hence it was appropriate to use the treatment mix in the IC arm as comparator. The company did not comply with the request for a fully incremental analysis with all comparators listed in the final scope modelled individually.[3, 6] According to the ERG, based on Tables 3 and 4 in the company's response to clarification question B4, the data to justify the assumption of equal effectiveness of pembrolizumab, ipilimumab, and dacarbazine does not seem compelling.[3] While being cautious regarding the lower number of patients in the ipilimumab stratum, the median OS and PFS and the 12-month OS rate [redacted] tebentafusp and ipilimumab. This warrants analyses stratified by IC treatment (incorporating treatment specific OS, PFS, and time to treatment discontinuation (TTD)), at least for pembrolizumab and ipilimumab as the patient numbers for dacarbazine may indeed be too small. The importance of such an analysis is further highlighted by the incremental analysis the company provided where the drug acquisition costs in the IC arm were modelled based on the costs of pembrolizumab, ipilimumab or dacarbazine while effectiveness was assumed to be equal (Table 12 clarification response to question C2b).[3] These analyses showed [redacted] costs for tebentafusp ([redacted]) than for ipilimumab ([redacted]) and pembrolizumab ([redacted]).

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model time horizon is 38 years (which equals lifetime).

ERG comment: None.

4.2.6 Treatment effectiveness and extrapolation

The main source of evidence on treatment effectiveness used for intervention and comparators is the IMCgp100-202 trial (NCT03070392). This is a multicentre open-label RCT in previously untreated HLA-A*02:01 positive adult patients with metastatic UM randomly assigned to either tebentafusp (n=252) or IC consisting of systemic dacarbazine, ipilimumab, or pembrolizumab (n=126). The most recent data cut-off, from August 2021, with a median follow-up time of [redacted] months, was used in the CS base-case analyses. This included [redacted] patients assigned to IC that had eventually crossed over to tebentafusp, which was permitted after the first interim analysis (of October 2020). No cross-over correction was applied but the October 2020 data cut off (without cross-over) was used (median follow-up time of 14.1 months) in scenario analyses.

To estimate OS, PFS and TTD over the 38-year time horizon, parametric survival curves were fitted to IMCgp100-202 patient-level data and used to extrapolate survival beyond the study time horizon. Six parametric models were considered (exponential, Weibull, Gompertz, log normal, log-logistic, and generalised gamma) and were assessed with regards 1) fit to the observed data based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) as well as visual comparison with the KM curves and 2) clinical plausibility of the extrapolated portion of the curve based on comparison with historical data for IC and clinical expert opinion for tebentafusp arm (as no historic data were available). The proportional hazards assumption was assessed statistically and visually through log-log plots and Schoenfeld residual plots, but results were not reported in the CS.[1, 7]

The process of selecting the approach to estimate and extrapolate OS, PFS and TTD for the ITT population is summarised in Table 4.4.

Table 4.4: Selection of approach to estimate and extrapolate OS, PFS and TTD for ITT population (based on August 2021 data cut-off)

	OS	PFS	TTD
General considerations	Company argues (without supporting information) that, for tebentafusp, none of the standard parametric models allowed to properly model the change in the survival profile around [redacted] Therefore, spline-based models were adopted by the company.	Due to a protocol-driven drop of PFS at week 12 corresponding to the first assessment, the compa	Although patients could stay on treatment beyond confirmed progression, treatment discontinuation was considered contingent on confirmed disease progression (illustrated in CS Figure 31). Hence, like PFS, a hybrid (or piecewise) approach is adopted using the KM curves (non-parametric) and the parametric curves (discussed below) only for extrapolation of the tail.

	OS	PFS	TTD
	No explicit justification was provided for using different approach for both treatments.	ny argues that the fit of the parametric distributions is limited and hence, a hybrid (or piecewise) approach is adopted using the KM curves (non-parametric) and the parametric curves (discussed below) only for extrapolation of the tail.	
Fit to the observed data based on AIC and BIC	**IC** The AIC and BIC are within two and five points respectively (CS Table 19). **Tebentafusp** Not provided for the standard parametric models.	**IC** The AIC and BIC of the log-logistic and generalised gamma	**IC** The models with the lowest AIC and BIC were the Gompertz and log-logistic (CS Table 32). **Tebentafusp** The AIC and BIC for the log-logistic was lowest with AIC and BIC for the second best (Gompertz) more than 10 points higher (CS Table 35).

	OS	PFS	TTD
	Provided for three knot spline model (hazard scale) in CS Table 22.	are within one point (CS Table 24) while the log-normal also provided a reasonable statistical fit to the observed data. **Tebentafusp** The AIC and BIC indicate that the generalised gamma has the best fit (CS Table 27)	
Fit to the observed data based on visual comparison with the Kaplan	**IC** The Weibull, Gompertz and generalised gamma provide a good fit over the trial period (CS Figure 25). **Tebentafusp** Comparison not provided for the	**IC** Based on visual inspection (CS Figure 28) the generalised gamma is	**IC** As can be observed in CS Figure 31, the PFS and TTD are almost identical in the IC arm, patients indeed discontinued based on confirmed disease progression. **Tebentafusp** The log-logistic provides a good fit over the trial period (CS Figure 32)

	OS	PFS	TTD
-Meier curves	standard parametric models. Provided for three knot spline model (hazard scale) in CS Figure 26.	preferred. **Tebentafusp** Based on visual inspection (CS Figure 28) the generalised gamma is preferred.	
Clinical plausibility of the extrapolation based on comparison with historical data	**IC** The extrapolations of the exponential, Gompertz, log-normal and log-logistic are unrealistic (CS Figure 25). **Tebentafusp** Not explicitly discussed.	**IC** Not explicitly discussed. **Tebentafusp** Not explicitly discussed.	**IC** Based on consistency with PFS (expecting similar TTD and PFS trajectories for IC) the generalised gamma is preferred. **Tebentafusp** It was noted that the choice of curve for the extrapolation of the tail in the tebentafusp arm has a little impact on the model results (potentially due to [redacted]).
Clinical plausibility of the extrapolation based on clinical expert opinion	**IC** The extrapolations of the log-normal and log-logistic are unrealistic. **Tebentafusp** Not explicitly discussed.	**IC** Not explicitly discussed. **Tebentafusp** Not explicitly discussed.	**IC** Gompertz may not be realistic **Tebentafusp** Gompertz may not be realistic
Base-case	CS Figure 26	CS Figure 29	CS Figure 33

	OS	PFS	TTD
approach	**IC** Weibull (generalised gamma in scenario analysis) **Tebentafusp** Three knot spline model with hazard scale and knots at [redacted] (default knot locations are used in scenario analysis)	**IC** KM + generalised gamma from the time point at which only 15% of the patients remain at risk (log-logistic and log-normal in scenario analyses) **Tebentafusp** KM + generalised gamma from the time point at which only 15% of the patients remain at risk (log-logistic and log-normal in	**IC** KM + generalised gamma from the time point at which only 15% of the patients remain at risk (log-logistic and Weibull in scenario analyses). **Tebentafusp** KM + generalised gamma from the time point at which only 15% of the patients remain at risk (log-logistic and exponential in scenario analyses).

	OS	PFS	TTD
		scenario analyses)	
Based on Section B.3.3 of the CS1 AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; IC = investigator's choice; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation			

4.2.6.1 Subgroup with the largest metastatic lesion recorded at baseline ≤30 mm

The process of selecting the approach to estimate and extrapolate OS, PFS and TTD for subgroup with the largest metastatic lesion recorded at baseline ≤30 mm is summarised in Table 4.5. The company notes that the median survival (August 2021 data cut-off) [redacted] for this subgroup [redacted]. The median PFS was [redacted] months for tebentafusp and IC respectively in this subgroup versus 3.4 and 2.9 months for tebentafusp and IC, respectively, in the ITT population. The median TTD was [redacted] months for tebentafusp and IC respectively in this subgroup versus 5.7 and 2.1 months for tebentafusp and IC respectively in the ITT population.

Table 4.5: Selection of approach to estimate and extrapolate OS, PFS and TTD for ≤30 mm subgroup (based on August 2021 data cut-off)

	OS	PFS	TTD
General considerations	No explicit justification was provided for using a different approach for both treatments.	Similar as for the ITT population, a hybrid (or piecewise) approach is adopted using the KM curves (non-parametric) and the parametric curves (discussed below) only for extrapolation of the tail.	Similar as for the ITT population, a hybrid (or piecewise) approach is adopted using the KM curves (non-parametric) and the parametric curves (discussed below) only for extrapolation of the tail.
Fit to the observed data based on AIC	**IC** The model with the lowest AIC and BIC was the Gompertz, although the generalised gamma and Weibull are reasonable (CS Table 40) **Tebentafusp** The model with the lowest AIC and BIC was the Weibull, although the log-logistic and Gompertz and generalised gamma were within five points (CS Table 43)	**IC** The models with the lowest AIC and BIC were the log-logistic and generalised gamma (CS Table 47). **Tebentafusp** The model with the lowest AIC and BIC was the generalised gamma (CS Table 50)	**IC** The models with the lowest AIC and BIC were the Gompertz and log-logistic (CS Table 54). **Tebentafusp** The AIC and BIC for the generalised gamma was lowest with the AIC and BIC for the log-logistic and log-normal within six

	OS	PFS	TTD
and BIC			points (CS Table 57).
Fit to the observed data based on visual comparison with the Kaplan-Meier curves	**IC** CS Figure 36 **Tebentafusp** The Gompertz model provides a good fit over the trial period (CS Figure 36).	**IC** Not explicitly discussed. **Tebentafusp** Not explicitly discussed.	**IC** The Gompertz provides a reasonable fit over the observed period (CS Figure 39). **Tebentafusp** [redacted]
Clinical plausibility of the extrapolation based	**IC** Not explicitly discussed. **Tebentafusp** Not explicitly discussed.	**IC** Not explicitly discussed. **Tebentafusp** Not explicitly discussed.	**IC** Not explicitly discussed. **Tebentafusp** Not explicitly discussed.

	OS	PFS	TTD
comparison with data			
Clinical plausibility of the extrapolation based on clinical expert opinion	**IC** [redacted] **Tebentafusp** [redacted]	**IC** [redacted] **Tebentafusp** [redacted]	**IC** [redacted] **Tebentafusp** [redacted]
Base-case approach (for subgroup)	CS Figure 36 **IC** Weibull **Tebentafusp** Log-logistic (log-normal in scenario analysis)	No Figure provided in CS section B.3.3 that provided a visual comparison with the Kaplan-Meier curves for this subgroup **IC** KM + generalised gamma **Tebentafusp** KM + generalised gamma	CS Figure 39 **IC** KM + generalised gamma **Tebentafusp** KM + generalised gamma

	OS	PFS	TTD
Based on Section B.3.3 of the CS[1] AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; IC = investigator's choice; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation			

ERG comment: The main concerns of the ERG relate to: a) approach to estimate OS; b) approach to estimate PFS and TTD; c) justification for approach to estimate OS, PFS and TTD for subgroup; d) using Rantala et al. 2019 to verify PFS and OS extrapolations; e) assuming no treatment waning in the CS base-case and f) lack of cross over correction.

a) The CS base-case estimated OS using a three-knot spline model with hazard scale (knots at [redacted]) for tebentafusp and a Weibull model for IC. Clarification response Figure 15 illustrates (based on the smoothed hazards over time) in general a monotonic increasing hazards for approximately the first 24 months (except a short dip around month 10 for IC).[3] Afterwards the number of patients at risk is limited (i.e. [redacted] patients for tebentafusp and IC respectively at 24 months are still at risk) and the decreasing hazard for tebentafusp afterwards should thus be interpreted with caution due to its uncertainty. Moreover, given clarification response Figure 18 (plotting the cumulative hazards over time) and clarification response Figure 27 (plotting the log survival odds) the exponential, Weibull, log-logistic and generalised gamma distribution might be candidates based on the observed data.[3] Moreover, the AIC for these distributions were very similar for IC (CS Table 19); the estimated AIC for tebentafusp (for the standard parametric models) were not provided.[1] Given the above, it is according to the ERG not warranted to diverge from the standard parametric models. Moreover, the company's justification not to use standard parametric models was that *"none allowed to appropriately model the* [redacted]*"* and *"to model* [redacted]*"*. According to the ERG this argument is flawed, given the very low number of patients at the risk at this time point, i.e. [redacted] patients for tebentafusp and IC respectively at 33 months. As illustrated in CS Figure 26, based on very few patients the knot at [redacted] results in a hazard function that is not consistent with the first 24 months.[1] Moreover, in response to clarification questions C5c and C5d, the company did not provide appropriate justifications for specifically selecting a three knots spline model with a hazards scale (i.e. why fewer knots and/or the "odds" and "normal" scale models were used) nor whether the linearity assumption (on a transformed scale of the survival function) is reasonable.[3] Thus, the ERG believes it is not appropriately justified that spline-based models are warranted, moreover if these spline-based models would be warranted no appropriate justification was provided why specifically the three knots spline model with a hazards scale (with the specific knot locations). In addition to this, assuming proportional hazards is not unreasonable for OS (Figure 10 in the clarification response) and the company did not provide *"substantial justification"* (as suggested in NICE DSU TSD 14) in case different types of parametric models are used for different treatment arms.[3, 26] This is particularly warranted since both tebentafusp and IC consist of immunotherapies (for IC 119 of 126 patients are treated with pembrolizumab or ipilimumab). Therefore, the ERG preferred to use standard parametric models, particularly the same distribution for both treatments.
As mentioned above, based on the company's clarification response Figures 18 and 27 the exponential, Weibull, log-logistic and generalised gamma were considered candidate distributions by the ERG.[3] However, given the shape of the smoothed hazard is not constant

(clarification response Figure 18), the Exponential distribution was not considered appropriate by the ERG.[3] Similarly, the Weibull distribution does not seem plausible given the IC extrapolations fall below the historic data reported by Rantala et al. 2019 (clarification response Table 41).[3, 22] Therefore, the ERG used the generalised gamma (used in scenario analyses by the company) and log-logistic distributions for two separate ERG analyses (adopting the same distribution for both treatments) as both distributions seem consistent with observed trial data and were considered reasonable given the historic data reported by Rantala et al. 2019 (used as 'lower limit benchmark'; see further details below).[22]

b) The hybrid approach (defined as piecewise approach in NICE DSU TSD 21) to estimate PFS and TTD for both tebentafusp and IC was justified by the company due to a *"protocol-driven drop of PFS at week 12 corresponding to the first assessment resulting in a limited fit of the parametric distributions"*.[1, 27] In general, the ERG does not prefer using KM curves (as done in the piecewise approach) for economic models as it might overfit the trial data which seems suboptimal for decision-making focussing on UK clinical practice. This might be specifically applicable to this case, given that the drop at 12 weeks was trial protocol-driven, which might not be representative for clinical practice. Moreover, NICE DSU TSD 21 on flexible methods for survival analysis highlights that the selected cut-point ([redacted] for tebentafusp and [redacted] for IC) may be arbitrary and potentially importantly influence the results of an analysis.[27] Potentially controversially, the cut-point in the current analyses was treatment dependent. In addition to the above, based on the company's response to clarification question C6a it became clear that the estimation and implementation of the piecewise models incorporated in the economic model deviates from common practice and the piecewise models described in NICE DSU TSD 21.[3, 27] The implemented piecewise models are using parametric survival models estimated from baseline (time = 0; using the full dataset) instead of being estimated specifically from the cut-point (using only data after [redacted] for tebentafusp and [redacted] for IC). This approach is flawed according to the ERG as these parametric survival models, estimated from baseline, are not intended to be used after the cut-point only as the proportion of patients surviving up to this cut-point (i.e. conditional survival) using these parametric survival models might differ from the conditional survival based on the KM curve. Given the aforementioned limitations of the company's piecewise approach, potentially controversial cut-points and flawed implementation by the company, the ERG prefers to use a standard parametric approach to estimate PFS and TTD in its base-case. Specifically, the generalised gamma distribution for both treatment arms and both outcomes (i.e. same distribution as used in the CS base-case while removing the KM curve component) was considered a plausible alternative and thus used in the ERG base-case.

c) For the ≤30 mm subgroup, inconsistencies are identified regarding the justifications provided by the company to support the selected approach to estimate OS, PFS and TTD. For instance, the company stated in the TTD section that [redacted]" while according to CS section B.3.9 a hybrid approach is adopted for the subgroup (KM + generalised gamma).[1] Moreover, there seem to be factual errors in this Section. For instance, in the Section related to OS it is stated *"the model with the best fit in the tebentafusp arm is the Gompertz"* while according to CS Table 43 the Weibull distribution has the best fit (August 2021 data cut-off which is used for the CS base-case).[1] Similarly, in the section related to PFS it was stated that *"the model with the best fit in the control arm is the log-logistic"* while according to CS Table 47 the [redacted] distribution has the best fit (August 2021 data cut-off which is used for the CS base-case).[1] Given these inconsistencies and apparent factual errors, combined with the

limited validation of the clinical plausibility of the extrapolations based on comparison with data, there is no compelling justification to deviate from the approached adopted for the ITT population. Therefore, for the ≤30 mm subgroup, the ERG adopted the same approach to estimate OS, PFS and TTD as was selected for the ERG base-case (ITT population). Notably, the extrapolations based on this approach should be verified further.

d) For validating the extrapolations with external data, the company stated that the data reported by Rantala et al. 2019 on first-line patients is the best benchmark available for comparison against IC (from IMCgp100-202).[22] However, the company appreciated that these patients were treated with conventional chemotherapy, chemoimmunotherapy, hepatic intra-arterial chemotherapy and transarterial chemoembolization and treatment modality thus differs from the IC arm of the IMCgp100-202 trial. Moreover, the ERG noted that this review potentially considered old studies (inclusion period 1980 to 2017) and most studies were retrospective analyses. Nevertheless, the ERG agrees that this is a useful benchmark (though it is unclear why the company digitised a plot from *"Supplemental digital content 4"* of the paper instead of from Figure 3 in the main manuscript). Given the above, the ERG believes this source should potentially be used as a 'lower limit benchmark' ruling out OS estimations of IC that fall below the OS estimated based on these historic data. Especially for the first 3 years as after 3 years data only few patients are at risk, see Figure 3 in Rantala et al. 2019.[22]
e) In the CS base-case no treatment waning was assumed, i.e. the PFS and OS were assumed to be different for tebentafusp and IC for the whole duration of the time horizon. This was not appropriately justified in the CS. Given i) it is unclear whether assuming a continued treatment effect over the lifetime horizon of the model is plausible; ii) the uncertainty related to the long-term extrapolations (only [redacted] patients were at risk at 36 months for tebentafusp and IC respectively, see clarification response Figure 3 considering OS) and; iii) the [redacted] of gains are accumulated beyond the observed data period.[3] Alternative assumptions related to extrapolation treatment waning should be explored by the company.
f) After the first interim analysis (of October 2020), [redacted] (out of 126) patients assigned to IC eventually crossed over to tebentafusp. The follow-up duration after cross-over for the August 2021 analyses as well as the initial IC treatment that was received by these patients is unclear based on clarification response C7.[3] Unfortunately, based on clarification response C7, the company did deprioritise this issue and the impact of cross-over on cost effectiveness is not explored in response to this clarification question. Hence, the anticipated impact of the cross-over is unclear.

4.2.7 Adverse events

The main source of evidence on AEs used for intervention and comparators was the IMCgp100-202 clinical trial. All grade ≥3 AEs with an occurrence of >3% (both treatment groups combined) were included as well as any grade endocrine disorders and colitis as these are associated with high costs even at lower grade and known to be related to the use of immune checkpoint inhibitors (CS Table 60).[1]

Cytokine-mediated AEs are commonly reported in patients treated with tebentafusp. For this reason, patients were monitored overnight after the first three doses during the dose escalation period to allow management of hypotension and other cytokine-related AEs. The most common cytokine-mediated AEs were pyrexia, chills, nausea, hypotension, and hypoxia. Out of the 805 distinct cytokine release syndrome episodes which occurred in 217 of 245 tebentafusp-treated patients, 99.6% were mild to moderate (grade 1 and 2). Out of the 60% of the patients who had grade 2+, only 49% required IV fluid. The number of patients requiring escalation of care (e.g. tocilizumab, vasopressor) was small (four patients out of 217 who had at least one cytokine release syndrome episode). Therefore, based on

clinical experts' opinion, the company assumed that no additional costs would be incurred related to these cytokine release syndrome episodes (in addition to the cost of inpatient monitoring for the first three doses captured within the administration costs for tebentafusp).

ERG comment: The company's assumption that no additional costs would be incurred related to cytokine release syndrome episodes (in addition to the cost of inpatient monitoring for the first three doses captured within the administration costs for tebentafusp) was regarded as the main ERG concern. However, in response to clarification question C8 the company provided a scenario analysis assuming the same proportion of inpatient vs. outpatient costs for tebentafusp as for IC.[3] This scenario indicated that the impact of this assumption (on the ICER) is likely to be very minor.

4.2.8 Health-related quality of life

The utility values were estimated based on time-to-death, rather than based on disease status. The time-to-death intervals used in the CEA model were based on technology appraisal (TA) 366 and included time-to-death ≥360 days, between 360 and 270 days, between 270 and 180 days, between 180 and 90 days, between 90 and 30 days, and less than 30 days until death.[28] Additionally, treatment related utility decrements were included for each treatment option. The EQ-5D-5L data that were collected in the IMCgp100-202 trial (see CS Tables 61 and 62) were not used directly in the CS base-case analysis.[1]

4.2.8.1 Health-related quality of life data identified in the review

According to the CS, the SLR identified six studies reporting HRQoL estimates for UM.[1] Out of these, the company considered that none of them was consistent with the NICE reference case and to be appropriate for the economic model, as none of the studies involved patients receiving tebentafusp or reported generic HRQoL utility values.

4.2.8.2 Time-to-death utility values

Based on the opinion of clinical experts and the study of Hatswell et al. 2014, utilities should be based on time-to-death rather than disease status.[29] Thus, base-case analysis was based on time-to-death (reported in CS Table 64), and the scenario analysis focused on the on-/off-treatment utilities values derived from the pivotal trial data (reported in CS Table 63).[1]

Based on the time-to-death utility values from TA366, the company calculated the relative reduction for the different periods until death (termed 'multipliers' in CS Table 64).[1, 28] Each of the 'multipliers' of each interval were subsequently applied to "on-treatment" utility derived from a regression analysis calculated with IMCgp100-202 data (CS Table 63).[1] These calculations assumed that the on-treatment utility reflected the utility of patients with a time-to-death ≥360 days. To calculate the proportion of patients alive in each cycle (>360, 360 to 270, 270 to 180, 180 to 90, 90 to 30, <30 days), an approach equivalent to tunnel states was implemented in the model.

4.2.8.3 Adverse event disutilities

Treatment related utility decrements, applied in the first model cycle only, are used in the model to reflect TRAEs. These utility decrements were retrieved from TA319 and TA384 for ipilimumab and dacarbazine respectively.[5, 30] Utility decrements for tebentafusp and pembrolizumab were assumed to be equal to the disutility for ipilimumab, based on clinical expert opinion. The company assumed that AEs would not impact patients' HRQoL significantly (in addition to the treatment related utility decrements), based on clinical expert opinion. Therefore, additional utility decrements explicitly linked to AE were not included in the CS base-case.

The on-/off-treatment utilities values used in a scenarios analysis were based on the IMCgp100-202 trial. Due to the high proportion of missing of European Quality of Life-5 Dimensions (EQ-5D) data (CS, Table 62), data were imputed using a combination of approaches (multiple imputation, mean imputation and no imputation) depending on the follow-up point.[1]

Additionally, an age-related utility decrease was introduced in the model in both base-case and scenario analyses. The model implements age adjustment considering the utility value of the mean population at baseline.

A summary of all utility values used in the cost effectiveness analysis is provided in Table 4.6.

Table 4.6: Health state utility values

State	Utility value*	Justification
≥ 360 days	[redacted]	Based on TA366 adjusted with on-treatment adjustment factor*,[28]
270-360 days	[redacted]	
180-270 days	[redacted]	
90-180 days	[redacted]	
30-90 days	[redacted]	
< 30 days	[redacted]	
Treatment effect of tebentafusp	-0.024	Assumption based on ipilimumab
Treatment effect of ipilimumab	-0.021	TA319[30]
Treatment effect of pembrolizumab	-0.021	Assumption based on ipilimumab
Treatment effect of dacarbazine	-0.024	TA384[5]
On-treatment	[redacted]	Based on statistical models fitted using EQ-5D data collected in IMCgp100-202 trial
Off-treatment	[redacted]	

	Utility value based on UK general population	Age adjustment factor used	Justification
18-24 years	0.92	1.13	Szende A. et al. 2014[31] adjusted by the company
25-34 years	0.92	1.12	
35-44 years	0.89	1.09	
45-54 years	0.86	1.05	
55-65 years	0.82	1.00	
65-74 years	0.79	0.96	
75-100 years	0.72	0.88	

*Adjusted utility values were used in the CEA. Utility values without adjustment can be found in CS Table 66.[1]

State	Utility value*	Justification
CEA = cost effectiveness analysis; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; UK = United Kingdom		

ERG comment: The main concerns of the ERG relate to: a) predominantly using TA366 utility values instead of IMCgp100-202 trial data; b) handling of EQ-5D IMCgp100-202 trial data; c) the time-to-death utility approach adopted by the company; and d) assumption of the limited impact of AE on patients HRQoL.

a) The CS base-case predominantly used utility values from TA366 instead of EQ-5D data from the IMCgp100-202 trial. This was justified by the company by stating a high proportion of missing EQ-5D data from the IMCgp100-202 trial, see Table 62 of the CS.[1] Thus, the CS base-case relied heavily on literature for obtaining utility values; however, the SLR they performed did not identify any relevant studies. The ERG considered that the justification on the use of utilities derived from TA366 (considering pembrolizumab in advanced melanoma not previously treated with ipilimumab) was insufficient, as the study focused on a different population with different treatment options.[28] In addition, the company did not elaborate on the suitability of the data from other NICE appraisals that were used (such as TA319 and TA384) in terms of different populations and treatment.[5, 30] This is particularly relevant given the company stated that there are no NICE TAs relevant to this decision problem (clarification response C24).[3] According to the company's response to the request for clarification, tebentafusp is the first treatment under evaluation by NICE for the treatment of metastatic UM.[3] The company stated that UM is biologically distinct from skin melanoma with different physiological, genetic, and epidemiologic characteristics. According to the ERG, these arguments, made by the company, underscore the importance of predominantly using the EQ-5D data from the IMCgp100-202 trial.

b) Due to the missing data from the EQ-5D-5L questionnaires on the IMCgp100-202 trial, data imputation was performed. Three imputation approaches were adopted by the company; data imputation was performed for baseline (mean imputation) and treatment phase (multiple imputation) but not for the survival follow-up period (i.e. assuming missingness is completely at random). However, the ERG considered that these approaches were not appropriately justified. Mean imputation should be avoided in general as it distorts the distribution of the imputated data in several ways. Particularly it can underestimate the variance and disturb relations between variables and biases any estimate other than the estimate of the mean, and the mean estimate itself when data is not missing completely at random (MCAR), as is most likely applicable in this case.[32] As seen in CS Tables 62 and Table 24 of the response to the clarification question, respectively, data are likely not MCAR.[1, 3] Indeed, more data from the IC arm are missing before end-of-treatment, and more data from the tebentafusp arm are missing for survival follow-up and missingness increases with increasing trial follow-up. Moreover, for the survival follow-up period the company removed incomplete data prior to analysis which is known as listwise deletion or complete-case analysis. Listwise deletion potentially introduces inconsistencies in the data and if the data are not MCAR (as is most likely the case), listwise deletion can severely bias estimates of means, regression coefficients and correlations.[32] Hence the imputation approach adopted by the company likely induces bias.

   In addition to the flawed imputation, the company did not fulfil the request of clarification C10, where the ERG requested the company to use the original EQ-5D data from the IMCgp100-202 trial (using the Van-Hout crosswalk algorithm) without imputation and apply a generalised linear mixed model (taking into account the nested data) that includes the covariates that are considered in the data imputation, as well as the covariates for the on/off treatment, and for being PFS or PD,

i.e. progression status.[6] Furthermore, the ERG requested an updated economic model and scenario analyses wherein these data are used (without applying the time-to-death utility values) and including a scenario analyses considering waning of treatment utility benefit for being on treatment. The ERG considered the company's approach to be flawed and believes induces bias. In addition, the incomplete clarification responses from the company were not helpful in this respect and hence the ERG is unable to resolve this key issue in the ERG analyses.[3]

c) According to the ERG the time-to-death utility approach adopted in the CS base-case is flawed from multiple perspectives: i) it is inconsistent with the model structure and common modelling practices; ii) the implementation is not transparent; and iii) the approach lacks face validity.
   i. Utility values were estimated based on time-to-death rather than based on disease status. However, the ERG considered that this approach was not appropriately justified. The decision of using time-to-death utility values is based on two arguments: clinical experts' opinion and literature. Nevertheless, the company did not explain the methods used to gather clinical experts' opinion, nor explained the reasoning of the clinical experts for this assumption. Moreover, the two sources for this choice were based on advanced melanoma (Hatswell et al. 2014, and TA366), not advanced UM.[28, 29] In addition, in TA366 the use of time-to-death utilities was criticised by the ERG.[28] Additionally, not implementing health state utilities differentiating between progression free and progressed disease arguably lacks face validity (as it does not reflect the decline in HRQoL after progression), is inconsistent with the model structure as well as common modelling practices. Given the increased post progression survival with tebentafusp, the use of time-to-death utilities is most likely not conservative.
   ii. To implement the time-to-death utilities in a partitioned survival model, the company stated to use an approach equivalent to tunnel states. Moreover, 'multipliers' were used to combine TA366 and IMCgp100-202 utility values. The ERG considered that these aspects (and the associated assumptions) related to the implementation of the time-to-death utilities were not appropriately explained and thus impedes the transparency of this approach.
   iii. The estimated time-to-death utility values from TA366 lack face validity as it leads to implausible high utility values.[28] The CS base-case applies an age adjustment factor to the QALY calculation based on utility values of the UK population to implement the utility decrement of age. Nevertheless, the on-treatment utility value of patients over the age of 62 years with metastatic UM ([redacted]) is higher than the average utility value of the UK population between 55 to 65 years (0.82). The company acknowledged this limitation in the clarification letter response and provided results of a scenario analysis that capped the baseline utility value at the norm of the age group, indicating the impact of this is minimal. Nevertheless, the face validity of the utility values used lacked face validity which might be related to the handling of EQ-5D IMCgp100-202 trial data (discussed above).

   Given the above, the ERG believes the time-to-death utility approach adopted in the CS base-case is flawed and as highlighted above the incomplete clarification responses from the company were not helpful in this respect and hence the ERG is unable to resolve this key issue in the ERG analyses.

d) The CS base-case only applied treatment utility decrements for the first cycle, and assumed that afterwards AEs did not have an impact on patients' HRQoL, based on clinical opinion. Nevertheless, serious AEs were reported in the study, especially in the tebentafusp arm: thus, a more comprehensive justification would be expected. Similarly, the utility decrements of both tebentafusp and IC are applied only for the first doses, even though, according to the CS, tebentafusp presented AEs during the first three doses.[1] Additionally, the ERG considered that the

suitability of the utility decrements of tebentafusp and pembrolizumab were not appropriately justified in the CS. Tebentafusp and pembrolizumab disutilities were assumed to be equal to the disutility for ipilimumab based on clinical expert opinion; however, no justification was provided on this assumption, nor the methods of gathering clinical experts' opinion were shared. Given the AE profile of tebentafusp, especially during the first doses, a higher utility decrement might have been expected.

4.2.9 Resources and costs

The cost categories included in the model were costs related to the intervention and IC (including treatment acquisition costs, and testing and administration costs), health state costs (routine management for pre-progression and BSC costs as well as one-off costs for management of progression for post-progression), costs of subsequent therapies, end of life costs, and costs of managing adverse events.

Unit prices were based on the National Health Service (NHS) reference prices, British National Formulary (BNF), and Personal Social Services Research Unit (PSSRU).

4.2.9.1 Resource use and costs data identified in the review

According to the CS, the SLR identified four studies reporting relevant resource use and costs for the treatment of UM.[1] Out of these, only one UK study was identified that fitted the decision problem. Nonetheless, the study was an abstract and omitted several significant costs of UM management. Therefore, none of the studies identified in the SLR were deemed appropriate for the CEA model.

4.2.9.2 Treatment costs

Drug acquisition costs in the economic model were related to tebentafusp and to the IC (i.e. ipilimumab, pembrolizumab, or dacarbazine), assuming the same dosage regimen as in the IMCgp100-202 trial. The drug acquisition costs were applied in the model based on the time-to-death curves. The estimated dosages per cycle for tebentafusp and the IC were derived from IMCgp100-202 protocol and are described in CS Table 68.[1] Dosage for IC was in line with the licensed and standard dosing regime in patients with advanced melanoma. It was assumed that vial sharing was not possible and drug quantities were rounded-up to the nearest vial size. The acquisition cost of tebentafusp was according to the list price, with patient access scheme (PAS), whereas other drug costs were sourced from the BNF. The CEA administration and monitoring costs were derived from the National Cost Collection for the NHS 2019/2020 version 2.

According to IMCgp100-202, the median relative dose intensity was 100% for both tebentafusp and IC. Thus, no correction for missed or delayed drug administrations was assumed for neither arm, and relative dose intensity ratio was not applied in the model (i.e., reflecting no missed drug consumption due to incomplete treatment cycles). Total costs for each treatment are described in Table 4.7 below.

4.2.9.3 Tebentafusp drug acquisition costs

The total treatment costs were calculated based on the cost per mcg of active pharmaceutical ingredient used and the estimated dosage per cycle and the number of cycles for each regimen. [redacted]

[redacted]. According to the company, [redacted] cap has no impact on the duration of treatment provided.

4.2.9.4 Investigator choice acquisition costs

The costs of the acquisition of investigator choice were calculated by weighting the percentage of patients receiving each treatment and multiplying them by their respective costs. The model considered that ipilimumab could only be administered four times. Ipilimumab and pembrolizumab were administered according to patients' weight. The mean weight of the IMCgp100-202 trial was used to estimate the dose in the CEA. Dacarbazine was administered based on BSA, which was derived from the mean weight and height (1.90 m^2) in the IMCgp100-202 trial.

4.2.9.5 Tebentafusp testing and administration costs

Tebentafusp was assumed to be administered in the inpatient setting for the first three doses and in a day case setting for the remaining doses. Administration for tebentafusp included: chemotherapy administration and hospital stay based on a weighted average cost of elective inpatient excess bed days for the first three doses, and subsequent administration thereafter. Other costs included for tebentafusp were the costs of human albumin for the preparation of the dose of tebentafusp, and one-off cost for HLA-A*02:01 testing based on the cost of HLA-A*31:01 reported by Plumpton et al. 2015.[33]

4.2.9.6 Investigator choice administration costs

Ipilimumab, pembrolizumab, and dacarbazine were assumed to be given in a day setting. All three treatments considered costs of first attendance and subsequent administrations. Ipilimumab administration costs included costs related to liver and thyroid function tests. Administration costs were weighted on the percentage of patients receiving each treatment.

4.2.9.7 Subsequent therapies

Subsequent therapies following discontinuation of the active treatment were accounted for in the economic model. The costs of these were applied as a one-off cost upon first line treatment discontinuation on each arm. Data on subsequent treatments was derived from IMCgp100-202 study data and are described in CS Table 73. The costs of nivolumab were obtained from the BNF (October 2021), and the combination therapy strategy (ipilimumab + nivolumab) dosage was based on the study by Najjar et al. 2020.[21] Patients could receive multiple subsequent therapies. Cost per therapy was calculated in the same way as described before and included drug acquisition and administration costs.

Table 4.7: Total treatment costs

Treatment	Dose	Tebentafusp	Ipilimumab (12.7%)	Pembrolizumab (81.7%)	Dacarbazine (5.6%)	Total Investigator choice
Acquisition costs	Dose 1-4	[redacted]	£18,750	£5,260	£150	[redacted]
	Dose 5+	[redacted]	N/A	[redacted]	[redacted]	[redacted]
Administration costs	Initial doses*	£2,803.28	£1,424.66	£1,386.03	£1,386.03	£1,390.93

Treatment	Dose	Tebentafusp	Ipilimumab (12.7%)	Pembrolizumab (81.7%)	Dacarbazine (5.6%)	Total Investigator choice
	Subsequent doses	£390.37	N/A	£363.37	£363.37	£317.23
Subsequent therapies cost		[redacted]				[redacted]

Based on Tables 71 to 73 of the CS[1]
* Doses 1-3 for tebentafusp, doses 1-4 for IC since ipilimumab can only be administered four times.
CS = company submission; IC = investigator's choice; N/A = not applicable

4.2.9.8 Health state costs

Pre-progression costs were derived from routine management during active treatment. Management progression was defined as an one-off cost for disease management, and post-progression costs consisted in BSC, see Table 4.8.

Unit costs were derived from the National Cost Collection for the NHS 2019/2020 version 2.[34] Health state resource utilisation was calculated based on published literature on metastatic melanoma and clinical experts' opinions due to the lack of UM health-care resource utilisation literature found in the SLR. Resource use per health states were based on McKendrick et al. 2016.[35] The data from McKendrick et al. 2016 was assumed applicable to UM based on clinical expert opinion who recommended removing resource utilisation related to brain and bone metastases and including costs specifics to UM; such as liver metastasis management and visits to ophthalmic surgeon during follow-up care.

The health state costs during active treatment pre-progression and during management progression included time devoted by different healthcare professionals to initiate treatment and monitor the patient, investigational tests and examinations typically conducted before treatment initiation, inpatient or outpatient hospital attendances, and clinical procedures. Post-progression included the same categories but excluded examinations resource use. The detailed resource utilisation are described in CS Table 74.[1]

Based on McKendrick et al. 2016 which reported BSC being provided for an average of 4 months, the CS base-case applied the monthly costs of BSC multiplied by four in the form of a one-off cost, after the cohort leaves the PFS at each cycle.[35] The estimated monthly resource utilisation per health state and unit costs are described in CS Tables 74 and 75.[1]

Table 4.8: Health state costs

Health state	Type	Costs	Justification
Pre-progression	Weekly cycle cost	£129.02	Costs: National Cost Collection for the NHS 2019/2020 version 2[34] Resource use: Clinical experience, McKendrick et al. 2016, Nathan et al. 2015[35, 36]
At progression	One-off cost	£389.70	
Post-progression (BSC)	One-off cost	£4,318.0	

Based on Table 76 of the CS[1]
BSC = best supportive care; CS = company submission; NHS = National Health Service

4.2.9.9 End of life costs

The CS base-case included the costs of end of life care as a one-off cost to the new death at each cycle. This cost estimate was taken from PSSRU 2020, and included hospital and social care costs for the patients final year; thus, palliative care was not included in the post-progression health state.[37] For patients living less than a year this cost was adjusted depending on the length of the time alive in the model. The company justified that the inclusion of end of life costs could lead to double counting.[1]

4.2.9.10 Event costs

The cost of managing grade ≥3AEs that occurred in more than 3%, endocrine disorders and colitis were included in the economic model. The costs of the different AEs were calculated with the incidence rate of each AE from IMCgp100-202 (CS Table 60), the proportion of patients managed in the in- and outpatient setting (CS Table 77), and the cost associated with the management of AEs (CS Table 78).[1] Unit costs of managing AEs were based on NHS reference costs, and if not available, clinical experts were asked, and targeted literature searches were conducted with priority to recent studies with a similar UK population.

Most AEs associated with tebentafusp were expected to occur within the first three doses; therefore, AEs weighted costs are applied as a one-off cost in the first cycle of the model. According to the CS, as patients are admitted overnight for monitoring after the first three doses, most costs are already accounted for in the tebentafusp administration costs. Thus, in the CS base-case, AEs of tebentafusp are derived from the assumption that patients were not admitted but used outpatient services instead. AEs are also applied as one-off cost in the first cycle for IC.

ERG comment: The main concerns of the ERG relate to: a) one-off application of BSC costs, b) unclear applicability to UK setting of subsequent therapies and population weight and height. c) tebentafusp AE costs, d) lack of analyses varying percentage of IC options, and e) lack of exploration on the [redacted] cap for tebentafusp.

a. BSC costs were applied in the model as a one-off cost after the cohort left the PFS state at each cycle. The one-off costs were based on the study by McKendrick et al. 2016 in which BSC was provided for an average of four months (for both treatments).[35] Hence, the one-off costs reflected the average BSC costs of 4 months, i.e. applied unrelated to the estimated time in the progressive disease (PD) health state. The company elaborated on the validity of the study of McKendrick and colleagues for the case of metastatic UM.[3] However, the explanation on why the BSC costs were not applied per cycle in the PD health state was not considered appropriate by the ERG. Since post-progression costs would most likely depend on how long patients stayed in the PD state, this approach would benefit tebentafusp, as patient after tebentafusp stayed longer in the PD health state than for IC (see also Table 5.1). Despite requested by the ERG (clarification question C16), the company did not provide a scenario analysis (and updated economic model) applying monthly BSC costs per cycle in the PD health state.[3, 6] The company stated that would be inappropriate as it would lead to double-counting with end of life costs, as patients incurred end of life costs at the point of death. However, in the clarification question C15, the company stated that end of life costs had a limited impact on the incremental cost effectiveness ratio (ICER; difference less than £50). Therefore, the ERG would prefer to implement monthly BSC costs per cycle in the PD health state while removing end of life costs to prevent potential double counting (also given the minimal impact of end of life costs on the estimated ICER).[3]
b. The ERG considered the applicability to UK practice to be uncertain for i) patients' weight and height, and ii) common subsequent therapies strategy.

i. Ipilimumab and pembrolizumab and dacarbazine acquisition costs were determined by the patient's weight, and BSA (i.e. patient weight and height), respectively. However, the company did not include the normal distribution for the UK population weight and height in their analyses (instead only the average patient weight and height are used). Incorporating these data would result in more accurate estimations of the average number of vials required per patient.

ii. Subsequent therapies following discontinuation of the active treatment were accounted for in the economic model from data of the IMCgp100-202 trial. In the clarification letter (C18a), the company elaborated on why the percentage of patients following different subsequent treatments (i.e. either dacarbazine or immunotherapy) exceeded the 100%.[3] However, the values of subsequent therapies used in the model were derived from the IMCgp100-202 trial, and potentially do not reflect the UK clinical practice presented by the company. Moreover, the calculation of subsequent therapies duration is unclear. Additionally, a scenario analysis using a survey with UK clinical experts to inform subsequent therapy proportions (clarification response Table 28) showed a decreased ICER (difference of approximately £5,000).[3]

c. AEs were applied as a one-off cost in the first cycle of the model for both tebentafusp and IC, even though CS stated that it does not reflect the clinical practice of IC. The ERG considered that the company did not appropriately justify this choice, nor included the clinical experts' reasoning for it. Although according to the CS, tebentafusp AE occur on the first three weeks (i.e. first three cycles), AE of IC should have been calculated according to their occurrence.

d. One of the main factors influencing IC acquisition costs was the percentage of patients using each treatment. Although the standard of care is not yet agreed for UM treatment, the company did not provide detailed analyses on the effect of varying this parameter in scenario analyses. In addition, tebentafusp, pembrolizumab, and dacarbazine acquisition and administration costs were determined by the duration of treatment. According to the IMCgp100-202 trial, intake of such treatment continued until radiographic progression, which differed in each arm. As the IC overall costs depend greatly on the proportion of treatment chosen (see Table 4.7), the company could have provided an analysis of the effect of different treatment proportions on the ICER.

e. According to the CS, tebentafusp acquisition costs were set to be zero after [redacted] due to the pricing approach between the company and the NHS. Therefore, only administration costs were included after [redacted]. The company indicated that this assumption was not related to any clinical aspects rather the company clarified this was part of the proposed pricing approach, in order reduce the uncertainty in the budget impact and overall treatment cost. However, the company failed to provide scenario analyses with an accompanying updated economic model that estimated drug acquisition costs without setting drug acquisition costs to zero after [redacted].

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The CS base-case cost effectiveness results (probabilistic) indicated that tebentafusp (with PAS) is both more costly (additional costs of [redacted]) and more effective (incremental QALYs of [redacted]) than the comparator amounting to an ICER of £[redacted] per QALY gained. Moreover, the 95% percentiles for the probabilistic incremental costs and QALYs were [redacted], respectively. The probabilities of tebentafusp being cost effective, at thresholds of £20,000, £30,000, and £50,000 per QALY gained, compared to the comparator are [redacted], respectively.

Overall, the technology is modelled to affect QALYs by:

- Increased PFS (time in the progression-free (PF) health state increased by [redacted] years; i.e. [redacted] years) and OS (survival increased by [redacted] years; i.e. [redacted] years) compared with the comparator. This resulted in [redacted] post-progression benefits of [redacted] (estimates retrieved from CS Appendix J).[7]
- Treatment benefit (in terms of OS, PFS and utility benefits) are maintained for the whole duration of the time horizon i.e. no waning of these treatment benefits.

Overall, the technology is modelled to affect costs by:

- The higher drug costs (additional costs of [redacted]) compared with the comparator, higher administration costs (additional costs of £[redacted]) as well as higher subsequent treatment costs (additional costs of £[redacted]; estimates retrieved from CS Appendix J).[7]
- The higher drug costs are driven by the higher unit costs and the TTD (combined with the [redacted] assumption).
- Notably, despite the increased post-progression survival, the post-progression costs are lower for tebentafusp compared with the comparator.

For the subgroup with the largest metastatic lesion recorded at baseline ≤30 mm the deterministic ICER was estimated to be £[redacted] per QALY gained (CS Table 89, using the log-logistic distribution to estimate OS as specified in CS Section B.3.3.2) which is a substantial increase compared with the deterministic base-case ICER of £[redacted] per QALY gained (CS Table 82).[1]

ERG comment: The main concerns of the ERG relate to: a) extent and plausibility of the observed gains accumulated beyond the observed data period and b) comparisons with all relevant comparators:

a) In clarification question C20, the ERG requested the company to provide a comparison of the observed survival as well as PFS for instance using restricted mean survival time (RMST) and the undiscounted life years (LYs) as well as undiscounted progression-free LY (PFLY) and elaborate on the plausibility of the differences (using template Tables provided by the company).[6] Unfortunately, the company did alter the template Tables provided by the ERG and did not provide the requested comparisons.[3] Therefore, the ERG calculated the proportion of observed gains accumulated beyond the observed data period beyond (Table 5.1; numbers might be subject to rounding errors). Based on these calculations it can be derived that the proportion of (PF)LY accumulated beyond the observed data is substantially larger for tebentafusp than for IC. Moreover, considering the increments, approximately [redacted] (or more depending on the truncation point) of the LYs are gained beyond the observed data period for tebentafusp compared with IC while this is approximately [redacted] (or more depending on the truncation point) for PFLY. The findings presented in Table 5.1 indicate that the [redacted] of gains are accumulated beyond the observed data

period and hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted (as requested but not provided in the company's response to clarification question C20).[3, 6] This includes verifying the plausibility of the partitioned survival model extrapolations (see Section 4.2.2).

b) The company did not provide results for all (appropriate comparisons) with all comparators listed in the scope (pembrolizumab, ipilimumab, nivolumab alone or in combination with ipilimumab, dacarbazine, and BSC for people who have had previous treatments). As highlighted in the ERG comments of Section 4.2.4, nivolumab alone or in combination with ipilimumab is not incorporated in the model as comparator nor for pembrolizumab, ipilimumab, and dacarbazine while not assuming equal effectiveness (as this assumption does not seem compelling based on clarification response Tables 3 and 4).[3]

Table 5.1: Comparison of the observed and modelled (progression free) survival expressed in months

	Observed	Modelled	
	Restricted mean survival time (RMST)	**Estimated (lifetime time horizon)**	**Proportion beyond observed data**
OS - RMST period / truncation point: 16.7 months (selected based on median in OS in control arm)			
Tebentafusp	[redacted]	[redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
OS - RMST period / truncation point: 21.2 months (selected based on at least 15% of patients at risk)			
Tebentafusp	[redacted]	[redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
OS - RMST period / truncation point: 27.3 months (selected based on maximum follow-up time in the control arm)			
Tebentafusp	[redacted]	[redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
PFS - RMST period / truncation point: 2.9 months (selected based on median PFS in control arm)			
Tebentafusp	[redacted]	[redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
PFS - RMST period / truncation point: 8.1 months (selected based on at least 15% of patients at risk)			
Tebentafusp	[redacted]	[redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
PFS - RMST period / truncation point: 21.9 months (selected based on maximum follow-up time in the control arm)			
Tebentafusp	[redacted]	[redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

OS = overall survival; PFS = progression-free survival; RMST = restricted mean survival time

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSAs), deterministic sensitivity analyses (DSAs) as well as scenario analyses. The parameters that have the greatest effect on the ICER (based on the company's sensitivity analyses) were:

- Age
- The baseline utility value
- Subsequent chemotherapy attendance

Consistently, modelling assumptions that relate to these parameters likely have the greatest effect on the ICER. This is illustrated by the following CS scenarios that have a substantial impact on the ICER:

- Approach to estimate OS (CS Table 87 and 88)
- Source of utility data (using the EQ-5D data collected in the IMCgp100-202 trial increased the ICER to £[redacted] per QALY gained)
- Choice of method of extrapolation of TTD (CS Tables 86)

5.3 Model validation and face validity check

In CS Section B.3.10 it is stated that cost effectiveness model was validated using two approaches.[1] First the internal validity of the model was assessed to verify whether the model performed the mathematical calculations according to its original specification. Secondly, the external validity of the model was tested by comparing the model's results against those reported in relevant clinical studies.

5.3.1 Face validity assessment

No face validity assessment was provided in CS section B.3.10.[1]

5.3.2 Technical verification

To ensure the internal validity of the model, a senior health economic modeler who was not previously involved in the submission, performed a thorough and systematic examination of multiple aspects of the model. First, the model was examined to ensure worksheets and formulas are programmed correctly. Subsequently, the model's behaviour was examined by running verification checks to assess the consistency of the modelled outputs, or indications of error in the results. The latter was achieved by using equal or extreme values in both treatment arms of the model and inspecting whether the results produced by the model matched the modeler's expectations. The results of these validation exercises were not presented in CS section B.3.10.[1]

5.3.3 Comparisons with other technology appraisals

No comparisons with other TAs were provided in CS section B.3.10.[1]

5.3.4 Comparison with external data

To examine the external validity of the model results the company compared the predicted OS and PFS with the 202 trial IC arm, and three studies of treatments for metastatic UM (results provided in CS Table 90).[1]

ERG comment: The main concerns of the ERG relate to: a) technical validation; b) cross validation and c) comparison with external data and plausibility of extrapolated gains.

a) In clarification response C23 the company elaborated on the internal validation performed and completed the TECH-VER checklist.[38] This reassured the ERG with regard the technical

verification of the economic model. However, the model submitted by the company did not allow the ERG to run probabilistic analyses for the ERG base-case, as the economic model did revert the input parameters to default values used for the CS base-case. It should be noted that the functionality *"Click to update default values with current values"* did not work appropriately (at least not for the OS, PFS and TTD switches).

b) In clarification response C24 the company indicated that no technical validation was performed as there are no NICE TAs relevant to this decision problem.[3] According to the company's response, tebentafusp is the first treatment under evaluation by NICE for the treatment of metastatic UM and the first proven effective treatment for metastatic UM supported by a registrational study. The company stated that UM is biologically distinct from skin melanoma with different physiological, genetic, and epidemiologic characteristics.

c) Tables 39 and 41 in the clarification responses provide additional comparisons with external data.[3] Although these Tables might be helpful to compare OS extrapolations for IC, this does not support the validity of extrapolated gains. As elaborated in the ERG comment of Section 5.1, the [redacted] of gains are accumulated beyond the observed data period and hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted (as requested but not provided in the company's response to clarification question C20).[3]

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020:[39]

- Transparency (e.g. lack of clarity in presentation, description, or justification)
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g. particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g. there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken, i.e. whether additional clarifications, evidence and/ or analyses might help to resolve the key issue. Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the ERG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this ERG report, the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous Sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler et al. 2016):[40]

a) Fixing errors (FE; correcting the model where the company's submitted model was unequivocally wrong)
b) Fixing violations (FV; correcting the model where the ERG considered that the NICE reference case, scope, or best practice had not been adhered to)
c) Matters of judgement (MJ; amending the model where the ERG considers that reasonable alternative assumptions are preferred)

6.1.1 ERG base-case

Adjustments made by the ERG, to derive the ERG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the ERG base-case. The 'fixing error' adjustments were combined and the other ERG analyses were performed also incorporating these 'fixing error' adjustments given the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

No errors were identified by the ERG

6.1.1.2 Fixing violations

1) Post progression health state costs (Section 4.2.9)
   The one-off application of BSC costs is flawed. The ERG adopted monthly BSC costs per cycle in the post progression health state and removed the end of life costs (to prevent potential double counting).

2) Extrapolation of PFS (Section 4.2.6)
   The hybrid/piecewise approach by the company is flawed. The ERG adopted the same distribution as used in the CS base-case (i.e., generalised gamma distribution) while removing the KM curve component.
3) Extrapolation of TTD (Section 4.2.6)
   The hybrid/piecewise approach by the company is flawed. The ERG adopted the same distribution as used in the CS base-case (i.e. generalised gamma distribution) while removing the KM curve component.

Matters of judgement

4) Extrapolation of OS (Section 4.2.6)
   The ERG used alternative standard parametric models to estimate and extrapolate OS (the same distribution was used for both treatments). Standard parametric models used were:
   a) The generalised gamma distribution (used in scenario analyses by the company)
   b) The log-logistic distribution.

6.1.2 ERG exploratory scenario analyses

The ERG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the ERG base-case.

6.1.2.1 Exploratory scenario analyses

5) Different source for utility data with alternative approach than the end of life utility values (Section 4.2.8)
   Scenario using IMCgp100-202 trial data implementing on and off treatment utility values instead of end of life utility values.
6) Alternative percentages of patients using each IC treatment
   Standard of care is not yet agreed for metastatic UM and the percentage of patients using each treatment (i.e. dacarbazine, pembrolizumab or ipilimumab) was considered one of the main factors influencing IC acquisition costs. This analysis explores the potential impact of alternative percentages.
   a) Assuming 100% pembrolizumab for IC treatment cost calculation (Section 4.2.9)
   b) Assuming 100% ipilimumab for IC treatment cost calculation (Section 4.2.9)
   c) Assuming 100% dacarbazine for IC treatment cost calculation (Section 4.2.9)
7) Adding 50 days to the subsequent treatment duration for tebentafusp (Section 4.2.9)
   It is unclear how the subsequent treatment duration is calculated (despite clarification responses to question C17a).[3] This analysis explores the potential impact of alternative subsequent treatment duration.

6.1.3 ERG subgroup analyses

No compelling justification was provided by the company to deviate from the approached adopted for the ITT population. Therefore, for the ≤30 mm subgroup, the ERG adopted the same approach to estimate OS, PFS and TTD as was described for the ERG base-case above.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Expected impact on ICER	Resolved in ERG base-case	Required additional evidence or analyses
The use of the treatment mix in the IC arm of the IMCgp100-202 study as single comparator and not including nivolumab as comparator	4.2.4	Methods	Unclear	No	Include all comparators listed in the final scope as separate comparators
Long-term PFS and OS extrapolations	4.2.6	Methods, unavailability	Depending on the scenario, the impact can be substantial.	Partly	Exploring alternative assumptions and using IMCgp100-202 trial data with additional follow-up.
Not primarily using the IMCgp100-202 trial EQ-5D data and time-to-death HRQoL approach being inconsistent with common modelling practices	4.2.8	Methods, bias & indirectness	The ERG is unable to determine the effect and magnitude on the ICER. Nevertheless, given the increased post-progression survival with tebentafusp, the use of time-to-death utilities is most likely not conservative.	No	The analyses requested in clarification question C10.
One-off application of BSC costs	4.2.9	Methods	Not conservative	Yes	
Percentage of patients using each IC treatment	4.2.9	Methods	Unclear	No	Scenario analyses exploring the effects on the ICER of each treatment option separately, also including treatment specific OS, PFS and TTD.
Proportion of (PF)LY accumulated beyond the observed data	5.1	Methods, unavailability	Unclear, alternative assumptions with less extrapolation would likely increase the ICER	No	Using IMCgp100-202 trial data with additional follow-up. Providing additional explanation and justification of the mechanism

Key issue	Section	Source of uncertainty	Expected impact on ICER	Resolved in ERG base-case	Required additional evidence or analyses
					by which the model generated the differences.
Probabilistic analyses for alternative OS, PFS and TTD assumptions	5.3	Methods	Unclear	No	Providing economic model, which includes the ERG preferred options and allows these analyses to be run probabilistically.

BSC = best supportive care; EQ-5D = European Quality of Life-5 Dimensions; ERG = Evidence Review Group; HRQoL = health-related quality of life; IC = investigator's choice; ICER = Incremental cost effectiveness ratio; OS = overall survival; PF(LY) = progression-free (life years); PFS = progression-free survival; TTD = time to treatment discontinuation

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In Section 6.1 the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on ERG base-case 1 (OS extrapolation using the generalised gamma distribution). The analyses numbers in Tables 6.2 and 6.3 correspond to the numbers reported in Section 6.1. Finally, Tables 6.4 and 6.5 provide the results of the subgroup analysis (described in Section 6.1.3). The submitted model file contains technical details on the analyses performed by the ERG (e.g. the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic ERG base-case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixing violation (1- Post progression health state costs)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixing violation (2- Extrapolation of PFS)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixing violation (3- Extrapolation of TTD)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Matter of judgement (4a-Extrapolation of OS – generalised gamma)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Matter of judgement (4a-Extrapolation of OS – log logistic)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case 1 (Extrapolation of OS – generalised gamma)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case 2 (Extrapolation of OS – log logistic)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IC = investigator's choice; OS = overall survival; PFS = progression-free survival; QALY = quality adjusted life years; TTD = time to treatment discontinuation

Table 6.3: Deterministic scenario analyses (conditional on ERG base-case 1)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base-case 1 (Extrapolation of OS – generalised gamma)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis 1 (5- Use of utility values from IMCgp100-202)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis 2 (6a- Only pembrolizumab in IC)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis 3 (6b- Only ipilimumab in IC)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis 4 (6c- Only dacarbazine in IC)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis 5 (7- Addition of 50 days of subsequent treatment for tebentafusp)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IC = investigator's choice; OS = overall survival; QALY = quality adjusted life years

Table 6.4: Deterministic subgroup analyses (conditional on ERG base-case)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixing violation (1- Post progression health state costs)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixing violation (2- Extrapolation of PFS)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixing violation (3- Extrapolation of TTD)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Matter of judgement (4a- Extrapolation of OS – generalised gamma)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Matter of judgement (4a- Extrapolation of OS – log logistic)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (Deterministic 1- Extrapolation of OS – generalised gamma)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (Deterministic 2- Extrapolation of OS – log logistic)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IC = investigator's choice; OS = overall survival; PFS = progression-free survival; QALY = quality adjusted life years; TTD = time to treatment discontinuation

Table 6.5: Deterministic subgroup scenario analyses (conditional on ERG base-case 1)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base-case 1 (Extrapolation of OS – generalised gamma)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis 1 (5-Use of utility values from IMCgp100-202)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis 2 (6a- Only pembrolizumab in IC)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis 3 (6b- Only ipilimumab in IC)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis 4 (6c- Only dacarbazine in IC)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis 5 (7- Addition of 50 days of subsequent treatment for tebentafusp)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IC = investigator's choice; OS = overall survival; QALY = quality adjusted life year

6.3 ERG's preferred assumptions

The estimated ERG base-case ICER (deterministic), based on the ERG preferred assumptions highlighted in Section 5.1, ranged between £[redacted] and £[redacted] per QALY gained. The most influential adjustments were related to the estimation of OS, post progression health state costs and the

TTD. The ICER increased most in the scenario analysis with alternative assumptions regarding different proportions for IC treatments.

6.4 Conclusions of the cost effectiveness section

The company's cost effectiveness model partly complied with the NICE reference case. Deviations from the NICE reference case related to the synthesis of evidence on health effects and source of data for measurement of HRQoL and relate to the key issues highlighted by the ERG. The most prominent issues highlighted by the ERG were 1) the estimation of OS, PFS and TTD; 2) the comparators considered; 3) the approach to incorporate HRQoL and 4) the approach to incorporate costs related to the post-progression health state.

Firstly, the overarching challenge was the immaturity of the OS data from IMCgp100-202 trial (NCT03070392) considering the uncertainty related to the extrapolated OS, which was the most influential issue. Related to this, given that a large proportion of life years gains could be attributed to the time period beyond available trial data, the company's approach of using a partitioned survival model was questioned. The ERG considered the company's spline-based approach for OS as well as the use of different approaches (i.e. spline-based versus standard parametric model with a Weibull distribution) for the intervention and comparator not appropriately justified. Moreover, the hybrid (or piecewise) approach for PFS and TTD was considered to be flawed. Hence, standard parametric survival models with the same distribution for both treatments were adopted in the ERG base-case. The ERG furthermore questioned the company's implicit assumption of a lifelong treatment effect (for OS and PFS). Moreover, the company did not explore alternative waning assumptions, but the ERG anticipates that alternative waning assumptions likely significantly impacts the ICER.

Secondly, the treatment mix in the IC arm of the IMCgp100-202 trial was used as the single comparator, while the different comparators included in the IC arm likely differ in costs and effectiveness. This seemed to be supported by the company's clarification responses, and therefore analyses stratified by IC treatment, incorporating treatment-specific cost and effectiveness estimates are warranted (despite requested by the ERG, these were unfortunately not provided by the company).[3, 6] This is also relevant given that in the current analyses, only incorporating treatment specific costs for the IC treatments, the proportions of specific IC treatments used (in the base-case these were pembrolizumab (82%), ipilimumab (13%) and dacarbazine (6%)) were considered influential in sensitivity analyses. Additionally, nivolumab, despite listed in the scope, was not included as comparator in the cost effectiveness analyses.

Thirdly, in terms of HRQoL, the cost effectiveness analyses predominantly used utility values 1) from TA366 instead of EQ-5D data from the IMCgp100-202 trial and 2) based on time-to-death rather than disease status. The ERG believes this approach was not appropriately justified and is flawed from multiple perspectives: firstly, it is inconsistent with the model structure and common modelling practices (criticised previously, e.g., in TA366) and does not reflect the decline in HRQoL after progression; secondly, the implementation is not transparent; and thirdly, it lacks face validity and leads to implausible high utility values. The ERG is unable to determine the effect and magnitude of this issue on the ICER. Nevertheless, given the increased post-progression survival with tebentafusp, the current approach is most likely not conservative. Additionally, the incomplete clarification responses from the company were not helpful to explore the expected effect on the cost effectiveness estimates.

Finally, regarding the costs, the company's approach of handling the post-progression health state costs, incorporated as one-off costs independent on the occupancy duration of this health state, is flawed according to the ERG. Since post-progression costs would most likely depend on how long patients

stayed in the post-progression health state, this approach would benefit tebentafusp, as patients after tebentafusp stayed longer in the post-progression health state than for the comparator.

The CS base-case probabilistic and deterministic ICERs were £[redacted] and £[redacted] per QALY gained, respectively. This was increased in the subgroup with the largest metastatic lesion recorded at baseline ≤30 mm (deterministic CS base-case ICER of £[redacted] per QALY gained). The estimated ERG base-case ICER range (deterministic), based on the ERG preferred assumptions highlighted in Section 6.1, was £[redacted] to £[redacted] per QALY gained. The ERG was unable to produce probabilistic base-case analyses (as highlighted in the model validation section). The most influential adjustments were related to the estimation of OS, post-progression health state costs and the TTD. The ICER increased most in the scenario analysis with alternative assumptions regarding different proportions for IC treatments.

There is large remaining uncertainty about the effectiveness and relative effectiveness of tebentafusp, which can be at least partly resolved by the company by conducting further analyses. According to the ERG the current approach (both in the CS and ERG base-case) to incorporate HRQoL is flawed and this could conceivably change, most likely increase, the ICER. Moreover, the current assessment does not provide an appropriate estimation of the comparators listed in the scope. Therefore, the ERG believes that the CS nor the ERG report contains an unbiased ICER of tebentafusp compared with relevant comparators.

7. END OF LIFE

The ERG noticed that the CS did not include any statement regarding tebentafusp potentially meeting the end of life criteria defined by NICE and asked for clarification.[6] In response to clarification question D1, the company provided details why end of life criteria should apply:[3]

i. *"The treatment is indicated for patients with a short life expectancy, normally less than 24 months*

> *The current life expectancy for patients with metastatic uveal melanoma is very short. The median survival from the time of development of metastatic disease is 12-15 months and 1-year survival is around 50% (Nathan et al., 2015, Kuk et al., 2016, Damato et al., 2019).*

ii. *There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment*

> *The Phase 3 RCT, study IMCgp-100-202, has demonstrated that patients randomised to tebentafusp as first-line therapy had a significant reduction of risk of death compared with those treated with investigator's choice therapies (i.e., pembrolizumab, ipilimumab or chemotherapeutic dacarbazine) after a median follow-up of 14.1 months. The estimated one-year OS rate was 73.2% among patients in the tebentafusp arm, compared with 58.5% in the investigator's choice arm. Historical data from two large meta-analyses examining a range of treatment options that have been tested in metastatic UM demonstrate 1-year overall survival for previously tested treatments is reported to be 52-56% (Khoja et al., 2019, Rantala et al., 2019).*[22, 41] *Current NICE approved clinical guidelines for metastatic UM suggest patients should be enrolled on clinical trials (Nathan et al., 2015).*[36] *In the absence of specific approved systemic treatments clinicians can employ treatments that are recommend for any type of metastatic melanoma such as ipilimumab, nivolumab or pembrolizumab. None of these treatments have shown demonstratable survival benefit, as single agents or in combination, that is comparable to tebentafusp for metastatic UM. Based on the cost-effectiveness model, the life-year gain is 2.33 years in the base-case. The incremental LYs range between 0.7-3.6 years (8-43 months), depending on the approach used to modelling OS.*

iii. *The treatment is licensed or otherwise indicated, for small patient populations.*

> *Uveal melanoma is a rare disease as recognised by the orphan designation for tebentafusp from the Committee for Orphan Medicinal Products (EMA, 2021) and the anticipated orphan designation of tebentafusp from the MHRA. The incidence of primary UM is 540 patients annually in the UK (ONS 2019), half these patients go on develop metastatic disease (Yang et al., 2018). The estimated incidence of metastatic UM patients who will be clinically eligible to receive tebentafusp, the indication for the technology being appraised is ~100 per year."*

ERG comment: The ERG reviewed the arguments presented in the response to the request for clarification.[3]

i. Based on the evidence provided by the company, it is likely that patients with metastatic UM meet the criterion outlined by NICE. However, it should be noted that the population defined in the NICE final scope is *"adults with advanced (unresectable or metastatic) HLA-A*0201-positive UM"*.[2] While the main study identified in the CS, IMCgp100-202, included participants with *"histologically or cytologically confirmed diagnosis of metastatic UM"*,[1] it is unclear whether this criterion would be met for patients with advanced but non-metastatic UM.

ii. As summarised in Section 3.2.3.1.1, results of IMCgp100-202 indicate that this criterion has been met in the comparison to IC. However, as highlighted in Section 3.2.3.5.1, treatment effects differ by drug used, i.e. the committee should consider this issue in light of the drugs usually used in the NHS setting. In particular, there appears to be little if any difference in median OS between tebentafusp and ipilimumab.

iii. This criterion is not part of the current criteria used by NICE and the ERG does not have any specific comments.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **12pm on Wednesday 2 February 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Incorrect name of treatment in table 1.6

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.6, Page 13 states '' The results of a separate analysis of each IC treatment in the IMCgp100-202 study could be used as inputs in CEAs of tafasitamab versus each of these treatments.''	Replace tafasitamab with tebentafusp	Incorrect treatment name. Tafasitamab is not relevant to this appraisal, we believe this is an error and it should read Tebentafusp.	Changed accordingly

Issue 2 Critique of company's definition of decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
2.1 Population, Page 24 The population in the decision problem of the company submission (CS) is: • Adults with advanced (unresectable or metastatic) HLA-A*02:01-positive UM.1 The population included in the identified trial evidence, the IMCgp-100-202 study, is: • Previously untreated patients with metastatic UM who were HLA-A* 02:01–positive to receive tebentafusp (intervention) or one of three investigator's choice	It should be noted that the population of patients with locally advanced disease alone is extremely small.	The reason to include this population in the indication was to provide this small number of patients a treatment option when there is clear reasoning that tebentafusp could be beneficial for them and no demonstrably effective systemic treatment options are available to these patients.	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
comparators: dacarbazine, ipilimumab, or pembrolizumab.			
2.1 Population, Page 24 ''Marketing authorisation for tebentafusp has not been approved anywhere in the world''	Tebentafusp was approved by the FDA on Wednesday 26th January 2022.	Tebentafusp is approved in the United States.	Not a factual inaccuracy NB: The ERG report was completed on 19th January 2022
[A] 2.3 Comparators, Page 25 - The ERG comments that nivolumab monotherapy should be considered a relevant comparator due to the NICE guidance that nivolumab alone is recommended for advanced (metastatic or unresectable) melanoma. [B] AND 3.6 Conclusions of the clinical effectiveness section Page 56 '' The ERG is also concerned about the lack of comparison to nivolumab monotherapy which has been identified as another key issue. (also noted in Issue 9)	[A] Propose amendment that nivolumab is not suggested to be included as a comparator. [B] Propose deletion of this statement	While nivolumab monotherapy is recommended for advanced (metastatic or unresectable) melanoma, the rare form of metastatic **uveal** melanoma was not included in the clinical trials that informed this guidance. The possibility of nivolumab monotherapy being included as a comparator was discussed in the scoping meeting and it was agreed that it was not considered relevant because (a) at this time no studies had been performed on nivolumab monotherapy in metastatic uveal melanoma patients as shown by the SLR outcomes, and (b) there is no evidence that clinicians in the UK employ nivolumab monotherapy for metastatic uveal melanoma in clinical practise (demonstrated by a clinician survey and advisory board with metastatic uveal melanoma clinical specialists). Nivolumab is an anti-PD-1 inhibitor and while there is	Not a factual inaccuracy Statement based on the documents submitted to the ERG.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		no evidence to suggest it is used in clinical practise for metastatic uveal melanoma in the UK, it has the same mechanism of action as pembrolizumab, which is included in the control arm of the tebentafusp clinical trial.	

Issue 3 Critique of decision problem (Other relevant factors)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
2.5 Other relevant factor, Page 25 – '' As the first three doses of tebentafusp will require administration and monitoring for 16 hours post-administration in a hospital setting, and weekly out-patient ambulatory care drug administration followed by 30 minutes of monitoring will only become appropriate once the patient tolerates the most recent infusion without grade ≥2 hypotension, in the context of short life expectancies among UM patients, **tebentafusp does not appear to be very innovative**.	Propose amendment or deletion of the statement that 'tebentafusp does not appear to be very innovative'.	The context of the statement suggests that innovation is only relevant to patient convenience which is a narrow interpretation of the term innovation. Tebentafusp is highly innovative in terms of the technology, as summarised in the CS. From a patient perspective, improved overall survival outcomes and reduced long term toxicity provide an innovative option to those with rare metastatic uveal melanoma. There are currently no approved effective systemic treatments specifically for metastatic uveal melanoma.	Not a factual inaccuracy Statement was made as an ERG comment, i.e. judgement by the ERG.

Issue 4 Incorrect reporting of detailed study characteristics for IMCgp100-202 study

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 3.4, Pages 34-36 - Incorrect reporting of detailed characteristics of IMCgp100-202. Including: Trial number, Trial design, Eligibility criteria for participants, Settings and locations where the data were collected, Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered), Intervention(s) (n=[x]) and comparator(s) (n=[x]), Primary outcomes (including scoring methods and timings of assessments), Other outcomes used in the economic model/specified in the scope, Pre-planned subgroups.	The table should be updated to describe the correct clinical trial being referred to in the title and text associated with this table. The details of study IMCgp100-202 have been included in Appendix 1 of this document: Table 1. Detailed characteristics of IMCgp100-202 study	The table title and text referring to the table state study IMCgp100-202, however the table itself reports detailed information on study IMCgp100-102 instead.	Changed accordingly NB: Changed based on Table 5 of the submission

Issue 5 Clarity of reporting overall survival data from study IMCgp100-202

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
3.2.2.1.1 IMCgp100-202 Overall Survival, Page 38 – The ERG state '' Figure 3.3B shows [redacted]	Insert '*the August 2021 data cut*' includes '*some':* Figure 3.3B shows the prolonged OS in the tebentafusp arm: [redacted] for investigator's choice (*the August*	Currently there is a lack of clarity that only the August data cut includes some crossover patients.	Not a factual inaccuracy NB: Wording in line with page 56 of the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
[redacted]	*2021 data cut* includes *some* patients who have crossed over from the IC to tebentafusp arm and has not been adjusted for).		

Issue 6 Clarification on patient numbers achieving OR in IC arm

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
3.2.3.4 Duration of Response,3.2.3.4.1 IMCgp100-202 - Page 43 ''It should be noted that in the CS, the text accompanying Table 10 stated that nine IC patients were considered in the analysis, however, the table states that six patients achieved OR.''	Addition of: 'As listed in the CSR, confirm that that the number of patients that achieved OR is six'.	Clarification of typo and confirmation of patient number as per CSR provided.	Not a factual inaccuracy

Issue 7 Clarity of statements relating to Adverse Event reporting

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
3.2.4.1 Adverse events; 3.2.4.1.1 Page 47 – The ERG states there is 'inconsistency in reported values'	Propose deletion of this statement, this is a misunderstanding of the difference between reported AEs and retrospective adjudication.	There is not inconsistent reporting. CRS (89%) is based on retrospective adjudication using ASTCT criteria, not reported AEs (this is in the footer of Table 3.12).	Changed accordingly
3.2.4.1 Adverse events; 3.2.4.1.1 Page 47 – The ERG states 'The inconsistency in reported values	Propose deletion of this statement, this is a misunderstanding of the clinical event definition, 'rash' (83%) is a composite of terms,	There is not inconsistent reporting. Rash (83%) is a composite of terms which included "rash	Changed accordingly

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
(e.g rash 55.1% vs. 83%) is of note.''	as described in the footer of Table 3.11 and 3.12.	maculo-papular" and "rash" - this composite is described in the footer of Table 3.11 and 3.12	
Page 55 The ERG states: ''The ERG also comments on the inconsistencies that were observed between the text and the information that was tabulated in the Tables, see above. While these may appear to be minor, it highlights that there might have been an error in reporting the frequency and occurrence of AEs.''	Propose deletion of this statement	This conclusion by the ERG is in reference to the above comments on discrepancies which are inaccurate.	Changed accordingly

Issue 8 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 54 – 3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison	We would recommend complete removal of this section. At minimum we would expect amendment of the section to provide a more balanced commentary, specifically we would expect it to: 1. better emphasise the naïve nature of the comparisons the ERG make across outcomes in the four potential comparator studies [Median OS is not useful measure	We appreciate that the similarity of results across the four studies the ERG have listed is surprising given the difference in treatment experience in the Piulats study. However, in line with many of the key points made by the ERG on the ITC throughout their review we would strongly argue against placing much interpretation on a naïve comparison of results across these four trials given high likelihood of confounding and effect modification. That is, there may have been various differences in	Not a factual inaccuracy. This is a matter of judgment.

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG comment</th></tr>
<tr><td></td><td>of OS in studies with small n-numbers (note CI's of in the list of study outcomes)]

2. note that confounding by other factors such as ECOG may explain the similarity in survival and the naïve comparisons therefore does not demonstrate that treatment experience is not prognostic.

3. Highlight that if treatment experience is prognostic (as is demonstrably the case) comparisons against the other 3 studies would not be recommended as it is not possible to account for this in those comparisons</td><td>patient characteristics beyond treatment experience that resulted in the patient populations across these four studies having similar prognosis. For example, in Piulats et al (2021) 15.4% of patients had an ECOG greater than 0 whereas in the other three studies there were a greater proportion of patients with an ECOG greater than 0 (see table below). This, and other imbalances like this, could explain the similar prognosis across these trials despite the differing treatment experience.
<table><tr><th>Study</th><th>ECOG>0*</th></tr><tr><td>Piulats et al (2021)</td><td>15.4%</td></tr><tr><td>Pelster et al (2021)</td><td>28.6%</td></tr><tr><td>Najjar et al (2020)</td><td>33.3%</td></tr><tr><td>Heppt et al (2019)</td><td>21.0%</td></tr></table>*% of those with known ECOG, n=14 missing ECOG in Najjar et al n=3 missing ECOG in Heppt et al.
Further to this, we made the decision to carry out our analysis against the Piulats study on the basis of study characteristics and availability of key variables, and independent of the study outcomes. As described in the CS and clarification response. We believe this is in keeping with a scientifically rigorous approach to conducting ITCs and do not believe that studies should be selected for inclusion in</td><td></td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		an ITC on the basis of their outcomes, as the comment appears to be suggesting. We therefore disagree with the relevance of a MAIC with the 3 studies [Pelster et al. (2021), Najjar et al. (2020) and Heppt et al. (2019)] because the study populations differed from the tebentafusp trial (Study 202) on at least one key factor (treatment experience) and did not meet the eligibility criteria for the ITC for a number of other important reasons, including the absence of or missing data on key variables, as exemplified by the missing ECOG data in the Najjar (2020) and Heppt (2019) studies.	

Issue 9 Critique of the indirect comparison and/or multiple treatment comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 56 3.4 - Relevance of quote to Hoaglin	Remove reference to Hoaglin quote or better link it to the commentary as at the moment its use is misleading. Provide a more balanced commentary on the possible reasons the HR was not observed to change, highlighting that it may be due to good population overlap and/or the existence of minimal	We broadly agree with the quoted text from Hogalin et al which is cited in TSD18 and which points to the difficulties in having confidence that systematic error has been fully accounted for in an analysis of this nature. However, we believe the Hoaglin et al text has been taken out of context somewhat in its use here as it is cited to justify a point the	Not a factual inaccuracy. Of course, it could be that the HR changes little because adjustment did reduce the bias, but there is little difference between the populations of the two studies. However, the similarity should not give any confidence that this is the case because an

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
	confounding effects of the covariates included in the MAIC	ERG make regarding the fact the absence of a meaningful shift in the HR following adjustment suggests that the result are not reliable. The Hogalin reference does not specifically support this point. We would also generally argue against this point made by the ERG, as a lack of movement in the HR may simply mean that there was minimal confounding of the original effect estimate, rather than suggesting a lack of validity of the results of the MAIC. We do however appreciate that taken together the absence of the details to diagnose population overlap (info on weights and ESS) and lack of movement in the HR render interpretation challenging. Based on our review of these outputs, we believe it is a function of small confounding effects and our having chosen a comparator study with relatively good baseline population overlap and therefore further supports our response to 3.3.	explanation that is similarly plausible is that the bias was not reduced.

Issue 10 Comparators and conclusions of the clinical effectiveness section

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 56 – ''The ERG is also concerned about the lack of comparison to nivolumab monotherapy which has been identified as another key issue.''	Propose deletion of this statement	Inclusion of an ITC on nivolumab monotherapy would not have been feasible as no studies on treatment of nivolumab monotherapy were identified in the systematic literature review, further comments relating to this are provided in the justification for amendment 'Issue 2' earlier in this document.	Not a factual inaccuracy

Issue 11 Cost effectiveness – selection approach to modelling OS, PFS, TTD

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.6, Table 4.4 (page 64) and page 68. The ERG reports that AIC and BIC for standard parametric models in the tebentafusp arm are not provided in the CS.	Amend this statement to reflect that: Goodness of fit measures were reported in Appendix L of the CS, as well as in the CEM where all models fitted are presented.	The statement is incorrect, the data is provided.	Not a factual inaccuracy AIC and BIC for standard parametric models in the tebentafusp arm were not provided in the CS nor in Appendix L

Issue 12 Cost effectiveness – selection approach to modelling OS, PFS, TTD

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.6, Table 4.4, page 64. The ERG reports that a comparison of standard	Amend this statement to reflect that:	The statement is incorrect, the data is provided.	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
parametric models with the KM curve in the tebentafusp was not provided.	Graphs of fitted parametric models, overlayed with KM curves, were reported in Appendix JL of the CS.		Plots with comparison of standard parametric models with the KM curve in the tebentafusp were not provided for the August 2021 data cut-off in the CS or in Appendix L

Issue 13 Cost effectiveness – selection approach to modelling OS, PFS, TTD

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.6, Table 4.4, page 64. The ERG reports that the clinical plausibility of the extrapolation in the control arm based on clinical expert opinion was not explicitly discussed.	Amend this statement: Based on clinical experts' opinion, the OS under current treatment modalities is between 0% and 5% at 5 years.	Discussed in Section B.3.3.1 of the CS.	This is adjusted in Table 4.4

Issue 14 Digitisation of Rantala et al. 2019

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 69. "it is unclear why the company digitised a plot from *"Supplemental digital content 4"* of the paper instead of from Figure 3 in the main manuscript"	Deleting this statement or describing more accurately what the supplementary content is.	Figure 3 presents three different KM curves of OS by treatment modality, for first line patients. The figure from the supplementary material, is the same data but pooled over all treatment modalities, giving more robust KM estimates given the higher number of patients from pooling the data.	Not a factual inaccuracy

Issue 15 Incorrect spelling of author name of a reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.8.2, page 71 "the study of Hatswall et al. 2014"	Correct the spelling of **Hatswell**	Error in the reference	Adjusted accordingly

Issue 16 Analysis method of EQ-5D data from the IMCgp100-202 clinical trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.8.2, page 73 Moreover, for the survival follow-up period the company removed incomplete data prior to analysis which is known as listwise deletion or complete-case analysis. Listwise deletion potentially introduces inconsistencies in the data and if the data are not MCAR (as is most likely the case), listwise deletion can severely bias estimates of means, regression coefficients and correlations.[32] Hence the imputation approach adopted by the company likely induces bias.	Deleting the statement or rephrasing. "For the survival follow-up period, data imputation was not conducted due to the high number of missing EQ-5D records. All available records for the period were complete with respect to the covariates included in the regression analysis (i.e., age, sex, treatment arm, and treatment status) and were included in the regression".	All records were complete with respect to the covariates included in the regression analysis (i.e., age, sex, treatment arm, and treatment status). No records were removed from the analysis.	Not a factual inaccuracy

Issue 17 Clinical expert opinion on time to death

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.8, page 73 "Nevertheless, the company did not explain the methods used to gather clinical experts' opinion, **nor explained the reasoning of the clinical experts for this assumption"**	The reasoning of the clinical experts for this assumption was explained although the company did not explain the methods used to gather clinical experts' opinion.	As stated in section B.3.4.3 of the CS, "Based on clinicals experts' opinion, the quality of life of patients with metastatic UM is maintained until approximately 6 months to death when symptoms start appearing heavily impacting on QoL."	Not a factual inaccuracy The CS quote might provide clinical opinion supporting that HRQoL diminishes at the end of life. It does not provide clinical opinion supporting to prefer an end-of-life utility approach over the more commonly used disease status utility approach.

Issue 18 End of life costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.2.9, page 77 "The company justified that the inclusion of end-of-life costs could lead to double counting"	Deleting this statement	Such a statement was not made in the CS.	Not a factual inaccuracy This statement was made in the company's clarification response.

Issue 19 Treatment duration of subsequent therapies

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 78, "Moreover, the calculation of subsequent therapies duration is unclear" Page 85 "It is unclear how the subsequent treatment duration is	Deleting this statement	No calculation was performed. The data is taken from the IMCgp100-202 CSR, which was provided to the ERG.	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
calculated (despite clarification responses to question C17a)."			

Issue 20 Treatment duration of subsequent therapies

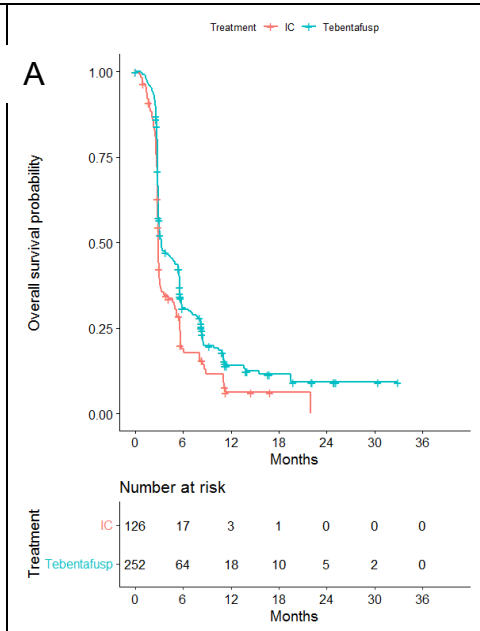
Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 79 "However, the company failed to provide scenario analyses with an accompanying updated economic model that estimated drug acquisition costs without setting drug acquisition costs to zero after [redacted].."	Deleting this statement (or rephrasing)	[redacted]	Not a factual inaccuracy

Issue 21 Exploratory scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 85 Assuming 100% dacarbazine for IC treatment cost calculation	Removing this scenario.	Such a scenario is irrelevant, dacarbazine use in the UK is very limited. Based on the NICE scope "people for whom immunotherapy is not suitable may have dacarbazine chemotherapy". Additionally, only seven patients (5.6%) received dacarbazine in the investigator's choice arm.	Not a factual inaccuracy

Amendments to AiC/CiC marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG comment
Page 11	No marking on: ‘‘higher administration costs (additional costs of £18,522) as well as higher subsequent treatment costs (additional costs of £10,350;’’	Add CiC, higher administration costs (additional costs of [redacted]) as well as higher subsequent treatment costs (additional costs of [redacted];	Changed accordingly
Page 41 Figure 3.5	Figure 3.5, Part B shows unpublished data from the August 2021 data cut and therefore should be marked AiC.	**Figure 0.1: Kaplan-Meier estimate of Progression Free Survival, (A) October 2020; (B) August 2021**	Changed accordingly

<table>
<tr>
<td></td>
<td></td>
<td> 

B [redacted]</td>
<td></td>
</tr>
<tr>
<td>Page 41 Figure 3.5, Tabular summary</td>
<td>The treatment arms in the table are incorrectly marked AiC when they do not need to be. The column showing the August 2021 data cut which is unpublished data should be marked AiC in this table.</td>
<td>
<table>
<tr><th></th><th colspan="2">Median (Months)(95% CI)</th></tr>
<tr><th></th><th>October 2020</th><th>August 2021</th></tr>
<tr><td><u>Tebentafusp (N=252)</u></td><td>3.3 (3.0 to 5.0)</td><td>[redacted]</td></tr>
<tr><td><u>Investigator’s choice (N=126)</u></td><td>2.9 (2.8 to 3.0)</td><td>[redacted]</td></tr>
</table>
</td>
<td>Amended accordingly</td>
</tr>
<tr>
<td>Page 47, 3.2.4 Safety</td>
<td>AiC marking not required</td>
<td>The frequency of treatment-emergent adverse events (TEAEs) from any cause was <u>100%</u> in the tebentafusp arm and <u>94.6%</u> in the investigator’s</td>
<td>Amended accordingly</td>
</tr>
</table>

results, 3.2.4.1 Adverse events, 3.2.4.1.1 Study IMCgp100-202		choice arm (see Table 3.11). Grade ≥3 AEs occurred in 54.3% and 36.0% of patients, respectively	

Appendix 1

Revised table for Issue 3

Table 1. Detailed characteristics of IMCgp100-202 study

Trial number	Study IMCgp100-202 (NCT03070392) (data on file)
Trial design	Phase 3 multi-centre, open-label, parallel, randomised controlled trial
Eligibility criteria for participants	Inclusion criteria 1. Male or female patients aged ≥18 years of age at the time of informed consent 2. Ability to provide and understand written informed consent prior to any study procedures 3. Histologically or cytologically confirmed metastatic UM 4. Had to meet the following criteria related to prior treatment: • No prior systemic therapy in the metastatic or advanced setting including chemotherapy, immunotherapy, or targeted therapy • No prior regional liver-directed therapy, including chemotherapy, radiotherapy, or embolisation • Prior surgical resection of oligometastatic disease was allowed • Prior neoadjuvant or adjuvant therapy was allowed provided administered in the curative setting in patients with localised disease. Patients must not have been retreated with an investigator's choice therapy that was administered as adjuvant or neoadjuvant treatment. Additionally, patients who received nivolumab as prior adjuvant/neoadjuvant treatment should not have received pembrolizumab as investigator's choice therapy 5. HLA-A*02:01 positive by central assay 6. Life expectancy of > 3 months as estimated by the investigator 7. ECOG performance status score of 0 or 1 at screening 8. Patients had measurable or non-measurable disease according to RECIST v1.1 9. All other relevant medical conditions had to be well-managed and stable, in the opinion of the investigator, for at least 28 days prior to first administration of study drug Key Exclusion criteria

<table>
<tr><td></td><td>Patient with any out-of-range laboratory values defined as:
1. Serum creatinine >1.5 × ULN and/or creatinine clearance <50 mL/minute
2. Total bilirubin >1.5 × ULN, except for patients with Gilbert's syndrome, who were excluded if total bilirubin >3.0 × ULN or direct bilirubin >1.5 × ULN
3. Alanine aminotransferase >3 × ULN
4. Aspartate aminotransferase >3 × ULN
5. Absolute neutrophil count <1.0 × 109/L
6. Absolute lymphocyte count <0.5 × 109/L
7. Platelet count <75 × 109/L
8. Hemoglobin <8 g/dL
9. History of severe hypersensitivity reactions (e.g., anaphylaxis) to other biologic drugs or monoclonal antibodies
10. Clinically significant cardiac disease or impaired cardiac function</td></tr>
<tr><td>Settings and locations where the data were collected</td><td>
<table>
<tr><th>United States and Canada</th><th>Australia</th></tr>
<tr><td>• UCLA Medical Center
• The Angeles Clinic and Research Institute
• Byers Eye Institute, Stanford University
• California Pacific Medical Center
• University of Colorado
• Mount Sinai Medical Center
• Winship Cancer Institute of Emory University
• Northwestern University
• The University of Chicago Medicine
• University of Iowa
• Massachusetts General Hospital</td><td>• Saint Vincent’s Hospital
• Melanoma Institute of Australia
• Central Adelaide Local Health Network, Royal Adelaide Hospital Cancer Center
• Peter MacCallum Cancer Center
Belgium
• Institut Roi Albert II Cliniques Universitaires St-Luc
France
• Centre Antoine Lacassagne
• Institut Curie
Germany</td></tr>
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</table>

	• Dana Farber Cancer Institute • Washington University School of Medicine • Roswell Park Cancer Institute • Columbia University Medical Center • Memorial Sloan Kettering Cancer Center • Duke University Health System • The Ohio State University • University of Oklahoma • Portland Providence Medical Center • Thomas Jefferson University Hospital • University of Pittsburgh Medical Center • Houston Methodist Cancer Center • Cross Cancer Institute • Princess Margaret Cancer Centre	• Universitaetsklinikum Koeln Dermatologie und Venerologie • Charite - Campus Benjamin Franklin • Universitätsklinikum Carl Gustav Carus • University Hospital Essen • University of Hamburg • Nationales Centrum für Tumorerkrankungen • Klinik und Poliklinik für Dermatologie und Allergolog
		Italy
		• Fondazione ICCRS • Istituto Nazionale Tumori - IRCCS Fondazione "G. Pascale" - UOC Melanoma, Immunoterapia Oncologica e Terapie Innovative
	Netherlands	**Switzerland**
	• LUMC Medical Oncology	• University of Zurich Hospital
	Poland	**United Kingdom**
	• Centrum Onkologii - Instytut im. Marii Sklodowskiej-C	• Mount Vernon Cancer Centre • The Clatterbridge Cancer Centre • Beatson West of Scotland Cancer Centre
	Russian Federation	**Ukraine**
	• Federal State Budgetary Institution N.N. Blokhin National Medical Research Center of Oncology	• Dnipropetrovsk State Medical Academy • Kyiv Munitipal Hospital

<table>
<tr><td></td><td colspan="2"><table>
<tr><td>• Federal State Budget Institution National Medical Research Center of Oncology
• State Budgetary Healthcare Institution Volgograd Regional Clinical Oncology Dispensary</td><td>• Uzhhorod Central City Clinical Hospital
• Zaporizhzhia Regional Clinical Oncology Center</td></tr>
<tr><td>Spain</td><td></td></tr>
<tr><td>• Institut Catala d'Oncologia (ICO) - L'Hospitalet
• Hospital Universitario La Paz
• Hospital Clínico Universitario de Santiago de Compostela
• Hospital Universitario General de Valencia
• Hospital Universitario Virgen Macarena</td><td></td></tr>
</table></td></tr>
<tr><td>Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x])
Permitted and disallowed concomitant medication</td><td colspan="2">From March 2017 to June 2020, a total of 442 HLA-A*02:01–positive patients were screened, with 378 patients being eligible for inclusion. Patients were randomised in a 2:1 ratio to either of two treatment groups (arms 1 and 2):
<u>Arm 1: tebentafusp (n=252)</u>
All patients randomised to arm 1 received tebentafusp by IV infusion following the intra-patient escalation regimen. Patients received 20 µg on C1D1, 30 µg on C1D8, and an escalated dose of 68 µg on C1D15 and weekly thereafter. Due to the anticipated cytokine release-associated toxicity with tebentafusp following the first three doses, patients were monitored for at least 16 hours after dosing as an inpatient following the weekly doses on C1D1, C1D8, and C1D15. Use of prophylactic steroids was not mandated.
<u>Arm 2: Investigator’s choice (n=126)</u>
All patients randomised to arm 2 received investigator’s choice of one of the following three options:
• Dacarbazine at the standard dosing regimen in UM of 1000 mg/m^2 given on Day 1 of each 21-day cycle (n=7)
• Ipilimumab at the dosing regimen for unresectable or metastatic melanoma of 3 mg/kg given on Day 1 of each 21-day cycle for a maximum of 4 doses (n=16)</td></tr>
</table>

	• Pembrolizumab at the dosing regimen of 2 mg/kg up to a maximum of 200 mg or 200 mg administered IV were approved locally given on Day 1 of each 21-day cycle. The preferred investigator's choice agent was selected prior to randomization. No extended monitoring after dosing was required in Arm 2 (n=103) Concomitant medications (e.g., anti-diarrhoeal drugs, antiemetics, or electrolyte supplementation) deemed necessary to provide adequate prophylactic or supportive care were allowed, except for medications identified as prohibited. There was no difference in drug restrictions between arms.
Primary outcomes (including scoring methods and timings of assessments)	The predefined, dual primary objectives were: • To compare the OS in all patients randomised to tebentafusp monotherapy versus all patients randomised to investigator's choice monotherapy • To compare the OS in all patients randomised to tebentafusp monotherapy who develop a rash within the first week of treatment versus all patients randomised to investigator's choice monotherapy Both objectives relate to HLA-A*02:01-positive patients with advanced UM with no prior treatment in the metastatic setting. The OS endpoint, which is used in the model, is defined as the time from randomisation until death by any cause.
	An additional primary objective was to compare the OS in all patients randomised to tebentafusp monotherapy who develop a rash within the first week of treatment versus all patients randomised to investigator's choice monotherapy. The rationale for this was related to the analysis of study IMCgp100-102, which reported that rash appeared to be associated with a clinical benefit across all efficacy endpoints including tumour shrinkage and PFS (both per an independent radiology committee) and OS. Therefore, this shared primary objective aimed to confirm these analyses by comparing OS in patients randomised to tebentafusp monotherapy who developed a rash within the first week of treatment, with those who did not.
Other outcomes used in the economic model/specified in the scope	The secondary outcome used in the study is PFS (comparison of arms 1 and 2). PFS was defined as the time from randomisation to the date of first documented progression (per RECIST v1.1.) as determined by investigator assessment or death due to any cause, whichever occurred first, regardless. Radiological assessments for PFS were performed as scheduled every 12 weeks, using a reference to C1D1 and were not to follow delays incurred during the treatment period. Other outcomes reported that were specified in the scope were:

	• ORR (using RECIST v1.1) • DOR (using RECIST v1.1) • Adverse effects of treatment • HRQoL (using the EQ-5D-5L for generic HRQoL and the EORTC QLQ-C30 for disease-specific HRQoL)
Co-primary endpoints	The following co-primary endpoint subgroup analyses were analysed for OS and PFS: ethnicity; gender; age; ECOG status; alkaline phosphatase status; LDH status; prior systemic therapy; largest metastatic lesion recorded at baseline; region; investigator's choice of chemotherapy (ipilimumab, dacarbazine and pembrolizumab)
Abbreviations: C, cycle; D, day; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; IV, intravenous; HLA, human leukocyte antigen; LDH, lactic dehydrogenase; metastatic UM, metastatic uveal melanoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PFS2, time to second disease progression; RECIST, Response Evaluation Criteria in Solid Tumours	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Thursday 10 March 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	Dr Chris Hoyle
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Immunocore Ltd.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Mixed therapy (IC) as comparator precludes separate evaluation of tebentafusp versus each comparator *Section 2.3 and 3.2*	Yes	In the response to the clarification questions, a breakdown of the clinical effectiveness results for each therapy in the IC arm were provided. The results included the median OS & PFS, 12-month OS & PFS and respective Hazard Ratios (HR) for each therapy (Section B4, Table 3 & Table 4, pages 10-11). While we agree that it would be desirable to have access to evidence regarding the comparative cost-effectiveness of tebentafusp versus each IC regimen separately, it would be both inappropriate and potentially misleading to attempt this for dacarbazine or ipilimumab. There are several related reasons why this is the case: • Patient numbers: During the technical engagement meeting the ERG argued that there was value in having the results of subgroup analyses regardless of the degree of uncertainty. By using the clinical data restricted to dacarbazine or ipilimumab it may be possible to obtain the necessary model inputs to generate cost and QALY outputs. However, the patient and event numbers are small: 16 patients received ipilimumab (11 events) and 7 patients received dacarbazine (7 events), from the August 2021 data cut. Consequently, the difference of one or two events occurring will likely yield

		dramatically different ICERs with high uncertainty. Therefore, we consider that provided ICERs based on such subgroup analyses may only either be irrelevant to the appraisal committee or misleading if the uncertainty of such estimates were not adequately emphasised. Furthermore, sub-group analysis of OS showed that tebentafusp was superior to all treatments used in the IC arm. • There is also the issue of potential differences in the characteristics of patients that receive each separate IC regimen. Patients were randomised to either tebentafusp or IC arms and the benefits of randomisation in clinical studies thus apply. However, randomisation was not stratified between the different IC regimens, therefore, we cannot expect baseline prognostic factors to be balanced on average. This is true of all such unstratified subgroup analyses, but the impact of this could be extreme in this case where such small samples are involved. • Modelling results for dacarbazine and ipilimumab separately would also not reflect UK clinical practice. Clinical opinion indicates that dacarbazine and ipilimumab are now rarely used and that pembrolizumab is the comparator of interest (see for example, [NICE. Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]. NHS England and NHS Improvement budget impact analysis submission. 2021]). The data in the IC arm of the trial is primarily driven by pembrolizumab. Figure 1 below provides an overlay of the IC and separated pembrolizumab data using the August 2021 dataset. As expected, given that most patients are on pembrolizumab in the IC arm, the Kaplan Maier (KM) curves and extrapolation model for pembrolizumab and the IC overlap. In terms of the ICER, it is increases slightly [redacted] compared to [redacted] in the base case. Figure 1: KM curves for IC and pembrolizumab fitted with standard parametric models

		[redacted]

Lack of comparison to nivolumab monotherapy *Section 2.3*	No	This issue was addressed in the call with ERG. The company re-stated that nivolumab monotherapy is not used in clinical practice in the UK. Noting the scoping workshop stated: • Systemic treatments used in clinical practice vary, in the absence of alternatives those with a broad license for melanoma are used (pembrolizumab, ipilimumab, nivolumab [**with** ipilimumab], systemic chemotherapy [dacarbazine]) • None have shown any survival benefit in randomised trials in patients with metastatic uveal melanoma • The drug class and mode-of-action of nivolumab and pembrolizumab are the same: both are PD-1 inhibitors
Frequency of adverse events in tebentafusp *Section 3.2.4*	No	(ERG report, Table 1.4, key issue 3) The ERG state that "Adverse events have been included in the economic model". Hence the cost-effectiveness results adequately reflect the balance of risks and benefits of tebentafusp.
Model structure – Use of a partitioned survival model *Section 4.2.2*	No	• We acknowledge that the assumption of structural independence of endpoints is a limitation of partitioned survival models. However, as noted in NICE DSU TSD 19, "in the context of a within-trial analysis or a case in which data have been fully observed, PSM and state transition modelling approaches are expected to produce similar results if modelling and fitting have been done appropriately, as relationships between endpoints are reflected within the data.". Therefore, we consider that this problem is mitigated by the relative maturity of the trial data. • We consider that using a PSM or state-transition model would produce very similar results in the control arm, given that a high proportion of the OS and PFS events have been observed over the trial period. o Most of the progression events have been observed over the trial period with PFS reaching [redacted] in the IC arm with the August 2021 data cut-off. Hence, there is limited uncertainty in the extrapolation of the PFS endpoint.

		○ In the IC arm, OS reached 10% at the end of the follow-up period with the October 2020 data cut-off (DCO), and [redacted] with the August 2021 DCO although this is not adjusted for the patients who crossed over from IC to tebentafusp after the October 2020 DCO. Additionally, we compared the extrapolation models with data from the literature (Rantala et al., 2019) and validated the choice of model with clinical experts. There is no significant uncertainty in the extrapolation of OS in the IC arm. • In the tebentafusp arm, PFS reached less than [redacted] at the end of the trial follow-up period with the August 2021 DCO. Hence, there is no significant uncertainty in the extrapolation of this endpoint. • We acknowledge that there is uncertainty in the extrapolation of OS in the tebentafusp arm. However, we note that the treatment effect size is larger for OS than for PFS, suggesting that PFS, defined as disease progression per RECIST v1.1 criteria, may be poorly correlated with OS. This has been documented for other types of immunotherapies like the checkpoint inhibitors, nivolumab and pembrolizumab (Gyawali and Prasad, 2017). Hence, the assumption of structural independence is likely to be less of a concern in this context. • Additionally, partitioned survival modelling is the most commonly used decision modelling approach used in NICE appraisals of advanced or metastatic cancers (Woods et al., 2017). • We note that in TA638 (July 2020), the ERG (Kleijnen Systematic Reviews – same ERG as in this current appraisal) made similar comments related to the limitations of PSM and questioned whether alternative modelling methods had been considered. The company replied that the main concern raised in NICE DSU TSD 19 was the assumption of structural independence between endpoints, which was mitigated by the relative maturity of the data. Consistent with TSD19, the ERG agreed with the Company that the partitioned survival model is the mainstay of cancer modelling.

The use of the treatment mix in the IC arm of the IMCgp100-202 study as single comparator and not including nivolumab as comparator *Section 4.2.4*	No	The ERG requested: "Scenario analyses exploring the effects on the ICER of each treatment option separately, also including treatment specific OS, PFS and TTD." However, we disagree that there is value in pursing this approach. The justification for this is that which is given in response to key issue 1. The question of including nivolumab monotherapy as a comparator was resolved in the technical engagement call (see response to Section 2.3 - Issue: Lack of comparison to nivolumab monotherapy).
Long-term PFS and OS extrapolations *Section 4.2.6*	No	Progression-free survival: • As detailed in response to issue 4, most of the progression events have been observed over the trial period with PD reaching [redacted] in the IC arm and [redacted] in the tebentafusp arm at the end of the trial follow-up period (August 2021 DCO). Hence, there is minimal uncertainty in the extrapolation of the PFS endpoint in either arm of the trial given the maturity of the data. • Six standard parametric models have been fitted (exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma) and have been implemented in the model to allow assessment of the choice of distribution on the model results. The choice of extrapolation model was made based on the visual and statistical fit to the trial data and clinical expert's opinion. Scenario analyses using different distributions were presented in the company submission and resulted in less than a 1% change in the ICER. Overall survival • A large proportion of events were observed in the investigator's choice arm, with OS reaching [redacted] at the end of the follow-up with the August 2021 DCO) (although this does not account for the patients crossing over from IC to tebentafusp). To support the choice of distribution the fitted extrapolation models were discussed with clinical experts and compared to historical data (Rantala et al., 2019), to which the trial data showed good overlap. Therefore, there is relatively low uncertainty in extrapolation of OS for the IC arm.

		• We acknowledge that there is uncertainty in the long-term extrapolation of OS in the tebentafusp arm. The plausibility of different extrapolation model fits was discussed with clinicians in the absence of an external data source for insight on the most appropriate model fit. The uncertainty and impact on the results was explored using a range of parametric models (e.g., DSA, PSA, scenarios).
Not primarily using the IMCgp100-202 trial EQ-5D data and time-to-death HRQoL approach being inconsistent with common modelling practices *Section 4.2.8*	No	• Based on clinical experts' opinion, disease progression assessed by RECIST v1.1 criteria is not a good marker for decline in quality of life (QoL) in this patient population. Clinicians have observed that patients maintain their quality of life until about 3-6 months before death when symptoms appear and impact on their QoL. We observed limited change in the EQ-5D utility value between baseline and end of treatment in the IMCgp100-202 Phase III trial, and similar for EORTC QLQ-C30 data, which supports this case. • Therefore, applying quality of life data based on time to death is more aligned with the clinical deterioration of patients, rather than by pre- and post-progression using PFS data. • The data presented is an early read out of the clinical trial (first interim analysis October 2021), EQ-5D data was limited and so published EQ-5D utilities were used. We used data from TA366 in advanced cutaneious melanoma, which was considered an acceptable proxy by clinical experts. • The baseline utility from the IMCgp100-202 clinical trial was used and combined with the published TTD utility from TA366, to derive utilities for the different times to death categories as a way of mitigating the use of utility data from a different patient population. • This approach has previously been accepted, for example in TA531 (July 2018) and TA650 (September 2020).
One-off application of BSC costs *Section 4.2.9*	No	The approach to accounting for the costs of BSC for patients with PD recommended by the ERG is to apply the same fixed cost to each month that patients are in PD, irrespective of the treatment arm. This assumes that the rate of

		healthcare consumption is equal regardless of whether patients were previously treated with tebentafusp or IC after disease progression, as captured by specific treatments used after progression in the clinical study and included in the model. The application of a one-off cost equivalent to four months of healthcare resource use (taken from (McKendrick et al., 2016)) makes the alternative assumption that each patient uses the same resource in PD regardless of the duration of time spent in this health state. This implies that the rate of healthcare resource utilisation is inversely proportional to the time spent in this state, so that although patients entering PD from tebentafusp may spend longer in PD this reflects the fact that their disease is less severe. This logic is also underpinning the time-to-death health state utilities approach and the application of end-of-life costs at the point of death to account for the decline in health status then. In the cancer treatment more broadly, there are studies that examine the variation in healthcare resource use. A trend of reduced monthly healthcare costs with delayed progression or increased follow-up has been reported, for example, in Reyes et al. (2019) and Ray et al. (2013) A further reason that we would expect the rate of healthcare resource use to be lower for patients in the tebentafusp arm is that 43.3% of patients continued to receive tebentafusp for some time following progression. As reported in the literature, variation in post-progression resource use and the use of tebentafusp post-progression, we do not consider that the ERG's assumption that PD following tebentafusp and PD following IC are equivalent in terms of resource use to be reasonable. We argue that, although evidence backing either assumption is limited, the approach of applying a fixed cost independent of time in PD is likely to be the most reasonable approach to handling BSC costs.
Percentage of patients using each IC treatment *Section 4.2.9*	No	• The mix of regimens and proportion of usage of these in the IC arm of the IMCgp100-202 trial were assessed by clinical experts and considered representative of UK clinical practice. • In the NHSE budget impact assessment the following was noted:

		"In practice dacarbazine is now rarely used in malignant melanoma so should not be used as a comparator in the BIT, similarly single agent ipilimumab is rarely used as ipilimumab is now preferred to be given in combination with nivolumab. This mirrors the trial in which the majority of patients (82%) received pembrolizumab, (13%) received ipilimumab and (6%) received dacarbazine." • Therefore, modelling the treatment mix as a single comparator, with the costs weighted by the proportion of treatments is appropriate to the decision problem. • Additionally, the proportion of patients on each of the regimen in the IC arm can be varied in the model with proportional adjustment of the treatment costs. Scenarios of this have been provided in the response to the clarification questions. • Incorporating treatment specific OS, PFS and TTD data is not appropriate. As explained in the responses to issue 1 and issue 5, the number of patients on ipilimumab (n=16) and dacarbazine (n=7), and the number of events are very low, which could lead to unreliable estimates of OS, PFS, and TTD and high level of uncertainty, and misleading model results.
Proportion of (PF)LYs accumulated beyond the observed data *Section 5.1*	No	As detailed in response to issue 6, most of the progression events were observed over the trial follow-up period in both arms, with progression reaching [redacted] in the tebentafusp arm and [redacted] in the IC arm with the August 2021 DCO. Hence, the PFS data is mature and PFLYs accumulated beyond the observed data is a small proportion of the total for both the tebentafusp arm and IC arm.
Probabilistic analyses for alternative OS, PFS and TTD assumptions *Section 5.3*	Yes	The model has been updated to allow running PSA for any combination of OS, PFS and TTD extrapolation models.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Addendum 1: Technical engagement response update of Document B3

Company evidence submission

4th May 2022

File name	Version	Contains confidential information	Date
NICE_ID1441_ Adden1_Technical engagement response update B3 040522 redacted	**V 1.2**	**Yes**	**4th May 2022**

Contents

Tables and figures 3
Summary 4
Overall Survival 5
B.3 Cost effectiveness 19
B.4 References 31
B.5 Appendices 32
Appendix J: Clinical outcomes and disaggregated results from the model 32
Appendix K: Checklist of confidential information 33
Appendix L: Overall survival plots 34

Tables and figures

Table 1 Summary of Baseline Covariates by Survival Status in Tebentafusp treated Subjects 8
Table 2. Proportion of usage of the different regimens in the IC arm 10
Table 3. Treatment duration by cohort based on enrolment cut-offs, IMCgp100-202 12
Table 4. Proportion of patients on treatment modelled vs. observed 12
Table 5. Dose interruptions and reductions – summary (Safety Analysis Set) 15
Table 6. Subsequent treatment usage 17
Table 7. Model updates 18
Table 8. Base-case results 20
Table 9. Results of the base-case PSA 22
Table 10. Results of the univariate sensitivity analysis 24
Table 11 Results of scenario analyses of alternative methods of extrapolating PFS 25
Table 12. Results of scenario analyses of alternative methods of extrapolating TTD 26
Table 13. Results of scenario analyses using alternative parametric survival models 27
Table 14. Results of scenario analyses using patients cure proportions for survival 28
Table 15. Results of scenario analysis on compliance 29
Table 16. Scenario analysis subgroup tumour ≤30mm 30
Table 17. Summary of QALY gain by health state 32
Table 18. Summary of predicted resource use by category of cost 33

Figure 1 Kaplan Meier curve of overall survival for study IMCgp100-202 from February 2022 data sweep 6
Figure 2 Overlay of KM curve (February 2022 DCO) and Log-normal and spline models (August 2021 DCO) 7
Figure 3 Prespecified Subgroup Analysis of Overall Survival. Shown are hazard ratios and 95% confidence intervals for overall survival in prespecified subgroups of patients, according to various baseline characteristics (Nathan et al. 2021) 8
Figure 4. Study IMCgp100-102: IMCgp100 Overall survival from the different data cut-offs - All patients (N=146) 10
Figure 5. Kaplan Meier curve and exponential model (August 2021 DCO) 11
Figure 6. Kaplan Meier curve for time to treatment discontinuation IMCgp100-202 (October 2020 DCO) 13
Figure 7. Cost-effectiveness plane – incremental costs vs. incremental QALYs 22
Figure 8. Cost-effectiveness acceptability curve for willingness-to-pay threshold 23
Figure 9. Tornado diagram 24
Figure 10. Overlay of KM curve (February 2022 DCO) and parametric survival models (August 2021 DCO) 34

NICE ID441 ADDENDUM

Summary

An update to the simple discount ([redacted]) on the list price of tebentafusp has been submitted to PASLU. The cost per QALY of tebentafusp with the company base case is £44,050 per QALY.

According to the NHSE/I BIA, the total drug costs for tebentafusp with the updated PAS are [redacted] at year 3 when uptake reaches 50% and are below the budget impact threshold.

The addendum comprises updates for:

- PAS update
- OS update
- Model updates
    - Proportion of usage of the comparators
    - Duration of treatment
    - Tebentafusp compliance
    - Cost of administration
    - Usage of subsequent therapies
    - Technical summary of model updates
- Updated Cost-effectiveness results (section B.3 of the submission dossier)

Overall Survival

Study IMCgp100-202

An updated survival data cut is provided from February 2022 (Figure 1). The modelled overall survival (OS) is overlaid with the KM plot from this most recent data cut, including 95%CI (Figure 2).

The company's base case estimation of OS uses the 3-knot spline. This model provides a good fit prior to 30 months. Between 30 and 48 months of the observed KM data, the 3-knot spline continues to fit within the 95%CI. Although the 3-knot spline model separates from the KM data, it is the company's view that the baseline characteristics of patients alive at the time of the survival data cut (Table 1, FEB-2022) favour a longer survival and an 'elongation' of the KM plot. The evidence for the likely 'elongation' of the KM plot is supported by:

- the prespecified study sub-group analysis of OS (Figure 3, Nathan et al., 2021) *and*
- the post-hoc supplementary analysis of patients remaining alive according to the prespecified sub-groups for analysis of OS

Sub-group analysis of OS, ALP<=ULN and LDH <=ULN, ECOG=0, Age=<65 and liver size / largest metastatic lesion <3 cm shows association with an improvement of survival outcome (i.e. lower HR for OS). This is particularly the case for ALP, LDH and largest tumour size < 3 cm (Figure 3).[1]

Analysis of the percentage of patients who died and who, therefore, inform the KM plot indicate that the percentage of patients with ALP<=ULN, LDH <=ULN, ECOG=0 and tumour size <3 cm is higher than the corresponding groups of patients who are alive and have survived >=30 months or <30 months following the start of treatment with tebentafusp. For example, the percentage of patients with LDH <=ULN who are dead is [redacted] % (Table 1, highlighted) whereas in the two groups that are alive, the percentages are [redacted] % and [redacted] % for the groups >=30 months or <30 months,

[1] ALP: Alkaline phosphatase, ULM: Upper limit of normal, LDH: lactate dehydrogenase, ECOG: Eastern Cooperative Oncology Group

respectively. A similar pattern is seen for ALP<=ULN, ECOG=0 and tumour size <3 cm and indicates that as the OS data matures, the KM plot will elongate, informing an improved estimation of the proportion of patients who will experience longer-term survival with tebentafusp and approximate to the 3-knot spline.

Figure 1 Kaplan Meier curve of overall survival for study IMCgp100-202 from a February 2022 data sweep

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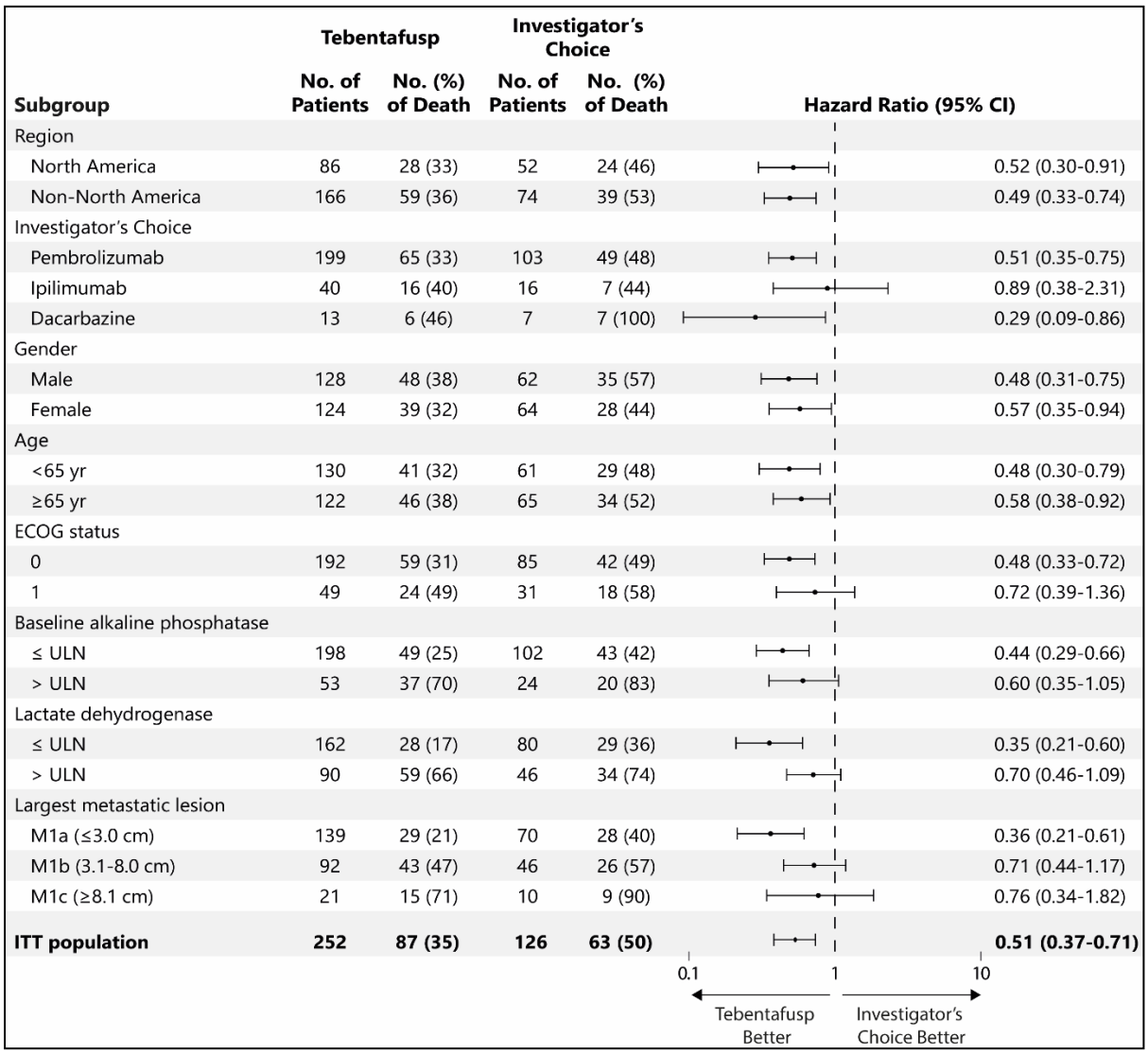
IMCgp100 – tebentafusp

Figure 2 Overlay of KM curve (February 2022 DCO) and Log-normal and spline models (August 2021 DCO)

Figure 3 Prespecified Subgroup Analysis of Overall Survival. Shown are hazard ratios and 95% confidence intervals for overall survival in prespecified subgroups of patients, according to various baseline characteristics (Nathan et al., 2021)



Subgroup	Tebentafusp No. of Patients	Tebentafusp No. (%) of Death	Investigator's Choice No. of Patients	Investigator's Choice 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)
ECOG 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)**

Table 1 Summary of Baseline Covariates by Survival Status in Tebentafusp treated Subjects

Safety Population. Output produced 05APR2022 10:32

		ALIVE (censored)		DEAD
Baseline Characteristics	Baseline Characteristics Description	OS >=30 months (N=33)	OS <30 months (N=56)	Deaths (N=156)
ALP	ALP <= ULN	[redacted]	[redacted]	[redacted]

		ALIVE (censored)		DEAD
Baseline Characteristics	**Baseline Characteristics Description**	**OS >=30 months (N=33)**	**OS <30 months (N=56)**	**Deaths (N=156)**
	ALP > ULN	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]
Age Group	<65	[redacted]	[redacted]	[redacted]
	>=65	[redacted]	[redacted]	[redacted]
ECOG	0	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]
Gender	F	[redacted]	[redacted]	[redacted]
	M	[redacted]	[redacted]	[redacted]
LDH	LDH =< ULN 250 U/L (n, %)	[redacted]	[redacted]	[redacted]
	LDH > ULN 250 U/L (n, %)	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]
Liver Size	< 3 cm	[redacted]	[redacted]	[redacted]
	>= 3 cm	[redacted]	[redacted]	[redacted]
	No liver lesion	[redacted]	[redacted]	[redacted]

IMCgp100-102

In study IMCgp100-102 the data available provides a longer follow up time for patients on tebentafusp treatment. There was elongation of the KM with a survival probability approximate to ~20% and ~10% at 36 months and 60 months respectively for this cohort, who received tebentafusp as a second line therapy (Figure 4).

Figure 4. Study IMCgp100-102: IMCgp100 Overall survival from the different data cut-offs - All patients (N=146)

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Model updates

Comparators

The proportion of patient on dacarbazine has been set to zero. Consistent with feedback from the NICE Scoping and Decision-problem meetings, dacarbazine is not used in England or the UK and it is inappropriate to include it as a comparator. The percentage of patients who were treated with dacarbazine were assumed to be treated with pembrolizumab (Table 2), as it is the most commonly used treatment regimen for the patient population in the UK. The comparator costs were adjusted accordingly.

Table 2. Proportion of usage of the different regimens in the IC arm

Investigator's choice	Prior	Updated

% on pembrolizumab	81.7%	87.3%
% on ipilimumab	12.7%	12.7%
% on dacarbazine	5.6%	0.0%

Treatment duration with tebentafusp

In the original model base-case, there was an 18-month cap on the treatment costs of tebentafusp. This feature was removed following feedback from NHSE. This change required some adjustment to the modelling of the treatment duration of tebentafusp.

The exponential distribution is applied instead of the generalized gamma in both arms, with a switch from the KM curve at 15% of patients at risk in the tebentafusp arm and 25% in the IC arm. Both provide reasonable fit over the trial period; however, the exponential provides a more plausible long-term extrapolation (year 3: 6% exponential vs. 8% generalized gamma; year 5: 1% exponential vs. 3% generalized gamma). Additionally, the exponential better aligns with the average observed duration of treatment and percentage of patients informing analysis (i.e. %pts at risk).

Figure 5. Kaplan Meier curve and exponential model (August 2021 DCO)

The mean duration of treatment in the model with an exponential distribution is 10.2 months (309 days). This is consistent with the observed duration of treatment (314 days ~10.3 months) in the IMCgp100-202 study, for the cohort of patients who were randomised prior to December 2018 and hence have the longest follow-up (Table 3). The modelled duration of treatment for study IMCgp100-202 is also consistent with the published duration of treatment for study IMCgp100-102 with longer follow up and mean duration of treatment of 9.5 months (Sacco J et al., 2021).

Table 3. Treatment duration by cohort based on enrolment cut-offs, IMCgp100-202

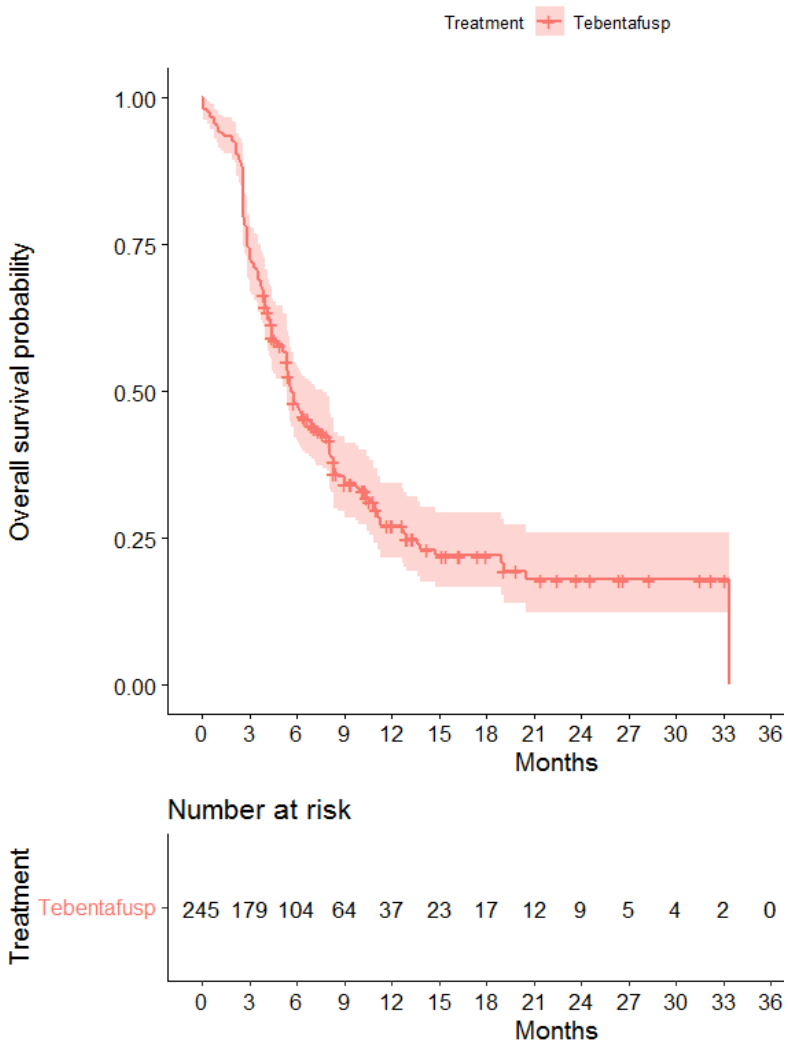
Obs	cutoff	n	mean	sd	max	q3	median	q1	min	n_ongoing	percent_ongoing
1	None (all patients)	245	219.547	191.612	1016	274	163	87	1	[redacted]	[redacted]
2	Randomised by end Dec 2019	179	243.352	215.391	1016	334	165	85	1	[redacted]	[redacted]
3	Randomised by end June 2019	114	275.114	244.892	1016	344	176	86	1	[redacted]	[redacted]
4	Randomised by end Dec 2018	61	313.984	289.655	1016	386	197	106	1	[redacted]	[redacted]

Data on file: datacut Study IMCgp100-202: Summary statistics for time on IMCgp100 treatment by time of randomisation - Safety population. output=f:\Biometrics\IMCgp100\imcgp100-202\2021-PA\output\a_timeontrt.rtf

Table 4. Proportion of patients on treatment modelled vs. observed

Model		Observed (Study-202)
Time (months)	Tebentafusp	Tebentafusp (%, [#risk])
12	26.2%	27.2% [37]
18	16.4%	22.1% [17]
24	9.5%	18% [9]
36 (3 years)	3.2%	0% [0]

Figure 6. Kaplan Meier curve for time to treatment discontinuation IMCgp100-202 (October 2020 DCO)



Tebentafusp stopping rule

Tebentafusp is administered on a weekly basis. Therefore, it is not expected that patients would be on treatment for longer than 24 months. It is anticipated that the clinical benefit will extend beyond the duration of treatment. This approach is consistent with the 2-year stopping rule used in a NICE appraisal of Nivolumab (TA655). It was noted that the clinical trial did not specify a stopping rule. The committee concluded that it was plausible that a survival benefit from nivolumab would continue after it is stopped at 2-years and that there was no evidence to show

that continuing for longer gave additional benefit. Therefore, the NICE committee concluded that a 2-year stopping rule was appropriate.

The company adopted the 24-month stopping rule consistent with the previous assessment of the immunotherapy (TA655). A treatment discontinuation rule is applied at 24 months in the model, time point beyond which no drug acquisition nor administration costs are accrued in the tebentafusp arm.

Tebentafusp compliance

Tebentafusp is administered weekly as an infusion. Compliance is unlikely to be 100% over the modelled time horizon, including during the 24-month proposed above. In study IMCgp100-202 42.4% (104 out of 245) of patients in the tebentafusp arm required a dose interruption (Table 5, highlighted). Of the 104 patients with an interruption, there were a total of 222 interruptions with a mean duration of 22.2 days (Table 5, highlighted).

Duration of treatment based on the date of first dose to date of discontinuation (i.e. time-to-discontinuation, TTD) does not account for missed doses or interruptions. The company adopted a compliance of less than 100% to reflect the interruptions seen in study IMCgp100-202 and adopted 95% to reflect approximately two 1 week breaks per year. The total combined costs of tebentafusp plus administration are weighted to account for the number of interruptions / missed doses for a compliance of 95%. Sensitivity analyses for compliance of 90% and 100% are provided (Table 15).

Table 5. Dose interruptions and reductions – summary (Safety Analysis Set)

		IMCgp100 (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	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 [1]		222		15	
Reason for interruption at any time	Missed Visit	89	(40.1)	2	(13.3)
	Adverse Event	50	(22.5)	12	(80.0)
	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

	IMCgp100 (N=245)		Investigator's Choice (N=111)	
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: Listing 16.2.5, Output: t-14-03-01-00-02-ex-dose.

Program: t03010ex0dose.sas Cutoff Date: 13OCT2020 05MAR2021 02:12

IC treatment duration

The exponential distribution was applied instead of the generalized gamma, to align with the modelling approach taken in the tebentafusp arm. We note that at 24 months, all patients have discontinued treatment based on the extrapolation (0.4%).

Administration costs

Administration costs were updated to align with the unit costs used in the budget assessment conducted by NHSE. The company adopted a single administration fee of £165 per infusion. The inpatient costs of the first 3 doses were captured within the costs of the overnight stay and hence the lower infusion cost of £165 per administration would avoid the risk of double-counting of extended infusions for the first cycle (i.e. 3 doses).

Patient access scheme

An updated PAS of [redacted] has been submitted to NHSE&I / PASLU and the model has been updated to reflect this new PAS. The list price of tebentafusp is [redacted] and [redacted] with PAS.

Subsequent therapies

The proportion of usage of the different regimens following discontinuation of the primary treatment have been updated to align with clinical practice in the UK. According to clinical input during the NICE Decision Problem meeting (Monday 16th August 2021), ipilimumab+nivolumab combination therapy is rarely used, therefore, the proportion of patients receiving the treatment after either tebentafusp or the IC was reduced to 10%. The percentage of patients assumed to receive pembrolizumab after tebentafusp was adjusted accordingly. For the IC arm, since the vast majority (26%) of patients received pembrolizumab, the percentage of patients assumed to receive ipilimumab as the subsequent treatment was adjusted (Table 6).

Table 6. Subsequent treatment usage

	Prior company case		Updated company case	
	Tebentafusp	IC	Tebentafusp	IC

% of usage of ipilimumab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
% of usage of ipilimumab (mono therapy)	[redacted]	[redacted]	[redacted]	[redacted]
% of usage of pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
% of usage of nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Total	100%	100%	100%	100%

Technical summary of model updates

Table 7 presented the changes which have been made in the model front-end input sheets.

Table 7. Model updates

Cell	Change	Rationale
Model Settings		
E84	87.30%	Alignment with clinical practice (dacarbazine not used in the UK), % increased to achieve a sum of 100%
E86	0%	Alignment with clinical practice, dacarbazine not used in the UK
E99	25%	% at risk by exponential
E104	24 months	Discontinuation rule to align with clinical expectation given weekly dose schedule
E106	95%	Compliance to align with clinical expectation given weekly dose schedule
Cost data		
D81	£165	Consistent with NHSEI BIM
D82	£165	Consistent with NHSEI BIM
D83	£165	Consistent with NHSEI BIM
L36	[redacted]%	Updated PAS submitted to PASLU
D111	10%	Alignment with clinical practice, ipi+nivo not used much in the UK
D112	10%	Alignment with clinical practice, pembrolizumab used more in UK
D113	68%	Alignment with clinical practice, pembrolizumab used more in UK
D114	12%	Alignment with clinical practice, pembrolizumab used more in UK
E111	10%	Alignment with clinical practice, ipi+nivo not used much in the UK
E112	43%	Alignment with clinical practice, pembrolizumab used more in UK
E113	42%	Alignment with clinical practice, pembrolizumab used more in UK
E114	5%	Alignment with clinical practice, pembrolizumab used more in UK

B.3 Cost effectiveness

B.3.7 Base-case results

Base-case results of the economic analysis for a 38-year time horizon and with a discount rate of 3.5% for both costs and outcomes, are presented in Table 8.

With the updated Company base case modelled over a lifetime horizon, tebentafusp provides a LYG of [redacted] years ([redacted] vs. [redacted]), and a QALY gain of [redacted] QALYs ([redacted]). Both the improvement in life expectancy and in HRQoL of patients with metastatic UM is considered substantial. This improvement in modelled outcomes of patients with metastatic UM is driven mainly by the proportion of patients experiencing longer survival compared with the comparator and is consistent with he published results of study IMCgp100-202.

Applying the PAS price of [redacted] per tebentafusp vial, the Company's base-case deterministic ICER was £44,050 per QALY (Table 8) and the PSA ICER was £42,176 per QALY (Table 9).

Table 8. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Tebentafusp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,050
Comparator	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to describe how uncertainty around input parameters is translated into uncertainty around the estimated outputs of the model. Hence, suitable probability distributions were assigned to model parameters to characterise uncertainty around their mean values and have been presented in section B3 of the company submission (November 2021). Values were sampled from the corresponding parameter distributions and were assigned to each parameter in an iterative process. This process was repeated for 10,000 times, and the results of each of these iterations were used to determine the distribution of incremental costs and incremental QALYs.

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

The results of the PSA were presented within the cost-effectiveness plane in the form of a joint distribution of costs and QALYs, along with a mean value of the ICER and a 95% confidence interval ellipse (Figure 7). It is apparent from that the largest spread is across the X axis of the scatter plot showing that the highest uncertainty is associated with the health benefits. The probability that each treatment is cost-effective, resulting in the highest net monetary benefit, is presented over different values of a cost-effectiveness threshold in the form of a cost-effectiveness acceptability curve (CEAC) in Figure 8.

Table 9 presents the mean incremental costs and QALYs as well as the ICER as estimated in the base-case PSA.

Table 9. Results of the base-case PSA

Technologies	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)
Tebentafusp	[redacted]	[redacted]	£42,176
Control	-	-	-
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years			

Figure 7. Cost-effectiveness plane – incremental costs vs. incremental QALYs

[redacted]

Figure 8. Cost-effectiveness acceptability curve for willingness-to-pay threshold

Deterministic sensitivity analysis

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.

Upper and lower values of model parameters were determined by their 95% CIs or ±1.96 standard errors, depending on format of source data reporting. When no information was available regarding a parameter's uncertainty then the variation around the mean value was modelled by varying the parameter by 25% or 10% of its mean value.

Figure 9 presents a tornado diagram indicating the 10 parameters with the greatest influence on the ICER in a descending order. Table 10 presents the ICER as a result of using an upper and lower estimate for these parameters.

We note that the parameter that has the most impact on the results is the age of a patient as it determines the time frame over which patients may derive benefit. The second parameter impacting the results is the baseline utility value as this is applied to patients until they are one year from death. The third parameter is the cost of administration of chemotherapy at subsequent attendance, related to the duration of

treatment of Tebentafusp which is administered on a weekly basis. All other parameters have very limited impact on the results.

Figure 9. Tornado diagram

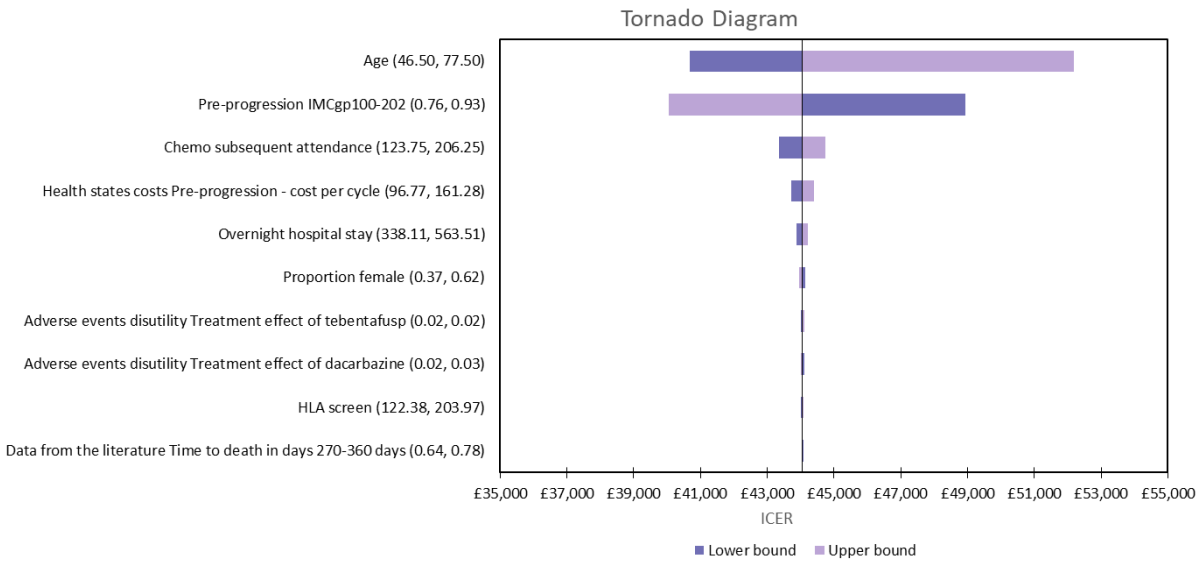


Table 10. Results of the univariate sensitivity analysis

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Age (46.50, 77.50)	£40,070	£52,274
Pre-progression IMCgp100-202 (0.76, 0.93)	£48,938	£40,050
Chemo subsequent attendance (123.75, 206.25)	£43,348	£44,752
Health states costs Pre-progression - cost per cycle (96.77, 161.28)	£43,708	£44,392
Overnight hospital stay (338.11, 563.51)	£43,881	£44,219
Proportion female (0.37, 0.62)	£44,136	£43,962
Adverse events disutility Treatment effect of tebentafusp (0.02, 0.02)	£44,000	£44,100
Adverse events disutility Treatment effect of dacarbazine (0.02, 0.03)	£44,099	£44,001
HLA screen (122.38, 203.97)	£44,006	£44,094
Data from the literature Time to death in days 270-360 days (0.64, 0.78)	£44,069	£44,031

Scenario analysis

The impact of both structural assumptions and choice of parameter values were further explored through a number of scenario analyses. The scenarios that were evaluated are outlined below.

Choice of method of extrapolation of PFS

We explored the choice of the method for the extrapolation of the PFS. We tested the log-logistic and lognormal curves, which were second best choice for the PFS curve as detailed in section B.3.3.1.2. We also tested the impact of the time-point at which there is a switch from the KM curves to the parametric curve, testing 10% of patients at risk in place of 15% of patients at risk in the base-case. We note that the impact on the results is very limited due to the difference in the costs between the two arms being driven by the TTD curves, and the difference in LY/QALYs being driven by the OS curve.

Table 11 Results of scenario analyses of alternative methods of extrapolating PFS

Scenario	ICER (£/QALY)	% change
Base-case KM + Generalised gamma	£44,050	NA
KM + log-logistic	£43,462	-1.34%
KM + log-normal	£43,366	-1.55%
Generalised gamma	£43,961	-0.20%
Log-logistic	£43,394	-1.49%
Log-normal	£43,393	-1.49%
Base-case (KM + generalised gamma; 10% at risk)	£44,055	0.01%

Choice of method of extrapolation of TTD

We explored the choice of the method for the extrapolation of the TTD. We tested the log-logistic, exponential and Weibull curves, which were second best choice for the TTD curve as detailed in section B.3.3.1.2. We also tested the impact of the time-point at which there is a switch from the KM curves to the parametric curve, testing 10% of patients at risk in place of 15% of patients at risk in the base-case.

We note that the difference in the ICER between the hybrid approach and using the parametric curves only is small. The choice of curve has a limited impact on the given the 24-month discontinuation rule.

Table 12. Results of scenario analyses of alternative methods of extrapolating TTD

Scenario	ICER (£/QALY)	% change
Base-case KM + Exponential	£44,050	NA
KM + log-logistic	£43,451	-1.36%
KM + Generalised gamma	£44,015	-0.08%
KM + Weibull	£43,839	-0.48%
Exponential	£48,359	9.78%
Log-logistic	£44,355	0.69%
Generalised gamma	£47,097	6.92%
Weibull	£47,969	8.90%
Base-case (KM + Exponential; 10% at risk)	£46,676	5.96%
Base-case (KM + Exponential; 15% at risk)	£46,319	5.15%
Base-case (KM + Exponential; 25% at risk)	£44,889	1.90%

Source of utility data

We conducted a scenario analysis using the utility values derived from the EQ-5D data collected in the IMCgp100-202 trial. The data is applied based on TTD rather than disease status as detailed in section B.3.4. The ICER is £47,971 which is equivalent to an 8.90% increase compared to the base-case.

Choice of method of extrapolation of overall survival and data-cut-off

The incremental LYs and QALYs are driven by the OS curve in the tebentafusp arm, hence the importance of testing the impact of the chosen method on the results. This section presents the results of a series of scenario analyses testing alternative combinations of standard parametric functions for extrapolating overall survival. A total of nine parametric function combinations have been examined for the tebentafusp and control arm.

The August 2021 DCO was used in the base-case providing the longest follow-up and therefore the most information on the clinical effectiveness of tebentafusp. However, the control arm was not adjusted for treatment cross-over, and [redacted] compared to historical data as presented in section B.3.3. Therefore, the series of scenarios based on standard parametric curves are presented for both DCO, for comparison. The preferred model is the Weibull for the control arm, which is consistent with the historical data of first-line patients reported in the meta-analysis conducted by Rantala et al. (2019) We also tested generalised gamma and Gompertz which provided second best and reasonable fits. In the tebentafusp arm, we tested the log-logistic distribution for OS which was the best fitting standard parametric model and gave a clinically plausible long-term extrapolation based on clinical experts' opinion. Generalised gamma and log-normal are also reasonable fits and tested. All other parameters are as per the base-case analysis. The resulting ICERs and change from the base case are presented Table 13.

Table 13. Results of scenario analyses using alternative parametric survival models

Scenario (Parametric models)	August 2021 DCO		October 2020 DCO	
	ICER (£/QALY)	% change	ICER (£/QALY)	% change
Base-case (August 2021 DCO) Spline (tebentafusp) Weibull (comparator)	£44,050	NA	£44,050	NA
Log-logistic (tebentafusp) Weibull (comparator)	£77,800	76.62%	£65,873	49.54%
Log-logistic (tebentafusp) Gompertz (comparator)	£75,133	70.56%	£63,230	43.54%
Log-logistic (tebentafusp) Generalised Gamma (comparator)	£87,046	97.61%	£70,296	59.58%
Lognormal (tebentafusp) Weibull (comparator)	£75,241	70.81%	£59,663	35.44%
Lognormal (tebentafusp) Gompertz (comparator)	£72,745	65.14%	£57,485	30.50%
Lognormal (tebentafusp) Generalised gamma (comparator)	£83,870	90.40%	£63,282	43.66%
Generalised Gamma (tebentafusp) Weibull (comparator)	£121,991	176.94%	£101,210	129.76%
Generalised Gamma (tebentafusp)	£115,456	162.10%	£95,081	115.85%

Gompertz (comparator)				
Generalised Gamma (tebentafusp) Generalised Gamma (comparator)	£146,237	231.98%	£111,942	154.12%

There is evidence to suggest a trend towards long-term survival for a fraction of patients treated with tebentafusp. This effect has been incorporated in the model by applying the mortality rates for the general population to a fraction of the patients treated with tebentafusp after a certain time point (e.g., survival probability of [redacted] equivalent to about [redacted] months, a time-point where we observe [redacted] with the August 2021 DCO). The results of varying the proportion of patients who living with their cancer, revert to normal life expectancy, from 50-90% (i.e., 50% of the patients alive at the specified time-point are applied background mortality, whereas the other patients are applied the mortality rate from the parametric curve) are presented in Table 14. The initial survival phase was modelled using parametric models assuming a Weibull hazard function in both arms since this provided a good fit in the early phase.

Table 14. Results of scenario analyses using patients cure proportions for survival

Scenario (cure fraction)	August 2021 DCO		October 2020 DCO	
	ICER (£/QALY)	% change	ICER (£/QALY)	% change
50%	£45,255	2.74%	£42,458	-3.62%
60%	£39,408	-10.54%	£37,128	-15.71%
70%	£34,884	-20.81%	£32,974	-25.14%
80%	£31,281	-28.99%	£29,644	-32.70%
90%	£28,342	-35.66%	£26,917	-38.90%

Summary of sensitivity analyses results

Extensive sensitivity and scenario analyses were conducted to explore the robustness of model results subject to changes in parameter values, and to consider the impact of structural uncertainties and choice of parameter values.

The results of the sensitivity analyses focussing on the methods of extrapolating PFS indicate that the model results are not sensitive to the choice of modelling approach.

This is not surprising, since, up to the end of the clinical trial study period, PFS is modelled based on the KM curves. It is only beyond the study period that parametric survival models are applied in order to extrapolate for the remainder of the time horizon. The number of patients progression-free at the beginning of the extrapolation phase, however, is relatively small and there are then only a small number of possible events that can be impacted by the choice of modelling approach.

In a DSA, the parameters with the most significant impact on the results are the baseline utility value as this is applied to patients until one year from death, and the cost of administration of subsequent attendance, related to the treatment duration of tebentafusp.

The ICER is most sensitive to the choice of model for the extrapolation of the OS in the tebentafusp arm, as this drives the size of the incremental QALYs, with ICERs varying between £146,237 and £26,917 depending on the extrapolation method and DCO chosen. Results from the PSA show that there is a significant level of uncertainty associated with the model chosen in the base-case for the extrapolation of the OS in the tebentafusp arm. The uncertainty is likely driven by the low number of patients at risk at the tail of the KM curves. The incremental costs are driven by the acquisition cost of tebentafusp.

Compliance

A compliance of 95% is applied in the base-case to reflect the interruptions seen in study IMCgp100-202. Scenario analyses for 90% and 100% compliance are presented in Table 15.

Table 15. Results of scenario analysis on compliance

Scenario	ICER (£/QALY)	% change
Base-case (95% compliance	£44,050	NA
90% compliance	£40,837	-7.29%
100% compliance	£47,263	7.29%

B.3.9 Subgroup analysis

There is a growing body of evidence documenting the associating between tumour burden and response to immunotherapies, thus the particular interest in this population subgroup (Dall'Olio et al., 2021).

The subgroup analysis examines the impact of implementing survival models based on restricted subpopulations of patients with baseline largest metastatic tumour with a diameter of less than 30mm.

PFS and TTD are modelled using KM curves and generalised gamma for the extrapolation of the tail in both arms. We model the OS in the control arm using Weibull which provided the best fit and present results for the log-logistic and log-normal in the tebentafusp arm. The results for both DCO are presented in Table 16, along with the ICER for the ITT set (using the same distributions) for comparison. The results of this scenario analysis demonstrate that for the patient subgroup with smaller tumour sizes (<30mm) the cost-effectiveness ratio is improved. Greater surveillance to detect smaller tumours could result in improved cost-effectiveness and better patient outcomes.

Table 16. Scenario analysis subgroup tumour ≤30mm

Scenario: **Parametric model for OS**	**August 2021 DCO ICER (£/QALY)**			**October 2020 DCO ICER (£/QALY)**		
	ITT	**Subgroup**	**% change**	**ITT**	**Subgroup**	**% change**
Log-normal (tebentafusp)	£78,189	£60,962	-22.03%	£60,636	£40,133	-33.81%
Log-logistic (tebentafusp)	£80,845	£78,647	-2.72%	£66,947	£57,687	-13.83%

B.4 References

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B.5 Appendices

Appendix J: Clinical outcomes and disaggregated results from the model

J1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 17. Summary of QALY gain by health state

Health state	Tebentafusp	Comparator	Increment	Absolute increment	% absolute increment
Life years					
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs					
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 18. Summary of predicted resource use by category of cost

Item	Tebentafusp	Comparator	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	£8,465	£971	£7,494	£7,494	772%
Subsequent therapy	£19,506	£16,017	£3,489	£3,489	22%
Healthcare Resources - PFS	£5,586	£3,039	£2,547	£2,547	84%
Healthcare Resources - PPS	£4,568	£4,632	-£64	-£64	-1%
Healthcare Resources - Death	£9,478	£9,431	£47	£47	0%
AE	£168	£363	-£195	-£195	-54%
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: Tech, technology; treat, treatment; admin, administration; mon, monitoring					

Appendix K: Checklist of confidential information

An updated confidential information checklist will be submitted as a separate document.

Appendix L: Overall survival plots

Figure 10. Overlay of KM curve (February 2022 DCO) and parametric survival models (August 2021 DCO)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Addendum 1: Technical engagement response update of Document B3

Clarification questions on ADDENDUM 1

4th May 2022

File name	Version	Contains confidential information	Date
NICE_ID1441_ Addendum 1: Technical engagement response update B3 – Clarification questions_updated 040522 redacted	**V 1.1**	**Yes**	**4th May 2022**

Contents

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE....1
Single technology appraisal....1
Addendum 1: Technical engagement response update of Document B3....1
Clarification questions on ADDENDUM 1....1
Contents....2
Tables and figures....3
NICE ID441 ADDENDUM....4
Clarification questions....4
References....31

Tables and figures

Table 1. Summary of intended model changes 4
Table 2. Increment results of intended changes 5
Table 12. Base-case results 6
Table 13. Results of the base-case PSA 8
Table 14. Results of the univariate sensitivity analysis 10
Table 15 Results of scenario analyses of alternative methods of extrapolating PFS 11
Table 16. Results of scenario analyses of alternative methods of extrapolating TTD 12
Table 17. Results of scenario analyses using alternative parametric survival models 13
Table 18. Results of scenario analyses using patients cure proportions for survival 14
Table 19. Scenario analysis subgroup tumour ≤30mm 15
Table 3. Treatment duration by cohort based on enrolment cut-offs, IMCgp100-202 16
Table 4. Proportion of patients on treatment modelled vs. observed 17
Table 5. Model updates 20
Table 6. Summary of additional model changes 21
Table 7. Analysis results of additional changes 22
Table 8. Proportion of usage of the different regimens in the IC arm 23
Table 9. Dose interruptions and reductions – summary (Safety Analysis Set) 25
Table 10. Subsequent treatment usage 27
Table 11. Model updates 27

Figure 3. Cost-effectiveness plane – incremental costs vs. incremental QALYs 8
Figure 4. Cost-effectiveness acceptability curve for willingness-to-pay threshold 9
Figure 5. Tornado diagram 10
Figure 1. Kaplan Meier curve and exponential model (August 2021 DCO) 16
Figure 2. Kaplan Meier curve for time to treatment discontinuation IMCgp100-202 (October 2020 DCO) 17

NICE ID441 ADDENDUM

Implementing all the changes detailed in question 1, intended changes, the ICER is £58,676. Implementing additional changes, detailed in question 2, the ICER is £44,054.

Clarification questions

Question 1

Provide an overview (tabulated) and analyses with only the intended changes (i.e. PAS, TTD, adjustment of infusion costs to match the NHSE BIT analysis) + extensive justification for the choices made (including an updated version of Table 4.4 from the ERG report) + instructions how to reproduce this based on the initially submitted model (or the ERG model).

Provide incremental results per adjustment (allowing to examine the impact of all individual changes).

Response 1

Overview of model changes and analyses results

Table 1. Summary of intended model changes

Parameter	Original model	Change made	Rational
PAS	[redacted]	[redacted]	Updated PAS submitted to PASLU
TTD	Tebentafusp: KM + generalized gamma from 15% of patients at risk IC: KM + generalized	Tebentafusp: KM + exponential from 25% of patients at risk IC: KM + exponential from	Exponential providing a more plausible long-term extrapolation (now that the treatment

	gamma from 15% of patients at risk	15% of patients at risk	cap has been removed)
Infusion costs	First attendance (<60 min): £295.92 First attendance (>60 min): £329.75 Subsequent attendance: £363.37	First attendance (<60 min): £165 First attendance (>60 min): £165 Subsequent attendance: £165	Consistent with NHSEI BIM

Table 2. Increment results of intended changes

Scenario	**ICER**	**% change**
Original base-case	[redacted]	NA
No cap on tebentafusp costs (reference)	[redacted]	NA
PAS	[redacted]	[redacted]
TTD	[redacted]	[redacted]
Infusion costs	[redacted]	[redacted]
All changes	£58,676	[redacted]

Model results (deterministic, DSA, PSA and scenarios) are provided in the following section.

Table 3. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Tebentafusp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,676
Comparator	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to describe how uncertainty around input parameters is translated into uncertainty around the estimated outputs of the model. Hence, suitable probability distributions were assigned to model parameters to characterise uncertainty around their mean values and have been presented in section B3 of the company submission (November 2021). Values were sampled from the corresponding parameter distributions and were assigned to each parameter in an iterative process. This process was repeated for 10,000 times, and the results of each of these iterations were used to determine the distribution of incremental costs and incremental QALYs.

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

The results of the PSA were presented within the cost-effectiveness plane in the form of a joint distribution of costs and QALYs, along with a mean value of the ICER and a 95% confidence interval ellipse (Figure 1). It is apparent from that the largest spread is across the X axis of the scatter plot showing that the highest uncertainty is associated with the health benefits. The probability that each treatment is cost-effective, resulting in the highest net monetary benefit, is presented over different values of a cost-effectiveness threshold in the form of a cost-effectiveness acceptability curve (CEAC) in

Figure 2.

Table 4 presents the mean incremental costs and QALYs as well as the ICER as estimated in the base-case PSA.

Table 4. Results of the base-case PSA

Technologies	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)
Tebentafusp	[redacted]	[redacted]	£56,715
Control	-	-	-
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years			

Figure 1. Cost-effectiveness plane – incremental costs vs. incremental QALYs

Figure 2. Cost-effectiveness acceptability curve for willingness-to-pay threshold

Deterministic sensitivity analysis

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.

Upper and lower values of model parameters were determined by their 95% CIs or ±1.96 standard errors, depending on format of source data reporting. When no information was available regarding a parameter's uncertainty then the variation around the mean value was modelled by varying the parameter by 25% or 10% of its mean value.

Figure 3 presents a tornado diagram indicating the 10 parameters with the greatest influence on the ICER in a descending order. Table 5 presents the ICER as a result of using an upper and lower estimate for these parameters.

We note that the parameter that has the most impact on the results is the age of a patient as it determines the time frame over which patients may derive benefit. The second parameter impacting the results is the baseline utility value as this is applied to patients until they are one year from death. The third parameter is the cost of

administration of chemotherapy at subsequent attendance, related to the duration of treatment of Tebentafusp which is administered on a weekly basis. All other parameters have very limited impact on the results.

Figure 3. Tornado diagram

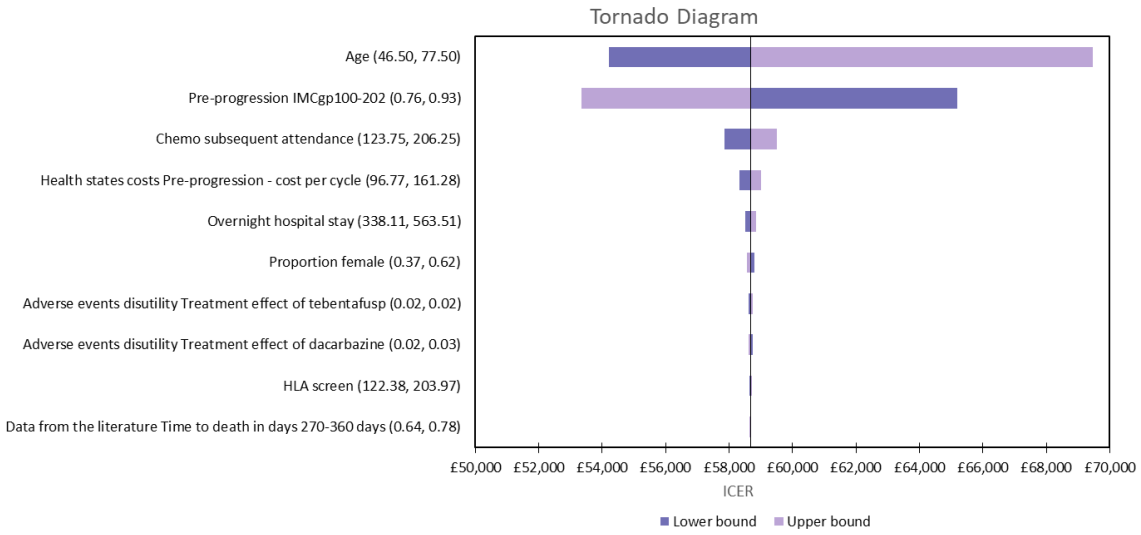


Table 5. Results of the univariate sensitivity analysis

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Age (46.50, 77.50)	£54,217	£69,476
Pre-progression IMCgp100-202 (0.76, 0.93)	£65,187	£53,348
Chemo subsequent attendance (123.75, 206.25)	£57,844	£59,508
Health states costs Pre-progression - cost per cycle (96.77, 161.28)	£58,334	£59,018
Overnight hospital stay (338.11, 563.51)	£58,498	£58,854
Proportion female (0.37, 0.62)	£58,790	£58,560
Adverse events disutility Treatment effect of tebentafusp (0.02, 0.02)	£58,610	£58,742
Adverse events disutility Treatment effect of dacarbazine (0.02, 0.03)	£58,741	£58,611
HLA screen (122.38, 203.97)	£58,630	£58,722
Data from the literature Time to death in days 270-360 days (0.64, 0.78)	£58,702	£58,650

Scenario analysis

The impact of both structural assumptions and choice of parameter values were further explored through a number of scenario analyses. The scenarios that were evaluated are outlined below.

Choice of method of extrapolation of PFS

We explored the choice of the method for the extrapolation of the PFS. We tested the log-logistic and lognormal curves, which were second best choice for the PFS curve as detailed in section B.3.3.1.2. We also tested the impact of the time-point at which there is a switch from the KM curves to the parametric curve, testing 10% of patients at risk in place of 15% of patients at risk in the base-case. We note that the impact on the results is very limited due to the difference in the costs between the two arms being driven by the TTD curves, and the difference in LY/QALYs being driven by the OS curve.

Table 6 Results of scenario analyses of alternative methods of extrapolating PFS

Scenario	ICER (£/QALY)	% change
Base-case KM + Generalised gamma	£58,676	NA
KM + log-logistic	£58,088	-1.00%
KM + log-normal	£57,992	-1.17%
Generalised gamma	£58,587	-0.15%
Log-logistic	£58,020	-1.12%
Log-normal	£58,019	-1.12%
Base-case (KM + generalised gamma; 10% at risk)	£58,681	0.01%

Choice of method of extrapolation of TTD

We explored the choice of the method for the extrapolation of the TTD. We tested the log-logistic, exponential and Weibull curves, which were second best choice for the TTD curve as detailed in section B.3.3.1.2. We also tested the impact of the time-point at which there is a switch from the KM curves to the parametric curve, testing 10% of patients at risk in place of 15% of patients at risk in the base-case.

We note that the difference in the ICER between the hybrid approach and using the parametric curves only is small. The choice of curve has a limited impact on the given the 24-month discontinuation rule.

Table 7. Results of scenario analyses of alternative methods of extrapolating TTD

Scenario	ICER (£/QALY)	% change
Base-case KM + Exponential	£58,676	NA
KM + log-logistic	£80,073	36.47%
KM + Generalised gamma	£64,602	10.10%
KM + Weibull	£59,935	2.15%
Exponential	£64,880	10.57%
Log-logistic	£82,936	41.35%
Generalised gamma	£70,034	19.36%
Weibull	£66,173	12.78%
Base-case (KM + Exponential; 10% at risk)	£65,405	11.47%
Base-case (KM + Exponential; 15% at risk)	£63,332	7.94%
Base-case (KM + Exponential; 25% at risk)	£59,491	1.39%

Source of utility data

We conducted a scenario analysis using the utility values derived from the EQ-5D data collected in the IMCgp100-202 trial. The data is applied based on TTD rather than disease status as detailed in section B.3.4. The ICER is £63,898 which is equivalent to an 8.90% increase compared to the base-case.

Choice of method of extrapolation of overall survival and data-cut-off

The incremental LYs and QALYs are driven by the OS curve in the tebentafusp arm, hence the importance of testing the impact of the chosen method on the results. This section presents the results of a series of scenario analyses testing alternative combinations of standard parametric functions for extrapolating overall survival. A total of nine parametric function combinations have been examined for the tebentafusp and control arm.

The August 2021 DCO was used in the base-case providing the longest follow-up and therefore the most information on the clinical effectiveness of tebentafusp. However, the control arm was not adjusted for treatment cross-over, and [redacted] compared to historical data as presented in section B.3.3. Therefore, the series of scenarios based on standard parametric curves are presented for both DCO, for comparison. The preferred model is the Weibull for the control arm, which is consistent with the historical data of first-line patients reported in the meta-analysis conducted by Rantala et al. (2019) We also tested generalised gamma and Gompertz which provided second best and reasonable fits. In the tebentafusp arm, we tested the log-logistic distribution for OS which was the best fitting standard parametric model and gave a clinically plausible long-term extrapolation based on clinical experts' opinion. Generalised gamma and log-normal are also reasonable fits and tested. All other parameters are as per the base-case analysis. The resulting ICERs and change from the base case are presented Table 8.

Table 8. Results of scenario analyses using alternative parametric survival models

Scenario (Parametric models)	August 2021 DCO		October 2020 DCO	
	ICER (£/QALY)	% change	ICER (£/QALY)	% change
Base-case (August 2021 DCO) Spline (tebentafusp) Weibull (comparator)	£58,676	NA	£58,676	NA
Log-logistic (tebentafusp) Weibull (comparator)	£103,488	76.37%	£85,654	45.98%
Log-logistic (tebentafusp) Gompertz (comparator)	£99,900	70.26%	£82,205	40.10%
Log-logistic (tebentafusp) Generalised Gamma (comparator)	£115,745	97.26%	£91,380	55.74%
Lognormal (tebentafusp) Weibull (comparator)	£111,556	90.12%	£77,608	32.27%
Lognormal (tebentafusp) Gompertz (comparator)	£96,753	64.89%	£74,766	27.42%
Lognormal (tebentafusp) Generalised gamma (comparator)	£111,556	90.12%	£82,294	40.25%
Generalised Gamma (tebentafusp) Weibull (comparator)	£162,286	176.58%	£131,554	124.20%
Generalised Gamma (tebentafusp) Gompertz (comparator)	£153,529	161.66%	£123,570	110.60%

Generalised Gamma (tebentafusp) Generalised Gamma (comparator)	£194,471	231.43%	£145,462	147.91%

There is evidence to suggest a trend towards long-term survival for a fraction of patients treated with tebentafusp. This effect has been incorporated in the model by applying the mortality rates for the general population to a fraction of the patients treated with tebentafusp after a certain time point (e.g., survival probability of [redacted] equivalent to about [redacted] months, a time-point where we observe [redacted] with the August 2021 DCO). The results of varying the proportion of patients who living with their cancer, revert to normal life expectancy, from 50-90% (i.e., 50% of the patients alive at the specified time-point are applied background mortality, whereas the other patients are applied the mortality rate from the parametric curve) are presented in Table 9. The initial survival phase was modelled using parametric models assuming a Weibull hazard function in both arms since this provided a good fit in the early phase.

Table 9. Results of scenario analyses using patients cure proportions for survival

Scenario (cure fraction)	August 2021 DCO		October 2020 DCO	
	ICER (£/QALY)	% change	ICER (£/QALY)	% change
50%	£60,274	2.72%	£55,260	-5.82%
60%	£52,510	-10.51%	£48,344	-17.61%
70%	£46,503	-20.75%	£42,953	-26.80%
80%	£41,718	-28.90%	£38,633	-34.16%
90%	£37,816	-35.55%	£35,093	-40.19%

Subgroup analysis

There is a growing body of evidence documenting the associating between tumour burden and response to immunotherapies, thus the particular interest in this population subgroup (Dall'Olio et al., 2021).

The subgroup analysis examines the impact of implementing survival models based on restricted subpopulations of patients with baseline largest metastatic tumour with a diameter of less than 30mm.

PFS and TTD are modelled using KM curves and generalised gamma for the extrapolation of the tail in both arms. We model the OS in the control arm using Weibull which provided the best fit and present results for the log-logistic and log-normal in the tebentafusp arm. The results for both DCO are presented in Table 10, along with the ICER for the ITT set (using the same distributions) for comparison. The results of this scenario analysis demonstrate that for the patient subgroup with smaller tumour size (<30mm) the cost-effectiveness ratio is improved. Greater surveillance to detect smaller tumours could result in improved cost-effectiveness and better patient outcomes.

Table 10. Scenario analysis subgroup tumour ≤30mm

Scenario: **Parametric model for OS**	**August 2021 DCO ICER (£/QALY)**			**October 2020 DCO ICER (£/QALY)**		
	ITT	**Subgroup**	**% change**	**ITT**	**Subgroup**	**% change**
Log-normal (tebentafusp)	£118,606	£115,750	-1.24%	£83,778	£64,571	-21.91%
Log-logistic (tebentafusp)	£122,586	£149,254	23.21%	£92,455	£92,660	1.55%

Justification for choices made

Patient access scheme

An updated PAS of [redacted] has been submitted to NHSE&I / PASLU and the model has been updated to reflect this new PAS. The list price of tebentafusp is [redacted] and [redacted] with PAS.

Treatment duration with tebentafusp

In the original model base-case, there was an 18-month cap on the treatment costs of tebentafusp. This feature was removed following feedback from NHSE. This change required some adjustment to the modelling of the treatment duration of tebentafusp.

The exponential distribution is applied instead of the generalized gamma in both arms, with a switch from the KM curve at 25% of patients at risk in the tebentafusp arm and 15% in the IC arm. Both provide reasonable fit over the trial period;

however, the exponential provides a more plausible long-term extrapolation (year 3: 6% exponential vs. 8% generalized gamma; year 5: 1% exponential vs. 3% generalized gamma). Additionally, the exponential better aligns with the average observed duration of treatment and percentage of patients informing analysis (i.e. %pts at risk).

Figure 4. Kaplan Meier curve and exponential model (August 2021 DCO)

The mean duration of treatment in the tebentafusp arm in the model with an exponential distribution is 10.2 months (309 days). This is consistent with the observed duration of treatment (314 days ~10.3 months) in the IMCgp100-202 study, for the cohort of patients who were randomised prior to December 2018 and hence have the longest follow-up (Table 11). The modelled duration of treatment for study IMCgp100-202 is also consistent with the published duration of treatment for study IMCgp100-102 with longer follow up and mean duration of treatment of 9.5 months (Sacco J et al., 2021).

Table 11. Treatment duration by cohort based on enrolment cut-offs, IMCgp100-202

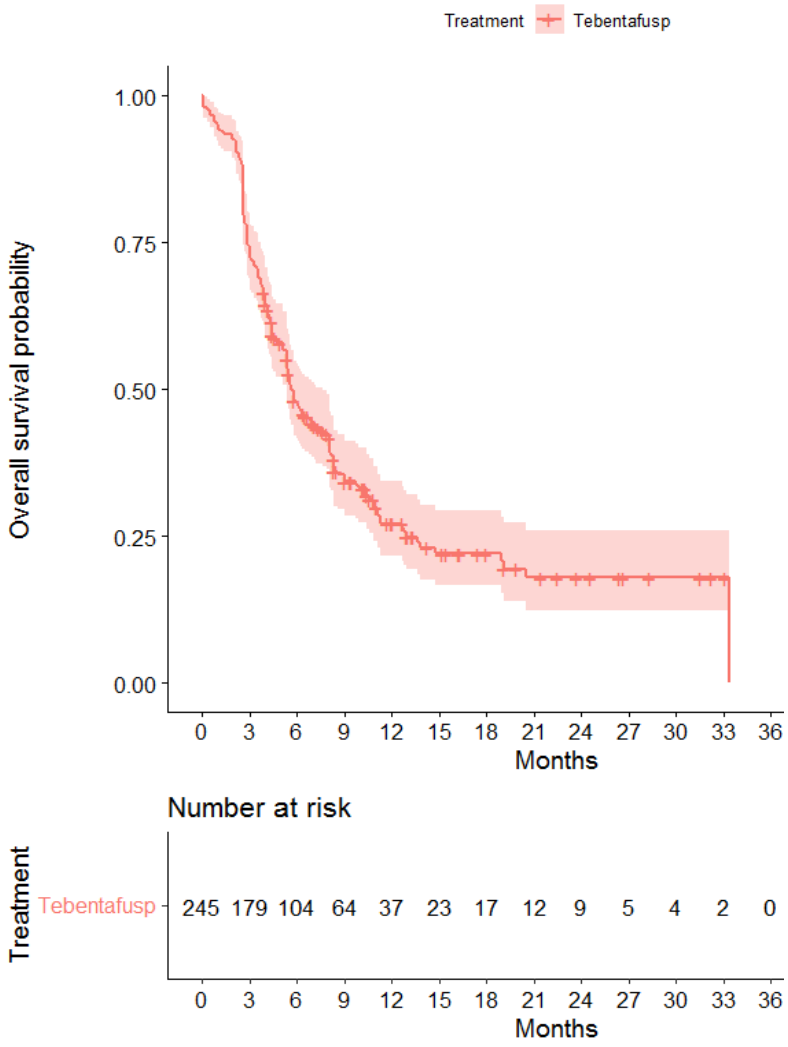
Obs	cutoff	n	mean	sd	max	q3	median	q1	min	n_ongoing	percent_ongoing
1	None (all patients)	245	219.547	191.612	1016	274	163	87	1	[redacted]	[redacted]
2	Randomised by end Dec 2019	179	243.352	215.391	1016	334	165	85	1	[redacted]	[redacted]
3	Randomised by end June 2019	114	275.114	244.892	1016	344	176	86	1	[redacted]	[redacted]
4	Randomised by end Dec 2018	61	313.984	289.655	1016	386	197	106	1	[redacted]	[redacted]

Data on file: datacut Study IMCgp100-202: Summary statistics for time on IMCgp100 treatment by time of randomisation - Safety population. output=f:\Biometrics\IMCgp100\imcgp100-202\2021-PA\output\a_timeontrt.rtf

Table 12. Proportion of patients on treatment modelled vs. observed

Model		Observed (Study-202)
Time (months)	Tebentafusp	Tebentafusp (%, [#risk])
12	26.2%	27.2% [37]
18	16.4%	22.1% [17]
24	9.5%	18% [9]
36 (3 years)	3.2%	0% [0]

Figure 5. Kaplan Meier curve for time to treatment discontinuation IMCgp100-202 (October 2020 DCO)



IC treatment duration

The exponential distribution was applied instead of the generalized gamma, to align with the modelling approach taken in the tebentafusp arm. We note that at 24 months, all patients have discontinued treatment based on the extrapolation (0.4%).

Administration costs

Administration costs were updated to align with the unit costs used in the budget assessment conducted by NHSE. The company adopted a single administration fee of £165 per infusion. The inpatient costs of the first 3 doses were captured within the costs of the overnight stay and hence the lower infusion cost of £165 per administration would avoid the risk of double-counting of extended infusions for the first cycle (i.e. 3 doses).

ERG report table4.4

Table 4.4 Selection of approach to estimate and extrapolate OS, PFS and TTD for ITT population (based on August 2021 data cut-off)

	OS	PFS	TTD
General considerations	Company argues (without supporting information) that, for tebentafusp, none of the standard parametric models allowed to properly model the change in the survival profile around [redacted] Therefore, spline-based models were adopted by the company. No explicit justification was provided for using different approach for both treatments.	Due to a protocol-driven drop of PFS at week 12 corresponding to the first assessment, the company argues that the fit of the parametric distributions is limited and hence, a hybrid (or piecewise) approach is adopted using the KM curves (non-parametric) and the parametric curves (discussed below) only for extrapolation of the tail.	Although patients could stay on treatment beyond confirmed progression, treatment discontinuation was considered contingent on confirmed disease progression (illustrated in CS Figure 31). Hence, like PFS, a hybrid (or piecewise) approach is adopted using the KM curves (non-parametric) and the parametric curves (discussed below) only for extrapolation of the tail.
Fit to the observed data based on AIC and BIC	**IC** The AIC and BIC are within two and five points respectively (CS Table 19). **Tebentafusp** Not provided for the standard parametric models.	**IC** The AIC and BIC of the log-logistic and generalised gamma are within one point (CS Table 24) while the log-normal also provided a reasonable statistical	**IC** The models with the lowest AIC and BIC were the Gompertz and log-logistic (CS Table 32). **Tebentafusp** The AIC and BIC for the log-logistic was

	OS	PFS	TTD
	Provided for three knot spline model (hazard scale) in CS Table 22.	fit to the observed data. **Tebentafusp** The AIC and BIC indicate that the generalised gamma has the best fit (CS Table 27)	lowest with AIC and BIC for the second best (Gompertz) more than 10 points higher (CS Table 35).
Fit to the observed data based on visual comparison with the Kaplan-Meier curves	**IC** The Weibull, Gompertz and generalised gamma provide a good fit over the trial period (CS Figure 25). **Tebentafusp** Comparison not provided for the standard parametric models. Provided for three knot spline model (hazard scale) in CS Figure 26.	**IC** Based on visual inspection (CS Figure 28) the generalised gamma is preferred. **Tebentafusp** Based on visual inspection (CS Figure 28) the generalised gamma is preferred.	**IC** As can be observed in CS Figure 31, the PFS and TTD are almost identical in the IC arm, patients indeed discontinued based on confirmed disease progression. **Tebentafusp** The log-logistic provides a good fit over the trial period (CS Figure 32)
Clinical plausibility of the extrapolation based on comparison with historical data	**IC** The extrapolations of the exponential, Gompertz, log-normal and log-logistic are unrealistic (CS Figure 25). **Tebentafusp** Not explicitly discussed.	**IC** Not explicitly discussed. **Tebentafusp** Not explicitly discussed.	**IC** Based on consistency with TTD in tebentafusp arm, the exponential is preferred. **Tebentafusp** Exponential provides more plausible long-term extrapolation.
Clinical plausibility of the extrapolation based on clinical expert opinion	**IC** Not explicitly discussed. **Tebentafusp** Not explicitly discussed.	**IC** Not explicitly discussed. **Tebentafusp** Not explicitly discussed.	**IC** Gompertz may not be realistic **Tebentafusp** Gompertz may not be realistic
Base-case approach	CS Figure 26 **IC** Weibull (generalised gamma in scenario analysis)	CS Figure 29 **IC** KM + generalised gamma from the time point at which only 15% of the	CS Figure 33 **IC** KM + exponential from the time point at which only 15% of the patients remain at

	OS	PFS	TTD
	Tebentafusp Three knot spline model with hazard scale and knots at [redacted] (default knot locations are used in scenario analysis)	patients remain at risk (log-logistic and log-normal in scenario analyses) **Tebentafusp** KM + generalised gamma from the time point at which only 15% of the patients remain at risk (log-logistic and log-normal in scenario analyses)	risk (log-logistic, Weibull and generalised gamma in scenario analyses). **Tebentafusp** KM + exponential from the time point at which only 25% of the patients remain at risk (log-logistic and generalised in scenario analyses).
Based on Section B.3.3 of the CS(Immunocore, 2021 [accessed 4.11.21]) AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; IC = investigator's choice; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation			

Instructions to update the model

Table 13 presented the changes which have been made in the model front-end input sheet (provided in Table 7 of the Addendum) and control sheet.

Table 13. Model updates

Cell	Change	Rationale
Model Settings		
E91	1	Selection of exponential in the drop-down menu in line 91. Exponential distribution chosen providing a more plausible long-term extrapolation (now that the treatment cap has been removed)
E93	1	Selection of exponential in the drop-down menu in line 93. Exponential distribution chosen providing a more plausible long-term extrapolation (now that the treatment cap has been removed)
E99	25%	% at risk by exponential
Cost data		
D81	£165	Consistent with NHSEI BIM
D82	£165	Consistent with NHSEI BIM
D83	£165	Consistent with NHSEI BIM
L36	[redacted]%	Updated PAS submitted to PASLU
Control		
C382	[redacted]%	Updated PAS submitted to PASLU
C333	£165	Consistent with NHSEI BIM
C334	£165	Consistent with NHSEI BIM
C335	£165	Consistent with NHSEI BIM
C341	25%	% at risk by exponential

Question 2

Provide a complete overview (tabulated) of additional changes made, with all instructions to reproduce this based on the initially submitted model (or the ERG model) + extensive justification for the choices made (and why these adjustments were made).

Provide incremental results per adjustment (allowing to examine the impact of all individual changes).

Response 2

Overview of model changes and analysis results

Table 14. Summary of additional model changes

Parameter	Original model	Change made	Rational
Proportion of usage of the different regimens in the IC arm	% on pembrolizumab 81.7% % on ipilimumab 12.7% % on dacarbazine 5.6%	% on pembrolizumab 87.3% % on ipilimumab 12.7% % on dacarbazine 0.0%	Consistent with feedback from the NICE Scoping and Decision-problem meetings, dacarbazine is not used in England or the UK and it is inappropriate to include it as a comparator.
Stopping rule	NA	No drug acquisition or administration costs accrued in the tebentafusp	Tebentafusp is administered on a weekly basis. Therefore, it is not expected that patients would be on treatment for

		arm beyond 24 months	longer than 24 months. 24-month stopping rule consistent with the previous assessment of the immunotherapy (TA655).
Compliance to tebentafusp	NA	95%	Compliance of less than 100% to reflect the interruptions seen in study IMCgp100-202, related to the weekly dose schedule
% of usage of subsequent therapies	See Table 18	See Table 18	To align with clinical practice in the UK, ipi+nivo rarely used.

Table 15. Analysis results of additional changes

Scenario	**ICER**	**% change**
Original base-case	[redacted]	NA
No cap on tebentafusp costs as requested by NHSE (reference)	[redacted]	NA

Comparators	[redacted]	[redacted]
Tebentafusp stopping rule	[redacted]	[redacted]
Tebentafusp compliance	[redacted]	[redacted]
Subsequent therapies	[redacted]	[redacted]
All changes above	[redacted]	[redacted]
All changes (Table 2 and Table 15)	£44,054	[redacted]

Justification for choices made

Comparators

The proportion of patient on dacarbazine has been set to zero. Consistent with feedback from the NICE Scoping and Decision-problem meetings, dacarbazine is not used in England or the UK and it is inappropriate to include it as a comparator. The percentage of patients who were treated with dacarbazine were assumed to be treated with pembrolizumab (Table 16), as it is the most commonly used treatment regimen for the patient population in the UK. The comparator costs were adjusted accordingly.

Table 16. Proportion of usage of the different regimens in the IC arm

Investigator's choice	Prior	Updated
% on pembrolizumab	81.7%	87.3%
% on ipilimumab	12.7%	12.7%
% on dacarbazine	5.6%	0.0%

Tebentafusp stopping rule

Tebentafusp is administered on a weekly basis. Therefore, it is not expected that patients would be on treatment for longer than 24 months. It is anticipated that the clinical benefit will extend beyond the duration of treatment. This approach is consistent with the 2-year stopping rule used in a NICE appraisal of Nivolumab (TA655). It was noted that the clinical trial did not specify a stopping rule. The committee concluded that it was plausible that a survival benefit from nivolumab would continue after it is stopped at 2-years and that there was no evidence to show that continuing for longer gave additional benefit. Therefore, the NICE committee concluded that a 2-year stopping rule was appropriate.

The company adopted the 24-month stopping rule consistent with the previous assessment of the immunotherapy (TA655). A treatment discontinuation rule is applied at 24 months in the model, time point beyond which no drug acquisition nor administration costs are accrued in the tebentafusp arm.

Tebentafusp compliance

Tebentafusp is administered weekly as an infusion. Compliance is unlikely to be 100% over the modelled time horizon, including during the 24-month proposed above. In study IMCgp100-202 42.4% (104 out of 245) of patients in the tebentafusp arm required a dose interruption (Table 17, highlighted). Of the 104 patients with an interruption, there were a total of 222 interruptions with a mean duration of 22.2 days (Table 17, highlighted).

Duration of treatment based on the date of first dose to date of discontinuation (i.e. time-to-discontinuation, TTD) does not account for missed doses or interruptions. The company adopted a compliance of less than 100% to reflect the interruptions seen in study IMCgp100-202 and adopted 95% to reflect approximately two 1 week breaks per year. The total combined costs of tebentafusp plus administration are weighted to account for the number of interruptions / missed doses for a compliance of 95%. Sensitivity analyses for compliance of 90% and 100% are provided.

Table 17. Dose interruptions and reductions – summary (Safety Analysis Set)

		IMCgp100 (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	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 [1]		222		15	
Reason for interruption at any time	Missed Visit	89	(40.1)	2	(13.3)
	Adverse Event	50	(22.5)	12	(80.0)
	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

	IMCgp100 (N=245)		Investigator's Choice (N=111)	
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: Listing 16.2.5, Output: t-14-03-01-00-02-ex-dose.

Program: t03010ex0dose.sas Cutoff Date: 13OCT2020 05MAR2021 02:12

Subsequent therapies

The proportion of usage of the different regimens following discontinuation of the primary treatment have been updated to align with clinical practice in the UK. According to clinical input during the NICE Decision Problem meeting (Monday 16th August 2021), ipilimumab+nivolumab combination therapy is rarely used, therefore, the proportion of patients receiving the treatment after either tebentafusp or the IC was reduced to 10%. The percentage of patients assumed to receive pembrolizumab after tebentafusp was adjusted accordingly. For the IC arm, since the vast majority (26%) of patients received pembrolizumab, the percentage of patients assumed to receive ipilimumab as the subsequent treatment was adjusted (Table 18).

Table 18. Subsequent treatment usage

	Prior company case		Updated company case	
	Tebentafusp	IC	Tebentafusp	IC
% of usage of ipilimumab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
% of usage of ipilimumab (mono therapy)	[redacted]	[redacted]	[redacted]	[redacted]
% of usage of pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
% of usage of nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Total	100%	100%	100%	100%

Instructions to update the model

Table 19 presented the changes which have been made in the model front-end input sheet (provided in Table 7 of the Addendum) and control sheet.

Table 19. Model updates

Cell	Change	Rationale
Model Settings		
E84	87.30%	Alignment with clinical practice (dacarbazine not used in the UK), % increased to achieve a sum of 100%
E86	0%	Alignment with clinical practice, dacarbazine not used in the UK
E104	24	Aligned with stopping rule consistent with the previous assessment of the immunotherapy (TA655)
Cost data		
D111	10%	Alignment with clinical practice, ipi+nivo not used much in the UK
D112	10%	Alignment with clinical practice, pembrolizumab used more in UK
D113	68%	Alignment with clinical practice, pembrolizumab used more in UK
D114	12%	Alignment with clinical practice, pembrolizumab used more in UK
E111	10%	Alignment with clinical practice, ipi+nivo not used much in the UK

E112	43%	Alignment with clinical practice, pembrolizumab used more in UK
E113	42%	Alignment with clinical practice, pembrolizumab used more in UK
E114	5%	Alignment with clinical practice, pembrolizumab used more in UK
Control sheet		
C10	87.30%	Alignment with clinical practice (dacarbazine not used in the UK), % increased to achieve a sum of 100%
C12	0%	Alignment with clinical practice, dacarbazine not used in the UK

- *Stopping rule*

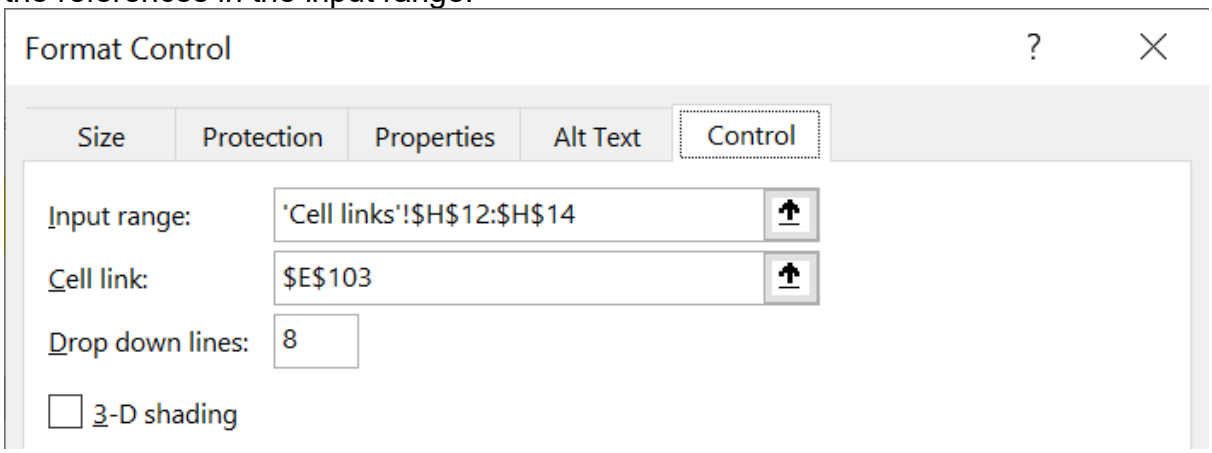
The drop-down box used for the cap in the tebentafusp costs in the original model was repurposed to programme the discontinuation rule. Please follow the following steps to update the model.

- Cell link tab: update the list options under cap on treatment duration

Cap on treatment duration
No rule
Cap on tebentafusp costs
Discontinuation - both arms

- Model settings tab

Select the drop-down box (line 103), right click and click on “Format control”. Update the references in the input range.



- Model setting tab
  Update the value in cell E104 to 24 (original model value 18)

- Tebentafusp engine

Column BC (Drug costs)
Replace using the following formula in cell BC13 and carry the formula over. The changes to the original formulas are in bold and underlined.

=IF(trtcap_switch**≥**1, IF(C13<Tebe_timecap,'Cost data'!$E$13,0),'Cost data'!$E$13)*AG13*adherence

Column BD (Administration costs)
Replace using the following formula in cell BD13 and carry the formula over. The changes to the original formulas are in bold and underlined.

=IF(A13=1,'Cost data'!$H$13,IF(OR(A13=2,A13=3),'Cost data'!$I$13,**IF(trtcap_switch>1, IF(C13<Tebe_timecap,'Cost data'!$J$13,0),'Cost data'!$J$13))**)*AG13*adherence

- IC engine

Column BC (Drug costs)
Replace using the following formula in cell BC13 and carry the formula over. The changes to the original formulas are in bold and underlined.

=IF(MOD(A13+2,3)<>0,0,IF((A13-1)/3<4, 'Cost data'!$E$18,'Cost data'!$F$18))*Y13***IF(AND(C13>Tebe_timecap,trtcap_switch=3),0,1)**

Column BD (Administration costs)
Replace using the following formula in cell BD13 and carry the formula over. The changes to the original formulas are in bold and underlined.

=IF(MOD(A13+2,3)<>0,0,IF((A13-1)/3=0,'Cost data'!$H$18,IF((A13-1)/3<4, 'Cost data'!$I$18,'Cost data'!$J$18)))*Y13***IF(AND(C13>Tebe_timecap,trtcap_switch=3),0,1)**

- *Compliance*

An additional model setting was created in the Model setting tab and changes were made in the 'Tebentafusp' engine to weight the drug and administration costs by the proportion of patients who received a dose. The changes to the original formulas are in bold and underlined.

- Model setting

  Create an additional setting to specify the proportion of patients who are adherent to treatment

- Tebentafusp engine

Column BC (Drug costs)

Replace using the following formula in cell BC13 and carry the formula over. The changes the original formulas are in bold and underlined.

=IF(trtcap_switch>1, IF(C13<Tebe_timecap,'Cost data'!$E$13,0),'Cost data'!$E$13)*AG13**<u>*adherence</u>**

Column BD (Administration costs)
Replace using the following formula in cell BD13 and carry the formula over.

=IF(A13=1,'Cost data'!$H$13,IF(OR(A13=2,A13=3),'Cost data'!$I$13,IF(trtcap_switch>1, IF(C13<Tebe_timecap,'Cost data'!$J$13,0),'Cost data'!$J$13)))*AG13***<u>adherence</u>**

References

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IMMUNOCORE 2021 [accessed 4.11.21]. Tebentafusp for treating advanced uveal melanoma [ID1441]: Document B. Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA).

RANTALA, E. S., HERNBERG, M. & KIVELÄ, T. T. 2019. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. *Melanoma research,* 29**,** 561-568.

SACCO J, CARVAJAL R & BUTLER M 2021. 538 Updated survival of patients with previously treated metastatic uveal melanoma who received tebentafusp. *Journal for ImmunoTherapy of Cancer* 9.

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Clinical expert statement and technical engagement response form

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma ID1441

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Clinical expert statement

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma ID1441

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Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **<<insert deadline>>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma ID1441

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma ID1441

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Part 1: Treating uveal melanoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Rumana Hussain
2. Name of organisation	Liverpool University Hospitals
3. Job title or position	Consultant Ophthalmologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with uveal melanoma? ☐ A specialist in the clinical evidence base for uveal melanoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	nil
8. What is the main aim of treatment for uveal melanoma?	Control the local tumour, retain vision, keep the eye, reduce the risk for development of metastatic disease

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction in tumour size on ultrasound (or complete removal of the tumour by surgical means) In terms of metastatic disease, this is out of my field of expertise
10. In your view, is there an unmet need for patients and healthcare professionals in uveal melanoma?	Yes, the main concern is metastatic disease which is as yet untreatable. 50% of uveal melanoma patients develop metastatic lesions
11. How is uveal melanoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	All uveal melanoma patients in the UK are treated in one of 4 supraregional specialist centres (London, Sheffield, Glasgow and Liverpool). The treatments can vary from focal radiotherapy (ruthenium-106 plaque brachytherapy, proton beam at clatterbridge, stereotactic radiation) to surgical methods (either tumour resection or enucleation of the eye). The methods of assessing and diagnosing these patients is quite consistent between clinicians, although the type of local treatment may vary to some minor extent depending on the surgeons preference or patient accessibility. There are ways of predicting the risk of developing metastatic disease, and these tests are undertaken routinely in Liverpool, less so elsewhere in the UK. Although we can predict the risk of developing metastatic disease, once there is systemic spread, this is almost universally lethal, with the majority of patients unsuitable for curative treatments such as localised liver resection. Systemic chemotherapy and immunotherapy has very little impact on survival. This is hugely problematic in a population in which 50% develop metastatic disease. Any progress in the treatment of metastatic uveal melanoma would have a huge impact on this patient group.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	Current care for metastatic uveal melanoma is variable due to the poor outcomes associated with the disease. There is not definitive standard of care. Multiple agents may be tried such as ipilimumab or pembrozilumab, but they often have little effect on disease progress. As such, new agents with better success rates would be welcomed and implemented. This would be undertaken in the hospital

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	setting under the care of medical oncologists with a specific interest in metastatic uveal melanoma, of which there are a few scattered across the country. As a relatively rare disease, it would be more appropriate to have centres of interest. As far as implementation, the cost of the drug would be the only change in procedure; otherwise the administration and monitoring of these patients would not be any different to the usual standard of care with other chemotherapeutic agents
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	As mentioned, the current standard of care has very poor outcomes. The results reported with tebentafusp are very promising, although it is only for a subgroup of these patients. This improvement in survival and fewer side effects is a significant improvement.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This drug is only for metastatic uveal melanoma patients with a very specifi HLA subtype, and would not be relevant to others.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	There are no additional practical considerations as the protocol of treatment would follow similar chemotherapy treatments; however a system would need to be set up to identify the correct patient subgroup with HLA subtype analysis
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There are specific inclusion criteria, predominantly the HLA subtyping

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	I think the QALY measures are sufficient
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This new drug is an improvement on the current available options for these patients
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	I do not have enough exposure to this drug to answer this
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The drugs used as the comparative treatment in the trials are appropriate for the standard of care for metastatic uveal melanoma. The outcomes measured include survival which is ultimately the most important factor in such studies. Long term outcomes are as yet unavailable. The comparisons to cutaneous melanoma is very questionable but does not detract from the outcomes described,

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. How do data on real-world experience compare with the trial data?	I have not had enough experience of this drug first hand to answer this
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	If this drug is to be administered in particular centres across the UK, rather than be utilised in every oncology unit in the country, there may be issues with transport and accessibility for more elderly and frail patients, and those of a lower socioeconomic group. This is not very different from current care, as specialist interest in this disease is not widely covered.

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Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Clinical expert statement

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma ID1441

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Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Mixed therapy (IC) as comparator precludes separate evaluation of tebentafusp versus each comparator ***Section 2.3 and 3.2***	There is no current standard of care for the treatment of metastatic uveal melanoma therefore the comparative to multiple other agents is not ideal but unavoidable.
Lack of comparison to nivolumab monotherapy ***Section 2.3***	See above. If they had compared individual agents. The numbers would have been too small to be meaningful in this small patient cohort
Frequency of adverse events in tebentafusp	Not my area of expertise

Section 3.2.4	
Model structure – Use of a partitioned survival model ***Section 4.2.2***	
The use of the treatment mix in the IC arm of the IMCgp100-202 study as single comparator and not including nivolumab as comparator ***Section 4.2.4***	See above
Long-term PFS and OS extrapolations ***Section 4.2.6***	The comparative to metastatic cutaneous melanoma is misled and inaccurate
Not primarily using the IMCgp100-202 trial EQ-5D data and time-to-death HRQoL approach being inconsistent with common modelling practices ***Section 4.2.8***	
One-off application of BSC costs ***Section 4.2.9***	

Percentage of patients using each IC treatment ***Section 4.2.9***	
Proportion of (PF)LYs accumulated beyond the observed data ***Section 5.1***	
Probabilistic analyses for alternative OS, PFS and TTD assumptions ***Section 5.3***	
Are there any important issues that have been missed in ERG report?	

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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Technical engagement response from Jo Gumbs, OcuMel

Differences in type of uveal melanoma

1. How does uveal melanoma differ from skin melanoma in prognosis, treatment and quality of life?
   Cutaneous and uveal melanoma are essentially two different diseases. Detection, surveillance, treatment, prognosis all differ, but especially quality of life. Differences also include
   - Vision loss. If the eye is treated, it is common for most patients to have reduced vision in the affected eye or up to a third of people loss their eye.
   - Consequences of treatment. Following treatment to the primary, many patients face daily pain and discomfort, but it also affects your appearance and confidence.
   - Rare Cancer. This complicates a patients journey as less is known about the disease, patients need to travel long distances to one of 4 hospitals in the UK for treatment, but isolation is often reported as so few patients are diagnosed.
   - Psychological distress. People have an uncertain future. We know 50% of patient will progress to incurable metastatic disease. Patients are aware of this, but current prognostication methods are not 100% accurate.
   -
2. Does metastatic disease differ in incidence, prognosis and current treatment options compared with non-metastatic, unresectable disease?
   50% of patients will become metastatic and the disease is known to be terminal.
   Liver disease that can be resected, is by its nature metastatic disease.

3. Would it be expected that Tebentafusp would have greater benefit in people who have no lesions more than 30mm when beginning treatment compared with people who have lesions bigger than 30mm?
   We cannot comment on this, but we do expect approval of this drug to bring a standard approach to how a person is monitored as there is no clear pathway for these patients.

Comparators

1. What is the current standard of care for metastatic or unresectable uveal melanoma?
   There is no standard of care and the comparators used in this trial are the current standard of choice treatments.

2. Are pembrolizumab, ipilimumab, nivolumab and dacarbazine used in practice?
   Yes

3. Do these treatment options have similar efficacy?
   They vary, as an organisation we do know patients on all of these treatments and they are seeing a response, or they at least have slower progression, but we cannot comment on why this is. These treatments are a valued option for patients as they are our only other systemic treatments, but from the data we've seen, Tebentafusp is more effective.

4. These medicines accessible for uveal melanoma treatment, (based on indication for melanoma in general or other reasons)?
   We cannot comment on this but know there is high unmet need for the treatment of metastatic uveal melanoma and so comparisons are difficult to do.

Evidence of clinical outcomes

1. Are the company's overall survival and progression free survival extrapolations beyond the trial data plausible?
   Yes, from memory as we were shown figures, but we'd expect patients to live longer once this treatment is standard of care.

2. Is long-term survival data for uveal melanoma available?
   We don't have any additional data

3. Is treatment waning with tebentafusp expected (i.e. Will the treatment benefits with a Tebentafusp compared with the immunotherapy/chemotherapy comparator seen in the trial be sustained long term)?
   We cannot answer this question, but this is an aggressive cancer and so this treatment is extending life.

Quality of life

1. Is it reasonable to expect the quality of life for people with uveal melanoma who were treated with Tebentafusp to be similar to quality of life for people treated with Pembrolizumab (considering quality of life both on and after treatment)?

   Patients report few side effects to us on Tebentafusp. Those that do experience them, are well managed and short lived comparably we do hear of side effects on immunotherapy.

2. Are there any impacts on quality of life which would not be captured by the quality adjusted life year calculation (which includes data on mobility self-care usual activities pain anxiety/depression)?

   People tend to feel very well and continue with daily activities, even with quite severe disease. Psychologically this is hard, and patients and family members tend to be unprepared for the final stages of life as they can deteriorate extremely rapidly.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma ID1441

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with uveal melanoma or caring for a patient with uveal melanoma. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **25 April 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with uveal melanoma

Table 1 About you, uveal melanoma, current treatments and equality

1. Your name	Jo Gumbs
2. Are you (please tick all that apply)	☐ A patient with uveal melanoma? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with uveal melanoma? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	OcuMel UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	I support people through the OcuMel UK Helpline and am the administrator of our online patient and family forums. I hear many views on the various aspects of this condition. ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with uveal melanoma? **If you are a carer (for someone with uveal melanoma) please share your experience of caring for them**	My dad was a young 61-year-old with uveal melanoma. He ran his own business, was looking forward to his retirement, and had just become a grandad. I spent the days with my mum, so I would see him most days when he finished work. He was always doing something and rarely sat still, so when he first said something wasn't right, his GP began ordering tests and referred him to an oncologist. Months passed as we waited for various tests and results, so by the time we learnt his cancer had spread, it was in his liver, spine, and two other places. This was only two years after his initial diagnosis. Even though most of his liver was affected, he felt very well, and tiredness was his only symptom for months, followed by oedema in his legs. It wasn't until the day before he died that he said he didn't feel great. That night we called an ambulance, and he died the following afternoon. We couldn't believe how quickly he deteriorated as we'd only been shopping for a few days beforehand, but I now hear similar experiences from other families. Since then, I formed OcuMel UK to help others. I supported a handful of families for the first couple of years, but we grew rapidly as the demand was so high. People with this rare cancer were unable to connect with others before OcuMel UK was formed, so initially, I dedicated most evenings to support work but after a few

	years, I had to leave my previous role to work for OcuMel UK full-time. I have since spoken to numerous families and patients with similar fears and needs.
7a. What do you think of the current treatments and care available for uveal melanoma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a. We do not have enough treatment options. There are even fewer available on the NHS. Once uveal melanoma spreads, it is incurable and aggressive, and psychologically it is difficult for most patients as they know there are few treatment options. Currently, only 10% of people can have a liver resection, and so without this treatment, the remaining patients hopefully have a chance at trying immunotherapy. That does help some people, but Tebentafusp is more effective and tolerable for HLA-0201 positive people. There is no clear treatment pathway, so it can take 3-4 months before starting any treatment. During this time, people deteriorate, so we need people in front of an oncologist able to arrange Tebentafusp in a timely manner. 7b. I believe most patients, family members and clinicians would agree wholeheartedly. Since my father's tragic death nearly thirteen years ago, I have supported numerous families and worked with many clinicians, and I have not heard of anyone disagreeing with how devastating and difficult it is to treat uveal melanoma.
8. If there are disadvantages for patients of current NHS treatments for uveal melanoma (for example, how tebentafusp is given or taken, side effects of treatment, and any others) please describe these	No, the risk of not having Tebentafusp would outweigh any side effects, and most people would tolerate more severe side effects if it meant they had more time. The scale of the side effects we have been told of ranges from manageable to a mild inconvenience. One lady said her hair is now white, so she now has to use hair dye. She has had some dry skin for a short while, but she would not class it as a side effect as she is alive two years on. Her difficulty now was knowing how to live her life as she had not expected to be alive.

	Another person experienced severe itchiness and a fever, but this stopped two days after treatment and lessened in severity with each treatment. Fortunately, most people report mild symptoms and from their scans they know the treatment is helping them. It is a weekly infusion, and so in time, I am sure people would appreciate having a few weeks without needing treatment, so their holidays are not restricted, but this isn't a major issue for people given the severity of the disease.
9a. If there are advantages of tebentafusp over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does tebentafusp help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	It helps the majority of HLA-0201 positive people. When people think about what they would want in a cancer treatment, it would be that it extends life and is tolerable. This treatment ticks both these boxes and allows people to live a good life. Patients have reported they have an excellent quality of life, and they can continue to work/education, have no issues with self-care, and still look after others. The Get Data Out team recently published eye cancer stats for 2019. Of the 444 uveal melanoma patients diagnosed that year, 285 people (64%) of patients were under 70, 180 people (40.5%) were under 60 and 85 people (19%) were under 50 years old. We know that these people are likely to have young families, have normal independent lives, contribute to society, and feel good health even when they have advanced disease. We also know half of them will have metastatic disease, and their time is precious. Every week that goes by is significant in terms of their time and in their cancer progression. I know many people in their twenties and in their teens who are diagnosed, and sadly people in their early thirties who have died from metastatic disease. They had their whole life ahead of them, so the main advantage of this treatment is incredibly

	important - we are finally seeing people in our community who are alive years later. This simply did not happen a few years ago before Tebentafusp.
10. If there are disadvantages of tebentafusp over current treatments on the NHS please describe these. For example, are there any risks with tebentafusp? If you are concerned about any potential side effects you have heard about, please describe them and explain why	None that we aware of, and we've regularly gained feedback over the past 12-18 months.
11. Are there any groups of patients who might benefit more from tebentafusp or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	If they are HLA-0201 positive, then this treatment has a high chance of helping them.
12. Are there any potential equality issues that should be taken into account when considering uveal melanoma and tebentafusp? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	No. Once we have approval, it will help access to the drug for everyone who is suitable for it.

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Having a rare cancer brings many challenges to the patient and in terms of the treatments available. There is significantly less research money and less data to evaluate treatments such as these than trials involving many more patients. We must accept that some data cannot be available if we want fair and ethical trials, and we are yet to find a widely accepted model for clinical trials for rare cancers. Until then, I hope you can see the overall data gathered by this trial is hugely significant for our community so that future people can benefit from the research that has brought us this far. Tebentafusp is the first systemic breakthrough we have seen in treating this terrible disease, and you can see from my answers that I support approval of this treatment. We have to stop people dying of uveal melanoma. It has crushed too many families, so I sincerely hope this evaluation sees the benefit of Tebentafusp.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Mixed therapy (IC) as comparator precludes separate evaluation of tebentafusp versus each comparator *Section 2.3 and 3.2*	There is no standard of care and the comparators used in this trial are the current standard of choice treatments. Data is limited in this rare cancer as many hospitals see patients throughout the UK. It is accepted the comparators used have similar efficacy rates. We know patients on these comparators and for some who have progression, the progression to us seems slower. We cannot comment on why this is. These treatments are still a valued option for patients as they are our only other systemic treatments, but from the data we've seen, Tebentafusp is more effective.

Patient expert statement

Lack of comparison to nivolumab monotherapy *Section 2.3*	As above
Frequency of adverse events in tebentafusp We consider patient perspectives may particularly help to address this issue. Please explain how the side effects with tebentafusp compare to the side effects with other treatments for uveal melanoma. *Section 3.2.4*	Patients report few side effects to us on Tebentafusp. Those that do experience them, are well managed and short lived, comparably, we do hear of side effects on immunotherapy. People tend to feel very well and continue with daily activities, even with quite severe disease. Psychologically this is hard, and patients and family members tend to be unprepared for the final stages of life as they can deteriorate extremely rapidly without tebentafusp.
Model structure – Use of a partitioned survival model *Section 4.2.2*	Although the trial has to show comparators against tebentasfusp, we should be fair to people on the comparator arm. They are all people with an aggressive cancer, so I feel it's right that oncologists were able to use their clinical judgement in choosing the most appropriate treatment for their patient. It's rare uveal melanoma patients have several lines of treatments. It's usually too late to opt for second or third lines as it's so aggressive.
The use of the treatment mix in the IC arm of the IMCgp100-202 study as single comparator and not including nivolumab as comparator	

Patient expert statement

Section 4.2.4	
Long-term PFS and OS extrapolations *Section 4.2.6*	From the data we were shown, the extrapolations seemed reasonable, but we'd expect patients to live longer once this treatment is standard of care.
Not primarily using the IMCgp100-202 trial EQ-5D data and time-to-death HRQoL approach being inconsistent with common modelling practices *Section 4.2.8*	The feedback we have received has consistently shown that people's quality of life is improved with this treatment. It extends life, but people have a good quality of life.
One-off application of BSC costs *Section 4.2.9*	
Percentage of patients using each IC treatment *Section 4.2.9*	
Proportion of (PF)LYs accumulated beyond the observed data *Section 5.1*	
Probabilistic analyses for alternative OS, PFS and TTD assumptions *Section 5.3*	

Patient expert statement

Are there any important issues that have been missed in ERG report?	We feel it is important for cutaneous and uveal melanoma to be viewed as two different diseases. Detection, surveillance, treatment, prognosis all differ, but especially Quality of Life. Differences also include - Vision loss. If the eye is treated, it is common for most patients to have reduced vision in the affected eye or up to a third of people loss their eye. - Consequences of treatment. Following treatment to the primary, many patients face daily pain and discomfort, but it also affects your appearance and confidence. - Rare Cancer. This complicates a patients journey as less is known about the disease, patients need to travel long distances to one of 4 hospitals in the UK for treatment, but isolation is often reported as so few patients are diagnosed. - Psychological distress. People have an uncertain future. We know 50% of patients will progress to incurable metastatic disease. Patients are aware of this, but current prognostication methods are not 100% accurate.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- People are dying every week because of uveal melanoma
- It is truly a devastating disease
- With Tebentafusp, we now have a systemic treatment that helps the majority of patients who are HLA-0201 positive
- Tebetafusp allows people to live, with a good quality of life, and continue to contribute to society
- Any delays in accessing this treatment will mean more deaths for people with this rare cancer.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma ID1441

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Deadline for comments by **5pm** on **3 May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Part 1: Living with this condition or caring for a patient with uveal melanoma

Table 1 About you, uveal melanoma, current treatments and equality

1. Your name	Patient expert
2. Are you (please tick all that apply)	☒ A patient with uveal melanoma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with uveal melanoma? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	OcuMel UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with uveal melanoma? **If you are a carer (for someone with uveal melanoma) please share your experience of caring for them**	I was diagnosed with Uveal Melanoma in March 2019. I attended a regular 12 monthly eye examination at my opticians due to my increased risk of Glaucoma. My optician notes a bruise-like structure on the retina in my left eye and I was referred urgently to my local eye clinic. There it was confirmed that there was a likelihood of malignant melanoma in my eye and I was referred to one of the four specialist centres. I waited a very long month to be seen but was treated the following day with radioactive brachytherapy, an uncomfortable painful experience but ultimately successful at treating the primary melanoma. I was left with a painful eye, double vision which affected my ability to read, eat, even drink a cup of coffee, exhaustion, and three months off work as a self-employed person. I was told before the surgery of the long-term risks associated with Uveal Melanoma, the requirement for regular eye examinations at a specialist centre, the risk of reoccurrence in the eye and the need for six monthly liver examinations because of the risk of secondary cancer spreading from the primary tumour. The consultant told me 50% of people will get metastatic Uveal Melanoma and there aren't any approved treatments if it does spread. It was an awful lot of information to take in and I found it hard to cope with. My hospital gave me a leaflet for OcuMel UK and I contacted them. It has been a lifeline for me for support and information I have needed over the past three years. My gp helped where she could but rare diseases are exactly that….rare! She had never had a patient with this disease, neither had my optician. I decided to retire early because I was still having difficulties with my vision and work was busy and stressful. I would most likely have carried on for another few years had I not been diagnosed with cancer that no approved treatment options. I

	had some counselling to help me deal with my diagnosis which was really helpful to me. I know not everyone can access this. Today my eyesight is good, I am well, I have a busy active life and still drive and do all the things I love. I am a volunteer Ambassador for OcuMel to help bring members together socially and give back some of the support given to me. Uveal Melanoma is a very lonely diagnosis, it is a rare disease and it is very unlikely you will meet anyone else with it. Unfortunately for 50% of us it will progress to Stage IV disease, most likely with metastases of the liver but also bones, lungs and brain.
7a. What do you think of the current treatments and care available for uveal melanoma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a.The initial treatment of the tumour in the eye is usually well organised into the four regional centres, but patients can travel long distances for treatment. However, I would say this is preferable to being treated in a local eye department with no experience of uveal melanoma. When metastases do occur, there is no set pathway of referral for treatment. There are no approved treatments available through the NHS for this terminal diagnosis and only 10% of patients are suitable for liver surgery to remove the tumours. There is a liver directed treatment which shows promise and has been assessed by NICE, but it is only available privately at £40,000 per treatment at specialist centres. Apart from that there are some clinical trials but it can take months to access them which uses up what time you have left. 7b. I do not have metastatic cancer but I have watched friends being diagnosed and die for lack of suitable treatments. It is hard to live with, it makes the six-monthly scans even more stressful knowing there is really very little you can be offered should it be you next. I have had the chance to talk to one patient who has been offered Chemostat, the liver directed therapy, which has a good effect on her. However, she had a very difficult time raising £40,000 for each treatment and she needed three treatments. I have also spoken to two patients who have been on the Tebentafusp trial. They have responded well and have been on treatment now for over two years. They are able to carry on their lives, look after their children and continue working. Their tumours are not solely in the liver so systemic treatment is crucial to them both. Their side effects from treatment have become more

	manageable and less debilitating with each treatment. They both had skin rashes and itching and both have lost hair colour, eyelashes and eye brows. But they felt it was a small price to pay for being alive and living well. I know one lady who had been treated with the immunotherapy ipi/nivo through a trial and has had severe side effects. She is more stable now thankfully and has responded to treatment.
8. If there are disadvantages for patients of current NHS treatments for uveal melanoma (for example, how tebentafusp is given or taken, side effects of treatment, and any others) please describe these	There are no currently NHS approved drug treatments available for metastatic uveal melanoma. NICE approval of tebentafusp would be a complete game changer. We know only 50% of patients would be suitable because of the HLA-0201 positive status requirement but the treatment has a good success rate and tolerability. The requirement for weekly infusion could be a problem for some people, but I am sure most patients would adjust to this knowing they were on a potentially life saving treatment. The 10% of patients who are suitable for surgery will have to take time to recover afterwards and know there is a high risk of the melanoma returning to the liver afterwards. Repeat surgery may be possible if this happens but it is major surgery each time.
9a. If there are advantages of tebentafusp over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does tebentafusp help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	9a. Tebentafusp helps the majority of patients who are HLA-0201 positive. The safety profile and side effect profile of tebentafusp appear to be comparable to or better than with any other treatments for Stage IV uveal melanoma. The side effects appear to become less of a problem with subsequent treatments and only last a couple of days. With supporting medication like antihistamines and emollient creams the rashes and itching can be well controlled. The ladies I have spoken to have a good quality of life, continue to work and look after their children. Most of all they are still alive and well and enjoying life! 9b. I think being alive must be the biggest advantage of tebentafusp! 9c. The fact that tebentafusp has been available for the last couple of years as a trial drug in the UK and may now become available on the NHS gives all of us hope when we go for our six-monthly scans. The discovery of metastases is still a

	terminal diagnosis of an aggressive cancer and life is precious. If tebetafusp is approved then for those able to be prescribed it, it will enable us to continue with a productive life, continue to work and care for our children or relatives. It will take the stress off our relatives and reduce the fear and stress form liver scans. We now need another drug like it to treat the other 50% of patients who are not HLA-0201 positive!
10. If there are disadvantages of tebentafusp over current treatments on the NHS please describe these. For example, are there any risks with tebentafusp? If you are concerned about any potential side effects you have heard about, please describe them and explain why	No not that I am aware of, the patients I have spoken to are prepared to put up with the inconvenience of having to dye their hair or have eye brows tattooed back on for the huge advantage of feeling well and being able to carry on their lives.
11. Are there any groups of patients who might benefit more from tebentafusp or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	No I am not aware of any. I think all patients who required treatment for stage IV uveal melanoma should be considered for this as long as they test HLA-020 positive. This treatment may be more suitable for patients who may not be suitable for major surgery.
12. Are there any potential equality issues that should be taken into account when considering uveal melanoma and tebentafusp? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	I don't know if this drug has been tested as suitable for patients who are pregnant. I think once approved it would be suitable for all patients who fitted the test criteria.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Diagnosis with a rare disease like uveal melanoma is difficult to come to terms with and a lonely place to be. Our treatments for the primary tumour in the eye are limited, a variety of radiation treatments are available but they all involve surgery and a degree of blunderbuss approach. We are often left with residual damage and eye sight which will deteriorate over time. I have been lucky so far but have the beginnings of radiation retinopathy. Uveal melanoma is rare, only about 600 patients per annum are diagnosed with it in the UK. Which means about 300 of those patients will be diagnosed with metastases over the next two to three years. If tebentafusp were to be approved, financially for the NHS it still only a small number of patients with stage IV uveal melanoma patients who will require treatment, I think this should be part of the consideration for approval of this drug. We are not talking about thousands of patients requiring it annually. However it could make a huge difference to the quality of life and prognosis to people like me who may require it. To be honest we all just get on with it, we may have adjustments made at work, some people loose confidence to drive or find things like stairs and uneven surfaces a problem. The issue we all share is the six-monthly MRI or Ultrasound scans of the liver to check for metastases. This a nasty aggressive cancer, 50% of people will succumb with no proven treatments approved for use on the NHS. We need there to be a better solution than the current one which is to get yourself on a trial and hope for the best. This is not an old person's disease, that is a common misconception. Young people are diagnosed too, they have a whole life to lead and want to be able to live it well and thrive. I feel lucky, I am well looked after by the NHS so far, but I have had to arrange private MRI scans for optimal surveillance. There is a lack of options in the UK on treatment and care of uveal melanoma patients. Approval of tebentafusp by

	NICE would go some way towards addressing that and giving us hope for the future.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Mixed therapy (IC) as comparator precludes separate evaluation of tebentafusp versus each comparator *Section 2.3 and 3.2*	
Lack of comparison to nivolumab monotherapy *Section 2.3*	
Frequency of adverse events in tebentafusp We consider patient perspectives may	We hear of short- lived side effects that are well managed by the teams treating the patients in the clinical trial. If the side effects are of a higher grade than the investigator's choice, then the fact that they are self-limiting and short lived implies that should not have long term impact on the patient's lives.

Patient expert statement

particularly help to address this issue. Please explain how the side effects with tebentafusp compare to the side effects with other treatments for uveal melanoma. *Section 3.2.4*	
Model structure – Use of a partitioned survival model *Section 4.2.2*	I cannot comment on the model structure used to predict the data you need, but I know we have patients alive who otherwise would not be without the trial of tebentafusp. We know the large majority of people with metastatic uveal melanoma disease die and we know this treatment is helping people to live more than any other treatments available. As I have mentioned already, this drug is a game changer for our community and I hope you can see how much we need it as an option to treat stage IV patients.
The use of the treatment mix in the IC arm of the IMCgp100-202 study as single comparator and not including nivolumab as comparator *Section 4.2.4*	
Long-term PFS and OS extrapolations *Section 4.2.6*	
Not primarily using the IMCgp100-202 trial EQ-5D data and time-to-	

Patient expert statement

death HRQoL approach being inconsistent with common modelling practices *Section 4.2.8*	
One-off application of BSC costs *Section 4.2.9*	
Percentage of patients using each IC treatment *Section 4.2.9*	
Proportion of (PF)LYs accumulated beyond the observed data *Section 5.1*	
Probabilistic analyses for alternative OS, PFS and TTD assumptions *Section 5.3*	
Are there any important issues that have been missed in ERG report?	

Patient expert statement

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Patients like me are dying every week from uveal melanoma
- The effect of this disease is devastating to patients and their families
- Tebentafusp will be the first systemic treatment to treat the majority of patients who are HLA-0201 positive
- Side effects of tebentafusp can be managed and are short lived in the main, allowing patients to lead a good quality of life and contribute to society
- Delaying access to this drug will mean more deaths for people with this rare and aggressive cancer

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

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Technical engagement response form

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Thursday 10 March 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1 About you

Your name	Dr. Paul Nathan on behalf of Melanoma Focus
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Melanoma Focus
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Mixed therapy (IC) as comparator precludes separate evaluation of tebentafusp versus each comparator *Section 2.3 and 3.2*	Yes	This criticism is flawed. The suggested separate evaluation would be worthwhile if the literature demonstrated significantly different activity between these treatments. It does not. Outcomes with each of these interventions are uniformly poor. Chemotherapy median OS 10.2 months (95% CI 9.5-11) and 1 year OS 43% (40-47) (Khoja et al). Ipilimumab median OS 5.2 – 9.8 months across 5 studies, 1 year OS approx. 30%. Pembrolizumab median OS 7.6m – 9.6m (Algazi et al, van der Kooij et al). The fact that no agreed systemic standard of care is in place for patients with metastatic UM reflects the fact that patient outcomes are uniformly poor. Obviously if one particular treatment was deemed superior an IC arm would not have been acceptable to patients or clinicians. This was not the case. In practice 82% of patients on the IC arm received pembrolizumab and small patient numbers receiving chemotherapy or ipilimumab in the IC arm would preclude such an analysis. Even if it were possible however, we know enough about these treatments to know such comparisons would not reveal any difference in the margin of superiority of tebentafusp.
Lack of comparison to nivolumab monotherapy	No	This is a surprising suggestion. Both nivolumab and pembrolizumab bind to PD-1 and interfere with the PDL-1 binding site. Both agents are licensed for the treatment of many

Section 2.3		cancers. Despite this, no clinical trial has been performed comparing the two antibodies as there is no clinical indication from cross-trial comparisons within identical indications that there are any clinically significant differences between them. I wonder whether the ERG took any clinical advice on this point.
Frequency of adverse events in tebentafusp *Section 3.2.4*		I wasn't aware that the ERG had the appropriate skill set to consider the AE profile of the agent, or that this was in their brief. No clinicians are amongst the authors.
Model structure – Use of a partitioned survival model *Section 4.2.2*	Yes/No	No comment
The use of the treatment mix in the IC arm of the IMCgp100-202 study as single comparator and not including nivolumab as comparator *Section 4.2.4*	Yes/No	See answer to section 2.3 & 3.2
Long-term PFS and OS extrapolations *Section 4.2.6*	Yes/No	No comment
Not primarily using the IMCgp100-202 trial EQ-5D data and time-to-death HRQoL approach being inconsistent with common modelling practices *Section 4.2.8*	Yes/No	No comment
One-off application of BSC costs *Section 4.2.9*		

Percentage of patients using each IC treatment *Section 4.2.9*		
Proportion of (PF)LYs accumulated beyond the observed data *Section 5.1*		
Probabilistic analyses for alternative OS, PFS and TTD assumptions *Section 5.3*		

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Lack of clinical guidance for ERG	All	No	Comments in the report regarding nivolumab, the focus on clinical activity of ipilimumab and chemotherapy as well as AEs imply that there has been minimal specialist melanoma oncology advice given to the ERG. I could not see any acknowledgement in the report of input from clinical advisors. I wonder if the committee should be explicit about the ERG constitution. This may have helped the ERG focus on relevant issues.
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

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Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Immunocore Ltd.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG comments
Mixed therapy (IC) as comparator precludes separate evaluation of tebentafusp versus each comparator *Section 2.3 and 3.2*	Yes	In the response to the clarification questions, a breakdown of the clinical effectiveness results for each therapy in the IC arm were provided. The results included the median OS & PFS, 12-month OS & PFS and respective Hazard Ratios (HR) for each therapy (Section B4, Table 3 & Table 4, pages 10-11). While we agree that it would be desirable to have access to evidence regarding the comparative cost-effectiveness of tebentafusp versus each IC regimen separately, it would be both inappropriate and potentially misleading to attempt this for dacarbazine or ipilimumab. There are several related reasons why this is the case: • Patient numbers: During the technical engagement meeting the ERG argued that there was value in having the results of subgroup analyses regardless of the degree of uncertainty. By using the clinical data restricted to dacarbazine or ipilimumab it may be possible to obtain the	The ERG acknowledges the uncertainty of the requested results but would have liked, as noted in the technical engagement call, the company to provide these results as "exploratory analyses" supporting the decision-making of the committee.

		necessary model inputs to generate cost and QALY outputs. However, the patient and event numbers are small: 16 patients received ipilimumab (11 events) and 7 patients received dacarbazine (7 events), from the August 2021 data cut. Consequently, the difference of one or two events occurring will likely yield dramatically different ICERs with high uncertainty. Therefore, we consider that provided ICERs based on such subgroup analyses may only either be irrelevant to the appraisal committee or misleading if the uncertainty of such estimates were not adequately emphasised. Furthermore, sub-group analysis of OS showed that tebentafusp was superior to all treatments used in the IC arm. • There is also the issue of potential differences in the characteristics of patients that receive each separate IC regimen. Patients were randomised to either tebentafusp or IC arms and the benefits of randomisation in clinical studies thus apply. However, randomisation was not stratified between the different IC regimens, therefore, we cannot expect baseline prognostic factors to be balanced on average. This is true of all such unstratified subgroup analyses, but the impact of this could be extreme in this case where such small samples are involved. • Modelling results for dacarbazine and ipilimumab separately would also not reflect UK clinical practice. Clinical opinion indicates that dacarbazine and ipilimumab are now rarely used and that pembrolizumab is the comparator of interest (see for example, [NICE. Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]. NHS England and NHS Improvement budget impact analysis submission. 2021]). The data in the IC arm of the trial is primarily driven by pembrolizumab. Figure 1 below provides an overlay of the IC and separated pembrolizumab data using the August 2021 dataset. As expected, given that most patients are on pembrolizumab in the IC arm, the Kaplan Maier (KM) curves and extrapolation	

		model for pembrolizumab and the IC overlap. In terms of the ICER, it is increases slightly [redacted] compared to [redacted] in the base case. Figure 1: KM curves for IC and pembrolizumab fitted with standard parametric models 	
Lack of comparison	No	This issue was addressed in the call with ERG. The company re-stated that nivolumab monotherapy is not used in clinical practice in the UK.	As stated in the TE call, nivolumab "(alone or in combination with

to nivolumab monotherapy *Section 2.3*		Noting the scoping workshop stated: • Systemic treatments used in clinical practice vary, in the absence of alternatives those with a broad license for melanoma are used (pembrolizumab, ipilimumab, nivolumab [**with** ipilimumab], systemic chemotherapy [dacarbazine]) • None have shown any survival benefit in randomised trials in patients with metastatic uveal melanoma • The drug class and mode-of-action of nivolumab and pembrolizumab are the same: both are PD-1 inhibitors	ipilimumab)" was included in the NICE final scope. Therefore, the ERG highlighted the discrepancy between the scope and the decision problem addressed in the CS.
Frequency of adverse events in tebentafusp *Section 3.2.4*	No	(ERG report, Table 1.4, key issue 3) The ERG state that "Adverse events have been included in the economic model". Hence the cost-effectiveness results adequately reflect the balance of risks and benefits of tebentafusp.	As detailed in the ERG report, e.g. in Table 1.4, the ERG aimed to bring this issue to the attention of the committee but highlighted that AEs were indeed included in the economic model.
Model structure – Use of a partitioned survival model *Section 4.2.2*	No	• We acknowledge that the assumption of structural independence of endpoints is a limitation of partitioned survival models. However, as noted in NICE DSU TSD 19, "in the context of a within-trial analysis or a case in which data have been fully observed, PSM and state transition modelling approaches are expected to produce similar results if modelling and fitting have been done appropriately, as relationships between endpoints are reflected within the data.". Therefore, we consider that this problem is mitigated by the relative maturity of the trial data. • We consider that using a PSM or state-transition model would produce very similar results in the control arm, given that a high proportion of the OS and PFS events have been observed over the trial period. ○ Most of the progression events have been observed over the trial period with PFS reaching [redacted] in the IC arm with the August 2021	No compelling new arguments/evidence provided. Hence the ERG perspective as described in the ERG report remains unchanged.

		data cut-off. Hence, there is limited uncertainty in the extrapolation of the PFS endpoint. ○ In the IC arm, OS reached 10% at the end of the follow-up period with the October 2020 data cut-off (DCO), and [redacted] with the August 2021 DCO although this is not adjusted for the patients who crossed over from IC to tebentafusp after the October 2020 DCO. Additionally, we compared the extrapolation models with data from the literature (Rantala et al., 2019) and validated the choice of model with clinical experts. There is no significant uncertainty in the extrapolation of OS in the IC arm. • In the tebentafusp arm, PFS reached less than [redacted] at the end of the trial follow-up period with the August 2021 DCO. Hence, there is no significant uncertainty in the extrapolation of this endpoint. • We acknowledge that there is uncertainty in the extrapolation of OS in the tebentafusp arm. However, we note that the treatment effect size is larger for OS than for PFS, suggesting that PFS, defined as disease progression per RECIST v1.1 criteria, may be poorly correlated with OS. This has been documented for other types of immunotherapies like the checkpoint inhibitors, nivolumab and pembrolizumab (Gyawali and Prasad, 2017). Hence, the assumption of structural independence is likely to be less of a concern in this context. • Additionally, partitioned survival modelling is the most commonly used decision modelling approach used in NICE appraisals of advanced or metastatic cancers (Woods et al., 2017). • We note that in TA638 (July 2020), the ERG (Kleijnen Systematic Reviews – same ERG as in this current appraisal) made similar comments related to the limitations of PSM and questioned whether alternative modelling methods had been considered. The company replied that the main concern raised in NICE DSU TSD 19 was the assumption of structural independence between endpoints, which was mitigated by the relative maturity of the data. Consistent with TSD19, the ERG agreed with the	

		Company that the partitioned survival model is the mainstay of cancer modelling.	
The use of the treatment mix in the IC arm of the IMCgp100-202 study as single comparator and not including nivolumab as comparator *Section 4.2.4*	No	The ERG requested: "Scenario analyses exploring the effects on the ICER of each treatment option separately, also including treatment specific OS, PFS and TTD." However, we disagree that there is value in pursing this approach. The justification for this is that which is given in response to key issue 1. The question of including nivolumab monotherapy as a comparator was resolved in the technical engagement call (see response to Section 2.3 - Issue: Lack of comparison to nivolumab monotherapy).	No compelling new arguments/evidence provided. Hence the ERG perspective as described in the ERG report remains unchanged.
Long-term PFS and OS extrapolations *Section 4.2.6*	No	Progression-free survival: • As detailed in response to issue 4, most of the progression events have been observed over the trial period with PD reaching [redacted] in the IC arm and [redacted] in the tebentafusp arm at the end of the trial follow-up period (August 2021 DCO). Hence, there is minimal uncertainty in the extrapolation of the PFS endpoint in either arm of the trial given the maturity of the data. • Six standard parametric models have been fitted (exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma) and have been implemented in the model to allow assessment of the choice of distribution on the model results. The choice of extrapolation model was made based on the visual and statistical fit to the trial data and clinical expert's opinion. Scenario analyses using different distributions were presented in the company submission and resulted in less than a 1% change in the ICER. Overall survival	No compelling new arguments/evidence provided. Hence the ERG perspective as described in the ERG report remains unchanged.

		• A large proportion of events were observed in the investigator's choice arm, with OS reaching [redacted] at the end of the follow-up with the August 2021 DCO) (although this does not account for the patients crossing over from IC to tebentafusp). To support the choice of distribution the fitted extrapolation models were discussed with clinical experts and compared to historical data (Rantala et al., 2019), to which the trial data showed good overlap. Therefore, there is relatively low uncertainty in extrapolation of OS for the IC arm. • We acknowledge that there is uncertainty in the long-term extrapolation of OS in the tebentafusp arm. The plausibility of different extrapolation model fits was discussed with clinicians in the absence of an external data source for insight on the most appropriate model fit. The uncertainty and impact on the results was explored using a range of parametric models (e.g., DSA, PSA, scenarios).	
Not primarily using the IMCgp100-202 trial EQ-5D data and time-to-death HRQoL approach being inconsistent with common modelling practices *Section 4.2.8*	No	• Based on clinical experts' opinion, disease progression assessed by RECIST v1.1 criteria is not a good marker for decline in quality of life (QoL) in this patient population. Clinicians have observed that patients maintain their quality of life until about 3-6 months before death when symptoms appear and impact on their QoL. We observed limited change in the EQ-5D utility value between baseline and end of treatment in the IMCgp100-202 Phase III trial, and similar for EORTC QLQ-C30 data, which supports this case. • Therefore, applying quality of life data based on time to death is more aligned with the clinical deterioration of patients, rather than by pre- and post-progression using PFS data. • The data presented is an early read out of the clinical trial (first interim analysis October 2021), EQ-5D data was limited and so published EQ-5D utilities were used. We used data from TA366 in advanced cutaneious melanoma, which was considered an acceptable proxy by clinical experts.	No compelling new arguments/evidence provided. Hence the ERG perspective as described in the ERG report remains unchanged.

		• The baseline utility from the IMCgp100-202 clinical trial was used and combined with the published TTD utility from TA366, to derive utilities for the different times to death categories as a way of mitigating the use of utility data from a different patient population. • This approach has previously been accepted, for example in TA531 (July 2018) and TA650 (September 2020).(July 2018) and TA650 (September 2020).	
One-off application of BSC costs *Section 4.2.9*	No	The approach to accounting for the costs of BSC for patients with PD recommended by the ERG is to apply the same fixed cost to each month that patients are in PD, irrespective of the treatment arm. This assumes that the rate of healthcare consumption is equal regardless of whether patients were previously treated with tebentafusp or IC after disease progression, as captured by specific treatments used after progression in the clinical study and included in the model. The application of a one-off cost equivalent to four months of healthcare resource use (taken from (McKendrick et al., 2016)) makes the alternative assumption that each patient uses the same resource in PD regardless of the duration of time spent in this health state. This implies that the rate of healthcare resource utilisation is inversely proportional to the time spent in this state, so that although patients entering PD from tebentafusp may spend longer in PD this reflects the fact that their disease is less severe. This logic is also underpinning the time-to-death health state utilities approach and the application of end-of-life costs at the point of death to account for the decline in health status then. In the cancer treatment more broadly, there are studies that examine the variation in healthcare resource use. A trend of reduced monthly healthcare costs with delayed progression or increased follow-up has been reported, for example, in Reyes et al. (2019) and Ray et al. (2013) A further reason that we would expect the rate of healthcare resource use to be lower for patients in the tebentafusp arm is that 43.3% of patients continued to receive tebentafusp for some time following progression.	No compelling new arguments/evidence provided. Hence the ERG perspective as described in the ERG report remains unchanged.

		As reported in the literature, variation in post-progression resource use and the use of tebentafusp post-progression, we do not consider that the ERG's assumption that PD following tebentafusp and PD following IC are equivalent in terms of resource use to be reasonable. We argue that, although evidence backing either assumption is limited, the approach of applying a fixed cost independent of time in PD is likely to be the most reasonable approach to handling BSC costs.	
Percentage of patients using each IC treatment *Section 4.2.9*	No	• The mix of regimens and proportion of usage of these in the IC arm of the IMCgp100-202 trial were assessed by clinical experts and considered representative of UK clinical practice. • In the NHSE budget impact assessment the following was noted: *"In practice dacarbazine is now rarely used in malignant melanoma so should not be used as a comparator in the BIT, similarly single agent ipilimumab is rarely used as ipilimumab is now preferred to be given in combination with nivolumab. This mirrors the trial in which the majority of patients (82%) received pembrolizumab, (13%) received ipilimumab and (6%) received dacarbazine."* • Therefore, modelling the treatment mix as a single comparator, with the costs weighted by the proportion of treatments is appropriate to the decision problem. • Additionally, the proportion of patients on each of the regimen in the IC arm can be varied in the model with proportional adjustment of the treatment costs. Scenarios of this have been provided in the response to the clarification questions. • Incorporating treatment specific OS, PFS and TTD data is not appropriate. As explained in the responses to issue 1 and issue 5, the number of patients on ipilimumab (n=16) and dacarbazine (n=7), and the number of events are very low, which could lead to unreliable estimates of OS, PFS, and TTD and high level of uncertainty, and misleading model results.	No compelling new arguments/evidence provided. Hence the ERG perspective as described in the ERG report remains unchanged.

Proportion of (PF)LYs accumulated beyond the observed data *Section 5.1*	No	As detailed in response to issue 6, most of the progression events were observed over the trial follow-up period in both arms, with progression reaching [redacted] in the tebentafusp arm and [redacted] in the IC arm with the August 2021 DCO. Hence, the PFS data is mature and PFLYs accumulated beyond the observed data is a small proportion of the total for both the tebentafusp arm and IC arm.	No compelling new arguments/evidence provided. Hence the ERG perspective as described in the ERG report remains unchanged.
Probabilistic analyses for alternative OS, PFS and TTD assumptions *Section 5.3*	Yes	The model has been updated to allow running PSA for any combination of OS, PFS and TTD extrapolation models.	The ERG thanks the company for updating the model

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

Reference list

- GYAWALI, B. & PRASAD, V. 2017. Combining drugs and extending treatment — a PFS end point is not sufficient. *Nature Reviews Clinical Oncology,* 14**,** 521-522.
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- RAY, S., BONTHAPALLY, V., MCMORROW, D., BONAFEDE, M. & LANDSMAN-BLUMBERG, P. 2013. Patterns of treatment, healthcare utilization and costs by lines of therapy in metastatic breast cancer in a large insured US population. *Journal of Comparative Effectiveness Research,* 2**,** 195-206.
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- WOODS, B., SIDERIS, E. B., PALMER, S., LATIMER, N. R. & SOARES, M. O. NICE-DSU TECHNICAL SUPPORT DOCUMENT 19 : PARTITIONED SURVIVAL ANALYSIS FOR DECISION MODELLING IN HEALTH CARE : A CRITICAL REVIEW REPORT BY THE DECISION SUPPORT UNIT 2 June 2017. 2017.

The updated ERG base-case results (deterministic) are provided below. Compared with the original ERG base-case the tebentafusp PAS was updated, the tebentafusp treatment duration cap was removed and the infusion costs were updated.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Original CS base-case					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Original ERG base-case 1 (Extrapolation of OS – generalised gamma)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Original ERG base-case 2 (Extrapolation of OS – log logistic)					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Original ERG base-case 1 + updated PAS + no treatment cap + updated infusion costs					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	238,748
Original ERG base-case 2 + updated PAS + no treatment cap + updated infusion costs					
Tebentafusp	[redacted]	[redacted]			
IC	[redacted]	[redacted]	[redacted]	[redacted]	230,366

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IC = investigator's choice; OS = overall survival; QALY = quality adjusted life years;