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NICE National Institute for Health and Care Excellence

Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID1504]

Second appraisal committee meeting

Evidence review group (ERG):	KSR Ltd
Technical team:	Stephen O'Brien (chair), Amy Crossley, Sally Doss, Frances Sutcliffe
Company:	Roche
Date:	5th December 2019

Atezolizumab (Tecentriq, Roche)

Marketing authorisation	Atezolizumab in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with ES-SCLC
Mechanism of action	Humanised anti-PD-L1 monoclonal antibody
Administration	Every three weeks for four cycles of: • Carboplatin: AUC 5 mg/ml/min, IV, Day 1 of each cycle • Etoposide: 100 mg per square meter of body surface area, IV, Days 1–3 of each cycle • Atezolizumab: 1200 mg, IV, Day 1 of each cycle Induction phase followed by maintenance therapy with atezolizumab 1200 mg IV every three weeks until loss of clinical benefit or unmanageable toxicity
Price	• List price: £3807.69 per 20 ml vial (1,200 mg) • Mean treatment cost of a course of treatment for an ES-SCLC patient is £32,798.39 for atezolizumab (at list price), £76.18 for carboplatin and £30.89 for etoposide. • Simple PAS approved for atezolizumab

[redacted]

AUC: area under the curve; ES-SCLC: extensive-stage small-cell lung cancer; IV: intravenous

Summary of 1st meeting

Main issues discussed at meeting	*Which extrapolation of overall survival (OS) is most appropriate (log-logistic or Weibull)?* *Do end-of-life (EOL) criteria apply in this indication?*
Outcomes	• Recommendation unable to be made • None of the standard parametric curves used to extrapolate OS were reliable for either arm – alternative more flexible models would provide more robust basis for decision making • Based on IMpower133 trial Kaplan-Meier (KM) data, may be no treatment benefit from ≈30 months • Further cost-effectiveness analyses needed to allow committee to identify most appropriate method for estimating mean OS • Unclear whether all EOL criteria were met

Additional analyses / information requested

Committee requested that company provide additional analyses and information, to allow for decision making:

- **Exploration of effect on model results of reducing duration of treatment benefit of atezolizumab**.
- **Further methods to estimate overall survival**, such as piecewise or mixture models.
- **Restricted means analysis of overall survival data from IMpower133** to inform estimation of extent that atezolizumab plus chemotherapy extends life compared to chemotherapy alone.
- **Clarification on source of real-world chemotherapy survival data** (as validated by advisory board), due to inconsistencies across different documents provided by company.
- **Further patient reported outcomes data from IMpower133**, with further detail on results (including statistical comparisons between arms) and methods to obtain data.

[redacted]

Patient-reported outcomes data

Company

- Patient-reported outcome (PRO) data collected via EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L.
- Provided information on data collection and PRO results.
- Changes in patient-reported treatment-related symptoms commonly associated with quality of life impairment similar during induction and most of maintenance phase. Patient-reported function and health-related quality of life (HRQoL) improved in both arms after initiating treatment, with more pronounced and persistent HRQoL improvements in atezolizumab arm.

Clarification on source of real-world chemotherapy survival data

Company

- Table validated by clinical experts in company's Appendix K is incorrect, not concordant with Flatiron data. Provided updated Flatiron data to clinical experts (Nov 2019) for validation, survival rates now match data in Flatiron curve.

[redacted]

Key issues for committee to consider

1. Which is the most plausible duration of treatment effect after initiation– 30, 36, 48 or 60 months?

2. Which extrapolation of overall survival is most appropriate – log-logistic, Kaplan-Meier + log-logistic, or one of the restricted cubic spline models?

3. Should end-of-life weighting be applied for this technology in this indication?

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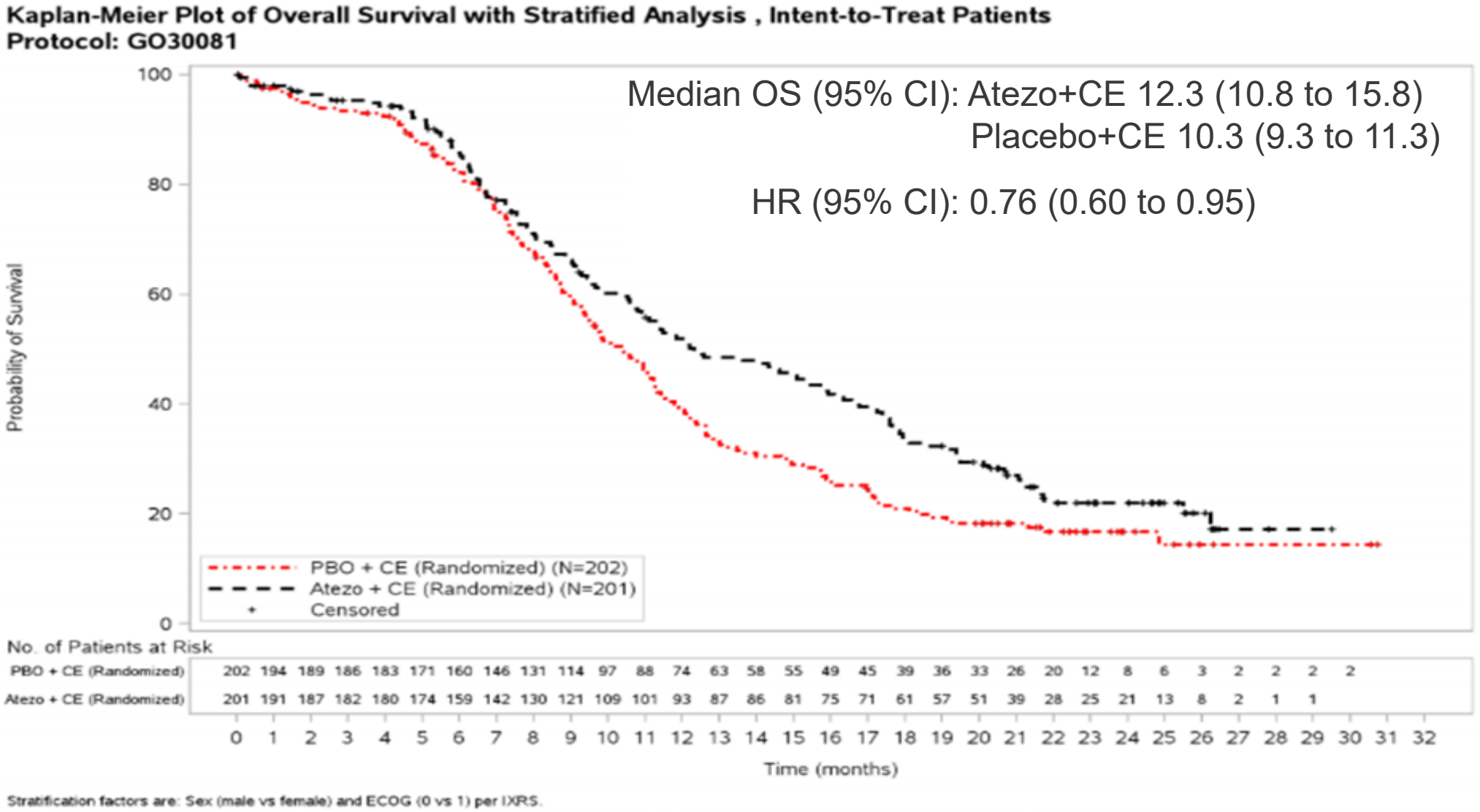
1. Duration of treatment effect

Kaplan-Meier data from IMpower133

(Jan 2019 data cut – as seen in 1st meeting)



[redacted]

Atezo: atezolizumab; CE: carboplatin+etoposide; CI: confidence interval; HR: hazard ratio; PBO: placebo

Reduced treatment effect duration – company new analyses

- 1st meeting - committee noted there may be no treatment benefit from ≈30 months (based on Kaplan-Meier OS plot from IMpower133). Median OS (Jan 2019 cut) 12.3 months for atezolizumab arm. Note no stopping rule was considered, treatment effect duration is **from initiation**.

Company

- Provided ICERs for reduced treatment effect (for original and updated OS extrapolation methods). At 30 months, there are 6 patients at risk on atezolizumab arm and 6 on comparator arm, so assessment of KM shape beyond this is unreliable due to censoring.

Treatment effect cut-off	ICER (£/QALY) – old company base case using log-logistic	ICER (£/QALY) – new company base case using KM+log-logistic (20 months)
No treatment effect cut-off	45,949	40,761
36 months	50,548	44,201
48 months	48,442	42,637
60 months (base case)	47,449	**41,894**

- Kept 60 months in base case, expect treatment effect from initiation to last at least this long due to prolonged benefit expected from immunotherapies. Company said used in previous lung cancer appraisal (TA483, nivolumab, squamous NSCLC). Company quoted TA428 and TA531 (pembrolizumab in PD-L1+ NSCLC indications) as examples where long-term treatment effect was considered potentially biologically plausible.
  - Note, in TA483, TA428 and TA531, consideration of continued treatment effect was in NSCLC (different disease pathway and evidence base).

Reduced treatment effect duration - new analyses

ERG

- Analysis showed that, as expected, ICER would increase if treatment benefit was curtailed, up to just over £50,000 with a cut-off of 36 months using log-logistic model.
- ERG conducted a further analysis that showed the **ICER might be as high as £52,646** if the **cut-off was as low as 30 months** (roughly the maximum follow-up in trial, and committee noted there may be no treatment benefit from ≈30 months in 1st meeting).

Technical team judgement:

Committee should also consider 30, 36, 48 and 60 months duration of treatment benefit from initiation. NSLC is a different disease pathway and evidence-base. The long-term treatment effect of any immunotherapy is uncertain in any indication.

Is 30, 36, 48 or 60 months the most appropriate atezolizumab treatment effect duration for modelling OS in this indication?

[redacted]

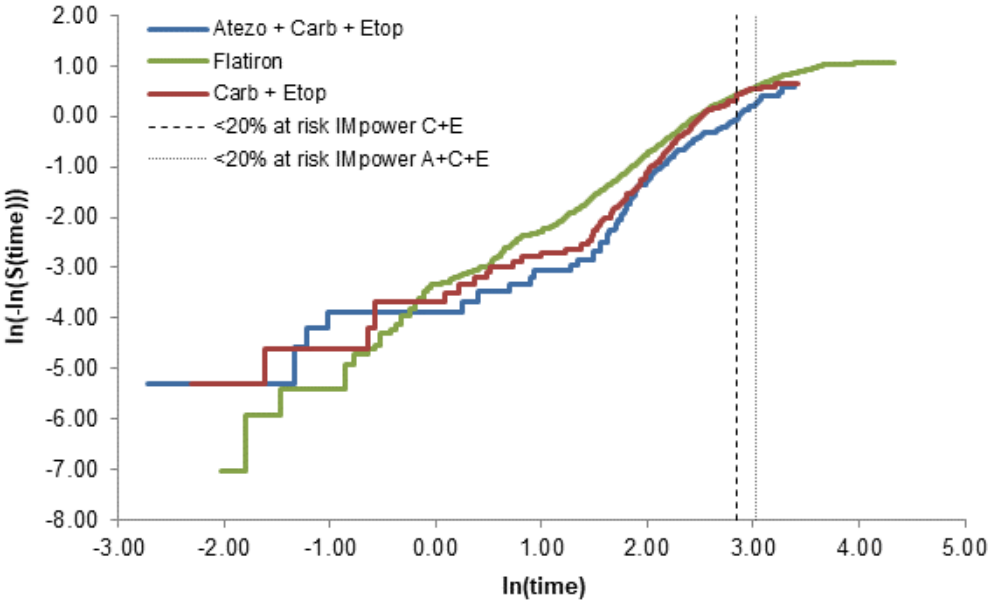
2. Survival extrapolation

Changing hazard function over time, with comparison to Flatiron data (1)

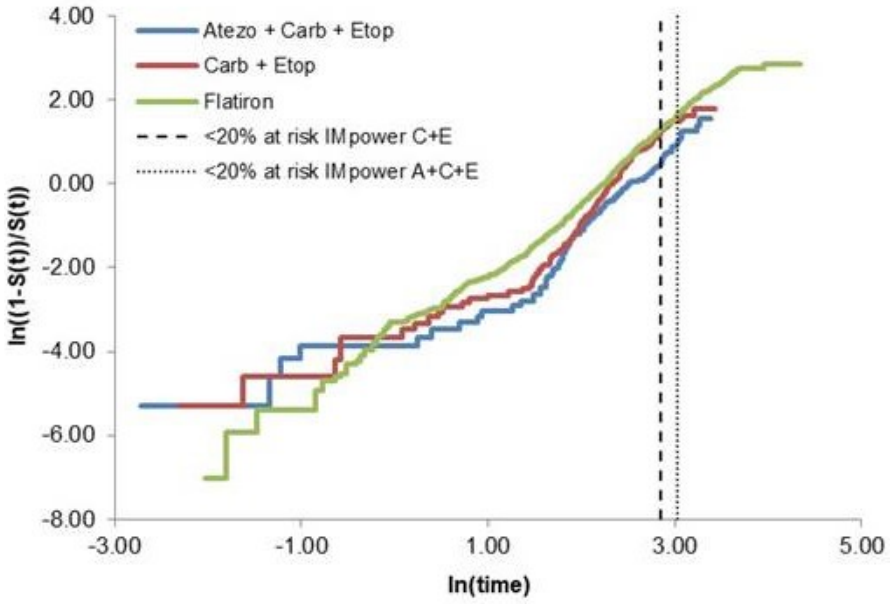
Company

- End of IMpower133 data follows similar shape to Flatiron long-term data.
- Cumulative hazards for IMpower133 arms cross within first 2 months, then no sign of convergence within interpretable section of trial data.
- **Long-term hazards decreasing** in all 3 data sources.
- For IMpower133 trial arms, different shape to curves before and after 5 months. **May be more appropriate to use Kaplan-Meier data prior to this point or look at piecewise fits**.
- Logit survival versus log time graph relatively linear in both Flatiron data and IMpower133 arms after 5 months, **suggests log-logistic model appropriate for extrapolation**.

Log cumulative hazard plot for OS



Logit (S(t)) vs Log-time



Changing hazard function over time, with comparison to Flatiron data (2)

ERG

Log cumulative hazard for OS versus log time plot:

- Straight line would be consistent with Weibull (gradient >1 implying increasing hazard). If gradient=1 this implies exponential model. Company claim long-term hazards decreasing, implies gradient <1. **Difficult to observe if this is the case due to graph fluctuations**.
- Gradient between last two data points=0 (given no mortality between these), but appears that gradient for comparator more clearly peaks then tails off toward end of follow-up. Calculated gradient between consecutive pairs of data points using KM data in company model. For atezolizumab arm ≈ last 12 months follow-up, there are 20 observations thus 20 consecutive pairs (6 with gradient <1). For comparator arm, for same period of last 12 months follow-up there are 9 observations thus 9 consecutive pairs (6 with gradient <1).

→ Hazards appear decreasing, most clearly in comparator arm. Provides evidence against Weibull and in favour of log-logistic, but particularly for comparator arm, although **any OS model with decreasing hazards would also be supported**.

Logit survival versus log time plot:

- Straight line would be consistent with log-logistic model, which is what company suggest after 5 months follow-up. **This is not implausible, although it is not entirely clear**.

Further methods to estimate overall survival

1st meeting - company preferred log-logistic extrapolation, ERG preferred Weibull (both for whole time horizon). Committee thought log-logistic may be too optimistic and Weibull too pessimistic for chemotherapy only group, did not consider either to be appropriate for decision making.

Company

- **Fitted same model to both arms**. Explored: Gamma, piecewise, KM + log-logistic, restricted cubic spline, mixture cure.
- Validated models with 8 consultant oncologists to understand how extrapolations reflected long-term OS in clinical practice. Sought opinions on generalisability of real-world Flatiron data to UK clinical practice.
- New company base case for OS modelling is **KM + log-logistic at 20 months (both arms)**.
- Based on external datasets and clinical expert opinion, key criteria company used for long-term validation of survival curves is **proportion of patients surviving in carboplatin-etoposide arm at 60 months**

A survival extrapolation for comparator arm deemed **clinically implausible** if:

- **< 0.5% remain alive at 60 months**
- **> 5% remain alive at 60 months**

[redacted]

KM: Kaplan-Meier

Further methods to estimate overall survival – Gamma, piecewise exponential

Company rejected gamma for modelling OS:

- Good statistical fit (similar to log-logistic and Weibull), but predicts 0.1% of patients alive at 60 months on comparator arm, underestimating long-term survival as seen with Weibull in 1st meeting.
- Half company's clinical experts thought survival at 60 months with gamma too pessimistic. Experts felt published figure of **1.3% ES-SCLC patients alive beyond 6 years plausible** (Souhami et al. 1990).
- Gamma extrapolation not associated with decreasing hazards, further discounting as a suitable extrapolation.

Company rejected piecewise model using KM estimates until 20 months (when ≈25% patients at risk in atezolizumab arm), extrapolating beyond with exponential function:

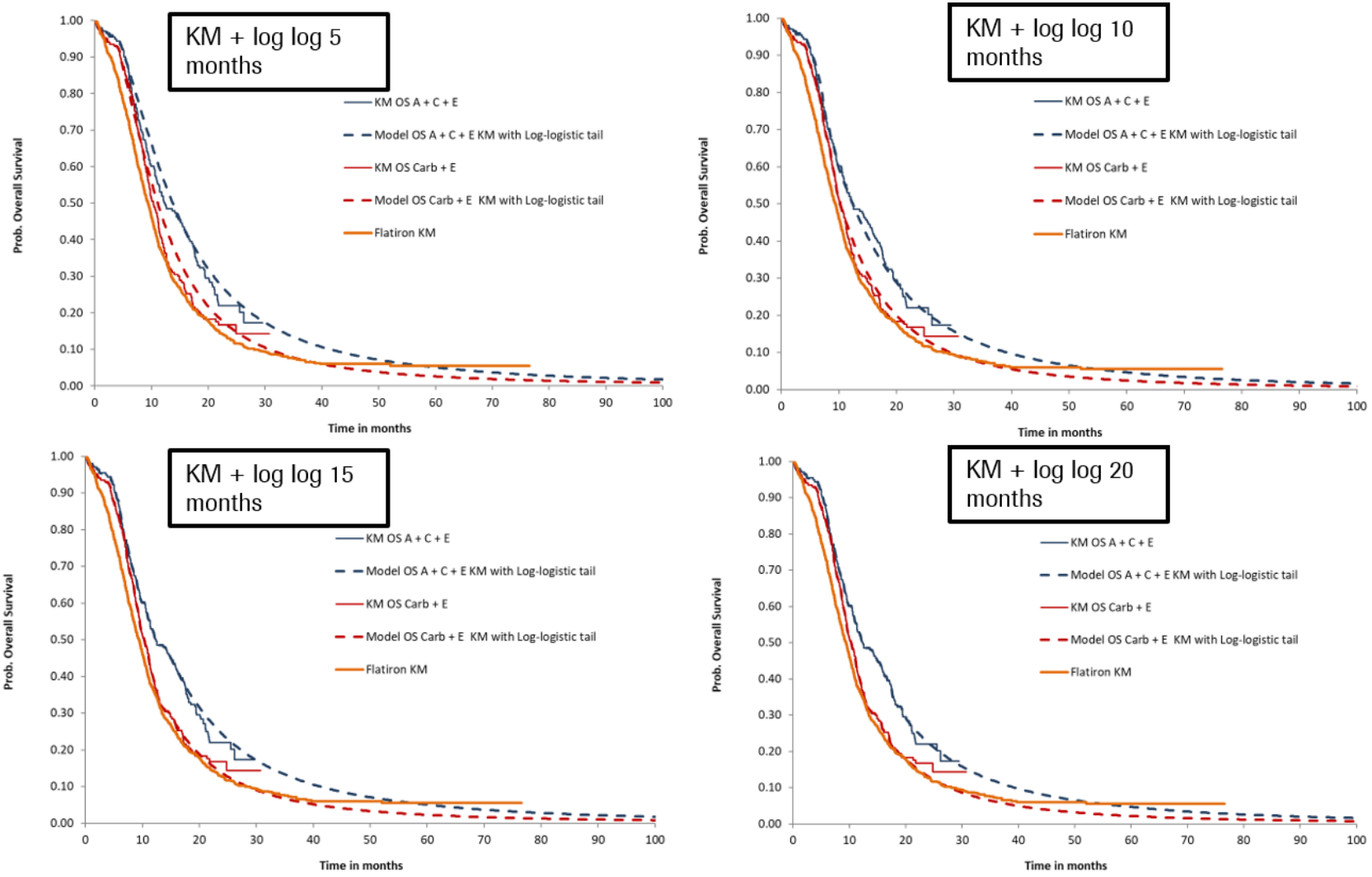
- Rate of exponential function estimated with data between 5 and 20 months, where plot of cumulative hazard appears linear, justifying use of exponential.
- Extrapolation too pessimistic, survival rate for comparator arm at 60 months is 0.2%. Around half of company's clinical experts thought this clinically implausible.
- Hazards do not decrease over time as available external data suggests it should.

[redacted]

A+C+E: atezolizumab+carboplatin+etoposide; AIC: Akaike information criterion; BIC: Bayesian information criterion; CE: carboplatin+etoposide

Further methods to estimate overall survival – KM + log-logistic (1)

Company investigated switching from KM data to log-logistic extrapolation at 5, 10, 15, and 20 months. Only considered log-logistic as Weibull confirmed as overly conservative at 1st meeting (predicts 0% survival at 60 months).



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Further methods to estimate overall survival – KM + log-logistic (2)

Company base case used a switch to extrapolation at 20 months, but sensitivity of ICER to cut-off point shown below:

Model (both arms, 60 months treatment effect duration)	ICER (£/QALY)	% remaining alive at 60 months (A+C+E arm)	% remaining alive at 60 months (C+E arm)	% remaining at risk A+C+E	% remaining at risk C+E
Log-logistic	47,449	4.9	2.5	n/a	n/a
KM switch at 5 months	43,806	5.2	2.7	86	90
KM switch at 10 months	50,635	4.7	2.4	54	59
KM switch at 15 months	38,904	5.1	2.3	40	45
KM switch at 20 months	**41,894**	**4.7**	**2.2**	**25**	**29**

Note: Assumption that hazards (survival curves) cannot cross in the model between A+C+E and C+E has been removed for these analyses due to the KM data being used for early time points of the survival model (this is referred to as alteration A in Table 3, page 482 of ACM1 Committee Papers).

- Extrapolation uses KM data for first portion of curve where hazard function differs to long-term data, and provides externally valid estimates - ≈2% patients remain alive at 60 months in comparator arm consistently. Over half of company's clinical experts felt at least one of KM + log-logistic extrapolations clinically plausible.
- Extrapolation shows decreasing long-term hazards on both arms. Overall, visual fit best for **KM switch to log-logistic at 20 months**, gives **ICER of £41,894**, **company's updated base case**.

[redacted]

Further methods to estimate overall survival – Restricted cubic spline (1)

Company

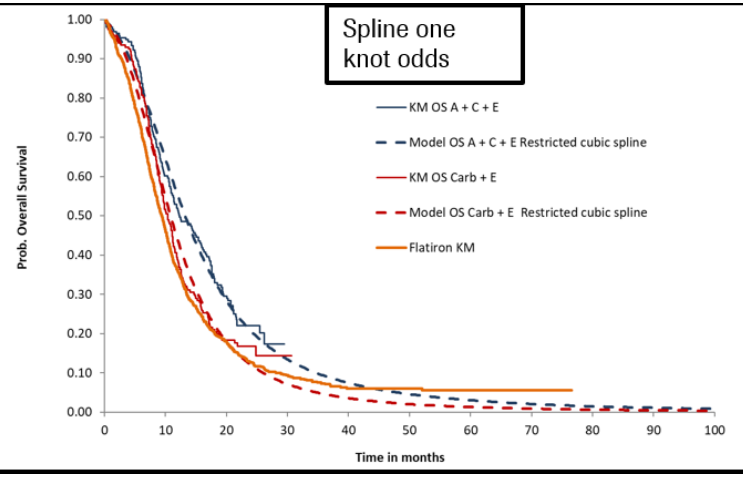
Majority of clinical experts thought two knot model estimates for survival at 60 months in comparator arm too optimistic (4.8% and 5.0% in two knot odds and two knot hazards, respectively). One knot odds model had an acceptable survival estimate of 1.3%.

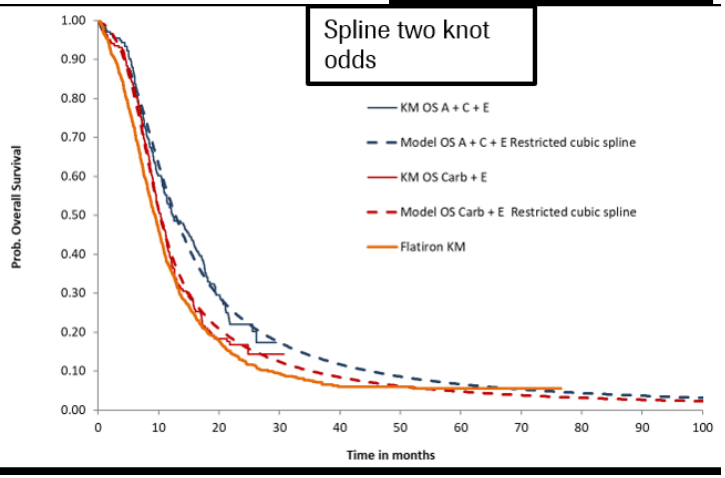
Three knot models provided minimal improved visual or statistical fit over two knot models. But over-fitted to carboplatin-etoposide tail, estimating 5 year survival >5% in all cases, which was not considered clinically plausible (so three knot models not included for consideration).

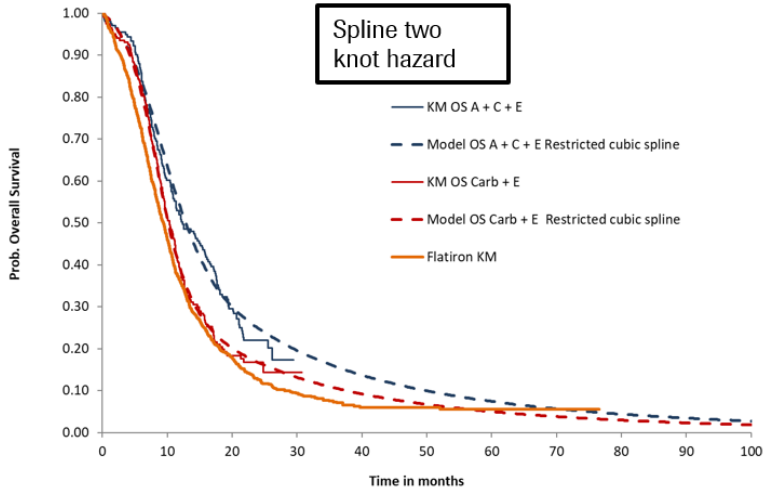
Model (both arms, 60 months treatment effect duration)	A+C+E		C+E	
Restricted Spline Model	AIC	BIC	AIC	BIC
One knot odds	**1081.373**	**1091.283**	**1134.843**	**1144.768**
One knot normal	1083.094	1093.004	1142.242	1152.167
One knot hazard	1089.305	1099.215	1154.956	1164.881
Two knots odds	**1080.935**	**1094.148**	**1125.977**	**1139.210**
Two knots normal	1083.613	1096.827	1134.597	1147.830
Two knots hazard	**1081.923**	**1095.137**	**1122.033**	**1135.266**
Three knots odds	1077.667	1094.184	1124.492	1141.033
Three knots normal	1095.123	1111.639	1128.552	1145.093
Three knots hazard	1077.918	1094.435	1123.050	1139.591
Note: Removal of the hazard assumption has been applied here for the two knot restricted spline models.				

Further methods to estimate overall survival – Restricted cubic spline (2)

Company







One knot odds: ICER £50,459

One of best statistical fits out of spline models, small number of patients alive at 5 years on carboplatin-etoposide.
Demonstrates decreasing hazards.
However, model did not improve in terms of visual fit over and above standard parametric curves.

Two knot odds: ICER £50,537

Good statistical fit, improved visual fit demonstrates decreasing hazards. Predict survival rate ≈5% at 5 years for comparator arm, higher than expected by clinicians.
Clinical experts do not anticipate that death rate for atezolizumab would exceed that of carboplatin (may be some crossing of curves in first 6 months). However, models report crossing of probability of death – atezolizumab arm assumed to have same probability of death as carboplatin-etoposide from 1.5 years (no treatment effect beyond this). Clinically implausible, considerable limitation of these models.

Two knot hazard: ICER £44,181

[redacted]

Further methods to estimate overall survival – Mixture cure

Company

- Investigated assumption of long-term survivorship ('cure') in OS extrapolation. Summary of estimated cure rates:

Distribution for survival in uncured patients	Cure fraction, % (min, max)		AIC	BIC	Ranking
	A+C+E	C+E			
Exponential	0 (0, 0)	0 (0, 0)	772.3965	1209.137	6
Generalised Gamma	19.9 (11.5, 22.7)	13.0 (0.1, 15.5)	703.1751	1341.779	2
Weibull	19.5 (19.4, 19.5)	12.7 (12.6, 12.8)	702.0928	1252.769	1
Log-normal	13.7 (9.7, 15.3)	6.3 (0, 8.3)	722.5114	1273.188	5
Log-logistic	3.0 (0, 10.4)	0.1 (0, 3)	709.1152	1259.792	3
Gompertz	21.3 (0, 22.6)	14.8 (0, 15.8)	711.1177	1261.794	4

- Clinical experts: long-term survival could be expected after 4-5 years, around 0.1–3% in patients on chemotherapy; log-logistic only distribution clinically plausible cure fraction.
- Considerable uncertainty around cure fraction depending on type of model fit to uncured population. Data available for atezolizumab not mature enough to visually observe plateau, model with cure fraction taken from trial data alone inappropriate for survival extrapolation.
- Scenario analyses with different cure fractions and mortality rates for those 'cured'.
- Cure models use the existing survival extrapolations - any additional 'cure' or long-term survivorship considered remains consistent in terms of fit. Long term survivorship deemed clinically plausible. However, as cure model provides a more optimistic view of long-term survivorship, and ICER only decreases under scenarios, KM + log-logistic (switch at 20 months) remains updated company base case.

Further methods to estimate overall survival

ERG

- Company's ICER for piecewise exponential could not be reproduced.
- Mixture cure models not justifiable given lack of trial data on patients who might demonstrate longevity (survival beyond 5 years in particular), but question validity of analyses where those who survive to 5 years are assumed to have a much lower mortality.
- Company's new base case OS model (KM data up to 20 months and log-logistic to extrapolate beyond this, for both arms) plausible, but **also any of the models considered by the company that fulfilled their own criteria of survival between 0.5% and 5% as well as with decreasing hazards:**
    - Log-logistic (as in original company base case)
    - Any KM+log-logistic
    - Spline based: one knot (odds or normal), two knots (odds or normal), three knots (odds only)
- Hazard versions of all spline models and normal version of three knots model eliminated due to 5 year survival <0.5% even for atezolizumab arm.

[redacted]

Further methods to estimate overall survival

ERG

- Two knots odds and hazard models applied to both arms gave ICERs of £78,080 and £226,106. Reported as lower by company, who curtailed treatment effect on mortality rate at 18 months. Company did this because these spline models resulted in mortality rate being higher for comparator for a period and their clinical experts believed this implausible.
- However, not impossible for there to be a change in direction of difference in mortality rate - supported by difference in shape of last 12 months of log cumulative hazard plot.

Most plausible model for extrapolation for **carboplatin + etoposide** would **still appear to be log-logistic** given its statistical fit, visual fit, decreasing hazards and survival at 5 years of 2.5%

Fitting OS models to the arms separately may be appropriate in this situation

[redacted]

Further methods to estimate overall survival – Different models for different arms

ERG Varying atezolizumab OS model (with log-logistic for comparator arm):

Model for atezolizumab arm (60 months treatment effect duration)	Survival at 60 months, atezolizumab arm	Survival at 60 months, comparator arm	ICER (£/QALY)
Log-logistic	[redacted]	[redacted]	47,449
KM+log-logistic, switch at:			
5 months	[redacted]	[redacted]	39,710
10 months	[redacted]	[redacted]	52,616
15 months	[redacted]	[redacted]	43,675
20 months	[redacted]	[redacted]	49,615
Restricted spline:			
1 knot odds	[redacted]	[redacted]	72,325
2 knot odds	[redacted]	[redacted]	50,287
2 knots normal	[redacted]	[redacted]	64,383
3 knots odds	[redacted]	[redacted]	75,544

Technical team judgement:

If fitting different models for the intervention and comparator arms is acceptable, then potential ICER range of all plausible models (assuming 60 month treatment effect) is £39,710-£75,544.

[redacted]

Is log-logistic, Kaplan-Meier+log-logistic, or one of the restricted cubic spline models the most appropriate extrapolation of OS? Should the arms have different OS models?

3. End of life considerations

End of life at ACM1

Scenario	Undiscounted mean overall survival, comparator arm	Undiscounted mean overall survival gain, atezolizumab
Issue: Long-term overall survival		
Using Weibull (technical team's preference)	12.8 months	+2.9 months
Use log-logistic	15.3 months	+4.4 months

IMpower133 study data

- 2.0 month median overall survival benefit for atezolizumab with carboplatin plus etoposide compared to carboplatin plus etoposide (12.3 months vs 10.3 months)

EOL:

- 'There is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.'
- 'Committees will need to be satisfied that estimates are sufficiently robust and the assumptions used are plausible, objective and robust.'

[redacted]

End of life - updated

	Scenario	Undiscounted mean overall survival, comparator arm	Undiscounted mean overall survival gain, atezolizumab
	Issue: Long-term overall survival		
	Company base case (KM+log-logistic, switch at 20 months, both arms)	14.6 months	+4.93 months
ERG	OS extrapolation for atezolizumab arm (with log-logistic for comparator arm):		
ERG	Log-logistic	15.3 months	+4.37 months
ERG	KM+log-logistic, switch at 5 months	15.3 months	+5.26 months
ERG	KM+log-logistic, switch at 10 months	15.3 months	+3.92 months
ERG	KM+log-logistic, switch at 15 months	15.3 months	+4.78 months
ERG	KM+log-logistic, switch at 20 months	15.3 months	+4.16 months
ERG	1 knot odds	15.3 months	+2.63 months
ERG	2 knot odds	15.3 months	+4.12 months
ERG	2 knots normal	15.3 months	+3.01 months
ERG	3 knots odds	15.3 months	+2.47 months

Restricted means analysis of trial data

- Committee requested restricted means analysis of overall survival data from IMpower133 to help estimate extent that atezolizumab plus carboplatin and etoposide extends life compared with carboplatin and etoposide alone.

Company

- Restricted mean survival times (RMSTs) at time of last event in trial show estimated difference of 2.1 months:

	Restricted mean survival time (RMST) at 26.22 months
Atezolizumab arm	14.4 months
Comparator arm	12.3 months

- One of the end-of-life (EOL) criteria is 'there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.'
- Difference of 2.1 months closer to EOL criteria than RMST difference estimated at 24 months (1.9 months difference). Suggests RMST increasing with further data cuts. Supported by clinician opinion on long-term survivors, implies RMST could be expected to continue increasing.

[redacted]

Restricted means analysis of trial data and end-of-life

Company (continued)

- Survival benefit as % of OS clinically meaningful, proportionally an important survival benefit improvement, supports atezolizumab as meeting EOL criteria. 2.1 months/12.3 months=17.1% versus EOL criteria (3 months/24 months=12.5%).
- When extrapolating for lifetime horizon of model in all alternative OS models presented, mean survival estimates for atezolizumab arm are 16.3-23.4 months (additional survival over SoC of 3.98-7.00 months, meeting EOL threshold).
- Using KM + log-logistic at 20 months, mean difference in OS is 4.93 months, above 3 months threshold required to meet EOL criteria.

ERG

- Restricted means analysis indicates that one of EOL criteria might not be met if difference in mean survival based on trial data only is used to estimate increase in life expectancy. Difference in means is larger the later the cut-off. Model predicts gain in life expectancy of <3 months using any of the log-logistic based models, **meeting EOL criteria possible although uncertain**.

Technical team judgement:

Additional survival for atezolizumab arm may eventually reach 3 months but this is uncertain. Previous guidance accept EOL criterion as being met with <3 months life extension, when survival gain is particularly important relative to average survival of people with the condition and committees were satisfied that estimates were sufficiently robust and assumptions used were plausible, objective and robust.

[redacted]

Should end-of-life weighting be applied for this technology in this indication?

Cost effectiveness results (1)

	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	Company updated base case (KM+log-logistic from 20 months, 60 months treatment effect)	[redacted]	[redacted]	41,894
ERG	Issue: Treatment effect duration			
ERG	a) 30 months (ERG generated)	N/R	N/R	52,646
ERG	b) 36 months	[redacted]	[redacted]	44,201
ERG	c) 48 months	[redacted]	[redacted]	42,637

[redacted]

Cost effectiveness results (2)

	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	Company updated base case (KM+log-logistic from 20 months for both arms, 60 months treatment effect)	[redacted]	[redacted]	41,894
ERG	Issue: OS extrapolation for atezolizumab arm (with log-logistic for comparator arm)			
	a) Log-logistic	[redacted]	[redacted]	47,449
	b) KM+log-logistic, switch at 5 months	[redacted]	[redacted]	39,710
	c) KM+log-logistic, switch at 10 months	[redacted]	[redacted]	52,616
	d) KM+log-logistic, switch at 15 months	[redacted]	[redacted]	43,675
	e) KM+log-logistic, switch at 20 months	[redacted]	[redacted]	49,615
	f) 1 knot odds	[redacted]	[redacted]	72,325
	g) 2 knot odds	[redacted]	[redacted]	50,287
	h) 2 knots normal	[redacted]	[redacted]	64,383
	i) 3 knots odds	[redacted]	[redacted]	75,544

[redacted]

Key issues for committee to consider

1. Which is the most plausible duration of treatment effect – 30, 36, 48 or 60 months?

2. Which extrapolation of overall survival is most appropriate – log-logistic, Kaplan-Meier + log-logistic, or one of the restricted cubic spline models?

3. Should end-of-life weighting be applied for this technology in this indication?

[redacted]