Redacted – contains no ACIC

NICE National Institute for Health and Care Excellence

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma

Lead team presentation

Lead team: Roger Whittaker, Alan Thomas, Brian Shine

ERG: Kleijnen Systematic Reviews

Chair: Jane Adam

Technical team: Albany Meikle, Mary Hughes, Janet Robertson

Company: Immunocore

10th May 2022

Key clinical issues

Comparator:

- Is a mixed treatment combination ('investigators choice'), including ipilimumab (13%), pembrolizumab (82%) and dacarbazine (6%), generalisable to current treatment of advanced uveal melanoma in the NHS?

Clinical effectiveness and how tebentafusp works:

- How does tebentafusp differ from immunotherapy currently used in treating uveal melanoma?
- PFS gains compared with individual immunotherapy agents are not statistically significant and QALYs are mainly gained post-progression – what is a possible explanation for this?

Subgroups:

- Are people with lesions ≤ 30mm a clinically relevant subgroup? Is this a measure of tumour burden used in clinical practice?

Adverse events

- Grade 3 adverse events more common with tebentafusp than comparator in trial; patient groups suggest tebentafusp has better adverse effect profile than current treatment
  - Is the adverse event profile acceptable?
  - How do the adverse events affect quality of life?

Abbreviations: PFS – progression-free survival; QALYs – quality-adjusted life years

Uveal melanoma: disease background

- Rare cancer arising from blood-rich structures in the middle of the eye
- Uveal melanoma is biologically distinct from skin melanoma; detection, surveillance, treatment, prognosis and quality of life all differ
- Around 600 to 700 people a year diagnosed with ocular melanoma (95% uveal melanoma)
- “Median patient age of diagnosis is 62 years; peak age range for diagnosis is between 70 and 79 years” – *company submission*
- Approximately 50% of people with uveal melanoma go on to develop metastatic disease
- Approximately 50% of people with metastatic uveal melanoma are HLA-A*02:01 positive
- Most metastatic disease occurs firstly in the liver and eventual liver failure is the predominant cause of death from the disease

Tebentafusp (KIMMTRAK, Immunocore)

Mechanism of action	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 Targets human leukocyte antigen-A*02:01 (HLA-A*02:01) uveal melanoma tumour cells, and activates T-cell anti-tumour activity
Expected GB marketing authorisation (wording as approved by European Commission April 22)	Indicated as 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	£[redacted] per vial; average cost of treatment course £[redacted]
Patient access scheme (PAS)	PAS discount agreed

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Does tebentafusp target uveal melanoma specifically?
Does tebentafusp cross the blood brain barrier?

Patient and professional group perspectives

Professional group perspectives

Royal College of Ophthalmologists and Royal College of Pathologists

Current care:

- Treatment of metastatic disease is limited with poor outcomes
- Long term control and treatment of metastatic disease would be ground breaking in this condition
- Prognostic markers (such as HLA) are well understood, but no guidelines on differential treatment of this group

Tebentafusp:

- Expected to prolong life and prolong the time that minimal medical intervention needed, due to better tumour control
- Treatment may require travel to be supervised by specialists in uveal melanoma
- Side effects similar to other chemotherapeutic agents

Patient group perspectives: living with the condition

OcuMel UK and Melanoma Focus

- Vision loss or difficulties and long-term fatigue is common
- May experience symptoms associated with liver cancer (if tumours spread to liver) and bone metastases are typically very painful
- No cure for metastatic uveal melanoma – know that cancer recurrence will come with a terminal diagnosis, so patients live with an immense psychological burden
- Rare cancer and little known, which complicates the patient journey
- Treatment options for metastatic disease are lacking: options include liver resection, immunotherapies and chemotherapy (which have side effects)
- Some people with metastatic disease have few symptoms and live active lives; others experience severe symptoms

"What do I think of treatments for stage 4 disease? Scared, as they are hardly in existence."

"At every corner we received conflicting advice, as there is so little known."

"We need some hope to reduce the despair of knowing we have no effective treatments available."

Patient group perspectives: tebentafusp

OcuMel UK and Melanoma Focus

- Tebentafusp has changed the direction of care for people with HLA-A2 positive tumours (around 50% of the uveal melanoma population) and has been very positively received by patients
- Initial side effects can be harsh (severe rash, hypotension, fever, blisters). Few consequent side effects experienced, unlike other systemic treatments (only rashes discussed on forums)
- Would positively change the physical and psychological impact of uveal melanoma
- Requires weekly infusion in hospital-based specialist centre – involves a lot of travel which is particularly difficult for those with vision impairment
- QALY may be insensitive to quality of life improvement with tebentafusp

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 I had side effects…"

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 licenses for melanoma in general which don't 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

Which treatment options are most commonly used for previously untreated uveal melanoma?

Decision problem

	Scope	Company model
Population	Adults with advanced (unresectable or metastatic) HLA-A*02:01-positive uveal melanoma (UM) *Aligned with marketing authorisation*	As in scope but: • only includes people who are treatment naïve
Intervention	Tebentafusp	Tebentafusp
Comparators	• Immunotherapies (pembrolizumab, ipilimumab, nivolumab [alone or with ipilimumab]) • Chemotherapy (dacarbazine) • Best supportive care (for people who have had previous treatment)	Investigators choice (blended comparator), including: • Dacarbazine *(costs not included in model)* • Pembrolizumab • Ipilimumab *Nivolumab (alone or with ipilimumab) not included in model*
Outcomes	• PFS • OS • Response rate • Duration of response • Adverse effects • HRQoL	As in scope

Would tebentafusp only be used for people who are treatment naïve for advanced uveal melanoma (as in trial)?

Abbreviations: PFS – progression-free survival; OS – overall survival; HRQoL – health related quality of life

Clinical effectiveness evidence

Pivotal trial: IMCgp100-202

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 factors	• Lactate dehydrogenase levels (associated with prognosis)	

IMCgp100-102 trial (not included in model): dose-finding and expansion single arm trial of tebentafusp including people with previously treated advanced melanoma (n=127)

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

Comparators in company submission based on IMCgp100-202

Company:

- Inappropriate to provide comparison with dacarbazine or ipilimumab individually due to small patient numbers, different characteristics of patients who receive each treatment and doesn't reflect clinical practice
- Dacarbazine not used in practice and therefore more appropriate to assume costs of pembrolizumab for proportion taking dacarbazine in IC arm in model
- Nivolumab can be assumed to have equal efficacy to pembrolizumab, so separate analysis not needed
- Mix of regimens and proportion of usage in IC arm representative of clinical practice

Patient and clinical experts:

- All comparators in scope are used in practice – but all are suboptimal

ERG:

- Treatment mix with IC arm assumes equal effectiveness of comparators
- All comparators in scope should be considered; comparison with comparators not in trial requires indirect treatment comparison

Is the clinical trial generalisable to NHS clinical practice (including comparators and age of population)?

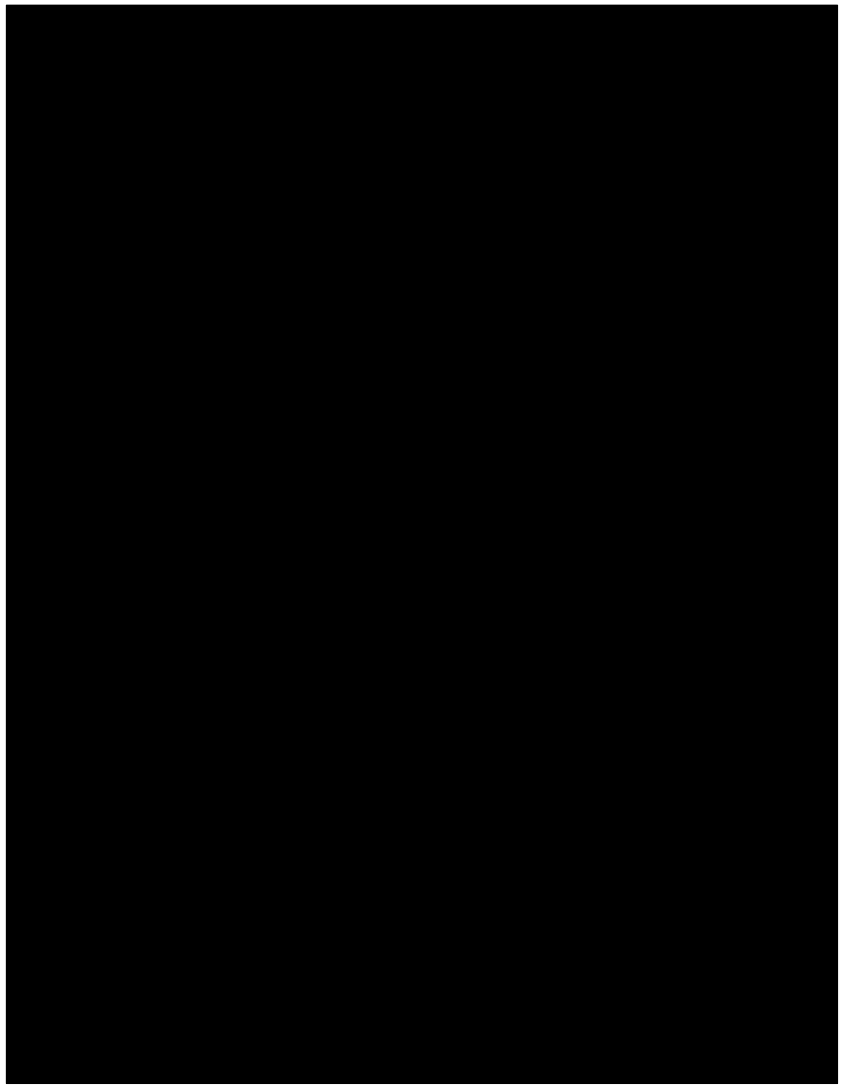
Abbreviations: IC – investigator choice

Overall survival results vs investigator choice

KM OS for August 2021 cut-off

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

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



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

†IC included dacarbazine, ipilimumab and pembrolizumab

February 2022 data cut for up to [redacted] supports treatment difference (submitted post technical engagement, not used in model)

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Abbreviations: KM – Kaplan-Meier; CI - confidence interval; OS – overall survival; IC – investigator choice

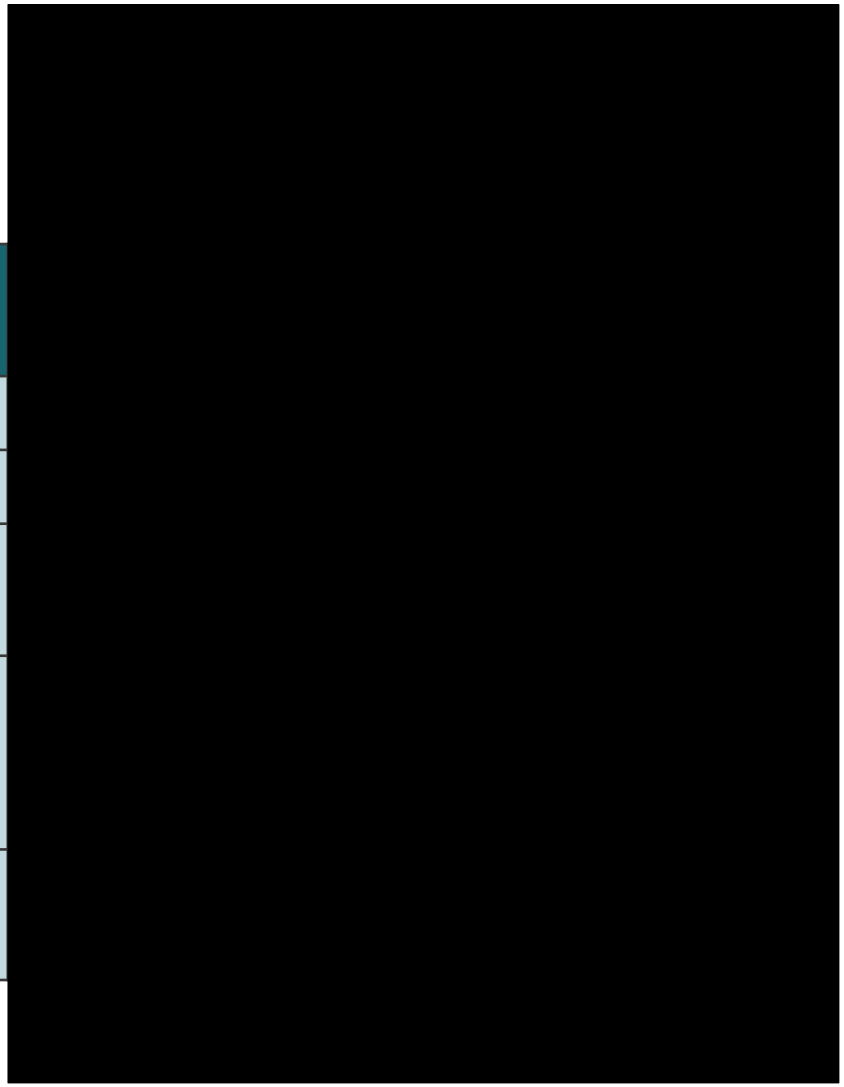
Progression-free survival results vs investigator choice

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)	
	October 2020 cut-off	August 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

KM PFS for August 2021 cut-off



OS benefit appears greater than PFS benefit – what is a possible explanation for this?

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

Subgroup analysis results by pre-choice of treatment in comparator arm

- **Trial data suggests relative effectiveness of treatments differ**
- Shorter OS and PFS with dacarbazine than immunotherapies and therefore greater benefit with tebentafusp
- Small sample size for dacarbazine and ipilimumab; OS estimates [redacted] for ipilimumab vs tebentafusp; PFS estimates [redacted] for pembrolizumab or ipilimumab vs tebentafusp

Choice of treatment (n, tebentafusp; n, comparator)	**Progression-free survival hazard ratio (95% CI)**
Dacarbazine (n=13, n=7)	[redacted]
Pembrolizumab (n=199, n=103)	[redacted]
Ipilimumab (n=40, n=16)	[redacted]
Pre-choice of treatment (n, tebentafusp; n, comparator)	**Overall survival hazard ratio (95% CI)**
Dacarbazine (n=13; n=7)	[redacted]
Pembrolizumab (n=199, n=103)	[redacted]
Ipilimumab (n=40, n=16)	[redacted]

ITT population overall survival hazard ratio used in model: [redacted]

Does relative effectiveness differ by comparator?
Is the blended comparator reflective of the relative benefit expected with tebentafusp in practice?

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Abbreviations: PFS – progression-free survival; OS – overall survival; CI – confidence interval; ITT – intention to treat

Subgroup analysis results: subgroup with the largest metastatic lesion recorded at baseline ≤30mm

- **Company** suggests association between tumour burden and response to immunotherapies
- It presented results for a subgroup of people who had no metastatic lesions bigger than 30mm at baseline

Median OS ITT (months; 95% CI)			Median OS largest lesion ≤30mm (months; 95% CI)		
Tebentafusp (n=252)	IC† (n=126)	Treatment difference	Tebentafusp (n=139)	IC† (n=70)	Treatment difference
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS ITT (months; 95% CI)			**Median PFS largest lesion ≤30mm (months; 95% CI)**		
Tebentafusp (n=252)	IC† (n=126)	Treatment difference	Tebentafusp (n=150)	IC† (n=126)	Treatment difference
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†IC included dacarbazine, ipilimumab and pembrolizumab

Overall survival and progression-free survival are [redacted] in the subgroup with less severe disease

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Is this subgroup relevant in clinical practice?

Abbreviations: PFS – progression-free survival; OS – overall survival; CI – confidence interval; IC – investigators choice

Adverse events in IMCgp100-202

Adverse event	Tebentafusp	Investigators choice
Any ≥ grade 3 treatment emergent adverse events	[redacted]	[redacted]
Adjudicated cytokine release syndrome (any grade)	[redacted]	[redacted]
Adjudicated cytokine release syndrome (≥ grade 3)	[redacted]	[redacted]
Rash (any grade)	[redacted]	[redacted]
Fatigue (any grade)	[redacted]	[redacted]
Pyrexia (≥ grade 3)	[redacted]	[redacted]
Pruritus (≥ grade 3)	[redacted]	[redacted]

ERG:

- Frequency of grade 3+ treatment emergent adverse events in IMCgp100-202 was [redacted] in tebentafusp arm ([redacted]) than in investigator choice arm ([redacted])
- Cytokine-mediated adverse events are commonly reported with tebentafusp so patients are monitored overnight after each of first 3 doses during dose escalation

Patient expert:

- Few side effects reported with tebentafusp and are easily managed

What is the typical duration of adverse events and what is the impact on quality of life?

Key clinical issues

Comparator:

- Is a mixed treatment combination ('investigators choice'), including ipilimumab (13%), pembrolizumab (82%) and dacarbazine (6%), generalisable to current treatment of advanced uveal melanoma in the NHS?

Clinical effectiveness and how tebentafusp works:

- How does tebentafusp differ from immunotherapy currently used in treating uveal melanoma?
- PFS gains compared with individual immunotherapy agents are not statistically significant and QALYs are mainly gained post-progression – what is a possible explanation for this?

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- Grade 3 adverse events more common with tebentafusp than comparator in trial; patient groups suggest tebentafusp has better adverse effect profile than current treatment
  - Is the adverse event profile acceptable?
  - How do the adverse events affect quality of life?

Abbreviations: PFS – progression-free survival; QALYs – quality-adjusted life years

Cost effectiveness issues

Key cost-effectiveness issues

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

Overall survival extrapolations

- Are the company's overall survival extrapolations that tebentafusp extends life by on average [redacted] plausible?
- Is the company's spline modelling or the ERG's standard parametric modelling approach preferred? (Approach has a very large effect on the ICER)
- Would the treatment effect of tebentafusp be expected to be maintained over the long term after stopping treatment, and is there a proportion of people who would be expected to have same survival as general population i.e. 'cured'?

End of life

- Have end of life criteria been met?

Stopping rule

- 24 month stopping rule (not included in MA or trial) was included by the company with no waning of effect thereafter - is this reasonable?

Time to treatment discontinuation

- Company and ERG use different approaches to modelling time on treatment. Which approach is preferred?
  - Company model includes average ~10 month tebentafusp treatment length

Abbreviations: ICER – incremental cost effectiveness ratio; MA – marketing authorisation

Further cost-effectiveness issues that contribute to uncertainty

Utilities

- Is the company's time-to-death utility approach appropriate for decision making?
- Has the company's model appropriately incorporated adverse events?
- Are there any benefits of tebentafusp not captured in the quality-of-life measure?

Starting age in model

- Model starting age is 62, in line with mean age in IMCgp-100-202. Is this the appropriate mean starting age in the model?

ERG also had different assumptions to the company on:

- **Progression-free survival extrapolation**
- **Best supportive care costs**
- **Subsequent treatment use**

Model structure

Model type	3-state partitioned survival model: • pre-progression • post-progression • death
Population	Adults with HLA-A*02:01 positive metastatic uveal melanoma, without prior treatment in the metastatic setting; mean start age 62
Intervention	Tebentafusp
Comparators	Investigator choice efficacy included ITT comparator distribution: ipilimumab (13%), pembrolizumab (82%) and dacarbazine (6%) Costs for ipilimumab (13%) and pembrolizumab (87%) used in model
Time horizon	38 years (equates to lifetime)

ERG:

- NICE DSU recommends also using a state transition model to assist verifying the plausibility of survival model extrapolations and to address uncertainty in the extrapolation
  Partitioned survival model uses independent modelling of PFS and OS

Company:

- Partitioned survival model appropriate because:
  - trial effect sizes show there may be low PFS and OS correlation
  - PFS and OS data in the investigator choice arm and PFS in tebentafusp arm are mature so similar results expected

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Abbreviations: ITT – intention to treat; DSU – decision support unit; PFS – progression-free survival; OS – overall survival

Overall survival extrapolations

- OS data comes from IMCgp100-202 trial August 2021 cut-off (median follow up [redacted] months)
- Approx. [redacted]% and [redacted]% of life years are gained beyond the observed data period for tebentafusp and IC arm, respectively
- **Company** used different curves for tebentafusp and IC arms

Company approach to OS extrapolation		Justification	Company model results (tebentafusp vs IC)
Tebentafusp	**Investigator choice**		
3 knot spline	Weibull model	Spline: standard parametric models can't capture change in survival profile at [redacted] Weibull: notes crossover in trial - Weibull gives projections consistent with meta-analysis of 1st line treatment options	[redacted] vs [redacted] years (OS increased by [redacted] years)

ERG:

- Prefers to use same curve for both arms - proportional hazards assumption holds
- Prefers to use a standard parametric model (generalised gamma or log-logistic) - company's justification is flawed; low numbers at risk at [redacted]; poor fit of spline model with observed hazards within first 24 months
- Most modelled life years are after observed data - question plausibility of maintained treatment effect of tebentafusp over lifetime

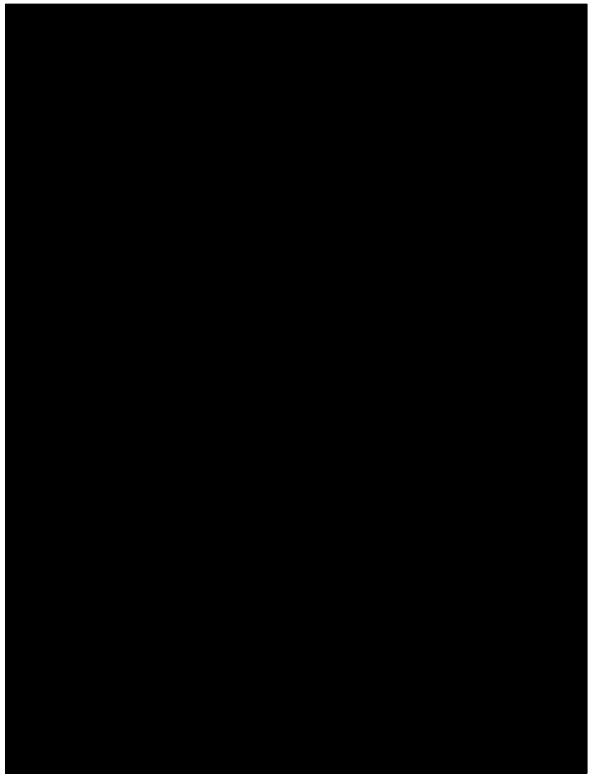
- **Is the use of different curves for extrapolating OS in each arm justified?**
- **Is the use of a 3 knot spline rather than a standard parametric model justified?**

Abbreviations: OS – overall survival; IC – investigators choice

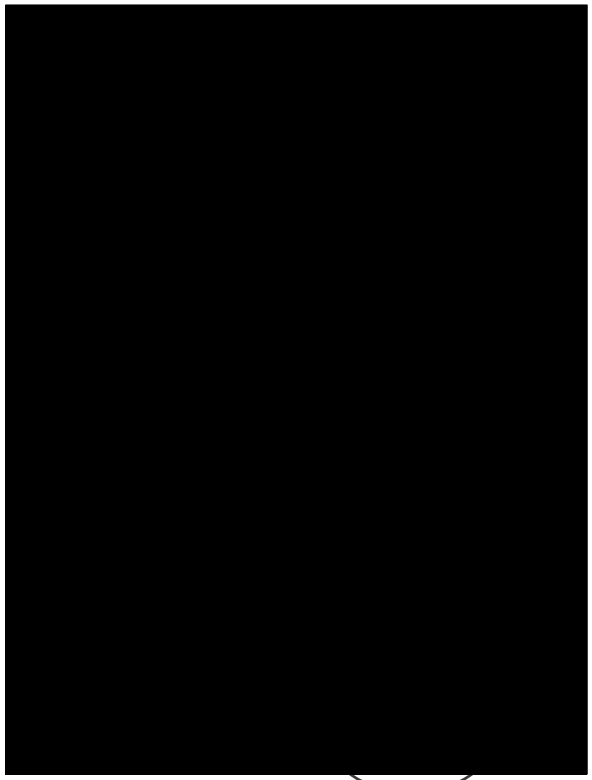
Company justification of spline approach for extrapolating tebentafusp OS

In response to technical engagement company showed different approaches to extrapolate August 21 data cut compared with Kaplan Meier data from new February 22 data cut

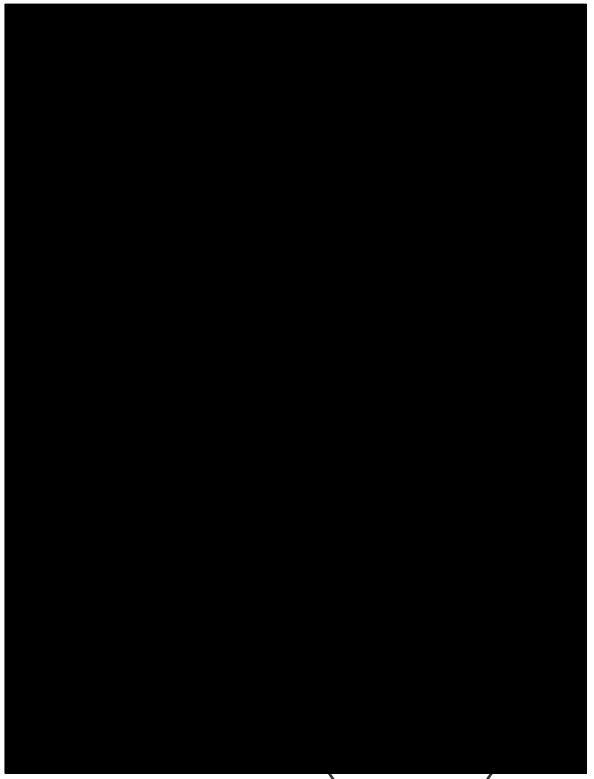
Kaplan Meier August 21



Feb 22 KM; 3 knot spline
(preferred by company)



Feb 22 KM; log-normal curve



Numbers at risk drop considerably from around month [redacted]

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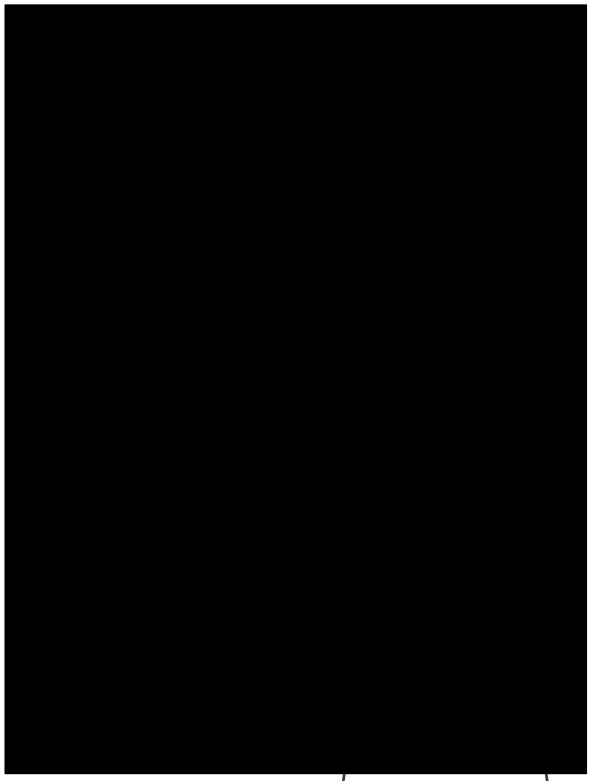
Abbreviations: OS – overall survival; IC – investigators choice

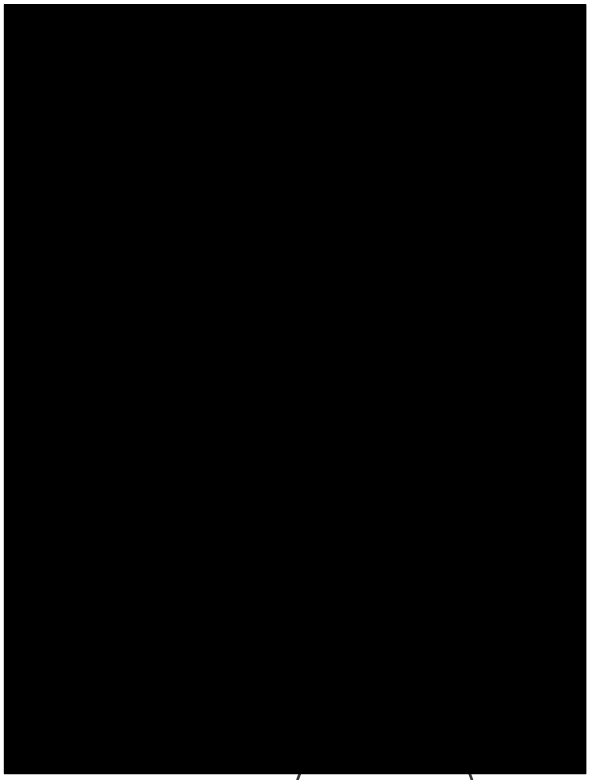
ERG's preferred OS extrapolation approaches

ERG prefers either log-logistic or generalised gamma extrapolation

Feb 22 KM; generalised gamma
(preferred by ERG)*



Feb 22 KM; log-logistic curve
(preferred by ERG)*



Numbers at risk drop considerably from around month [redacted]

Abbreviations: OS – overall survival

End of life

End of life:

Short life expectancy criteria (normally less than 24 months with current care):

- Modelled OS (investigator choice): [redacted] years; median OS (IC) in trial: [redacted] months

Extension to life criteria (mean increase in life of at least 3 months expected compared with current care):

- Modelled difference in OS: [redacted] years; median difference in OS in trial: [redacted] months
- Data based on comparison with investigators choice, assuming equal treatment effect for each comparator drug

Are both end of life criteria met?

Abbreviations: OS – overall survival; IC – investigators choice

Time on treatment and stopping rule

Company ToT approach		Company justification	ERG comments
IC	**Tebentafusp**		
KM + exponential curve (cut off at time only 15% remain at risk)	KM + exponential curve (cut off at time only 25% remain at risk)	Provides plausible long-term extrapolation: treatment discontinuation in tebentafusp arm 94% after 3 years and 99% after 5 years	• Piecewise modelling may over fit trial data; estimating parametric curve from full dataset is flawed • Cut point is arbitrary • Prefers standard parametric modelling without KM data

Extrapolated time to treatment discontinuation from trial: KM data then exponential parametric tail

Tebentafusp mean treatment duration: 10.2 months

IC: 0.4% on treatment at 24 months

Stopping rule
After 24 months no drug or administration costs modelled in tebentafusp arm. No stopping rule in trial, but company do not expect patients to be taking tebentafusp past 24 months in practice

- **Is average 10 month tebentafusp treatment duration plausible?**
- **Will tebentafusp be stopped after 24 months if successful in practice?**

Abbreviations: KM – Kaplan Meier; IC – investigators choice

Utility values (1)

	Company approach	Company scenario	ERG scenario
How change in utility modelled over time	Utility decreases depending on how close to dying a person is		Models utility for pre-progression health state and post-progression health state
Data source	TA366 (pembrolizumab for advanced melanoma)	IMgp100-202 EQ-5D-5L with data imputation	IMgp100-202 EQ-5D-5L with data imputation
Utility decrements	Treatment related utility decrements applied as a 1 off in first cycle - additional utility decrements linked to adverse events not included in analysis		

ERG:
- Skin melanoma distinct condition to uveal melanoma
- Produces implausible values: on-treatment utility aged 62+ ([redacted]) > general population aged 55 to 65 (0.82)

ERG:
- Imputation methods flawed

Company:
- Disease progression (RESIST criteria) not good marker of decline in QoL
- QoL maintained until about 3 to 6 months before death when symptoms appear and impact QoL

Patient expert:
- People often feel very well and continue with daily activities even with severe disease
- Deterioration can happen extremely rapidly at the end of life

Abbreviations: QoL – quality of life

Utility values (2)

	Utility value
Time to death	
≥ 360 days	[redacted]
270-360 days	[redacted]
180-270 days	[redacted]
90-180 days	[redacted]
30-90 days	[redacted]
< 30 days	[redacted]
Treatment effect disutility	
Tebentafusp	-0.021
Ipilimumab	-0.021
Pembrolizumab	-0.021
Dacarbazine	-0.024
Health state	
On-treatment	[redacted]
Off-treatment	[redacted]

ERG key issue summary on utilities:

- Company approach using utility values from TA366* instead of EQ-5D data from IMCgp100-202 is not appropriately justified as uveal melanoma biologically distinct to skin melanoma
- Data imputation methods introduce bias
- Use of time-to-death approach is inconsistent with model structure and common practices, not transparent and lacks face validity

*TA366: pembrolizumab for advanced melanoma not previously treated with ipilimumab

Overview: key company and ERG assumptions (1)

Parameter	Company base case	ERG base case
OS extrapolation 	Tebentafusp arm: spline model IC arm: Weibull model	Fully parametric model (same in each arm) 2 approaches: • Generalised gamma • Log-logistic
Time on treatment extrapolation	Piecewise KM + exponential extrapolation (cut off at time only 15% [IC arm] or 25% [tebentafusp arm] remain at risk)	Fully parametric generalised gamma extrapolation
Stopping rule	No drug or administration costs modelled in tebentafusp arm after 24 months	No stopping rule included
Utilities ?	Time to death approach using TA366 (skin melanoma) data	Time to death approach using TA366 (skin melanoma) data
PFS extrapolation	Piecewise KM + generalised gamma extrapolation	Fully parametric generalised gamma extrapolation
Best supportive care costs	One-off costs applied (plus end of life costs)	Monthly costs applied per cycle in post progression state (end of life costs removed)

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

Abbreviations: OS – overall survival; IC – investigators choice; KM – Kaplan Meier; PFS – progression-free survival; ICER – incremental cost effectiveness ratio

Overview: key company and ERG assumptions (2)

	Company base case			ERG base case		
Compliance	Costs associated with 95% compliance with tebentafusp to account for interruptions and missed doses			100% compliance assumed		
Subsequent treatments (following tebentafusp or IC)		**Tebentafusp**	**IC**		**Tebentafusp**	**IC**
	ipi+nivo	[redacted]	[redacted]	ipi+nivo	[redacted]	[redacted]
	ipi	[redacted]	[redacted]	ipi	[redacted]	[redacted]
	pembro	[redacted]	[redacted]	pembro	[redacted]	[redacted]
	nivo	[redacted]	[redacted]	nivo	[redacted]	[redacted]
Administration costs	Lower infusion cost for 1st cycle as costs counted in overnight stay costs			Accepted in ERG base case		
Comparator treatments	Assumes everyone on dacarbazine in trial (5.6%) given pembrolizumab (costs only)			Costs for each comparator included as in distribution in trial		

Which of these assumptions should be accepted?

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

Company cost effectiveness results

Summary of company's cost effectiveness results, including model updates following technical engagement

Includes patient access scheme for tebentafusp but not comparators (results including these patient access schemes will be presented in Part 2)

		Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company deterministic base case	Tebentafusp	[redacted]	[redacted]	-	-	-
	IC	[redacted]	[redacted]	[redacted]	[redacted]	44,050
Company probabilistic base case	Tebentafusp	-	-	-	-	-
	IC	-	-	[redacted]	[redacted]	42,176

Abbreviations: IC – investigators choice; ICER – incremental cost effectiveness ratio; QALY – quality-adjusted life year

ERG exploratory base cases (using generalised gamma or log-logistic OS extrapolation)

		Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company deterministic base case	Tebentafusp	[redacted]	[redacted]	-	-	-
	IC	[redacted]	[redacted]	[redacted]	[redacted]	44,050
ERG base case						
Overall survival generalised gamma	Tebentafusp	[redacted]	[redacted]			
	IC	[redacted]	[redacted]	[redacted]	[redacted]	238,748
Overall survival log-logistic	Tebentafusp	[redacted]	[redacted]			
	IC	[redacted]	[redacted]	[redacted]	[redacted]	230,366

NICE

Abbreviations: OS – overall survival; IC – investigators choice; ICER – incremental cost effectiveness ratio; QALY – quality-adjusted life year

Impact of company updates following technical engagement

Uncertainties resulting in biggest impact on ICER

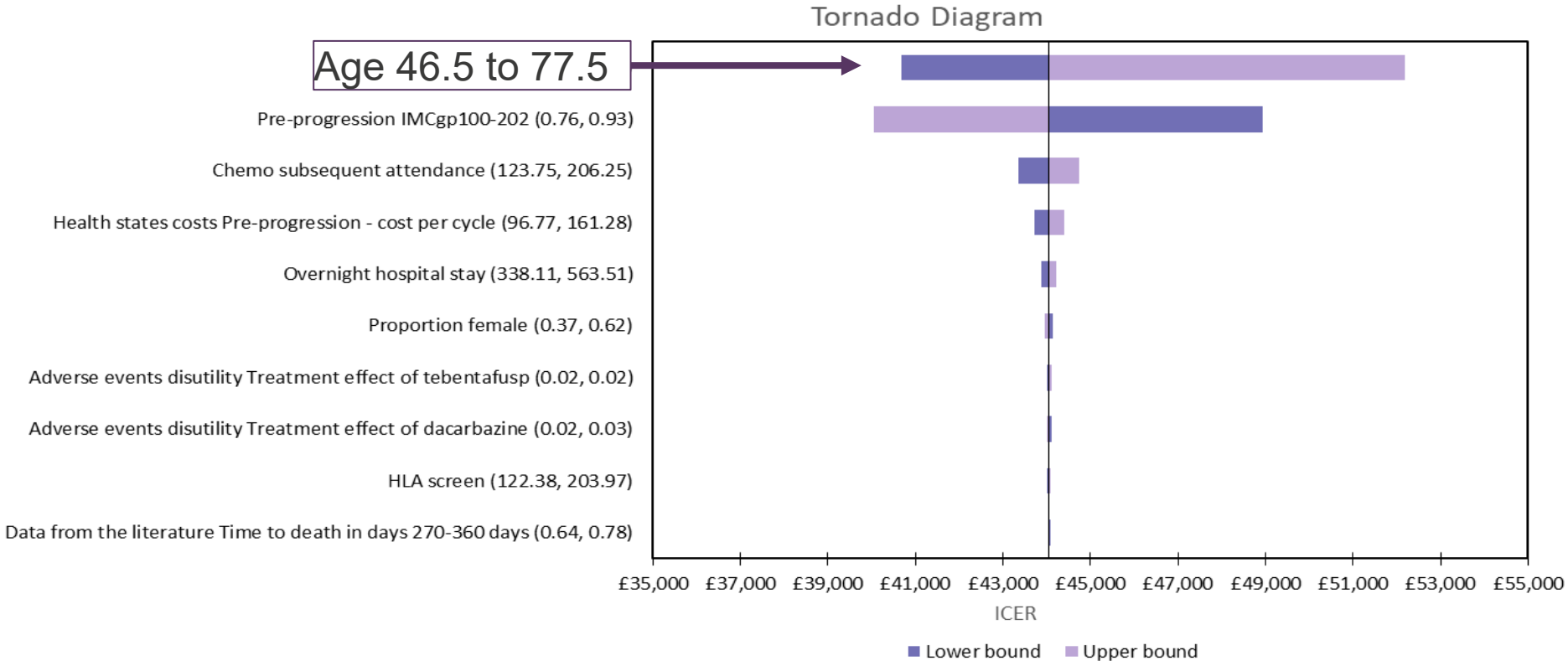
	ICER (£/QALY)	% change
Original base case without treatment cap (reference)	[redacted]	NA
Updated PAS	[redacted]	[redacted]
Including tebentafusp stopping rule	[redacted]	[redacted]
Time to treatment discontinuation update	[redacted]	[redacted]
Assuming 95% tebentafusp compliance	[redacted]	[redacted]
Updating subsequent treatments	[redacted]	[redacted]
Updated administration costs	[redacted]	[redacted]
Replacing dacarbazine with pembrolizumab treatment costs	[redacted]	[redacted]
Company base case (including all changes above)	44,050	[redacted]

Abbreviations: ICER – incremental cost effectiveness ratio; PAS – patient access scheme

Deterministic sensitivity analysis shows largest effect is from varying age

- Average age in model is 62 years – aligns with median age in IMCgp-102-202 but peak age in trial is between 70 to 79 years
- Varying average starting age in model impacts ICER
- Patient expert: most patients were under 70 in 2019 stats

Mean age in model	ICER
46.5 years	40,070
62 years (base case)	44,054
77.5 years	52,274



Is the average age in the model (62 years) appropriate?

Abbreviations: ICER – incremental cost effectiveness ratio

Company scenario: assuming proportion of people will be cured

Company:

- Suggest trend towards long-term survival for a fraction of patients treated with tebentafusp
- Note in the August 2021 there was a flattening of [redacted]
- Ran scenarios in which 50% to 90% of people alive at this point (around [redacted] of ITT population) were assumed to have the same mortality rates as the general population at this time point (i.e they were assumed to be 'cured')

Scenario (cure fraction)	August 2021 DCO	
	ICER (£/QALY)	% change
50%	45,255	2.74%
60%	39,408	-10.54%
70%	34,884	-20.81%
80%	31,281	-28.99%
90%	28,342	-35.66%

Kaplan- Meier August 21

[redacted]

Will some people have the same risk of dying as the general population after treatment?

NICE

Abbreviations: IC – investigators choice; KM – Kaplan Meier; ITT – intention to treat; ICER – incremental cost effectiveness ratio; QALY – quality-adjusted life year

Innovation

Company:

- Tebentafusp is 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

Patient expert:

- There is no clear pathway for this population – tebentafusp would bring in a standard approach

Clinical expert:

- Results with tebentafusp are promising, for a subgroup of people with uveal melanoma (HLA-A*02:01)
- Improvement in survival and fewer side effects is a significant improvement

Is tebentafusp an innovative medicine and how should this be considered as part of decision making?

Key cost-effectiveness issues

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

Overall survival extrapolations

- Are the company's overall survival extrapolations that tebentafusp extends life by on average [redacted] plausible?
- Is the company's spline modelling or the ERG's standard parametric modelling approach preferred? (Has a very large effect on the ICER)
- Would the treatment effect of tebentafusp be expected to be maintained over the long term after stopping treatment, and is there a proportion of people who would be expected to have same survival as general population i.e. 'cured'?

End of life

- Have end of life criteria been met?

Stopping rule

- 24 month stopping rule (not included in MA or trial) was included by the company with no waning of effect thereafter - is this reasonable?

Time to treatment discontinuation

- Model includes average ~10 month tebentafusp treatment length, and adjusts for missed doses
  - Is average 10 month tebentafusp treatment duration plausible?

Abbreviations: ICER – incremental cost effectiveness ratio; MA – marketing authorisation