EAG cost-comparison report

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small cell lung cancer (Review of TA662) [ID6404]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 168879

Completed 3 October 2024
Updated 22 October 2024

CONTAINS CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small cell lung cancer (Review of TA662) [ID6404]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Nigel Fleeman, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Samuel Bryning, Economic Modeller, LRiG, University of Liverpool

Sophie Beale, Director, HARE Research, North Yorkshire

Angela Boland, Director, LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Ashley Marsden, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

John Green, Consultant Medical Oncologist, The Clatterbridge Cancer Centre, Liverpool

Correspondence to: Nigel Fleeman, Senior Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 3 October 2024; updated 22 October 2024 following company factual accuracy check

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 168879

Acknowledgements: The authors would like to thank Lynn Campbell, Medical Oncologist, Belfast City Hospital, Belfast who provided feedback on a draft version of 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 Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Declared competing interests of the authors: None.

Declared competing interests of peer reviewers: Lynn Campbell has received reimbursement from Roche for attending the All Ireland Lung Cancer Conference (2022), reimbursement from Takeda for attending the World Conference on Lung Cancer (2022) and reimbursement from MSD for attending the European Society for Medical Oncology Congress (2023).

This report should be referenced as follows: Fleeman N, Bryning S, Beale S, Boland A, Dundar Y, Marsden A, Green J. Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small cell lung cancer (Review of TA662) [ID6404]: A Cost-comparison Technology Appraisal. LRiG, University of Liverpool, 2024

Contributions of authors:

Nigel Fleeman	Project lead, critical appraisal of the clinical and statistical evidence and supervised the final report
Samuel Bryning	Critical appraisal of the economic model and economic evidence
Sophie Beale	Critical appraisal of the clinical, statistical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical, statistical and economic evidence, editorial input
Yenal Dundar	Conduct of searches for the EAG and critical appraisal of the company systematic review
Ashley Marsden	Critical appraisal of the company submission
John Green	Clinical advice and critical appraisal of the clinical evidence

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AUC	area under the curve
BSA	body surface area
CNS	central nervous system
CS	company submission
DUR+ET+CAR	durvalumab+etoposide+carboplatin
DUR+ET+CIS	durvalumab+etoposide+cisplatin
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EP	etoposide plus platinum-based chemotherapy
ES-SCLC	extensive-stage small cell lung cancer
ET+CAR	etoposide+carboplatin
ET+CIS	etoposide+cisplatin
HRQoL	health-related quality of life
imAE	immune-modulated adverse event
IPD	individual patient data
ITC	indirect treatment comparison
IO	immunotherapy
ITT	intention to treat
IV	intravenous
K-M	Kaplan-Meier
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
ORR	objective response rate
OS	overall survival
PCI	prophylactic cranial irradiation
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand
PFS	progression-free survival
PH	proportional hazards
RCT	randomised controlled trial
RDI	relative dose intensity
SC	subcutaneous
SCLC	small cell lung cancer
STA	Single Technology Appraisal
TA	Technology Appraisal

1 EXECUTIVE SUMMARY

The National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) of durvalumab in combination with etoposide and platinum-based chemotherapy (EP) for untreated extensive stage small cell lung cancer (ES-SCLC) (TA662) was terminated in 2020; NICE was unable to make a recommendation because the company's evidence submission was withdrawn. In 2024, the company asked NICE to review TA662 using cost-comparison methods, with atezolizumab+EP (TA638) as the comparator. Following review and consultation with stakeholders, NICE determined that durvalumab+EP for untreated ES-SCLC should be appraised via the cost-comparison process and that atezolizumab+EP was the appropriate comparator.

1.1 Decision problem

In line with the final scope issued by NICE, for patients with ES-SCLC, the company has provided evidence to compare the clinical effectiveness of durvalumab+EP versus atezolizumab+EP. The External Assessment Group (EAG) agrees with the company and NICE that the appropriate comparator to durvalumab+EP is atezolizumab+EP.

Durvalumab and atezolizumab belong to the same class of drugs. The frequency that durvalumab+EP and atezolizumab+EP are administered is the same during the induction phase (in combination with EP every 3 weeks for 4 cycles); however, during the maintenance phase, durvalumab monotherapy is delivered every 4 weeks and atezolizumab monotherapy is typically delivered every 3 weeks. Durvalumab can only be administered via intravenous (IV) infusion, whilst atezolizumab can be administered by IV infusion or subcutaneous (SC) injection. The two treatments can also differ in terms of platinum-based chemotherapy used during the induction phase of treatment; durvalumab can be administered in combination with carboplatin or cisplatin whilst atezolizumab can only be administered in combination with carboplatin. The company and EAG agree that carboplatin and cisplatin can be considered similarly efficacious; however, clinical advice to the EAG is that, in the NHS, carboplatin is preferred to cisplatin as it is considered to have a better safety profile.

1.2 Clinical effectiveness evidence

There is no direct evidence to compare the clinical effectiveness of durvalumab+EP versus atezolizumab+EP; the company, therefore, carried out indirect treatment comparisons (ITCs). The company and EAG agree that CASPIAN trial (durvalumab+EP) and IMpower133 trial (atezolizumab+EP) patient and trial characteristics are comparable. However, the EAG considers that within-trial overall survival (OS) and progression-free survival (PFS)

proportional hazards (PH) assumptions are violated, which may mean that ITC results are unreliable.

Company base case and sensitivity analysis unadjusted ITC OS and PFS results for the comparison of durvalumab+EP versus atezolizumab+EP showed that there were no statistically significant differences in efficacy. However, confidence intervals were wide; further, there is ongoing debate around whether confidence intervals that include 1 should be used to support claims of similar health benefits. Results from 3/24 company safety ITCs were statistically significant; all three of these results suggested that patients treated with durvalumab+EP experienced fewer adverse events (AEs) than patients treated with atezolizumab+EP.

The EAG asked the company (clarification questions A2 and A3) to provide statistical evidence to demonstrate the similarity of survival outcomes for patients treated with durvalumab+EP and atezolizumab+EP. The company provided Kaplan-Meier data but did not carry out the requested across trial log-rank tests and restricted mean survival time analyses.

The EAG considers that, based on the available clinical effectiveness evidence, it is appropriate to carry out a cost-comparison analysis (durvalumab+EP versus atezolizumab+EP).

1.3 Economic evidence

The company developed a cost-comparison model in Microsoft® Excel. With the exception of treatment cycle numbering (see Section 5.2), the EAG is satisfied that the company model algorithms are accurate and that the parameter values used in the model match the values presented in the company submission (CS) and in the original sources. The EAG considers that the company model is robust and generates reliable cost-comparison analysis results for the comparison of durvalumab+EP versus atezolizumab+EP. EAG revisions only had a small effect on company base case results.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) of durvalumab in combination with etoposide and platinum-based chemotherapy (EP) for untreated extensive stage small cell lung cancer (ES-SCLC) (TA662[1]) was terminated in 2020; NICE was unable to make a recommendation because the company's evidence submission was withdrawn. In 2024, the company asked NICE to review TA662[1] using cost-comparison methods, with atezolizumab+EP (TA638[2]) as the comparator.[3] Following review and consultation with stakeholders, NICE determined that durvalumab+EP for untreated ES-SCLC should be appraised via the cost-comparison process and that atezolizumab+EP was the appropriate comparator.[3]

The External Assessment Group (EAG) critique of the company submission (CS) is presented in this report. All references to the CS are to the company's Document B, which is the company's full evidence submission. Additional evidence was provided by the company in response to the clarification letter.

2.2 Background

SCLC is an aggressive form of lung cancer and is associated with a poor prognosis; symptoms include cough, chest pain, dyspnoea, arm/shoulder pain, fatigue and appetite loss (CS, Table 6). There are two categories of SCLC: limited-stage (LS) and extensive stage (ES) (CS, Table 4). SCLC is less common than non-small cell lung cancer (NSCLC), is almost universally related to smoking and has a worse 5-year survival than NSCLC (CS, Table 3). Recommendations for the management of SCLC differ from those for the management of NSCLC.

2.3 Clinical pathway

European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines[4,5] recommend immunotherapy (IO) for treating ES-SCLC. The recommended treatment with IO (atezolizumab or durvalumab) is four cycles of induction treatment in combination with EP (the NCCN guidelines[5] permit up to six cycles of induction treatment if deemed necessary) followed by IO monotherapy as maintenance treatment until disease progression or unacceptable toxicity. Recommended treatment for patients ineligible for IO is four to six cycles of EP. Currently, the only NICE recommended IO for ES-SCLC is atezolizumab+EP for patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1.[2] In this appraisal, durvalumab+EP is being considered as an alternative to atezolizumab+EP for ES-SCLC for patients with ECOG PS 0 to 1.

3 EAG CRITIQUE OF THE COMPANY DECISION PROBLEM

The decision problem addressed by the company in the CS matches the final scope[3] issued by NICE (Table 1). See Section 3.1 to Section 3.5 for EAG comments on the evidence base, population, intervention, comparators, outcomes, economic analysis and subgroups.

Table 1 The final scope issued by NICE and the company decision problem

Element	Final scope[3] issued by NICE and addressed by the company
Population	Adults with untreated ES-SCLC
Intervention	Durvalumab+EP
Comparator(s)	Atezolizumab+EP
Outcomes	Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life
Economic analysis	Cost comparison
Subgroups	No subgroups were specified in the final scope[3] issued by NICE

EP=etoposide+platinum-based chemotherapy; ES=extensive stage; SCLC=small cell lung cancer; NICE=National Institute for Health and Care Excellence

3.1 Sources of clinical effectiveness evidence

The two main sources of the clinical effectiveness data presented in the CS are the CASPIAN trial[6] (durvalumab+EP) and the IMpower133 trial[7] (atezolizumab+EP).

CASPIAN trial

The CASPIAN trial is a phase III, open-label, international, multicentre, randomised controlled trial (RCT) that enrolled previously untreated adults with ES-SCLC (Eastern Cooperative Oncology Group performance status [ECOG PS] 0 to 1 who were allowed to have treated or asymptomatic brain/central nervous system [CNS] metastases). The trial has three arms, two of which provide data that are relevant to this appraisal: durvalumab+EP (n=268) and EP (n=269). The primary outcome is overall survival (OS) (median OS follow-up: 39.4 months).

IMpower133 trial

The IMpower133 trial is a phase I/III, double-blind, placebo-controlled, international, multicentre, RCT that enrolled previously untreated adults with ES-SCLC (ECOG PS 0 to 1 and no evidence of untreated active brain/CNS metastases). The trial has two arms: atezolizumab+EP (n=201) and placebo+EP (n=202). There are two primary outcomes, progression-free survival (PFS) and OS (median OS follow-up: 22.9 months).

3.2 Population

Clinical advice to the EAG is that the patients enrolled in the CASPIAN and IMpower133 trials have the characteristics of patients with untreated ES-SCLC who would be considered eligible for treatment with an IO in NHS clinical practice.

3.3 Intervention

The intervention is durvalumab+EP (carboplatin or cisplatin). Durvalumab is a high-affinity, human, recombinant immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that selectively binds to programmed cell death-ligand 1 (PD-L1) and blocks the interaction of PD-L1 with programmed cell death-1 (PD-1) and cluster of differentiation 80 (CD80) receptors. By inhibition of the immune responses in the tumour micro-environment, treatment with durvalumab leads to prolonged T-cell activation and anti-tumour activity (CS, Table 2).

The durvalumab+EP induction phase (4 x 21 day treatment cycles) treatment protocol is as follows:

- durvalumab: 1500mg, IV, administered Day 1 of each cycle
- carboplatin: area under curve (AUC) 5-6 mg/ml/min, IV or cisplatin 75–80mg/m² on Day 1 of each cycle
- etoposide: 80–100mg/m^2 of body surface area (BSA), IV, Days 1 through Day 3 of each cycle

The induction phase is followed by maintenance therapy: durvalumab 1500mg, IV, every 4 weeks until loss of clinical benefit or unmanageable toxicity.

In 2020, durvalumab+EP was licensed by the European Medicines Agency (EMA)[8] as a first-line treatment option for adults with ES-SCLC; the EMA licence was issued prior to the Medicines Healthcare products Regulatory Agency (MHRA) carrying out licensing for new medicines (January 2021).

3.4 Comparators

The comparator is atezolizumab+EP (carboplatin) which was recommended by NICE[2] as an option for untreated ES-SCLC in adults with ECOG PS 0 or 1 in July 2020 (based on evidence largely derived from the IMpower133 trial). Clinical advice to the EAG is that NHS patients who would be considered for treatment with durvalumab+EP have the same characteristics as NHS patients currently considered for treatment with atezolizumab+EP.

Atezolizumab is a monoclonal antibody designed to target PD-1. It blocks the PD-L1 protein, preventing it from binding to PD-1 and B7-1, allowing T-cells to attack cancer cells.

In the IMpower133 trial, the atezolizumab+EP induction phase (4 x 21 day treatment cycles) treatment protocol is as follows:

- atezolizumab: 1200mg, IV, administered Day 1 of each cycle
- carboplatin: AUC 5mg/ml/min, IV, Day 1 of each cycle
- etoposide: 100mg/m^2 of BSA, IV, Days 1 through Day 3 of each cycle

The induction phase is followed by maintenance therapy: atezolizumab 1200mg, IV, every 3 weeks until loss of clinical benefit or unmanageable toxicity.

The only platinum chemotherapy that is used in combination with atezolizumab during the induction phase is carboplatin.[2] Most clinicians consider that the efficacy of carboplatin is similar to the efficacy of cisplatin; this assumption is supported by OS, PFS and objective response rate (ORR) meta-analysis results published in 2012[9] and by US cohort study OS results published in 2022.[10] Clinical advice to the EAG is that, in NHS clinical practice, the preferred platinum-based chemotherapy tends to be carboplatin as it is considered less toxic than cisplatin. Published results[9] show that carboplatin and cisplatin have different toxicity profiles; haematological adverse events (AEs) (e.g., myelosuppression including neutropenia, anaemia, and thrombocytopenia) were more common for patients treated with carboplatin, whilst nausea/vomiting, neurotoxicity and renal toxicity were more common for patients treated with cisplatin. The different toxicity profiles may affect clinician and patient treatment choices.

Additional treatment regimens for atezolizumab+EP are described in the Summary of Product Characteristics (SmPC) for atezolizumab.[11] These include IV atezolizumab (840mg) every 2 weeks or IV atezolizumab (1680mg) every 4 weeks. A subcutaneous (SC) injection of atezolizumab (1875mg every 3 weeks) was also approved in 2023.[12] Compared with IV atezolizumab, SC atezolizumab is less invasive and has lower service delivery costs (e.g., clinic costs, health professional time). According to the NICE medicines optimisation briefing,[13] it is anticipated that most people starting atezolizumab treatment will have the SC injection. However, people who are receiving IV chemotherapy in combination with atezolizumab may remain on the IV infusion.[14]

In the CS, all clinical effectivenessresults for durvalumab+EP versus atezolizumab+EP have been generated using data from patients who received IV atezolizumab (as in the IMpower133 trial); no comparative results have been generated using SC atezolizumab. However, results from the phase III IMscin001 trial (SC atezolizumab versus IV atezolizumab for patients with NSCLC)[15] show that efficacy, safety and immunogenicity SC outcomes were similar to, and consistent with, IV outcomes.[15]

3.5 Outcomes

Evidence for all the outcomes specified in the final scope issued by NICE[3] is presented in the CS. Comparative durvalumab+EP versus atezolizumab+EP effectiveness (OS and PFS) and some adverse events (AE) evidence was generated using indirect treatment comparisons (ITCs), whilst a naïve treatment comparison was conducted by the EAG to generate comparative health-related quality of life (HRQoL) data. Additional ITC evidence for OS and naïve comparisons of OS and PFS was presented by the company in response to clarification questions A2 and A3.

Details about the company ITCs and naïve comparisons, the EAG's critique of the company ITCs and naïve comparisons and the EAG's own naïve comparisons are presented in Section 4 and/or Appendix 2 (Section 10.2).

3.6 Economic analysis

The EAG agrees with the company and NICE that it is appropriate to carry out a cost-comparison analysis comparing durvalumab+EP versus atezolizumab+EP. The EAG's consideration of the economic evidence provided by the company is presented in Section 6.

4 CLINICAL EFFECTIVENESS EVIDENCE

4.1 Critique of the methods of review(s)

The EAG considers that the company's systematic literature review (SLR) was conducted to a good standard (Table 2); searches carried out by the EAG did not identify any additional relevant studies.

Table 2 Company SLR: EAG appraisal of the review methods

Review process	EAG response	EAG comment
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes CS, Appendix D.1 and CS, Appendix D.1.2	The study question was specified using the PICOS framework
Were appropriate sources searched?	Yes CS, Appendix D.1.1	Electronic searches of Embase, MEDLINE, The Cochrane Library, and hand searches of registries and conference proceedings were carried out
Was the timespan of the searches appropriate?	Yes CS, Appendix D.1.1	Date of most recent search: 17 May 2024
Were appropriate search terms used?	Yes CS, Appendix D.1.3	Search strings included keywords, medical subject headings and free text words
Were the eligibility criteria appropriate to the decision problem?	Yes CS, Appendix D.1.2	Eligibility criteria were wide (and therefore sufficient) to find studies relevant to the decision problem addressed by the company; only RCTs were included
Was study selection applied by two or more reviewers independently?	Yes CS, Appendix D.1.4	All title/abstract and full-text publications were reviewed by a second independent reviewer, with discrepancies resolved via discussion
Was data extracted by two or more reviewers independently?	Unclear	Not reported
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes CS, Appendix D.1.7	Conducted in accordance with the CRD recommended tool[16]
Was the quality assessment conducted by two or more reviewers independently?	Unclear	Not reported
Were attempts to synthesise evidence appropriate?	Yes CS, Section B.3.9 CS, Appendix D.3	ITCs (see Section 4.3 of this EAG report)

CRD=Centre for Reviews and Dissemination; CS=company submission; EAG=External Assessment Group; ITC=indirect treatment comparison; PICOS=Population, Intervention, Comparator, Outcome, and Study type; RCT=randomised controlled trial; SLR=systematic literature review

4.2 Included studies

The company identified two RCTs: one durvalumab+EP trial (CASPIAN trial) and one atezolizumab+EP trial (IMpower133 trial). Key trial sources and publications are listed in Table 3.

Table 3 Included studies: key trial references and data extracted from these sources

Trial Treatment	Key reference	Outcomes relevant to the decision problem presented and data cut-off date
CASPIAN Durvalumab+EP	CASPIAN trial CSR 2019: primary analysis[17]	Outcome data from this data-cut (April 2019) did not inform clinical effectiveness in the CS but AE data were used to inform treatment-emergent AE probabilities applied in the company's economic analysis
	Paz-Ares 2019[18]	Outcome data (April 2019) are the same as reported in CSR primary analysis[17]
	Goldman 2020[19]	HRQoL (April 2019)*
	CASPIAN trial CSR 2020: final analysis[20]	PFS, HRQoL, AEs (March 2020)
	Goldman 2021[21]	PFS, HRQoL, AEs (March 2020) as reported in CSR: final analysis[20]
	CASPIAN trial CSR 2021 addendum[22]	Updated OS (March 2021)
	Paz-Ares 2022[23]	Updated OS (March 2021) as reported in CSR 2021 addendum[22]
IMpower133 Atezolizumab+EP	Horn 2018[24]	OS, PFS and AEs (April 2018): final analysis for PFS
	TA638[2] including committee papers[25]	OS, PFS, AEs and HRQoL (April 2018): primary analysis
	Reck 2019[26]	Updated OS (January 2019) reported as conference abstract
	Mansfield 2020[27]*	HRQoL (April 2018) as reported in Califano 2018[28]
	Liu 2021[29]	Updated OS (January 2019) as reported in Reck 2019[26] plus updated AE data

* Results from this paper were not reported by the company, only baseline data in CS, Section B.1.3.2.1 (Symptom burden); results from this paper have been cited by EAG (Appendix 2, Section 10.2.6)
AE=adverse event; CS=company submission; CSR=clinical study report; EAG=External Assessment Group; EP=etoposide+platinum-based chemotherapy; HRQoL=health-related quality of life; OS=overall survival; PFS=progression-free survival; SAE=serious adverse events

4.2.1 CASPIAN and IMpower133 trial characteristics

Key CASPIAN and IMpower133 trial characteristics are presented in CS, Appendix 1 (Section 10.1). Both trials enrolled patients with ES-SCLC. The main differences between the CASPIAN and IMpower133 trials are:

- the CASPIAN trial was open-label and the IMpower133 trial was double-blind (open-label trials may be subject to bias)
- stratification factors differed; however, the baseline patient characteristics that could be compared were broadly similar (Section 4.2.3)
- CASPIAN trial patients could have been treated with carboplatin or cisplatin, although most patients were treated with carboplatin (75% were randomised to carboplatin and 78% received cisplatin during the trial[18]). In the IMpower133 trial, all patients were treated with carboplatin (Section 4.2.3)
- prophylactic cranial irradiation (PCI) was not permitted in the CASPIAN trial Intervention arms but was permitted in the IMpower133 trial (the clinical impact of this difference is not known); NICE has recommended (NG122[30]) that PCI should be considered for patients with ES-SCLC who have had a partial or complete response to chemotherapy within the thorax and at distant sites (and also following response to first-line treatment if they have PS 0-2)
- CASPIAN trial median OS follow-up was longer (39.4 months) than IMpower133 trial median OS follow-up (22.9 months); however, data were available after approximately 1-year and 2-years of follow-up from both trials

4.2.2 CASPIAN and IMpower133 trial eligibility criteria

A comparison of the CASPIAN and IMpower133 trial eligibility criteria is presented in the CS (CS, Appendix D.3.1.2.4, Table 14 and Table 15). Complete eligibility criteria for both trials have been published (Paz-Ares 2019[18] [CASPIAN trial], Horn 2018[24] [IMpower133] and the European Medicines Agency [EMA] Assessment Reports for durvalumab+EP for ES-SCLC[31] and atezolizumab+EP for ES-SCLC[11]). Clinical advice to the EAG agrees with the company that CASPIAN trial and IMpower133 trial eligibility criteria were broadly similar.

4.2.3 CASPIAN and IMpower133 trial patient characteristics

A comparison of baseline CASPIAN and IMpower133 trial patient characteristics is provided in the CS (CS, Appendix D.3.1.2.5, Table 16). Where comparable data are available, baseline characteristics appear similar (Table 4). Clinical advice to the EAG agrees with the company that CASPIAN trial and IMpower133 trial patient baseline characteristics were broadly similar.

Table 4 CASPIAN and IMpower133 trials: baseline characteristics

Baseline characteristic	CASPIAN trial		IMpower133 trial	
	Durvalumab+ EP (n=268)	EP (n=269)	Atezolizumab+ EP (n=201)	Placebo+ EP (n=202)
Median age (range), years	62 (28 to 82)	63 (35 to 82)	64 (28 to 90)	64 (26 to 87)
Age group				
<65 years	167 (62.3%)	157 (58.4%)	111 (55.2%)	106 (52.5%)
≥65 years	101 (37.7%)	112 (41.6%)	90 (44.8%)	96 (47.5%)
Male	190 (70.9%)	184 (68.4%)	129 (64.2%)	132 (65.3%)
WHO/ECOG PS				
0	99 (36.9%)	90 (33.5%)	73 (36.3%)	67 (33.2%)
1	169 (63.1%)	179 (66.5%)	128 (63.7%)	135 (66.8%)
Smoking status				
Non-smoker	22 (8.2%)	15 (5.6%)	9 (4.5%)	3 (1.5%)
Ex-smoker	126 (47.0%)	128 (47.6%)	118 (58.7%)	124 (61.4%)
Current smoker	120 (44.8%)	126 (46.8%)	74 (36.8%)	75 (37.1%)
Disease-related characteristics				
AJCC stage IV disease	240 (89.6%)	245 (91.1%)	Not reported	Not reported
Brain metastases	28 (10.4%)	27 (10.0%)	17 (8.5%)	18 (8.9%)
Liver metastases	108 (40.3%)	104 (38.7%)	77 (38.3%)	72 (35.6%)
Platinum chemotherapy (induction phase)*				
Carboplatin	201 (75.0%)	201 (74.7%)	201 (100%)	202 (100%)
Cisplatin	67 (25.0%)	68 (25.5%)	0	0

* It is reported in Paz-Ares 2019[18] (Table 2) that patients were allowed to switch between cisplatin and carboplatin at the investigator's discretion and hence slightly more patients received carboplatin (208 [78.5%] in intervention arm and 208 [77.3%] in comparator arm) and slightly fewer received cisplatin (65 [24.3%] in intervention arm and 67 [24.9%] in comparator arm) than as randomised

AJCC=American Joint Committee on Cancer; CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; EP=etoposide+platinum-based chemotherapy; NICE=National Institute for Health and Care Excellence; WHO =World Health Organization

Source (CASPIAN): Paz-Ares 2019;[23] CS, Section B.3.3.2 (Table 12, Table 13); CS, Appendix D.3.1.2.5 (Table 16)

Source (IMpower133): TA638[2] NICE Committee papers (Roche CS, Table 9)

4.2.4 CASPIAN and IMpower133 trial quality assessment

The company conducted quality assessments of the CASPIAN and IMpower133 trials using criteria recommended in the NICE Guide to the Methods of Technology Appraisal;[32] these methods are consistent with the methods recommended by the Centre for Reviews and Dissemination (CRD).[16] The EAG agrees with the company's assessments (Table 5) and considers that both trials are of good quality (i.e., well-designed and well-conducted).

Table 5 CASPIAN and IMpower133 trials: quality assessment

Quality assessment item	CASPIAN trial	IMpower133 trial
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	n/a	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No*	Yes
Were there any unexpected imbalances in dropouts between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis?	Yes	Yes

* The company highlights that although the CASPIAN trial was open-label and trial investigators and patients were not blinded to treatment allocation, the company study team was blinded to aggregate treatment information
CS=company submission; n/a=not applicable
Source CS, Table 15; CS, Appendix D.1.7 (Figure 4)

4.2.5 CASPIAN and IMpower133 trial results

CASPIAN and IMpower133 trial OS, PFS, ORR, HRQoL and safety results are summarised in Appendix 2 (Section 10.2). For all intention to treat (ITT) efficacy outcomes, except ORR for patients treated with atezolizumab+EP, point-estimates favoured the Interventions (durvalumab+EP or atezolizumab+EP) versus EP. For HRQoL, patients in the Intervention arms experienced a numerically reduced burden for most symptoms over time. Longer median time to treatment deterioration was observed for patients in the Intervention arms compared with those in the EP arms for treatment-related or lung-cancer related symptoms.

4.3 Indirect treatment comparisons

The company carried out OS, PFS and AE ITCs to compare the relative clinical effectiveness of durvalumab+EP versus atezolizumab+EP (CS, Section B.3.9). Results for the analyses of the following treatment-related Grade 3/4 AEs are presented in CS, Appendix D.3.4.3: febrile neutropenia, thrombocytopenia, leukopenia, anaemia, neutropenia and decreased neutrophil count. The ITCs were carried out using a frequentist Bucher approach.[33] The EAG considers that the methods used by the company to conduct (unadjusted) ITCs were appropriate; the EAG's only concern is that the within-trial (CASPIAN trial and IMpower133 trial) PFS and OS proportional hazard (PH) assumptions do not hold (see Section 4.3.5).

4.3.1 Treatment effect modifiers and/or prognostic factors

The company's ad-hoc literature review did not identify any treatment effect modifiers and/or prognostic factors for patients with ES-SCLC (CS, Appendix D.3.1). The company assessed whether CASPIAN trial patient baseline characteristics were treatment effect modifiers and/or prognostic factors for OS and PFS by examining individual CASPIAN trial individual patient

data (IPD). A list of the baseline characteristics examined, and whether the company considered the characteristic to be a potential treatment effect modifier and/or prognostic factor, is provided in Table 6.

Table 6 CASPIAN trial: potential treatment effect modifiers and/or prognostic factors*

Characteristic	Potential treatment effect modifiers and/or prognostic factor	
	Overall survival	Progression-free survival
Gender	**Yes**	**Yes**
Age	No	No
Performance status	**Yes**	**Yes**
Smoking status	No	No
Brain metastases	No	**Yes**
Disease stage	No	No
Race	No	**Yes**
Liver metastases	**Yes**	**Yes**
LDH level	**Yes**	No

* Characteristics were considered potential treatment effect modifiers and/or prognostic factors if the Cox model interaction term was <0.05
LDH=lactate dehydrogenase
Source: CS, Appendix D.3.1.1 (Table 8, Table 9)

The company considered that, as CASPIAN trial and IMpower133 trial baseline patient characteristics were similar, it was appropriate to carry out unadjusted ITCs; the company highlights that data were not available to compare race or lactate dehydrogenase (see also Table 4).

Clinical advice to the EAG is that the potential treatment effect modifiers and/or prognostic factors identified by the company are important; however, the EAG considers that as these are evenly distributed between the CASPIAN and IMpower133 trials, the approach taken by the company was appropriate.

4.3.2 Comparability of CASPIAN and IMpower133 trial and patient characteristics

The company's trial and patient characteristic comparability assessments are reported in CS, Appendix D.3.1.2. The company considered that the characteristics of patients enrolled in the CASPIAN and IMpower133 trials were broadly comparable. The EAG agrees with this conclusion (see Sections 4.2.1 to 4.2.3).

4.3.3 Comparability of CASPIAN and IMpower133 trial EP arms

The CASPIAN and IMpower133 trials are linked via EP arms; however, the CASPIAN trial and IMpower133 trial EP arms differ:

- CASPIAN trial: placebo was not included as part of the EP arm, and patients were permitted treatment with carboplatin or cisplatin

- IMpower133 trial: the EP arm included placebo, and patients were only permitted treatment with carboplatin

The company tested the assumption of equivalence of the EP arms by:

1. sourcing evidence from an ad-hoc literature review
2. using CASPIAN trial IPD (Cox PH regression models) to compare the effectiveness (OS and PFS) of treatment with carboplatin versus cisplatin

Following these two assessments, the company concluded that efficacy was similar but that carboplatin and cisplatin had different safety profiles (CS, Appendix D.3.1.2.7 [p70]). The company carried out unadjusted ITC sensitivity analyses using results from the following CASPIAN trial subgroup analyses (rather than the ITT analysis) for OS and PFS:

- durvalumab+etoposide+carboplatin (DUR+ET+CAR) versus etoposide+carboplatin (ET+CAR)
- DUR+ET+CAR versus etoposide+cisplatin (ET+CIS)
- durvalumab+etoposide+cisplatin (DUR+ET+CIS) versus ET+CAR
- DUR+ET+CIS versus ET+CIS

Sensitivity analysis results were then presented by the company for:

- DUR+ET+CAR versus atezolizumab+EP
- DUR+ET+CIS versus atezolizumab+EP

The EAG considers that the approach taken by the company was appropriate.

4.3.4 Indirect treatment comparison inputs

The data inputs used in the company ITCs is summarised in Table 7.

Table 7 Data inputs in the company ITCs presented in the CS

Trial	Overall survival	Progression-free survival	Adverse events
CASPIAN trial	HR 3-year follow-up	HR 2-year follow-up	OR 2-year follow-up
IMpower133 trial	HR 2-year follow-up	HR 1-year follow-up*	OR 1-year follow-up

* 2-year follow-up point-estimate is identical, see Appendix 2, Section 10.2.3 (Table 19)
CS=company submission; HR=hazard ratio; ITC=indirect treatment comparison; OR=odds ratio

As the company OS ITC was populated with CASPIAN trial 3-year follow-up data and IMpower133 trial 2-year follow-up data, the EAG asked the company to also carry out an OS ITC using 2-year follow-up data from the CASPIAN and IMpower133 trials (clarification question A1).

4.3.5 Validity of the OS and PFS proportional hazards assumptions

As described in CS, Appendix D.3.1.2.6, the validity of the PH assumption was investigated using CASPIAN trial IPD and IMpower133 trial reconstructed IPD (derived from digitising

Kaplan-Meier [K-M] data) based on:

- the cumulative hazard plot and Schoenfeld residual plot (visual assessment)
- the global Schoenfeld residuals test (statistical assessment, $p<0.05$ suggesting the PH assumption is violated)

The company concluded that the within-trial PH assumptions did not hold for the CASPIAN and IMpower133 trial survival data (OS and PFS) (CS, Appendix D.3.1.2.6). The EAG considers that as within-trial OS and PFS PH assumptions were violated, ITC results may be unreliable.

4.3.6 OS and PFS ITC results

Company OS and PFS results are presented in Table 8. Base case and sensitivity analysis OS and PFS results showed that, in all cases, efficacy did not differ statistically significantly between durvalumab+EP and atezolizumab+EP. However, confidence intervals are wide; further, there is ongoing debate around whether confidence intervals that include 1 should be used to support claims of similar health benefits.

Table 8 Company OS and PFS ITC results

Outcome HR (95% CI)	**Base case (assumption of equivalence)**	**Sensitivity analysis (without assumption of equivalence)**	
	DUR+EP vs ATEZ+EP	**DUR+ET+CAR vs ATEZ+ET+CAR**	**DUR+ET+CIS vs ATEZ+ET+CAR**
Overall survival	[redacted]	[redacted]	[redacted]
Progression-free survival	[redacted]	[redacted]	[redacted]

ATEZ=atezolizumab; CAR=carboplatin; CI=confidence interval; CIS=cisplatin; CS=company submission; DUR=durvalumab; EP=etoposide+platinum-based chemotherapy; ET=etoposide; HR=hazard ratio
Source: CS, Section 3.9.2 (Table 16); CS, Section 3.9.3 (Table 17); CS, Appendix D.3.4.1.2, (Table 20); CS, Appendix D.3.4.2.2, (Table 22)

While non-statistically significant results do not provide evidence of similarity, the null hypothesis (which the analyses aim to disprove) is that there is no difference between durvalumab+EP and atezolizumab+EP. However, the test for statistical significance relies on the PH assumption holding between the within trial arms (durvalumab+EP versus EP and atezolizumab+EP versus placebo+EP). The company have found this not to be the case for OS and PFS, which makes interpreting these ITC results problematic.

4.3.7 Safety ITC results

Company's safety results are present in Table 9. Results from 3/24 comparisons were statistically significant (bold text); all three of these results suggested that patients treated with durvalumab+EP experienced fewer AEs than patients treated with atezolizumab+EP.

Table 9 Company safety ITC results

Outcome OR (95% CI)	Base case	Sensitivity analyses	
	DUR+EP vs ATEZ+EP	DUR+ET+CAR vs ATEZ+ET+CAR	DUR+ET+CIS vs ATEZ+ET+CAR
TR-SAEs	[redacted]	[redacted]	[redacted]
TR-Grade 3/4 AEs			
All	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Decreased neutrophil count	[redacted]	[redacted]	[redacted]

Results denoted in bold are statistically significantly different, favouring durvalumab
AE=adverse event; ATEZ=atezolizumab; CAR=carboplatin; CI=confidence interval; CIS=cisplatin; CS=company submission; DUR=durvalumab; EP=etoposide+platinum-based chemotherapy; ET=etoposide; OR=odds ratio; SAE=serious adverse event; TR=treatment-related
Source: CS, Section 3.9.4 (Table 18); CS, Appendix D.3.4.3 (Table 23 to Table 26)

4.4 Additional clinical effectiveness evidence

4.4.1 OS ITC: 2-year follow-up data

The company presented OS ITC results generated using CASPIAN trial 2-year follow-up data in response to clarification question A1. These results were similar to company base case OS results, i.e., the difference between durvalumab+EP and atezolizumab+EP was not statistically significant; again, confidence intervals are wide (Table 10).

Table 10 Company OS ITC results (2-year follow-up)

Outcome HR (95% CI)	Base case (assumption of equivalence)	Sensitivity analysis (without assumption of equivalence)	
	DUR+EP vs ATEZ+EP	DUR+ET+CAR vs ATEZ+ET+CAR	DUR+ET+CIS vs ATEZ+ET+CAR
Overall survival	[redacted]	[redacted]	[redacted]

ATEZ=atezolizumab; CAR=carboplatin; CI=confidence interval; CIS=cisplatin; DUR=durvalumab; EP=etoposide +platinum-based chemotherapy; ET=etoposide; HR=hazard ratio
Source: company response to clarification question A1 (Table 1, Table 2)

4.4.2 K-M charts using 2-years follow-up data

In response to clarification question A2, the company provided OS and PFS K-M data comparing data from the CASPIAN and IMpower133 trial Intervention arms and CASPIAN and IMpower133 trial comparator arms. The EAG considers that the OS and PFS K-M data provided by the company support the view that durvalumab+EP and atezolizumab+EP are similar (and the two EP arms are similar).

The EAG also asked the company to carry out between trial log-rank tests to provide statistical evidence of the similarity of survival outcomes from both trials; the company did not provide this information.

4.4.3 Restricted mean survival time analysis

As the company within-trial PH assessments did not hold, the EAG asked the company to carry out OS and PFS restricted mean survival time (RMST) analyses for the comparison of durvalumab+EP versus atezolizumab+EP (2-year follow-up data) (clarification question A3). The company only provided within-trial RMST differences for these analyses and did not provide statistical test results for the comparison of durvalumab+EP versus atezolizumab+EP. Examination of the within-trial RMST differences add weight to the company's argument that durvalumab+EP and atezolizumab+EP are clinically similar; in both trials, the within-trial RMST difference was approximately [redacted] for OS and [redacted] for PFS.

4.5 Published network meta-analysis results

The EAG has identified eight published network meta-analyses (NMAs)[34-41] that compared the efficacy and safety of durvalumab+EP and atezolizumab+EP. These NMAs[34-41] considered data from between four and ten RCTs (as additional treatments were included in these NMAs) which included between 1547[34] and 5544[35] patients, in total. An EAG summary of published ITC results is presented in Table 11. Published OS, PFS and Grade 3/4 AE ITC results are in line with company ITC results.

Table 11 EAG summary of published network meta-analysis results

Outcome	Number of NMAs	Summary published ITC results: durvalumab+EP versus atezolizumab+EP
OS	8[a]	No statistically significant difference found from any NMA[34-41]
PFS	8[a]	No statistically significant difference found from any NMA[34-41]
ORR	5	Four NMAs[34,35,40,41] found ORR was statistically significantly superior for patients treated with durvalumab+EP; one NMA[38] found no statistically significant difference
Grade ≥3 AEs	8[b]	No statistically significant difference found from any NMA[34-41]
imAEs	2	Results from one NMA[39] showed that patients treated with durvalumab+EP experienced statistically significantly more any Grade imAEs (but no difference in Grade 3/4 imAEs)[c] Results from one NMA[34] found no statistically significant difference in any Grade imAEs

[a] One NMA[40] utilised the fractional polynomial model to evaluate the adjusted HRs for OS and PFS, an approach that does not required the proportional hazards assumption to hold
[b] Seven studies[34-38,40,41] reported AEs of any causality, one study reported treatment-related AEs[39]
[c] The EAG considers it to be surprising that the difference in any Grade imAEs was found to be statistically significantly in favour of atezolizumab+EP versus durvalumab+EP when the trial publications show fewer imAEs reported by patients with durvalumab+EP than atezolizumab+EP (see Appendix 2, Section 10.2.7, Table 21)
AE=adverse event; EAG=External Assessment Group; EP=etoposide+platinum-based chemotherapy; imAE=immune-modulated adverse event; NMA=network meta-analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

4.6 Summary statement

A comparison of durvalumab+EP and atezolizumab+EP is presented in Table 12.

Table 12 Comparison of durvalumab+EP and atezolizumab+EP

Metric	Durvalumab+EP	Atezolizumab+EP
Company	AstraZeneca	Roche
Brand name	Imfinzi	Tecentriq
Drug class	Monoclonal antibody, immune checkpoint inhibitor	Monoclonal antibody, immune checkpoint inhibitor
Mechanism of action	PD-L1 blocking antibody. Blocks PD-L1 interaction with both PD-1 and CD80 on T cells	PD-L1 blocking antibody. Inhibits binding of PD-L1 to both PD-1 and CD80
Given with (as induction treatment)	EP: Etoposide+carboplatin or etoposide+cisplatin	EP: Etoposide+carboplatin
Maintenance treatment	Monotherapy treatment every 4 weeks	Monotherapy treatment every 3 weeks
Administrative route	Intravenous infusion	Intravenous infusion or subcutaneous injection
Frequency of administration in main trials	Durvalumab+EP every 3 weeks for 4 cycles, followed by durvalumab every 4 weeks as monotherapy	Atezolizumab+EP every 3 weeks for 4 cycles, followed by atezolizumab every 3 weeks as monotherapy
Contraindications	Severe hypersensitivity to durvalumab or any of its components	Severe hypersensitivity to atezolizumab or any of its components
Results		
Within-trial: OS	Results from all within-trial analyses show that the Intervention is statistically significantly superior to the EP comparator	
Within-trial: PFS		
Unadjusted ITC: PFS	Results from all unadjusted ITCs show that there are no statistically significant differences between durvalumab+EP and atezolizumab+EP	
Unadjusted ITC: OS		
K-M charts	Visual inspection of the four K-M charts provided by the company in response to clarification question A2, support the view that Intervention and EP comparator data from the CASPIAN and IMpower133 trials are similar	
AEs	Results from 3/24 company AE ITCs are statistically significant; all three of these results suggested that patients treated with durvalumab+EP experienced fewer AEs than patients treated with atezolizumab+EP	
HRQoL	Over time, the burden of most symptoms experienced by patients in the durvalumab+EP and atezolizumab+EP arms of the CASPIAN trial and IMpower133 trial decreased	

AE=adverse event; CD80=cluster of differentiation 80; EP=etoposide+platinum-based chemotherapy; HRQoL=health-related quality of life; ITC=indirect treatment comparison; K-M=Kaplan-Meier; OS=overall survival; PD-L1=programmed cell death-ligand1; PD-1=programmed cell death-1; PFS=progression-free survival

The EAG agrees with the company and NICE that the appropriate comparator to durvalumab+EP is atezolizumab+EP. The EAG also considers that, based on the available clinical effectiveness evidence, it is appropriate to carry out a cost-comparison analysis (durvalumab+EP versus atezolizumab+EP).

5 EAG CRITIQUE OF COMPANY COST COMPARISON EVIDENCE

5.1 Company approach to cost comparison analysis

The company submitted an economic model, developed in Microsoft® Excel, to generate cost effectiveness results for durvalumab+EP versus atezolizumab+EP for patients with untreated ES-SCLC. The EAG agrees with the company and NICE that it is appropriate to carry out a cost-comparison analysis of durvalumab+EP versus atezolizumab+EP (see Section 3 and Section 4).

With the exception of treatment cycle numbering (see Section 5.2), the EAG is satisfied that the company model algorithms are accurate and that the parameter values used in the model match the values presented in the CS and in the original sources.

The EAG considers that the time horizon used in the company model (15 years) is appropriate as only a small proportion of patients ([redacted]%) are estimated to remain on treatment beyond this time point. The company generated cost-comparison analysis results using a partitioned survival model and assumed that there were no differences in OS, PFS, treatment duration, subsequent treatments or the incidence of AEs. In the model, it was assumed that 75% of patients were treated with SC atezolizumab and 25% of patients were treated with IV atezolizumab; clinical advice to the EAG is that this assumption was appropriate. As efficacy and safety outcomes for patients treated with durvalumab+EP and patients treated with atezolizumab+EP appear to be similar, the company modelling assumptions are appropriate.

The key drivers of the company's cost-comparison analysis results are the costs of purchasing durvalumab and atezolizumab (and, to a lesser extent, drug administration and radiotherapy costs).

5.2 EAG correction and revisions

The EAG has identified and corrected one minor error: company model Markov traces treatment cycle numbering. The EAG made three revisions to the company model (see Section 5.2.1 to Section 5.2.3).

5.2.1 Platinum chemotherapy costs

In the company model, it is assumed that [redacted]% of patients treated with durvalumab+EP receive carboplatin and [redacted]% receive cisplatin (this is in line with CASPIAN trial data) and all patients treated with atezolizumab+EP receive carboplatin-based chemotherapy (this is in line with the IMpower133 trial data). Clinical advice to the company and the EAG is that, in NHS clinical practice, there appears to be no substantial efficacy differences between these two platinum

agents; however, there is a strong clinical preference to use carboplatin as cisplatin is considered more toxic than carboplatin. To more accurately reflect expected NHS costs, the EAG has revised the model so that all patients treated with durvalumab+EP are treated with carboplatin.

5.2.2 Relative dose intensity

The company applied relative dose intensity (RDI) multipliers to durvalumab and atezolizumab; this approach implicitly models the potential reduction in costs due to missed doses (Table 13). The durvalumab and atezolizumab RDI multipliers are similar (95.4% and 94.9%, respectively); this suggests that missed doses are similar.

Durvalumab and atezolizumab are modelled using fixed doses (1500mg and 1200mg, respectively). The company has, incorrectly, used the RDI multipliers to calculate average doses (in mg) of durvalumab and atezolizumab (1431mg and 1139mg, respectively) and then calculated the whole number of vials needed to provide these average doses. This has reduced the cost of durvalumab and made no change to the cost of atezolizumab. The EAG has therefore applied the correct approach, i.e., applied the RDI multipliers to the costs of the fixed doses.

Table 13 Durvalumab and atezolizumab drug acquisition costs

Drug	Fixed dose	RDI	Cost per administration	
			Company base case: RDI applied to doses (mg)	EAG base case: RDI applied to fix dose
Durvalumab (120mg and 500mg)	1500mg	95.4% (1431mg)	1431mg: [redacted] (2x500mg+4x120mg vials)	[redacted] (95.4% of 3x500mg)
Atezolizumab (840mg and 1200mg)	1200mg*	94.9% (1139mg)	1139mg: £3,808 (1x1200mg vial)	£3,614 (94.9% of 1x1200mg)

* IV and SC unit costs are the same
EAG=External Assessment Group; IV=intravenous; RDI=relative dose intensity; SC=subcutaneous
Source: Company model

5.2.3 Radiotherapy costs

In the company base case analysis, the cost of PCI was only applied to patients treated with atezolizumab+EP; PCI was not permitted in the durvalumab+EP arm of the CASPIAN trial. Clinical advice to the EAG is that, in NHS clinical practice, it is likely that similar proportions of patients treated with durvalumab and atezolizumab would receive PCI. The EAG has therefore presented results from a company scenario analysis (CS, Table 48) in which the same proportion of patients treated with durvalumab+EP and atezolizumab+EP receive PCI (10.9%).

Based on CASPIAN trial data, the company included the cost of other radiotherapy (10 fractions); this other radiotherapy cost (£3,293.82) was applied as a one-off cost after progression to 25.7% of all patients. Clinical advice to the EAG is that radiotherapy offered to patients after progression is typically palliative, with the intent of relieving symptoms, and consists of one fraction or a course of five fractions. Since the same proportions of patients treated with durvalumab+EP and atezolizumab+EP receive post-progression radiotherapy, there is no impact on cost-comparison analysis results from changing the cost of radiotherapy and therefore no change has been made to costs to reflect this lower level of radiotherapy usage.

6 COMPANY AND EAG COST-COMPARISON ANALYSIS RESULTS

The EAG has made the following revisions to the company base case cost comparison analysis:

- all patients treated with durvalumab+EP receive carboplatin (R1)
- correctly applied RDI multipliers (R2)
- PCI cost also applied to 10.9% of patients treated with durvalumab+EP (R3)

Details of the EAG corrections and revisions to the company model are presented in Appendix 3 (Section 10.3). EAG cost-comparison analysis results (durvalumab confidential commercial agreement price) are presented in Table 15. Cost-comparison results using the confidential commercial agreement price for durvalumab, the confidential commercial agreement price for atezolizumab and electronic Market Information Tool (eMIT) prices for all other drugs are provided in a confidential appendix. The sources of the prices used in the confidential appendix are presented in Table 14.

Table 14 Pricing sources used in confidential appendix

Treatment	Price source/type of commercial arrangement
Durvalumab	Confidential commercial agreement
Atezolizumab	Confidential commercial agreement
Carboplatin	eMIT price
Cisplatin	eMIT price
Etoposide	eMIT price
Cyclophosphamide	eMIT price
Doxorubicin	eMIT price
Vincristine	eMIT price

eMIT=electronic Market Information Tool.
Source: Price-tracker (September 2024)

6.1 EAG cost-comparison analysis conclusions

The EAG considers that the company cost-comparison model generates robust cost effectiveness results. EAG revisions only had a small effect on company base case results.

Table 15 Company base case and EAG cost comparison results (durvalumab confidential commercial agreement price)

Scenario/EAG revision	Durvalumab+EP				Atezolizumab+EP				Incremental costs[c]	Change from (A2) base case
	Drug costs (1st line)[a]	HCRU[b]	Subsequent treatment	Total costs	Drug costs[a] (1st line)	HCRU[b]	Subsequent treatment	Total costs		
A1. Company base case	[redacted]	**£18,921**	**£862**	[redacted]	**£90,528**	**£19,260**	**£862**	**£110,651**	[redacted]	-
A2. Corrected company base case	[redacted]	**£18,921**	**£862**	[redacted]	**£90,410**	**£19,260**	**£862**	**£110,532**	[redacted]	-
R1) All patients treated with durvalumab+EP receive carboplatin	[redacted]	£18,921	£862	[redacted]	£90,410	£19,260	£862	£110,532	[redacted]	[redacted]
R2) Correctly apply RDI multipliers	[redacted]	£18,921	£862	[redacted]	£86,157	£19,260	£862	£106,279	[redacted]	[redacted]
R3) PCI cost also applied to durvalumab+EP arm	[redacted]	£19,260	£862	[redacted]	£90,410	£19,260	£862	£110,532	[redacted][d]	[redacted]
B. EAG preferred scenario (R1-R3)	[redacted]	**£19,260**	**£862**	[redacted]	**£86,157**	**£19,260**	**£862**	**£106,279**	[redacted]	[redacted]

[a] Includes administration costs
[b] Includes radiotherapy, monitoring and terminal care costs
[c] All costs are discounted
[d] Incremental cost differs from company scenario analysis due to corrections implemented in company model
EAG=External Assessment Group; EP=etoposide+platinum-based chemotherapy; HCRU=healthcare resource use; PCI=prophylactic cranial irradiation

7 EQUALITIES AND INNOVATION

The company has not reported any equality issues and clinical advice to the EAG is that there are no obvious equality issues.

The evidence suggests that durvalumab+EP and atezolizumab+EP are similar treatments (in terms of mechanism of action, efficacy and safety). Atezolizumab was recommended by NICE as a treatment option for patients with untreated ES-SCLC in 2020[2] and, therefore, durvalumab+EP cannot be considered an innovative treatment.

8 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

8.1 Clinical effectiveness evidence

The company has provided evidence from two good quality RCTs (CASPIAN trial: durvalumab+EP versus EP; IMpower133 trial: atezolizumab+EP versus EP). Durvalumab+EP and atezolizumab+EP have similar mechanisms of action.

Clinical advice to the EAG is that it is appropriate to compare CASPIAN and IMpower133 trial data and the patients enrolled in these trials have characteristics that are similar to the characteristics of NHS patients who are treated with atezolizumab+EP (and who could, if recommended by NICE, be treated with durvalumab+EP).

There is no direct evidence to compare the clinical effectiveness of durvalumab+EP versus atezolizumab+EP and therefore the company has carried out unadjusted OS, PFS and AE ITCs. For survival outcome comparisons, the within-trial PH assumptions do not hold and therefore the efficacy ITC results may be unreliable. However, the company has provided other evidence to support the similarity of durvalumab+EP and atezolizumab+EP and all company efficacy ITC results are in line with published NMA results.

8.2 Cost effectiveness evidence

The EAG considers that company cost-comparison methods were largely appropriate and model results are robust. The EAG correction and revisions were minor and only had a small effect on the size of the company base case results.

8.3 Overall conclusion

The EAG considers that the available clinical effectiveness evidence is sufficiently robust to suggest that durvalumab+EP can be considered similar to atezolizumab+EP. EAG revisions to the company model only had a small effect on the size of the company base case results.

9 REFERENCES

1. National Institute for Health and Care Excellence (NICE). Durvalumab in combination for untreated extensive-stage small-cell lung cancer (terminated appraisal). Technology appraisal. Reference number:TA662. Published: 25 November 2020. Available from: https://www.nice.org.uk/guidance/ta662. Accessed 28 August 2024.
2. National Institute for Health and Care Excellence (NICE). Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer. Technology appraisal guidance. Reference number:TA638. Published: 01 July 2020. Available from: https://www.nice.org.uk/guidance/ta638. Accessed 4 June 2024.
3. National Institute for Health and Care Excellence (NICE). Review proposal paper and final scope for durvalumab in combination with platinum-based chemotherapy for untreated extensive stage small-cell lung cancer (Review of TA662) [ID6404]. Issue date: July 2024. Available from: https://www.nice.org.uk/guidance/gid-ta11515/documents/final-scope. Accessed 28 August 2024.
4. Dingemans AC, Fruh M, Ardizzoni A, Besse B, Faivre-Finn C, Hendriks LE*, et al.* Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). Ann Oncol. 2021; 32:839-53.
5. Ganti AKP, Loo BW, Bassetti M, Blakely C, Chiang A, D'Amico TA*, et al.* Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021; 19:1441-64.
6. AstraZeneca. ClinicalTrials.gov ID NCT03043872: Durvalumab ± Tremelimumab in Combination With Platinum Based Chemotherapy in Untreated Extensive-Stage Small Cell Lung Cancer (CASPIAN) (CASPIAN), Last Update Posted 2024-06-26. Available from: https://clinicaltrials.gov/study/NCT03043872. Accessed 1 October 2024.
7. Hoffmann-La Roche. ClinicalTrials.gov ID NCT02763579: A Study of Carboplatin Plus Etoposide With or Without Atezolizumab in Participants With Untreated Extensive-Stage (ES) Small Cell Lung Cancer (SCLC) (IMpower133). Last Update Posted 2023-07-28. Available from: https://clinicaltrials.gov/study/NCT02763579. Accessed 1 October 2024.
8. European Medicines Agency (EMA). Imfinzi: durvalumab. 2024; Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/imfinzi#overview. Accessed 2024 June 4.
9. Rossi A, Di Maio M, Chiodini P, Rudd RM, Okamoto H, Skarlos DV*, et al.* Carboplatin- or Cisplatin-Based Chemotherapy in First-Line Treatment of Small-Cell Lung Cancer: The COCIS Meta-Analysis of Individual Patient Data. J Clin Oncol. 2012; 30:1692-8.
10. Azar I, Yazdanpanah O, Jang H, Austin A, Kim S, Chi J*, et al.* Comparison of Carboplatin With Cisplatin in Small Cell Lung Cancer in US Veterans. JAMA Netw Open. 2022; 5:e2237699-e.
11. European Medicines Agency (EMA). EMA/CHMP/557475/2019. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Tecentriq. International non-proprietary name: atezolizumab. Procedure No. EMEA/H/C/004143/II/0018. 25 July 2019. Available from: https://www.ema.europa.eu/en/documents/variation-report/tecentriq-h-c-004143-ii-0018-epar-assessment-report-variation_en.pdf. Accessed 5 September 2024.
12. European Medicines Agency (EMA). Tecentriq 1,875 mg solution for injection. 2023; Available from: https://www.medicines.org.uk/emc/product/15037/smpc#gref. Accessed 2024 September 24.
13. National Institute for Health and Care Excellence (NICE). Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small-cell lung cancer [ID6404]. NICE medicines optimisation briefing. May 2024.

14. NHS England (NHSE). NHS world first rollout of cancer jab that cuts treatment time by up to 75%. Published: 29 August 2023. Available from: https://www.england.nhs.uk/2023/08/nhs-world-first-rollout-of-cancer-jab-that-cuts-treatment-time-by-up-to-75/. Accessed 28 August 2024.
15. Burotto M, Zvirbule Z, Mochalova A, Runglodvatana Y, Herraez-Baranda L, Liu SN, *et al.* IMscin001 Part 2: a randomised phase III, open-label, multicentre study examining the pharmacokinetics, efficacy, immunogenicity, and safety of atezolizumab subcutaneous versus intravenous administration in previously treated locally advanced or metastatic non-small-cell lung cancer and pharmacokinetics comparison with other approved indications. Ann Oncol. 2023; 34:693-702.
16. Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in health care. CRD, University of York; 2009; Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed 3 October 2024.
17. AstraZeneca. A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment In Patients with Extensive Disease Small-Cell Lung Cancer (SCLC) (CASPIAN) - Clinical Study Report. 2019.
18. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, *et al.* Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019; 394:1929-39.
19. Goldman JW, Garassino MC, Chen Y, Özgüroğlu M, Dvorkin M, Trukhin D, *et al.* Patient-reported outcomes with first-line durvalumab plus platinum-etoposide versus platinum-etoposide in extensive-stage small-cell lung cancer (CASPIAN): a randomized, controlled, open-label, phase III study. Lung Cancer. 2020; 149:46.
20. AstraZeneca. A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment In Patients with Extensive Disease Small-Cell Lung Cancer (SCLC) (CASPIAN) - Clinical Study Report Final Anaylsis 2020.
21. Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, *et al.* Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2021; 22:51.
22. AstraZeneca. A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment In Patients with Extensive Disease Small-Cell Lung Cancer (SCLC) (CASPIAN) - Clinical Study Report Addendum. 2021.
23. Paz-Ares L, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, *et al.* Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. ESMO open. 2022; 7:100408.
24. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, *et al.* First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018; 379:2220-9.
25. National Institute for Health and Care Excellence (NICE). Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID1504] Committee Papers, 11 February 2019. Available from: https://www.nice.org.uk/guidance/ta638/documents/committee-papers. Accessed 28 August 2024.

26. Reck M, Liu S, Mansfield A, Mok T, Scherpereel A, Reinmuth N*, et al.* IMpower133: Updated overall survival (OS) analysis of first-line (1L) atezolizumab (atezo) + carboplatin + etoposide in extensive-stage SCLC (ES-SCLC). Ann Oncol. 2019; 30:v710-v1.
27. Mansfield AS, Każarnowicz A, Karaseva N, Sánchez A, De Boer R, Andric Z*, et al.* Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): a randomized phase I/III trial. Ann Oncol. 2020; 31:310-7.
28. Califano R, Każarnowicz A, Karaseva N, Sánchez A, Liu SV, Horn L*, et al.* IMpower133: patient-reported outcomes (PROs) in a ph1/3 study of first-line (1L) atezolizumab (atezo) + carboplatin + etoposide (CP/ET) in extensive-stage small cell lung cancer. Ann Oncol. 2018; 29:x17–x23.
29. Liu SV, Reck M, Mansfield AS, Mok T, Scherpereel A, Reinmuth N*, et al.* Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133). J Clin Oncol. 2021; 39:619-30.
30. National Institute for Health and Care Excellence (NICE). Lung cancer: diagnosis and management. NICE guideline [NG122]. Published: 28 March 2019. Last updated: 08 March 2024. Available from: https://www.nice.org.uk/guidance/ng122. Accessed 3 October 2024.
31. European Medicines Agency (EMA). EMA/CHMP/210563/2020. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Imfinzi. International non-proprietary name: durvalumab. Procedure No. EMEA/H/C/004771/II/0014/G. 23 July 2020. Available from: https://www.ema.europa.eu/en/documents/variation-report/imfinzi-h-c-4771-ii-0014-g-epar-assessment-report-variation_en.pdf. Accessed 5 September 2024.
32. National Institute for Health and Care Excellence (NICE). Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy. Technology appraisal guidance. Reference number:TA655. Published: 21 October 2020. Available from: https://www.nice.org.uk/guidance/ta655. Accessed.
33. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997; 50:683-91.
34. Chen J, Wang J, Xu H. Comparison of atezolizumab, durvalumab, pembrolizumab, and nivolumab as first-line treatment in patients with extensive-stage small cell lung cancer: A systematic review and network meta-analysis. Medicine (Baltimore). 2021; 100(15):E25180.
35. Yang C, Xuan T, Gong Q, Dai X, Wang C, Zhang R*, et al.* Efficacy and safety of novel immune checkpoint inhibitor-based combinations versus chemotherapy as first-line treatment for patients with extensive-stage small cell lung cancer: A network meta-analysis. Thorac Cancer. 2024; 15(15):1246-62.
36. Zhu Y, Liu K, Yang Q, Zeng M, Peng L. First-line Immuno-chemotherapy for extensive-stage small-cell lung cancer: A network meta-analysis and cost-effectiveness analysis. Front Public Health. 2023; 11:1028202.
37. Wang S, Li Y, Liu Z, Tian W, Zeng Y, Liu J*, et al.* Efficacy and safety of firwst-line immune checkpoint inhibitors combined with chemotherapy for extensive-stage small cell lung cancer: A network meta-analysis. Lung Cancer. 2023; 178:47-56.
38. Zhang T, Li W, Diwu D, Chen L, Chen X, Wang H. Efficacy and safety of first-line immunotherapy plus chemotherapy in treating patients with extensive-stage small cell lung cancer: a Bayesian network meta-analysis. Front Immunol. 2023; 14:1197044.
39. Zhu Y, Liu K, Zhu H, Cao H, Zhou Y. Comparative efficacy and safety of novel immuno-chemotherapy for extensive-stage small-cell lung cancer: a network meta-analysis of randomized controlled trial. Ther Adv Med Oncol. 2023; 15:1-16.

40. Chen HL, Tu YK, Chang HM, Lee TH, Wu KL, Tsai YC*, et al.* Systematic Review and Network Meta-Analysis of Immune Checkpoint Inhibitors in Combination with Chemotherapy as a First-Line Therapy for Extensive-Stage Small Cell Carcinoma. Cancers (Basel). 2020; 12(12):1-17.
41. Wang BC, Xiao BY, Li PC, Kuang BH, Chen WB, Li PD*, et al.* Efficacy and Safety of First-Line Immunotherapy in Combination with Chemotherapy for Patients with Extensive-Stage Small Cell Lung Cancer: A Systematic Review and Network Meta-Analysis. J Oncol. 2020; 2020:2368164.

10 APPENDICES

10.1 Appendix 1: CASPIAN and IMPower133 trial characteristics

CASPIAN and IMpower133 trial characteristics are summarised in Table 16.

Table 16 CASPIAN and IMpower133 trials: key characteristics

Characteristic	CASPIAN trial	IMpower133 trial
Study design	Phase III, open-label, international, multicentre RCT	Phase I/III, double-blind, placebo-controlled, international, multicentre RCT
Location	209 sites across 23 countries in Europe (but not in the UK), Asia, North and South America	106 sites across 21 countries in Europe (including 10 patients from the UK), Asia, North and Central America and Australia
Recruitment	27 March 2017 to 29 May 2018	6 June 2016 to 31 May 2017
Patients	Previously untreated adults with histologically or cytologically documented ES-SCLC, T3 or T4 and WHO PS 0 or 1 with body weight >30kg and life expectancy >12 weeks Patients with brain metastases at baseline needed to be asymptomatic, or treated and stable off steroids and anticonvulsants for at least 1 month prior to study treatment	Previously untreated adults with histologically or cytologically confirmed ES-SCLC as defined according to the Veterans Administration Lung Study Group staging system, measurable ES-SCLC according to RECIST v1.1, and ECOG PS 0 or 1 Patients with treated asymptomatic CNS metastases were eligible provided specific criteria were met[b]
Trial arms	Durvalumab+EP (n=268) Durvalumab+tremelimumab+EP (n=268)[a] EP (n=269)	Atezolizumab+EP (n=201) Placebo+EP (n=202)
Stratification factors	Planned platinum chemotherapy (carboplatin or cisplatin)	Sex and ECOG PS (0 or 1) and presence of brain metastases (yes or no
Immunotherapy schedule (intravenous)	Induction: up to 4 cycles of durvalumab+EP 1500mg every 3 weeks Maintenance: durvalumab 1500mg every 4 weeks	Induction: up to 4 cycles of atezolizumab+EP 1200mg every 3 weeks Maintenance: atezolizumab 1200mg every 3 weeks Patients in the EP arm also received placebo every 3 weeks in both induction and maintenance trial phases
EP schedule (intravenous)	Up to 4 (or 6 in EP arm) 21-day cycles of: • carboplatin AUC 5–6mg/mL per min or cisplatin 75–80mg/m² on day 1 of each cycle • etoposide 80–100mg/m² on days 1–3 of each cycle	Up to 4 21-day cycles of: • carboplatin AUC 5mg/mL per min on day 1 of each cycle • etoposide 100mg/m² on days 1–3 of each cycle
Radiotherapy	During the maintenance phase and post-discontinuation of study drug, PCI was only permitted in the EP arm	During the maintenance phase, palliative PCI was permitted but thoracic radiation therapy was not

Characteristic	CASPIAN trial	IMpower133 trial
	Post-discontinuation of study drug, thoracic radiation was permitted for patients who had been randomised to any trial arm	permitted Use of radiotherapy post-discontinuation of study drug was not limited
Median follow-up times for outcomes, months	**OS: 25.1 and 39.4[c]** PFS: 25.1[c] ORR: 25.1[c] AEs: 25.1[c] HRQoL: 25.1[c]	**OS: 13.9 and 22.9[d]** **PFS: 13.9 and 22.9[d]** ORR: 13.9[e] AEs: 13.9 and 22.9[d] HRQoL: 13.9[e]

Primary outcomes denoted in bold. The IMpower133 trial had co-primary outcomes. The final OS has not been published for the IMpower133 trial. However, the updated OS analysis was conducted after 302 deaths had occurred, the final analysis was planned after 306 deaths had occurred

[a] Patients in this treatment arm are not relevant to this appraisal

[b] Patients with a history of treated asymptomatic CNS metastases were eligible, provided they meet all 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 randomization
- 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

[c] CASPIAN trial data have also been reported after a median follow-up of 14.2 months but these data did not inform the CS; the company did not report OS results after a median 25.1 months follow-up, however the EAG have reported these data in Section 10.2.2 and also requested analyses using OS data from this data-cut during the clarification process

[d] Company only used data from 13.9 months follow-up in ITCs presented in the CS (but highlighted that OS and PFS data after 22.9 months was very similar); EAG presented OS, PFS and some AE data from 22.9 months follow-up in in Section 10.2

[e] The company did not report results for ORR or HRQoL for the IMpower133 trial; data presented by EAG in Section 10.2

AUC=area under the curve; CNS=central nervous system; CS=company submission; CSR=clinical study report; ECOG PS=Eastern Cooperative Oncology Group performance status; EAG=External Assessment Group EP=etoposide+platinum-based chemotherapy; ES-SCLC=extensive-stage small cell lung cancer; ITC=indirect treatment comparison; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; RECIST=Response Evaluation Criteria in Solid Tumors; PCI=prophylactic cranial irradiation; WHO PS=World Health Organization performance status

Source (CASPIAN): CASPIAN trial CSR 2019;[17] Paz-Ares 2019;[18] Goldman 2020;[19] CASPIAN CSR 2020;[20] Goldman 2021;[21] CASPIAN CSR addendum[22]

Source (IMpower133): Horn 2018;[24] TA638[2] including committee papers;[25] Reck 2019;[26] Mansfield 2020;[27] Liu 2021[29]

10.2 Appendix 2: CASPIAN and IMPower133 trial results

10.2.1 Drug exposure

Exposure to study drugs in the CASPIAN and IMpower133 trials is reported in Table 17.

Table 17 CASPIAN and IMpower133 trial: patient drug exposure

Trial	Treatment	Cycles Median (range)
CASPIAN trial 3 year follow-up	Durvalumab+EP	Durvalumab: 7 (1 to 52) Platinum (carboplatin or cisplatin): 4 (1 to 6)
	EP	Carboplatin: 6 (1 to 6) Cisplatin: 6 (1 to 7)
IMpower133 trial 2 year follow-up	Atezolizumb+EP	Atezolizumab: 7 (1 to 39) Carboplatin: 4 (1 to 6)
	EP	Carboplatin: 4 (1 to 5)

CS=company submission; EMA=European Medicines Agency; EP=etoposide+platinum-based chemotherapy
Source (CASPIAN): CS, Section B.3.10.1; Durvalumab EMA Assessment Report[23] (Table 46)
Source (IMpower133): Committee Papers for TA638[2] (Roche CS, p44); Atezolizumab EMA Assessment Report[11] (Table 39, Table 40); Liu 2021[29]

10.2.2 Overall survival

CASPIAN trial and IMpower133 trial OS results at the latest data-cuts and over a similar follow-up period are summarised in Table 18.

Table 18 CASPIAN and IMpower133 trials: overall survival results

Outcome	CASPIAN		IMpower133	
	Durvalumab+EP (n=268)	EP (n=269)	Atezolizumab+EP (n=201)	Placebo+EP (n=202)
Overall survival after approximately 2 years				
Number of deaths	441 (82.1%)		302 (74.9%)	
Median, months[a]	12.9	10.5[b]	12.3	10.3
HR	0.75 (0.63 to 0.91)		0.76 (0.60 to 0.95)	
Overall survival after approximately 3 years				
Number of deaths	[redacted]		-	
Median, months[a]	12.9	10.5[b]	-	-
HR	0.71 (0.60 to 0.86)		-	

[a] Median overall surviva results for the CASPIAN trial are incorrectly presented for the IMpower133 trial and vice versa in CS, Appendix D.3.1.2.2 (Table 12)
[b] Median overall survival reported for all patients in comparator arm, i.e., treated with carboplatin or cisplatin
CI=confidence interval; CS=company submission; HR=hazard ratio
Source (both trials): CS, Section B.3.3.1 (Table 10); CS, Section 3.9.2 (Table 16); CS, Appendix D.3.1.2.2 (Table 12); CS, Appendix D.3.4.1.1 (Table 19)
Source (CASPIAN): Goldman 2021;[21] Paz-Ares 2022[23]
Source (IMpower133): Liu 2021[29]

10.2.3 Progression-free survival

CASPIAN trial and IMpower133 trial PFS results at the latest data-cuts and over a similar follow-up period are summarised in Table 19.

Table 19 CASPIAN and IMpower133 trials: progression-free survival results

Outcome	CASPIAN		IMpower133	
	Durvalumab+EP (n=268)	EP (n=269)	Atezolizumab+EP (n=201)	Placebo+EP (n=202)
Progression-free survival after approximately 1-year				
Median, months[a]	5.1	5.4[b]	5.2	4.3
HR	0.78 (0.65 to 0.94)		0.77 (0.62 to 0.96)	
Progression-free survival after approximately 2-years				
Median, months[a]	5.1	5.4[b]	5.2	4.3
HR	0.80 (0.67 to 0.96)		0.77 (0.63 to 0.95)	

[a] Median progression-free survival results for the CASPIAN trial are incorrectly presented for the IMpower133 trial and vice versa in CS, Appendix D.3.1.2.2 (Table 12)
[b] Median progression-free survival reported for all patients in comparator arm, i.e., treated with carboplatin or cisplatin
CI=confidence interval; CS=company submission; HR=hazard ratio
Source (both trials): CS, Section 3.9.3 (Table 17); CS, Appendix D.3.1.2.2 (Table 12); CS, Appendix D.3.4.2.1 (Table 21)
Source (CASPIAN): Paz-Ares 2019;[18] Goldman 2021[21]
Source (IMpower133): Horn 2018;[24] Liu 2021[29]

10.2.4 Key CASPIAN trial subgroup results (different EP formulations)

Subgroup results for durvalumab+EP versus ET+CAR or ET+CIS

CASPIAN trial subgroup results for durvalumab+EP versus ET+CAR or ET+CIS are summarised in Table 20.

Table 20 CASPIAN trial: OS and PFS for durvalumab+EP versus ET+CAR or ET+CIS

Outcome	Durvalumab+EP vs ET+CAR	Durvalumab+EP vs ET+CIS
HR (95% CI) after approximately 2-years		
Overall survival	0.79 (0.63 to 0.98)	0.67 (0·46 to 0.97)
Progression-free survival	[redacted]	[redacted]
HR (95% CI) after approximately 3-years		
Overall survival	0.74 (0.60 to 0.91)	0.65 (0.45 to 0.94)
Progression-free survival	-	-

CAR=carboplatin; CI=confidence interval; CIS=cisplatin; CSR=clinical study report; DUR=durvalumab; EP=etoposide+platinum-based chemotherapy; ET=etoposide; HR=hazard ratio
Source: CASPIAN 2020 CSR[20] (Table 14.2.2.15); Goldman 2021;[21] Paz-Ares 2022[23]

Subgroup results for DUR+ET+CAR or DUR+ET+CIS versus ET+CAR

CASPIAN trial subgroup results for DUR+ET+CAR or DUR+ET+CIS versus ET+CAR are summarised in Table 21.

Table 21 CASPIAN trial: OS and PFS for DUR+ET+CAR or DUR+ET+CIS versus ET+CAR

Outcome	DUR+ET+CAR vs ET+CAR	DUR+ET+CIS vs ET+CAR
HR (95% CI) after approximately 2-years		
Overall survival	[redacted]	[redacted]*
Progression-free survival	[redacted]	[redacted]*
HR (95% CI) after approximately 3-years		
Overall survival	[redacted]	[redacted]*
Progression-free survival	-	-

* HR estimated with the digitalization of KM curves
CAR=carboplatin; CI=confidence interval; CIS=cisplatin; CS=company submission; DUR=durvalumab; ET=etoposide; HR=hazard ratio
Source: CS, Appendix D.3.4.1.2 (Table 20); CS, Appendix D.3.4.2.2 (Table 22); company response to clarification question A1 (Table 2)

10.2.5 Objective response rate

CASPIAN trial and IMpower133 trial ORR results at the latest data-cuts for which data were published are summarised in Table 22.

Table 22 CASPIAN and IMpower133 trials: objective response rate*

Objective response rate	CASPIAN trial (2 year follow-up)		IMpower133 trial (1 year follow-up)	
	Durvalumab+EP (n=268)	EP (n=269)	Atezolizumab+EP (n=201)	Placebo+EP (n=202)
Confirmed* %	67.9	58.0	60.2	64.4
OR (95% CI)	1.53 (1.078 to 2.185)		Not reported	

* Confirmed objective response rate was a post-hoc analysis in the CASPIAN trial, unconfirmed objective response rate was a protocol-defined outcome for this trial
CI=confidence interval; CS=company submission; EP=etoposide+platinum-based chemotherapy; OR=odds ratio
Source (CASPIAN): CS, Section B.3.6.3.2 (Figure 9a)
Source (IMpower133): Horn 2018[24]

10.2.6 Health-related quality of life

Patient reported outcome (PRO) data were collected as part of the CASPIAN and IMpower133 trials using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core module (EORTC QLQ-C30) and the EORTC Quality of Life Questionnaire, Lung module (EORTC QLQ-LC13). The company only presented results from the CASPIAN trial. The differences in how PROs were reported and the difference in follow-up at which results were reported in the CS for the CASPIAN trial (2-years) versus the IMpower133 trial publications (1-year) make comparisons between treatment arms across

trials difficult. However, the following general observations can be made when comparing 1-year follow-up data from both trials:

- patients in both the durvalumab+EP and EP arms of the CASPIAN trial experienced a numerically reduced burden for most symptoms over time,; similar results were found between atezolizumab+EP and EP for the same symptoms in the IMpower133 trial (alopecia notably worsened over the first 30-33 weeks in both arms of the IMpower133 trial; this outcome was excluded from the published CASPIAN trial analysis by Goldman 2020[19])
- longer median time to treatment deterioration was observed for patients in the durvalumab+EP arm compared with those in the EP arm for global health status/QoL and all functioning scales, as well as for all QLQ-C30 and QLQ-LC13 symptom scales; similar results were found between atezolizumab+EP and EP for treatment-related or lung-cancer related symptoms in the IMpower133 trial (TTD for global health status/QoL and functional scales were not reported in this trial)

10.2.7 Safety results

The overall safety profiles of the CASPIAN trial durvalumab+EP and EP arms were comparable and consistent with the known safety profiles of individual treatment components. Similar safety conclusions were reported in the Roche CS (TA638[2] Committee papers) for the comparison of atezolizumab+EP versus placebo+EP. The following three tables (Table 23 to Table 25) provide a summary of key CASPIAN and IMpower133 trial AE data, including immune-mediated AE (imAE) data. The company also presented information on the types of adverse events of special interest (AESIs) reported in the CASPIAN trial in CS, Section B.3.10.2 (Table 22).

The EAG considers that, where it was possible to carry out a naïve comparison of AEs experienced by patients treated with durvalumab+EP and patients treated with atezolizumab+EP, AEs were largely comparable and often seemed to favour treatment with durvalumab+EP. However, the EAG considers that results from naïve comparisons of AESI and imAE data are difficult to interpret due to differences in how these AEs were defined in the trials (see Table 26).

Table 23 CASPIAN and IMpower133 trials: summary of adverse events (2 year follow-up)

Adverse event %	CASPIAN trial		IMpower133 trial	
	Durvalumab+EP (n=265)	EP (n=266)	Atezolizumab+EP (n=198)	Placebo+EP (n=196)
All any-cause AEs	98.1	97.0	100.0	96.4
TR-AEs	89.4	89.8	94.9	92.3
All Grade 3/4 AEs	[redacted][a]	[redacted][a]	67.7	63.3
TR-Grade 3/4 AEs	45.7	51.9	57.1	56.1
Any SAE	32.1[b]	36.5	37.4	34.7
TR-SAEs	13.2	18.8	22.7[c]	18.9[c]
Any AESI	[redacted]	[redacted]	41.4	24.5
Any Grade 3/4 AESI	11.3	5.6	8.1	2.6
Any imAE	20.0	2.6	39.9[c]	24.5[c]
Any Grade 3/4 imAE	4.9	0.4	Not reported	Not reported
AEs leading to treatment discontinuation				
TR-AEs	6.0	4.9	Not reported	Not reported
Any-cause AE	10.2	9.4	12.1	3.1
AESIs	[redacted][d]	[redacted]	4.0	1.0
imAEs	[redacted][e]	[redacted]	4.0	1.0
TR-deaths	2.3	0.8	1.5	1.5

[a] In Goldman 2021,[21] data reported to be 59.6% in durvalumab+EP arm versus 59.4% in EP arm
[b] After 3-years follow-up, SAEs increased to 32.5% in durvalumab+EP arm
[c] Data from 1-year follow-up reported as data not available from 2-years follow-up
[d] Date reported to be [redacted]% in company response to clarification question A7
[e] Date reported to be [redacted]% in company response to clarification question A7
AE=adverse event; AESI=AE of special interest; CS=company submission; CSR=clinical study report; imAE=Immune mediated; SAE=serious AE; TR=treatment-related
Source (CASPIAN): CS, Section B.3.10.2 (Table 19); CASPIAN CSR 2020,[20] Section 12.2.3 (Table 46); Goldman 2021[21] including supplementary appendix
Source (IMpower133): Committee Papers for TA638[2] (Roche CS, Table 15); Liu 2021[29]

Table 24 CASPIAN and IMpower133 trials: summary of imAEs (1 year follow-up)*

imAE %	CASPIAN trial		IMpower133 trial	
	Durvalumab+EP (n=265)	EP (n=266)	Atezolizumab+EP (n=198)	Placebo+EP (n=196)
Hypothyroid events	9.1	0.8	Not reported	Not reported
Hypothyroidism	Not reported	Not reported	12.6	0.5
Hyperthyroid events	5.3	0	Not reported	Not reported
Hyperthyroidism	Not reported	Not reported	5.6	2.6
Pneumonitis	2.6	0.8	2.0	2.6
Hepatitis	Not reported	Not reported	7.1	4.6
Hepatic events	2.6	0	Not reported	Not reported
Dermatitis/rash	1.5	0.8	18.7	10.2
Diarrhoea/colitis	1.5	0.4	1.5	0
Thyroiditis	1.5	0	Not reported	Not reported
Type 1 diabetes	1.5	0	0.5	0
Adrenal insufficiency	0.4	0	0	1.0
Pancreatic events	0.4	0	Not reported	Not reported
Pancreatitis	Not reported	Not reported	0.5	1.0
Nephritis	Not reported	Not reported	0.5	0.5
Hypophysitis	Not reported	Not reported	0.5	0,5
Rhabdomyolysis	Not reported	Not reported	1.0	0
Vasculitis	Not reported	Not reported	0	0.5
Arthritis	0.8	0	Not reported	Not reported
Severe cutaneous reaction	Not reported	Not reported	1.0	0
Infusion-related reactions	[redacted]	[redacted]	5.5	2.6

* It is apparent from the CASPIAN final analysis CSR 2020 (2-years follow-up) that additional patients experienced the following imAEs: [redacted] after 2-years follow-up; see CASPIAN final analysis CSR 2020, Table 14.3.6.5
CS=company submission; CSR=clinical study report; imAE=Immune mediated adverse event
Source (CASPIAN): Paz-Ares 2019[18] (Table S8)
Source (IMpower133): Horn 2018[24] (Table S10)

Table 25 CASPIAN and IMpower133 trials: summary of Grade 3/4 imAEs (1 year follow-up)*

imAE %	CASPIAN		IMpower133	
	Durvalumab+EP (n=265)	EP (n=266)	Atezolizumab+EP (n=198)	Placebo+EP (n=196)
Hypothyroid events	0	0	Not reported	Not reported
Hypothyroidism	Not reported	Not reported	0	0
Hyperthyroid events	0	0	Not reported	Not reported
Hyperthyroidism	Not reported	Not reported	0	0
Pneumonitis	0.8	0.4	0.5	1.0
Hepatitis	Not reported	Not reported	1.5	0
Hepatic events	1.9	0	Not reported	Not reported
Dermatitis/rash	0.0	0	2.0	0
Diarrhoea/colitis	0.4	0	1.0	0
Thyroiditis	0.0	0	Not reported	Not reported
Type 1 diabetes	1.5	0	0	0
Adrenal insufficiency	0.0	0	0	0
Pancreatic events	0.4	0	Not reported	Not reported
Pancreatitis	Not reported	Not reported	0.5	1.0
Nephritis	Not reported	Not reported	0.5	0
Hypophysitis	Not reported	Not reported	0.5	0
Rhabdomyolysis	Not reported	Not reported	0.5	0
Vasculitis	Not reported	Not reported	0	0
Arthritis	0	0	Not reported	Not reported
Severe cutaneous reaction	Not reported	Not reported	0	0
Infusion-related reactions	[redacted]	[redacted]	2.0	1.0

It is apparent from the CASPIAN final analysis CSR 2020 (2-years follow-up) that additional patients experienced the following Grade 3/4 imAEs: [redacted] after 2-years follow-up; see CASPIAN final analysis CSR 2020, Table 14.3.6.5
CS=company submission; CSR=clinical study report; imAE=Immune mediated adverse event
Source (CASPIAN): CASPIAN CSR 2019;[12] Paz-Ares 2019[18] (Table S8)
Source (IMpower133): Horn 2018[24] (Table S10)

Table 26 CASPIAN and IMpower133 trials: Definition of AESIs and imAEs

AE type	CASPIAN	IMpower133
AESI	AEs that include, but are not limited to, events with a potential inflammatory or immune mediated mechanism as a result of the mechanism of action of durvalumab that may require more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy	Immune-related AEs defined based on the mechanism of action of atezolizumab, organized by medical concepts
imAE	AE associated with drug exposure and consistent with an immune-mediated mechanism of action, where there is no clear alternate aetiology and required treatment with systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy	Immune-related AEs that were consistent with an immune-mediated mechanism of action of atezolizumab and required treatment with systemic corticosteroids

AE= adverse event; AESI=AE of special interest; imAE=Immune mediated AE
Source (CASPIAN): Paz-Ares 2019[18] (Table S8); CASPIAN CSR 2020 (p183)
Source (IMpower133): Mansfield 2020;[27] Liu 2021[29]

10.3 Appendix 3: EAG revisions to the company model

EAG revisions	Implementation instructions
Correction to treatment cycle numbering in Markov traces	**Insert sheet 'EAG Revisions'** Set value in cell C4 = "C1" Set value in cell D4 = 1 In Sheet 'D +EP' Copy range G27:G1575 Paste values to range H27:H1575 Set value in cell I27=MOD(SEQUENCE(4*(ROUNDUP(C$1575,0)*52-12)/4,,0),4)+1 Copy formula in cell I27 and paste to range I27:I1575 Set value in cell G27=IF('EAG Revision'!D$4=1,I27,H27) Copy formula in cell G27 and paste to range G27:G1575 In Sheet 'Atez + Chemo' Copy range G27:G1575 Paste values to range H27:H1575 Set value in cell I27=MOD(SEQUENCE(3*(ROUNDUP(C$1575,0)*52-12)/3,,0),3)+1 Copy formula in cell I27 and paste to range I27:I1575 Set value in cell G27=IF('EAG Revision'!D$4=1,I27,H27) Copy formula in cell G27 and paste to range G27:G1575
R1) 100% carboplatin in durvalumab+EP arm	In Sheet 'EAG Revisions' Set value in cell C5 = "R1" Set value in cell D5 =1 In Sheet 'Dosing & Adminstration' Set value in cell E14 =IF('EAG Revision'!D5=1,1,201/268) Set value in cell E15 =IF('EAG Revision'!D5=1,0,67/268)
R2) Apply RDI to durvalumab and atezolizumab fixed dose costs	In Sheet 'EAG Revisions' Set value in cell C6 = "R2" Set value in cell D6 =1 In Sheet 'Dosing & Adminstration' Set value in cell D103 =IF('EAG Revision'!D6=1,"Total Vial Sharing", vial_sharing_yn) Set value in cell D109 =IF('EAG Revision'!D6=1,"Total Vial Sharing", vial_sharing_yn)
R3) PCI applied to durvalumab+EP arm	In Sheet 'EAG Revisions' Set value in cell C7 = "R3" Set value in cell D7 = 1 In Sheet 'HCRU' Set value in cell D68 =IF('EAG Revision'!D7=1,D69,0%)

EP=etoposide+platinum-based chemotherapy; PCI=prophylactic cranial irradiation therapy; RDI=relative dose intensity