Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma

For public– contains redacted information

Technology appraisal committee A [04th July 2023]

Chairs' Presentation

Chair: Dr Radha Todd

Vice chair: Dr James Fotheringham

Evidence assessment group: Kleijnen Systematic Reviews

Technical team: Vicky Gillis-Elliott, Christian Griffiths, Janet Robertson

Company: Immunocore

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Tebentafusp is not recommended for routine use and did not meet criteria for inclusion in CDF

RECAP

Clinical effectiveness

- No standard care: the 82% of people who had pembrolizumab in trial are most relevant to NHS clinical practice
- Tebentafusp improves OS and seems to have a benefit after progression but reason for this is unclear

Cost effectiveness

- Highly uncertain OS modelling but standard parametric approaches are most appropriate
- 2-year stopping rule not appropriate in model
- Cost-effectiveness estimates higher than what NICE considers a cost-effective use of NHS resources. Most plausible ICER was over £250,000 per QALY gained

Cancer Drugs Fund

- ICERs had no plausible potential to be cost effective
- If included in CDF, end of life criteria would not apply in future review and it's unknown if severity modifier is applicable

Abbreviations: CDF, Cancer Drugs Fund; ICER, incremental cost effectiveness ratio; OS, overall survival.

Key issues

= main driver of the difference between the company and ERG's results

Overall survival extrapolations

- Do committee agree that OS results should not be adjusted for crossover?
- Should a piecewise approach be used to extrapolate OS in the tebentafusp arm?

Progression-free survival and time to treatment discontinuation

- Should a piecewise approach be applied for PFS and TTD?

Other model updates: costs

- Should BSC costs be applied as one-off costs or applied per cycle?

Abbreviations: BSC, best supportive care; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation

Recap from 1st meeting

Including updated data from company's response to ACD

NICE National Institute for Health and Care Excellence

Tebentafusp (KIMMTRAK, Immunocore)

Mechanism of action	Targets human leukocyte antigen-A*02:01 (HLA-A*02:01) uveal melanoma tumour cells, and activates T-cell anti-tumour activity
Marketing authorisation	Monotherapy for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma
Administration & dose	Intravenous infusion Day 1: 20 µg Day 8: 30 µg Day 15 and then once a week: 68 µg First 3 doses to be followed by monitoring for at least 16 hours for the signs and symptoms of cytokine release syndrome
List price	£10,114 per vial; average cost of treatment course £326,888
Patient access scheme	PAS discount agreed amended after ACD consultation

Abbreviations: µg microgram; ACD, appraisal consultation document; PAS, patient access scheme

Treatment pathway

Based on company submission and clinical expert statement:
There is no nationally accepted standard of care for metastatic uveal melanoma
Immunotherapy or chemotherapy can be offered, based on licences for melanoma in general which do not distinguish between cutaneous and uveal melanoma

Options include:

- Pembrolizumab
- Ipilimumab
- Nivolumab with ipilimumab (company state nivolumab monotherapy not used in clinical practice)
- Dacarbazine

Best supportive care may also be considered

At ACM1 the committee concluded pembrolizumab should be key comparator in the model

Pivotal trial: IMCgp100-202

RECAP

Trial design	Randomised, open-label, phase 3 trial	
Population	• Adults with uveal melanoma (UM) • No prior therapy for metastatic or advanced UM (prior therapy for localised disease allowed) • Mean age, 62	
Intervention/ comparator	**Tebentafusp (n=252)** IV infusion with dose escalation, up to day 15	**Investigators choice (n=126):** • Dacarbazine (n=7, 6%) • Ipilimumab (n=16, 13%) • Pembrolizumab (n= 103, 82%)
Outcomes	• Overall survival (primary endpoint) • Overall survival in people randomised to tebentafusp who develop rash within 1st week of treatment	• Progression-free survival • Overall response rate • Duration of response • Adverse effects
Stratification	• Lactate dehydrogenase levels (associated with prognosis)	

NICE Professional org: clinical trials for tebentafusp do not reflect current UK clinical practice

Company's analyses

NICE National Institute for Health and Care Excellence

Company's analyses

- At ACM 1, the company provided the following data from the IMCgp100-202 trial
  - PFS data comparing tebentafusp with IC (October 2020 and August 2021 data cut-off)
  - OS data comparing tebentafusp with IC (October 2020, August 2021 and February 2022 data cut-off)
- After consultation, the company updated its cost-effectiveness analyses with data from IMCgp100-202 (April 2022 data cut-off). It also updated the modelling based on a comparison of tebentafusp with pembrolizumab
- The company provided additional data based upon the most recent survival data from IMCgp100-202 (November 2022 data cut-off). This was used to support its updated analyses but was not included in the company's model

Abbreviations: ACM, appraisal committee meeting; OS, overall survival; PFS, progression-free survival; IC, investigator choice

Progression-free survival results vs investigator choice

Tebentafusp associated with median improvement in progression-free survival of [redacted] months

Progression-free survival (investigator assessed) IMCgp100-202		
	Median (months) KM estimates (95% CI)	
	Oct 2020 cut-off	Aug 2021 cut-off
Tebentafusp (n=252)	3.3 (3.0 to 5.0)	[redacted]
Investigator choice† (n=126)	2.9 (2.8 to 3.0)	[redacted]
Hazard ratio	0.73 (0.58 to 0.94)	[redacted]

†IC included dacarbazine, ipilimumab and pembrolizumab

Company's response to ACD: PFS not collected for Apr 22 data cut off. For the model base-case, tebentafusp PCP subgroup and pembrolizumab subgroup were used

KM PFS for August 2021 cut-off

[redacted]

Abbreviations: KM, Kaplan-Meier; CI, confidence interval; PFS, progression-free survival; IC, investigator choice; OS, overall survival.

Overall survival for ITT results vs investigator choice (1)

Tebentafusp associated with median improvement in overall survival of [redacted] months

IMCgp100-202 OS (ITT)				
	Median (months) KM estimates (95% CI)			
	Oct 2020 cut-off	Aug 2021 cut-off*	Feb 2022 cut-off*	**April 2022 cut-off***
Tebentafusp (n=252)	21.7 (18.6 to 28.6)	[redacted]	[redacted]	[redacted]
Investigator choice† (n=126)	16.0 (9.7 to 18.4)	[redacted]	[redacted]	[redacted]
Hazard ratio	0.51 (0.37 to 0.71)	[redacted]	[redacted]	[redacted]

*Cross over was allowed in IC arm from Oct 2020 (planned interim OS data cut off);
by Aug 2021, [redacted] had crossed over – no adjustment

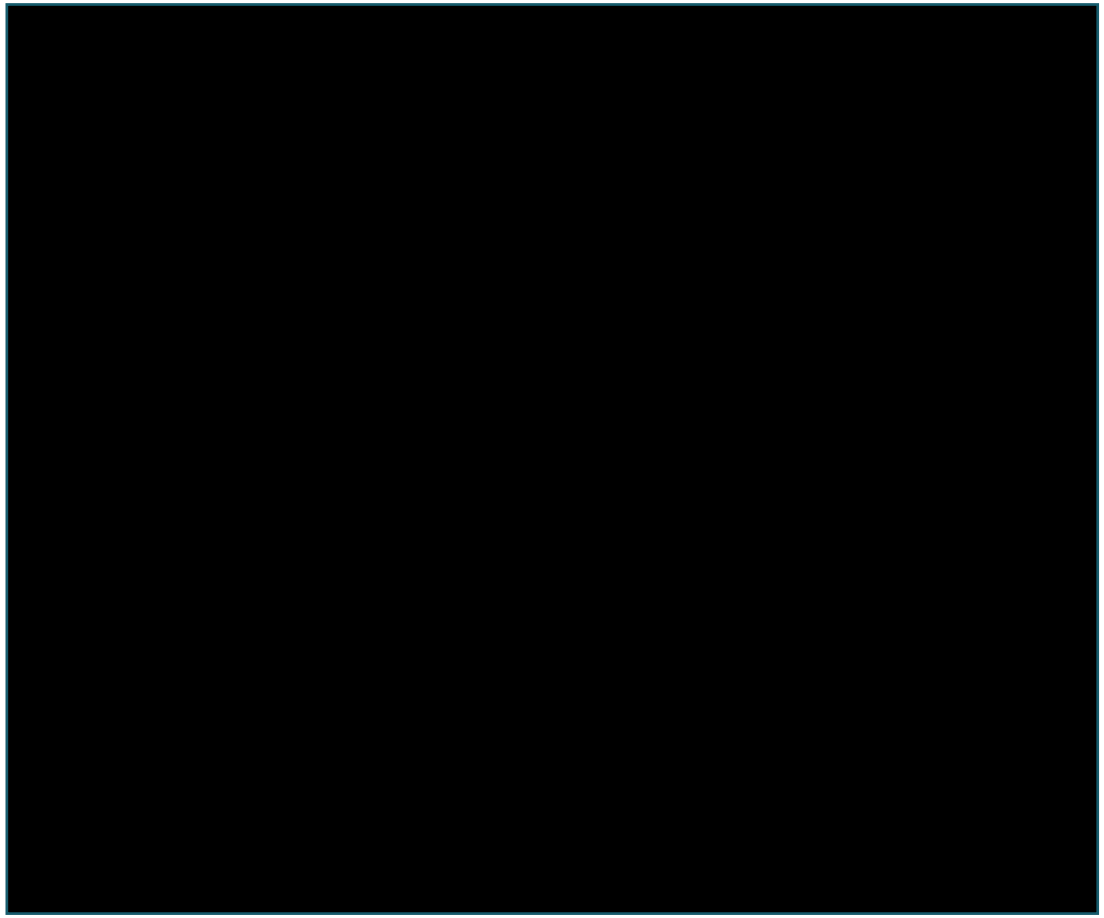
April 2022 cut off: Of 126 in IC arm, there were [redacted] deaths; [redacted] were censored

†IC included dacarbazine, ipilimumab and pembrolizumab

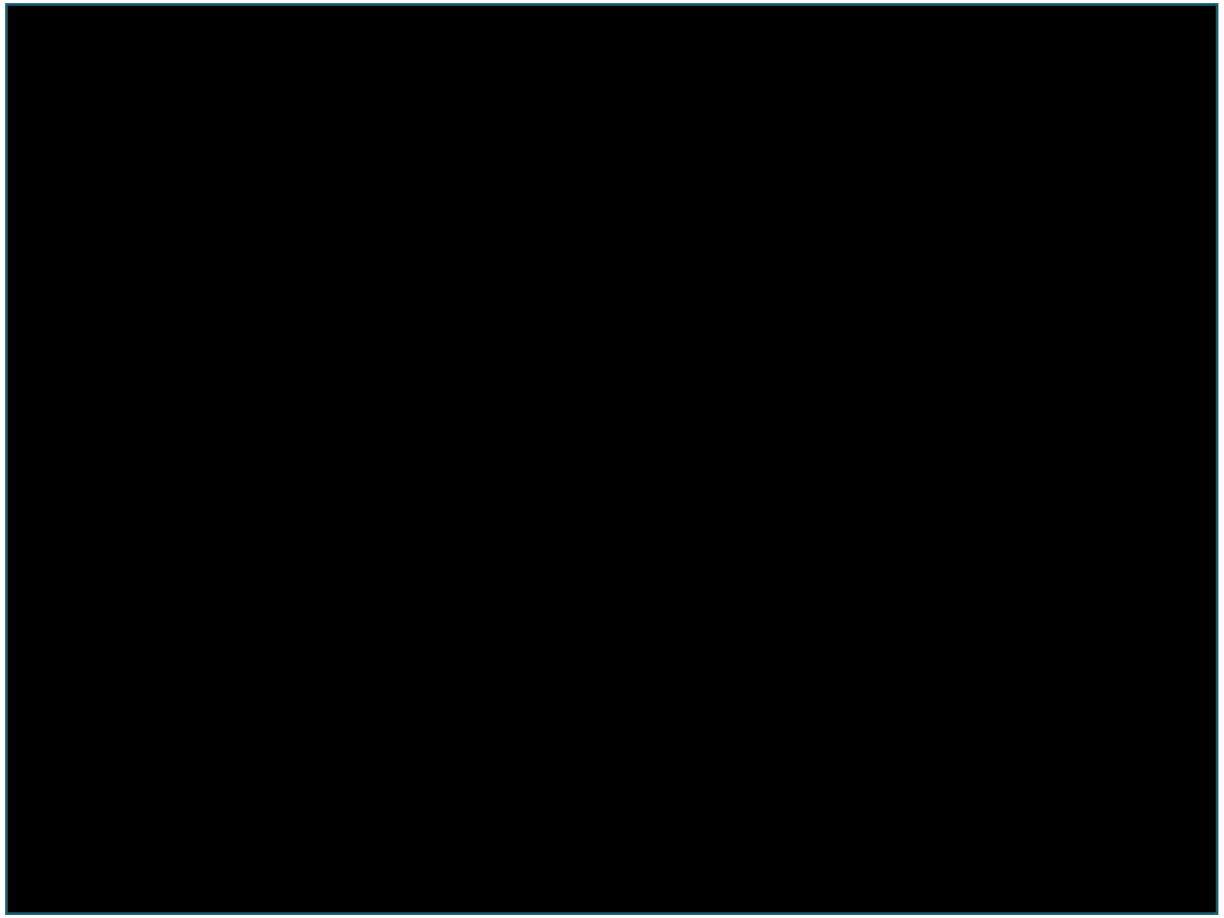
Abbreviations: KM, Kaplan-Meier; CI, confidence interval; IC, investigator choice; ITT, intention-to-treat; OS, overall survival.

Overall survival for ITT results vs investigator choice (2)

KM OS April 2022 ITT dataset



KM OS Nov 2022 ITT dataset



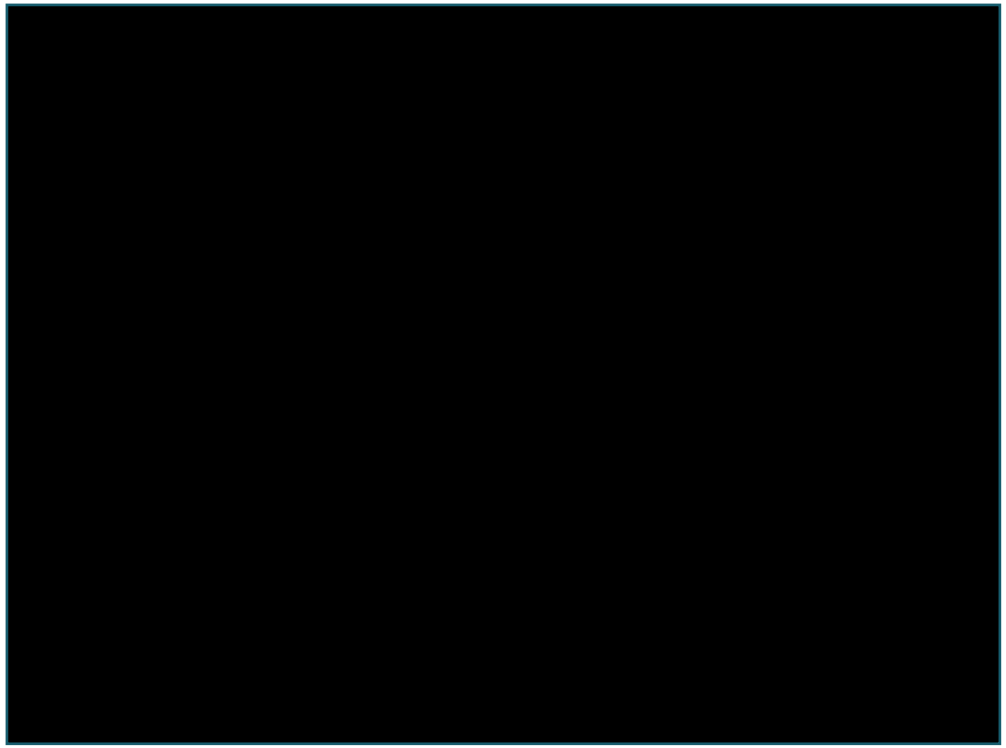
†IC included dacarbazine, ipilimumab and pembrolizumab
Abbreviations: KM, Kaplan-Meier; CI, confidence interval; IC, investigator choice; ITT, intention-to-treat; OS, overall survival.

Overall survival for subgroup tebentafusp PCP vs pembrolizumab

IMCgp100-202 OS (pre choice pembrolizumab population)	
	Median (months) KM estimates (95% CI)
Nov 2022 cut-off	
Tebentafusp PCP (n=252)	[redacted]
Pembrolizumab (n=103) *	[redacted]

*includes 14 patients who crossed over to tebentafusp arm

KM OS Nov 2022 PCP subgroup



Company response to ACD:

- KM data show survival probability reaches 0 at 5 years in pembrolizumab arm

ERG:
Sudden drop in numbers at risk in pembrolizumab arm at same time point can explain sudden reduction but data uncertain due to lack of precision estimates

NICE

Abbreviations: CI, confidence interval; OS, overall survival.; PCP, pre choice pembrolizumab

Consultation responses

NICE National Institute for Health and Care Excellence

ACD consultation responses

Received from

- **Company:** Immunocore
- **2 patient organisations:**
  - OcuMel
  - Melanoma Focus, including a clinical expert testimony
- **1 patient expert**
- **Web comments (n=2)**

Abbreviations:

Patient organisations, web comments and patient expert (1/2)

Population

- Pleased tebentafusp could be used as first line treatment and can be used second line treatment if required
- Ocular melanoma is usually seen as affecting older people but many who are diagnosed are working age and still work through the diagnosis

Unmet need and burden of disease

- Welcome recognition of severity of condition, burden from regular scans and anxiety about developing metastases
- Concerned recommendation does not fully recognise unmet need of metastatic uveal melanoma patients who have no other treatment option that gives tangible benefit
- Given short life span, increase in median OS would make a huge difference to patients and their families
- Very rare condition - evidence will never be as robust as a more common cancer

Testing for HLA-A*02:01

- Can take up to 6 weeks to get test results. Would it be possible to improve delay at all?

Abbreviations: ACD, appraisal consultation documernt; OS, overall survival.

Patient organisations, web comments and patient expert (2/2)

CDF

- Uncertainty about OS is common for new oncology treatments. Any clinical uncertainty could form basis of referral to CDF rather than patients having no treatment options

2 year stopping rule

- Agree a 2-year stopping rule lacks a clear clinical rationale and not appropriate to include in guidance to the NHS
- Treatment should be available to those that benefit beyond an arbitrary 2 year cut off

Modelling OS

- Acknowledge concern with modelling OS and hopes Immunocore will submit data using the preferred approach to address this and improve the overall clinical and cost effectiveness of Tebentafusp
- Request for longer follow up of patients up to 5 years from start of treatment suggests committee do not understand the very short survival without treatment. Prospect of living beyond 2 years, maybe up to 5 years would be a fantastic for any patient with stage 4 uveal melanoma
- Reasonable to consider different models to best fit each curve

Abbreviations: CDF, Cancer Drugs Fund; OS, overall survival.

Company updated base case (1)

Issue	Committee preference from ACM1	Company updated base case	ERG preferred base case
Analysis set	Clinical effectiveness data for 82% in trial who had pembrolizumab	Tebentafusp arm = subgroup pre-selected for pembrolizumab IC arm = pembrolizumab subgroup	ERG were satisfied with company updated base case
Clinical effectiveness data	Longer-term evidence with up to 5-years follow up would help reduce uncertainty with overall survival extrapolation	IMCgp100-202 study data cut updated to April 2022 for OS and PFS in model Provided additional supportive data for Nov 2022 data cut off	
Stopping rule	Exclude 2-year stopping rule	Updated model to remove stopping rule	

Abbreviations IC, investigator choice; OS overall survival;. PFS, progression free survival

Company updated base case (2)

Issue	Committee preferences at ACM1	Company updated base case	ERG preferred base case
Modelling OS	Standard parametric curves in both treatment arms	Tebentafusp arm = piecewise model (KM + log-normal) IC arm – no change (Weibull)	Fully parametric model in each arm (Generalised gamma or Log-logistic)
	Adjust for crossover	Company did not adjust for crossover; ERG consider this mirrors clinical practice	
Modelling PFS and TTD	Either piecewise or fully parametric models	PFS Not changed from ACM1 TTD uses April, 2022 data cut Piecewise model in each arm (KM + exponential for each arm)	Fully parametric model in each arm (Generalised gamma)
Compliance adjustment	Did not comment	Company = 92% tebentafusp; 100% pembrolizumab ERG = applied company assumption but consider adjustment should be equal or excluded for both arms	

Abbreviations: ACM, appraisal committee meeting; IC, investigator choice; ITT, intention to treat; KM, Kaplan Meier; OS overall survival; PFS, progression free survival; TTD, time to treatment discontinuation

Key issue: Updated comparator and population

ACD

- Subgroup data from main trial suggested worse outcomes with dacarbazine, and better outcomes for ipilimumab compared with pembrolizumab but data was highly uncertain
- Model included some that crossed over from IC arm to tebentafusp, but did not adjust OS
- Committee conclude pembrolizumab should be key comparator and model should be adjusted for crossover

Company response

Updated control arm

- Updated model to compare tebentafusp with pembrolizumab
- Base case uses pembrolizumab subgroup, including survival follow-up when patients had crossed-over from pembrolizumab to tebentafusp.

ERG comments

- Company used ITT without censoring to account for participants crossing over
- ERG consider this is the most robust approach that mirrors clinical practice

Do committee agree that OS results should not be adjusted for cross-over?

Abbreviations: ITT, intention to treat, OS, overall survival

Key issue: Modelling overall survival (1)

ACD

- Company originally used 3-knot spline for extrapolation of OS in tebentafusp arm and a Weibull model for IC arm
- Committee considered this might over-estimate proportion of long-term survival and preferred a standard parametric approach to extrapolate OS in both treatment arms

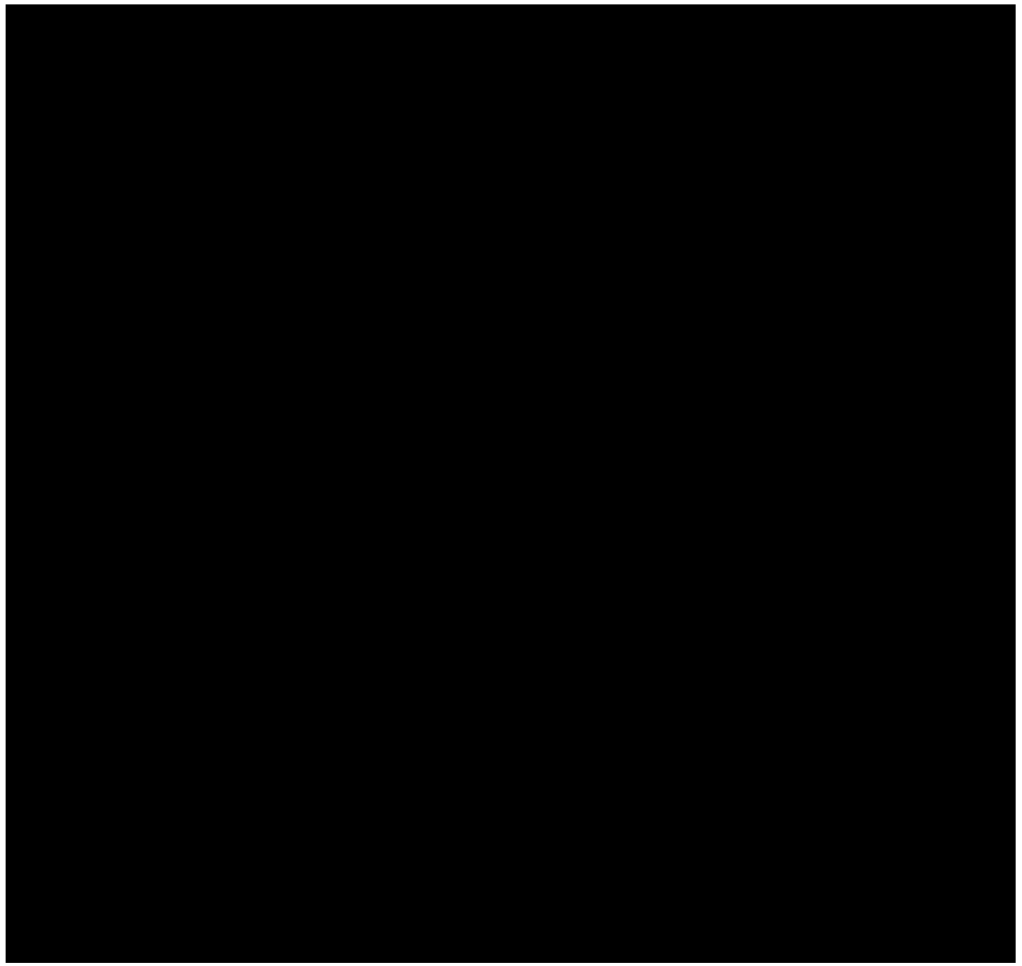
Company response

- Updated base case with more recent data cut (April 2022) to reduce uncertainty
- Tebentafusp arm uses piecewise model (separate survival models are fitted to defined portions of survival data)
  - KM data for 1st phase (increasing hazard) and standard parametric (lognormal) for 2nd phase (decreasing hazard)
  - Piecewise approach more robust and provides best fit to data
- Pembrolizumab arm uses standard parametric (Weibull) model in line with ACD recommendation and NICE TSD 21
  - Weibull is most clinically plausible estimate and likely over-estimation of survival, compared to historical data for 1st line treatments (based on Rantala et al. 2019)

Abbreviations: ACD, Appraisal Consultation Document; ERG, Evidence Review Group; IC, investigator choice; OS, overall survival; PCP, pre-choice pembrolizumab; TSD, technical support document

Key issue: Modelling overall survival (2)

KM OS for tebentafusp PCP for April 2022, Nov 2022 and piecewise extrapolation



ERG comments

- Piecewise approach has several limitations
  - Using KM curves might overfit trial data - suboptimal for decision-making
  - Conditional survival (proportion surviving up to cut-point) in parametric model might differ from that from KM curve
  - Cut-point used was treatment-dependent but NICE TSD 21 notes a limitation of using cut-points because they may be arbitrary and could influence results
- ERG prefers standard parametric approach (generalised gamma or log-logistic
- Agree Rantala et al (2019) is a useful benchmark but it contained retrospective analyses so should be 'lower limit benchmark'

Notes: *, pre-choice pembrolizumab. Abbreviations: ACD, Appraisal Consultation Document; ERG, Evidence Review Group; OS, overall survival

Company justification of piecewise model for extrapolating tebentafusp overall survival

- Increase followed by a decrease in hazards suggests a piecewise model is most suitable for tebentafusp
  - Dataset split at 28 months, point from which hazard is monotonically decreasing
- Distinct hazards plots between treatment arms supports use of different parametric modelling for tebentafusp and pembrolizumab arms

Kaplan Meier (04-April-2022 data-cut)

Hazard plot (04-April-2022 data-cut)

Should a piecewise approach be used to extrapolate OS in the tebentafusp arm?

Modelling progression free survival and time to treatment discontinuation

ACD

- Company used piecewise (KM and generalised gamma) to model PFS and TTD ERG preferred fully parametric (generalised gamma) for both arms
- Committee considered both extrapolation methods were reasonable

Company response

- Did not update modelling of PFS from the original Company base case.
  - Based on August 2021 data, piecewise model with KM data and generalised gamma
- Updated TTD in model with April 2022 data set
  - Tebentafusp PCP arm [redacted] events from 92 patients and pembrolizumab arm [redacted] events from 91patients were observed
- Piecewise approach retained (Kaplan-Meier curve plus exponential in both arms. (at cut off 25% at risk in tebentafusp PCP arm and 15% in pembrolizumab arm)

ERG comments

- standard parametric extrapolation is most appropriate

Should a piecewise approach be applied for PFS and TTD?

NICE

Abbreviations: ACD, Appraisal Consultation Document; DCO, data cut off; ERG, Evidence Review Group; OS, overall survival; PCP, pre-choice pembrolizumab; PFS, progression free survival; TTD time to treatment discontinuation

Other model updates: costs

ACD

- Company applied BSC costs as one-off costs and ERG applied monthly costs but this had little impact on cost-effectiveness results

Company response

Retained original assumption at ACM 1:

- Applied one-off costs based on McKendrick et al. 2016 to reflect average BSC costs (4 months) assumes each patient uses the same resource in progressive disease regardless of time in this health state.
- Applying fixed cost independent of time in PD is most reasonable for BSC costs

ERG comments

- Company did not provide appropriate justification why BSC costs were not applied per cycle in the PD health state
- Post-progression costs will likely depend on how long people stay in PD state
- Prefer monthly BSC costs per cycle in PD health state (removing end of life costs to prevent potential double counting) but could not include in updated analyses

Should BSC costs be applied as one-off costs or applied per cycle?

Abbreviations: ACD, appraisal consultation document; ACM, appraisal committee meeting; BSC, best supportive care, PD, progressive disease

Other uncertainties: utility values (1)

ACD

- Company used utility values from TA366 but ERG suggested using EQ-5D data from trial
- Committee noted both company and ERG base cases used time to death approach and consider estimates of utility values is unlikely to be important driver of CE results.

Company response

No changes in how utility data were modelled

- high proportion of missing EQ-5D data from trial (missing observations at baseline, missing at end of treatment and in survival follow-up)
- Carried out imputation for missing data but based on clinical opinion took utility values from TA366 (advanced melanoma) based on time to death instead of disease status

Missing observations in IMCgp100-202

Phase of trial	Missing observations (%)	Imputation performed
Baseline	[redacted]	mean imputation
End of treatment phase	[redacted]	multiple imputation
Survival follow up	[redacted]	MCAR

Abbreviations: ACD, Appraisal Consultation Document;, CE, cost-effectiveness; MCAR missing completely at random; OS, overall survival; PCP, pre-choice pembrolizumab; PFS, progression free survival; TTD time to treatment discontinuation

Other uncertainties: utility values (2)

ERG comments

ERG had concerns with company's approach

- Company did not justify appropriateness of using TA366 (advanced melanoma) utility values instead of trial data
  - It is a different population with different treatment options
  - Company did not explore other potentially relevant TAs
- Imputation approaches were not appropriately justified
  - Mean imputation distorts the distribution of imputed data
  - Company removed incomplete data before analysis which could bias estimates
- Time to death utility approach inconsistent with the model structure; implementation not transparent and lacks face validity
- Based on clinical opinion, company only applied treatment utility decrements for the first cycle, and assumed that AEs have no impact on HRQoL after that
  - ERG consider there was no comprehensive justification for this but retained company's modelling approach

Abbreviations: ACD, Appraisal Consultation Document; AE, adverse event; CE, cost-effectiveness; HRQOL, Health-related quality of life; OS, overall survival; PCP, pre-choice pembrolizumab; PFS, progression free survival; TTD time to treatment discontinuation

Unchanged assumptions:

At ACM1 Committee considered assumptions had little impact on CE results at ACM1 but ERG consider still uncertainty

Parameter	ACD	Company base case	ERG
PFS and TTD extrapolation	• Company used piecewise model ERG preferred fully parametric • Committee considered both methods were reasonable	Retained original piecewise approach PFS data not updated TTD data uses April 2022	Standard parametric approach is most appropriate
Utility values	• company and ERG used time to death approach and Committee considered unlikely to be important driver of CE results.	Used utility values based on time-to-death, High proportion of missing EQ-5D data from main trial so imputed data using 3 imputation methods but used utility values from TA366 instead of EQ-5D data	Retained company assumption but queried approach to impute missing data Suggest EQ-5D data from trial was more appropriate to use

Abbreviations: ACD, appraisal consultation document; CE, cost effectiveness; OS, overall survival; PFS, progression free survival

Other model updates:

At ACM1 Committee noted the following assumptions differed for company and ERG but noted this had little impact on cost effectiveness results

Parameter	Assumption in ACD	Company updates	ERG
Treatment adherence	Company assumed 95% adherence for tebentafusp. ERG assumed same adherence in both arms.	Tebentafusp = 92% adherence (sensitivity analyses 90% and 95%) Based on Schlaak et al. (2022). Adjustment not applied to pembrolizumab as interruption was limited	Could not replicate 92% estimate as methods company used were unclear No compelling evidence why pembrolizumab adherence was not included

Abbreviations: ACD appraisal consultation document; BSC, best supportive care

Key cost-effectiveness issues

The ERG carried out several adjustments to the company's base case:

- OS extrapolation
- PFS extrapolation
- TTD extrapolation
- Post progression health state costs

Uncertainties resulting in biggest impact on ICER

Scenario	impact (%)
ERG preferred TTD generalised gamma in both arms	[redacted]
ERG preferred OS log-logistic in pembrolizumab arm	[redacted]
ERG preferred OS log-logistic in tebentafusp PCP arm	[redacted] *
ERG preferred OS generalised gamma in pembrolizumab arm	[redacted]
ERG preferred OS generalised gamma tebentafusp PCP	[redacted] *

ERG's original base case had carried out a further change to post-progression health-state costs, but it was not able to include this in its updated CE analyses due to limitations in model functionality

* **These had the biggest impact on the ICER which was within a similar realm to results originally described in the ACD**

Abbreviations: ACD, appraisal consultation document; CE, cost effectiveness; OS, overall survival; PCP, PCP, pre-choice pembrolizumab; TTD, time to treatment discontinuation; ICER – incremental cost effectiveness ratio

Overview: key company and ERG assumptions (1)

Parameter	Company base case	ERG preferences
OS extrapolation	Tebentafusp arm: Kaplan-Meier + log-normal distribution; cut-off: xx months). IC arm: Weibull model (consistent with original CS)	Fully parametric model (same in each arm) 2 approaches: • Generalised gamma • Log-logistic
PFS extrapolation	Piecewise KM + generalised gamma extrapolation	Fully parametric generalised gamma extrapolation
TTD extrapolation	Piecewise KM + exponential extrapolation	Fully parametric generalised gamma extrapolation
Stopping rule	No stopping rule included	
Utilities* ?	Time to death approach using TA366 (skin melanoma) data*	
BSC costs** ?	One-off costs applied (plus end of life costs)	Monthly costs applied per cycle in post progression state (end of life costs removed)

Notes: * ERG disagreed with company approach but did not amend in their CE analyses
** ERG could not implement preferred analyses in updated base case so retained company assumption

= small impact on ICER = biggest impact on ICER ? = ERG note major area of uncertainty

NICE Abbreviations: IC, investigator choice; OS – overall survival; IC – investigators choice; KM – Kaplan Meier; PFS – progression-free survival; ICER – incremental cost effectiveness ratio; PCP, pre-choice pembrolizumab

Overview: key company and ERG assumptions (2)

	Company base case	ERG preferences
Compliance	Costs with 92% compliance with tebentafusp to account for interruptions and missed doses and 100% pembrolizumab	Not included in base case
Subsequent treatments (following tebentafusp or IC) *	See table below	See table below
Administration costs *	Lower infusion cost for 1st cycle as costs counted in overnight stay costs	

Company base case:

	Tebentafusp	IC
ipi+nivo	xxx	xxx
ipi	xxx	xxx
pembro	xxx	xxx
nivo	xxx	xx

ERG preferences:

	Tebentafusp	IC
ipi+nivo	xxx	xxx
ipi	xxx	xxx
pembro	xxx	xxx
nivo	xxx	xx

Notes: * no change from original model

= small impact on ICER = biggest impact on ICER ? = ERG note major area of uncertainty

Abbreviations: IC – investigators choice; ipi – ipilimumab; nivo – nivolumab; pembro - pembrolizumab

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Key issues

= main driver of the difference between the company and ERG's results

Overall survival extrapolations

- Do committee agree that OS results should not be adjusted for crossover?
- Should a piecewise approach be used to extrapolate OS in the tebentafusp arm?

Progression-free survival and time to treatment discontinuation

- Should a piecewise approach be applied for PFS and TTD?

Other model updates: costs

- Should BSC costs be applied as one-off costs or applied per cycle?

Abbreviations: BSC, best supportive care; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation

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