NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Roche Products**
   a. Response form
   b. Revised PAS

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Royal College of Physicians

4. **Comments on the Appraisal Consultation Document from experts:**
   a. Samreen Ahmed – clinical expert, nominated by the Royal College of Physicians

5. **Comments on the Appraisal Consultation Document received through the NICE website**

6. **Evidence Review Group critique of company comments on the ACD**
   a. ERG Addendum

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	Roche Products Ltd	*(see comment 1 in the company's consultation response for tables and figures)* **<u>Long term benefit on overall survival</u>** The ACD states: "…the trial data showed that atezolizumab with carboplatin and etoposide improves overall and progression-free survival compared with standard chemotherapy, but the long-term benefit on overall survival is uncertain." The IMpower133 trial showed that first-line extensive-stage small cell lung cancer (ES-SCLC) patients treated with atezolizumab plus carboplatin and etoposide had statistically significant and clinically meaningful overall survival versus those treated with carboplatin and etoposide. Although Roche agrees with the committee that there is uncertainty regarding the extent of long-term survival, the following considerations can help establish a clinically plausible incremental cost effectiveness ratio (ICER). These are summarised as follows with further details presented below: • Roche's response following the first committee meeting in the 'Request for additional analyses' submission clearly describes how the Kaplan Meier plus switch to log-logistic model at 20 months was selected, and maintain that this is the most appropriate choice that is well-supported by the evidence provided previously and reiterated in this document • The ERG analysis of survival extrapolations and resulting committee-preferred assumptions allows for the probability of death on the atezolizumab arm to exceed that of carboplatin and etoposide arm, which is clinically implausible • Exploring tumour growth inhibition (TGI) metrics from the IMpower133 trial supports Roche's rationale as to why the committee preferred assumptions are overly conservative, hence atezolizumab plus carboplatin and etoposide can be considered a cost-effective use of NHS resources **Kaplan-Meier with switch to log-logistic extrapolation at 20 months is suitable for appraising the cost-effectiveness of atezolizumab** As presented in the Roche's "Request for additional analyses" submission, our base case extrapolation is Kaplan-Meier + log-logistic at 20 months, which we maintain is the most appropriate to appraise the cost effectiveness of atezolizumab (ICER of £41,894).	The committee were aware of the data from tables and figures provided in this consultation comment, but this did not alter their preferred extrapolations for the atezolizumab arm or the chemotherapy arm. The committee were concerned that the company's hybrid modelling was inappropriate, because the event hazard rate had been applied for the whole model duration, rather than a hazard rate related to a specific cut-point in time. It considered that the chemotherapy group hazard reduced over time, but this was not reflected in the company's preferred hybrid model (Kaplan-Meier with switch to log-logistic extrapolation at 20 months) (see FAD section 3.6).

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			This extrapolation uses the Kaplan Meier data directly for the first portion of the curve where the hazard function differs to the long-term data and provides externally valid estimates. The extrapolation chosen for the tail of the curve is the log-logistic as this had one of the best statistical fits, shows good visual fit, and long-term survival estimates are validated by clinical experts, available literature and real-world (Flatiron) data. The event hazard rate applied in the tail of the curve has been generated from the entire dataset, further increasing robustness. It would not be appropriate to consider the hazard rate from the cut-point of 20 months since this ignores valuable data from the trial - at 20 months, there are 24.9% patients remaining in the atezolizumab arm and 16.8% in the comparator arm. The evidence used to support the use of the Kaplan-Meier with switch to log-logistic extrapolation at 20 months is summarised in Table 1 (*see Table 1 box in comment 1 in the company's consultation response*). This includes additional evidence collated through a survey sent to Early Access To Medicines Scheme (EAMS) investigators in January 2020. **The committee's preferred models are not appropriate for appraising atezolizumab** The committee stated in the ACD that restricted spline models might be the best method for modelling long-term survival for atezolizumab in first-line ES-SCLC and agreed with the ERG that the use of the log-logistic extrapolation for the chemotherapy arm and a more flexible model for the atezolizumab arm was suitable for decision-making. Roche does not consider these models to be appropriate for the following reasons which will be addressed in turn below: 1. The models chosen allow for crossing of the probability of death, in doing so, it is assumed that the rate of death for atezolizumab arm can exceed that of the chemotherapy arm – which is clinically implausible 2. Allowing the use of different parametric models for the treatment arms is not recommended in the NICE Decision Support Unit (DSU) guidance (Technical Support Document 14) [1] ***Crossing of intervention and comparator probability of death*** As detailed in the ACD, the committee considered a log-logistic extrapolation for the chemotherapy arm plus a spline-based model for the atezolizumab arm was plausible, with ICERs ranging between just over £50,000 per QALY gained and £75,544 per QALY gained. This ICER range includes the assumption that the probability of mortality can cross. As stated by the ERG in slide 22 of the public committee slides, "…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." However, during 1:1 consultations with 8 clinical experts (held during November 2019) to support the "Request for additional analyses" submission, the clinical experts did not anticipate that the rate of mortality for atezolizumab arm would exceed that of the comparator arm (although there may be some crossing in the first 6 months). Therefore, in Roche's analyses, it was assumed that these cannot cross, and the probability of mortality	

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			was equal from the point at which the arms meet. By allowing the crossing of probabilities of mortality, an assumption is made that chemotherapy alone is actually providing a survival benefit over atezolizumab from this point onwards (until 60 months, when the model limits overall survival to be equal on both arms). This lacks clinical or biologic rationale, as supported by the following points: • Trial evidence shows no evidence of the cumulative hazard curves converging within the interpretable section of the data; • Clinical expert opinion gathered by Roche has confirmed that the probability of death for patients treated with atezolizumab exceeding that for patients treated with carboplatin plus etoposide in the long term is implausible; • The intervention arm includes the same active treatments as the comparator arm plus an immunotherapy, therefore an efficacy that is improved or at least equal is expected • TGI metrics (see section heading: "Tumour growth inhibition (TGI) metrics" below) suggest there is a [redacted] and that crossing of probability of mortality at or before 2 years is not an appropriate assumption Furthermore, although the ERG commented that the shape of the last 12 months of the log cumulative plot supports a change in different of mortality rate, this portion of the plot should be interpreted with caution. The last 12 months of the cumulative hazard plot is informed by only a small number of patients at risk and a lot of censoring; from 18 months, there are only 61 patients with 21 events on the atezolizumab arm and 39 patients with 8 events on the chemotherapy arm (Figure 1 and Figure 2) (*see Figure 1 and Figure 2 in comment 1 in the company's consultation response*) . For these reasons, Roche considers survival models that include the crossing of probabilities to be implausible and not reflective of the survival benefit observed in the clinical data or clinical expert opinion. Three of the four models used to generate the ICERs ranging between just over £50,000 per QALY gained and £75,544 per QALY gained (1 knot odds, 2 knots normal, and 3 knots odds in the atezolizumab arm and log-logistic in the chemotherapy arm) are not clinically plausible as there is crossing of the probability of mortality between the treatment arms. The remaining 2 knot odds spline model did not show crossing of the probability of mortality, however, this model was not strongly considered a clinically plausible model in the survey of EAMS investigators (see Appendix 1). Furthermore, the 2 knot odds spline model does not fit better over and above the fully log-logistic model. ***The same parametric model should be used for the treatment arms*** According to the DSU Technical Support Document, "fitting different types of parametric model…to different treatment arms would require substantial justification". However, Roche has not seen a clear rationale given as to why different parametric models have been used for each treatment arm. This assumption lacks biological plausibility and has not been underpinned by clinical expert	

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			judgment, or robust statistical analysis. Furthermore, the shape of the log cumulative hazard plots in Figure 1 are similar and support the use of the same model for both treatment arms. Roche strongly believes that the committee should re-consider using the same parametric model for both treatment arms in absence of a substantial justification. **Tumour growth inhibition (TGI) metrics** To further support the relative efficacy of atezolizumab in ES-SCLC, tumour growth inhibition (TGI) data are presented below. TGI metrics are estimated using the sum of longest diameters of target lesions per response evaluation criteria in solid tumours (RECIST) criteria (5). These can be used to model longitudinal tumour size, and to capture the rates of tumour growth and shrinkage over time (6). This allows the examination of differential response patterns seen with different types of therapy; such as with immunotherapies where a delayed response or initial tumour growth before regression (pseudoprogression) may be observed (7). TGI metrics have previously been shown to predict overall survival (OS) in colorectal cancer, non-small cell lung cancer (NSCLC) and other tumour types (6, 8-11). TGI metrics have also been investigated using data from the POPLAR study, showing that patients with NSCLC treated with atezolizumab had slower tumour growth than those treated with chemotherapy, and that these metrics were predictive of overall survival (12). This study hypothesised that as anti-PD-L1/PD-1 therapies have been shown in NSCLC to improve OS relative to chemotherapy, a TGI model could provide a complementary assessment of response to evaluate the efficacy of immunotherapies. To estimate TGI profiles for the atezolizumab and chemotherapy arms using IMpower133 data, the same methods as detailed in Claret et al. 2009 (8) were followed by describing tumour size (the sum of the longest diameters of target lesions) as a function of time (Figure 3) (*see Figure 3 in comment 1 in the company's consultation response*). [redacted] Considering the predictive quality of TGI metrics with overall survival, there is reason to believe that the separation of TGI profiles would lead to a continued treatment effect, and overall survival benefit, up to and beyond 2 years. This would further suggest that models demonstrating a crossing of probability of mortality at or before 2 years are too conservative, and suggests that there is a realistic prospect of some differential long-term survivorship in favour of atezolizumab plus carboplatin and etoposide. Incorporating long-term survivorship on top of survival extrapolations In Roche's "Request for additional analyses" submission, we included a section on mixture	

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			cure models. The inclusion of the cure fraction was backed up by literature, Flatiron registry data, and clinical expert opinion. The TGI metrics data presented above provides further support for including an assumption of long-term survivorship. Only a small number of patients would need to experience long-term survivorship for atezolizumab to be cost-effective. Table 2 shows the cost-effectiveness results for survival models where no crossing of mortality of probability between arms is present, with and without an assumption of long-term survivorship. All these survival models estimate long-term survival for the comparator between 0.5% and 5% and support an assumption of decreasing long-term hazards in both arms. All models are in the range of cost-effectiveness for end-of-life medicines. More importantly, by assuming that 50% of patients remaining alive at 60 months have double the risk of mortality to the general population , all the ICERs fall below the £50k threshold (*see Table 4 in comment 1 in the company's consultation response*). Appendix 2 presents this information as a visual representation. **Atezolizumab plus carboplatin and etoposide for first-line ES-SCLC is plausibly cost-effective** Roche acknowledges that there are a few alternative viable options to extrapolate overall survival presented in the "Request for additional analyses" submission that are a good fit both visually and statistically, and clinically plausible. Table 4 displays the cost-effectiveness results of survival models that do not result in any crossing or meeting of the probability of mortality across the two model arms. These results show that the majority of these options provide ICERs below £50,000, and if an assumption is made that atezolizumab patients receive a small incremental long-term survivorship benefit (~2% for atezolizumab patients and ~1% for chemotherapy), as suggested by the TGI profiles, all of these options would be below the £50,000 threshold.	
2	Consultee (company)	Roche Products Ltd	Generalisibility to patients with ECOG performance status 2 or higher The ACD states: "Data from IMpower133 are not generalisable to people with an ECOG performance status score of 2 or higher which is likely in clinical practice in England." Whilst we agree there are patients in the NHS in England who are ECOG performance status 2 or higher at diagnosis, clinical experts during an advisory board in November 2018 estimated a range of 20–55% ES-SCLC patients are diagnosed as ECOG performance status 0–1. Importantly, during the first appraisal committee meeting, it was stated that if atezolizumab plus carboplatin and etoposide was available on the NHS, the Blueteq system will limit access to atezolizumab using ECOG performance status 0–1 criteria, therefore IMpower133 data are generalisable for patients in England. An Early Access to Medicines Scheme for first line ES-SCLC, with ECOG performance status 0-1 opened on 10th June 2019. Since the EAMS began, 79 patients have already been treated in the scheme across 38 sites in England and Wales, highlighting that there are patients who are eligible for treatment in England.	The wording of the FAD has been amended to make it clearer that the committee considered the trial data to not be representative of people of ECOG performance status of 2 or higher – see FAD section 3.4. Wording in section 3.4 changed to 'some' instead of 'many', so sentence now reads 'some people with untreated ES SCLC in the NHS in England are likely to have an ECOG performance status of 2 or higher.'

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			Roche sent out a survey to 51 EAMS investigators in England and Wales at 35 different hospitals across England and Wales, who have treated patients with atezolizumab in first line ES-SCLC to determine the proportion of patients with ES-SCLC who are diagnosed as ECOG performance status 0–1. The survey asked the following question (email communication provided in Appendix 1): Question: The IMpower133 trial recruited patients with ES-SCLC that were ECOG performance status 0–1. What percentage of your 1L ES-SCLC patients are ECOG performance status 0-1? a. 0–10% b. 11–20% c. 21–30% d. 31–40% e. 41–50% f. >50% From the 51 EAMS investigators who were sent the survey, 7 responded. The collated responses were as follows (please see : Estimated proportion of patients with ECOG performance status 0–1 (number of responses) 0–10% (0) 11–20% (2) 21–30% (2) 31–40% (0) 41–50% (1) >50% (2) The advisory board, the EAMS, and the survey to EAMS investigators confirm that a meaningful proportion of patients in England are diagnosed with 1L ES-SCLC with ECOG performance status of 0 or 1. Therefore, atezolizumab plus carboplatin and etoposide is an important addition to the treatment of 1L ES-SCLC patients in England.	
3	Consultee (company)	Roche Products Ltd	**Duration of treatment benefit** The ACD states: "…based on a Kaplan-Maier data plot of overall survival from IMpower133, there may be no treatment benefit from approximately 30 months." However, there is no evidence that treatment benefit may stop from 30 months. As detailed earlier in this response, the data at 30 months are subject to an extremely high level of censoring and considered to be unreliable. Specifically, the last observed events are at 26.2 and 24.8 months for the atezolizumab and comparator arms, respectively, at which point there are only 6 patients left at risk on both arms. The censored patients are either lost to follow up or have not experienced progression or death at the time of analysis (i.e., not necessarily dead).	Comment noted. Section 3.6 of the FAD states that 'The company's preferred 60-month treatment effect duration from starting treatment was plausible but uncertain because follow up was still short.' The committee used a 60-month cut off of treatment benefit in their decision making, as opposed to a shorter duration such as 30 months, as varying the treatment effect duration did not have a large effect on the

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			Furthermore, the tumour growth inhibition (TGI) metrics presented (**Error! Reference source not found.**) shows clearly there is a [redacted] As presented in the "Request for additional analyses" submission, the scenario analysis for different treatment effect cut off times showed that this had little impact on the ICER. Overall, there is no evidence to support or refute using 60 months as the treatment effect cut-off. We have previously provided evidence of other immunotherapies for lung cancer where NICE had accepted that long-term treatment effect was biologically plausible (TA428, TA531) (13, 14). Prolonged treatment benefit is expected from immunotherapies, as supported by clinical experts; therefore Roche's base case remains at 60 months, as has been used in previous lung cancer appraisals (TA483) (15).	ICER overall (see section 3.6 of FAD).
4	Consultee (company)	Roche Products Ltd	In summary, we discuss in the preceding sections the reasons we maintain that the Kaplan-Meier plus a switch to log-logistic extrapolation at 20 months is the most appropriate model to appraise the cost-effectiveness of atezolizumab (ICER of £41,894). In addition, we explain why it is not possible for there to be a crossing of probability of mortality between the treatment arms in the long term and that there is no strong support for different extrapolations on each arm. We also present tumour inhibition (TGI) metrics [redacted]. By assuming long-term survivorship rates, the ICERs presented in the scenario analysis (**Error! Reference source not found.**) all fall below the £50k threshold. Atezolizumab with carboplatin plus etoposide is considered to meet NICE's end-of-life criteria, highlighting that it is a valuable treatment for those with first-line ES-SCLC who have a poor prognosis and do not have the option of life-extending innovative treatments. As stated by a patient expert at the first appraisal committee meeting, "any treatment that could extend life, even only for a short period, would allow more time for advanced care planning" (16), so although the benefit of atezolizumab with carboplatin plus etoposide may be considered modest, the impact will be great for patients, carers, and their families.	Comment noted. The committee took into account clinical and patient expert evidence, and considered that the criteria to be considered an end of life treatment had been met. The revised patient access scheme means that the ICER results for the range of extrapolations considered plausible by the committee, are now all below the threshold used for end of life treatments, so atezolizumab can be considered cost effective in this indication.
1	Consultee (national professional organisations)	Clinical expert representing BTOG/RCP/ACP/NCRN	All relevant data has been considered: IMPOWER 133 has been thoroughly scrutinised. Data recently presented for CASPIAN (using durvalumab with chemotherapy) has almost identical HR=0.73 in extensive SCLC. This was brought to the Committee's attention by the clinical experts. This suggests that immunotherapy has a biological effect in SCLC as 2 trials of IO have produced consistent and confirmatory results	Comment noted.
2	Consultee (national professional organisations)	Clinical expert representing BTOG/RCP/ACP/NCRN	The evidence and models used are representative and as closely interpreted as possible without bias. The assumptions made are clinically reliable	Comment noted.

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3	Consultee (national professional organisations)	Clinical expert representing BTOG/RCP/ACP/NCRI	I am disappointed that this treatment will NOT be available for patients in the UK as this is the only advance made in this disease area for over 30 years. This is presumably made solely on cost effectiveness grounds. The performance status of patient in the trial was 0/1 so would exclude the majority of patient in the UK for this treatment anyway. It is unfortunate that this treatment breakthrough will not be available for this small proportion of fit patients	The revised patient access scheme discount has resulted in the benefit being sufficient to justify the cost, so the treatment has been recommended. The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when formulating its recommendations.
4	Public	(Web commenter 1)	**Has all of the relevant evidence been taken into account?** Yes	Comment noted.
5		(Web commenter 1)	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The comment about performance status and the IMpower133 not being applicable to clinical practice in England is misleading. ES-SCLC is an aggressive cancer and a lot of patient will present with a compromised performance status. However this is the case globally and not just for England. It is the biology of the disease. As per the rest of the world there is still a significant population of good performance status ES-SCLC patients who would stand to benefit from the IMpower133 regime.	The wording of the FAD has been amended to make it clear that the committee considered the trial data to not be representative of people of ECOG performance status of 2 or higher – see FAD section 3.4
6	Public	(Web commenter 1)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** In my opinion the decision to not recommend the treatment is incorrect. ES-SCLC is a disease with high unmet need and with no therapeutic gains for decades. The IMpower133 regime and trial readout is the first positive step forward for this group of patients with an improvement in PFS and OS The end of life modelling meets NICE's criteria. On this basis I would strongly support a positive recommendation from NICE	The revised patient access scheme has resulted in the benefit being sufficient to justify the cost, so the treatment has been recommended. The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when formulating its recommendations.
7	Public	(Web commenter 2)	**Has all of the relevant evidence been taken into account?** As a mother whose son died 3 years ago from small cell lung cancer aged 29. I would like to say because of the length of time it actually took for my son to be diagnosed , this hampered his treatment. He was given chemotherapy, 3 different concoctions. Which unfortunately didn't work at all even though his oncologist was adamant he could fix it this time ? If having this new drug could have prolonged his life for a few short months would have made a lot of difference to us as a family and my son. We could have made more memories and maybe given him a better quality of life. From diagnosis to death was only 4 month's. Too quick and heartbreaking, the disease is too aggressive and caused him so much discomfort and pain. No parent should have to witness this. If you can help give further patients a few more months if required and without further pain and discomfort why should that be denied????	The revised patient access scheme has resulted in the benefit being sufficient to justify the cost, so the treatment has been recommended. The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when formulating its recommendations. The Committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness.

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				Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (see point 4, and principle 7, NICE principles).
8	Public	(Web commenter 2)	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** As I said earlier who gives the right to deny someone with the will to live life, just because of cost?????? Cancer is ruining and killing people's loved ones every second of every day. A y more time that can be given to them is precious and no amount of money matters.	Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (see point 4, and principle 7, NICE principles).
9	Public	(Web commenter 2)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** If all the trials are proven conclusive and sound then it's a no brainer. Yes allow the NBA to use it. Too many of us are having to find our own life saving treatments.	Comment noted.
10	Public	(Web commenter 2)	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** I don't believe there is? It should be available to all.	Comment noted.

References:

1. Latimer N. Nice DSU technical support document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data 2011 [Date Accessed 23rd December 2019]. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments: **5pm** on **Tuesday 28 January 2020. Email:** TACommC@nice.org.uk **/** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Roche Products Ltd; hereinafter “Roche”
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Chui-ying Yip

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	Roche is disappointed with the provisional negative recommendation, although we recognise the uncertainties presented by the committee in the ACD. **Technical engagement** There were 5 key issues that were considered during Technical Engagement and 4 of these issues were resolved during this stage of the appraisal as follows: • Carboplatin with etoposide is the most relevant comparator for this appraisal • Because carboplatin with etoposide is the most relevant comparator for this appraisal, clinical data from the IMpower133 trial is acceptable for decision making • Roche's approach of using time-to-death to estimate utility values, using the ERG's preferred model, is acceptable for decision making • It is appropriate for disutilities associated with adverse events to be incorporated in the model. **First appraisal committee meeting** The remaining issue, which was a main point of discussion at the first appraisal committee meeting, was uncertainty regarding the long-term survival estimates. **Second appraisal committee meeting** Roche provided further clarification and analyses ahead of the second committee meeting to address the uncertainties around long-term survival estimates. In addition, treatment effect duration and end of life were also addressed. Following the second committee meeting, atezolizumab was deemed to meet NICE's criteria to be considered a life-extending treatment for the end of life. However, the following issues remain: • The long-term benefit on overall survival is uncertain • IMpower133 data are not generalisable to patients with ECOG performance status score of 2 or higher • Duration of treatment benefit is uncertain Our response provided below address these remaining issues in turn.
1	**<u>Long term benefit on overall survival</u>** The ACD states: "…the trial data showed that atezolizumab with carboplatin and etoposide improves overall and progression-free survival compared with standard chemotherapy, but the long-term benefit on overall survival is uncertain." The IMpower133 trial showed that first-line extensive-stage small cell lung cancer (ES-SCLC) patients treated with atezolizumab plus carboplatin and etoposide had statistically significant and clinically meaningful overall survival versus those treated with carboplatin and etoposide. Although Roche agrees with the committee that there is uncertainty regarding the extent of long-term survival, the following considerations can help establish a clinically plausible incremental cost effectiveness ratio (ICER). These are summarised as follows with further details presented below:

- Roche's response following the first committee meeting in the 'Request for additional analyses' submission clearly describes how the Kaplan Meier plus switch to log-logistic model at 20 months was selected, and maintain that this is the most appropriate choice that is well-supported by the evidence provided previously and reiterated in this document
- The ERG analysis of survival extrapolations and resulting committee-preferred assumptions allows for the probability of death on the atezolizumab arm to exceed that of carboplatin and etoposide arm, which is clinically implausible
- Exploring tumour growth inhibition (TGI) metrics from the IMpower133 trial [redacted], hence atezolizumab plus carboplatin and etoposide can be considered a cost-effective use of NHS resources

Kaplan-Meier with switch to log-logistic extrapolation at 20 months is suitable for appraising the cost-effectiveness of atezolizumab

As presented in the Roche's "Request for additional analyses" submission, our base case extrapolation is Kaplan-Meier + log-logistic at 20 months, which we maintain is the most appropriate to appraise the cost effectiveness of atezolizumab (ICER of £41,894).

This extrapolation uses the Kaplan Meier data directly for the first portion of the curve where the hazard function differs to the long-term data and provides externally valid estimates. The extrapolation chosen for the tail of the curve is the log-logistic as this had one of the best statistical fits, shows good visual fit, and long-term survival estimates are validated by clinical experts, available literature and real-world (Flatiron) data. The event hazard rate applied in the tail of the curve has been generated from the entire dataset, further increasing robustness. It would not be appropriate to consider the hazard rate from the cut-point of 20 months since this ignores valuable data from the trial - at 20 months, there are 24.9% patients remaining in the atezolizumab arm and 16.8% in the comparator arm.

The evidence used to support the use of the Kaplan-Meier with switch to log-logistic extrapolation at 20 months is summarised in Table 1. This includes additional evidence collated through a survey sent to Early Access To Medicines Scheme (EAMS) investigators in January 2020.

Table 1: Supporting evidence for the Kaplan-Meier with switch to log-logistic extrapolation at 20 months

Reasons	Supporting evidence
One of the best statistical fits	*Table 2: Ranking of overall survival distributions based on AIC, BIC* and visual fit*

	A+C+E		Ranking	C+E		Ranking
Distribution	**AIC (R)**	**BIC (R)**		**AIC (R)**	**BIC (R)**	
exponential	1108.41	1111.72	5	1174.54	1177.84	6
weibull	**1085.40**	**1092.01**	**1**	**1146.84**	**1153.45**	**3**
log-normal	1116.28	1122.89	7	1173.89	1180.51	7
gamma	**1086.36**	**1092.97**	**2**	**1145.85**	**1152.47**	**2**
generalised gamma	1087.35	1097.26	4	1147.64	1157.56	4

		log-logistic | **1086.40** | **1093.00** | **3** | **1140.26** | **1146.88** | **1** | gompertz | 1093.11 | 1099.71 | 6 | 1162.48 | 1169.10 | 5 *Survival analysis have been re-run using R, version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria), rather than SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA), therefore, AIC/BIC are presented on a different scale compared to those in Roche's submission. No point estimates of the models in the original submission have changed.
	Good visual fit	Between the Kaplan-Meier with switch to log-logistic extrapolation at 5, 10, 15, and 20 months, the visual fit was best for the Kaplan-Meier with switch to log-logistic extrapolation at 20 months.
	Clinical validation	During 1:1 consultations with eight clinicians, over half of the clinicians felt that at least one of the Kaplan Meier + log-logistic extrapolations was clinically plausible. The mean 5-year survival estimate for patients receiving carboplatin-etoposide from these consultations was 1.26±0.91 which aligns with the 5-year survival estimate from the Kaplan Meier + log-logistic extrapolation at 20 months of 2.2%. In January 2020, Roche sent out a survey to 51 EAMS investigators at 35 hospitals across England and Wales to further assess the most appropriate extrapolation with which to estimate long-term survival. Investigators were asked to evaluate ten different models, including log-logistic, Kaplan-Meier plus log-logistic and restricted spline models, by commenting on whether they thought comparator arm survival estimates were clinically plausible, clinically implausible or if they were uncertain (Table 3). Seven EAMS investigators responded to the survey and two models were deemed clinically plausible by all seven of the investigators: the log-logistic extrapolation and the Kaplan-Meier plus log-logistic extrapolation at 20 months (see Appendix 1 for the full results). The EAMS investigators were also asked to rank the models from 1 to 10 (1=most clinically plausible, 10=most clinically implausible); the models ranked 1 and 2 were a mixture of log-logistic, Kaplan-Meier plus log-logistic, and spline one knot (see Appendix 1 for full results). *Table 3: Survival estimates for the comparator arm using different extrapolations** **Extrapolations** | **Months** **12** | **24** | **36** | **48** | **60** Log-logistic | 43.8% | 15.3% | 7.1% | 4.0% | 2.5% KM + log-log (5 months) | 45.8% | 16.0% | 7.4% | 4.2% | 2.7% KM + log log (10 months) | 42.0% | 14.6%% | 6.8% | 3.8% | 2.4% KM + log log (15 months) | 39.0% | 13.8% | 6.4% | 3.6% | 2.3% KM + log log (20 months) | 39.0% | 13.2% | 6.1% | 3.5% | 2.2% Spline one knot odds | 44.1% | 12.1% | 4.6% | 2.3% | 1.3% Spline two knots odds | 40.6% | 16.6% | 9.8% | 6.5% | 4.8% Spline two knots hazard | 39.2% | 16.8% | 10.6% | 7.1% | 5.0% Spline two knots normal | 41.4% | 16.8% | 8.9% | 5.3% | 3.3% Spline three knots odds | 39.5% | 16.6% | 11.3% | 8.5% | 6.7% *Same extrapolations used for both treatment arms

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

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Literature	Collectively, the literature presented in the Technical Engagement Report (1-3), support our assumption that patients with ES-SCLC alive at 4/5 years could experience long-term survivorship on carboplatin + etoposide of approximately 1.1%–2.3% of patients, which aligns with the 5-year survival estimate from the Kaplan Meier + log-logistic extrapolation at 20 months of 2.2%.
Flatiron data	The Flatiron real-world data provided further evidence that survival at 4/5 years is plausible and that there is evidence of a survival plateau, demonstrating that long-term survival exists for a small group of patients.

The committee's preferred models are not appropriate for appraising atezolizumab
The committee stated in the ACD that restricted spline models might be the best method for modelling long-term survival for atezolizumab in first-line ES-SCLC and agreed with the ERG that the use of the log-logistic extrapolation for the chemotherapy arm and a more flexible model for the atezolizumab arm was suitable for decision-making. Roche does not consider these models to be appropriate for the following reasons which will be addressed in turn below:

1. The models chosen allow for crossing of the probability of death, in doing so, it is assumed that the rate of death for atezolizumab arm can exceed that of the chemotherapy arm – which is clinically implausible
2. Allowing the use of different parametric models for the treatment arms is not recommended in the NICE Decision Support Unit (DSU) guidance (Technical Support Document 14) (4)

Crossing of intervention and comparator probability of death

As detailed in the ACD, the committee considered a log-logistic extrapolation for the chemotherapy arm plus a spline-based model for the atezolizumab arm was plausible, with ICERs ranging between just over £50,000 per QALY gained and £75,544 per QALY gained. This ICER range includes the assumption that the probability of mortality can cross. As stated by the ERG in slide 22 of the public committee slides, *"…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."*

However, during 1:1 consultations with 8 clinical experts (held during November 2019) to support the "Request for additional analyses" submission, the clinical experts did not anticipate that the rate of mortality for atezolizumab arm would exceed that of the comparator arm (although there may be some crossing in the first 6 months). Therefore, in Roche's analyses, it was assumed that these cannot cross, and the probability of mortality was equal from the point at which the arms meet.

By allowing the crossing of probabilities of mortality, an assumption is made that chemotherapy alone is actually providing a survival benefit over atezolizumab from this point onwards (until 60 months, when the model limits overall survival to be equal on both arms). This lacks clinical or biologic rationale, as supported by the following points:

- Trial evidence shows no evidence of the cumulative hazard curves converging within the interpretable section of the data;
- Clinical expert opinion gathered by Roche has confirmed that the probability of death for patients treated with atezolizumab exceeding that for patients treated with carboplatin plus etoposide in the long term is implausible;
- The intervention arm includes the same active treatments as the comparator arm plus an immunotherapy, therefore an efficacy that is improved or at least equal is expected
- TGI metrics (see section heading: "Tumour growth inhibition (TGI) metrics" below) suggest there is [redacted] and that crossing of probability of mortality at or before

2 years is not an appropriate assumption

Furthermore, although the ERG commented that the shape of the last 12 months of the log cumulative plot supports a change in different of mortality rate, this portion of the plot should be interpreted with caution. The last 12 months of the cumulative hazard plot is informed by only a small number of patients at risk and a lot of censoring; from 18 months, there are only 61 patients with 21 events on the atezolizumab arm and 39 patients with 8 events on the chemotherapy arm (Figure 1 and Figure 2).

Figure 1: Log-cumulative hazard of IMpower133 trial data

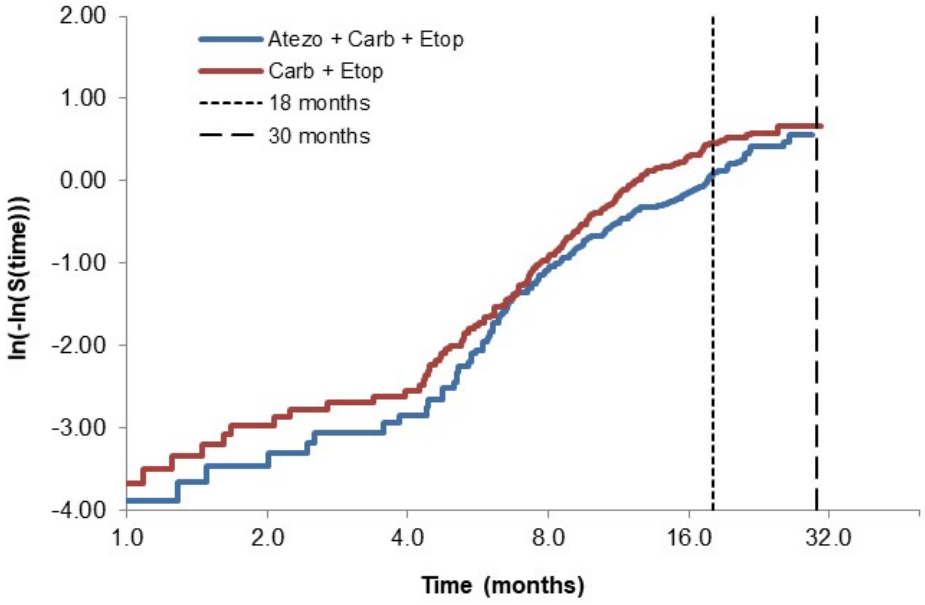
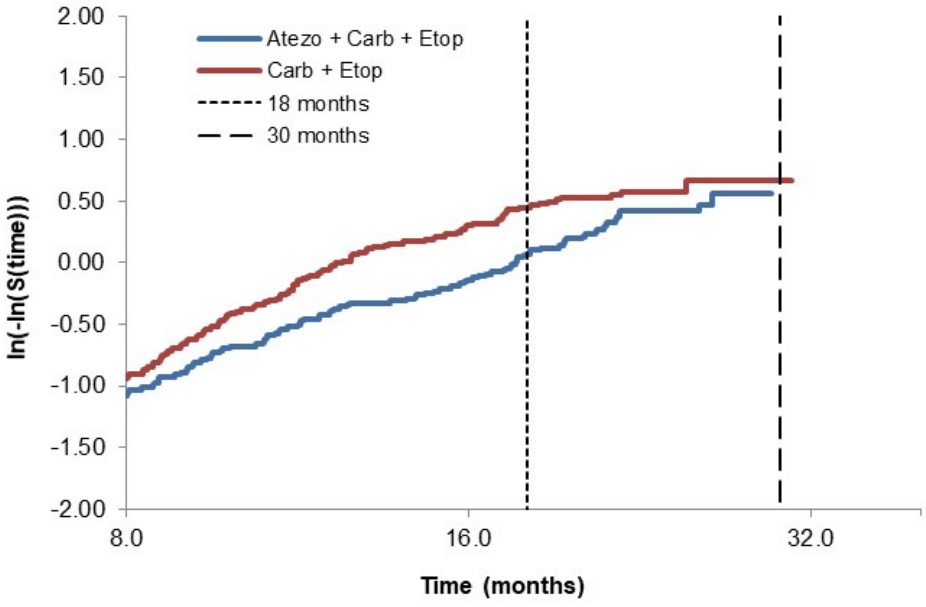


Figure 2: Logit (S(t)) vs Log-time plot of IMpower133 trial data



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

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For these reasons, Roche considers survival models that include the crossing of probabilities to be implausible and not reflective of the survival benefit observed in the clinical data or clinical expert opinion. Three of the four models used to generate the ICERs ranging between just over £50,000 per QALY gained and £75,544 per QALY gained (1 knot odds, 2 knots normal, and 3 knots odds in the atezolizumab arm and log-logistic in the chemotherapy arm) are not clinically plausible as there is crossing of the probability of mortality between the treatment arms. The remaining 2 knot odds spline model did not show crossing of the probability of mortality, however, this model was not strongly considered a clinically plausible model in the survey of EAMS investigators (see Appendix 1). Furthermore, the 2 knot odds spline model does not fit better over and above the fully log-logistic model.

The same parametric model should be used for the treatment arms

According to the DSU Technical Support Document, "fitting different types of parametric model…to different treatment arms would require substantial justification". However, Roche has not seen a clear rationale given as to why different parametric models have been used for each treatment arm.

This assumption lacks biological plausibility and has not been underpinned by clinical expert judgment, or robust statistical analysis. Furthermore, the shape of the log cumulative hazard plots in Figure 1 are similar and support the use of the same model for both treatment arms. Roche strongly believes that the committee should re-consider using the same parametric model for both treatment arms in absence of a substantial justification.

Tumour growth inhibition (TGI) metrics

To further support the relative efficacy of atezolizumab in ES-SCLC, tumour growth inhibition (TGI) data are presented below. TGI metrics are estimated using the sum of longest diameters of target lesions per response evaluation criteria in solid tumours (RECIST) criteria (5). These can be used to model longitudinal tumour size, and to capture the rates of tumour growth and shrinkage over time (6). This allows the examination of differential response patterns seen with different types of therapy; such as with immunotherapies where a delayed response or initial tumour growth before regression (pseudoprogression) may be observed (7).

TGI metrics have previously been shown to predict overall survival (OS) in colorectal cancer, non-small cell lung cancer (NSCLC) and other tumour types (6, 8-11). TGI metrics have also been investigated using data from the POPLAR study, showing that patients with NSCLC treated with atezolizumab had slower tumour growth than those treated with chemotherapy, and that these metrics were predictive of overall survival (12). This study hypothesised that as anti-PD-L1/PD-1 therapies have been shown in NSCLC to improve OS relative to chemotherapy, a TGI model could provide a complementary assessment of response to evaluate the efficacy of immunotherapies.

To estimate TGI profiles for the atezolizumab and chemotherapy arms using IMpower133 data, the same methods as detailed in Claret et al. 2009 (8) were followed by describing tumour size (the sum of the longest diameters of target lesions) as a function of time (Figure 3). [redacted]

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Figure 3: Tumour growth inhibition profile from IMpower133 between 0 and 100 weeks (January 2019 data cut) (Data on file)

CE: carboplatin and etoposide

Considering the predictive quality of TGI metrics with overall survival, [redacted] of atezolizumab plus carboplatin and etoposide.

Incorporating long-term survivorship on top of survival extrapolations
In Roche's "Request for additional analyses" submission, we included a section on mixture cure models. The inclusion of the cure fraction was backed up by literature, Flatiron registry data, and clinical expert opinion. [redacted].

Only a small number of patients would need to experience long-term survivorship for atezolizumab to be cost-effective. Table 4 shows the cost-effectiveness results for survival models where no crossing of mortality of probability between arms is present, with and without an assumption of long-term survivorship. All these survival models estimate long-term survival for the comparator between 0.5% and 5% and support an assumption of decreasing long-term hazards in both arms. All models are in the range of cost-effectiveness for end-of-life medicines. More importantly, by assuming that 50% of patients remaining alive at 60 months have double the risk of mortality to the general population[1], all the ICERs fall below the £50k threshold. Appendix 2 presents this information as a visual representation.

[1] During 1:1 consultations (November 2019), clinical experts stated that long-term survivors of ES-SCLC are expected to have a higher risk of mortality than the general population.

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Table 4: Cost-effectiveness results using survival extrapolations that do not demonstrate crossing of probabilities of mortality, with and without an assumption of long-term survivorship

Extrapolations	No long-term survivorship assumed ICER (£/QALY)	Long-term survivorship assumed*		
		Overall % of A+C+E patients with long-term survivorship	Overall % of C+E patients with long-term survivorship	ICER (£/QALY)
Using the same survival extrapolation for both A+C+E and C+E				
Log-logistic	47,449	2.5%	1.3%	42,881
KM+ logistic, switch at 5 months	43,806	2.6%	1.3%	39,637
KM+ logistic, switch at 10 months	50,635	2.3%	1.2%	45,703
KM+ logistic, switch at 15 months	38,904	2.5%	1.1%	35,215
KM+ logistic, switch at 20 months	41,894	2.3%	1.1%	38,065
Spline one knot odds	50,459	1.5%	0.6%	46,586
Using different extrapolations for A+C+E and log-logistic for C+E				
KM+ logistic, switch at 5 months	39,710	2.6%	1.3%	36,103
KM+ logistic, switch at 10 months	52,616	2.3%	1.3%	47,533
KM+ logistic, switch at 15 months	43,675	2.5%	1.3%	39,453
KM+ logistic, switch at 20 months	49,615	2.3%	1.3%	45,005
Spline two knot odds	50,287	2.4%	1.3%	45,330

Note: * At 60 months, 50% of patients remaining alive are assumed to have mortality double that of the general population (standard mortality rate = 2).
A+C+E: atezolizumab + carboplatin + etoposide; C+E: carboplatin + etoposide; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year

Atezolizumab plus carboplatin and etoposide for first-line ES-SCLC is plausibly cost-effective

Roche acknowledges that there are a few alternative viable options to extrapolate overall survival presented in the "Request for additional analyses" submission that are a good fit both visually and statistically, and clinically plausible. Table 4 displays the cost-effectiveness results of survival models that do not result in any crossing or meeting of the probability of mortality across the two model arms. These results show that the majority of these options provide ICERs below £50,000, and if an assumption is made that atezolizumab patients receive a small incremental long-term survivorship benefit (~2% for atezolizumab patients and ~1% for chemotherapy), [redacted], all of these options would be below the £50,000 threshold.

2

Generalisibility to patients with ECOG performance status 2 or higher

The ACD states: "Data from IMpower133 are not generalisable to people with an ECOG performance status score of 2 or higher which is likely in clinical practice in England."

Whilst we agree there are patients in the NHS in England who are ECOG performance status 2 or higher at diagnosis, clinical experts during an advisory board in November 2018 estimated a range of 20–55% ES-SCLC patients are diagnosed as ECOG performance status 0–1. Importantly, during the first appraisal committee meeting, it was stated that if atezolizumab plus carboplatin and etoposide was available on the NHS, the Blueteq system will limit access to atezolizumab using ECOG performance status 0–1 criteria, therefore IMpower133 data are generalisable for patients in

England.

An Early Access to Medicines Scheme for first line ES-SCLC, with ECOG performance status 0-1 opened on 10th June 2019. Since the EAMS began, 79 patients have already been treated in the scheme across 38 sites in England and Wales, highlighting that there are patients who are eligible for treatment in England.

Roche sent out a survey to 51 EAMS investigators in England and Wales at 35 different hospitals across England and Wales, who have treated patients with atezolizumab in first line ES-SCLC to determine the proportion of patients with ES-SCLC who are diagnosed as ECOG performance status 0–1. The survey asked the following question (email communication provided in Appendix 1):

Question: The IMpower133 trial recruited patients with ES-SCLC that were ECOG performance status 0–1. What percentage of your 1L ES-SCLC patients are ECOG performance status 0-1?

a. 0–10%
b. 11–20%
c. 21–30%
d. 31–40%
e. 41–50%
f. >50%

From the 51 EAMS investigators who were sent the survey, 7 responded. The collated responses were as follows:

Estimated proportion of patients with ECOG performance status 0–1	Number of responses
0–10%	0
11–20%	2
21–30%	2
31–40%	0
41–50%	1
>50%	2

The advisory board, the EAMS, and the survey to EAMS investigators confirm that a meaningful proportion of patients in England are diagnosed with 1L ES-SCLC with ECOG performance status of 0 or 1. Therefore, atezolizumab plus carboplatin and etoposide is an important addition to the treatment of 1L ES-SCLC patients in England.

3

Duration of treatment benefit

The ACD states: "…based on a Kaplan-Maier data plot of overall survival from IMpower133, there may be no treatment benefit from approximately 30 months."

However, there is no evidence that treatment benefit may stop from 30 months. As detailed earlier in this response, the data at 30 months are subject to an extremely high level of censoring and considered to be unreliable. Specifically, the last observed events are at 26.2 and 24.8 months for the atezolizumab and comparator arms, respectively, at which point there are only 6 patients left at risk on both arms. The censored patients are either lost to follow up or have not experienced progression or death at the time of analysis (i.e., not necessarily dead).

Furthermore, the tumour growth inhibition (TGI) metrics presented (Figure 3) shows clearly there is a [redacted]

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	As presented in the "Request for additional analyses" submission, the scenario analysis for different treatment effect cut off times showed that this had little impact on the ICER. Overall, there is no evidence to support or refute using 60 months as the treatment effect cut-off. We have previously provided evidence of other immunotherapies for lung cancer where NICE had accepted that long-term treatment effect was biologically plausible (TA428, TA531) (13, 14). Prolonged treatment benefit is expected from immunotherapies, as supported by clinical experts; therefore Roche's base case remains at 60 months, as has been used in previous lung cancer appraisals (TA483) (15).
4	**Conclusion** In summary, we discuss in the preceding sections the reasons we maintain that the Kaplan-Meier plus a switch to log-logistic extrapolation at 20 months is the most appropriate model to appraise the cost-effectiveness of atezolizumab (ICER of £41,894). In addition, we explain why it is not possible for there to be a crossing of probability of mortality between the treatment arms in the long term and that there is no strong support for different extrapolations on each arm. We also present tumour inhibition (TGI) metrics [redacted]. By assuming long-term survivorship rates, the ICERs presented in the scenario analysis (Table 4) all fall below the £50k threshold. Atezolizumab with carboplatin plus etoposide is considered to meet NICE's end-of-life criteria, highlighting that it is a valuable treatment for those with first-line ES-SCLC who have a poor prognosis and do not have the option of life-extending innovative treatments. As stated by a patient expert at the first appraisal committee meeting, "any treatment that could extend life, even only for a short period, would allow more time for advanced care planning" (16), so although the benefit of atezolizumab with carboplatin plus etoposide may be considered modest, the impact will be great for patients, carers, and their families.

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

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Appendix 1: Email and questions to UK clinical experts

Email

Dear Dr XX,

As an oncologist who submitted a patient request for the Early Access to Medicines Scheme (EAMS) for atezolizumab in ES-SCLC, you may be aware that NICE have issued an appraisal consultation document (ACD) (draft decision) from NICE in which they do not recommend this treatment.

"Atezolizumab with carboplatin and etoposide is not recommended, within its marketing authorisation, for untreated extensive-stage small-cell lung cancer in adults."

In order for Roche to respond to this ACD we would be extremely grateful if you could answer a brief questionnaire in the form provided (link below). This information will help us to respond to specific issues that have arisen in the ACD. Please can you provide your response by Monday 27th January 9am.

[*Link to Google form*]

For information, the next NICE committee meeting will take place on 18th February 2020, we expect a final decision (FAD) at the end of February.

Before the FAD, and in addition to our response, NICE will first consider all comments, made before Tuesday 28th January 5pm, by any member of the public or health care professional through the usual process (https://www.nice.org.uk/guidance/indevelopment/gid-ta10400/consultation/html-content-2).

[redacted]

If you have any questions please do not hesitate to get in touch,

Many thanks,

xxxx

Questions and results

1. The IMpower133 trial recruited patients with ES-SCLC that were ECOG performance status 0-1. What percentage of your 1L ES-SCLC patients are ECOG performance status 0-1?
   a. 0–10%
   b. 11–20%
   c. 21–30%
   d. 31–40%
   e. 41–50%
   f. >50%

Answer:

Response no.	Estimation of proportion of patients with ECOG performance status
1	21 - 30%
2	41 - 50%

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3	11 - 20%
4	11 - 20%
5	>50%
6	>50%
7	21 - 30%

2. Please study the table provided which presents the results of different economic models used to estimate long-term survival of 1L ES-SCLC patients that are ECOG PS 0-1. The estimated overall survival rates for these patients are presented from 12 to 60 months. For each model, please respond as to whether the overall survival rates are clinically plausible or clinically implausible[2] for this group of patients.

Survival extrapolations (**Comparator arm**)	**Models**	**Months**				
		12	**24**	**36**	**48**	**60**
	Log-logistic	43.8%	15.3%	7.1%	4.0%	2.5%
	KM + log-log (5 mths)	45.8%	16.0%	7.4%	4.2%	2.7%
	KM + log log (10 months)	42.0%%	14.6%%	6.8%	3.8%	2.4%
	KM + log log (15 months)	39.0%	13.8%	6.4%	3.6%	2.3%
	KM + log log (20 months)	39.0%	13.2%	6.1%	3.5%	2.2%
	Spline one knot odds	44.1%	12.1%	4.6%	2.3%	1.3%
	Spline two knots odds	40.6%	16.6%	9.8%	6.5%	4.8%
	Spline two knots hazard	39.2%	16.8%	10.6%	7.1%	5.0%
	Spline two knots normal	41.4%	16.8%	8.9%	5.3%	3.3%
	Spline three knots odds	39.5%	16.6%	11.3%	8.5%	6.7%

Answer:

	Clinically plausible	**Clinically implausble**	**Uncertain**
Log-logistic	100%	-	-
KM + log-log (5 months)	85.7%	-	14.3%
KM + log-log (10 months)	85.7%	-	14.3%
KM + log-log (15 months)	85.7%	-	14.3%
KM + log-log (20 months)	100%	-	-
Spline one knot odds	57.1%	-	42.9%

[2] An option of 'Uncertain' was included in the drop down list that the clinical experts could choose from

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

Consultation on the appraisal consultation document – deadline for comments: **5pm** on **Tuesday 28 January 2020. Email:** TACommC@nice.org.uk **/** NICE DOCS

Spline two knot odds	57.1%	-	42.9%
Spline two knots hazards	42.9%	-	57.1%
Spline two knots normal	57.1%	-	42.9%
Spline three knots odds	57.1%	-	42.9%

3. Looking at the same table of overall survival rates, please rank the models from 1 (1 being the most clinically plausible) to 10 (being the most clinically implausible).

Answer:

	Rank									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Log-logistic	28.6%	-	-	14.3%	-	14.3%	-	-	-	-
KM + log-log (5 months)	-	28.6%	-	14.3%	14.3%	-	14.3%	-	14.3%	-
KM + log-log (10 months)	14.3%	14.3%	42.9%	14.3%	-	-	-	-	-	14.3%
KM + log-log (15 months)	14.3%	28.6%	14.3%	28.6%	14.3%	-	-	-	42.9%	-
KM + log-log (20 months)	28.6%	28.6%	14.3%	-	28.6%	-	-	-	-	-
Spline one knot odds	14.3%	-	-	-	14.3%	28.6%	-	14.3%	-	-
Spline two knot odds	-	-	-	-	14.3%	28.6%	71.4%	-	14.3%	-
Spline two knots hazards	-	-	14.3%	-	-	-	-	28.6%	-	-
Spline two knots normal	-	-	-	14.3%	14.3%	28.6%	14.3%	28.6%	14.3%	14.3%
Spline three knots odds	-	-	14.3%	14.3%	-	-	-	14.3%	14.3%	71.4%

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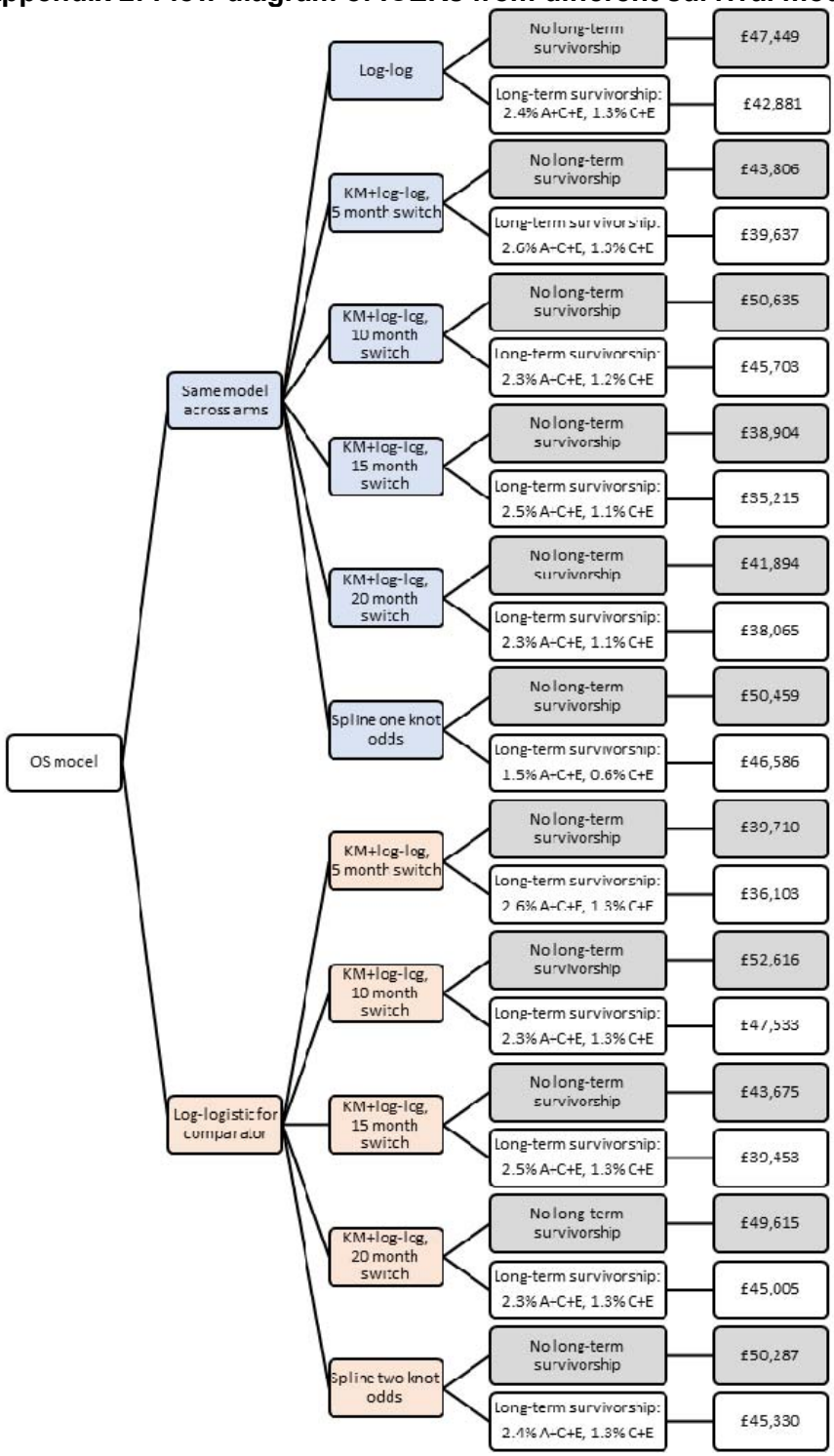
Appendix 2: Flow diagram of ICERs from different survival models



Note: Only survival models that do not demonstrate crossing of probabilities of mortality are included, with and without assumption of long-term survivorship

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Single technology appraisal

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

20th February 2020

Dear Frances,

As you will be aware, Roche has been in discussions with NHSE regarding a commercial arrangement for atezolizumab. I can now confirm we have made our best and final offer to enable access for small-cell lung cancer (SCLC [ID1504]) [redacted]. We propose a [redacted] to the list price of atezolizumab, comprising [redacted]

This offer is on the basis [redacted]

Whilst we have not received formal sign off from NHSE on this offer, our understanding is that it is currently going through their approval and governance process.

As such, we now feel it is important to share with NICE the details of our offer, and provide updated cost effectiveness results for the committee's consideration. Given the unmet need, and considerable delays this appraisal has already faced, we feel it is important to bring this to a conclusion – whether the decision be positive or negative.

As you will see from the results below, the [redacted] now means all scenarios are cost effective under the End of Life threshold. Given this, with specific reference to the provisions of Section 3.5.42 (NICE "Guide to the processes of technology

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appraisal"), we would ask whether this could proceed without a third committee meeting and the FAD be signed off by the committee electronically. We believe this would ensure patient access in a timely manner, whilst also conserving key NICE and committee resources. Nevertheless, if the Chair feels this is not appropriate, we request to be scheduled for the 18th March 2020 committee meeting.

We hope the updated analyses will support the committee in making a positive recommendation, allowing SCLC patients the opportunity to access the first new therapy in over 20 years. Please let us know if NICE requires any more information. We look forward to hearing from you shortly.

Kind regards,

Jessica Purchase

Group Health Economic Manager
Roche Products Ltd

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Updated company base case pairwise ICERs, including the [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER incremental (£/QALY)
				Costs (£)	LYG	QALYs	
Atezolizumab plus carboplatin-etoposide	[redacted]	[redacted]	[redacted]				
Carboplatin-etoposide	[redacted]	1.16	0.75	[redacted]	[redacted]	[redacted]	£26,998

Updated summary of different scenario analyses, including the [redacted][a]

Extrapolations	No long-term survivorship assumed ICER (£/QALY)	Long-term survivorship assumed[b]		
		Overall % of A+C+E patients with long-term survivorship	Overall % of C+E patients with long-term survivorship	ICER (£/QALY)
Using the same survival extrapolation for both A+C+E and C+E				
Log-logistic	30,613	2.4%	1.3%	27,656
KM+ logistic, switch at 5 months	28,233	2.6%	1.3%	25,535
KM+ logistic, switch at 10 months	32,645	2.3%	1.2%	29,455
KM+ logistic, switch at 15 months	25,066	2.5%	1.1%	22,680
KM+ logistic, switch at 20 months (base case)	26,998	2.3%	1.1%	24,521
Spline one knot odds	32,564	1.5%	0.6%	30,056
Spline two knots odds[c]	32,607	3.3%	2.4%	29,965
Spline two knots normal[c]	38,172	1.6%	1.7%	35,749
Spline three knots odds[c]	19,143	5.5%	3.4%	17,373

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Extrapolations	No long-term survivorship assumed ICER (£/QALY)	Long-term survivorship assumed[b]		
		Overall % of A+C+E patients with long-term survivorship	Overall % of C+E patients with long-term survivorship	ICER (£/QALY)
ERG preferred scenarios - Using different extrapolations for A+C+E and log-logistic for C+E				
KM+ logistic, switch at 5 months	25,567	2.6%	1.3%	23,235
KM+ logistic, switch at 10 months	33,898	2.3%	1.3%	30,613
KM+ logistic, switch at 15 months	28,127	2.5%	1.3%	25,397
KM+ logistic, switch at 20 months	31,961	2.3%	1.3%	28,981
Spline one knot odds	46,674	1.5%	1.3%	45,031
Spline two knot odds	32,433	2.4%	1.3%	29,225
Spline two knot normal	41,554	1.6%	1.3%	40,127
Spline three knot odds	48,770	1.3%	1.3%	48,368

[a] The spline one knot normal was excluded as the carboplatin arm had a 5-year survival of <0.5% which is clinically implausible.
[b] At 60 months, 50% of patients remaining alive are assumed to have mortality double that of the general population (standard mortality rate = 2).
[c] Clinical experts did not anticipate that the rate of mortality for atezolizumab arm would exceed that of the comparator arm in the long term. Therefore, for these analyses, it was assumed that the arms do not cross, and the probability of mortality is equal from the point at which the arms meet

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

Consultation on the appraisal consultation document – deadline for comments: **5pm** on **Tuesday 28 January 2020. Email:** TACommC@nice.org.uk **/** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**BTOG/ACP/RCR/NCRI)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments**

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Consultation on the appraisal consultation document – deadline for comments: **5pm** on **Tuesday 28 January 2020. Email:** TACommC@nice.org.uk **/** NICE DOCS

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Small cell lung cancer patients will not have access to this combination despite showing an overall survival advantage (statistically significant) above that of chemotherapy alone
2	Many patients will not have access despite being fit enough to receive the chemo/IO combination ie. PS0-1
3	No treatment advances in this disease for the last 30 years
4	No prospect of this being available on the Cancer Drugs Fund either
5	CASPIAN study with Durvalumab in SCLC has almost identical outcome in OS. Confirming that immunotherapy is likely to have a biological effect on SCLC
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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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Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID1504]

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NICE Appraisal Consultation Document (ACD): consultees and commentators: Lung cancer (small-cell, extensive stage, untreated) - atezolizumab (with carboplatin and etoposide) [ID1504]

Comments on the ACD from Professor Samreen Ahmed

Clinical expert representing BTOG/RCP/ACP/NCRN:

- All relevant data has been considered: IMPOWER 133 has been thoroughly scrutinised. Data recently presented for CASPIAN (using durvalumab with chemotherapy) has almost identical HR=0.73 in extensive SCLC. This was brought to the Committee's attention by the clinical experts. This suggests that immunotherapy has a biological effect in SCLC as 2 trials of IO have produced consistent and confirmatory results
- The evidence and models used are representative and as closely interpreted as possible without bias. The assumptions made are clinically reliable
- I am disappointed that this treatment will NOT be available for patients in the UK as this is the only advance made in this disease area for over 30 years. This is presumably made solely on cost effectiveness grounds. The performance status of patient in the trial was 0/1 so would exclude the majority of patient in the UK for this treatment anyway. It is unfortunate that this treatment breakthrough will not be available for this small proportion of fit patients

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
The comment about performance status and the IMpower133 not being applicable to clinical practice in England is misleading.
ES-SCLC is an aggressive cancer and a lot of patient will present with a compromised performance status. However this is the case globally and not just for England. It is the biology of the disease. As per the rest of the world there is still a significant population of good performance status ES-SCLC patients who would stand to benefit from the IMpower133 regime.

Are the recommendations sound and a suitable basis for guidance to the NHS?
In my opinion the decision to not recommend the treatment is incorrect.
ES-SCLC is a disease with high unmet need and with no therapeutic gains for decades.
The IMpower133 regime and trial readout is the first positive step forward for this group of patients with an improvement in PFS and OS
The end of life modelling meets NICE's criteria.
On this basis I would strongly support a positive recommendation from NICE

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
n/a

Name	[redacted]
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
As a mother whose son died 3 years ago from small cell lung cancer aged 29. I would like to say because of the length of time it actually took for my son to be diagnosed , this hampered his treatment. He was given chemotherapy, 3 different concoctions. Which unfortunately didn't work at all even though his oncologist was adamant he could fix it this time ? If having this new drug could have prolonged his life for a few short months would have made a lot of difference to us as a family and my son. We could have made more memories and maybe given him a better quality of life. From diagnosis to death was only 4 month's. Too quick and heartbreaking, the disease is too aggressive and caused him so much discomfort and pain. No parent should have to witness this. If you can help give further patients a few more months if required and without further pain and discomfort why should that be denied????

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
As I said earlier who gives the right to deny someone with the will to live life, just because of cost?????? Cancer is ruining and killing people's loved ones every second of every day. A y more time that can be given to them is precious and no amount of money matters.

Are the recommendations sound and a suitable basis for guidance to the NHS?
If all the trials are proven conclusive and sound then it's a no brainer. Yes allow the NBA to use it. Too many of us are having to find our own life saving treatments.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
I don't believe there is? It should be available to all.

Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer (addendum before ACM 3)

Produced by Kleijnen Systematic Reviews Ltd

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Date completed 21/04/2020 (this addendum)

Source of funding: This report was commissioned by the NIHR HTA Programme as project number STA 12/85/73.

Declared competing interests of the authors

None.

Acknowledgements

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.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This addendum is the ERG response to the company revised PAS before ACM 3, including a [redacted].[1] The ERG can confirm that all of the results presented in this document are reproduceable, including the new company base case ICER of £26,998, based on the following assumptions:

- OS extrapolation using KM + log-logistic at 20 months for both the intervention and the comparator,
- The ERG's suggested fixes (corrected PFS and AE disutilities from the literature) in their updated cost-effectiveness analysis.

For comparison, using the previous PAS ([redacted]), these assumptions produced a company base case ICER of £41,894, which was presented in the company's additional analyses report post-ACM 1.[2] In response to these additional analyses, the ERG concluded that the company base case analysis assumption of KM + log-logistic at 20 months for both the intervention and the comparator was plausible.[3] However, the ERG still preferred the log-logistic for the comparator and any one of a number of extrapolations, including spline-based models, for the intervention, with which the committee at ACM 2 largely agreed.[4] The ERG can confirm that all of these scenarios have been reproduced with the company revised PAS in the table, "Updated summary of different scenario analyses, including the [redacted] in the column "No long-term survivorship assumed". In the same table, the company has also presented results where "Long-term survivorship" is assumed with an explanation that at 60 months, 50% of patients remaining alive are assumed to have mortality double that of the general population (standard mortality rate = 2). The most obvious effect of this is to reduce 5-year survival by up to about half depending on the extrapolation model. For example, with the log-logistic for the comparator, the 5-year survival reduces from 2.5% to 1.3%. It is unclear to the ERG what the motivation for this analysis is, although, importantly, it has little effect on the ICER. Without the "long-term survivorship" and using the ERG preferred log-logistic model for the comparator, the ICER varies from £25,567 to £48,770 according to any of the models considered plausible for the intervention. For comparison, using the previous PAS, the highest ICER was £75,544 instead of £48,770 for the 3 knots odds model.

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