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:

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

1. **Company submission** from **Roche Products**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Roy Castle Lung Cancer Foundation
   b. The Royal College of Pathologists
   c. The Royal College of Physicians

4. **Expert personal perspectives** from:
   a. Dr Alastair Greystoke, consultant medical oncologist – clinical expert, nominated by Roche Products
   b. Professor Samreen Ahmed, consultant medical oncologist – clinical expert, nominated by The Royal College of Physicians
   c. Carol Davies, lung cancer nurse specialist – patient expert, nominated by National Lung Cancer Forum of Nurses

5. **Evidence Review Group report** prepared by **Kleijnen Systematic Reviews Ltd**

6. **Company and Evidence Review Group factual accuracy check responses**

7. **Evidence Review Group erratum**

8. **Technical engagement response** from **Roche Products**

9. **Technical engagement responses from experts:**
   a. Professor Samreen Ahmed, consultant medical oncologist – clinical expert, nominated by The Royal College of Physicians

   Technical engagement response from consultees and commentators:
   None

10. **Evidence Review Group critique of company response to technical**

engagement prepared by Kleijnen Systematic Reviews Ltd

11. Final Technical Report

12. Additional analyses submitted by the company following Appraisal Committee Meeting 1

13. Evidence Review Group critique of company additional analyses

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

First-line atezolizumab plus carboplatin and etoposide in ES-SCLC

ID1504

Document B

Company evidence submission

February 2019

File name	Version	Contains confidential information	Date
ID1504_first-line atezolizumab plus carboplatin and etoposide in ES-SCLC_Doc B	**V1**	**Yes**	**15 February 2019**

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Abbreviations

AE	adverse event
AIC	Akaike information criteria
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BIC	Bayesian information criteria
BNF	British National Formulary
BSA	body surface area
BTOG	British Thoracic Oncology Group
CCOD	clinical cut-off date
CE	Conformité Européene
CG	clinical guidance
CI	confidence interval
CNS	central nervous system
CP	carboplatin
CR	complete response
CT	computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
DOR	duration of response
DSU	decision support unit
EAMS	early access to medicines scheme
ECG	electrocardiography
ECOG	Eastern Cooperative Oncology Group
EGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
eMIT	electronic market information tool
EOL	end-of-life
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic patient reported outcomes
EQ-5D-5L	Euro quality of Life 5 dimensions 5-level
ERG	evidence review group
ES-SCLC	extensive stage small cell lung cancer
ESMO	European Society for Medical Oncology
ET	etoposide
FDA	Food and Drug administration
GP	general practitioner
HBV	hepatitis B virus

HCHS	hospital & community health services
HCV	hepatitis B virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRG	Healthcare Resource Group
HSUV	health state utility values
HTA	health technology assessment
IASLC	International Association for the Study of Lung Cancer
ICER	incremental cost-effectiveness ratio
INR	International Normalised Ratio
ITC	indirect treatment comparison
ITT	intent-to-treat
IV	intravenous
KM	Kaplan-Meier
LS	limited stage
LYG	life years gained
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLCA	National Lung Cancer Audit
NMA	network meta-analysis
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PartSA	Partitioned survival analysis
PAS	patient access scheme
PCI	prophylactic cranial irradiation
PCR	polymerase chain reaction
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PIM	promising innovative medicine
PR	partial response
PS	performance score
PSA	probabilistic sensitivity analysis
PSS	personal social services
PSSRU	Personal Social Services Research Unit
PUVA	psoralen and ultraviolet A radiation

QALY	quality adjusted life years
QLQ	quality of life questionnaire
RDI	relative dose intensity
RECIST	response evaluation criteria in solid tumours
RNA	ribonucleic acid
RR	response rate
RSI	request for supplementary information
SCLC	small cell lung cancer
SD	standard deviation
SE	standard error
SLR	systematic literature review
TA	technology appraisal
TAE	therapy area expert
TC	tumour cell
TMB	tumour mutational burden
TNF	tumour necrosis factor
TNM	tumour node metastasis
TTD	time to deterioration
TTO	time trade-off
TTOT	time-to-off-treatment
UC	urothelial carcinoma
UICC	Union for International Cancer Control
UK	United Kingdom
ULN	upper limit of normal
US	United States
VALG	Veterans Administration Lung Study Group
WCLC	World Conference on Lung Cancer
WHO	World Health Organisation

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

B.1.1 Decision problem

This submission covers the technology's anticipated full marketing authorisation for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). The indication wording proposed by Roche is "Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)."

According to UK-practising clinical experts, NHS practice is to treat [redacted] of first-line ES-SCLC patients, who are eligible to receive chemotherapy, with 4–6 cycles of carboplatin-etoposide (engagement with UK-practising clinical experts is detailed in Appendix K), therefore this is the only comparator considered to be appropriate and relevant to the decision problem. [redacted] of first-line, ES-SCLC patients are expected to receive 4–6 cycles of cisplatin-etoposide chemotherapy (Appendix K). We have also been advised by UK-practising clinical experts treating first-line ES-SCLC patients within England that [redacted] when the disease is considered to be borderline limited-stage (LS) or ES-SCLC, or when radiation therapy may follow (Appendix K). Therefore, clinical experts consider the control arm of the pivotal IMpower133 trial to adequately reflect NHS practice and the appraisal decision problem. As such, although the final NICE scope states the comparators are 'platinum-based combination chemotherapy regimens', a comparison to cisplatin-etoposide is only presented for transparency and as a secondary comparator (1).

Subgroup data are presented in Appendix E for the populations that were pre-specified in the pivotal IMpower133 trial, specifically: demographics (e.g. age, sex, and race/ethnicity, etc.) and baseline prognostic characteristics (e.g., ECOG [Eastern Cooperative Oncology Group] performance status [PS], smoking status, presence of brain metastases, etc.) (2). However, it is important to note that these subgroups were not statistically powered to detect a difference in clinical efficacy. In addition, exploratory subgroup analyses were carried out to evaluate the tumour mutation burden (TMB) levels of patients within the IMpower133 trial and no predictive correlation between TMB and a patient's response to atezolizumab with carboplatin and etoposide was observed (3). UK-practising clinical experts who reviewed this

IMpower133 subgroup data considered it appropriate to only consider the full ITT population within this submission and the cost-effectiveness analyses).

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated ES-SCLC	As detailed in the final scope	As detailed in the final scope
Intervention	Atezolizumab with carboplatin and etoposide	As detailed in the final scope Induction phase comprises atezolizumab in combination with carboplatin and etoposide every three weeks for 4 cycles, followed by a maintenance phase of atezolizumab every three weeks until loss of clinical benefit or unmanageable toxicity.	As detailed in the final scope
Comparator(s)	Platinum-based combination chemotherapy regimens	Carboplatin-etoposide for up to 4 cycles – as included in the IMpower133 trial control arm. UK-practising clinical experts advise Roche this reflects NHS standard of care and is the only comparison of relevance in this submission (Appendix K). An NMA has been included and a secondary comparison to cisplatin-etoposide has been presented for transparency purposes. However, the anticipated marketing authorisation wording would restrict atezolizumab in this setting to combination with carboplatin-etoposide and [redacted]	As detailed in the final scope and aligned with the anticipated MA wording and UK-practising clinical expert opinion (Appendix K).

Outcomes	The outcome measures to be considered include: • OS • PFS • RR • AE • HRQoL	All the outcomes stated in the final scope are considered in this submission. In addition, we present data for treatment discontinuation.	While the outcomes listed in the final scope are considered to be of relevance, however treatment discontinuation is an important outcome for the accurate reporting of cost-effectiveness.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	Cost-effectiveness is herein expressed in terms of incremental cost per quality-adjusted life year. No additional tests for biological markers are considered to be appropriate. A time horizon of 20 years is included in the base case, which is sufficiently long to reflect any differences in costs or outcomes between these treatment approaches. The perspective taken is UK NHS and Personal Social Services. A PAS for atezolizumab has been approved by the Department of Health during 2018. The price for chemotherapy regimens are taken from the eMIT database to reflect costs to the NHS.	As detailed in the final scope
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on biological markers.	The efficacy of atezolizumab is presented for the ITT population from the IMpower133 trial, as well as for the pre-specified subgroups (3). However, it is important to note that these subgroups were not statistically powered to detect a difference in	As detailed in the final scope

		clinical efficacy. These are presented here for transparency. Furthermore, exploratory subgroup efficacy data are presented in relation to TMB expression, however this was also not prognostic of clinical outcome. A post-hoc exploratory analysis will be performed to investigate efficacy according to PD-L1 IHC status, with results due in Q2 2019. This analysis is being performed due to a final RSI from the EMA. Since this is a post-hoc exploratory analysis, only a limited number of samples are available for testing (approximately 35%). Therefore, the cost-effectiveness is only considered for the ITT population from IMpower133 trial in this submission.	
Special considerations including issues related to equity or equality	N/A	N/A	N/A

AE: adverse event; EMA: European Regulatory Agency; eMIT: electronic marketing information tool; ES-SCLC: extensive-stage small cell lung cancer; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; ITT: intent-to-treat; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; RR: response rate; RSI: request for supplementary information; TMB: tumour mutational burden

B.1.2 Description of the technology being appraised

The summary of product characteristics or information for use, and the European public assessment report, scientific discussion or drafts is included in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	UK approved name: Atezolizumab Brand name: Tecentriq®
Mechanism of action	**Atezolizumab** Atezolizumab is a humanised anti-PD-L1 monoclonal antibody that inhibits the binding of PD-L1 to its receptors, PD-1 and B7.1 (4) • PD-1 is an inhibitory receptor expressed on T cells following T-cell activation and binds to PD-L1 which inhibits T-cell proliferation, cytokine production, and cytolytic activity (5, 6) • B7.1 is a receptor expressed on antigen-presenting cells and activated T cells and by binding to PD-L1, can downregulate the immune response, including inhibition of T-cell activation and cytokine production (7, 8) Therefore, when atezolizumab binds to PD-L1, which is overexpressed on TCs, this can enhance the anti-tumour immune response (4, 9). **Carboplatin** Carboplatin is a cytotoxic chemotherapy agent which acts by forming DNA crosslinks to interrupt cellular DNA functioning, which leads to apoptosis (10, 11). **Etoposide** Etoposide targets topoisomerase II activities and inhibits DNA re-ligation, which leads to DNA breaks; this elicits a response that disrupts cell metabolism (12).
Marketing authorisation/CE mark status	An application for licence extension of atezolizumab for the following indication was submitted to the EMA on 11th October 2018. "Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with ES-SCLC." Marketing authorisation for this indication is currently expected in August 2019.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Atezolizumab as monotherapy is indicated for the treatment of patients with locally advanced or metastatic UC after prior platinum-containing chemotherapy or who are considered cisplatin ineligible and whose tumours have a PD-L1 expression of ≥5% (13)

	Atezolizumab as monotherapy is indicated for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR activating mutations or ALK positive tumour mutations should also have received targeted therapy before receiving atezolizumab (13)
Method of administration and dosage	Every three weeks for four cycles of: • **Carboplatin:** AUC 5 mg/ml/min, intravenously administered, Day 1 of each cycle) • **Etoposide:** 100 mg per square meter of body surface area, intravenously administered, Days 1–3 of each cycle • **Atezolizumab:** 1200 mg, intravenously administered, Day 1 of each cycle The induction phase is followed by maintenance therapy with atezolizumab 1200 mg, intravenously delivered every three weeks until loss of clinical benefit or unmanageable toxicity
Additional tests or investigations	None
List price and average cost of a course of treatment	Atezolizumab: £3807.69 per 20 ml vial (1,200 mg) ([redacted]). Carboplatin: £3.18 per 5 ml vial (50 mg); £28.24 per 60 ml vial (600 mg) (14). Etoposide: £2.30 per 5 ml vial (100 mg); £9.65 per 25 ml vial (500 mg) (14). The mean treatment cost of a course of treatment for an ES-SCLC patient is £32,798.39 for atezolizumab [redacted] £76.18 for carboplatin and £30.89 for etoposide. The carboplatin-etoposide costs are in line with current standard of care.
Patient access scheme (if applicable)	A simple PAS discount of [redacted] has already been implemented as a result of three previous NICE appraisals (TA492, TA520, TA525) for atezolizumab. We do not propose to change or otherwise amend this existing PAS as part of this appraisal.

ALK: anaplastic lymphoma kinase; AUC: area under the curve; CE: Conformité Européene; DNA: deoxyribonucleic acid; EGFR: epidermal growth factor receptor; EMA: European Medicines Agency; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; PAS; Patient access scheme; PD-1: programmed death-1; PD-L1: programmed death-ligand 1; TC: tumour cell; UC: urothelial cancer; UK: United Kingdom

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

B.1.3.1 Clinical overview

Lung cancer is the most common cause of cancer death in the UK; it is more than the two next common causes of cancer death combined (bowel and prostate). In England, there were 39,038 new cases of lung cancer (2017) and 28,566 deaths from lung cancer (2016) (15, 16). Lung cancer is divided into two types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (17). SCLC is an aggressive neuroendocrine tumour characterised by early metastasis (18) and accounts for 10% of all lung cancers (15). SCLC is a more aggressive cancer than NSCLC and can lead to early widespread metastases (19), SCLC occurs almost exclusively in smokers, with only ~2% patients with SCLC who are never smokers (20, 21).

There are two methods used to stage lung cancer: VALG (Veterans Administration Lung Study Group) and TNM (tumour, node, metastases). The IMpower133 trial used the VALG classification and is widely used by the National Institute of Health and Care Excellence (NICE) and oncologists for staging in the UK. However, the International Association for the Study of Lung Cancer (IASLC) and European Society for Medical Oncology (ESMO) guidelines now recommend staging and treatment decisions based on TNM staging (22-24). A description of TNM staging is provided in Table 3. Using the VALG classification, SCLC can be divided into limited stage and extensive stage (Table 4) (25). Two-thirds of SCLC diagnoses are ES-SCLC due to the tendency to metastasise early (26). LS-SCLC is disease that is confined to an area of tissue that can be treated with a single beam of external radiation (25, 27). ES-SCLC is defined as metastatic disease that extends beyond the boundaries of a single radiation port (23, 25). For the IMpower133 trial, ES-SCLC in patients was defined according to VALG classification, in alignment with NICE guidelines (3).

Table 3: Description of TNM staging

	T – Tumour	N – Node	M – Metastasis
Description	The size of the primary cancer and how far it has spread into nearby tissue – it can be 1, 2, 3 or 4 (1 being small and 4 being large)	Whether the cancer has spread to the lymph nodes – it can be between 0 (no lymph nodes containing cancer cells) and 3 (lots of lymph nodes containing cancer cells)	Whether the cancer has spread to another part of the body – it can either be 0 (the cancer hasn't spread) or 1 (the cancer has spread)

Table 4: Veterans Administration Lung Study Group (VALG) staging system

Stage	Characteristics
Limited small-cell lung cancer (LS-SCLC)	• Disease confined to one hemithorax, although local extensions may be present; • No extrathoracic metastases except for possible ipsilateral, supraclavicular nodes if they can be included in the same portal as the primary tumour; and • Primary tumour and regional nodes that can be adequately treated and totally encompassed in every portal
Extensive small-cell lung cancer (ES-SCLC)	• Inoperable patients who cannot be classified as having limited disease

Survival from SCLC in England is worse than in some European countries (28-30), with a 5-year survival rate of only 5% (24). With the 5-year survival rate being lower for ES-SCLC patients, than for all SCLC patients, at less than 1% with current standard of care carboplatin and etoposide (see Section B.3.3.4). Analysis of National Lung Cancer Audit (NLCA) data from 2004–2011 showed that median survival was 4 months for ES-SCLC (PS 0–4) patients (31). It is worth noting that in this audit, 69% of all SCLC patients (PS 0–4) received chemotherapy (in 2017, this figure was 68% (32)) and the proportion of ES-SCLC patients who did not receive chemotherapy likely had worse survival outcomes than those who received chemotherapy (31). In addition, there has been little improvement in the survival rates of SCLC patients in recent years as demonstrated by analysis of data from a US cancer centre, where the 5-year overall survival rates have increased from 8.3% (1986–1999) to 11.0% (2000–2008) (33).

Patients with SCLC typically present with symptoms of dyspnoea and persistent cough (34). Common comorbidities include: pulmonary disease, hypertension, cardiac disease, and diabetes (35). Poor prognostic factors for survival in patients with SCLC include extensive-stage disease, poor Eastern Cooperative Oncology Group performance status (ECOG PS), weight loss, and markers associated with excessive bulk of disease (e.g., elevated lactate dehydrogenase) (36, 37).

In the treatment of lung cancer, it is important to both increase survival and ease symptoms because disease symptoms have a negative impact on HRQoL (38-40). A systematic review on the humanistic burden of SCLC found that the impact on HRQoL was greatest in treatment-naïve ES-SCLC patients (41).

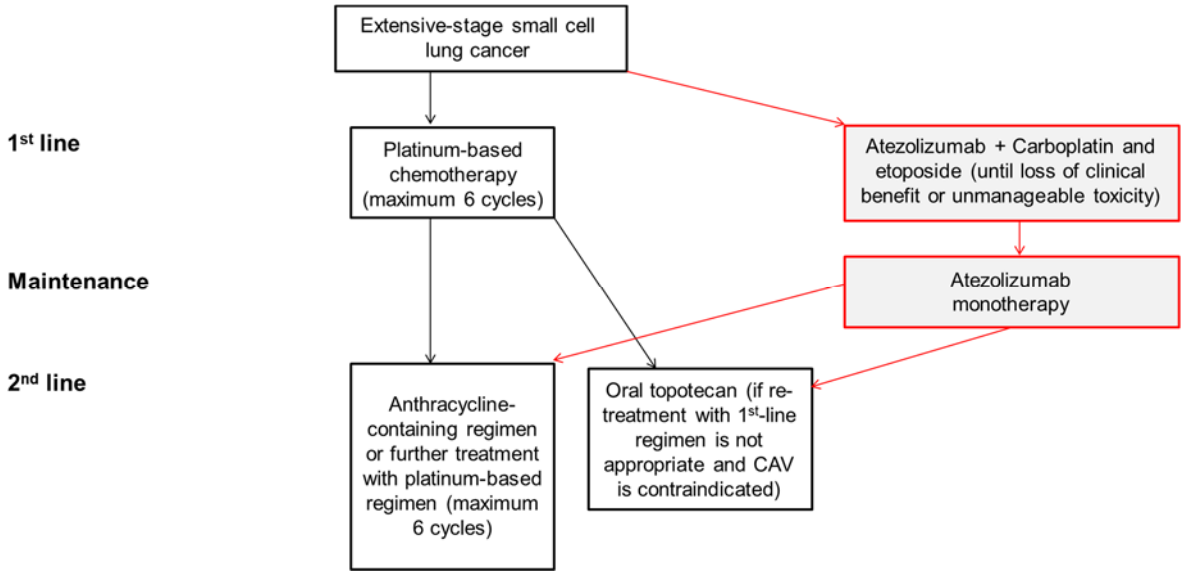
SCLC is highly sensitive to initial chemotherapy, with tumour response rates as high as 60%–80% (42, 43), however, systemic treatment for patients with SCLC has not changed significantly in the past 30 years (19, 23). Indeed, no new treatment has emerged for first-line SCLC since platinum-etoposide chemotherapy was introduced over 30 years ago (44) and recent trials have been unsuccessful in improving survival in patients with SCLC (45). Most recently, a press release from Bristol-Myers Squibb announced that the Phase III trial of nivolumab in combination with ipilimumab as maintenance therapy for patients with ES-SCLC (without disease progression after completion of 1L platinum-based chemotherapy) did not meet its primary endpoint of overall survival (OS) (46).

B.1.3.2 Clinical pathway of care

The National Institute for Health and Care Excellence (NICE) Clinical Guidance CG121 was last updated in 2011 and is currently being reviewed, with an expected publication date of 13th March 2019 (47). It defines ES-SCLC as broadly similar to lung cancer TNM staging: T1–4, N0–3, M1a/b – including cerebral metastases (48). For ES-SCLC, NICE recommend a maximum of 6 cycles of platinum-based chemotherapy if the patient is fit enough (48). UK-practising clinical experts attending a Roche-organised advisory board advised that [redacted] first-line ES-SCLC patients are treated with carboplatin and etoposide chemotherapy (Appendix K) for 4–6 cycles. A recent real-world study looking into the clinical benefit of four or more cycles of platinum and etoposide chemotherapy for stage 4 SCLC patients (who make up the majority of ES-SCLC patients) at a UK cancer centre found that there were no statistically significant differences in the clinical outcomes of patients receiving four cycles versus more than four cycles of chemotherapy (49). NICE also recommend thoracic radiotherapy and prophylactic cranial irradiation (PCI) for selected patients with ES-

SCLC after chemotherapy (48). Figure 1 shows a flow diagram of the NICE clinical pathway of care and where atezolizumab is expected to fit into this pathway.

Figure 1: NICE clinical pathway of care and the proposed indication for atezolizumab



Red boxes and arrows indicate the proposed indication for atezolizumab.

CAV: cyclophosphamide, Adriamycin, vincristine

The ESMO guidelines were published in 2013 and recommend platinum-based chemotherapy with etoposide for first-line treatment in patients with ES-SCLC (22).

The full ESMO recommendations for SCLC (TNM staging by UICC [Union for International Cancer Control] version 7: T1-4 N1-3 M1a, b multiple or confirmed) are listed below (22):

- Chemotherapy: 4-6 cycles carboplatin + etoposide OR 4-6 cycle cisplatin + etoposide (in young patients and patients with localised disease, etoposide–cisplatin is recommended)
- Alternate platinum doublets, if etoposide is contraindicated: irinotecan–cisplatin, gemcitabine–carboplatin (in poor prognostic patients only) and IV (intravenous) or oral topotecan–cisplatin – this population is not considered to be a comparable to the IMpower133 population as the patients in the trial were only included if they were etoposide-eligible (3)
- Patients with a reasonably good PS with any response to first-line treatment should be evaluated for PCI
- The routine use of thoracic irradiation in patients with metastatic SCLC is not recommended

B.1.4 Equality considerations

No equality issues have been identified.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1 Phase I trial

Study PCD4989g is a Phase Ia, multicentre, first-in-human, open-label, dose escalation study of atezolizumab monotherapy to patients with locally advanced or metastatic solid malignancies or haematologic malignancies (Table 5). The results for the cohort of patients with refractory or relapsed SCLC showed promising durability of response and had an acceptable side-effect and safety profile (50). This study will not be discussed further in this submission as it was a single arm trial for atezolizumab monotherapy.

B.2.2.2 Phase I/III trial

The IMpower133 trial is a multinational Phase I (safety) and III (efficacy), double-blind, randomised, placebo-controlled study (Table 5). The trial evaluated the efficacy and safety of adding atezolizumab or placebo to first-line treatment with carboplatin and etoposide in patients with ES-SCLC. In this submission, we report the planned interim analysis of OS and a final analysis of progression-free survival (data cutoff 24th April, 2018) (3).

Table 5: Clinical effectiveness evidence

Study	PCD4989g (50)	IMpower133 Phase I/III trial (3)
Study design	Phase Ia, multicentre, first-in-human, open label, dose escalation study	A Phase I/III, randomised, double-blind, placebo-controlled study
Population	SCLC cohort of patients with locally advanced or metastatic solid malignancies or haematologic malignancies	Patients with untreated extensive-stage small cell lung cancer
Intervention(s)	Atezolizumab monotherapy	Atezolizumab with carboplatin plus etoposide
Comparator(s)	N/A	Carboplatin plus etoposide

Study	PCD4989g (50)		IMpower133 Phase I/III trial (3)	
Indicate if trial supports application for marketing authorisation	Yes		Yes	✓
	No	✓	No	
Indicate if trial used in the economic model	Yes		Yes	✓
	No	✓	No	
Rationale for use/non-use in the model	Phase I study Atezolizumab monotherapy		Phase I/III study of atezolizumab with carboplatin plus etoposide versus carboplatin plus etoposide (standard of care is platinum chemotherapy)	
Reported outcomes specified in the decision problem	N/A		• OS • PFS • RR • AE • HRQoL	
All other reported outcomes	N/A		N/A	

N/A: not applicable; SCLC: Small cell lung cancer

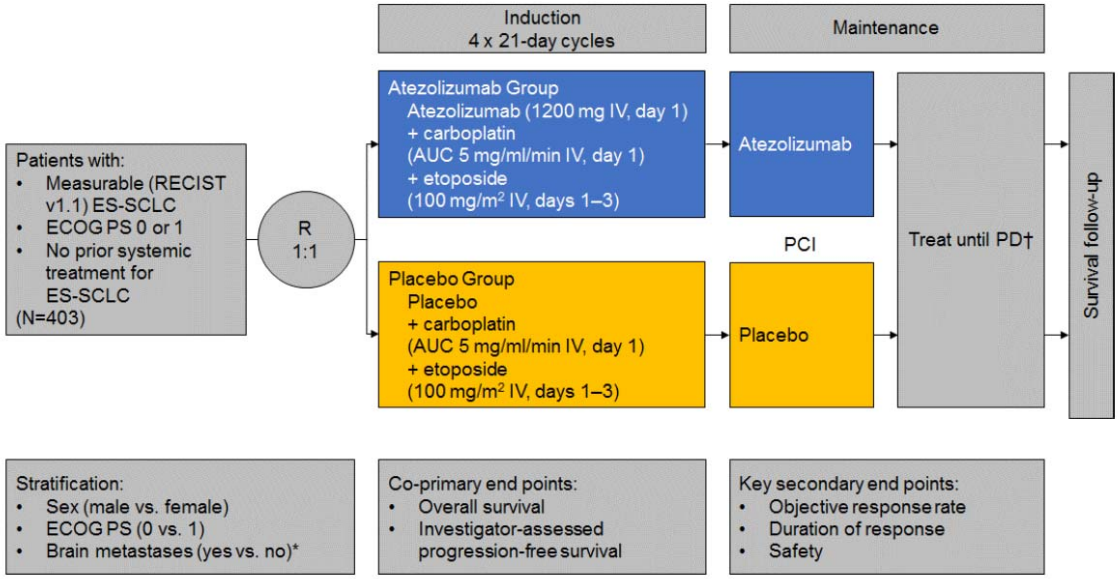
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Unless otherwise stated, the information in Section B2.3 is taken from the protocol (51).

B.2.3.1 Trial design

The IMpower133 trial study design is summarised in Figure 2 (3).

Figure 2: Study design of IMpower133 (3)



AUC: area under curve; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ES-SCLC: extensive-stage small cell lung cancer; PCI: prophylactic cranial irradiation; PD: disease progression; R: randomised; RECIST: response evaluation criteria in solid tumours

* Only patients with treated asymptomatic central nervous system metastases were eligible

† Maintenance continued until occurrence of unacceptable toxic effects or disease progression according to RECIST, however, patients who met prespecified criteria were allowed to be treated beyond disease progression per RECIST v1.1 criteria until loss of clinical benefit in a blinded fashion.

Patients may be considered for treatment beyond radiographic disease progression per response evaluation criteria in solid tumours (RECIST), at the discretion of the investigator and after appropriate discussion with the patient and obtaining informed consent, only if all of the following criteria are met:

- Evidence of clinical benefit as assessed by the investigator
- No decline in Eastern Cooperative Oncology Group performance status (ECOG PS) that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

- Patients must provide written consent to acknowledge deferring other treatment options in favour of continuing study treatment at the time of initial progression

Randomisation was performed with the use of a permuted-block randomisation method. PD-L1 testing was not performed during screening owing to the expected high rate of inadequate sample types (e.g., fine-needle aspirates, bronchoscopy findings), the low prevalence of PD-L1 expression on tumour cells, and the lack of an association between response and PD-L1 expression in the phase I trial of atezolizumab in ES-SCLC (3, 50). In addition, there is often an urgent need to begin treatment on this aggressive disease and this further limits the opportunity for prospective biomarker testing before initiating first-line therapy.

Phase I of the trial was carried out to establish the side-effect and adverse-event profile of the treatment regimens. A minimum of 12 patients were assigned to each treatment regimen and received at least two cycles of treatment (at full dose) (3). Unblinded safety data were reviewed by an independent data and safety monitoring committee for assessment of the side-effect profile; on the basis of the findings of the committee, the trial continued as a randomised phase III trial (3).

Table 6: Summary of IMpower133 trial

	IMpower133 trial (NCT02763579)
Trial design	Phase I/III double-blind, randomised, placebo-controlled trial (N=403)
Settings and locations where the data were collected	106 centres in 21 countries. Number of patients randomised per country (number of centres in parentheses): United States of America 86 (22), Poland 45 (6), Japan 42 (13), Russia 30 (6), Spain 25 (6), Austria 20 (4), Hungary 19 (4), Czech Republic 17 (3), South Korea 17 (4), Italy 15 (6), Serbia 15 (3), Australia 11 (3), Greece 11 (3), United Kingdom 10* (4), Germany 9 (5), Taiwan 9 (3), France 7 (4), Chile 6 (2). Brazil 4 (3), Mexico 4 (1), China 1 (1)
Trial drugs	Four 21-day cycles of: • Carboplatin (area under the curve of 5 mg per millilitre per minute, administered intravenously on day 1 of each cycle) • Etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle) • Atezolizumab (at a dose of 1200 mg, administered intravenously on day 1 of each cycle) or placebo The induction phase was followed by a maintenance phase during which patients received either atezolizumab (1200 mg every three weeks) or placebo (according to the previous random assignment) until

	the occurrence of unacceptable toxic effects or disease progression per RECIST v1.1. Continuation of the trial regimen after the occurrence of disease progression during either phase was allowed if evidence of clinical benefit existed
Permitted and disallowed concomitant medication	The following medications were prohibited while in the study, unless otherwise noted: • Denosumab • Any live, attenuated vaccine (e.g. FluMist®) within 4 weeks prior to randomisation, during treatment, and for 5 months following the last dose of atezolizumab/placebo • Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance) • The concomitant use of herbal therapies The following therapies were permitted while patients were in the study: • Oral contraceptives • Hormone-replacement therapy • Prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level) • Palliative radiotherapy (e.g., treatment of known bony metastases) provided it does not interfere with the assessment of tumour target lesions • Inactive influenza vaccinations • Megestrol administered as an appetite stimulant • Inhaled corticosteroids for chronic obstructive pulmonary disease • Mineralocorticoids (e.g., fludrocortisone) • Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency • Premedication with antihistamines could be administered for any atezolizumab/placebo infusions after Cycle 1
Pre-planned subgroups	To assess the consistency of the study results in subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline prognostic characteristics (e.g., ECOG performance status, smoking status, presence of brain metastases etc.)

* 4 patients in the atezolizumab arm and 6 patients in the placebo arm

ECOG: Eastern Cooperative Oncology Group, OS: overall survival; PD-L1: programmed death-ligand 1, PFS: progression-free survival

B.2.3.2 Efficacy outcome measures

The primary and secondary endpoints are shown in Table 7.

Table 7: Primary and secondary endpoints for the IMpower133 trial

Co-primary endpoints	Secondary endpoints
• OS (the time from randomisation to death from any cause) • Investigator-assessed PFS per RECIST v1.1 (time from randomisation to disease progression or death from any cause, whichever occurred first)	• ORR (either an unconfirmed CR or a PR, as determined by the investigator using RECIST v1.1) • DOR (an objective response as determined by the investigator using RECIST v1.1) • 6- and 12-month PFS rates • 12- and 24-month OS rates • TTD using EORTC QLQ-C30 and QLQ-LC13

CR: complete response; DOR: duration of response; EORTC: European Organization for the Research and Treatment of Cancer; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: quality of life questionnaire lung cancer 13; RECIST: Response Evaluation Criteria in Solid Tumours; TTD: time to deterioration

Exploratory analyses included the assessment of efficacy according to tumour mutational burden (using a blood-based assay). Tumour assessments were conducted at baseline and every 6 weeks for the first 48 weeks starting from day 1 of cycle 1, and every 9 weeks thereafter until the occurrence of disease progression according to RECIST. Patients who continued the trial regimen beyond radiographic disease progression continued to undergo tumour assessments every 6 weeks until the regimen was discontinued. Adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The investigators determined whether adverse events (AEs) were related to the trial regimen (3).

Table 8: Inclusion/exclusion criteria for IMpower133 (3)

Inclusion criteria	Exclusion criteria
• Signed Informed Consent Form • Male or female, 18 years of age or older • ECOG performance status of 0 or 1 • Histologically or cytologically confirmed ES-SCLC (per the VALG staging system) • No prior systemic treatment for ES-SCLC • Patients who have received prior chemoradiotherapy for LS-SCLC must have been treated with curative intent and experienced a treatment-free interval of at least 6 months since last chemotherapy, radiotherapy, or chemoradiotherapy cycle from diagnosis of ES-SCLC • Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria: – Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord) – No ongoing requirement for corticosteroids as therapy for CNS disease – No evidence of interim progression between the completion of CNS-directed therapy and randomisation – Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomisation, if all other criteria are met • Measurable disease, as defined by RECIST v1.1	• Active or untreated CNS metastases as determined by CT or MRI evaluation during screening and prior radiographic assessments • Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥1 week prior to randomisation • Leptomeningeal disease • Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently) – Patients with indwelling catheters (e.g., PleurX®) are allowed regardless of drainage frequency • Uncontrolled or symptomatic hypercalcemia – Patients who are receiving denosumab prior to randomisation must be willing and eligible to discontinue its use and replace it with a bisphosphonate while in the study • Malignancies other than SCLC within 5 years prior to randomisation, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS >90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous-cell skin cancer, localised prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent) • Women who are pregnant, lactating, or intending to become pregnant during the study • History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus

– Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of disease • Adequate haematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to randomisation: – ANC ≥1500 cells/μL without granulocyte colony-stimulating factor support – Lymphocyte count ≥500/μL – Platelet count ≥100,000/μL without transfusion – Haemoglobin ≥9.0 g/dL ◊ Patients may be transfused to meet this criterion. – INR or aPTT ≤1.5 × ULN ◊ This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose – AST, ALT, and alkaline phosphatase ≤2.5 × ULN, with the following exceptions: ◊ Patients with documented liver metastases: AST and/or ALT ≤5 × ULN ◊ Patients with documented liver or bone metastases: alkaline phosphatase ≤5 × ULN – Serum bilirubin ≤1.25 × ULN ◊ Patients with known Gilbert disease who have serum bilirubin level ≤3 × ULN may be enrolled. – Serum creatinine ≤1.5 × ULN	erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis – Patients with a history of autoimmune-related hypothyroidism on thyroid replacement hormone therapy are eligible – Patients with controlled Type I diabetes mellitus on an insulin regimen are eligible – Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are eligible for the study provided that they meet the following conditions: ◊ Rash must cover less than 10% of body surface area ◊ Disease is well controlled at baseline and only requires low potency topical steroids ◊ No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus PUVA, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency, or oral steroids) • History of idiopathic pulmonary fibrosis, organising pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan – History of radiation pneumonitis in the radiation field (fibrosis) is permitted • Positive test result for HIV – All patients must be tested for HIV; patients who test positive for HIV will be excluded

• Patients must submit a pre-treatment tumour tissue sample. Any available tumour tissue sample can be submitted. The tissue sample should be submitted before or within 4 weeks after randomisation; however, patients may be enrolled into the study before the pre-treatment tumour tissue sample is submitted • For women of childbearing potential: agreement to remain abstinent or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 months after the last dose of study treatment – A woman was considered to be of childbearing potential if she was postmenarcheal, had not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and had not undergone surgical sterilisation (removal of ovaries and/or uterus). – Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilisation, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices – The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal were not acceptable methods of contraception • For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as defined below: – With female partners of childbearing potential or pregnant female partners, men had to remain abstinent or use a condom during treatment with chemotherapy (i.e., carboplatin and etoposide) and for at least 6 months after the last dose of chemotherapy to avoid exposing the embryo	• Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test result at screening) or HCV – Patients with past HBV infection or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) were eligible. HBV DNA should be obtained in these patients prior to randomisation – Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA • Active tuberculosis • Severe infections at the time of randomisation, including but not limited to hospitalisation for complications of infection, bacteraemia, or severe pneumonia • Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to randomisation, unstable arrhythmias, or unstable angina – Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on a stable medical regimen that is optimised in the opinion of the treating physician, in consultation with a cardiologist if appropriate • Major surgical procedure other than for diagnosis within 28 days prior to randomisation or anticipation of need for a major surgical procedure during the course of the study • Prior allogeneic bone marrow transplantation or solid organ transplant • Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an

– The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal were not acceptable methods of contraception	investigational drug or that may affect the interpretation of the results or render the patient at high risk for treatment complications • Patients with illnesses or conditions that interfered with their capacity to understand, follow, and/or comply with study procedures • Treatment with any other investigational agent with therapeutic intent within 28 days prior to randomisation • Administration of a live, attenuated vaccine within 4 weeks before randomisation or anticipation that such a live attenuated vaccine will be required during the study – Patients could not receive live, attenuated influenza vaccines (e.g., FluMist®) within 4 weeks prior to randomisation, during treatment, and for 5 months following the last dose of atezolizumab/placebo • Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–PD-1, and anti–PD-L1 therapeutic antibodies • Treatment with systemic immunosuppressive medications (including, but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumour necrosis factor [anti-TNF] agents) within 1 week prior to randomisation – Patients who received acute systemic immunosuppressant medications (e.g., use of corticosteroids for nausea, vomiting, or management of or premedication for allergic reactions) may be enrolled in the study after discussion with and approval by the Medical Monitor. In those patients, the need and length of the washout period prior to randomisation were also established in conjunction with the Medical Monitor – The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for

	patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency were allowed • History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanised antibodies or fusion proteins • Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation • History of allergic reactions to carboplatin or etoposide

aPTT: activated Partial Thromboplastin Time; ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate aminotransferase; ; CNS: central nervous system; CT: Computed tomography; DNA: deoxyribonucleic acid; ECOG: European Cooperative Oncology Group; ES-SCLC: extensive-stage small cell lung cancer; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; INR: International Normalised Ratio; MRI: magnetic resonance imaging; OS: overall survival; PCR: polymerase chain reaction; PUVA: psoralen and ultraviolet A radiation; RNA: ribonucleic acid; VALG: Veterans Administration Lung Study Group; ULN: upper limit of normal

B.2.3.3 Baseline characteristics

A total of 403 patients were enrolled at 106 sites in 21 countries and were randomly assigned to the atezolizumab group (201 patients) or the placebo group (202 patients) (3). Baseline characteristics were well balanced between the groups (Table 9). Twenty-two patients in each group received PCI.

Table 9: Baseline characteristics of all enrolled patients (ITT population) (3)

Characteristic	Atezolizumab Group (n = 201)	Placebo Group (n = 202)
Median age (range) — yr	64 (28–90)	64 (26–87)
Age group — no. (%)		
<65 yr	111 (55.2)	106 (52.5)
≥65 yr	90 (44.8)	96 (47.5)
Male sex — no. (%)†	129 (64.2)	132 (65.3)
ECOG performance-status score — no. (%)†‡		
0	73 (36.3)	67 (33.2)
1	128 (63.7)	135 (66.8)
Smoking status — no. (%)		
Never smoked	9 (4.5)	3 (1.5)
Current smoker	74 (36.8)	75 (37.1)
Former smoker	118 (58.7)	124 (61.4)
Brain metastasis at enrolment — no. (%)†	17 (8.5)	18 (8.9)
Blood-based tumour mutational burden — no./total no. (%)§		
<10 mutations/Mb	71/173 (41.0)	68/178 (38.2)
≥10 mutations/Mb	102/173 (59.0)	110/178 (61.8)
<16 mutations/Mb	133/173 (76.9)	138/178 (77.5)
≥16 mutations/Mb	40/173 (23.1)	40/178 (22.5)
Median sum of longest diameter of target lesions at baseline (range)	113.0 (12.0–325.0)	105.5 (15.0–353.0)
Previous anticancer treatments — no. (%)		
Chemotherapy or nonanthracycline¶	8 (4.0)	12 (5.9)
Radiotherapy	25 (12.4)	28 (13.9)
Cancer-related surgery	33 (16.4)	25 (12.4)

Mb: megabases

† The data were determined from electronic case-report forms.

‡ ECOG PS scores range from 0 to 5, with higher scores reflecting greater disability.

§ Of the 403 patients in the two groups, 374 had plasma available for blood-based analysis of tumour mutational burden; 351 of the samples (173 in the atezolizumab group and 178 in the placebo group) yielded high-quality data for analysis of tumour mutational burden.

¶ Previous chemotherapy or nonanthracycline treatments included cisplatin, etoposide, and concurrent radiation (in six patients in the atezolizumab group and seven patients in the placebo group) and carboplatin, etoposide, and concurrent radiation (in two patients in the atezolizumab group and six patients in the placebo group).

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

Unless otherwise stated, the information in Section B.2.4 is taken from the statistical analysis plan (52).

B.2.4.1 Determination of sample size

This study planned to randomise 400 patients during the global enrolment phase.

[redacted]

To control the overall two-sided type I error rate at 0.05 in the analyses of patients enrolled during the global enrolment phase, a group sequential weighted Holm procedure (53) was used wherein the two-sided significance levels of 0.005 and 0.045 were allocated to the primary comparisons for progression-free survival (PFS) and OS, respectively. If PFS in the ITT population was statistically significant at the two-sided α level of 0.005, OS in the ITT population was tested at a two-sided α level of 0.05. Additionally, if OS in the ITT population was statistically significant at the two-sided α level of 0.045, PFS in the ITT population was tested at a two-sided α level of 0.05.

The sample size of the study was determined by the analysis of OS. To detect an improvement of HR = 0.68 in OS using a log-rank test, approximately 306 deaths in the ITT population will be required to achieve an 91% power at a two-sided significance level of 0.045. One OS interim analysis was performed when approximately 240 OS events in the ITT population were observed, which was estimated to occur at approximately 25 months after the first patient was randomised.

The primary analysis of PFS was planned to be conducted at the time of the OS interim analysis and was estimated to occur when approximately 295 PFS events in the ITT population had occurred, which was expected at approximately 25 months after the first patient was randomised. This provides a 99% power to detect an improvement of HR = 0.55 in PFS at a two-sided significance level of 0.005. There were no interim analyses for PFS.

B.2.4.2 Progression-free survival

PFS was defined as the time from randomisation to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first. Patients who did not experience disease progression or death at the time of analysis were censored at the time of the last tumour assessment. Patients with no post-baseline tumour assessment were censored at the date of randomisation plus 1 day.

Treatment comparisons were based on the stratified log-rank test. If the null hypothesis of the OS testing was rejected at a two-sided significance level of 0.045, PFS were tested at the two-sided significance level of 0.05. Otherwise, PFS were tested at the two-sided significance level of 0.005.

The null and alternative hypotheses can be phrased in terms of the survival functions S_{PFS_A} (t) and S_{PFS_B} (t) in Arm A and Arm B, respectively:

H_0: S_{PFS_A} (t) =S_{PFS_B} (t) versus H_1: S_{PFS_A} (t) ≠S_{PFS_B} (t)

Kaplan-Meier methodology were used to estimate median PFS for each treatment arm and to construct survival curves for each treatment arm. The Brookmeyer-Crowley methodology and log-log transformation for normal approximation were used to construct the 95% CI for the median PFS for each treatment arm (54).

The HR, $\lambda_{PFS\_A}/\lambda_{PFS\_B}$, where λ_{PFS_A} and λ_{PFS_B} represented the hazard of the PFS event in Arm A and Arm B, respectively, were estimated with a stratified Cox regression model and the same stratification variables used for the stratified log-rank test and the 95% CI were estimated by normal approximation.

B.2.4.3 Overall survival

The other co-primary endpoint for this study is OS, which is defined as the time from randomisation to death from any cause. Patients who were not reported as having died were censored at the date when they were last known to be alive. Patients who did not have post-baseline information were censored at the date of randomisation plus 1 day.

OS was analysed with the same methodologies as PFS. Treatment comparisons were based on the stratified log-rank test, and if the null hypothesis of the PFS testing was rejected at a two-sided significance level of 0.005, OS was tested at the two-sided significance level of 0.05. Otherwise, OS was tested at the two-sided significance level of 0.045. Two analyses for OS were planned, including one interim analysis. If the two-sided p-

value corresponding to the stratified log-rank test was less than or equal to the two-sided level of significance at the corresponding analysis, the null hypothesis was rejected. The null and alternative hypotheses can be phrased in terms of the survival functions SOS_A (t) and SOS_B (t) in Arm A and Arm B, respectively:

H0: SOS_A (t) =SOS_B (t) versus H1: SOS_A (t) ≠SOS_B (t)

B.2.4.4 Study groups

Randomisation occurred in a 1:1 ratio using a permuted-block randomisation method. Patients were randomised to one of two treatment arms:

- Atezolizumab + carboplatin + etoposide
- Placebo + carboplatin + etoposide

The randomisation scheme was designed to ensure that an approximately equal number of patients would be enrolled in each treatment arm within the baseline characteristics of the following stratification factors:

- Sex (male vs. female)
- ECOG PS (0 vs. 1)
- Presence of brain metastases (yes vs. no)

Patients received their first dose of study drug on the day of randomisation if possible. If this was not possible, the first dose occurred within 5 days after randomisation (51).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The complete quality assessment for IMpower133 provided in appendix D.1.3 shows that the overall risk of bias is low.

B.2.6 Clinical effectiveness results of IMpower133

The IMpower133 trial evaluated the efficacy and safety of adding atezolizumab or placebo to first-line treatment with carboplatin and etoposide (hereafter referred to as the atezolizumab group and placebo group) in patients with ES-SCLC. The planned interim analysis of OS and a final analysis of PFS is reported below (data cutoff 24th April, 2018). Unless otherwise stated, the clinical data presented here is from the Horn et al. 2018 publication "First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer" (3).

B.2.6.1 Overview of efficacy

The study met the co-primary endpoints of OS and investigator-assessed PFS, demonstrating a statistically significant and clinically meaningful improvement in OS and a statistically significant improvement in investigator-assessed PFS with the atezolizumab group compared with the placebo group, in patients with chemotherapy-naïve ES-SCLC. The objective response rate (ORR) and median duration of response (DOR) were similar between the treatment arms, however, more patients in the atezolizumab group had an ongoing response at the time of data cutoff (Table 10).

Table 10: Overview of efficacy (ITT population), data cutoff date 24th April 2018

		Atezolizumab group	Placebo group
Co-primary efficacy objectives	**Overall survival**		
	ITT population	n=201	n=202
	Patients with event (%)	104 (51.7%)	134 (66.3%)
	Median duration of survival (95%) (months)	12.3 (10.8, 15.9)	10.3 (9.3, 11.3)
	Stratified hazard ratio (95%)	0.70 (0.54, 0.91)	
	p-value (log-rank)	0.007[a]	
	1-year event-free rate (%)	51.7	38.2
	(95% CI)	(44.4, 59.0)	(31.2, 45.3)
	Progression-free survival		
	ITT population	n=201	n=202
	Patients with event (%)	171 (85.1%)	189 (93.6%)
	Median duration of PFS (95%) (months)	5.1 (4.4, 5.6)	4.3 (4.2, 4.5)
	Stratified hazard ratio (95%)	0.77 (0.62, 0.96)	
	p-value (log-rank)	0.02[b]	
	6-month event-free rate	30.9	22.4
	(95% CI)	(24.3, 37.5)	(16.6, 28.2)

	1-year event-free rate (%)	12.6	5.4
	(95% CI)	(7.9, 17.4)	(2.1, 8.6)
	Objective response rate		
	ITT population	n=201	n=202
	No. of responders (%)	121 (60.2%)	130 (64.4%)
	95% Clopper-Pearson	(53.1, 67.0)	57.3, 71.0)
Other efficacy objectives	**Duration of response**		
	ITT population responders	n=121	n=130
	Patients with event (%)	103 (85.1%)	123 (94.6%)
	Median DOR (months[c])	4.2	3.9
	Range	(1.4[d], 19.5)	(2.0, 16.1[d])
	Ongoing response at data cutoff (%)	18 (14.9)	7 (5.4)

CI: confidence interval; DOR: duration of response; ITT: intent-to-treat; OS: overall survival; PFS: progression-free survival.

[a] Interim Analysis OS was tested at two-sided α of 0.0193 (with 238 observed OS events at CCOD) to control the overall two-sided type I error for OS at 0.045 by Lan DeMets function approximating O'Brien-Fleming boundary.

[b] Since null hypothesis for OS was rejected at an overall two-sided significance level of 0.045, PFS was tested at two-sided type I error of 0.05.

[c] Duration of response was assessed in patients who had an objective confirmed response and was defined as the time from the first occurrence of a documented objective response to the time of disease progression as determined by the investigator (according to RECIST) or death from any cause, whichever occurred first.

[d] Data for the lower range of the response in the atezolizumab group and the upper range of the response in the placebo group are censored.

Table 11 shows subsequent cancer therapies for patients in the IMpower133 trial; overall, 104 patients in the atezolizumab group and 116 patients in the placebo group received at least one subsequent therapy.

Table 11: Subsequent cancer therapies, data cutoff date 24th April 2018

Line of therapy (%)	Atezolizumab group (n=201)	Placebo group (n=202)
Second	101 (50.2)	116 (57.4)
Third	29 (14.4)	38 (18.8)
Fourth	3 (1.5)	15 (7.4)
Therapy type		
Total number of patients with at least one treatment	104 (51.7)	116 (57.4)
Total number of treatments	138	176
Chemotherapy/non-anthracycline	81 (40.3)	88 (43.6)
Chemotherapy/anthracycline	31 (15.4)	46 (22.8)

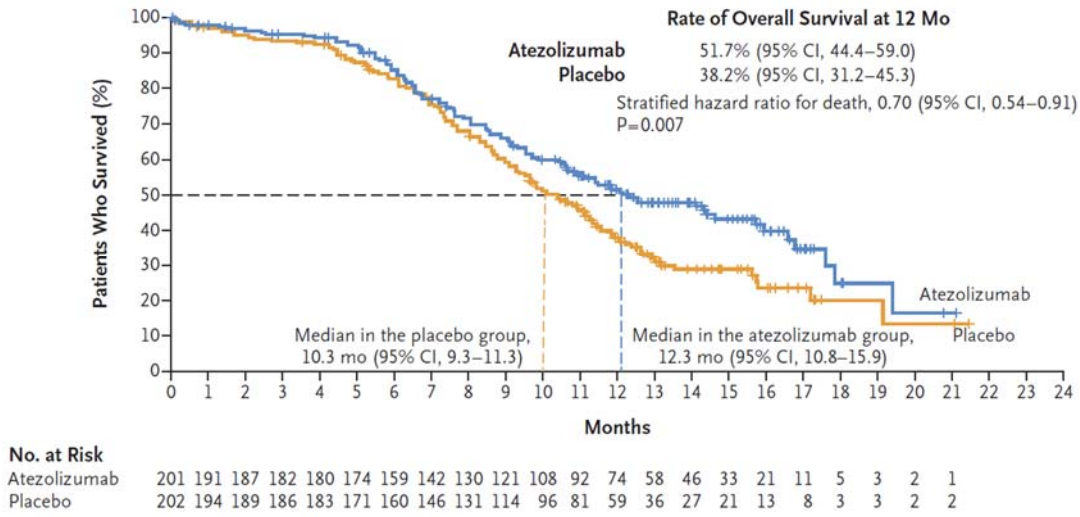
Immunotherapy	6 (3.0)	15 (7.4)
Other	2 (1.0)	2 (1.0)
Targeted therapy	2 (1.0)	1 (0.5)

Data are number of patients with at least one treatment (%) unless otherwise specified.
Multiple cases within a specific line of therapy and regimen for a patient were counted once for the frequency of line of therapy or regimen name. A patient was counted more than once if that patient received more than one therapy type under each line and regimen.

B.2.6.2 Overall survival analysis

At the time of data cutoff, 24th April 2018. the median follow-up was 13.9 months. A total of 104/201 patients (51.7%) in the atezolizumab group and 134/202 patients (66.3%) in the placebo group had died. OS reported to date was clinically and significantly longer in the atezolizumab group (median, 12.3 months; 95% CI, 10.8 to 15.9) than in the placebo group (median, 10.3 months; 95% CI, 9.3 to 11.3) (Figure 3). The stratified HR for death was 0.70 (95% CI, 0.54 to 0.91; P = 0.007) (Figure 3), and the 1-year OS rate was 51.7% (95% CI, 44.4–59.0) in the atezolizumab group and 38.2% (95% CI, 31.2–45.3) in the placebo group.

Figure 3: Kaplan-Meier plot of OS in ITT population, data cutoff date 24th April 2018

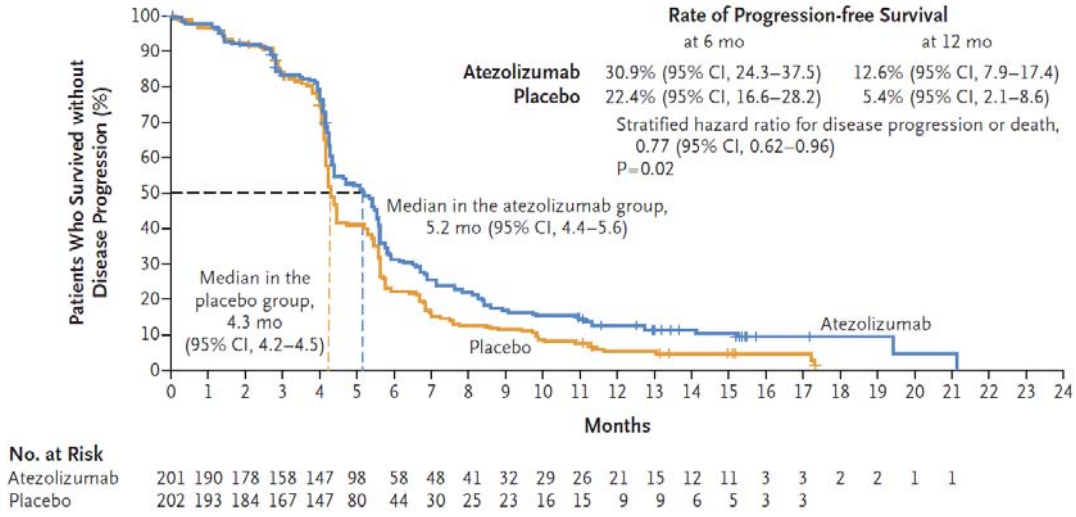


mo: Months; CI: Confidence interval

B.2.6.3 Progression-free survival analysis

A total of 171/201 patients (85.1%) in the atezolizumab group and 189/202 patients (93.6%) in the placebo group had disease progression or had died. Progression-free survival was longer in the atezolizumab group (median, 5.2 months; 95% CI, 4.4 to 5.6) than in the placebo group (median, 4.3 months; 95% CI, 4.2 to 4.5). The stratified hazard ratio for disease progression or death was 0.77 (95% CI, 0.62 to 0.96; P = 0.02) (Figure 4).

Figure 4: Kaplan-Meier plot of PFS in ITT population, data cutoff date 24th April 2018



mo: Months; CI: Confidence interval

B.2.6.4 Confirmed objective response rate and duration of response

Investigator-assessed confirmed objective response rates and median duration of response were similar in the two groups. In total, five patients (2.5%) in the atezolizumab group and two patients (1.0%) in the placebo group had a complete response (Table 12).

Table 12: Response rate, duration of response, and disease progression, data cutoff date 24th April 2018

Variable	Atezolizumab group (n = 201)	Placebo group (n = 202)
Objective confirmed response† — no. (% [95% CI])	121 (60.2 [53.1–67.0])	130 (64.4 [57.3–71.0])
Complete response — no. (% [95% CI])	5 (2.5 [0.8–5.7])	2 (1.0 [0.1–3.5])
Partial response — no. (% [95% CI])	116 (57.7 [50.6–64.6])	128 (63.4 [56.3–70.0])
Median duration of response (range) — mo‡	4.2 (1.4§–19.5)	3.9 (2.0–16.1§)

Ongoing response at data cutoff — no./total no. (%)	18/121 (14.9)	7/130 (5.4)
Stable disease — no. (% [95% CI])	42 (20.9 [15.5–27.2])	43 (21.3 [15.9–27.6])
Progressive disease — no. (% [95% CI])	22 (10.9 [7.0–16.1])	14 (6.9 [3.8–11.4])

CI: confidence interval

* The date of data cutoff was April 24, 2018.

† The objective confirmed response rate was assessed in patients in the intention-to-treat population who had measurable disease at baseline. Objective response was defined as confirmed complete response or partial response as determined by the investigator according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1.

‡ Duration of response was assessed in patients who had an objective confirmed response and was defined as the time from the first occurrence of a documented objective response to the time of disease progression as determined by the investigator (according to RECIST) or death from any cause, whichever occurred first.

§ Data for the lower range of the response in the atezolizumab group and the upper range of the response in the placebo group are censored.

B.2.6.5 Patient-reported outcomes – Baseline disease burden

At baseline, mean disease-related symptoms, treatment-related symptoms, functioning, and HRQoL scores were comparable between treatment arms (Table 13) (55). Patients generally had worse disease-related symptoms relative to normative scores of patients with ES-SCLC (56). Completion rates were high (≥ 85%) at baseline and ≥ 70% in both arms until Week 75 (n=6) (55).

Table 13: Baseline patient-reported outcome scores, data cutoff date 24th April 2018 (55)

	Atezolizumab arm (n=201)	**Placebo arm (n=202)**
	Mean scores (SD)	
Lung cancer-related symptoms		
Coughing	42.2 (27.7)	42.9 (29.2)
Pain in chest	22.9 (26.6)	22.2 (25.7)
Dyspnoea	34.3 (25.9)	29.6 (25.9)
Pain in arm or shoulder	22.2 (30.6)	19.4 (27.4)
Fatigue	42.0 (26.4)	38.7 (26.9)
Appetite loss	28.9 (32.3)	27.4 (31.9)
Treatment-related symptoms		
Constipation	22.7 (30.5)	22.7 (32.8)
Dysphagia	11.2 (20.4)	10.1 (22.4)
Peripheral neuropathy	9.9 (20.3)	9.9 (21.8)
Nausea and vomiting	9.6 (18.9)	10.5 (21.8)

Diarrhoea	6.3 (15.7)	7.4 (17.9)
Sore mouth	5.5 (14.7)	8.9 (19.8)
Function		
Physical functioning	70.7 (22.7)	71.9 (23.5)
HRQoL		
Global health status	51.6 (22.4)	53.7 (23.4)

HRQoL: health-related quality of life, SD: standard deviation

The score range for each QLQ-C30 orQLQ-LC13 scale is 0 to 100, with higher scores indicating either worse symptoms, better functioning, or better HRQoL.

B.2.6.6 Patient-reported outcomes – Lung cancer and treatment-related symptoms

TTD (time to deterioration: the time from baseline to the first time the patient's score shows a ≥10-point increase above baseline maintained for at least two consecutive assessments or followed by death within 3 weeks of the last assessment) between the treatment arms were similar in patient-reported lung cancer symptoms of cough, chest pain, or arm/shoulder pain, although a trend towards delayed worsening of dyspnoea favoured the atezolizumab group versus the placebo group (stratified HR=0.75 [95% CI: 0.55, 1.02]) (55).

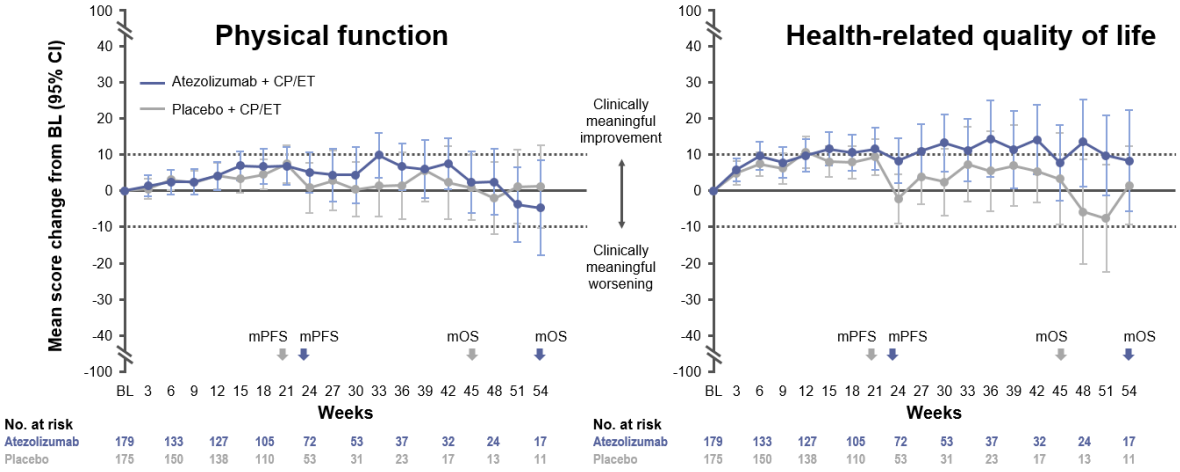
Change from baseline analyses suggested that, in general, patients in both treatment arms experienced immediate improvements in disease-related symptoms after beginning study treatment. At induction visits (i.e., from baseline up to but not including Week 12), improvements from baseline in cough, chest pain, dyspnoea, arm/shoulder pain, dysphagia, fatigue, and appetite loss were numerically greater in the atezolizumab arm. At visits during maintenance (i.e., Week 12 to Week 54), numeric improvements in lung cancer-related symptoms were either comparable between arms or larger in the atezolizumab arm than in the placebo arm (55). In addition, patients in the atezolizumab arm experienced clinically meaningful improvements (i.e., >10-point score decrease from baseline) in cough, chest pain, and dyspnoea earlier, and generally reported more enduring improvements than patients in the placebo arm (2). There were no differences between the treatment arms at most visits through Week 54 in the following treatment-related symptoms: nausea, vomiting, sore mouth, diarrhoea, dysphagia, and peripheral neuropathy (55). Changes in constipation were also similar between the two arms in the first 6 months (55).

B.2.6.7 Patient-reported outcomes – Function and health-related quality of life

Patients in both the atezolizumab arm and the placebo arm reported immediate and notable improvements in function and HRQoL (Figure 5). There were clinically meaningful improvements in HRQoL that were sustained through Week 54 in the atezolizumab arm (55).

In contrast, improvements in the placebo group were small and tapered off after Week 21 (2).

Figure 5: Change from baseline in function and health-related quality of life (55)



CP: carboplatin; ET: etoposide; mOS: median overall survival; mPFS: median progression-free survival

B.2.6.8 Summary of patient-reported outcomes

There was a trend of greater improvements in patient-reported lung cancer-related symptoms and physical function, with minimal impact from treatment-related toxicities observed in the atezolizumab arm versus the placebo arm (55). HRQoL improvements were also reported by patients in the atezolizumab arm, suggesting that the addition of atezolizumab did not increase toxicity related to carboplatin/etoposide, or adversely contribute to symptom burden (55).

B.2.7 Pre-planned subgroup analysis

The consistency of the study results in subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline prognostic characteristics (e.g., ECOG performance status, smoking status, presence of brain metastases at baseline), and pre-specified bTMB biomarker expression cutoffs (>10 or <10 and >16 or <16), was assessed by investigating the duration of OS and PFS in these subgroups (51).

OS and PFS benefit associated with treatment with atezolizumab was consistent across key subgroups (see Appendix E) (3). An exploratory analysis of TMB showed a consistent OS and PFS benefit above and below the prespecified cutoffs of 10 and 16 mutations per megabase (3).

A summary of the results for the subgroups is provided in appendix E.

B.2.8 Meta-analysis

The efficacy and safety of atezolizumab plus carboplatin-etoposide in first-line ES-SCLC patients has only been investigated in one RCT: the IMpower133 trial. Therefore, a meta-analysis of relevant trials was not required.

B.2.9 Indirect and mixed treatment comparisons

Appendix F includes full details of the methodology and results for the indirect comparison or mixed treatment comparison.

The decision problem for this appraisal states the relevant comparators are 'platinum-based combination chemotherapy regimens' (1). However, as outlined above, UK-practising clinical experts advise Roche that cisplatin-etoposide is not a relevant comparator for this appraisal. This is due to a consensus that [redacted] of ES-SCLC patients in the UK will be treated with carboplatin-etoposide chemotherapy (Appendix K).

[redacted] Moreover, since the marketing authorisation for atezolizumab to treat first-line ES-SCLC is

[redacted] Consequently, cisplatin-etoposide is not considered to be a key comparator in this appraisal.

However, since the final scope states the relevant comparators are 'platinum-etoposide chemotherapy regimens', for the purpose of transparency a network meta-analysis and indirect treatment comparison for cisplatin-etoposide are presented in Appendix F. The base case cost-effectiveness analysis for atezolizumab plus carboplatin-etoposide versus cisplatin-etoposide is presented in Appendix L.

B.2.10 Adverse reactions

Unless otherwise specified, the information in Section B.2.10 comes from the Horn et al. 2018 paper, "First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer". The date of data cutoff was 24th April, 2018 (3).

An iDMC was used to evaluate safety during the study. The population that could be evaluated for safety included 198 patients who received at least 1 dose of atezolizumab and 196 patients who received placebo. The median duration of treatment with atezolizumab was 4.7 months (range, 0–21), and the median number of atezolizumab doses received was 7 (range, 1–30). The median number of doses of chemotherapy was the same in the two groups (median, 4 doses of carboplatin and 12 doses of etoposide). The median dose intensity and total cumulative dose of chemotherapy were similar in the two groups. Table 14 details the treatment exposure to atezolizumab.

Table 14: Treatment exposure, data cutoff date 24th April 2018

	Atezolizumab group (n=198)			**Placebo group (n=196)**		
	Atezolizumab	**Carboplatin**	**Etoposide**	**Placebo**	**Carboplatin**	**Etoposide**
Median treatment duration						
Median — months	4.7	2.3	2.3	4.1	2.2	2.2
0–3 months (%)	47 (23.7)	193 (97.5)	191 (96.5)	41 (20.9)	191 (97.4)	191 (97.4)
3–6 months (%)	87 (43.9)	5 (2.5)	7 (3.5)	113 (57.7)	5 (2.6)	5 (2.6)
6–12 months (%)	41 (20.7)	0	0	30 (15.3)	0	0
>12 months (%)	23 (11.6)	0	0	12 (6.1)	0	0
Median dose intensity %	94.9	92.3	89.4	94.7	93.3	90.3
Median doses	7	4	12	6	4	12
Total cumulative dose — mg						
Mean (SD)	10193 (7166.6)	2019.2 (642.2)	1965.8 (539.8)	0	2145.7 (645.0)	2034.5 (477.2)
Median	8400	2062.5	2055.2	0	2175	2131.7

SD: standard deviation

Dose intensity is the number of doses actually received divided by the expected number of doses.

The proportion of patients with AEs related to any component of the trial regimen was comparable between the treatment groups and occurred in 188 patients (94.9%) in the atezolizumab group and in 181 patients (92.3%) in the placebo group (Table 15). The most common grade 3 or 4 AEs related to the trial regimen were neutropenia (22.7%), anaemia (14.1%), and decreased neutrophil count (14.1%) (Table 16).

The proportion of patients who experienced SAEs (serious adverse events) was similar between the atezolizumab group (37.4%) and the placebo group (34.7%) (Table 17). The most frequently reported SAEs were haematologic toxicities or infections. There were no SAEs which occurred at a higher (>2%) incidence in the atezolizumab group.

A total of 49/201 patients (24.4%) in the atezolizumab group were treated beyond investigator-assessed disease progression per RECIST v1.1. The median duration of atezolizumab treatment following investigator-assessed disease progression was 0.7 months (range: 0–16 months) (2). In the atezolizumab group, 7/49 (14.3%) of patients treated with atezolizumab beyond disease progression were still receiving atezolizumab treatment at the time of the data cutoff date (2).

Table 15: Summary of adverse events, data cutoff date 24th April 2018 (3, 57)

Patients — no. (%)	Atezolizumab Group (n=198)	Placebo Group (n=196)
Patients with ≥1 AE	198 (100)	189 (96.4)
Grade 3–4 AEs	133 (67.2)	125 (63.8)
Grade 5 AEs	4 (2.0)	11 (5.6)
Treatment-related AEs*	188 (94.9)	181 (92.3)
Treatment-related Grade 3–4 AEs	112 (56.6)	110 (56.1)
Treatment-related Grade 5 AEs	3 (1.5)	3 (1.5)
Serious AEs	74 (37.4)	68 (34.7)
Treatment-related serious AEs*	45 (22.7)	37 (18.9)
Immune-related AEs	79 (39.9)	48 (24.5)
AEs leading to withdrawal from any treatment*	22 (11.1)	6 (3.1)
AEs leading to withdrawal from atezolizumab/placebo	21 (10.6)	5 (2.6)
AEs leading to withdrawal from carboplatin	5 (2.5)	1 (0.5)
AEs leading to withdrawal from etoposide	8 (4.0)	2 (1.0)
Treatment-related deaths	3 (1.5)	3 (1.5)

AE: adverse event

* Incidence of treatment-related AEs, serious treatment-related AEs, and AEs leading to withdrawal from any treatment are for any treatment component. Multiple occurrences of the same AE in one patient were counted once at the highest grade for the preferred term.

Table 16: Treatment-related adverse events, data cutoff date 24th April 2018*

	Atezolizumab group (n=198)			Placebo group (n=196)		
Patients — no. (%)	**Grade 1–2**	**Grade 3–4**	**Grade 5**	**Grade 1–2**	**Grade 3–4**	**Grade 5**
Treatment-related AEs	73 (36.9)	112 (56.6)	3 (1.5)	68 (34.7)	110 (56.1)	3 (1.5)
Treatment-related AEs with an incidence of ≥10% in any arm, grade 3–4 severity with incidence of ≥1% in any arm, or grade 5 severity						
Neutropenia	26 (13.1)	45 (22.7)	1 (0.5)	20 (10.2)	48 (24.5)	0
Anaemia	49 (24.7)	28 (14.1)	0	41 (20.9)	24 (12.2)	0

Alopecia	69 (34.8)	0	0	66 (33.7)	0	0
Nausea	62 (31.3)	1 (0.5)	0	58 (29.6)	1 (0.5)	0
Fatigue	39 (19.7)	3 (1.5)	0	37 (18.9)	1 (0.5)+	0
Neutrophil count decreased	7 (3.5)	28 (14.1)	0	12 (6.1)	33 (16.8)	0
Decreased appetite	39 (19.7)	2 (1.0)	0	26 (13.3)	0	0
Thrombocytopenia	12 (6.1)	20 (10.1)	0	14 (7.1)	15 (7.7)	0
Platelet count decreased	17 (8.6)	7 (3.5)	0	21 (10.7)	7 (3.6)	0
Vomiting	25 (12.6)	2 (1.0)	0	19 (9.7)	3 (1.5)	0
Constipation	19 (9.6)	1 (0.5)	0	25 (12.8)	0	0
Leukopenia	15 (7.6)	10 (5.1)	0	10 (5.1)	8 (4.1)	0
White blood cell count decreased	10 (5.1)	6 (3.0)	0	16 (8.2)	9 (4.6)	0
Diarrhoea	15 (7.6)	4 (2.0)	0	18 (9.2)	1 (0.5)	0
Asthenia	14 (7.1)	3 (1.5)	0	12 (6.1)	2 (1.0)	0
Febrile neutropenia	0	6 (3.0)	0	0	12 (6.1)	0
Infusion-related reaction	6 (3.0)	4 (2.0)	0	9 (4.6)	1 (0.5)	0
Hypomagnesemia	7 (3.5)	0	0	5 (2.6)	2 (1.0)	0
Peripheral neuropathy	4 (2.0)	2 (1.0)	0	4 (2.0)	0	0
Hypokalaemia	2 (1.0)	0	0	4 (2.0)	2 (1.0)	0
Pneumonia	1 (0.5)	3 (1.5)	1 (0.5)	2 (1.0)	0	1 (0.5)
Pneumonitis	2 (1.0)	1 (0.5)	0	2 (1.0)	2 (1.0)	0
Pancytopenia	1 (0.5)	1 (0.5)	0	1 (0.5)	3 (1.5)	0
Lung infection	1 (0.5)	0	0	0	2 (1.0)	0
Cardiopulmonary failure	0	0	0	0	0	1 (0.5)
Death	0	0	1 (0.5)	0	0	0
Septic shock	0	0	0	0	0	1 (0.5)

* Incidence of treatment-related adverse events for any treatment. Multiple occurrences of the same AE in one patient were counted once at the highest grade for the preferred term.

AE: adverse event

Table 17: Serious treatment-related adverse events, data cutoff date 24th April 2018*

	Atezolizumab group (n=198)			**Placebo group (n=196)**		
Patients — no. (%)	**Grade 1–2**	**Grade 3–4**	**Grade 5**	**Grade 1–2**	**Grade 3–4**	**Grade 5**

Neutropenia	0	6 (3.0)	1 (0.5)	0	8 (4.1)	0
Febrile neutropenia	0	4 (2.0)	0	0	9 (4.6)	0
Thrombocytopenia	0	5 (2.5)	0	0	4 (2.0)	0
Pneumonia	0	3 (1.5)	1 (0.5)	0	0	1 (0.5)
Anaemia	0	3 (1.5)	0	0	2 (1.0)	0
Pancytopenia	0	0	0	1 (0.5)	3 (1.5)	0
Vomiting	0	2 (1.0)	0	0	2 (1.0)	0
Diarrhoea	1 (0.5)	2 (1.0)	0	0	0	0
Leukopenia	0	2 (1.0)	0	0	1 (0.5)	0
Infusion-related reaction	0	1 (0.5)	0	2 (1.0)	0	0
Pneumonitis	0	1 (0.5)	0	0	2 (1.0)	0
Lung infection	0	0	0	0	2 (1.0)	0
Platelet count decreased	0	0	0	1 (0.5)	1 (0.5)	0
Acute kidney injury	0	2 (1.0)	0	0	0	0
Asthenia	0	2 (1.0)	0	0	0	0
Autoimmune thyroiditis	2 (1.0)	0	0	0	0	0
Death	0	0	1 (0.5)	0	0	0
Cardiopulmonary failure	0	0	0	0	0	1 (0.5)
Septic shock	0	0	0	0	0	1 (0.5)
Acute pancreatitis	0	1 (0.5)	0	0	0	0
Atrioventricular block complete	0	1 (0.5)	0	0	0	0
Colitis	0	1 (0.5)	0	0	0	0
Dehydration	0	1 (0.5)	0	0	0	0
Fatigue	0	1 (0.5)	0	0	0	0
Ileus	0	1 (0.5)	0	0	0	0
Jaundice	0	1 (0.5)	0	0	0	0
Liver function test increased	0	1 (0.5)	0	0	0	0
Lower respiratory tract infection	0	1 (0.5)	0	0	0	0
Nausea	0	1 (0.5)	0	0	0	0
Peripheral neuropathy	0	1 (0.5)	0	0	0	0
Pulmonary oedema	0	1 (0.5)	0	0	0	0
Skin toxicity	0	1 (0.5)	0	0	0	0
Transaminases increased	0	1 (0.5)	0	0	0	0
Trigeminal neuralgia	0	1 (0.5)	0	0	0	0
Tubulointerstitial nephritis	0	1 (0.5)	0	0	0	0
Hypokalaemia	0	0	0	0	1 (0.5)	0
Hypomagnesemia	0	0	0	0	1 (0.5)	0
Neutropenic sepsis	0	0	0	0	1 (0.5)	0
Neutrophil count decreased	0	0	0	0	1 (0.5)	0
Pancreatitis	0	0	0	0	1 (0.5)	0

Urinary tract infection	0	0	0	0	1 (0.5)	0
White blood cell count decreased	0	0	0	0	1 (0.5)	0
Autoimmune colitis	1 (0.5)	0	0	0	0	0
Blood creatinine increased	1 (0.5)	0	0	0	0	0
Bronchitis	1 (0.5)	0	0	0	0	0
Cytomegalovirus infection	1 (0.5)	0	0	0	0	0
Diverticular perforation	1 (0.5)	0	0	0	0	0
Guillain−Barre syndrome	0	1 (0.5)	0	0	0	0
Haemoptysis	1 (0.5)	0	0	0	0	0
Pleural effusion	1 (0.5)	0	0	0	0	0

* Incidence of treatment-related adverse events for any treatment. Multiple occurrences of the same AE in one patient were counted once at the highest grade for the preferred term.

Immune-related AEs were reported regardless of whether it was treatment related (investigator-assessed) (2). The most common immune-related AE for both groups was rash occurring in 18.7% in the atezolizumab group and 10.2% in the placebo group (of which 2.0% and 0% were considered to be grade 3-4 respectively), followed by hypothyroidism in the atezolizumab group (25 [12.6%]) and infusion-related reaction in the placebo group (10 [5.1%]) (Table 18).

Table 18: Immune-related adverse events, data cutoff date 24th April 2018

Patients — no. (%)	**Atezolizumab Group (N=198)**	**Placebo Group (N=196)**
Rash All grades Grade 3–4	 37 (18.7) 4 (2.0)	 20 (10.2) 0
Hypothyroidism All grades Grade 3–4	 25 (12.6) 0	 1 (0.5) 0
Hepatitis (diagnosis) All grades Grade 3–4	 14 (7.1) 3 (1.5)	 9 (4.6) 0
Hepatitis (laboratory abnormalities) All grades Grade 3–4	 14 (7.1) 3 (1.5)	 9 (4.6) 0
Infusion-related reaction All grades Grade 3–4	 11 (5.6) 4 (2.0)	 10 (5.1) 1 (0.5)
Hyperthyroidism All grades Grade 3–4	 11 (5.6) 0	 5 (2.6) 0

Pneumonitis All grades Grade 3–4	 4 (2.0) 1 (0.5)	 5 (2.6) 2 (1.0)
Colitis All grades Grade 3–4	 3 (1.5) 2 (1.0)	 0 0
Pancreatitis All grades Grade 3–4	 1 (0.5) 1 (0.5)	 2 (1.0) 2 (1.0)
Severe cutaneous reaction All grades Grade 3–4	 2 (1.0) 0	 0 0
Adrenal insufficiency All grades Grade 3–4	 0 0	 2 (1.0) 0
Rhabdomyolysis All grades Grade 3–4	 2 (1.0) 1 (0.5)	 0 0
Nephritis All grades Grade 3–4	 1 (0.5) 1 (0.5)	 1 (0.5) 0
Hypophysitis All grades Grade 3–4	 1 (0.5) 0	 0 0
Vasculitis All grades Grade 3–4	 0 0	 1 (0.5) 0
Diabetes mellitus All grades Grade 3–4	 1 (0.5) 0	 0 0
Guillain−Barre Syndrome All grades Grade 3–4	 1 (0.5) 1 (0.5)	 0 0

Immune-related AEs were defined using MedDRA Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of immune-related events, regardless of investigator-assessed causality.

Deaths deemed related to the trial regimen occurred in 3 patients (1.5%) in the atezolizumab group (death was due to neutropenia in 1 patient, pneumonia in 1 patient, and an unspecified cause in 1 patient) and in 3 patients (1.5%) in the placebo group (death was due to pneumonia in 1 patient, septic shock in 1 patient, and cardiopulmonary failure in 1 patient).

B.2.11 Ongoing studies

The final analysis of OS in the IMpower133 trial will occur after approximately 306 OS events in the ITT population have occurred; this analysis is anticipated in Q2 2019 and will be made available to NICE.

A post-hoc exploratory analysis will be performed to investigate efficacy according to PD-L1 IHC status, with results due in Q2 2019. This analysis is being performed due to a final request for supplementary information (RSI) from the European Medicines Agency (EMA). Since this is a post-hoc exploratory analysis, only a limited number of samples were available for testing (approximately 35% remaining).

B.2.12 Innovation

The IMpower133 Phase I/III trial demonstrated significantly longer OS and PFS in patients with first-line ES-SCLC who were treated with atezolizumab and chemotherapy compared with chemotherapy alone (3, 58). It is the first significant advance in the treatment of ES-SCLC in 20 years (3, 58) and represents a step change in the management of ES-SCLC (59). Although IMpower133 is not yet approved by the European Medicine Agency (EMA), the addition of the IMpower133 regimen in the National Comprehensive Cancer Network (NCCN) guidelines only 15 days after the presentation of the data at the World Conference on Lung Cancer (WCLC) reflects the significance of these data and the unmet need for the patients (57, 60). The results of the trial suggest that atezolizumab plus carboplatin and etoposide is a new standard of care for first-line ES-SCLC and can improve outcomes beyond those achieved with platinum chemotherapy (3, 48, 60).

The improvement in OS and PFS via the addition of immunotherapy to chemotherapy supports the proposal that immunotherapy may enhance anti-tumour immunity when added to chemotherapy (3, 4, 61). The rationale for combining atezolizumab (an antibody that binds to PD-L1 and blocks its interaction with PD-1) with chemotherapy was that tumour cell killing by cytotoxic chemotherapy can reasonably be expected to expose the immune system to high levels of tumour antigens. Therefore, invigorating tumour-specific T-cell immunity by inhibiting PD-L1/PD-1 interaction may result in more durable responses compared with standard chemotherapy alone (62).

Atezolizumab plus carboplatin and etoposide for first-line treatment of ES-SCLC was granted a promising innovation medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency (MHRA) on 23rd November 2018, indicating that this treatment regimen has the potential to address an unmet clinical need for patients with a life-

threatening condition. An application for an early access to medicines scheme (EAMS) for atezolizumab plus carboplatin and etoposide for first-line treatment of ES-SCLC was submitted on 10th December 2018; the outcome of this submission is expected in Q2 2019. In addition, a supplemental biologic licence application (sBLA) for atezolizumab has been granted a priority review by the Food and Drug Administration (FDA) based on IMpower133 for use in combination with carboplatin and etoposide for the frontline treatment of patients with ES-SCLC (63); the FDA action date for this decision is 18th March 2019.

There have been very few developments in SCLC treatment in the past few decades and most of the changes made so far are related to improved radiation approaches (43). Several trials in ES-SCLC have failed to reach statistical significance in recent years in addition to the Phase III trial of nivolumab in combination with ipilimumab (46). There was a Phase III trial in 2016, evaluating ipilimumab or placebo in combination with etoposide and platinum therapy which found that ipilimumab did not prolong OS versus chemotherapy alone (64) and a Phase II trial in 2018 which showed that maintenance therapy with pembrolizumab after treatment with platinum and etoposide did not appear to improve median PFS compared with the historical data (65). This highlights the clinical significance of the positive IMpower133 trial results.

B.2.13 Interpretation of clinical effectiveness and safety evidence

The primary analysis of PFS and the interim analysis of OS from the IMpower133 phase I/III trial demonstrated that atezolizumab plus carboplatin and etoposide as first-line treatment in patients with ES-SCLC, was associated with significantly longer PFS and OS compared to chemotherapy alone (3). There was a 2-month statistically and clinically significant benefit in median OS with atezolizumab group compared to the placebo group (HR for death: 0.7, 95% CI, 0.54–0.91); the 1-year OS rate was approximately 13% higher in the atezolizumab group than in the placebo group (3). PFS was longer in the atezolizumab group versus the placebo group and the HR for disease progression or death was 0.77 (95% CI, 0.62–0.96). The landmark PFS analysis showed that 1 year after randomisation, the event-free rate was numerically higher in the atezolizumab arm compared with the placebo arm (12.6% vs. 5.4%) after randomisation (3). The benefits of including atezolizumab in the chemotherapy regimen with respect to OS and PFS were consistent across key patient subgroups (3). Objective response rates and median duration of response were similar in the two groups; however, more patients in the atezolizumab group had an ongoing response at data cutoff than the placebo group (14.9% vs. 5.4%) (3). In summary, results from the IMpower133 trial

suggest that combining checkpoint inhibition with cytotoxic therapy during induction will significantly improve outcomes beyond those seen with the current standard of care (3).

The IMpower133 trial also showed that blood-based tumour mutational burden levels at either cutoff (10 or 16 mutations per megabase) was not predictive of benefit in patients receiving atezolizumab (3). This result adds to previous observations that there is lack of targetable mutations for treating SCLC (43).

A trend of greater improvements in patient-reported lung cancer-related symptoms and physical function, with minimal impact from treatment-related toxicities, was observed in patients from the atezolizumab arm versus the placebo arm (55). The notable HRQoL improvements reported by patients in the atezolizumab arm suggest that the addition of atezolizumab did not increase toxicity related to carboplatin/etoposide, or adversely contribute to symptom burden (55).

Atezolizumab in combination with carboplatin and etoposide was well tolerated and the safety profile was consistent with the well-known toxic effects of the individual agents (3). There were no new or unexpected safety signals identified for the combination (3). The most common AEs were haematological and reflective of known safety effects of chemotherapy (66). The frequency of AEs leading to carboplatin or etoposide withdrawal were higher in the atezolizumab arm compared to the placebo arm (4.0% vs. 1.0% for etoposide and 2.5% vs 0.5% for carboplatin) (3). However, this frequency was generally low and in line with published chemotherapy withdrawal rate in first-line ES-SCLC patients (67, 68). A similar proportion of patients completed the four cycles of scheduled induction chemotherapy in both the atezolizumab and the placebo arm (carboplatin: 86.4% vs. 88.8%; etoposide: 84.8% vs. 88.3%, respectively) (2), demonstrating that the addition of atezolizumab did not affect the number of cycles administered. The incidence and types of immune-related AEs were similar to those seen with atezolizumab monotherapy (3, 69-71).

The IMpower 133 trial is relevant to UK clinical practice as it investigates the addition of atezolizumab to the current standard of care - carboplatin and etoposide. Limitations associated with the IMpower133 data presented are that the OS data are immature (a data update will be available Q2 2019) and that the patient population excludes those with ECOG PS 2 and higher.

The improved OS and PFS in patients with ES-SCLC through the use of first-line treatment with atezolizumab, carboplatin and etoposide represents a step change in the treatment of a disease which currently results in a very poor prognosis. As noted by the British Thoracic

Oncology Group (BTOG) in the response to consultee and commentator comments on the draft remit and draft scope (59), “Whereas the majority of patients with extensive-stage SCLC respond to first-line platinum-based chemotherapy, relapse of disease is universal and usually swift. The majority of patients in the real-world setting are too unwell to receive 2nd line chemotherapy. Consequently, any technology that improves PFS and OS, this is likely to be associated with an improvement in QALY.”

Roche considers the survival gain reported for atezolizumab plus carboplatin-etoposide to meet the end-of-life (EOL) criteria within this appraisal (Table 19). The first EOL criterion is for normal life expectancy to be shorter than 24 months. The median OS associated with ES-SCLC is 4–10 months, so it is substantially within the criterion of less than 24 months (3, 31). The IMpower133 trial reports a median OS for the current standard of care (i.e., the placebo group) of 10.3 months (95% CI 9.3–11.3), for patients with ECOG PS 0-1 (3). However, the median OS for ES-SCLC patients reported by the UK-based NLCA for all PS is just 4 months (31).

The second EOL criterion requires there to be sufficient evidence that atezolizumab offers an extension to life compared to current NHS treatment – typically with a survival benefit of 3 months or more. The primary analysis of the IMpower133 trial has already reported a clinically meaningful and statistically significant improvement in median OS of 2.0 months from the addition of atezolizumab to the current standard of care treatment in ES-SCLC patients (3). Moreover, [redacted]. The final IMpower133 study analysis will be available during Q2 2019. Some UK-practising clinical experts speculated that atezolizumab in ES-SCLC patients could be associated with a long survival tail, as has been seen for immuno-oncology therapies in other tumour types.

The 2.0-month median OS benefit reported to date from the IMpower133 trial is less than the 3-month benefit typically awarded the EOL criteria during NICE appraisals. However, this is based on the trial follow-up only, where not all OS events have been observed; therefore it is likely to be an underestimation of the OS benefit with this regimen across patients’ lifetime. Meanwhile, there is precedence in conditions with severe unmet need and extremely short life expectancy with current treatments, for shorter survival benefits from treatment to be awarded this status during a NICE appraisal (72). Given the severe unmet need in ES-SCLC and the lack of treatment benefits prior to theIMpower133 study, Roche considers this submission to warrant consideration on the EOL criteria.

Importantly, when assessing EOL criteria, the NICE Committee should also be considering the modelled OS benefit, particularly when trials are not complete - as with the IMpower133 study. Standard cost-effectiveness methodologies have been used to extrapolate the study data beyond the current trial follow-up period (B.3), with robust real-world data and UK-practising clinical experts validating the survival assumptions included in the submitted base case (B.3.3). In our base-case analysis, the expected difference in mean OS with the atezolizumab combination is 4.8 months, whilst the expected difference in median OS is 2.5 months. The difference in mean OS has been more commonly used in NICE committee decisions when evaluating the criteria for EOL therapies, we therefore believe that the atezolizumab combination in this appraisal could meet the EOL criteria.

Table 19: End-of-life criteria

<table>
<tr><th>Criterion</th><th>Data available</th><th>Reference in submission (section and page number)</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>Data from the NLCA from 2004–2011 reported the median survival for all ES-SCLC patients (ECOG PS 0–4) was just 4 months (31).

The IMpower133 trial data available to date, reported a median OS of 10.3 months (95% CI, 9.3–11.3) in the comparator arm, which is the same regimen as NHS standard of care (3).</td><td>Section B.2.6.2, page 38</td></tr>
<tr><td>There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment</td><td>The IMpower133 study has to date reported a 2.0-month median survival benefit from atezolizumab treatment in ES-SCLC patients. The final analysis is expected for the IMpower133 trial in Q2 2019.

Using the preferred base case described below (Section B.3.6), the modelled OS is as follows:
mean OS is 13.3 months for comparator arm vs 18.1 months for atezolizumab group – a difference of 4.8 months;
median OS is 10.3 for comparator arm and 12.9 for atezolizumab group – a difference of 2.5 months.
The modelled proportion of patients alive is as follows:<table><tr><th>Months</th><th>Comparator group</th><th>Atezolizumab group</th></tr><tr><td>12</td><td>42%</td><td>54%</td></tr><tr><td>24</td><td>13%</td><td>23%</td></tr><tr><td>36</td><td>5%</td><td>12%</td></tr><tr><td>48</td><td>2%</td><td>7%</td></tr><tr><td>60</td><td>1%</td><td>5%</td></tr></table></td><td>Section B.2.6.2, page 38

Appendix K
Section B.3.3, page 62
Section B.3.6, page 94</td></tr>
</table>

CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; NCLA: National Lung Cancer Audit; OS: overall survival.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

In appendix G, the methods and results of any published cost-effectiveness analyses available for atezolizumab and relevant comparators are presented.

Four published cost-effectiveness studies met the systematic literature review (SLR) inclusion criteria and were screened as full text articles. These were published in Canada, China, the Netherlands and the US (73-76). None of these four studies evaluated the costs and benefits of chemotherapy versus atezolizumab in ES-SCLC, which would reflect the clinical advancement of atezolizumab in the treatment of first-line ES-SCLC. A summary of these four studies is provided in Appendix G.

B.3.2 Economic analysis

The cost-effectiveness studies identified in Section B.3.1 and described in Appendix G, as well as the previous NICE technology appraisal for topotecan to treat relapsed SCLC (TA184, (77)), were reviewed for their potential to inform this submission dossier and the associated cost-effectiveness modelling. However, since there are no published economic analyses for first-line ES-SCLC from a UK perspective a *de novo* economic model was built to inform decision making. Many of the key modelling assumptions were informed by either the IMpower133 trial or through targeted engagement with UK-practising clinical experts treating ES-SCLC patients (Appendix K).

The model inputs of efficacy, safety and tolerability are based on data reported from the pivotal phase I/III IMpower133 trial for atezolizumab plus carboplatin-etoposide. Model results are reported in terms of cost per life years gained (LYG) and costs per quality adjusted life years (QALY) gained. This appropriately reflects the decision problem summarised in Section B.1.1.

B.3.2.1 Patient population

The *de novo* model considers the improvement in OS and PFS from atezolizumab plus carboplatin-etoposide induction, followed by atezolizumab monotherapy maintenance in first-line, adult ES-SCLC patients, versus carboplatin-etoposide induction treatment only. This population is consistent with the ITT population of the IMpower133 study, the NICE final scope for this appraisal (1), the appraisal decision problem and the anticipated EMA Marketing Authorisation (the draft SmPC provided in a separate document).

In terms of patient subgroups, the IMpower133 study results were assessed for consistency between the ITT population and pre-defined subgroups (demographics [e.g., age, sex, and race/ethnicity] or baseline prognostic characteristics [e.g., ECOG performance status, smoking status, presence of brain metastases]). In addition, an exploratory subgroup analysis of TMB was performed. Only the ITT population is evaluated for cost-effectiveness in this appraisal since UK-practising clinical experts treating ES-SCLC have advised this is the most clinically relevant population. This is due to the limited differentiation between the subgroups (3), and that no change in prescribing practice is expected according to patient subgroups.

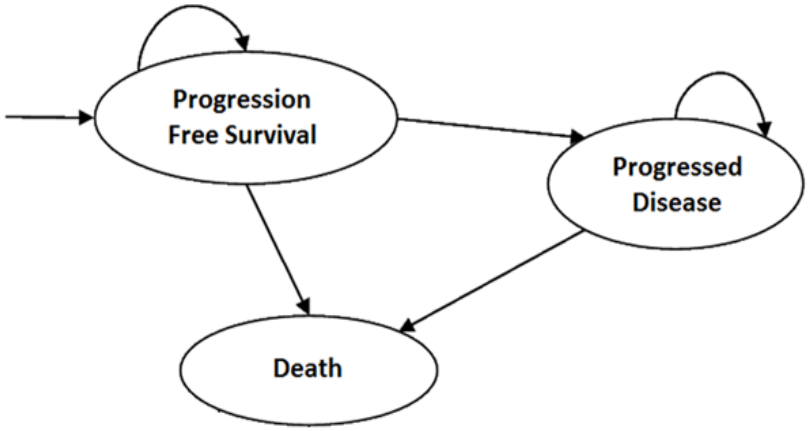
B.3.2.2 Model structure

The cost-effectiveness model submitted with this appraisal to evaluate the costs and benefits of ES-SCLC patients, is a 3-health state partitioned survival analysis (PartSA) model; also known as an area-under-the-curve (AUC) model. These 3 health states are mutually exclusive, and are consistent with previous appraisals accepted by NICE to evaluate first-line lung cancer, as well as other oncology indications (78-82): “PFS”, “Progressed Disease (PD)” and “Death” (Figure 6).

[redacted]

All patients start in the PFS health state and remain there until either disease progression or death. Upon disease progression patients transition from PFS into the PD health state, where they remain until death (Figure 6). Patients cannot transition to an improved health state – i.e., from progression back to PFS. This restriction is consistent with previous economic modelling in oncology and is considered clinically relevant (Appendix K).

Figure 6: Economic model structure with 3 mutually exclusive health states



The model structure was selected, as per NICE DSU (decision support unit) guidance (83), to allow the PFS and OS data from the IMpower133 trial to be fully incorporated. This model assumes: (i) all endpoints – including OS and PFS – are modelled and extrapolated independently; and (ii) trends in the hazard of each endpoint and treatment effects on these hazards observed within the trial can be generalised to the extrapolation period.

This model structure prevents the patient's transitions between the health states being explicitly modelled, instead the proportion of patients within each health state was calculated based on the PFS and OS survival curves from the IMpower133 trial, with the proportion of patients in the progressed health state being the difference between these two. The model approach allows for modelling of OS and PFS based on study-observed events, which is expected to accurately reflect disease progression during the period of the study duration. However, the main limitation of this approach is that OS and PFS are modelled as independent end points, and since transitions are not explicitly modelled, the model structure is rigid and does not allow for sensitivity or scenario analyses to be explored by altering the transition probability in specific health states. Although transitions are not explicitly modelled, the proportion of patients in each health state is driven by parametric survival curves, which are varied in scenario analysis, and parameters varied in the PSA to evaluate the impact on the ICER.

PFS, OS and TTOT data from the IMpower133 trial are incorporated into the model. This modelling approach does not directly consider post-progression survival, and not all events have been observed to date within the IMpower133 trial. Therefore, the long-term survival of ES-SCLC patients treated with chemotherapy has been modelled using standard parametric methods and confirmed against [redacted] (Appendix K) and real-world data (Section B.3.3.6). In order to demonstrate the clinical plausibility of the chosen extrapolation approach, scenario analyses are presented where the real-world data is incorporated directly into the control arm of the model (described in more detail in Section B.3.3.6) with the resulting atezolizumab benefit based on the benefit reported in the IMpower133 study. Similarly, the PartSA model principle is applied between time–to-off-treatment (TTOT) and OS, to assess the states on and off treatment. This is considered to be a transparent approach because PFS, TTOT and OS data are directly applied from the pivotal phase I/III trial – IMpower133.

Treatment duration measured during the IMpower133 trial is applied directly within the model so as to accurately report the costs associated with the resulting efficacy. This is due to maintenance with atezolizumab monotherapy being allowed to continue beyond evidence of

disease progression, until loss of clinical benefit if certain criteria were met. These criteria were defined in the trial protocol (Section B.2.3.1 and Appendix C).

The model also enables external evidence for secondary comparators to be included via the NMAs proportional hazard ratios (Appendix F). The indirect hazard ratios resulting from the NMA are applied to the survival estimates of the atezolizumab plus carboplatin-etoposide arm to calculate the mean cost and effects for cisplatin-etoposide. With the atezolizumab plus carboplatin-etoposide arm being informed by the IMpower133 study plus a parametric extrapolation. Since cisplatin-etoposide was not evaluated within the IMpower133 trial, information on treatment discontinuation was not available, so the discontinuation rate for carboplatin-etoposide was used as a proxy. However, [redacted], cisplatin-etoposide is only presented as a secondary analysis for the purpose of transparency (Appendix L).

The model structure has a weekly cycle length, meaning the proportion of patients in each health state is calculated per week. Transition between health states can occur at any time within the cycle. In order to account for any over or under estimation of transitions occurring at the beginning or end of the cycle, a half-cycle correction was applied.

Utilities are applied within the model linked to time to death (Section B.3.4).

The results of the cost-effectiveness analysis are reported in terms of cost per life years gained and costs per QALY gained (Section B.3.7 and B.3.8).

The economic model uses a 20-year time horizon in the base case, after which >99% of first-line ES-SCLC patients are expected to be dead. This long time horizon ensures that all the benefits and costs accrued by ES-SCLC patients are captured.

Costs and health outcomes are discounted at 3.5% in the base case and the perspective of the NHS and personal social services (PSS) is assumed. These are in line with the NICE reference case (84). Alternative discount levels are considered in the scenario analysis (Section B.3.8.3).

An overview of the economic analysis for this appraisal is provided in Table 20. Since there are no previous NICE technology appraisals in first-line, ES-SCLC patients, no comparison between appraisals has been made here.

Table 20: Features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Time horizon	Lifetime (20 years)	NICE reference case. Time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies being compared
Cycle length	1 week	In line with previous NICE appraisals of lung cancer treated with cancer immunotherapy treatments
Half-cycle correction	Included	In line with previous NICE appraisals of lung cancer treated with cancer immunotherapy treatments and included here to mitigate potential bias
Were health effects measured in QALYs; if not, what was used?	Yes	NICEs reference case (84). Only direct health effects related to patients were considered, with no wider societal impact or impact on carers are included
Discount of 3.5% for utilities and costs	Yes	NICEs reference case (84)
Perspective (NHS/PSS)	Yes	NICEs reference case (84)
Treatment benefit cap	Treatment benefit capped at 5 after diagnosis	[redacted]). Removal of this assumption is considered in Section B.3.8.
Source of utilities	IMpower133 trial, EQ-5D individual patient level data	NICEs reference case (84)
Source of costs	[redacted] Unit costs derived from NHS reference costs (85) and eMIT (14)	Expert opinion sought in the absence of published literature. Widely accepted sources of cost and resource use data of relevance to the NHS

CE: cost-effectiveness; EQ-5D: Euro quality of life-5 dimensions; eMIT: electronic marketing information tool; ERG: Evidence Review Group; ES-SCLC: extensive-stage small cell lung cancer; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; QALY: quality-adjusted life years

B.3.2.3 Intervention technology and comparators

The final NICE scope states the relevant comparators in this appraisal are 'platinum-based combination chemotherapy regimens' (1). As outlined in Section B.1.1. UK-practising clinical

experts who treat ES-SCLC patients in the NHS advise Roche that [redacted] of first-line ES-SCLC patients eligible to receive chemotherapy will be prescribed carboplatin-etoposide (Appendix K) for a maximum of 6 cycles. Carboplatin-etoposide is the control arm of IMpower133, therefore the cost-effectiveness model and subsequent incremental cost-effectiveness ration (ICER) values are based on the pivotal trial in this indication, which is directly relevant to NHS practice (3).

Roche were advised the [redacted] of first-line ES-SCLC patients eligible to receive chemotherapy are likely to be prescribed cisplatin-etoposide for a maximum of 6 cycles (Appendix K). However, UK-practising clinical experts stated a [redacted] was typically chosen when borderline LS-SCLC was suspected, or radiotherapy may be considered later in treatment (Appendix K). Therefore, cisplatin-etoposide is not considered a relevant comparator in this appraisal. Although cisplatin-etoposide is not the standard of care in the UK and not considered a relevant comparator in this appraisal, an NMA was conducted to enable a comparison with cisplatin-etoposide, for the purpose of transparency of decision-making. This should be considered as supportive data, provided for completeness. The NMA presented in Appendix F demonstrates that carboplatin-etoposide and cisplatin-etoposide regimens have equivalent clinical efficacy in ES-SCLC patients. However, Roche were advised that the AE profiles differed significantly between these platinum-etoposide regiments, which clinicians considered when making treatment decisions (Appendix K). In addition, cisplatin-etoposide has greater service implications, given it requires up to 10 hours to infuse, whereas carboplatin-etoposide requires just 2 hours (Appendix K). Furthermore, UK-practising clinical experts reported an increased risk of heart failure following the prolonged infusion of cisplatin-etoposide and the hydration required (Appendix K). Although cisplatin-etoposide is not considered a relevant comparator in this appraisal, for transparency a cost-effectiveness evaluation is presented in comparison to atezolizumab plus carboplatin-etoposide (Appendix L).

The NICE final scope for this appraisal considers the broad ES-SCLC treatment pathway, and current UK treatment guidelines (1). However, since atezolizumab is expected to receive marketing authorisation specifically in combination with carboplatin-etoposide, then etoposide-intolerant patients are outside the scope of this submission. For example, patients treated with carboplatin-irinotecan.

Within the model:

- Atezolizumab plus carboplatin-etoposide is modelled in line with the dosing schedule for the IMpower133 study, which is aligned with the anticipated EMA marketing authorisation. Specifically, atezolizumab was given at a fixed dose of 1200 mg on Day 1 of every 3 week (Q3W) cycle until loss of clinical benefit or unacceptable toxicity, in combination with carboplatin AUC of 5 mg/ml/min on Day 1 of each of the Q3W cycles for four cycles, plus etoposide 100 mg/m^2 of body surface area on Days 1, 2 and 3 the Q3W cycles for four cycles.

- The control arm reflects current standard of care within the NHS for first-line ES-SCLC patients. Specifically, carboplatin AUC of 5 mg/mL/min on Day 1 of each of the Q3W for four cycles, plus etoposide 100 mg/m^2 on Days 1, 2 and 3 of Q3W cycles for four cycles. NHS practice follows published treatment guidelines, allowing a maximum of 6 cycles of carboplatin-etoposide to be administered, if the patient is showing clinical benefit and an acceptable toxicity profile. Yet, clinical practice differs across the NHS with some clinicians preferring to administer only 4 chemotherapy cycles to minimise the AEs.

- [redacted] Therefore, cisplatin-etoposide is not considered to be relevant to the decision problem, so is only presented as supplementary evidence, for transparency (Appendix L).

The cost-effectiveness model incorporates treatment discontinuation rates from the IMpower133 trial – these are considered to be clinically relevant to NHS practice (49). In addition, the relative dose intensity reported in the IMpower133 trial is considered when the dose is calculated for atezolizumab, carboplatin and etoposide.

B.3.3 Clinical parameters and variables

B.3.3.1 Incorporation of clinical data into the model and overview of the chosen parametric extrapolations

The primary data source for the model is the pivotal IMpower133 study, comparing atezolizumab plus carboplatin and etoposide induction followed by atezolizumab monotherapy maintenance versus carboplatin and etoposide induction treatment only. Data

are currently available from the 24th April 2018 data cut, which have been used to inform the clinical parameters of the model, including OS, PFS, TTOT and AE (3). An event-based data update is anticipated from the ongoing IMpower133 study during Q2 2019.

Costs and benefits for treating ES-SCLC were extrapolated from the IMpower133 trial to the 20-year time-horizon of the model, as lifetime results are not available currently. Guidance from the NICE DSU (86) was followed to identify the best fit parametric survival extrapolations for OS, PFS and TTOT in the model base-case.

The following process was used to select the most relevant extrapolation options for OS and PFS:

- Check for proportional hazards;
- Inspection of visual fit;
- Assessment of statistical fit (Akaike Information Criterion (AIC) within 5 data points of the lowest AIC value are considered to have a similar goodness of fit);
- Consideration of whether different curve types per arm may be justifiable;
- Plausibility of extrapolation beyond the trial data:
    - Crossing curves (OS extrapolation should not cross the PFS or TTOT extrapolations; this is applied as a restriction on the selection of OS curves which cross either PFS or TOT when >1% of patients remain alive);
    - Survival estimates against expert clinical opinion and real-world data;
    - Comparison to general mortality rates for OS.

Since the IMpower133 trial has not yet completed, extrapolation of PFS and OS are required. This extrapolation is made more challenging since the available real-world data shows a change in the shape of the Kaplan-Meier / hazard function at around 30 months, i.e. beyond the duration of current IMpower133 trial evidence. However, since there are no NICE DSU guidelines regarding the incorporation of real-world data into cost-effectiveness modelling, then standard parametric approaches have been applied in the model base case with real-world data scenarios presented to validate the extrapolation choice.

Analyses are presented for extrapolation using either the Kaplan-Meier data with parametric survival extrapolations or fully parametric survival extrapolations. The standard parametric distributions are fitted, including: Exponential, Weibull, log-logistic, log-normal, generalised gamma and Gompertz. Since the IMpower133 OS data are not fully matured, a fully parametric extrapolation approach was taken here, to avoid the need for assumptions regarding the time to switch between KM and parametric functions.

The extrapolation methods and extrapolation results for PFS and OS results are outlined below in Sections B.3.3.2 and B.3.3.3, with the real-world data scenarios and validation presented in Section B.3.3.4.

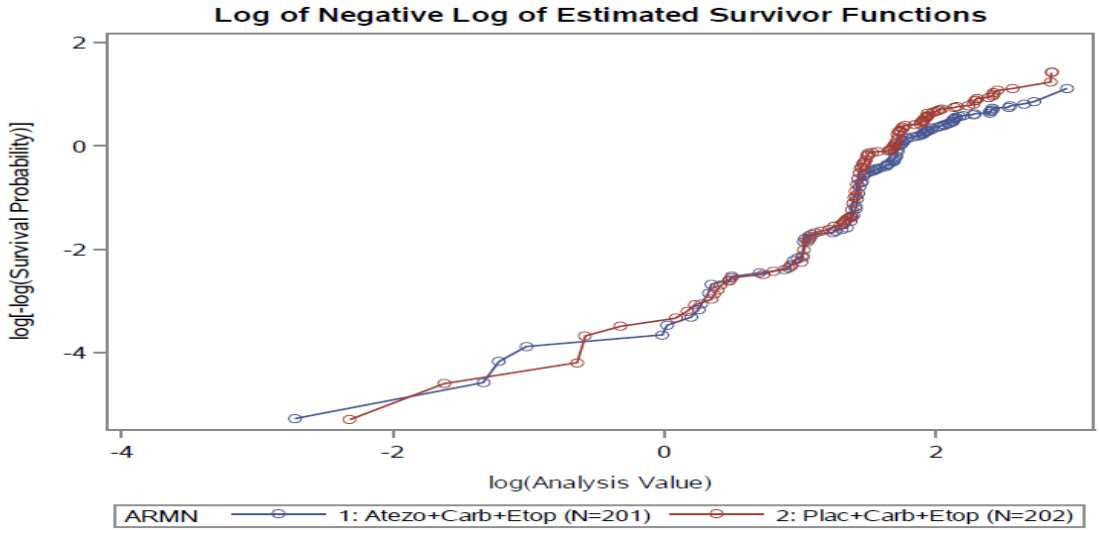
B.3.3.2 Probability of remaining in PFS and PFS extrapolation

As stated above, patients enter the model in the PFS health state and remain there until disease progression (as defined by RECIST v.1.1), or death (Figure 6).

Assessment of proportional hazards

To justify fitting an unstratified parametric function, the proportional hazards assumption must be demonstrated. The proportional hazard assumption requires the hazard in arm A to be a constant proportion to the hazard in arm B, this proportion is then the hazard ratio. Therefore, although the hazard may vary with time, the ratio of the hazard rates is constant. A diagnostic plot of the log cumulative hazard for PFS over the log of time for the IMpower133 arms was assessed to test the proportional hazards assumption. Based on the log cumulative hazard plot in Figure 7, it was determined that the proportional hazards assumption does not hold for PFS, given the curves cross each other at multiple time points. In order to address the non-proportionality of the hazards, independent parametric models for PFS have been applied, as per NICE DSU guidance (86).

Figure 7: PFS log-cumulative hazard plot from IMpower133



Visual and statistical goodness of fit of the parametric functions

Parametric distributions (Table 21) were assessed for their goodness of fit to the data using the AIC, Bayesian Information Criteria (BIC), graphical assessment of each parametric function. Low values for AIC and BIC indicate a better statistical assessment of the fit of the parametric function to the actual data. The log-logistic curve provided the best statistical fit on AIC and BIC, no other curves provided a similar statistical fit (AIC within 5).

In terms of visual fit, all the standard parametric curves provided a similarly poor visual fit to the Kaplan Meier due to steep drops within the first 5 months at the time of each scan. For this reason, Kaplan-Meier data was used for the first 5 months in both arms of the model. At this timepoint approximately 50% of patients remain at risk on both arms.

Given the similarity of long-term projections, and the fact that the best statistical fit was consistent for the two model arms, the same parametric extrapolation was applied to both arms.

Table 21: Ranking of PFS distributions based on AIC, BIC, visual fit and clinical plausibility

Parametric distribution	AIC Atezo	BIC Atezo	AIC control	BIC control	Visual fit to KM	Ranking overall
Log-logistic	**428.6**	**435.2**	**376.1**	**382.7**	**Best fit**	**1**
Generalised gamma	448.3	458.2	399.8	409.7	Poor fit	2
Weibull	455.6	462.2	408.6	415.2	Poor fit	3
Log-normal	464.7	471.3	425.5	432.1	Poor fit	4
Gompertz	483.3	489.9	452.8	459.4	Poor fit	5
Exponential	493.9	497.2	482.6	485.9	Poor fit	6

AIC: Akaike information criteria; BIC: Bayesian information criteria; KM: Kaplan-Meier.
Text in bold refers to best fit extrapolations.

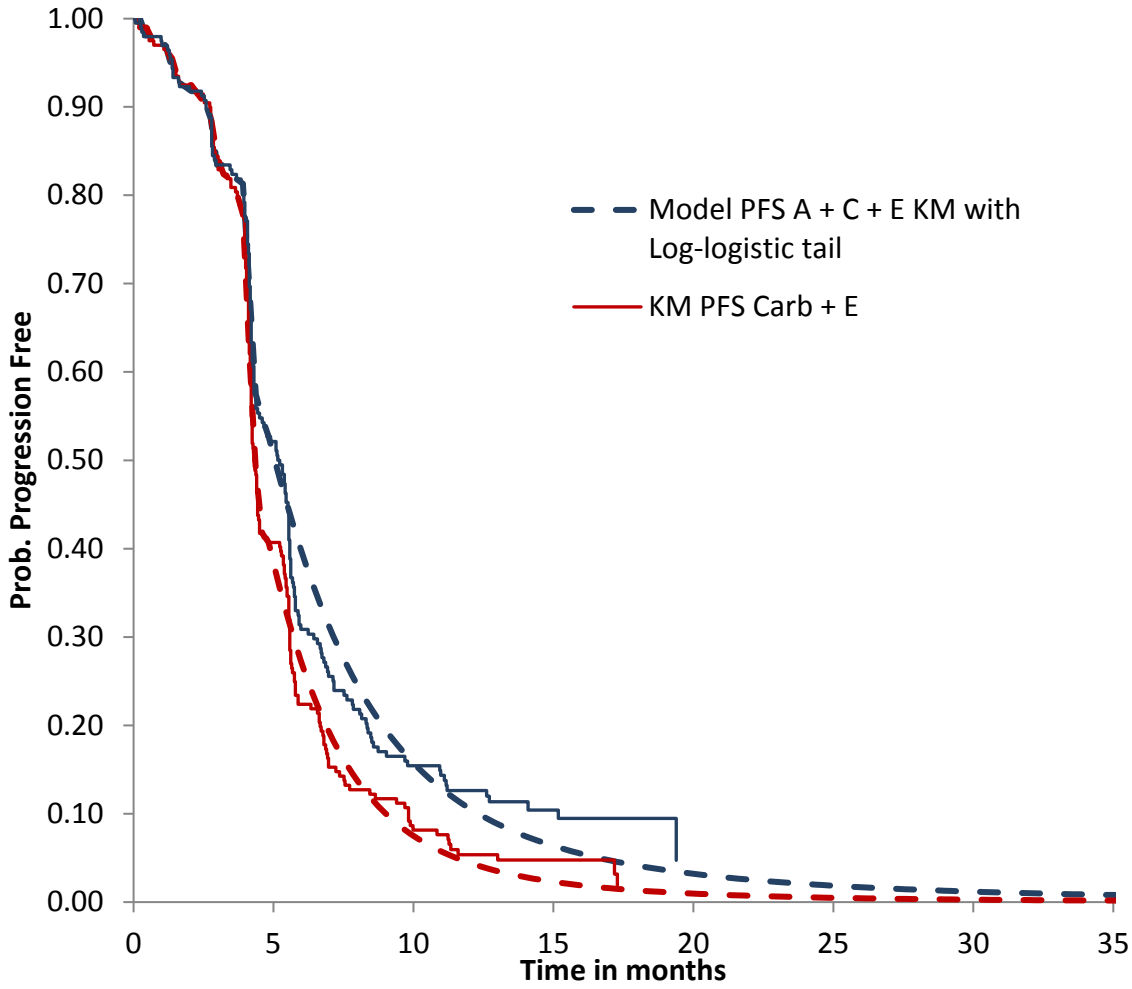
Plausibility of extrapolation beyond trial

The quality and plausibility of the extrapolation beyond the observed data should not only be assessed mathematically based on the AIC and BIC, since this does not allow any conclusion to be drawn around the appropriateness for the tail of the distribution.

Model base case

Figure 8 shows the curve selection in the model base case (Kaplan-Meier for 5 months followed by the log-logistic extrapolation on both arms). Alternative parametric extrapolations are provided within the model for comparison.

Figure 8. Log-logistic PFS extrapolation



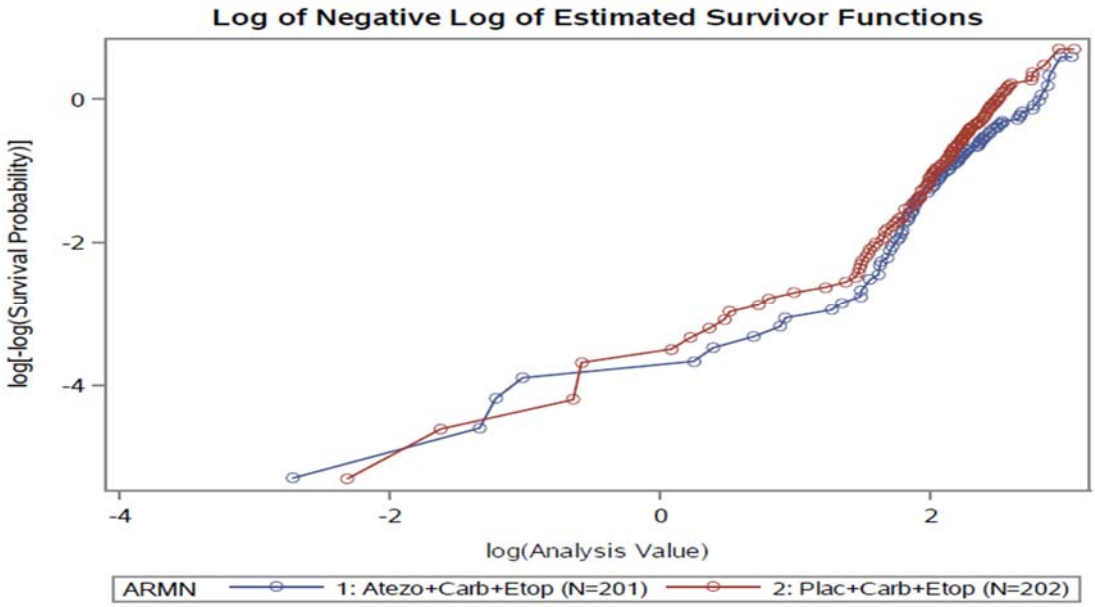
A: atezolizumab; C: carboplatin; E: etoposide; KM: Kaplan-Meier; PFS: progression-free survival

B.3.3.3 Probability of remaining in OS and OS extrapolation

Assessment of proportional hazards

As above, a diagnostic plot of the log cumulative hazard for OS over the log of time for the treatment arms was assessed to test the proportional hazards assumption for OS. Based on this graphical assessment, the log plots were not considered to be parallel, and hence the proportional hazards assumption also does not appear to be validated for OS (Figure 9).

Figure 9: OS log-cumulative hazard plot in IMpower133



Visual and statistical goodness of fit of the parametric functions

The AIC and BIC goodness of fit results for the functions used to model OS are presented in Table 22. According to AIC and BIC criteria alone, the best overall fit to the existing OS data would be either the Weibull, Gompertz generalised gamma or log-logistic extrapolations for the atezolizumab arm (all have AIC within 5 values of the lowest) and the Weibull, Gompertz or generalised gamma curves for the comparator arm.

The Weibull, Log-logistic, Gompertz and generalised gamma extrapolation curves were all considered to have good visual fit to the existing trial data. As a result, only fully parametric extrapolations were considered for OS in the model base case, however functionality is included in the model to assess the impact of applying the Kaplan Meier data for the initial period before switching to parametric extrapolation.

Table 22: Ranking of OS parametric distributions from IMpower133 trial data based on AIC, BIC, visual fit and clinical plausibility

Parametric distribution	AIC Atezo	BIC Atezo	AIC Control	BIC Control	Visual fit to KM	Clinical plausibility	Ranking overall
Log-logistic	**409.8**	**416.4**	**437.4**	**444.0**	**Good fit to existing data**	**Best fit**	**1**
Weibull	**406.4**	**413.0**	**428.6**	**435.2**	**Best fit to existing data**	**Too conservative**	**2**
Gompertz	**407.4**	**414.0**	**430.4**	**437.0**	**Good fit to existing data**	**Too conservative**	**Poor fit**
Generalised gamma	**407.7**	**417.6**	**429.1**	**439.0**	**Good fit to existing data**	**Too conservative**	**Poor fit**
Exponential	430.1	433.4	472.7	476.0	Poor fit to existing data	Too optimistic	Poor fit
Log-normal	436.6	443.2	472.9	479.6	Poor fit to existing data	Too optimistic	Poor fit

AIC: Akaike information criteria; BIC: Bayesian information criteria; KM: Kaplan-Meier
Text in bold refers to best fit(s) extrapolations.

Plausibility of extrapolation beyond trial

As above, the quality and plausibility of any extrapolation beyond the observed data cannot be assessed with AIC and BIC statistical fit alone, as these do not inform the appropriateness of the tail of any distribution. Validation of the clinical plausibility of long-term OS extrapolations is therefore critical when long-term trial data are missing. Here, validation of the chosen parametric extrapolation is based firstly on expert clinical opinion, then secondly on real-world data sources. Some published literature also reports the long-term survival associated with ES-SCLC treated with chemotherapy at 2 years and 5 years, but it is unclear the data source this is based upon (27).

[redacted]

[redacted]. These long-term survival estimates are important to take into account, since they are not observable from the current IMpower133 data cut (or from any of the other identified studies).

The real-world data evaluated by these clinical experts was from the Flatiron Health database, which reports individual patient-level data for ES-SCLC patients with ECOG 0-1, treated with platinum-etoposide chemotherapy (Figure 10).

[redacted] The Flatiron Health database is a US-based, observational, longitudinal database containing electronic health record data from over 265 cancer clinics (~800 sites of care) including more than 2 million active U.S. cancer patients, available for analysis. Although this is an entirely US-based cohort, the baseline patient characteristics were restricted to reflect the IMpower133 trial in terms of patients' being ES-SCLC, ECOG 0-1, and treated with platinum-etoposide regimens and survival probability was reported (Figure 10). The Flatiron Health data differ to the IMpower133 trial in that they include both carboplatin-etoposide and cisplatin-etoposide treatments. However, this is considered to be appropriate; firstly, because it accurately reflects real-world treatment patterns and secondly, the efficacy of these regimens is considered to be comparable - as per the results of the NMA (Appendix F).

Comparing the control arm of IMpower133 trial and the real-world data shows that initially the IMpower133 trial OS is better, with the survival profile with the 2 KMs converging and showing similar survival from approximately 12 months until the end of the availability of IMpower133 study data, which as a maximum follow-up currently of 21 months (Figure 10 and Figure 11). There is then a flattening in the KM curve and change in the hazard function within the real-world dataset at around 30 months, with proportion of patient still remaining alive after 60 months.

Figure 10: Flatiron Health database, long-term survival for ES-SCLC patients with ECOG 0-1, treated with a platinum-etoposide regimen

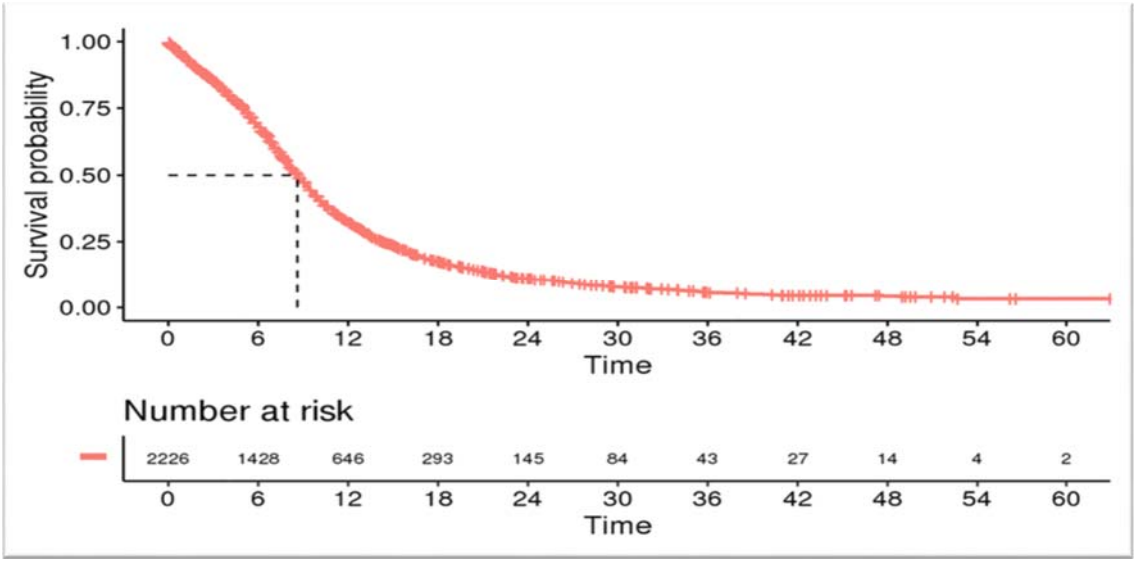


Figure 11: Kaplan Meier comparing Flatiron Health database survival and the IMpower133 study OS

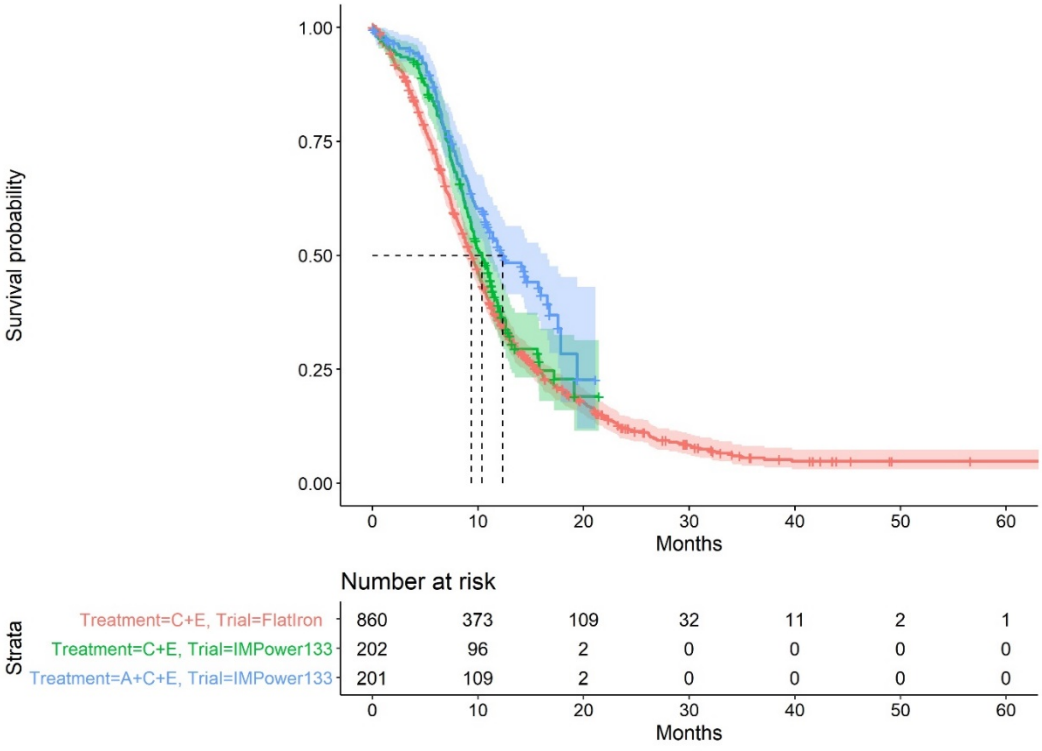


Table 23 compares the modelled OS from standard parametric extrapolation approaches in the chemotherapy arm against the real-world data [redacted], at different time points. This shows the Weibull,

Gompertz and generalised gamma – which are the best fit according to AIC and BIC criteria for the reported data - are all too conservative in their long-term chemotherapy survival estimates to be considered clinically plausible beyond 2-years. Meaning, the estimation of data not yet reported in IMpower133 is poor with the Weibull, Gompertz and generalised gamma extrapolations. This is due to an underestimation of the long-term survival of ES-SCLC patients with ECOG 0-1, treated with platinum-etoposide chemotherapy – i.e. the current standard of care. Conversely, the exponential and log-normal curves were considered too optimistic in their long-term survival estimates. The next best fit according to AIC and BIC criteria was the log-logistic extrapolation, which from a visual fit gave the closest estimate of long-term survival to the real-world data, although this was on the optimistic side.

In addition to the log-logistic extrapolation being the best fit for OS estimates of the chemotherapy arm, it also provides the best fit for the expected atezolizumab benefit long-term (Table 24) providing both a good statistic fit and the best fit to estimates based on clinical opinion.

The selection of different parametric distributions for the chemotherapy and atezolizumab arms may be justifiable given the different mechanisms of action of the two drugs and potential for long-term survival with atezolizumab as an immunotherapy, however, as the Flatiron Health data shows some plateau even with chemotherapy the same functional form was decided to be used for both. This is also consistent with existing NICE DSU guidance.

Table 23: Parametric extrapolations of the proportion of patients alive (OS) following carboplatin-etoposide treatment, using only IMpower133 data to inform the extrapolation

Time (months)	Parametric extrapolations						Real-world data of chemotherapy survival [redacted]
	Weibull	Gompertz	Generalised gamma	Log-logistic	Exponential	Log-normal	
12	42%	44%	42%	42%	43%	44%	33%
24	5%	1%	3%	14%	19%	19%	7%
36	0%	0%	0%	6%	8%	10%	2%
48	0%	0%	0%	3%	4%	6%	0.5%
60	0%	0%	0%	2%	2%	3%	0.1%

*Appendix K

In the model base case, the long-term survival of the atezolizumab arm was estimated by extrapolating the IMpower133 trial benefit until 5 years after treatment initiation. At which time the treatment effect of the atezolizumab combination over chemotherapy is assumed to

stop, and the conditional survival probability is set to equal the chemotherapy arm.

[redacted], plus it aligned with previous Committee decisions on when immuno-oncology treatment effect becomes more uncertain. Alternative assumptions for treatment effect duration are considered in the scenario analysis in Section B.3.8.3

Conclusion

In summary, because the IMpower133 trial is not yet fully mature and available real-world data shows a change in the hazard function beyond the trial data follow-up period, the best-fitting parametric extrapolation approaches based on trial data alone are not fully informative, here resulting in an overly conservative estimation of long-term survival on chemotherapy from just the AIC and BIC criteria. The almost complete mortality at 30 months for the Weibull, Gompertz and generalised gamma are all too conservative and not consistent with the [redacted], ES-SCLC real-world data, and published literature (27).

When extrapolating only the IMpower133 trial data, the log-logistic extrapolation approach – whilst rather optimistic - has the closest long-term survival estimates to that expected from UK-practising clinical experts for current standard of care, and most closely matches the Flatiron Health real-world data. In addition, the log-logistic extrapolation assumes a decreasing risk over time, which is a conservative assumption.

Table 24: Parametric extrapolations of the proportion of patients alive (OS) following atezolizumab plus carboplatin-etoposide treatment, using only IMpower133 data to inform the extrapolation

Time (months)	Parametric extrapolations						UK-practising clinical experts opinion, based on real-world data and IMpower133 benefit*
	Weibull	Gompertz	Generalised gamma	Log-logistic	Exponential	Log-normal	
12	54%	56%	55%	54%	54%	55%	[redacted]
24	15%	7%	13%	23%	29%	31%	[redacted]
36	3%	0%	1%	12%	16%	19%	[redacted]
48	0%	0%	0%	7%	9%	13%	[redacted]
60	0%	0%	0%	5%	5%	9%	[redacted]

*Appendix K

B.3.3.4 Use of real-world data to inform OS

An alternative approach to modelling just the IMpower133 trial data is presented here, where long-term OS estimates are informed by the IMpower133 trial and Flatiron Health datasets jointly or just the Flatiron Health data. However, since the NICE DSU TSD on the use of non-randomised data does not include any specific recommendations for incorporating real-world data into modelling OS alongside RCT data, a conservative approach has been taken here and the base case model only incorporated a parametric function for the IMpower133 OS data.

Since there is no NICE DSU guidance on the incorporation of real-world data for modelling time-to-event data within a cost-effectiveness model, the base case of our submission only extrapolates the IMpower133 trial data using fully parametric approaches. However, as detailed in Section B.3.3.3, although the log-logistic extrapolation of OS is the best fit for both the comparator and atezolizumab arms, it is somewhat optimistic for the standard of care long-term survival compared to the real-world data from the Flatiron Health database (Table 23).

To more fully consider the real-world data for long-term survival from current chemotherapy regimens, two approaches are presented below which incorporate the Flatiron Health data into the model extrapolation. These are presented as scenario analysis for evaluating cost-effectiveness (B.3.8.3).

The following methods were adapted from the published literature (87). NICE DSU 17 relates to the use of non-randomised data (i.e. observational), however this does not include any guidance on how to combine RCT data with observational data (88).

Since there is no NICE DSU guidance on the incorporation of observational data into a model, different methodological approaches have been applied here for comparison. The use of different methodologies to incorporate these data will allow assessment of (i) consistency of the results between these approaches, (ii) validation of the preferred parametric model extrapolating the IMpower133 OS data, and (iii) the magnitude of impact in terms of economic model results.

Two different approaches have been applied for incorporating the real-world data into the control arm of the model, with these two approaches being applied either at week 1 in the model or at a set time point (19 months; see below for rationale). The resulting 2 approaches are then compared with the fully parametric log-logistic extrapolation (for OS) approach using only the IMpower133 trial data (as outlined in Section B.3.3.3). In these two approaches, the conditional survival probabilities for the chemotherapy arm of the model are

either replaced entirely with Flatiron Health data or informed by projections based upon both the Flatiron Health and the IMpower133 chemotherapy arm data. These survival analysis approaches use the two most robust data sources to estimate long-term survival for carboplatin-etoposide, with both methods suggested in a recent publication on the use of external datasets to inform survival prediction (87).

To maintain the randomised controlled data from the IMpower133 study for as long as it's considered robust, the preferred approach for this scenario analysis was to use only data from the IMpower133 trial until 20% of patients remain at risk in the study (here 19 months). This time point was chosen as a compromise between not disregarding randomised controlled data, until the censoring at the end of the follow-up. Maximum follow-up for the IMpower133 study is 21 months with the current data cut.

Approach 1: incorporates data from Flatiron Health real-world database pooled with IMpower133 trial data, to inform long-term survival in the chemotherapy arm

In the preferred scenario analysis approach, pooled patient-level data for both sources was used to predict the form of long-term survival with all 6 standard parametric models assessed using the pooled data and a covariate included for trial (i.e. assuming a common shape).

Based upon inspection of the log-cumulative hazard plot and Q-Q plot (Figure 12) the assumption of proportional hazards was not deemed to hold, however, the assumption required for a constant shape for an AFT model (e.g. log-normal, log-logistic, Gompertz) could be reasonably assumed, due to the QQ plot being approximately 45 degrees. Statistical fit criteria showed the log-logistic and generalised gamma models to have the best statistical fit for the incorporated data. The generalised gamma model was selected as this had the best within-trial fit and is also more clinically plausible given the reducing hazard over time. The AIC and BIC values are reported in Table 25.

Figure 12: QQ plot comparing Flatiron Health data and IMpower133

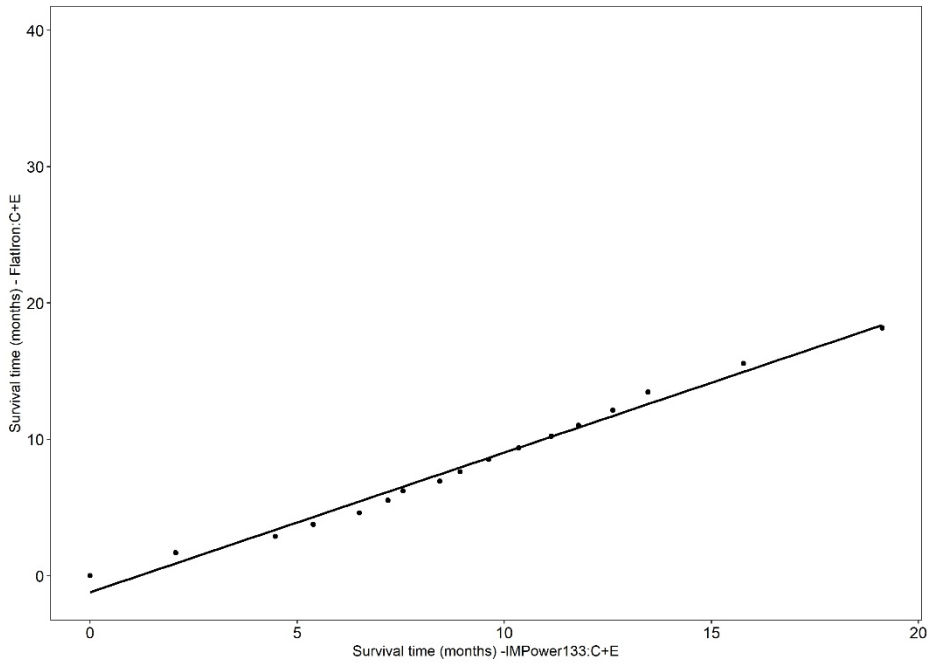


Table 25: AIC and BIC values for pooled Flatiron Health and IMpower133 data extrapolations for the chemotherapy arm

Method	AIC	BIC
Exponential	6096.742	6106.678
Weibull	6012.488	6027.391
Gompertz	6085.448	6100.351
Log-logistic	5960.39	5975.294
Log-normal	6037.419	6052.323
Generalised gamma	**5983.466**	**6003.338**

AIC: Akaike information criteria; BIC: Bayesian information criteria

Approach 2: incorporate data from only the Flatiron Health database to inform long-term survival for the chemotherapy arm

The same approach is used when fitting the standard parametric curves for the extrapolation of OS to the Flatiron dataset only (Table 26). Based upon the AIC / BIC the log-logistic curve is used in this scenario.

Table 26: The parametric curve fits AIC and BIC for Flatiron Health data alone

Distribution	AIC	BIC
Exponential	5109.62	5114.38
Weibull	5054.07	5063.58
Log normal	5051.97	5061.49
Generalised gamma	5022.52	5036.79

Log-logistic	**5006.45**	**5015.96**
Gompertz	5105.70	5115.21

AIC: Akaike information criteria; BIC: Bayesian information criteria

Comparison of chemotherapy survival estimates

Similar long-term survival estimates were reported for the chemotherapy arm via these three approaches: extrapolation of IMpower133 data only; combining Flatiron Health and IMpower133 data; and replacing the IMpower133 trial arm with Flatiron Health data, (Appendix J). This demonstrates the robustness of the projections to the data source used, and validates the choice of the log-logistic fully parametric approach for the IMpower133 data in the control arm.

Estimating OS for the atezolizumab arm

[redacted]. [redacted] and the best visual fit was achieved with a log-logistic parametric extrapolation of the IMpower133 data (for both the atezolizumab and chemotherapy arms), with incorporation of the merged IMpower133 and real-world data at 19 months for chemotherapy, followed with a generalised gamma extrapolation.

The selected OS curves do not cross the TTOT curves (see Section B.3.3.5) and do not cross the PFS curves when there are still 1% of patients alive. When 0.01% of patients remain alive the selected curves do cross, at this time the model limits PFS to be the same as OS.

Figure 13 shows the final model predictions for OS and Figure 14 compares the cycle mortality probability to that of the general population demonstrating that these curves do not cross.

Figure 13: OS in the model base case, comparing IMpower133 study KM, Flatiron Health data and the best fit parametric extrapolations

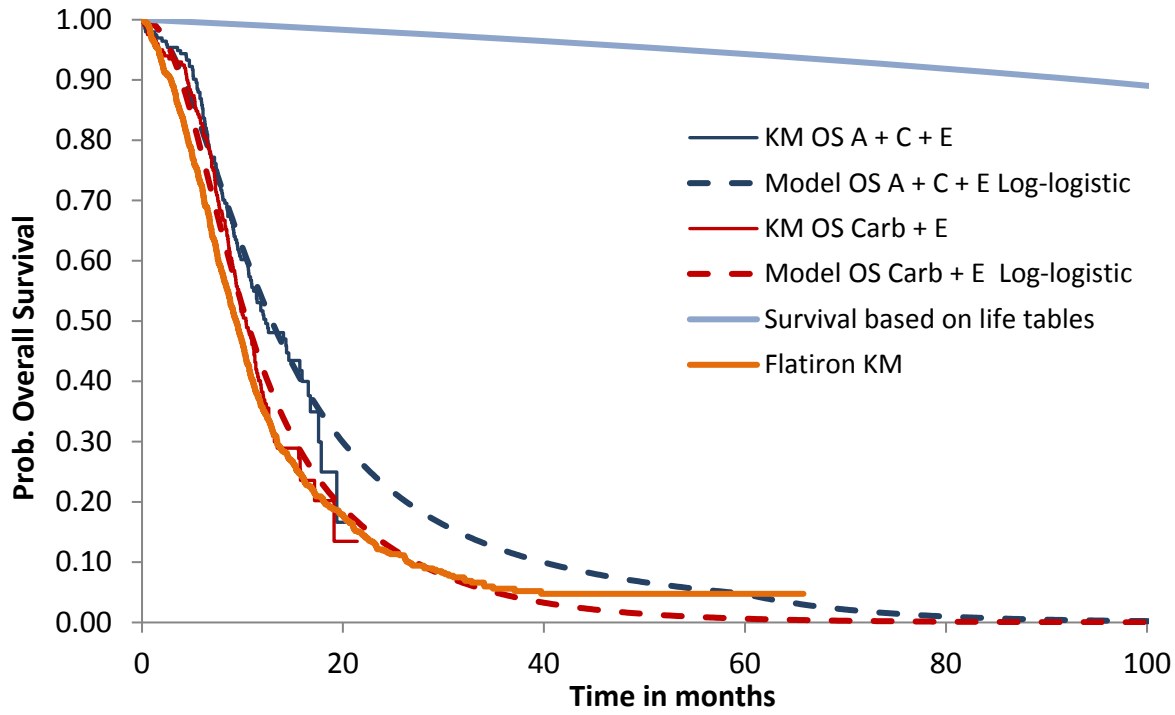
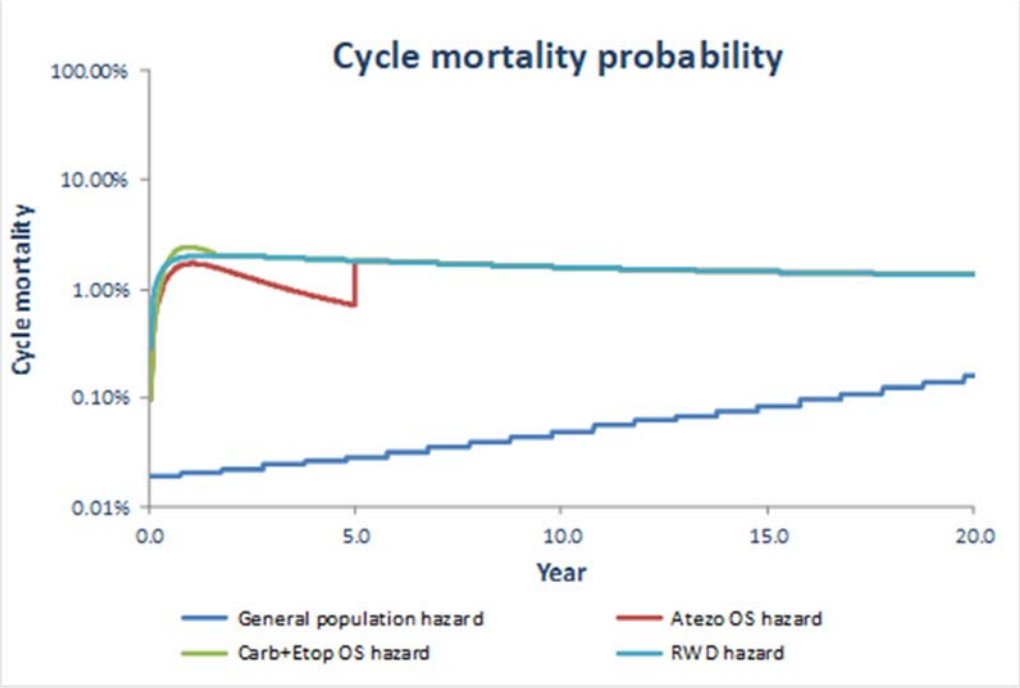


Figure 14: Cycle mortality probability in the model base case compared to the general population



B.3.3.5 Time-to-off-treatment extrapolation

The model incorporates time-to-off-treatment (TTOT) directly from the IMpower133 study as a measure of treatment duration, this TTOT is then extrapolated to estimate the missing data. This approach is considered the most plausible and transparent since it directly applies the trial data. TTOT is calculated as the difference between the times whene the patient is receiving the last dose and when the patient is receiving the first dose. In both arms of the pivotal trial, no extrapolation is needed for either carboplatin or etoposide treatments, since the time to treatment discontinuation has been observed for the entire cohort during the 12-month follow up period (3). For atezolizumab, at the time of the IMpower133 data cut, only 11.7% of patients were still receiving treatment at 12 months.

Goodness of fit of the parametric functions

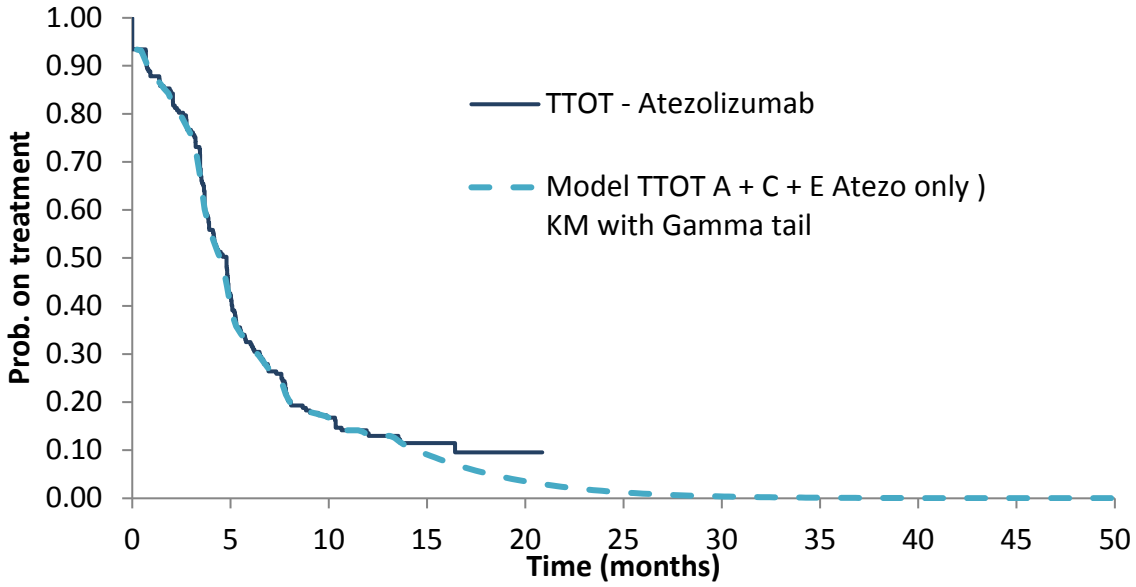
Since TTOT is only modelled for atezolizumab treatment, no proportional hazards assumption is required. The AIC and BIC values for the common parametric methods on the TTOT observations for atezolizumab, show the generalised gamma approach is the optimal statistical fit (Table 27). Since the initial portion of a fully parametric extrapolation is not an optimal fit – likely due to the effect of study visits – a KM curve is applied for the first 14 months, allowed by an extrapolated tail based on Gamma fitting then onwards (Figure 15) (89).

Table 27: AIC and BIC for TTOT for atezolizumab from IMpower133

Parametric distribution	AIC	BIC	Visual fit to KM	Clinical plausibility	Ranking
Generalised gamma	701.5	711.4	Best fit overall but poor fit to initially data	Plausibility increased by KM with generalised gamma tail	1
Weibull	717.5	724.1	Poor fit	Low	2
Exponential	721.7	725.0	Poor fit	Low	3
Gompertz	723.7	730.3	Poor fit	Low	4
Log-logistic	762.1	768.7	Poor fit	Low	5
Log-normal	844.7	851.3	Poor fit	Low	6

AIC: Akaike information criteria; BIC: Bayesian information criteria; KM: Kaplan-Meier

Figure 15. Kaplan-Meier estimates of PFS and TTOT in IMpower133 (24 April 2018 data cut)



A: atezolizumab; C: carboplatin; E: etoposide; KM: Kaplan-Meier; PFS: progression-free survival; TTOT: time-to-off-treatment

No time-based treatment discontinuation rule was applied in this appraisal; this approach is in line with the IMpower133 study protocol which describes atezolizumab discontinuation in terms of treatment benefit (Section B.2.3.1). Moreover, since very few patients remain on atezolizumab monotherapy beyond 1 year in IMpower133, a time-based treatment discontinuation rule would not substantially impact the cost-effectiveness calculations (Table 28).

Table 28: Proportion of patients still receiving treatment, based on KM and Gamma tail extrapolation

Time (months)	Atezolizumab	Carboplatin + etoposide
1	89%	94%
12	14%	0%
24	2%	0%
36	0%	0%

B.3.3.6 Population subgroups

As outlined in Section B.1.1, no ES-SCLC population subgroups are considered within this appraisal. This is in agreement with UK-practising clinical expert opinion and the final scope for this appraisal (1).

B.3.3.7 Adverse events

AEs included in the model were either treatment-related Grade 3–5 AEs or serious AEs, with an occurrence of more than 2% in either arm. The frequencies of AEs were obtained from the IMpower133 trial for the first patients randomised (primary population) who had received at least one dose of trial drug (Table 29). The rates applied in the model are calculated based on the total number of patient weeks at risk, which in turn is based on the median reported follow up of 13.9 months then multiplied by the safety population in each arm (n = 197 for each treatment arm).

Table 29: AEs included in the model: Grade ≥3 treatment related AEs, with incidence ≥2% in either arm of IMpower133 study

AE	Atezolizumab plus carboplatin-etoposide			Carboplatin-etoposide		
	Number of patients with AE (N)	**Occurrence of the AE**	**Probability of event (weekly)**	**Number of patients with AE (N)**	**Occurrence of the AE**	**Probability of event (weekly)**
Anaemia	28	31	0.0026	24	26	0.0022
Diarrhoea	5	5	0.0004	1	2	0.0002
Febrile neutropenia	6	6	0.0005	12	13	0.0011
Infusion-related reaction	4	5	0.0004	3	3	0.0003
Leukopenioa	10	15	0.0013	8	11	0.0009
Neutropenia	46	72	0.0060	48	69	0.0058
Neutrophil count decreased	28	50	0.0042	33	56	0.0047
Pancytopenia	1	1	0.0001	4	4	0.0003
Platelet count decreased	7	11	0.0009	8	11	0.0009
Pneumonia	4	4	0.0003	1	1	0.0001
Thrombocytopenia	20	22	0.0018	15	18	0.0015
Vomiting	2	3	0.0003	3	3	0.0003
White blood cell count decreased	6	8	0.0007	9	12	0.0010

AE: adverse event.

B.3.4 Measurement and valuation of health effects

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

During the IMpower133 study a total of 403 patients were randomised to the two treatment arms. The study protocol stipulated all patients should complete the Euro quality of life 5 dimensions 5-level version (EQ-5D-5L) questionnaires on the electronic Patient Reported Outcomes (ePRO) tablet at each scheduled study visit, prior to administration of study drug and prior to any other study assessment(s). During the trial's survival follow-up, the EQ-5D-5L questionnaire was completed at 3 and 6 months following radiographic disease progression per RECIST v1.1.

In total 96.8% of the patients completed the EQ-5D-5L at least once. The EQ-5D-5L index scores were calculated using tariffs from the UK. In total 3,199 utility index scores were calculated for the 390 patients within the IMpower133 trial who completed one or more EQ-5D questionnaires.

This submission applies utility values based on UK utility tariffs and on converting the EQ-5D-5L into EQ-5D-3L values using the crosswalk algorithm (90, 91).

Utility was incorporated into the model using the same time to death approach as has been accepted during previous NICE appraisals of lung cancer treatments, this was validated [redacted]. HRQoL data is incorporated directly from the IMpower133 trial, for proximity to death and on or off treatment (Table 30).

Table 30: Utilities applied in the model base case, reported from the IMpower133 study

Proximity to death	On treatment	Off treatment
≤ 5 weeks before death	[redacted]	[redacted]
> 5 & ≤ 15 weeks before death	[redacted]	[redacted]
> 15 & ≤ 30 weeks before death	[redacted]	[redacted]
> 30 weeks before death	[redacted]	[redacted]

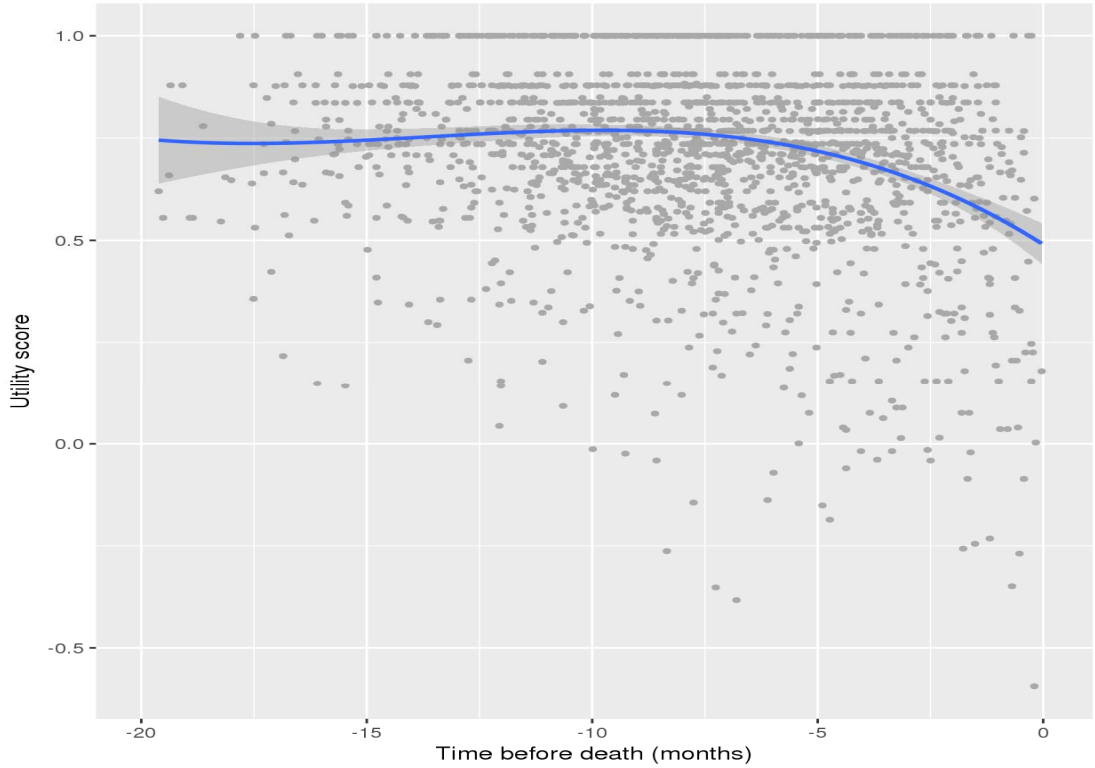
This approach was based on patients' 'proximity to death' rather than utility estimates based on whether patients had remained progression free. A scatter plot of utility by proximity to death was used, using a non-parametric lowess smoother which declines as time approaches death (set as zero) (Figure 16). A visual assessment of the plot was used to select proximity to death categories. Categories too close to death were avoided as there are very few observations available to estimate a robust utility estimate. Four 'proximity to

death' sub-states were used to capture patient HRQoL as a proxy of time until death and were categorised by visual assessment.

The 'proximity to death' sub states were further stratified according to whether patients were on or off treatment. A mixed linear model was fitted for each of the four 'proximity to death' groups, adjusting for baseline EQ-5D values. The on/off treatment status was an effect modifier in the regression, e.g. a factor or covariate. The estimates were computed in a Least-Square means sense (SAS 9.4, Cary, NC). Each category included patient records regardless of deaths being observed or censored after reporting their EQ-5D scores. UK preference based scores were used for patient data from the trial and the time trade-off (TTO) technique was used to develop the UK scoring functions.

At time of clinical data cut-off for IMpower133, [redacted] of patients were still alive, those patients provided almost ten thousand utility scores to date.

Figure 16. Proximity to death utility plot



B.3.4.2 Mapping

According to the IMpower133 study protocol, patients were required to complete the EQ-5D-5L questionnaire at each scheduled study visit, prior to the administration of study drug and prior to any other study assessments. In line with the NICE reference case, the utility results

from the EQ-5D-5L questionnaire were mapped to the EQ-5D-3L using the crosswalk algorithm and UK tariffs were applied (90, 91).

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

A SLR was conducted to identify HRQoL evidence in first-line ES-SCLC patients. Detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies are provided in Appendix H.

B.3.4.4 Summary of identified studies and results

Overall, a total of six publications were identified which met the eligibility criteria of the review and reported relevant health state utility values (HSUV) data (full publications, n=3; conference abstracts, n=3) (92-97). Countries from which the utility data were derived were restricted to Europe (France and the UK) and North America (Canada and the US). Only two studies reported utilities specifically for patients with ES-SCLC, one of which considered ES-SCLC as a sub-group of the overall cohort. Patient populations considered across the remaining studies included mixed LS- and ES-SCLC and advanced/metastatic lung cancer. This limits the direct applicability of these publications to the decision problem for this appraisal.

With regard to the relevance of the identified utilities for HTA purposes, none of the studies fully met the requirements of the NICE reference case; that is, utilities derived directly from patients using the preferred preference-based EQ-5D instrument, and health states valued using UK societal preferences elicited using the direct time trade-off (TTO) method. Therefore, alternative scenarios using utilities from the published literature were not considered.

Furthermore, no previous NICE TA have been conducted in first-line ES-SCLC patients, so utilities available from the appraisal of topotecan are not considered to be applicable. However, these are expected to be in line with those for progressed patients in IMpower133, [redacted] in the IMpower133 analysis, [redacted] baseline used in TA184 for relapsed patients for B.3.4.6.

B.3.4.5 Adverse reactions

Two alternative approaches can be taken regarding the inclusion of the impact of AEs on HRQoL:

1. Assume any AE disutility has already been incorporated into the base case health state utilities through the trial derived EQ-5D utilities, and incorporating an additional disutility could be considered double counting;

2. Assume the averaged trial-derived utilities underestimate disutility's associated with AEs which occur in a proportion of patients, and therefore an additional disutility must be applied for completeness.

Consistent with previous NICE lung cancer appraisals, the base case analysis takes the former assumption and does not include any additional disutility for AEs (78, 79, 81).

B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

Table 31 reports the utility values applied within the model submitted with this appraisal dossier.

Table 31. Utility values reported within the IMpower133 trial and analysed according to both proximity to death and on or off treatment

State	Utility value: mean	Reference in submission	Justification
≤ 5 weeks before death; on treatment	[redacted]	B.3.4.1	Derived from analysis of the EQ-5D data collected during IMpower133 study. Methodology as per NICE reference case
≤ 5 weeks before death; off treatment	[redacted]		
> 5 & ≤ 15 weeks before death; on treatment	[redacted]		
> 5 & ≤ 15 weeks before death; off treatment	[redacted]		
> 15 & ≤ 30 weeks before death; on treatment	[redacted]		
> 15 & ≤ 30 weeks before death; off treatment	[redacted]		
> 30 weeks before death; on treatment	[redacted]		
> 30 weeks before death; off treatment	[redacted]		

The utilities in the model were age adjusted in the base case, the impact of this was considered in a scenario analysis (B.3.8.3).

B.3.4.7 Consistency of literature utility values with values derived from the IMpower133 study

Since atezolizumab is the first available treatment for first-line ES-SCLC patients, no relevant utility values are reported in the literature to make a comparison here.

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

An SLR was conducted to identify studies presenting novel cost and resource use data associated with ES-SCLC for previously first-line patients, relevant to the economic model presented herein. Detailed descriptions of the search strategy, search terms and extraction methods, as well as details of the included studies, are provided in Appendix I.

B.3.5.1 Summary of identified studies and results

A total of 32 publications were considered to be eligible for inclusion from the costs and resource use SLR: 28 full publications and 4 abstracts. The reported cost studies from the literature are either not considered to be relevant to the decision problem or are not considered to reflect current clinical practice. Therefore, NHS resource use has been calculated from the IMpower133 study and from UK-practising clinical expert opinion (Appendix K).

To best reflect the likely impact on the NHS, the base case model includes the actual dosing from IMpower133 study and vial sharing assumptions (i.e., no wastage) for the administration of chemotherapy drugs in the model. Atezolizumab is given at a fixed dose. The impact of these assumptions are considered in scenario analyses in Section B.3.8. Relative dose intensity has been applied according to the IMpower133 study (Table 34) to account for missed doses.

Drug acquisition costs for the treatments included in this submission and model are summarised in Table 32. Since carboplatin, etoposide and cisplatin are all available to the NHS as generic medicines, prices are taken from eMIT, which reports the average price paid by the NHS for a generic medicine (14). The only other medicine price included in this submission was for atezolizumab which is presented inclusive of the confidential PAS discount (see Table 2 for further details).

The dosing schedule from the IMpower133 study protocol, is described for each of these drugs in Table 2. The average weight (75.5 kg) and CG.84 m^2 using the Dubois formula) from the IMpower133 study were applied to estimate the average cost per dose per patient for the treatments that are dosed according to weight or BSA. The drug costs of the combination therapies were assumed to be equal to the sum of individual drug's costs included in a combination therapy, e.g., the costs for the combination of carboplatin-

etoposide therapy per administration is the sum of drug costs for carboplatin per administration plus the drug costs for etoposide per administration). Since TTOT data were not available for cisplatin-etoposide, the same discontinuation rate is assumed as for carboplatin-etoposide.

Table 32: Drug acquisition costs

Drug	Vial/pack concentration and volume	Cost per vial/pack	Standard deviation	Source
Atezolizumab with PAS	20 mL/1,200 mg	[redacted]	N/A	BNF list price
Carboplatin	5 mL/50 mg	£3.18	£0.43	eMIT (14)
Carboplatin	60 mL/600 mg	£28.24	£19.64	eMIT (14)
Etoposide	5 mL/100 mg	£2.30	£1.14	eMIT (14)
Etoposide	25 mL/500 mg	£9.65	£6.37	eMIT (14)
Cisplatin	10 mL/10 mg	£1.84	£1.44	eMIT (14)
Cisplatin	100 mL/100 mg	£10.13	£8.93	eMIT (14)

eMIT: 12-month period until end of June 2017

BNF: British National Formulary; eMIT: electronic marketing information tool; N/A: not applicable

Table 33: Dosing schedule and dose per administration

Drug	Dosing per administration	Frequency of administration	Source
Atezolizumab	1,200 mg	Q3W	Appendix C
Carboplatin	5 mg/mL/min (AUC)*	Q3W	Appendix C
Etoposide	100 mg/m^2	Q3W	Appendix C
Cisplatin	80 mg/m^2	Q3W	Appendix C

*Dose is calculated based on the Calvert Formula: Target AUC * {[Sex * ((140 - Age) / (Serum Creat)) * (Weight / 72)] + 25} --> Male = 1 / Female = 0.85.

AUC: Area under the curve; Q3W: once every 3 weeks; SmPC: summary of product characteristics

Table 34: Relative dose intensity reported in the Impower133 study

Treatments	Regimen	RDI	SE
Atezolizumab	Atezolizumab plus carboplatin-etoposide	92.1%	0.7%
Carboplatin	Carboplatin-etoposide with or without atezolizumab	91.5%	0.6%
Etoposide	Etoposide with or without atezolizumab	88.8%	0.6%
Cisplatin	Cisplatin-etoposide	91.5%	0.6%

RDI: Relative dose intensity; SE: standard error.

Table 35: Drug cost per treatment cycle for interventions used in the cost-effectiveness model

Comparator	Method and frequency of administration	Drug cost per combination partner per cycle*	Total drug cost per cycle before discounting*
Atezolizumab** plus carboplatin-etoposide	IV, Q3W	Atezolizumab: [redacted] Carboplatin: £27.70 Etoposide: £10.05	£1,223
Carboplatin-etoposide	IV, Q3W	Carboplatin: £27.70 Etoposide: £10.05	£38
Cisplatin-etoposide	IV, Q3W	Cisplatin: £17.21 Etoposide: £27.70	£27

IV: intravenous; Q3W: once every 3 weeks

*Assuming vial sharing, actual dose and proportion of missed doses from IMpower133 study. **With PAS.

Subsequent therapies

Subsequent treatment costs have been incorporated into the model according to the IMpower133 study as this was deemed to balance the efficacy and cost estimates from the study appropriately. This incorporated limited use of subsequent immuno-oncology treatments, and subsequent treatment rates were largely balanced between the two study arms.

[redacted] and did not expect to prescribe immune-oncology treatments at second line. For comparison, a scenario analysis considering this expert opinion is presented in section B.3.8.3.

Drug administration costs

The costs for drug administration incorporated into the model is reported in Table 36. The administration cost for the first cycle of treatment for any of the three regimens is costed as a complex chemotherapy day case procedure including prolonged infusion due to being the first attendance – SB13Z of the NHS reference costs (98). For all three regimens, the subsequent drug administration is costed for the comparable procedure, but at standard infusion duration – SB15Z of the NHS reference costs (98). Since the infusion of atezolizumab alone requires less time this is costed as a simple infusion SB12Z of the NHS reference cost (98). [redacted]

[redacted]

Table 36: Administration costs incorporated into the CEM

Drug	Type of administration	NHS reference code	Cost per administration	Source
First administration of treatment cycle for all combination regiments	Daycase and Reg Day/Night: Deliver more Complex Parenteral Chemotherapy at First Attendance	SB13Z	£309.22	NHS reference cost 2017/18 (98)
Subsequent elements of etoposide treatment, i.e. Day 2 and 3 of each treatment cycle	Deliver complex chemotherapy, day case, standard infusion rate for subsequent treatment	SB15Z	£312.34	NHS reference cost 2017/18 (98)
Atezolizumab monotherapy administration	Deliver simple parenteral chemotherapy at first attendance as outpatient	SB12Z	£173.99	NHS reference cost 2017/18 (98)
First administration of cisplatin-etoposide	Daycase and Reg Day/Night: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	£374.52	NHS reference cost 2017/18 (98)

NHS: National Health Service

B.3.5.2 Health-state unit costs and resource use

NHS resource use data was not available for first-line ES-SCLC, due to there being no previous NICE appraisals for this condition. Moreover, as stated in Section B.3.5.1, no relevant published costs studies were identified of relevance to the decision problem and reflecting current NHS practice.

To address this data gap, [redacted]

[redacted]

Unit costs were derived from NHS reference costs (98) and PSSRU published costs (99), Table 38(100)(100)(102). Table 37 details the resource use for different treatment options and disease stages, including: on carboplatin-etoposide treatment; on atezolizumab plus

carboplatin-etoposide treatment; on surveillance only; on atezolizumab monotherapy only. This was surveyed from clinicians as the expected average resource use of a patient in this stage of treatment and disease, therefore the average duration of treatment has already been considered here to align with the modelled time in different treatment stages. As a result, each cost is applied within the model once, as the patient moves into this stage. Table 38 presents the unit cost for each resource use element.

Table 37: Resource use for ES-SCLC treatment and disease stages, per patient

Resource	Receiving carboplatin-etoposide treatment: first 4 cycles		Receiving atezolizumab plus carboplatin-etoposide treatment: first 4 cycles		Receiving surveillance only*: e.g. after 4 chemo cycles		Receiving atezolizumab monotherapy: after first 4 chemo cycles	
	Number of appointments (mean±SD)	% of patients requiring these appointments (mean±SD)	Number of appointments (mean±SD)	% of patients requiring these appointments (mean±SD)	Number of appointments (mean±SD)	% of patients requiring these appointments (mean±SD)	Number of appointments (mean±SD)	% of patients requiring these appointments (mean±SD)
Estimated time frame	4 cycles		4 cycles		3-4 months		4-5 months	
Outpatient visit	5.0 ± 1.5	100 ± 0	5.0 ± 1.5	100 ± 0	3.6 ± 2.1	86 ± 19	5.0 ± 2.1	100 ± 0
GP visit – surgery	1.9 ± 1.3	71 ± 39	1.9 ± 1.3	71 ± 39	2.3 ± 1.4	69 ± 38	1.5 ± 1.3	71 ± 39
GP visit – home	0.6 ± 1.5	68 ± 43	0.7 ± 0.8	68 ± 43	1.6 ± 1.3	66 ± 40	1.2 ± 1.3	68 ± 43
Cancer nurse visit	1.6 ± 1.4	67 ± 37	1.6 ± 1.4	75 ± 32	2.1 ± 1.3	54 ± 34	2.0 ± 1.5	61 ± 40
Community nurse visit	1.6 ± 1.5	64 ± 37	1.7 ± 1.5	68 ± 31	1.5 ± 1.4	47 ± 39	1.1 ± 1.1	61 ± 40
ECG	0.3 ± 0.5	64 ± 48	0.5 ± 0.5	66 ± 45	0.1 ± 0.4	50 ± 50	0.2 ± 0.4	51 ± 48
Chest X-ray	2.0 ± 1.9	78 ± 32	2.0 ± 1.9	75 ± 30	2.4 ± 1.3	74 ± 21	2.8 ± 1.7	71 ± 32
CT scan	1.6 ± 0.5	96 ± 9	1.6 ± 0.5	89 ± 20	1.6 ± 1.0	69 ± 28	1.9 ± 1.1	86 ± 20
MRI scan	0.4 ± 0.5	48 ± 45	0.4 ± 0.5	61 ± 48	0.3 ± 0.5	49 ± 48	0.4 ± 0.8	51 ± 48
Blood tests	4.0 ± 0	100 ± 0	4.4 ± 0	35 ± 0	6 ± 0	80 ± 0	2.2 ± 3.1	100 ± 0

CG: clinical guidance; CT: computerised tomography; ECG: electrocardiogram; GP: general practitioner; SD: standard deviation

*Monitored for disease progression but not receiving active treatment, i.e., after chemotherapy or atezolizumab treatment .

Table 38: Unit costs for both PFS and PD health states

Resource	Unit cost	Unit	Source
Outpatient follow-up visit	£140.87	per visit	NHS Reference Costs 2017-2018, Outpatient attendance data, Consultant Led, Service code 800, Clinical Oncology (98)
GP surgery visit	£37.40	per visit	PSSRU 2018, p.134: Cost per patient contact lasting 9.22 minutes, including direct care staff costs (including qualifications) (99)
GP home visit	£93.28	per visit	PSSRU 2016, p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel - inflated to 2017/18 using the PSSRU HCHS index (99)
Cancer nurse visit	£42.02	per visit	Assumed to be 66.7% of community nurse cost
Community nurse visit	£63.00	per visit	PSSRU 2018, p.130: Cost per hour Band 8a (99)
ECG	£250.10	per visit	NHS Reference Costs 2017–2018, Complex ECG, HRG code EY50Z (98)
Chest X-ray	£106.88	per case	NHS Reference Costs 2017-2018, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)
CT scan	£106.88	per case	NHS Reference Costs 2017-2018, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast) (98)
MRI scan	£202.64	per scan	NHS Reference Costs 2017–2018, Diagnostic Imaging, Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast, Outpatient, RD05Z (98)
Blood tests	£2.51	per test	NHS Reference Costs 2017–2018, Directly Accessed Pathology Services, Haematology, DAPS05 (98)

CT: computerised tomography; ECG: electrocardiogram; GP: general practitioner; HCHS: hospital & community health services; HRG: Healthcare Resource Group; MRI: magnetic resonance imaging; NHS: National Health Service; PSSRU: Personal Social Services Research Unit.

The expected cost for a typical patient in each of these stages of treatment is as follows: on carboplatin-etoposide treatment = £1191.97 expected to represent 4 cycles of treatment; on atezolizumab plus carboplatin-etoposide treatment = £1232.53 expected to represent 4 cycles of treatment; on surveillance only = £1216.40 expected to represent 3-4 months' treatment; on atezolizumab monotherapy only = £903.84 expected to represent 4-5 months' treatment.

The cost of PCI was also considered within the model and applied separately, with 90% of patients receiving PCI every 3 weeks for a maximum of 5 doses. A PCI frequency of 3 weeks was incorporated, since this was reported for the majority of the IMpower133 cohort (101). A specific cost for PCI is not available in the NHS reference costs, therefore

radiotherapy is costed in the model using the NHS reference costs for preparation and delivery of radiotherapy (codes SC47Z = £375.000 and SC22Z = £113.00, (98). The cost is applied for the PFS state only.

Cost of terminal care

A cost for terminal care is applied within the model. This is based on terminal care costs specific to SCLC (102). These data are limited given that they are not published recently, however inflating to 2018 PSSRU indices can put this into current costs (99). The average cost of palliative care reported was £3,495 in 1998 prices, which is here inflated using the PSSRU inflation index for Hospital and Community Health Services – giving £6,174.81 in 2018 prices (99).

B.3.5.3 Adverse reaction unit costs and resource use

Rates and severity of AEs are taken directly from the IMpower133 trial data. AEs may occur at any time during treatment exposure, therefore the associated AE costs are applied for the duration of time in which a patient is considered to be on treatment (Table 39). The AEs included were considered to be treatment related and were of Grade 3 to 5 or serious AEs, with an occurrence of 2% or more in either arm of the IMpower133 study (Table 15). The weekly AE rate is calculated from the number of AEs divided by the total time at risk in weeks. This time at risk is the sum of the follow-up exposure for each patient in the trial, the median follow-up of 13.9 months is applied. The NMA was not able to map safety events, so cisplatin-etoposide AE rates have been matched to those for carboplatin-etoposide. According to UK-practising clinical experts, this is likely to be an underestimate of the AEs for cisplatin.

The number of AEs included in the model base case differs from the AEs reported in the adverse reactions section (Section B.2.10). This is due to the economic model needing to calculate multiple occurrences of an AE per patient, to then calculate the probability of an AE occurring. In contrast, when reporting the clinical study, the convention is to count only once any AE that occurs in an individual, at the highest grade for this patient.

The costs associated with AE management are multiplied by the rate of AEs and summed to calculate total AE cost by treatment arm (Table 39). The safety analysis is based on 197 patients in the primary population per arm in IMpower133 who received any dose of study drug at the primary analysis time.

Grade 3-5 AEs and serious AEs have a treatment cost included in the model. Furthermore, AE data were only available for the treatment arms in IMpower133, so no comparison with cisplatin was possible via the NMA.

Table 39: Unit cost per AE used in the model

AE	Cost	Reference
Anaemia	£2,749	TA531 - inflated to 2016/17 using the PSSRU HCHS index (78)
Diarrhoea	£182	NHS reference costs, WF01B, Consultant Led, Non-Admitted Face-to-Face Attendance, First, Gastroenterology (98)
Febrile neutropenia	£7,097	NICE TA531 - inflated to 2016/17 using the PSSRU HCHS index (78)
Infusion-related reaction	£0	Clinical opinion
Leukopenia	£377	NICE TA531 - inflated to 2016/17 using the PSSRU HCHS index (78)
Neutropenia	£601	Brown 2013 (inflated to 2016-17 using PSSRU inflation indices) (103)
Neutrophil count decreased	£449	NICE TA428 (79)
Pancytopenia	£601	Assumed same as neutropenia
Platelet count decreased	£449	Assumed same as neutrophil count decreased
Pneumonia	£2,784	TA531 - inflated to 2016/17 using the PSSRU HCHS index (78)
Thrombocytopenia	£124	NICE TA484, NICE TA520, NICE TA525 (80-82)
Vomiting	£182	NHS reference costs, WF01B, Consultant Led, Non-Admitted Face-to-Face Attendance, First, Gastroenterology (98)
White blood cell count decreased	£449	NICE TA484, NICE TA520, NICE TA525 (80-82)

AE : adverse event.

Miscellaneous unit costs and resource use

No direct or indirect unit costs are included, other than those described in Sections B.3.5.1 – B.3.5.3.

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

B.3.6.1 Summary of base-case analysis inputs

The full list of variables applied in the model is reported in Table 40.

Table 40: Summary of variables applied in the model base case

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General model parameters			
Time horizon	20 years	Fixed	B.3.2
Discount rate - efficacy	3.5%	Fixed	
Discount rate - costs	3.5%	Fixed	
Population parameters			
Age	63.7 years	Fixed	B.2.3
Body weight	75.5 kg	Fixed	B.3.5.1
Height	168.24 cm	Fixed	CEM
Body surface area	1.84 m^2	Fixed	B.3.5
Utilities – base case – IMpower133			
≤ 5 weeks before death on treatment	0.65	N/A	B.3.4.1
> 5 & ≤ 15 weeks before death on treatment	0.73	N/A	
> 15 & ≤ 30 weeks before death on treatment	0.72	N/A	
> 30 weeks before death on treatment	0.73	N/A	
≤ 5 weeks before death off treatment	0.33	N/A	
> 5 & ≤ 15 weeks before death off treatment	0.53	N/A	
> 15 & ≤ 30 weeks before death off treatment	0.70	N/A	
> 30 weeks before death off treatment	0.75	N/A	
OS extrapolation approach			
Control and atezolizumab arms were both extrapolated using a fully parametric log-logistic approach based on IMpower133 trial data	Table 23 Table 24	N/A	B.3.3.3
Drug acquisition costs per pack (list price)			
Atezolizumab; 20mL/1,200mg	[redacted]	Fixed	B.3.5.1
Carboplatin; 5mL/50mg	£3.18	Fixed	

Carboplatin; 60mL/600mg	£28.24	Fixed	
Etoposide; 5mL/100mg	£2.30	Fixed	
Etoposide; 25mL/500mg	£9.65	Fixed	
Cisplatin; 10mL/10mg	£1.84	Fixed	
Cisplatin; 100mL/100mg	£10.13	Fixed	
Drug administration costs – per cycle			
Atezolizumab plus carboplatin-etoposide	[redacted]	95% CI of point estimate assumed (Normal distribution)	B.3.5.1
Carboplatin-etoposide	£37.80		
Cisplatin-etoposide	£28.30		
Drug administration costs			
Daycase and Reg Day/Night: Deliver more Complex Parenteral Chemotherapy at First Attendance - SB13Z: for first administration treatments	£309.22	N/A	B.3.5.1.2
Daycase and Reg Day/Night: Subsequent Elements of Chemotherapy Cycle - SB15Z: for subsequent elements of the cycle, ie etoposide on Day 2 and 3.	£312.34	N/A	
SB12Z; Deliver simple parenteral chemotherapy at first attendance as outpatient: for atezolizumab monotherapy.	£173.99	N/A	
Daycase and Reg Day/Night: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (SB14Z): for cisplatin-etoposide.	£374.52	N/A	
Resource use costs			
Typical resource use on carboplatin-etoposide treatment	£1191.97	95% CI of point estimate assumed (Normal distribution)	B.3.5.2
Typical resource use on atezolizumab plus carboplatin-etoposide treatment	£1232.53		
Typical resource use on surveillance only	£1216.40		

Typical resource use on atezolizumab monotherapy only	£903.84		
Terminal care cost			
Terminal care cost	£6,174.81	95% CI of point estimate assumed (Normal distribution)	B.3.5.2
Adverse event management costs			
Anaemia	£2,749	95% CI of point estimate assumed (Normal distribution)	B.3.5.3
Diarrhoea	£182		
Febrile neutropenia	£7,097		
Infusion-related reaction	£0		
Leukopenioa	£377		
Neutropenia	£601		
Neutrophil count decreased	£449		
Pancytopenia	£601		
Platelet count decreased	£449		
Pneumonia	£2,784		
Thrombocytopenia	£124		
Vomiting	£182		
White blood cell count decreased	£449		

CI: confidence interval; N/A: not applicable; OS: overall survival

B.3.6.2 Assumptions

The key assumptions applied in the model base case are summarised is in Table 41.

Table 41: Key assumptions used in the economic model base case

Area	Assumption	Justification
Time horizon	20 years	The average age of patients in the model is 64 years. The 20-year time horizon in the model allows >99% of deaths to have occurred in ES-SCLC. This is to fully capture the difference in costs and outcomes between the interventions being compared in this appraisal dossier. It is also consistent with previous NICE appraisals in this indication (78, 81, 104)
Subsequent therapies	Subsequent therapies are modelled here to reflect the IMpower133 trial	IMpower133 subsequent therapies are in the base case to balance efficacy and costs. [redacted]

		[redacted] therefore it is not expected to impact the ICER calculation
Comparators considered in the model	Carboplatin-etoposide is the relevant comparator treatment	See Section B.1.1, UK-practising clinical experts advise Roche that [redacted] more of first-line ES-SCLC patients are prescribed carboplatin-etoposide in the NHS (Appendix K). The remaining patients are likely to [redacted] this is related to being suspected of having borderline LS-SCLC – this is included as a secondary analysis for transparency. Moreover, atezolizumab is expected to only be licensed in combination with carboplatin-etoposide. Therefore, etoposide ineligible patients are considered to be outside the scope of this appraisal
IMpower133 clinical efficacy and safety applied in the model	IMpower133 study results were applied within the model to measure lifetime costs and benefits of treatment	The selected trial population is generalisable to the real-world population, with the only caveat that the trial population is restricted according to the inclusion and exclusion criteria (Section B.2.3.1). The IMpower133 study includes UK trial sites.
IMpower133 clinical efficacy and safety is representative of NHS practice	IMpower efficacy and safety results are considered to be generalisable to the NHS population	[redacted]
Extrapolation of TTOT, PFS and OS data	The best fit according to AIC/BIC criteria, visual fit to observed data and long-term clinical plausibility guides the choice of extrapolation method when the majority of the data are available. Clinical expert opinion is critical to validating all extrapolations assumptions, especially beyond the observed trial data.	Based on NICE DSU recommendation (86) and [redacted]
Long-term extrapolation for chemotherapy treatment	A fully parametric log-logistic extrapolation is applied to the IMpower133 trial data	A small but meaningful proportion of first-line ES-SCLC patients are expected to survive long-term in response to chemotherapy. The best fit extrapolation to include this is the log-

		logistic extrapolation approach, which also has a decreasing risk over time
Long-term survival extrapolation for atezolizumab treatment	A fully parametric log-logistic extrapolation is applied to the IMpower133 trial data	[redacted]. Also the log-log has a decreasing risk over time
Long-term survival restriction for atezolizumab treatment	Atezolizumab mortality rate can never be worse than the chemotherapy arm and cannot be better than age matched population mortality rate	Clinically implausible that atezolizumab arm will perform better than general population mortality or worse than standard of care – [redacted]
No time-based treatment stopping rule for atezolizumab	Atezolizumab monotherapy following combination induction treatment with carboplatin-etoposide treatment does not have a time-based treatment stopping rule applied	This is in line with the IMpower133 study design
Duration of treatment	IMpower133 study data is used to model the duration of treatment	To accurately reflect how atezolizumab plus carboplatin-etoposide will be used in the NHS, the treatment duration (TTOT) from the IMpower133 study have been applied in the model.
Duration of treatment benefit	The treatment benefit has been capped at 5 years after start of treatment	[redacted]
HRQoL	Based on EQ-5D data collected during the IMpower133 study. Proximity to death and on/off treatment approach used in the base-case analysis for utility	[redacted]
NHS resource use	NHS oncologists reported the expected average resource use for a ES-SCLC patient at different stages of disease progression and treatment. These are then applied as a one-off cost as the patient moves into that state.	[redacted]
Safety	Grade 3 to 5 treatment related AE experienced by ≥2% of patients in the IMpower133 study were included in the CEM.	The threshold of 2% for AE inclusion is conservative as an approach.

AE: adverse event; CEM: cost-effectiveness model; DSU: decision support unit; EQ-5D: EuroQol-5 dimensions; ES-SCLC: extensive-stage small cell lung cancer; HRQoL: health-related quality of life; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; NMA: network meta-analysis

B.3.7 Base-case results

Key information and limitations for economic results sections

- Cost-effectiveness results are only presented for the ITT population of IMpower133, this is in line with UK-practising clinical expert opinion regarding population subgroups for ES-SCLC patients (Appendix K)
- Since both carboplatin and etoposide are available generically to the NHS, eMIT average costs are incorporated to estimate the true cost to the NHS for these comparator treatments. Atezolizumab is presented both at list price and with the confidential PAS approved by the Department of Health during 2018
- For consistency with previous atezolizumab dossiers submitted to NICE, a treatment benefit cap has been implement here 5 years after diagnosis, although few ES-SCLC patients will still be alive so the impact on the ICER is negligable
- The IMpower133 utility values are applied within the model and dossier linked to time to death and on/off treatment, again this is consistent with previous atezolizumab dossiers submitted to NICE and [redacted]
- Atezolizumab plus carboplatin-etoposide for the treatment of first-line ES-SCLC patients meets the criteria for an end of life treatment, since the majority of these patients live for substantially less than 2 years following their diagnosis and atezolizumab is associated with a clinically meaningful and statistically significant extension to normal life expectancy. Therefore, atezolizumab plus carboplatin-etoposide for the treatment of first-line ES-SCLC patients represents a cost-effective use of NHS resources
- Extensive sensitivity and scenario analyses were conducted in the model to demonstrate the uncertainty around the parameters used, assess the plausibility of different scenarios and approaches, and help understand what key variables and assumptions potentially have a major impact on the cost-effectiveness results

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

Base-case results of the model are presented in Table 42 and Table 43, comparing atezolizumab plus carboplatin-etoposide versus carboplatin-etoposide for first-line ES-SCLC patients, with the atezolizumab PAS and at list price respectively. Including the PAS and considering the threshold for EOL therapies, atezolizumab plus carboplatin-etoposide represents a cost-effective use of NHS resources for the treatment of first-line ES-SCLC patients.

Table 42: Base-case results for first-line ES-SCLC patients including the PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab plus carboplatin-etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,175
Carboplatin-etoposide	[redacted]	1.15	0.76				

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 43: Base-case results for first-line ES-SCLC patients at list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab plus carboplatin-etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin-etoposide	[redacted]	1.15	0.76				

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted with 1,000 iterations to determine the uncertainty surrounding the base case ICERs (Table 44 and Table 45). All model variables that had an assigned distribution are presented in Table 41. Uncertainty was characterised by standard error. Atezolizumab acquisition costs were fixed, however since carboplatin and etoposide costs are derived from eMIT these have a reported variance (105).

Table 44: Base-case results for first-line ES-SCLC patients at PAS price, PSA approach

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Atezolizumab plus carboplatin-etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,893
Carboplatin-etoposide	[redacted]	1.16	0.77				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 45: Base-case results for first-line ES-SCLC patients at list price, PSA approach

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Atezolizumab plus carboplatin-etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin-etoposide	[redacted]	1.16	0.77				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

The incremental cost-effectiveness plane and the corresponding cost-effectiveness acceptability curves - with PAS and at list price - are shown in Figure 17, Figure 18, Figure 19, and Figure 20.

The range of uncertainty is consistent across the considered variables, and are all beneath the EOL cost-effectiveness threshold of up to £50,000/QALY.

The probabilistic base case ICER was £116,931/QALY [redacted] which is very comparable to the deterministic base case ICER (B.3.7).

Figure 17: Incremental cost and QALY base case results, with atezolizumab PAS

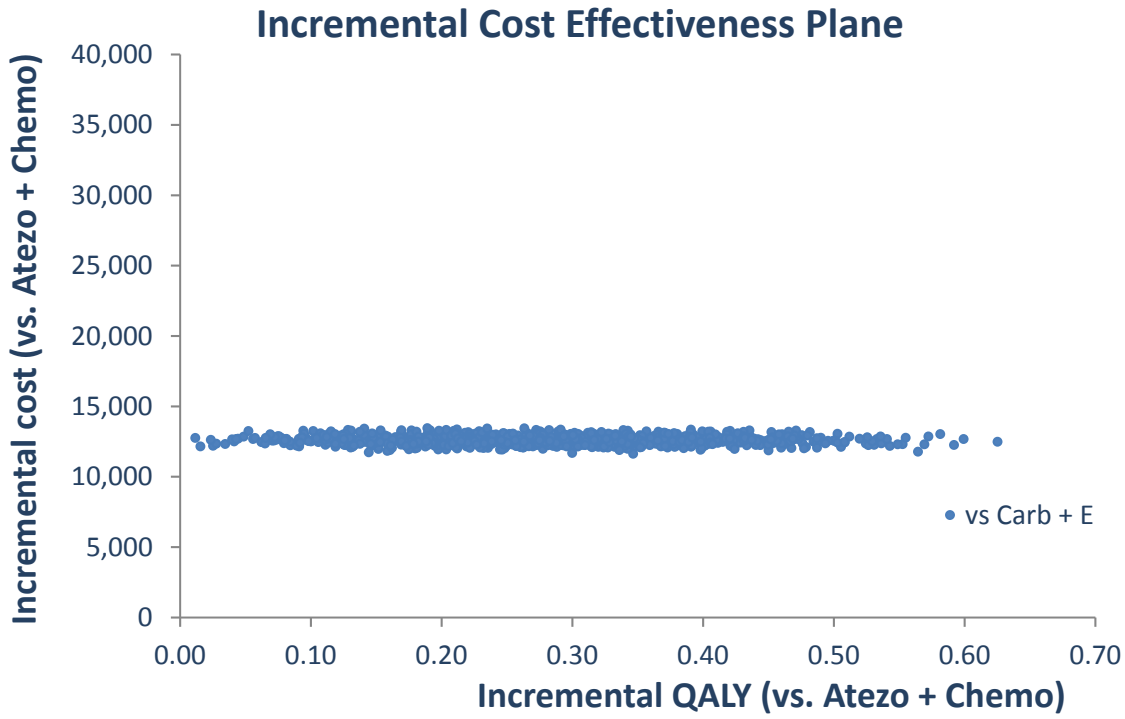


Figure 18: Cost-effectiveness acceptability curve, with atezolizumab PAS

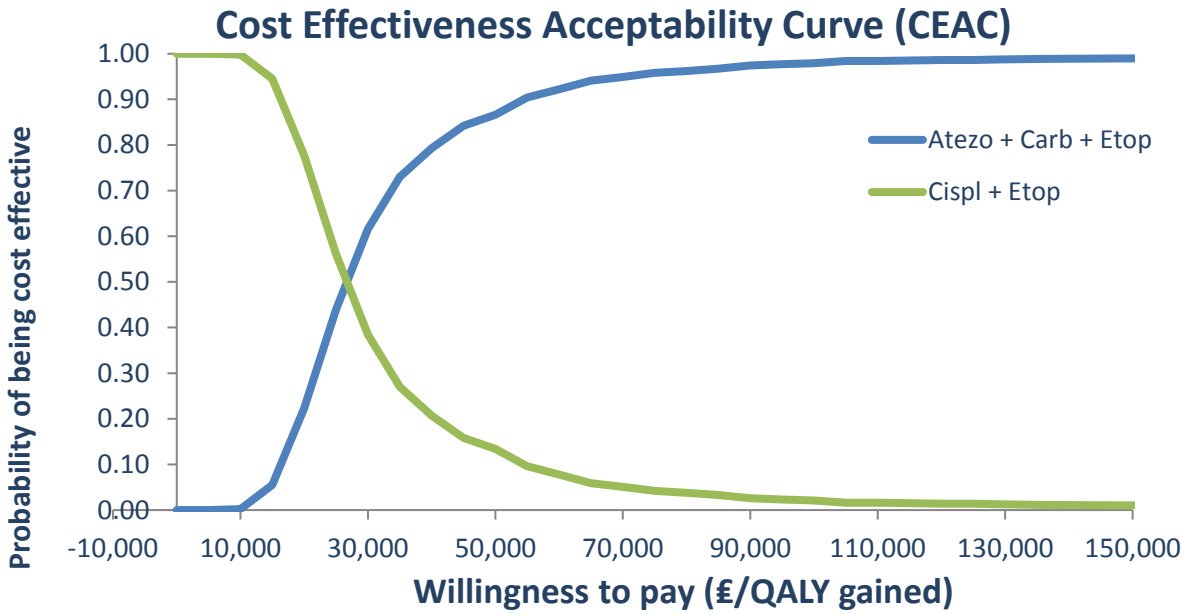


Figure 19: Incremental cost and QALY base case results, at atezolizumab list price

Figure 20: Cost-effectiveness acceptability curve, at atezolizumab list price

The results from the deterministic and the probabilistic sensitivity analyses are comparable in their result that atezolizumab plus carboplatin-etoposide is cost-effective to treat ES-SCLC when considering the EOL threshold.

B.3.8.2 Deterministic sensitivity analysis

A deterministic sensitivity analysis is presented in Table 46 and Table 47. The results of the deterministic sensitivity analysis are shown in the tornado diagrams in Figure 21 and Figure 22. The output variables have varied around the base case value, subject to the influence of each variable on the ICER (Table 40).

The minimal impact on the cost-effectiveness calculation demonstrates that the model and analysis are robust against variation in these parameters, both at list price and with the atezolizumab PAS. The most impactful inputs are the utility off treatment immediately before death and the discounting of benefits.

Table 46: Deterministic sensitivity analysis, with atezolizumab PAS

Parameter modified	Base case value	Lower value	Lower ICER	Upper value	Upper ICER	Justification
Discounted costs	3.50%	2%	£45,604	5%	£44,766	Assumption
Discounted benefits	3.50%	2%	£43,222	5%	£47,128	Assumption
Subsequent administration costs	£312.28	£312.28	£45,175	£312.40	£45,175	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on A+C+E	£1232.53	£1,105.03	£44,685	£1,387.64	£44,685	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on C+E	£1191.97	£1,064.28	£45,670	£1,333.11	£44,651	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on atezo monotherapy	£903.84	£755.74	£44,731	£1,059.29	£45,628	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on surveillance only	£1216.40	£1,022.90	£45,158	£1,409.56	£45,193	Base case is from IMpower133 study, sensitivity is from TAE opinion

≤ 5 weeks before death on treatment	0.65	0.61	£45,353	0.69	£45,007	IMpower133 study
> 5 & ≤ 15 weeks before death on treatment	0.73	0.70	£45,356	0.75	£44,993	IMpower133 study
> 15 & ≤ 30 weeks before death on treatment	0.72	0.71	£45,300	0.74	£45,043	IMpower133 study
> 30 weeks before death on treatment	0.73	0.71	£45,625	0.74	£44,720	IMpower133 study
≤ 5 weeks before death off treatment	0.33	0.22	£44,751	0.43	£45,598	IMpower133 study
> 5 & ≤ 15 weeks before death off treatment	0.53	0.45	£44,626	0.62	£45,736	IMpower133 study
> 15 & ≤ 30 weeks before death off treatment	0.70	0.63	£44,704	0.77	£45,608	IMpower133 study
> 30 weeks before death off treatment	0.75	0.67	£47,164	0.83	£43,281	IMpower133 study

ICER: Incremental cost-effectiveness ratio; TAE: therapy area expert

Table 47: Deterministic sensitivity analysis, at atezolizumab list price

Parameter modified	Base case value	Lower value	Lower ICER	Upper value	Upper ICER	Justification
Discounted costs	3.50%	2%	[redacted]	5%	[redacted]	Assumption
Discounted benefits	3.50%	2%	[redacted]	5%	[redacted]	Assumption
Subsequent administration costs	£312.34	£312.28	[redacted]	£312.40	[redacted]	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on A+C+E	£1232.53	1,088.63	[redacted]	1,386.77	[redacted]	Base case is from IMpower133 study, sensitivity is from TAE opinion

Resource use cost on C+E	£1191.97	1,053.88	[redacted]	1,335.51	[redacted]	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on atezo monotherapy	£903.84	760.13	[redacted]	1,063.44	[redacted]	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on surveillance only	£1216.40	1,055.70	[redacted]	1,411.72	[redacted]	Base case is from IMpower133 study, sensitivity is from TAE opinion
≤ 5 weeks before death on treatment	0.65	0.61	[redacted]	0.69	[redacted]	IMpower133 study
> 5 & ≤ 15 weeks before death on treatment	0.73	0.70	[redacted]	0.75	[redacted]	IMpower133 study
> 15 & ≤ 30 weeks before death on treatment	0.72	0.71	[redacted]	0.74	[redacted]	IMpower133 study
> 30 weeks before death on treatment	0.73	0.71	[redacted]	0.74	[redacted]	IMpower133 study
≤ 5 weeks before death off treatment	0.33	0.22	[redacted]	0.42	[redacted]	IMpower133 study
> 5 & ≤ 15 weeks before death off treatment	0.53	0.44	[redacted]	0.62	[redacted]	IMpower133 study
> 15 & ≤ 30 weeks before death off treatment	0.70	0.62	[redacted]	0.77	[redacted]	IMpower133 study
> 30 weeks before death off treatment	0.75	0.66	[redacted]	0.83	[redacted]	IMpower133 study

ICER: Incremental cost-effectiveness ratio; TAE: therapy area expert

Figure 21: Deterministic sensitivity analysis for the base case, with atezolizumab PAS

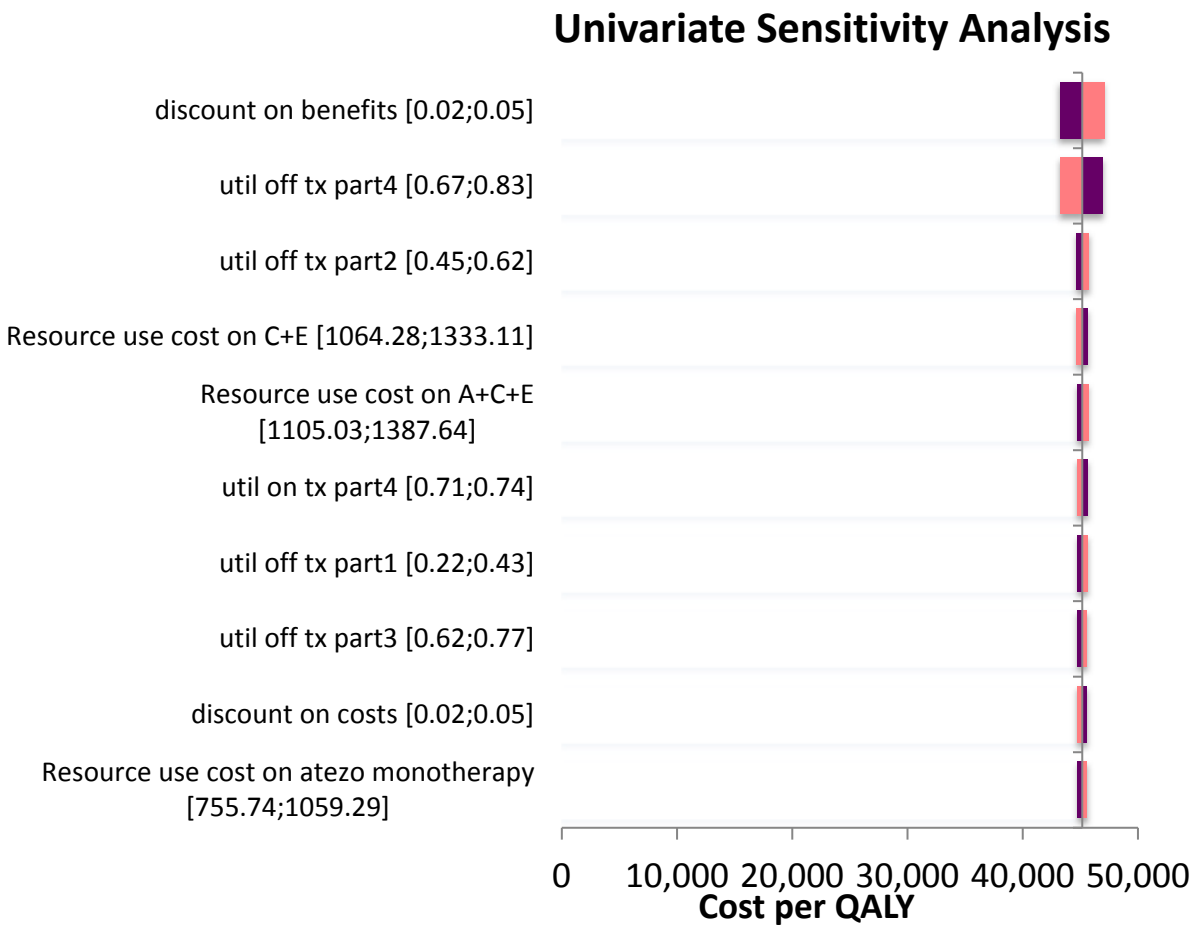


Figure 22: Deterministic sensitivity analysis for the base case, at atezolizumab list price

B.3.8.3 Scenario analysis

Different scenario analyses have been performed on the base-case and are illustrated in Table 48 and Table 49 for atezolizumab PAS price and list price, respectively. These scenarios assessed different parametric models for OS extrapolation, model time horizon, approaches and timepoints for incorporating Flatiron Health data into the chemotherapy arm extrapolation. Several of these scenarios are more cost effective than the chosen base case – shoeing that clinically plausible assumptions have been made. Furthermore, the scenarios that are less cost-effective are considered to be overly conservative.

Table 48: Summary of different scenario analysis, with atezolizumab PAS

Parameter	Value	ICER (£/QALY)	Justification
OS comparator + atezolizumab arm	Exponential	£45,450	Not clinically plausible

	Weibull	£67,177	Not clinically plausible
	Log-normal	£33,358	Not clinically plausible
	Gen Gamma	£72,437	Not clinically plausible
	Log-logistic	£45,166	Best fit + base case
	Gompertz	£85,119	Not clinically plausible
OS comparator + atezolizumab arm	KM-Exponential	£40,533	Fully parametric better fit
	KM-Weibull	£66,064	Fully parametric better fit
	KM-Log-normal	£30,516	Fully parametric better fit
	KM-Gen Gamma	£70,814	Fully parametric better fit
	KM-Log-logistic	£43,921	Fully parametric better fit
	KM-Gompertz	£81,154	Fully parametric better fit
Real-world (FI) data incorporation for the chemotherapy arm	Replace control arm with FI data from week 1	£38,196	Replaces all IMpower study data
	Replace control arm with FI data from 10% at risk	£47,111	Only replaces IMpower133 data at maximum follow-up
	Replace control arm with FI and IMpower133 combined from week 1	£44,472	Replaces all IMpower study data
	Replace control arm with FI and IMpower133 combined from 10% at risk	£44,872	Only replaces IMpower133 data at maximum follow-up
Time horizon	5	£53,603	Few patients still alive
	10	£46,978	Few patients still alive
	15	£45,632	Few patients still alive
	20 – base case	£45,175	Allows all data to be considered

FI: Flatiron Health data; ICER: incremental cost-effectiveness ratio.

Table 49: Summary of different scenario analysis, at atezolizumab list price

Parameter	Value	ICER (£/QALY)	Justification
OS comparator + atezolizumab arm	Exponential	[redacted]	Not clinically plausible

	Weibull	[redacted]	Not clinically plausible
	Log-normal	[redacted]	Not clinically plausible
	Gen Gamma	[redacted]	Not clinically plausible
	Log-logistic	[redacted]	Best fit + base case
	Gompertz	[redacted]	Not clinically plausible
OS comparator + atezolizumab arm	KM-Exponential	[redacted]	Fully parametric better fit
	KM-Weibull	[redacted]	Fully parametric better fit
	KM-Log-normal	[redacted]	Fully parametric better fit
	KM-Gen Gamma	[redacted]	Fully parametric better fit
	KM-Log-logistic	[redacted]	Fully parametric better fit
	KM-Gompertz	[redacted]	Fully parametric better fit
Real-world (FI) data incorporation for the chemotherapy arm	Replace control arm with FI data from week 1	[redacted]	Replaces all IMpower study data
	Replace control arm with FI data from 10% at risk	[redacted]	Only replaces IMpower133 data at maximum follow-up
	Replace control arm with FI and IMpower133 combined from week 1	[redacted]	Replaces all IMpower study data
	Replace control arm with FI and IMpower133 combined from 10% at risk	[redacted]	Only replaces IMpower133 data at maximum follow-up
Time horizon	5	[redacted]	Few patients still alive
	10	[redacted]	Few patients still alive
	15	[redacted]	Few patients still alive
	20 – base case	[redacted]	Allows all data to be considered

FI: Flatiron Health data; ICER: incremental cost-effectiveness ratio.

Table 50: Scenario analysis of relevance to this appraisal, with PAS

Scenario	Value	ICER (£/QALY gained)	Rationale

Treatment discontinuation rule	2-years	£44,810	Not aligned with the IMpower133 study design
Cycles of carboplatin-etoposide	6 cycles	£45,077	Guidelines recommend up to 6 chemotherapy cycles
Subsequent treatment source	UK-practising clinical expert opinion	£45,226	Reflective of possible future NHS costs
Age adjusted utilities	Excluded	£44,368	Conservative assumption
Treatment benefit cap	Excluded	£43,228	Not clinically plausible

ICER: incremental cost-effectiveness ratio.

Table 51: Scenario analysis of relevance to this appraisal, at list price

Scenario	Value	ICER (£/QALY Gained)	Rationale
Treatment discontinuation rule	2-years	[redacted]	Not aligned with the IMpower133 study design
Cycles of carboplatin-etoposide	6 cycles	[redacted]	Guidelines recommend up to 6 chemotherapy cycles
Subsequent treatment source	UK-practising clinical expert opinion	[redacted]	Reflective of possible future NHS costs
Age adjusted utilities	Excluded	[redacted]	Conservative assumption
Treatment benefit cap	Excluded	[redacted]	Not clinically plausible

ICER: incremental cost-effectiveness ratio.

B.3.8.4 Summary of sensitivity analyses results

All scenario and sensitivity analysis presented demonstrate that the chosen base case is plausibly cost-effective and clinically plausible. Many of the alternative scenarios have comparable ICERs to the chosen base case: e.g., including a 2-year treatment discontinuation rule. Moreover, there are possible scenarios where the ICER is more cost-effective than in the chosen base case: e.g., having a treatment benefit beyond 5 years after diagnosis. The scenarios where the cost-effectiveness is considered to be worse, are not considered to be clinically plausible: exponential extrapolation of OS.

B.3.9 Subgroup analysis

As described in Section B.3.2.1, only the cost-effectiveness of the ITT population is considered from the IMpower133 study. This is consistent with the opinion of UK-practising clinical experts.

B.3.10 Validation of cost-effectiveness analysis

The appropriate statistical distributions for time-to-event endpoints were selected based on best fit, using AIC and BIC criteria as well as visual inspection against KM. Importantly, clinical plausibility of each outcome was also a key component of decision making. All outcomes of the model were extensively compared to and validated against all best evidence, as well as clinical expert opinion, to assess the accuracy of the modelled results (See Section B.3.3 and Appendices).

The economic model was developed from the UK NHS and PSS perspective to comply with NICE requirements. The structure is consistent with other cancer immunotherapy models and previous lung cancer submissions to NICE, plus all costs are sourced from UK published sources. In addition, the model approach and inputs were validated by a number of UK clinical experts to ensure the model is reflective of clinical practice. This includes, but is not limited to: health state inclusion, relevant treatment comparators, NHS resource use, OS and PFS projections and extrapolation techniques.

Quality control and validation of the model structure, inputs and assumptions was conducted by an agency external to Roche. Cell by cell validation was conducted which included formula checking, cell references and all aspects of model functionality. A number of validation tests were also conducted, often using extreme values. The results of the model using these values were then compared to expected outputs to assess functional accuracy.

B.3.11 Interpretation and conclusions of economic evidence

ES-SCLC is a severe, fatal condition with extremely short life expectancy with currently available treatments. Life expectancy is reported to range between just 4 months for ES-SCLC patients of ECOG PS 0–4 (31), and 10.3 months for the IMpower133 trial population (3). Atezolizumab has already shown in the IMpower133 interim analysis a statistically significant and clinically meaningful benefit to OS for patients, offering the first change in treatment practice in decades. Given the unmet need and lack of treatment alternatives, Roche requests that NICE consider awarding the EOL criteria for this appraisal, to allow flexibility in the ICER threshold.

The pivotal IMpower133 trial is compared to standard of care in the UK, allowing direct consideration of the cost-effectiveness results from the RCT to UK clinical practice. Moreover, UK-practising clinical experts report that [redacted] of ES-SCLC patients are expected to be treated with carboplatin-etoposide (Appendix K).

The base case submitted here is cost-effective when considering the EOL ICER threshold. Furthermore, many alternative scenarios and the PSA presented show comparable cost-effectiveness to the chosen base case. In addition, some scenarios are most cost-effective, demonstrating that the chosen base case is clinical plausible. The scenarios that report less cost-effective ICERs are overly conservative in estimating OS for current standard of care.

In summary, this *de novo* cost-effectiveness model presents a clinically plausible base case which demonstrates that atezolizumab is a reasonable use of NHS resources for the treatment of ES-SCLC. Furthermore, the budget impact model (see separate documentation) associated with this submission also demonstrates a minimal expected budget impact in NHS England in this severely morbid condition.

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B.5 Appendices

The Appendices are provided in a separate document.

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Indirect treatment comparison and network meta-analysis

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Engagement with UK-practising oncologists treating patients with ES-SCLC within the NHS

Appendix L: Cisplatin-etoposide cost-effectiveness results

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

First-line atezolizumab plus carboplatin and etoposide in ES-SCLC

ID1504

Clarification questions

May2019

File name	Version	Contains confidential information	Date
ID1504 Atezolizumab clarification response – stage 2	**V3.** **Here including PD-L1 clinical data from the IMpower133 study**	**Yes**	**24 May 2019**

Section A: Clarification on effectiveness data

Search strategies

A1. For transparency please supply the original search strategies for the clinical effectiveness searches detailed in appendix D and run on 1 July 2018. Only strategies conducted for the 4 November 2018 update have been provided in appendix D.

Please see Appendix 1 for the search strategies for the clinical effectiveness searches. For ease of comparison, appendix A here includes both the search strategies for the original searches conducted on 1 July 2018, and for the update conducted on 4 November 2018. Please note these search strategies are the same, but were run on different dates. The purpose of re-running the clinical effectiveness searches was to ensure any publication of significance was included in the review, including the publication of the pivotal IMpower133 study (1).

Trial IMpower133

A2. Priority question**:** Please provide the full clinical study report including all of its appendices of IMpower133. It would be helpful if these could be sent electronically and if possible, ahead of the other requested analysis to assist the review team with the information previously submitted.

As requested, the clinical study report was uploaded via NICE docs on Wednesday 20th March 2019. For ease of record keeping, it has also been uploaded via NICE Docs along with this ERG response.

A3. Priority question**:** The protocol for the IMpower 133 trial is referred to on page 22 of the company submission as reference 51. However, this reference does not seem to be included in the reference pack. Please provide the protocol and the Statistical Analysis Plan (reference #52 in the company submission). Please check if any other references from documents A (summary), B (main submission) and C (appendices) are missing. If so, please provide PDFs for these references. We also noticed that most of the 73 publications mentioned in table 5 of appendix D (pages 22-28) are missing, these are references 6-9 and 12-80 in the appendices.

Please see a compiled list of missing references (sent as an appendix to this letter) and provide them with your response.

The statistical analysis plan (reference 51) and protocol (reference 52) for IMpower133 have been uploaded via NICE Docs, along with this ERG response. In addition, all references listed in the appendix to the ERG's clarification questions have been uploaded via NICE docs along with this response.

A4. The submission mentions phase 1 of the trial (company submission, page 24) which included at least 12 patients for each treatment regimen and safety data. Please provide full data for this phase of the trial, including how many patients were included in each arm; how were patients assigned to each arm; were these patients also included in the randomised part of the trial; and please provide full safety data for each arm.

The IMpower133 study was designed as a phase 3 trial with a phase 1 safety portion in order to establish tolerability of the study treatment. The phase 1 part consisted of an independent data monitoring committee (iDMC) assessing safety data after at least 12 patients in each arm of the trial had received at least 2 cycles of treatment. This occurred without a pause in enrolment for the trial. The feedback received from this iDMC safety review at this time was to continue with the study as planned. The data from this small group of patients was incorporated into the overall safety results of the safety evaluable population of 403 patients presented in the submission.

The method used to assign patients to each arm of the phase 1 part of the study was the same as the method used in the phase 3 part of the trial. Eligible patients were stratified by sex (male vs. female), ECOG performance status (0 vs. 1), and presence of brain metastases (yes vs. no) and randomised 1:1 to either the atezolizumab arm or the placebo arm.

Table 1 below includes a summary of the safety data included in the iDMC review when at least 12 patients in each arm had received at least 2 cycles of treatment. Please refer to Table 31 for the immune-related adverse events and Table 32 for Serious Adverse Events by Highest NCI-CTCAE Grade, Treated Patients.

Table 1: Summary of Adverse Events

Patients — no. (%)	Atezolizumab Group (n=18)	Placebo Group (n=17)	Total
Serious AEs	XXXXXXX	XXXXXXX	XXXXXXX
Immune-related AEs	XXXXXXX	XXXXXXX	XXXXXXX
AEs leading to withdrawal from any treatment	X	XXXXXXX	XXXXXXX
Death	X	XXXXXXX	XXXXXXX

XXXXXXXXXXXXXXXX

A5. Can the company provide evidence that the proportion of patients undergoing previous cancer treatments in the IMpower 133 trial is representative of what is observed in a UK setting?

The proportion of patients undergoing previous cancer treatments in the IMpower133 trial was presented and discussed at a recent Roche advisory board meeting attended by 11 practising oncologists from a range of hospitals across the UK. The consensus from this group of clinical experts was that these proportions are representative of what is observed in their clinical practice in the UK. Please refer to appendix 3 where we have included an anonymised list of the attendees, for your reference.

A6. The submission mentions (company submission, page 17): "For the IMpower133 trial, ES-SCLC in patients was defined according to [Veterans Administration Lung Study Group] VALG classification, in alignment with NICE guidelines (3)". As far as we can see, NICE guideline 121 describes extensive stage small cell lung cancer (ES-SCLC), according to the [tumour node metastasis] TNM classification, as broadly corresponding to T1–4, N0–3, M1a/b. Please explain how the definition of ES-SCLC in the IMpower133 trial was in alignment with NICE guideline 121.

An advisory board meeting of 11 UK practicing oncologists held in March 2019 confirmed the correlation of the VALG staging definition for ES-SCLC used as an inclusion criterion for the IMpower133 study with the NICE guidance for TNM classification of "broadly T1–4, N0–3, M1a/b." This correlation is because of the requirement in the VALG definition of LS-SCLC

(definition provided in answer to A7) that the disease is encompassed by the radiation field in every portal.

The use of the VALG staging system reflects current NHS practice where it is used to classify patients with small cell lung cancer (SCLC) as either limited or extensive stage disease - as corroborated at an advisory board.

In addition, the use of the VALG staging system is also applied in other clinical trials investigating the use of immunotherapies in ES-SCLC including those that have UK sites enrolling patients (2, 3).

A7. Please provide details of how ES-SCLC are distinguished from LS-SCLC? Additionally, please provide evidence that this method of distinguishing the two populations is universally applied (specifically that the method in the trial is the same as that used throughout the UK)?

During the screening assessment for the IMpower133 study, to determine eligibility for the study patients had a CT scan with contrast (unless contraindicated) or MRIs of the chest, abdomen and pelvis. To evaluate CNS metastasis, a CT scan with contrast (unless contraindicated) or MRI of the head was also performed. The investigator was then responsible for determining whether the patient had LS-SCLC or ES-SCLC using the following VALG classification system:

Limited stage

- Disease confined to one hemithorax, although local extensions may be present;
- No extrathoracic metastases except for possible ipsilateral, supraclavicular nodes if they can be included in the same portal as the primary tumour; and
- Primary tumour and regional nodes that can be adequately treated and totally encompassed by the radiation field in every portal

Extensive stage

- Inoperable patients who cannot be classified as having limited disease

Consultation with 11 UK oncologists confirmed that in their clinical practice they would request a chest, abdomen and pelvis CT scan in order to stage a patient with suspected or known SCLC as either LS-SCLC or ES-SCLC.

With respect to performing a brain scan to stage patients with SCLC, NICE clinical guideline 121 (4, 5) only recommends performing brain scans in patients with symptoms or signs of intracranial pathology. Whilst this does highlight a disparity between the guideline and the IMpower133 trial protocol this is primarily due to the exclusion criteria of patients with active or untreated CNS metastases which meant that all patients, irrespective of their clinical presentation, were required to have a brain scan at screening.

It is important to note that these inclusion/exclusion criteria in relation to the patient with brain metastases and therefore the need for a CT/MRI of the head at baseline is not unique to the IMpower133 study and is common practice amongst other immunotherapy studies in ES-SCLC (2, 3, 6-8).

A8. Please clarify whether in the IMpower133 trial, progression-free survival (PFS) was only assessed as investigator-assessed PFS, or whether it was also assessed using an Independent Review Committee (IRC-assessed). If it was also assessed using an IRC then please provide the results for each treatment arm, including the KM-plot.

In the IMpower133 trial, progression-free survival (PFS) was only assessed by investigators and not by an Independent Review Committee. Since the study is double-blinded and placebo-controlled, the risk of investigator bias during response assessment was considered to be low. Investigator-assessed PFS is also more likely to reflect decision making in clinical practice and so this endpoint is expected to more accurately reflect the treatment pathway in the NHS, and therefore the calculation of cost-effectiveness.

The study did however include overall survival (OS) as a co-primary endpoint, which is an objective endpoint and now considered to be the “gold standard” in cancer immunotherapy trials. Whilst traditional endpoints including PFS can be used to assess the activity of agents that are likely to elicit rapid control of tumour growth it may be less suitable for therapies where tumour control may develop over time, such as immunotherapies which therefore can lead to an improvement in OS after progressive disease (9). Furthermore, clinical expert advice from a group of 11 UK practising oncologists have also validated OS as being the critical and preferred endpoint for this trial regimen.

A9. Please present the difference in means for objective response rate and duration of response (as presented in table 10 of the company submission, page 36-37) with the 95% confidence interval and p-value.

Table 2 reports the confirmed overall response rate (ORR) per RECIST v1.1 by Investigator for the ITT population, including the 95% confidence interval (CI) and p-value. Table 3 reports the time to event summary for objective confirmed response duration. Both of these data sets can also be searched in the CSR.

Table 2: Confirmed overall response rate (ORR) per RECIST v1.1 by Investigator for the ITT population

	Placebo arm (n=202)	Atezolizumab arm (n=201)
Responders	XXXXXXXX	XXXXXXXX
Non-responders	XXXXXXXX	XXXXXXXX
95% CI for response rate (Clopper-Pearson)	XXXXXXXX	XXXXXXXX
Difference in response rates	XXXXXXXX	
95% CI for Difference in Response Rates (Wald with Continuity Correction)	XXXXXXXX	
p-value*(Cochran-Mantel-Haens zel)	XXXXXXXX	

Table 3: Time to event summary for objective confirmed response duration

	Placebo arm (n=155)	Atezolizumab arm (n=149)
Patients with event	[redacted]	[redacted]
Patients without event	[redacted]	[redacted]
Time to event, median (months)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Mean duration of confirmed response	[redacted]	[redacted]
Standard error	[redacted]	[redacted]
Hazard ratio	[redacted]	
Stratified analysis p-value (log-rank)	[redacted]	

Note: The mean and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time

A10. Priority question: According to section B.2.6.1 the latest database lock is April 2018 for PFS and overall survival (OS). Could the company please update all analyses using the most recently available data?

At the primary analysis, the IMpower133 study met the co-primary endpoints of OS and investigator-assessed PFS, demonstrating a statistically significant and clinically meaningful improvement in OS and a statistically significant improvement in investigator-assessed PFS in the atezolizumab group compared with the placebo group in patients with chemotherapy-naïve ES-SCLC. At the planned interim OS analysis, the OS endpoint passed its statistical boundary and the co-primary endpoints were [redacted]

[redacted]

Table 4 includes [redacted] with a median follow up of [redacted]. The data included in the original submission was the primary analysis at the CCOD 24th April 2018 with a median follow up time of 13.9 months.

[redacted]

[redacted]

[redacted] Subgroup analysis of OS at the CCOD [redacted] is provided in Appendix 4 however as discussed in the original submission this analysis is not powered to detect statistical significance.

Table 4: Overview of efficacy (ITT population), primary analysis CCOD 24th April 2018 and latest analysis CCOD [redacted]

	CCOD 24th April 2018		CCOD [redacted]	
	Atezolizumab group	Placebo group	Atezolizumab group	Placebo group
Overall survival				
ITT population	n=201	n=202	n=201	n=202
Patients with event (%)	104 (51.7%)	134 (66.3%)	[redacted]	[redacted]
Median duration of survival (95%) (months)	12.3 (10.8, 15.9)	10.3 (9.3, 11.3)	[redacted]	[redacted]
Stratified hazard ratio (95% CI)	0.70 (0.54, 0.91)		[redacted]	
p-value (log-rank)	0.007		[redacted]	
6 months event-free rate (%)	[redacted]	[redacted]	[redacted]	[redacted]
(95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
12 months event-free rate (%)	51.7	38.2	[redacted]	[redacted]
(95% CI)	(44.4, 59.0)	(31.2, 45.3)	[redacted]	[redacted]

18 months event-free rate (%)	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX
(95% CI)	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX
24 months event-free rate (%)	XXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX
(95% CI)	XXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX

*This value is descriptive

Figure 1: Kaplan-Meier plot of OS in the ITT population, data cut-off date XXXXXX XXXXXX

Table 5 includes updated information regarding subsequent cancer therapies from the CCOD XXXXXXXXXX. The proportion of patients having at least XXXXXXXX XXXXXXXX XXXXXXXX in the atezolizumab group and XXXXX in the placebo group. XXXXX XXXXX XXXXX XXXXX XXXXX XXXXX XXXXX in the placebo arm (XXX) compared with the atezolizumab arm (XXXXX) This data is not reflective of NHS clinical practice, as immunotherapies are currently not licenced nor reimbursed in this setting. Clinical expert opinion is that chemotherapy, either by re-challenge with platinum based chemotherapy or topetecan, would be prescribed for patients with relapsing disease.

Clarification questions

Table 5: Subsequent cancer therapies, data cut-off date XXXXXXXXXXXX

	Atezolizumab group (n=201)	Placebo group (n=202)
Line of therapy (%)		
Maintenance	XXXX	XXXX
Second	XXXX	XXXX
Third	XXXX	XXXX
Fourth	XXXX	XXXX
Missing	XXXX	XXXX
Therapy type (%)		
Total number of patients with at least one treatment	XXXX	XXXX
Total number of treatments	XXXX	XXXX
Chemotherapy/non-anthracycline	XXXX	XXXX
Chemotherapy/anthracycline	XXXX	XXXX
Immunotherapy	XXXX	XXXX
Other	XXXX	XXXX
Targeted therapy	XXXX	XXXX

A11.Please provide stratified analysis for PFS and OS, including median survival and hazard ratios, by previous anticancer treatments, Eastern Cooperative Oncology Group performance status (ECOG PS) and smoking status.

The stratified analyses for PFS and OS by previous anticancer treatments was provided in the previous response to the clarification questions.

The stratified analyses for PFS and OS according to ECOG performance status and smoking status are provided below (Table 6, Table 7) at the CCOD 24th April 2018. As highlighted in our previous response to the clarification questions, subgroup analyses in the IMpower133 trial were not powered to detect a statistically significant treatment effect and the results should be interpreted with caution. Also note that in the subgroups as compared with the ITT population, the forced balance or homogeneity within strata introduced by the stratified

randomization no longer holds, thus the unstratified analysis is the more appropriate method for the subgroup analyses. Unstratified analysis results are also provided in the table below for consideration.

Table 6: Subgroup analysis of PFS, ITT patients, data cut-off date 24th April 2018

		Placebo arm			Atezolizumab arm			Unstratified Hazard Ratio	95% CI	Stratified Hazard Ratio	95% CI
	TOTAL n	n	Events	Median (months)	n	Events	Median (months)				
Baseline ECOG											
0	140	67	XX	4.3	73	XX	4.9	0.84	0.59,1.20	XX	XXXX
1	263	135	XX	4.3	128	XX	5.4	0.72	0.55, 0.94	XX	XXXX
Tobacco Use											
Never	XX	XX	XX	XX	XX	XX	XX	XXXX	XXXX	XXXX	XXXX
Current	XX	XX	XX	XX	XX	XX	XX	XXXX	XXXX	XXXX	XXXX
Previous	XX	XX	XX	XX	XX	XX	XX	XXXX	XXXX	XXXX	XXXX

Table 7: Subgroup analysis of OS, intent-to-treat patients

		Placebo arm			Atezolizumab arm			Unstratified Hazard Ratio	95% CI	Stratified Hazard Ratio	95% CI
	TOTAL n	n	Events	Median (months)	n	Events	Median (months)				
Baseline ECOG											
0	140	67	XX	12.4	73	XX	16.6	0.79*	0.49, 1.27	XXXX	XXXX
1	263	135	XX	9.3	128	XX	11.4	0.68	0.50, 0.93	XXXX	XXXX
Tobacco Use											
Never	XX	XX	XX	XX	XX	XX	XX	XX	XXXX	XXXX	XXXX
Current	XX	XX	XX	XX	XX	XX	XX	XX	XXXX	XXXX	XXXX
Previous	XX	XX	XX	XX	XX	XX	XX	XX	XXXX	XXXX	XXXX

* This number was incorrectly stated as 0.78 in the previous version of this document

A12. Priority question**:** We note that programmed death-ligand 1 (PD-L1) testing was not conducted during screening. One of the reasons cited was the 'lack of an association between response and PD-L1 expression in the phase I trial of atezolizumab in ES-SCLC (3, 50)" (page 24). Reference 3 refers to a phase III trial and seems to be an incorrect reference for this point. Reference 50 refers to phase I trial which was based on only 17 patients, therefore constitutes weak evidence. Furthermore, in reference 50, the ERG notices a numerical increase in efficacy with an increase of PD-L1 receptors, which seems intuitively to be expected. [redacted]

The IMpower133 study was designed for an all-comer population and not designed to statistically test [redacted] therefore this [redacted] and the results should be interpreted with caution. The results from the primary analysis of the IMpower133 study showed that the addition of atezolizumab to carboplatin and etoposide as first-line treatment for patients with ES-SCLC resulted in a statistically significant improvement in PFS and a statistically significant and clinically meaningful improvement in OS compared to chemotherapy alone in the overall ITT population.

With regards to the absence of PD-L1 testing at screening, [redacted] (10).

Roche has [redacted] was selected over the [redacted] Note that [redacted]

Since there is currently [redacted] established for SCLC, [redacted] were [redacted] was defined as the [redacted].

In total [redacted] of the intent-to-treat [ITT] population) [redacted] Following [redacted] was reported for a total of [redacted] of ITT). Furthermore, [redacted] of ITT) produced a [redacted] and [redacted] patients [redacted] of ITT) produced [redacted] To limit the risk of [redacted] associated with [redacted] was evaluated [redacted] and from [redacted] Analysis of the [redacted] can be found in Appendix 5.

The [redacted] patients enrolled in the IMpower133 study is a result of multiple factors, including [redacted] (i.e., approximately [redacted]), and [redacted]. Importantly, the [redacted] in [redacted] of the patients enrolled in the IMpower133 study greatly [redacted] from the [redacted] presented.

[redacted] were defined based on [redacted] on [redacted]. The [redacted] in the [redacted] and within each treatment arm are shown in XXXXXXXXXX XXXXXXXXXX [redacted]

Table 8. [redacted] within [redacted] defined as [redacted] within [redacted] defined as [redacted] The majority of [redacted] were attributed to [redacted], as only [redacted] had any [redacted] Of note, in both [redacted] there was only [redacted] with a [redacted] that had [redacted] Due to the limited number of patients in this [redacted], OS efficacy analyses have been [redacted]

Table 8: [redacted]

[redacted]

[redacted]

Demographic and baseline characteristics were generally balanced between the two treatment arms within the [redacted]). Baseline characteristics were also [redacted] (see Table 16 in CSR for baseline characteristics of the ITT).

Table 9: [redacted]

[redacted]

[redacted]

This section describes OS results [redacted]. Data are based on an [redacted], and [redacted] were defined using the [redacted], as described above.

The HR for OS in the [redacted] was [redacted], compared to that observed in the overall ITT population ([redacted], see Figure 2). [redacted] were observed between the [redacted]. The OS HR and median OS in the [redacted] and [redacted] are also available in Figure 2.

An OS [redacted] The OS HR was [redacted] with median OS [redacted] in the Atezo + CE arm [redacted] compared to the PBO + CE arm [redacted] The OS HR was [redacted] with median OS [redacted] in the Atezo + CE arm [redacted] compared to the PBO + CE arm [redacted]. The OS HR was [redacted] with [redacted] in the Atezo + CE arm [redacted] compared with the PBO + CE arm [redacted]. However, due to the [redacted] in the [redacted], results should be interpreted with caution.

Kaplan-Meier OS curves for [redacted] are shown in Figure 3, Figure 4, Figure 5 and Figure 6[redacted] for [redacted] (see Figure 2 and Appendix 5 Figure 15, Figure 16, Figure 17, and Figure 18).

Clarification questions

Figure 2: [redacted]

Figure 3: [redacted]

Figure 4: [redacted]

Figure 5: [redacted]

Figure 6: [redacted]

[redacted]

This section describes [redacted] based on the first primary analysis CCOD of 24 April 2018. [redacted] were [redacted]. The HR for [redacted] compared to the overall ITT population [redacted] The [redacted] and [redacted] in the [redacted] and [redacted] are also available in Figure 7.

[redacted] with Atezo + CE compared with PBO + CE was observed [redacted] suggesting [redacted] in the overall ITT population (Figure 7). The [redacted] was [redacted] with [redacted] in the Atezo + CE arm [redacted] compared to the PBO + CE arm [redacted] The [redacted] with [redacted] in the Atezo + CE arm [redacted] and PBO + CE arm [redacted] for [redacted].

[redacted] for [redacted] and [redacted] are shown in Figure 8 and Figure 9, respectively. [redacted] were observed for [redacted] (see Figure 7 and Appendix 5, Figure 19 and Figure 20).

Figure 7: [redacted]

[redacted]

Figure 8: [redacted]

Figure 9: [redacted]

[redacted]

This section describes [redacted] results by [redacted] as assessed by the [redacted] and determined in [redacted]. In addition, [redacted] was evaluated. Data are based on the primary analysis CCOD of 24 April 2018, and [redacted]

The proportion of patients with [redacted] or [redacted] is shown in Table 10 according to [redacted] For [redacted] in the Atezo + CE arm [redacted] compared with the PBO + CE arm [redacted] For [redacted] in the Atezo + CE arm [redacted] compared with the PBO + CE arm [redacted] However, [redacted].

The proportion of patients with [redacted] is shown in [redacted]. For [redacted] in the Atezo + CE arm [redacted] compared with the PBO + CE arm [redacted] with [redacted] For [redacted] In the Atezo + CE arm [redacted] compared with the PBO + CE arm [redacted] with [redacted]

[redacted] results were observed [redacted] (see Appendix 5 Table 35 and **Error! Reference source not found.**).

[Table 10: XXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXX XXXXXXXXX XXXXXXXXXXXXX XXXXXXXXXXXXXX]

[Table 10: XXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXX XXXXXXXXX XXXXXXXXXXXXX XXXXXXXXXXXXX]

Table 11: [redacted]

Table 11: XXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXX

Time to off treatment by [redacted]

Data reporting [redacted] is presented for atezolizumab (Figure 21, Figure 22, Table 36, Table 37) in the atezolizumab arm, and for carboplatin (Table 38, Table 39, Figure 23, Figure 24), and etoposide (Figure 25, Figure 26, Table 40, Table 41) in the atezolizumab arm and the placebo arm.
The tables and figures [redacted] These tables and figures can be found in Appendix 6.

Summary

The results of this [redacted] should [redacted] and the fact that the IMpower133 trial was not designed to statistically [redacted]. Furthermore, [redacted] of the ITT population had [redacted]; presenting an additional limiting factor in the interpretation of these results.

Based on the totality of the data from the ITT population and [redacted] the IMpower133 regimen demonstrates meaningful clinical benefit in an all-comer population [redacted]. In addition, the clinical benefit in the ITT population [redacted].

Network meta-analyses (NMA)

A13. Priority question: Could the company please provide the Winbugs code including data and initial values for all NMAs.

The Winbugs code for the full literature searches, including the data and initial values for all NMAs, has been uploaded via NICE Docs along with this response. Since these are developed for a Global audience, ES-SCLC treatment approaches have been included that do not reflect NHS clinical practice. For clarity, only the treatments relevant to NHS clinical practice have been reported within the submitted dossier. Please see the responses to questions A14 and A15 for further information.

A14. Priority question: The submission states (company submission, appendix D, page 41) that "chemotherapy regimens excluding etoposide are outside of the scope of this appraisal, so are not considered further here". However, the scope only mentions "Platinum-based combination chemotherapy regimens" as relevant

comparators. Therefore, chemotherapy regimens excluding etoposide are within the scope of this appraisal. Please explain and rectify if a mistake was made.

Roche have been advised by over 20 practising NHS oncologists during individual consultation meetings and two separate advisory board meetings that the standard of care in the NHS for untreated, ES-SCLC is carboplatin plus etoposide. Moreover, that the control arm of the IMpower133 study is reflective of NHS clinical practice. Roche have also been advised that across the NHS, cisplatin plus etoposide is the standard of care for patients diagnosed with LS-SCLC and those considered to be borderline LS-SCLC and ES-SCLC. Therefore, only carboplatin plus etoposide treatment is considered to be within the scope of this appraisal, since all other treatments listed in the final scope are not considered standard NHS practice (13). NICEs guide to the methods of technology appraisal 2013 state the scope should be inclusive in terms of comparators but that the Committee will normally be guided by established practice in the NHS when identifying the appropriate comparator, therefore we expect this approach to be in line with the NICE appraisal process (14).

A15. Priority question: On page 42 of appendix F, the company states: "Irinotecan plus carboplatin, paclitaxel plus carboplatin and best supportive care were reported in the clinical studies included in the SLR, but these regimens were not relevant to this appraisal." Please clarify why irinotecan plus carboplatin and paclitaxel plus carboplatin are not relevant to this appraisal when the NICE scope describes relevant comparators as "Platinum-based combination chemotherapy regimens", which includes irinotecan plus carboplatin and paclitaxel plus carboplatin. Please rectify if a mistake was made.

Roche have been advised by over 20 practising NHS oncologists during individual consultation meetings and advisory board meetings that the standard of care in the NHS for untreated, ES-SCLC is carboplatin plus etoposide. Moreover, that the control arm of the IMpower133 study is reflective of NHS clinical practice. Regimens such as irinotecan plus carboplatin, paclitaxel plus carboplatin and best supportive care are not considered standard clinical practice by the broad range of NHS oncologists advising Roche.

Moreover, as stated in page 61 of the submission alternate platinum doublets (e.g. irinotecan plus carboplatin and paclitaxel plus carboplatin) are only used in patients who are etoposide-intolerant. These patients also cannot receive the atezolizumab, carboplatin, etoposide combination as this contains etoposide. Therefore, these are not relevant comparators.

Clarification questions

As such, only carboplatin plus etoposide is considered to be within the scope of this appraisal, since all other treatments listed in the final scope are not considered standard NHS practice in the relevant patient population (13). NICE guide to the methods of technology appraisal 2013 state the scope should be inclusive in terms of comparators but that the Committee will normally be guided by established practice in the NHS when identifying the appropriate comparator, therefore we expect this approach to be in line with the NICE appraisal process (14).

Section B: Clarification on cost-effectiveness data

Updated base case results with the IMpower133 data analysis update

The [redacted] reported for untreated ES-SCLC patients in the April 2018 analysis (see section A10). Although, the [redacted] in this updated analysis. Hence, there is [redacted] among untreated ES-SCLC patients. However, [redacted]

The comparative efficacy reported in the IMpower133 trial (see A10) is confounded by increased use of immuno-oncology (IO) treatments in the control arm versus the atezolizumab arm. [redacted], for the atezolizumab versus the control arms respectively. This [redacted]. The costs associated with all second-line treatments have been updated in the cost-effectiveness model submitted here, in order to correspond with the reported efficacy. However, [redacted]. Moreover, the control arm of the IMpower133 study has [redacted] for chemotherapy treated patients, which reports the survival rate of over 3,000 untreated ES-SCLC patients with PS 0-1. [redacted]. This further demonstrates that the survival rate

reported in the control arm of IMpower133 is [redacted]

In addition, to the updated OS and second-line treatment rates, the [redacted] IMpower133 study analysis provided additional data for the measurement of utility, which has also been incorporated here (see B4).

In summary, the [redacted] updated analysis of IMpower133 gives updated base case cost-effectiveness results, as described above. The new base case results are presented in Table 12. The results presented below are both the base case comparison versus carboplatin-etoposide and the exploratory comparison versus cisplatin-etoposide. A full set of updated results versus carboplatin-etoposide are presented in Appendix 7.

Table 12: Updated company base case pairwise ICERs, including the PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER incremental (£/QALY)
				Costs (£)	LYG	QALYs	
Atezolizumab plus carboplatin-etoposide	[redacted]	[redacted]	[redacted]				
Carboplatin-etoposide	[redacted]	1.21	0.83	[redacted]	[redacted]	[redacted]	£49,588
Cisplatin-etoposide	[redacted]	1.20	0.82	[redacted]	[redacted]	[redacted]	£47,477

Utilities

B1. Priority question**:** Section 3.4.1 states "…time to death approach as has been accepted during previous NICE appraisals of lung cancer treatments". Please list these previous appraisals.

The approach applied here of measuring utility difference as a function of time to death has been repeatedly accepted during previous NICE appraisals for lung cancer treatments. Specifically, this approach was accepted during the appraisal of atezolizumab to treat both first-line and second-line non-small cell lung cancer, and pembrolizumab for the treatment of

non-small cell lung cancer as first-line monotherapy and combination therapy, and as second-line therapy, including: TA520, TA428, TA531, TA557 and ID1210 (15-19).

B2. Priority question: When considering adverse events, it is important to include decrements in HRQoL associated with grade 3-4 adverse events (NICE technical support document 12). In the "IMpower 133" study 67.2% of patients in Atezolizumab + CP/ET arm and 63.8% in placebo + CP/ET arm experienced grade 3-4 adverse events. However, in the company submission section B.3.4.5 it was stated "… the base case analysis takes the former assumption and does not include any additional disutility for AEs". Therefore, please provide a scenario analysis using additional disutility for AEs.

To demonstrate the sensitivity of the model to the assumption that there is no difference in disutility due to adverse events between treatment arms, an additional scenario analysis has been included, whereby individual adverse event disutilities have been added. Disutilities are included in the scenario using the AEs and their relative probabilities of occurring per week (while on treatment) as reported in Table 29 of Document B (Grade ≥3 treatment related AEs, with incidence ≥2% in either arm of IMpower133 study), with disutility values sourced from NICE lung cancer appraisals (Table 13). This method assumes an average AE duration of 1 week, aligned with the method used in the recent company submissions for lung cancer appraisals TA520, TA484 and TA483.

Table 13: Adverse event disutilities included in this scenario

	Disutility	Probability of event (weekly)		NICE TA	Original source cited
		Atezo+C+E	Carbo+E		
Anaemia	-0.07346	0.0026	0.0022	TA520, Company submission, Table 62 (16)	Nafees et al, 2008 (20)
Diarrhoea	-0.0468	0.0004	0.0002	TA484, Company submission, Table 57 (21)	Nafees et al, 2008 (20)
Febrile neutropenia	-0.09002	0.0005	0.0011	TA520, Company submission, Table 62 (16)	Nafees et al, 2008 (20)
Infusion related reaction	-0.05	0.0004	0.0003	Assumed the same as dyspnoea	Doyle et al, 2008 (22)

Leukopenia	-0.08973	0.0013	0.0009	TA520, Company submission, Table 62 (16)	Assumed equal to neutropenia
Neutropenia	-0.08973	0.0060	0.0058	TA520, Company submission, Table 62 (16)	Nafees et al, 2008 (20)
Neutrophil count decreased	0	0.0042	0.0047	TA520, Company submission, Table 62 (16)	Assumption
Pancytopenia	-0.08973	0.0001	0.0003	Assume same as neutro/leuko/thrombocytopenia	Nafees et al, 2008 (20)
Platelet count decreased	-0.05	0.0009	0.0009	TA416, committee papers, Table 5.18 (23)	Assumption based on Nintedanib NICE appraisal (TA347)
Pneumonia	-0.008*	0.0003	0.0001	TA484, Company submission, Table 57 (21)	Marti et al, 2013 (24)
Thrombo-cytopenia	-0.08973	0.0018	0.0015	TA406, committee papers, Table 50 (25)	Assumed same as fatigue from Nafees (20) (as per TA181)
Vomiting	-0.048	0.0003	0.0003	TA416, committee papers, Table 5.18 (23)	Nafees et al, 2008 (20)
White blood cell count decreased	-0.05	0.0007	0.0010	TA520, Company submission, Table 62 (16)	Assumption based on Nintedanib NICE appraisal (TA347)
Notes: *, although the disutility for pneumonia does not match the severity of the condition considering the other AEs and their disutilities, this value has been left unchanged, to keep consistency with previous appraisals. As pneumonia is one of the least frequently experienced AEs on both arms, any change in this value is not thought to greatly impact the model results.					

The switch for this scenario can be found in Cell F45 of the Model Inputs sheet. This scenario has a limited impact on the ICER with the base case changing from £49,588 to £49,664 per QALY for Atezo+C+E versus carboplatin plus etoposide (Table 14).

Table 14: Scenario analysis including AE disutilities from the literature

Parameter	Value	inc. vs Carb + Etop		inc. vs Cispl + Etop		ICER vs	
		QALYs	Costs	QALYs	Costs	Carb + Etop	Cispl + Etop
Include AE disutilities from literature	Yes	[redacted]	[redacted]	[redacted]	[redacted]	£49,664	£47,546
	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	£49,588	£47,477

In addition, a scenario analysis modelling utility as a function of progression status, treatment arm and inclusion of adverse events (whether or not a patient had a treatment related adverse event grade 3 or more before progression) using trial EQ-5D data is provided in response to question B5.

B3. In the company submission health state utility values were stratified according to whether patients were on or off treatment (Table 30 in the company submission). Please clarify which treatment this is referring to (e.g. atezolizumab, atezolizumab + CP/ET).

The approach of measuring a patient's utility according to whether they are on or off treatment, was applied based on whether patients had discontinued all treatment or not: for patients treated with atezolizumab, the patient needed to have discontinued all three agents, and for a patient receiving only chemotherapy they needed to have discontinued both treatments.

B4. Priority question: Health state utility values were estimated as a function of proximity to death in four categories. However, in the Utility tab in the model the mean values of utilities at almost each time point are higher in the placebo arm than in the atezolizumab arm. This is counterintuitive given that the health state utility values for

off treatment patients having ≤ 5weeks before death are much lower than for 'on treatment' patients (0.33 vs 0.65).

a) Please provide an explanation for this apparent discrepancy and details of the analysis by which the health state utility values in each of the four categories are derived. This should include the precise specification of the statistical model and measures of goodness of fit.

We do not consider there to be a discrepancy between the information presented. The descriptive statistics provided in the Utility sheet in cells H23:Q56 provide limited information on the comparison between arms considering that these do not account for patient baseline utility, or repeated measures. In fact, the mean baseline utility on the placebo arm is higher than that of the atezolizumab arm (0.6891 versus 0.6708), so it is not surprising that some of the subsequent time points in the descriptive analysis are also higher for the placebo arm.

The specification of the statistical model used for the time to death utilities is as follows: two repeated measurements models were fitted, one for patients off-treatment and one for patients on-treatment. Both models included time before death group, assessment time, treatment arm and baseline utility score as covariates and assumed an exchangeable working correlation. For both models, utilities were included for patients who had died during the trial and also patients who had over 211 day's follow-up. This differs to the previous approach for estimating utility, where only patients who had died were included. The approach to utility measurement has been amended here since over 40% of utility data were discarded by restricting to only those patients who had died. The updated IMpower133 analysis with the longer follow-up here allows for more patients to be included, providing a more robust analysis.

The fixed effects models are presented in Table 15 and Table 16. Health state utilities were then produced based upon the mean estimates for all variables apart from the time to death categories (i.e. average time of baseline assessment, average EQ-5D at baseline and pooled across the two treatment arms). These are presented in Table 17 and Table 18 for the off-treatment and on-treatment utilities, respectively.

Table 15: Fixed effect coefficients in the proximity to death model on-treatment

Effect	Estimate	Standard Error	Lower limit 95% CI	Upper limit 95% CI
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	[redacted]
Plac + Carb + Etop	[redacted]	[redacted]	[redacted]	[redacted]
1:<35 days BD	[redacted]	[redacted]	[redacted]	[redacted]
2: 35-74 days BD	[redacted]	[redacted]	[redacted]	[redacted]
3: 75-210 days BD	[redacted]	[redacted]	[redacted]	[redacted]
4: > 210 days BD	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]

Table 16: Fixed effect coefficients in the proximity to death model off-treatment

Effect	Estimate	Standard Error	Lower limit 95% CI	Upper limit 95% CI
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	[redacted]
Plac + Carb + Etop	[redacted]	[redacted]	[redacted]	[redacted]
1:<35 days BD	[redacted]	[redacted]	[redacted]	[redacted]
2: 35-74 days BD	[redacted]	[redacted]	[redacted]	[redacted]
3: 75-210 days BD	[redacted]	[redacted]	[redacted]	[redacted]
4: > 210 days BD	[redacted]			
Baseline	[redacted]	[redacted]	[redacted]	[redacted]

Table 17: Model-based coefficients in the proximity to death model off-treatment by treatment arm

Effect	Estimate	Standard Error	Lower limit 95% CI	Upper limit 95% CI
BD Group 1: less than 35 days BD	[redacted]	[redacted]	[redacted]	[redacted]
BD Group 2: more than 34 and less than 75 days	[redacted]	[redacted]	[redacted]	[redacted]
BD Group 3: more than 74 and less than 210 days	[redacted]	[redacted]	[redacted]	[redacted]
BD Group 4: more than 211 days*	[redacted]	[redacted]	[redacted]	[redacted]
Atezo + Carb + Etop BD Group 1	[redacted]	[redacted]	[redacted]	[redacted]
Atezo + Carb + Etop BD Group 2	[redacted]	[redacted]	[redacted]	[redacted]
Atezo + Carb + Etop BD Group 3	[redacted]	[redacted]	[redacted]	[redacted]
Atezo + Carb + Etop BD Group 4*	[redacted]	[redacted]	[redacted]	[redacted]
Plac + Carb + Etop BD Group 1	[redacted]	[redacted]	[redacted]	[redacted]
Plac + Carb + Etop BD Group 2	[redacted]	[redacted]	[redacted]	[redacted]
Plac + Carb + Etop BD Group 3	[redacted]	[redacted]	[redacted]	[redacted]
Plac + Carb + Etop BD Group 4*	[redacted]	[redacted]	[redacted]	[redacted]
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	[redacted]
Plac + Carb + Etop	[redacted]	[redacted]	[redacted]	[redacted]
Off-treatment	[redacted]	[redacted]	[redacted]	[redacted]

Table 18: Model-based estimates of utility on treatment according to time before death and treatment

Effect	Estimate	Standard Error	Lower limit 95% CI	Upper limit 95% CI
BD Group 1: less than 35 days BD	xxxxxx	xxxxxx	xxxxxx	xxxxxx
BD Group 2: more than 34 and less than 75 days	xxxxxx	xxxxxx	xxxxxx	xxxxxx
BD Group 3: more than 74 and less than 210 days	xxxxxx	xxxxxx	xxxxxx	xxxxxx
BD Group 4: more than 211 days*	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Atezo + Carb + Etop BD Group 1	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Atezo + Carb + Etop BD Group 2	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Atezo + Carb + Etop BD Group 3	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Atezo + Carb + Etop BD Group 4*	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Plac + Carb + Etop BD Group 1	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Plac + Carb + Etop BD Group 2	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Plac + Carb + Etop BD Group 3	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Plac + Carb + Etop BD Group 4*	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Atezo + Carb + Etop	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Plac + Carb + Etop	xxxxxx	xxxxxx	xxxxxx	xxxxxx
On-treatment	xxxxxx	xxxxxx	xxxxxx	xxxxxx

Table 19 and Table 20 present the sum of on and off treatment patient numbers. These exceed the total number of randomised patients per arm, since some patients may have observations during both the on and off treatment period.

Table 19: Number of patients per treatment arm included in proximity to death model off-treatment

Treatment arm	Number of patients, when counting only those who had died	Number of patients including patients dead or alive with over 211 day's follow-up in January 2019
Atezo + Carb + Etop	XXXXXX	XXXXXX
Plac + Carb + Etop	XXXXXX	XXXXXX

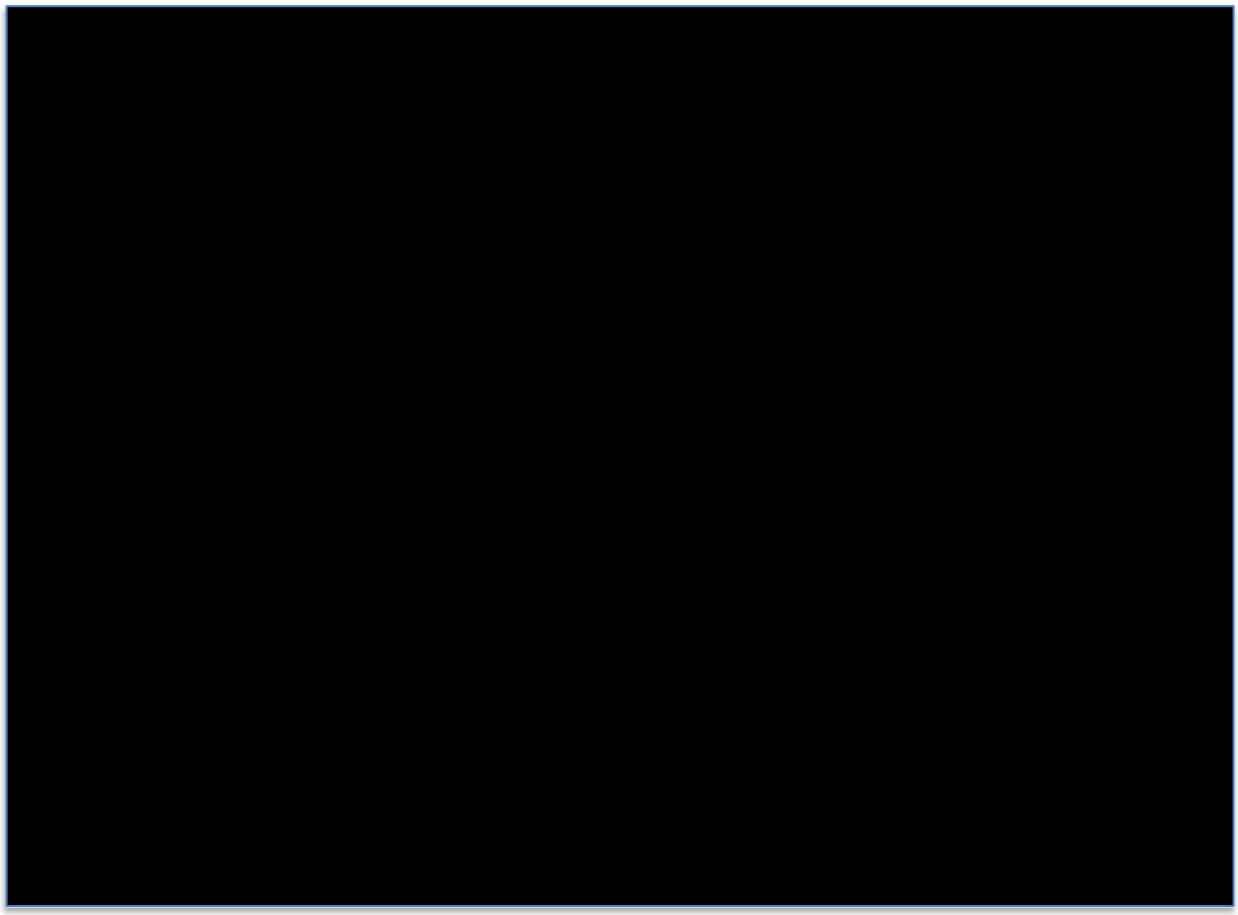
Table 20: Number of patients per treatment arm included in proximity to death model on-treatment

Treatment arm	Number of patients, when counting only those who had died	Number of patients including patients dead or alive with over 211 day's follow-up in January 2019
Atezo + Carb + Etop	XXXXXX	XXXXXX
Plac + Carb + Etop	XXXXXX	XXXXXX

b) The company submission section B.3.4.1 states: "a visual assessment of the plot was used to select proximity to death categories". Please provide a scatter plot of utility by proximity to death for both patients on treatment and off treatment.

A scatterplot of utility by proximity to death for patients on treatment and off treatment is provided in Figure 10. This includes patients who have died and patients who have over 211 days' follow-up.

Figure 10: Utilities according to treatment status, based on proximity to death approach



c) Please explain how utilities as a function of proximity to death are incorporated in the model given the challenge of knowing time to death at any point in the time horizon.

Time to death at any point in the time horizon is known for the cohort as a whole based upon the overall survival curve. The model uses this to calculate the proportion of patients who die each cycle (see column AY of the Atezo+C+E sheet for example). The proportion of patients who die in future cycles (categorised by the TTD groups) are summed (see columns AZ:BC of the Atezo+C+E sheet for example) and multiplied by the utilities provided by the time to death utility model to calculate utilities by TTD. Although there are challenges in knowing the time to death of patients in the clinical setting, for the purposes of modelling, this accurately captures the utility as a function of proximity to death.

B5. Priority question**:** Utility was estimated as a function of arbitrary categories of time to death. It also is not a function of progression status and thus does not respond to changes in the rate of progression as either a result of different survival curves or assumptions regarding the duration of the treatment effect. This method is also not referred to in any technical support document from the NICE Decision Support Unit, and appendix K provides inadequate grounds for expert clinical validation, providing only a single statement that: "…the approach for calculating quality of life and proximity to death was considered standard, as this reflected the atezolizumab submission for [non-small cell lung cancer] NSCLC." Therefore, the method conceptually and in its implementation, lacks validation. The ERG requests that the company please re-estimate utility as a function of progression status as well as time to death as a continuous variable and whether on treatment as covariates. Such a model specification may also be compared to one in which time to death is incorporated in categories. One of the approaches suggested by Basu, 2012 (26) may be used to ensure that estimated values do not exceed 1. Details of the specification of estimated models and measures of goodness of fit should also be provided. The cost-effectiveness analysis (CEA) model should then be updated accordingly with the model that is most plausible and the best fit.

No NICE technical support document yet exists on how to specify utility analysis based on patient level data, therefore such guidance could not be used to determine what models should be fitted. We do not agree that the method lacks conceptual validity as this method arose from a lack of conceptual validity to the use of pre- and post-progression utilities based on RECIST during the ipilimumab appraisals (the first I-O to be appraised) and was suggested as a better measure at that time by the consulted clinicians. As stated in the response to question B1, this approach has since been used in numerous appraisals.

We do agree that providing sensitivity analysis looking at the impact of progression status on utilities is a valuable exercise to determine its usefulness based upon the data available. Additional utility analyses have therefore been added in to the cost-effectiveness model. Further utility analysis based on IMpower 133 trial data is now available for selection, modelling utility as a function of treatment arm and treatment status, treatment arm and progression status, and treatment arm with progression status and adverse event status (whether or not a patient had an AE pre-progression).

Since pre-progression and post-progression, and on-treatment and off-treatment utilities were modelled independently of each other, comparing statistical fit between them using AIC/BIC is not possible. However, the new options allow the user to test model sensitivity to the utility model approach. There is little utility impact between pre- and post-progression using the approach (0.7416 and 0.7364 for Atezo+C+E and Carbo+E, respectively, versus 0.7276). This suggests that within the data available, progression has had little impact on quality of life. Since time to death was previously accepted in the atezolizumab NSCLC appraisal (16), and clinicians supported the use of time to death utilities in this model, this approach has been kept as the base case.

There were no instances of utility values exceeding 1 therefore application of the approach suggested by Basu, 2012 (26) was not needed.

Scenario analysis has been conducted using the alternative utility models, with the results presented in Table 21. The switch for these alternative utility model options can be found in cell F37 of the Model Inputs sheet.

Table 21: Scenario analysis using alternative utility models

Parameter	Value	inc. vs Carb + Etop		inc. vs Cispl + Etop		ICER vs	
		QALYs	Costs	QALYs	Costs	Carb + Etop	Cispl + Etop
Utility model	IMpower 133 (proximity to death) - base case	XXX	XXX	XXX	XXX	£49,588	£47,477
	IMpower133 (On/Off treatment)	XXX	XXX	XXX	XXX	£52,557	£50,485
	IMpower133 (Off/On progression)	XXX	XXX	XXX	XXX	£53,724	£51,314
	IMpower133 (Off/On progression)+ AE3+	XXX	XXX	XXX	XXX	£53,822	£51,404

Model structure

B6. The company uses a partitioned survival model approach, which has been criticised in technical support document 19 from the Decision Support Unit. Could the

company explain whether alternative model approaches were considered (e.g. state transition model) and justify why these were not considered in the company submission.

As stated in Section B3.2.2.2 of the submission given the relative maturity of both OS and PFS data from the IMpower133 study and the short time frame during which this high proportion of observed events is achieved (due to the aggressive nature of this disease), it was considered that a standard partitioned survival analysis was the most appropriate approach.

The key concern raised within TSD19 is that "the lack of structural link between endpoints in partitioned survival analysis models may increase the potential for inappropriate extrapolation, and may make it difficult to understand the mechanisms underpinning extrapolations and therefore to assess their clinical and biological plausibility."

In our case the level of data maturity is high meaning that the reliance on extrapolation and therefore the potential for inappropriate extrapolation is lower than in many other recent immuno-oncology submissions. This is particularly the case when the fact that data is available from the Flatiron Health database is available to validate and inform projections.

TSD19 also recognises that the methods used for robust implementation of state transition modelling are still emerging. We did consider whether using this type of modelling would add benefit for atezolizumab, however, concluded that it would not based on the data maturity available and the significantly overlapping log cumulative hazard plots between treatment arms in post-progression survival which further supported the view that an alternative structure such as a state transition model with tunnel states, would give no additional accuracy to this data set. Finally, given the monotonic hazard trend observed in log cumulative hazard plots of all the survival estimates (OS, PFS, PPS) and the fact that these endpoints are modelled separately, without a proportionality assumption, the accuracy of the fit and the extrapolation are very robust for a partition survival model. We believe that both progression free and post-progression transitions can be very accurately captured in this data set, via a PartSA approach. There is neither immature OS (hence PPS) data or biomarker/medical hints post-progression indicating potential non-monotonic hazard trends, to suggest that a different modelling approach would add any more value.

B7. Priority question**:** Please provide parametric survival curve graphs for all parametric distributions assessed so that the ERG can validate the fit by visual inspection.

Graphs plotting the Kaplan Meier and parametric survival curve fits are available in the 'KM PFS' and 'KM OS' tabs of the cost-effectiveness model, submitted along with this response.

Since the OS extrapolation is the most impactful on the cost-effectiveness calculation, graphs plotting these curve fits are presented below. Figure 11 for the OS extrapolation of the atezolizumab arm and Figure 12 for the control arm. A visual inspection of the curve fit is one aspect of the choice of optimal parametric extrapolation, but should not be considered in isolation. Consideration should also be given to AIC and BIC criteria and most importantly to clinical plausibility. These have been considered as a whole in B.3.3.2 and B.3.3.3 of the submitted Document B, and although the IMpower133 data are updated here the recommendation of a log-logistic extrapolation for OS remains unchanged.

Figure 11: Fully parametric extrapolations of OS for the atezolizumab treated arm

Figure 12: Fully parametric extrapolations of OS for the control arm

Pocock et al (27) states that visual inspection is only relevant until the point where 10–20% of the original number at risk remain within the KM. For the XXXXXXXXX IMpower133 study analysis update, where there are fewer censored data points, this point for the OS extrapolation is now around XXXXXXXXX in the atezolizumab arm and XXXXXXXXX arm (see A10).

B8. Priority question: Please update all analyses of survival data, including OS, PFS and TTOT in response to any changes to data requested in Section A, specifically questions A10 to A12. Please therefore also update the CEA model accordingly.

The updated OS data from the [redacted] IMpower133 study have been incorporated into the cost-effectiveness model submitted with this response, and are detailed in response to question A10.

As with the submitted appraisal dossier, the best-fit parametric extrapolations for the updated IMpower133 trial OS analysis are Log-logistic and Weibull approaches. A comparison of the AIC and BIC values are reported in Table 22. Although the Weibull and the Log-logistic extrapolations have similar statistical measures of goodness of fit – according to AIB and BIC criteria - the Weibull extrapolation does not report clinically plausible OS results, due to the convergence of the atezolizumab and control arm curves at 50 months. Of these two parametric extrapolations, only the Log-logistic approach modelled the continued benefit of

atezolizumab in untreated, ES-SCLC patients reported in the updated IMpower133 analysis and expected by clinicians.

Table 22: Comparison of fit and plausibility for OS parametric extrapolations approaches

	AIC Atezo	BIC Atezo	AIC control	BIC control	Visual fit and clinical plausibility	Overall Ranking
Log-logistic	469	476	483	490	Best fit and most plausible	1
Weibull	468	475	490	497	Good fit for data but not plausible tail	2
Gen Gamma	470	480	491	501	Poor fit	3
Gompertz	476	482	506	512	Poor fit	4
Exponential	491	494	518	521	Poor fit	5
Log normal	499	506	517	524	Poor fit	6

The plot of the IMpower133 updated OS data is presented with a Log-logistic or a Weibull extrapolation parametric below (Figure 13, Figure 14). This clearly demonstrates how the Weibull extrapolation has a clinically implausible absence of sustained atezolizumab benefit over time. Only the Log-logistic extrapolation has a good AIC and BIC fit and reports a clinically plausible long-term survival rate and ongoing atezolizumab benefit.

Figure 13: Log-logistic extrapolation of IMpower133 OS data

Figure 14: Weibull extrapolation of IMpower133 OS data

As in the originally submitted appraisal dossier, having the long-term OS estimates informed by the IMpower133 trial and Flatiron Health datasets jointly or just the Flatiron Health data improves the clinical plausibility of the OS extrapolation as well as the cost-effectiveness. However, since there are no established methods published in the NICE methods guide for incorporating RWD into a NICE cost-effectiveness model, a conservative approach has been taken here and only the fully parametric extrapolation is applied to the base case model. Table 23 summarises the alternative RWD scenarios presented here to validate the Log-logistic extrapolation approach.

In line with the appraisal dossier submitted in February 2019, Roche consider the end of life criteria to be applicable to this appraisal. Using the base case model assumptions, atezolizumab is associated with a mean benefit of 4.8 months and a median benefit of 2.5 months. This is consistent across different extrapolation approaches (Table 23). As with the previous NICE appraisal of paclitaxel with gemcitabine for untreated metastatic pancreatic cancer (TA476), Roche consider ES-SCLC to be a sufficiently severe disease to warrant flexibility in the interpretation of the end of life criteria.

Table 23: Survival extrapolations for the control arm, using different statistic approaches and data sources

Time (months)	Parametric extrapolations		Real-world data of chemotherapy survival validated as appropriate by UK practising experts*		
	Log-logistic control arm – February submission	Log-logistic updated, control arm – base case		Log-logistic (updated) with Flatiron data after 22 months (generalised gamma)*	Log-logistic (updated) with Flatiron data after 22 months (Log-logistic)*
12	XXX	XXX	XXX	XXX	XXX
24	XXX	XXX	XXX	XXX	XXX
36	XXX	XXX	XXX	XXX	XXX
48	XXX	XXX	XXX	XXX	XXX
60	XXX	XXX	XXX	XXX	XXX
ICER	£45,893	£49,588	N/A	£45,873	£53,191
Mean difference in survival (months)	XXX	XXX	N/A	XXX	XXX
Median difference in survival (months)	XXX	XXX	N/A	XXX	XXX

*FlatIron Health cycle probability of death is applied from data-cut off

No cost-effectiveness analysis is presented for the XXXX XXXX XXXX due to the data limitations outlined in response to question A12 and B16.

B9. Section B3.2 in the company submission states that a de novo model was constructed because: "…there are no published economic analyses for first-line ES-SCLC from a UK perspective…". However, there was one by Uyl-de-Groot, 2006, from a Netherlands perspective, which might be informative in terms of model structure. Also, TA184 modelled relapsed small cell lung cancer (SCLC), which might be informative in terms of model structure and parameterisation later in any model for this appraisal. Therefore, could the company please validate their de novo model by comparison with both the Uyl-de-Groot, 2006 and TA184 models?

To make the comparison between SCLC models requested here, the 'features of the economic analysis' table submitted with Document B (Section B.3.3.2, Table 20) has been reproduced

below. As requested, a comparison is made here between Uyl-de-Groot 2006 hypothetical drug model and the NICE appraisal of topotecan to treat relapsed SCLC (TA184).

The model details described in Table 24 outline the limitations of comparing these model approaches, and demonstrate further why a *de novo* model was required here for the appraisal of atezolizumab for untreated ES-SCLC. The key limitations in terms of relevance for this appraisal are the study populations which do not match the population for this appraisal and the age of the two studies.

Table 24: Features of the economic analysis

	Previous appraisals	**Published models**	**Current appraisal: ID1504**	
Factor	**NICE TA184 (28)**	**Uyl-de-Groot 2006 (29)**	**Chosen values**	**Justification**
Condition	Relapsed SCLC	Advanced SCLC (it is unclear how advanced SCLC has been classified)	Untreated ES-SCLC	Matches pivotal trial data and expected to match MA
Intervention	Topotecan	Hypothetical drug	Atezolizumab in combination with carboplatin-etoposide, followed by atezolizumab monotherapy	Matches pivotal trial data and expected to match MA
Country perspective	England; NICE	Netherlands	England; NICE	NICE submission
Publication year	2009	2006	2019	In line with the expected MA
Model structure	Survival model with the entry health state as relapsed SCLC; progression and death.	Markov chain model with four states: 'Response', 'Stable disease', 'Progressive disease', 'Death' Since this if for a hypothetical	Partitioned survival analysis (area under the curve approach)	Commonly accepted by NICE committees as appropriate for modelling the costs and benefits of treatments for lung oncology, and fits the data available (see response to question B6)

		drug, the probabilities of these events were based on expert opinion		
Time horizon	Lifetime (5 years for relapsed SCLC)	Not specified	Lifetime (20 years for untreated ES-SCLC)	NICE reference case. Time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies being compared
Cycle length	21 days	Model cycle length not specified, however the treatment cycles referred to are 28 days	1 week	In line with previous NICE appraisals of lung cancer treated with cancer immunotherapy treatments
Half-cycle correction	Not specified	Not specified	Included	In line with previous NICE appraisals of lung cancer treated with cancer immunotherapy treatments and included here to mitigate potential bias
Were health effects measured in QALYs; if not, what was used?	Yes	Yes	Yes	NICEs reference case (84). Only direct health effects related to patients were considered, with no wider societal impact or impact on carers are included
Discount of 3.5% for utilities and costs	Not specified, but expected to match NICE's methods Guidance of 3.5%	Discount applied; unspecified what the base case discount value is but a scenario using 4% discount rate was considered	Yes	NICEs reference case (84)
Perspective (NHS/PSS)	Yes	Societal perspective but focused on direct	Yes	NICEs reference case (84)

		medical cost		
Treatment benefit cap	Not specified	Not specified	Treatment benefit capped at 5 after diagnosis	XXXXXXXXXx XXXXXXXXX XXXXXXX). Removal of this assumption is considered in Section B.3.8.
Source of utilities	Reported in the relevant RCTs	Utilities were derived from an overview study in patients with lung cancer and expert opinion	IMpower133 trial, EQ-5D individual patient level data	NICEs reference case (84)
Source of costs	Cost year 2007-2008	Dutch healthcare price sources for 2002 cost year presented in €	XXXXX XXXX XXX XXX XXX XXX XXX XX XXX XXX Unit costs derived from NHS reference costs (85) and eMIT (14)	Expert opinion sought in the absence of published literature. Widely accepted sources of cost and resource use data of relevance to the NHS

B10. Priority question**:** Could the company please explain what happens to patients "off treatment"? The ERG would like know when patients come off therapy what happens next in the care pathway.

a) Do they go to 2nd line treatment? If so could the company, please provide details as to the proportion of patients receiving each treatment.

b) NICE Technology Appraisal 184 recommends topotecan for recurrent SCLC. Could the company explain why this is not incorporated in the CEA model.

c) Do they have palliative therapy? If so could the company, please provide details as to the proportion of patients receiving each treatment.

Due to this appraisal being the first for the treatment of untreated ES-SCLC, not all relevant information is readily available, as it would be in conditions that have been appraised more often, such as NSCLC. As such, Roche has sought the advice of practicing NHS oncologists to inform model assumptions that are not defined within published literature. Subsequent therapies after relapse of ES-SCLC is one of these areas where expert clinical advice has constituted the best available evidence to inform model assumptions. The dossier submitted

to NICE included expert advice on subsequent treatment rates surveyed at an advisory board held in November 2018; this is described in section B.3.5.1 of the submitted dossier and is presented as a scenario in the cost-effectiveness model. To further consider the questions posed here, a subsequent advisory board meeting was held in March 2019 where subsequent treatment rates for relapsed ES-SCLC were discussed once more. The responses from this March 2019 advisory board are summarised below and included in the cost-effectiveness model submitted alongside this response.

a) Advice from UK practising oncologists is that after completion of first-line treatment, approximately 10-20% patients move to second-line treatment once their disease has relapsed. The pathway for treatment at second line is not standardised, however, in general in UK clinical practice patients are treated by either a re-challenge with their first-line chemotherapy, treated with topotecan or treated with cyclophosphamide, doxorubicin and vincristine (CAV). There is variation between treatment centres in terms of the proportion of patients receiving each of these treatments. The consensus from the advisory board meeting in March 2019 was that a third of patients would be attributed to each of the three predominant second-line therapies: re-challenge, topotecan and CAV. It is important to note that although topotecan is recommended by NICE for relapsed ES-SCLC, few patients receive topotecan as it is not regarded as an efficacious treatment in this setting by this group of advisors.
b) Topotecan therapy was included as a subsequent treatment in the submitted cost-effectiveness model, with treatment rates in the model base case taken from the IMpower133 study. As stated in Section B.3.5.1 of the submission in order to match the information provided on costs and effectiveness subsequent therapy information included in the economic model was taken from the IMpower 133 study. The most frequently used therapies were platinum combinations (particularly platinum and etoposide), topotecan and CAV which is in line with UK clinical practice. As discussed above, this trend is in line with the experience of over 20 UK practising NHS oncologists who informed Roche that in UK clinical practice topotecan is not the preferred choice of second line treatment, as it is not deemed to be efficacious in this group of patients. Furthermore, the NICE clinical guideline suggests topotecan be used only in patients for whom CAV is contraindicated or re-treatment with first-line therapy is not appropriate.
c) Advice from UK practising oncologists suggests that after first-line treatment, approximately 80-90% of patients will either receive palliative care or surveillance only. Hence, no further active treatment will be given to 80-90% of ES-SCLC patients in the NHS, following their relapse. This is discussed further in the response to question B20.

Due to the differences in expert opinion regarding the proportion of patients receiving subsequent therapy between advisory board meetings held in November 2018 and March 2019 and the IMpower133 trial, an additional scenario analysis has been included here to test the model sensitivity to this input (Table 25). This uses the switch found in cell F126 of the Cost Inputs sheet. As can be seen in Table 10, this variation in expert clinical option has minimal impact on the cost-effectiveness calculation.

Table 25: Scenario analysis for source of proportion of patients receiving subsequent therapy

Parameter	Value	inc. vs Carb + Etop		inc. vs Cispl + Etop		ICER vs	
		QALYs	Costs	QALYs	Costs	Carb + Etop	Cispl + Etop
	IMpower133 - base case	XXXX	XXXX	XXXX	XXXX	£49,588	£47,477
	Clinical opinion Nov-18	XXXX	XXXX	XXXX	XXXX	£49,759	£47,641
Data source for post-discontinuation therapy	Clinical opinion Mar-19	XXXX	XXXX	XXXX	XXXX	£49,789	£47,670

B11. Priority question**:** The formula for probability of surviving in column AO of the tab Atezo+C+E includes the max() function, which ensures that the probability of surviving with atezolizumab can never be less than that for the comparator carboplatin + etoposide. This appears to be a bias in favour of atezolizumab. Therefore, could the company please remove this function in the CEM.

The formula described in B11 is required within the base case of the cost-effectiveness model to ensure clinically implausible results are not generated when estimating long-term survival of ES-SCLC patients. This formula implements the clinical assumption that patients who have received atezolizumab plus carboplatin-etoposide will not at any time have a greater risk of death than patients who have received only carboplatin-etoposide therapy. This assumption was supported as being clinically appropriate at both the November 2018 and March 2019 clinical advisory board meetings attended by practicing NHS oncologists from across the UK (see Appendix K of the original submission dossier).

However, to demonstrate the minimal impact on the cost-effectiveness calculation of this assumption, a scenario has been included here where it can be considered without this assumption. The switch for this scenario is found in cell F145 of the Model Inputs sheet. The resulting ICER values are presented in Table 26, where it is demonstrated that there is minimal impact on the cost-effectiveness.

Table 26: Scenario analysis allowing the Atezo+C+E cycle hazard to exceed Carbo+E

Parameter	Value	inc. vs Carb + Etop		inc. vs Cispl + Etop		ICER vs	
		QALYs	Costs	QALYs	Costs	Carb + Etop	Cispl + Etop
Allow Atezo+C+E cycle hazard to exceed the cycle hazard for Carbo+Etop	Yes	XXXX	XXXX	XXXX	XXXX	£49,588	£47,476
	No (base case)	XXXX	XXXX	XXXX	XXXX	£49,588	£47,477

Comparators

B12. Priority question**:** The scope does not exclude cisplatin-based regimens. Appendix K indicates that the clinical experts who were questioned, believe that about 5% of patients in the UK would be prescribed cisplatin-etoposide. However, this implies that for at least some patients this is standard care. Therefore, the ERG requests that the company incorporate a comparison with cisplatin plus etoposide in all analyses including a full incremental analysis as part of the base case of the CEA.

The NICE methods guide states that ""Standard decision rules should be followed when combining costs and QALYs. *When appropriate*, these should reflect when dominance or extended dominance exists, presented thorough incremental cost–utility analysis."

The purpose of performing fully incremental analysis is to be able to determine the ICER of your intervention vs the relevant (next most cost-effective) therapy in the decision problem population. In order for a fully incremental analysis to be appropriate therefore all therapies included in the analysis should be used to treat the same patient population (i.e. a choice exists between these therapies and they all apply to the same decision problem population). A fully incremental analysis is not appropriate where comparators are used for different sub-populations within the decision problem population as this choice does not exist. This is the

case for the 5% of patients who receive cisplatin plus etoposide, since they are considered to be borderline LS-SCLC patients. As described in response to question A14, Roche has been advised that cisplatin plus etoposide is not standard of care for untreated, ES-SCLC patients. Therefore, an incremental analysis with carboplatin plus etoposide is not considered to be appropriate within this appraisal.

However, for the purpose of this response, a fully incremental cost-effective analysis has been presented for the company base case deterministic analysis in Table 27. As cisplatin plus etoposide provides less QALYs and is more expensive to administer than carboplatin plus etoposide, it is dominated. Hence, excluding cisplatin plus etoposide is a conservative approach in terms of the ICER calculation.

Table 27: Full incremental cost-effectiveness analysis, company base case, PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Strong dominance	Dominance	ICERs
Carboplatin-etoposide	[redacted]	[redacted]	[redacted]						
Cisplatin-etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Strictly dominated	Strictly dominated
Atezolizumab plus carboplatin-etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,477		£49,588

B13. NICE Clinical Guideline 121 states that etoposide is usually added to chemotherapy and so this indicates that some people do not receive etoposide. It does not explicitly state that only those for whom etoposide is contraindicated do not receive it. Therefore, could the company please either provide evidence to support the exclusion of chemotherapy without etoposide as a comparator or conduct a cost-effectiveness analysis with chemotherapy without etoposide as a comparator.

Roche have been advised by over 20 practising NHS oncologists during individual consultation meetings and two advisory board meetings that the standard of care in the NHS for untreated, ES-SCLC is up to 6 cycles of carboplatin plus etoposide. Therefore, UK clinicians will

preferentially use etoposide in combination with carboplatin for this patient population, unless etoposide is contraindicated. Furthermore, since patients that are unable to receive etoposide would not be eligible to receive the regimen in the IMpower133 trial this is therefore not in scope for this appraisal. This is in line with the response to question A14.

B14. According to the NICE care pathway for treating small-cell lung cancer, up to six cycles of carboplatin-etoposide is offered depending on response and toxicity. See Treating small-cell lung cancer

a) Could the company please explain why carboplatin-etoposide is restricted to up to 4 cycles in the company submission and explain the implications, in terms of costs and benefits of allowing up to 6 cycles.

b) Please amend the base case to include up to 6 cycles of carboplatin-etoposide.

In line with the IMpower 133 trial, the cost-effectiveness model analysis restricts carboplatin-etoposide use to 4 cycles. This matches the costs and effectiveness data from the pivotal study. This restriction was included in IMpower133 to allow an international standard for the trial and broad inclusion of patients (30, 31). Clinical opinion from the November 2018 and March 2019 advisory board meetings report that within the NHS, the number of chemotherapy treatment cycles varied between centres, but it was acknowledged that there was no evidence of an OS from >4 chemotherapy cycles in ES-SCLC patients (32). What evidence there is available comparing effectiveness shows no statistically significant differences in clinical outcomes between 4 cycles and greater than 4 cycles of chemotherapy in stage IV SCLC patients (32)

Based upon this, a scenario analysis is provided in the updated model using the time to off treatment data from IMpower133 to estimate the impact of a small number of patients receiving up to 6 cycles of chemotherapy. This only impacts the costs, and not the efficacy as there is no evidence to suggest a benefit from 6 chemotherapy cycles. If 6 cycles of chemotherapy are used in clinical practice, the base case model assumption of 4 cycles can therefore be considered conservative, as the incremental costs for the carbo+E and cispl+E arms would increase due to the additional administration costs that atezolizumab already incurs to some extent due to atezolizumab monotherapy during the maintenance phase.

The scenario analysis result showing the impact of increasing the maximum duration of chemotherapy is shown in Table 28 (using the switch in cell F39 on the Cost Inputs sheet).

Table 28: Scenario analysis increasing the maximum duration of chemotherapy

Parameter	Value	inc. vs Carb + Etop		inc. vs Cispl + Etop		ICER vs	
		QALYs	Costs	QALYs	Costs	Carb + Etop	Cispl + Etop
Maximum duration of carbo/cispl+etoposide treatment	4 cycles (base case)	XXXX	XXXX	XXXX	XXXX	£49,588	£47,477
	6 cycles	XXXX	XXXX	XXXX	XXXX	£49,476	£47,360

B15. In reference to table 1 in the company submission, could the company please clarify how unmanageable toxicity has been defined.

Whether toxicity was unmanageable, and therefore warranted discontinuation, was determined by the investigator on a case-by-case basis. In the IMpower133 trial protocol it is advised that investigators had the responsibility to determine intolerable toxicity and unacceptable immune-mediated adverse events, given each individual patient's potential response to therapy and the severity of the event.

Please note that unmanageable toxicity from atezolizumab is only one of several conditions that necessitated study treatment discontinuation, as outlined in the protocol.

Population

B16. Priority question: Table 1 in the company submission (pages 12-14) states "[redacted]

[redacted]" Could the company please ensure that the results of these analyses are incorporated in the CEA.

No cost-effectiveness analysis is presented for the [redacted] due to the data limitations outlined in response to question A12. Particularly it is important to re-iterate that only [redacted] were included in the [redacted] and that the IMpower133 trial was not designed to statistically test clinical benefit [redacted]. Meaning, this exploratory data provided should be interpreted with caution.

B17. Section B.3.5.2 of the company submission states that 90% of the cohort were assumed to receive prophylactic cranial irradiation (PCI). PCI was assumed to be received every 3 weeks for a maximum of 5 doses.

a) Could the company please provide a justification for 90% receipt of PCI and if it is uncertain then conduct sensitivity analyses over a range that is also justified.

This response is incorporated into the response to B17b.

b) NICE Clinical Guideline121 states that PCI should be offered to those with ES-SCLC and WHO performance status 2 or less, if their disease has not progressed on first-line treatment. Therefore, could the company indicate the percentage of the cohort for whom this is the case if not 90% and conduct the CEA with this revised percentage.

The March 2019 advisory board of practicing NHS oncologists highlighted that the proportion of patients receiving PCI is highly variable across the UK. However, overall it was agreed that PCI rates were falling due to conflicting evidence in the literature of the survival benefits of PCI, whilst the risk of AEs were clearly reported (33). At the November 2018 advisory board the consensus was that 90% of patients would receive PCI, however at the March 2019 advisory board consensus was that only 55% of patients would receive PCI. In addition, the rate of PCI in the IMpower133 trial was only 11% (1)ho. Based on this variability and the latest expert clinical opinion, the base case analysis has been updated to 55% of patients receiving PCI, with uncertainty incorporated within PSA using a uniform distribution between 0% and 100% given the large amount of variation. The one-way sensitivity analysis (OWSA) for these inputs are shown in Table 14.

c) Could the company please conduct sensitivity analysis to show the effect of variation in PCI frequency on the incremental cost-effectiveness ratio (ICER).

The frequency of PCI has been varied using a uniform distribution with limits of between 1 and 5 weeks, and the OWSA results shown in Table 14.

d) Could the company please explain how the number of doses was determined in the model and, if this is uncertain then conduct sensitivity analysis to show the effect of variation on the ICER.

A base case input of a maximum of 5 doses was assumed in the model based on the feedback from the November 2018 advisory board. In order to test the model sensitivity to the number of doses, the maximum number of doses has been varied using a uniform distribution with limits of 5 and 12 doses (based on the max number of doses for standard PCI identified in the Schild review (33)), and the results presented in Table 29.

Table 29: One-way sensitivity analysis for PCI parameters for Atezo+C+E versus Carbo+E, PAS price

Parameter	Base case value	Base case ICER	Lower value (0%)	Lower ICER	Upper value (100%)	Upper ICER
Proportion of patients with PCI	0.55	£49,588	0.10	£49,581	0.91	£49,594
Frequency of PCI	3.00		1.42	£49,587	4.56	£49,724
Max dose of PCI	5.00		5.75	£49,614	11.32	£50,238

B18. NICE Clinical Guideline 121 states that thoracic radiotherapy should be considered after chemotherapy if there has been a complete response at distant sites and at least a good partial response within the thorax. Therefore, could the company please incorporate this for the applicable percentage of the cohort in the CEA model.

The IMpower133 trial did not allow patients to receive consolidative or curative thoracic radiotherapy as described in the NICE guidance. This decision was made based on evidence from the CREST trial which failed to meet its primary endpoint. The CREST trial is a phase 3 international randomised control trial that included 22 sites in the UK. The trial included patients with ES-SCLC that had responded to chemotherapy and investigated whether

treatment with consolidative thoracic radiotherapy would lead to an improvement in overall survival. The study failed to meet its primary endpoint of overall survival at 1 year (34).

Consultation with over 20 practising NHS oncologists has also suggested that the use of consolidative thoracic radiotherapy across hospitals in the UK is extremely varied. In addition, they highlighted the lack of supporting evidence of the use of consolidative thoracic radiotherapy with the IMpower133 regimen requiring caution in combining these two treatments from a patient safety perspective.

Palliative thoracic radiotherapy however was permitted in the IMpower133 trial, with 3 (1.5%) patients in the atezolizumab arm and 4 (2.0%) patients in the placebo arm receiving this treatment.

We did not incorporate these percentages into the cost effective model as they are representative of palliative thoracic radiotherapy and not consolidative radiotherapy as outlined in the NICE guidance, also they were infrequent and balanced across the two treatment arms.

Costs

B19. Proximity to death is used as a way of classifying utilities. One would also expect higher levels of palliation/terminal care for patients with lower utility. Therefore, could the company provide cost estimates relating to proximity to death and incorporate in the CEA model.

Roche are not aware of any cost sources for SCLC that report costs as a function of time to death. However, it is clear that higher levels of palliation/terminal care will be required for patients with lower utility, at the end of their lives. We capture this using a one-off cost for terminal care as described in Section B.3.5.2 of the company submission.

B20. Priority question: The company estimates the cost of terminal care as a fixed cost i.e. independent of number of days in receipt of terminal care.

a) Could the company please provide more details of what constitutes terminal care using a framework similar to that in TA483 (Nivolumab for NSCLC)?

In TA483 (35), terminal care was assumed to be comprised of hospitalisation, in home care (MacMillian nurse) or hospice care. These costs were individually itemised, with a total cost calculated by weighting the proportion of time spent in each setting. This total was applied as a one-off cost.

The details of terminal care included as part of this submission are provided in the reference pack for this submission. The chosen source for this input is from small-cell lung cancer patients – Oliver et al. 2001 (36):

> *Bone pain was treated with radiotherapy and/or intravenous bisphosphonates, spinal cord compression mainly with radiotherapy and steroids. Short stays in hospital or hospice became more frequent over time once the disease became progressive. The palliative care service provided support for patients at home through district nurses, palliative care physicians, dietary advice, and psychological support. Social services provided in home assistance of various kinds and day hospice care was also available.*

Unfortunately, this reference does not report itemised frequency of resources included for terminal care costs, as per the TA483 submission.

However, at the March 2019 advisory board, clinicians did not agree with the use of the terminal care costs from Oliver et al. 2001, stating that these costs were out-of-date and not applicable to current NHS practice. Therefore, the company base case analysis has been updated to use the terminal care cost used for TA483, inflated to 2018 costs.

b) Could the company use this framework to estimate cost per day and incorporate this in the CEA model?

The method used to apply terminal care costs (one-off cost upon death) is consistent with recent previous lung cancer appraisals (16, 21, 35). Applying the cost of terminal care as a cost per day, rather than a one off cost, is likely to favour the atezolizumab arm, as more discounting will apply – those patients living longer (on the atezolizumab arm) will have more heavily discounted terminal care costs. A scenario has been presented in Table 30, to show the limited impact of changing terminal care costs to those used in TA483 or removing them

entirely, demonstrating that this is not a key driver of cost-effectiveness. The switch for this scenario has been added to F139 of the Cost Inputs sheet.

Table 30: Scenario analysis removing terminal care costs

Parameter	Value	inc. vs Carb + Etop		inc. vs Cispl + Etop		ICER vs	
		QALYs	Costs	QALYs	Costs	Carb + Etop	Cispl + Etop
Terminal care cost options	None	XXXX	XXXX	XXXX	XXXX	£49,761	£47,651
	Oliver et al. 2001	XXXX	XXXX	XXXX	XXXX	£49,475	£47,363
	TA483 - base case	XXXX	XXXX	XXXX	XXXX	£49,588	£47,477

B21. Section B.3.5.1 of the company submission states (page 86): "To best reflect the likely impact on the NHS, the base case model includes the actual dosing from IMpower133 study and vial sharing assumptions (i.e., no wastage) for the administration of chemotherapy drugs in the model. Atezolizumab is given at a fixed dose. The impact of these assumptions is considered in scenario analyses in Section B.3.8."

a. Could the company please provide any scenario analyses on degree of vial sharing.

b. Given that vial sharing can be difficult in clinical practice, could the company please include a scenario where there is no vial sharing.

The option for vial sharing in the cost-effectiveness model is only applied to carboplatin and etoposide treatments, as atezolizumab is given as a fixed dose. These are generic and frequently used drugs. The option to exclude or modify vial sharing assumptions is available on the 'Cost Inputs' sheet in cell F35 and F37 - this allows vial sharing to be excluded from the analysis of cost-effectiveness (F35) or for the ERG to input a different proportion of vial sharing (F37).

Section C: Textual clarification and additional points

Model errors

C1. Priority question: The equation for PFS probability in column W included a test, which resembled that for OS probability e.g. IF(AND(effect_dur_pfs=Settings!I11,options_trt,D267≤t_effect_dur_pfs)

However, it is incorrect and thus prevented any response to variation in duration of treatment effect. Instead it should be:

IF(AND(effect_dur_pfs=Settings!I$10,options_trt,D267>t_effect_dur_pfs)

Could the company please make this correction.

Roche have submitted a cost-effectiveness model with this ERG response which includes the amended formula described in C1.

In addition, a second error was identified in the model, in the VBA code that creates the cost-effectiveness acceptability curve. This has been corrected in the submitted model, and an updated CEAC diagram is presented on page 112 in Appendix 7 (Figure 29).

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Appendix 1: Response to question A1

Original search strategies - performed on 1 July 2018.

Embase 1974 to 2018 June 29: accessed July 1st 2018

#	Searches	Results
1	exp small cell lung cancer/ or exp lung small cell cancer/	6077
2	(small cell lung adj (cancer or tumo?r or carcinoma or malignan*)).mp.	102415
3	(oat cell adj (cancer or tumo?r or carcinoma or malignan*)).mp.	1228
4	1 or 2 or 3	103607
5	exp carboplatin/	60689
6	(carboplat* or carbosin or carbotec or erbakar or ercar or oncocarbin or paraplatin).mp.	62997
7	exp cisplatin/	164235
8	(cisplatin or cismaplat or cisplatina or 'cis-platinum' or cysplatyna or 'peyrones chloride' or 'peyrones salt' or platinoxan or platinol or abipltin or blastolem or briplatin or cisplatyl or citoplatino or citosin or lederplatinOR metaplatin or neoplatin or placis or platamine or platiblastin or platinex or platiran or platistin or platosin).mp.	171564
9	exp etoposide/	81150
10	(etoposide or lastet or 'vp-16' or 'vp-16-213').mp.	84034
11	exp irinotecan/	33478
12	(irinotecan or calmtop or campto or camptosar or irinotel or topotecin).mp.	34545
13	(Atezolizumab or Tecentriq).mp.	1819
14	exp atezolizumab/	1758
15	(paclitaxel or taxol or anzatax or asotax or bristaxol or praxel).mp.	98163
16	exp paclitaxel/	93057
17	5 or 6	62997
18	7 or 8	171564
19	9 or 10	84034
20	11 or 12	34545
21	15 or 16	98163
22	17 and 19	19078

23	18 and 19	35482
24	17 and 20	5720
25	17 and 21	29375
26	13 or 14 or 22 or 23 or 24 or 25	69034
27	Clinical trial/	968071
28	Randomized controlled trial/	507666
29	Randomization/	78496
30	Single blind procedure/	31699
31	Double blind procedure/	151259
32	Crossover procedure/	55930
33	Placebo/	327123
34	Randomi?ed controlled trial$.tw.	183545
35	Rct.tw.	28932
36	Random allocation.tw.	1844
37	Randomly allocated.tw.	30149
38	Allocated randomly.tw.	2352
39	(allocated adj2 random).tw.	883
40	Single blind$.tw.	21333
41	Double blind$.tw.	190510
42	((treble or triple) adj blind$).tw.	821
43	Placebo$.tw.	276157
44	Prospective study/	457424
45	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	1939551
46	Case study/	55089
47	Case report.tw.	366652
48	Abstract report/ or letter/	1066236
49	46 or 47 or 48	1479221
50	45 not 49	1890528
51	4 and 26 and 50	5041

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to June 27, 2018: accessed July 1st 2018

#	Searches	Results
1	exp Small Cell Lung Carcinoma/	3129
2	exp Carcinoma, Small Cell/	16973
3	(small cell lung adj (cancer or tumo?r or carcinoma or malignan*)).mp.	59796
4	(oat cell adj (cancer or tumo?r or carcinoma or malignan*)).mp.	760
5	1 or 2 or 3 or 4	70332
6	exp CARBOPLATIN/	10753
7	(carboplat* or carbosin or carbotec or erbakar or ercar or oncocarbin or paraplatin).mp.	16110
8	exp CISPLATIN/	47936
9	(cisplatin or cismaplat or cisplatina or 'cis-platinum' or cysplatyna or 'peyrones chloride' or 'peyrones salt' or platinoxan or platinol or abipltin or blastolem or briplatin or cisplatyl or citoplatino or citosin or lederplatinOR metaplatin or neoplatin or placis or platamine or platiblastin or platinex or platiran or platistin or platosin).mp.	69014
10	exp ETOPOSIDE/	15927
11	(etoposide or lastet or 'vp-16' or 'vp-16-213').mp.	24593
12	(irinotecan or calmtop or campto or camptosar or irinotel or topotecin).mp.	9832
13	(Atezolizumab or Tecentriq).mp.	386
14	exp PACLITAXEL/	24025
15	(paclitaxel or taxol or anzatax or asotax or bristaxol or praxel).mp.	34985
16	6 or 7	16110
17	8 or 9	69014
18	10 or 11	24593
19	14 or 15	34985
20	17 and 18	8094
21	16 and 18	3216
22	12 and 16	427
23	16 and 19	5498
24	13 or 20 or 21 or 22 or 23	15509

Clarification questions

25	Randomized controlled trials as Topic/	116849
26	Randomized controlled trial/	463068
27	Random allocation/	94832
28	Double blind method/	146265
29	Single blind method/	25302
30	Clinical trial/	510879
31	exp Clinical Trials as Topic/	314947
32	25 or 26 or 27 or 28 or 29 or 30 or 31	1078074
33	(clinic$ adj trial$1).tw.	309231
34	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	157340
35	Placebos/	33981
36	Placebo$.tw.	196042
37	Randomly allocated.tw.	24414
38	(allocated adj2 random).tw.	778
39	33 or 34 or 35 or 36 or 37 or 38	554782
40	32 or 39	1308611
41	Case report.tw.	272719
42	Letter/	991385
43	Historical article/	345438
44	41 or 42 or 43	1595296
45	40 not 44	1277204
46	5 and 24 and 45	1929

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#	Searches	Results
1	exp Small Cell Lung Carcinoma/	274
2	exp Carcinoma, Small Cell/	726

3	(small cell lung adj (cancer or tumo?r or carcinoma or malignan*)).mp.	9924
4	(oat cell adj (cancer or tumo?r or carcinoma or malignan*)).mp.	41
5	1 or 2 or 3 or 4	10169
6	exp CARBOPLATIN/	1869
7	(carboplat* or carbosin or carbotec or erbakar or ercar or oncocarbin or paraplatin).mp.	5182
8	exp CISPLATIN/	4367
9	(cisplatin or cismaplat or cisplatina or 'cis-platinum' or cysplatyna or 'peyrones chloride' or 'peyrones salt' or platinoxan or platinol or abipltin or blastolem or briplatin or cisplatyl or citoplatino or citosin or lederplatinOR metaplatin or neoplatin or placis or platamine or platiblastin or platinex or platiran or platistin or platosin).mp.	11312
10	exp ETOPOSIDE/	1588
11	(etoposide or lastet or 'vp-16' or 'vp-16-213').mp.	3748
12	(irinotecan or calmtop or campto or camptosar or irinotel or topotecin).mp.	2209
13	(Atezolizumab or Tecentriq).mp.	257
14	exp PACLITAXEL/	2735
15	(paclitaxel or taxol or anzatax or asotax or bristaxol or praxel).mp.	7557
16	6 or 7	5182
17	8 or 9	11312
18	10 or 11	3748
19	14 or 15	7557
20	17 and 18	1599
21	16 and 18	833
22	12 and 16	136
23	16 and 19	2482
24	13 or 20 or 21 or 22 or 23	4561
25	5 and 24	1951

Updated search strategies - performed on 4 November 2018.

Embase 1974 to 2018 November 02: accessed November 4th 2018

#	Searches	Results
1	exp small cell lung cancer/ or exp lung small cell cancer/	6741
2	(small cell lung adj (cancer or tumo?r or carcinoma or malignan*)).mp.	107588
3	(oat cell adj (cancer or tumo?r or carcinoma or malignan*)).mp.	1143
4	1 or 2 or 3	108695
5	exp carboplatin/	62025
6	(carboplat* or carbosin or carbotec or erbakar or ercar or oncocarbin or paraplatin).mp.	64403
7	exp cisplatin/	167000
8	(cisplatin or cismaplat or cisplatina or 'cis-platinum' or cysplatyna or 'peyrones chloride' or 'peyrones salt' or platinoxan or platinol or abipltin or blastolem or briplatin or cisplatyl or citoplatino or citosin or lederplatinOR metaplatin or neoplatin or placis or platamine or platiblastin or platinex or platiran or platistin or platosin).mp.	174507
9	exp etoposide/	81603
10	(etoposide or lastet or 'vp-16' or 'vp-16-213').mp.	84579
11	exp irinotecan/	34025
12	(irinotecan or calmtop or campto or camptosar or irinotel or topotecin).mp	35141
13	(Atezolizumab or Tecentriq).mp.	2269
14	exp atezolizumab/	2192
15	(paclitaxel or taxol or anzatax or asotax or bristaxol or praxel).mp.	100069
16	exp paclitaxel/	94824
17	5 or 6	64403
18	7 or 8	174507
19	9 or 10	84579
20	11 or 12	35141
21	15 or 16	100069
22	17 and 19	19412
23	18 and 19	35836
24	17 and 20	5788
25	17 and 21	30049
26	13 or 14 or 22 or 23 or 24 or 25	70538

Clarification questions

27	Clinical trial/	950818
28	Randomized controlled trial/	521459
29	Randomization/	79994
30	Single blind procedure/	32954
31	Double blind procedure/	154896
32	Crossover procedure/	57164
33	Placebo/	325911
34	Randomi?ed controlled trial$.tw.	189663
35	Rct.tw.	30055
36	Random allocation.tw.	1869
37	Randomly allocated.tw.	31060
38	Allocated randomly.tw.	2385
39	(allocated adj2 random).tw.	876
40	Single blind$.tw.	21858
41	Double blind$.tw.	192180
42	((treble or triple) adj blind$).tw.	866
43	Placebo$.tw.	280271
44	Prospective study/	481579
45	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	1965032
46	Case study/	57363
47	Case report.tw.	366655
48	Abstract report/ or letter/	1079088
49	46 or 47 or 48	1494051
50	45 not 49	1915061
51	4 and 26 and 50	5120
52	limit 51 to yr="2018 -Current"	171

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to November 02, 2018: accessed November 4th 2018

Clarification questions

#	Searches	Results
1	exp Small Cell Lung Carcinoma/	3253
2	exp Carcinoma, Small Cell/	17025
3	(small cell lung adj (cancer or tumo?r or carcinoma or malignan*)).mp.	61676
4	(oat cell adj (cancer or tumo?r or carcinoma or malignan*)).mp.	760
5	1 or 2 or 3 or 4	72253
6	exp CARBOPLATIN/	10888
7	(carboplat* or carbosin or carbotec or erbakar or ercar or oncocarbin or paraplatin).mp.	16382
8	exp CISPLATIN/	48649
9	(cisplatin or cismaplat or cisplatina or 'cis-platinum' or cysplatyna or 'peyrones chloride' or 'peyrones salt' or platinoxan or platinol or abipltin or blastolem or briplatin or cisplatyl or citoplatino or citosin or lederplatinOR metaplatin or neoplatin or placis or platamine or platiblastin or platinex or platiran or platistin or platosin).mp.	70219
10	exp ETOPOSIDE/	16049
11	(etoposide or lastet or 'vp-16' or 'vp-16-213').mp.	24841
12	(irinotecan or calmtop or campto or camptosar or irinotel or topotecin).mp.	10012
13	(Atezolizumab or Tecentriq).mp.	486
14	exp PACLITAXEL/	24479
15	(paclitaxel or taxol or anzatax or asotax or bristaxol or praxel).mp.	35729
16	6 or 7	16382
17	8 or 9	70219
18	10 or 11	24841
19	14 or 15	35729
20	17 and 18	8170
21	16 and 18	3252
22	12 and 16	433
23	16 and 19	5605
24	13 or 20 or 21 or 22 or 23	15811
25	Randomized controlled trials as Topic/	119218
26	Randomized controlled trial/	470768

27	Random allocation/	96381
28	Double blind method/	148092
29	Single blind method/	25855
30	Clinical trial/	513070
31	exp Clinical Trials as Topic/	318844
32	25 or 26 or 27 or 28 or 29 or 30 or 31	1093397
33	(clinic$ adj trial$1).tw.	318082
34	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	159784
35	Placebos/	34134
36	Placebo$.tw.	199226
37	Randomly allocated.tw.	25114
38	(allocated adj2 random).tw.	782
39	33 or 34 or 35 or 36 or 37 or 38	567226
40	32 or 39	1331346
41	Case report.tw.	278550
42	Letter/	1004878
43	Historical article/	347980
44	41 or 42 or 43	1616913
45	40 not 44	1299532
46	5 and 24 and 45	1947
47	limit 46 to yr="2018 - 2019"	36

EBM Reviews - Cochrane Database of Systematic Reviews 2005 to October 31, 2018, EBM Reviews - ACP Journal Club 1991 to October 2018, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews - Cochrane Clinical Answers October 2018, EBM Reviews - Cochrane Central Register of Controlled Trials September 2018, EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews - Health Technology Assessment 4th Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016: accessed November 4th 2018

#	Searches	Results
1	exp Small Cell Lung Carcinoma/	277
2	exp Carcinoma, Small Cell/	726
3	(small cell lung adj (cancer or tumo?r or carcinoma or malignan*)).mp.	10115

Clarification questions

4	(oat cell adj (cancer or tumo?r or carcinoma or malignan*)).mp.	40
5	1 or 2 or 3 or 4	10360
6	exp CARBOPLATIN/	1885
7	(carboplat* or carbosin or carbotec or erbakar or ercar or oncocarbin or paraplatin).mp.	5301
8	exp CISPLATIN/	4419
9	(cisplatin or cismaplat or cisplatina or 'cis-platinum' or cysplatyna or 'peyrones chloride' or 'peyrones salt' or platinoxan or platinol or abipltin or blastolem or briplatin or cisplatyl or citoplatino or citosin or lederplatinOR metaplatin or neoplatin or placis or platamine or platiblastin or platinex or platiran or platistin or platosin).mp.	11531
10	exp ETOPOSIDE/	1594
11	(etoposide or lastet or 'vp-16' or 'vp-16-213').mp.	3776
12	(irinotecan or calmtop or campto or camptosar or irinotel or topotecin).mp.	2268
13	(Atezolizumab or Tecentriq).mp.	272
14	exp PACLITAXEL/	2765
15	(paclitaxel or taxol or anzatax or asotax or bristaxol or praxel).mp.	7750
16	6 or 7	5301
17	8 or 9	11531
18	10 or 11	3776
19	14 or 15	7750
20	17 and 18	1625
21	16 and 18	840
22	12 and 16	140
23	16 and 19	2573
24	13 or 20 or 21 or 22 or 23	4680
25	5 and 24	1989
26	limit 25 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	103

Appendix 2: Response to question A4.

Table 31: Immune-Related Adverse Events by Highest NCI-CTCAE Grade, Treated Patients

Adverse Event	Grade	Atez+Carb+Etop (N = 18)	Pbo+Carb+Etop (N = 17)	Total (N = 35)
Any Immune-Related Adverse Event	XXXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Skin And Subcutaneous Tissue Disorders	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Rash	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Pruritus	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX

	XXX	XXX	XXX	XXX
Dry Skin	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Rash Maculo-Papular	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Respiratory, Thoracic And Mediastinal Disorders	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX

Dyspnoea	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Vascular Disorders	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Hypotension	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Flushing	XXX	XXX	XXX	XXX

Clarification questions

	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Endocrine Disorders	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Hyperthyroidism	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Hypothyroidism	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX

	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
General Disorders And Administration Site Conditions	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Face Oedema	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Pyrexia	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Eye Disorders	XXX	XXX	XXX	XXX

Clarification questions

	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Periorbital Oedema	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Investigations	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Alanine Aminotransferase Increased	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX

	XXX	XXX	XXX	XXX
Metabolism And Nutrition Disorders	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Hyperglycaemia	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX

Table 32: Serious Adverse Events by Highest NCI-CTCAE Grade, Treated Patients

Adverse Event	Grade	Atezolizumab +Carb+Etop (N = 18)	Pbo+Carb+Etop (N = 17)	Total (N = 35)
Any Serious Adverse Event	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX

	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Blood And Lymphatic System Disorders	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Febrile Neutropenia	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Anaemia	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Infections And Infestations	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Pneumonia	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX

	XXX	XXX	XXX	XXX
Septic Shock	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Urinary Tract Infection	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Psychiatric Disorders	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
Depression	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX
NCI CTCAE v 4.0 NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events. Note: Atez+Carb+Etop = Atezolizumab + Carboplatin + Etoposide, Pbo+Carb+Etop = Placebo + Carboplatin + Etoposide. Note: Subjects with multiple Adverse Events in the same System Organ Class/Preferred Term category will be counted only once at the occurring highest grade.				

Appendix 3: Anonymised list of attendees at the Roche Lung Cancer advisory board meeting held March 2019

This appendix is referred to in response to question A5.

Professional title	Affiliation	Speciality
Consultant Medical Oncologist	Midlands	Lung, colorectal and hepatobiliary cancer
Consultant Medical Oncologist	Oxfordshire	Lung and prostate cancer
Consultant Medical Oncologist	Scotland	Lung cancer
Specialist Registrar in Oncology	London	Lung, breast and gynaecological cancers
Consultant Clinical Oncologist	West Yorkshire	Lung cancer
Consultant Medical Oncologist	London	Lung and gynaecological cancer
Consultant Clinical Oncologist	West Midlands	Lung and breast cancer
Consultant Medical Oncologist	London	Lung cancer
Consultant Medical Oncologist	Scotland	Lung cancer
Consultant Medical Oncologist	East of England	Lung cancer and mesothelioma
Consultant Medical Oncologist	Somerset	Lung cancer

Appendix 4: IMpower133 subgroup data from [redacted]

This appendix is referred to in response to question A10.

Table 33: Subgroup analysis of OS, ITT population data cut-off date XXXXXXXXXXXX

		Placebo group			Atezolizumab group			Unstratified Hazard Ratio	95% CI
	Total n	n	Events	Median (months)	n	Events	Median (months)		
Sex									
Male	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Female	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Age									
<65 yr	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
≥65 yr	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Baseline ECOG score									
0	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
1	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Brain metastases									
Yes	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
No	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

Liver Metastases									
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bTMB Biomarker Expression									
<10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The risk of death was [redacted] in the patients in the atezolizumab group compared with the placebo group, [redacted]

Appendix 5: [redacted] Analyses

This appendix is referred to in response to question A12.

Table 34: Demographic and Baseline Disease Characteristic XXXXXXXXx XXXXXXXX XXXXXXXx

Figure 15: Kaplan-Meier Curves for Overall Survival in XXXXXXXXXXXXXXx XXXXXXXXXXXxXXXXXXXXX

Figure 16: Kaplan-Meier Curves for Overall Survival in XXXXXXXXXXXXXXx XXXXXXXXXXXxXXXXXXXXX

Figure 17: Kaplan-Meier Curves for Overall Survival in XXXXXXXXXXXXXXx XXXXXXXXXXXxXXXXXXXXX

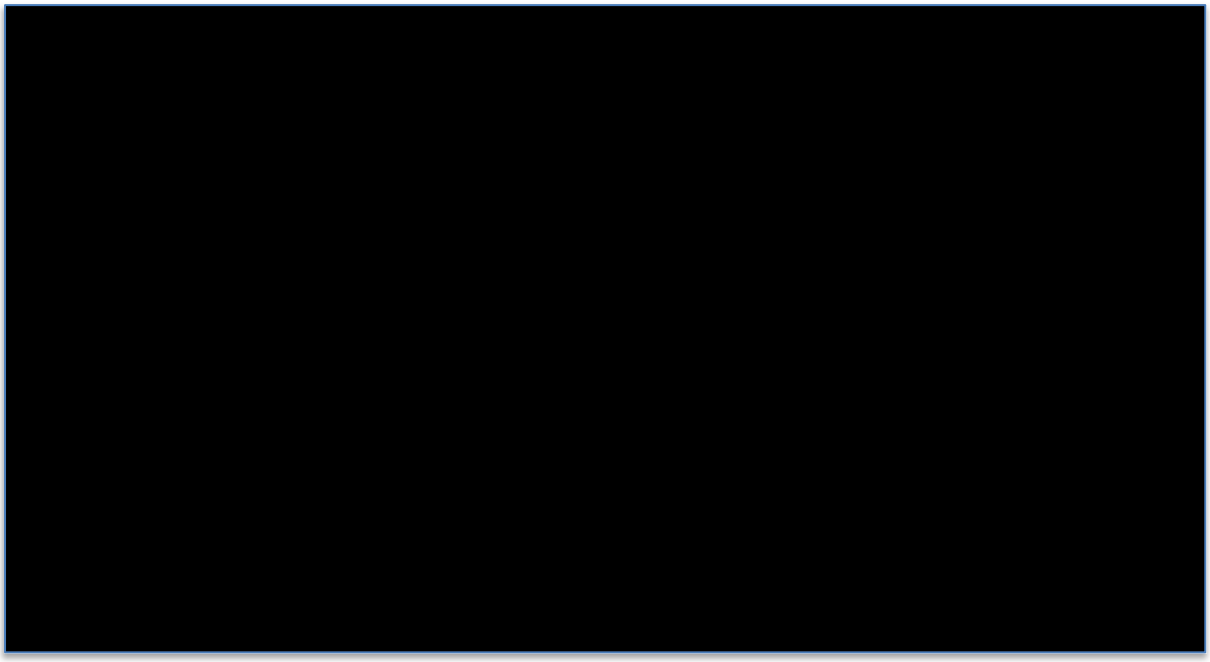


Figure 18: Kaplan-Meier Curves for Overall Survival in XXXXXXXXXXXxXXXXXXXXX

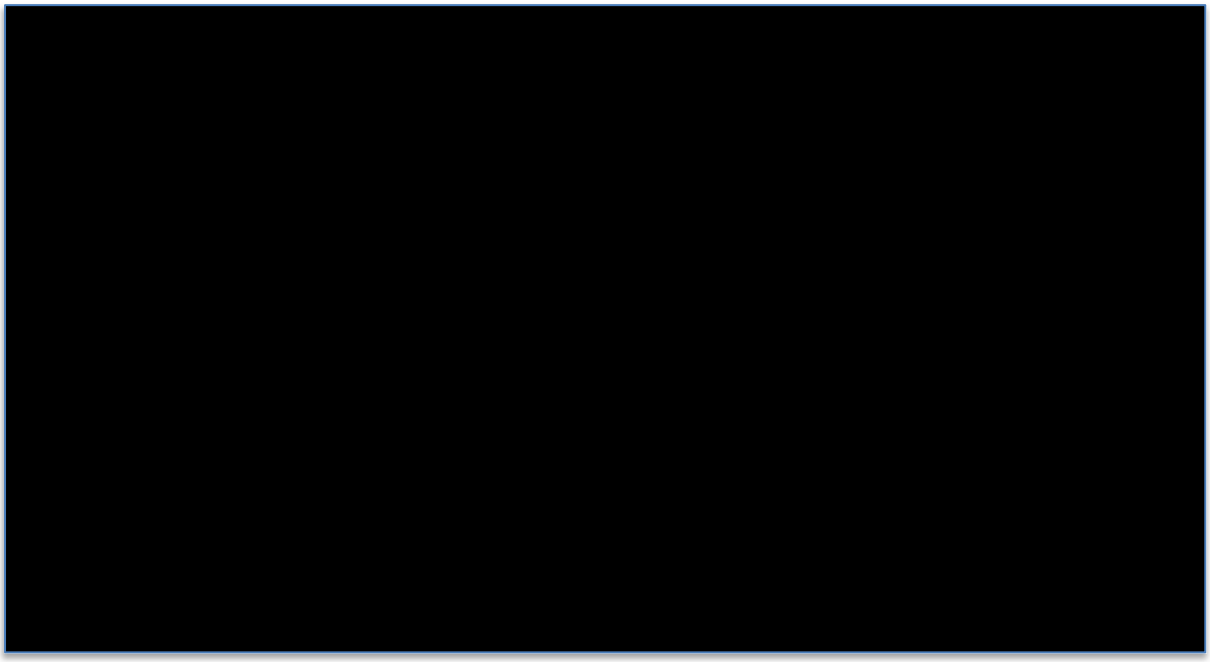


Figure 19: Kaplan-Meier Curves for Progression-Free Survival in XXXXXXXXXXXxXXXXXXXXX

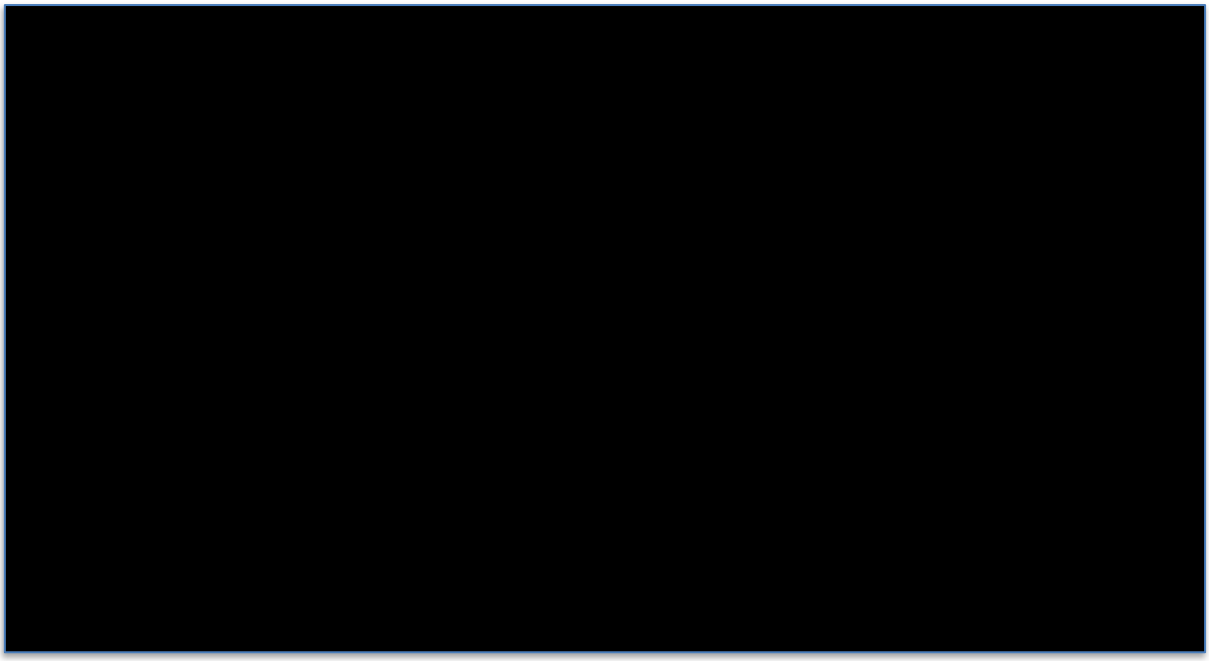


Figure 20: Kaplan-Meier Curves for Progression-Free Survival in XXXXXXXXXXXXxXXXXXXXXX

Table 35_Overview of Unconfirmed Response Rate by XXXXXXXXXXx XXXXXXXXXXXXXXx XXXXXXXXXXXxXXXXXXXXX

Table 35 [redacted]

[redacted]

Error! Reference source not found.**Overview of Confirmed Response Rate by XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXxx**

Error! Reference source not found.**Overview of Confirmed Response Rate by XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXxx**

Appendix 6: Time to off treatment

Figure 21: Kaplan-Meier Curve for Time to off treatment with Atezolizumab in [redacted] in the Atezolizumab arm

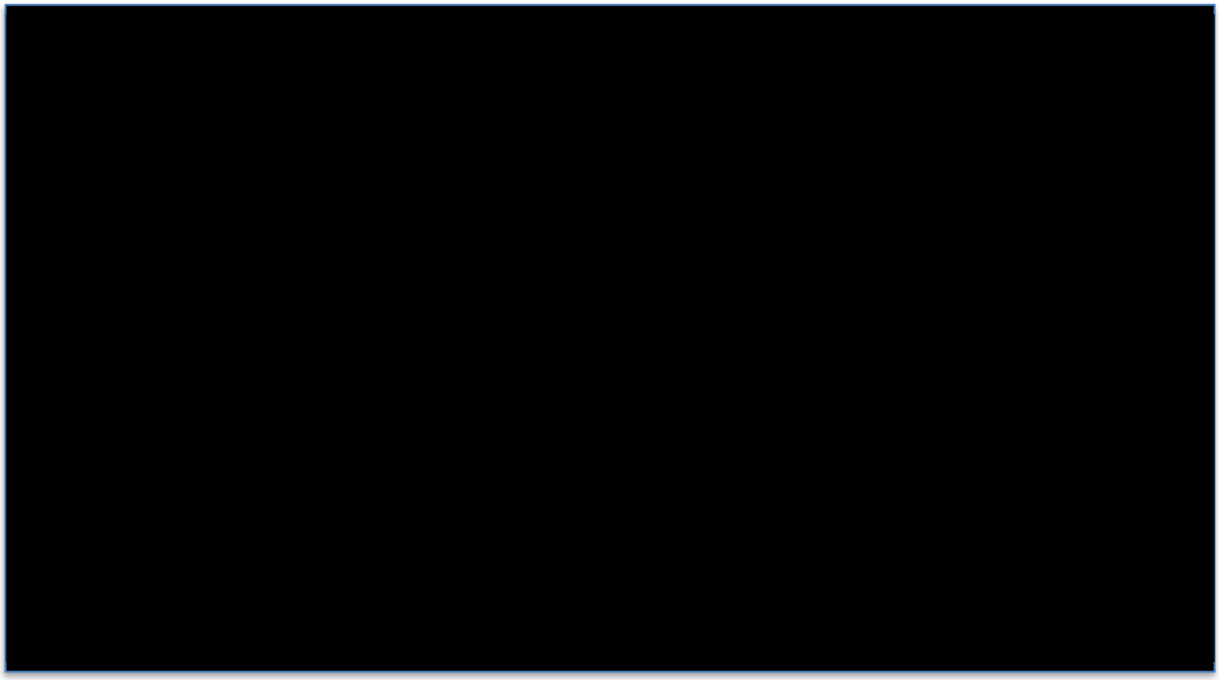


Table 36: Time to off treatment with Atezolizumab in [redacted] in the Atezolizumab arm

Treatment Arm	Median TTO Atezolizumab (months)	95% CI for median TTO Atezolizumab
Atezo + Carbo + Etop	[redacted]	[redacted]

Figure 22: Kaplan-Meier Curve for Time to off treatment with Atezolizumab in [redacted] in the Atezolizumab arm

Table 37: Time to off treatment with Atezolizumab in [redacted] in the Atezolizumab arm

Treatment Arm	[redacted]	[redacted]
Atezo + Carbo + Etop	[redacted]	[redacted]

Figure 23: Kaplan-Meier Curve for Time to off treatment with Carboplatin [redacted] in the Atezolizumab and Placebo arms

Table 38: Time to off treatment with Carboplatin in [redacted] in the Atezolizumab and Placebo arms

Treatment Arm	[redacted]	[redacted]
Atezo + Carbo + Etop	[redacted]	[redacted]
Plac + Carbo + Etop	[redacted]	[redacted]

Figure 24: Kaplan-Meier Curve for Time to off treatment with Carboplatin in [redacted] in the Atezolizumab and Placebo arm

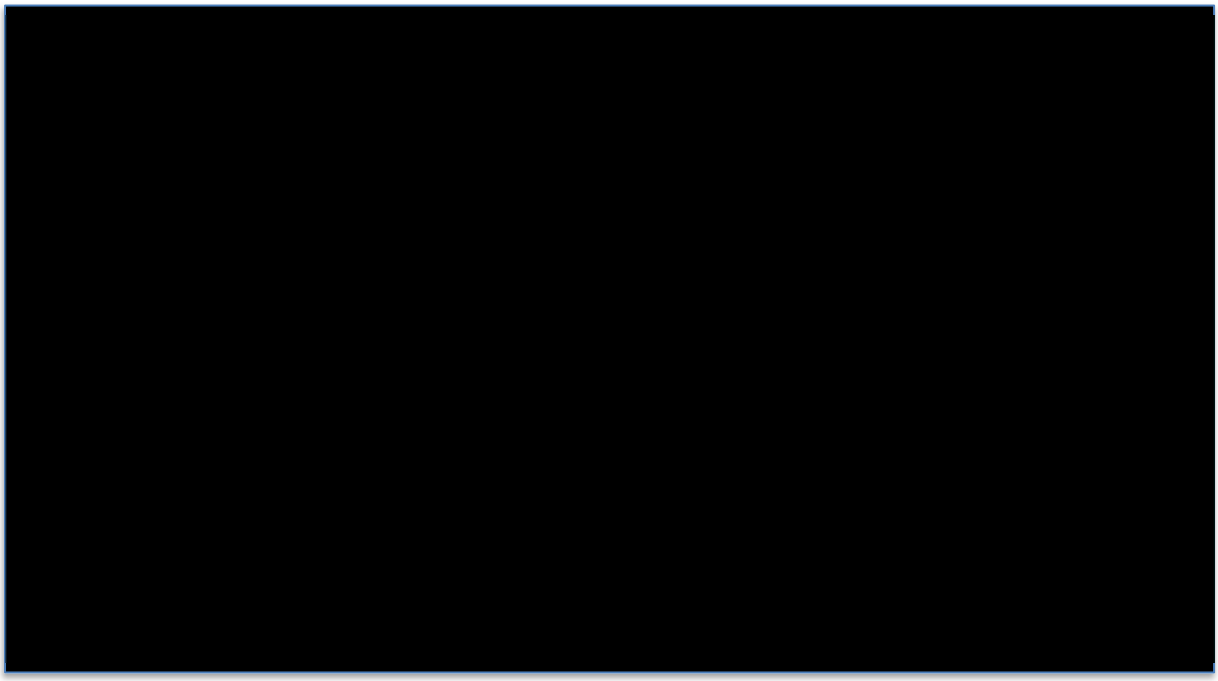


Table 39: Time to off treatment with Carboplatin in [redacted] in the Atezolizumab and Placebo arm

Treatment Arm	[redacted]	[redacted]
Atezo + Carbo + Etop	[redacted]	[redacted]
Plac + Carbo + Etop	[redacted]	[redacted]

Figure 25 Kaplan-Meier Curve for Time to off treatment with Etoposide in [redacted] in the Atezolizumab and Placebo arms

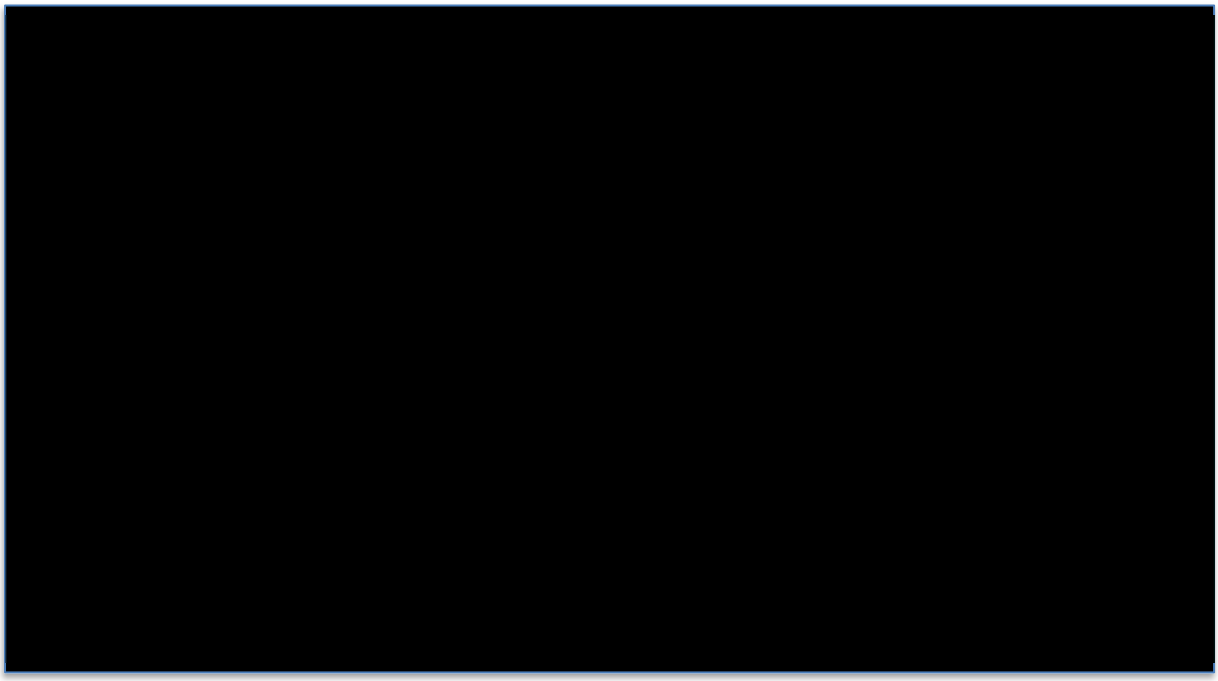


Table 40: Time to off treatment with Etoposide in [redacted] in the Atezolizumab and Placebo arms

Treatment Arm	[redacted]	[redacted]
Arm A: Atezo + Carbo + Etop	[redacted]	[redacted]
Arm B: Plac + Carbo + Etop	[redacted]	[redacted]

Figure 26: Kaplan-Meier Curve for Time to off treatment with Etoposide in [redacted] in the Atezolizumab and Placebo arms

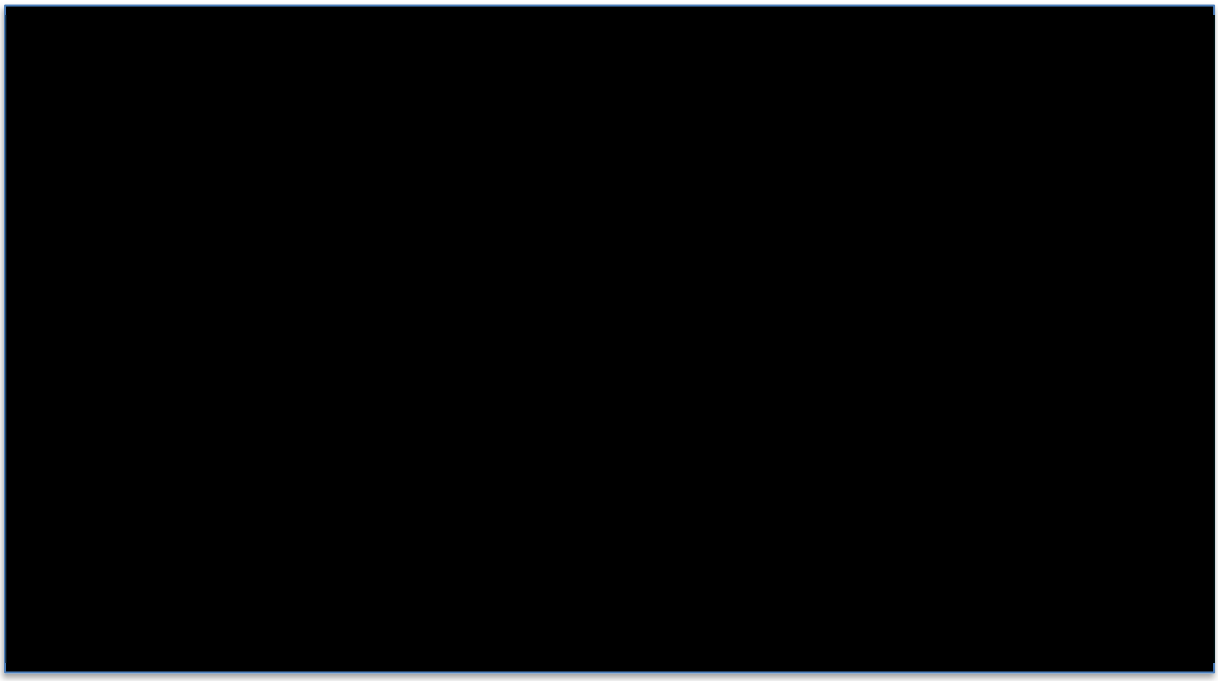


Table 41: Time to off treatment with Etoposide in [redacted] in the Atezolizumab and Placebo arms

Treatment Arm	Median TTO Etoposide (months)	Median TTO Etoposide (months)
Arm A: Atezo + Carbo + Etop	[redacted]	[redacted]
Arm B: Plac + Carbo + Etop	[redacted]	[redacted]

Appendix 7: Updated ICER results

This appendix is provided in the context of section B cost-effectiveness amendments.

Base-case incremental cost-effectiveness analysis results

Table 42: Base-case results for first-line ES-SCLC patients including the PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab plus carboplatin-etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,588
Carboplatin-etoposide	[redacted]	1.21	0.83				

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 43: Base-case results for first-line ES-SCLC patients, list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab plus carboplatin-etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin-etoposide	[redacted]	1.21	0.83				

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Probabilistic sensitivity analysis

Table 44: Base-case results for first-line ES-SCLC patients at PAS price, PSA approach

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Atezolizumab plus carboplatin-etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,045
Carboplatin-etoposide	[redacted]	1.21	0.84				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 45: Base-case results for first-line ES-SCLC patients at list price, PSA approach

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Atezolizumab plus carboplatin-etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin-etoposide	[redacted]	1.22	0.84				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 27: Incremental cost and QALY base case results, with atezolizumab PAS

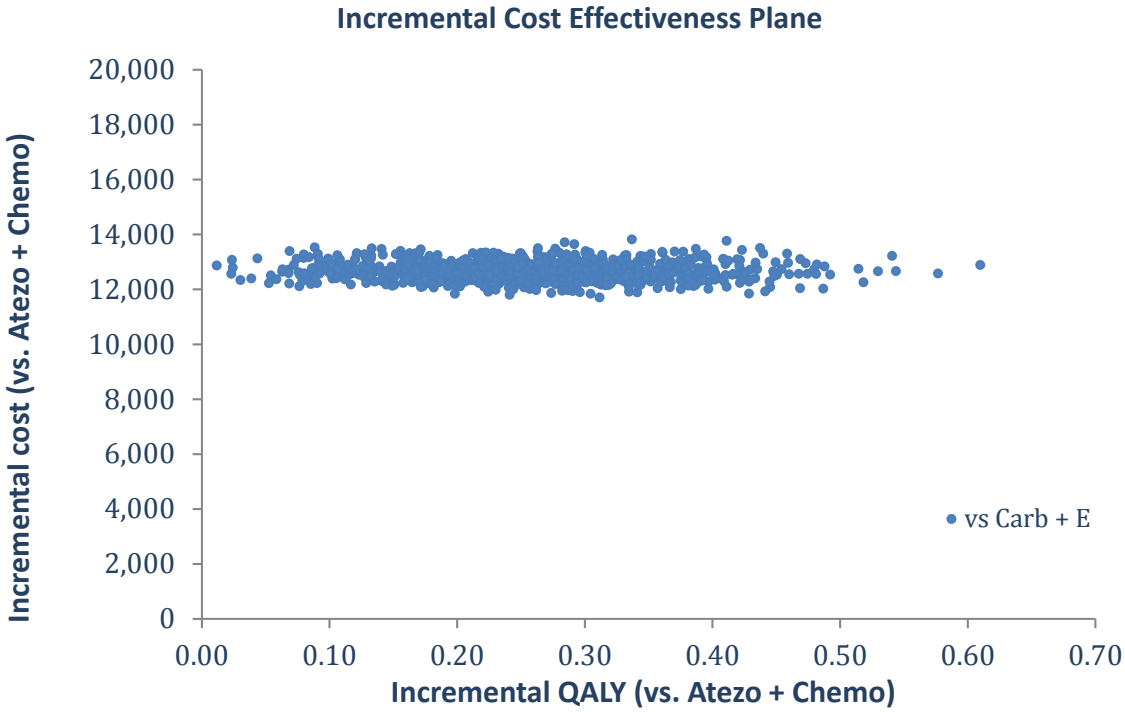


Figure 28: Incremental cost and QALY base case results, with atezolizumab list price

[redacted]

Figure 29: Cost-effectiveness acceptability curve, with atezolizumab PAS

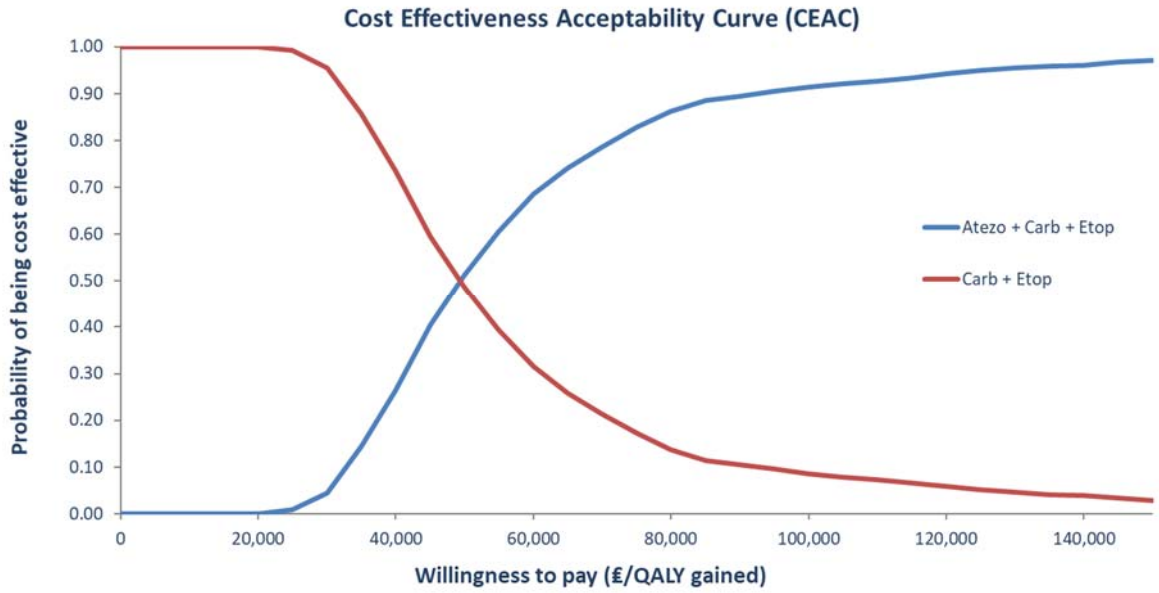
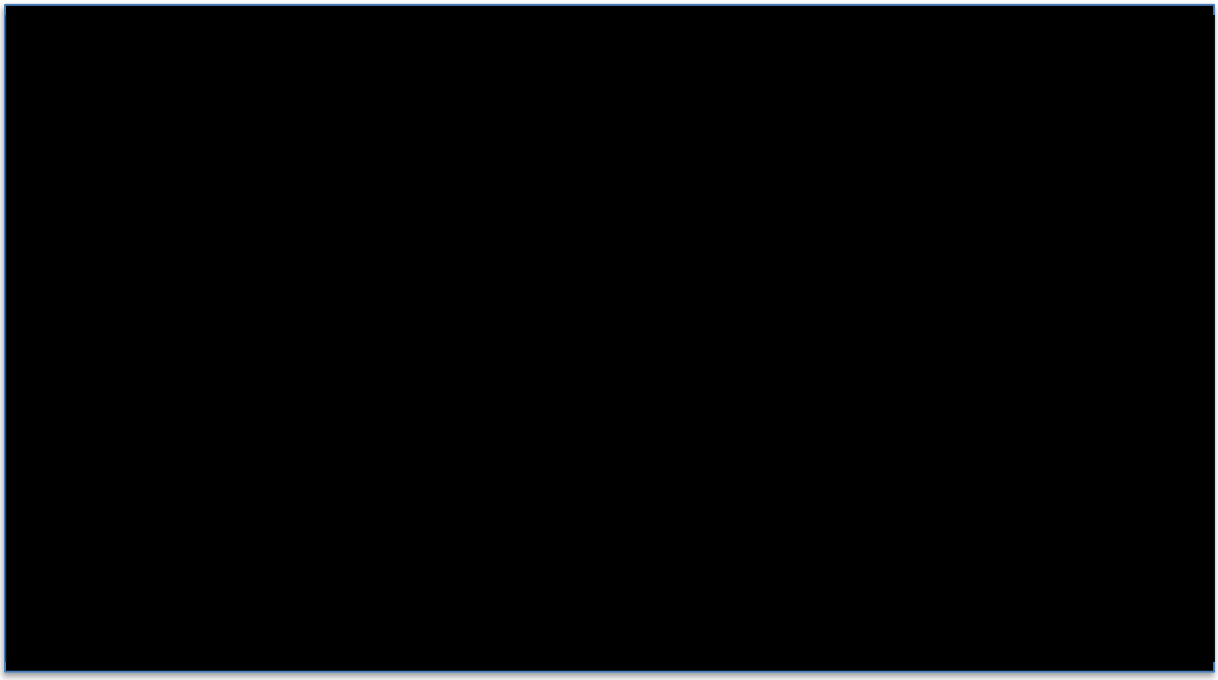


Figure 30: Cost-effectiveness acceptability curve, with atezolizumab list price



Deterministic sensitivity analysis

Table 46: Deterministic sensitivity analysis, with atezolizumab PAS

Parameter modified	Base case value	Lower value	Lower ICER	Upper value	Upper ICER	Justification
Discounted costs	3.50%	2%	£50,004	5%	£49,187	Assumption
Discounted benefits	3.50%	2%	£47,456	5%	£51,720	Assumption
Subsequent administration costs	312.34	£312.27	£49,588	£312.40	£49,588	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on A+C+E	£1232.53	£1,092.41	£49,067	£1,375.35	£50,095	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on C+E	£1191.97	£1,052.13	£50,161	£1,335.74	£49,022	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on atezo monotherapy	£903.84	£741.83	£49,079	£1,063.84	£50,057	Base case is from IMpower133 study, sensitivity is from TAE opinion

Parameter modified	Base case value	Lower value	Lower ICER	Upper value	Upper ICER	Justification
Resource use cost on surveillance only	£1216.40	£1,035.35	£49,549	£1,404.60	£49,629	Base case is from IMpower133 study, sensitivity is from TAE opinion
≤ 5 weeks before death on treatment	0.65	0.61	£49,791	0.69	£49,405	IMpower133 study
> 5 & ≤ 15 weeks before death on treatment	0.73	0.70	£49,771	0.76	£49,407	IMpower133 study
> 15 & ≤ 30 weeks before death on treatment	0.72	0.71	£49,703	0.74	£49,461	IMpower133 study
> 30 weeks before death on treatment	0.73	0.71	£50,017	0.74	£49,149	IMpower133 study
≤ 5 weeks before death off treatment	0.33	0.23	£49,265	0.42	£49,908	IMpower133 study
> 5 & ≤ 15 weeks before death off treatment	0.53	0.45	£49,237	0.62	£49,977	IMpower133 study
> 15 & ≤ 30 weeks before death off treatment	0.70	0.63	£49,306	0.77	£49,840	IMpower133 study
> 30 weeks before death off treatment	0.75	0.66	£50,329	0.82	£48,833	IMpower133 study

ICER: Incremental cost-effectiveness ratio; TAE: therapy area expert

Figure 31: Deterministic sensitivity analysis for the base case, with atezolizumab PAS

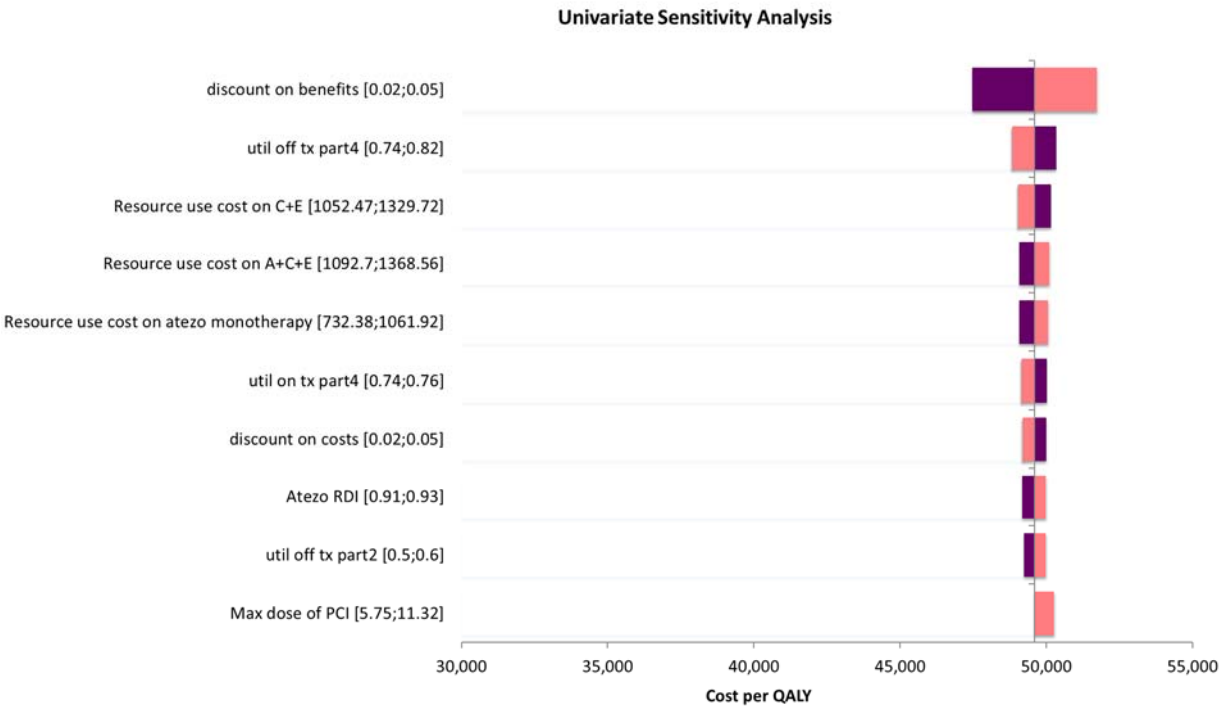


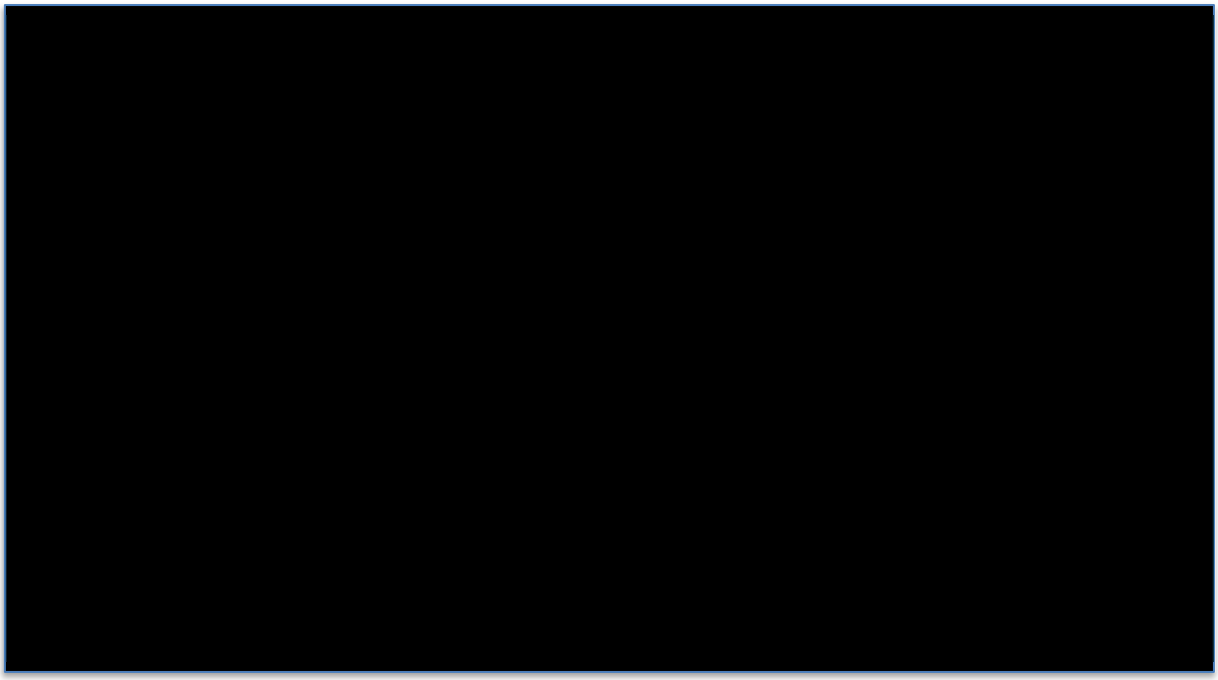
Table 47: Deterministic sensitivity analysis, with atezolizumab list price

Parameter modified	Base case value	Lower value	Lower ICER	Upper value	Upper ICER	Justification
Discounted costs	3.50%	2%	[redacted]	5%	[redacted]	Assumption
Discounted benefits	3.50%	2%	[redacted]	5%	[redacted]	Assumption
Subsequent administration costs	312.34	312.28	[redacted]	312.40	[redacted]	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on A+C+E	£1232.53	1,072.63	[redacted]	1,379.79	[redacted]	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on C+E	£1191.97	1,051.83	[redacted]	1,330.10	[redacted]	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on atezo monotherapy	£903.84	749.19	[redacted]	1,069.81	[redacted]	Base case is from IMpower133 study, sensitivity is from TAE opinion
Resource use cost on	£1216.40	1,034.44	[redacted]	1,409.27	[redacted]	Base case is from IMpower133

Parameter modified	Base case value	Lower value	Lower ICER	Upper value	Upper ICER	Justification
surveillance only						study, sensitivity is from TAE opinion
≤ 5 weeks before death on treatment	0.65	0.61	[redacted]	0.69	[redacted]	IMpower133 study
> 5 & ≤ 15 weeks before death on treatment	0.73	0.70	[redacted]	0.76	[redacted]	IMpower133 study
> 15 & ≤ 30 weeks before death on treatment	0.72	0.71	[redacted]	0.74	[redacted]	IMpower133 study
> 30 weeks before death on treatment	0.73	0.71	[redacted]	0.74	[redacted]	IMpower133 study
≤ 5 weeks before death off treatment	0.33	0.22	[redacted]	0.43	[redacted]	IMpower133 study
> 5 & ≤ 15 weeks before death off treatment	0.53	0.44	[redacted]	0.62	[redacted]	IMpower133 study
> 15 & ≤ 30 weeks before death off treatment	0.70	0.63	[redacted]	0.77	[redacted]	IMpower133 study
> 30 weeks before death off treatment	0.75	0.67	[redacted]	0.83	[redacted]	IMpower133 study

ICER: Incremental cost-effectiveness ratio; TAE: therapy area expert

Figure 32: Deterministic sensitivity analysis for the base case, with atezolizumab list price



Scenario analysis

Table 48: Summary of different scenario analysis, with atezolizumab PAS

Parameter	Value	ICER (£/QALY)	Justification
OS atezolizumab arm	Exponential	£46,988	Not clinically plausible
	Weibull	£61,865	Not clinically plausible
	Log-normal	£35,260	Not clinically plausible
	Gen Gamma	£62,317	Not clinically plausible
	Log-logistic	£49,588	Best fit + base case
	Gompertz	£56,563	Not clinically plausible
	KM-Exponential	£33,882	Fully parametric better fit
	KM-Weibull	£62,718	Fully parametric better fit
	KM-Log-normal	£29,881	Fully parametric better fit
	KM-Gen Gamma	£62,951	Fully parametric better fit

Parameter	Value	ICER (£/QALY)	Justification
	KM-Log-logistic	£49,286	Fully parametric better fit
	KM-Gompertz	£53,874	Fully parametric better fit
Real-world (FI) data incorporation for the chemotherapy arm	Replace control arm with FI data from week 1	£49,588	Replaces all IMpower study data
	Replace control arm with FI data from 10% at risk	£49,588	Only replaces IMpower133 data at maximum follow-up
	Replace control arm with FI and IMpower133 combined from week 1	£49,588	Replaces all IMpower study data
	Replace control arm with FI and IMpower133 combined from 10% at risk	£49,588	Only replaces IMpower133 data at maximum follow-up
Time horizon	5	£59,300	Few patients still alive
	10	£51,768	Few patients still alive
	15	£50,155	Few patients still alive
	20 – base case	£49,588	Allows all data to be considered

FI: Flatiron Health data; ICER: incremental cost-effectiveness ratio.

Table 49: Summary of different scenario analysis, with atezolizumab list price

Parameter	Value	ICER (£/QALY)	Justification
OS atezolizumab arm	Exponential	[redacted]	Not clinically plausible
	Weibull	[redacted]	Not clinically plausible
	Log-normal	[redacted]	Not clinically plausible
	Gen Gamma	[redacted]	Not clinically plausible
	Log-logistic	[redacted]	Best fit + base case
	Gompertz	[redacted]	Not clinically plausible
	KM-Exponential	[redacted]	Fully parametric better fit
	KM-Weibull	[redacted]	Fully parametric better fit

Parameter	Value	ICER (£/QALY)	Justification
	KM-Log-normal	[redacted]	Fully parametric better fit
	KM-Gen Gamma	[redacted]	Fully parametric better fit
	KM-Log-logistic	[redacted]	Fully parametric better fit
	KM-Gompertz	[redacted]	Fully parametric better fit
Real-world (FI) data incorporation for the chemotherapy arm	Replace control arm with FI data from week 1	[redacted]	Replaces all IMpower study data
	Replace control arm with FI data from 10% at risk	[redacted]	Only replaces IMpower133 data at maximum follow-up
	Replace control arm with FI and IMpower133 combined from week 1	[redacted]	Replaces all IMpower study data
	Replace control arm with FI and IMpower133 combined from 10% at risk	[redacted]	Only replaces IMpower133 data at maximum follow-up
Time horizon	5	[redacted]	Few patients still alive
	10	[redacted]	Few patients still alive
	15	[redacted]	Few patients still alive
	20 – base case	[redacted]	Allows all data to be considered

FI: Flatiron Health data; ICER: incremental cost-effectiveness ratio.

Table 50: Scenario analysis of relevance to this appraisal, with PAS

Scenario	Value	ICER (£/QALY gained)	Rationale
Treatment discontinuation rule	2-years	£49,188	Not aligned with the IMpower133 study design
Cycles of carboplatin-etoposide	6 cycles	£49,476	Guidelines recommend up to 6 chemotherapy cycles
Subsequent treatment source	UK-practising clinical expert opinion (Nov-18)	£49,759	Reflective of possible future NHS costs

Scenario	Value	ICER (£/QALY gained)	Rationale
Age adjusted utilities	Excluded	£48,701	Conservative assumption
Treatment benefit cap (at 5 years after start of treatment)	Included	£49,623	Not clinically plausible

ICER: incremental cost-effectiveness ratio.

Table 51: Scenario analysis of relevance to this appraisal, with list price

Scenario	Value	ICER (£/QALY gained)	Rationale
Treatment discontinuation rule	2-years	[redacted]	Not aligned with the IMpower133 study design
Cycles of carboplatin-etoposide	6 cycles	[redacted]	Guidelines recommend up to 6 chemotherapy cycles
Subsequent treatment source	UK-practising clinical expert opinion (Nov-18)	[redacted]	Reflective of possible future NHS costs
Age adjusted utilities	Excluded	[redacted]	Conservative assumption
Treatment benefit cap (at 5 years after start of treatment)	Included	[redacted]	Not clinically plausible

ICER: incremental cost-effectiveness ratio.

NICE National Institute for Health and Care Excellence

Patient organisation submission – Roy Castle Lung Cancer Foundation

Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer (ID1504)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

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2. Name of organisation	ROY CASTLE LUNG CANCER FOUNDATION
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity). Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of Small Cell Lung Cancer (SCLC).
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Foundation has contact with patients/carers through its UK wide network of over 55 monthly Lung Cancer Patient Support Groups, patient/carer panel, online forums and its Lung Cancer Information Helpline.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The National Lung Cancer Audit (2017), reported 10% of lung cancer being of small cell pathological sub type. SCLC is widely accepted to be around 10 to 15% of lung cancer cases. A diagnosis of extensive SCLC is devastating. Small cell is a particularly aggressive type of cancer, patients often being very symptomatic at presentation. Chemotherapy (and combination chemo-radiotherapy) with Cisplatin/Carboplatin and Etoposide is the usual first line of therapy. This is a rapidly progressive disease and as such, patients should be assessed quickly and systemic anticancer treatment started quickly. SCLC is very responsive to chemotherapy. However, despite the sometimes dramatic response to chemotherapy, many patients relapse and die within six months of diagnosis. The overall 5 year survival for SCLC (limited and extensive stage disease) is only about 5%. . Thus, this group of lung cancer patients have a particularly poor outlook. with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In recent years, we have seen new therapy options for some patients with Non Small Cell Lung Cancer – Target Therapies and Immunotherapies. Treatment option however, have remained unchanged for SCLC for decades. As such, there is a huge need for therapies with better outcomes than currently available.
8. Is there an unmet need for patients with this condition?	Most definitely.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The IMpower 133 study, showed that first line treatment, with a combination of Atezolizumab plus chemotherapy (carboplatin and etoposide), helped people with extensive stage SCLC live significantly longer compared to chemotherapy alone. After a median follow up of 13.9 months, the median overall survival was 12.3 months (95% CI, 10.8-15.9) in the Atezolizumab arm, compared to 10.3 months (95% CI, 9.3-11.3) in the chemotherapy only arm (HR, 0.70: CI, 0.54-0.91: P=.0069). Median progression free survival was 5.2 months (95% CI, 4.4-5.6) in the Atezolizumab arm, compared with 4.3 months (95% CI, 4,2-4,5) in the chemotherapy arm (HR, 0.77: 95% CI, 0.62-0.96: P= .017). Atezolizumab was associated with a higher 6 month PFS rate (30.9%. vs 22,4%) and 12 month PFS rate (12.6% vs 5,4%), as compared with the chemotherapy only arm. Though relatively modest, the potential for extensions in life, is of paramount importance to this patient population and their families. New therapy options provide much needed hope in this patient group.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The side effects of the treatment. Side effects are obviously greater with the addition of Atezolozumab, as, compared with chemotherapy alone. .

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- The outcome from current standard treatment, for this patient group, is woefully poor. There is massive unmet need.
- The addition of Atezolizumab to initial chemotherapy, is the first immunotherapy to show benefit in extensive stage small cell lung cancer.
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional Organisation Submission Template

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**ROYAL COLLEGE OF PATHOLOGISTS**

NICE National Institute for Health and Care Excellence

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☒ other (please specify): pathologist who deals with testing for those who might receive the drug
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

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The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce disease and slow progression
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Not for pathologist
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Not for pathologist
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Not for pathologist
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	

• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Not for pathologist
• Do you expect the technology to increase length of life more than current care?	

• Do you expect the technology to increase health-related quality of life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	**Data for NSCLC suggest that those with greater immunostaining of the tumour for PD-L1 have a better response. I am not sure what data there are for SCLC** **If this is the case and it is a companion diagnostic, pathologists will have to be trained in interpretation and systems for validaton will need to be put in place, as well as the cost of the test (and possible rebiopsy) taken into account.** **Impact on biomedical scientists workloads/staff will also need to be taken into account.** **RCPath would therefore need to know if a test is part of the requirement and, if so, which one?** **If there is not, then I do not think we need to be involved.**
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical	This depends on whether there will be a companion diagnostic and if so, which one.

implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not for pathologist
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not for pathologist

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Not for pathologist
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Not for pathologist

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Not for pathologist
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not for pathologist
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	

23. Is pemetrexed in combination with cisplatin/carboplatin, with or without pemetrexed, maintenance the appropriate UK chemotherapy in this setting?	
24. Is it reasonable to include a two year stopping rule to treatment with atezolizumab plus bevacizumab, paclitaxel and carboplatin? Is this representative of clinical practice in the UK?	Not for pathologist
Key messages	

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25. In up to 5 bullet points, please summarise the key messages of your statement.

- Impact on the RCPath community will depend on whether there is a companion diagnostic and, if so, which one the company want the pathologist to use
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted], **submitting on behalf of:**
2. Name of organisation	**BTOG-NCRI-ACP-RCP-RCR**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NONE**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	There have been no improvements to the treatment of Small cell lung cancer in the last 30 years. There is a small chance of a cure/prolonged remission in limited stage SCLC when concurrent chemoradiotherapy is given. Limited stage SCLC excluded from this appraisal. Majority of these patients present with extensive stage SCLC (meaning it is not able to be treated in one radiotherapy field). For this SOC has been platinum doublet, most commonly etoposide, but irinotecan and gemcitabine have also been used in trials with equal effectiveness. After 4-6 cycles if there is a good response, radiotherapy consolidation to the mediastinum is recommended and prophylactic cranial

disability.)	irradiation (PCI). There is a high response rate 80-90% but recurrence is inevitable and often deterioration is rapid. Response to second line treatment is dependent on the disease free interval. Often the cancer acquires resistance to second line treatment
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Radiological response and clinical improvement generally go together particularly in SCLC, patients immediately feel better with introduction of chemotherapy. 20% reduction is considered response
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There has been a great unmet need for this group of patients for the last 3 decades as no improvement in outcome has been here
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	As above
• Are any clinical guidelines used in the treatment of the condition, and if so,	NICE lung cancer guidance ESMO/ASCO guidance for SCLC

which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is very little variability in the treatment as the options and lines of treatment have been so limited
• What impact would the technology have on the current pathway of care?	It would be seamlessly absorbed into the pathway as no extra testing is required. Atezolizumab requires 60 minutes for first infusion and then 30 minute IV infusion for subsequent treatments. Treatment time will be increased for each patient.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Additional to standard chemotherapy with platinum/etoposide
• How does healthcare resource use differ between the technology and current care?	As above
• In what clinical setting should the technology be used? (For example,	Chemotherapy suite treatment

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Immunotherapy well established so will increase chair time for administration but does not represent extra line of treatment
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes Impower 133 met its co-primary endpoints of PFS and OS. 200 patients in each treatment arm. At median FU of 13.9 months, OS was 12.3m for atezolizumab/chemotherapy versus 10.3 for the chemotherapy/placebo arm (HR 0.70 p= 0.007). Median PFS 5.2m vs 4.3m (HR=0.77 p=0.02)
• Do you expect the technology to increase length of life more than current care?	Overall survival difference is small but clinically meaningful and statistically significant. The main intrigue for the study will be whether there is a tail on the survival curve and what proportion of patients will get prolonged remission with immunotherapy.
• Do you expect the technology to increase health-related quality of life more than current care?	Quality of life is likely to remain better for longer due to delay in progression of disease

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not from the preplanned subgroup analyses.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Longer time of administration for each cycle

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Radiological assessment likely to guide therapy as previously
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	None
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current	Yes: likely to produce clinically meaningful difference with possibility of long term survival for responders. Currently very short follow up

need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes significant change after no therapy change in 20-30 years
• Does the use of the technology address any particular unmet need of the patient population?	None
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Immune mediated adverse events need to be recognised and dealt with promptly
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes SOC: platinum/etoposide followed by radiotherapy to mediastinum + PCI
• If not, how could the results be extrapolated to	

the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS and OS were primary endpoints which were both met. Mediastinal RT in IMPOWER 133 was excluded
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None
21. How do data on real-world experience compare with the trial data?	All patients were PS0-1 which does not represent the patients presenting in reall life in the UK

Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
22b. Consider whether these issues are different from issues with current care and why.	None
Key messages	
24. In up to 5 bullet points, please summarise the key messages of your submission. • New standard of care for treating extensive stage SCLC witth chemotherapy and atezolizumab • Use of mediastinal RT was excluded in study • Chair time increase by 60 mins and 30 mins subsequently • Early median FU 13 m, await to see what proportion of patients alive at 5 years, currently 2% with extensive stage SCLC	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Alastair Greystoke**
2. Name of organisation	**Newcastle University**

3. Job title or position	**Senior Lecturer**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Palliate symptoms, shrink tumours and prevent progression as long as possible and improve overall surivival.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An improvement in Progression Free or Overall Survival by 2 months or an increase in the patients alive at 2 years by 5%.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. These patients at presentation are often significantly unwell. Without treatment or in patients with primary progressive disease life expectancy is very short. High initial response rates are seen to 1st line chemotherapy but may patients will have already progressed at the end of chemotherapy or after a very short interval. 2nd line treatments are poor with much lower response rates and can be associated with significant toxicity. Because of this many patients or clinicians do not undertake/ advise 2nd line therapy/ These patients have a very high symptom burden often with problematic respiratory symptoms, brain

	metastases and bone metastases. There has not been an advance in the systemic treatment of these patients for at least 10 years.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Guidelines include the recently updated NICE guidance of diagnosis and management of Lung Cancer NG122 and the ESMO guidelines (Annals of Oncology, Volume 24, Issue suppl_6, October 2013, Pages vi99–vi105).
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The most common regimen used in the 1st line setting are based around platinum and etoposide. Most centres would use carboplatin rather than cisplatin in this setting. They may be variations in doses of etoposide used (100mg/m2 vs 120mgm2) and whether the etoposide is given orally or as an IV infusion on days 2-3 of each cycle. There has been recent problems with the supply of oral etoposide. There is variation in the number of cycles that are initially planned at the start of treatment between 4 and 6 cycles, theer is no evidence of any survival benefit in offering 6 cycles rather than 4. Some centres will offer most patients thoracic radiotherapy and prophylactic cranial irradiation following the completion of chemotherapy as suggested in the recent update of NICE guidance but this will vary with centre. 2nd line chemotherapy rates are low. Some centres use anthracycline based regimes normally in combination with vincristine and cyclophosphamide (CAV or VAC), others will use oral Toptecan.
• What impact would the	In patients who are PS0-1 at the onset of therapy atezolizumab would be added into standard 1st line

technology have on the current pathway of care?	chemotherapy and in patients with response carried on until progression.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	There will be additional treatment and pharmacy time required in each of the 1st 4 cycles of therapy to deliver the atezolizumab in addition to the chemotherapy. There may also be additional health care resources used in the investigation and management of any immune related adverse events. The main impact will be the requirement for additional "maintenance" treatments with atezolizumab on completion of chemotherapy, given until progression or toxicity, this will involve monitoring and administration every 3 weeks which would be additional input over the present standard. It is not clear what would happen to the delivery of thoracic radiotherapy in this setting, which is now recommended by NICE. It was not allowed in IMPOWER-133. However studies using concurrent thoracic radiotherapy and immuno-oncology agents such as atezolizumab are ongoing. Use of radiotherapy in this setting may depend on emerging evidence and the exact wording of blue-teq criteria if approved.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist cancer centre
• What investment is needed to introduce the	None. Atezolizumab given routinely to patients with NSCLC and chemo-therapy in conjunction with immunotherapy approved in non squamous NSCLC. It would be the same medical and nursing teams

technology? (For example, for facilities, equipment, or training.)	looking after these patients.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	In the study the use of atezolizumab was associated with a 2 month increase in overall survival. There is no reason why this benefit should not be maintained when used in routine clinical practice.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Active SCLC is associated with a heavy symptom burden, often requiring inpatient admission or specialist palliative care. Any treatment that prolongs disease control will be associated with improved quality of life. In general atezolizumab is a well tolerated agent.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No.

The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The main implications will be the additional time on treatment for some patients with 3 weekly visits for treatment until progression. This is unlikely to have a major impact on patients who understand they have an incurable condition with an anticipated short life expectancy, and are enthusiastic for any treatment that can give them more time. It will have implications for medical staff, pharmacies and oncology treatment units due to the extra treatments delivered as described above.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients who are PS0-1 and who have no contra-indications for immunotherapy will be offered this treatment, and so no additional testing will be required. Treatment will be until progression which may require additional CT scans. However as the disease free interval following chemotherapy with present care is short, many patients end up needing CT scans anyway

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
• Is the technology a 'step-change' in the management of the condition?	This is the first significant improvement in the systemic management of SCLC since the 1990s. This is despite a number of clinical trials assessing a number of different agents. It is also the 1st time that immunotherapy has been associated with a significant benefit in SCLC. Outcomes with extensive stage SCLC are extremely poor and haven't improved in recent years.

• Does the use of the technology address any particular unmet need of the patient population?	Yes. As described above active SCLC is associated with a heavy symptom burden. This treatment offers a longer period of disease control for some patients.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In general atezolizumab is well tolerated. A small number of patients will experience severe immune related adverse events which will require investigation, management with steroids and occasionally other immune modifying agents such as infliximab. Overall rates of severe immune related advents are estimated to be between 5 and 10% of patients.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Not precisely. In patients with active brain disease they were required to have these treated prior to embarking on the study. In UK practice these patients would go straight onto systemic therapy. Also rates of prophylactic cranial irradiation were lower than would be expected in UK practice. This reflects a move away from PCI in some countries. Lastly as described above thoracic radiotherapy following completion of chemotherapy was not allowed but is given in some UK centres.
• If not, how could the results be extrapolated to the UK setting?	I do not think of any of the differences above will have a major impact on how atezolizumab may give added value in the UK practice. Patients were allowed to receive PCI in the study and it is likely that

	patients with untreated brain disease will be excluded from any approval. The question to how atezolizumab may interact with thoracic radiotherapy is discussed above.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival, progression free survival, response rate adverse events and health related quality of life. All were assessed in the study.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world	None available as yet

experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Small Cell Lung Cancer is more common in patients with lower socio-economic status (PMID: 24586771) and therefore has a higher impact on this group who are also less likely to be given chemotherapy.
22b. Consider whether these issues are different from issues with current care and why.	The availability of atezolizumab may emphasise inequities in access, as patients with higher socio-economic status are more likely to ask for newer innovative treatments.
Key messages	
24. In up to 5 bullet points, please summarise the key messages of your statement. • Atezolizumab when given in combination with carboplatin etoposide chemotherapy improves survival in extensive stage SCLC • This is the 1st significant change in the systemic management of SCLC since the 1990s • SCLC is associated with a heavy disease burden and high healthcare resource use • The use of consolidation radiotherapy following completion of chemotherapy was not allowed in the registration study. How this will impact in routine practice is not known. •	

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NICE National Institute for Health and Care Excellence

Clinical expert statement

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Samreen Ahmed**
2. Name of organisation	**BTOG/NCRN/RCP**

3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• Improve quality of life and delay progression of lung cancer
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	• Small cell lung cancer presents late as it progresses very quickly. Patients are often very symptomatic at presentation and have very extensive disease. Any treatment that has high and quick response rates will improve patients symptoms quickly and improve QOL. Response rates are good with chemotherapy but resistance is inevitable and period of remission can be short, this is of prognostic significance. >20% reduction in lesions constitutes response by RECIST. This is often very closely aligned to improvement in symptoms.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	• Yes • There has been no meaningful development in SCLC for last 30 years. The SOC is Chemotherapy for advanced disease, concurrent chemoradiotherapy for limited disease. Chemotherapy in advanced disease is followed by radiotherapy to consolidate mediastinal disease and prophylactic cranial irradiation (PCI). Median overall survival for these patients can vary from 9-18 months dependent on response to treatment. There are very few 5 year survivors <5%.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	• As above
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	• NICE SCLC guidelines ESMO guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	• No real options so treatment is generally very clearly defined and similar throughout the country. The rates of treatment after diagnosis can vary between the regions in the UK due to fitness of population. It would be expected that 80-90% of SCLC patients should be treated at presentation.
• What impact would the technology have on the current pathway of care?	• None
11. Will the technology be used (or is it already used) in	• Would be incorporated in current practice. I would suggest that there is some latitude in terms of adding this after the 1st cycle as the 1st cycle is often given in an emergency or whilst patient is hospitalised. In this setting an extra drug maybe difficult to prepare and administer. In

the same way as current care in NHS clinical practice?	this case the most vulnerable and unwell patients from the disease may miss out on this valuable addition to the small cell lung cancer treatment
• How does healthcare resource use differ between the technology and current care?	• Additional cost and longer time on chemosuite chair. More monitoring of immune mediated adverse events
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	• Specialist oncology
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	• Well established currently. No testing/biomarker required in addition

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	• Yes • Impower 133 met its co-primary endpoints of PFS and OS. 200 patients in each treatment arm. At median FU of 13.9 months, OS was 12.3m for atezolizumab/chemotherapy versus 10.3 for the chemotherapy/placebo arm (HR 0.70 p= 0.007). • Median PFS 5.2m vs 4.3m (HR=0.77 p=0.02) • Overall survival difference is small but clinically meaningful and statistically significant. The main intrigue for the study will be whether there is a tail on the survival curve and what proportion of patients will get prolonged remission with immunotherapy. • Quality of life is likely to remain better for longer due to delay in progression of disease
• Do you expect the technology to increase length of life more than current care?	• Yes as above
• Do you expect the technology to increase health-related quality of life more than current care?	• Yes as response rates higher and risk of relapse is lower. QOL as a consequence will be better for longer.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• No biomarker to predict response

The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Immune mediated AEs will be monitored. This is standard in lung cancer generally.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	RECIST / iRECIST criteria for radiological progression and clinical benefit assessment.

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Rapid and sustained QOL improvement may not be reflected in QALY
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	As above
• Is the technology a 'step-change' in the management of the condition?	Yes only change in therapy showing benefit for the last 20+ years
• Does the use of the technology address any	Median survival has been around 10-12 months with current therapy for the last 2 -3 decades

particular unmet need of the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes Impower 133 however did not allow mediastinal radiotherapy for consolidation in either arm which is the only deviation from standard practice
• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS and OS HRQOL Yes assessed in trial

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None unexpected and tolerated as well as the chemotherapy alone
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	Comparative standard arm PS2 patients were excluded but untreated brain mets were allowed and this would be SOC. Patients with brain mets detected would start chemotherapy which is as effective as radiotherapy
Equality	
22a. Are there any potential equality issues that should be	None

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	None

Key messages

24.

In up to 5 bullet points, please summarise the key messages of your statement.

- New standard of care for treating extensive stage SCLC witth chemotherapy and atezolizumab: Early median FU 13 m, await to see what proportion of patients alive at 5 years, currently 2% with extensive stage SCLC
- Use of mediastinal RT was excluded in study in both arms: disparate from SOC in UK
- Chair time increase by 60 mins and 30 mins subsequently, over that of chemotherapy alone
- These patients present late and very unwell and therefore can often require inpatient treatment/sometimes as emergency: consider allowing addition of atezo after first cycle
- Toxicities are no worse than that of chemotherapy alone

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer (ID1504)

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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To help you give your views, please use this questionnaire with our guide for patient submissions.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Carol A Davies**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ ✓ other (please specify): Macmillan Lung Cancer Nurse Specialist and NLCFN committee member
3. Name of your nominating organisation	NLCFN
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ ✓ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ ✓other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ ✓ I am drawing on others' experiences. Please specify how this information was gathered: I work with Patients (and carers) with lung cancer and keep myself up to date with relevant trial results
Living with the condition	
What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Small cell lung cancer is a more aggressive disease than nsclc. Extensive stage SCLC has metastasised before the patient is diagnosed. So people are diagnosed with metastatic disease – incurable disease. It often comes with a high burden of side effects: Individuals frequently feel unwell, symptoms can be non-specific and difficult for patients to describe. They often have weight loss, loss of appetite, low energy levels with worsening performance status. Many patients are breathless with noticeable deterioration in their breathing – (often due to extensive nodal disease). There is a need for rapid treatment as the disease can worsen very quickly. Guidelines suggest treatment needs should start within a week of diagnosis.

	Challenge is that many people are unwell at diagnosis. The patient and their family don't have much time to emotionally come to terms with diagnosis/treatment plan. SCLC is highly associated with smoking; as such these patients will have smoking related co-morbidities. Not necessarily any difference in ages between small cell and non-small cell. A high proportion of ES SCLC patients are diagnosed whilst an inpatient, having been admitted as so unwell. These patients have high burden of disease, side effects and worsening performance status.
Current treatment of the condition in the NHS	
What do patients or carers think of current treatments and care available on the NHS?	**Chemotherapy (carboplatin and etoposide) is the first line treatment with a high level of** initial **response**. The degree and duration of response is unpredictable. Sometimes because the patients is feeling so unwell, when chemotherapy is commenced the cancer related symptoms can improve, which can initially result in them feel better overall. This does change, chemotherapy comes with side effects which impact/affect the individual's The main burden of chemotherapy include; increased infection risk (the chemo affects the immune system so the white cell count is lower). Fatigue, nausea, vomiting, constipation, sore mouth, taste changes, poor appetite, neurological changes. Etoposide causes hair loss which has a psychological effect; it is very visual women generally find this harder to cope with although both find this hard. In the non -smoking population prognosis is generally worse than it is in smokers – this came out of a European study. Chemotherapy is administered every 3 weeks for 4 to 6 cycles. The majority have 4 cycles or less. Very fit patients with a good radiological response to chemotherapy and a low burden of side effects may have up to 6 cycles. Treatment is given as an outpatient, patients will be in the unit for a few hours.

	On day 1 chemotherapy an intravenous infusion of both drugs is administer with oral etoposide tablets dispensed to been taken at home for the next two consecutive days. Side effects tend to escalate the more chemotherapy cycles given. Normal activities become much more of an effect. A small number of people are capable of continuing work but this is a very low percentage ***What happens if somebody has had first line and relapsed.*** If someone has had a prolonged response from chemo, and performance status remains suitable, they may receive 2nd line chemotherapy. If their performance status has worsened they may be unfit for further chemo therapy. They may be offered radio therapy for specific symptoms, but it's generally chemo followed by palliative care.
Is there an unmet need for patients with this condition?	Definitely There is nothing first line except for the double chemotherapy regime. The diagnosis is particularly hard as patient's usually present with extensive Stage disease, it is not curable with one treatment option. Chemotherapy can initially reduce the cancer burden, this can improve the presenting cancer related symptoms as such temporarily improve the individual's quality of life and performance status. Unfortunately this improvement is often short. Occasionally the response can be prolonged,(No relapse of cancer in excess of 6 months after completion of treatment) – Only a small proportion of patients have this prolonged benefit. Unfortunately, small cell lung cancer will relapse and symptoms will return. Very distressing for the family who hear the diagnosis, may see their family member temporarily improve and then have to cope with the deterioration again.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Trial didn't have any UK centres. Patient and family perception - Immunotherapy is thought to be the 'magic treatment', expectations often very high; patients and family have often read about immunotherapy online, in media or on patient blogs. As atezolizumab is given at the same time as the current treatment, it would eliminate need for additional hospital visits. This will be an advantage; it fits with the current schedule.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	One of the disadvantages is that immunotherapy has potential added side effects. There may be a worry that these side effects may result in chemotherapy having to be stopped or postponed. ES-SCLC is aggressive, if this should occur the cancer could worsen during the break in treatment? Immunotherapy side effects can increase fatigue levels and cause autoimmune symptoms including joint inflammation, gastritis, lung fibrosis and alter thyroid levels; treatment may need to be stopped or postponed.

Patient population	
Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The addition of atezolizumab could perhaps just be considered in patients with a performance status of 0 - 1 as they are generally fitter better able to better cope with the additional side effects.
Equality	
Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that can be identified.

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

Produced by Kleijnen Systematic Reviews Ltd

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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.

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Contributions of authors

Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nigel Armstrong acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Dhwani Shah, Titas Buksnys and Steve Ryder acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Annette Chalker, Heike Raatz and Vanesa Huertas Carrera acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Janine Ross critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse events
AIC	Akaike Information Criterion
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BI	Budget impact
BIC	
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
BTOG	British Thoracic Oncology Group
CCOD	Clinical cut-off date
CTCAE	Common terminology criteria for adverse events
CE	Conformité Européene/Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CG	Clinical guidance
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CP	Carboplatin
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSU	Decision Support Unit
EAMS	Early access to medicines scheme
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
eMIT	Electronic market information tool
EOL	End-of-life
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European public assessment report
ePRO	Electronic patient reported outcomes
EQ-5D-5L	European Quality of Life-5 Dimensions, 5-level
ERG	Evidence review group
ES-SCLC	Extensive stage small cell lung cancer
ESMO	European Society for Medical Oncology
ET	Etoposide
FDA	Food and Drug Administration
GP	General practitioner
HBV	Hepatitis B virus
HCHS	Hospital and community health services
HCV	Hepatitis B virus
HIV	Human immunodeficiency virus

HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HRU	Healthcare resource use
HSUV	Health state utility values
HTA	Health technology assessment
IASLC	International Association for the Study of Lung Cancer
IC	Indirect comparison
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
INR	International normalised ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LS	Limited stage
LYG	Life year gained
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging
MTC	Mixed treatment comparison
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NLCA	National Lung Cancer Audit
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
OR	Objective response/odds ratio
ORR	Objective response rate
OS	Overall survival
PartSA	Partitioned survival analysis
PAS	Patient access scheme
PCI	Prophylactic cranial irradiation
PCR	Polymerase chain reaction
PD-1	Programmed death 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PICOS	Population – intervention - comparators - outcomes- study
PIM	Promising innovative medicine
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PS	Performance score
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PUVA	Psoralen and ultraviolet A radiation
QALY(s)	Quality-adjusted life year(s)
QLQ	Quality of life questionnaire
QoL	Quality of life

RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
RNA	Ribonucleic acid
RR	Response rate/relative risk/risk ratio
RSI	Request for supplementary information
SAE	Serious adverse events
ScHARR	School of Health and Related Research
SCLC	Small cell lung cancer
SD	Standard deviation
SE	Standard error
SHTAC	Southampton Health Technology Assessments Centre
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology assessment/technology appraisal
TAE	Therapy area expert
TC	Tumour cell
TEAE	Treatment-emergent adverse event
TMB	Tumour mutational burden
TNF	Tumour necrosis factor
TNM	Tumour node metastasis
TTD	Time to deterioration
TTO	Time trade-off
TTOT	Time-to-off-treatment
UC	Urothelial carcinoma
UICC	Union for International Cancer Control
UK	United Kingdom
ULN	Upper limit of normal
UMC	University Medical Centre
USA	United States of America
VALG	Veterans Administration Lung Study Group
WCLC	World Conference on Lung Cancer
WHO	World Health Organisation
WTP	Willingness-to-pay

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The National Institute for Health and Care Excellence (NICE) scope describes the decision problem as the clinical and cost effectiveness of atezolizumab with carboplatin and etoposide within its marketing authorisation for untreated extensive-stage small-cell lung cancer (ES-SCLC). The anticipated license is: atezolizumab [redacted] The main trial (IMpower133) included patients with untreated extensive-stage small cell lung cancer.

The intervention described in the NICE scope is atezolizumab with carboplatin and etoposide. However, in the company submission (CS), the intervention is atezolizumab with carboplatin and etoposide for four 21-day cycles followed by a maintenance phase during which patients receive atezolizumab monotherapy until the occurrence of unacceptable toxic effects or disease progression.

The description of the comparators in the NICE scope is as follows: Platinum-based combination chemotherapy regimens. However, in the CS the company states that "chemotherapy regimens excluding etoposide are outside of the scope of this appraisal" (CS, Appendix D, page 41). This means treatment regimens such as carboplatin plus paclitaxel, irinotecan plus cisplatin, topotecan plus cisplatin, and paclitaxel plus cisplatin are not considered as comparators in the CS. The only other comparator considered in the CS is cisplatin plus etoposide in a scenario analysis.

1.2 Summary of clinical effectiveness evidence submitted by the company

In their submission the company focussed on results from the IMpower133 trial. IMpower133 (NCT02763579) is a multinational Phase I (safety) and III (efficacy), double-blind, randomised, placebo-controlled study, evaluating the efficacy and safety of adding atezolizumab or placebo to first-line treatment with carboplatin and etoposide in patients with ES-SCLC. In the submission, the company reported the planned interim analysis of overall survival (OS) and a final analysis of progression-free survival (data cut-off 24 April 2018). The trial included adults with histologically or cytologically confirmed ES-SCLC as defined according to the VALG staging system, measurable ES-SCLC according to RECIST, version 1.1, and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher numbers reflecting greater disability) who had not received previous systemic treatment for ES-SCLC. The study included 403 patients from 106 centres in 21 countries (USA, Europe, South America and Asia), with 10 patients from the UK (four (2%) patients in the atezolizumab arm and six (3%) patients in the placebo arm).

The co-primary outcomes were overall survival (OS; the time from randomisation to death from any cause) and investigator-assessed progression-free survival (PFS, per RECIST v1.1; time from randomisation to disease progression or death from any cause, whichever occurred first). A final analysis of OS in the IMpower133 trial was planned after approximately 306 OS events in the Intention to treat (ITT) population had occurred; this analysis was made available to NICE by the company in May 2019.

A total of 201 patients were randomly assigned to the atezolizumab group, and 202 patients to the placebo group. Based on [redacted] data and at a median follow-up of [redacted] months, the median overall survival was [redacted] months in the atezolizumab group and [redacted] months in the placebo group (hazard ratio (HR) = [redacted] (95% confidence interval (CI): [redacted] to [redacted]). Based on April 2018 data, the median progression-free survival was 5.1 months and 4.3 months, respectively (HR = 0.77 (95% CI:

0.62 to 0.96). The objective response rate (ORR, Difference in response rates: [redacted]) and median duration of response (DOR, Median duration 4.2 months for atelozumab versus 3.9 months for placebo) were similar between the treatment arms. Patients in both the atezolizumab arm and the placebo arm reported improvements in function and health related quality of life (HRQoL). However, statistical significance of differences between treatment arms was not reported in the CS. Time to deterioration (TTD) showed no statistically significant differences between treatment arms in patient-reported lung cancer symptoms (cough, chest pain, dyspnoea, arm/shoulder pain, fatigue and loss of appetite) or treatment-related symptoms (constipation, dysphagia, peripheral neuropathy, nausea/vomiting, diarrhoea and sore mouth).

Adverse events related to any component of the trial regimen occurred in 188 patients (94.9%) in the atezolizumab group and in 181 patients (92.3%) in the placebo group. The most common grade 3 or 4 adverse events related to the trial regimen were neutropenia, anaemia, and decreased neutrophil count. Deaths related to the trial regimen occurred in three patients (1.5%) in the atezolizumab group and in three patients (1.5%) in the placebo group. Immune-related adverse events occurred in 79 patients (39.9%) in the atezolizumab group and in 48 patients (24.5%) in the placebo group, with rash and hypothyroidism being the most common. The proportion of patients who experienced serious adverse events (SAEs) was 37.4% in the atezolizumab group and 34.7% in the placebo group. The most frequently reported SAEs were haematologic toxicities or infections.

In addition, the company stated that "[redacted]" (CS, page 50).

The company presented an indirect comparison of atezolizumab plus carboplatin-etoposide versus cisplatin-etoposide. However, we believe that the results from the indirect comparison presented by the company in Appendix F are unreliable and should not be used by NICE for decision making.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted as part of the systematic review to identify clinical effectiveness studies. A wide range of databases and additional resources were searched. The searches included limited comparators and was not in line with the broader comparator definition in the final scope.

Baseline characteristics in the IMpower133 trial were well balanced between the groups. However, the population included in the IMpower133 trial may not be representative of the ES-SCLC patient population in UK practice. According to clinical experts employed by the company fewer than [redacted] of ES-SCLC patients in UK clinical practice would be diagnosed with an ECOG status of 0. In the IMpower133 trial, 35% of patients had an ECOG performance status of 0. Furthermore, all included patients in the IMpower133 trial had an ECOG performance status of 0-1. In Appendix K, the company reports that "some advisors stated in their experience the probable proportions of UK ES-SCLC patients diagnosed as ECOG 0–1 would be as high as [redacted], with others reporting that in their clinical experience it could be as low as [redacted]." Therefore, the population included in the IMpower133 trial might only represent a third of ES-SCLC patients in the UK.

Based on the most recent data from 2019, and a median follow-up of [redacted] months, the stratified (gender and ECOG) HR for death was [redacted] and a difference in median

overall survival of [redacted]. Progression free survival (PFS) also showed a statistically significant improvement in investigator-assessed PFS in favour of the atezolizumab group compared with the placebo group (HR = 0.77 (95% CI: 0.62 to 0.96)). Objective response rate (ORR) and median duration of response (DOR) were similar between the treatment arms; while statistical significance of differences between treatment arms was not reported in the CS for health-related quality of life.

The proportion of patients who experienced SAEs (serious adverse events) was 37.4% in the atezolizumab group and 34.7% in the placebo group. The most frequently reported SAEs were haematologic toxicities or infections.

The company provided subgroup analysis by [redacted]. This included [redacted] data. At a [redacted], atezolizumab [redacted] in terms of [redacted] when compared to placebo. However, these results are based on [redacted] and exploratory subgroup analyses.

The IMpower133 trial compares atezolizumab plus carboplatin and etoposide with placebo plus carboplatin and etoposide. The NICE scope describes the comparators as 'platinum-based combination chemotherapy regimens'. However, in the CS the company states that "chemotherapy regimens excluding etoposide are outside of the scope of this appraisal" (CS, Appendix D, page 41). This means treatment regimens such as carboplatin plus paclitaxel, irinotecan plus cisplatin, topotecan plus cisplatin, and paclitaxel plus cisplatin are not considered as comparators in the CS. The only comparators considered in the CS are carboplatin plus etoposide as reported in the IMpower133 trial and cisplatin plus etoposide based on an indirect comparison. The ERG believes that the results from this indirect comparison are unreliable and should not be used by NICE for decision making.

The company argues that "only carboplatin plus etoposide treatment is considered to be within the scope of this appraisal" (Response to clarification, Question A.4). This is based on advice from over 20 practising NHS oncologists that the standard of care in the NHS for untreated, ES-SCLC is carboplatin plus etoposide. In addition, the evidence for a comparison of atezolizumab plus carboplatin/etoposide versus carboplatin/etoposide is based on a head-to-head comparison (the IMpower133 trial), while evidence for other comparisons will have to rely on weaker evidence based on indirect comparisons. Therefore, the ERG would agree that carboplatin/etoposide is probably the most relevant comparator for this appraisal.

However, if the committee decides that all comparators mentioned in the NICE scope are relevant comparators, we have conducted an indirect comparison based on a limited search performed by the company (see Section 4.5 of this report), which shows that results for irinotecan plus carboplatin are similar to atezolizumab plus carboplatin/etoposide in terms of OS, PFS, and response.

1.4 Summary of cost effectiveness evidence submitted by the company

Separate sets of searches were undertaken to identify economic, resource use and HRQoL evidence. The CS provided sufficient details for the ERG to appraise the searches. An extensive range of databases and additional resources were searched.

The CEA was structured as a three-health state partitioned survival analysis (PartSA) model. These three health states were consistent with previous appraisals accepted by NICE to evaluate first-line lung cancer, as well as other oncology indications: "PFS", "Progressed Disease (PD)" and "Death". The population in the CEA was first-line, adult ES-SCLC patients, which is consistent with the ITT population of the IMpower133 study, the NICE final scope for this appraisal, the appraisal decision

problem and the anticipated EMA Marketing Authorisation (the draft SmPC provided in a separate document). The intervention was atezolizumab with carboplatin and etoposide, given for up to four cycles and the comparator was carboplatin and etoposide, given for up to four cycles. In response, the company provided the results of a scenario analysis involving six cycles, which showed a decrease in the incremental cost effectiveness ratio (ICER). Also in a scenario analysis, comparison with cisplatin instead of carboplatin was employed. This was performed as a full incremental analysis in the response to the clarification letter. However, as described in Section 5.2.3 of this report, the company argued that the comparison was inappropriate due to cisplatin being indicated for only "…borderline LS-SCLC patients." The economic model uses a 20-year time horizon in the base case. Costs and health outcomes are discounted at 3.5% in the base case and the perspective of the NHS and personal social services (PSS) is assumed.

The company stated that they followed step by step guidance from the NICE DSU TSD 14 to identify the best fit parametric extrapolations for OS, PFS and time-to-off-treatment (TTOT) in the model base case. For TTOT, in both arms of the pivotal trial, no extrapolation was needed for either carboplatin or etoposide treatments, since the time to treatment discontinuation had been observed for the entire cohort during the 12-month follow up period. Therefore, parametric extrapolation was only required for TTOT for atezolizumab. Because TTOT extrapolation only applied to the intervention, a test for proportional hazards was not required. For OS and PFS, the company first tested whether the proportional hazard assumption held between treatment arms by inspecting the log cumulative hazard (odds, and standardised normal curve) plots and computing the log cumulative hazard over the log of time. Based on those tests, the proportional hazard assumption was rejected for both OS and PFS because the curves cross each other at multiple time points. Therefore, separate parametric time-to-event models were fitted to each treatment arm for each endpoint, OS, PFS and TTOT. Visual inspection and statistical fit (Akaike Information Criterion (AIC) and Bayesian information criterion (BIC)) were used to select the most relevant extrapolations. The plausibility of extrapolation beyond trial data was also assessed by checking the crossing of curves (OS should not cross PFS or TTOT) and for OS comparison, external validation with expert opinion and/or real-world data and general mortality rates.

For PFS, the log-logistic curve provided the best statistical fit of the parametric function to the actual data. This continued to be the case with the [redacted] data: PFS analysis was considered final at the primary analysis. The company noted that all the standard parametric curves provided a similarly poor visual fit to the Kaplan-Meier data, as there were steep drops within the first five months at the time of each scan. [redacted], at this specific time point approximately 50% of patients remain at risk in both arms. No external validation was performed for PFS.

For OS, in terms of statistical fit, the CS stated the best overall fit to the existing OS data would be either Weibull, Gompertz, generalised gamma or log-logistic extrapolations for the atezolizumab arm and Weibull, Gompertz or generalised gamma curves for the comparator arm. The company argued in the CS that the visual fit of these extrapolation curves was good enough not to use the KM data even for the initial period, as they did for PFS. In response to clarification letter part 2 and the data from [redacted] the company stated that the best fit was obtained from the Weibull and log-logistic extrapolations. For the comparator, the company finally chose the log-logistic from the set of parametric curves on the basis of external validity of the extrapolations by comparison with data from the Flatiron study, validated by clinical expert opinion, although it did also provide the best statistical fit based on the data from [redacted]. For the intervention, the company cited the clinical expert opinion as to long term survival and on this basis chose the log-logistic model, although the Weibull had a minor advantage in terms of statistical fit based on the data from [redacted].

For TTOT, for atezolizumab only, as explained above, the generalised gamma provided the best statistical fit of the parametric function to the actual data. The company noted that all the standard parametric curves provided a similarly poor visual fit to the Kaplan-Meier data. [redacted]. No external validation was performed for TTOT.

The main source of evidence on treatment adverse events (AEs) used for atezolizumab was the IMpower133 trial data. AEs were included in the model if they had an occurrence of more than 2% in either arm in the IMpower133 trial and a severity of Grade 3-5 or if they were classified as serious AEs. AEs were included in the model in terms of their costs and not their impact on health-related quality of life (HRQoL) in the CS. The company argued that any AE disutility had already been incorporated into the base case health state utilities through the trial derived EQ-5D utilities estimated as a function of time to death only, and incorporating an additional disutility could be considered double counting.

For utilities, the company used the EQ-5D-5L data from the IMpower133 trial. In line with NICE's position statement on EQ-5D-5L data, the obtained data were mapped to EQ-5D-3L using the indirect mapping approach according to van Hout et al. 2012. The company stated that utility was incorporated into the model using the same time to death approach as has been accepted during previous NICE appraisals of lung cancer treatments, this was validated [redacted]. In response to the request for clarification, the company included AE disutilities in a scenario analysis.

The base case model includes the actual dosing from IMpower133 study and vial sharing assumptions (i.e. no wastage) for the administration of chemotherapy drugs in the model. Atezolizumab is given at a fixed dose. Relative dose intensity has been applied according to the IMpower133 study to account for missed doses. Since carboplatin, etoposide and cisplatin are all available to the NHS as generic medicines, prices are taken from eMIT, which reports the average price paid by the NHS for a generic medicine. The only other medicine price included in this submission was for atezolizumab which is presented inclusive of the confidential PAS discount. Subsequent treatment costs have been incorporated into the model according to the IMpower133 study as this was deemed to balance the efficacy and cost estimates from the study appropriately. Drug administration costs were also included based on NHS reference costs. The cost of PCI was also considered within the model and applied separately, with 90% of patients receiving PCI every three weeks for a maximum of five doses with the NHS reference cost for radiotherapy used. A cost for terminal care is applied within the model. In the CS, this had been based on terminal care costs specific to SCLC from the literature. In response to clarification, the company stated that at a March 2019 Advisory Board meeting, clinicians felt that these terminal care costs were too out of date to be reliable. Instead the company decided to use the terminal care costs from TA483, inflated to 2018 costs.

As reported in the deterministic base case cost effectiveness results of treatment with atezolizumab plus carboplatin and etoposide with PAS compared with just carboplatin and etoposide included an ICER of [redacted] per quality adjusted life year (QALY) gained. The main share of the [redacted] QALY increment stemmed from the large accrual of QALYs in the PFS/on treatment health state. The incremental costs of atezolizumab plus carboplatin and etoposide compared with carboplatin and etoposide were [redacted]. However, following response to clarification letter part 2, these values changed to an increased ICER of [redacted] with a lower QALY increase of [redacted] and a cost increase of [redacted]. The ICER for atezolizumab plus carboplatin and etoposide versus cisplatin and etoposide was lower at [redacted] with higher cost and lower QALYs for this cisplatin in comparison to carboplatin. This implies that cisplatin would be dominated by carboplatin plus etoposide. The probabilistic sensitivity analysis (PSA) results

were similar with ICERs about 1% and 8% higher, of [redacted] and [redacted], versus carboplatin plus etoposide and cisplatin plus etoposide respectively. Scenario analysis revealed that the ICER was most sensitive to the parametric model for TTOT for atezolizumab. However, none of these models provided a good visual or statistical fit and the one that fitted best i.e. the generalised gamma produced an ICER under £50,000. The next most influential input was the parametric model for OS for atezolizumab and the Gompertz does provide a plausible alternative to the log-logistic and did produce an ICER well in excess of £50,000. However, the Weibull did provide the best statistical fit and, in the view of the ERG, is the most clinically plausible.

In the clarification letter the ERG requested that a subgroup analysis be conducted based on the results of the "…[redacted]". In their response of 28 May 2019, the company declined to do so citing limitations in the data.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers the population, intervention and comparator considered by the company in their CEA to be largely appropriate. However, as the company identify in the response to clarification letter, there might be a subgroup of "…borderline LS-SCLC patients" for whom cisplatin plus etoposide instead of carboplatin plus etoposide would be appropriate. On this basis, the ERG would concur that cisplatin plus etoposide is probably not an appropriate comparator for the index population. Also, the company showed that, if cisplatin is compared with atezolizumab and carboplatin, that it would be dominated. However, no data on the effectiveness of atezolizumab in this 'borderline population' were provided either from the IMpower133 trial or any other source. Therefore the ERG would argue that, if such a borderline LS-SCLC population exists, then one can make no evidence-based decision as to whether atezolizumab is cost effective in this population.

For PFS, the ERG considers the choice of model to be appropriate and, although the point at which the KM curve is replaced by the log-logistic model is arbitrary, there is little difference in the ICER by replacing with log-logistic for the whole time horizon (£35.92 on the company base-case). The ERG has a similar opinion of the choice of model for TTOT, although the difference between ICERs is not so easily dismissed, it being £1,026.11 lower on the company base-case by replacing with generalised gamma for the whole time horizon. Nevertheless, this implies that the model chosen by the company (KM for first 14 months) is conservative with regards to the cost effectiveness of atezolizumab. For OS and for the comparator, the ERG would disagree with the company judgement regarding clinical plausibility. Given that the log-logistic already overestimates OS as estimated in the Flatiron study and the Flatiron study probably overestimates OS compared to UK clinical practice, the log-logistic almost certainly overestimates OS compared to UK clinical practice. In contrast, the Weibull, which, whilst it also overestimates OS in comparison to the Flatiron study for years 1 to 2, it does provide estimates that are almost identical to the Flatiron study for years 3 to 5. Therefore, its overestimation of UK clinical practice is likely to be less than that by the log-logistic. Therefore, the ERG would argue that the Weibull is likely to be have greater clinical plausibility and it provides nearly as good a statistical fit, which is why it has been chosen for the comparator in the ERG base-case. For the intervention, the ERG also disagrees with the choice of the log-logistic on the basis of clinical plausibility as well as it having a marginally worse statistical fit than the Weibull. The main reason for this judgement is that there are no real-world data by which any estimates can be externally validated and the ERG questions the validity of clinical expert opinion as to the effect of a treatment for which they would have had no clinical experience. However, as with the comparator, one can compare the percentages surviving at each of the five time points from the clinical experts with those from the log-logistic and the model with the best statistical fit, the Weibull. When one does that it can be seen that the values for the Weibull are

all higher than those elicited from the clinical experts, but by more than the log-logistic only in year 1 and by less in all other years. Therefore, the ERG would argue that the Weibull is likely to have greater clinical plausibility and it provides a better statistical fit, which is why it has been chosen for the intervention in the ERG base-case.

The ERG considers that the company appropriately identified the AEs that were most important to include in terms of the potential impact on cost and utility. However, the ERG believes the justification provided by the company stating that AEs are implicitly captured by EQ-5D is questionable. According to NICE TSD 12 it is important to include decrements on HRQoL associated with AEs of at least Grade 3. The ERG therefore included AE disutilities. The ERG also questions the validity of the 'time to death' method employed by the company, although in the clarification letter response, the company provided references to previous STAs that used the 'time to death' approach. The ERG would argue that, despite use of the approach in previous STAs, it still remains an unvalidated method as evidenced by no mention of it in any of the NICE TSDs. It neglects the more established method of using progression status to determine utility value, it incorporates the effect of being on or off treatment with questionable clinical validity especially not having statistically tested the effect of both treatment and progression status and it is implemented by the arbitrary division into four time to death categories. In response to clarification letter, the company failed to provide what the ERG requested i.e. full statistical analysis of various models including both on/off treatment and progressed/not progressed as well as time to death as a continuous variable. Therefore, the ERG chose the more conservative approach of measuring utility as a function of progression status and not time to death as its ERG base-case.

The ERG believe that costs were generally estimated in a way that seemed plausible. The ERG has some concerns over the unit costs used for adverse events. This being said, the impact of using alternative unit cost estimates on the final ICER is very limited. However, alternative more costly estimates were used in TA531 (equating to £998 for diarrhoea and £788 for vomiting). It is not clear why the company chose the specific unit costs for adverse events.

The ERG base-case resulted in an ICER of £75,585 for atezolizumab plus carboplatin and etoposide versus carboplatin and etoposide only. This increase from the company base-case is due mainly to the decrease in the incremental QALYs from 0.25 to 0.17. Most of this decrease is due to the Weibull instead of the log-logistic, which by itself resulted in an ICER of £69,290. None of the scenario analyses chosen by the ERG made much difference and none decreased the ICER to below the £50,000 threshold.

Finally, the ERG would contend that, given evidence of variation in effectiveness according to PD-L1 subgroup that the subgroup analysis of cost effectiveness is still relevant, particularly given the possibility that atezolizumab might not be cost effective as shown in the ERG base-case.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

A wide range of resources was searched and the searches were well documented making them transparent and reproducible. An extensive range of additional searches were conducted for grey literature.

The evidence for atezolizumab with carboplatin and etoposide versus placebo with carboplatin and etoposide is based on a good quality randomised controlled trial (IMpower133) including 403 patients from 21 countries, with 10 patients from the UK. Results are based on the most recent data from 2019, and a median follow-up of [redacted] months.

The company model was generally well constructed and largely transparent with easy ability to conduct sensitivity analyses. Most of the data were obtained from a source i.e. the IMPower133 trial that was consistent with the scope and of good quality. Other data sources, such as for those used for costs, were appropriately justified and explored. The ICER was not very sensitive to plausible variation in most parameters.

1.6.2 Weaknesses and areas of uncertainty

The list of comparators searched was not exhaustive or in line with the final scope.

The population included in the IMpower133 trial might only represent a third of ES-SCLC patients in the UK. The company presented an indirect comparison of atezolizumab plus carboplatin-etoposide versus cisplatin-etoposide. However, we believe that the results from the indirect comparison presented by the company are unreliable and should not be used by NICE for decision making.

Regarding the comparators, etoposide plus carboplatin is a relevant comparator and no indirect comparison will present more reliable data than the data from the IMpower133 trial comparing atezolizumab plus carboplatin and etoposide with carboplatin and etoposide. However, it is possible that among the relevant comparators ignored by the company there is a more cost effective option than carboplatin and etoposide, which means the evidence presented in the CS might overestimate the relative cost effective of atezolizumab plus carboplatin and etoposide.

The ICER was most sensitive to plausible variation in parametric survival curves required to extrapolate beyond the trial follow-up. In particular, the ICER might be considerably higher than the £50,000 threshold given adoption of the curves considered to be the most plausible i.e. the Weibull for both intervention and comparator. This uncertainty would be reduced by further follow-up in the IMPower133 trial. The ICER was also reasonably sensitive to the method of estimating utilities, the uncertainty in which would be reduced by estimating a model that incorporated all plausible independent variables including both time to death and progression status.

There is also the possibility that irinotecan might be more effective than carboplatin plus etoposide as shown by some exploratory work by the ERG. However, whether atezolizumab plus etoposide and carboplatin is cost effective in comparison to irinotecan would require the performance of an indirect comparison as well as the inclusion of other parameters, such as AE risks and irinotecan specific costs.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Table 1.1 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 1.2. These are all conditional on the ERG base-case.

Table 1.1: Deterministic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,588
Carb + Etop	[redacted]	[redacted]			
Fixing error (Corrects PFS not starting at 1 in first cycle)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,577

Carb + Etop	[redacted]	[redacted]			
Fixing error (Corrects OS for intervention always being at least as high as comparator)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,588
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Uses Weibull for OS for both intervention and comparator)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.18	£69,260
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Utility is a function of progression status and not time to death)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.23	£53,724
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (AE disutilities from literature)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,664
Carb + Etop	[redacted]	[redacted]			
ERG base-case					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,585
Carb + Etop	[redacted]	[redacted]			
AE = adverse event; Atezo = atezolizumab; Carb = carboplatin; CS = company submission; ERG = Evidence Review Group; Etop = etoposide; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS =progression-free survival; QALY = quality-adjusted life year.					

Table 1.2: Deterministic scenario analyses conditional on ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Matter of judgement (Ensures that TTOT does not sink lower than PFS after 14 months (limit of K-M data))					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£77,891
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Change time at which PFS moves from K-M to Log-logistic)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,585
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Diarrhoea unit cost £998)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,631
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Vomiting unit cost £788)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,601
Carb + Etop	[redacted]	[redacted]			
Atezo = atezolizumab; Carb = carboplatin; ERG = Evidence Review Group; Etop = etoposide; ICER = incremental cost effectiveness ratio; K-M = Kaplan-Meier; PFS = progression-free survival; QALY = quality-adjusted life year; TTOT = time to of treatment.					

2. BACKGROUND

2.1 Critique of company's description of underlying health problem.

The company submission (CS) identifies lung cancer to be the most common cause of cancer-related death in the United Kingdom (UK), surpassing the next two common causes of cancer death, being bowel and prostate.[1, 2] According to the company submission 39,038 new cases of lung cancer were reported for England in 2017, and 28,566 deaths from lung cancer in 2016.[2, 3] Based on the information sheet from the Royal College of Physicians, the incidence data are for the year 2016 though and not 2017.[3]

The company distinguishes lung cancer by two types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[4] SCLC is identified as an aggressive neuroendocrine tumour which is characterised by early metastasis, accounting for 10% of all lung cancers.[3, 4] The two methods used to stage lung cancer include the Veterans Administration Lung Study Group (VALSG) classification and tumour, node, metastases (TNM).[1] The CS presents the IMpower133 trial as using the VALG classification system and states that this is widely used by the National Institute of Health and Care Excellence (NICE) and UK oncologists.[1] However, according to the company this does not align with the current recommendations from the International Association for the Study of Lung cancer (IASLC) and the European Society for Medical Oncology (ESMO), which recommend staging and treatment decisions be based on TNM status (CS, page 17).[5-8] The ERG wanted clarification regarding this matter and the company replied that an "advisory board meeting of 11 UK practicing oncologists held in March 2019 confirmed the correlation of the VALG staging definition for ES-SCLC used as an inclusion criterion for the IMpower133 study with the NICE guidance for TNM classification of 'broadly T1–4, N0–3, M1a/b'. This correlation is because of the requirement in the VALG definition of LS-SCLC that the disease is encompassed by the radiation field in every portal" (Response to clarification letter, Question A6).[9] By using the VALG identification system, SCLC can be further classified into either limited stage (LS) or extensive stage (ES).[10] The CS[1] notes LS-SCLC to be identified by its confinement to an area of tissue and its ability to be treated with a single beam of external radiation, while ES-SCLC is a metastatic disease and extends beyond the boundaries of a single radiation port. The IMpower133 trial focuses on ES-SCLC patients.[1]

The company states that the five-year survival for SCLC in England is only 5%.[1] However, the cited paper by Nicholson et al. (2016)[8] does not seem to provide any country specific data. The CS presents the five-year survival rate for ES-SCLC patients at less than 1% when treated with current standard of care carboplatin and etoposide.[1] According to data based on the National Lung Cancer Audit (NLCA) from 2004 to 2011, the median survival for the 68% of ES-SCLC patients who had received chemotherapy was shown to be 4 months.[11] This is under the assumption that the ES-SCLC patients who did not receive chemotherapy had worse survival outcomes than those who were treated with chemotherapy.

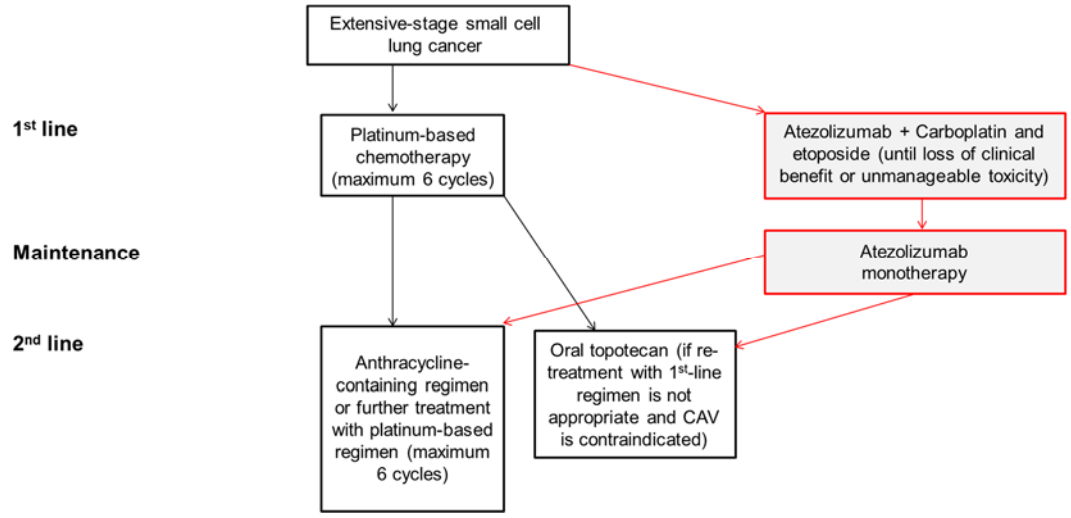
The CS notes SCLC patients experience symptoms such as dyspnoea and persistent cough.[12] The common comorbidities associated with SCLC include pulmonary disease, hypertension, cardiac disease, and diabetes.[13]

The CS describes that the purpose of lung cancer treatment is to increase survival and improve symptoms resulting in a negative impact on health-related quality of life (HRQoL).[14-16] The company emphasises the lack of innovation in treatment strategies for SCLC, either as systemic treatment or first-line treatment, within the last 30 years.[7, 17, 18]

2.2 Critique of company's overview of current service provision

Figure 2.1 shows the NICE clinical pathway of care and the proposed indication for atezolizumab as presented in the CS.[1] The company based the submission on NICE Clinical Guidance CG121, which was last updated in 2011. This clinical guidance was in the process of being reviewed at the time the ERG received the CS, with a publication date of 28 March 2019.[19]

Figure 2.1: NICE clinical pathway of care and the proposed indication for atezolizumab



Source: Section A.2 of the CS (Document A).[20]
CAV = cyclophosphamide, Adriamycin, vincristine.

For fit patients with ES-SCLC, NICE recommended a maximum of six cycles of platinum-based chemotherapy.[5] According to UK clinical experts attending a Roche-organised advisory board, [redacted] of ES-SCLC patients are treated with carboplatin and etoposide chemotherapy for 4-6 cycles as a first-line treatment.[1] After chemotherapy, NICE recommended thoracic radiotherapy and prophylactic cranial irradiation (PCI) for selected patients.[5]

The company presents the pathway alongside the NICE Scope.[1] However, the ERG noticed some inconsistencies within the CS and the NICE scope. The company states that "chemotherapy regimens excluding etoposide are outside the scope of this appraisal, so are not considered further here."[1] This does not coincide with the scope, which mentions "platinum-based combination chemotherapy regimens," as relevant comparators. The ERG noted this inconsistency in the letter of clarification to which the company responded that "Roche have been advised by over 20 practising NHS oncologists during individual consultation meetings and two separate advisory board meetings that the standard of care in the NHS for untreated, ES-SCLC is carboplatin plus etoposide. Moreover, that the control arm of the IMpower133 study is reflective of NHS clinical practice. Roche have also been advised that across the NHS, cisplatin plus etoposide is the standard of care for patients diagnosed with LS-SCLC and those considered to be borderline LS-SCLC and ES-SCLC. Therefore, only carboplatin plus etoposide treatment is considered to be within the scope of this appraisal, since all other treatments listed in the final scope are not considered standard NHS practice" (Response to clarification letter, Question A15).[9] The ERG noted another inconsistency between the CS and the NICE scope. In the CS the company states "Irinotecan plus carboplatin, paclitaxel plus carboplatin and best supportive care were reported in the clinical studies included in the systematic literature review (SLR), but these regimens were not relevant to this appraisal."[1] However, due to the NICE scope including all relevant comparators as "platinum-based combination chemotherapy regimens," this would also include irinotecan plus carboplatin and paclitaxel plus carboplatin.[5] The ERG addressed this issue also in the

letter of clarification to the company, to which the company responded that "regimens such as irinotecan plus carboplatin, paclitaxel plus carboplatin and best supportive care are not considered standard clinical practice by the broad range of NHS oncologists advising Roche" (Response to clarification letter, Question A15).[9] The company refers to the 2013 ESMO guidelines for SCLC in their submission.[6] The first section of the listed recommendations covers two cycles for chemotherapy. One method consisted of 4-6 cycles of carboplatin + etoposide, while the other method consisted of 4-6 cycles of cisplatin + etoposide. The second section notes the use of alternative platinum doublets, in the case of etoposide being contraindicated. The CS notes that in that case, irinotecan-cisplatin, gemcitabine-carboplatin, and IV or oral topotecan-cisplatin would not be considered comparable to the IMpower133 trial population.[1] The third recommendation states that patients with a reasonably good PS should be evaluated for PCI if there was any response to first-line treatment.[1] The fourth statement indicates that patients with metastatic SCLC are not recommended to have thoracic irradiation.[1]

The CS presents atezolizumab plus carboplatin and etoposide as a first-line treatment alongside platinum-based chemotherapy, for a maximum of six cycles.[1] The pathway also presents atezolizumab in the form of a monotherapy in the maintenance component of treatment.[1] Upon completion of the maintenance phase (atezolizumab monotherapy), patients would then enter the second-line treatment stage.[1] This could include an anthracycline-containing regimen/further platinum-based treatment regimen or oral topotecan in the event that retreatment with the first-line regimen is not appropriate and CAV is contraindicated.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	Adults with untreated ES-SCLC	As detailed in the final scope.	As detailed in the final scope	[redacted] Therefore, the relevant population for this appraisal is currently unclear. The proposed indication is: [redacted]
Intervention	Atezolizumab with carboplatin and etoposide	As detailed in the final scope Induction phase comprises atezolizumab in combination with carboplatin and etoposide every three weeks for 4 cycles, followed by a maintenance phase of atezolizumab every three weeks until loss of clinical benefit or unmanageable toxicity.	As detailed in the final scope	The intervention is atezolizumab with carboplatin and etoposide for four 21-day cycles followed by a maintenance phase during which patients receive atezolizumab monotherapy until the occurrence of unacceptable toxic effects or disease progression.
Comparator(s)	Platinum-based combination chemotherapy regimens	Carboplatin-etoposide for up to 4 cycles – as included in the IMpower133 trial control arm. UK-practising clinical experts advise Roche this reflects NHS standard of care and is the only comparison of relevance in this submission (Appendix K).	As detailed in the final scope and aligned with the anticipated MA wording and UK-practising clinical expert opinion (Appendix K).	The company has limited the comparators to 'platinum-etoposide chemotherapy regimens' (CS, page 43). Therefore, most relevant

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
		An NMA has been included and a secondary comparison to cisplatin-etoposide has been presented for transparency purposes. [redacted]		comparators are excluded from the CS.
Outcomes	The outcome measures to be considered include: • OS • PFS • RR • AE • HRQoL	All the outcomes stated in the final scope are considered in this submission. In addition, we present data for treatment discontinuation.	While the outcomes listed in the final scope are considered to be of relevance, however treatment discontinuation is an important outcome for the accurate reporting of cost-effectiveness.	The outcomes reported are in line with the NICE scope.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If appropriate, the appraisal should include consideration of the costs and implications of additional testing for	Cost-effectiveness is herein expressed in terms of incremental cost per quality-adjusted life year. No additional tests for biological markers are considered to be appropriate. A time horizon of 20 years is included in the base case, which is sufficiently long to reflect any differences in costs or outcomes between these treatment approaches.	As detailed in the final scope	In line with the reference case.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	biological markers, but will not make recommendations on specific diagnostic tests or devices. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	The perspective taken is UK NHS and Personal Social Services. A PAS for atezolizumab has been approved by the Department of Health during 2018. The price for chemotherapy regimens is taken from the eMIT database to reflect costs to the NHS.		
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on biological markers.	The efficacy of atezolizumab is presented for the ITT population from the IMpower133 trial, as well as for the pre-specified subgroups.[21] However, it is important to note that these subgroups were not statistically powered to detect a difference in clinical efficacy. These are presented here for transparency. Furthermore, exploratory subgroup efficacy data are presented in relation to TMB expression, however this was also not prognostic of clinical outcome. [redacted]	As detailed in the final scope	[redacted] However, the CEA was not performed for these subgroups.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
		[redacted] Therefore, the cost effectiveness is only considered for the ITT population from IMpower133 trial in this submission.		
Special considerations including issues related to equity or equality	N/A	N/A	N/A	

Source: CS, Table 1, pages 12-14.

AE = adverse event; EMA = European Regulatory Agency; eMIT = electronic marketing information tool; ES-SCLC = extensive-stage small cell lung cancer; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; ITT = intent-to-treat; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; OS = overall survival; PAS = patient access scheme; PFS = progression-free survival; RR = response rate; RSI = request for supplementary information; TMB = tumour mutational burden

3.1 Population

The population defined in the scope is: Adults with untreated extensive-stage small-cell lung cancer.[22]

The proposed indication for atezolizumab as described in the company submission (CS) is: [redacted] However, [redacted] Therefore, the relevant population for this appraisal is currently unclear.

3.2 Intervention

The intervention described in the NICE scope is atezolizumab with carboplatin and etoposide. However, in the CS, the intervention is atezolizumab with carboplatin and etoposide for four 21-day cycles followed by a maintenance phase during which patients receive atezolizumab monotherapy until the occurrence of unacceptable toxic effects or disease progression.

During the induction phase, patients receive four 21-day cycles of:

- Atezolizumab (at a dose of 1200 mg, administered intravenously on day 1 of each cycle)
- Carboplatin (area under the curve of 5 mg per millilitre per minute, administered intravenously on day 1 of each cycle)
- Etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle)

The induction phase is followed by a maintenance phase during which patients receive atezolizumab (1200 mg every three weeks) until the occurrence of unacceptable toxic effects or disease progression per RECIST v1.1. In the IMpower133 trial, continuation of the trial regimen after the occurrence of disease progression during either phase was allowed if evidence of clinical benefit existed.[21, 23]

No additional tests or investigations are required according to the company (CS, page 16).

Atezolizumab is a humanised anti-PD-L1 monoclonal antibody that inhibits the binding of PD-L1 to its receptors, PD-1 and B7.1.[24]

- PD-1 is an inhibitory receptor expressed on T cells following T-cell activation and binds to PD-L1 which inhibits T-cell proliferation, cytokine production, and cytolytic activity.[25, 26]
- B7.1 is a receptor expressed on antigen-presenting cells and activated T cells and by binding to PD-L1, can downregulate the immune response, including inhibition of T-cell activation and cytokine production.[27, 28]

Therefore, when atezolizumab binds to PD-L1, which is overexpressed on tumour cells, this can enhance the anti-tumour immune response.[24, 29]

Carboplatin is a cytotoxic chemotherapy agent which acts by forming DNA crosslinks to interrupt cellular DNA functioning, which leads to apoptosis.[30, 31]

Etoposide targets topoisomerase II activities and inhibits DNA re-ligation, which leads to DNA breaks; this elicits a response that disrupts cell metabolism.[32]

3.3 Comparators

The description of the comparators in the NICE scope is as follows: Platinum-based combination chemotherapy regimens. However, in the CS the company states that "chemotherapy regimens excluding etoposide are outside of the scope of this appraisal" (CS, Appendix D, page 41). This means

treatment regimens such as carboplatin plus paclitaxel, irinotecan plus cisplatin, topotecan plus cisplatin, and paclitaxel plus cisplatin are not considered as comparators in the CS.

The only comparators considered in the CS are carboplatin plus etoposide and cisplatin plus etoposide.

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- overall survival
- progression-free survival
- response rate
- adverse effects of treatment
- health-related quality of life.

These were all assessed in the IMpower133 trial. In addition, data for treatment discontinuation were reported.

3.5 Other relevant factors

A simple PAS discount of [redacted] has already been implemented as a result of three previous NICE appraisals (TA492,[33] TA520,[34] and TA525[35]) for atezolizumab. The company does not propose to change or otherwise amend this existing PAS as part of this appraisal (CS, Table 2, page 16).[1]

According to the company, atezolizumab meets the NICE end of life criteria for the first-line treatment of adult patients with ES-SCLC (see: CS, Table 19, page 55).[1] The ERG is not sure there is robust evidence to assess this (see Section 7 in this report).

According to the company no equality concerns have been identified or are anticipated with the introduction of atezolizumab (CS, Section B.1.4, page 21).[1]

The company does claim that atezolizumab is an innovative treatment for first-line ES-SCLC patients because "the IMpower133 Phase I/III trial demonstrated significantly longer OS and PFS in patients with first-line ES-SCLC who were treated with atezolizumab and chemotherapy compared with chemotherapy alone" (CS, Section B.2.12, page 50).[1] The company states that this is "the first significant advance in the treatment of ES-SCLC in 20 years and represents a step change in the management of ES-SCLC" (CS, page 50).[1] The IMpower133 study has to date reported a 2-month median survival benefit from atezolizumab treatment in ES-SCLC patients (CS, Table 19, page 55).[1] However, the OS data from the IMpower133 trial as presented in the CS are immature; the final analysis for the IMpower133 trial is expected in [redacted]. Based on the final analysis for the IMpower133 trial, the Kaplan-Meier estimated median OS was [redacted] in the atezolizumab group ([redacted]) vs. the placebo group ([redacted]).

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D.1.1 of the CS details a systematic search of the literature used to identify clinical effectiveness literature undertaken on 1 July 2018 and an updated (electronic databases and congress proceedings) on 4 November 2018. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the clinical effectiveness systematic review

Search strategy element	Resource	Host/Source	Date Range	Date searched
Electronic Databases	Medline	OVID	1946-2018/11/2	1 July 2018 Update searches on 4 November 2018
	Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations			
	Medline Daily			
	Embase		1974- 2018/11/2	
	Cochrane CENTRAL	EBM Reviews via OVID	July 2017	
	CDSR		2005 – 16 August 2016	
	DARE		Up to 1st Quarter 2016	
	HTA Database		Up to 4th Quarter 2016	
	NHS EED		Up to 1st Quarter 2016	
Conference Proceedings	ASCO	Not reported	Last 3 years	1 July 2018 Update searches on 4 November 2018
	ESMO			
	AACR			
HTA Agencies	NICE	Not reported		1 July 2018
	SMC			
	PBAC			
	CADTH (including pCODR)			
Trials Registries	WHO ICTRP	Not reported		1 July 2018
Reference lists of relevant studies, recent systematic reviews, and meta-analyses were searched to identify further relevant studies				

AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; CADTH = Canadian Agency for Drugs and Technologies in Health; CDSR = Cochrane Database Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; ESMO = European Society for Medical Oncology; HTA Database = Health Technology Assessment Database; NHS EED = NHS Economic Evaluation Database; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicine Consortium.

ERG comment:

- The selection of databases searched was comprehensive, and searches were clearly reported and reproducible. The database name, host and date searched were provided. An extensive range of resources additional to database searches was included in the SLR to identify further relevant studies and grey literature.
- Restricted list of comparators in the search strategies, some possible comparators were not included in the searches (e.g. irinotecan plus cisplatin, topotecan plus cisplatin, and paclitaxel plus cisplatin are not included).
- Study design filters to identify clinical trials were applied. The filters were not referenced, so it was unclear whether they were published objectively-derived filters. The filters contained a combination of subject heading terms (MeSH and Emtree) and free text terms, and the ERG deemed them to be adequate.
- A broad range of additional sources were 'hand' searched, the sources and terms used were not reported in full detail (i.e. website addresses and terms used to search them).

4.1.2 Inclusion criteria

The eligibility criteria used for inclusion in the systematic literature review (SLR) are presented in Table 4.2.

Table 4.2: Eligibility criteria for inclusion in the SLR

Criteria	Inclusion criteria
Population	The primary population of interest were aligned with patients enrolled in the IMpower133 study, namely adult patients (≥ 18 years) with histologically or cytologically confirmed ES-SCLC with no prior systemic treatment for ES-SCLC.
Interventions	The investigational medicinal products of interest were: • Atezolizumab • Carboplatin plus etoposide Comparators of interest included the following: • Cisplatin plus etoposide • Carboplatin plus irinotecan • Carboplatin plus paclitaxel • Best supportive care
Outcomes	The following outcomes were of interest: **Efficacy**: Overall survival (OS), Progression-free survival (PFS), Time to progression, Duration of response (DOR), Response rates (Complete response (CR), partial response (PR), stable disease (SD)), Objective response rate (ORR), Disease control rate (DCR), Duration of treatment and duration of treatment beyond progression, Time in response (TIR), Time to deterioration (TTD), HRQoL and patient reported outcomes measures. **Safety**: All-grade treatment related adverse events (AE), Treatment related Grade 3 or 4 AEs, Treatment related serious adverse events (SAE) and Tolerability: Dose reductions and interruptions, discontinuation (any reason), discontinuation (due to AEs).
Study design	Prospective RCTs (Phases II to IV with active or placebo or BSC controls with no restriction on blinding).
Territory of interest	No restriction.

Criteria	Inclusion criteria
Date of publication	No restriction.
Language of publication	No restriction. The primary focus was English language publications or non-English language publications with an English abstract.
Source: CS, Appendix D, Table 1, pages 11-12.	

ERG comment: Interventions of interest were restricted to atezolizumab, carboplatin or cisplatin plus etoposide, carboplatin plus irinotecan or paclitaxel, and best supportive care (BSC). This means interventions such as: topotecan plus carboplatin or cisplatin, irinotecan plus cisplatin, paclitaxel plus cisplatin with or without etoposide, gemcitabine plus carboplatin or cisplatin, pemetrexed plus carboplatin or cisplatin, and bevacizumab plus cisplatin with or without etoposide were all ignored in the SLR. The company does not discuss the omission of these treatments and provides no justification for the inclusion of the treatments mentioned in the table above.

4.1.3 Critique of data extraction

Relevant data were extracted into an Excel-based data extraction table (DET). Data were extracted as reported and no calculations to obtain additional data were performed, calculations to obtain values for meta-analysis were reported in the meta-analysis report. Data extraction was conducted by an analyst and all data inputs were independently checked against the source document by a second analyst (CS, Appendix D, page 18).[1]

ERG comment: The process of data extraction appears sufficient. The checking of extracted data by a second reviewer minimises the risk of error and bias.

4.1.4 Quality assessment

In Section 1.3 of Appendix D of the CS, the company describes the results of the quality assessment of the IMpower133 trial.[36] The overall result of this assessment is reported in Section B.2.5 of the CS.[1] This assessment was performed against a checklist developed by the Centre for Reviews and Dissemination (CRD) for the assessment of risk of bias in RCTs as part of their guidance for undertaking reviews in health care.[37] The checklist addresses four dimensions of bias (selection, performance, attrition and detection bias) using the following seven signalling questions:[36]

- Was randomisation carried out appropriately?
- Was the concealment of treatment allocation adequate?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

The company rated the overall risk of bias as low.

ERG comment: The ERG agrees that the overall risk of bias of the IMpower133 trial is low. However, the study population may not be representative for the UK population (see also Section 4.2.3 (Baseline characteristics) of this report).

4.1.5 Evidence synthesis

The company mentions two types of evidence synthesis. Firstly, the company addresses the possibility of a meta-analysis of atezolizumab studies. The company concludes that: "The efficacy and safety of atezolizumab plus carboplatin-etoposide in first-line ES-SCLC patients has only been investigated in one RCT: the IMpower133 trial. Therefore, a meta-analysis of relevant trials was not required." (CS, Section B.2.8, page 43).[1]

ERG comment: Firstly, we agree that a meta-analysis of atezolizumab studies is not relevant.

Secondly, the company addresses the possibility of performing indirect and mixed treatment comparisons to compare the intervention (atezolizumab with carboplatin and etoposide) with the comparators described in the NICE scope (platinum-based combination chemotherapy regimens). However, first the company limits the comparators to 'platinum-etoposide chemotherapy regimens' and then the company concludes that cisplatin-etoposide is not a relevant comparator for this appraisal based on expert advice (CS, page 43). Nevertheless, the company presents a network meta-analysis and indirect treatment comparison for cisplatin-etoposide in Appendix F.

ERG comment: As mentioned in Sections 4.1.1 and 4.1.2 of this report, a large number of potentially relevant comparators have not been included in the literature searches. Therefore, no evidence for these interventions will have been retrieved. It is beyond the remit of the ERG to repeat the systematic review for the company, which means that the ERG have no idea what the impact of this omission is.

Based on the limited searches performed by the company, 73 publications were retrieved. However, most of these were excluded by the company because the intervention did not include etoposide. It is unclear why the company has limited the comparators to 'platinum-etoposide chemotherapy regimens' because the NICE scope is quite clear in describing the comparator as: 'platinum-based combination chemotherapy regimens'. Therefore, we will describe the possibilities of performing a mixed treatment comparison of atezolizumab with carboplatin and etoposide versus the comparators described in the NICE scope in Section 4.5 (Additional work on clinical effectiveness undertaken by the ERG) of this report.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Included studies

Two studies are mentioned in the CS as relevant to the technology being appraised:

- A Phase Ia, multicentre, first-in-human, open-label, dose escalation study of atezolizumab monotherapy to patients with locally advanced or metastatic solid malignancies or haematologic malignancies (Study PCD4989g). This study will not be discussed further in this submission as it was a single arm trial for atezolizumab monotherapy.
- A multinational Phase I (safety) and III (efficacy), double-blind, randomised, placebo-controlled study (IMpower133 trial), evaluating the efficacy and safety of adding atezolizumab or placebo to first-line treatment with carboplatin and etoposide in patients with ES-SCLC. In the submission, the company report the planned interim analysis of OS and a final analysis of progression-free survival (data cut-off 24 April, 2018).

These two studies are listed in Table 4.3.

Table 4.3: Clinical effectiveness evidence as presented in the CS

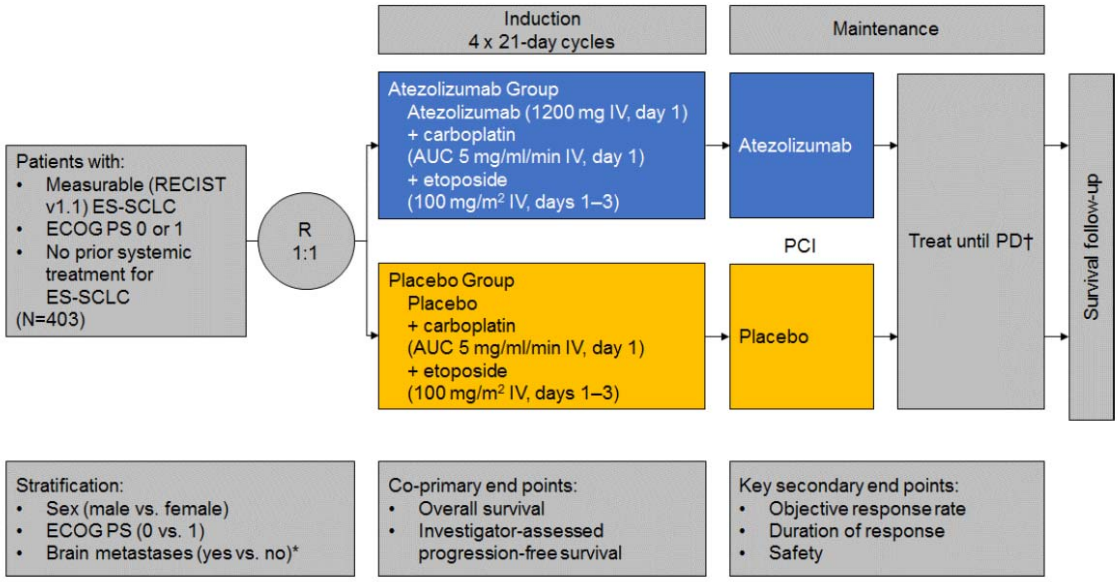
Study	PCD4989g[38]	IMpower133 Phase I/III trial[21, 23]
Study design	Phase Ia, multicentre, first-in-human, open label, dose escalation study	A Phase I/III, randomised, double-blind, placebo-controlled study
Population	SCLC cohort of patients with locally advanced or metastatic solid malignancies or haematologic malignancies	Patients with untreated extensive-stage small cell lung cancer
Intervention(s)	Atezolizumab monotherapy	Atezolizumab with carboplatin plus etoposide
Comparator(s)	N/A	Carboplatin plus etoposide
Study used in the economic model	No	Yes
Reported outcomes	N/A	Overall survival, progression-free survival, response rate, adverse events, health-related quality of life.
Source: CS, Table 5, pages 21-22. N/A = not applicable; SCLC = Small cell lung cancer		

ERG comment: The ERG agrees with the company that Study PCD4989g does not need to be discussed further for this appraisal, and to focus on the IMpower133 trial.

4.2.2 Methodology of included studies

The IMpower133 trial study design is summarised in the Figure below.

Figure 4.1: Study design of IMpower133



Source: CS, Figure 2, page 23.

AUC = area under curve; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ES-SCLC = extensive-stage small cell lung cancer; PCI = prophylactic cranial irradiation; PD = disease progression; R = randomised; RECIST = response evaluation criteria in solid tumours

* Only patients with treated asymptomatic central nervous system metastases were eligible.

† Maintenance continued until occurrence of unacceptable toxic effects or disease progression according to RECIST, however, patients who met prespecified criteria were allowed to be treated beyond disease progression per RECIST v1.1 criteria until loss of clinical benefit in a blinded fashion.

ERG comment: As can be seen in Figure 4.1, the intervention is not "atezolizumab with carboplatin and etoposide" as described in the NICE scope, but atezolizumab with carboplatin and etoposide for about three months (four x 21-day cycles) followed by atezolizumab monotherapy (maintenance phase, until disease progression or unacceptable toxic effects). In the control arm, patients received carboplatin and etoposide for about three months followed by placebo (until disease progression or unacceptable toxic effects).

The methodology of the IMpower133 trial is described in Table 4.4.

Table 4.4: Summary of methodology for the IMpower133 trial

Study	IMpower133 trial (NCT02763579)[21, 23]
Trial design	Phase I/III double-blind, randomised, placebo-controlled trial (N=403)
Eligibility criteria for participants	Adults with histologically or cytologically confirmed ES-SCLC as defined according to the VALG staging system, measurable ES-SCLC according to RECIST, version 1.1, and an ECOG performance-status score of 0 or 1 (on a 5-point scale, with higher numbers reflecting greater disability) who had not received previous systemic treatment for ES-SCLC. Patients with treated asymptomatic central nervous system metastases were eligible. Key exclusion criteria were a history of autoimmune disease and previous treatment with CD137 agonists or immune-checkpoint blockade therapies.
Settings and locations where data were collected	106 centres in 21 countries. Number of patients randomised per country (number of centres in parentheses): United States of America 86 (22), Poland 45 (6), Japan 42 (13), Russia 30 (6), Spain 25 (6), Austria 20 (4), Hungary 19 (4), Czech Republic 17 (3), South Korea 17 (4), Italy 15 (6), Serbia 15 (3), Australia 11 (3), Greece 11 (3), United Kingdom 10* (4), Germany 9 (5), Taiwan 9 (3), France 7 (4), Chile 6 (2). Brazil 4 (3), Mexico 4 (1), China 1 (1)
Trial drugs	Four 21-day cycles of: • Carboplatin (area under the curve of 5 mg per millilitre per minute, administered intravenously on day 1 of each cycle) • Etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle) • Atezolizumab (at a dose of 1200 mg, administered intravenously on day 1 of each cycle) or placebo The induction phase was followed by a maintenance phase during which patients received either atezolizumab (1200 mg every three weeks) or placebo (according to the previous random assignment) until the occurrence of unacceptable toxic effects or disease progression per RECIST v1.1. Continuation of the trial regimen after the occurrence of disease progression during either phase was allowed if evidence of clinical benefit existed.
Permitted and disallowed concomitant medication	The following medications were prohibited while in the study, unless otherwise noted: • Denosumab • Any live, attenuated vaccine (e.g. FluMist®) within 4 weeks prior to randomisation, during treatment, and for 5 months following the last dose of atezolizumab/placebo

Study	IMpower133 trial (NCT02763579)[21, 23]
	• Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance) • The concomitant use of herbal therapies The following therapies were permitted while patients were in the study: • Oral contraceptives • Hormone-replacement therapy • Prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level) • Palliative radiotherapy (e.g., treatment of known bony metastases) provided it does not interfere with the assessment of tumour target lesions • Inactive influenza vaccinations • Megestrol administered as an appetite stimulant • Inhaled corticosteroids for chronic obstructive pulmonary disease • Mineralocorticoids (e.g., fludrocortisone) • Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency • Premedication with antihistamines could be administered for any atezolizumab/placebo infusions after Cycle 1
Co-primary outcomes	• OS (the time from randomisation to death from any cause) • Investigator-assessed PFS per RECIST v1.1 (time from randomisation to disease progression or death from any cause, whichever occurred first)
Secondary outcomes	• ORR (either an unconfirmed CR or a PR, as determined by the investigator using RECIST v1.1) • DOR (an objective response as determined by the investigator using RECIST v1.1) • 6- and 12-month PFS rates • 12- and 24-month OS rates • TTD using EORTC QLQ-C30 and QLQ-LC13
Pre-planned subgroups	To assess the consistency of the study results in subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline prognostic characteristics (e.g., ECOG performance status, smoking status, presence of brain metastases etc.)
Source: CS, Table 6, 7 and 8, pages 24-31 CR = complete response; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for the Research and Treatment of Cancer; ES-SCLC = extensive-stage small-cell lung cancer, ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; QLQ-C30 = Quality of Life Questionnaire-Core 30; QLQ-LC13 = quality of life questionnaire lung cancer 13; RECIST = Response Evaluation Criteria in Solid Tumours; TTD = time to deterioration; VALG = Veterans Administration Lung Study Group . Notes: * 4 patients in the atezolizumab arm and 6 patients in the placebo arm	

ERG comment: The trial included 403 patients (201 patients in the atezolizumab arm and 202 patients in the placebo arm), including 10 from the UK (four patients in the atezolizumab arm and six patients in the placebo arm).

4.2.3 Baseline characteristics

A total of 403 patients were enrolled in the IMpower133 trial and were randomly assigned to the atezolizumab group (201 patients) or the placebo group (202 patients). Baseline characteristics seem well balanced between the groups (see Table 4.5).

Table 4.5: Baseline characteristics of all enrolled patients (ITT population)

Characteristic	Atezolizumab Group (n = 201)	Placebo Group (n = 202)
Median age (range) — yr	64 (28–90)	64 (26–87)
Age group — no. (%)		
<65 yr	111 (55.2)	106 (52.5)
≥65 yr	90 (44.8)	96 (47.5)
Male sex — no. (%)†	129 (64.2)	132 (65.3)
ECOG performance-status score — no. (%)†‡		
0	73 (36.3)	67 (33.2)
1	128 (63.7)	135 (66.8)
Smoking status — no. (%)		
Never smoked	9 (4.5)	3 (1.5)
Current smoker	74 (36.8)	75 (37.1)
Former smoker	118 (58.7)	124 (61.4)
Brain metastasis at enrolment — no. (%)†	17 (8.5)	18 (8.9)
Blood-based tumour mutational burden — no./total no. (%)§		
<10 mutations/Mb	71/173 (41.0)	68/178 (38.2)
≥10 mutations/Mb	102/173 (59.0)	110/178 (61.8)
<16 mutations/Mb	133/173 (76.9)	138/178 (77.5)
≥16 mutations/Mb	40/173 (23.1)	40/178 (22.5)
Median sum of longest diameter of target lesions at baseline (range)	113.0 (12.0–325.0)	105.5 (15.0–353.0)
Previous anticancer treatments — no. (%)		
Chemotherapy or nonanthracycline¶	8 (4.0)	12 (5.9)
Radiotherapy	25 (12.4)	28 (13.9)
Cancer-related surgery	33 (16.4)	25 (12.4)

Source: CS, Table 9, page 32.
Mb = megabases
† The data were determined from electronic case-report forms.
‡ ECOG PS scores range from 0 to 5, with higher scores reflecting greater disability.
§ Of the 403 patients in the two groups, 374 had plasma available for blood-based analysis of tumour mutational burden; 351 of the samples (173 in the atezolizumab group and 178 in the placebo group) yielded high-quality data for analysis of tumour mutational burden.
¶ Previous chemotherapy or nonanthracycline treatments included cisplatin, etoposide, and concurrent radiation (in six patients in the atezolizumab group and seven patients in the placebo group) and carboplatin, etoposide, and concurrent radiation (in two patients in the atezolizumab group and six patients in the placebo group).

ERG comment: Baseline characteristics were well balanced between the groups. However, the population included in the IMpower133 trial may not be representative of the ES-SCLC patient

population in UK practice. In Appendix K the company stated that "discussion among the advisory board attendees highlighted that, in their experience, fewer ES-SCLC patients in a real-world situation within the UK would be diagnosed with an ECOG status of 0 than was reported in the cohort of US patients included in the Flatiron study (Appendix K, page 6).[39] This means that fewer than [redacted] of ES-SCLC patients in a real-world situation within the UK would be diagnosed with an ECOG status of 0 according to 8 out of 9 oncologists consulted by Roche. In the IMpower133 trial, 35% of patients had an ECOG performance status of 0. Furthermore, all included patients in the IMpower133 trial had an ECOG performance status of 0-1. In appendix K, the company reports that "some advisors stated in their experience the probable proportions of UK ES-SCLC patients diagnosed as ECOG 0–1 would be as high as [redacted], with others reporting that in their clinical experience it could be as low as [redacted]."[39] Therefore, the population included in the IMpower133 trial might only represent a third of ES-SCLC patients in the UK.

4.2.4 Statistical analyses

Randomisation occurred in a 1:1 ratio using a permuted-block randomisation method. Patients were randomised to one of two treatment arms: atezolizumab + carboplatin + etoposide or placebo + carboplatin + etoposide. The randomisation scheme was designed to ensure that an approximately equal number of patients would be enrolled in each treatment arm within the baseline characteristics of the following stratification factors: gender (male vs. female), ECOG PS (0 vs. 1) and presence of brain metastases (yes vs. no). Patients received their first dose of the study drug on the day of randomisation if possible. If this was not possible, the first dose occurred within five days after randomisation.[40]

The two co-primary endpoints of the IMpower133 study were OS and investigator-assessed PFS. OS was defined as the time from randomisation to death from any cause. Patients who were not reported as having died were censored at the date when they were last known to be alive. Patients who did not have post-baseline information were censored at the date of randomisation plus one day.

PFS was defined as the time from randomisation to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first. Patients who did not experience disease progression or death at the time of analysis were censored at the time of the last tumour assessment. Patients with no post-baseline tumour assessment were censored at the date of randomisation plus one day.

The sample size calculation was based on the analysis of OS. To detect a HR = 0.68 for atezolizumab versus placebo using a log-rank test, approximately 306 deaths in the ITT population provided 91% power at a two-sided 0.045 significance level. One interim analysis was performed after 240 deaths. The primary PFS analysis was planned at the time of the interim OS analysis after approximately 295 PFS events had occurred. This provided 99% power to detect an improvement in PFS of a HR = 0.55 at a two-sided significance level of 0.005. There were no interim analyses for PFS.

To control the overall two-sided type I error rate at 0.05 in the analyses of patients enrolled during the global enrolment phase, a group sequential weighted Holm procedure[41] was used wherein the two-sided significance levels of 0.005 and 0.045 were allocated to the primary comparisons for progression-free survival (PFS) and OS, respectively. If PFS in the ITT population was statistically significant at the two-sided α level of 0.005, OS in the ITT population was tested at a two-sided α level of 0.05. Additionally, if OS in the ITT population was statistically significant at the two-sided α level of 0.045, PFS in the ITT population was tested at a two-sided α level of 0.05.

OS and PFS were analysed using the same methods. Treatments were compared with a stratified log-rank test and the Kaplan-Meier methodology was used to estimate median PFS for each treatment arm and to construct survival curves. The Brookmeyer-Crowley methodology and log-log transformation for normal approximation were used to construct the 95% CI for the median PFS for each treatment arm.[42] HR were estimated with a stratified Cox regression model with 95% CI estimated by normal approximation.

ERG comment: The statistical analysis of the IMpower133 was appropriate and the ERG have no concerns.

4.2.5 Results

The IMpower133 trial evaluated the efficacy and safety of adding atezolizumab or placebo to first-line treatment with carboplatin and etoposide (hereafter referred to as the atezolizumab group and placebo group) in patients with ES-SCLC. Results below are based on a planned interim analysis of OS and a final analysis of PFS (data cut-off 24 April 2018).

A final analysis of OS in the IMpower133 trial will occur after approximately 306 OS events in the ITT population have occurred; this analysis is anticipated in [redacted] and will be made available to NICE according to the company.

In addition, the company stated that "[redacted]" (CS, page 50).[1]

4.2.5.1 Overall survival

The study met the co-primary endpoint of OS, demonstrating a statistically significant improvement in OS in favour of the atezolizumab group compared with the placebo group (HR = 0.70 (95% CI: 0.54 to 0.91)), in patients with chemotherapy-naïve ES-SCLC at the time of data cut-off (see Table 4.6).

Table 4.6: Overall survival in the ITT population, data cut-off date 24 April 2018

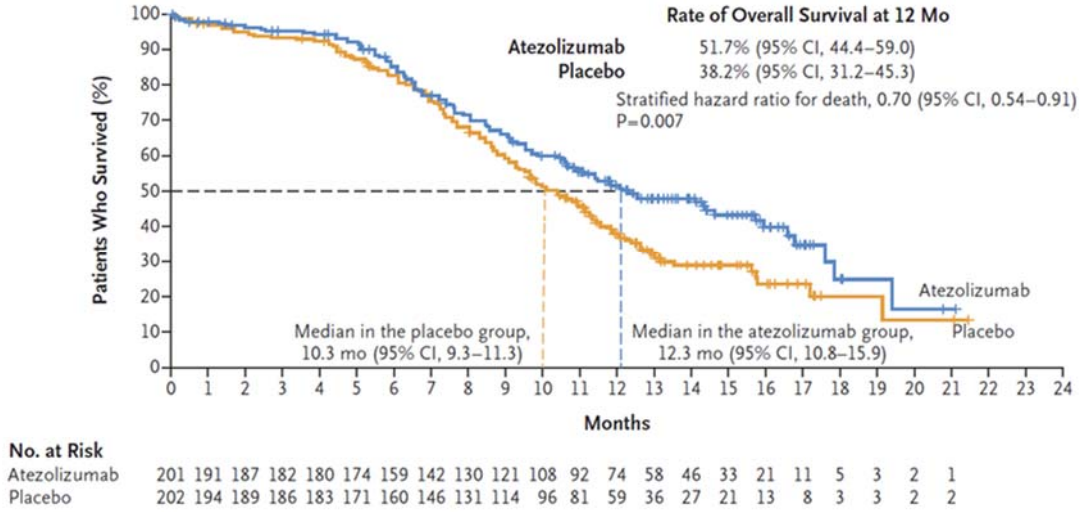
	Atezolizumab group	Placebo group
ITT population	n=201	n=202
Patients with event (%)	104 (51.7%)	134 (66.3%)
Median duration of survival (95%) (months)	12.3 (10.8, 15.9)	10.3 (9.3, 11.3)
Stratified hazard ratio (95%)	0.70 (0.54, 0.91)	
p-value (log-rank)	0.007[a]	
1-year event-free rate (%) (95% CI)	51.7 (44.4, 59.0)	38.2 (31.2, 45.3)

Source: CS, Table 10, pages 36-37.
CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
[a] Interim Analysis OS was tested at two-sided α of 0.0193 (with 238 observed OS events at CCOD) to control the overall two-sided type I error for OS at 0.045 by Lan DeMets function approximating O'Brien-Fleming boundary.

At the time of data cut-off, 24 April 2018, the median follow-up was 13.9 months. A total of 104/201 patients (51.7%) in the atezolizumab group and 134/202 patients (66.3%) in the placebo group had died. The stratified HR for death was 0.70 (95% CI, 0.54 to 0.91; P = 0.007) (see Figure 4.2), and the one-

year OS rate was 51.7% (95% CI, 44.4–59.0) in the atezolizumab group and 38.2% (95% CI, 31.2–45.3) in the placebo group.

Figure 4.2: Kaplan-Meier plot of OS in ITT population, data cut-off date 24 April 2018



Source: CS, Figure 3, page 38.
Mo = Months; CI = Confidence interval

The company performed subgroup analyses for demographics (e.g., age, gender and race/ethnicity), baseline prognostic characteristics (e.g., ECOG performance status, smoking status, presence of brain metastases at baseline), and pre-specified blood tumour mutational burden (bTMB) biomarker expression cut-offs (>10 or <10 and >16 or <16), by investigating the duration of OS in these subgroups. Results are reported in Appendix E of the CS and show that the hazard ratios for overall survival are better for older patients (HR=0.53 (95% CI: 0.36 to 0.77) for ≥65 yr versus HR=0.92 (95% CI: 0.64 to 1.32) for <65 yr); and for those without brain or liver metastases (Brain: HR=0.68 (95% CI: 0.52 to 0.89) for no metastases versus HR=1.07 (95% CI: 0.47 to 2.43) for those with metastases; Liver: HR=0.64 (95% CI: 0.45 to 0.90) for no metastases versus HR=0.81 (95% CI: 0.55 to 1.20) for those with metastases).

ERG comment: At the time of the company submission to NICE (February 2019), OS data were almost a year old. Therefore, we asked the company for updated OS and PFS data in the clarification letter. Updated OS data are presented below.

Updated overall survival data

As part of the response to clarification, the company provided updated OS data, with a clinical cut-off date (CCOD) of [redacted] (Table 4.7).[43] This updated exploratory analysis for OS was conducted, based on a pre-specified number of events (306 OS events) in the Statistical Analysis Plan Version 3 (dated 14 May 2018). [redacted] Overall, [redacted].

Table 4.7: Overall survival in the ITT population, data cut-off date [redacted]

	Atezolizumab group	Placebo group
ITT population	n=201	n=202
Patients with event (%)	[redacted]	[redacted]
Median duration of survival (95%) (months)	[redacted]	[redacted]
Stratified hazard ratio (95%)	[redacted]	
p-value (log-rank)	[redacted]	
1-year event-free rate (%) (95% CI)	[redacted]	[redacted]
2-year event-free rate (%) (95% CI)	[redacted]	[redacted]

Source: Response to Clarification Letter, version 2, Question A10.
CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
[a] This value is descriptive.

At the time of data cut-off, [redacted], the median follow-up was [redacted] months. A total of [redacted] patients ([redacted]) in the atezolizumab group and [redacted] patients ([redacted]) in the placebo group had died. The stratified (gender and ECOG) HR for death was [redacted] (see Figure 4.3), and the two-year OS rate was [redacted] in the atezolizumab group and [redacted] in the placebo group.

The Kaplan-Meier estimated median OS was [redacted] in the atezolizumab group ([redacted]) vs. the placebo group ([redacted]) (see Figure 4.3).

Figure 4.3: Kaplan-Meier plot of OS in the ITT population, data cut-off date [redacted]

4.2.5.2 Progression-free survival

The study met the co-primary endpoint of PFS, demonstrating a statistically significant improvement in investigator-assessed PFS in favour of the atezolizumab group compared with the placebo group (HR

= 0.77 (95% CI: 0.62 to 0.96)), in patients with chemotherapy-naïve ES-SCLC at the time of data cut-off (see Table 4.8).

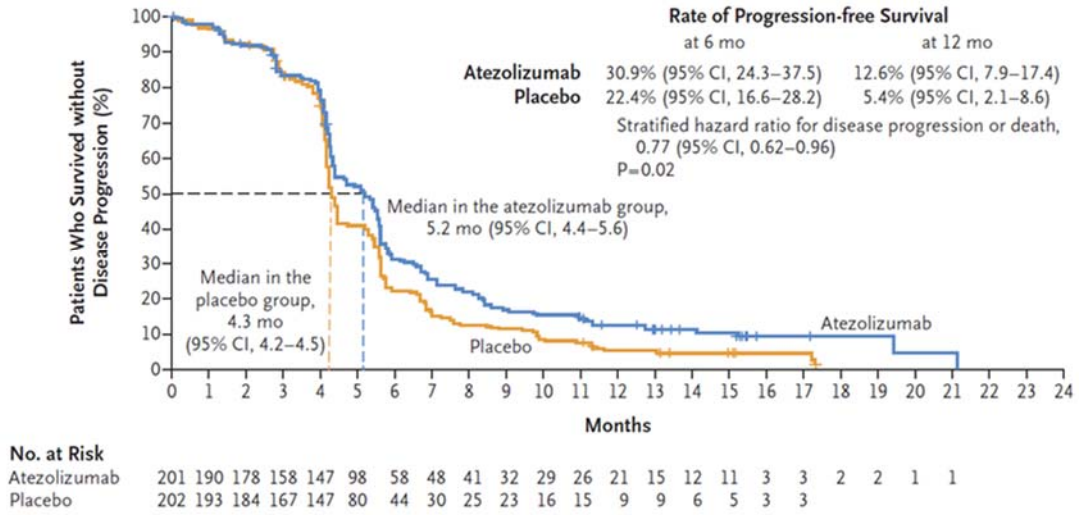
Table 4.8: Progression-free survival in the ITT population, data cut-off date 24 April 2018

	Atezolizumab group	Placebo group
ITT population	n=201	n=202
Patients with event (%)	171 (85.1%)	189 (93.6%)
Median duration of PFS (95%) (months)	5.1 (4.4, 5.6)	4.3 (4.2, 4.5)
Stratified hazard ratio (95%)	0.77 (0.62, 0.96)	
p-value (log-rank)	0.02[a]	
6-month event-free rate (95% CI)	30.9 (24.3, 37.5)	22.4 (16.6, 28.2)
1-year event-free rate (%) (95% CI)	12.6 (7.9, 17.4)	5.4 (2.1, 8.6)

Source: CS, Table 10, pages 36-37.
CI = confidence interval; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival.
[a] Since null hypothesis for OS was rejected at an overall two-sided significance level of 0.045, PFS was tested at two-sided type I error of 0.05.

A total of 171/201 patients (85.1%) in the atezolizumab group and 189/202 patients (93.6%) in the placebo group had disease progression or had died. Progression-free survival was longer in the atezolizumab group (median, 5.2 months; 95% CI, 4.4 to 5.6) than in the placebo group (median, 4.3 months; 95% CI, 4.2 to 4.5). The stratified hazard ratio for disease progression or death was 0.77 (95% CI, 0.62 to 0.96; P = 0.02) (see Figure 4.4).

Figure 4.4: Kaplan-Meier plot of PFS in ITT population, data cut-off date 24 April 2018



Source: CS, Figure 4, page 39.
Mo = Months; CI = Confidence interval

The company performed subgroup analyses for demographics (e.g., age, gender, and race/ethnicity), baseline prognostic characteristics (e.g., ECOG performance status, smoking status, presence of brain metastases at baseline), and pre-specified bTMB biomarker expression cut-offs (>10 or <10 and >16 or <16), by investigating the duration of PFS in these subgroups. Results are reported in Appendix E of the CS and show that the hazard ratios for PFS are better for female patients (HR=0.59 (95% CI: 0.41 to 0.85) for females versus HR=0.87 (95% CI: 0.67 to 1.13) for males); and for those without brain

metastases (HR=0.75 (95% CI: 0.60 to 0.93) for no metastases versus HR=0.98 (95% CI: 0.49 to 2.00) for those with metastases).

ERG comment: In the IMpower133 trial, progression-free survival (PFS) was only assessed by investigators and not by an Independent Review Committee.

As specified by the company in the response to clarification (received 7 May 2019),[43] these data were '[redacted]'.

4.2.5.3 Objective response rate and duration of response

The objective response rate (ORR) and median duration of response (DOR) were similar between the treatment arms (see Table 4.9) In total, five patients (2.5%) in the atezolizumab group and two patients (1.0%) in the placebo group had a complete response.

Table 4.9: Response in the ITT population, data cut-off date 24 April 2018

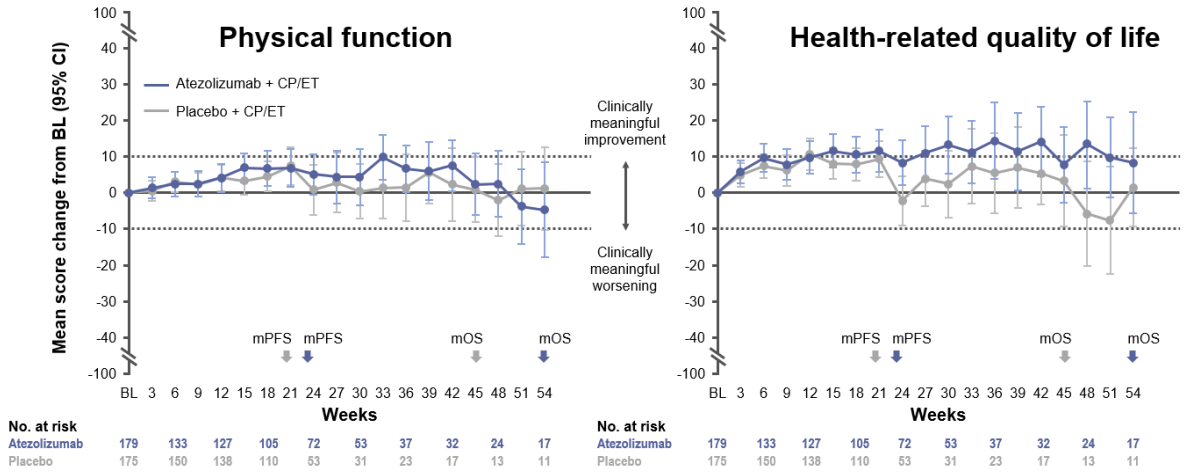
	Atezolizumab group	Placebo group
Objective response rate		
ITT population	n=201	n=202
No. of responders (%)	121 (60.2%)	130 (64.4%)
95% Clopper-Pearson	(53.1, 67.0)	57.3, 71.0)
Difference in response rates[a]	[redacted]	
Duration of response		
ITT population responders	n=121	n=130
Patients with event (%)	103 (85.1%)	123 (94.6%)
Median DOR (months)[b]	4.2	3.9
Range	(1.4[c], 19.5)	(2.0, 16.1[c])
Ongoing response at data cut-off (%)	18 (14.9)	7 (5.4)

Source: CS, Table 10, pages 36-37.
DOR = duration of response; ITT = intent-to-treat.
[a] 95% CI for Difference in Response Rates (Wald with Continuity Correction)
[b] Duration of response was assessed in patients who had an objective confirmed response and was defined as the time from the first occurrence of a documented objective response to the time of disease progression as determined by the investigator (according to RECIST) or death from any cause, whichever occurred first.
[c] Data for the lower range of the response in the atezolizumab group and the upper range of the response in the placebo group are censored.

4.2.5.4 Health-related quality of life

Patients in both the atezolizumab arm and the placebo arm reported improvements in function and HRQoL (See Figure 4.5). The company stated that "There was a trend of greater improvements in patient-reported lung cancer-related symptoms and physical function, with minimal impact from treatment-related toxicities observed in the atezolizumab arm versus the placebo arm" (CS, page 42).[1] However, statistical significance of differences between treatment arms was not reported in the CS.

Figure 4.5: Change from baseline in function and health-related quality of life



Source: CS, Figure 5, page 42.
CP = carboplatin; ET = etoposide; mOS = median overall survival = mPFS: median progression-free survival.

4.2.5.5 Other outcomes

Time to deterioration (TTD) is defined as the time from baseline to the first time the patient's score shows a ≥10-point increase above baseline maintained for at least two consecutive assessments or followed by death within three weeks of the last assessment. TTD showed no statistical significant differences between treatment arms in patient-reported lung cancer symptoms (cough, chest pain, dyspnoea, arm/shoulder pain, fatigue and loss of appetite) or treatment-related symptoms (constipation, dysphagia, peripheral neuropathy, nausea/vomiting, diarrhoea and sore mouth).

4.2.6 Adverse events

The population that could be evaluated for safety included 198 patients who received at least one dose of atezolizumab and 196 patients who received placebo. The median duration of treatment with atezolizumab was 4.7 months (range, 0 to 21), and the median number of atezolizumab doses received was seven (range, 1 to 30). The median number of doses of chemotherapy was the same in the two groups (median, four doses of carboplatin and 12 doses of etoposide). The median dose intensity and total cumulative dose of chemotherapy were similar in the two groups.

A total of 49/201 patients (24.4%) in the atezolizumab group were treated beyond investigator-assessed disease progression per RECIST v1.1. The median duration of atezolizumab treatment following investigator-assessed disease progression was 0.7 months (range: 0–16 months).[23] In the atezolizumab group, 7/49 (14.3%) of patients treated with atezolizumab beyond disease progression were still receiving atezolizumab treatment at the time of the data cut-off date.[23]

Adverse events related to any component of the trial regimen occurred in 188 patients (94.9%) in the atezolizumab group and in 181 patients (92.3%) in the placebo group (Table 4.10). The most common grade 3 or 4 adverse events related to the trial regimen were neutropenia, anaemia, and decreased neutrophil count (Table 4.11).

Table 4.10: Summary of adverse events, data cut-off date 24 April 2018

AE type	Atezolizumab Group (n=198)	Placebo Group (n=196)
Patients with ≥1 AE	198 (100)	189 (96.4)
Grade 3–4 AEs	133 (67.2)	125 (63.8)
Grade 5 AEs	4 (2.0)	11 (5.6)
Treatment-related AEs*	188 (94.9)	181 (92.3)
Treatment-related Grade 3–4 AEs	112 (56.6)	110 (56.1)
Treatment-related Grade 5 AEs	3 (1.5)	3 (1.5)
Serious AEs	74 (37.4)	68 (34.7)
Treatment-related serious AEs*	45 (22.7)	37 (18.9)
Immune-related AEs	79 (39.9)	48 (24.5)
AEs leading to withdrawal from any treatment*	22 (11.1)	6 (3.1)
AEs leading to withdrawal from atezolizumab/placebo	21 (10.6)	5 (2.6)
AEs leading to withdrawal from carboplatin	5 (2.5)	1 (0.5)
AEs leading to withdrawal from etoposide	8 (4.0)	2 (1.0)
Treatment-related deaths	3 (1.5)	3 (1.5)

Source: CS, Table 15, page 45.
AE = adverse event
* Incidence of treatment-related AEs, serious treatment-related AEs, and AEs leading to withdrawal from any treatment are for any treatment component. Multiple occurrences of the same AE in one patient were counted once at the highest grade for the preferred term

Table 4.11: Treatment-related adverse events, data cut-off date 24 April 2018*

	Atezolizumab group (n=198)			Placebo group (n=196)		
AE type	**Grade 1–2**	**Grade 3–4**	**Grade 5**	**Grade 1–2**	**Grade 3–4**	**Grade 5**
Treatment-related AEs	73 (36.9)	112 (56.6)	3 (1.5)	68 (34.7)	110 (56.1)	3 (1.5)
Treatment-related AEs with an incidence of ≥10% in any arm, grade 3–4 severity with incidence of ≥1% in any arm, or grade 5 severity						
Neutropenia	26 (13.1)	45 (22.7)	1 (0.5)	20 (10.2)	48 (24.5)	0
Anaemia	49 (24.7)	28 (14.1)	0	41 (20.9)	24 (12.2)	0
Alopecia	69 (34.8)	0	0	66 (33.7)	0	0
Nausea	62 (31.3)	1 (0.5)	0	58 (29.6)	1 (0.5)	0
Fatigue	39 (19.7)	3 (1.5)	0	37 (18.9)	1 (0.5)+	0
Neutrophil count decreased	7 (3.5)	28 (14.1)	0	12 (6.1)	33 (16.8)	0
Decreased appetite	39 (19.7)	2 (1.0)	0	26 (13.3)	0	0
Thrombocytopenia	12 (6.1)	20 (10.1)	0	14 (7.1)	15 (7.7)	0
Platelet count decreased	17 (8.6)	7 (3.5)	0	21 (10.7)	7 (3.6)	0

	Atezolizumab group (n=198)			Placebo group (n=196)		
AE type	**Grade 1–2**	**Grade 3–4**	**Grade 5**	**Grade 1–2**	**Grade 3–4**	**Grade 5**
Vomiting	25 (12.6)	2 (1.0)	0	19 (9.7)	3 (1.5)	0
Constipation	19 (9.6)	1 (0.5)	0	25 (12.8)	0	0
Leukopenia	15 (7.6)	10 (5.1)	0	10 (5.1)	8 (4.1)	0
White blood cell count decreased	10 (5.1)	6 (3.0)	0	16 (8.2)	9 (4.6)	0
Diarrhoea	15 (7.6)	4 (2.0)	0	18 (9.2)	1 (0.5)	0
Asthenia	14 (7.1)	3 (1.5)	0	12 (6.1)	2 (1.0)	0
Febrile neutropenia	0	6 (3.0)	0	0	12 (6.1)	0
Infusion-related reaction	6 (3.0)	4 (2.0)	0	9 (4.6)	1 (0.5)	0
Hypomagnesemia	7 (3.5)	0	0	5 (2.6)	2 (1.0)	0
Peripheral neuropathy	4 (2.0)	2 (1.0)	0	4 (2.0)	0	0
Hypokalaemia	2 (1.0)	0	0	4 (2.0)	2 (1.0)	0
Pneumonia	1 (0.5)	3 (1.5)	1 (0.5)	2 (1.0)	0	1 (0.5)
Pneumonitis	2 (1.0)	1 (0.5)	0	2 (1.0)	2 (1.0)	0
Pancytopenia	1 (0.5)	1 (0.5)	0	1 (0.5)	3 (1.5)	0
Acute kidney injury	2 (1.0)	2 (1.0)	0	1 (0.5)	0	0
Lung infection	1 (0.5)	0	0	0	2 (1.0)	0
Cardiopulmonary failure	0	0	0	0	0	1 (0.5)
Death	0	0	1 (0.5)	0	0	0
Septic shock	0	0	0	0	0	1 (0.5)

Source: CS, Table 16, pages 45-46.
AE = adverse event
* Incidence of treatment-related adverse events for any treatment. Multiple occurrences of the same AE in one patient were counted once at the highest grade for the preferred term.

Deaths related to the trial regimen occurred in three patients (1.5%) in the atezolizumab group (death was due to neutropenia in one patient, pneumonia in one patient, and an unspecified cause in one patient) and in three patients (1.5%) in the placebo group (death was due to pneumonia in one patient, septic shock in one patient, and cardiopulmonary failure in one patient). Immune-related adverse events occurred in 79 patients (39.9%) in the atezolizumab group and in 48 patients (24.5%) in the placebo group, with rash and hypothyroidism being the most common.

The proportion of patients who experienced SAEs (serious adverse events) was 37.4% in the atezolizumab group and 34.7% in the placebo group. The most frequently reported SAEs were haematologic toxicities or infections (Table 4.12).

Table 4.12: Serious treatment-related adverse events, data cut-off date 24 April 2018*

	Atezolizumab group (n=198)			Placebo group (n=196)		
AE type	**Grade 1–2**	**Grade 3–4**	**Grade 5**	**Grade 1–2**	**Grade 3–4**	**Grade 5**
Neutropenia	0	6 (3.0)	1 (0.5)	0	8 (4.1)	0
Febrile neutropenia	0	4 (2.0)	0	0	9 (4.6)	0
Thrombocytopenia	0	5 (2.5)	0	0	4 (2.0)	0
Pneumonia	0	3 (1.5)	1 (0.5)	0	0	1 (0.5)
Anaemia	0	3 (1.5)	0	0	2 (1.0)	0
Pancytopenia	0	0	0	1 (0.5)	3 (1.5)	0
Vomiting	0	2 (1.0)	0	0	2 (1.0)	0
Diarrhoea	1 (0.5)	2 (1.0)	0	0	0	0
Leukopenia	0	2 (1.0)	0	0	1 (0.5)	0
Infusion-related reaction	0	1 (0.5)	0	2 (1.0)	0	0
Pneumonitis	0	1 (0.5)	0	0	2 (1.0)	0
Lung infection	0	0	0	0	2 (1.0)	0
Platelet count decreased	0	0	0	1 (0.5)	1 (0.5)	0
Acute kidney injury	0	2 (1.0)	0	0	0	0
Asthenia	0	2 (1.0)	0	0	0	0
Autoimmune thyroiditis	2 (1.0)	0	0	0	0	0
Death	0	0	1 (0.5)	0	0	0
Cardiopulmonary failure	0	0	0	0	0	1 (0.5)
Septic shock	0	0	0	0	0	1 (0.5)
Acute pancreatitis	0	1 (0.5)	0	0	0	0
Atrioventricular block complete	0	1 (0.5)	0	0	0	0
Colitis	0	1 (0.5)	0	0	0	0
Dehydration	0	1 (0.5)	0	0	0	0
Fatigue	0	1 (0.5)	0	0	0	0
Ileus	0	1 (0.5)	0	0	0	0
Jaundice	0	1 (0.5)	0	0	0	0
Liver function test increased	0	1 (0.5)	0	0	0	0
Lower respiratory tract infection	0	1 (0.5)	0	0	0	0
Nausea	0	1 (0.5)	0	0	0	0
Peripheral neuropathy	0	1 (0.5)	0	0	0	0
Pulmonary oedema	0	1 (0.5)	0	0	0	0
Skin toxicity	0	1 (0.5)	0	0	0	0
Transaminases increased	0	1 (0.5)	0	0	0	0

	Atezolizumab group (n=198)			Placebo group (n=196)		
AE type	**Grade 1–2**	**Grade 3–4**	**Grade 5**	**Grade 1–2**	**Grade 3–4**	**Grade 5**
Trigeminal neuralgia	0	1 (0.5)	0	0	0	0
Tubulointerstitial nephritis	0	1 (0.5)	0	0	0	0
Hypokalaemia	0	0	0	0	1 (0.5)	0
Hypomagnesemia	0	0	0	0	1 (0.5)	0
Neutropenic sepsis	0	0	0	0	1 (0.5)	0
Neutrophil count decreased	0	0	0	0	1 (0.5)	0
Pancreatitis	0	0	0	0	1 (0.5)	0
Urinary tract infection	0	0	0	0	1 (0.5)	0
White blood cell count decreased	0	0	0	0	1 (0.5)	0
Autoimmune colitis	1 (0.5)	0	0	0	0	0
Blood creatinine increased	1 (0.5)	0	0	0	0	0
Bronchitis	1 (0.5)	0	0	0	0	0
Cytomegalovirus infection	1 (0.5)	0	0	0	0	0
Diverticular perforation	1 (0.5)	0	0	0	0	0
Guillain−Barre syndrome	0	1 (0.5)	0	0	0	0
Haemoptysis	1 (0.5)	0	0	0	0	0
Pleural effusion	1 (0.5)	0	0	0	0	0

Source: CS, Table 17, pages 46-48.
* Incidence of treatment-related adverse events for any treatment. Multiple occurrences of the same AE in one patient were counted once at the highest grade for the preferred term.

4.2.7 Additional PD-L1 analyses

In response to the clarification letter (question A12) the company reported details of their analysis by [redacted] results. This included [redacted] data.

[redacted] were defined by applying [redacted] to raw scores. Because of the [redacted]. This is reported as 'TC' (tumour cells) or 'IC' (tumour infiltrating immune cells).

As some of the slides tested were [redacted]. The sample defined as [redacted] and the sample defined as [redacted] is that of [redacted]. In this section of the ERG report we report results for [redacted]; full results can be found in the company's response to the clarification letter.

In terms of OS [redacted]

[redacted]. This is based on the updated analysis with cut-off date of [redacted] (see Table 4.13). The Kaplan-Meier plot is not reported for the BEP2 sample.

Table 4.13: Overall survival by PD-L1 status in BEP2 population, data cut-off date [redacted]

	PD-L1 expression <1%		PD-L1 expression ≥1%	
Group	**Atezolizumab**	**Placebo**	**Atezolizumab**	**Placebo**
BEP2 population	[redacted]	[redacted]	[redacted]	[redacted]
Patients with event (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median duration of survival (months)	[redacted]	[redacted]	[redacted]	[redacted]
Stratified hazard ratio (95% Wald CI)	[redacted]		[redacted]	
Source: Clarification response, Question A12, Figure 2 BEP = biomarker evaluable population; CI = confidence interval				

Similarly, in terms of PFS [redacted]. To note these are results for the analysis performed with cut-off date 24 April 2018 (see Table 4.14). The Kaplan-Meier plot is not reported for the BEP2 sample.

Table 4.14: Progression free survival by PD-L1 status in BEP2 population, data cut-off date 24 April 2018

	PD-L1 expression <1%		PD-L1 expression ≥1%	
Group	**Atezolizumab**	**Placebo**	**Atezolizumab**	**Placebo**
BEP2 population	[redacted]	[redacted]	[redacted]	[redacted]
Patients with event (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median duration of survival (months)	[redacted]	[redacted]	[redacted]	[redacted]
Stratified hazard ratio (95% Wald CI)	[redacted]		[redacted]	
Source: Clarification response, Question A12, Figure 4 BEP = biomarker evaluable population; CI = confidence interval				

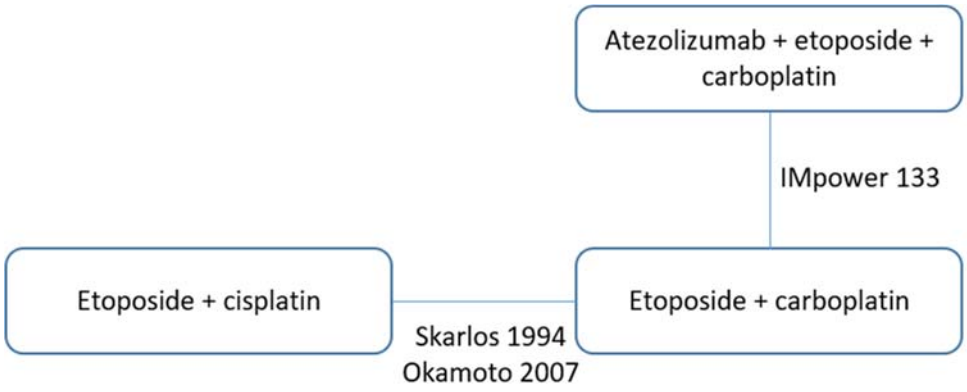
ERG comment: As can be seen from these results, at a cut-off of 1%, atezolizumab [redacted] in terms of [redacted] when compared to placebo. However, these results are based on [redacted] and exploratory subgroup analyses.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company included three trials in their indirect comparisons (See Figure 4.6):

- IMpower133[21, 23] (atezolizumab + carboplatin/etoposide versus carboplatin/etoposide)
- Skarlos 1994[44] (carboplatin/etoposide versus cisplatin/etoposide)
- Okamoto 2007[45] (carboplatin/etoposide versus cisplatin/etoposide)

Figure 4.6: Best-case evidence network – as presented by the company



Source: CS, Appendix F, Figure 6, page 42.

ERG comment: There are two fundamental problems with the studies included in the indirect comparison performed by the company:

1. The search did not include all relevant comparators (See Section 4.1.1 of this report).
2. The company restricted the inclusion criteria to 'platinum-etoposide chemotherapy regimens' instead of all 'platinum-based combination chemotherapy regimens' as mentioned in the final NICE scope (See Section 4.1.2 of this report).

Therefore, the indirect comparison in the CS does not include all trials that could have been included according to the NICE scope. As the ERG do not have the resources to do full searches and a full systematic review of the evidence, we are not able to provide a full overview of all trials that have been missed.

The company argues that "only carboplatin plus etoposide treatment is considered to be within the scope of this appraisal" (Response to clarification, Question A14).[9] This is based on advice from over 20 practising NHS oncologists that the standard of care in the NHS for untreated, ES-SCLC is carboplatin plus etoposide. In addition, the evidence for a comparison of atezolizumab plus carboplatin/etoposide versus carboplatin/etoposide is based on a head-to-head comparison (the IMpower133 trial), while evidence for other comparisons will have to rely on weaker evidence based on indirect comparisons.

The committee needs to decide whether carboplatin plus etoposide is indeed the only relevant comparator, or whether all comparators mentioned in the NICE scope are relevant comparators. In Sections 4.4 and 4.5 of this report we have presented some information which might be relevant if the committee decides more comparators need to be taken into consideration.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company stated that they do not consider cisplatin-etoposide to be a key comparator in this appraisal because they estimated that [redacted] of ES-SCLC patients in the UK will be treated with carboplatin-etoposide chemotherapy. Nevertheless, they presented an indirect comparison of atezolizumab plus carboplatin-etoposide versus cisplatin-etoposide (CS, Appendix F).[1]

According to the company "the final NICE scope restricts the interventions of interest for this appraisal to atezolizumab, carboplatin or cisplatin plus etoposide. Therefore, whilst carboplatin plus paclitaxel, best supportive care (BSC), irinotecan plus cisplatin, topotecan plus cisplatin, and paclitaxel plus cisplatin were initially considered in the meta-analysis feasibility assessment, following confirmation of the NICE scope these were subsequently excluded from further consideration" (CS, Appendix F, page 42).[1] This seems to be a misunderstanding. The NICE scope describes the comparators as

'platinum-based combination chemotherapy regimens', which means that interventions such as carboplatin plus paclitaxel, irinotecan plus cisplatin, topotecan plus cisplatin, and paclitaxel plus cisplatin are all within the scope of this appraisal. The company responded to the request for cclarification letter, Question A15, that "Roche have been advised by over 20 practising NHS oncologists during individual consultation meetings and two separate advisory board meetings that the standard of care in the NHS for untreated, ES-SCLC is carboplatin plus etoposide. Moreover, that the control arm of the IMpower133 study is reflective of NHS clinical practice. Roche have also been advised that across the NHS, cisplatin plus etoposide is the standard of care for patients diagnosed with LS-SCLC and those considered to be borderline LS-SCLC and ES-SCLC. Therefore, only carboplatin plus etoposide treatment is considered to be within the scope of this appraisal, since all other treatments listed in the final scope are not considered standard NHS practice".[9]

Based on the restrictions to the NICE scope and a limited search, the company produced a network of three studies allowing an indirect comparison of atezolizumab plus carboplatin-etoposide versus cisplatin-etoposide (see Figure 4.6).

As stated by the company (CS, Appendix F, page 42), "the validity of meta-analysis relies on non-systematic differences within or between direct treatment comparisons, particularly in terms of patient or disease characteristics which are known treatment-effect modifiers."[1] As shown in Figure 4.6, the indirect comparison relies on two studies evaluating cisplatin-etoposide: Skarlos 1994[44] and Okamoto 2007[45].

Skarlos 1994[44] is a randomised comparison of etoposide plus cisplatin (E/Cis) versus etoposide plus carboplatin (E/Car) and irradiation in previously untreated patients with small-cell lung cancer. Patients aged less than 75 years and with a ECOG performance status of less than three were eligible. Patients received cisplatin 50 mg/m^2 on days 1-2 or carboplatin 300 mg/m^2 on day 1, both combined with etoposide 300 mg/m^2 on days 1-3 every 21 days for six treatment cycles. The fast majority of responding limited disease patients and complete responders (CR) with extensive disease, also received thoracic irradiation (TI) and prophylactic cranial irradiation (PCI) concurrently with the third cycle. The trial included 82 patients with limited disease (LD) and 61 with extensive disease (30 E/Cis and 31 E/Car). Overall response rate (ORR) is the only outcome separately reported for patients with extensive disease. Outcome data for OS and PFS were not separately reported for the ES-SCLC subpopulation in Skarlos 1994[44]. Therefore, ORR is the only outcome that can be used in an indirect comparison. Patient characteristics are only reported for the full SCLC population in this trial; therefore, it is not possible to assess how comparable the patient populations are in the Skarlos trial[44] and the IMpower133 trial[21, 23].

Okamoto 2007[45] is a randomised phase III trial of carboplatin plus etoposide versus split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer. The E/car arm received carboplatin area under the curve of five intravenously (IV) on day 1 and etoposide 80 mg/m^2 IV on days 1–3. The E/Cis arm received cisplatin 25 mg/m^2 IV on days 1–3 and etoposide 80 mg/m^2 IV on days 1–3. Both regimens were given with granulocyte colony-stimulating factor support in a 21–28 day cycle for four courses. A total of 220 patients were randomised. There are considerable differences in patient characteristics between the IMpower133 trial[21, 23] and the Okamoto trial[45]. The Okamoto trial[45] was conducted in an elderly, high-risk population and included patients with an age range of 55-86 years and 92% of patients were ≥70 years. A majority of the patients (52.5%) enrolled in the IMpower133 trial were aged <65 years.[21, 23] Okamoto enrolled patients with an ECOG PS of 0-2 in those aged ≥70 years and an ECOG PS of 3 for those aged <70 years. [45] The IMpower133 trial enrolled patients with an ECOG PS of 0 or 1.[21, 23]

Therefore, results from both studies are not comparable with results from the IMpower133 trial[21, 23]. Skarlos 1994[44] is more than 20 years older than the IMpower133 trial[21, 23] and only one outcome measure is the same in both trials: overall response rate. In addition, results in Skarlos 1994[44] are based on only 61 patients with extensive disease and patient characteristics are not reported for these 61 patients. Okamoto 2007[45] included elderly and poor-risk patients, which is a completely differently population from that included in the IMpower133 trial[21, 23]. In conclusion, although the ERG does not agree with the company that cisplatin-etoposide is not a relevant comparator for this appraisal, we do believe that the results from the indirect comparison presented by the company in Appendix F are unreliable and should not be used by NICE for decision making.

4.5 Additional work on clinical effectiveness undertaken by the ERG

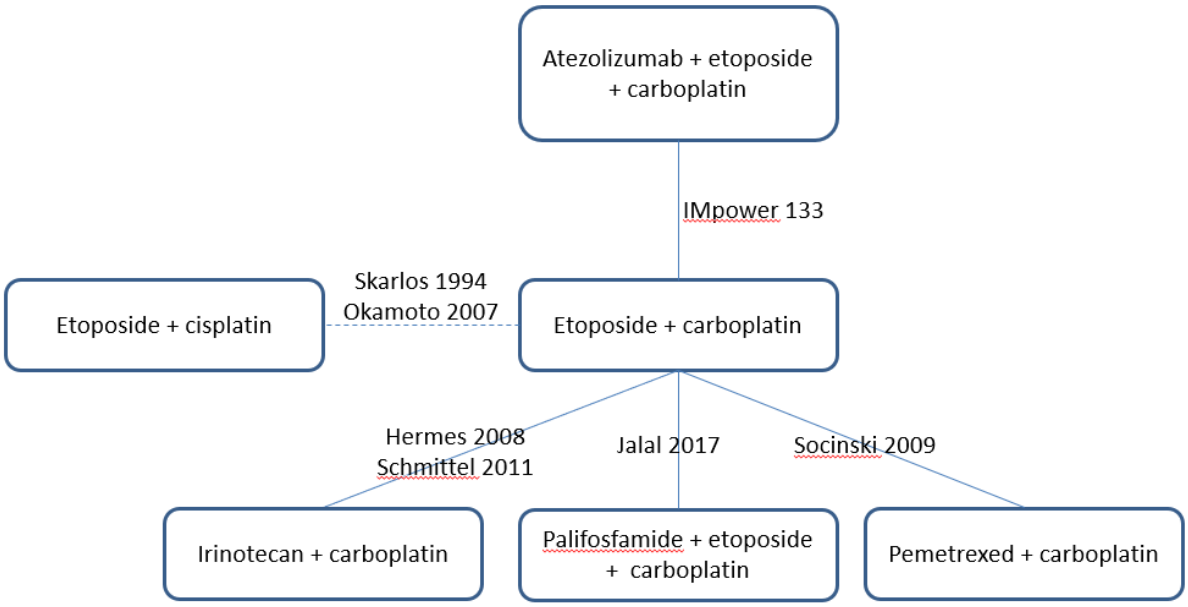
As stated before (Section 4.1.5 of this report), the company retrieved 73 publications based on limited searches. However, most of these were excluded by the company because the intervention did not include etoposide. In favour of this approach are the advice Roche received from over 20 practising NHS oncologists that the standard of care in the NHS for untreated ES-SCLC is carboplatin plus etoposide, and ESMO guidelines[6] recommending four to six cycles of etoposide plus cisplatin or carboplatin for first-line treatment of metastatic SCLC disease. The main argument against this approach is the NICE final scope which describes the comparator as: 'platinum-based combination chemotherapy regimens' and the NICE guideline for the diagnosis and management of lung cancer,[46] which recommends platinum-based combination chemotherapy to people with extensive stage disease SCLC if they are fit enough.

As stated before, the committee needs to decide whether carboplatin plus etoposide is indeed the only relevant comparator, or whether all comparators mentioned in the NICE scope are relevant comparators.

The section below describes the possibilities of performing a mixed treatment comparison of atezolizumab with carboplatin and etoposide versus all relevant comparators as described in the NICE scope. However, it should be taken into account that this is based on the limited searches for comparators as presented by the company in the CS.

As described in Section 4.4 of this report, we do not believe that the results from the indirect comparison of atezolizumab plus carboplatin-etoposide versus cisplatin-etoposide are reliable. Therefore, we have not included any other studies comparing relevant comparators with cisplatin-etoposide. This means we checked the 73 studies for studies that had carboplatin-etoposide as one of the treatment arms. This resulted in a network allowing comparisons of atezolizumab plus carboplatin-etoposide versus three platinum-based combination chemotherapy regimens: irinotecan plus carboplatin, palifosfamide plus carboplatin-etoposide and pemetrexed plus carboplatin (see Figure 4.7). We further checked the 73 studies to see if any other studies compared relevant comparators with either of these three comparators, but no studies were found.

Figure 4.7: Possible evidence network – based on ERG assessment of company's searches



Based on this network it might be possible to do indirect comparisons of atezolizumab plus carboplatin-etoposide versus irinotecan plus carboplatin (using Hermes 2008[47] & Schmittel 2011[48]), palifosfamide plus carboplatin-etoposide (using Jalal 2017[49]) and pemetrexed plus carboplatin (using Socinski 2009[50]). However, it needs to be stressed here that these treatments are probably not the only treatments that can be compared with atezolizumab, because the company's searches did not include all relevant comparators and inclusion criteria in the CS were restricted to 'platinum-etoposide chemotherapy regimens'.

As stated in Section 4.4, and by the company (CS, Appendix F, page 42), "the validity of meta-analysis relies on non-systematic differences within or between direct treatment comparisons, particularly in terms of patient or disease characteristics which are known treatment-effect modifiers."[1] Table 4.15 shows the study characteristics of the studies that could be included in an indirect comparison. In terms of population and outcomes reported the studies are comparable. There are some differences in settings and treatment characteristics (most markedly etoposide being administered orally in Hermes 2008), but generally these differences are small enough to allow the studies to be included in an indirect comparison.[47]

Table 4.16 shows the patient characteristics of the studies that could be included in an indirect comparison. For a number of variables there is little or no information for most studies (smoking status, blood-based tumour mutational burden and previous anticancer treatments). In terms of age and gender, the studies are comparable. However, there are some differences in terms of ECOG performance-status score and the percentage of patients with brain metastasis at enrolment. ECOG performance-status is best in the IMpower133 trial[21, 23] with all patients having a score of 0 or 1. For the Socinski 2009[50] and Jalal 2017[49] trials, almost 90% of patients in each trial had a score of 0 or 1; while this was about 53% in the Hermes 2008[47] trial, and Schmittel 2011[48] only reported Karnofsky performance scores. The percentage of patients with brain metastasis at enrolment was lowest in the IMpower133 trial[21, 23] (8.7%), similar in the Socinski 2009[50] trial (9.3%), but higher in the Jalal 2017[49] (17%), Hermes 2008[47] (21%) and Schmittel 2011[48] (25%) trials. The ERG considers that the studies are comparable enough to be included in an indirect comparison. However, these differences in populations should be taken into account when considering the results.

Table 4.15: Study characteristics of trials included in the indirect comparison

Study	IMpower133[21, 23]		Hermes 2008[47]		Schmittel 2011[48]		Socinski 2009[50]		Jalal 2017[49]	
Characteristics	**At-EP (n = 201)**	**Pbo-EP (n = 202)**	**IP (n = 105)**	**EP (n = 104)**	**IP (n = 106)**	**EP (n = 110)**	**PemP (n = 453)**	**EP (n = 455)**	**Pa-EP (n = 94)**	**EP (n = 94)**
Population	Patients with untreated extensive-stage small cell lung cancer.		Patients with untreated extensive-stage small cell lung cancer.		Patients with untreated extensive-stage small cell lung cancer.		Patients with untreated extensive-stage small cell lung cancer.		Patients with untreated extensive-stage small cell lung cancer.	
Reported outcomes	OS, PFS, ORR, AEs, HRQoL, DOR, TTD.		OS, CR, QoL, AEs		OS, PFS, Response rate, AEs		OS, PFS, Response rate, AEs		OS, PFS, ORR, DOR, AEs	
Setting	106 centres in 21 countries: America, Europe (UK), Asia, Australia		Bergen, Norway		Eight centres in Germany		USA (no details)		70 study sites in 13 countries: North-America, Europe (UK), Asia, Australia.	
Carboplatin-Etoposide	Four 21-day cycles of: Carboplatin (AUC of 5 mg per millilitre per minute, administered intravenously on day 1 of each cycle). Etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle)		Four 21-day cycles of: carboplatin (AUC = 4 by the Chatelut formula; roughly corresponding to AUC = 5 by the Calvert formula) on day 1 and Etoposide (120 mg/m^2) orally on days 1 through 5 every 21 days.		Up to 6 cycles repeated on day 22 of: Carboplatin at a dose of AUC 5 mg min/ml in 500 ml 5% glucose over 1 h on day 1 (using Calvert's formula). Etoposide 140 mg/m2 was administered on days 1, 2, and 3 in 1000 ml NaCl 0.9% i.v. over 90 min.		Up to 6 cycles every 3 weeks of: Carboplatin at area under the serum concentration-time curve 5 on day 1 and Etoposide 100mg/m2 on days 1, 2, and 3.		Up to 6 cycles every 3 weeks of: Carboplatin administered at AUC 4 on day 1, Etoposide at 100 mg/m^2 on days 1 to 3.	

Source: CS, Table 6, 7 and 8, pages 24-31, Hermes 2008[47], Schmittel 2011[48], Socinski 2009[50], and Jalal 2017[49].
AEs = Averse Events; At=Atezolizumab; AUC = area under the curve; CR = Complete response; DOR = Duration of response; ECOG = Eastern Cooperative Oncology Group; EP = etoposide and carboplatin; HRQoL = Health-related quality of life; IP = irinotecan and carboplatin; Mb = megabases; ORR = Objective response rate; OS = Overall survival; Pa = Palifosfamide; PemP, Pemetrexed and carboplatin; PFS = Progression-free survival; TTD = Time to deterioration.

Table 4.16: Baseline characteristics of patients in the studies included in the indirect comparison

Study	IMpower133[21, 23]		Hermes 2008[47]		Schmittel 2011[48]		Socinski 2009[50]		Jalal 2017[49]	
Characteristics	**At-EP (n = 201)**	**Pbo-EP (n = 202)**	**IP (n = 105)**	**EP (n = 104)**	**IP (n = 106)**	**EP (n = 110)**	**PemP (n = 453)**	**EP (n = 455)**	**Pa-EP (n = 94)**	**EP (n = 94)**
Median age (range) — yr	64 (28–90)	64 (26–87)	67 (46-81)	68 (42-82)	60 (34-80)	63 (39-80)	63 (35-89)	63 (38-86)	61 (42-82)	61 (32-88)
Age group — no. (%)										
<65 yr	111 (55.2)	106 (52.5)	NR	NR	NR	NR	267 (59)	275 (60)	NR	NR
≥65 yr	90 (44.8)	96 (47.5)	NR	NR	NR	NR	186 (41)	180 (40)	NR	NR
≥70 yr	NR	NR	31 (30)	43 (41)	12 (11)	17 (15)	NR	NR	NR	NR
Male sex — no. (%)	129 (64.2)	132 (65.3)	66 (63)	72 (69)	70 (66)	71 (65)	325 (72)	330 (73)	66 (70)	66 (70)
ECOG performance-status score — no. (%)†										
0	73 (36.3)	67 (33.2)	NR	NR	NR	NR	NR	NR	24 (25)	21 (22)
1	128 (63.7)	135 (66.8)	NR	NR	NR	NR	NR	NR	60 (64)	62 (66)
2	0	0	31 (30)	31 (30)	NR	NR	54 (12)	55 (12)	10 (11)	9 (10)
3	0	0	NR	NR	NR	NR	0	0	0	0
4	0	0	NR	NR	NR	NR	0	0	0	0
0 or 1	201 (100)	202 (100)	56 (53)	54 (52)	NR	NR	398 (88)	398 (88)	84 (89)	83 (88)
3 or 4	0	0	18 (17)	19 (18)	NR	NR	0	0	0	0
Smoking status — no. (%)										
Never smoked	9 (4.5)	3 (1.5)	NR	NR	NR	NR	NR	NR	5 (5.3)	7 (7.4)
Current smoker	74 (36.8)	75 (37.1)	NR	NR	NR	NR	NR	NR	46 (49)	44 (47)
Former smoker	118 (58.7)	124 (61.4)	NR	NR	NR	NR	NR	NR	36 (38)	33 (35)
Brain metastasis at enrolment — no. (%)	17 (8.5)	18 (8.9)	17 (16)	12 (12)	31 (29)	23 (21)	43 (9.5)	41 (9.1)	14 (15)	17 (18)
Blood-based tumour mutational burden — no./total no. (%)										

Study	IMpower133[21, 23]		Hermes 2008[47]		Schmittel 2011[48]		Socinski 2009[50]		Jalal 2017[49]	
Characteristics	**At-EP (n = 201)**	**Pbo-EP (n = 202)**	**IP (n = 105)**	**EP (n = 104)**	**IP (n = 106)**	**EP (n = 110)**	**PemP (n = 453)**	**EP (n = 455)**	**Pa-EP (n = 94)**	**EP (n = 94)**
<10 mutations/Mb	71/173 (41.0)	68/178 (38.2)	NR	NR	NR	NR	NR	NR	NR	NR
≥10 mutations/Mb	102/173 (59.0)	110/178 (61.8)	NR	NR	NR	NR	NR	NR	NR	NR
<16 mutations/Mb	133/173 (76.9)	138/178 (77.5)	NR	NR	NR	NR	NR	NR	NR	NR
≥16 mutations/Mb	40/173 (23.1)	40/178 (22.5)	NR	NR	NR	NR	NR	NR	NR	NR
Median sum of longest diameter of target lesions at baseline (range)	113.0 (12.0–325.0)	105.5 (15.0–353.0)	NR	NR	NR	NR	NR	NR	NR	NR
Previous anticancer treatments — no. (%)										
Chemotherapy or nonanthracycline	8 (4.0)	12 (5.9)	0	0	NR	NR	0	0	0	0
Radiotherapy	25 (12.4)	28 (13.9)	NR	NR	NR	NR	NR	NR	NR	NR
Cancer-related surgery	33 (16.4)	25 (12.4)	NR	NR	NR	NR	NR	NR	NR	NR

Source: CS, Table 9, page 32, Hermes 2008[47], Schmittel 2011[48], Socinski 2009[50], and Jalal 2017[49].
At = Atezolizumab; ECOG = Eastern Cooperative Oncology Group; EP = etoposide and carboplatin; IP = irinotecan and carboplatin; Mb = megabases; Pa = Palifosfamide; PemP = Pemetrexed and carboplatin.
† ECOG PS scores range from 0 to 5, with higher scores reflecting greater disability.

The results from individual studies are shown in Table 4.17. Based on overall survival results, it can be concluded that pemetrexed plus carboplatin and palifosfamide plus carboplatin/etoposide are both inferior to carboplatin/etoposide and therefore also inferior to atezolizumab plus carboplatin/etoposide. Thus it is unlikely that pemetrexed and palifosfamide will be cost effective in comparison to atezolizumab. However, results for irinotecan plus carboplatin are similar to atezolizumab plus carboplatin/etoposide in terms of OS, PFS, and response. Therefore, an indirect comparison with irinotecan plus carboplatin seems feasible and warranted if the NICE committee decides that carboplatin plus etoposide is not the only relevant comparator, and that all comparators mentioned in the NICE scope should be considered relevant comparators.

Table 4.17: Main results from the studies included in the indirect comparison

	Atezolizumab	Irinotecan	Pemetrexed	Palifosfamide
OS (HR, 95% CI)	0.70 (0.54, 0.91)**	H: 0.71 (0.53, 0.94) S: 0.75 (0.54, 1.03)	1.56 (1.27, 1.92)	1.30 (0.95, 1.78)
PFS (HR, 95% CI)	0.77 (0.62, 0.96)**	H: NR S: 0.78 (0.58, 1.04)	1.85 (1.58, 2.17)	NR
Difference in response rates (95% CI)*	[redacted]	H: NR S: 2.00 (NR)	-19 (NR)	NR
Median DOR (months) (range)	4.2 (1.4, 19.5)	H: NR S: NR	NR	NR

Source: CSR Atezolizumab[23], Hermes 2008[47], Schmittel 2011[48], Socinski 2009[50], and Jalal 2017[49].
CI = confidence interval; DOR = duration of response; H = Hermes 2008; HR = hazard ratio; NR = not reported; OS = overall survival; PFS = progression-free survival; S = Schmittel 2011.
* Positive results favour the intervention over carboplatin plus etoposide; ** Stratified analyses (sex and ECOG).

It should be taken in to account that this network is based on searches performed by the company and that these searches did not include all relevant comparators. Therefore, it is possible that some relevant comparators have been missed.

Finally, the ERG wants to point out that etoposide plus carboplatin is a relevant comparator and no indirect comparison will present more reliable data than the data from the IMpower133 trial comparing atezolizumab plus carboplatin and etoposide with carboplatin and etoposide. However, it is possible that among the relevant comparators excluded by the company there is a more effective option than carboplatin and etoposide, which means the evidence presented in the CS might overestimate the relative effectiveness of atezolizumab plus carboplatin and etoposide.

4.6 Conclusions of the clinical effectiveness section

The searches included limited comparators and was not in line with the broader comparator definition in the final scope. Therefore, relevant studies may have been missed.

In their submission the company focusses on results from the IMpower133 trial. IMpower133 (NCT02763579) is a multinational Phase I (safety) and III (efficacy), double-blind, randomised, placebo-controlled study, evaluating the efficacy and safety of adding atezolizumab or placebo to first-line treatment with carboplatin and etoposide in patients with ES-SCLC. In the submission, the company report the planned interim analysis of OS and a final analysis of progression-free survival (data cut-off 24 April 2018). The trial included adults with histologically or cytologically confirmed ES-SCLC as defined according to the VALG staging system, measurable ES-SCLC according to RECIST, version 1.1, and an ECOG performance-status score of 0 or 1 (on a five-point scale, with higher numbers reflecting greater disability) who had not received previous systemic treatment for ES-

SCLC. The study included 403 patients from 106 centres in 21 countries (USA, Europe, South America and Asia), with 10 patients from the UK (4 (2%) patients in the atezolizumab arm and 6 (3%) patients in the placebo arm).

The co-primary outcomes were overall survival (OS; the time from randomisation to death from any cause) and investigator-assessed progression-free survival (PFS, per RECIST v1.1; time from randomisation to disease progression or death from any cause, whichever occurred first). A final analysis of OS in the IMpower133 trial will occur after approximately 306 OS events in the ITT population have occurred; this analysis is anticipated in [redacted] and will be made available to NICE according to the company.

Baseline characteristics in the IMpower133 trial were well balanced between the groups. However, the population included in the IMpower133 trial may not be representative of the ES-SCLC patient population in UK practice. According to clinical experts employed by the company fewer than [redacted] of ES-SCLC patients in UK clinical practice would be diagnosed with an ECOG status of 0. In the IMpower133 trial, 35% of patients had an ECOG performance status of 0. Furthermore, all included patients in the IMpower133 trial had an ECOG performance status of 0-1. In appendix K, the company reports that "some advisors stated in their experience the probable proportions of UK ES-SCLC patients diagnosed as ECOG 0–1 would be as high as [redacted], with others reporting that in their clinical experience it could be as low as [redacted]".[39] Therefore, the population included in the IMpower133 trial might only represent a third of ES-SCLC patients in the UK.

A total of 201 patients were randomly assigned to the atezolizumab group, and 202 patients to the placebo group. Based on [redacted] data and at a median follow-up of [redacted] months, the median overall survival was [redacted] months in the atezolizumab group and [redacted] months in the placebo group (hazard ratio (HR) = [redacted] (95% confidence interval (CI): [redacted] to [redacted]). Based on April 2018 data, the median progression-free survival was 5.1 months and 4.3 months, respectively (HR = 0.77 (95% CI: 0.62 to 0.96). The objective response rate (ORR, Difference in response rates: [redacted])) and median duration of response (DOR, Median duration 4.2 months for atelozumab versus 3.9 months for placebo) were similar between the treatment arms. Patients in both the atezolizumab arm and the placebo arm reported improvements in function and HRQoL. However, statistical significance of differences between treatment arms was not reported in the CS. Time to deterioration (TTD) showed no statistically significant differences between treatment arms in patient-reported lung cancer symptoms (cough, chest pain, dyspnoea, arm/shoulder pain, fatigue and loss of appetite) or treatment-related symptoms (constipation, dysphagia, peripheral neuropathy, nausea/vomiting, diarrhoea and sore mouth).

Adverse events related to any component of the trial regimen occurred in 188 patients (94.9%) in the atezolizumab group and in 181 patients (92.3%) in the placebo group. The most common grade 3 or 4 adverse events related to the trial regimen were neutropenia, anaemia, and decreased neutrophil count. Deaths related to the trial regimen occurred in three patients (1.5%) in the atezolizumab group and in three patients (1.5%) in the placebo group. Immune-related adverse events occurred in 79 patients (39.9%) in the atezolizumab group and in 48 patients (24.5%) in the placebo group, with rash and hypothyroidism being the most common. The proportion of patients who experienced serious adverse events (SAEs) was 37.4% in the atezolizumab group and 34.7% in the placebo group. The most frequently reported SAEs were haematologic toxicities or infections.

In addition, the company stated that "[redacted]

[redacted]" (CS, page 50).[1] Results by PD-L1 testing for OS and PFS showed that, at a [redacted], atezolizumab produced [redacted] in terms of [redacted] when compared to placebo. However, these results are based on [redacted] and exploratory subgroup analyses.

The IMpower133 trial compares atezolizumab plus carboplatin and etoposide with placebo plus carboplatin and etoposide. The NICE scope describes the comparators as 'platinum-based combination chemotherapy regimens'. However, in the CS the company states that "chemotherapy regimens excluding etoposide are outside of the scope of this appraisal (CS, Appendix D, page 41).[1] This means treatment regimens such as carboplatin plus paclitaxel, irinotecan plus cisplatin, topotecan plus cisplatin, and paclitaxel plus cisplatin are not considered as comparators in the CS. The only comparators considered in the CS are carboplatin plus etoposide as reported in the IMpower133 trial and cisplatin plus etoposide based on an indirect comparison. The ERG believes that the results from this indirect comparison are unreliable and should not be used by NICE for decision making.

The company argues that "only carboplatin plus etoposide treatment is considered to be within the scope of this appraisal" (Response to clarification, Question A14).[9] This is based on advice from over 20 practising NHS oncologists that the standard of care in the NHS for untreated, ES-SCLC is carboplatin plus etoposide. In addition, the evidence for a comparison of atezolizumab plus carboplatin/etoposide versus carboplatin/etoposide is based on a head-to-head comparison (the IMpower133 trial), while evidence for other comparisons will have to rely on weaker evidence based on indirect comparisons. Therefore, the ERG would agree that carboplatin/etoposide is probably the most relevant comparator for this appraisal.

However, if the committee decides that all comparators mentioned in the NICE scope are relevant comparators, we have conducted an indirect comparison based on a limited search performed by the company (see Section 4.5 of this report), which shows that results for irinotecan plus carboplatin are similar to atezolizumab plus carboplatin/etoposide in terms of OS, PFS, and response.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (Section 5.1.1 of this report) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

5.1.1.1 Searches for cost effectiveness analysis review

Appendices G, H and I of the CS detail systematic searches of the literature used to identify cost effectiveness, HRQol and resource use studies. Separate sets of searches were run for each section. Searches were undertaken on 26/27 July 2018. A summary of the sources searched is provided in Table 5.1.

Table 5.18: Data sources for the systematic review of cost effectiveness

Search strategy element	Resource	Host/Source	Date Range	Date Searched
Electronic Databases	Medline	OVID	1946- 2018/July/Wk 3	26 July 2018
	Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations		Up to 25 July 2018	
	Medline Daily			
	Embase		1974- 2018/wk30	27 July 2018
	HTA Database	EBM Reviews via OVID	Up to 4th Quarter 2016	26 July 2018
	NHS EED		Up to 1st Quarter 2016	
	Econlit	OVID	1886-July 19 2018	26 July 2018
Conference proceedings	ASCO	Not reported	2016-2018	26/27 July 2018
	ESMO			
	HTAi			
	SMDM			
HTA Body Websites	NICE, SMC, PBAC, CADTH, TLV	Not reported		26/27 July 2018
Additional Resources (cost effectiveness)	CEA Registry, RePEc, INAHTA, NIHR	Not reported		26/27 July 2018

Search strategy element	Resource	Host/Source	Date Range	Date Searched
	HTA database, CRD databases, Google Scholar			
Additional Resources to those above for HRQol searches	EuroQoL website, ScHARRHUD database	Not reported		26/27 July 2018
Additional Resources to those above for resource use searches	ISPOR Conference abstracts	Not reported		26/27 July 2018
Source: based on CS, Appendix G ASCO = American Society of Clinical Oncology; CADTH = Canadian Agency for Drugs and Technologies in Health; ESMO = European Society for Medical Oncology; HTA Database = Health Technology Assessment Database; HTAi = Health Technology Assessment International; INAHTA = International Network of Agencies for Health Technology Assessment; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NHS EED = NHS Economic Evaluation Database; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; RePEc = Research Papers in Economics; SMC = Scottish Medicine Consortium; SMDM = Society for Medical Decision Making; TLV = Tandvårds- och läkemedelsförmånsverket.				

ERG comments:

- The ERG considers the database searches and methodology reported in the CS to support the systematic review of cost effectiveness data, HRQol and resource use to be comprehensive, transparent, reproducible and fit for purpose.
- Additional economics terms were included in the strategy designed to find economic studies in NHS EED and the HTA database. These are already filtered sources and using these terms will have restricted recall.
- A broad range of additional sources were 'hand' searched, the sources and terms used were not reported in detail (i.e. website addresses and terms used to search them)

5.1.2 Inclusion/exclusion criteria used in the study selection

The eligibility criteria used for inclusion in the economic evaluation reviews are presented in Table 5.2.

Table 5.19: Included/excluded studies in the cost effectiveness review

Criteria	Include	Exclude
Population	The primary population of interest was that aligned with patients enrolled in the IMpower133 study, namely adult patients (≥ 18 years) with histologically or cytologically confirmed, previously untreated, ES- SCLC. *At citation screening stage, the population of interest was kept broad and included adult patients with SCLC, regardless of disease stage or line of therapy.*	• Paediatric patients (age <18 years) • NSCLC
Intervention(s)/ comparator(s)	The investigational medicinal products of interest were:	Interventions not listed

Criteria	Include	Exclude
	• Atezolizumab • Carboplatin plus etoposide The comparators of interest were: • Cisplatin plus etoposide • Carboplatin plus irinotecan • Carboplatin plus paclitaxel • BSC	
Outcomes	• Summary costs and health outcomes (e.g. LYG, QALYs) • ICERs: cost/QALY, cost/LYG, cost/DALY, cost/event avoided • Model summary and structure – Model type – Perspective – Discounting – Time horizon • Assumptions underpinning model structures • Sources of model inputs • Main drivers of costs as reported in deterministic/probabilistic sensitivity analyses	Outcomes not listed
Study design	• Cost-utility analyses • Cost-effectiveness analyses • Cost-benefit analyses • Cost-minimisation analyses	• Reviews/editorials • Budget impact analyses
Territory of interest	No restriction	NA
Date of publication	No restriction	NA
Language of publication	English language publications or non-English language publications with an English abstract	Foreign language papers without an English abstract
Source: CS, Appendix G, Table 26		

ERG comment: Interventions of interest were restricted to atezolizumab, carboplatin or cisplatin plus etoposide, carboplatin plus irinotecan or paclitaxel, and best supportive care (BSC). This means interventions such as: topotecan plus carboplatin or cisplatin, irinotecan plus cisplatin, paclitaxel plus cisplatin with or without etoposide, gemcitabine plus carboplatin or cisplatin, pemetrexed plus carboplatin or cisplatin, and bevacizumab plus cisplatin with or without etoposide were all ignored in the SLR. The company did not discuss the omission of these treatments and provided no justification for the inclusion of the treatments mentioned in the table above. All other criteria seem appropriate.

5.1.3 Conclusions of the cost effectiveness review

The electronic database searches identified a total of 625 citations. Following removal of 69 duplicates, 556 citations were screened on the basis of title and abstract. A total of 16 citations were considered to be potentially relevant and were obtained for full text review. At this stage, a further 12 citations were excluded. Hand searching yielded no additional relevant citations. Therefore, a total of four economic evaluations were identified for final inclusion in the review. The generalisability of results from these studies was questioned by the company on the grounds of retrospective study design, small sample sizes

and the derivation of data from single centres. None of these four studies evaluated the costs and benefits of chemotherapy versus atezolizumab in ES-SCLC, which would reflect the clinical advancement of atezolizumab in the treatment of first-line ES-SCLC.

ERG comment: The ERG agrees with the conclusions of the company's cost effectiveness review. Indeed, the age of the included studies is an additional factor which limits their usefulness.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

No details were provided as to how many reviewers were involved in the screening and/or data extraction stages of the review.

ERG comment: The ERG notes that there may be a risk of bias associated with the review process undertaken for the economic evaluation systematic review which means that useful evidence may have been overlooked. The ERG also notes that there is a misalignment of stated exclusion criteria and those applied on full text review. The latter suggests cost analysis as a rationale for exclusion, yet this reason is not a pre-stated explicit exclusion criterion. This being said, it does appear that studies excluded for this reason would not have added any meaningful evidence in support of the review's objectives.

5.2.1 NICE reference case checklist

The summary of the company's economic evaluation is set out in Table 5.3. Comparison to the NICE reference case is set out in Table 5.4.

Table 5.20: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	3-health state partitioned survival analysis (PartSA) model	Consistent with previous appraisals accepted by NICE to evaluate first-line lung cancer, as well as other oncology indications. [redacted]	Section B.3.2.2
States and events	"PFS", "Progressed Disease (PD)" and "Death"	Consistent with previous appraisals accepted by NICE to evaluate first-line lung cancer, as well as other oncology indications.	Section B.3.2.2
Comparators	Platinum-based combination chemotherapy regimens: carboplatin and etoposide only in the base case; cisplatin plus etoposide in a scenario analysis	Consistent with Lung Cancer (2016) NICE pathway	Section B.3.2.3
Population	Adults with untreated ES-SCLC	Reflective of patients in the IMpower133 trial (NCT02763579).	Section B.3.2.1
Treatment effectiveness	OS and PFS as measured by disease progression (as defined by RECIST v 1.1)	The primary data source for the model is the pivotal IMpower133 study, comparing atezolizumab plus carboplatin and etoposide induction followed by atezolizumab	Sections B.3.3.1 to B.3.3.4

	Approach	Source/Justification	Signpost (location in CS)
		monotherapy maintenance versus carboplatin and etoposide induction treatment only. For OS and PFS the company: • Checked for proportional hazards; • Inspected visual fit; • Assessed statistical fit (Akaike Information Criterion (AIC) within 5 data points of the lowest AIC value are considered to have a similar goodness of fit); • Considered whether different curve types per arm may be justifiable; • Assessed plausibility of extrapolation beyond the trial data: o Tested survival estimates against expert clinical opinion and real-world data; o Compared to general mortality rates for OS.	
Adverse events	Treatment-related Grade 3-5AEs or serious AEs were included in the cost effectiveness model.	Grade 3-5 AEs or serious AEs with an occurrence of more than 2% in either arm of the IMpower133 trial were included in the cost effectiveness model. The rates applied in the model are calculated based on the total number of patient weeks at risk, which in turn is based on the median reported follow up.	Section B.3.3.7
Health related QoL	Patient Reported Outcomes (PRO) were based on the Euro quality of life 5 dimensions 5-level version (EQ-5D-5L) questionnaires. The submission applies utility values based on UK utility tariffs and on converting the EQ-5D-5L into EQ-5D-3L values using a crosswalk algorithm	Utility was incorporated into the model using the same time to death approach as has been accepted during previous NICE appraisals of lung cancer treatments. This approach was based on patients' 'proximity to death' rather than utility estimates based on whether patients had remained progression free. Four 'proximity to death' sub-states were used to capture patient HRQoL as a proxy of time until death and were categorised by visual assessment.	Section B.3.4
Resource utilisation and costs	Cost comprised drug acquisition costs, the cost of subsequent therapies, drug administration costs, the costs of terminal care and the costs of adverse events, Unit prices were based on the National Health Service (NHS)	An SLR was conducted to identify studies presenting novel cost and resource use data associated with ES-SCLC for previously first-line patients, relevant to the economic model. However, no relevant studies were identified. Therefore, NHS resource use has been calculated from the IMpower133 study and from UK-practising clinical expert opinion. NHS resource use data was not available for first-line ES-SCLC, due to there being no previous NICE appraisals for this condition.	Section B.3.5

	Approach	Source/Justification	Signpost (location in CS)
	reference prices, Personal Social Services Research Unit (PSSRU) and British National Formulary (BNF)	To address this data gap, associated NHS activity was systematically surveyed from 9 UK-practising clinical experts' opinions to correspond to different stages of ES-SCLC disease.	
Discount rates	Discount of 3.5% for utilities and costs.	As per NICE reference case	Table 40
Subgroups	No subgroup analysis was performed.	Only the ITT population was evaluated since, according to the company, UK-practising clinical experts treating ES-SCLC advised this as the most clinically relevant population. A post-hoc exploratory analysis will be performed to investigate efficacy according to PD-L1 IHC status, with results due in Q2 2019. This analysis is being performed due to a final RSI from the EMA. Since this is a post-hoc exploratory analysis, only a limited number of tissue samples are available for testing (approximately 35%).	Section B.3.9 and Section B.3.2.1
Sensitivity analysis	Both DSA and PSA were performed as well as scenario analyses	As per NICE reference case	Section B.3.8

AE = adverse events; AIC = Akaike Information Criterion; BNF = British national formulary; EMA = European medicines agency; ES-SCLC = Extensive-stage small cell lung cancer; EQ-5D-5L = Euro quality of life 5 dimensions 5-level version; IHC = ImmunoHistoChemistry; NICE = National Institute for Health and Care Excellence; OS = Overall survival; PDL1 = Programmed death-ligand 1; PFS = Progression free survival; PRO = Patient reported outcomes; RECIST = Response evaluation criteria in solid tumours; RSI = Request for supplementary information; SA = Survival analysis;

Table 5.21: Comparison of the CS model with the NICE reference case

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Intervention	Atezolizumab with carboplatin and etoposide	Yes	Requirements largely met. However, the model considers carboplatin-etoposide for up to 4 cycles – as included in the IMpower133 trial control arm. This is not consistent with recent NICE guidance http://pathways.nice.org.uk/pathways/lung-cancer suggests that recommends up to a maximum of six cycles, depending on response and toxicity. The impact of allowing up to 6 cycles was explored in a scenario analysis following request for clarification.
Comparators	Platinum-based combination chemotherapy	No	The scope does not exclude cisplatin-based regimens. Also, Appendix K indicates that

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
	regimens: carboplatin and etoposide only in the base case; cisplatin plus etoposide in a scenario analysis		the clinical experts who were questioned, believe that about [redacted] of patients in the UK would be prescribed cisplatin-etoposide. However, this implies that for at least some patients this is standard care. Therefore, in the clarification letter, the ERG requested that the company incorporate a comparison with cisplatin plus etoposide in all analyses including a full incremental analysis as part of the base case of the CEA. In the company's response they stated that this was inappropriate given that they had been advised that cisplatin plus etoposide is not standard of care for untreated, ES-SCLC patients. Nevertheless, it was carried out as a deterministic analysis only. No other platinum-based chemotherapy regimens were compared.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	Yes	All outcomes that were required for the model structure were included, the only caveat being that AE disutilities were only included as a scenario analysis.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be	Yes	ICERs using QALYs were estimated. The time horizon was lifetime and costs were considered from an NHS and Personal Social Services perspective

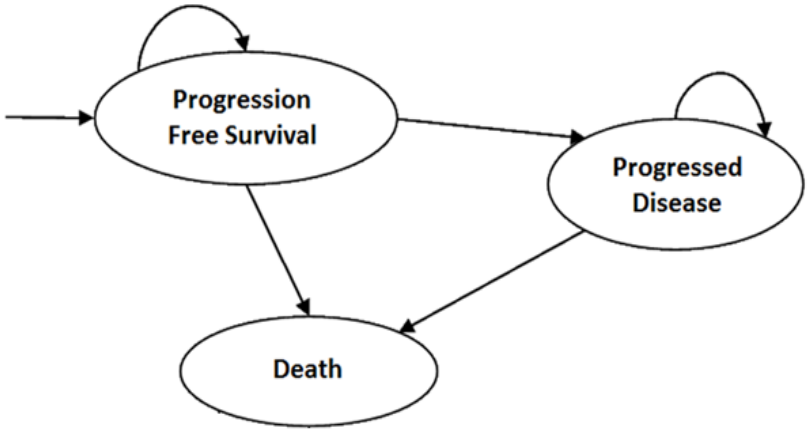
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
	sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.		
Other considerations	If the evidence allows, consideration will be given to subgroups based on biological markers. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	No	[redacted] However, the CEA was not performed for these subgroups.
CS = Company submission; NHS = National Health Service; PSS = Personal Social Services; QALY = quality-adjusted life year; TSS = total symptom score; TTO = time trade-off			

5.2.2 Model structure

The CEA was structured as a three-health state partitioned survival analysis (PartSA) model (See CS, B3.2.2). These three health states were consistent with previous appraisals accepted by NICE to evaluate first-line lung cancer, as well as other oncology indications: "PFS", "Progressed Disease (PD)" and "Death" (2). [redacted].

All patients start in the PFS health state and remain there until either disease progression or death. Upon disease progression patients transition from PFS into the PD health state, where they remain until death (Figure 5.1). Patients cannot transition to an improved health state – i.e., from progression back to PFS. This restriction is consistent with previous economic modelling in oncology and is considered clinically relevant (Appendix K of the CS).

Figure 5.1: Economic model structure with three mutually exclusive health states



Source: CS, Figure 8

ERG comment: The ERG considers this model structure to be appropriate. In the clarification letter, the ERG had requested the company to explain whether alternative model approaches were considered (e.g. state transition model) and justify why these were not considered in the company submission. The company argued that TSD19 states the main concern with this approach is that "the lack of structural link between endpoints in partitioned survival analysis models may increase the potential for inappropriate extrapolation, and may make it difficult to understand the mechanisms underpinning extrapolations and therefore to assess their clinical and biological plausibility."[51] They go on to argue that this problem is mitigated by the relative maturity of the trial data. The ERG concurs and also admit, as TSD19 elucidates, that the mainstay of cancer modelling is the partitioned survival model.

5.2.3 Population

The population in the CEA was first-line, adult ES-SCLC patients (See CS, B3.2.1). which is consistent with the ITT population of the IMpower133 study, the NICE final scope for this appraisal, the appraisal decision problem and the anticipated EMA Marketing Authorisation (the draft SmPC provided in a separate document).[22]

ERG comment: The ERG considers this CEA population to be largely appropriate. The only caveat is that, as the company identified in the response to clarification letter, there might be a subgroup of "…borderline LS-SCLC patients." for whom cisplatin plus etoposide instead of carboplatin plus etoposide would be appropriate. However, no data on the effectiveness of atezolizumab in this 'borderline population' was provided either from the IMpower133 trial or any other source. Therefore, the ERG would argue that, if such a borderline LS-SCLC population exists, then one can make no evidence-based decision as to whether atezolizumab is cost effective in this population.

5.2.4 Interventions and comparators

The intervention and comparators are presented in CS, B3.2.3. The intervention was atezolizumab with carboplatin and etoposide, given for up to four cycles and the comparator was carboplatin and etoposide, given for up to four cycles. The ERG identified that according to the NICE care pathway for treating small-cell lung cancer up to six cycles of carboplatin-etoposide are offered depending on response and toxicity for treating small-cell lung cancer.[52] In response, the company provided the results of a scenario analysis assuming six cycles, which showed a decrease in the ICER.[9] Additionally, a scenario analysis which compared cisplatin instead of carboplatin was modelled. This was performed as a full incremental analysis in the response to clarification letter.[9] However, as described in Section 5.2.3, the company

argued that the comparison was inappropriate due to cisplatin being indicated for only borderline LS-SCLC patients.

ERG comment: The ERG considers the intervention and comparator to be largely appropriate. The ERG also agrees that, if the effectiveness evidence was derived from the IMpower133 study, in which patients received no more than four cycles of chemotherapy, then the only effect of six instead of four cycles would increase the cost of chemotherapy. However, if clinical practice is to prescribe six instead of four cycles, as recommended in the NICE guideline 24,[19] then the ERG would argue that this is how the model should be parameterised and the effectiveness of six versus four cycles remains pertinent and in doubt. Nevertheless, the ERG was inclined to accept that the data for six cycles were unavailable.

The company showed that, if cisplatin plus etoposide is compared with carboplatin plus etoposide, it would be dominated. However, the ERG agrees that for the index population for cisplatin plus etoposide is probably not appropriate and, as argued in Section 4.4, the indirect comparison is unreliable.

The ERG would also point out that the results of the individual studies that might be used for an indirect comparison performed by the ERG, as described in Section 4.5 indicate that the inclusion of irinotecan as a comparator might mean that atezolizumab is not cost effective. However, this would require the performance of the indirect comparison as well as updating other parameters in the model such as AE rates and costs.

5.2.5 Perspective, time horizon and discounting

The economic model uses a 20-year time horizon in the base case. Costs and health outcomes are discounted at 3.5% in the base case and the perspective of the NHS and personal social services (PSS) is assumed.

ERG comment: The ERG considers the time horizon, discount rates and perspective to be appropriate since they are consistent with the NICE reference case.[53] The time horizon is consistent with the lifetime specified in the NICE reference case since no more than 2 in 1000 patients are still alive at 20 years.

5.2.6 Treatment effectiveness and extrapolation

As described in Section B.3.3 of the CS, to estimate the endpoints OS, PFS and TTOT for the company's CEA, data from the IMpower133 trial were used (with a data base lock at 24 April 2018) comparing atezolizumab plus carboplatin and etoposide induction followed by atezolizumab monotherapy maintenance versus carboplatin and etoposide induction treatment only. In response to request for clarification the OS data were updated to [redacted].[43]

The company stated that they followed step by step guidance from the NICE DSU TSD 14 to identify the best fit parametric extrapolations for OS, PFS and TTOT in the model base case.[54] For TTOT, as stated in Section B.3.3.5 of the CS, in both arms of the pivotal trial, no extrapolation was needed for either carboplatin or etoposide treatments, since the time to treatment discontinuation had been observed for the entire cohort during the 12-month follow up period. Therefore, parametric extrapolation was only required for TTOT for atezolizumab.

Because TTOT extrapolation only applied to the intervention, a test for proportional hazards was not required. For OS and PFS, the company first tested whether the proportional hazard assumption held between treatment arms by inspecting the log-cumulative hazard (odds, and standardised normal curve) plots and computing the log cumulative hazard over the log of time. Based on those tests, the proportional hazard assumption was rejected for both OS and PFS because the curves cross each other at multiple time points. Therefore, separate parametric time-to-event models were fitted to each

treatment arm for each endpoint, OS, PFS and TTOT. Visual inspection, The Akaike and Bayesian Information Criterion (AIC and BIC) were used to selects the most relevant extrapolations. The plausibility of extrapolation beyond trial data was also assessed by checking the crossing of curves (OS should not cross PFS or TTOT) and, for OS comparison external validation with expert opinion and/or real-world data and general mortality rates.

5.2.6.1 Progression free survival

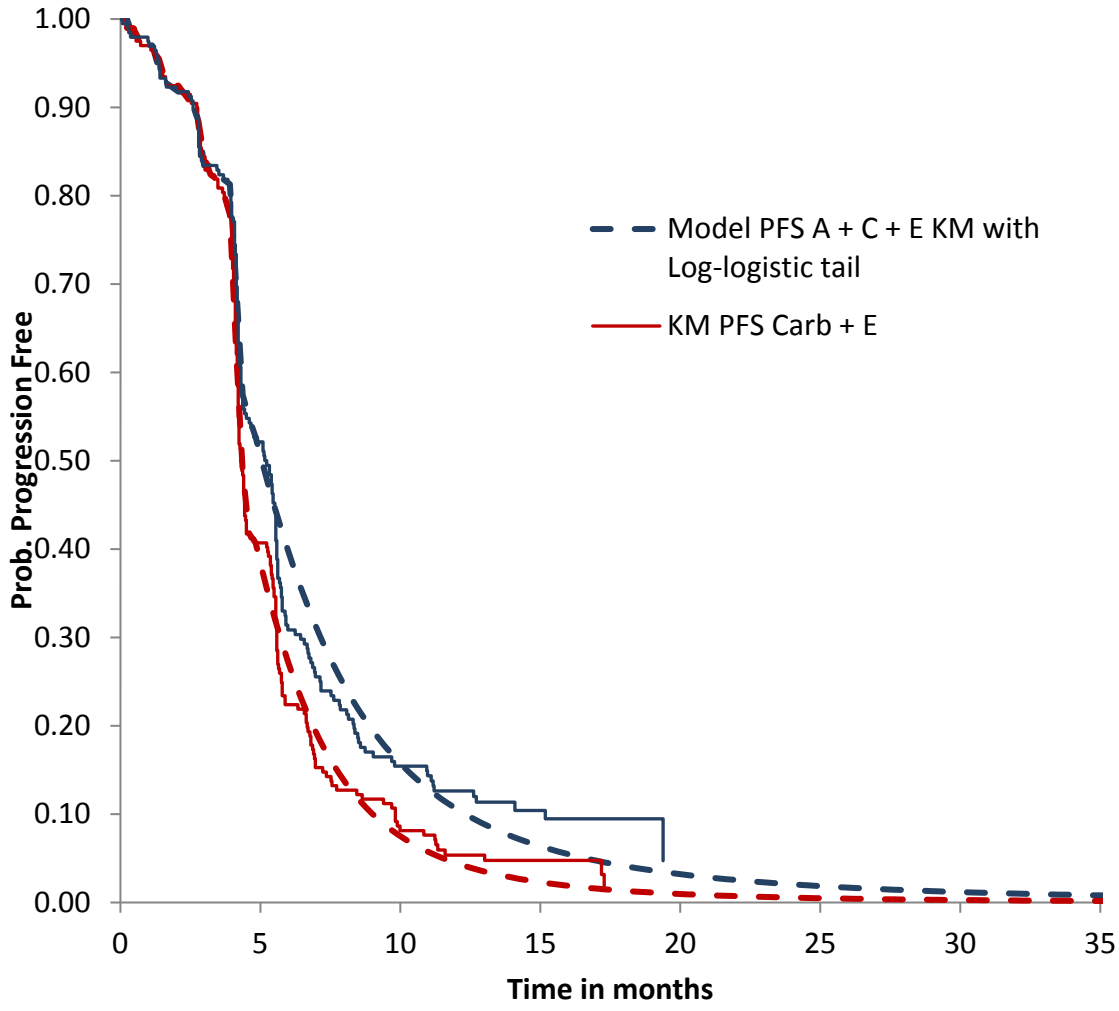
For PFS, the log-logistic curve provided the best statistical fit of the parametric function to the actual data (Table 5.5). This continued to be the case with the [redacted] data: [redacted] Figure 5.2 shows the selected parametric time-to-event models compared to Kaplan Meier. The company noted that all the standard parametric curves provided a similarly poor visual fit to the Kaplan-Meier data, as there were steep drops within the first five months at the time of each scan. [redacted], at this specific time point approximately 50% of patients remain at risk in both arms. Figure 5.2 shows the curve selection in the model base case, Kaplan-Meier for the first five months followed by log-logistic extrapolation on both arms. No external validation was performed for PFS.

Table 5.22: Ranking of PFS distributions based on AIC, BIC, visual fit and clinical plausibility of PFS

Parametric distribution	AIC Atezo	BIC Atezo	AIC control	BIC control	Visual fit to KM	Ranking overall
Log-logistic	**428.6**	**435.2**	**376.1**	**382.7**	**Best fit**	**1**
Generalised gamma	448.3	458.2	399.8	409.7	Poor fit	2
Weibull	455.6	462.2	408.6	415.2	Poor fit	3
Log-normal	464.7	471.3	425.5	432.1	Poor fit	4
Gompertz	483.3	489.9	452.8	459.4	Poor fit	5
Exponential	493.9	497.2	482.6	485.9	Poor fit	6

Source: CS, Table 21
AIC = Akaike information criteria; BIC = Bayesian information criteria; KM = Kaplan-Meier.

Figure 5.2: Kaplan-Meier curves and selected parametric time-to-event models for PFS of Atezolizumab + carboplatin + etoposide and carboplatin + etoposide based on IMpower133



Source: CS, Figure 8.
A = atezolizumab; C = carboplatin; E = etoposide; KM = Kaplan-Meier; PFS = progression-free survival

5.2.6.2 Overall survival

For OS, fully parametric survival extrapolations were used by the company. The following functions were fitted to both OS and PFS: Exponential, Weibull, log-logistic, log-normal, generalised gamma and Gompertz. In terms of statistical fit, the CS stated the best overall fit to the existing OS data would be either Weibull, Gompertz, generalised gamma or log-logistic extrapolations for the atezolizumab arm and Weibull, Gompertz or generalised gamma curves for the comparator arm. The company argued in the CS that the visual fit of the Weibull, Log-logistic, Gompertz and generalised gamma extrapolation curves was good enough not to use the KM data even for the initial period, as they did for PFS. In response to clarification letter stage 2 and the data from [redacted] the company stated that the best fit was obtained from the Weibull and log-logistic extrapolations, as shown in Table 5.6.[43]

For the comparator, the company finally chose the log-logistic from the set of parametric curves on the basis of external validity of the extrapolations by comparison with data from the Flatiron study. These data were based on 2,161 extensive-stage small-cell lung cancer (ES-SCLC) patients diagnosed since the 1 January 2013 in the USA. Data from this study were presented to an expert panel, as described in Appendix K. The company argued that these patients were representative of UK clinical practice, although clinical experts stated that ECOG performance status in the UK would be worse. Also 16% of

patients in the Flatiron study received cisplatin instead of carboplatin, the former being argued by the company to not be a comparator on the grounds that it would only be suitable for borderline LS-SCLC patients. The company provided a comparison of survival estimates based on various parametric extrapolations with the data from the Flatiron study referred to as "Real-world data of chemotherapy survival validated as appropriate by UK-practising experts", which was reported in Appendix K.[39] This has been updated by the ERG using the version of the model, ID1504 Atezolizumab Roche CE model PAS price v2 070519 JM [PAS], containing the updated OS data (see Table 5.7). A similar table was also provided in the response to clarification letter stage 2 (see Table 5.8).[43] However, it was not clear why the company adjusted these values in this second table (e.g. compare 33% with 40% at 12 months) given that they were supposed to have been estimated from the Flatiron study and these unadjusted estimates were the ones validated by the clinical experts as presented in Appendix K. The company provided the footnote: "FlatIron Health cycle probability of death is applied from data-cut off", but it is not clear what this means. Also, based on the [redacted] data, the company argued differently that the Weibull extrapolation does not report clinically plausible OS results, due to the convergence of the atezolizumab and control arm curves at 50 months. They stated in response to clarification letter stage 2 that "…only the log-logistic approach modelled the continued benefit of atezolizumab in untreated, ES-SCLC patients reported in the updated IMpower133 analysis and expected by clinicians."[43] They attempted to demonstrate this "…clinically implausible absence of sustained atezolizumab benefit over time." in two figures shown below, which compared the log-logistic with the Weibull (see Figures 5.3 and 5.4).

For the intervention, the company cited the clinical expert opinion as to long term survival (see Appendix K) and on this basis chose the log-logistic model.[39] As with the comparator, the company compared survival estimates from each of the parametric models with those elicited by clinical experts in Appendix K and the ERG updated these using the version of the model, ID1504 Atezolizumab Roche CE model PAS price v2 070519 JM [PAS] (Table 5.9). In the model base case, at five years the treatment effect of the atezolizumab combination over chemotherapy is assumed to stop, and the conditional survival probability is set to equal the chemotherapy arm. [redacted] as being relevant to ES-SCLC. It was also stated to have been aligned with previous committee decisions on when immuno-oncology treatment effect becomes more uncertain. Alternative assumptions for treatment effect duration were considered in the scenario analysis.

As described in Section B.3.3.4, in a scenario analysis, the company also incorporated real-world data from the Flatiron study to estimate OS only for the comparator. This was achieved by one of two methods. The first, referred to as Approach 1, involved pooling these data with the IMpower133 individual patient data and then fitting parametric curves. The second involved using the Flatiron data only after using the KM data for a period of time, which was chosen as until 20% of patients remain at risk in the IMpower133 trial (here 19 months). This was chosen to maintain the randomised controlled data from the IMpower133 study for as long as it was "…considered robust…" In fact, in the scenario analysis, the figure 10% was stated instead of 20% as the cut-off in Table 48 of the CS, although the Excel model shows the time to be 19 months at which 20% of the cohort are still alive. As there is no guidance in TSD 14 about the use of this approach, the company choose to present this analysis as a scenario analysis rather than in the base-case.[54]

Table 5.23: Ranking of OS parametric distributions from IMpower133 trial data based on AIC, BIC, visual fit and clinical plausibility

Parametric distribution	AIC Atezo	BIC Atezo	AIC Control	BIC Control	Visual fit to KM	Ranking overall
Log-logistic	469	476	483	490	Best fit and most plausible	1
Weibull	468	475	490	497	Good fit for data but not plausible tail	2
Gen Gamma	470	480	491	501	Poor fit	3
Gompertz	476	482	506	512	Poor fit	4
Exponential	491	494	518	521	Poor fit	5
Log normal	499	506	517	524	Poor fit	6

Source: Table 18, response to clarification letter stage 2.[43]
AIC = Akaike information criteria; BIC = Bayesian information criteria; KM = Kaplan-Meier

Table 5.24: Parametric extrapolations of the proportion of patients alive (OS) following carboplatin-etoposide treatment, using only IMpower133 data to inform the extrapolation

Time (months)	Parametric extrapolations						Real-world data of chemotherapy survival validated as appropriate by UK-practising experts	Difference between real-world data and parametric extrapolation	
	Weibull	Gompertz	Generalised gamma	Log-logistic	Exponential	Log-normal		Weibull	Log-logistic
12	47%	47%	46%	44%	43%	44%	[redacted]	14%	11%
24	1[redacted]%	12%	12%	15%	18%	19%	[redacted]	[redacted]%	8%
36	[redacted]%	1%	3%	7%	8%	10%	[redacted]	[redacted]%	5%
48	0%	0%	1%	4%	4%	6%	[redacted]	0%	3%
60	0%	0%	0%	3%	2%	3%	[redacted]	0%	2%

Source: Adapted from Table 23 of the CS using the company model, ID1504 Atezolizumab Roche CE model PAS price v2 070519 JM [PAS]

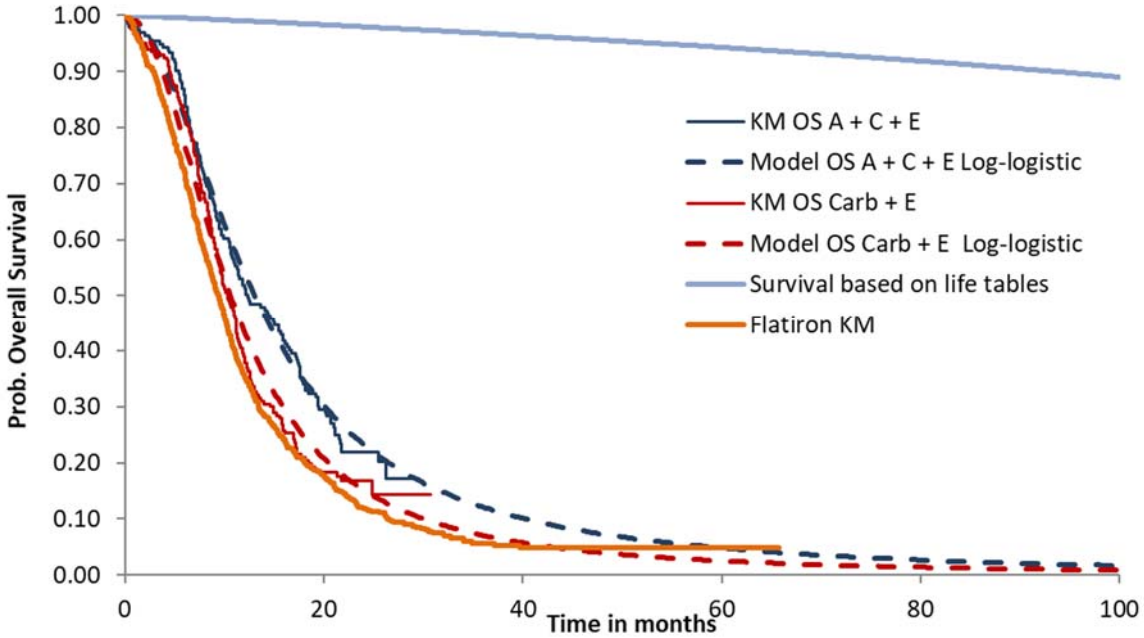
Table 5.25: Survival extrapolations for the control arm, using different statistical approaches and data sources

Time (months)	Parametric extrapolations		Real-world data of chemotherapy survival validated as appropriate by UK practising experts*		
	Log-logistic control arm – February submission	Log-logistic updated, control arm – base case		Log-logistic (updated) with Flatiron data after 22 months (generalised gamma)*	Log-logistic (updated) with Flatiron data after 22 months (Log-logistic)*
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time (months)	Parametric extrapolations		Real-world data of chemotherapy survival validated as appropriate by UK practising experts*		
	Log-logistic control arm – February submission	Log-logistic updated, control arm – base case		Log-logistic (updated) with Flatiron data after 22 months (generalised gamma)*	Log-logistic (updated) with Flatiron data after 22 months (Log-logistic)*
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	£45,893	£49,588	N/A	£45,873	£53,191
Mean difference in survival (months)	[redacted]	[redacted]	N/A	[redacted]	[redacted]
Median difference in survival (months)	[redacted]	[redacted]	N/A	[redacted]	[redacted]

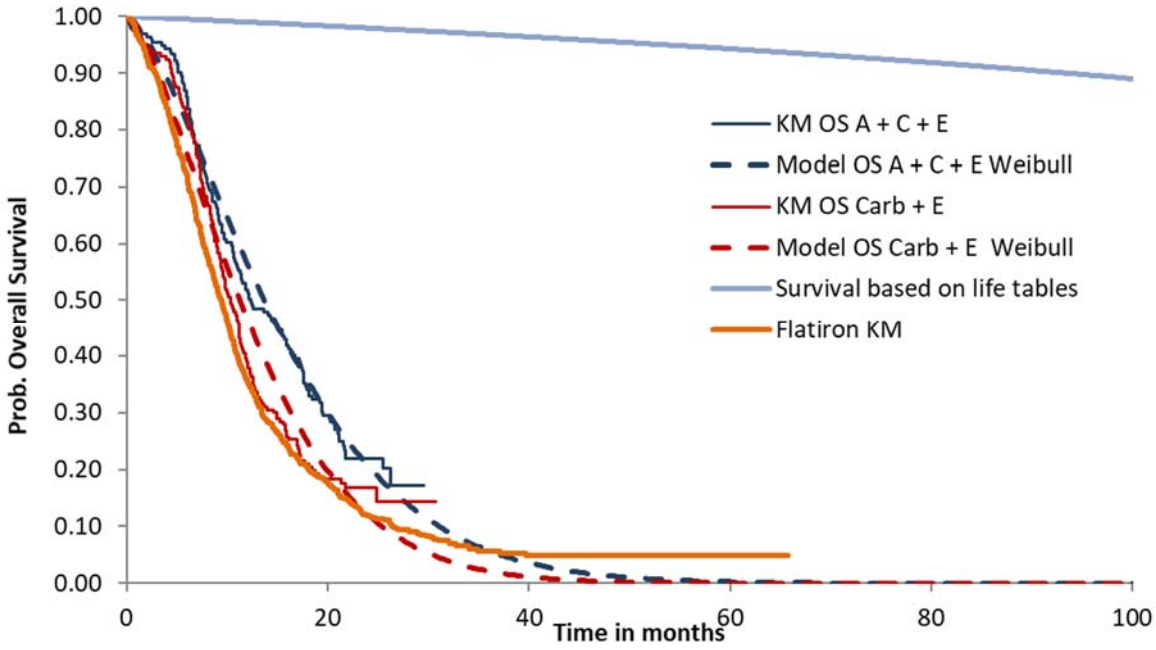
Source: Table 19, Response to clarification letter stage 2.[43]
*FlatIron Health cycle probability of death is applied from data-cut off

Figure 5.3: Log-logistic extrapolation of IMpower133 OS data



Source: Figure 5, response to clarification letter stage 2.[43]

Figure 5.4: Weibull extrapolation of IMpower133 OS data



Source: Figure 6, response to clarification letter stage 2.[43]

Table 5.26: Parametric extrapolations of the proportion of patients alive (OS) following atezolizumab plus carboplatin-etoposide treatment, using only IMpower133 data to inform the extrapolation

Time (months)	Parametric extrapolations						UK-practising clinical experts' opinion, based on real-world data and IMpower133 benefit	Difference between clinical expert opinion and parametric extrapolation*	
	Weibull	Gompertz	Generalised gamma	Log-logistic	Exponential	Log-normal		Weibull	Log-logistic
12	57%	58%	56%	54%	52%	53%	[redacted]	17%	14%
24	22%	23%	22%	23%	26%	27%	[redacted]	10%	11%
36	10%	11%	10%	12%	14%	16%	[redacted]	5%	7%
48	6%	6%	6%	7%	8%	10%	[redacted]	3%	5%
60	4%	4%	4%	5%	5%	7%	[redacted]	2%	3%

Source: Adapted from Table 24 of the CS using the company model, ID1504 Atezolizumab Roche CE model PAS price v2 070519 JM [PAS]
*Midpoint of clinical expert opinion used where range given

5.2.6.3 Time to off treatment

For TTOT, for atezolizumab only, as explained above, the generalised gamma provided the best statistical fit of the parametric function to the actual data (Table 5.10). The company noted that all the standard parametric curves provided a similarly poor visual fit to the Kaplan-Meier data. [redacted]. No external validation was performed for TTOT.

Table 5.27: Ranking of TTOT distributions based on AIC, BIC and visual fit

Parametric distribution	AIC Atezo	BIC Atezo	AIC control	BIC control	Visual fit to KM	Ranking overall
Generalised gamma	701.5	711.4	Best fit overall but poor fit to initially data	Plausibility increased by KM with generalised gamma tail	Generalised gamma	1
Weibull	717.5	724.1	Poor fit	Low	Weibull	2
Exponential	721.7	725.0	Poor fit	Low	Exponential	3
Gompertz	723.7	730.3	Poor fit	Low	Gompertz	4
Log-logistic	762.1	768.7	Poor fit	Low	Log-logistic	5
Log-normal	844.7	851.3	Poor fit	Low	Log-normal	6
Source: CS, Table 27. AIC = Akaike information criteria = BIC: Bayesian information criteria = KM: Kaplan-Meier.						

ERG comment: The company appropriately applied the criteria specified in the TSD 14 in terms of testing for proportional hazards, statistical and visual fit.[54] They also correctly considered external validity.

For PFS, the ERG considers the choice of model appropriate, although the point at which the KM curve is replaced by the log-logistic model is arbitrary. Therefore, and given no external validation of PFS, the ERG conducted a scenario analysis by using 15 instead of five months. The ERG has a similar opinion of the choice of model for TTOT. However, given that there was no external validation of TTOT, the ERG conducted a scenario analysis that assumed TTOT is at least equal to PFS after 14 months on the basis that progression will probably be the main reason for ending treatment in the long term (see Section 5.3).

For OS and for the comparator the ERG would disagree with the judgement regarding clinical plausibility. Specifically, the ERG would argue that the log-logistic curve is actually too optimistic to estimate OS for the comparator i.e. as would be observed in clinical practice on the following grounds:

1) The percentage surviving to the end of every year of comparison presented in Table 5.7 using the log-logistic is higher than in the Flatiron study "Real-world data of chemotherapy survival validated as appropriate by UK-practising experts" (by 11%, 8%, 5%, 3% and 2% for years 1 to 5 respectively).
2) The clinical expert panel noted that ECOG performance status would be worse in the UK than in the Flatiron study.
3) The ERG also located a conference abstract[55] based on this study that showed a survival advantage to those patients taking cisplatin compared to carboplatin and the evidence to inform the effectiveness of both intervention and comparator is that based on only taking carboplatin.

Therefore, given that the log-logistic already overestimates OS as estimated in the Flatiron study and the Flatiron study probably overestimates OS compared to UK clinical practice, the log-logistic almost certainly overestimates OS compared to UK clinical practice. Indeed, the company also make the point that the control arm of the IMpower133 study has [redacted].[43] There is, on the other hand, the Weibull, which, whilst it also overestimates OS in comparison to the Flatiron study for years 1 to 2, it provides estimates that are almost identical to the Flatiron study

for years 3 to 5 (Table 5.7). Therefore, its overestimation of UK clinical practice is likely to be less than that by the log-logistic given, as described in points (2) and (3), Flatiron is likely to produce an overestimate of OS. Therefore, the ERG would argue that the Weibull is likely to be more clinically plausible and it provides nearly as good a statistical fit, which is why it has been chosen for the comparator in the ERG base-case (see Section 5.3 below). It is true that, in response to clarification letter stage 2, a completely different set of figures was provided in the column for "Real-world data of chemotherapy survival validated as appropriate by UK-practising experts" and that these data are closer to the estimates from the log-logistic extrapolation.[43] However, the ERG believe that this is not an appropriate method to validate an extrapolation based on the trial data. Adjusting these data in any way undermines their status as providing "real-world" external validation. Adjusting those data after they had been presented to the clinical experts undermines their status has having been "validated as appropriate by UK-practising experts". Nevertheless, given the marginally better statistical fit of the log-logistic, the ERG has included this in a scenario analysis (see Section 5.3).

For the intervention, the ERG also disagrees with the choice of the log-logistic on the basis of clinical plausibility as well as it having a marginally worse statistical fit than the Weibull. The main reason for this judgement is that there is in fact are no real-world data by which any estimates can be externally validated and the ERG questions the validity of clinical expert opinion as to the effect of a treatment for which they would have had no clinical experience. However, as with the comparator, one can compare the percentages surviving at each of the five time points (shown in Table 5.9) elicited from the clinical experts with those from the log-logistic and the model with the best statistical fit, the Weibull. When one does that it can be seen that, as for the comparator, the values for the log-logistic are all higher than those elicited from the clinical experts. The same is also true for the Weibull, but by more than the log-logistic only in year 1 and by less in all other years. Therefore, the ERG would argue that the Weibull is likely to be more clinically plausible and it provides a better statistical fit, which is why it has been chosen for the intervention in the ERG base-case (see section 5.3 below).

The company also claim that the [redacted] However, the ERG would argue that whilst such a bias would seem plausible it is impossible to estimate its size and adjust for it directly. Indeed, the ERG have located a conference abstract that showed no survival advantage to one of those immunotherapies i.e. nivolumab at second line for advanced SCLC.[56] One can, however, choose the most plausible curve for each of the comparator and the intervention as described above, which is the Weibull, based both on statistical fit and clinical plausibility. This will be used in the ERG base-case (see Section 5.3).

The ERG also questioned the implementation in the model of OS for the intervention, which included a formula that ensured that it would always be at least as high as that for the comparator, carboplatin plus etoposide. In response to clarification the company defended this by stating the this was supported by clinical expert opinion.[9] However, the ERG would argue that it is impossible for any clinical expert to predict the relative survival at any time point by any means other than based on empirical data, the only source of which is the IMpower133 study. Therefore, the ERG chose to remove this formula and inform OS only by the survival model fit to the trial data (see Section 5.3 below).

The ERG also identified an error with the implementation of PFS estimation on the model, which was stated to have been corrected by the company in the response to clarification letter.[9] On examination by the ERG, it was noticed that it had not been corrected. However, the error has no effect on the base-case or any scenario except one where the treatment effect for PFS is assumed to be finite, the effect of

which is trivial. Another error was identified in the post-response to clarification model in the VBA code relating to TTOT. This prevented change to the parametric model. The error was in the code associated with worksheet 3 (Model Inputs):

If WorksheetFunction.Match(Sheet3.Range("tx_dur"), Sheet17.Range("options_tx_dur"), 0) = 1 Then

This was corrected by the ERG to:

If WorksheetFunction.Match(Sheet3.Range("dist_ttd"), Sheet17.Range("options_TTD"), 0) = 1 Then

For TTOT the ERG agreed that the fit to the K-M data was poor for any of the parametric curves. No justification was given for the choice of 14 months, although the ERG noticed that this was the reliable limit of the K-M data there being only one point after this and with some censoring. However, in the absence of data beyond 14 months the ERG performed a scenario analysis by assuming that patients would stay on treatment at least until progression (see Section 5.3).

5.2.7 Adverse events

As described in Section B.3.3.7 of the CS, the main source of evidence on treatment adverse events (AEs) used for atezolizumab was the IMpower133 trial data. AEs were included in the model if they had an occurrence of more than 2% in either arm in the IMpower133 trial and a severity of Grade 3-5 or if they were classified as serious AEs (see Table 5.11 for the list of included AEs). AEs were included in the model in terms of their costs and not their impact on health-related quality of life (HRQoL) in the CS. The company argued that any AE disutility had already been incorporated into the base-case health state utilities through the trial derived EQ-5D utilities estimated as a function of time to death only, and incorporating an additional disutility could be considered double counting.

Table 5.28: AEs included in the model: Grade ≥3 treatment related AEs, with incidence ≥2% in either arm of IMpower133 study

AE	Atezolizumab plus carboplatin-etoposide			Carboplatin-etoposide		
	Number of patients with AE (N)	Occurrence of the AE	Probability of event (weekly)	Number of patients with AE (N)	Occurrence of the AE	Probability of event (weekly)
Anaemia	28	31	0.0026	24	26	0.0022
Diarrhoea	5	5	0.0004	1	2	0.0002
Febrile neutropenia	6	6	0.0005	12	13	0.0011
Infusion-related reaction	4	5	0.0004	3	3	0.0003
Leukopenioa	10	15	0.0013	8	11	0.0009
Neutropenia	46	72	0.0060	48	69	0.0058
Neutrophil count decreased	28	50	0.0042	33	56	0.0047
Pancytopenia	1	1	0.0001	4	4	0.0003
Platelet count decreased	7	11	0.0009	8	11	0.0009
Pneumonia	4	4	0.0003	1	1	0.0001

AE	Atezolizumab plus carboplatin-etoposide			Carboplatin-etoposide		
	Number of patients with AE (N)	Occurrence of the AE	Probability of event (weekly)	Number of patients with AE (N)	Occurrence of the AE	Probability of event (weekly)
Thrombocytopenia	20	22	0.0018	15	18	0.0015
Vomiting	2	3	0.0003	3	3	0.0003
White blood cell count decreased	6	8	0.0007	9	12	0.0010

Source: CS, Table 29.
AE = adverse event.

ERG comment: The ERG considers that the company appropriately identified the AEs that were most important to include in terms of the potential impact on cost and utility. The rule by which they were included i.e. according to frequency (see Section 4.2.6 of this report) would not per se result in a bias towards or against atezolizumab. Also, the ERG knows of no reason to include any rarer event and a review of both the previous NICE technology appraisal in SMLC, TA184[57] and the CEAs included in the review (see Section 5.1.3) shows that the list included in this appraisal was more comprehensive. A description and critique of the methods of estimation of utility and cost as a function of AEs is presented below in Sections 5.2.8 and 5.2.9 respectively.

5.2.8 Health-related quality of life

According to the CS, Section B.3.4.4, the SLR identified six studies which met the eligibility criteria of the review and reported relevant health state utility values (HSUV) data. Out of these, the company considered that none of the studies fully met the requirements of the NICE reference case. Therefore, alternative scenarios using utilities from the published literature were not conducted (see the CS, Section B.3.4.4).

Instead, as described in Section B.3.4.1, the company used the data from the IMpower133 trial in which the EQ-5D-5L questionnaire on the electronic Patient Reported Outcomes (ePRO) tablet at each scheduled study visit, prior to administration of study drug and prior to any other study assessment(s).

In line with NICE's position statement on EQ-5D-5L data, the obtained data were mapped to EQ-5D-3L using the indirect mapping approach according to van Hout et al. 2012.[58]

The company stated that utility was incorporated into the model using the same time to death approach as has been accepted during previous NICE appraisals of lung cancer treatments, this was validated [redacted]. The values used in the model are shown in Table 5.12. As clarified in the response to clarification letter, off treatment referred to being off all components of the combination i.e. not on atezolizumab or carboplatin or etoposide.[9]

Table 5.29: Utilities applied in the model base case, reported from the IMpower133 study

Proximity to death	On treatment	Off treatment
≤ 5 weeks before death	0.65	0.37
> 5 & ≤ 15 weeks before death	0.73	0.55
> 15 & ≤ 30 weeks before death	0.73	0.71
> 30 weeks before death	0.75	0.78

Source: CS, CE model

As described in Section B3.4.5 of the CS, the company did not apply a separate disutility for each AE on the basis that this would imply double counting given that utilities as estimated as described above are already a function of AEs.

ERG comment: The ERG questions the validity of the 'time to death' method employed by the company, although in the clarification letter response, the company provided references to previous STAs that used the 'time to death' approach, which were the appraisal of atezolizumab to treat both first-line and second-line non-small cell lung cancer, and pembrolizumab for the treatment of non-small cell lung cancer as first-line monotherapy and combination therapy, and as second-line therapy.[34, 59-62] The main reasons for this are:

1) Despite previous use of the approach in previous STAs, it still remains unvalidated as evidenced by no mention in the NICE TSD on utilities.[63]
2) It neglects the more established method of using progression status to determine utility value
3) It incorporates the effect of being on or off treatment with questionable clinical validity especially not having statistically tested the effect of both treatment and progression status
4) It is implemented by the arbitrary division into four time to death categories without statistically testing the fit of such a model or any other model.

In response to clarification letter, the company failed to provide what the ERG had requested i.e. full statistical analysis of various models including both on/off treatment and progressed/not progressed as well as time to death as a continuous variable.[9] Instead, the company estimated separate models for each of "on or off" treatment and "progressed or not progressed" scenarios so that the independent effect of each of these factors could not be estimated and they retained the arbitrary time to death categories. Therefore, the ERG chose the more conservative approach of measuring utility as a function of progression status and not time to death in the ERG base-case (see Section 5.3).

The ERG believes the justification provided by the company stating that AEs are implicitly captured by EQ-5D is questionable. According to NICE TSD 12[63] it is important to include decrements on HRQoL associated with AEs of at least Grade 3. Therefore, the ERG requested this in the clarification letter. As a result, in response the company included all AEs as included for costs (Table 5.13).[9] The ERG therefore included AE disutilities with progression status to calculate utilities for the ERG base-case (see Section 5.3).

Table 5.30: Adverse event disutilities

	Disutility	Probability of event (weekly)		NICE TA	Original source cited
		Atezo+C+E	Carbo+E		
Anaemia	-0.07346	0.0026	0.0022	TA520, Company submission, Table 62[34]	Nafees et al, 2008[64]
Diarrhoea	-0.0468	0.0004	0.0002	Ta484, Company submission, Table 57[65]	Nafees et al, 2008[64]
Febrile neutropenia	-0.09002	0.0005	0.0011	TA520, Company submission, Table 62[34]	Nafees et al, 2008[64]

	Disutility	Probability of event (weekly)		NICE TA	Original source cited
		Atezo+C+E	Carbo+E		
Infusion related reaction	-0.05	0.0004	0.0003	Assumed the same as dyspnoea	Doyle et al, 2008[66]
Leukopenia	-0.08973	0.0013	0.0009	TA520, Company submission, Table 62[34]	Assumed equal to neutropenia
Neutropenia	-0.08973	0.0060	0.0058	TA520, Company submission, Table 62[34]	Nafees et al, 2008[64]
Neutrophil count decreased	0	0.0042	0.0047	TA520, Company submission, Table 62[34]	Assumption
Pancytopenia	-0.08973	0.0001	0.0003	Assume same as neutro/leuko/thrombocytopenia	Nafees et al, 2008[64]
Platelet count decreased	-0.05	0.0009	0.0009	TA416, committee papers, Table 5.18[67]	Assumption based on Nintedanib NICE appraisal (TA347)[68]
Pneumonia	-0.008*	0.0003	0.0001	TA484, Company submission, Table 57[65]	Marti et al, 2013[69]
Thrombo-cytopenia	-0.08973	0.0018	0.0015	TA406 committee papers, Table 50[70]	Assumed same as fatigue from Nafees,[64] (as per TA181)
Vomiting	-0.048	0.0003	0.0003	TA416, committee papers, Table 5.18[67]	Nafees et al, 2008[64]
White blood cell count decreased	-0.05	0.0007	0.0010	TA520, Company submission, Table 62[34]	Assumption based on Nintedanib NICE appraisal (TA347)[68]

Source: Table 7, Clarification letter response[9]

These are the Notes from this source: "*, although the disutility for pneumonia does not match the severity of the condition considering the other AEs and their disutilities, this value has been left unchanged, to keep consistency with previous appraisals. As pneumonia is one of the least frequently experienced AEs on both arms, any change in this value is not thought to greatly impact the model results."

5.2.9 Resources and costs

A SLR was conducted to identify studies presenting novel cost and resource use data associated with ES-SCLC for previously first-line patients, relevant to the economic model presented herein. Detailed descriptions of the search strategy, search terms and extraction methods, as well as details of the included studies were provided in Appendix I of the CS.[36]

As reported in Section B.3.5.1 of the CS, a total of 32 publications were considered to be eligible for inclusion from the costs and resource use SLR: 28 full publications and four abstracts. According to the company, the reported cost studies from the literature were either not considered to be relevant to the decision problem or not considered to reflect current clinical practice. Therefore, NHS resource use has been calculated from the IMpower133 study and from UK-practising clinical expert opinion (Appendix K of CS).[39] The base-case model includes the actual dosing from IMpower133 study and vial sharing assumptions (i.e., no wastage) for the administration of chemotherapy drugs in the model. Atezolizumab is given at a fixed dose. The impact of these assumptions was stated to have been considered in scenario analyses in CS, Section B.3.8.

Drug acquisition costs for the treatments included in this submission and model are summarised in Table 5.14 and schedule dosing administration costs in Table 5.15. Since carboplatin, etoposide and cisplatin are all available to the NHS as generic medicines, prices are taken from eMIT, which reports the average price paid by the NHS for a generic medicine.[71] The only other medicine price included in this submission was for atezolizumab which is presented inclusive of the confidential PAS discount (see Table 2 of the CS for further details).

The dosing schedule from the IMpower133 study protocol, is described for each of these drugs in Table 5.15. The average weight (75.5 kg) and CG.84 m2 using the Dubois formula) from the IMpower133 study were applied to estimate the average cost per dose per patient for the treatments that are dosed according to weight or BSA. The drug costs of combination therapies were assumed to be equal to the sum of individual drug's costs included in a combination therapy, e.g., the costs for the combination of carboplatin-etoposide therapy per administration is the sum of drug costs for carboplatin per administration plus the drug costs for etoposide per administration). Since TTOT data were not available for cisplatin-etoposide, the same discontinuation rate is assumed as for carboplatin-etoposide.

Relative dose intensity has been applied according to the IMpower133 study (see Table 5.16) to account for missed doses. Drug cost per treatment cycle for interventions used in the cost effectiveness model are summarised in Table 5.17.

Table 5.31: Drug acquisition costs

Drug	Vial/pack concentration and volume	Cost per vial/pack	Standard deviation	Source
Atezolizumab with PAS	20 mL/1,200 mg	[redacted]	N/A	BNF list price
Carboplatin	5 mL/50 mg	£3.18	£0.43	eMIT 2018[71]
Carboplatin	60 mL/600 mg	£28.24	£19.64	
Etoposide	5 mL/100 mg	£2.30	£1.14	
Etoposide	25 mL/500 mg	£9.65	£6.37	
Cisplatin	10 mL/10 mg	£1.84	£1.44	
Cisplatin	100 mL/100 mg	£10.13	£8.93	

Source: CS Table 32.
BNF = British National Formulary; eMIT = electronic marketing information tool; N/A = not applicable
eMIT: 12-month period until end of June 2017

Table 5.32: Dosing schedule and dose per administration

Drug	Dosing per administration	Frequency of administration	Source
Atezolizumab	1,200 mg	Q3W	CS Appendix C
Carboplatin	5 mg/mL/min (AUC)*	Q3W	CS Appendix C
Etoposide	100 mg/m^2	Q3W	CS Appendix C
Cisplatin	80 mg/m^2	Q3W	CS Appendix C

Source: CS Table 33.
AUC = Area under the curve; Q3W = once every 3 weeks; SmPC = summary of product characteristics.
*Dose is calculated based on the Calvert Formula: Target AUC * ([Sex * ((140 - Age) / (Serum Creat)) * (Weight / 72)] + 25) --> Male = 1 / Female = 0.85.

Table 5.33: Relative dose intensity reported in the IMpower133 study

Treatments	Regimen	RDI	SE
Atezolizumab	Atezolizumab plus carboplatin-etoposide	92.1%	0.7%
Carboplatin	Carboplatin-etoposide with or without atezolizumab	91.5%	0.6%
Etoposide	Etoposide with or without atezolizumab	88.8%	0.6%
Cisplatin	Cisplatin-etoposide	91.5%	0.6%

Source: CS, Table 34.
RDI = Relative dose intensity; SE = standard error.

Table 5.34: Drug cost per treatment cycle for interventions used in the cost effectiveness model

Comparator	Method and frequency of administration	Drug cost per combination partner per cycle*	Total drug cost per cycle before discounting*
Atezolizumab** plus carboplatin-etoposide	IV, Q3W	Atezolizumab: [redacted] Carboplatin: £27.70 Etoposide: £10.05	£1,223
Carboplatin-etoposide	IV, Q3W	Carboplatin: £27.70 Etoposide: £10.05	£38
Cisplatin-etoposide	IV, Q3W	Cisplatin: £17.21 Etoposide: £27.70	£27

Source: CS, Table 35.
IV= intravenous; Q3W = once every 3 weeks
*Assuming vial sharing, actual dose and proportion of missed doses from IMpower133 study.
**With PAS.

5.2.9.1 Subsequent therapies

Subsequent therapy treatment costs have been incorporated into the model according to the IMpower133 study as this was deemed to balance the efficacy and cost estimates from the study appropriately. This incorporated limited use of subsequent immuno-oncology treatments, and subsequent treatment rates were largely balanced between the two study arms. UK-practising clinical experts stated they did not expect a difference between subsequent treatment prescribing practices according to whether atezolizumab had been prescribed first-line (Appendix K of CS)[39] and did not

expect to prescribe immune-oncology treatments at second line. For comparison, a scenario analysis considering this expert opinion is presented in Section B.3.8.3 of the CS.

5.2.9.2 Drug administration costs

The cost for drug administration incorporated into the model is reported in Table 5.18. The administration cost for the first cycle of treatment for any of the three regimens is costed as a complex chemotherapy day case procedure including prolonged infusion due to being the first attendance – SB13Z of the NHS reference costs.[72] For all three regimens, the subsequent drug administration is costed for the comparable procedure, but at standard infusion duration – SB15Z of the NHS reference costs.[72] Since the infusion of atezolizumab alone requires less time this is costed as a simple infusion SB12Z of the NHS reference costs.[72] However, UK-practising clinical experts advised Roche that cisplatin-etoposide requires 10 hours to infuse, so this has been costed as complex chemotherapy – SB14Z of NHS reference costs. This approach is in line with advice from UK-practising clinical experts (Appendix K).[39]

Table 5.35: Administration costs incorporated into the CEM

Drug	Type of administration	NHS reference code	Cost per administration	Source
First administration of treatment cycle for all combination regiments	Daycase and Reg Day/Night: Deliver more Complex Parenteral Chemotherapy at First Attendance	SB13Z	£309.22	NHS reference cost 2017/18[72]
Subsequent elements of etoposide treatment, i.e. Day 2 and 3 of each treatment cycle	Deliver complex chemotherapy, day case, standard infusion rate for subsequent treatment	SB15Z	£312.34	
Atezolizumab monotherapy administration	Deliver simple parenteral chemotherapy at first attendance as outpatient	SB12Z	£173.99	
First administration of cisplatin-etoposide	Daycase and Reg Day/Night: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	£374.52	
Source: CS, Table 36. NHS = National Health Service				

NHS resource use data were not available for first-line ES-SCLC, due to there being no previous NICE appraisals for this condition. Moreover, as stated in Section B.3.5.1 of the CS, no relevant published costs studies were identified of relevance to the decision problem and reflecting current NHS practice.

To address this data gap, associated NHS activity was systematically surveyed from nine UK-practising clinical experts' opinions to correspond to different stages of ES-SCLC disease progression and different treatment options relevant to this appraisal. Unit costs were derived from NHS reference costs[72] and PSSRU published costs.[73] Table 5.19, details the resource use for different treatment options and disease stages, including: on carboplatin-etoposide treatment; on atezolizumab plus carboplatin-etoposide treatment; on surveillance only; on atezolizumab monotherapy only. This was surveyed from clinicians as the expected average resource use of a patient in this stage of treatment and disease, therefore the average duration of treatment has already been considered here to align with the modelled time in different treatment stages. As a result, each cost is applied within the model once, as the patient moves into this stage. Table 5.20 presents the unit cost for each resource use element.

ERG comment: No explicit scenarios were located in the CS that tested the effect of the vial sharing assumption. However, since vial sharing does not apply to atezolizumab and can only occur with the chemotherapy, an assumption of vial sharing seems reasonable given that said chemotherapy will be commonly prescribed. Whilst scenario analysis does not include different vial sharing scenarios, there is a facility in the model (via switches) to explore the impact of four different scenarios: cohort based (w/wo vial sharing) and individual based (w/wo vial sharing). Choosing any one of these scenarios makes no material difference to the ICER.

The assumption made of 92.1% RDI (percentage of the planned dose actually administered) for treatment was found in IMPower133 and the ERG are not aware of any evidence to suggest this is unreasonable. In the company's economic model, an assumption of a lower RDI for atezolizumab would produce a lower ICER. The ERG also noted that varying the RDIs for carboplatin, etoposide and cisplatin has no impact at all on ICERs. The ERG feels that the RDI should ideally be linked to effectiveness and adverse event rates as well as costs. However, as the assumptions for RDI seem reasonable (as input parameters) neither individual scenarios nor base case adjustment were considered necessary.

Table 5.36: Resource use for ES-SCLC treatment and disease stages, per patient

Resource	Receiving carboplatin-etoposide treatment: first 4 cycles		Receiving atezolizumab plus carboplatin-etoposide treatment: first 4 cycles		Receiving surveillance only*: e.g. after 4 chemo cycles		Receiving atezolizumab monotherapy: after first 4 chemo cycles	
	Number of appointments (mean±SD)	% of patients requiring these appointments (mean±SD)	Number of appointments (mean±SD)	% of patients requiring these appointments (mean±SD)	Number of appointments (mean±SD)	% of patients requiring these appointments (mean±SD)	Number of appointments (mean±SD)	% of patients requiring these appointments (mean±SD)
Estimated time frame	4 cycles		4 cycles		3-4 months		4-5 months	
Outpatient visit	5.0 ± 1.5	100 ± 0	5.0 ± 1.5	100 ± 0	3.6 ± 2.1	86 ± 19	5.0 ± 2.1	100 ± 0
GP visit – surgery	1.9 ± 1.3	71 ± 39	1.9 ± 1.3	71 ± 39	2.3 ± 1.4	69 ± 38	1.5 ± 1.3	71 ± 39
GP visit – home	0.6 ± 1.5	68 ± 43	0.7 ± 0.8	68 ± 43	1.6 ± 1.3	66 ± 40	1.2 ± 1.3	68 ± 43
Cancer nurse visit	1.6 ± 1.4	67 ± 37	1.6 ± 1.4	75 ± 32	2.1 ± 1.3	54 ± 34	2.0 ± 1.5	61 ± 40
Community nurse visit	1.6 ± 1.5	64 ± 37	1.7 ± 1.5	68 ± 31	1.5 ± 1.4	47 ± 39	1.1 ± 1.1	61 ± 40
ECG	0.3 ± 0.5	64 ± 48	0.5 ± 0.5	66 ± 45	0.1 ± 0.4	50 ± 50	0.2 ± 0.4	51 ± 48
Chest X-ray	2.0 ± 1.9	78 ± 32	2.0 ± 1.9	75 ± 30	2.4 ± 1.3	74 ± 21	2.8 ± 1.7	71 ± 32
CT scan	1.6 ± 0.5	96 ± 9	1.6 ± 0.5	89 ± 20	1.6 ± 1.0	69 ± 28	1.9 ± 1.1	86 ± 20
MRI scan	0.4 ± 0.5	48 ± 45	0.4 ± 0.5	61 ± 48	0.3 ± 0.5	49 ± 48	0.4 ± 0.8	51 ± 48
Blood tests	4.0 ± 0	100 ± 0	4.4 ± 0	35 ± 0	6 ± 0	80 ± 0	2.2 ± 3.1	100 ± 0

Source: CS, Table 37.
CG = clinical guidance; CT = computerised tomography; ECG = electrocardiogram; GP = general practitioner; SD = standard deviation
*Monitored for disease progression but not receiving active treatment, i.e., after chemotherapy or atezolizumab treatment

Table 5.37: Unit costs for both PFS and PD health states

Resource	Unit cost	Unit	Source
Outpatient follow-up visit	£140.87	per visit	NHS Reference Costs 2017-2018, Outpatient attendance data, Consultant Led, Service code 800, Clinical Oncology[72]
GP surgery visit	£37.40	per visit	PSSRU 2018, p.134: Cost per patient contact lasting 9.22 minutes, including direct care staff costs (including qualifications)[73]
GP home visit	£93.28	per visit	PSSRU 2016, p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel - inflated to 2017/18 using the PSSRU HCHS index[73]
Cancer nurse visit	£42.02	per visit	Assumed to be 66.7% of community nurse cost
Community nurse visit	£63.00	per visit	PSSRU 2018, p.130: Cost per hour Band 8a[73]
ECG	£250.10	per visit	NHS Reference Costs 2017–2018, Complex ECG, HRG code EY50Z[72]
Chest X-ray	£106.88	per case	NHS Reference Costs 2017-2018, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)[72]
CT scan	£106.88	per case	
MRI scan	£202.64	per scan	NHS Reference Costs 2017–2018, Diagnostic Imaging, Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast, Outpatient, RD05Z[72]
Blood tests	£2.51	per test	NHS Reference Costs 2017–2018, Directly Accessed Pathology Services, Haematology, DAPS05[72]

Source: CS, Table 38.
CT = computerised tomography; ECG = electrocardiogram; GP = general practitioner; HCHS = hospital & community health services; HRG = Healthcare Resource Group; MRI = magnetic resonance imaging; NHS = National Health Service; PSSRU = Personal Social Services Research Unit.

The expected cost for a typical patient in each of these stages of treatment is as follows: on carboplatin-etoposide treatment = £1,191.97 expected to represent four cycles of treatment; on atezolizumab plus carboplatin-etoposide treatment = £1,232.53 expected to represent four cycles of treatment; on surveillance only = £1,216.40 expected to represent three to four months' treatment; on atezolizumab monotherapy only = £903.84 expected to represent four to five months' treatment.

The cost of prophylactic cranial irradiation (PCI) was also considered within the model and applied separately, with 90% of patients receiving PCI every three weeks for a maximum of five doses. A PCI frequency of three weeks was incorporated, since this was reported for the majority of the IMpower133 cohort.[74] A specific cost for PCI is not available in the NHS reference costs, therefore radiotherapy is costed in the model using the NHS reference costs for preparation and delivery of radiotherapy (codes SC47Z = £375.000 and SC22Z = £113.00.[72] The cost is applied for the PFS state only.

5.2.9.3 Cost of terminal care

A cost for terminal care is applied within the model. This is based on terminal care costs specific to SCLC.[75] These data are of limited applicability given that they are not recently published. Nevertheless, inflating to 2018 using PSSRU indices can express this at current pricess.[73] The average cost of palliative care reported was £3,495 in 1998 prices, which is here inflated using the PSSRU inflation index for Hospital and Community Health Services – giving £6,174.81 in 2018 prices.[73]

In response to clarification, the company stated that at a March 2019 Advisory board meeting, clinicians felt that terminal care costs derived from Oliver 2001[75] were too out-of-date to be reliable. Instead, the company decided to use the terminal care costs from TA484, inflated to 2018 costs i.e.£3,739 as a fixed cost.[65]

ERG comment: The ERG have been unable to find any reference to validate the frequency of PCI (55%) from the IMpower133 cohort which has been incorporated in the model. However, the company demonstrated, in a sensitivity analysis, that there was little effect on the ICER of quite a wider variation in PCI frequency (see Table 5.26).

At clarification, the ERG requested that the company review the way terminal care costs were incorporated into the model. The ERG are satisfied with the responses provided. In their response, the company stated that applying the cost per day, rather than a one-off cost is likely to favour the atezolizumab arm as those living longer will have more heavily discounted terminal care costs. The company also provided analysis whereby terminal care costs were removed altogether. This demonstrated the impact of selecting the most conservative of all scenarios for terminal care. The ERG are pleased that the company has demonstrated these effects and the chosen costs of terminal care seem reasonable in the light of other reviews (see below), even though they are based on a study which costed only certain elements of terminal care.

The Topetecan assessment report (NICE)[57] also provided cost estimates for terminal care which included drug costs, chemotherapy, monitoring costs, adverse events management and imaging costs to produce an estimate of palliative care of 4,977 at 2007/8 prices. When this is inflated to 2018 prices it produces an estimate of £6,022 which is similar to that used in the original CS. However, the revised assumptions now provided by the company appear to be more reflective of current costs estimates (even though documentation of the March 2019 Advisory board meeting has not been provided, meaning this can in no way be validated). They are also more conservative than the alternative scenarios. No change to base-case is implied.

5.2.9.4 Adverse event unit costs and resource use

Rates and severity of AEs are taken directly from the IMpower133 trial data. AEs may occur at any time during treatment exposure, therefore the associated AE costs are applied for the duration of time in which a patient is considered to be on treatment (Table 5.21). The AEs included were considered to be treatment related and were of Grade 3 to 5 or serious AEs, with an occurrence of 2% or more in either arm of the IMpower133 study (Table 15 of the CS). The weekly AE rate is calculated from the number of AEs divided by the total time at risk in weeks. This time at risk is the sum of the follow-up exposure for each patient in the trial, the median follow-up of 13.9 months is applied. The NMA was not able to map safety events, so cisplatin-etoposide AE rates have been matched to those for carboplatin-etoposide. According to UK-practising clinical experts, this is likely to be an underestimate of the AEs for cisplatin.

The number of AEs included in the model base case differs from the AEs reported in the adverse reactions section (Section B.2.10 of the CS). This is due to the economic model needing to calculate multiple occurrences of an AE per patient, and to then calculate the probability of an AE occurring. In contrast, when reporting the clinical study, the convention is to count only once any AE that occurs in an individual, at the highest grade for this patient.

The costs associated with AE management (Table 5.21) are multiplied by the rate of AEs and summed to calculate total AE cost by treatment arm. The safety analysis is based on 197 patients in the primary population per arm in IMpower133 who received any dose of study drug at the primary analysis time.

Grade 3-5 AEs and serious AEs have a treatment cost included in the model. Furthermore, AE data were only available for the treatment arms in IMpower133, so no comparison with cisplatin was possible via the NMA.

Table 5.38: Unit cost per AE used in the model

AE	Cost	Reference
Anaemia	£2,749	TA531 - inflated to 2016/17 using the PSSRU HCHS index[60, 73]
Diarrhoea	£182	NHS reference costs, WF01B, Consultant Led, Non-Admitted Face-to-Face Attendance, First, Gastroenterology[72]
Febrile neutropenia	£7,097	NICE TA531 - inflated to 2016/17 using the PSSRU HCHS index[60, 73]
Infusion-related reaction	£0	Clinical opinion
Leukopenia	£377	NICE TA531 - inflated to 2016/17 using the PSSRU HCHS index[60, 73]
Neutropenia	£601	Brown 2013 (inflated to 2016-17 using PSSRU inflation indices[73, 76]
Neutrophil count decreased	£449	NICE TA428[59]
Pancytopenia	£601	Assumed same as neutropenia
Platelet count decreased	£449	Assumed same as neutrophil count decreased
Pneumonia	£2,784	TA531 - inflated to 2016/17 using the PSSRU HCHS index[60, 73]
Thrombocytopenia	£124	NICE TA484, NICE TA520, NICE TA525[34, 35, 65]
Vomiting	£182	NHS reference costs, WF01B, Consultant Led, Non-Admitted Face-to-Face Attendance, First, Gastroenterology[72]

AE	Cost	Reference
White blood cell count decreased	£449	NICE TA484, NICE TA520, NICE TA525[34, 35, 65]
Source: CS, Table 39. AE = adverse event.		

ERG comment: The ERG has some concerns over the unit costs used for adverse events. This being said, the impact of using alternative unit cost estimates on the final ICER is very limited. Nevertheless, alternative unit cost estimates could have been used for diarrhoea, neutrophil count decreased, platelet count decreased, thrombocytopaenia, vomiting and white blood cell count decreased. In the case of decreased counts of neutrophil, platelets and white blood cell counts the CS quotes NICE TA428[59] as the source. However, on review of this source, the correct unit cost appears to have been £179.83 at 2014/15 prices – which when inflated to 2018 prices – yields an estimate of £186.50. Unit costs estimated for diarrhoea and vomiting were based on NHS reference costs, WF01B, Consultant Led, Non-Admitted Face-to-Face Attendance, First, Gastroenterology. However, alternative more costly estimates were used in TA531 (equating to £998 for diarrhoea and £788 for vomiting).[60] It is not clear why the company chose the specific unit costs for adverse events. However, using any of the suggested alternatives has minimal impact on the resulting ICER and so no specific scenarios are necessary to model changes in assumptions.

The ERG base case will use £998 for diarrhoea and £788 for vomiting adverse events to demonstrate the impact of higher adverse event unit costs. See Section 5.3 of this report.

5.2.9.4 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

The full list of variables applied in the model is reported in Table 5.22.

Table 5.39: Summary of variables applied in the model base-case (CS)

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General model parameters			
Time horizon	20 years	Fixed	B.3.2
Discount rate - efficacy	3.5%	Fixed	
Discount rate - costs	3.5%	Fixed	
Population parameters			
Age	63.7 years	Fixed	B.2.3
Body weight	75.5 kg	Fixed	B.3.5.1
Height	168.24 cm	Fixed	CEM
Body surface area	1.84 m2	Fixed	B.3.5
Utilities – base-case – IMpower133			
≤ 5 weeks before death on treatment	0.65	N/A	B.3.4.1
> 5 & ≤ 15 weeks before death on treatment	0.73	N/A	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
> 15 & ≤ 30 weeks before death on treatment	0.72	N/A	
> 30 weeks before death on treatment	0.73	N/A	
≤ 5 weeks before death off treatment	0.33	N/A	
> 5 & ≤ 15 weeks before death off treatment	0.53	N/A	
> 15 & ≤ 30 weeks before death off treatment	0.70	N/A	
> 30 weeks before death off treatment	0.75	N/A	
OS extrapolation approach			
Control and atezolizumab arms were both extrapolated using a fully parametric log-logistic approach based on IMpower133 trial data	Survival curves	N/A	B.3.3.3
Drug acquisition costs per pack (list price)			
Atezolizumab; 20mL/1,200mg	[redacted]	Fixed	B.3.5.1
Carboplatin; 5mL/50mg	£3.18	Fixed	
Carboplatin; 60mL/600mg	£28.24	Fixed	
Etoposide; 5mL/100mg	£2.30	Fixed	
Etoposide; 25mL/500mg	£9.65	Fixed	
Cisplatin; 10mL/10mg	£1.84	Fixed	
Cisplatin; 100mL/100mg	£10.13	Fixed	
Drug administration costs – per cycle			
Atezolizumab plus carboplatin-etoposide	£1,227.41	95% CI of point estimate assumed (Normal distribution)	B.3.5.1
Carboplatin-etoposide	£37.80		
Cisplatin-etoposide	£28.30		
Drug administration costs			
Daycase and Reg Day/Night: Deliver more Complex Parenteral Chemotherapy at First Attendance - SB13Z: for first administration treatments	£309.22	N/A	B.3.5.1.2
Daycase and Reg Day/Night: Subsequent Elements of Chemotherapy Cycle -	£312.34	N/A	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
SB15Z: for subsequent elements of the cycle, i.e. etoposide on Day 2 and 3.			
SB12Z; Deliver simple parenteral chemotherapy at first attendance as outpatient: for atezolizumab monotherapy.	£173.99	N/A	
Daycase and Reg Day/Night: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (SB14Z): for cisplatin-etoposide.	£374.52	N/A	
Resource use costs			
Typical resource use on carboplatin-etoposide treatment	£1191.97	95% CI of point estimate assumed (Normal distribution)	B.3.5.2
Typical resource use on atezolizumab plus carboplatin-etoposide treatment	£1232.53		
Typical resource use on surveillance only	£1216.40		
Typical resource use on atezolizumab monotherapy only	£903.84		
Terminal care cost			
Terminal care cost	£6,174.81	95% CI of point estimate assumed (Normal distribution)	B.3.5.2
Adverse event management costs			
Anaemia	£2,749	95% CI of point estimate assumed (Normal distribution)	B.3.5.3
Diarrhoea	£182		
Febrile neutropenia	£7,097		
Infusion-related reaction	£0		
Leukopenioa	£377		
Neutropenia	£601		
Neutrophil count decreased	£449		
Pancytopenia	£601		
Platelet count decreased	£449		
Pneumonia	£2,784		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Thrombocytopenia	£124		
Vomiting	£182		
White blood cell count decreased	£449		
Source: CS, Table 40. CI = confidence interval; N/A = not applicable; OS = overall survival			

5.2.10 Cost effectiveness results

5.2.10.1 Base-case deterministic results

As reported in the deterministic base-case cost effectiveness results of treatment with atezolizumab plus carboplatin and etoposide with PAS compared with just carboplatin and etoposide included an ICER of [redacted] per quality adjusted life year (QALY) gained. The main share of the [redacted] QALY increment stemmed from the large accrual of QALYs in the PFS/on treatment health state. The incremental costs of atezolizumab plus carboplatin and etoposide compared with carboplatin and etoposide were [redacted]. However, following response to clarification letter stage 2, these values changed to an increased ICER of [redacted] with a lower QALY increase of [redacted] and a cost increase of [redacted] (Table 5.23). [43] This table also shows the comparison with cisplatin plus etoposide. The probabilistic sensitivity analysis (PSA) results were similar with ICERs about 1% and 8% higher, of [redacted] and [redacted], versus carboplatin plus etoposide and cisplatin plus etoposide respectively.

Table 5.40: Company's deterministic base-case cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALY	Incremental ICER (£/QALY)
Atezolizumab plus carboplatin-etoposide	[redacted]	1.53	1.09				
Carboplatin-etoposide	[redacted]	1.21	0.83	[redacted]	0.32	0.25	[redacted]
Cisplatin-etoposide	[redacted]	1.20	0.82	[redacted]	0.34	0.26	[redacted]
Source: Table 8, response to clarification letter stage 2.[43] ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = Quality adjusted life years.							

ERG comment: Although the company argued that cisplatin plus etoposide was not an appropriate comparator they did make the comparison. This analysis showed that cisplatin plus etoposide would be dominated by carboplatin plus etoposide and thus, if this is credible, only the ICER versus carboplatin plus etoposide need be considered. This conclusion would be the same regardless of deterministic or probabilistic analysis.

5.2.11 Company's sensitivity analyses

5.2.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted with 1,000 iterations to determine the uncertainty surrounding the base case ICERs. Results are set out in Table 5.24 below. All model variables that had an assigned distribution are presented in Table 5.22 of this report. Uncertainty was characterised by standard error. Atezolizumab acquisition costs were fixed, however since carboplatin and etoposide costs are derived from eMIT these have a reported variance.[71]

Table 5.41: Company base-case probabilistic cost effectiveness results at PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Atezolizumab plus carboplatin-etoposide	[redacted]	1.54	1.09	[redacted]	0.33	0.26	£49,045
Carboplatin-etoposide	[redacted]	1.21	0.84				
Source: ID1504 Atezolizumab Roche CE model PAS price v2 070519 JM [PAS]							

The incremental cost effectiveness plane and the corresponding cost effectiveness acceptability curves (with PAS) are shown in Figure 5.5 and Figure 5.6.

The probabilistic base-case ICER was £49,045 which is comparable to the deterministic base-case ICER (£49,588) see Table 5.23.

Figure 5.5: Scatterplot form the probabilistic sensitivity analysis iterations

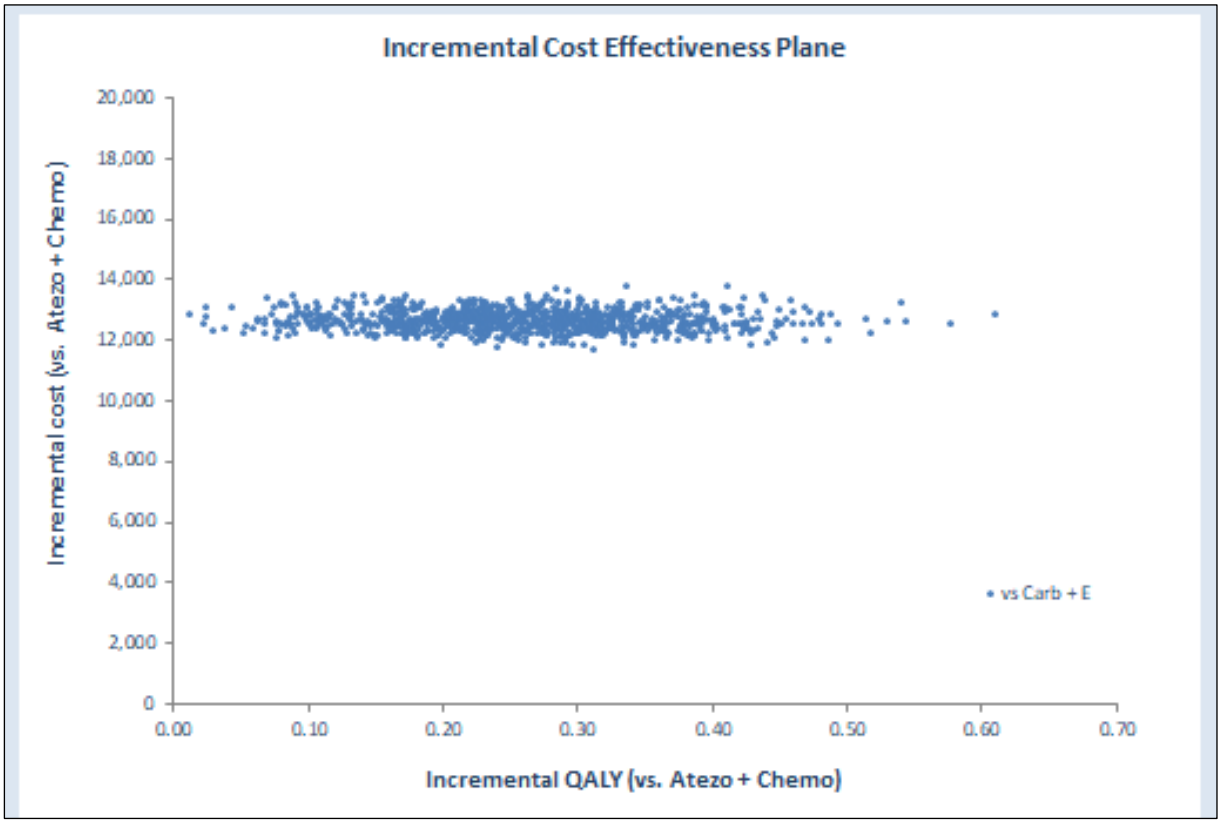
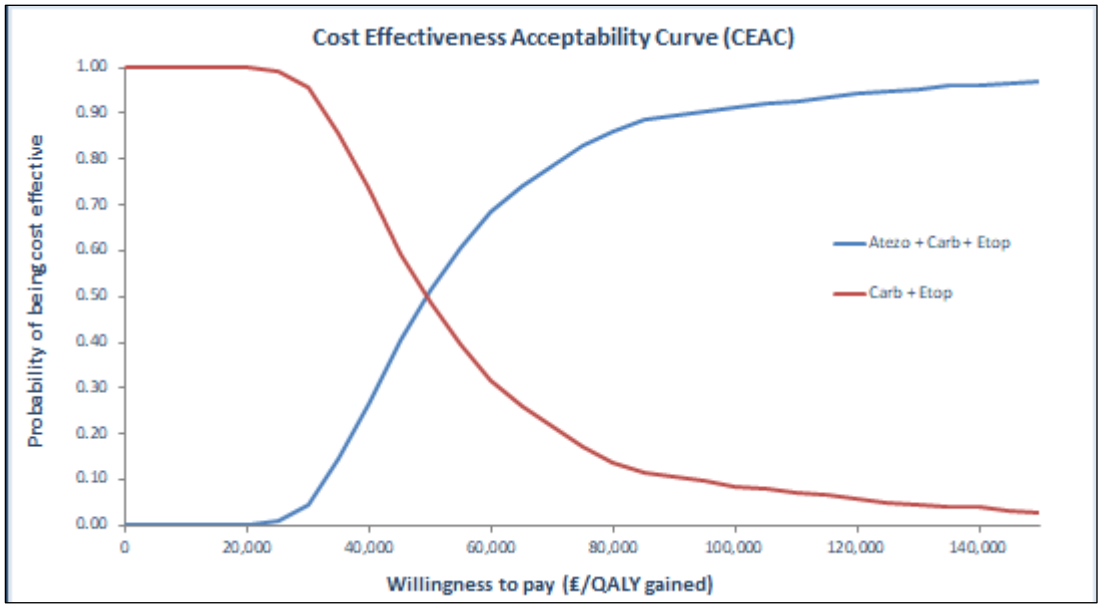


Figure 5.6: Cost effectiveness acceptability curve

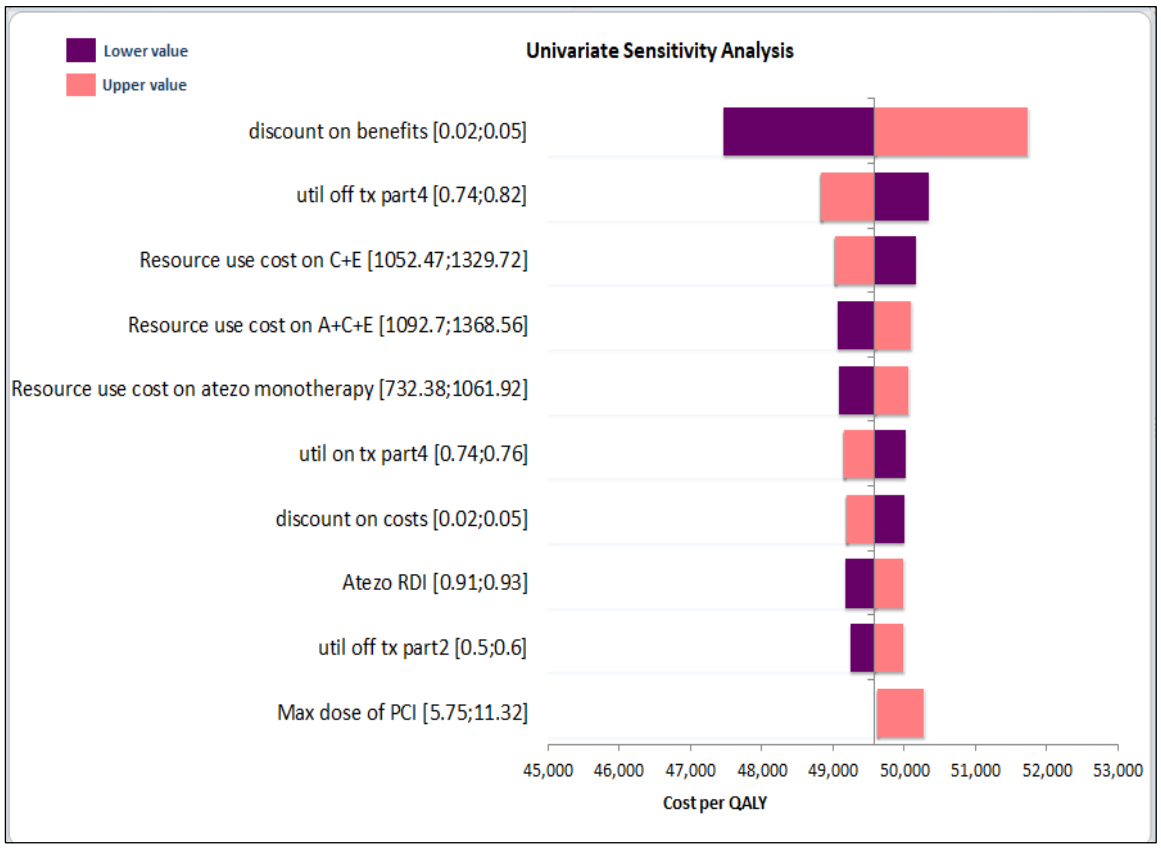


5.2.11.2 Deterministic sensitivity analysis

The results of the deterministic sensitivity analysis are shown below in the tornado diagram in Figure 5.7. The output variables have varied around the base-case value, subject to the influence of each variable on the ICER (as listed in Table 5.22 of this report).

The most impactful inputs are the utility off treatment immediately before death and the discounting of benefits.

Figure 5.7: Tornado diagram – company's preferred assumptions



5.2.11.3 Scenario analyses

The original CS presented 15 separate sensitivity analyses (Table 46, CS).[1] In addition to the 15 separate sensitivity analyses, the company also provided scenario analyses associated mostly with varying parametric curves for OS, PFS and TTOT and varying the time horizon (See Table 48, CS).[1] However, none of these analyses were updated with the response to clarification that incorporated the updated OS data from [redacted].[43] They were only available in the model that was submitted with the response to clarification, named ID1504 Atezolizumab Roche CE model PAS price v2 070519 JM [PAS]. None of the sensitivity analyses resulted in major variation in the resulting ICER, one producing the larges variation being the discount rate applied to benefits (Table 5.25). The scenario analyses that produced the largest variation in the ICER were those related to TTOT, but since none of these were based on parametric models that produced a good fit either statistically or visually (see Section 5.3), they have not been reproduced here. Those for OS that are the lowest and highest for each of the intervention and the comparator are shown in Table 5.25. This Table also contains scenario analyses reported in response to the ERG request for clarification.[43]

ERG comment: The ERG considered the sensitivity and scenario analyses to be appropriate. Only those related to OS parametric model choice and which had at least a reasonable fit to the data (Table 5.6) produced substantial variation in the ICER. Although the log normal is not very plausible given its poor statistical fit (Table 5.6) and visual fit, for the intervention the generalised gamma produced a fit that was not too inferior to the base-case i.e. log-logistic. It was only because of the superiority of the Weibull and that it was not further considered for the ERG base-case (see Section 5.3). The Gompertz lacked plausibility because it produced a relatively poor statistical fit (Table 5.6) and visual fit.

Table 5.42: Sensitivity and scenario analyses conducted by the company

Parameter modified	Base-case value	Lower value	Lower ICER	Upper value	Upper ICER	Source
Company's sensitivity analysis which resulted in lowest and highest ICERs						
Discounted benefits – produced both the lowest and highest ICERs of any scenario	3.50%	2%	£47,456	5%	£51,720	Source: ID1504 Atezolizumab Roche CE model PAS price v2 070519 JM [PAS]
Company's scenarios which resulted in lowest and highest ICERs						
Overall survival model without using the KM curve (Atezolizumab)	Log-logistic	Log normal	£35,260	Generalised gamma	£62,317	Source: ID1504 Atezolizumab Roche CE model PAS price v2 070519 JM [PAS]
Overall survival models using KM with parametric curve in the tail of the distribution (Atezolizumab)	Log-logistic	KM with Log-normal tail	£29,881	KM with Weibull tail	£62,718	

Parameter modified	Base-case value	Lower value	Lower ICER	Upper value	Upper ICER	Source
Overall survival model without using the KM curve (comparator)	Log-logistic	Gompertz	£41,653	Log-normal	£68,986	
Overall survival models using KM with parametric curve in the tail of the distribution (comparator)	Log-logistic	KM with Weibulll tail	£39,068	KM with Log-normal tail	£75,568	
Company scenarios following suggestions from ERG						
Survival extrapolation using only Flatiron data after 22 months	Parametric extrapolation based on IMpower and Flatiron data	Generalised gamma distribution	£45,873	Log-logistic distribution	£53,191	Source: Table 19 response to clarification letter stage 2.[43]
Proportion of patients receiving subsequent therapy	Source: IMpower133	Source: Clinical opinion Nov-18	£49,759	Source: Clinical opinion Mar-19	£49,789	Source: Table 21 response to clarification letter stage 2.[43]
Changing the maximum duration of chemotherapy	4 cycles	NA	NA	6 cycles	£49,476	Source: Table 24 response to clarification letter stage 2.[43]
Proportion of patients with PCI	0.55	0.11	£49,581	0.91	£49,594	Source: Table 25 response to clarification letter stage 2.[43]
Frequency of PCI	3.00	1.42	£49,587	4.56	£49,724	
Maximum dose of PCI	5.00	5.75	£49,614	11.32	£50,238	
ICER = incremental cost effectiveness ratio; KM = Kaplan Meier; PCI = prophylactic cranial irradiation.						

5.2.11.4 Subgroup analyses

In the clarification letter the ERG requested that a subgroup analysis be conducted based on the results of the "… [redacted]. In their response of 28 May 2019, the company declined to do so citing limitations in the data.

ERG comment: The ERG would contend that, given evidence of variation in effectiveness according to subgroup, particularly applying a cut-off at 1% expression (see Section 4.2.7 of this report), that the subgroup analysis of cost effectiveness is still relevant and particularly given the possibility that atezolizumab might cost effective as shown in the ERG base-case (See Section 5.3 of this report).

5.2.12 Model validation and face validity check

The company validated the model in the following ways, as described in Section B.3.10 of the CS:

1) Multiple means to validate time to event distribution including the use of clinical expert opinion
2) Compliance with NICE requirements
3) Consistency with previous cancer immunotherapy models and lung cancer NICE submissions
4) Clinical expert opinion to validate the overall model approach
5) Quality control via a team external to Roche

ERG comment: The ERG consider that the model was generally validated appropriately. In particular, there was explicit employment of clinical expert opinion on model structure as well as many of the inputs including those that were particularly influential on the ICER i.e. OS distributions as reported in Appendix K of the CS.[43] The process as recommended by the NICE DSU was also followed, although the judgement of the ERG was different to that of the company.[54] The model also adheres to the NICE reference case.[53] Some errors and violations, in accordance with Kaltenhaler 2016 were identified by the ERG, although the effect on the ICER of their correction was relatively small (see Section 5.3).[77] The ERG also differed in their judgement regarding the validity of the time to death approach for the incorporation of utilities largely because of a lack of statistical validation in comparison to the more established approach (see Section 5.2.8).[63]

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations discussed in Section 5.2 of this report (summarised in Table 5.26), the ERG defined a new base-case. This base-case included multiple adjustments to the company base-case submitted with the latest OS data i.e. 'ID1504 Atezolizumab Roche CE model list price v2 070519 JM [ACIC]'. These adjustments are subdivided into three categories (derived from Kaltenthaler 2016).[77]

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Fixing errors

1) PFS in first cycle for comparator set to 1

Fixing violations

2) Removed formula to ensure OS for intervention always being at least as high as comparator so that, according to the parametric model, it might for some cycles be lower than for the comparator. The one exception is the scenario (1) of additional exploratory analyses because of implausible crossing of the intervention and comparator survival curves.

Matters of judgment

3) Weibull as opposed to log-logistic chosen for parametric model for OS for intervention and comparator
4) Utility estimated as a function of progression status as opposed to time to death
5) AE disutilities from literature incorporated

Table 6.1 in Section 6 shows how individual adjustments impact the results plus the combined effect of all above mentioned adjustments simultaneously, resulting in the (deterministic) ERG base-case.

Table 5.43: Company and ERG base-case preferred assumptions

Base-case preferred assumptions	Company-base case	Justification*	ERG	Justification for change
PFS in first cycle for comparator	PFS not starting at 1 in the first cycle for comparator	This appears to be a mistake in that it is 1 for atezolizumab plus carboplatin-etoposide	PFS starts at 1 in the first cycle for comparator	In order to achieve consistency between intervention and comparator
OS for intervention relative to comparator	OS for intervention always being at least as high as comparator	Based on clinical expert opinion	Removed formula to ensure OS for intervention always being at least as high as comparator	Section 5.2.6
OS extrapolation model	Log-logistic chosen for intervention and comparator	Visual and statistical fit External validation of comparator arm using the Flatiron study, itself validated by clinical expert opinion	Weibull chosen for intervention and comparator	Section 5.2.6
Utility estimation	Based on time to death	This is in line with previous NICE appraisals, and clinical expert opinion	Based on progression status	Section 5.2.8
AE disutilities	Not included	Effect already included in time to death approach	Included	Section 5.2.8

AE = adverse event; OS = overall survival; PFS = progression free survival

5.3.1 ERG base case results

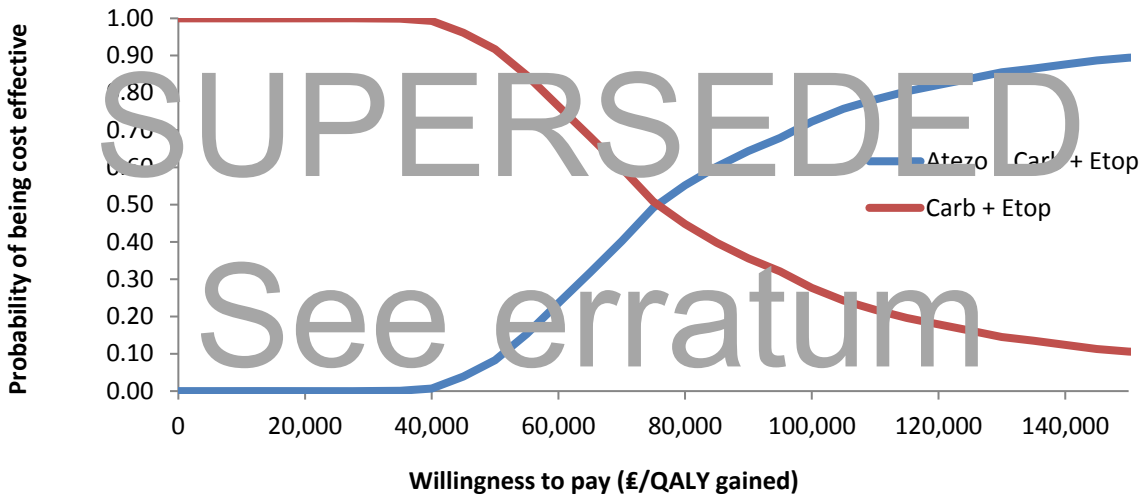
The results of the deterministic ERG base case showed that incremental costs were [redacted] and incremental QALYs were 0.17 (Table 5.27). This result is an ICER of £75,585, which was mainly driven by using the Weibull distribution for OS in both intervention and comparator arms instead of Log-logistic.

Compared with the deterministic ERG base-case results, the ERG PSA with 5,000 iterations resulted in higher incremental QALYs and slightly higher incremental costs, which resulted in an ICER that was less than 2% higher than the deterministic result of £76,930. The cost effectiveness acceptability curve showed that atezolizumab approximately had a 0.0% and 8.3% probability of being cost effective at willingness-to-pay (WTP) thresholds of £30,000 and £50,000 respectively (Figure 5.5).

Table 5.44: ERG base-case results

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Deterministic ERG-base case					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,585
Carb + Etop	[redacted]	[redacted]			
Probabilistic ERG base-case					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.16	£76,930
Carb + Etop	[redacted]	[redacted]			
Atezo = atezolizumab; Carb = carboplatin; ERG = Evidence Review Group; Etop = etoposide; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year.					

Figure 5.8: ERG base-case cost effectiveness acceptability curve



5.3.2 Additional exploratory analyses performed based on the ERG base-case

The ERG also conducted exploratory analyses based on the ERG base-case and as a matter of judgement:

1) Weibull model for OS for intervention and log-logistic for comparator, as discussed in Section 5.2.6. This does not include element (2) of the ERG base-case. This is because of implausible crossing of the intervention and comparator survival curves.
2) Switch from K-M to parametric curve for PFS at 15 instead of 5 months, as discussed in Section 5.2.6
3) Ensure that TTOT does not sink lower than PFS after 14 months (limit of K-M data), as discussed in Section 5.2.6
4) Unit cost of diarrhoea £998 instead of £182, as discussed in Section 5.2.9
5) Unit cost of vomiting £788 instead of £182, as discussed in Section 5.2.9

The results are shown in Table 6.2 in Section 6.

5.4 Conclusions of the cost effectiveness section

The CEA was structured as a three-health state partitioned survival analysis (PartSA) model. These three health states were consistent with previous appraisals accepted by NICE to evaluate first-line lung cancer, as well as other oncology indications: "PFS", "Progressed Disease (PD)" and "Death". The population in the CEA was first-line, adult ES-SCLC patients, which is consistent with the ITT population of the IMpower133 study, the NICE final scope for this appraisal, the appraisal decision problem and the anticipated EMA marketing authorisation (the draft SmPC provided in a separate document). The intervention was atezolizumab with carboplatin and etoposide, given for up to four cycles and the comparator was carboplatin and etoposide, given for up to four cycles. In response, the company provided the results of a scenario analysis, which showed a decrease in the ICER. Also in a scenario analysis, comparison with cisplatin instead of carboplatin was employed. This was performed as a full incremental analysis in the response to clarification letter. However, as described in Section 5.2.3, the company argued that the comparison was inappropriate due to cisplatin being indicated for only borderline LS-SCLC patients. The economic model uses a 20-year time horizon in the base case. Costs and health outcomes are discounted at 3.5% in the base case and the perspective of the NHS and personal social services (PSS) is assumed.

The company stated that they followed step by step guidance from the NICE DSU TSD 14 to identify the best fit parametric extrapolations for OS, PFS and TTOT in the model base case.[77] For TTOT, in both arms of the pivotal trial, no extrapolation was needed for either carboplatin or etoposide treatments, since the time to treatment discontinuation had been observed for the entire cohort during the 12-month follow up period. Therefore, parametric extrapolation was only required for TTOT for atezolizumab. Because TTOT extrapolation only applied to the intervention, a test for proportional hazards was not required. For OS and PFS, the company first tested whether the proportional hazard assumption held between treatment arms by inspecting the log-cumulative hazard (odds, and standardised normal curve) plots and computing the log cumulative hazard over the log of time. Based on those tests, the proportional hazard assumption was rejected for both OS and PFS because the curves cross each other at multiple time points. Therefore, separate parametric time-to-event models were fitted to each treatment arm for each endpoint, OS, PFS and TTOT. Visual inspection and statistical fit (AIC and BIC) were used to selects the most relevant extrapolations. The plausibility of extrapolation beyond trial data was also assessed by checking the crossing of curves (OS should not cross PFS or TTOT) and, for OS comparison external validation with expert opinion and/or real-world data and general mortality rates.

For PFS, the log-logistic curve provided the best statistical fit of the parametric function to the actual data. This continued to be the case with the [redacted] data: [redacted] The company noted that all the standard parametric curves provided a similarly poor visual fit to the Kaplan-Meier data, as there were steep drops within the first five months at the time of each scan. [redacted], at this specific time point approximately 50% of patients remain at risk in both arms. No external validation was performed for PFS.

For OS, in terms of statistical fit, the CS stated the best overall fit to the existing OS data would be either Weibull, Gompertz, generalised gamma or log-logistic extrapolations for the atezolizumab arm and Weibull, Gompertz or generalised gamma curves for the comparator arm. The company argued in the CS that the visual fit of the Weibull, Log-logistic, Gompertz and generalised gamma extrapolation curves was good enough not to use the KM data even for the initial period, as they did for PFS. In response to clarification letter stage 2 and the data from [redacted] the company stated that the best fit was obtained from the Weibull and log-logistic extrapolations. For the comparator, the company

finally chose the log-logistic from the set of parametric curves on the basis of external validity of the extrapolations by comparison with data from the Flatiron study, validated by clinical expert opinion, although it did also provide the best statistical fit based on the data from [redacted].[39] For the intervention, the company cited the clinical expert opinion as to long term survival and, on this basis, chose the log-logistic model, although the Weibull had a minor advantage in terms of statistical fit based on the data from [redacted].

For TTOT, for atezolizumab only, as explained above, the generalised gamma provided the best statistical fit of the parametric function to the actual data. The company noted that all the standard parametric curves provided a similarly poor visual fit to the Kaplan-Meier data. [redacted]. No external validation was performed for TTOT.

The main source of evidence on treatment adverse events (AEs) used for atezolizumab was the IMpower133 trial data. AEs were included in the model if they had an occurrence of more than 2% in either arm in the IMpower133 trial and a severity of Grade 3-5 or if they were classified as serious AEs. AEs were included in the model in terms of their costs and not their impact on health-related quality of life (HRQoL) in the CS. The company argued that any AE disutility has already been incorporated into the base case health state utilities through the trial derived EQ-5D utilities estimated as a function of time to death only, and incorporating an additional disutility could be considered double counting.

For utilities, the company used the EQ-5D-5L data from the IMpower133 trial. In line with NICE's position statement on EQ-5D-5L data, the obtained data were mapped to EQ-5D-3L using the indirect mapping approach according to van Hout et al. 2012.[58] The company stated that utility was incorporated into the model using the same time to death approach as has been accepted during previous NICE appraisals of lung cancer treatments, this was validated [redacted] (Appendix K).[39] In response to the request for clarification, the company included AE disutilities in a scenario analysis.

The base-case model includes the actual dosing from IMpower133 study and vial sharing assumptions (i.e., no wastage) for the administration of chemotherapy drugs in the model. Atezolizumab is given at a fixed dose. Relative dose intensity has been applied according to the IMpower133 study to account for missed doses. Since carboplatin, etoposide and cisplatin are all available to the NHS as generic medicines, prices are taken from eMIT, which reports the average price paid by the NHS for a genericmedicine.[71] The only other medicine price included in this submission was for atezolizumab which is presented inclusive of the confidential PAS discount. Subsequent treatment costs have been incorporated into the model according to the IMpower133 study as this was deemed to balance the efficacy and cost estimates from the study appropriately. Drug administration costs were also included based on NHS reference costs. The cost of PCI was also considered within the model and applied separately, with 90% of patients receiving PCI every three weeks for a maximum of five doses with the NHS reference cost for radiotherapy used. A cost for terminal care is applied within the model. In the CS, this had been based on terminal care costs specific to SCLC from the literature. In response to clarification, the company stated that at a March 2019 Advisory Board meeting, clinicians felt that these terminal care costs were too out of date to be reliable. Instead the company decided to use the terminal care costs from TA484, inflated to 2018 costs.[65]

As reported in the deterministic base-case, cost effectiveness results of treatment with atezolizumab plus carboplatin and etoposide with PAS compared with just carboplatin and etoposide resulted in an ICER of [redacted] per quality adjusted life year (QALY) gained. The main share of the [redacted] QALY increment stemmed from the large accrual of QALYs in the PFS/on treatment health state. The

incremental costs of atezolizumab plus carboplatin and etoposide compared with carboplatin and etoposide were [redacted]. However, following response to clarification letter stage 2, these values changed to an increased ICER of [redacted] with a lower QALY increase of [redacted] and a cost increase of [redacted]. The ICER for atezolizumab plus carboplatin and etoposide versus cisplatin and etoposide was lower at [redacted] with higher cost and lower QALYs for this cisplatin in comparison to carboplatin. This implies that cisplatin would be dominated by carboplatin plus etoposide. The probabilistic sensitivity analysis (PSA) results were similar with ICERs about 1% and 8% higher, of [redacted] and [redacted], versus carboplatin plus etoposide and cisplatin plus etoposide respectively. Scenario analysis revealed that the ICER was most sensitive to parametric model for TTOT for atezolizumab. However, none of these models provided a good visual or statistical fit and the one that fit best i.e. the generalised gamma produced an ICER under £50,000. The next most influential input is parametric model for OS for atezolizumab and the Gompertz provided a plausible alternative to the log-logistic and did produce an ICER well in excess of £50,000. However, the Weibull did provide the best statistical fit and, in the view of the ERG, is the most clinically plausible.

In response to the ERG request that a subgroup analysis be conducted based on the results of the "…[redacted]" the company declined to do so citing limitations in the data.[43]

The ERG considers the population, intervention and comparator considered by the company in their CEA to be largely appropriate. However, as the company identified in the response to clarification letter, there might be a subgroup of borderline LS-SCLC patients for whom cisplatin plus etoposide instead of carboplatin plus etoposide would be appropriate. On this basis ERG would concur that cisplatin plus etoposide is probably not an appropriate comparator for the index population. Also, the company showed that if cisplatin is compared with atezolizumab and carboplatin that it would be dominated. However, no data on the effectiveness of atezolizumab in this 'borderline population' was provided either from the IMpower133 trial or any other source. Therefore, the ERG would argue that, if such a borderline LS-SCLC population exists, then one can make no evidence-based decision as to whether atezolizumab is cost effective in this population.

For PFS, the ERG considers the choice of model appropriate and, although the point at which the KM curve is replaced by the log-logistic model is arbitrary, there is little difference in the ICER (£35.92 on the company base-case) by replacing with log-logistic for the whole time horizon. The ERG has a similar opinion of the choice of model for TTOT, although the difference between ICERs is not so easily dismissed, it being £1,026 lower on the company base-case by replacing with generalised gamma for the whole time horizon. Nevertheless, this implies that the model chosen by the company (KM for first 14 months) is conservative with regards to the cost effectiveness of atezolizumab. For OS and for the comparator, the ERG would disagree with the company judgement regarding clinical plausibility. Given that the log-logistic already overestimates OS, as estimated in the Flatiron study, and the Flatiron study probably overestimates OS compared to UK clinical practice, the log-logistic almost certainly overestimates OS compared to UK clinical practice. In contrast, the Weibull, which, whilst it also overestimates OS in comparison the Flatiron study for years 1 to 2, it provides estimates that are almost identical to the Flatiron study for years 3 to 5. Therefore, its overestimation of UK clinical practice is likely to be less than that derived via the log-logistic. Therefore, the ERG would argue that the Weibull is more likely to be clinically plausible and it provides nearly as good a statistical fit, which is why it has been chosen for the comparator in the ERG base-case. For the intervention, the ERG also disagrees with the choice of the log-logistic on the basis of clinical plausibility as well as it having a marginally worse statistical fit than the Weibull. The main reason for this judgement is that there is in fact no real-world data by which any estimates can be externally validated and the ERG questions the validity of

clinical expert opinion as the effect of a treatment for which they would have had no clinical experience. However, as with the comparator, one can compare the percentages surviving at each of the five time points from the clinical experts with those from the log-logistic and the model with the best statistical fit, the Weibull. When one does that it can be seen that the values for the Weibull are all higher than those elicited from the clinical experts, but by more than the log-logistic only in year 1 and by less in all other years. Therefore, the ERG would argue that the Weibull is more likely to be clinically plausible and it provides a better statistical fit, which is why it has been chosen for the intervention in the ERG base-case.

The ERG considers that the company appropriately identified the AEs that were most important to include in terms of the potential impact on cost and utility. However, the ERG believes the justification provided by the company stating that AEs are implicitly captured by EQ-5D is questionable. According to NICE TSD 12 it is important to include decrements on HRQoL associated with AEs of at least Grade 3.[63] The ERG therefore included AE disutilities. The ERG also questions the validity of the 'time to death' method employed by the company, although in the clarification letter response, the company provided references to previous STAs that used the 'time to death' approach. The ERG would argue that, despite use of the approach in previous STAs, it still remains unvalidated as evidenced by no mention in any of the NICE TSDs. It neglects the more established method of using progression status to determine utility value, it incorporates the effect of being on or off treatment with questionable clinical validity especially not having statistically tested the effect of both treatment and progression status and it is implemented by the arbitrary division into four time to death categories. In response to clarification letter, the company failed to provide what the ERG requested i.e. full statistical analysis of various models including both on/off treatment and progressed/not progressed as well as time to death as a continuous variable. Therefore, the ERG chose the more conservative approach of measuring utility as a function of progression status and not time to death in the ERG base-case.

The ERG believe that costs were generally estimated in a way that seemed plausible. The ERG has some concerns over the unit costs used for adverse events. This being said, the impact of using alternative unit cost estimates on the final ICER is very limited. However, alternative more costly estimates were used in TA531 (equating to £998 for diarrhoea and £788 for vomiting). It is not clear why the company chose the specific unit costs for adverse events.[60]

The ERG base-case resulted in an ICER of £75,585 for atezolizumab plus carboplatin and etoposide versus carboplatin and etoposide only. This increase from the company base-case is due mainly to the decrease in the incremental QALYs from 0.25 to 0.17. Most of this decrease is due to the Weibull instead of the log-logistic, which by itself resulted in an ICER of £69,290. None of the scenario analyses chosen by the ERG made much difference and none decreased the ICER to below the £50,000 threshold.

Finally, the ERG would contend that, given evidence of variation in effectiveness according PD-L1 subgroup, the subgroup analysis of cost effectiveness is still relevant and particularly given the possibility that atezolizumab might not be cost effective for the whole population as shown in the ERG base-case.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.1 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.2. These are all conditional on the ERG base-case.

Table 6.1: Deterministic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,588
Carb + Etop	[redacted]	[redacted]			
Fixing error (Corrects PFS not starting at 1 in first cycle)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,577
Carb + Etop	[redacted]	[redacted]			
Fixing error (Corrects OS for intervention always being at least as high as comparator)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,588
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Uses Weibull for OS for both intervention and comparator)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.18	£69,260
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Utility is a function of progression status and not time to death)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.23	£53,724
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (AE disutilities from literature)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,664
Carb + Etop	[redacted]	[redacted]			
ERG base-case					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,585
Carb + Etop	[redacted]	[redacted]			

AE = adverse event; Atezo = atezolizumab; Carb = carboplatin; CS = company submission; ERG = Evidence Review Group; Etop = etoposide; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year.

Table 6.2: Deterministic scenario analyses conditional on ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Matter of judgement (Weibull for intervention and log-logistic for comparator for OS)*					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.14	£67,654
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Ensures that TTOT does not sink lower than PFS after 14 months (limit of K-M data))					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£77,891
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Change time at which PFS moves from K-M to Log-logistic)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,585
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Diarrhoea unit cost £998)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,631
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Vomiting unit cost £788)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,601
Carb + Etop	[redacted]	[redacted]			

Atezo = atezolizumab; Carb = carboplatin; ERG = Evidence Review Group; Etop = etoposide; ICER = incremental cost effectiveness ratio; K-M = Kaplan-Meier; PFS = progression-free survival; QALY = quality-adjusted life year; TTOT = time to of treatment.
*Excluding element (2) of ERG base case because of implausible crossing of the intervention and comparator survival curves.

7. END OF LIFE

The company claims that: "Roche considers the survival gain reported for atezolizumab plus carboplatin-etoposide to meet the end-of-life (EOL) criteria within this appraisal" (CS, page 53).[1]

For the first EOL criterion (short life expectancy, normally less than 24 months), this is based on data from the National Lung Cancer Audit (NLCA) from 2004–2011, which reported a median survival for all ES-SCLC patients (ECOG PS 0–4) of just four months.[11] The population described in the final NICE scope includes "Adults with untreated extensive-stage small-cell lung cancer" without reference to ECOG PS. Therefore, it can be assumed that all grades of ECOG PS (0-4) are included. However, the IMpower133 trial only includes patients with EGOG PS 0 (Fully active, able to carry on all pre-disease performance without restriction) or 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work). Nevertheless, The IMpower133 trial data available to date (data cut-off date 24 April 2018), reported a median OS of 10.3 months (95% CI, 9.3–11.3) in the comparator arm (carboplatin plus etoposide for four 21-day cycles followed by placebo until the occurrence of unacceptable toxic effects or disease progression),[21] which according to the company is the same regimen as NHS standard of care (CS, Table 19, page 55).[1]

For the second EOL criterion (an extension to life of at least three months), this is based on results from the IMpower133 study, which has to date (data cut-off date 24 April 2018) reported a 2.0-month median survival benefit for atezolizumab with carboplatin plus etoposide compared to carboplatin plus etoposide in ES-SCLC patients. The final analysis is expected for the IMpower133 trial in [redacted]. In addition, the company refers to the results of the economic model, which show a mean OS of [redacted] months for the comparator arm versus [redacted] months for the atezolizumab group – a difference of [redacted] months; and a median OS of [redacted] months for the comparator arm and [redacted] for the atezolizumab group – a difference of [redacted] months.

Updated results from the IMpower133 study, (data cut-off date [redacted]) also reported a 2.0-month median survival benefit for atezolizumab with carboplatin plus etoposide compared to carboplatin plus etoposide in ES-SCLC patients. In addition, the economic model with updated OS data (data cut-off date [redacted]), shows a mean OS of [redacted] months for the comparator arm versus [redacted] months for the atezolizumab group – a difference of [redacted] months; and a median OS of [redacted] months for the comparator arm and [redacted] for the atezolizumab group – a difference of [redacted] months.

ERG comment: The ERG agrees that the first EOL criterion is most likely met. However, the ERG base-case shows that the extension to life produced by atezolizumab is [redacted] months. Therefore, at the moment there is no robust evidence to show that the second criterion has been met.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

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

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Wednesday 3 July 2019** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Clarifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2 .5.2 page 40 "The study met the co-primary endpoint of PFS, demonstrating a statistically significant improvement in investigator-assessed PFS in favour of the atezolizumab group compared with the placebo group (HR = 0.77 (95% CI: 0.62 to 0.96))"	*Amend to:* *"The study met the co-primary endpoint of PFS, demonstrating a statistically significant improvement in investigator-assessed PFS in favour of the atezolizumab group compared with the placebo group (HR = 0.77 (95% CI: 0.62 to 0.96; p = 0.02))"*	Clarification for transparency The Log-rank p-value associated with PFS result is missing. Suggest including this figure.	Not a factual error. We think the CI is sufficient.
Table 4.9 page 42 Unclear that the Objective response rate, 95% Clopper-Pearson values are % as oppose to the number of patients.	*Amend to:* *95% Clopper Pearson **(%)***	Clarification for transparency	Percentage has been added.
Section 4.1.5, page 32 'It is unclear why the company has limited the comparators to 'platinum-etoposide chemotherapy regimens' because the NICE scope is quite clear in describing the comparator as: 'platinum-based combination chemotherapy regimens'.'	*Amend to:* *'The company described during the NICE scoping engagement, the decision problem meeting, and the checkpoint teleconference that according to practicing NHS oncologists the relevant comparator was platinum-based combination regimens, and that the anticipated marketing authorisation would restrict to use with carboplatin-etoposide chemotherapy. Given the final NICE scope still included treatments not used in the NHS for*	Clarification for transparency The ERG do not summarise the evidence presented within the company's submission.	Not a factual error. Even if the marketing authorisation would restrict the use of atezolizumab to use with carboplatin-etoposide chemotherapy, comparators could still include other 'platinum-based combination chemotherapy regimens' according to the scope.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.5 page 50 "results for irinotecan plus carboplatin are similar to atezolizumab plus carboplatin/etoposide in terms of OS, PFS, and response. Therefore, an indirect comparison with irinotecan plus carboplatin seems feasible"	*treatment of first-line ES-SCLC the manufacturer described through clinician survey's why it was not considered to be a relevant comparator in the NHS.'* *Amend to:* *"results for irinotecan plus carboplatin are similar to atezolizumab plus carboplatin/etoposide in terms of OS, PFS, and response. However, an indirect comparison with irinotecan plus carboplatin would not be feasible given the differences in cycles of chemotherapy (up to 6 cycles for Schmittel 2011) and dosing of etoposide (140 mg/m^2 on days 1–3 in Schmittel 2011 and 120 mg/m^2/d on days 1–5 in Hermes 2008) (1, 2)"*	Clarification for transparency The ERG do not discuss the differences between the studies where the number of chemotherapy cycles and dosage of etoposide varies.	Not a factual error. We have left the decision whether an indirect comparison is warranted to the NICE committee.
ERG exploratory analysis 1 Section 5.2.6, page 76 'Nevertheless, given the marginally better statistical fit of the log-logistic, the ERG has included this in a scenario analysis (see Section 5.3).' Section 5.3.2, Exploratory analysis 1, Weibull model for OS for intervention and log-logistic for comparator	*The scenario should investigate the use of log-logistic for both model arms*	This scenario has not been conducted in line with conclusions from NICE DSU TSD 14. Conclusion 6 for NICE DSU TSD 14 is, *'Where parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model, that is if a Weibull model is fitted to one treatment arm a Weibull should also be fitted to the other treatment arm… If different types*	Not a factual error. We have left the decision as to which curve is most appropriate to the NICE committee. We have highlighted that choice of curve used for extrapolation is a key factor determining the final ICER.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		of model seem appropriate for each treatment arm this should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis.' For the intervention arm, although the ERG has argued that the statistical fit is best with Weibull, log-logistic is still a good statistical fit to the data, with similar fit according to AIC/BIC. No further clinical expert judgement has been provided by the ERG, and arguably, by using Weibull, they have failed to consider the plateauing of the KM curve from the Flatiron data for their base case survival model. Therefore, a scenario using log-logistic for both arms is the most appropriate method to investigate the uncertainty regarding long-term survival, and is aligned with NICE DSU TSD 14 guidance analysis. Using the ERGs base case with this scenario would result in an ICER of £53,802	
ERG exploratory analysis results Section 1.5, page 17, and Section 5.4,	*This statement should be removed, and the ERG should provide a scenario for alternative survival curve fits for the*	Currently, the ERG only tests alternative overall survival curve fits for the comparator arm	This is not a factual error and, indeed there may be value in NICE considering different

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
page 103 'None of the scenario analyses chosen by the ERG made much difference and none decreased the ICER to below the £50,000 threshold.'	*intervention, rather than just the comparator (for example log-logistic).*	(Weibull and log-logistic), and not the intervention. The company believes that if the ERG consider it appropriate to model survival using different types of curve extrapolations between model arms, they should consider varying curve choice for both arms. If the ERG were conduct a scenario using the next statistically best fitting curve for the intervention arm (log-logistic) within their base case, this would result in an ICER of £45,137 (below the £50,000 threshold).	curves for different arms if they deem it to be justified "using clinical expert judgement, biological plausibility, and robust statistical analysis".
End of life, Extension to life Section 7, page 106 'The ERG agrees that the first EOL criterion is most likely met. However, the ERG base-case shows that the extension to life produced by atezolizumab is [redacted] months. Therefore, at the moment there is no robust evidence to show that the second criterion has been met.'	*Amend to:* *"The ERG agrees that the first EOL criterion is most likely met. The ERG base-case shows that the extension to life estimated by the cost-effectiveness model produced by atezolizumab is [redacted] months,* ***with exploratory analysis 1 showing that this could rise to [redacted] months****. Therefore, the second criterion* ***could also*** *be met according to ERG analysis."*	The base case analysis is not the sole criteria used for decision making, and therefore, the full extent of analyses conducted should be considered when deciding on whether specific criteria are met. A scenario analysis conducted by the ERG has provided incremental LYs of 3.1 months. Therefore, it is feasible that the second EOL criterion is met. Incremental LYs from scenarios suggested above are 3.9 months (both arms log-logistic for OS) and 4.6 months (intervention arm	Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		log-logistic and comparator Weibull for OS) There is precedence in conditions with severe unmet need and extremely short life expectancy with current treatments, for shorter survival benefits from treatment to be awarded EOL criteria status during a NICE appraisal (3)	
Interpretation of Flatiron real-world evidence Section 5.2.6, page 75 '3) The ERG also located a conference abstract based on this study that showed a survival advantage to those patients taking cisplatin compared to carboplatin' Section 5.2.6, page 76 Therefore, its overestimation of UK clinical practice is likely to be less than that by the log-logistic given, as described in points (2) and (3), Flatiron is likely to produce an overestimate of OS.	*Amend to:* *"The ERG also located a conference abstract based on this study that showed in countries where cisplatin was prescribed more often than the UK, this tended to be in younger fitter patients, giving a misleading survival advantage to those patients taking cisplatin compared to carboplatin"* *Amend to:* *"Therefore, its overestimation of UK clinical practice is likely to be less than that by the log-logistic given, as described in point (2), Flatiron is likely to produce an overestimate of OS."*	Misleading The abstract in question (4) actually concludes the following: *Pts who received cis + etop had numerically increased OS vs pts who received carbo + etop, as did pts with ECOG PS 0-1. However, these findings may be due to pts receiving cis + etop being fitter (younger and lower ECOG PS) at baseline.* Considering the differences in patient characteristics between the two arms of this analysis, the company do not believe this abstract provides any strong rationale as to why the Flatiron data would overestimate UK clinical practice, and thus do not provide any strong rationale as to why log-logistic would not be a	Not a factual error. This is a matter of judgement.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		suitable base case curve for extrapolation of overall survival on the comparator arm.	
Real-world data for chemotherapy survival Section 5.2.6, page 76 'It is true that, in response to clarification letter stage 2, a completely different set of figures was provided in the column for "Real-world data of chemotherapy survival validated as appropriate by UK-practising experts" and that these data are closer to the estimates from the log-logistic extrapolation.' 'However, the ERG believe that this is not an appropriate method to validate an extrapolation based on the trial data. Adjusting these data in any way undermines their status as providing "real-world" external validation. Adjusting those data after they had been presented to the clinical experts undermines their status has having been "validated as appropriate by UK-practising experts".'	*Amend to:* *"It is true that, in response to clarification letter stage 2, a completely different set of figures was provided in the column for "Real-world data of chemotherapy survival validated as appropriate by UK-practising experts" and that these data are closer to the estimates from the log-logistic extrapolation, but the manufacturer have confirmed this was an error on their behalf, as these were the clinician estimates from the intervention arm."* *Remove text:* *"However, the ERG believe that this is not an appropriate method to validate an extrapolation based on the trial data. Adjusting these data in any way undermines their status as providing "real-world" external validation. Adjusting those data after they had been presented to the clinical experts undermines their status has having been "validated as appropriate by UK-practising experts"."*	Interpretation error The company used the incorrect data for comparison, rather than adjusting any previously validated estimates of long term survival. Therefore, it is not factually accurate to describe the values as having been amended by the company when this error is recognised here.	The ERG thank the company for pointing out that they had made an error in their original submission which they have now rectified. The report can be amended to reflect this

Issue 2 Factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.1 page 14 Table 3.1 1st row, page 23 Section 3.1 page 27 Incorrect date for marketing authorisation	*Amend to:* "[redacted]."	Factual inaccuracy	This was correct at the time of writing the report. Our information was based on the CS (page 15): "Marketing authorisation for this indication is currently expected in [redacted]." We checked the version of the CS dated 18 February and the version dated 28 May.
Section 1.1 page 14 Table 3.1 1st row, page 23 "The intervention described in the NICE scope is atezolizumab with carboplatin and etoposide. However, in the company submission (CS), the intervention is atezolizumab with carboplatin and etoposide for four 21-day cycles followed by a maintenance phase during which patients receive atezolizumab monotherapy until the occurrence of unacceptable toxic effects or disease progression."	*Amend to:* *"The intervention described in the NICE scope is atezolizumab with carboplatin and etoposide. However, in the company submission (CS), the intervention is atezolizumab with carboplatin and etoposide for four 21-day cycles followed by a maintenance phase during which patients receive atezolizumab monotherapy until the occurrence of* ***loss of clinical benefit or unmanageable toxicity****."*	Factual inaccuracy Duration of treatment described incorrectly: As per the IMPower133 clinical trial, and anticipated license, patients receive treatment until loss of clinical benefit or unmanageable toxicity	This was correct at the time of writing the report. Our information was based on the CS (page 23, and 24-25): "Maintenance continued until occurrence of unacceptable toxic effects or disease progression …" We checked the version of the CS dated 18 February and the version dated 28 May.
Section 4.2.2 page 34	*Amend to:*		See above.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
"As can be seen in Figure 4.1, the intervention is not "atezolizumab with carboplatin and etoposide" as described in the NICE scope, but atezolizumab with carboplatin and etoposide for about three months (four x 21-day cycles) followed by atezolizumab monotherapy (maintenance phase, until disease progression or unacceptable toxic effects). In the control arm, patients received carboplatin and etoposide for about three months followed by placebo (until disease progression or unacceptable toxic effects)."	*"As can be seen in Figure 4.1, the intervention is not "atezolizumab with carboplatin and etoposide" as described in the NICE scope, but atezolizumab with carboplatin and etoposide for about three months (four x 21-day cycles) followed by atezolizumab monotherapy (maintenance phase, until loss of clinical benefit or unacceptable toxic effects)."*		
Section 1.5, page 16, and Section 5.4, page 102 'The ERG would argue that, despite use of the approach in previous STAs, it still remains an unvalidated method as evidenced by no mention of it in any of the NICE TSDs' Section 5.2.8, page 78 1) 'Despite previous use of the approach in previous STAs, it still remains unvalidated as evidenced by no mention in the NICE TSD on utilities'	*Amend to:* *"The ERG would argue that, despite use of the approach in previous STAs, it still remains an unvalidated method"* *Amend to:* *1) Despite use of the approach in previous STAs, it still remains an unvalidated method*	Incorrect logic The company respects that the choice of utility analysis used by the ERGs in the base case is based on their opinion on the validity of this utility approach, but the absence of this method from any TSD documentation should not lead to the assumption that it is invalid. Indeed, as mentioned in the company's response to clarification question B5, there is not yet a NICE TSD on how to specify utility analysis based on patient level data, thus this should not be the factor of whether any method is	Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		validated or not. Moreover, given atezolizumab can be given to patients beyond treatment progression, it seems unreasonable to assume that utility is linked to progression status in this condition. Furthermore, previous NCIE appraisals have endorsed this approach as being relevant for decision-making, when evaluating the cost-effectiveness of immune-oncology treatments (including the most recently published: TA584).	
Section 2.2 page 22 The ERG have stated the incorrect number of treatment cycles as 6 when the number should be 4.	Amend to: "The CS presents atezolizumab plus carboplatin and etoposide as a first-line treatment alongside platinum-based chemotherapy, for a maximum of four cycles."	Factual inaccuracy	This has been corrected.
Section 4.2.4 page 37 Incorrect information included regarding the number of deaths at the time of interim analysis recorded in our statistical analysis plan. "One interim analysis was performed after	Amend to: One interim analysis was performed after **approximately** 240 deaths.	Factual inaccuracy	This has been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
240 deaths."			
Change in the date of the availability of the final analysis OS data Section 4.2.5 page 38 "A final analysis of OS in the IMpower133 trial will occur after approximately 306 OS events in the ITT population have occurred; this analysis is anticipated in [redacted] and will be made available to NICE according to the company" AND Section 4.6 para 3 "A final analysis of OS in the IMpower133 trial will occur after approximately 306 OS events in the ITT population have occurred; this analysis is anticipated in [redacted] and will be made available to NICE according to the company."	Amend to: "A final analysis of OS in the IMpower133 trial will occur after approximately 306 OS events in the ITT population have occurred; this analysis is anticipated in [redacted]"	Factual inaccuracy Incorrect date for anticipated final analysis of OS data. These data have already been provided to NICE, however, it will remain AIC until [redacted].	This was correct at the time of writing the report. Our information was based on the CS (page 50): "The final analysis of OS in the IMpower133 trial will occur after approximately 306 OS events in the ITT population have occurred; this analysis is anticipated in [redacted] and will be made available to NICE." We checked the version of the CS dated 18 February and the version dated 28 May.
Description of ERG amend Fixing error (Corrects OS for intervention always being at least as high as comparator) Table 1.1 (Section 1.7, page 19) and Table 6.1 (Section 6, page 104) Section 5.2.6, page 76	Remove from ERG base case Remove from ERG base case or amend to:	Factually inaccurate and contradicted within the ERG exploratory analysis This is listed as an assumption in Table 41 of the CS and therefore should not be deemed an error. In addition, Section 5.3 of the ERG report, page 96, defines this as a	Not a factual error. This is a matter of judgement. It is also clear when this is included or excluded from each ERG scenario.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
'Therefore, the ERG chose to remove this formula and inform OS only by the survival model fit to the trial data'	*"Therefore, the ERG chose to remove this formula and inform OS only by the survival model fit to the trial data* ***(aside from when modelling in ERG exploratory analysis 1)****"*	violation rather than an error. Further, the ERG removes this base case change in their exploratory analysis 1: *'This is because of implausible crossing of the intervention and comparator survival curves.'* If this ERG change allows implausible crossing of the two curves, then the original model assumption preventing this should remain as part of the base case.	
Updated parametric extrapolations and proportion of patients alive over time Section 5.2.6.2, Table 5.7 (page 72) and Table 5.9 (page 74)	Proposed amendments provided in Table 1 and Table 2 of this document	Incorrect See Table 1 and Table 2 for location of errors. These updated tables show that Weibull actually underpredicts survival when compared to UK clinician estimates, and could be considered a conservative estimate of comparator survival	Thank-you for identifying these errors. The tables have been corrected, as has the text in Section 1.5, 5.2.6 and 5.4.
Company base case ICER £45,893, Incremental QALYs of 0.38 Section 1.4, page 15 Section 5.2.6.2, Table 5.8, page 73	Original company base case ICER should be £44,175, with incremental QALYs of 0.28	Factually inaccurate	The revised figures will be used referencing the company submission dated 18.02.19 page 101 stating that this is the deterministic approach.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 5.2.10.1, page 91 Section 5.4, page 101			The values quoted by the ERG were those derived via the PSA approach
ERG exploratory analysis 2 Matter of judgement (Change time at which PFS moves from K-M to Log-logistic), ICER £75,585 Section 1.7, Table 1.2, page 19 Section 6, Table 6.2, page 105	The ICER should be £75,5**06**	Factually inaccurate Using switches B2:B6 and B9 on the ERG sheet of ID1504 Atezolizumab ERG CE model with PAS v0.1 200619 PS [ACIC].xlsb gives an ICER of £75,506	Thank-you for identifying this error. It has now been corrected in Tables 1.2 and 6.2.

Issue 3 Factual inaccuracies related to the PD-L1 data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.3 page 13 "atezolizumab produced [redacted]." Inappropriate conclusion, and incorrect marking of commercial in confidence information.	*Amend to:* *"The company provided subgroup analysis by [redacted] This included [redacted]. At a [redacted] atezolizumab [redacted] in terms of [redacted] when compared to placebo. However, these results are based on [redacted] and exploratory subgroup analyses and are therefore not powered to detect statistical significance"*	Factual inaccuracy and incorrect marking of confidential data The data provided on PD-L1 expression is exploratory and therefore not statistically powered to detect a difference in clinical efficacy. Furthermore, the lack of tissue available for PD-L1 IHC assessment in more	Not a factual error. However, text has been updated for clarity. CiC marking added.

		than half of the patients in the ITT population limits the ability to interpret and draw reliable conclusions. As such, this is an inappropriate conclusion: there is insufficient evidence to be able to draw any conclusion regarding this subgroup data. Further, text needs to be marked as commercial in confidence.	
Section 4.2.7 page 47 "In terms of OS [redacted]). This is based on the updated analysis with cut-off date of [redacted] (see Table 4.13)." The date for data cut-off has not been marked as commercial in confidence	*Amend to:* *"OS is reported [redacted] This is based on the updated analysis with cut-off date of [redacted]"*	Factual inaccuracy and incorrect marking of confidential data This data is exploratory and therefore not statistically powered to be detect a difference in clinical efficacy. As such, it cannot be claimed that a statistically significant result is reported. Furthermore, the lack of tissue available for PD-L1 IHC assessment in more than half of the patients in the ITT population limits the ability to interpret and draw reliable conclusions. In addition, incorrect values for 95% CI are reported, and the date for data cut off has not been marked as academic in confidence	Not a factual error. However, the text has been updated. AiC marking has been added.

Section 4.2.7 page 47 "The Kaplan-Meier plot is not reported for the BEP2 sample."	*Suggest deleting "The Kaplan-Meier plot is not reported for the BEP2 sample".*	Factual inaccuracy The Kaplan-Meier plot for the BEP2 sample was made available in the ERG clarification response appendix 5.	The sentence has been deleted.
Section 4.2.7 page 48 "As can be seen from these results, , atezolizumab in terms of when compared to placebo. However, these results are based on and exploratory subgroup analyses"	*Amend to:* *"As can be seen from these results, , atezolizumab produces in terms of when compared to placebo. However, these results are based on and exploratory subgroup* ***analyses and are therefore not powered to detect statistical significance****"*	This data is exploratory and therefore not statistically powered to be detect a difference in clinical efficacy. Furthermore, the lack of tissue available for PD-L1 IHC assessment in more than half of the patients in the ITT population limits the ability to interpret and draw reliable conclusions. For transparency purposes for the reader, this should be made clear. Further text needs to be marked as commercial in confidence.	Not a factual error. However, the text has been updated. CiC marking has been added.
Section 4.6 page 58 "Results by showed that, at a , atezolizumab produced in terms of when compared to placebo. However, these results are based on and exploratory subgroup analyses."	*Amend to:* *"Results by showed that, at a , atezolizumab produced results for patients with in terms of when compared to placebo. However, these results are based on and exploratory subgroup analyses."*		Not a factual error. CiC marking has been added.

Issue 4 Typographical grammatical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.1 page 14 The word "is" is missing from the anticipated licence for the submission.	*Amend to:* [redacted]"	Grammatical error	We do not think 'is' is necessary in our sentence: "The anticipated license is: atezolizumab [redacted]."
Section 1.2 page 11 "Based on April 2018 data, the median progression-free survival was 5.1 months and 4.3 months, respectively (HR = 0.77 (95% CI: 0.62 to 0.96)" AND Table 4.8 has incorrect median PFS value of 5.1 in instead of 5.2.	*Amend to:* *"Based on April 2018 data, the median progression-free survival was 5.2 months and 4.3 months, respectively (HR = 0.77 (95% CI: 0.62 to 0.96; P = 0.02)."*	Factual inaccuracy Incorrect value assigned to median PFS result for atezolizumab. Current reads 5.1 when it should be 5.2. In addition, we suggest incorporating p values.	This was based on information reported in the CS (Table 10, page 36). We checked the version of the CS dated 18 February and the version dated 28 May. We do not think P-values add anything when CIs are reported.
Section 4.6 page 57 P value associated with the median PFS result is missing and the median PFS for atezolizumab is incorrect as it should be 5.2 not 5.1. Suggest including p value "Based on April 2018 data, the median progression-free survival was 5.1 months and 4.3 months, respectively (HR = 0.77 (95% CI: 0.62 to 0.96)."	*Amend to:* *"Based on April 2018 data, the median progression-free survival was 5.2 months and 4.3 months, respectively (HR = 0.77 (95% CI: 0.62 to 0.96; p=0.02)."*		Same as above.
Section 1.4, page 14	*Amend to:*	Factually inaccurate	The ERG thanks the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
'The intervention was atezolizumab with carboplatin and etoposide, given for up to four cycles and the comparator was carboplatin and etoposide, given for up to four cycles.'	*"The intervention was atezolizumab with carboplatin and etoposide, given for up to four cycles* ***followed by monotherapy atezolizumab****, and the comparator was carboplatin and etoposide, given for up to four cycles."*	The intervention arm is triple therapy followed by monotherapy	for pointing out this factual error and will make the change.
Section 1.6.2, page 18 'However, it is possible that among the relevant comparators ignored by the company'	*Amend to:* *"However, it is possible that among the* ***comparators from the NICE scope not stated as being relevant by NHS oncologists****"*	Clarity In section 1.3, page 13, the ERG states that, *'the ERG would agree that carboplatin/etoposide is probably the most relevant comparator for this appraisal.'* The ERG have not provided any evidence that there are any other relevant comparators for this appraisal, but the company recognise that there are some comparators that would be included within the definition listed in the NICE scope that have not be included in the CS. Evidence provided in the company submission clearly reports that numerous NHS oncologists stated that carboplatin-etoposide is the only comparator of relevance.	Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		This was also stated directly to NICE and the ERG during the scope consultation stage of this appraisal.	
Section 1.3, page 12 'According to clinical experts employed by the company…'	*Amend to:* *"According to clinical experts **engaged** by the company…"*	Clarity Employed suggests that the clinical experts work for the company, which is incorrect.	Not a factual error.
Section 1.5, page 17, and section 5.4, page 102 'The ERG therefore included AE disutilities.'	*Amend to:* *"The ERG therefore included AE disutilities **in their base case**."*	Clarity Without the addition proposed, it is implied that the ERG added the disutilities themselves, but these were provided by the company upon request	Not a factual error. The "implication" is a matter of opinion.
ERG base case ICER, £75,585 Section 1.5, page 16 Section 1.7, Table 1.1 and 1.2, page 18 and 19 Section 5.3.1, page 97 and Table 5.2.7, page 98 Section 5.4, page 102 Section 6, Table 6.1 and 6.2, page 104 and 105	*The ICER should be £75,58**6***	Rounding error Using switches B2:B6 in the 'ERG' sheet of *ID1504 Atezolizumab ERG CE model with PAS v0.1 200619 PS [ACIC].xlsb* gives an ICER of £75,585.77. Rounding to 0dp would be £75,586, rather than £75,585.	The ERG thanks the company for identifying this error and has made the correction to Section 1.5, Table 1.1, Section 5.3.1, Table 5.2.7, Section 5.4 and Table 6.2.
Table 4.11 page 44 The incidence of grade 3-4 fatigue in the	*Remove +*	Typographical error	Thank you for pointing this out. We think these are obvious mistakes, no change to the

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
placebo group is stated as 1(0.5)+			ERG report is warranted.
Section 4.4, page 49 'cclarification'	*"clarification"*	Typographical error	Same as above
Section 4.4, page 50 'The fast majority'	*"The **v**ast majority"*	Typographical error	Same as above
Section 5.2.6, page 68, and Section 4.4, page 99 'Visual inspection, The Akaike and Bayesian Information Criterion (AIC and BIC) were used to selects the most relevant extrapolations'	*"…were used to select the most relevant extrapolations"*	Typographical error	Same as above

Issue 5 Incorrect marking of ACIC information

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.3 page 12 Incorrect marking of academic in	*Amend to:* *"Based on the most recent data from 2019,*	Information needs to be marked as academic in	AiC marking has been added.

confidence information. "Based on the most recent data from 2019, and a median follow-up of [redacted] months, the stratified (gender and ECOG) HR for death was [redacted] and a difference in median overall survival of [redacted]."	*and a median follow-up of [redacted] months, the stratified (gender and ECOG) HR for death was [redacted] and a difference in median overall survival of [redacted]"*	confidence and redacted.	
Section 1.4 page 14 No requirement for confidential marking. "[redacted]"	*Suggest removing highlighting and underlining:* *"PFS analysis was considered final at the primary analysis."*	Not confidential information	We have removed the CiC marking. However, the was marked CiC in the response to the clarification letter by the company (Question A10, page 8)
Table 4.7 (page 40), Figure 4.3 (page 40) and Table 4.13 (page 47) The cut-off date in the titles of these figures must be marked as academic in confidence and redacted from public versions of the document. AND The Kaplan-Meier curve itself in Figure 4.3 must be marked as academic in confidence and redacted from public versions of this document.	*Include confidential marking:* ***Table 4.7: Overall survival in the ITT population, data cut-off date [redacted]*** ***Figure 4.3: Kaplan-Meier plot of OS in the ITT population, data cut-off date [redacted]*** ***Table 4.13: Overall survival by PD-L1 status in BEP2 population, data cut-off date [redacted]***	Confidential information has not been marked as such.	AiC marking has been added.

Section 1.3 page 12 and Section 4.6 page 57 Incorrect marking of commercial in confidence information. "…fewer than [redacted] of ES-SCLC patients in UK clinical practice would be diagnosed with an ECOG status of 0" AND "In Appendix K, the company reports that "some advisors stated in their experience the probable proportions of UK ES-SCLC patients diagnosed as ECOG 0–1 would be as high as [redacted] with others reporting that in their clinical experience it could be as low as [redacted]"	*Amend to:* *"…fewer than [redacted] of ES-SCLC patients in UK clinical practice would be diagnosed with an ECOG status of 0"* *AND* *"In Appendix K, the company reports that "some advisors stated in their experience the probable proportions of UK ES-SCLC patients diagnosed as ECOG 0–1 would be as high as [redacted] with others reporting that in their clinical experience it could be as low as [redacted]"*	Confidential information has not been marked as such.	CiC marking has been added.
Section 4.2.5.1 page 39 "This updated [redacted]"	*Suggested amend:* *"This updated exploratory analysis for OS was conducted, based on a pre-specified number of events (306 OS events) in the Statistical Analysis Plan Version 3 (dated 14 May 2018)."*	Remove confidential marking	We have removed the CiC marking. However, the was marked CiC in the response to the clarification letter by the company (Question A10, page 8)
Section 4.2.7 page 47 Incorrect marking of commercial in confidence information. [redacted] were defined by applying [redacted] to raw scores. Because of the [redacted]	*In response to the clarification letter (question A12) the company reported details of their analysis by [redacted] results. This included [redacted] data.* *[redacted] were defined by applying [redacted] to raw scores.*	Further information needs to be marked as commercial in confidence.	CiC marking has been added.

[redacted]. This is reported as 'TC' (tumour cells) or 'IC' (tumour infiltrating immune cells). As some of the slides tested were [redacted]. The sample defined as [redacted] and the sample defined as [redacted] is that of [redacted] In this section of the ERG report we report results for [redacted]; full results can be found in the company's response to the clarification letter."	*Because of the [redacted]. This is reported as 'TC' (tumour cells) or 'IC' (tumour infiltrating immune cells).* *As some of the slides tested were [redacted]. The sample defined as [redacted] and the sample defined as [redacted] is that of [redacted] In this section of the ERG report we report results for [redacted]; full results can be found in the company's response to the clarification letter."*		

Corrected tables – included here due to an error found in the ERG tab in cells B26, B28 + B29.

Table 1: Parametric extrapolations of the proportion of patients alive (OS) following carboplatin-etoposide treatment, using only IMpower133 data to inform the extrapolation

Time (months)	Parametric extrapolations						Real-world data of chemotherapy survival validated as appropriate by UK-practising experts	Difference between real-world data and parametric extrapolation	
	Weibull	Gompertz	Generalised gamma	Log-logistic	Exponential	Log-normal		Weibull	Log-logistic
12	47%	47%	46%	44%	43%	44%	[redacted]	14%	11%
24	12%	12%	12%	15%	19%	19%	[redacted]	5%	8%
36	2%	1%	3%	7%	8%	10%	[redacted]	0%	5%
48	0%	0%	1%	4%	4%	6%	[redacted]	0%	3%
60	0%	0%	0%	3%	2%	3%	[redacted]	0%	2%
Source: Adapted from Table 23 of the CS using the company model, ID1504 Atezolizumab Roche CE model PAS price v2 070519 JM [PAS]									

Table 2: Parametric extrapolations of the proportion of patients alive (OS) following atezolizumab plus carboplatin-etoposide treatment, using only IMpower133 data to inform the extrapolation

Time (months)	Parametric extrapolations						UK-practising clinical experts' opinion, based on real-world data and IMpower133 benefit	Difference between clinical expert opinion and parametric extrapolation*	
	Weibull	Gompertz	Generalised gamma	Log-logistic	Exponential	Log-normal		Weibull	Log-logistic
12	57%	58%	56%	54%	52%	53%	[redacted]	17%	14%
24	20%	20%	20%	23%	26%	27%	[redacted]	8%	11%
36	6%	3%	6%	12%	14%	16%	[redacted]	1%	7%
48	1%	0%	1%	7%	7%	10%	[redacted]	-1%	5%
60	0%	0%	0%	5%	4%	7%	[redacted]	-1%	3%
Source: Adapted from Table 24 of the CS using the company model, ID1504 Atezolizumab Roche CE model PAS price v2 070519 JM [PAS] *Midpoint of clinical expert opinion used where range given									

1. Schmittel A, Sebastian M, Fischer von Weikersthal L, Martus P, Gauler TC, Kaufmann C, et al. A German multicenter, randomized phase III trial comparing irinotecan-carboplatin with etoposide-carboplatin as first-line therapy for extensive-disease small-cell lung cancer. Annals of Oncology. 2011;22(8):1798-804.
2. Hermes A, Bergman B, Bremnes R, Ek L, Fluge S, Sederholm C, et al. Irinotecan plus carboplatin versus oral etoposide plus carboplatin in extensive small-cell lung cancer: a randomized phase III trial. Journal of Clinical Oncology. 2008;26(26):4261-7.
3. National Institute for Health and Care Excellence. Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [TA476] 2017 [Date Accessed 31st January 2019]. Available from: https://www.nice.org.uk/guidance/ta476/resources/paclitaxel-as-albuminbound-nanoparticles-with-gemcitabine-for-untreated-metastatic-pancreatic-cancer-pdf-82604969382085.
4. M. Sebastian, F. Barlesi, Califano. R, Mansfield. A, F. Blackhall, E. Flahavan, et al. Treatment (tx) characteristics and clinical outcomes in patients (pts) with extensive-stage small cell lung cancer (ES-SCLC) treated with carboplatin (carbo) or cisplatin (cis) in combination with etoposide (etop) in US clinical practice 2019 [Date Accessed 7th July 2019]. Available from: https://cslide.ctimeetingtech.com/elcc2019/attendee/confcal/show/session/66#presentation-abstract-309878370428.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

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

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual accuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
12	CiC added (3x) and AiC added (1x)
13	CiC added (5x)
14	CiC removed (1x) and added "followed by monotherapy atezolizumab"
16-17	Added text and changed '£75,585' to '£75,585'
19	Changed '£75,585' to '£75,585' and changed '£75,585' to '£75,506'
22	'six cycles' changed to 'four cycles'
37	The word 'approximately' added
39	CiC removed (1x)
40	AiC added (2x)
42	'%' added
47	CiC added (10x)
48	AiC added (2x), CiC added (3x) and sentence removed ('The Kaplan-Meier plot is not reported for the BEP2 sample.')
57	CiC added (3x)
58	CiC added (5x)
72	Updated percentages
74	Updated percentages
76	Added text
98-99	Changed '£75,585' to '£75,585' and changed '£75,585' to '£75,506'
103	Added text
104-105	Changed '£75,585' to '£75,585' and changed '£75,585' to '£75,506'

0.62 to 0.96). The objective response rate (ORR, Difference in response rates: [redacted]) and median duration of response (DOR, Median duration 4.2 months for atelozumab versus 3.9 months for placebo) were similar between the treatment arms. Patients in both the atezolizumab arm and the placebo arm reported improvements in function and health related quality of life (HRQoL). However, statistical significance of differences between treatment arms was not reported in the CS. Time to deterioration (TTD) showed no statistically significant differences between treatment arms in patient-reported lung cancer symptoms (cough, chest pain, dyspnoea, arm/shoulder pain, fatigue and loss of appetite) or treatment-related symptoms (constipation, dysphagia, peripheral neuropathy, nausea/vomiting, diarrhoea and sore mouth).

Adverse events related to any component of the trial regimen occurred in 188 patients (94.9%) in the atezolizumab group and in 181 patients (92.3%) in the placebo group. The most common grade 3 or 4 adverse events related to the trial regimen were neutropenia, anaemia, and decreased neutrophil count. Deaths related to the trial regimen occurred in three patients (1.5%) in the atezolizumab group and in three patients (1.5%) in the placebo group. Immune-related adverse events occurred in 79 patients (39.9%) in the atezolizumab group and in 48 patients (24.5%) in the placebo group, with rash and hypothyroidism being the most common. The proportion of patients who experienced serious adverse events (SAEs) was 37.4% in the atezolizumab group and 34.7% in the placebo group. The most frequently reported SAEs were haematologic toxicities or infections.

In addition, the company stated that "[redacted]" (CS, page 50).

The company presented an indirect comparison of atezolizumab plus carboplatin-etoposide versus cisplatin-etoposide. However, we believe that the results from the indirect comparison presented by the company in Appendix F are unreliable and should not be used by NICE for decision making.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted as part of the systematic review to identify clinical effectiveness studies. A wide range of databases and additional resources were searched. The searches included limited comparators and was not in line with the broader comparator definition in the final scope.

Baseline characteristics in the IMpower133 trial were well balanced between the groups. However, the population included in the IMpower133 trial may not be representative of the ES-SCLC patient population in UK practice. According to clinical experts employed by the company fewer than [redacted] of ES-SCLC patients in UK clinical practice would be diagnosed with an ECOG status of 0. In the IMpower133 trial, 35% of patients had an ECOG performance status of 0. Furthermore, all included patients in the IMpower133 trial had an ECOG performance status of 0-1. In Appendix K, the company reports that "some advisors stated in their experience the probable proportions of UK ES-SCLC patients diagnosed as ECOG 0–1 would be as high as [redacted], with others reporting that in their clinical experience it could be as low as [redacted]." Therefore, the population included in the IMpower133 trial might only represent a third of ES-SCLC patients in the UK.

Based on the most recent data from 2019, and a median follow-up of [redacted] months, the stratified (gender and ECOG) HR for death was [redacted] and a difference in median

overall survival of [redacted]. Progression free survival (PFS) also showed a statistically significant improvement in investigator-assessed PFS in favour of the atezolizumab group compared with the placebo group (HR = 0.77 (95% CI: 0.62 to 0.96)). Objective response rate (ORR) and median duration of response (DOR) were similar between the treatment arms; while statistical significance of differences between treatment arms was not reported in the CS for health-related quality of life.
The proportion of patients who experienced SAEs (serious adverse events) was 37.4% in the atezolizumab group and 34.7% in the placebo group. The most frequently reported SAEs were haematologic toxicities or infections.

The company provided subgroup analysis by [redacted]. This included [redacted] data. At a [redacted], atezolizumab [redacted] in terms of [redacted] when compared to placebo. However, these results are based on [redacted] and exploratory subgroup analyses.

The IMpower133 trial compares atezolizumab plus carboplatin and etoposide with placebo plus carboplatin and etoposide. The NICE scope describes the comparators as 'platinum-based combination chemotherapy regimens'. However, in the CS the company states that "chemotherapy regimens excluding etoposide are outside of the scope of this appraisal" (CS, Appendix D, page 41). This means treatment regimens such as carboplatin plus paclitaxel, irinotecan plus cisplatin, topotecan plus cisplatin, and paclitaxel plus cisplatin are not considered as comparators in the CS. The only comparators considered in the CS are carboplatin plus etoposide as reported in the IMpower133 trial and cisplatin plus etoposide based on an indirect comparison. The ERG believes that the results from this indirect comparison are unreliable and should not be used by NICE for decision making.

The company argues that "only carboplatin plus etoposide treatment is considered to be within the scope of this appraisal" (Response to clarification, Question A14). This is based on advice from over 20 practising NHS oncologists that the standard of care in the NHS for untreated, ES-SCLC is carboplatin plus etoposide. In addition, the evidence for a comparison of atezolizumab plus carboplatin/etoposide versus carboplatin/etoposide is based on a head-to-head comparison (the IMpower133 trial), while evidence for other comparisons will have to rely on weaker evidence based on indirect comparisons. Therefore, the ERG would agree that carboplatin/etoposide is probably the most relevant comparator for this appraisal.

However, if the committee decides that all comparators mentioned in the NICE scope are relevant comparators, we have conducted an indirect comparison based on a limited search performed by the company (see Section 4.5 of this report), which shows that results for irinotecan plus carboplatin are similar to atezolizumab plus carboplatin/etoposide in terms of OS, PFS, and response.

1.4 Summary of cost effectiveness evidence submitted by the company

Separate sets of searches were undertaken to identify economic, resource use and HRQoL evidence. The CS provided sufficient details for the ERG to appraise the searches. An extensive range of databases and additional resources were searched.

The CEA was structured as a three-health state partitioned survival analysis (PartSA) model. These three health states were consistent with previous appraisals accepted by NICE to evaluate first-line lung cancer, as well as other oncology indications: "PFS", "Progressed Disease (PD)" and "Death". The

population in the CEA was first-line, adult ES-SCLC patients, which is consistent with the ITT population of the IMpower133 study, the NICE final scope for this appraisal, the appraisal decision

problem and the anticipated EMA Marketing Authorisation (the draft SmPC provided in a separate document). The intervention was atezolizumab with carboplatin and etoposide, given for up to four cycles followed by monotherapy atezolizumab, and the comparator was carboplatin and etoposide, given for up to four cycles. In response, the company provided the results of a scenario analysis involving six cycles, which showed a decrease in the incremental cost effectiveness ratio (ICER). Also in a scenario analysis, comparison with cisplatin instead of carboplatin was employed. This was performed as a full incremental analysis in the response to the clarification letter. However, as described in Section 5.2.3 of this report, the company argued that the comparison was inappropriate due to cisplatin being indicated for only "…borderline LS-SCLC patients." The economic model uses a 20-year time horizon in the base case. Costs and health outcomes are discounted at 3.5% in the base case and the perspective of the NHS and personal social services (PSS) is assumed.

The company stated that they followed step by step guidance from the NICE DSU TSD 14 to identify the best fit parametric extrapolations for OS, PFS and time-to-off-treatment (TTOT) in the model base case. For TTOT, in both arms of the pivotal trial, no extrapolation was needed for either carboplatin or etoposide treatments, since the time to treatment discontinuation had been observed for the entire cohort during the 12-month follow up period. Therefore, parametric extrapolation was only required for TTOT for atezolizumab. Because TTOT extrapolation only applied to the intervention, a test for proportional hazards was not required. For OS and PFS, the company first tested whether the proportional hazard assumption held between treatment arms by inspecting the log-cumulative hazard (odds, and standardised normal curve) plots and computing the log cumulative hazard over the log of time. Based on those tests, the proportional hazard assumption was rejected for both OS and PFS because the curves cross each other at multiple time points. Therefore, separate parametric time-to-event models were fitted to each treatment arm for each endpoint, OS, PFS and TTOT. Visual inspection and statistical fit (Akaike Information Criterion (AIC) and Bayesian information criterion (BIC)) were used to select the most relevant extrapolations. The plausibility of extrapolation beyond trial data was also assessed by checking the crossing of curves (OS should not cross PFS or TTOT) and, for OS comparison, external validation with expert opinion and/or real-world data and general mortality rates.

For PFS, the log-logistic curve provided the best statistical fit of the parametric function to the actual data. This continued to be the case with the [redacted] data: PFS analysis was considered final at the primary analysis. The company noted that all the standard parametric curves provided a similarly poor visual fit to the Kaplan-Meier data, as there were steep drops within the first five months at the time of each scan. [redacted], at this specific time point approximately 50% of patients remain at risk in both arms. No external validation was performed for PFS.

For OS, in terms of statistical fit, the CS stated the best overall fit to the existing OS data would be either Weibull, Gompertz, generalised gamma or log-logistic extrapolations for the atezolizumab arm and Weibull, Gompertz or generalised gamma curves for the comparator arm. The company argued in the CS that the visual fit of these extrapolation curves was good enough not to use the KM data even for the initial period, as they did for PFS. In response to clarification letter part 2 and the data from [redacted] the company stated that the best fit was obtained from the Weibull and log-logistic extrapolations. For the comparator, the company finally chose the log-logistic from the set of parametric curves on the basis of external validity of the extrapolations by comparison with data from the Flatiron study, validated by clinical expert opinion, although it did also provide the best statistical fit based on the data from [redacted]. For the intervention, the company cited the clinical expert opinion as

to long term survival and on this basis chose the log-logistic model, although the Weibull had a minor advantage in terms of statistical fit based on the data from [redacted].

were similar with ICERs about 1% and 8% higher, of [redacted] and [redacted], versus carboplatin plus etoposide and cisplatin plus etoposide respectively. Scenario analysis revealed that the ICER was most sensitive to the parametric model for TTOT for atezolizumab. However, none of these models provided a good visual or statistical fit and the one that fitted best i.e. the generalised gamma produced an ICER under £50,000. The next most influential input was the parametric model for OS for atezolizumab and the Gompertz does provide a plausible alternative to the log-logistic and did produce an ICER well in excess of £50,000. However, the Weibull did provide the best statistical fit and, in the view of the ERG, is the most clinically plausible.

In the clarification letter the ERG requested that a subgroup analysis be conducted based on the results of the "…[redacted]". In their response of 28 May 2019, the company declined to do so citing limitations in the data.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers the population, intervention and comparator considered by the company in their CEA to be largely appropriate. However, as the company identify in the response to clarification letter, there might be a subgroup of "…borderline LS-SCLC patients" for whom cisplatin plus etoposide instead of carboplatin plus etoposide would be appropriate. On this basis, the ERG would concur that cisplatin plus etoposide is probably not an appropriate comparator for the index population. Also, the company showed that, if cisplatin is compared with atezolizumab and carboplatin, that it would be dominated. However, no data on the effectiveness of atezolizumab in this 'borderline population' were provided either from the IMpower133 trial or any other source. Therefore, the ERG would argue that, if such a borderline LS-SCLC population exists, then one can make no evidence-based decision as to whether atezolizumab is cost effective in this population.

For PFS, the ERG considers the choice of model to be appropriate and, although the point at which the KM curve is replaced by the log-logistic model is arbitrary, there is little difference in the ICER by replacing with log-logistic for the whole time horizon (£35.92 on the company base-case). The ERG has a similar opinion of the choice of model for TTOT, although the difference between ICERs is not so easily dismissed, it being £1,026.11 lower on the company base-case by replacing with generalised gamma for the whole time horizon. Nevertheless, this implies that the model chosen by the company (KM for first 14 months) is conservative with regards to the cost effectiveness of atezolizumab. For OS and for the comparator, the ERG would disagree with the company judgement regarding clinical plausibility. Given that the log-logistic already overestimates OS as estimated in the Flatiron study and the Flatiron study probably overestimates OS compared to UK clinical practice, the log-logistic almost certainly overestimates OS compared to UK clinical practice. In contrast, the Weibull, which, whilst it also overestimates OS in comparison to the Flatiron study for years 1 to 2, it does provide estimates that are almost identical to the Flatiron study for years 3 to 5. Therefore, its overestimation of UK clinical practice is likely to be less than that by the log-logistic. Therefore, the ERG would argue that the Weibull is likely to be have greater clinical plausibility and it provides nearly as good a statistical fit, which is why it has been chosen for the comparator in the ERG base-case. For the intervention, the ERG also disagrees with the choice of the log-logistic on the basis of clinical plausibility as well as it having a marginally worse statistical fit than the Weibull. The main reason for this judgement is that there are no real-world data by which any estimates can be externally validated and the ERG questions the validity of clinical expert opinion as to the effect of a treatment for which they would have had no clinical experience. However, as with the comparator, one can compare the percentages surviving at each of the five time points from the clinical experts with those from the log-logistic and the model with the best statistical fit, the Weibull. When one does that it can be seen that the values for the Weibull for

only the first three time points are all higher than those elicited from the clinical experts, but by more than the log-logistic only in year 1 and they are different by less than the log-logistic in all other years i.e. 2 to 5. Therefore, the ERG would argue that the Weibull is likely to have greater clinical plausibility and it provides a better statistical fit, which is why it has been chosen for the intervention in the ERG base-case.

The ERG considers that the company appropriately identified the AEs that were most important to include in terms of the potential impact on cost and utility. However, the ERG believes the justification provided by the company stating that AEs are implicitly captured by EQ-5D is questionable. According to NICE TSD 12 it is important to include decrements on HRQoL associated with AEs of at least Grade 3. The ERG therefore included AE disutilities. The ERG also questions the validity of the 'time to death' method employed by the company, although in the clarification letter response, the company provided references to previous STAs that used the 'time to death' approach. The ERG would argue that, despite use of the approach in previous STAs, it still remains an unvalidated method as evidenced by no mention of it in any of the NICE TSDs. It neglects the more established method of using progression status to determine utility value, it incorporates the effect of being on or off treatment with questionable clinical validity especially not having statistically tested the effect of both treatment and progression status and it is implemented by the arbitrary division into four time to death categories. In response to clarification letter, the company failed to provide what the ERG requested i.e. full statistical analysis of various models including both on/off treatment and progressed/not progressed as well as time to death as a continuous variable. Therefore, the ERG chose the more conservative approach of measuring utility as a function of progression status and not time to death as its ERG base-case.

The ERG believe that costs were generally estimated in a way that seemed plausible. The ERG has some concerns over the unit costs used for adverse events. This being said, the impact of using alternative unit cost estimates on the final ICER is very limited. However, alternative more costly estimates were used in TA531 (equating to £998 for diarrhoea and £788 for vomiting). It is not clear why the company chose the specific unit costs for adverse events.

The ERG base-case resulted in an ICER of £75,586 for atezolizumab plus carboplatin and etoposide versus carboplatin and etoposide only. This increase from the company base-case is due mainly to the decrease in the incremental QALYs from 0.25 to 0.17. Most of this decrease is due to the Weibull instead of the log-logistic, which by itself resulted in an ICER of £69,290. None of the scenario analyses chosen by the ERG made much difference and none decreased the ICER to below the £50,000 threshold.

Finally, the ERG would contend that, given evidence of variation in effectiveness according to PD-L1 subgroup that the subgroup analysis of cost effectiveness is still relevant, particularly given the possibility that atezolizumab might not be cost effective as shown in the ERG base-case.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

A wide range of resources was searched and the searches were well documented making them transparent and reproducible. An extensive range of additional searches were conducted for grey literature.

The evidence for atezolizumab with carboplatin and etoposide versus placebo with carboplatin and etoposide is based on a good quality randomised controlled trial (IMpower133) including 403 patients

from 21 countries, with 10 patients from the UK. Results are based on the most recent data from 2019, and a median follow-up of [redacted] months.

Carb + Etop	[redacted]	[redacted]			
Fixing error (Corrects OS for intervention always being at least as high as comparator)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,588
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Uses Weibull for OS for both intervention and comparator)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.18	£69,260
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Utility is a function of progression status and not time to death)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.23	£53,724
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (AE disutilities from literature)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,664
Carb + Etop	[redacted]	[redacted]			
ERG base-case					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,586
Carb + Etop	[redacted]	[redacted]			
AE = adverse event; Atezo = atezolizumab; Carb = carboplatin; CS = company submission; ERG = Evidence Review Group; Etop = etoposide; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS =progression-free survival; QALY = quality-adjusted life year.					

Table 1.2: Deterministic scenario analyses conditional on ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Matter of judgement (Ensures that TTOT does not sink lower than PFS after 14 months (limit of K-M data))					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£77,891
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Change time at which PFS moves from K-M to Log-logistic)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,506
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Diarrhoea unit cost £998)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,631
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Vomiting unit cost £788)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,601
Carb + Etop	[redacted]	[redacted]			
Atezo = atezolizumab; Carb = carboplatin; ERG = Evidence Review Group; Etop = etoposide; ICER = incremental cost effectiveness ratio; K-M = Kaplan-Meier; PFS = progression-free survival; QALY = quality-adjusted life year; TTOT = time to of treatment.					

letter of clarification to the company, to which the company responded that "regimens such as irinotecan plus carboplatin, paclitaxel plus carboplatin and best supportive care are not considered standard clinical practice by the broad range of NHS oncologists advising Roche" (Response to clarification letter, Question A15).[9] The company refers to the 2013 ESMO guidelines for SCLC in their submission.[6] The first section of the listed recommendations covers two cycles for chemotherapy. One method consisted of 4-6 cycles of carboplatin + etoposide, while the other method consisted of 4-6 cycles of cisplatin + etoposide. The second section notes the use of alternative platinum doublets, in the case of etoposide being contraindicated. The CS notes that in that case, irinotecan-cisplatin, gemcitabine-carboplatin, and IV or oral topotecan-cisplatin would not be considered comparable to the IMpower133 trial population.[1] The third recommendation states that patients with a reasonably good PS should be evaluated for PCI if there was any response to first-line treatment.[1] The fourth statement indicates that patients with metastatic SCLC are not recommended to have thoracic irradiation.[1]

The CS presents atezolizumab plus carboplatin and etoposide as a first-line treatment alongside platinum-based chemotherapy, for a maximum of four cycles.[1] The pathway also presents atezolizumab in the form of a monotherapy in the maintenance component of treatment.[1] Upon completion of the maintenance phase (atezolizumab monotherapy), patients would then enter the second-line treatment stage.[1] This could include an anthracycline-containing regimen/further platinum-based treatment regimen or oral topotecan in the event that retreatment with the first-line regimen is not appropriate and CAV is contraindicated.

population in UK practice. In Appendix K the company stated that "discussion among the advisory board attendees highlighted that, in their experience, fewer ES-SCLC patients in a real-world situation within the UK would be diagnosed with an ECOG status of 0 than was reported in the cohort of US patients included in the Flatiron study (26%, Appendix K, page 6).[39] This means that fewer than 26% of ES-SCLC patients in a real-world situation within the UK would be diagnosed with an ECOG status of 0 according to 8 out of 9 oncologists consulted by Roche. In the IMpower133 trial, 35% of patients had an ECOG performance status of 0. Furthermore, all included patients in the IMpower133 trial had an ECOG performance status of 0-1. In appendix K, the company reports that "some advisors stated in their experience the probable proportions of UK ES-SCLC patients diagnosed as ECOG 0–1 would be as high as 55%, with others reporting that in their clinical experience it could be as low as 20–30%.".[39] Therefore, the population included in the IMpower133 trial might only represent a third of ES-SCLC patients in the UK.

4.2.4 Statistical analyses

Randomisation occurred in a 1:1 ratio using a permuted-block randomisation method. Patients were randomised to one of two treatment arms: atezolizumab + carboplatin + etoposide or placebo + carboplatin + etoposide. The randomisation scheme was designed to ensure that an approximately equal number of patients would be enrolled in each treatment arm within the baseline characteristics of the following stratification factors: gender (male vs. female), ECOG PS (0 vs. 1) and presence of brain metastases (yes vs. no). Patients received their first dose of the study drug on the day of randomisation if possible. If this was not possible, the first dose occurred within five days after randomisation.[40]

The two co-primary endpoints of the IMpower133 study were OS and investigator-assessed PFS. OS was defined as the time from randomisation to death from any cause. Patients who were not reported as having died were censored at the date when they were last known to be alive. Patients who did not have post-baseline information were censored at the date of randomisation plus one day.

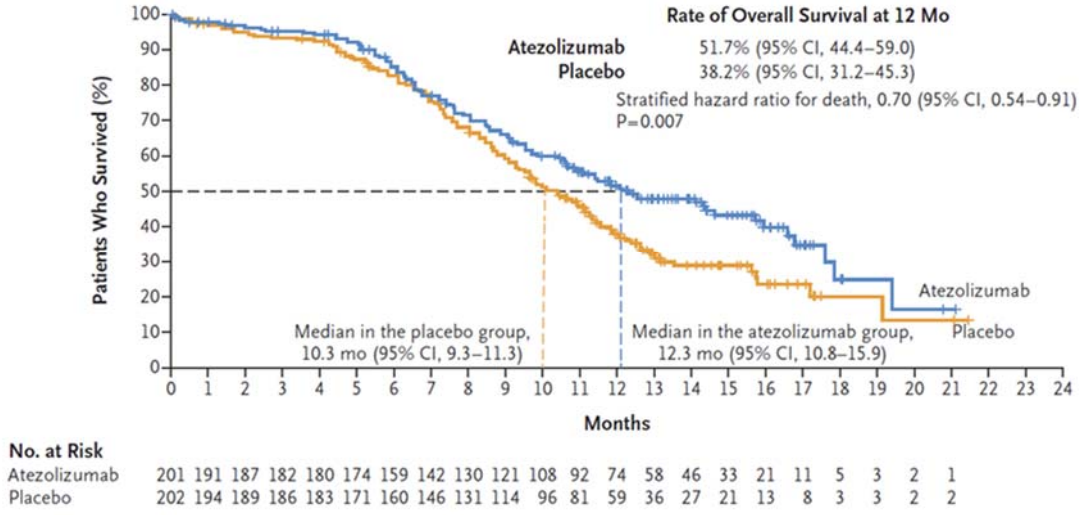
PFS was defined as the time from randomisation to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first. Patients who did not experience disease progression or death at the time of analysis were censored at the time of the last tumour assessment. Patients with no post-baseline tumour assessment were censored at the date of randomisation plus one day.

The sample size calculation was based on the analysis of OS. To detect a HR = 0.68 for atezolizumab versus placebo using a log-rank test, approximately 306 deaths in the ITT population provided 91% power at a two-sided 0.045 significance level. One interim analysis was performed after approximately 240 deaths. The primary PFS analysis was planned at the time of the interim OS analysis after approximately 295 PFS events had occurred. This provided 99% power to detect an improvement in PFS of a HR = 0.55 at a two-sided significance level of 0.005. There were no interim analyses for PFS.

To control the overall two-sided type I error rate at 0.05 in the analyses of patients enrolled during the global enrolment phase, a group sequential weighted Holm procedure[41] was used wherein the two-sided significance levels of 0.005 and 0.045 were allocated to the primary comparisons for progression-free survival (PFS) and OS, respectively. If PFS in the ITT population was statistically significant at the two-sided α level of 0.005, OS in the ITT population was tested at a two-sided α level of 0.05. Additionally, if OS in the ITT population was statistically significant at the two-sided α level of 0.045, PFS in the ITT population was tested at a two-sided α level of 0.05.

year OS rate was 51.7% (95% CI, 44.4–59.0) in the atezolizumab group and 38.2% (95% CI, 31.2–45.3) in the placebo group.

Figure 4.2: Kaplan-Meier plot of OS in ITT population, data cut-off date 24 April 2018



Source: CS, Figure 3, page 38.
Mo = Months; CI = Confidence interval

The company performed subgroup analyses for demographics (e.g., age, gender and race/ethnicity), baseline prognostic characteristics (e.g., ECOG performance status, smoking status, presence of brain metastases at baseline), and pre-specified blood tumour mutational burden (bTMB) biomarker expression cut-offs (>10 or <10 and >16 or <16), by investigating the duration of OS in these subgroups. Results are reported in Appendix E of the CS and show that the hazard ratios for overall survival are better for older patients (HR=0.53 (95% CI: 0.36 to 0.77) for ≥65 yr versus HR=0.92 (95% CI: 0.64 to 1.32) for <65 yr); and for those without brain or liver metastases (Brain: HR=0.68 (95% CI: 0.52 to 0.89) for no metastases versus HR=1.07 (95% CI: 0.47 to 2.43) for those with metastases; Liver: HR=0.64 (95% CI: 0.45 to 0.90) for no metastases versus HR=0.81 (95% CI: 0.55 to 1.20) for those with metastases).

ERG comment: At the time of the company submission to NICE (February 2019), OS data were almost a year old. Therefore, we asked the company for updated OS and PFS data in the clarification letter. Updated OS data are presented below.

- *Updated overall survival data*

As part of the response to clarification, the company provided updated OS data, with a clinical cut-off date (CCOD) of [redacted] (Table 4.7).[43] This updated exploratory analysis for OS was conducted, based on a pre-specified number of events (306 OS events) in the Statistical Analysis Plan Version 3 (dated 14 May 2018).

[redacted] Overall, [redacted].

Table 4.7: Overall survival in the ITT population, data cut-off date [redacted]

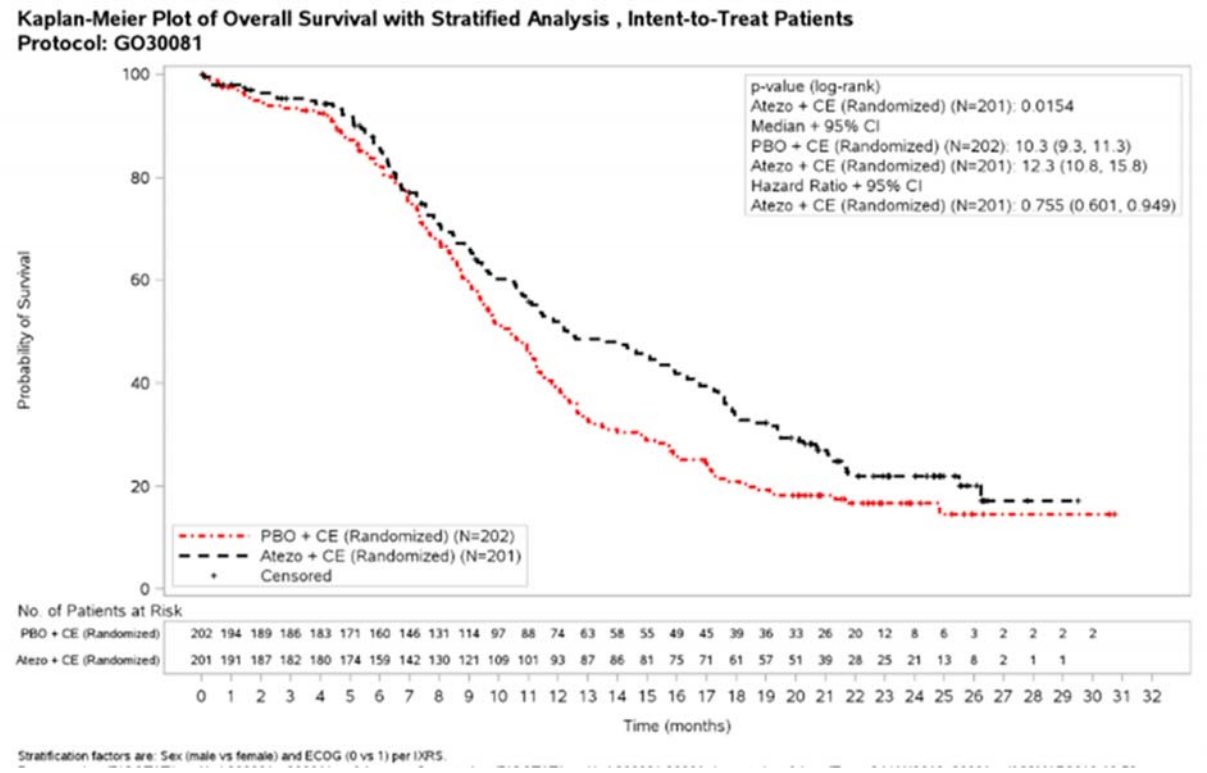
	Atezolizumab group	Placebo group
ITT population	n=201	n=202
Patients with event (%)	[redacted]	[redacted]
Median duration of survival (95%) (months)	[redacted]	[redacted]
Stratified hazard ratio (95%)	[redacted]	
p-value (log-rank)	[redacted]	
1-year event-free rate (%) (95% CI)	[redacted]	[redacted]
2-year event-free rate (%) (95% CI)	[redacted]	[redacted]

Source: Response to Clarification Letter, version 2, Question A10.
CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
[a] This value is descriptive.

At the time of data cut-off, [redacted], the median follow-up was [redacted] months. A total of [redacted] patients ([redacted]) in the atezolizumab group and [redacted] patients ([redacted]) in the placebo group had died. The stratified (gender and ECOG) HR for death was [redacted] (see Figure 4.3), and the two-year OS rate was [redacted] in the atezolizumab group and [redacted] in the placebo group.

The Kaplan-Meier estimated median OS was [redacted] in the atezolizumab group ([redacted]) vs. the placebo group ([redacted]) (see Figure 4.3).

Figure 4.3: Kaplan-Meier plot of OS in the ITT population, data cut-off date [redacted]



4.2.5.2 Progression-free survival

The study met the co-primary endpoint of PFS, demonstrating a statistically significant improvement in investigator-assessed PFS in favour of the atezolizumab group compared with the placebo group (HR

metastases (HR=0.75 (95% CI: 0.60 to 0.93) for no metastases versus HR=0.98 (95% CI: 0.49 to 2.00) for those with metastases).

ERG comment: In the IMpower133 trial, progression-free survival (PFS) was only assessed by investigators and not by an Independent Review Committee.

As specified by the company in the response to clarification (received 7 May 2019),[43] these data were
‘[redacted]’.

4.2.5.3 Objective response rate and duration of response

The objective response rate (ORR) and median duration of response (DOR) were similar between the treatment arms (see Table 4.9) In total, five patients (2.5%) in the atezolizumab group and two patients (1.0%) in the placebo group had a complete response.

Table 4.9: Response in the ITT population, data cut-off date 24 April 2018

	Atezolizumab group	Placebo group
Objective response rate		
ITT population	n=201	n=202
No. of responders (%)	121 (60.2%)	130 (64.4%)
95% Clopper-Pearson (%)	(53.1, 67.0)	(57.3, 71.0)
Difference in response rates[a]	[redacted]	
Duration of response		
ITT population responders	n=121	n=130
Patients with event (%)	103 (85.1%)	123 (94.6%)
Median DOR (months)[b]	4.2	3.9
Range	(1.4[c], 19.5)	(2.0, 16.1[c])
Ongoing response at data cut-off (%)	18 (14.9)	7 (5.4)

Source: CS, Table 10, pages 36-37.
DOR = duration of response; ITT = intent-to-treat.
[a] 95% Cl for Difference in Response Rates (Wald with Continuity Correction)
[b] Duration of response was assessed in patients who had an objective confirmed response and was defined as the time from the first occurrence of a documented objective response to the time of disease progression as determined by the investigator (according to RECIST) or death from any cause, whichever occurred first.
[c] Data for the lower range of the response in the atezolizumab group and the upper range of the response in the placebo group are censored.

4.2.5.4 Health-related quality of life

Patients in both the atezolizumab arm and the placebo arm reported improvements in function and HRQoL (See Figure 4.5). The company stated that “There was a trend of greater improvements in patient-reported lung cancer-related symptoms and physical function, with minimal impact from treatment-related toxicities observed in the atezolizumab arm versus the

placebo arm" (CS, page 42).[1] However, statistical significance of differences between treatment arms was not reported in the CS.

	Atezolizumab group (n=198)			Placebo group (n=196)		
AE type	**Grade 1–2**	**Grade 3–4**	**Grade 5**	**Grade 1–2**	**Grade 3–4**	**Grade 5**
Trigeminal neuralgia	0	1 (0.5)	0	0	0	0
Tubulointerstitial nephritis	0	1 (0.5)	0	0	0	0
Hypokalaemia	0	0	0	0	1 (0.5)	0
Hypomagnesemia	0	0	0	0	1 (0.5)	0
Neutropenic sepsis	0	0	0	0	1 (0.5)	0
Neutrophil count decreased	0	0	0	0	1 (0.5)	0
Pancreatitis	0	0	0	0	1 (0.5)	0
Urinary tract infection	0	0	0	0	1 (0.5)	0
White blood cell count decreased	0	0	0	0	1 (0.5)	0
Autoimmune colitis	1 (0.5)	0	0	0	0	0
Blood creatinine increased	1 (0.5)	0	0	0	0	0
Bronchitis	1 (0.5)	0	0	0	0	0
Cytomegalovirus infection	1 (0.5)	0	0	0	0	0
Diverticular perforation	1 (0.5)	0	0	0	0	0
Guillain−Barre syndrome	0	1 (0.5)	0	0	0	0
Haemoptysis	1 (0.5)	0	0	0	0	0
Pleural effusion	1 (0.5)	0	0	0	0	0

Source: CS, Table 17, pages 46-48.
* Incidence of treatment-related adverse events for any treatment. Multiple occurrences of the same AE in one patient were counted once at the highest grade for the preferred term.

4.2.7 Additional PD-L1 analyses

In response to the clarification letter (question A12) the company reported details of their analysis by [redacted] results. This included [redacted] data.

[redacted] were defined by applying [redacted] to raw scores. Because of the [redacted]. This is reported as 'TC' (tumour cells) or 'IC' (tumour infiltrating immune cells).

As some of the slides tested were [redacted]. The sample defined as [redacted] and the sample defined as [redacted] is that of [redacted]. In this section of the ERG report we report results for [redacted]; full results can be found in the company's response to the clarification letter.

In terms of OS [redacted]

[redacted]. This is based on the updated analysis with cut-off date of [redacted] (see Table 4.13).

Table 4.13: Overall survival by PD-L1 status in BEP2 population, data cut-off date [redacted]

	PD-L1 expression <1%		PD-L1 expression ≥1%	
Group	**Atezolizumab**	**Placebo**	**Atezolizumab**	**Placebo**
BEP2 population	[redacted]	[redacted]	[redacted]	[redacted]
Patients with event (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median duration of survival (months)	[redacted]	[redacted]	[redacted]	[redacted]
Stratified hazard ratio (95% Wald CI)	[redacted]		[redacted]	
Source: Clarification response, Question A12, Figure 2 BEP = biomarker evaluable population; CI = confidence interval				

Similarly, in terms of PFS [redacted] To note, these are results for the analysis performed with cut-off date 24 April 2018 (see Table 4.14). The Kaplan-Meier plot is not reported for the BEP2 sample.

Table 4.14: Progression free survival by PD-L1 status in BEP2 population, data cut-off date 24 April 2018

	PD-L1 expression <1%		PD-L1 expression ≥1%	
Group	**Atezolizumab**	**Placebo**	**Atezolizumab**	**Placebo**
BEP2 population	[redacted]	[redacted]	[redacted]	[redacted]
Patients with event (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median duration of survival (months)	[redacted]	[redacted]	[redacted]	[redacted]
Stratified hazard ratio (95% Wald CI)	[redacted]		[redacted]	
Source: Clarification response, Question A12, Figure 4 BEP = biomarker evaluable population; CI = confidence interval				

ERG comment: As can be seen from these results, [redacted], atezolizumab [redacted] in terms of [redacted] when compared to placebo. However, these results are based on [redacted] and exploratory subgroup analyses.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company included three trials in their indirect comparisons (See Figure 4.6):

- IMpower133[21, 23] (atezolizumab + carboplatin/etoposide versus carboplatin/etoposide)
- Skarlos 1994[44] (carboplatin/etoposide versus cisplatin/etoposide)
- Okamoto 2007[45] (carboplatin/etoposide versus cisplatin/etoposide)

SCLC. The study included 403 patients from 106 centres in 21 countries (USA, Europe, South America and Asia), with 10 patients from the UK (4 (2%) patients in the atezolizumab arm and 6 (3%) patients in the placebo arm).

The co-primary outcomes were overall survival (OS; the time from randomisation to death from any cause) and investigator-assessed progression-free survival (PFS, per RECIST v1.1; time from randomisation to disease progression or death from any cause, whichever occurred first). A final analysis of OS in the IMpower133 trial will occur after approximately 306 OS events in the ITT population have occurred; this analysis is anticipated in [redacted] and will be made available to NICE according to the company.

Baseline characteristics in the IMpower133 trial were well balanced between the groups. However, the population included in the IMpower133 trial may not be representative of the ES-SCLC patient population in UK practice. According to clinical experts employed by the company fewer than [redacted] of ES-SCLC patients in UK clinical practice would be diagnosed with an ECOG status of 0. In the IMpower133 trial, 35% of patients had an ECOG performance status of 0. Furthermore, all included patients in the IMpower133 trial had an ECOG performance status of 0-1. In appendix K, the company reports that "some advisors stated in their experience the probable proportions of UK ES-SCLC patients diagnosed as ECOG 0–1 would be as high as [redacted], with others reporting that in their clinical experience it could be as low as [redacted].".[39] Therefore, the population included in the IMpower133 trial might only represent a third of ES-SCLC patients in the UK.

A total of 201 patients were randomly assigned to the atezolizumab group, and 202 patients to the placebo group. Based on [redacted] data and at a median follow-up of [redacted] months, the median overall survival was [redacted] months in the atezolizumab group and [redacted] months in the placebo group (hazard ratio (HR) = [redacted] (95% confidence interval (CI): [redacted] to [redacted]). Based on April 2018 data, the median progression-free survival was 5.1 months and 4.3 months, respectively (HR = 0.77 (95% CI: 0.62 to 0.96). The objective response rate (ORR, Difference in response rates: [redacted]) and median duration of response (DOR, Median duration 4.2 months for atelozumab versus 3.9 months for placebo) were similar between the treatment arms. Patients in both the atezolizumab arm and the placebo arm reported improvements in function and HRQoL. However, statistical significance of differences between treatment arms was not reported in the CS. Time to deterioration (TTD) showed no statistically significant differences between treatment arms in patient-reported lung cancer symptoms (cough, chest pain, dyspnoea, arm/shoulder pain, fatigue and loss of appetite) or treatment-related symptoms (constipation, dysphagia, peripheral neuropathy, nausea/vomiting, diarrhoea and sore mouth).

Adverse events related to any component of the trial regimen occurred in 188 patients (94.9%) in the atezolizumab group and in 181 patients (92.3%) in the placebo group. The most common grade 3 or 4 adverse events related to the trial regimen were neutropenia, anaemia, and decreased neutrophil count. Deaths related to the trial regimen occurred in three patients (1.5%) in the atezolizumab group and in three patients (1.5%) in the placebo group. Immune-related adverse events occurred in 79 patients (39.9%) in the atezolizumab group and in 48 patients (24.5%) in the placebo group, with rash and hypothyroidism being the most common. The proportion of patients who experienced serious adverse events (SAEs) was 37.4% in the atezolizumab group and 34.7% in the placebo group. The most frequently reported SAEs were haematologic toxicities or infections.

In addition, the company stated that "[redacted]

[redacted]

[redacted]" (CS, page 50).[1] Results by [redacted] showed that, at a [redacted], atezolizumab produced [redacted] in terms of [redacted] when compared to placebo. However, these results are based on [redacted] and exploratory subgroup analyses.

The IMpower133 trial compares atezolizumab plus carboplatin and etoposide with placebo plus carboplatin and etoposide. The NICE scope describes the comparators as 'platinum-based combination chemotherapy regimens'. However, in the CS the company states that "chemotherapy regimens excluding etoposide are outside of the scope of this appraisal (CS, Appendix D, page 41).[1] This means treatment regimens such as carboplatin plus paclitaxel, irinotecan plus cisplatin, topotecan plus cisplatin, and paclitaxel plus cisplatin are not considered as comparators in the CS. The only comparators considered in the CS are carboplatin plus etoposide as reported in the IMpower133 trial and cisplatin plus etoposide based on an indirect comparison. The ERG believes that the results from this indirect comparison are unreliable and should not be used by NICE for decision making.

The company argues that "only carboplatin plus etoposide treatment is considered to be within the scope of this appraisal" (Response to clarification, Question A14).[9] This is based on advice from over 20 practising NHS oncologists that the standard of care in the NHS for untreated, ES-SCLC is carboplatin plus etoposide. In addition, the evidence for a comparison of atezolizumab plus carboplatin/etoposide versus carboplatin/etoposide is based on a head-to-head comparison (the IMpower133 trial), while evidence for other comparisons will have to rely on weaker evidence based on indirect comparisons. Therefore, the ERG would agree that carboplatin/etoposide is probably the most relevant comparator for this appraisal.

However, if the committee decides that all comparators mentioned in the NICE scope are relevant comparators, we have conducted an indirect comparison based on a limited search performed by the company (see Section 4.5 of this report), which shows that results for irinotecan plus carboplatin are similar to atezolizumab plus carboplatin/etoposide in terms of OS, PFS, and response.

Table 5.6: Ranking of OS parametric distributions from IMpower133 trial data based on AIC, BIC, visual fit and clinical plausibility

Parametric distribution	AIC Atezo	BIC Atezo	AIC Control	BIC Control	Visual fit to KM	Ranking overall
Log-logistic	469	476	483	490	Best fit and most plausible	1
Weibull	468	475	490	497	Good fit for data but not plausible tail	2
Gen Gamma	470	480	491	501	Poor fit	3
Gompertz	476	482	506	512	Poor fit	4
Exponential	491	494	518	521	Poor fit	5
Log normal	499	506	517	524	Poor fit	6

Source: Table 18, response to clarification letter stage 2.[43]
AIC = Akaike information criteria; BIC = Bayesian information criteria; KM = Kaplan-Meier

Table 5.7: Parametric extrapolations of the proportion of patients alive (OS) following carboplatin-etoposide treatment, using only IMpower133 data to inform the extrapolation

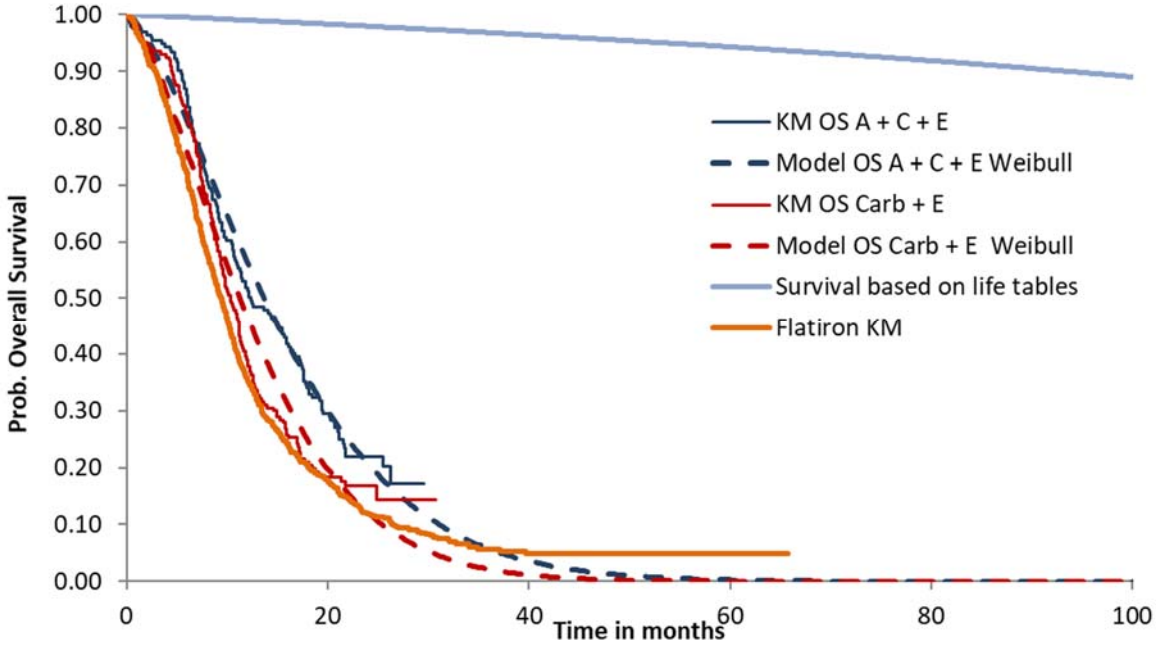
Time (months)	Parametric extrapolations						Real-world data of chemotherapy survival validated as appropriate by UK-practising experts	Difference between real-world data and parametric extrapolation	
	Weibull	Gompertz	Generalised gamma	Log-logistic	Exponential	Log-normal		Weibull	Log-logistic
12	47%	47%	46%	44%	43%	44%	[redacted]	14%	11%
24	12%	12%	12%	15%	18%	19%	[redacted]	5%	8%
36	2%	1%	3%	7%	8%	10%	[redacted]	0%	5%
48	0%	0%	1%	4%	4%	6%	[redacted]	0%	3%
60	0%	0%	0%	3%	2%	3%	[redacted]	0%	2%

Source: Adapted from Table 23 of the CS using the company model, ID1504 Atezolizumab Roche CE model PAS price v2 070519 JM [PAS]

Table 5.8: Survival extrapolations for the control arm, using different statistical approaches and data sources

Time (months)	Parametric extrapolations		Real-world data of chemotherapy survival validated as appropriate by UK practising experts*		
	Log-logistic control arm – February submission	Log-logistic updated, control arm – base case		Log-logistic (updated) with Flatiron data after 22 months (generalised gamma)*	Log-logistic (updated) with Flatiron data after 22 months (Log-logistic)*
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 5.4: Weibull extrapolation of IMpower133 OS data



Source: Figure 6, response to clarification letter stage 2.[43]

Table 5.9: Parametric extrapolations of the proportion of patients alive (OS) following atezolizumab plus carboplatin-etoposide treatment, using only IMpower133 data to inform the extrapolation

Time (months)	Parametric extrapolations						UK-practising clinical experts' opinion, based on real-world data and IMpower133 benefit	Difference between clinical expert opinion and parametric extrapolation*	
	Weibull	Gompertz	Generalised gamma	Log-logistic	Exponential	Log-normal		Weibull	Log-logistic
12	57%	58%	56%	54%	52%	53%	[redacted]	17%	14%
24	20%	23%	22%	23%	26%	27%	[redacted]	8%	11%
36	6%	11%	10%	12%	14%	16%	[redacted]	1%	7%
48	1%	6%	6%	7%	8%	10%	[redacted]	-1%	5%
60	0%	4%	4%	5%	5%	7%	[redacted]	-1%	3%

Source: Adapted from Table 24 of the CS using the company model, ID1504 Atezolizumab Roche CE model PAS price v2 070519 JM [PAS]
*Midpoint of clinical expert opinion used where range given

5.2.6.3 Time to off treatment

For TTOT, for atezolizumab only, as explained above, the generalised gamma provided the best statistical fit of the parametric function to the actual data (Table 5.10). The company noted that all the standard parametric curves provided a similarly poor visual fit to the Kaplan-Meier data. [redacted]. No external validation was performed for TTOT.

for years 3 to 5 (Table 5.7). Therefore, its overestimation of UK clinical practice is likely to be less than that by the log-logistic given, as described in points (2) and (3), Flatiron is likely to produce an overestimate of OS. Therefore, the ERG would argue that the Weibull is likely to be more clinically plausible and it provides nearly as good a statistical fit, which is why it has been chosen for the comparator in the ERG base-case (see Section 5.3 below). It is true that, in response to clarification letter stage 2, a completely different set of figures was provided in the column for "Real-world data of chemotherapy survival validated as appropriate by UK-practising experts" and that these data are closer to the estimates from the log-logistic extrapolation.[43] However, the ERG believe that this is not an appropriate method to validate an extrapolation based on the trial data. Adjusting these data in any way undermines their status as providing "real-world" external validation. Adjusting those data after they had been presented to the clinical experts undermines their status has having been "validated as appropriate by UK-practising experts". Nevertheless, given the marginally better statistical fit of the log-logistic, the ERG has included this in a scenario analysis (see Section 5.3).

For the intervention, the ERG also disagrees with the choice of the log-logistic on the basis of clinical plausibility as well as it having a marginally worse statistical fit than the Weibull. The main reason for this judgement is that there is in fact are no real-world data by which any estimates can be externally validated and the ERG questions the validity of clinical expert opinion as to the effect of a treatment for which they would have had no clinical experience. However, as with the comparator, one can compare the percentages surviving at each of the five time points (shown in Table 5.9) elicited from the clinical experts with those from the log-logistic and the model with the best statistical fit, the Weibull. When one does that it can be seen that, as for the comparator, the values for the log-logistic are all higher than those elicited from the clinical experts. The same is also true for the Weibull for the first three time points, but by more than the log-logistic only in year 1 and by less in all other years. Indeed the difference between the Weibull and those elicited from the clnical experts is only 1% for the last three time points, either above or below. Therefore, the ERG would argue that the Weibull is likely to be more clinically plausible and it provides a better statistical fit, which is why it has been chosen for the intervention in the ERG base case (see Section 5.3 below).

The company also claim that the [redacted] However, the ERG would argue that whilst such a bias would seem plausible it is impossible to estimate its size and adjust for it directly. Indeed, the ERG have located a conference abstract that showed no survival advantage to one of those immunotherapies i.e. nivolumab at second line for advanced SCLC.[56] One can, however, choose the most plausible curve for each of the comparator and the intervention as described above, which is the Weibull, based both on statistical fit and clinical plausibility. This will be used in the ERG base-case (see Section 5.3).

The ERG also questioned the implementation in the model of OS for the intervention, which included a formula that ensured that it would always be at least as high as that for the comparator, carboplatin plus etoposide. In response to clarification the company defended this by stating the this was supported by clinical expert opinion.[9] However, the ERG would argue that it is impossible for any clinical expert to predict the relative survival at any time point by any means other than based on empirical data, the only source of which is the IMpower133 study. Therefore, the ERG chose to remove this formula and inform OS only by the survival model fit to the trial data (see Section 5.3 below).

The ERG also identified an error with the implementation of PFS estimation on the model, which was stated to have been corrected by the company in the response to clarification letter.[9] On examination by

the ERG, it was noticed that it had not been corrected. However, the error has no effect on the base-case or any scenario except one where the treatment effect for PFS is assumed to be finite, the effect of

Table 5.26: Company and ERG base-case preferred assumptions

Base-case preferred assumptions	Company-base case	Justification*	ERG	Justification for change
PFS in first cycle for comparator	PFS not starting at 1 in the first cycle for comparator	This appears to be a mistake in that it is 1 for atezolizumab plus carboplatin-etoposide	PFS starts at 1 in the first cycle for comparator	In order to achieve consistency between intervention and comparator
OS for intervention relative to comparator	OS for intervention always being at least as high as comparator	Based on clinical expert opinion	Removed formula to ensure OS for intervention always being at least as high as comparator	Section 5.2.6
OS extrapolation model	Log-logistic chosen for intervention and comparator	Visual and statistical fit External validation of comparator arm using the Flatiron study, itself validated by clinical expert opinion	Weibull chosen for intervention and comparator	Section 5.2.6
Utility estimation	Based on time to death	This is in line with previous NICE appraisals, and clinical expert opinion	Based on progression status	Section 5.2.8
AE disutilities	Not included	Effect already included in time to death approach	Included	Section 5.2.8
AE = adverse event; OS = overall survival; PFS = progression free survival				

5.3.1 ERG base case results

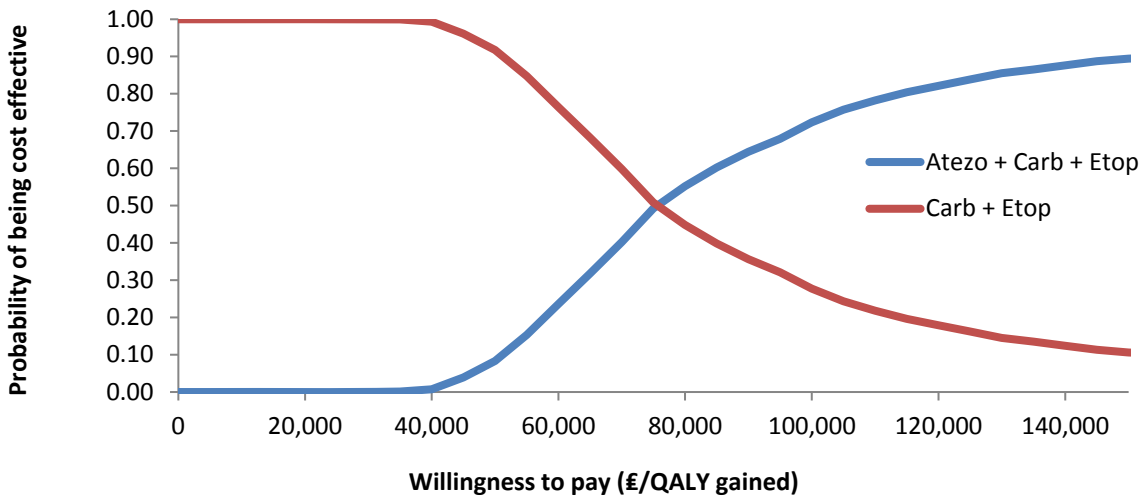
The results of the deterministic ERG base case showed that incremental costs were [redacted] and incremental QALYs were 0.17 (Table 5.27). This result is an ICER of £75,586, which was mainly driven by using the Weibull distribution for OS in both intervention and comparator arms instead of Log-logistic.

Compared with the deterministic ERG base-case results, the ERG PSA with 5,000 iterations resulted in higher incremental QALYs and slightly higher incremental costs, which resulted in an ICER that was less than 2% higher than the deterministic result of £76,930. The cost effectiveness acceptability curve showed that atezolizumab approximately had a 0.0% and 8.3% probability of being cost effective at willingness-to-pay (WTP) thresholds of £30,000 and £50,000 respectively (Figure 5.5).

Table 5.27: ERG base-case results

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Deterministic ERG-base case					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,586
Carb + Etop	[redacted]	[redacted]			
Probabilistic ERG base-case					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.16	£76,930
Carb + Etop	[redacted]	[redacted]			
Atezo = atezolizumab; Carb = carboplatin; ERG = Evidence Review Group; Etop = etoposide; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year.					

Figure 5.1: ERG base-case cost effectiveness acceptability curve



5.3.2 Additional exploratory analyses performed based on the ERG base-case

The ERG also conducted exploratory analyses based on the ERG base-case and as a matter of judgement:

1) Weibull model for OS for intervention and log-logistic for comparator, as discussed in Section 5.2.6. This does not include element (2) of the ERG base-case. This is because of implausible crossing of the intervention and comparator survival curves.
2) Switch from K-M to parametric curve for PFS at 15 instead of 5 months, as discussed in Section 5.2.6
3) Ensure that TTOT does not sink lower than PFS after 14 months (limit of K-M data), as discussed in Section 5.2.6
4) Unit cost of diarrhoea £998 instead of £182, as discussed in Section 5.2.9
5) Unit cost of vomiting £788 instead of £182, as discussed in Section 5.2.9

The results are shown in Table 6.2 in Section 6.

clinical expert opinion as the effect of a treatment for which they would have had no clinical experience. However, as with the comparator, one can compare the percentages surviving at each of the five time points from the clinical experts with those from the log-logistic and the model with the best statistical fit, the Weibull. When one does that it can be seen that the values for the Weibull for only the first three time points are higher than those elicited from the clinical experts, but by more than the log-logistic only in year 1 and they are different by less than the log-logistic in all other years i.e. 2 to 5. Therefore, the ERG would argue that the Weibull is more likely to be clinically plausible and it provides a better statistical fit, which is why it has been chosen for the intervention in the ERG base-case.

The ERG considers that the company appropriately identified the AEs that were most important to include in terms of the potential impact on cost and utility. However, the ERG believes the justification provided by the company stating that AEs are implicitly captured by EQ-5D is questionable. According to NICE TSD 12 it is important to include decrements on HRQoL associated with AEs of at least Grade 3.[63] The ERG therefore included AE disutilities. The ERG also questions the validity of the 'time to death' method employed by the company, although in the clarification letter response, the company provided references to previous STAs that used the 'time to death' approach. The ERG would argue that, despite use of the approach in previous STAs, it still remains unvalidated as evidenced by no mention in any of the NICE TSDs. It neglects the more established method of using progression status to determine utility value, it incorporates the effect of being on or off treatment with questionable clinical validity especially not having statistically tested the effect of both treatment and progression status and it is implemented by the arbitrary division into four time to death categories. In response to clarification letter, the company failed to provide what the ERG requested i.e. full statistical analysis of various models including both on/off treatment and progressed/not progressed as well as time to death as a continuous variable. Therefore, the ERG chose the more conservative approach of measuring utility as a function of progression status and not time to death in the ERG base-case.

The ERG believe that costs were generally estimated in a way that seemed plausible. The ERG has some concerns over the unit costs used for adverse events. This being said, the impact of using alternative unit cost estimates on the final ICER is very limited. However, alternative more costly estimates were used in TA531 (equating to £998 for diarrhoea and £788 for vomiting). It is not clear why the company chose the specific unit costs for adverse events.[60]

The ERG base-case resulted in an ICER of £75,585 for atezolizumab plus carboplatin and etoposide versus carboplatin and etoposide only. This increase from the company base-case is due mainly to the decrease in the incremental QALYs from 0.25 to 0.17. Most of this decrease is due to the Weibull instead of the log-logistic, which by itself resulted in an ICER of £69,290. None of the scenario analyses chosen by the ERG made much difference and none decreased the ICER to below the £50,000 threshold.

Finally, the ERG would contend that, given evidence of variation in effectiveness according PD-L1 subgroup, the subgroup analysis of cost effectiveness is still relevant and particularly given the possibility that atezolizumab might not be cost effective for the whole population as shown in the ERG base-case.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.1 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.2. These are all conditional on the ERG base-case.

Table 6.1: Deterministic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,588
Carb + Etop	[redacted]	[redacted]			
Fixing error (Corrects PFS not starting at 1 in first cycle)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,577
Carb + Etop	[redacted]	[redacted]			
Fixing error (Corrects OS for intervention always being at least as high as comparator)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,588
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Uses Weibull for OS for both intervention and comparator)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.18	£69,260
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Utility is a function of progression status and not time to death)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.23	£53,724
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (AE disutilities from literature)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.25	£49,664
Carb + Etop	[redacted]	[redacted]			
ERG base-case					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,586
Carb + Etop	[redacted]	[redacted]			

AE = adverse event; Atezo = atezolizumab; Carb = carboplatin; CS = company submission; ERG = Evidence Review Group; Etop = etoposide; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year.

Table 6.2: Deterministic scenario analyses conditional on ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Matter of judgement (Weibull for intervention and log-logistic for comparator for OS)*					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.14	£67,654
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Ensures that TTOT does not sink lower than PFS after 14 months (limit of K-M data))					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£77,891
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Change time at which PFS moves from K-M to Log-logistic)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,506
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Diarrhoea unit cost £998)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,631
Carb + Etop	[redacted]	[redacted]			
Matter of judgement (Vomiting unit cost £788)					
Atezo + Carb + Etop	[redacted]	[redacted]	[redacted]	0.17	£75,601
Carb + Etop	[redacted]	[redacted]			

Atezo = atezolizumab; Carb = carboplatin; ERG = Evidence Review Group; Etop = etoposide; ICER = incremental cost effectiveness ratio; K-M = Kaplan-Meier; PFS = progression-free survival; QALY = quality-adjusted life year; TTOT = time to of treatment.
*Excluding element (2) of ERG base case because of implausible crossing of the intervention and comparator survival curves.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm on Monday 2 September 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche Products Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nothing to disclose**

Questions for engagement

Issue 1: Comparators	
Is carboplatin plus etoposide the only relevant comparator?	Roche have been advised by over 20 practising NHS oncologists during individual consultation meetings and two separate advisory board meetings in 2018 and 2019 that the standard of care in the NHS for untreated, extensive-stage small cell lung cancer (ES-SCLC) is 4–6 cycles of carboplatin plus etoposide (Appendix K of Submission Document). Furthermore, during the Technical Engagement teleconference on the 6th August, Dr Alastair Greystoke (Consultant Medical Oncologist, Sir Bobby Robson Clinical Trials Unit, Freeman Hospital) confirmed that cisplatin is not used for ES-SCLC and that in clinical practice, virtually 100% of patients with ES-SCLC receive carboplatin-etoposide. Dr Greystoke stated that a comparison to cisplatin-etoposide would be out of scope in this appraisal as it is typically used with borderline limited-stage small cell lung cancer patients, rather than ES-SCLC patients. Moreover, the anticipated marketing authorisation wording is "Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with ES-SCLC." Therefore, patients typically receiving cisplatin (i.e., limited-stage patients) cannot receive atezolizumab. It is also worth noting that Roche have presented an exploratory comparison to cisplatin-etoposide in both our original submission and response to clarification questions including the January 2019 data cut. This showed a similar cost-effectiveness to that when comparing to carboplatin + etoposide (ICER £47,477 for cisplatin + etoposide vs £49,588 for carboplatin+ etoposide; Table 12 clarification response). Roche do, however, consider this comparison to be unreflective of current clinical practice (as per above) and also less robust due to lack of ability to fully consider the side effects and the reliance on indirect comparison rather than head-to-head trial data. All other platinum-based combination chemotherapies are not considered relevant to this appraisal as they are either not used in the UK (irinotecan-based therapies) or would only be given to carboplatin-ineligible patients, who would be outside of the anticipated licence for the atezolizumab plus carboplatin and etoposide regimen.

What proportion of patients have cisplatin plus etoposide?	During the Technical Engagement teleconference on the 6th August, Dr Greystoke confirmed that cisplatin is not used for ES-SCLC and that in clinical practice, virtually 100% of patients with ES-SCLC receive carboplatin-etoposide. It was noted by UK clinical experts at an advisory board in November 2018 (Appendix K of the Submission Document) that up to [redacted] of untreated ES-SCLC patients received cisplatin-etoposide and whilst the efficacy benefits are similar between cisplatin and carboplatin, the low use of cisplatin is due to safety and service implications: specifically increased risk of heart failure associated with longer infusion times for cisplatin-etoposide, a reportedly more severe adverse event profile, and increased administration costs to the NHS.
Issue 2: Network meta-analysis and Indirect comparison	
Are the results from the company's network meta-analysis and indirect comparison for the comparison of carboplatin-etoposide with cisplatin-etoposide reliable for decision-making?	Roche agrees with the ERG and NICE's Technical Team regarding the limitations of the network meta-analysis submitted for this appraisal. However, it is worth highlighting, this does not have a bearing on the appraisal if it is considered that carboplatin-etoposide is the only relevant comparator, as detailed in response to Issue 1. Dr Greystoke confirmed during the Technical Engagement teleconference that although the literature in the network meta-analysis are not very recent, clinical practice has not changed since these studies were published. Furthermore, it was agreed during the Technical Engagement teleconference that although the network meta-analysis has limitations, there are no additional studies available that can improve the current analysis. At the ERG clarification stage, a fully incremental cost-effective analysis was presented for the company base case deterministic analysis of atezolizumab plus carboplatin-etoposide and cisplatin-etoposide (Table 27 of the clarification response – Version 3). In line with clinical opinion, the assumptions used were as follows: equivalent progression-free survival of cisplatin to carboplatin (due to lack of progression-free survival data informing the network meta-analysis), cisplatin drug costs, and increased administration time. In addition, an assumption of equivalent safety profiles was required; this was not in line with clinical opinion but there was a lack of reliable data. Assuming equal efficacy between cisplatin plus etoposide and carboplatin plus etoposide, cisplatin plus etoposide will be dominated by carboplatin plus etoposide. Therefore, although the cisplatin-etoposide comparison may be difficult to accurately quantify without a reliable network meta-analysis and safety data, it can be assumed that the

	incremental cost effectiveness ratio (ICER) would be more favourable for carboplatin-etoposide. Hence, excluding cisplatin plus etoposide is a conservative approach in terms of the ICER calculation within this appraisal. The network meta-analysis was included by Roche solely for completeness and for transparency of decision making. Given cisplatin is not a relevant comparator for this appraisal and the exploratory analysis presented indicate that cisplatin is dominated by carboplatin (including if we assume the two therapies have equal effectiveness in line with clinical opinion), the fact that a robust comparison cannot be presented versus cisplatin is anticipated to have little impact on this appraisal.
Issue 3: Time-to-death approach for estimating utilities	
Is the time-to-death approach a reliable method for estimating utilities?	In order to address the ERG and NICE technical team's concerns over the validity and suitability of the time to death approach and its statistical fit, further analysis has been conducted in line with the request made by the ERG in clarification question B5. Whilst the use of progression status to predict utility is common in NICE appraisals, use of progression status in isolation has been shown to be sub-optimal in a variety of prior immune-oncology appraisals. The evidence available for this appraisal indicates that this is also the case here: progression status has only a minor impact on utilities (~0.015 in the analysis using progression status alone) and, as is shown below, is less useful in prediction than time to death with, at best, borderline significance and small effect size. **Categorical vs continuous time** A repeated measures model, estimating utility as a function of treatment arm, baseline utility, progression status, treatment status and time to death as a continuous variable was fitted to the IMpower133 EQ-5D utility data (including patients who died only). This shows that progression status and treatment arm are not significant predictors of patient utility, but treatment status and time to death are. In the previous company analysis, each category included records for patients who had died during the trial and censored patients who had over 30 weeks' follow-up who were assigned to the time to death category of >30 weeks. However, in this analysis, in order to be able to look at whether a continuous model fitted better than models using time banding, censored patients were excluded.

Table 1: Repeated measures model for utility, including progression status, treatment status and time to death as a continuous variable

Effect	Estimate	Standard Error	Pr > |t|
Atezolizumab + Carboplatin + Etoposide	[redacted]	0.01623	0.4497
Placebo + Carboplatin + Etoposide			
Baseline utility	[redacted]	0.03563	<.0001
Intercept	[redacted]	0.02847	<.0001
Progression-free	[redacted]	0.01413	0.3907
Progressed			
Time to death (weeks)	[redacted]	0.000277	0.0153
On treatment	[redacted]	0.01377	<.0001
Off treatment			
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1413.7	[redacted]	-1409.7	-1402.6

The same model was run using categories for time to death (using the same time categories as used in the company base case, and two additional models for time categories one week earlier and one week later to test sensitivity), rather than using a continuous variable.

All of the models using time categories provided a better statistical fit according to AIC and BIC, and were therefore carried forward.

Table 2: Repeated measures model for utility, including progression status, treatment status and time to death as a categorical variable using categories as per the company base case

Effect	Estimate	Standard Error	Pr > |t|
Atezolizumab + Carboplatin + Etoposide	[redacted]	0.01609	0.5065
Placebo + Carboplatin + Etoposide			
Baseline utility	[redacted]	0.03531	<.0001
≤ 5 weeks before death	[redacted]	0.02538	<.0001
> 5 & ≤ 15 weeks before death	[redacted]	0.01798	0.0017
> 15 & ≤ 30 weeks before death	[redacted]	0.009906	0.0211
> 30 weeks before death			
Intercept	[redacted]	0.03076	<.0001
Progression-free	[redacted]	0.01366	0.1884

Progressed			
On treatment		0.01364	0.001
Off treatment			
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1472.6		-1468.6	-1461.5

Table 3: Repeated measures model for utility, including progression status, treatment status and time to death as a categorical variable using categories one week earlier than the company base case

Effect	Estimate	Standard Error	Pr > |t|
Atezolizumab + Carboplatin + Etoposide		0.01613	0.461
Placebo + Carboplatin + Etoposide			
Baseline utility		0.03536	<.0001
≤ 4 weeks before death		0.0298	<.0001
> 4 & ≤ 14 weeks before death		0.01843	0.0006
> 14 & ≤ 29 weeks before death		0.00984	0.0192
> 29 weeks before death			
Intercept		0.03065	<.0001
Progression-free		0.01364	0.1642
Progressed			
On treatment		0.01358	0.002
Off treatment			
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1487.4		-1483.4	-1476.3

Table 4: Repeated measures model for utility, including progression status, treatment status and time to death as a categorical variable using categories one week later than the company base case

Effect	Estimate	Standard Error	Pr > |t|
Atezolizumab + Carboplatin + Etoposide		0.01598	0.4583
Placebo + Carboplatin + Etoposide			
Baseline utility		0.03508	<.0001
≤ 6 weeks before death		0.02285	<.0001
> 6 & ≤ 16 weeks before death		0.01739	0.0005
> 16 & ≤ 31 weeks before death		0.009929	0.0194
> 31 weeks before death			

Intercept	[redacted]	0.03065	<.0001
Progression-free	[redacted]	0.0137	0.2609
Progressed			
On treatment	[redacted]	0.01363	0.0007
Off treatment			
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1465.0	[redacted]	-1461.0	-1453.9

The impact of progression status

In each of the categorical models carried forward, treatment arm and progression status were not significant predictors of utility.

Interaction terms between the significant categorical variables (time to death and treatment status) were tested and included in each of the utility models using time to death as a categorical variable. Non-significant variables ($p<0.1$) were then removed to create a final utility model.

In all three models, treatment arm was non-significant and was therefore not included in the regression equations. Progression status was also removed as non-significant in the model with time categories one week later than the company base case (Table 5). In the other two models, progression status was retained but had only borderline significance and a small effect size (~0.02) (Table 6 and Table 7). The model with time categories one week earlier than those in the company base case provided a marginally better statistical fit than the other two models.

Table 5: Repeated measures model for utility, including treatment status and time to death as a categorical variable using categories one week later than the company base case, and interaction terms

Effect	Estimate	Standard Error	Pr > |t|
Baseline utility	[redacted]	0.03473	<.0001
≤ 6 weeks before death	[redacted]	0.03358	<.0001
> 6 & ≤ 16 weeks before death	[redacted]	0.02881	<.0001
> 16 & ≤ 31 weeks before death	[redacted]	0.02228	0.0843
> 31 weeks before death			
Intercept	[redacted]	0.03072	<.0001
On treatment	[redacted]	0.01683	0.1604
Off treatment			
On treatment * ≤ 6 weeks before death	[redacted]	0.04296	<.0001

On treatment * > 6 & ≤ 16 weeks before death	[redacted]	0.03383	0.0066
On treatment * > 16 & ≤ 31 weeks before death	[redacted]	0.02375	0.6378
On treatment * > 31 weeks before death			
Off treatment * ≤ 6 weeks before death			
Off treatment * > 6 & ≤ 16 weeks before death			
Off treatment * > 16 & ≤ 31 weeks before death			
Off treatment * > 31 weeks before death			
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1494.6	[redacted]	-1490.6	-1483.5

Table 6: Repeated measures model for utility, including progression status, treatment status, and time to death as a categorical variable using categories as per the company base case, and interaction terms

Effect	Estimate	Standard Error	Pr > |t|
Baseline utility	[redacted]	0.03492	<.0001
≤ 5 weeks before death	[redacted]	0.03606	<.0001
> 5 & ≤ 15 weeks before death	[redacted]	0.02929	<.0001
> 15 & ≤ 30 weeks before death	[redacted]	0.02189	0.0452
> 30 weeks before death			
Intercept	[redacted]	0.03127	<.0001
Progression-free	[redacted]	0.01364	0.0726
Progressed			
On treatment	[redacted]	0.01881	0.6839
Off treatment			
On treatment * ≤ 5 weeks before death	[redacted]	0.04873	<.0001
On treatment * > 5 & ≤ 15 weeks before death	[redacted]	0.03508	0.001
On treatment * > 15 & ≤ 30 weeks before death	[redacted]	0.02341	0.3788
On treatment * > 30 weeks before death			
Off treatment * ≤ 5 weeks before death			
Off treatment * > 5 & ≤ 15 weeks before death			
Off treatment * > 15 & ≤ 30 weeks before death			
Off treatment * > 30 weeks before death			
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1493.2	[redacted]	-1489.1	-1482

Table 7: Repeated measures model for utility, including progression status, treatment status, and time to death as a categorical variable using categories one week earlier than the company base case, and interaction terms

Effect	Estimate	Standard Error	Pr > |t|
Baseline utility	[redacted]	0.03496	<.0001
≤ 4 weeks before death	[redacted]	0.03953	<.0001
> 4 & ≤ 14 weeks before death	[redacted]	0.02948	<.0001
> 14 & ≤ 29 weeks before death	[redacted]	0.02136	0.0243
> 29 weeks before death			
Intercept	[redacted]	0.03107	<.0001
Progression-free	[redacted]	0.01359	0.0934
Progressed			
On treatment	[redacted]	0.01828	0.6581
Off treatment			
On treatment * ≤ 4 weeks before death	[redacted]	0.05845	<.0001
On treatment * > 4 & ≤ 14 weeks before death	[redacted]	0.03625	0.0005
On treatment * > 14 & ≤ 29 weeks before death	[redacted]	0.02276	0.244
On treatment * > 29 weeks before death			
Off treatment * ≤ 4 weeks before death			
Off treatment * > 4 & ≤ 14 weeks before death			
Off treatment * > 14 & ≤ 29 weeks before death			
Off treatment * > 29 weeks before death			
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1502.7	[redacted]	-1498.7	-1491.6

Table 8 presents the utility values based on the new analysis vs the company base case. Health states were defined by the variables included in corresponding final models.

Table 8: Health state utility values for repeated measures models

Health state			Company base case	New utility regression models		
Time	Treatment	Progression		TTD using base case categories	TTD using categories one week earlier	TTD using categories one week later
1	0	0	[redacted]	[redacted]	[redacted]	[redacted]
1	0	1		[redacted]	[redacted]	
2	0	0	[redacted]	[redacted]	[redacted]	[redacted]
2	0	1			[redacted]	
3	0	0	[redacted]	[redacted]	[redacted]	[redacted]
3	0	1		[redacted]	[redacted]	
4	0	0	[redacted]	[redacted]	[redacted]	[redacted]
4	0	1		[redacted]	[redacted]	
1	1	0	[redacted]	[redacted]	[redacted]	[redacted]
1	1	1		[redacted]	[redacted]	
2	1	0	[redacted]	[redacted]	[redacted]	[redacted]
2	1	1		[redacted]	[redacted]	
3	1	0	[redacted]	[redacted]	[redacted]	[redacted]
3	1	1			[redacted]	
4	1	0	[redacted]	[redacted]	[redacted]	[redacted]
4	1	1		[redacted]	[redacted]	

Key: Time (base case), 1=<35 days before death, 2=>= 35 and <75 days before death, 3=>= 75 and <210 days before death, 4=>210 days before death; Treatment, 0=on treatment, 1=off treatment; Progression, 0=progression-free, 1=progressed.

The health state utilities for all of the time cut offs tested were similar to the company base case values, showing that the model is not sensitive to the time cut-offs used for the categories.

Impact on the ICER

All three new models (Table 5, Table 6, and Table 7) which investigated the inclusion of progression status as well as time to death using time in a categorical format have been added into the cost-effectiveness model as scenario analyses (with the master switch placed in B15 of the ERG sheet, and individual model selections made using cell L142 in the Utility sheet), with resulting ICERs as follows (including the ERG correction for fixing PFS starting at the first cycle, and including AE disutilities):

Table 9: Incremental cost-effectiveness ratios using alternative utility models

Scenario	ICER (Atezo+C+E versus Carb+Etop)
Company base case	£49,654
Using ERG requested utility model with TTD categories as per company base case	£51,060
Using ERG requested utility model with TTD categories one week earlier	£50,918 (best statistical fit)
Using ERG requested utility model with TTD categories one week later	£50,819

Conclusion

This analysis demonstrates that treatment status and time to death are significant predictors of health-related quality of life for ES-SCLC patients, that progression status is of borderline additional value, and that the original utility analysis presented by the company is a viable method, providing reasonable health state utility values. The ICERs produced by the model with the best statistical fit using the new analysis much more closely resemble those of the original company base case than those provided by the ERG based on progression status alone. This analysis supports the conclusion that the original company base case provides a more appropriate estimate of the ICER than the ERG analysis when all clinically relevant variables are taken into account.

	Additionally, we hope that the lack of model sensitivity to the cut-offs chosen reassures the technical team that the use of visual assessment to determine proximity-to-death categories has not had a major impact on modelled results. Given the borderline significance of progression status in the additional analysis presented and the ability to include more data in the original company model (censored patients with longer follow-up) we would recommend using the company's base case analysis as most appropriate.
Issue 4: Utilities associated with adverse events	
Should the economic model include disutilities associated with adverse events?	Roche agree to incorporate disutilities associated with adverse events into the model. Roche's submitted cost-effectiveness evaluation did not include additional disutility values for the adverse events reported in IMpower133 so as to avoid the risk of double-counting the effects of treatment (which were already included within the quality of life analysis from the trial) within the cost-effectiveness model. Given the minor differences in the adverse event profiles between the intervention and comparator arms of the IMpower133 trial (1), including additional disutilities for adverse events has a minimal impact on the ICER – as expected. This was demonstrated with an additional scenario analysis during the ERG clarification response, whereby individual adverse event disutilities were added (Table 14 of the clarification response – version 3). This scenario resulted in the base case changing from £49,588 to £49,664 per QALY for atezolizumab plus carboplatin and etoposide versus carboplatin and etoposide.
Issue 5: Long-term overall survival estimates	
Which extrapolation of overall survival is clinically plausible?	The preliminary judgement of NICE's Technical Team was that the Weibull extrapolation approach *could* be more clinically plausible for modelling the long-term overall survival (OS) of both arms of the IMpower133 study. However, as presented below, available data supports the log-logistic extrapolation approach being more appropriate. Whilst the Weibull extrapolation may have comparable Akaike Information Criterion and Bayesian Information Criterion (AIC/BIC) fit to the log-logistic extrapolation for the atezolizumab arm (1 point difference), the fit is notably

poorer in the control arm (7 point difference which warrants more consideration; Table 22 of the clarification response – version 3).

Further, and importantly the Weibull curve does not provide clinically plausible OS estimates for untreated ES-SCLC patients, as shown by the evidence sources detailed below.

To demonstrate that the Weibull extrapolation provides an overly conservative estimate of the long-term survival for both current standard of care and atezolizumab and that the log-logistic extrapolation better reflects this long-term survival, we provide data as follows:

- Published literature
- FlatIron registry data
- Clinical expert opinion
- Immuno-oncology trials

Published literature demonstrates the implausibility of the Weibull curve

The ERG states that the 'log-logistic extrapolation of IMpower133 overestimates OS'. Conversely, with the Weibull extrapolation predicting all ES-SCLC patients are dead by 40 months, Roche believe the Weibull is overly conservative.

To assess the validity of these conflicting views, pragmatic literature searches were performed to identify UK-specific data and in addition, US lung cancer databases (SEER, Cancer Treatment Centres of America [CTCA]) were reviewed. Search strategies are detailed in Appendix 2.

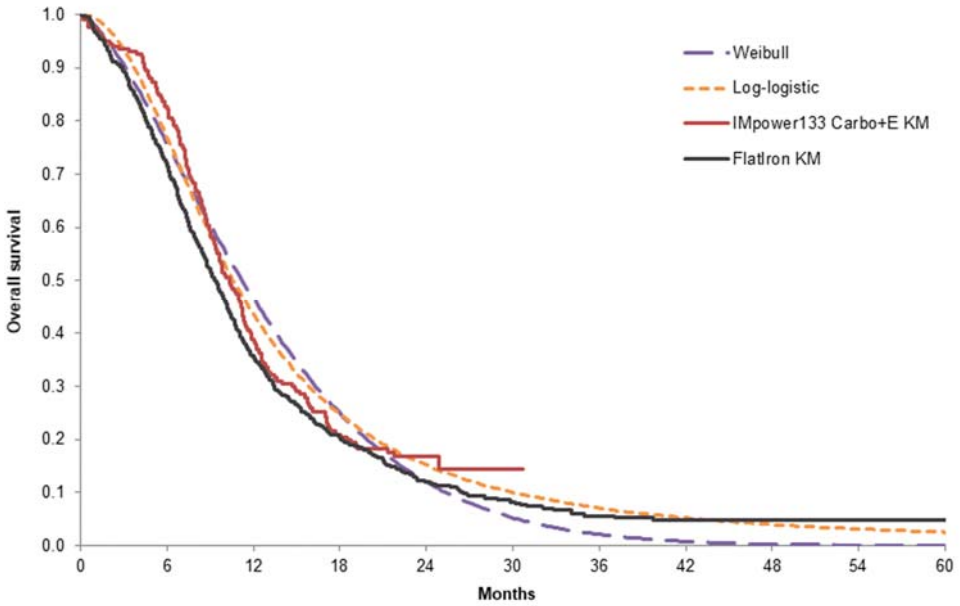
UK data:

Souhami and Law 1990 analysed the long-term results of 3,681 patients with SCLC from major centres in the UK during the period 1978–1986. Two-year survival for patients with extensive-stage disease was 2.2% (n=36), and of these patients, approximately 60% were still alive beyond 6 years. Importantly, a plateauing of the cumulative survival curve was reported here, showing a small number of patients surviving long term, even during the 1970's and 1980's (2).

	US data: Maneenil et al. 2017 is a retrospective analysis conducted on an ES-SCLC patient cohort diagnosed and followed from 1997 to 2015 at Mayo Clinic in Minnesota. Overall, there were 1.13% ES-SCLC patients with >3 year's survival (5). *Sweden and Denmark data:* Lassen et al. 1995 explored the characteristics of patients with SCLC who survive ≥5 years, to identify long-term prognostic factors. A cohort of 1,714 unselected patients (comprising LS-SCLC and ES-SCLC) treated with combination chemotherapy were included. Among these, the ES-SCLC cohort of patients had 5- and 10-year survival rates of 2.3% and 1.2%, respectively (4). *US lung cancer databases:* USA-based lung cancer databases (SEER and the Cancer Treatment Centres of America [CTCA]) were reviewed for survival rates in patients with distant (metastatic) SCLC (see Appendix 3, Figure 3) (3). Based on the CTCA database, approximately 6% and 3% of patients with distant (metastatic) SCLC were estimated to be alive at 3 and 5 years, respectively; whilst SEER reports 4% and 2% survival at the 3 and 5-year landmarks. Collectively, the published data identified via the pragmatic literature searches from large patient registries provide consistent evidence of a small but meaningful long-term survival rate among ES-SCLC patients. These survival estimates are based on a broader patient population than was targeted in the IMpower133 study, particularly regarding Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–1. Therefore, results from the IMpower133 study could be expected to be more favourable, with even higher proportions surviving long term. This demonstrates that the Weibull extrapolation provides overly conservative estimates of OS, and that the log-logistic extrapolation is the most clinically plausible as this curve allows for a small proportion of longer-term survivors.

	FlatIron registry data is consistent with the published literature in demonstrating a small proportion of long-term survivors The ERG states the 'FlatIron study probably overestimates OS compared to UK clinical practice'. The rationale behind this statement is unclear. Baseline characteristics data for the FlatIron cohort submitted were provided in the original submission documentation for this appraisal, showing similarity to the characteristics of the IMpower133 study population. It can therefore be concluded that the FlatIron cohort is a reasonable data source to estimate long-term survival beyond IMpower133. Roche have previously validated the Flatiron data cohort and results with UK clinical experts who consider these data to reflect NHS practice. During the Technical Engagement teleconference, Dr Greystoke also stated he considered the FlatIron data cohort to be 'useful for decision-making' in this appraisal. A visible comparison of observed OS outcomes for carboplatin-etoposide in IMpower133 and platinum-etoposide in FlatIron, show similar proportions of patients alive at 12 months (38%, IMpower133 carboplatin-etoposide vs 36%, platinum-etoposide Flatiron) and at the 13.9-month median study follow-up (29% IMpower133 carboplatin-etoposide vs 29%, platinum-etoposide Flatiron) (**Error! Reference source not found.**).

Figure 1: IMpower133 Kaplan-Meier OS, log-logistic and Weibull extrapolations vs FlatIron platinum+etoposide OS



Similar to the published literature presented above, present-day registry data from Flatiron conclusively demonstrate long-term survival among a small proportion of ES-SCLC patients treated with current standard of care (Table 10). This further demonstrates the appropriate use of the log-logistic extrapolation to determine long-term carboplatin-etoposide survival outcomes.

Table 10: Comparison of estimated survival and observed survival from databases

	ES-SCLC population	1-year OS	2-year OS	3-year OS	5-year OS
IMpower133, carboplatin-etoposide arm, **Weibull** survival extrapolation	PS 0-1 only	47%	12%	2%	0%

IMpower133, carboplatin-etoposide arm, **log-logistic** survival extrapolation	PS 0-1 only	44%	15%	7%	3%
Flatiron cohort	PS 0-1 only	36%	12%	5%	5%
CTCA observed	**PS unselected**	38%	13%	6%	3%
SEER observed	**PS unselected**	21%	7%	4%	2%

Clinical expert opinion

In line with the published data and evidence from Flatiron, expert clinical opinion has consistently reported a small but meaningful percentage of ES-SCLC patients treated with carboplatin-etoposide survive long term.

Specifically, expert clinical opinion was sought from over 20 practicing NHS oncologists gathered during individual consultations and two separate advisory board meetings held during 2018 and 2019, with consensus regarding there being a small but meaningful long-term survival among ES-SCLC patients treated on the NHS currently. Specifically, attendees at the November 2018 advisory board meeting (report provided in Appendix K of Submission Document) stated some long-term survivors were expected to survive beyond 2 years, with the attendees stating some had a few patients at 5-year and 10-year follow-up who were being discharged from ongoing monitoring for their ES-SCLC diagnosis.

Additionally, during this current Technical Engagement consultation period, 4 practicing Senior Lung Oncologists again confirmed they expected survival for some ES-SCLC patients beyond 40 months when treated with carboplatin-etoposide on the NHS (Appendix 1 – please note 3 of these 4 oncologists attended the advisory board meeting reported within Appendix K of the Submission Document).

Furthermore, the clinician and patient representative expert statements from the Technical Engagement Papers agree that a small proportion of patients are alive at 5 years:

- ‘The overall 5-year survival for SCLC (limited and extensive stage disease) is only about 5%’ Dr Jesme Fox, Roy Castle Lung Foundation

- '…proportion of patients alive at 5 years, [is] currently 2% with extensive stage SCLC.' Professor Samreen Ahmed, Clinical Expert and Professor Donal O'Donoghue (on behalf of British Thoracic Oncology Group)

Conclusion: the Weibull is an unrealistically conservative representation of survival on standard of care

The available published data and clinical expert opinion are consistent in their conclusion that a small proportion of patients can be expected to survive long term (5 years+) on current care.

Further, the patient population targeted in this appraisal - patients with previously untreated ES-SCLC with an ECOG PS score of ≤1 - is expected to have even more favourable long-term survival than the broader ES-SCLC population presented in the historical published information.

Together, the evidence presented clearly demonstrates that the Weibull extrapolation provides overly conservative estimates of OS (predicting all ES-SCLC patients are dead by 40 months), and that the log-logistic extrapolation is the most clinically plausible, allowing for a small proportion of longer-term survivors in line with the available data.

Evidence from immuno-oncology trials also demonstrate the implausibility of the Weibull curve for atezolizumab

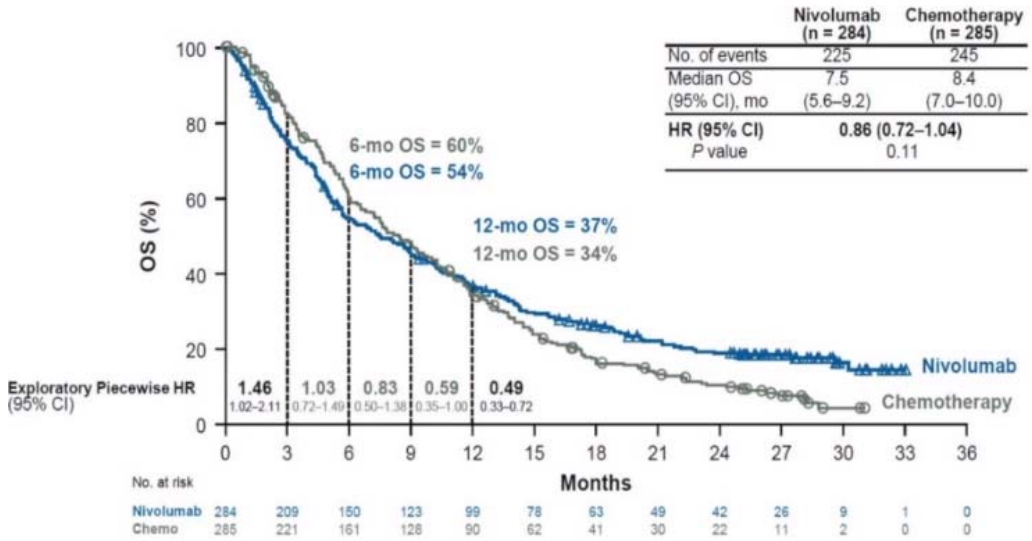
Roche have already demonstrated above that the Weibull extrapolation is overly conservative and under-predicts long term survival associated with the current SoC. This is equally true in the prediction of long term survival for atezolizumab: disregarding any potential for sustained benefit over time.

The log-logistic curve provides a more reasonable long-term extrapolation in line with both literature on the long-term performance of immuno-oncology therapies in ES-SCLC, clinical expert opinion provided to Roche and the observed sustained response in the IMpower133 trial. Rather, the use of the log-logistic function allows the extrapolation to assume a decrease in hazards over time, consistent with the plateauing of OS curves in the immuno-oncology therapy trials.

In the absence of longer-term data for atezolizumab in SCLC, other immune-oncology trials can be explored to provide insight into the long-term survival of patients treated with immunotherapies in SCLC:

CHECKMATE-331 is a randomised controlled open-label phase III trial of nivolumab monotherapy vs chemotherapy and despite being negative, has highlighted the different survival curve characteristics between cancer immunotherapy and chemotherapy. With longer study follow-up, there is an ongoing separation of the curves, representing a greater reduction in the risk of death for the immunotherapy arm over time (Figure 2) (11). Consequently, it is reasonable to expect an ongoing separation with the combination immunotherapy and chemotherapy vs chemotherapy alone, more specifically as is being considered in this appraisal.

Figure 2: Overall survival in relapsed SCLC patients (CHECKMATE-331)



Source: Slide 9, (11)
Notes: 15.8 month minimum follow-up, 59 patients (21%) in the nivolumab arm, 40 patients (14%) in the chemotherapy arm were censored

	Other studies have explored the use of immuno-oncology therapies in later lines of SCLC treatment, with similar conclusions. Appendix 3 summarises three single-arm studies (CHECKMATE-032 (7), KEYNOTE-028, KEYNOTE-158 (8, 9)), all of which show a promising flattening of the survival curves with longer follow-up, consistent with that observed with immuno-oncology therapies in other solid tumour types. Importantly, these outcomes were observed in more heavily pre-treated populations with poorer survival prognosis than the indication for this appraisal. It is therefore reasonable to assume that a similar plateauing of survival curves would be seen in patients treated with atezolizumab and carboplatin-etoposide in first-line ES-SCLC, consistent with the log-logistic extrapolation utilised. **Conclusion** Roche considers the log-logistic to be the most appropriate extrapolation for both comparator and intervention arms for this appraisal. The log-logistic has demonstrated good AIC/BIC fit, good visual fit, and most importantly, clinical plausibility of the long-term survival tail for both the chemotherapy and atezolizumab arms: consistent with available literature, clinical expert opinion and real-world data analysis. The Weibull curves favoured by the ERG have been demonstrated to be overly conservative: they do not reflect the potential for long-term survivorship in a small proportion of patients either as directly observed from studies of platinum-etoposide combinations or as expected for atezolizumab based on clinical opinion and published literature for other immune-oncology products in SCLC.
Additional issue: End of life criteria	
	The ERG agree that this appraisal meets the first requirement in the end-of-life criteria of a life expectancy of less than 24 months. The IMpower133 trial data available to date, reported a median OS of 10.3 months (95% CI, 9.3–11.3) in the comparator arm, significantly below the 24-month threshold. The modelled mean is also substantially below 24 months (14.5 months using the latest data cut; Table 12 clarification response). Finally, data from the NLCA from 2004–2011 reported 4 months for the median survival of all ES-SCLC patients (ECOG PS 0–4). Across

	all analyses, these data show that life expectancy is much lower than 24 months for patients with ES-SCLC treated with NHS standard of care. Regarding the second criteria of extension to life (an additional 3 months), Roche's economic model predicts a mean incremental OS benefit of 4.37 months and a median incremental overall survival benefit of 2.53 months. Use of mean OS data is more meaningful when considering immunotherapies because it considers the small proportion of patients who experience long-term survival (12). As detailed in response to Issue 5, the log-logistic extrapolation used to estimate the mean and median overall survival is the most clinically plausible extrapolation and should be utilised within this appraisal. However, even under the conservative assumption utilising the Weibull extrapolation, mean survival of atezolizumab is 2.7 months over the current SoC. The survival gain seen for atezolizumab and carboplatin-etoposide in SCLC should be considered both in the context of the maturity of the available data and in the context of the poor prognosis of the patients with this extremely severe type of lung cancer. As supported by the expert statements in the Technical Engagement Papers submitted during this appraisal to date the survival gain seen here is particularly important relative to the average survival of people with this condition (e.g., 'Though relatively modest, the potential for extensions in life, is of paramount importance to this patient population and their families' – Professor Jesme Fox). Moreover, this is reflective of the improved landmark analysis seen from the January 2019 analysis of the IMpower133 study, reporting the longer-term landmark survival rates being stable with longer follow-up: with an 18-month survival rate of 34.0% in the atezolizumab group compared with 21.0% in the placebo group. Similar to the end-of-life considerations made in TA476, Roche believe that the survival gain provided by atezolizumab and carboplatin-etoposide in this indication is particularly important, considering the severity of the condition, and the average life expectancy of these patients (13). As such, Roche would consider it appropriate for the extension-to-life criterion to be met, given the mean OS is > 3 months and mean OS benefit is a more appropriate measure when considering immunotherapies.

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Appendix 1

The following expect oncologists have agreed they consider there to be a small but meaningful percentage of ES-SCLC patients with an ECOG PS score of 0–1 who survive long-term within the NHS following carboplatin-etoposide treatment.

Appendix 2

Search terms

To identify UK-based data, a targeted literature search was performed in Embase and Medline using the following MESH search terms; 'small cell lung cancer'[Mesh], 'United Kingdom'[Mesh], 'overall survival'[Mesh], 'survival analysis'[Mesh], 'extensive stage small cell lung cancer'" OR "extensive stage small cell lung carcinoma" on 14th August 2019 to identify sources of literature that included long-term OS data for patients with ES-SCLC. Articles analysing data from FlatIron databases have been excluded to avoid duplication of the data.

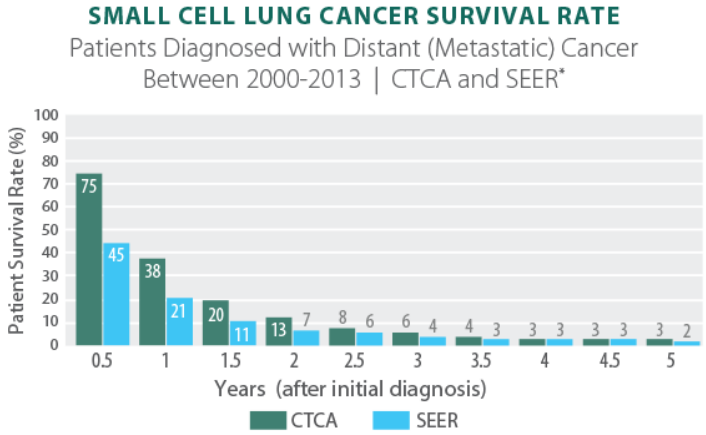
Appendix 3

Summaries of relevant literature

The durability of response, long-term survival among ES-SCLC patients and ongoing benefit following immuno-oncology agents has been reported in the literature, to support assumptions of atezolizumab survival benefit made within this appraisal.

CTCA and SEER

Figure 3: Distant (metastatic) small cell lung cancer survival reported in CTCA and SEER



**The SEER data represent national results over a large number of institutions and have been included for illustrative purposes. They are not intended to represent a controlled study and/or a perfect analysis of the CTCA data because of variability in the sample sizes of the two databases, the clinical condition(s) of the patients treated, and other factors.*

Source: (3)
Note: SEER, CTAC and FlatIron databases may include some of the same patients, but these cohorts cannot be disentangled

CHECKMATE-032

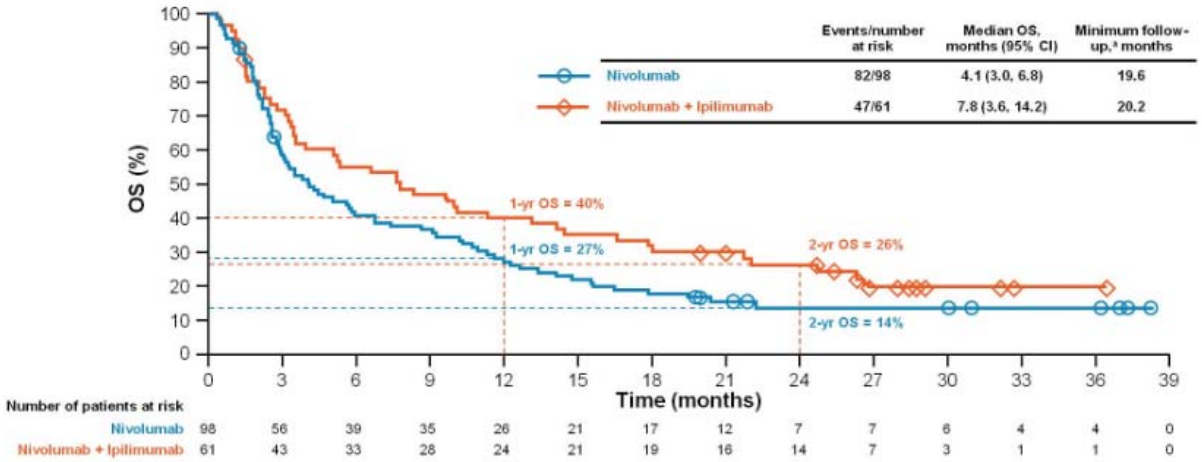
Antonia (2016) reports the safety and activity of nivolumab +/- ipilimumab in patients with SCLC who progressed after one or more previous regimens (CHECKMATE-032). It was concluded that nivolumab monotherapy and nivolumab plus ipilimumab showed anti-tumour activity with durable responses and manageable safety profiles in previously treated patients with SCLC (7).

The CHECKMATE-032 authors highlighted: '*consistent with other trials with immune-checkpoint inhibitors across multiple solid tumours, and unlike trials of topotecan, findings from our study showed a flattening of the overall survival curves for the nivolumab 3 mg/kg and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohorts, suggesting a survival benefit in a subset of patients. However, because of the small numbers in this trial, it is difficult to determine when this occurs. Also consistent with findings from previous randomised trials of immuno-oncology agents, there seems to be a greater effect of nivolumab or ipilimumab treatment on overall survival than progression-free survival*' (7). On this basis, the data supported the inclusion of nivolumab +/- ipilimumab in the NCCN Guidelines.

Hellman (2017) reports the updated survival of nivolumab +/- ipilimumab at a longer duration of study follow-up (23.3 months nivolumab, 28.6 months nivolumab + ipilimumab study median follow-up). It was again noted that a further randomised cohort was added (in addition to the non-randomised cohort) to further evaluate nivolumab +/- ipilimumab. Summarising the results, Hellman (2007) concluded: '*with longer follow-up in the non-randomised cohort, responses remained durable and survival promising*'.

Overall survival in the non-randomised cohort is presented in Figure 4. For nivolumab monotherapy, the ORR was 11% (95% CI: 6, 19) with a median DOR of 17.9 months (range: 2.8, 34.6).

Figure 4: Overall survival of nivolumab +/- ipilimumab treated SCLC patients (CHECKMATE-032, non-randomised cohort)

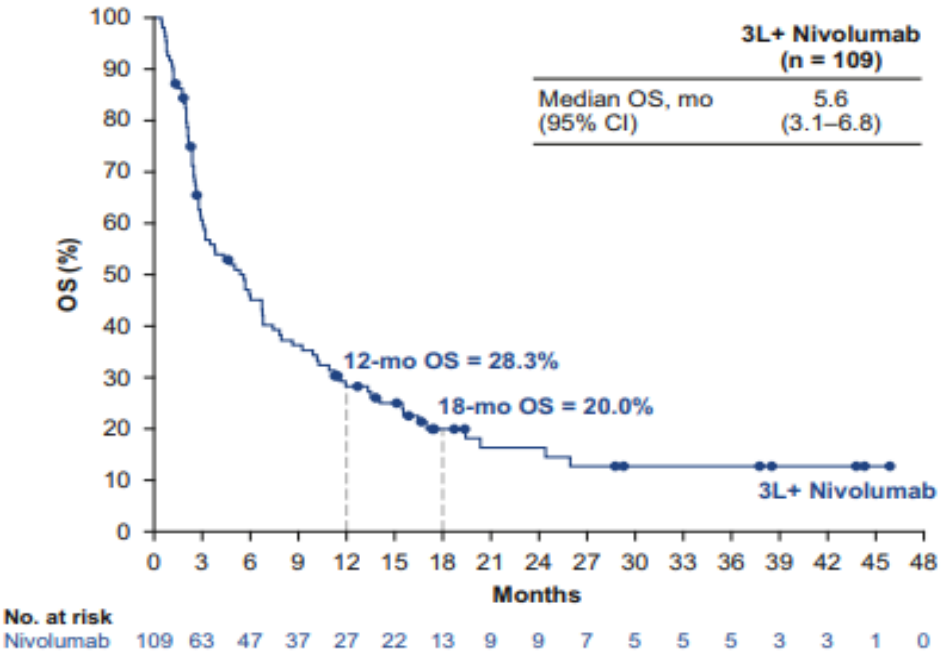


Source: Slide 7, (14)

Ready (2018) reported the efficacy and safety of third- or later-line nivolumab monotherapy from pooled non-randomised and randomised cohorts of patients from CHECKMATE-032. The 12-month and 18-month OS rates were 28.3% and 20.0%, respectively (Figure 5).

Publications commenting on CHECKMATE-032 noted '*the most striking feature of this trial was not the median survival but the high survival rates at 1 and 2 years, indicating that while a minority of patients benefited, those that benefited had long-term benefit' p.8, (6)*.

Figure 5: Overall survival of 3L+ nivolumab treated SCLC patients (CHECKMATE-032, pooled randomised and non-randomised cohort)



Source: Figure 3, p.5 (15)

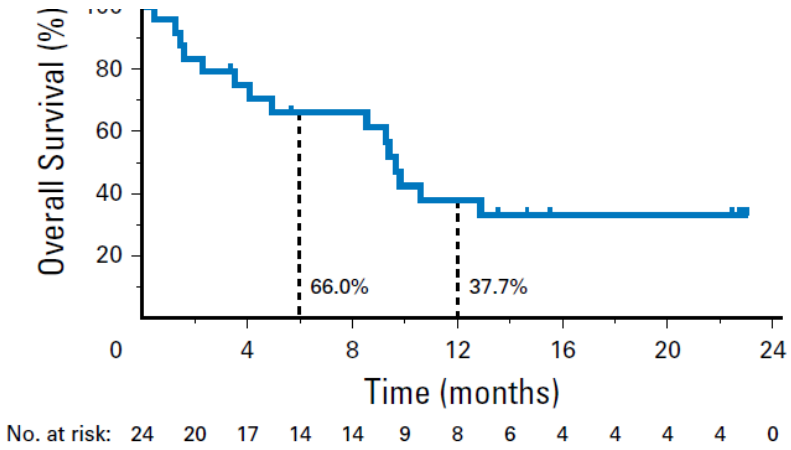
KEYNOTE-028

KEYNOTE-028 reported safety and efficacy for pembrolizumab in an open-label, phase Ib multicohort study in patients with PD-L1–positive advanced solid tumours (PD-L1 ≥1%) who experienced treatment failure, or were unable to receive standard therapy (8).

Ott (2017) noted that '*objective responses seen were robust and durable, consistent with the presumed mechanism of action of anti–PD-1 antibodies*' (p.3828, (8)), as '*notably, tumour responses were rapid and durable. The median onset of response was 2 months, and the median duration of response was 19.4 months. The responses were durable, and three patients were still on treatment at the time of data cutoff. This contrasts with the typically short duration of response seen with chemotherapy in this setting*', (p. 3826, (8)). Further, '*there is quite an encouraging plateau of the survival curve going out to 24 months*' (16), represented in Figure 6.

At the data cut-off date, the median duration of follow-up was 9.8 months (range: 0.5, 24). An ORR of 33.3% was demonstrated, with responses lasting for a median of 19.4 months (8). The median PFS was 1.9 months (95% CI: 1.7, 5.9); the 6- and 12-month PFS rates were 28.6% and 23.8%, respectively (8). The median OS was 9.7 months (95% CI: 4.1 months to not reached); the 6- and 12-month OS rates were 66.0% and 37.7%, respectively (8). The clear plateau of the response shown support assumptions included in this appraisal.

Figure 6: Overall survival of pembrolizumab-treated ES-SCLC patients (KEYNOTE-028)

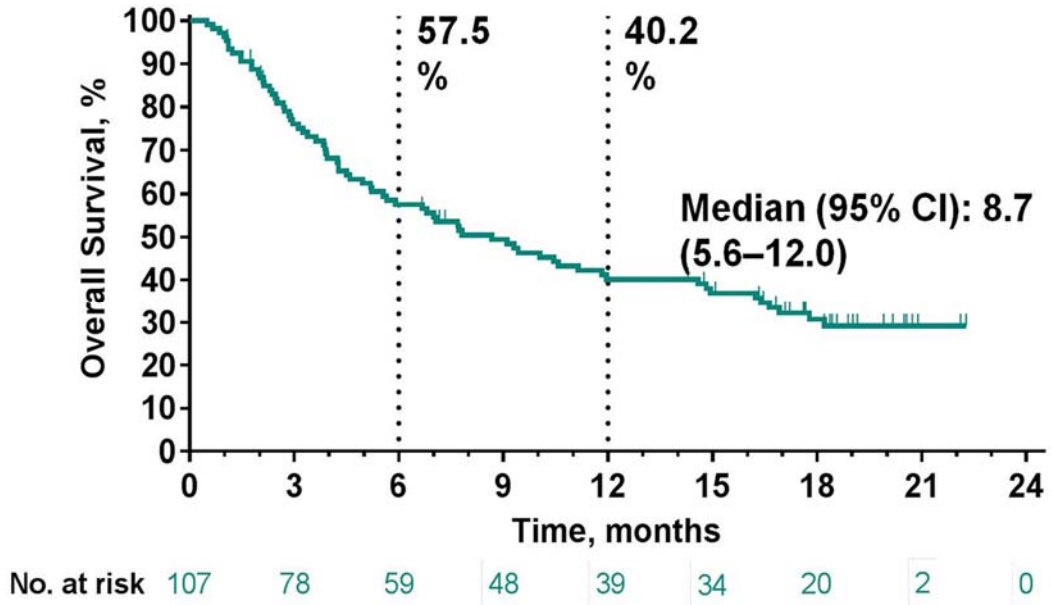


Source: B, Figure 3, p. 3828, (8)

KEYNOTE-158

KEYNOTE-158 evaluated the anti-tumour activity of pembrolizumab in a phase 2 basket study of 11 cancer types. Figure 7 presents the OS of pembrolizumab-treated advanced SCLC patients, before 15 months (and before censoring) the shape of the curve clearly demonstrates decreasing likelihood of death. This is again in line with a log-logistic extrapolation of OS included in the appraisal for IMpower133.

Figure 7: Overall survival of pembrolizumab treated advanced SCLC patients (KEYNOTE-158)



Source: Slide 14, (9)

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm on Monday 2 September 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Professor Samreen Ahmed**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**BTOG/RCP/NCRI** I note my name is not on any of the documents, eventhough I am the independent clinical expert from specialist societies.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Comparators	
Is carboplatin plus etoposide the only relevant comparator?	**Yes in UK practice this is the standard of care for extensive stage SCLC**
What proportion of patients have cisplatin plus etoposide?	**<5% This is used as a radiosensitiser when patients receive concurrent chemoradiotherapy for limited stage SCLC.**
Issue 2: Network meta-analysis and Indirect comparison	
Are the results from the company's network meta-analysis and indirect comparison for the comparison of carboplatin-etoposide with cisplatin-etoposide reliable for decision-making?	**Comparison is valid for decision making but the range of toxicities will be different and time of administration is very different.** 7 hours for cisplatin and 1 hour for carboplatin
Issue 3: Time-to-death approach for estimating utilities	
Is the time-to-death approach a reliable method for estimating utilities?	**Yes as DFS fairly representative of OS: very limited lines of treatment** I would estimate that 20-30% of patients are likely to have subsequent line of treatment. Has this been captured in IMPOWER 133? Response rates are determined by time to relapse from first line treatment.
Issue 4: Utilities associated with adverse events	
Should the economic model include disutilities associated with adverse events?	This is likely to be the excess immunotherapy SEs and lethargy over and above that of carb/etop alone

Issue 5: Long-term overall survival estimates	
Which extrapolation of overall survival is clinically plausible?	<5% alive at 5years are the only estimate we have of long term survival

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

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We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche Products Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nothing to disclose**

Questions for engagement

Issue 1: Comparators		ERG comment
Is carboplatin plus etoposide the only relevant comparator?	Roche have been advised by over 20 practising NHS oncologists during individual consultation meetings and two separate advisory board meetings in 2018 and 2019 that the standard of care in the NHS for untreated, extensive-stage small cell lung cancer (ES-SCLC) is 4–6 cycles of carboplatin plus etoposide (Appendix K of Submission Document). Furthermore, during the Technical Engagement teleconference on the 6th August, Dr Alastair Greystoke (Consultant Medical Oncologist, Sir Bobby Robson Clinical Trials Unit, Freeman Hospital) confirmed that cisplatin is not used for ES-SCLC and that in clinical practice, virtually 100% of patients with ES-SCLC receive carboplatin-etoposide. Dr Greystoke stated that a comparison to cisplatin-etoposide would be out of scope in this appraisal as it is typically used with borderline limited-stage small cell lung cancer patients, rather than ES-SCLC patients. Moreover, the anticipated marketing authorisation wording is “Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with ES-SCLC.” Therefore, patients typically receiving cisplatin (i.e., limited-stage patients) cannot receive atezolizumab. It is also worth noting that Roche have presented an exploratory comparison to cisplatin-etoposide in both our original submission and response to clarification questions including the January 2019 data cut. This showed a similar cost-effectiveness to that when comparing to carboplatin + etoposide (ICER £47,477 for cisplatin + etoposide vs £49,588 for carboplatin+ etoposide; Table 12 clarification	This is in line with the ERG understanding.

	response). Roche do, however, consider this comparison to be unreflective of current clinical practice (as per above) and also less robust due to lack of ability to fully consider the side effects and the reliance on indirect comparison rather than head-to-head trial data. All other platinum-based combination chemotherapies are not considered relevant to this appraisal as they are either not used in the UK (irinotecan-based therapies) or would only be given to carboplatin-ineligible patients, who would be outside of the anticipated licence for the atezolizumab plus carboplatin and etoposide regimen.	
What proportion of patients have cisplatin plus etoposide?	During the Technical Engagement teleconference on the 6th August, Dr Greystoke confirmed that cisplatin is not used for ES-SCLC and that in clinical practice, virtually 100% of patients with ES-SCLC receive carboplatin-etoposide. It was noted by UK clinical experts at an advisory board in November 2018 (Appendix K of the Submission Document) that up to [redacted] of untreated ES-SCLC patients received cisplatin-etoposide and whilst the efficacy benefits are similar between cisplatin and carboplatin, the low use of cisplatin is due to safety and service implications: specifically increased risk of heart failure associated with longer infusion times for cisplatin-etoposide, a reportedly more severe adverse event profile, and increased administration costs to the NHS.	This is in line with the ERG understanding.
Issue 2: Network meta-analysis and Indirect comparison		
Are the results from the company's network meta-analysis and indirect	Roche agrees with the ERG and NICE's Technical Team regarding the limitations of the network meta-analysis submitted for this appraisal. However, it is worth highlighting, this does not have a bearing on the appraisal if it is considered that carboplatin-etoposide is the only relevant comparator, as detailed in response to Issue 1. Dr Greystoke confirmed during the Technical Engagement teleconference that although the literature in the network meta-analysis are not very recent, clinical	This is in line with the ERG understanding.

comparison for the comparison of carboplatin-etoposide with cisplatin-etoposide reliable for decision-making?	practice has not changed since these studies were published. Furthermore, it was agreed during the Technical Engagement teleconference that although the network meta-analysis has limitations, there are no additional studies available that can improve the current analysis. At the ERG clarification stage, a fully incremental cost-effective analysis was presented for the company base case deterministic analysis of atezolizumab plus carboplatin-etoposide and cisplatin-etoposide (Table 27 of the clarification response – Version 3). In line with clinical opinion, the assumptions used were as follows: equivalent progression-free survival of cisplatin to carboplatin (due to lack of progression-free survival data informing the network meta-analysis), cisplatin drug costs, and increased administration time. In addition, an assumption of equivalent safety profiles was required; this was not in line with clinical opinion but there was a lack of reliable data. Assuming equal efficacy between cisplatin plus etoposide and carboplatin plus etoposide, cisplatin plus etoposide will be dominated by carboplatin plus etoposide. Therefore, although the cisplatin-etoposide comparison may be difficult to accurately quantify without a reliable network meta-analysis and safety data, it can be assumed that the incremental cost effectiveness ratio (ICER) would be more favourable for carboplatin-etoposide. Hence, excluding cisplatin plus etoposide is a conservative approach in terms of the ICER calculation within this appraisal. The network meta-analysis was included by Roche solely for completeness and for transparency of decision making. Given cisplatin is not a relevant comparator for this appraisal and the exploratory analysis presented indicate that cisplatin is dominated by carboplatin (including if we assume the two therapies have equal effectiveness in line with clinical opinion), the fact that a robust comparison cannot be presented versus cisplatin is anticipated to have little impact on this appraisal.	
Issue 3: Time-to-death approach for estimating utilities		

Is the time-to-death approach a reliable method for estimating utilities?	In order to address the ERG and NICE technical team's concerns over the validity and suitability of the time to death approach and its statistical fit, further analysis has been conducted in line with the request made by the ERG in clarification question B5. Whilst the use of progression status to predict utility is common in NICE appraisals, use of progression status in isolation has been shown to be sub-optimal in a variety of prior immune-oncology appraisals. The evidence available for this appraisal indicates that this is also the case here: progression status has only a minor impact on utilities (~0.015 in the analysis using progression status alone) and, as is shown below, is less useful in prediction than time to death with, at best, borderline significance and small effect size. **Categorical vs continuous time** A repeated measures model, estimating utility as a function of treatment arm, baseline utility, progression status, treatment status and time to death as a continuous variable was fitted to the IMpower133 EQ-5D utility data (including patients who died only). This shows that progression status and treatment arm are not significant predictors of patient utility, but treatment status and time to death are. In the previous company analysis, each category included records for patients who had died during the trial and censored patients who had over 30 weeks' follow-up who were assigned to the time to death category of >30 weeks. However, in this analysis, in order to be able to look at whether a continuous model fitted better than models using time banding, censored patients were excluded. **Table 1: Repeated measures model for utility, including progression status, treatment status and time to death as a continuous variable** See table below	The ERG acknowledge that these new analyses presented by the company are an adequate response to what the ERG had requested, as reported in Section 5.2.8 of the ERG report, i.e. a full statistical analysis of various models including both on/off treatment and progressed/not progressed as well as time to death as a continuous variable. The ERG therefore recommends the utility model described as: "Using ERG requested utility model with TTD categories one week earlier".

Effect	Estimate	Standard Error	Pr > |t|
Atezolizumab + Carboplatin + Etoposide	0.01229	0.01623	0.4497
Placebo + Carboplatin + Etoposide	0		
Baseline utility	0.5709	0.03563	<.0001
Intercept	0.2316	0.02847	<.0001

Progression-free	0.01217	0.01413	0.3907
Progressed	0		
Time to death (weeks)	-0.00067	0.000277	0.0153
On treatment	0.06486	0.01377	<.0001
Off treatment	0		
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1413.7	-1409.7	-1409.7	-1402.6

The same model was run using categories for time to death (using the same time categories as used in the company base case, and two additional models for time categories one week earlier and one week later to test sensitivity), rather than using a continuous variable.

All of the models using time categories provided a better statistical fit according to AIC and BIC, and were therefore carried forward.

Table 2: Repeated measures model for utility, including progression status, treatment status and time to death as a categorical variable using categories as per the company base case

Effect	Estimate	Standard Error	Pr > |t|
Atezolizumab + Carboplatin + Etoposide	0.0107	0.01609	0.5065
Placebo + Carboplatin + Etoposide	0		
Baseline utility	0.5523	0.03531	<.0001
≤ 5 weeks before death	-0.2122	0.02538	<.0001
> 5 & ≤ 15 weeks before death	-0.05694	0.01798	0.0017
> 15 & ≤ 30 weeks before death	-0.02299	0.009906	0.0211
> 30 weeks before death	0		
Intercept	0.3026	0.03076	<.0001
Progression-free	0.01807	0.01366	0.1884
Progressed	0		
On treatment	0.04557	0.01364	0.001
Off treatment	0		
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1472.6	-1468.6	-1468.6	-1461.5

Table 3: Repeated measures model for utility, including progression status, treatment status and time to death as a categorical variable using categories one week earlier than the company base case

Effect	Estimate	Standard Error	Pr > |t|
Atezolizumab + Carboplatin + Etoposide	0.01191	0.01613	0.461
Placebo + Carboplatin + Etoposide	0		
Baseline utility	0.5515	0.03536	<.0001
≤ 4 weeks before death	-0.2733	0.0298	<.0001
> 4 & ≤ 14 weeks before death	-0.06416	0.01843	0.0006
> 14 & ≤ 29 weeks before death	-0.02321	0.00984	0.0192
> 29 weeks before death	0		
Intercept	0.3037	0.03065	<.0001
Progression-free	0.01908	0.01364	0.1642
Progressed	0		
On treatment	0.04276	0.01358	0.002
Off treatment	0		
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1487.4	-1483.4	-1483.4	-1476.3

Table 4: Repeated measures model for utility, including progression status, treatment status and time to death as a categorical variable using categories one week later than the company base case

Effect	Estimate	Standard Error	Pr > |t|
Atezolizumab + Carboplatin + Etoposide	0.01187	0.01598	0.4583
Placebo + Carboplatin + Etoposide	0		
Baseline utility	0.5522	0.03508	<.0001
≤ 6 weeks before death	-0.1792	0.02285	<.0001
> 6 & ≤ 16 weeks before death	-0.06175	0.01739	0.0005
> 16 & ≤ 31 weeks before death	-0.02336	0.009929	0.0194
> 31 weeks before death	0		
Intercept	0.3044	0.03065	<.0001
Progression-free	0.01547	0.0137	0.2609
Progressed	0		
On treatment	0.04686	0.01363	0.0007
Off treatment	0		

-2 Res Log Likelihood	AIC	AICC	BIC
-1465.0	-1461.0	-1461.0	-1453.9

The impact of progression status

In each of the categorical models carried forward, treatment arm and progression status were not significant predictors of utility.

Interaction terms between the significant categorical variables (time to death and treatment status) were tested and included in each of the utility models using time to death as a categorical variable. Non-significant variables ($p<0.1$) were then removed to create a final utility model.

In all three models, treatment arm was non-significant and was therefore not included in the regression equations. Progression status was also removed as non-significant in the model with time categories one week later than the company base case (Table 5). In the other two models, progression status was retained but had only borderline significance and a small effect size (~0.02) (Table 6 and Table 7). The model with time categories one week earlier than those in the company base case provided a marginally better statistical fit than the other two models.

Table 5: Repeated measures model for utility, including treatment status and time to death as a categorical variable using categories one week later than the company base case, and interaction terms

Effect	Estimate	Standard Error	Pr > |t|
Baseline utility	0.5493	0.03473	<.0001
≤ 6 weeks before death	-0.3093	0.03358	<.0001
> 6 & ≤ 16 weeks before death	-0.1302	0.02881	<.0001
> 16 & ≤ 31 weeks before death	-0.03848	0.02228	0.0843
> 31 weeks before death	0		
Intercept	0.3464	0.03072	<.0001
On treatment	0.02364	0.01683	0.1604
Off treatment	0		
On treatment * ≤ 6 weeks before death	0.2297	0.04296	<.0001

On treatment * > 6 & ≤ 16 weeks before death	0.09197	0.03383	0.0066
On treatment * > 16 & ≤ 31 weeks before death	0.01118	0.02375	0.6378
On treatment * > 31 weeks before death	0		
Off treatment * ≤ 6 weeks before death	0		
Off treatment * > 6 & ≤ 16 weeks before death	0		
Off treatment * > 16 & ≤ 31 weeks before death	0		
Off treatment * > 31 weeks before death	0		
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1494.6	-1490.6	-1490.6	-1483.5

Table 6: Repeated measures model for utility, including progression status, treatment status, and time to death as a categorical variable using categories as per the company base case, and interaction terms

Effect	Estimate	Standard Error	Pr > |t|
Baseline utility	0.5513	0.03492	<.0001
≤ 5 weeks before death	-0.3334	0.03606	<.0001
> 5 & ≤ 15 weeks before death	-0.1357	0.02929	<.0001
> 15 & ≤ 30 weeks before death	-0.04388	0.02189	0.0452
> 30 weeks before death	0		
Intercept	0.3353	0.03127	<.0001
Progression-free	0.02451	0.01364	0.0726
Progressed	0		
On treatment	0.007661	0.01881	0.6839
Off treatment	0		
On treatment * ≤ 5 weeks before death	0.2315	0.04873	<.0001
On treatment * > 5 & ≤ 15 weeks before death	0.1158	0.03508	0.001
On treatment * > 15 & ≤ 30 weeks before death	0.02061	0.02341	0.3788
On treatment * > 30 weeks before death	0		
Off treatment * ≤ 5 weeks before death	0		
Off treatment * > 5 & ≤ 15 weeks before death	0		
Off treatment * > 15 & ≤ 30 weeks before death	0		
Off treatment * > 30 weeks before death	0		
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1493.2	-1489.2	-1489.1	-1482

Table 7: Repeated measures model for utility, including progression status, treatment status, and time to death as a categorical variable using categories one week earlier than the company base case, and interaction terms

Effect	Estimate	Standard Error	Pr > |t|
Baseline utility	0.5506	0.03496	<.0001
≤ 4 weeks before death	-0.375	0.03953	<.0001
> 4 & ≤ 14 weeks before death	-0.1467	0.02948	<.0001
> 14 & ≤ 29 weeks before death	-0.04815	0.02136	0.0243
> 29 weeks before death	0		
Intercept	0.3361	0.03107	<.0001
Progression-free	0.02282	0.01359	0.0934
Progressed	0		
On treatment	0.008093	0.01828	0.6581
Off treatment	0		
On treatment * ≤ 4 weeks before death	0.2285	0.05845	<.0001
On treatment * > 4 & ≤ 14 weeks before death	0.1263	0.03625	0.0005
On treatment * > 14 & ≤ 29 weeks before death	0.02652	0.02276	0.244
On treatment * > 29 weeks before death	0		
Off treatment * ≤ 4 weeks before death	0		
Off treatment * > 4 & ≤ 14 weeks before death	0		
Off treatment * > 14 & ≤ 29 weeks before death	0		
Off treatment * > 29 weeks before death	0		
-2 Res Log Likelihood	**AIC**	**AICC**	**BIC**
-1502.7	-1498.7	-1498.7	-1491.6

Table 8 presents the utility values based on the new analysis vs the company base case. Health states were defined by the variables included in corresponding final models.

Table 8: Health state utility values for repeated measures models

Health state			Company base case	New utility regression models		
Time	Treatment	Progression		TTD using base case categories	TTD using categories one week earlier	TTD using categories one week later
1	0	0	0.6548	0.6015	0.5536	0.6061
1	0	1		0.5770	0.5308	
2	0	0	0.7281	0.6981	0.7010	0.6788
2	0	1		0.6736	0.6782	
3	0	0	0.7311	0.7038	0.7027	0.7097
3	0	1		0.6793	0.6799	
4	0	0	0.7525	0.7540	0.7525	0.7555
4	0	1		0.7295	0.7297	
1	1	0	0.3708	0.2994	0.2487	0.3688
1	1	1		0.2749	0.2259	
2	1	0	0.5483	0.5233	0.5333	0.5699
2	1	1		0.4988	0.5105	
3	1	0	0.7082	0.7205	0.6885	0.7194
3	1	1		0.6960	0.6657	
4	1	0	0.7764	0.7712	0.7688	0.7676
4	1	1		0.7467	0.7460	

Key: Time (base case), 1=<35 days before death, 2=>= 35 and <75 days before death, 3=>= 75 and <210 days before death, 4=>210 days before death; Treatment, 0=on treatment, 1=off treatment; Progression, 0=progression-free, 1=progressed.

The health state utilities for all of the time cut offs tested were similar to the company base case values, showing that the model is not sensitive to the time cut-offs used for the categories.

Impact on the ICER

All three new models (Table 5, Table 6, and Table 7) which investigated the inclusion of progression status as well as time to death using time in a categorical format have been added into the cost-effectiveness model as scenario analyses (with the master switch placed in B15 of the ERG sheet, and individual model selections made using cell L142 in the Utility sheet), with resulting ICERs as follows (including the ERG correction for fixing PFS starting at the first cycle, and including AE disutilities):

Table 9: Incremental cost-effectiveness ratios using alternative utility models

Scenario	ICER (Atezo+C+E versus Carb+Etop)
Company base case	£49,654
Using ERG requested utility model with TTD categories as per company base case	£51,060
Using ERG requested utility model with TTD categories one week earlier	£50,918 (best statistical fit)
Using ERG requested utility model with TTD categories one week later	£50,819

Conclusion

This analysis demonstrates that treatment status and time to death are significant predictors of health-related quality of life for ES-SCLC patients, that progression status

	is of borderline additional value, and that the original utility analysis presented by the company is a viable method, providing reasonable health state utility values. The ICERs produced by the model with the best statistical fit using the new analysis much more closely resemble those of the original company base case than those provided by the ERG based on progression status alone. This analysis supports the conclusion that the original company base case provides a more appropriate estimate of the ICER than the ERG analysis when all clinically relevant variables are taken into account. Additionally, we hope that the lack of model sensitivity to the cut-offs chosen reassures the technical team that the use of visual assessment to determine proximity-to-death categories has not had a major impact on modelled results. Given the borderline significance of progression status in the additional analysis presented and the ability to include more data in the original company model (censored patients with longer follow-up) we would recommend using the company's base case analysis as most appropriate.	
Issue 4: Utilities associated with adverse events		
Should the economic model include disutilities associated with adverse events?	Roche agree to incorporate disutilities associated with adverse events into the model. Roche's submitted cost-effectiveness evaluation did not include additional disutility values for the adverse events reported in IMpower133 so as to avoid the risk of double-counting the effects of treatment (which were already included within the quality of life analysis from the trial) within the cost-effectiveness model. Given the minor differences in the adverse event profiles between the intervention and comparator arms of the IMpower133 trial (1), including additional disutilities for adverse events has a minimal impact on the ICER – as expected. This was demonstrated with an additional scenario analysis during the ERG clarification response, whereby individual adverse event disutilities were added (Table 14 of the clarification response – version 3). This scenario resulted in the base case changing from £49,588 to	The incorporation of adverse event disutilities is in line with the ERG base case.

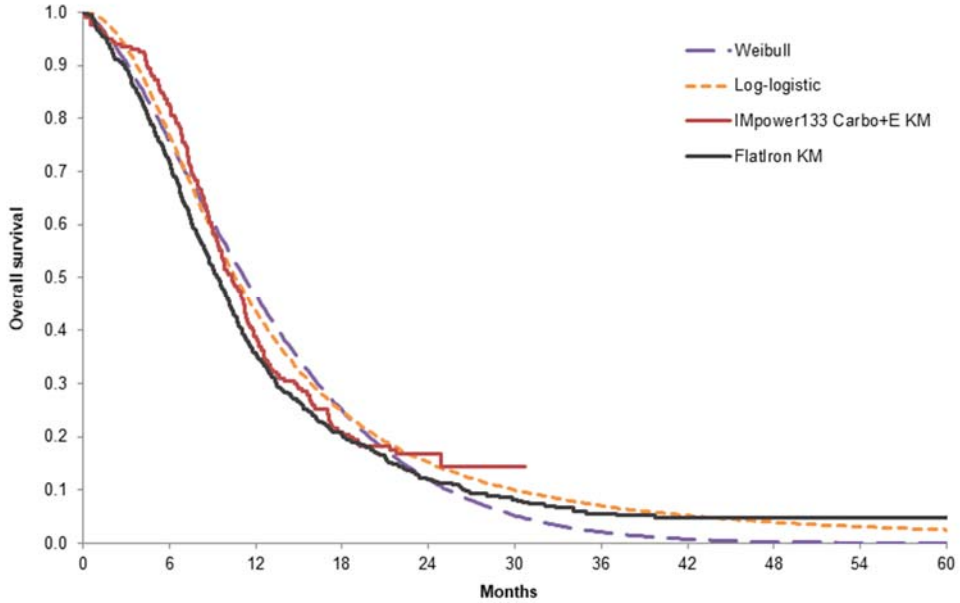
	£49,664 per QALY for atezolizumab plus carboplatin and etoposide versus carboplatin and etoposide.	
Issue 5: Long-term overall survival estimates		
Which extrapolation of overall survival is clinically plausible?	The preliminary judgement of NICE's Technical Team was that the Weibull extrapolation approach *could* be more clinically plausible for modelling the long-term overall survival (OS) of both arms of the IMpower133 study. However, as presented below, available data supports the log-logistic extrapolation approach being more appropriate. Whilst the Weibull extrapolation may have comparable Akaike Information Criterion and Bayesian Information Criterion (AIC/BIC) fit to the log-logistic extrapolation for the atezolizumab arm (1 point difference), the fit is notably poorer in the control arm (7 point difference which warrants more consideration; Table 22 of the clarification response – version 3). Further, and importantly the Weibull curve does not provide clinically plausible OS estimates for untreated ES-SCLC patients, as shown by the evidence sources detailed below. To demonstrate that the Weibull extrapolation provides an overly conservative estimate of the long-term survival for both current standard of care and atezolizumab and that the log-logistic extrapolation better reflects this long-term survival, we provide data as follows: • Published literature • FlatIron registry data • Clinical expert opinion • Immuno-oncology trials **<u>Published literature demonstrates the implausibility of the Weibull curve</u>**	The ERG questions the conclusion by the company that because the Weibull underestimates long term survival that the log-logistic is the appropriate choice for "untreated ES-SCLC" patients, which the ERG takes to mean those treated by the comparator to atezolizumab. The essential point is not so much whether one curve under or over estimates survival, but the closeness to the best available external validation data. Indeed, whilst recognising the limitations of those external data, the ERG used those supplied by the company and validated by the company's own advisory board, i.e. from the Flatiron study (See Table 5.7 of the ERG report). This showed that the Weibull, which, whilst it also overestimates OS in comparison

	The ERG states that the 'log-logistic extrapolation of IMpower133 overestimates OS'. Conversely, with the Weibull extrapolation predicting all ES-SCLC patients are dead by 40 months, Roche believe the Weibull is overly conservative. To assess the validity of these conflicting views, pragmatic literature searches were performed to identify UK-specific data and in addition, US lung cancer databases (SEER, Cancer Treatment Centres of America [CTCA]) were reviewed. Search strategies are detailed in Appendix 2. *UK data:* Souhami and Law 1990 analysed the long-term results of 3,681 patients with SCLC from major centres in the UK during the period 1978–1986. Two-year survival for patients with extensive-stage disease was 2.2% (n=36), and of these patients, approximately 60% were still alive beyond 6 years. Importantly, a plateauing of the cumulative survival curve was reported here, showing a small number of patients surviving long term, even during the 1970's and 1980's (2). *US data:* Maneenil et al. 2017 is a retrospective analysis conducted on an ES-SCLC patient cohort diagnosed and followed from 1997 to 2015 at Mayo Clinic in Minnesota. Overall, there were 1.13% ES-SCLC patients with >3 year's survival (5). *Sweden and Denmark data:* Lassen et al. 1995 explored the characteristics of patients with SCLC who survive ≥5 years, to identify long-term prognostic factors. A cohort of 1,714 unselected patients (comprising LS-SCLC and ES-SCLC) treated with combination chemotherapy were included. Among these, the ES-SCLC cohort of patients had 5- and 10-year survival rates of 2.3% and 1.2%, respectively (4).	to the Flatiron study for years 1 to 2, provides estimates that are almost identical to the Flatiron study for years 3 to 5. The ERG also maintains that there are grounds for believing that the Flatiron data might be an overestimate of survival in UK clinical practice at least partly according to the findings of the company's own advisory board, where 5/8 advisors said rates would be similar and 3/8 said that survival would be worse in clinical practice (See Appendix K). This was further supported by the finding that survival was greater on cisplatin than carboplatin in the Flatiron study in the context of the belief that most if not all patients with ES-SCLC would receive carboplatin. The company have provided additional studies for external validation. However, one of these studies, Southami and Law 1990, provide estimates of survival that are closer to those of the Weibull. Two-year survival is much lower than either the

	US lung cancer databases: USA-based lung cancer databases (SEER and the Cancer Treatment Centres of America [CTCA]) were reviewed for survival rates in patients with distant (metastatic) SCLC (see Appendix 3, Figure 3) (3). Based on the CTCA database, approximately 6% and 3% of patients with distant (metastatic) SCLC were estimated to be alive at 3 and 5 years, respectively; whilst SEER reports 4% and 2% survival at the 3 and 5-year landmarks. Collectively, the published data identified via the pragmatic literature searches from large patient registries provide consistent evidence of a small but meaningful long-term survival rate among ES-SCLC patients. These survival estimates are based on a broader patient population than was targeted in the IMpower133 study, particularly regarding Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–1. Therefore, results from the IMpower133 study could be expected to be more favourable, with even higher proportions surviving long term. This demonstrates that the Weibull extrapolation provides overly conservative estimates of OS, and that the log-logistic extrapolation is the most clinically plausible as this curve allows for a small proportion of longer-term survivors. **<u>FlatIron registry data is consistent with the published literature in demonstrating a small proportion of long-term survivors</u>** The ERG states the 'FlatIron study probably overestimates OS compared to UK clinical practice'. The rationale behind this statement is unclear. Baseline characteristics data for the FlatIron cohort submitted were provided in the original submission documentation for this appraisal, showing similarity to the characteristics of the IMpower133 study population. It can therefore be concluded that the FlatIron cohort is a reasonable data source to estimate long-term survival beyond IMpower133.	Weibull or the log-logistic. 1.1% survive to at least six years, but clearly all of the estimates of survival in each year between two and six would logically have to be much lower than those estimated by the log-logistic (compare values between 2.2% and 1.1% with those in Table 5.7 of 7%, 4% and 2.5% for the Weibull). Of course, this is an old study and so it might be expected to underestimate survival. However, the second study presented by the company by Maneenil et al. 2017, which is much more recent, also supports the Weibull in that three-year survival in the study is lower than that with the Weibull. The "Sweden and Denmark data" do provide more support for the log-logistic. However, it is interesting to note that the data from Sweden and Denmark are roughly contemporaneous with those UK data from Southami and Law 1990 (1973-1991 vs. 1978-1986). Finally, the company provide data from "US

	Roche have previously validated the Flatiron data cohort and results with UK clinical experts who consider these data to reflect NHS practice. During the Technical Engagement teleconference, Dr Greystoke also stated he considered the FlatIron data cohort to be 'useful for decision-making' in this appraisal. A visible comparison of observed OS outcomes for carboplatin-etoposide in IMpower133 and platinum-etoposide in FlatIron, show similar proportions of patients alive at 12 months (38%, IMpower133 carboplatin-etoposide vs 36%, platinum-etoposide Flatiron) and at the 13.9-month median study follow-up (29% IMpower133 carboplatin-etoposide vs 29%, platinum-etoposide Flatiron) (**Error! Reference source not found.**).	lung cancer databases", which do also appear to support the log-logistic. However, whilst these data are the most recent, it is unclear which treatments the patients received and how comparable it is with standard care in the UK. The company also cite further clinical expert opinion to support 5-year survival that is more consistent with the log-logistic. Nevertheless, the ERG consider that the most reliable evidence in terms of whether it is from the UK (Southami and Law 1990) or where it is known how comparable the treatment is to UK clinical practice (Flatiron study, validated by clinical expert opinion) provide support for the Weibull being a better approximation of UK clinical practice than the log-logistic. For atezolizumab, the ERG consider that the company have not provided any persuasive data that are useful for supporting one curve fit over another. Firstly, the extent of the analogy between other immunotherapies in different

Figure 1: IMpower133 Kaplan-Meier OS, log-logistic and Weibull extrapolations vs FlatIron platinum+etoposide OS



Similar to the published literature presented above, present-day registry data from Flatiron conclusively demonstrate long-term survival among a small proportion of ES-SCLC patients treated with current standard of care (Table 10). This further demonstrates the appropriate use of the log-logistic extrapolation to determine long-term carboplatin-etoposide survival outcomes.

Table 10: Comparison of estimated survival and observed survival from databases

	ES-SCLC population	1-year OS	2-year OS	3-year OS	5-year OS

populations and atezolizumab in ES-SCLC in the shape of the survival curve is questionable. Secondly, the assertion of "flattening" of the survival curve or separation between other immunotherapies and the comparator is insufficient evidence to support the precise shape of the extrapolated curve. Indeed, the log-logistic implies a decrease in the hazard rate over time as opposed to the Weibull, which implies the opposite. However, although the long-term data are not available for atezolizumab, an exploration of the K-M data reveals that at least up to 26 months the hazard rate increases (calculated as the number of deaths divided by the number at risk, obtained from the KM OS tab of the company model).

In conclusion, the ERG consider that the company have provided some additional evidence of treatment that resembles UK clinical practice in the correct population, supported by clinical expert opinion that does support the adoption of the log-logistic instead of the Weibull curve for

IMpower133, carboplatin-etoposide arm, **Weibull** survival extrapolation	PS 0-1 only	47%	12%	2%	0%	the comparator, although on balance we would still recommend the Weibull. In contrast, the company have not supplied any additional evidence of long-term survival of atezolizumab in ES-SCLC. Instead, they have only provided some evidence of a flattening of survival curve with other immunotherapies in other populations. Therefore, the ERG continues to believe that the ERG base case assumptions of the Weibull for both intervention and comparator are the most plausible.
IMpower133, carboplatin-etoposide arm, **log-logistic** survival extrapolation	PS 0-1 only	44%	15%	7%	3%	
Flatiron cohort	PS 0-1 only	36%	12%	5%	5%	
CTCA observed	**PS unselected**	38%	13%	6%	3%	
SEER observed	**PS unselected**	21%	7%	4%	2%	

Clinical expert opinion

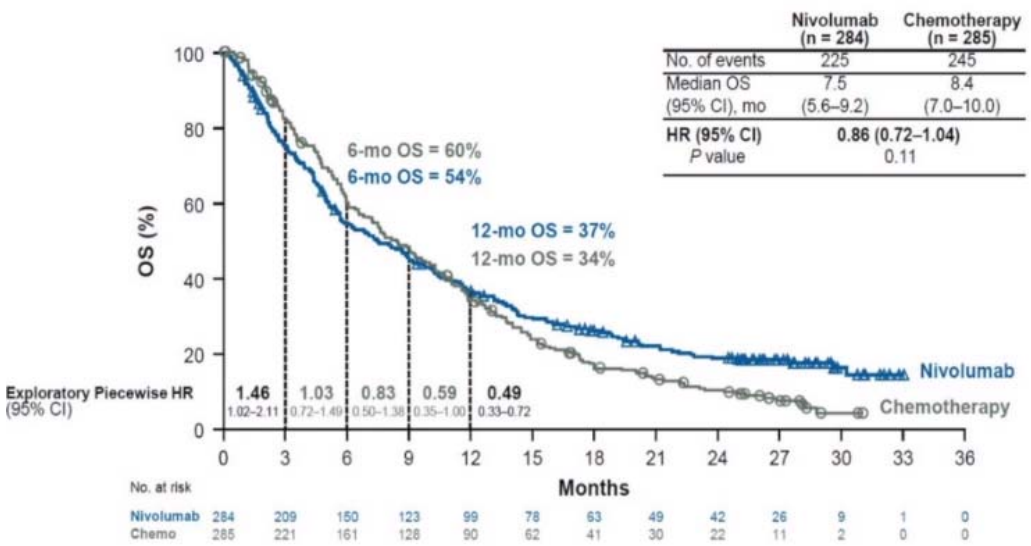
In line with the published data and evidence from Flatiron, expert clinical opinion has consistently reported a small but meaningful percentage of ES-SCLC patients treated with carboplatin-etoposide survive long term.

Specifically, expert clinical opinion was sought from over 20 practicing NHS oncologists gathered during individual consultations and two separate advisory board meetings held during 2018 and 2019, with consensus regarding there being a small but meaningful long-term survival among ES-SCLC patients treated on the NHS currently. Specifically, attendees at the November 2018 advisory board meeting (report provided in Appendix K of Submission Document) stated some long-term survivors were expected to survive beyond 2 years, with the attendees stating some had a few patients at 5-year and 10-year follow-up who were being discharged from ongoing monitoring for their ES-SCLC diagnosis.

Additionally, during this current Technical Engagement consultation period, 4 practicing Senior Lung Oncologists again confirmed they expected survival for some ES-SCLC patients beyond 40 months when treated with carboplatin-etoposide on the NHS

	(Appendix 1 – please note 3 of these 4 oncologists attended the advisory board meeting reported within Appendix K of the Submission Document). Furthermore, the clinician and patient representative expert statements from the Technical Engagement Papers agree that a small proportion of patients are alive at 5 years: • 'The overall 5-year survival for SCLC (limited and extensive stage disease) is only about 5%' Dr Jesme Fox, Roy Castle Lung Foundation • '…proportion of patients alive at 5 years, [is] currently 2% with extensive stage SCLC.' Professor Samreen Ahmed, Clinical Expert and Professor Donal O'Donoghue (on behalf of British Thoracic Oncology Group) **Conclusion: the Weibull is an unrealistically conservative representation of survival on standard of care** The available published data and clinical expert opinion are consistent in their conclusion that a small proportion of patients can be expected to survive long term (5 years+) on current care. Further, the patient population targeted in this appraisal - patients with previously untreated ES-SCLC with an ECOG PS score of ≤1 - is expected to have even more favourable long-term survival than the broader ES-SCLC population presented in the historical published information. Together, the evidence presented clearly demonstrates that the Weibull extrapolation provides overly conservative estimates of OS (predicting all ES-SCLC patients are dead by 40 months), and that the log-logistic extrapolation is the most clinically plausible, allowing for a small proportion of longer-term survivors in line with the available data.	

	Evidence from immuno-oncology trials also demonstrate the implausibility of the Weibull curve for atezolizumab Roche have already demonstrated above that the Weibull extrapolation is overly conservative and under-predicts long term survival associated with the current SoC. This is equally true in the prediction of long term survival for atezolizumab: disregarding any potential for sustained benefit over time. The log-logistic curve provides a more reasonable long-term extrapolation in line with both literature on the long-term performance of immuno-oncology therapies in ES-SCLC, clinical expert opinion provided to Roche and the observed sustained response in the IMpower133 trial. Rather, the use of the log-logistic function allows the extrapolation to assume a decrease in hazards over time, consistent with the plateauing of OS curves in the immuno-oncology therapy trials. In the absence of longer-term data for atezolizumab in SCLC, other immune-oncology trials can be explored to provide insight into the long-term survival of patients treated with immunotherapies in SCLC: CHECKMATE-331 is a randomised controlled open-label phase III trial of nivolumab monotherapy vs chemotherapy and despite being negative, has highlighted the different survival curve characteristics between cancer immunotherapy and chemotherapy. With longer study follow-up, there is an ongoing separation of the curves, representing a greater reduction in the risk of death for the immunotherapy arm over time (Figure 2) (11). Consequently, it is reasonable to expect an ongoing separation with the combination immunotherapy and chemotherapy vs chemotherapy alone, more specifically as is being considered in this appraisal. **Figure 2: Overall survival in relapsed SCLC patients (CHECKMATE-331)**	



Source: Slide 9, (11)

Notes: 15.8 month minimum follow-up, 59 patients (21%) in the nivolumab arm, 40 patients (14%) in the chemotherapy arm were censored

Other studies have explored the use of immuno-oncology therapies in later lines of SCLC treatment, with similar conclusions. Appendix 3 summarises three single-arm studies (CHECKMATE-032 (7), KEYNOTE-028, KEYNOTE-158 (8, 9)), all of which show a promising flattening of the survival curves with longer follow-up, consistent with that observed with immuno-oncology therapies in other solid tumour types.

Importantly, these outcomes were observed in more heavily pre-treated populations with poorer survival prognosis than the indication for this appraisal. It is therefore reasonable to assume that a similar plateauing of survival curves would be seen in patients treated with atezolizumab and carboplatin-etoposide in first-line ES-SCLC, consistent with the log-logistic extrapolation utilised.

	Conclusion Roche considers the log-logistic to be the most appropriate extrapolation for both comparator and intervention arms for this appraisal. The log-logistic has demonstrated good AIC/BIC fit, good visual fit, and most importantly, clinical plausibility of the long-term survival tail for both the chemotherapy and atezolizumab arms: consistent with available literature, clinical expert opinion and real-world data analysis. The Weibull curves favoured by the ERG have been demonstrated to be overly conservative: they do not reflect the potential for long-term survivorship in a small proportion of patients either as directly observed from studies of platinum-etoposide combinations or as expected for atezolizumab based on clinical opinion and published literature for other immune-oncology products in SCLC.	
Additional issue: End of life criteria		
	The ERG agree that this appraisal meets the first requirement in the end-of-life criteria of a life expectancy of less than 24 months. The IMpower133 trial data available to date, reported a median OS of 10.3 months (95% CI, 9.3–11.3) in the comparator arm, significantly below the 24-month threshold. The modelled mean is also substantially below 24 months (14.5 months using the latest data cut; Table 12 clarification response). Finally, data from the NLCA from 2004–2011 reported 4 months for the median survival of all ES-SCLC patients (ECOG PS 0–4). Across all analyses, these data show that life expectancy is much lower than 24 months for patients with ES-SCLC treated with NHS standard of care. Regarding the second criteria of extension to life (an additional 3 months), Roche's economic model predicts a mean incremental OS benefit of [redacted] months and a median incremental overall survival benefit of [redacted] months. Use of mean OS data is more meaningful when considering immunotherapies because it considers the small	As stated in our report: "However, the ERG base-case shows that the extension to life produced by atezolizumab is [redacted] months. Therefore, at the moment there is no robust evidence to show that the second criterion has been met."

	proportion of patients who experience long-term survival (12). As detailed in response to Issue 5, the log-logistic extrapolation used to estimate the mean and median overall survival is the most clinically plausible extrapolation and should be utilised within this appraisal. However, even under the conservative assumption utilising the Weibull extrapolation, mean survival of atezolizumab is [redacted] months over the current SoC. The survival gain seen for atezolizumab and carboplatin-etoposide in SCLC should be considered both in the context of the maturity of the available data and in the context of the poor prognosis of the patients with this extremely severe type of lung cancer. As supported by the expert statements in the Technical Engagement Papers submitted during this appraisal to date the survival gain seen here is particularly important relative to the average survival of people with this condition (e.g., 'Though relatively modest, the potential for extensions in life, is of paramount importance to this patient population and their families' – Professor Jesme Fox). Moreover, this is reflective of the improved landmark analysis seen from the January 2019 analysis of the IMpower133 study, reporting the longer-term landmark survival rates being stable with longer follow-up: with an 18-month survival rate of 34.0% in the atezolizumab group compared with 21.0% in the placebo group. Similar to the end-of-life considerations made in TA476, Roche believe that the survival gain provided by atezolizumab and carboplatin-etoposide in this indication is particularly important, considering the severity of the condition, and the average life expectancy of these patients (13). As such, Roche would consider it appropriate for the extension-to-life criterion to be met, given the mean OS is > 3 months and mean OS benefit is a more appropriate measure when considering immunotherapies.	

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Appendix 1

The following expect oncologists have agreed they consider there to be a small but meaningful percentage of ES-SCLC patients with an ECOG PS score of 0–1 who survive long-term within the NHS following carboplatin-etoposide treatment.

Appendix 2

Search terms

To identify UK-based data, a targeted literature search was performed in Embase and Medline using the following MESH search terms; 'small cell lung cancer'[Mesh], 'United Kingdom'[Mesh], 'overall survival'[Mesh], 'survival analysis'[Mesh], 'extensive stage small cell lung cancer'" OR "extensive stage small cell lung carcinoma" on 14th August 2019 to identify sources of literature that included long-term OS data for patients with ES-SCLC. Articles analysing data from FlatIron databases have been excluded to avoid duplication of the data.

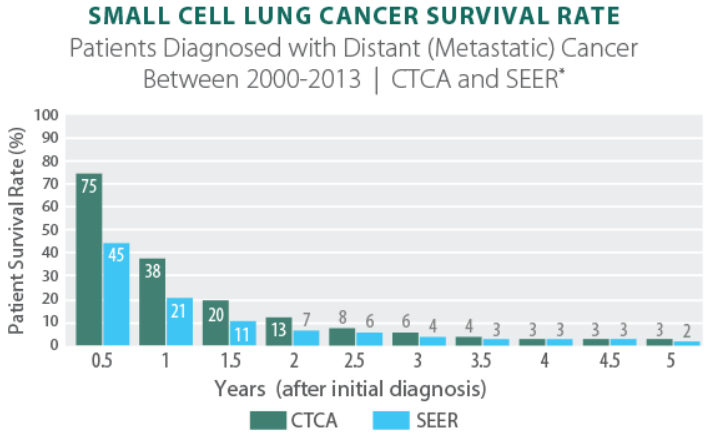
Appendix 3

Summaries of relevant literature

The durability of response, long-term survival among ES-SCLC patients and ongoing benefit following immuno-oncology agents has been reported in the literature, to support assumptions of atezolizumab survival benefit made within this appraisal.

CTCA and SEER

Figure 3: Distant (metastatic) small cell lung cancer survival reported in CTCA and SEER



**The SEER data represent national results over a large number of institutions and have been included for illustrative purposes. They are not intended to represent a controlled study and/or a perfect analysis of the CTCA data because of variability in the sample sizes of the two databases, the clinical condition(s) of the patients treated, and other factors.*

Source: (3)
Note: SEER, CTAC and FlatIron databases may include some of the same patients, but these cohorts cannot be disentangled

CHECKMATE-032

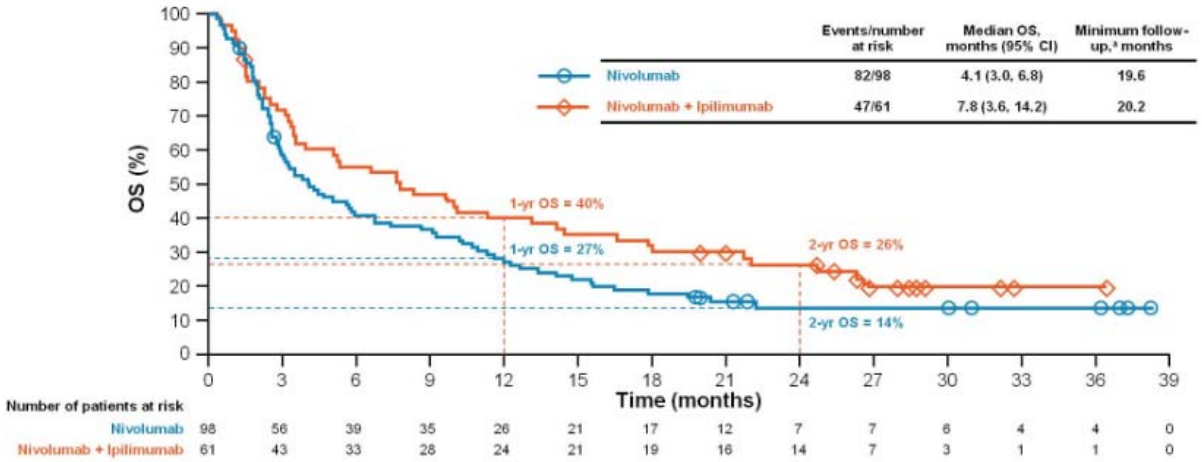
Antonia (2016) reports the safety and activity of nivolumab +/- ipilimumab in patients with SCLC who progressed after one or more previous regimens (CHECKMATE-032). It was concluded that nivolumab monotherapy and nivolumab plus ipilimumab showed anti-tumour activity with durable responses and manageable safety profiles in previously treated patients with SCLC (7).

The CHECKMATE-032 authors highlighted: '*consistent with other trials with immune-checkpoint inhibitors across multiple solid tumours, and unlike trials of topotecan, findings from our study showed a flattening of the overall survival curves for the nivolumab 3 mg/kg and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohorts, suggesting a survival benefit in a subset of patients. However, because of the small numbers in this trial, it is difficult to determine when this occurs. Also consistent with findings from previous randomised trials of immuno-oncology agents, there seems to be a greater effect of nivolumab or ipilimumab treatment on overall survival than progression-free survival*' (7). On this basis, the data supported the inclusion of nivolumab +/- ipilimumab in the NCCN Guidelines.

Hellman (2017) reports the updated survival of nivolumab +/- ipilimumab at a longer duration of study follow-up (23.3 months nivolumab, 28.6 months nivolumab + ipilimumab study median follow-up). It was again noted that a further randomised cohort was added (in addition to the non-randomised cohort) to further evaluate nivolumab +/- ipilimumab. Summarising the results, Hellman (2007) concluded: '*with longer follow-up in the non-randomised cohort, responses remained durable and survival promising*'.

Overall survival in the non-randomised cohort is presented in Figure 4. For nivolumab monotherapy, the ORR was 11% (95% CI: 6, 19) with a median DOR of 17.9 months (range: 2.8, 34.6).

Figure 4: Overall survival of nivolumab +/- ipilimumab treated SCLC patients (CHECKMATE-032, non-randomised cohort)

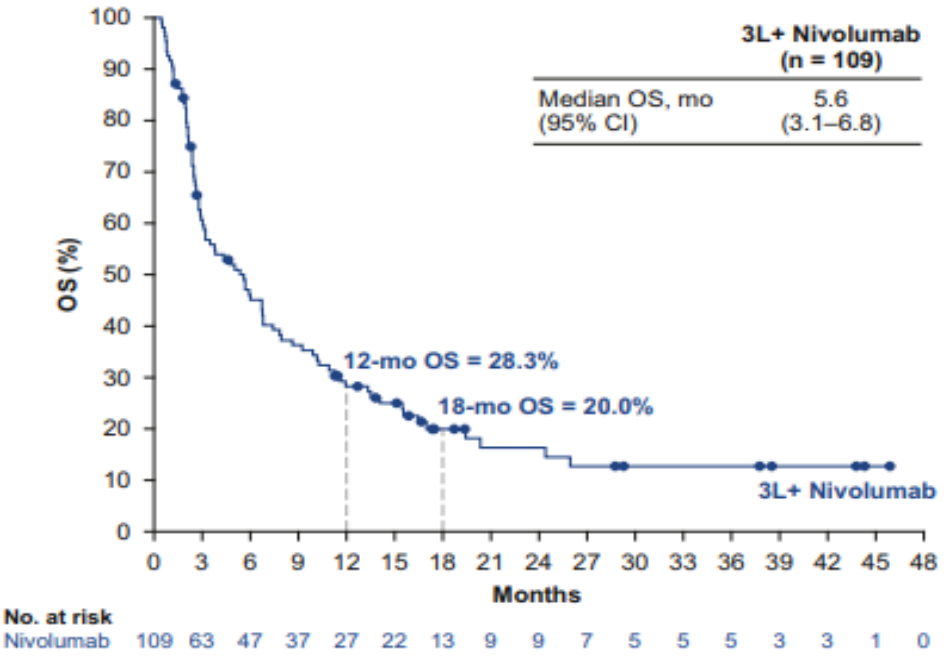


Source: Slide 7, (14)

Ready (2018) reported the efficacy and safety of third- or later-line nivolumab monotherapy from pooled non-randomised and randomised cohorts of patients from CHECKMATE-032. The 12-month and 18-month OS rates were 28.3% and 20.0%, respectively (Figure 5).

Publications commenting on CHECKMATE-032 noted '*the most striking feature of this trial was not the median survival but the high survival rates at 1 and 2 years, indicating that while a minority of patients benefited, those that benefited had long-term benefit' p.8, (6)*.

Figure 5: Overall survival of 3L+ nivolumab treated SCLC patients (CHECKMATE-032, pooled randomised and non-randomised cohort)



Source: Figure 3, p.5 (15)

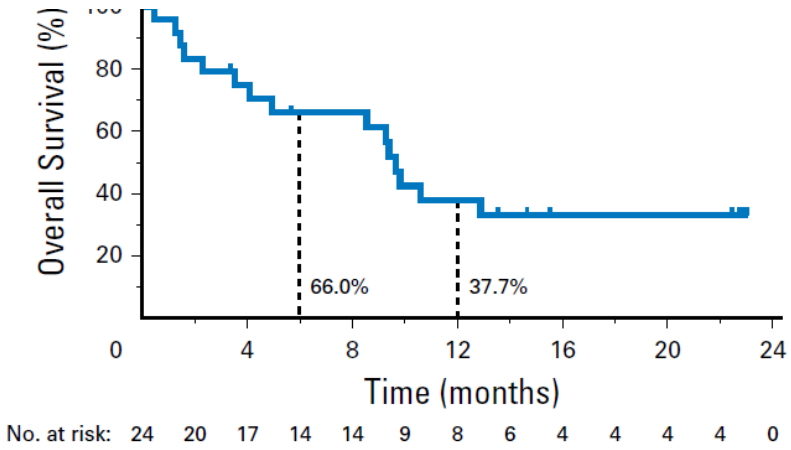
KEYNOTE-028

KEYNOTE-028 reported safety and efficacy for pembrolizumab in an open-label, phase Ib multicohort study in patients with PD-L1–positive advanced solid tumours (PD-L1 ≥1%) who experienced treatment failure, or were unable to receive standard therapy (8).

Ott (2017) noted that '*objective responses seen were robust and durable, consistent with the presumed mechanism of action of anti–PD-1 antibodies*' (p.3828, (8)), as '*notably, tumour responses were rapid and durable. The median onset of response was 2 months, and the median duration of response was 19.4 months. The responses were durable, and three patients were still on treatment at the time of data cutoff. This contrasts with the typically short duration of response seen with chemotherapy in this setting*', (p. 3826, (8)). Further, '*there is quite an encouraging plateau of the survival curve going out to 24 months*' (16), represented in Figure 6.

At the data cut-off date, the median duration of follow-up was 9.8 months (range: 0.5, 24). An ORR of 33.3% was demonstrated, with responses lasting for a median of 19.4 months (8). The median PFS was 1.9 months (95% CI: 1.7, 5.9); the 6- and 12-month PFS rates were 28.6% and 23.8%, respectively (8). The median OS was 9.7 months (95% CI: 4.1 months to not reached); the 6- and 12-month OS rates were 66.0% and 37.7%, respectively (8). The clear plateau of the response shown support assumptions included in this appraisal.

Figure 6: Overall survival of pembrolizumab-treated ES-SCLC patients (KEYNOTE-028)

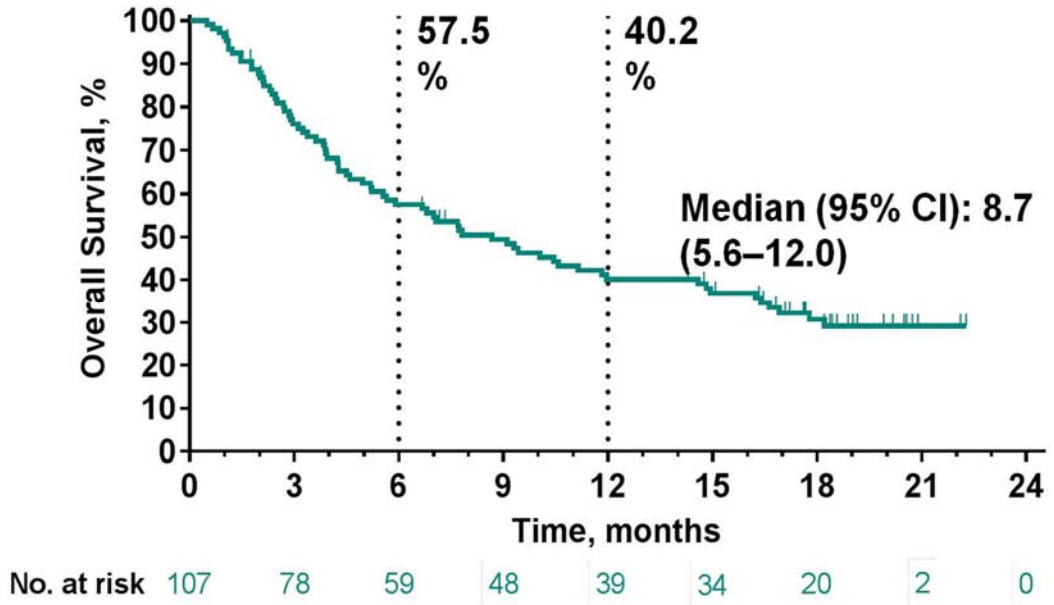


Source: B, Figure 3, p. 3828, (8)

KEYNOTE-158

KEYNOTE-158 evaluated the anti-tumour activity of pembrolizumab in a phase 2 basket study of 11 cancer types. Figure 7 presents the OS of pembrolizumab-treated advanced SCLC patients, before 15 months (and before censoring) the shape of the curve clearly demonstrates decreasing likelihood of death. This is again in line with a log-logistic extrapolation of OS included in the appraisal for IMpower133.

Figure 7: Overall survival of pembrolizumab treated advanced SCLC patients (KEYNOTE-158)



Source: Slide 14, (9)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

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

The technical report should be read with the full supporting documents for this appraisal.

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

Issue date: September 2019

Contents

1. Summary

1.1. After technical engagement the technical team has collated the comments received and, if relevant, updated the judgement made by the technical team and it's rationale. Judgements that have been updated after engagement are highlighted in bold below.

1.2. In summary, the technical team considered the following:

Issue		Technical team's preliminary judgement
1	**Comparators**	The technical team accepts the company's approach that carboplatin plus etoposide is the **most relevant** comparator.
2	**Network meta-analysis and indirect comparison**	**The company's indirect treatment comparison is not suitable for decision-making and given that carboplatin plus etoposide is the most relevant comparator, clinical data from the Impower133 trial is more relevant**.
3	**Time to death approach for estimating utilities**	The technical team **accepts the company's approach of using time to death to estimate utility values, and prefers using the ERG's preferred model to do so.**
4	**Utilities associated with adverse events**	It is appropriate for disutilities associated with adverse events to be incorporated in the model.
5	**Long-term overall survival estimates**	**The technical team prefer the Weibull curve to extrapolate overall survival for both treatment groups because the long-term survival predictions are more aligned with clinical expert predictions compared with the log-logistic curve.**

1.3. The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- Patients in the IMpower133 trial had an ECOG status of 0-1 but in UK clinical practice it is rare for patients to have an ECOG status of 0 when they are diagnosed.

1.4. The cost-effectiveness results include a commercial arrangement (simple discount patient access scheme) for atezolizumab.

1.5. Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) in excess of £70,000 per QALY gained (see table 1).

1.6. The company did not make a case for inclusion of atezolizumab with carboplatin and etoposide in the Cancer Drugs Fund (CDF).

1.7. Based on the company's economic model, it is uncertain whether atezolizumab meets the life extension end-of-life criterion specified in NICE's guide to the methods of technology appraisal (see table 5).

1.8. Atezolizumab is unlikely to be considered innovative. All relevant benefits associated with the drug are adequately captured in the model (see table 5).

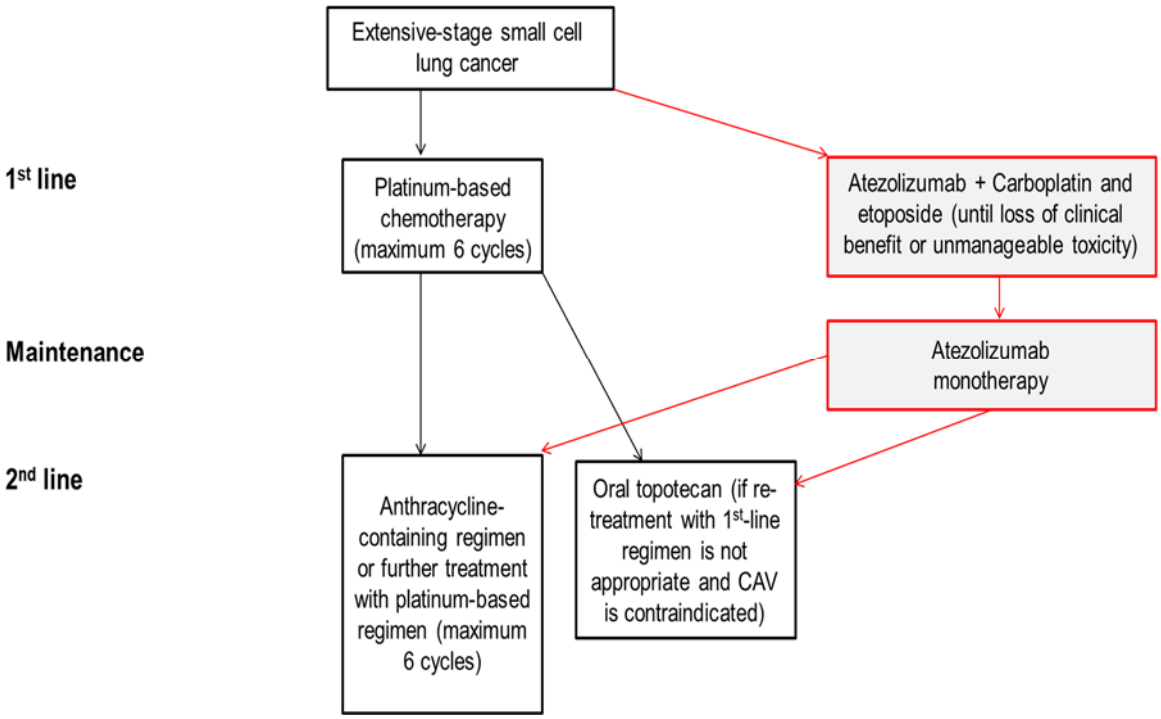
1.9. No relevant equality issues were identified.

2. Background

2.1 Disease background: Extensive-stage small-cell lung cancer (ES-SCLC)

- Small-cell lung cancer (SCLC) is a type of lung cancer that grows rapidly and spreads quickly to other parts of the body.
- Common symptoms of SCLC include weight loss, malaise, bone pain, breathlessness and coughing up blood.
- Extensive-stage disease (cancer that has spread beyond a single area that can be treated with radiotherapy, for example to the other lung or to other parts of the body).
- In 2016 there were 38,381 cases of lung cancer registered in England.
- Around 12% of lung cancer cases are SCLC.

2.2 Treatment pathway: ES-SCLC



2.3 Atezolizumab

Marketing authorisation (granted 6 September 2019)	Atezolizumab, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small-cell lung cancer (ES-SCLC).
Mechanism of action	Humanised anti-PD-L1 monoclonal antibody
Administration	Induction phase, every 3 weeks for 4 cycles: Atezolizumab: 1,200 mg, intravenously administered, day 1 of each cycle with Carboplatin: (area under the curve 5 mg/ml/min), intravenously administered, day 1 of each cycle and with Etoposide: 100 mg/m^2, intravenously administered, days 1–3 of each cycle Maintenance phase follows the induction phase, every 3 weeks until loss of clinical benefit or unmanageable toxicity: Atezolizumab monotherapy without chemotherapy: 1,200 mg is administered intravenously day 1 of each cycle
Price	List price: £3807.69 per 1,200 mg vial (excluding VAT; BNF online, assessed July 2019). The company has a commercial arrangement (simple discount patient access scheme). This makes atezolizumab available to the NHS with a discount. The size of the discount is commercial in confidence.
EAMS	Atezolizumab received a positive opinion from the early access to medicines scheme in June 2019.

2.4 Patient and professional views

- Patients with ES-SCLC are very unwell when diagnosed and have short life expectancy. Patients often require admission to hospital or need specialist palliative care.

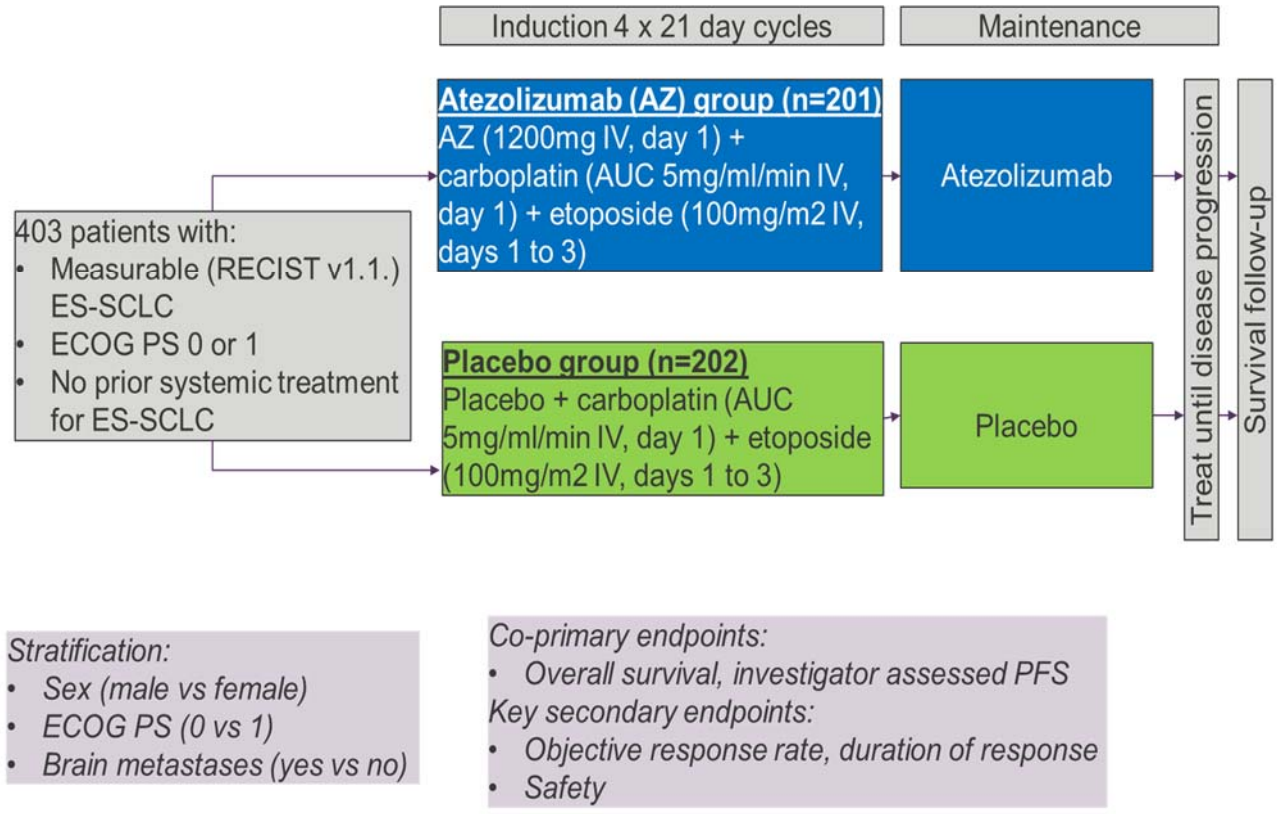
- There is an unmet need since there have been no improvements to the treatment of SCLC in over 10 years. Chemotherapy (carboplatin/cisplatin plus etoposide) can result in 80-90% response rate but recurrence is likely, and patients then deteriorate quickly.

- The overall 5-year survival for SCLC (limited and extensive stage disease) is about 5%.

- Atezolizumab can easily be added to existing standard chemotherapy but will increase treatment time.
- Immunotherapy- adverse events need to be recognised and treated.

2.5 Impower133 trial

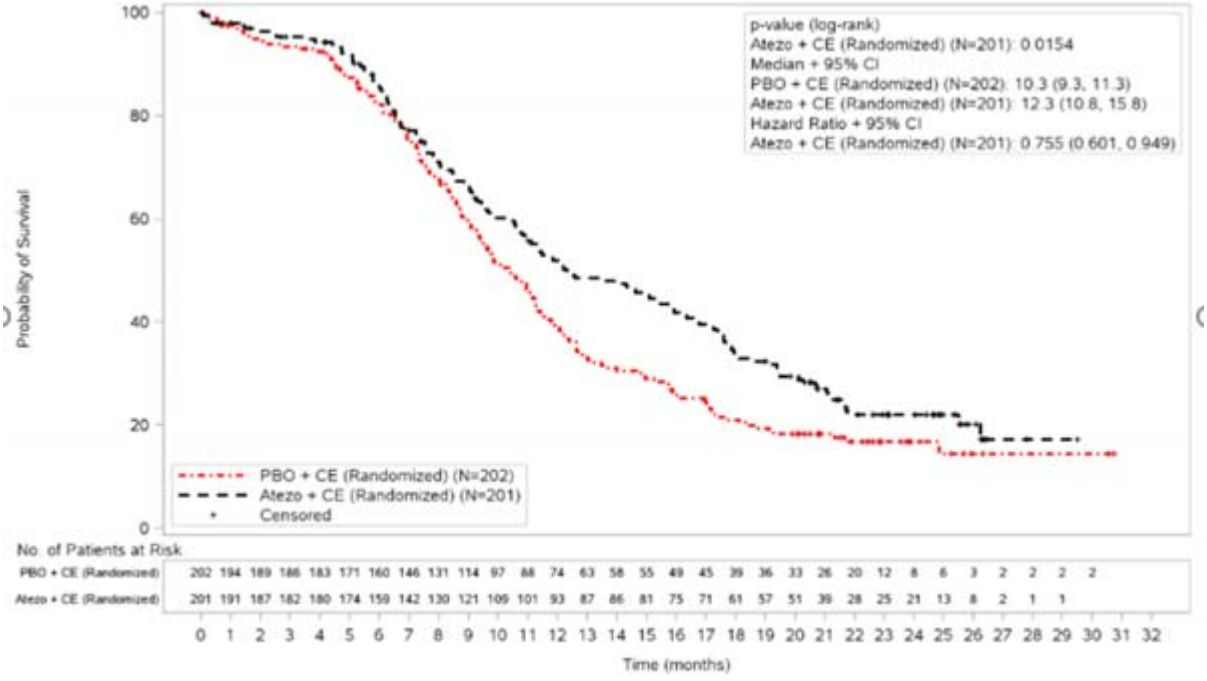
- Double-blind, randomised, placebo-controlled trial



2.6 Summary of key results from Impower133 trial

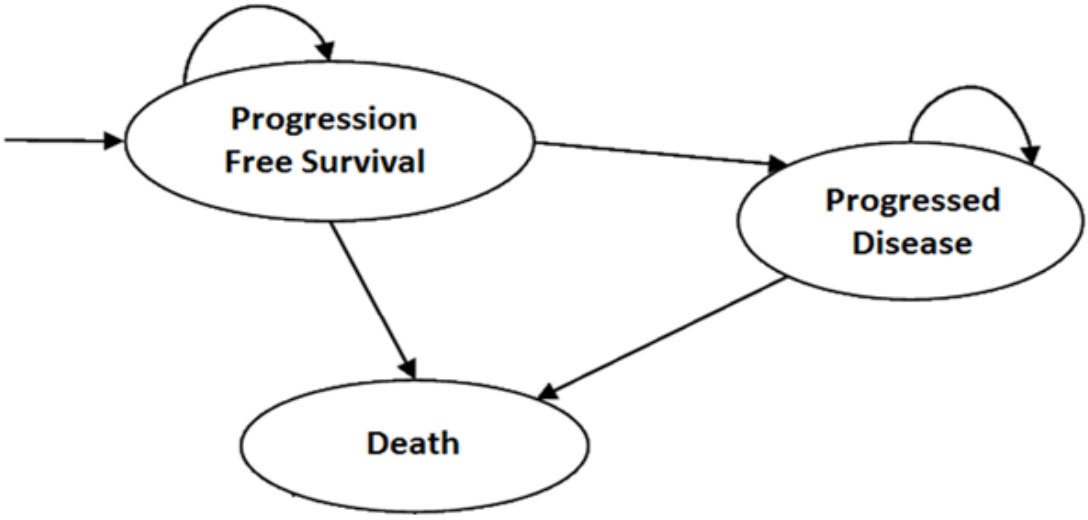
	April 2018 data cut (median 13.9 months follow up)		Jan 2019 data cut (median 22.9 months follow up)	
Outcome	**Atezolizumab**	**Placebo**	**Atezolizumab**	**Placebo**
Median OS (months)	12.3 (10.8 to 15.9)	10.3 (9.3 to 11.3)	12.3 (10.8 to 15.8)	10.3 (9.3 to 11.3)
1-year OS rate	51.7% (44.4% to 59.0%)	38.2% (31.2% to 45.3%)	[redacted]	[redacted]
2-year OS rate	Not reported	Not reported	[redacted]	[redacted]
OS	HR 0.70 (0.54 to 0.91)		HR 0.76 (0.60 to 0.95)	
Median PFS (months)	5.1 (4.4 to 5.6)	4.3 (4.2 to 4.5)	Not reported	Not reported
1-year PFS rate	12.6 (7.9 to 17.4)	5.4 (2.1 to 8.6)	Not reported	Not reported
PFS	HR 0.77 (0.62 to 0.96)		Not reported	Not reported
ORR	60.2%	64.4%	Not reported	Not reported
Abbreviations: HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival				

Kaplan-Meier for overall survival with stratified analysis in intention to treat population using Jan 2019 data cut



2.7 Company's model structure and inputs

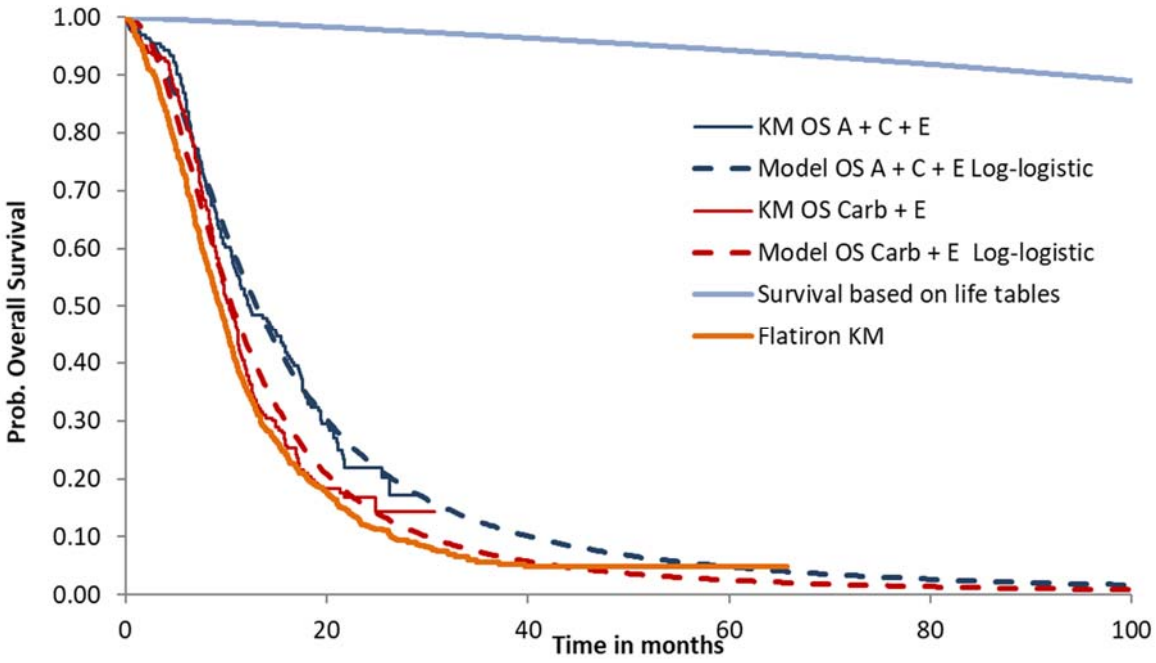
- Partitioned survival model with 3 health states and weekly cycle length
- Comparator: carboplatin and etoposide (4 cycles)
- Clinical effectiveness data from IMpower133 trial including updated overall survival, all other data from April 2018
- Extrapolations:
  - Overall survival: log-logistic extrapolation for both groups
  - Progression-free survival: Kaplan-Meier data for first 5 months then log-logistic extrapolation for both groups
  - Time to off-treatment (TTOT): extrapolation only needed for atezolizumab. Kaplan-Meier data for first 14 months then Gamma extrapolation
- Utility values from IMpower133 (EQ-5D-5L mapped to EQ-5D-3L)
- Excludes disutility for adverse events.
- 20-year time horizon and 3.5% discount rate



2.8 Treatment effectiveness in the model

- Updated overall survival data, introduced prior to technical engagement, suggests Weibull or log-logistic curves provide the best fit to the data

- Company prefers to use a log-logistic extrapolation for both treatment groups. For atezolizumab, this was supported by clinical expert opinion on long-term survival. For the comparator group this was supported by external validation by clinical experts of the Flatiron study (database including 2,161 people in USA with ES-SCLC, ECOG 0-1 and who were treated with platinum-etoposide chemotherapy).



3. Key issues for consideration

Issue 1 – Comparators

Questions for engagement	1. Is carboplatin plus etoposide the only relevant comparator? 2. What proportion of patients have cisplatin plus etoposide?
Background/description of issue	**The company** considers carboplatin plus etoposide to be the only relevant comparator. The company noted that it consulted with over 20 practising NHS oncologists who agreed that the standard of care in the NHS for untreated, extensive stage small cell lung cancer (ES-SCLC) is carboplatin plus etoposide. All other treatments, such as cisplatin plus etoposide, irinotecan plus carboplatin, paclitaxel plus carboplatin and best supportive care, are not considered standard NHS practice. The company further explained that platinum double regimens (e.g. irinotecan plus carboplatin and paclitaxel plus carboplatin) are used only if patients are etoposide-intolerant and cannot receive carboplatin-etoposide combination. **The ERG** notes that the NICE scope specifies platinum-based combination chemotherapy regimens as relevant comparators. Other treatment regimens such as carboplatin plus paclitaxel, irinotecan plus cisplatin, topotecan plus cisplatin, and paclitaxel plus cisplatin are not considered as comparators in the company submission. The ERG notes that in Appendix K in the company submission the clinical experts said that [redacted] of patients in the UK would receive cisplatin-etoposide. The ERG also notes that there might be a subgroup of people with borderline limited-stage SCLC (LS-SCLC) who would receive cisplatin plus etoposide. **The technical team** heard from clinical experts that carboplatin plus etoposide is the most commonly used chemotherapy regimen in the UK. Cisplatin plus etoposide is rarely used. The experts advised that irinotecan (one of the comparators listed by the ERG) is not used in the UK.
Why this issue is important	All relevant comparators should be accounted for and modelled appropriately. This can have a significant effect on the appraisal decision-making process as different comparators can lead to different cost-effectiveness estimates.
Technical team preliminary scientific judgement and rationale	The technical team accepts the company's approach that carboplatin plus etoposide is the main comparator. However, it would be useful to know the clinical and cost effectiveness of atezolizumab with carboplatin and etoposide compared with cisplatin and etoposide for the small number of patients who receive this combination in

<table>
<tr><td></td><td>NHS practice in England. The positive CHMP opinion for atezolizumab was for the first-line treatment of ES-SCLC so all possible comparators should be included.</td></tr>
<tr><td>Summary of comments</td><td>
<table>
<tr><th>Stakeholder</th><th>Summary of comments</th></tr>
<tr><td>Clinical expert</td><td>Agree, in UK clinical practice carboplatin plus etoposide is the standard of care for extensive stage SCLC. Less than 5% of people will be offered cisplatin plus etoposide. This is used as a radiosensitiser when patients receive concurrent chemoradiotherapy for limited stage SCLC.</td></tr>
<tr><td>Company</td><td>• Received clinical expert advice that the standard of care in the NHS for untreated, extensive-stage small cell lung cancer (ES-SCLC) is 4–6 cycles of carboplatin plus etoposide (see Appendix K of company submission). Also noted the efficacy of cisplatin and carboplatin are similar, and the low use of cisplatin is due to safety (more severe adverse event profile) and service implications
• During the technical engagement teleconference 1 clinical expert confirmed that cisplatin is not used for ES-SCLC and that in clinical practice, virtually 100% of patients with ES-SCLC receive carboplatin-etoposide.
• In line with the marketing authorisation, patients typically receiving cisplatin (i.e. limited-stage disease) cannot receive atezolizumab.
• The company presented an exploratory comparison with cisplatin-etoposide in both the original submission and response to clarification questions including the January 2019 data cut. This showed a similar cost-effectiveness estimate to that when comparing to carboplatin plus etoposide (atezolizumab ICER £47,477 vs cisplatin plus etoposide and £49,588 vs carboplatin plus etoposide; see table 12 of the clarification response).</td></tr>
<tr><td>ERG</td><td>In its critique of the company's response to technical engagement, the ERG noted that the company's response is in line with its own understanding.</td></tr>
</table>
</td></tr>
<tr><td>Technical team judgement after engagement</td><td>The technical team agrees that carboplatin plus etoposide is the most relevant comparator.</td></tr>
</table>

Issue 2 – Network meta-analysis and Indirect comparison

Questions for engagement	3. Are the results from the company's network meta-analysis and indirect comparison for the comparison of carboplatin-etoposide with cisplatin-etoposide reliable for decision-making?
Background/description of issue	The Impower133 trial compared atezolizumab plus carboplatin and etoposide with placebo plus carboplatin and etoposide. The company did not think that cisplatin plus etoposide is a relevant comparator for this appraisal based on clinical expert advice, who said that [redacted]% of people with ES-SCLC are treated with carboplatin plus etoposide. **The company** performed a network meta-analysis and an indirect comparison based on 2 studies comparing carboplatin-etoposide with cisplatin-etoposide for the purpose of transparency. The company also included a base-case cost-effectiveness analysis for atezolizumab plus carboplatin and etoposide versus cisplatin and etoposide as an appendix. **The ERG** noted that the studies included in the indirect comparison had the relevant comparator, but they think that the results are not comparable with the results from the IMpower133 trial because of the following: • The Skarlos 1994 study is more than 20 years old and the results are based on small patient sample whose characteristics are not reported. There is only one outcome measure, overall response rate, that is present in both Skarlos 1994 and IMpower133. • The study from Okamoto 2007 had patients who were elderly and had poor performance status. This population does not match the IMpower133 trial population. The ERG therefore considers that the results of the company indirect comparison are not reliable for decision making. The ERG performed its own mixed treatment comparison of atezolizumab with carboplatin and etoposide versus all relevant comparators as described in the scope but using the searches for comparators presented by the company which the ERG considered to have limitations. Based on this network it might be possible to do indirect comparisons of atezolizumab plus carboplatin-etoposide versus irinotecan plus carboplatin, palifosfamide plus carboplatin-etoposide and pemetrexed plus carboplatin. However, the ERG stressed that these treatments are probably not the only treatments that can be compared with atezolizumab, because the company's searches did not include all relevant comparators. **The technical team** acknowledges the challenges associated with performing an indirect comparison. However, the concerns raised by the ERG are valid.

<table>
<tr><td>Why this issue is important</td><td>A lack of direct evidence adds uncertainty to the true comparative efficacy of atezolizumab versus standard of care. The Impower133 trial compared atezolizumab plus carboplatin and etoposide with placebo plus carboplatin and etoposide and there was no comparison with cisplatin plus etoposide.</td></tr>
<tr><td>Technical team preliminary scientific judgement and rationale</td><td>Even though most people with ES-SCLC receive carboplatin and etoposide, it would be useful to know the clinical and cost effectiveness of atezolizumab with carboplatin and etoposide compared with cisplatin and etoposide for the small number of patients who receive this combination in NHS practice in England. The positive CHMP opinion for atezolizumab was for the first-line treatment of ES-SCLC so all possible comparators should be included. The technical team agree that the company's indirect comparison comparing carboplatin-etoposide with cisplatin-etoposide is not suitable for decision making.</td></tr>
<tr><td>Summary of comments</td><td>
<table>
<tr><th>Stakeholder</th><th>Summary of comments</th></tr>
<tr><td>Clinical expert</td><td>The indirect comparison is valid for decision making but the range of toxicities will be different and time of administration is very different (7 hours for cisplatin and 1 hour for carboplatin).</td></tr>
<tr><td>Company</td><td>• The company agrees regarding the limitations of the network meta-analysis submitted for this appraisal but notes this does not have a bearing on the appraisal if carboplatin-etoposide is the only relevant comparator, see Issue 1.
• 1 clinical expert confirmed during the technical engagement teleconference that although the literature in the network meta-analysis are not very recent, clinical practice has not changed since these studies were published.
• The network meta-analysis was included solely for completeness and for transparency of decision making. Given cisplatin is not a relevant comparator for this appraisal and the exploratory analysis presented indicates that cisplatin is dominated by carboplatin (including if we assume the two therapies have equal effectiveness in line with clinical opinion), the fact that a robust comparison cannot be presented versus cisplatin is anticipated to have little impact on this appraisal.</td></tr>
<tr><td>ERG</td><td>In its critique of the company's response to technical engagement, the ERG noted that the company's response is in line with its own understanding.</td></tr>
</table>
</td></tr>
<tr><td>Technical team judgement after engagement</td><td>The company's indirect treatment comparison is not suitable for decision-making and given that carboplatin plus etoposide is the most relevant comparator, clinical data from the Impower133 trial is most relevant.</td></tr>
</table>

Issue 3 – Time-to-death approach for estimating utilities

Questions for engagement	4. Is the time-to-death approach a reliable method for estimating utilities?
Background/description of issue	**The company** used a time-to-death approach to obtain utility values. The company explained that the method was used and accepted during the appraisal of atezolizumab to treat both first-line and second-line non-small cell lung cancer, and pembrolizumab for the treatment of non-small cell lung cancer as first-line monotherapy and combination therapy, and as second-line therapy (TA520, TA428, TA531, TA557 and ID1210). **The ERG** is unsure of the validity of the time-to-death method for estimating utilities. Despite being used in previously approved appraisals, the method is not mentioned in any of the NICE TSDs. The ERG has questioned the validity of the approach because it does not statistically test the effect of both treatment and progression status but still incorporates the effect of being on or off treatment. The ERG notes that it relies on an arbitrary division into four time-to-death categories without statistically testing the fit of such a model. Using progression status to obtain utilities is more widely accepted method and the ERG has run an exploratory analysis using this approach. **The technical team** The company selected the proximity-to-death categories based on a visual assessment of the utility scatter plot. The technical team is unsure of the reliability of this method.
Why this issue is important	Using different methods to estimate utility values results in different cost-effectiveness results. The ERG's exploratory analysis including its preferred approach increases the company's ICER from £49,588 to £53,724 per QALY gained.
Technical team preliminary scientific judgement and rationale	Even though the time-to-death approach has been accepted in other appraisals, it is not mentioned in the NICE TSDs and the technical team is unsure about the reliability of this method. The technical team prefers the ERG's approach of using progression status to estimate utilities.
Summary of comments	**Stakeholder** | **Summary of comments**

<table>
<tr><td></td><td>Clinical expert</td><td>• Agree that the time-to-death approach is reliable because disease-free survival is fairly representative of OS: very limited lines of treatment.
• Estimates that 20-30% of patients are likely to have subsequent line of treatment, but it is unclear whether this been captured in IMPOWER 133.
• Response rates are determined by time to relapse from first line treatment.</td></tr>
<tr><td></td><td>Company</td><td>In order to address the ERG and NICE technical team's concerns over the validity and suitability of the time to death approach and its statistical fit, further analysis has been conducted in line with the request made by the ERG in clarification question B5 (data not reported here, see company response to technical report for more details). Whilst the use of progression status to predict utility is common in NICE appraisals, use of progression status in isolation has been shown to be sub-optimal in a variety of prior immune-oncology appraisals. The evidence available for this appraisal indicates that this is also the case here: progression status has only a minor impact on utilities (~0.015 in the analysis using progression status alone) and is less useful in prediction than time to death with, at best, borderline significance and small effect size.
The company reports data comparing categorical vs continuous time which show that progression status and treatment group are not significant predictors of patient utility, but treatment status (on/off treatment) and time to death are.
All three new models which investigated the inclusion of progression status as well as time to death using time in a categorical format have been added into the cost-effectiveness model as scenario analyses, with resulting ICERs as follows (including the ERG correction for fixing PFS starting at the first cycle, and including AE disutilities):
Table 1: Incremental cost-effectiveness ratios using alternative utility models
<table>
<tr><th>Scenario</th><th>ICER (Atezo+C+E versus Carb+Etop)</th></tr>
<tr><td>Company base case</td><td>£49,654</td></tr>
<tr><td>Using ERG-requested utility model with TTD categories as per company base case</td><td>£51,060</td></tr>
<tr><td>Using ERG-requested utility model with TTD categories one week earlier</td><td>£50,918 (best statistical fit)</td></tr>
</table></td></tr>
</table>

		Using ERG-requested utility model with TTD categories one week later: £50,819 This analysis demonstrates that treatment status and time to death are significant predictors of health-related quality of life for ES-SCLC patients, that progression status is of borderline additional value, and that the original utility analysis presented by the company is a viable method, providing reasonable health state utility values. The ICERs produced by the model with the best statistical fit using the new analysis much more closely resemble those of the original company base case than those provided by the ERG based on progression status alone. In addition, the use of visual assessment to determine proximity-to-death categories has not had a major impact on modelled results.
	ERG	In its critique of the company's response to technical engagement, the ERG acknowledged that the analyses provided by the company were an adequate response to what the ERG had requested. The ERG therefore recommended the utility model described as: "Using ERG requested utility model with TTD categories one week earlier".
Technical team judgement after engagement	The technical team prefers the ERG's preferred approach of using the ERG requested utility model with TTD categories one week earlier to estimate utility values.	

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Issue 4 – Utilities associated with adverse events

Questions for engagement	5. Should the economic model include disutilities associated with adverse events?
Background/description of issue	**The company** has not included adverse events disutilities in its model. It assumes that AE disutilities have already been incorporated into the base case health state utilities when EQ-5D utilities were derived from the IMpower133 trial. They consider that including additional utilities would constitute double counting. In its clarification response, the company explained that there is no difference in disabilities due to the adverse events between the different treatment groups, and provided a scenario analysis showing that adverse events disutilities have a small impact on the

<table>
<tr><td></td><td>ICERs (although the company base case which has no adverse events disutilities leads to lower ICER).

The ERG noted that the company's analyses did not include adverse events disutilities. It explained that if a significant proportion of patients experience grade 3-4 adverse events, the resulting disutilities should be accounted for. The ERG provided an exploratory analysis with adverse events disutilities from trial data in addition to utility as a function of progression status.</td></tr>
<tr><td>Why this issue is important</td><td>Incorporating different utility values may lead to different cost effectiveness results. It is important that the values used are transparent and reflect the clinical state. Including adverse event disutilities from trial data increased the company's ICER from £49,588 to £49,664 per QALY gained.</td></tr>
<tr><td>Technical team preliminary scientific judgement and rationale</td><td>It seems reasonable that disutilities associated with adverse events should be incorporated into the model.</td></tr>
<tr><td>Summary of comments</td><td>
<table>
<tr><th>Stakeholder</th><th>Summary of comments</th></tr>
<tr><td>Clinical expert</td><td>Adverse events are likely to be the excess immunotherapy side effects and lethargy over and above that of carboplatin and etoposide alone</td></tr>
<tr><td>Company</td><td>The company agree to incorporate disutilities associated with adverse events into the model (these were not included to avoid the risk of double counting the effects of treatment, which were already included within the quality of life analysis from the trial).</td></tr>
<tr><td>ERG</td><td>In its critique of the company's response to technical engagement, the ERG confirmed that the company's response is in line with its preferred approach.</td></tr>
</table>
</td></tr>
<tr><td>Technical team judgement after engagement</td><td>Disutility values associated with adverse events should be included into the model, to ensure they are not underestimated.</td></tr>
</table>

Issue 5 – Long-term overall survival estimates

Questions for engagement	6. Which extrapolation of overall survival is clinically plausible?

<table>
<tr><td>Background/description of issue</td><td>The company stated that for the extrapolation of overall survival, the best fit for both the atezolizumab and the comparator groups was provided by the log-logistic curve. For the comparator group, the company compared survival estimates from the extrapolation with data from the Flatiron study, a US study of over 2,000 ES-SCLC patients. However, the company had received clinical advice which stated that the ECOG performance status in the UK would be worse than in the US.

The ERG disagreed with the company choice of the log-logistic curve for the comparator group. It considered that the log-logistic curve overestimates overall survival in UK clinical practice (because it overestimates survival in the Flatiron study, which is itself likely to overestimate UK survival), and is therefore too optimistic. The ERG considered that the Weibull extrapolation is likely to have better clinical plausibility.

The technical team heard from clinical experts who agreed that the log-logistic curve overestimates overall survival in UK clinical practice and that the Weibull extrapolation was more plausible for the comparator group.</td></tr>
<tr><td>Why this issue is important</td><td>The choice of data source and statistical method used to estimate longer term OS has a considerable impact on the ICER. It is important that the methods used result in clinically plausible survival probabilities and a valid rationale is given for the choice of any statistical method used. Most alternative curve functions for extrapolating OS mean the ICER increases from the company's base case analysis. Using the Weibull extrapolation from both the intervention and comparator increases the company's ICER from £49,588 to £69,260 per QALY gained.</td></tr>
<tr><td>Technical team preliminary scientific judgement and rationale</td><td>It is plausible that the company's base case model overestimates the long-term survival benefit and that the Weibull extrapolation increases the ICER from the company's base case.</td></tr>
<tr><td>Summary of comments</td><td>
<table>
<tr><th>Stakeholder</th><th>Summary of comments</th></tr>
<tr><td>Clinical expert</td><td>The only estimate we have of long-term survival suggests less than 5% of people are alive at 5 years.</td></tr>
<tr><td>Company</td><td>The company presented data to support the log-logistic extrapolation approach being the most appropriate:
Published literature (collectively, the published data identified via the pragmatic literature searches from large patient registries provide consistent evidence of a small but meaningful long-term survival rate</td></tr>
</table>
</td></tr>
</table>

among ES-SCLC patients. The company believes the Weibull is overly conservative, by predicting all ES-SCLC patients are dead by 40 months)

- Flatiron registry data (similar to the published literature, updated registry data from Flatiron conclusively demonstrate long-term survival among a small proportion of ES-SCLC patients treated with current standard of care, see table 2 below)
- Clinical expert opinion (in line with the published data and evidence from Flatiron, expert clinical opinion has consistently reported a small but meaningful percentage of ES-SCLC patients treated with carboplatin-etoposide survive long term)
- Immuno-oncology trials (with longer study follow-up, there is an ongoing separation of the curves, representing a greater reduction in the risk of death for the immunotherapy group over time)

Table 2: Comparison of estimated survival and observed survival from databases

	ES-SCLC population	1-year OS	2-year OS	3-year OS	5-year OS
IMpower133, carboplatin-etoposide arm, **Weibull** survival extrapolation	PS 0-1 only	47%	12%	2%	0%
IMpower133, carboplatin-etoposide arm, **log-logistic** survival extrapolation	PS 0-1 only	44%	15%	7%	3%
Flatiron cohort, present day	PS 0-1 only	36%	12%	5%	5%
CTCA observed	**PS unselected**	38%	13%	6%	3%

		SEER observed | **PS unselected** | 21% | 7% | 4% | 2% The company considers the log-logistic to be the most appropriate extrapolation for both comparator and intervention groups (the Weibull extrapolation may have comparable statistical fit (AIC/BIC) for the atezolizumab group (1-point difference), the fit is notably poorer in the control group (7-point difference)). The log-logistic extrapolation has demonstrated good AIC/BIC fit, good visual fit, and most importantly, clinical plausibility of the long-term survival tail for both the chemotherapy and atezolizumab groups: consistent with available literature, clinical expert opinion and real-world data analysis.
	ERG	In its critique of the company's response to technical engagement, the ERG maintained that its preferred assumption of using the Weibull for both intervention and comparator remains the most plausible.
Technical team judgement after engagement	The technical team prefers the Weibull curve to extrapolate overall survival for both treatment groups, rather than the log-logistic curve, because its long-term survival predictions are more aligned with clinical expert predictions. The log-logistic curve overestimates long-term survival observed in the US Flatiron study, which itself is likely to have higher survival than the population that would be treated in the NHS in England.	

4 Issues for information

Tables 3 to 5 are provided to stakeholders for information only and not included in the Technical Report comments table provided.

Table 3: Technical team preferred assumptions and impact on the cost-effectiveness estimates

Alteration	Technical team rationale	ICER[1]	Change from base case
Company revised base case (includes fixing error for PFS not starting at 1 in 1st cycle & using AE disutility values from literature)	**–**	**£50,513**	
A. Fixing error (OS for intervention always being at least as high as comparator)	Technical team agrees with ERG corrections	£50,513	£0
B. A + Overall survival extrapolation (using Weibull for both intervention and comparator)	Technical team agrees with ERG preference	£70,593	+£20,080
C. A + utility values estimated using time to death (ERG's preferred model)	Technical team agrees with ERG preference	£51,800	+£1,287
D. **Impact of the technical team's preferred assumptions on the cost-effectiveness estimate (A + B + C)**	**–**	**£72,077**	**+£21,564**
[1] Results from corrected model (provided 24/09/2019)			

Table 4: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
ECOG status of patients enrolled in IMpower133	Patients in the IMpower133 trial had an ECOG status of 0-1 but in UK clinical practice it is rare for patients to have an ECOG status of 0 when they are diagnosed.	People with an ECOG status of 0 are likely to have better outcomes so the survival estimates from the trial could be overestimated. It is unknown what impact this could have on the cost-effectiveness estimates.

Table 5: Other issues for information

Issue	Comments
Innovation	The company considers the drug to be innovative. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model and the QALY calculation.
Equality considerations	No relevant equalities issues were identified by the company, consultees or nominated clinical and patient experts.
Cancer Drugs Fund	The company has not proposed a case for atezolizumab being considered for funding through the Cancer Drugs Fund.
End of life criteria	The company states that atezolizumab meets the end of life criteria. ERG comments: • Short life expectancy, normally less than 24 months, without atezolizumab with carboplatin and etoposide Data from the NLCA from 2004–2011 reported the median survival for all ES-SCLC patients (ECOG PS 0–4) was 4 months. The IMpower133 trial data available to date, reported a median OS of 10.3 months (95% CI, 9.3–11.3) in the comparator group, which is the same regimen as NHS standard of care.

	• Extension to life, normally of at least an additional 3 months, compared with current NHS treatment. The IMpower133 study reported a 2-month median survival benefit for atezolizumab with carboplatin and etoposide treatment in ES-SCLC patients (12.3 months vs 10.3 months). The company's economic model predicts OS as: o mean OS is [redacted] months for the comparator group and [redacted] months for the atezolizumab group – a difference of [redacted] months o median OS is [redacted] for the comparator group and [redacted] for the atezolizumab group – a difference of [redacted] months. The model using the technical team's preferred assumptions (see table 3) predicts OS as: o mean OS is [redacted] months for the comparator group and [redacted] months for the atezolizumab group – a difference of [redacted] months o median OS is [redacted] for comparator group and [redacted] for the atezolizumab group – a difference of [redacted] months. While it is likely that atezolizumab meets the life expectancy criterion, it is uncertain whether it also meets the life extension criterion.

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Lead team member

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Lead team member

NICE National Institute for Health and Care Excellence

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

Request for additional analyses

Deadline for comments 5pm on Thursday 14 November 2019 via NICE Docs.

Contents

Additional information request from NICE

Following the 1st Appraisal Committee Meeting for atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID1504], the committee requested further clarification and analyses to be made available for the next appraisal committee meeting. These requests for further information include:

1. Further methods of estimating overall survival:
    a. Flatiron data to assess hazard over time
    b. Alternative models (including gamma, piecewise, restricted cubic spline, and mixture models)
    c. Clinical validation of alternative models
    d. Restricted mean analysis
2. Exploration of the effect of reducing duration of treatment benefit in the model
3. Clarification of the source of real-world chemotherapy survival data (as validated by an advisory board)
    a. Address the factual inaccuracy that was raised at the committee meeting
    b. Explain difference in initial number of patients at risk
    c. Address inconsistency regarding the source of the real-world data as referenced in the Company submission and validated at the advisory board
4. Further patient reported outcomes data from IMpower133

This document provides the Roche response to these requests. Sections below follow the same structure as the requests above.

1. Further methods of estimating overall survival

Introduction

The committee had concluded that none of the standard parametric models used provided a good representation of the observed IMpower133 KM data in either arm, leading to uncertainty in the reliability of overall survival extrapolations derived from the models. Therefore, alternative, more flexible models have been provided below. The models explored include:

1) Gamma
2) Piecewise
3) KM + log-logistic
4) Restricted cubic spline
5) Mixture cure

This may allow for a better representation of the available survival data and provide a more robust basis for decision-making. These models have been assessed in the context of:

1) How the hazard function within the clinical trial data changes over time;
2) How the hazard function within the external data (i.e. Flatiron data) changes over time; and
3) Statistical fit, visual fit, and clinical plausibility as per NICE Decision Support Unit (DSU) guidance (Technical Support Document 14 (1))

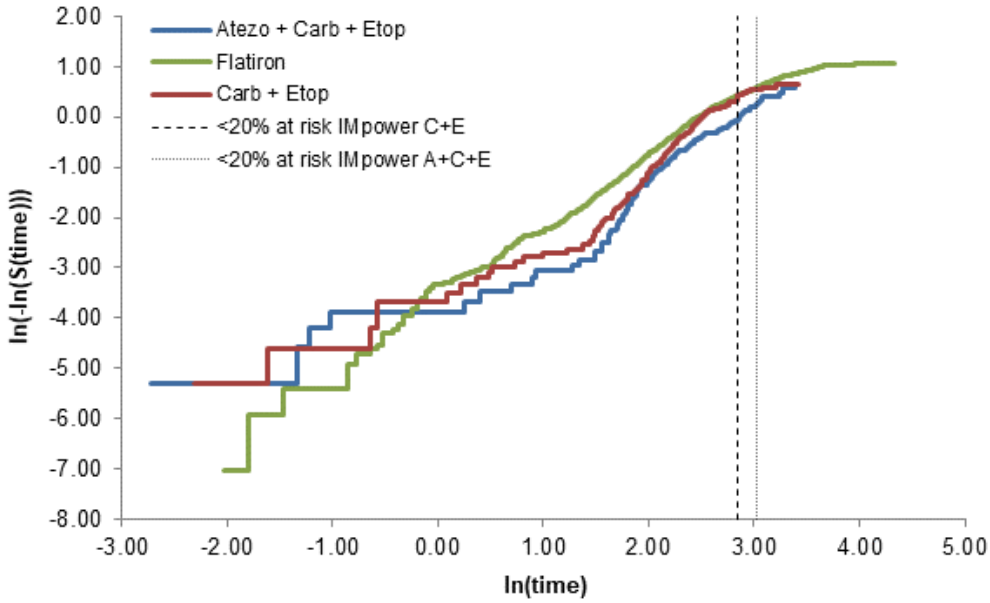
The models detailed were validated with 8 Consultant Oncologists during 1:1 consultations between 5-12th November 2019 (see Appendices, Page 30) to understand how the survival extrapolations reflected long-term overall survival of patients with ES-SCLC in their clinical practice. In addition, Roche sought their opinion regarding the generalisability of the real-world Flatiron data to UK clinical practice (Data on file).

Changing of the hazard function over time

The Committee requested that further analyses should include comparison with external (Flatiron) data to understand what is happening to the hazard over time to help validate the choice of model.

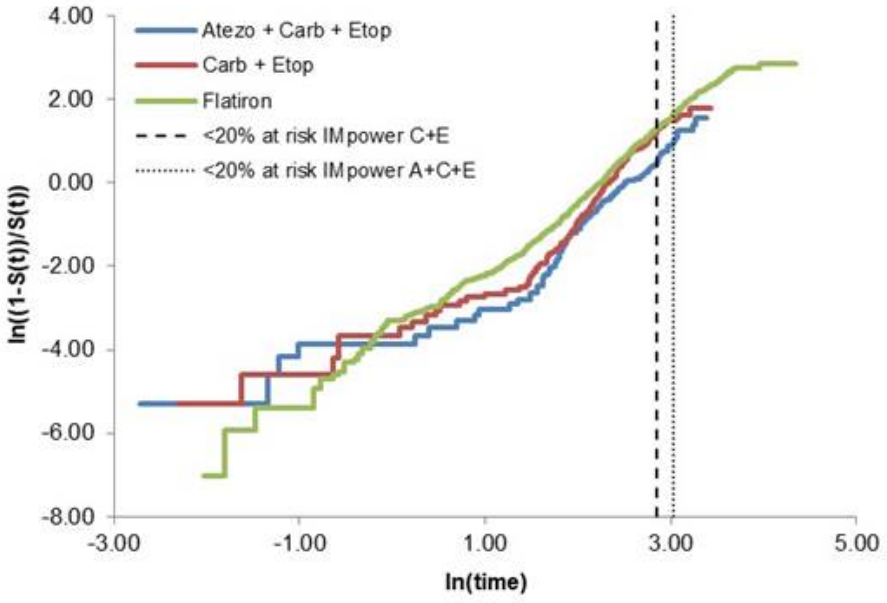
Figure 1 and Figure 2 show the log cumulative hazard (i.e. log(-log(S(t))) and logit(S(t) vs log-time plots) of the IMpower133 and Flatiron data (updated with follow up to July 2019). These demonstrate decreasing hazards over time. Notably, the end of the IMpower133 data follows a very similar shape to the Flatiron long-term data.

Figure 1: Log cumulative hazard plot for OS – IMpower133 and Flatiron data



Note: Dashed and grey vertical lines in the graph indicate <20% remaining at risk, i.e. at approximately 18 months for the comparator arm and 21 months for the atezolizumab arm

Figure 2: Logit (S(t)) vs Log-time – IMpower133 and Flatiron data



Note: Dashed and grey vertical lines in the graph indicate <20% remaining at risk, i.e. at approximately 18 months for the comparator arm and 21 months for the atezolizumab arm

To evaluate which parametric models may be more appropriate, visual assessment can be conducted as follows:

- if the log cumulative hazard is approximately a straight line, then a Weibull is justified and the slope is an estimate of the shape parameter. If the shape parameter is less than one (as it probably is at the end of the time interval), then the hazards are decreasing
- if the logit(S(t) vs log-time plot is approximately a straight line, then the log-logistic is justified (2)

In the plots presented in Figure 1 and Figure 2, the following can be observed:

- The cumulative hazards for the two IMpower133 arms cross within the first 2 months, after which there is no sign of convergence within the interpretable section of the trial data (see Figure 1 and Figure 2 for indication of when there is <20% remaining at risk, i.e. approximately 18 months for the comparator arm, 21 months for the atezolizumab arm - criterion of 20% based on Pocock et al (3))
- The long-term hazards are decreasing in all 3 data sources
- In both graphs, for the IMpower133 trial arms, there is a different shape to the curves before and after 5 months. It may be more appropriate to use KM data prior to this point or look at piecewise fits
- The logit(S(t)) vs log(time) graph has a relatively linear shape in both the Flatiron data and the IMpower133 arms after 5 months, suggesting that a log-logistic model is appropriate for extrapolation

The following sections will explore additional flexible models and the most plausible model will be chosen as the company base case.

Additional Survival Models

As discussed above, the models have been assessed in the context of: 1) how the hazard function within the clinical trial data changes over time; 2) how the hazard function within the external data (i.e. Flatiron data) changes over time; and 3) statistical fit, visual fit, and clinical plausibility as per NICE Decision Support Unit (DSU) guidance (Technical Support Document 14 (1)).

Following assessment of the hazard functions for IMpower133 and Flatiron data (the external data set), we can conclude a model with decreasing hazards is most appropriate.

The following section details the new survival models and assesses them based on point 3) above: NICE DSU TSD14 (1). Specifically, clinical plausibility is assessed based on external data available for validation:

- Clinical expert opinion from NHS oncologists
- Published literature
- Updated Flatiron registry data
- Data from other Immuno-oncology trials

Key criteria for validation of the survival curve

Based upon the external datasets available and clinical expert opinion[1], the key criteria used for long-term validation of survival curves is the proportion of patients surviving in the carboplatin-etoposide arm at 60 months. The survival extrapolation is deemed clinically implausible if:

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

[1] During 1:1 consultation with clinical experts, the vast majority agreed that a range of survival estimates between 0.5–5% was plausible for patients with ES-SCLC, ECOG PS 0–1, when considering their clinical experience and available literature (4).

1) ***Simple model – Gamma distribution***

A gamma distribution was fitted to the IMpower133 trial data (CCOD January 2019) as shown in Figure 3, and the AIC/BIC goodness of fit of the gamma and other OS distributions are presented in Table 1 for comparison. Gamma has a good statistical fit, similar to the log-logistic and Weibull, but it predicts 0.1% of patients alive at 60 months on the comparator arm, similarly underestimating long-term survival as seen with the Weibull distribution. During 1:1 consultations with clinical experts, around half of the experts commented that survival at 60 months with the gamma distribution was too pessimistic. In addition, all the clinicians felt that the published figure of 1.3% ES-SCLC patients alive beyond 6 years in Souhami et al. 1990 was plausible (4). The Gamma extrapolation is also not associated with decreasing hazards, further discounting this as a suitable extrapolation. The ICER using the gamma distribution for both arms is £46,916.

Figure 3: Gamma extrapolation of the IMpower133 OS data

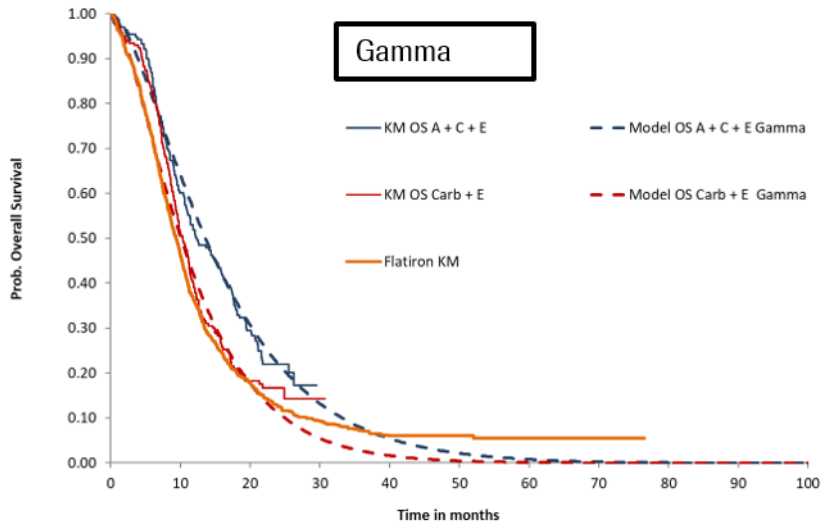


Table 1: Ranking of OS distributions based on AIC, BIC* and visual fit

	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

*New survival analysis (including AIC/BIC statistics) 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) in order to incorporate the gamma distribution, therefore, AIC/BIC are presented on a different scale compared to those in the Company submission. No point estimates of the models in the Company original submission have changed.

2) Piecewise model – piecewise exponential (KM plus exponential)

A piecewise model was fitted considering the KM estimates until 20 months (when ~25% patients are at risk in the atezolizumab arm) and extrapolating further by using an exponential function (Figure 4). The rate of the exponential function was estimated with the data between 5 and 20 months, where the plot of the cumulative hazard (-ln(S(t))) appears to be linear, justifying the use of an exponential (Figure 5). However, this extrapolation is too pessimistic as the survival rate for the comparator arm at 60 months is 0.2%. Around half of the clinical experts supported the view that this was clinically implausible during 1:1 consultations and as discussed before, clinical experts agreed with the survival estimate reported in Souhami et al (4). In addition, the hazards do not decrease over time as the available external data suggests it should. The piecewise model results in an ICER of £46,069.

Figure 4: Piecewise exponential extrapolation of IMpower133 data (using KM data between 5-20 months)

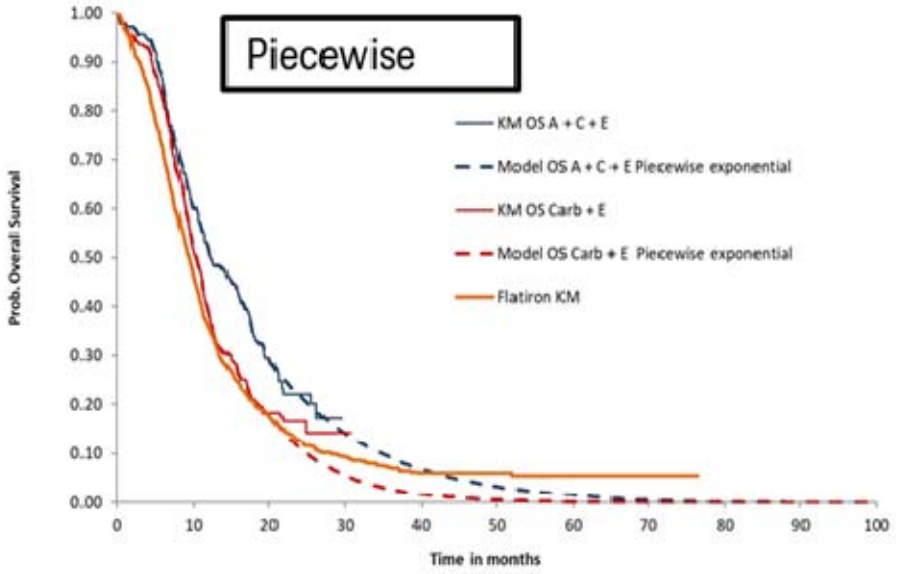
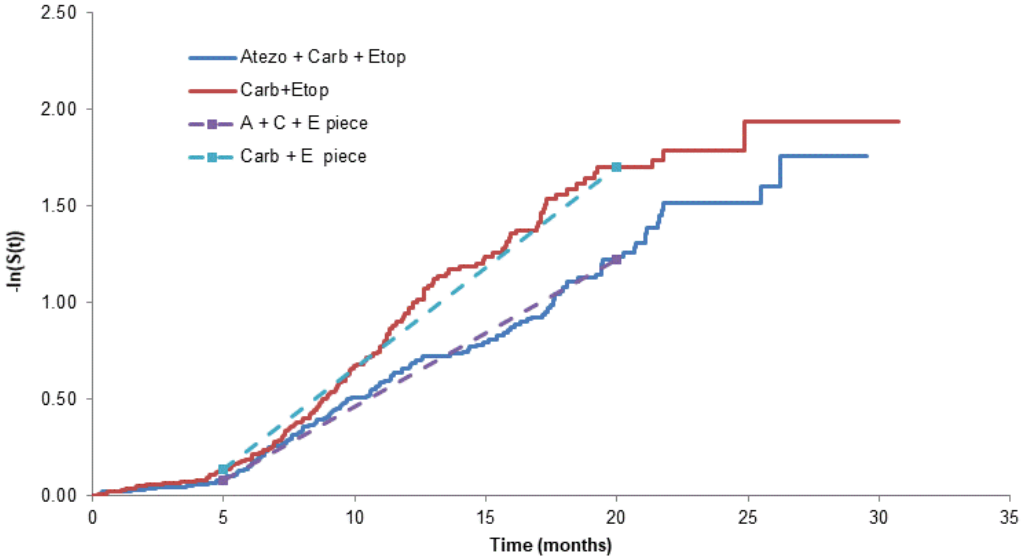


Figure 5: Cumulative hazard plot for OS: IMpower133 and piecewise (5 to 20 months*)



*25% patients at risk at 20 months

3) KM + log-logistic

Functionality was already included in the model to assess the impact of applying the KM data until a specific cut-off point before switching to transition probabilities of the parametric extrapolations (derived from the entirety of the IMpower133 trial data). Only the log-logistic extrapolation (Figure 6) has been considered here, as the Weibull was confirmed as overly conservative at the first committee meeting (predicts 0% survival at 60 months). During Technical Engagement, the Company discussed that whilst the Weibull extrapolation has comparable AIC/BIC fit to the log-logistic extrapolation, the fit of the curve is poorer in the control arm of the Weibull extrapolation. In addition, the Weibull survival curve did not provided clinically plausible overall survival estimates in relation to available long-term data (literature, Flatiron, and clinical opinion). To test the sensitivity to the cut-off point, Table 2 shows ICERs when switching from KM data to a log-logistic extrapolation at 5, 10, 15, and 20 months.

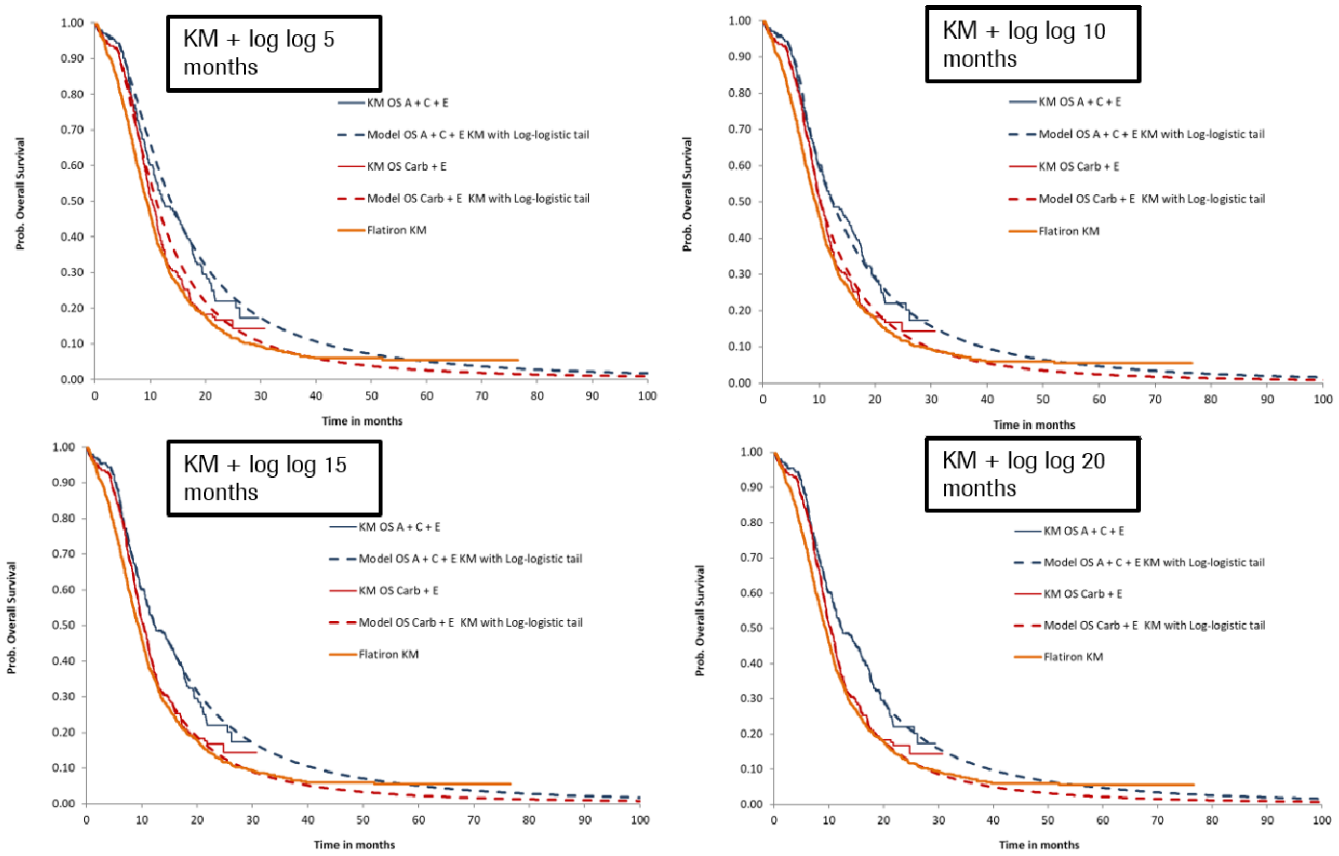
This extrapolation has the benefit of using the KM data directly for the first portion of the curve where the hazard function differs to the long-term data and providing externally valid estimates. With this approach, it is estimated that ~2% patients remain alive at 60 months in the comparator arm consistently (Table 2). During 1:1 consultations with clinicians, over half of the clinicians felt that at least one of the KM + log-logistic extrapolations was clinically plausible. The extrapolation also shows decreasing long-term hazards on both arms. Overall, the visual fit is best for KM switch to log-logistic extrapolation at 20 months, which provides an ICER of £41,894 (Figure 6).

Table 2: ICERs for KM + log-logistic at various cut-off points

Model (log-logistic extrapolation)	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 the ID1504 Atezolizumab Committee Papers).

Figure 6: KM + log-logistic extrapolation of the IMpower133 OS data, switch at 5-20 months



4) Restricted cubic spline model

Spline-based functions were explored as more flexible models that may better accommodate the changes in shape of the KM than traditional parametric approaches. One, two, and three knot spline models were fitted, following guidance on number and positioning of knots from Royston and Parmer (5). AIC and BIC values for all spline models are presented in Table 3, and the one knot odds, two knots odds, and two knots hazard are the best fit according to AIC/BIC. The same survival model was used for both arms in these analyses as is recommended in NICE DSU TSD 14. Table 4 presents the statistical and visual fit, as well as the ICER for the one knot odds, two knots odds, and two knots hazard; the corresponding graphs are presented in Figure 7. During 1:1 consultations, the majority of clinical experts considered the two knot model estimates for survival at 60 months in the comparator arm to be too optimistic (4.8% and 5.0% in the two knot odds and two knot hazards, respectively), however, the one knot odds model had an acceptable survival estimate of 1.3%.

The three knot models provided minimal improved visual or statistical fit over the two knot models. They also over-fitted to the carboplatin-etoposide tail, estimating 5 year survival >5% in all cases, which was not considered clinically plausible and are not included for consideration (although functionality remains in the model).

Table 3: AIC and BIC values for restricted spline survival models

	A+C+E		C+E	
Restricted Spline Model	**AIC**	**BIC**	**AIC**	**BIC**
Restricted spline one knot odds	**1081.373**	**1091.283**	**1134.843**	**1144.768**
Restricted spline one knot normal	1083.094	1093.004	1142.242	1152.167
Restricted spline one knot hazard	1089.305	1099.215	1154.956	1164.881
Restricted spline two knots odds	**1080.935**	**1094.148**	**1125.977**	**1139.21**
Restricted spline two knots normal	1083.613	1096.827	1134.597	1147.83

	A+C+E		C+E	
Restricted Spline Model	**AIC**	**BIC**	**AIC**	**BIC**
Restricted spline two knots hazard	**1081.923**	**1095.137**	**1122.033**	**1135.266**
Restricted spline three knots odds	1077.667	1094.184	1124.492	1141.033
Restricted spline three knots normal	1095.123	1111.639	1128.552	1145.093
Restricted spline three knots hazard	1077.918	1094.435	1123.05	1139.591

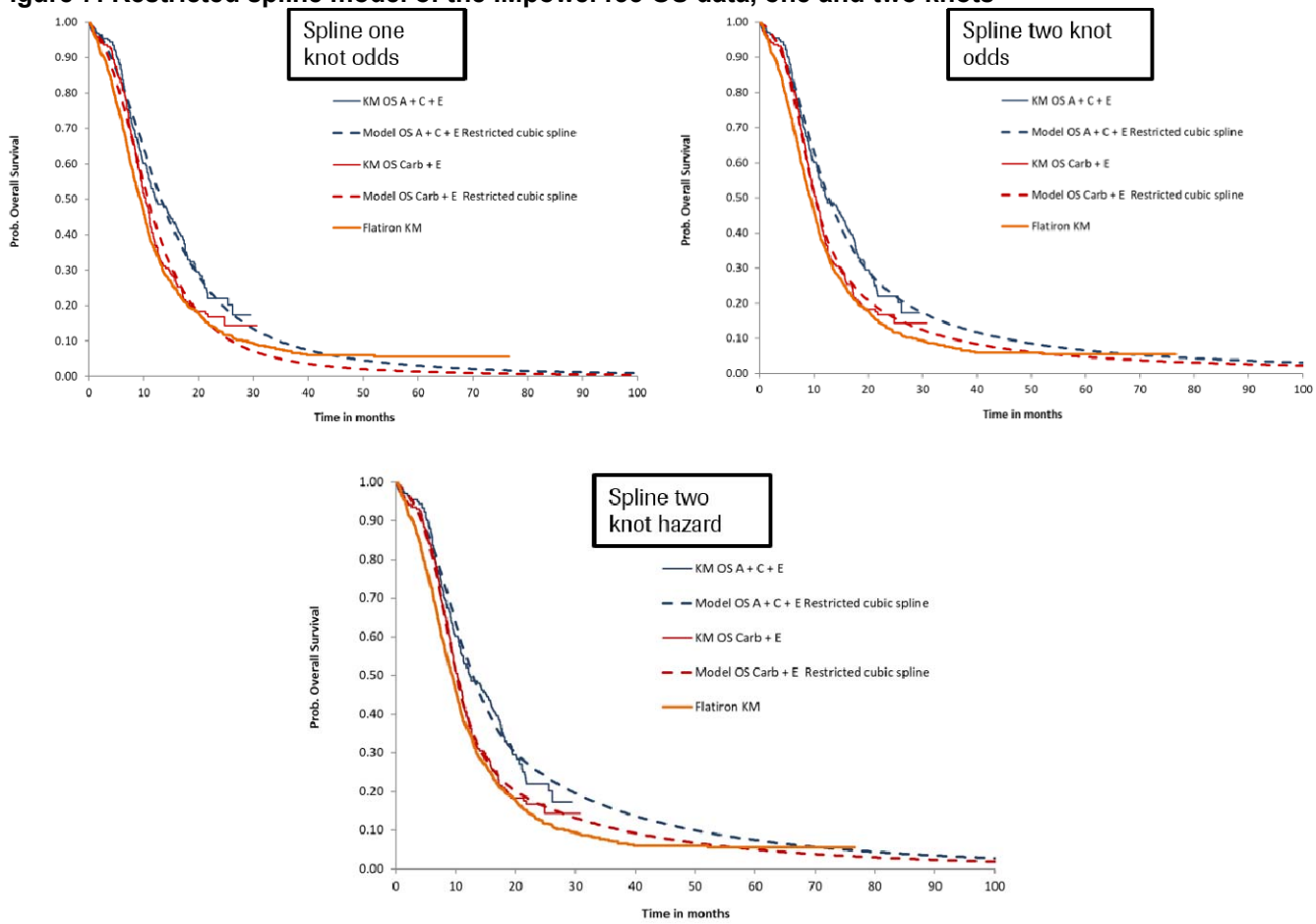
Note: Highlighted in bold are the models with the best statistical fit out of the spline models; odds, normal, and hazard are different functions for the restricted cubic splines. The text from the R package used to fit these are:

- The proportional odds model (scale="odds") defines g(S(t, z))= log(S(t, z) −1 − 1), the log cumulative odds.
- The probit model (scale="normal") defines g(S(t, z)) =−Φ−1(S(t, z)), where Φ−1() is the inverse normal distribution function qnorm.
- The proportional hazards model (scale="hazard") defines g(S(t, z)) = log(− log(S(t, z))) = log(H(t, z)), the log cumulative hazard.

Table 4: Statistical and visual fit and ICERs for selected restricted spline models

Restricted Spline Model	Statistical and visual fit	ICER
Restricted spline one knot odds	One of the best statistical fits out of the spline models and a small number of patients remain alive at 5 years on carboplatin-etoposide. Demonstrates decreasing hazards. However, the model did not improve in terms of visual fit over and above the standard parametric curves	£50,459
Restricted spline two knot odds	Good statistical fit and improved visual fit demonstrates decreasing hazards. These models predict survival rate of ~5% at 5 years for patients in the comparator arm, which is considered by clinicians to be higher than expected. Based on feedback from clinical experts, it is not anticipated that the rate of death for atezolizumab would exceed that of carboplatin (there may be some crossing of the curves in the first 6 months). However, these models report a crossing of the probability of death – therefore, the atezolizumab arm is assumed to have the same probability of death as carboplatin-etoposide from 1.5 years (no treatment effect beyond this). This is clinically implausible and thus a considerable limitation of these models. Similar to the explanation in the footnote of Table 2, the removal of the hazard assumption has been applied here for the two knot restricted spline models.	£44,181
Restricted spline two knot hazards		£50,537

Figure 7: Restricted spline model of the IMpower133 OS data, one and two knots



5) ***Mixture cure model***

We have investigated incorporating an assumption of long-term survivorship into overall survival extrapolation (mixture model). Mixture models are suited to extrapolation where we believe there are two groups of patients: those who experience poor long-term outcomes and those who experience good long-term outcomes (long-term survivorship). Immunotherapies have previously been associated with the potential for long-term survival in other indications (melanoma and NSCLC) and data from CHECKMATE-032. KEYNOTE-028, and KEYNOTE-158 (6-8) indicates some potential for long-term survivorship in SCLC (see Technical Engagement Response for more details). The clinical experts that we engaged with for this response would refrain from using the word “cured”, however, the majority agreed that some of their patients survive long-term (beyond 5 years) and in some cases, are discharged from their care. Most clinical experts consider these long-term survivors to have worse background mortality to that of the general population without cancer due to the high incidence of smoking in patients with ES-SCLC which leads to co-morbidities, e.g. cardiovascular disease, chronic lung diseases, and a higher risk of other types of lung cancer. For the remainder of this section, when the term “cure” is used, this refers to long-term survival. Roche do not consider atezolizumab to be curative.

Mixture cure models were built using the IMpower133 trial data (CCOD 24th January 2019) and background survival data. General population life tables were used to estimate background survival and mortality in cure patients. This data came from the Human Mortality Database (HMD) (9).

The cure fraction was estimated using maximum likelihood for different parametric specifications of the mortality hazard function. Since the estimation process showed instability, the analysis was re-run 100 times and the summary of the estimated cure rates is presented in Table 5.

Table 5: Estimates of the cure fraction for different parametric specifications using IMpower133 data

Distribution for survival in uncured patients	Cure fraction, % (min, max)		AIC	BIC	Ranking
	A + CE	P + CE			
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
Lognormal	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

During the 8 clinical expert consultations between 5th and 12th November 2019, the clinicians' opinion was that long-term survival could be expected once patients survive 4-5 years and the percentage estimate of ES-SCLC patients who reach this stage, in their clinical experience, is around 0.1–3% in patients receiving chemotherapy. From these consultations, the only distribution with a clinically plausible cure fraction is the log-logistic. However, there is considerable uncertainty around the cure fraction dependent upon the type of model fit to the uncured population. This is unsurprising given that the data available for atezolizumab are not mature enough to be able to visually observe a plateau, let alone have the confidence that would be appropriate in the cast of a long plateau containing a large number of data points (10, 11). We conclude that using a mixture cure model with the cure fraction taken from trial data alone is inappropriate for survival extrapolation.

However, there is an alternative option for including long-term survivorship within survival extrapolation:

Impact of incorporating long-term survivorship on top of survival extrapolations

In order to provide some sensitivity analysis around the impact of potential long-term survivorship, a cure fraction can be used as an input into the model: located in F178 and F180 of the Model Inputs tab.

As discussed above, consultation with clinical experts did highlight the potential for long-term survivorship. Generally, it was felt that if a patient reached 4–5 years, their risk of death associated with SCLC decreases, closer (albeit not equal to) general mortality. As such, we explored the potential implications of this assumption in a scenario analyses.

To explore what cure fractions could be included in the scenario analyses, the Company has considered the literature, external data and clinical expert opinion.

Literature

As presented in the Technical Engagement Report, a small but meaningful percentage of patients treated with chemotherapy survive long term according to Souhami et al 1990 (4), with UK data showing 1.3% ES-SCLC patients alive beyond 6 years, and Mannenil et al, 2017 (12), with US data showing 1.1% ES-SCLC patients alive beyond 3 years. Data from Sweden and Denmark also show that the ES-SCLC cohort of patients had 5- and 10-year survival rates of 2.3% and 1.2%, respectively (13). Collectively, these literature support our assumption that patients with ES-SCLC alive at 4/5 years could experience long-term survivorship on carboplatin + etoposide – generally 1.1%–2.3% of patients.

Also presented during Technical Engagement, was a number of supporting literature that were related to long-term survival rates seen with immunotherapies. This included Antonia et al. 2016, which showed a long term survival curve following treatment with nivolumab monotherapy and nivolumab plus ipilimumab (CheckMate-032 trial); Chung et al. 2018, which similarly showed long term survival after treatment with pembrolizumab (KEYNOTE-158); and finally, the KEYNOTE-028 trial also demonstrated a clear OS

plateau in ES-SCLC patients. Atezolizumab data in other indications also support the OS plateau (See Appendices, Page 31). These studies collectively show a flattening of the survival curve, or OS plateau for immunotherapy trials, suggesting that long-term survivorship could be further enhanced beyond that already documented for current standard of care.

Flatiron registry data

As was described in Document B of the Company submission, the Flatiron Health Database is a US-based, observational, longitudinal database containing electronic health record data from over 265 cancer clinics (~800 sites of care) including more than 2 million active U.S. cancer patients, available for analysis. To align with the IMpower133 data, the baseline patient characteristics were restricted in terms of patients being ES-SCLC, ECOG 0–1, and treated with platinum-etoposide regimens. These Flatiron data are presented in Section 3 and are updated data compared with what was submitted previously (initiated treatment from January 2013 to July 2018 with follow-up to July 2019). At 5 years, there were 5.6% patients alive and this survival tail remains up to the maximum follow up of 76 months. This real-world data provides 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.

Clinical expert opinion

During the 1:1 consultations with 8 clinical experts (carried out 5–12th November 2019), they were asked what their estimated percentage was for patients, treated with carboplatin-etoposide, who survive up to 5 years. The majority of clinical experts considered patients who reach 5 years' survival to be long-term survivors (one clinician has observed a maximum overall survival of 4 years in their clinical practice but agreed that survival beyond 4 years was plausible). The average survival estimates of the 8 clinical experts are presented in Table 6. All but one clinical expert considered patients who survive beyond 4/5 years to be long-term survivors. The majority of clinical experts expect it is unlikely that patients who survive up to 4 or 5 years are at risk of death from SCLC.

Table 6: Averaged survival estimates at 4 and 5 years from 8 clinical experts

Years	Survival estimate for A+C+E arm	Survival estimate for C+E arm
4	6.38±4.57%	2.5±1.28%
5	3.53±2.25%	1.26±0.91%

Scenario analyses exploring cure fractions

The evidence above from literature, external data, and clinical expert opinion, show that a long-term overall survival benefit is clinically and pharmacologically plausible for patients with ES-SCLC that receive carboplatin and etoposide or atezolizumab in combination with carboplatin and etoposide. Therefore, scenario analyses have been conducted to reflect the range in survival seen in the evidence provided (Table 7).

For the scenario analyses detailed here, the KM + Log logistic (switch at 20 months) is used as the underlying survival extrapolation.

At 60 months, using the KM + Log logistic (switch at 20 months), 2.2% of patients are alive on carboplatin + etoposide, and 4.7% are alive on atezolizumab + carboplatin + etoposide (Table 8 and Table 9). These are within the range of anticipated survival estimates from clinical expert consultation (Table 6).

Aligned with clinical expert feedback, assuming 100% of patients experience long-term survivorship (with the same mortality risk as the general population mortality) - if they reach 60 months survival on either the intervention or comparator arm, the ICER reduces significantly to £31,956 (Table 7).

It is worth noting that in some of the evidence shown above (e.g. Flatiron and Denmark/Swedish data); the survival predictions are even higher than the 2.2% patients alive at 60 months on carboplatin + etoposide. However, we are unable to account for this (i.e., assuming >100% of patients experience long-term survivorship at 60 months). Nevertheless, it is important to highlight the ICER could decrease further if the literature and Flatiron is deemed plausible.

Table 7 summarises the cure fraction scenarios explored based on the literature and clinical opinion. Two key assumptions are explored: Firstly, that long term survivors experience the same mortality hazard as the general population (standard mortality ratio of 1). Secondly, long-term survivors experience an increased risk to the general population: When consulting with clinical experts, some explained that long-term survivors are still expected to have a higher risk of death than the general population, and instead, should have the same mortality as, for example, a chronic obstructive pulmonary disease (COPD) or a smoking population. This assumption was explored by applying a standardised mortality ratio of 2; this equates to double the risk of death compared to the general population (Table 7). As demonstrated, this has little impact on the ICER.

Table 7: Inputs for cure fractions as supported by literature and clinical expert opinion (using KM + log-logistic, switch at 20 months)

Standardised mortality ratio	% of patients at 60 months who experience cure	Equivalent % of all patients achieving cure (A+C+E)	Equivalent % of all patients achieving cure (C+E)	ICER (£ Cost/QALY)
1	100	4.7	2.2	31,956
	50	2.3	1.1	38,039
	25	1.2	0.5	40,204
2	100	4.7	2.2	32,539
	50	2.3	1.1	38,065
	25	1.2	0.5	40,097

Summary of survival extrapolations

Presented in Table 8 are the survival rates and ICERs from the additional parametric extrapolations that have been discussed in the previous sections, alongside data available from the original company and ERG base case extrapolations, IMpower133 trial and Flatiron registry (discussion of Flatiron data is further discussed in Section 4). In addition, the estimations of survival rates for ES-SCLC patients with ECOG PS 0-1 from clinical experts (obtained during 1:1 consultations) have been averaged and presented.

Table 8: Survival extrapolations using alternative models for the comparator arm

	Data	12 mths	24 mths	36 mths	48 mths	60 mths	ICER (£/QALY)
Validation information	IMPower133 Carbo + Etop arm	38.9%	16.8%	-	-	-	-
	Flatiron C+E (updated July 2019)	35.9% (33.1–38.9)	12.6% (10.6-14.9)	7.1% (5.4-9.2)	6.0% (4.4-8.2)	5.6% (3.9-7.9)	-
	Mean estimates from 1:1 consultations with 8 clinical experts	41.3±8.7%	14.4±7.3%	5.4±2.4%	2.5±1.3%	1.3±0.9%	-
Original extrapolations	Weibull	46.8%	12.1%	2.2%	0.3%	0%	66,032
	Log-logistic	43.8%	15.3%	7.1%	4.0%	2.5%	47,449
Survival extrapolations (**Comparator arm**)	Gamma	41.6%	11.3%	2.7%	0.6%	0.1%	49,916
	Piecewise exponential	39.0%	11.3%	2.8%	0.7%	0.2%	46,069
	KM + log-log (5 mths)	45.8%	16.0%	7.4%	4.2%	2.7%	43,806
	KM + log log (10 months)	42.0%	14.6%	6.8%	3.8%	2.4%	50,635
	KM + log log (15 months)	39.0%	13.8%	6.4%	3.6%	2.3%	38,904
	KM + log log (20 months)	39.0%	13.2%	6.1%	3.5%	2.2%	41,894
	Spline one knot odds	44.1%	12.1%	4.6%	2.3%	1.3%	50,459
	Spline two knots odds	40.6%	16.6%	9.8%	6.5%	4.8%	50,537
	Spline two knots hazard	39.2%	16.8%	10.6%	7.1%	5.0%	44,181
	100% cure fraction* (SMR=1)	39.0%	13.2%	6.1%	3.5%	2.2%	31,956
	50% cure fraction* (SMR=1)	39.0%	13.2%	6.1%	3.5%	2.2%	38,039
	25% cure fraction* (SMR=1)	39.0%	13.2%	6.1%	3.5%	2.2%	40,204
	100% cure fraction* (SMR=2)	39.0%	13.2%	6.1%	3.5%	2.2%	32,539

	50% cure fraction* (SMR=2)	39.0%	13.2%	6.1%	3.5%	2.2%	38,065
	25% cure fraction* (SMR=2)	39.0%	13.2%	6.1%	3.5%	2.2%	40,097

* Using KM + log-logistic, switch at 20 months

The revised Company base case

At the appraisal committee meeting, the Committee felt that the log-logistic curve did not align with the estimates provided by the clinical experts who were present and that it provided a poor visual fit to KM data. Based on the information presented above regarding the AIC/BIC and visual fit of the additional overall survival extrapolations, and clinical plausibility based on:

- The estimated proportion of long term survivors,
- Decreasing hazards to reflect the trial, and external data
- Clinical validation from 8 consultations

Roche considers the **KM + log-logistic at 20 months** as the most plausible extrapolation.

At 60 months, using the revised Company base case (KM + log-logistic, switch at 20 months), there are 4.7% of patients alive on the atezolizumab arm and 2.2% on the carboplatin arm. These figures are comparable to the proportion of patients with an ongoing response at latest follow-up from IMpower133 (11/201 [5.5%] A+C+E and 3/202 [1.5%] on C+E) (14) providing further validation of the plausibility of the estimates.

During the 1:1 consultations, clinical experts were presented with the alternative models and provided their opinion on the clinical plausibility of the survival extrapolations. Most clinical experts chose the most clinically plausible extrapolation(s) through a process of elimination; early on in this process, some clinicians discounted the gamma, piecewise, spline 2 knot odds, and spline 2 knot hazards extrapolations as they considered the 5-year survival estimation to be either too pessimistic (gamma and piecewise) or too optimistic (spline 2 knot odds and spline 2 knot hazards). In addition, the crossing of the death hazards for the restricted spline models are clinically implausible. This leaves the KM + log-logistic for 5, 10, 15, and 20 months and the Spline 1 knot odds extrapolations as remaining potential options.

By looking at the curves for these remaining extrapolations, the KM + log-logistic (20 months) best fits the data and provides the improved visual fit the Committee requested as well as clinically plausible long-term outcomes. In addition, as can be seen from the survival extrapolation of the comparator arm in Table 8, the survival rates are comparable to the estimates provided by the clinical experts.

In terms of the cure models, those implemented within the model utilise the existing survival extrapolations. Hence, any additional “cure” or “long-term survivorship” considered remains consistent in terms of fit. Based on the evidence presented, the long term survivorship is also deemed clinically plausible (Table 7). However, as the cure model provides a more optimistic view of long-term survivorship, and the ICER only decreases under these scenarios (Table 9), the KM + log-logistic (switch at 20 months) remains the updated company base case.

Conclusion

Overall, out of the additional flexible models we have provided, the KM + log-logistic (20 months) is the best fitting extrapolation, in terms of statistical and visual fit, and clinical plausibility.

Given that 80% of the scenarios the Company have provided in Table 8 are below the threshold of £50k, this supports the conclusion that atezolizumab plus carboplatin and etoposide for untreated 1L ES-SCLC patients (ECPG PS 0–1) is a cost effective use of NHS resources.

Restricted means analysis and implications for end of life

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

The restricted mean survival time (RMST) at 26.22 months (time of the last event in the trial) is 14.4 months and 12.3 months for the atezolizumab arm and the placebo arm, respectively, with an estimated difference of 2.1 months. Given one of the two end-of-life (EOL) criterion is: extension to life of normally at least an additional 3 months, this difference of 2.1 months is closer to the EOL criteria than the RMST difference estimated at 24 months (i.e 1.9 months difference). This suggests that RMST is increasing with further data cuts. This is also supported by clinician opinion regarding long-term survivors, implying that RMST could be expected to continue increasing.

Looking at this survival benefit as a percentage of the overall survival, it is clinically meaningful and proportionally an important improvement survival benefit, which supports atezolizumab plus carboplatin and etoposide as meeting EOL criteria:

- 2.1/12.3 = **17.1%** vs. EOL criteria 3/24 = **12.5%**

In all alternative survival models considered here, when extrapolating for the lifetime horizon of the economic model, mean survival estimates for atezolizumab range from 16.3–23.4 equating to an additional survival over standard of care of 3.98–7.00 months, comfortably meeting the EOL threshold (see Table 9).

The overall proportion of improvement in OS is high at when we look at the proportional difference in mean OS generated from the updated company base case extrapolation: 33.8% (4.93 months/14.6 months) compared to the 12.5% improvement (3 months/24 months) required for the EOL criteria. With our base case extrapolation using KM + log-logistic at 20 months, the mean difference in OS is 4.93 months which is above the 3 months threshold required to meet the EOL criteria.

Table 9: Scenario of difference survival analysis, with PAS price

Survival extrapolations	Arm	Total LYG	Total QALYs	Incremental LYG	Incremental QALYs	% alive at 5 years in A+C+E arm	Mean OS in atezolizumab arm	Mean OS improvement between treatment arms (months)	ICER (£/QALY)
Log-logistic (Original Company base case)	A+C+E	1.53	[redacted]	0.32	[redacted]	4.89	19.7	4.37	47,449
	C+E	1.21	0.79						
Weibull (ERG base-case)	A+C+E	1.26	[redacted]	0.23	[redacted]	0.24	15.7	2.88	66,032
	C+E	1.04	0.67						
Gamma	A+C+E	1.31	[redacted]	0.33	[redacted]	0.85	16.3	4.19	46,916
	C+E	0.98	0.63						
Piecewise exponential	A+C+E	1.35	[redacted]	0.44	[redacted]	1.66	16.8	4.24	46,069
	C+E	1.02	0.65						
KM + log-log (5 months)	A+C+E	1.60	[redacted]	0.35	[redacted]	5.16	20.6	4.76	43,806
	C+E	1.25	0.82						
KM + log log (10 months)	A+C+E	1.50	[redacted]	0.30	[redacted]	4.66	19.2	4.06	50,635
	C+E	1.20	0.78						
KM + log log (15 months)	A+C+E	1.56	[redacted]	0.39	[redacted]	5.10	20.1	5.35	38,904
	C+E	1.17	0.76						
KM + log log (20 months) – base case	**A+C+E**	**1.52**	[redacted]	**0.36**	[redacted]	**4.70**	**19.5**	**4.93**	**41,894**
	C+E	**1.16**	**0.75**						
Spline one knot odds	A+C+E	1.40	[redacted]	0.30	[redacted]	3.06	17.7	3.98	50,459
	C+E	1.10	0.71						
Spline two knots odds	A+C+E	1.68	[redacted]	0.30	[redacted]	6.65	22.1	4.15	50,537
	C+E	1.38	0.90						
Spline two knots hazards	A+C+E	1.69	[redacted]	0.34	[redacted]	7.46	21.9	4.54	44,181
	C+E	1.34	0.88						
Cure fractions (% patient at 60 months who experience cure)*									
100% (SMR=1) Equivalent to 2.2% patients achieving cure	A+C+E	1.73	[redacted]	0.48	[redacted]	4.70	24.5	7.6	31,956
	C+E	1.25	0.82						

50% (SMR=1) Equivalent to 1.1% patients achieving cure	A+C+E	1.59	[redacted]	0.40	[redacted]	4.70	21.0	5.74	38,039
	C+E	1.19	0.77						
25% (SMR=1) Equivalent to 0.5% patients achieving cure	A+C+E	1.55	[redacted]	0.38	[redacted]	4.70	20.1	5.26	40,204
	C+E	1.17	0.76						
100% (SMR=2) Equivalent to 2.2% patients achieving cure	A+C+E	1.73	[redacted]	0.48	[redacted]	4.70	23.4	7.00	32,539
	C+E	1.25	0.82						
50% (SMR=2) Equivalent to 1.1% patients achieving cure	A+C+E	1.59	[redacted]	0.40	[redacted]	4.70	20.8	5.62	38,065
	C+E	1.19	0.77						
25% (SMR=2) Equivalent to 0.5% patients achieving cure	A+C+E	1.55	[redacted]	0.38	[redacted]	4.70	20.0	5.22	40,097
	C+E	1.17	0.76						
*Using KM + log-logistic, 20 months as base-case									

2. Exploration of duration of treatment benefit in the model

The committee requested exploration of the effect on model results of reducing the duration of treatment benefit (5 years after starting treatment in the base case). For example, the committee noted that, based on a Kaplan-Meier data plot of overall survival from IMpower133 (Figure 1 in the Clarification response, shown on slides 10 and 19 in the committee meeting presentation), there may be no treatment benefit from around 30 months.

However, it should be noted that at 30 months, there are only 6 patients at risk on the atezolizumab arm and 6 on the comparator arm. Any assessment of the shape of KM after this point is subject to an extremely high level of censoring, and therefore is considered to be unreliable. Furthermore, the censored patients are either lost to follow up or have not experienced progression or death at the time of the analysis (i.e., not necessarily dead). Visual fit should only be assessed where 10-20% remain at risk (3). At this time point (21-22 months), the KMs do not cross and the hazard functions do not look to be converging (Figure 1 and Figure 2).

In response to the request for further information, ICERs have been provided using a reduced treatment effect cut-off (Table 10). This shows that changes to this cut off make little difference to the ICER, even with a cut off at 36 months. Roche has also provided a scenario with no treatment effect cap, in alignment with the committee conclusions in the ACD for ID1522: Atezolizumab with nab-paclitaxel for treating PD-L1-positive, triple-negative, advanced breast cancer (15).

Table 10: Scenario analysis for treatment effect cut-off

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

Other immunotherapy treatments for lung cancer have been appraised by NICE where it was accepted that a long-term treatment effect was biologically plausible; these appraisals are listed in Table 11. Previous immunotherapy appraisals in other indications have considered a relationship between long-term immunotherapy effect and patients with a durable treatment response (i.e., CheckMate 214 trial (16)). As discussed previously the proportion of patients surviving to 5 years in the revised company base case aligns well with the proportion of patients with durable treatment response in the IMpower133 trial.

Table 11: NICE lung cancer appraisals that have discussed plausibility of long-term immunotherapy effect

Appraisal	Comments from Committee
TA428 - Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (17)	"…in the March 2016 data submitted by the company at consultation all patients had stopped taking pembrolizumab and that the hazard ratios for both overall survival and progression-free survival were essentially unchanged from the original September 2015 data, supporting the company's preferred assumption that there is a long-term treatment effect"
TA531 - Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (18)	"The committee agreed that although it was biologically plausible for the treatment effect to continue after stopping pembrolizumab, its duration was uncertain."

Conclusion

Due to the prolonged treatment benefit expected from immunotherapies therapies, Roche expects the treatment effect to last at least 60 months, and keeps this as the company's base case, as has been used in previous lung cancer appraisals (19).

3. Clarification of the source of real-world chemotherapy survival data (as validated by an advisory board)

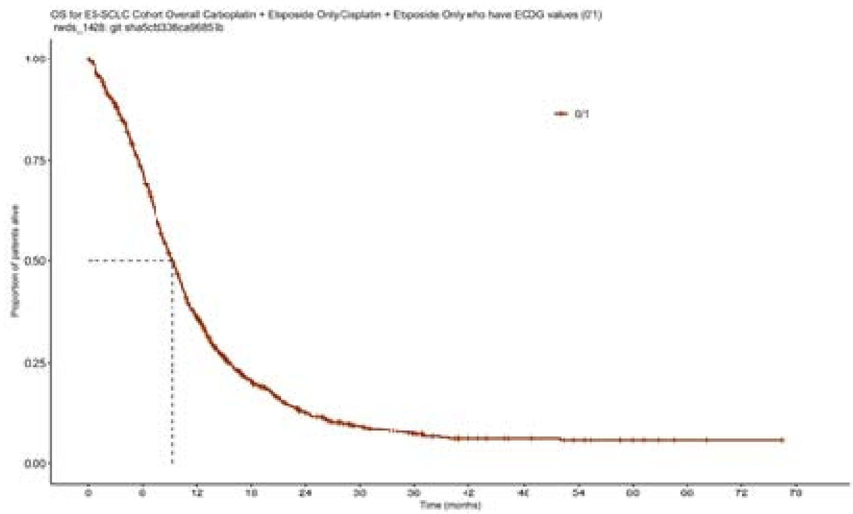
The committee requested clarification of the source of the Flatiron registry data regarding:

- 'Flatiron data' presented in Document B, Page 71, Table 23 – does not match KM Flatiron plot in Document B, Figure 13
- Sample size of the data – Figure 10, number at risk starts at 2,226

Clinical validation of Flatiron data

The table validated by clinical experts in Question 9 of the report in Appendix K is incorrect due to calculation of survival rates based on the percentage of patients at risk rather than the rates from the Kaplan-Meier curve of the data, which also account for censoring. Therefore, the results from Question 9 of the report in Appendix K are not concordant with the Flatiron data (these data were published in Sebastian et al 2019 (20)). During 5–12th November 2019, we have had 1:1 consultations with 8 clinical experts and we provided updated Flatiron data (initiated treatment from January 2013 to July 2018 with follow-up to July 2019) for their validation. As shown in Figure 9, the survival rates now match the data in the Flatiron curve.

Figure 8: Flatiron Health database (updated to July 2019), long-term survival for ES-SCLC patients with ECOG 0-1, treated with a platinum-etoposide regimen



Time (Months)	0	6	12	18	24	30	36	42	48	54	60	66
Survival rates	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Number at risk	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	n 15	n 10	n 5	n 2

Clinical experts were asked to look at the updated Flatiron data and determine whether they thought that the long-term survival for UK patients with ES-SCLC and ECOG 0-1 would be:

1) Better than described, with an increased number of patients surviving at 2 years and later;
2) Approximately the same as the described number of patients surviving at 2 years and later;
3) Worse than described, with a reduced number of patients surviving at 2 years and later.

Some clinical experts considered the long-term survival rates from the Flatiron data to be similar to UK patients in the initial proportion of the data (up to 24-36 months), however, the tail of the curve after 24-36 months was considered to be more optimistic than they would expect for UK patients. It should be noted that the tail on the KM curve at 42 months is representative of 19 patients and there is censoring of the data. This is because patients enter the dataset at different times meaning that for some patients there are many years of data for, however for others, follow-up ends quickly within the database and many patients are therefore, censored.

Sample size of the Flatiron data

The committee asked for clarification on Figure 10 (page 70) of Doc B due to the discrepancy in the population number. The discrepancy is because an incorrect graph was presented. The graph represented a wider Flatiron population (i.e., the whole cohort treated with any platinum therapy), hence, there are 2226 patients at risk. Whereas the number 860 is a subset analysis of more trial-like patients from the 5,600 patients diagnosed with SCLC (from 1st Jan 2013 to 31st Aug 2017). The 'trial-like' subset is derived by selecting for patients treated with 1st-line carboplatin-etoposide or cisplatin-etoposide with ES-SCLC and baseline ECOG PS 0–1. This generated the 860 patient included in the analysis. In the updated Flatiron data presented above, using the same criteria, the number of patients in the 'trial-like' population is 1,122.

Clinical expert opinion was sought on whether the Flatiron data could be used as a proxy for the carboplatin-etoposide arm and whether it was appropriate to incorporate Flatiron data with IMpower133 data. Some clinicians generally thought that the Flatiron patient population were similar to the UK patients, however, they felt that there was uncertainty in the tail of the survival curve due to the censoring, therefore the 5-year survival rate higher than they would expect in their clinical practice (estimations available in Table 6).

Despite this uncertainty, the real-world evidence we have available is the best data available for long-term survival of patients treated with platinum-etoposide and we have presented a scenario analysis of the Flatiron data merged with the IMpower133 data in order to use the strength of the additional dataset available to directly inform extrapolations (Document B, Section B.3.3.3). It is evident from this that use of Flatiron data to directly inform extrapolations (rather than for validation) improves the ICER.

Table 12: Survival extrapolations for the control arm compared with Flatiron data and merged IMpower133/Flatiron (July 2019) data

Time (months)	Modelled KM + log-logistic using trial data alone (20 months)	Flatiron data	IMpower133 KM + log-logistic Flatiron/IMpower133 extrapolation (20 months)
12	39.0%	35.9% (33.1-38.9)	38.9%
24	13.2%	12.6% (10.6-14.9)	13.8%
36	6.1%	7.1% (5.4-9.2)	7.1%
48	3.5%	6.0% (4.4-8.2)	4.3%
60	2.2%	5.6% (3.9-7.9)	2.9%

ICER (£/QALY)	**41,894**	**-**	**46,120***
Mean difference in survival (months)	4.93	-	4.44

*The survival extrapolations use IMpower133 KM data up to 20 months (~20% remaining at risk), and then the A+C+E arm extrapolates using a log-logistic parametric distribution fitted to the entirety of the IMpower133 A+C+E data, whereas the C+E arm extrapolates using a log-logistic informed fits model with data from the entirety of the IMpower133 C+E data informed by the Flatiron data.

4. Patient reported outcomes data from IMpower133

The committee requested that further data on patient reported outcomes from IMpower133 be provided. Specifically, it was requested that this should include further detail on the methods used to obtain the data, and further detail of results, including any statistical comparisons between the atezolizumab and placebo arms.

The below provides the additional information that is available from the CSR and the protocol (21, 22). Figures have been provided from an unpublished manuscript based on data from the CSR ([redacted]). No additional information beyond this is available.

Protocol

Secondary efficacy objective: To determine the impact of atezolizumab as measured by time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnoea (single-item and multi-item subscales), chest pain, arm/shoulder pain, or fatigue using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) in patients treated with atezolizumab plus carboplatin and etoposide compared with placebo plus carboplatin and etoposide in the ITT population.

Exploratory objective: To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 5-Level (EQ-5D-5L) questionnaire to generate utility scores for use in economic modelling.

Methodology

The methodology for collecting patient-reported outcome data is described in the clinical study report as belw (21).

PRO data was collected via the EORTC QLQ-C30, the EORTC QLQ-LC13, and the EQ-5D-5L using an electronic PRO (ePRO) device. To ensure instrument validity and that data standards met health authority requirements, questionnaires scheduled for administration during a clinic visit were completed in their entirety by the patient prior to the performance of non-PRO assessments and the administration of study treatment.

Patients whose native language was not available on the ePRO device or who were deemed by the investigator incapable of inputting their ePRO assessment after undergoing appropriate training were exempted from completing all ePRO assessments.

Only identified and trained users could view the data, and their actions would become part of the audit trail. The Sponsor had view access only. Regular data transfers occurred from the centralized database at the vendor to the database at the Sponsor.

EORTC QLQ-C30, EORTC QLQ-LC13, and the EQ-5D-5L questionnaires were completed by the patients on the ePRO tablet at each scheduled study visit prior to administration of study drug and prior to any other study assessment(s).

During survival follow-up, the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires were completed at 3 and 6 months following radiographic disease progression per RECIST v1.1 (or at 3 [± 30 days] and 6 months [± 30 days] after treatment was discontinued for patients who continued treatment after disease progression per RECIST v1.1). For patients who discontinued study treatment for any reason other than radiographic disease progression, PRO assessments continued at the same frequency as would have been followed if the patient had remained on study treatment until radiographic disease progression, withdrawal of consent, death, or study termination by the Sponsor, whichever occurred first. Study personnel reviewed all questionnaires for completeness before the patient left the investigational site.

PROs of HRQoL, lung cancer-related symptoms, and health status were measured using EORTC QLQ-C30 and EORTC QLQ-LC13. Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) and the mean change from baseline of linear-transformed scores would be reported for all of the items and subscales of the EORTC QLQ-C30 questionnaire and the QLQ-LC13 according to the EORTC scoring manual guidelines. Completion and compliance rates would be summarised at each timepoint by treatment arm. The analysis populations for PRO changes would be all randomised patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment

Time to death (TTD) using EORTC is defined as the time from baseline to the first time the patient's score shows a ≥10-point increase above baseline in any of the following EORTC-transformed symptom subscale scores (whichever occurs first): cough, dyspnoea (single item), dyspnoea (multi-item subscale), chest pain, or arm/shoulder pain, whichever occurs first. The linear transformation gives each individual symptom subscale a possible score of 0–100. In order for the symptom to be considered "deteriorated," a score increase of ≥10 points above baseline must be held for at least two consecutive assessments or an initial score increase of ≥10 points is followed by death within 3 weeks from the last assessment. A ≥10-point change in the symptoms subscale score is perceived by patients as clinically significant(23). Patients were censored at the last time when they completed an assessment if they had not deteriorated. If no post-baseline assessment was performed, patients were censored at the randomisation date plus 1 day. TTD using the EORTC scale were analysed using the same methods as for PFS. The analysis populations for TTD included all randomised patients with a non-missing baseline PRO assessment.

Results

The following section presents the results of the PRO data, as provided in the CSR – no statistical comparisons were carried out.

At baseline, 175 patients in the atezolizumab plus CP/ET arm (87%) and 179 in the placebo plus CP/ET arm (89%) completed the QLQ-C30, and 176 (88%) and 168 (83%), respectively, completed the QLQ-LC13. Completion rates remained above 80% up to week 24 in the placebo arm and up to week 36 in the atezolizumab arm. At week 54, 34 (8%) of the 403 randomized patients remained on study treatment and were eligible to complete PRO assessments. At baseline (i.e., before initiating study treatment), mean disease-related symptom, functioning, and HRQoL scores were comparable between treatment arms (Table 13). Compared to normative scores of ES-SCLC patients (24), patients in the study reported worse symptoms at baseline.

Table 13: Baseline Patient-reported outcome scores

	Placebo + carbo-etop	Atezolizumab + carbo-etop
	Mean scores (SD)	
Select EORTC QLQ-LC13 scales	**n = 168**	**n = 176**
Coughing	42.9 (29.2)	42.2 (27.7)
Pain in chest	22.2 (25.7)	22.9 (26.6)
Dyspnea	29.6 (25.9)	34.3 (25.9)
Pain in arm or shoulder	19.4 (27.4)	22.2 (30.6)
Select EORTC QLQ-C30 scales	**n = 175**	**n = 179**
Fatigue	38.7 (26.9)	42.0 (26.4)
Appetite loss	27.4 (31.9)	28.9 (32.3)
Physical functioning	71.9 (23.5)	70.7 (22.7)
Role functioning	66.4 (32.9)	67.1 (31.3)
Social functioning	73.3 (28.8)	71.1 (29.1)
Emotional functioning	69.9 (24.0)	68.6 (23.9)
Cognitive functioning	83.3 (20.6)	81.8 (21.1)
Global health status or HRQoL	53.7 (23.4)	51.6 (22.4)

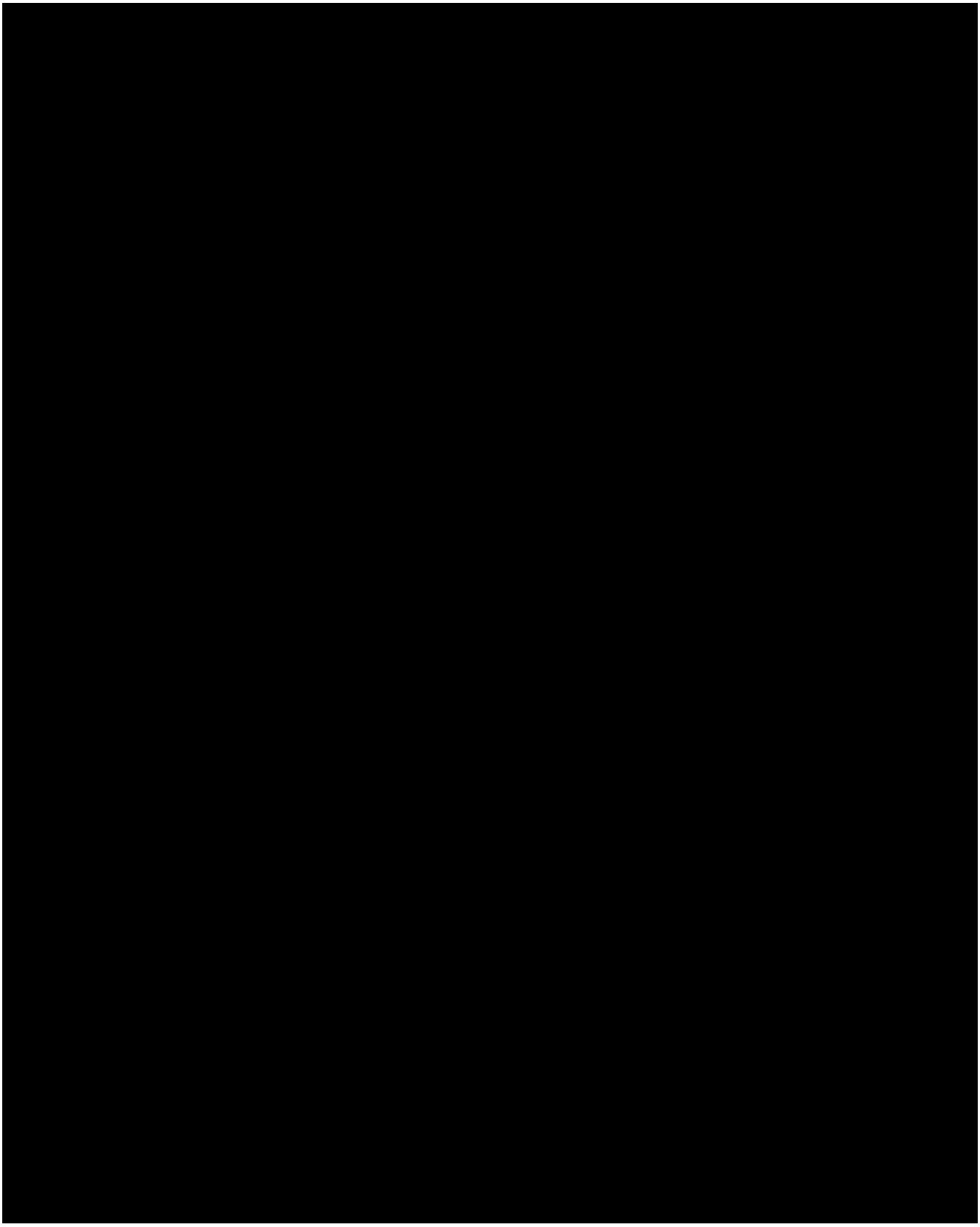
Lung cancer and treatment related symptoms

No apparent differences between treatment arms were observed in TTD (defined as a > 10-point increase from baseline maintained for at least two consecutive assessments or followed by death within 3 weeks of the last assessment) in patient-reported lung cancer symptoms of cough, chest pain, or arm/shoulder pain. Although a trend towards delayed worsening of dyspnoea favoured the atezolizumab arm vs. the placebo arm (stratified HR = 0.75 [95% CI: 0.55, 1.02]).

Change from baseline analyses suggests that, on average, patients in both treatment arms experienced immediate improvements in disease-related symptoms after beginning study treatment. At induction visits (i.e., Baseline up to but not including Week 12), improvements from baseline in cough, chest pain, dyspnoea, arm/shoulder pain, dysphagia, fatigue, and appetite loss were numerically greater in the atezolizumab arm than in the placebo arm. At visits during maintenance (i.e., Week 12 to end-of-treatment), numeric improvements in lung cancer-related symptoms were either comparable between arms or larger in the atezolizumab arm than in the placebo arm. In addition, patients receiving atezolizumab plus carboplatin and etoposide experienced clinically meaningful improvements (i.e., > 10-point score decrease from baseline) in cough, chest pain, and dyspnoea earlier and generally reported more enduring improvements than patients in the placebo arm. For example, patients in the atezolizumab arm vs. placebo arm reported clinically meaningful improvement by Week 3 vs. Week 6 (cough), Week 15 vs. Week 24 (chest pain), Week 15 vs. Week 33 (dyspnoea), Week 15 vs. Week 60 (fatigue), and Week 9 vs. Week 21 (appetite loss). Improvement above baseline was sustained for a longer duration of time in the atezolizumab arm vs. placebo arm for cough (Week 87 vs. Week 72), chest pain (Week 60 vs. Week 48), arm/shoulder pain (Week 27 vs. Week 18), and fatigue (Week 60 vs. Week 24).

Mean score changes in diarrhoea, nausea and vomiting, sore mouth, and peripheral neuropathy were numerically similar between treatment arms during induction and most visits through Week 54 (Figure 9).

Figure 9: Changes from baseline through week 54 in treatment-related symptoms



Possible scores are 0–100 (i.e. maximum possible change is +100 to –100).

Functional and HRQoL

Mean score changes from baseline in physical functioning and role functioning suggest similar degrees of improvement in both treatment arms during induction (Figure 10). At visits during the maintenance phase, patients treated with atezolizumab plus carboplatin and etoposide reported similar or greater improvements in both physical and role function compared to patients treated with placebo plus carboplatin and etoposide. On average, improved physical function was sustained until Week 51 in atezolizumab arm (vs. Week 48 in the placebo arm) and improved role function was sustained until Week 30 in the atezolizumab arm (vs. Week 27 in the placebo arm).

Descriptive changes in mean cognitive, social, and emotional functioning scores suggest numerically comparable or greater improvements in the atezolizumab arm vs. placebo arm during induction until Week 21 (emotional, social) or Week 30 (cognitive). On average, patients in both treatment arms reported social and emotional functioning better than pre-treatment functioning through at least Week 42. At visits through Week 27 (when 25% of randomised patients remained on study treatment and were available to complete PRO assessments), patients in the atezolizumab arm reported improved cognitive functioning, whereas patients in the placebo arm reported either nominal improvements or worsening. Patients in both treatment arms reported improved HRQoL immediately after starting study treatment, with more pronounced HRQoL benefit in the atezolizumab arm vs. placebo arm after Week 21. Clinically meaningful improvement in HRQoL was achieved early (by Week 12 [placebo arm] or Week 15 [atezolizumab arm]), and was sustained in the atezolizumab arm at most visits through Week 57, whereas improvements in the placebo arm were small and generally not clinically meaningful (i.e., <10-point score increases from baseline)

Figure 10: Changes from baseline through week 54 in function and HRQoL

Possible scores are 0–100 (i.e. maximum possible change is +100 to –100).

Summary of patient-reported outcomes data

Changes in patient-reported treatment-related symptoms commonly associated with quality of life impairment were generally similar during induction and most of the 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 the atezolizumab arm.

Overall summary of Company response

Roche have provided additional survival extrapolations and analysed each of these extrapolations in turn using a combination of:

- Statistical and visual fit
- Clinical expert opinion

- Hazards over time
- Comparability to relevant clinical trial evidence for atezolizumab and other immunotherapies
- Real-world evidence from Flatiron data

After consideration of each of these additional extrapolations, Roche's revised company base case extrapolation is **KM + log-logistic at 20 months**, which is considered the most appropriate to appraise the cost effectiveness of atezolizumab (ICER of £41,894, Figure 6). This extrapolation uses the KM data directly for the first portion of the curve where the hazard function differs to the long-term data, providing a solution to the Committee's challenge on visual fit to the KM. It then utilises the best statistical fit of all curves for the extrapolation portion. During 1:1 consultations with clinicians, the majority of clinicians felt that at least one of the KM + log-logistic extrapolations was clinically plausible of all the extrapolations presented. The extrapolation also shows decreasing long-term hazards on both arms, and the estimation of long-term survival for both the intervention (atezolizumab + carboplatin + etoposide) and comparator (carboplatin + etoposide) is supported by literature and FlatIron data.

The revised base case is associated with 4.7% surviving to 60 months on the atezolizumab arm vs 2.2% on comparator arm, consistent with the anticipated long-term survival from clinical experts. Additional scenario analysis shows that if even a small proportion of these patients can be deemed "cured" – either experiencing the same mortality rate of the general population, or double the mortality rate for the general population post-60 months, this has the potential to considerably improve upon these cost-effectiveness estimates.

Finally, the updated base case provides a 4.93 month mean overall survival improvement of atezolizumab over current standard of care, demonstrating atezolizumab meets the End of Life criteria.

As such, atezolizumab can be considered is a cost-effective use of NHS resource for the treatment of untreated ES-SCLC, and has an opportunity to:

- Be the first new treatment available to patients with ES-SCLC in 20 years
- Provide patients with a proportionally substantial extension to what is currently an extremely poor overall survival, without compromising quality of life (proportional difference: RMST 17.1% vs. EOL 12.5%)

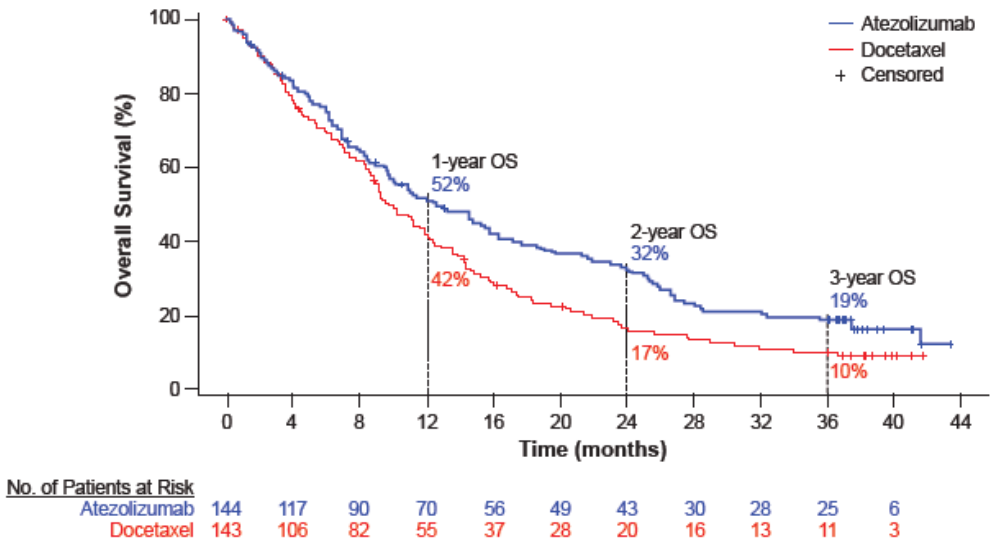
Roche understand that the committee required a better fitting survival extrapolation to inform decision making and have explored a series of more flexible models to address this. We believe that our revised base case extrapolation is well supported in terms of plausibility and invite the committee to consider this new evidence and hopefully enable all patients who can benefit from treatment to access to atezolizumab.

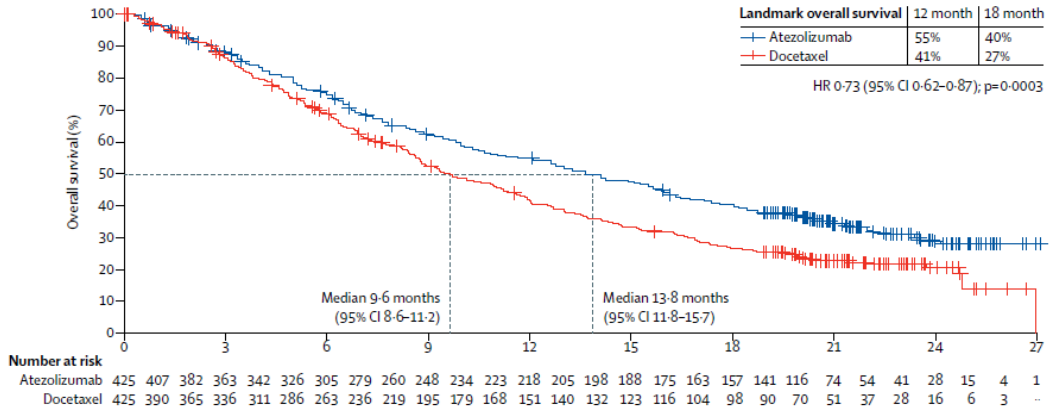
Appendices

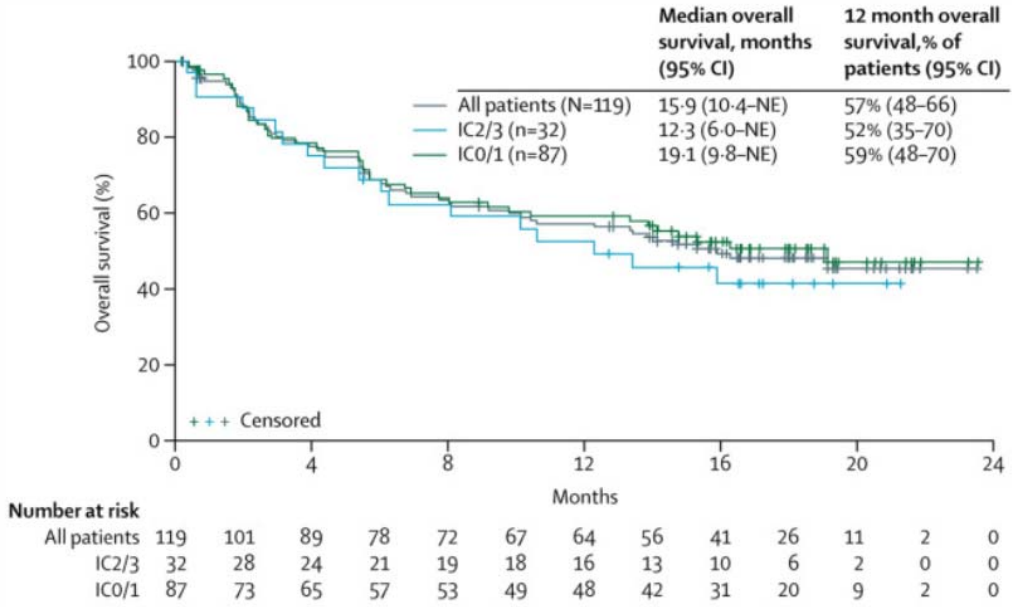
Clinical experts

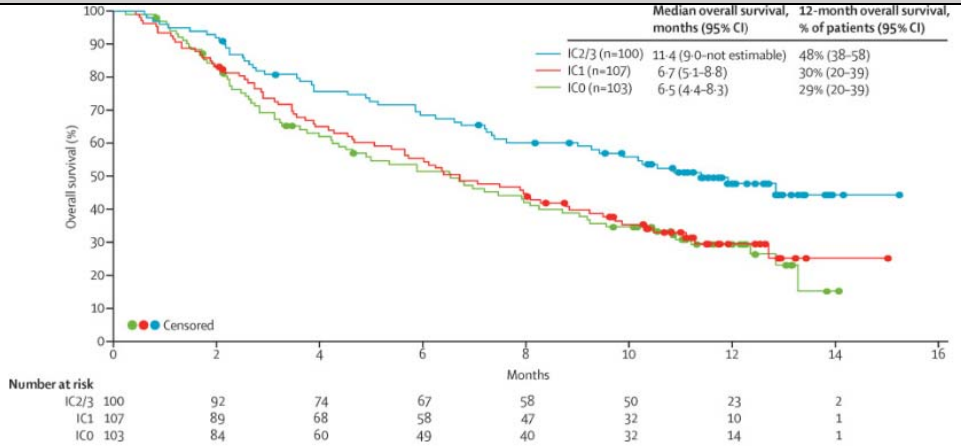
Clinical expert	Affiliation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

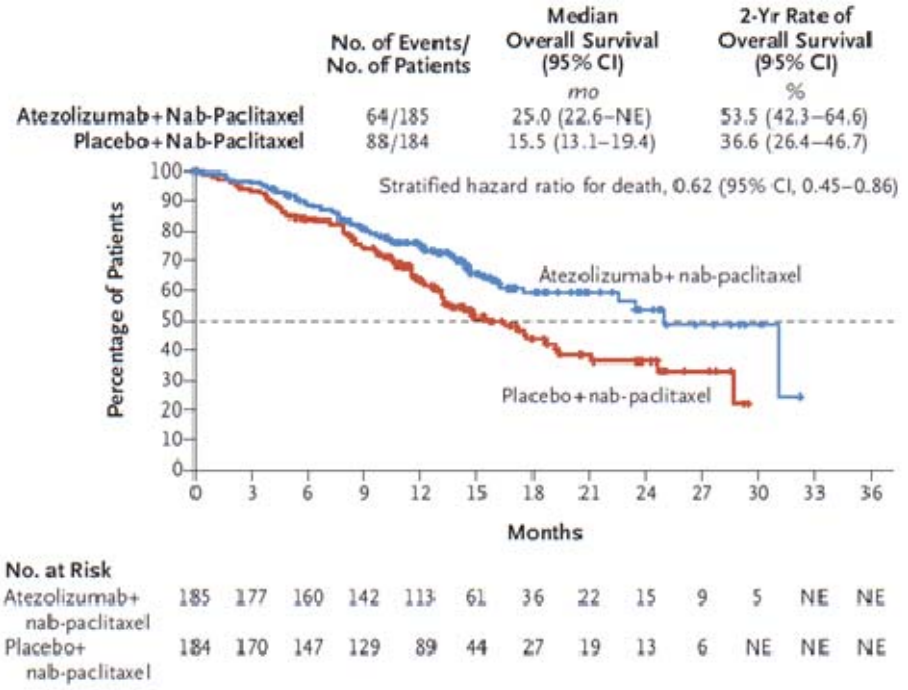
Atezolizumab trial results for various indications

Trial	Reference	Results
POPLAR	Mazières, J. et al. 3-year survival and duration of response in randomized phase II study of atezolizumab (atezo) vs docetaxel (doc) in 2L+ NSCLC (POPLAR). Journal of Thoracic Oncology, Volume 13, Issue 4, S79 (25)	The 2-year and 3-year survival with atezolizumab vs docetaxel were 32.2% vs 16.6% and 18.7% vs 10.0%, respectively (Figure 11). The long-term OS benefit of atezolizumab vs docetaxel was observed across histology and PD-L1 expression subgroups. **Figure 11: Landmark OS rates from POPLAR** 
OAK	Rittmeyer, Achim et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial.	In the ITT population, overall survival was improved with atezolizumab compared with docetaxel (median overall survival was 13·8 months [95% CI 11·8–15·7] vs 9·6 months [8·6–11·2]; hazard ratio [HR] 0·73 [95% CI 0·62–0·87], p=0·0003). **Figure 12: Overall survival in the ITT population of OAK**

Trial	Reference	Results
	The Lancet, Volume 389, Issue 10066, 255 - 265 (26)	
IMvigor210 (cohort 1 first-line treatment)	Balar, AV et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. The Lancet, Volume 389, Issue 10064, 2017, Pages 67-76 (27)	The median overall survival was 15.9 months (95% CI 10.4 to not estimable) in all patients, 12·3 months (6.0 to not estimable) in IC2/3 patients, and 19.1 months (9.8 to not estimable) in IC0/1 patients (Figure 13). With longer follow-up, in the PD-L1-selected subgroup, several patients had further tumour shrinkage, leading to new complete and partial responses. **Figure 13: Overall survival in patients given atezolizumab according to PD-L1 status on immune cells – Imvigor210 Cohort**

Trial	Reference	Results
		
IMvigor210 (cohort 2 previously treated)	Rosenberg, JE et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. The Lancet, Volume 387, Issue 10031, 2016, Pages 1909-1920 (28)	The median overall survival was 11.4 months (95% CI 9.0–not estimable) in patients in the IC2/3 group, 8·8 months (7.1–10.6) in the IC1/2/3 group, and 7.9 months (6.6–9.3) for the entire cohort of patients (Figure 14). **Figure 14: Kaplan-Meier overall survival curves for the IC0, IC1, and IC2/3 groups – Imvigor210 Cohort 2**

Trial	Reference	Results
		
IMpassion130	Schmid, P et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. New England Journal of Medicine. 2018 Nov 29;379(22):2108-2121. (29)	The IMpassion130 trial established the benefit of adding a checkpoint inhibitor to standard chemotherapy for the first-line treatment of metastatic triple-negative breast cancer, with most of the benefit realized in the PD-L1–positive subgroup. The first interim OS analysis is shown in Figure 15. At the second interim analysis, 9% of patients in the atezolizumab arm and 3% in the placebo arm were still on treatment (median duration of 18.5 months and 17.5 months, respectively). A 7.0-month improvement in median OS was observed in PD-L1+ patients with 25.0 months in the atezo arm vs 18.0 months in the placebo arm (HR, 0.71 [95% CI: 0.54, 0.93]) (30). **Figure 15: Kaplan-Meier overall survival curves in the PD-L1–Positive Subgroup for IMpassion130**

Trial	Reference	Results
		

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Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer (response post appraisal committee meeting)

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Rider on responsibility for report

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Following the first appraisal committee meeting (ACM), the company were asked to submit additional analyses and explanation, which has been provided in a report by the company according to the following structure[1]:

1. Further methods of estimating overall survival:
    a. Flatiron data to assess hazard over time
    b. Alternative models (including gamma, piecewise, restricted cubic spline, and mixture models)
    c. Clinical validation of alternative models
    d. Restricted mean analysis
2. Exploration of the effect of reducing duration of treatment benefit in the model
3. Clarification of the source of real-world chemotherapy survival data (as validated by an advisory board)
    a. Address the factual inaccuracy that was raised at the committee meeting
    b. Explain difference in initial number of patients at risk
    c. Address inconsistency regarding the source of the real-world data as referenced in the Company submission and validated at the advisory board
4. Further patient reported outcomes data from IMpower133

The following is a critique by the ERG of the company's additional analyses report.[1]

1. Further methods of estimating overall survival

a. Flatiron data to assess hazard over time

Figure 1 in the Roche report is the log cumulative hazard for OS vs. log time plot, which provides an indication as to the rate at which the hazard changes over time.[1] A straight line is consistent with the Weibull model, with a gradient greater than one implying a monotonically increasing hazard. If this gradient is 1 then this implies the exponential model. The company claim that the long-term hazards are decreasing, which would therefore imply a gradient that is less than 1 in Figure 1. Given the fluctuations in the graph it is difficult to observe if this is the case. Although the gradient between the very last two data points is zero (given no mortality between these two observations), it does appear that the gradient for carboplatin + etoposide more clearly peaks and then tails off toward the end of the follow-up period. Using the Kaplan-Meier (KM) data provided in the company Excel model, the ERG calculated the gradient between consecutive pairs of data points. For atezolizumab + carboplatin + etoposide, this shows that for about the last 12 months follow-up (from an observation at17.94 months and until the latest observation at 29.5 months) there are 20 observations and thus 20 consecutive pairs. Out of these 20, 6 have a gradient below 1. For carboplatin + etoposide, for the same period of the last 12 months follow-up (from an observation at 17.68 months and until the latest observation at 30.72 months) there are 9 observations and thus 9 consecutive pairs. Out of these 9, 6 have a gradient below 1. The ERG would therefore concur with the company that the hazards appear to be decreasing in both arms of the trial, but most clearly in carboplatin + etoposide arm. This does provide evidence against the Weibull and in favour of the log-logistic model, but particularly for carboplatin + etoposide arm, although any model with decreasing hazards would also be supported (see restricted cubic spline in section b.)

Figure 2 is the logit survival vs. log time plot.[1] A straight line on this plot is consistent with the log-logistic model, which is what the company suggest after 5 months follow-up. It appears to the ERG that this is not implausible, although it is not entirely clear.

b./c. Alternative models (including gamma, piecewise, restricted cubic spline, and mixture models) and their clinical validation

The company considered several survival models not presented in the original submission.[1] The results of these analyses were presented in Tables 8 and 9 and the ERG can confirm that all results could be reproduced except the incremental cost-effectiveness ratio (ICER) for two models. The one for gamma model in Table 8 must be a typo given that the value reported in Table 9 was reproduced by the ERG. The one for the piecewise exponential could not be reproduced.

The company stated that they judged the validity of each model according to the rule of thumb informed by clinical expert opinion that survival at 5 years should lie between 0.5% and 5%. The ERG concur with the company that mixture cure models are not justifiable given lack of trial data on patients who might demonstrate longevity, in particular, survival beyond 5 years. The ERG also questions the validity of the analyses where those who survive to 5 years are assumed to have a much lower mortality (general population or twice general population) (see section entitled: "Impact of incorporating long-term survivorship on top of survival extrapolations" in the Roche report).[1]

The company suggested a new base case, which uses the KM data for a period up to 20 months and the log-logistic model to extrapolate beyond this for both intervention and comparator. This seemed to be on the basis mainly of visual fit and the survival at 5 years being deemed plausible by their clinical expert panel. The ERG considers that such a model is 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. These would include:

- 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)

The hazard versions of all spline base models and the normal version of the three knots model are elimintated due to 5 year survival being less than 0.5% even for atezolizumab + carboplatin + etoposide. The two knots odds and hazard models applied to both arms were found by the ERG to produce ICERs of £78,080 and £226,106 respectively. They were reported as £50,459 and £44,181 in Table 8, but this seems to be because the treatment effect (difference between intervention and comparator) on mortality rate was curtailed at 18 months. The company stated that this was done because these spline based models resulted in the mortatlity rate being higher for carboplatin + etoposide for a period and that the clinical experts believe that this was implausible. The ERG would argue that it is not impossible for there to be a change in the direction of the difference in mortality rate and indeed this is supported by the difference in shape of the last 12 months of the log cumulative hazard plot (see section 1.a).

Therefore, the ERG would argue that the most plausible model for extrapolation for carboplatin + etoposide would still appear to be the log-logisitic given its statisitical fit, visual fit, decreasing hazards and survival at 5 years of 2.5%.[2] For atezolizumab + carboplatin + etoposide, the choice is less clear. The log-logistic or any of the KM + log-logistic models would appear to be plausible, all of which would produce an ICER that is either under or just over £50,000 per QALY and which include the company's new base case using the KM + log-logistic at 20 months. However, four spline based models for atezolizumab + carboplatin + etoposide also have good visual fit and decreasing hazards, the results of comparison to the log-logistic for carboplatin + etoposide , are shown in Table 1. The ERG would elimite the 1 knot normal model because survival at 5 years for atezolizumab + carboplatin + etoposide is 1.9%, which would be below that for carboplatin + etoposide using the log-logistic model.

Table 1: comparison of different plausible spline based models for atezolizumab + carboplatin + etoposide vs. log-logistic for carboplatin + etoposide

Model for carboplatine + etoposide	Survival at 5 years, atezolizumab + carboplatin + etoposide	Survival at 5 years, carboplatin + etoposide	ICER
Log-logistic	[redacted]	[redacted]	£47,449
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

d. Restriced means analysis

The restricted means analysis does indicate that one of the end of life (EOL) criteria might not be met if the difference in mean survival based on the trial data only is used to estimate increase in life expectancy.[1] However, as the company show, the difference in means is larger the later the cut-off, i.e 2.1 months at 26.22 months and 1.9 months aty 24 months. Also, the model predicts a gain in life expectancy of over 3 months using any of the log-logistic based models. On this basis, meeting the EOL criteria is possible although uncertain.

2. Exploration of duration of treatment benefit in the model

This analysis showed that, as expected, the ICER would increase if treatment benefit was curtailed, up to just over £50,000 with a cut-off of 36 months using the log-logistic model.[1] The 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, which is roughly the maximum follow-up in the trial.

3. Clarification of the source of real-world chemotherapy survival data (as validated by an advisory board)

The company explained that the data presented in Appendix K of the company submission to the clinical expert panel on survival at different time points from the Flatiron study were incorrect.[1, 3] The ERG can confirm that the data that the company claim should have been presented, as estimated using KM analysis, can be found in the KM OS tab of the original company model with number of patients at risk at time zero of n=860. This has now been updated in the latest version of the company model to [redacted], as also reported by the company's additional analyses report. This shows that the percentage surviving to [redacted] by which one can infer that the percentage surviving to 5 years is approximately as the company report, i.e. [redacted]

4. Further patient reported outcomes data from IMpower13

The company provided additional analyses of patient-reported outcomes.[1] They re-stated their conclusion in the original CS that there was no statisitically significant difference between intervention and comparator in either time to deterioration (TTD) or any other patient-reported outcomes.[4] The ERG would agree that this is the case.

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