CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Atezolizumab (Tecentriq) for Small Cell Lung Cancer

January 30, 2020

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding atezolizumab (Tecentriq) in combination with carboplatin and etoposide for extensive stage small cell lung cancer (ES-SCLC) The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding atezolizumab (Tecentriq) in combination with carboplatin and etoposide for ES-SCLC conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on atezolizumab (Tecentriq) in combination with carboplatin and etoposide for ES-SCLC, a summary of submitted Provincial Advisory Group Input on atezolizumab (Tecentriq) in combination with carboplatin and etoposide for ES-SCLC, and a summary of submitted Registered Clinician Input on atezolizumab (Tecentriq) in combination with carboplatin and etoposide for ES-SCLC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the safety and effect of atezolizumab in combination with carboplatin plus etoposide on patient outcomes compared to appropriate comparators for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).

Atezolizumab is a fully humanized, engineered monoclonal antibody of IgG1 isotype against the protein programmed cell death-ligand 1. Atezolizumab has the following pCODR requested reimbursement criteria: Atezolizumab in combination with a platinum-based chemotherapy and etoposide for the first-line treatment of patients with extensive stage small cell lung cancer (ES-SCLC). Maintenance TECENTRIQ should be continued until loss of clinical benefit or unacceptable toxicity. Health Canada has a issued marketing authorisation without conditions for: Atezolizumab in combination with a carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). Note that the Health Canada approved indication differs slightly from the reimbursement criteria, in that it specifies 'atezolizumab in combination with *carboplatin and etoposide*' instead of 'atezolizumab in combination with a *platinum-based chemotherapy and etoposide'*.

During the induction phase the recommended daily dose of atezolizumab is 1200 mg administered by intravenous infusion followed by carboplatin, and then etoposide administered by intravenous infusion on day 1. Etoposide is administered by intravenous infusion on days 2 and 3. This regimen is administered every 3 weeks for four cycles.

The maintenance phase follows the induction phase. During the maintenance phase atezolizumab without chemotherapy is administered at 1200 mg by intravenous infusion every 3 weeks. Patients are treated with atezolizumab until loss of clinical benefit or unacceptable toxicity.

Please refer to the full prescribing information for carboplatin and etoposide, in their respective product monographs.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

IMpower133 is an ongoing multinational, phase III, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of atezolizumab in combination with carboplatin plus etoposide compared with carboplatin and etoposide plus placebo as a first-line treatment for extensive-stage small-cell lung cancer (ES-SCLC). The trial randomized 403 patients in total and assigned 201 patients in a 1:1 ratio to the atezolizumab in combination with carboplatin and etoposide and 202 patients to carboplatin and etoposide plus placebo. According to the study authors, the baseline patient characteristics were well balanced between the study groups. The median age was 64 years (range 28-90 years) in both the atezolizumab and carboplatin and etoposide groups. The use of prophylactic cranial irradiation (PCI) was balanced between arms in IMpower133, 22 (10.9%) patients in the atezolizumab containing treatment arm and 22 (10.9%) patients in the carboplatin and etoposide plus placebo arm received PCI. Randomization was stratified by according sex, ECOG performance-status score (0 or 1), and presence of brain metastases (yes or no). The trial publication did not mention about treatment crossover.

Treatment assignments were blinded. In the induction phase, four 21-day cycles of carboplatin and etoposide with either atezolizumab administered intravenously on day 1 of each cycle or placebo was provided. Maintenance phase followed the induction phase whereby patients received either atezolizumab or placebo based on previous randomized assignment until a toxic effect or disease progression occurred according to RECIST.[1] At the discretion of the investigator patients were allowed to continue their trial regimen after the occurrence of disease progression during either the induction of maintenance phase if evidence of clinical benefit existed. During the maintenance phase, prophylactic cranial irradiation was allowed, but thoracic radiation therapy was not.[1]

For patients with concomitant conditions present at baseline, dose modifications will be applied according to the corresponding shift in toxicity grade, based on the investigator's discretion.[2] Nearly all patients received at least one concomitant medication initiated on or after randomization date, and this was balanced between both treatment arms. The most commonly used classes of drugs included: [redacted].[2] (*Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by sponsor that it can be publicly disclosed.*)

No dose reductions were permitted for patients that received either atezolizumab in combination with carboplatin and etoposide or carboplatin and etoposide plus cisplatin.[2] In the event a patient experienced an adverse event that required a dose to be held, study treatment may be suspended for up to 105 days following the last dose. The patient will be discontinued from either atezolizumab in combination with carboplatin and etoposide or carboplatin and etoposide plus placebo if the adverse event due to treatment exceeds 105 days following the last dose.[2] For the management of adverse events associated with

atezolizumab, toxicities should be treated adhering to standard medical practice. However, additional tests (e.g., autoimmune serology or biopsies) should be used to identify a possible immunogenic etiology.[3]

The primary end points were overall survival and investigator-assessed progression-free survival in the intention-to-treat population. Key secondary end points included investigator-assessed objective response rate (according to RECIST) and the duration of response. Confirmation of responses was not required per protocol but confirmed response rates were reported in the interest of rigor and to protect against potential bias.

Patient reported outcomes were assessed using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), the supplemental lung cancer module (QLQ-LC13), and the EuroQol 5 Dimensions 5-Level (EQ-5D-5L) questionnaire. The EORTC QLQ-C30 and EORTC QLQ-LC13 instruments measure the following four criteria: (1) Disease-related symptoms, (2) treatment-related symptoms, (3) physical function, and (4) health-related quality of life. The EQ-5D-5L instrument is used to elicit utility scores for the submitted cost-effectiveness evaluation. Patient reported outcomes were descriptively analyzed using time to deterioration (TTD) in patient-reported lung cancer-related symptoms and change from baseline in lung cancer- and treatment-related symptoms.[4]

1.2.1.1 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Progression Free Survival

Results reported for progression free survival are based on the primary analysis (Clinical Data Cut-off April 24, 2018). At a median follow-up of 13.9 months, patients that received atezolizumab in combination with carboplatin plus etoposide had statistically significantly longer PFS compared to patients that were treated with carboplatin plus etoposide and placebo (stratified HR: 0.77, 95% CI 0.62-0.96, p=0.017). The median PFS was 5.2 months (95% CI 4.4 to 5.6) in patients that received atezolizumab in combination with carboplatin plus etoposide compared to a median PFS of 4.3 months (95% CI 4.2 to 4.5) for patients that were treated with carboplatin and etoposide plus placebo.

Overall Survival

Results reported for overall survival are based on a planned interim analysis. There were 104 (51.7%) patients that died in the atezolizumab in combination with carboplatin plus etoposide group compared to 134 (66.3%) patients that died in the placebo plus carboplatin plus etoposide group. At a median follow-up of 13.9 months, patients that received atezolizumab in combination with carboplatin plus etoposide had statistically significantly longer OS compared to patients that were treated with carboplatin and etoposide plus placebo (stratified HR: 0.70, 95% CI 0.54-0.91, p=0.0069). The OS endpoint met the statistical boundary (HR ≤ 0.7453). Overall survival was significantly longer in the atezolizumab in combination with carboplatin and etoposide group (median, 12.3 months; 95% CI: 10.8 -15.9) than in the carboplatin and etoposide plus placebo group (median, 10.3 months; 95% CI: 9.3 - 11.3).

At the clinical cut-off date January 24, 2019, 302 of the planned 306 death events of the final analysis of OS had occurred, at a median follow-up of 22.9 months (stratified HR of 0.76, 95% CI: 0.601-0.949). The median OS was 2 months longer in the atezolizumab in

combination with carboplatin plus etoposide group (12.3 months) compared with the carboplatin and etoposide plus placebo group (10.3 months).

This is considered an updated exploratory analysis with longer follow-up. The results from the updated exploratory analysis of OS with longer follow-up were consistent with the OS results of the interim analysis.

In their feedback on the initial recommendation, the sponsor noted that the IMpower133 OS data from the updated exploratory analysis (data cut-off date: January 24, 2019) is mature and no additional analyses are planned or possible at the official study completion date (data cut-off date March 24, 2020) to form the basis of a resubmission to CADTH. Specifically, the sponsor explained that additional survival follow-up analyses are not possible as study sites have been in clinical closure since the second quarter of 2019. According to the sponsor, all patients were unblinded over a year ago and there are no longer any placebo patients being enrolled on the study. Further, the sponsor noted that the official study completion date of March 24, 2020 is the study closing date for safety reporting purposes and is based on the last patient's last visit. In response to the submitter's feedback the CADTH Methods Team noted that based on the information reported in the IMpower133 trial statistical analysis plan (SAP) as well as in direct communications with the sponsor (i.e., checkpoint meeting responses) the Methods Team had been under the impression that an additional final OS analysis was planned to occur in the future, at the latest, at the formal study completion date of March 24, 2020: Firstly, the SAP (Version 3) states that *"The final OS analysis will be conducted when approximately 306 OS events in the ITT population have been observed."* At the time of the updated exploratory OS analysis (data cut-off date: January 24, 2019) only 302 (and not as pre-planned 306) events had been reached. Secondly, the sponsor's checkpoint meeting response [Tecentriq_SCLC_Checkpoint_Responses_FINAL.docx], states that *"At an updated clinical cut-off date (CCOD) of 24 January 2019, 302 death events had been observed (…) With this longer follow-up, the updated OS results continued to demonstrate (…)"*. There was no indication in the sponsor's response at checkpoint meeting that these updated exploratory OS analyses were to be considered 'final' OS analyses. However, in response to a clarification request on the sponsor's feedback on the initial recommendation, the sponsor noted that the number of target events for the final analysis was an "approximate projection" and that the analysis at the January 24, 2019 data cut-off date, with 302 events, represented the final OS analysis. The study site closures were therefore initiated as no further follow-up analysis was required. Furthermore, the sponsor, in their feedback, referred to an abstract by Reck et al.,[5] from the ESMO 2019 Congress which presented the *"updated OS analysis"* (data cut-off date: January 24, 2019). The CADTH Methods Team noted that this abstract was not submitted to CADTH during the review process and was published (September 28, 2019) after the date of the initial pERC meeting (September 19, 2019). The abstract was therefore considered 'new information' and was not considered by pERC in their Reconsideration of the Initial Recommendation of atezolizumab for extensive stage SCLC. The Methods Team noted that, although the abstract had not been provided to CADTH, information regarding the updated exploratory OS analysis from data cut-off date January 24, 2019, had been included in the initial Clinical Guidance Report (CGR) based on information provided by the sponsor at the time of checkpoint meeting [Tecentriq_SCLC_Checkpoint_Responses_FINAL.docx].

CADTH received a procedural review request from the sponsor for atezolizumab for ES-SCLC on December 16, 2019, which CADTH accepted on the grounds that it failed to act in accordance with its procedures in conducting the review. Specifically, the sponsor alleged that data from a recent publication (Reck et al. [2019])[5] regarding 18-month survival rates were not new data and should have been considered by pERC at the reconsideration meeting on November 21, 2019. The sponsor also noted that this information had been

provided as part of the Checkpoint Meeting Responses dated May 6, 2019. CADTH acknowledged that the relevant data had been provided in the Checkpoint Meeting Responses. In view of this finding, it was determined that the submission needed to be re-deliberated by pERC at its next available meeting on January 16, 2020. The OS landmark analysis results at 24 months had also been provided in the Checkpoint meeting material. The European Public Assessment Report[6] (EPAR) on atezolizumab (Tecentriq) for ES-SCLC was published on October 23, 2019 after the posting of the initial recommendation (October 3, 2019), and outlines the OS landmark analysis results for 12, 18, and 24 months (please see Table 1.1 below). As shown in Table 1.1, at 12 months and 18 months (January 2019 data cut off date) there is an estimated 13% absolute improvement in OS in favour of treatment with atezolizumab in combination with carboplatin and etoposide. At 24 months, the absolute improvement in OS was 5% in favour of treatment with atezolizumab in combination with carboplatin and etoposide (22% vs 17%).

Table 1.1: Overview of Overall Survival (ITT population)

Parameter	Interim OS Analysis (CCOD 24 April 2018)		Updated OS Analysis (CCOD 24 January 2019)	
	PBO+CE	Atezo+CE	PBO+CE	Atezo+CE
Co-Primary Efficacy Objective: Overall Survival				
ITT Population	N=202	N=201	N = 202	N = 201
Patients with event (%)	134 (66.3)	104 (51.7)	160 (79.2)	142 (70.6)
Median duration of survival - months (95% CI)	10.3 (9.3, 11.3)	12.3 (10.8, 15.9)	10.3 (9.3, 11.3)	12.3 (10.8, 15.8)
Stratified Hazard Ratio (95% CI) p-value (log-rank)	0.701 (0.541, 0.909) 0.0069[a]		0.755 (0.601, 0.949) 0.0154[b]	
Patients remaining at risk	59	74	74	93
12-month event-free rate - % (95% CI)	38.2 (31.2, 45.3)	51.7 (44.4, 59.0)	39.0 (32.1, 45.9)	51.9 (44.6, 59.1)
Patients remaining at risk	3	5	39	61
18-month event-free rate - % (95% CI)	20.2 (11.1, 29.4)	25.0 (11.2, 38.7)	21.0 (15.2, 26.8)	34.0 (27.1, 40.9)
Patients remaining at risk	NE	NE	8	21
24-month event-free rate - % (95% CI)	NE (NE, NE)	NE (NE, NE)	16.8 (11.3, 22.2)	22.0 (15.7, 28.3)

Atezo = atezolizumab; CCOD = clinical cut-off date; CE = carboplatin – etoposide; CI = confidence interval; DOR = duration of response; ITT = intent-to-treat; OS = overall survival; NE = not estimable; PBO = placebo.

[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] Descriptive purposes only

Source: EPAR[6]

The overall response rate was similar for patients that received atezolizumab in combination with carboplatin plus etoposide (60.2%) compared to patients that received

carboplatin and etoposide plus placebo (64.4%). There were five patients (2.5%) in the atezolizumab in combination with carboplatin and etoposide group and two patients (1.0%) in the carboplatin and etoposide plus placebo group who had a complete response.

The median duration of response for patients that received atezolizumab in combination with carboplatin plus etoposide was 4.2 months (range 1.4-19.5 months) and 3.9 months (range 2.0-16.1 months) for patients treated with carboplatin and etoposide plus placebo.

There was a greater improvement from baseline in patient-reported lung cancer-related symptoms (i.e., chest pain, dyspnea, arm/shoulder pain) for patients that received treatment with atezolizumab in combination with carboplatin and etoposide compared to patients that received carboplatin and etoposide plus placebo. There was a delay in worsening of dyspnea symptoms for patients treated with atezolizumab in combination with carboplatin and etoposide compared to patients that received carboplatin and etoposide plus placebo (HR: 0.75, 95% CI 0.55, 1.02). The data from the EORTC QLQ-C30 showed an immediate improvement in physical function and HRQoL in favour of patients that received atezolizumab in combination with carboplatin and etoposide compared with patients who received carboplatin and etoposide plus placebo. The improvement in HRQoL was sustained through Week 54 in patients that received atezolizumab in combination with carboplatin and etoposide. Improvements observed in the patients treated with carboplatin and etoposide plus placebo were small and generally not clinically meaningful.

Safety Outcomes

Safety data were not blinded and reviewed by an independent data and safety monitoring committee for assessment of the side-effect profile. There were 22 patients in the atezolizumab in combination with carboplatin plus etoposide and 6 patients in the carboplatin and etoposide plus placebo that experienced AEs that led to withdrawal from any treatment component. There were 3 mortalities among patients that were treated with atezolizumab in combination with carboplatin plus etoposide (death was due to neutropenia in 1 patient, pneumonia in 1 patient, and an unspecified cause in 1 patient) and 3 mortalities among patients in the carboplatin and etoposide plus placebo group (death was due to pneumonia in 1 patient, septic shock in 1 patient, and cardiopulmonary failure in 1 patient). The proportion of treatment-related adverse events was similar between patients treated with atezolizumab in combination with carboplatin plus etoposide (94.9%) and patients that received carboplatin and etoposide plus placebo (92.3%). There were 112 patients (56.6%) that experienced treatment-related Grade 3-4 adverse events in the atezolizumab in combination with carboplatin and etoposide compared to 110 patients (56.1%) in the carboplatin and etoposide plus placebo group. Serious adverse events occurred in 74 patients (37.4%) that received atezolizumab in combination with carboplatin and etoposide compared to 68 patients (34.71%) in the carboplatin and etoposide plus placebo group. There were 45 patients (22.7%) that experienced Grade 3-4 neutropenia that received treatment with atezolizumab in combination with carboplatin plus etoposide compared to 48 patients (24.5%) that received carboplatin and etoposide plus placebo. The most commonly reported immune related adverse events were rash followed by hypothyroidism (atezolizumab in combination with carboplatin plus etoposide vs. carboplatin and etoposide plus placebo: all grades rash 18.7% vs. 10.2%; all grades hypothyroidisms: 12.6% vs. 0.5%).

Limitations

Although this phase III trial was a randomized, double-blinded study, there are limitations associated with the study design and methodology. While the sample size of the trial was

based on the analysis of OS, the secondary efficacy endpoints and subgroup analyses were not adequately powered to determine statistical significance. Specifically, sample size calculations were outlined for OS and investigator assessed PFS. Thus, the results for secondary endpoints should be interpreted with caution. In addition, an amendment was made to the stopping boundary for OS interim and final analyses from HR ≤ 0.665 to HR ≤ 0.745 to observe a smaller effect size, however, the rationale provided in the protocol is unclear. The amendment was dated May 14, 2018 following the first data cut-off on April 24, 2018. The Although methods for testing for multiplicity were outlined in the protocol for primary endpoints, it is unclear whether these were carried out in the statistical analysis for secondary endpoints. Results related to patient-reported outcomes were descriptive only. In addition, the proportion of patients that did not complete the EORTC QLQ C30 is not reported and whether these patients may have responded differently to patients that completed the questionnaire is uncertain. Lastly, due to the sponsor involved in various aspects of the trial (e.g., data collection, performing data analysis, authorship), there is a possible conflict of interest.

Table 1.2: Highlights of Key Outcomes

	IMpower133			
	Atezolizumab and carboplatin and etoposide group	Carboplatin and etoposide and placebo group	Atezolizumab and carboplatin and etoposide group	Carboplatin and etoposide and placebo group
Data cut-off date	April 24, 2018 (primary data cut)		January 24, 2019 (updated exploratory data cut)	
Median duration of follow-up, Months	13.9		22.9	
Co-primary endpoint – PFS				
Events n (%)	171 (85.1)	189 (93.6)	Not assessed	
Median PFS, months (95% CI)	5.2 (4.4 - 5.6)	4.3 (4.2- 4.5)		
HR (95% CI)	0.77 (0.62 - 0.96) p=0.017			
Co-primary endpoint - OS				
Events n (%)	104 (51.7)	134 (66.3)	(70.6)	(79.2)
Median OS, months (95% CI)	12.3 (10.8 - 15.9)	10.3 (9.3- 11.3)	12.3	10.3
HR (95% CI)	0.70 (0.54- 0.91) p=0.0069		0.76 (0.60- 0.95) p=0.0154	
Tumour Response				
Duration of Response			Not assessed	
Median, months (95% CI)	4.2 (1.4- 19.5)	3.9 (2.0- 16.1)		
Overall Response Rate %	60.2	64.4	Not assessed	
Complete Response %	2.5	1.0		

	IMpower133			
	Atezolizumab and carboplatin and etoposide group	Carboplatin and etoposide and placebo group	Atezolizumab and carboplatin and etoposide group	Carboplatin and etoposide and placebo group
Safety				
Patients with ≥ 1 AE	198 (100)	189 (96.4)		
Grade 3–4 AEs	133 (67.2)	125 (63.8)		
Treatment-related AEs	188 (94.9)	181 (92.3)	Not assessed	
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)	Not assessed	
Treatment related deaths	3 (1.5)	3 (1.5)		
Immune-related AEs	79 (39.9)	48 (24.5)		
Notes: AEs = adverse events; OS = overall survival; PFS = progression-free survival				

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

Two patient advocacy groups, Lung Cancer Canada (LCC) and the Ontario Lung Association (OLA), provided input for atezolizumab with etoposide and a platinum-based chemotherapy for the first-line treatment of patients with small cell lung cancer (SCLC).

LCC and OLA noted that, from a patient's perspective, SCLC is an aggressive condition with limited treatment options available for patients. The fear and stress experienced by patients and caregivers related to receiving a diagnosis of SCLC was mentioned by both LCC and OLA, as SCLC is associated with poor survival. Symptoms of lung cancer were stated to impact patient's ability to engage with family and friends, take part in daily activities or work. Immunotherapy and chemotherapy were treatments patients had received to treat their SCLC. Both chemotherapy and immunotherapy were stated to be effective, however side effects of immunotherapy were much more tolerable, with some patients being able to resume their daily tasks. Only patients on behalf of LCC reported having experience with atezolizumab, however, quotes and experiences were mostly reported by patients diagnosed with NSCLC; only one patient had received atezolizumab in combination with chemotherapy and was diagnosed with SCLC. LCC stated that they did not believe there to be any reason why experiences would differ greatly between patients with NSCLC and SCLC, however, no evidence was provided to support their belief. Patients reported that atezolizumab was effective, with some patients experiencing positive responses relatively quickly. Side effects were few, tolerable and manageable. In general, patients found that they were able to engage in daily activities, including going back to work. The patient who was diagnosed with SCLC and received atezolizumab in combination

with chemotherapy reported significant tumour shrinkage, but experienced significant side effects that required hospitalization. Despite the experienced side effects and hospitalization, this patient expressed that receiving atezolizumab was a good opportunity.

In terms of expectations for alternative treatment options, OLA and LCC highlighted the following patient values: extension of life, improvement of QoL, manageable side effects, and additional and affordable treatment choices. An overarching theme of hope was discussed, as patients and caregivers felt grateful to have a treatment that allowed them to partake in normal daily tasks and allow them to live longer in hopes of receiving a new treatment if needed in the future.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Generalizability of trial results to cisplatin/etoposide

Economic factors:

- Treatment duration and stopping rules for maintenance atezolizumab

Registered Clinician Input

One joint clinician input on behalf of five clinicians from Lung Cancer Canada (LCC) and one single clinician input were provided for the review of atezolizumab (Tecentriq) in combination with chemotherapy for first-line treatment of extensive stage small cell lung cancer (ES-SCLC).

Both inputs indicated having experience with using atezolizumab. The current standard of care for patients with ES-SCLC in the first-line was stated to be platinum-based chemotherapy. Eligibility criteria for patients from the IMpower133 trial were stated to be reasonable and reflective of clinical practice. However, the clinicians expressed a desire to extrapolate evidence from the IMpower133 trial to patients with an ECOG performance status of 2 or 3, as the IMpower133 trial included only patients with an ECOG performance status of 0 or 1. The IMpower133 trial also only included patients who received carboplatin, the clinicians providing input suggested that patients also receiving cisplatin should be eligible for atezolizumab. Finally, treatment with atezolizumab and chemotherapy for patients with brain metastases was supported by both clinician inputs. General stopping rules for immunotherapy were stated to be reasonable stopping rules for atezolizumab in this setting.

Summary of Supplemental Questions

The Submitter conducted a systematic literature review which provided input for the network meta-analysis (NMA) which was also provided by the Submitter. The primary objective of the NMA was to compare atezolizumab in combination with etoposide and a platinum-based chemotherapy for the first-line treatment of extensive stage small cell lung cancer (ES-SCLC) with relevant platinum doublet therapies used in clinical practice globally.

Quality (risk of bias) assessment of RCTs assessed the following items: randomization allocation, if groups were similar at the outset of the study, blinding, attrition, statistical

analysis and conflicts of interest. A Bayesian approach was used to conduct the NMA analyses which encompassed the formal combination of a prior probability distribution. Since the evidence networks included few studies, there was insufficient data to apply the random effects model correctly. Therefore, it was not feasible to assess heterogeneity using meta-regression and subgroup analyses in the current project. Fixed effects models were applied for all analyses. Median hazard ratios (HRs) and associated 95% credible intervals (CrIs) were rereported for time-to-event outcomes. The outcomes investigated included progression free survival (PFS) at 6 months, 1 year, overall survival (OS) at 1 year and objective response rate. For the purpose of alignment with the pharmacoeconomic evaluation, data for PFS and OS are reported below. In addition, the surface under the cumulative ranking (SUCRA) was calculated for each treatment.

The systematic literature review search revealed 8, 291 articles and 7, 848 articles were excluded. Based on the 112 articles identified as potentially relevant, a total of 72 publications met the inclusion criteria for the systematic review. Of the 72 publications included in the SR, 68 were excluded from the meta-analysis feasibility assessment.

Conclusions

Atezolizumab in combination with etoposide plus carboplatin is associated with a statistically significantly longer PFS compared with etoposide plus carboplatin (HR=0.77, 95% CrI 0.62-0.95). The NMA base case result of PFS is the same as the PFS result reported in IMpower133 trial. Atezolizumab in combination with etoposide plus carboplatin is associated with a higher odds of PFS at 6 months compared with etoposide plus carboplatin (OR= 1.57, 95% CrI 1.00- 2.46). There was a statistically significant higher odds of PFS at 1 year in favour of atezolizumab in combination with etoposide plus carboplatin compared with etoposide plus carboplatin (OR=2.51, 95% CrI 1.22, 5.45). There was no statically significant difference in PFS at 6 months (OR=0.59, 95% CrI 0.34-1.02) and 1 year (OR=0.47, 95% CrI 0.17-1.23) between atezolizumab in combination with etoposide plus carboplatin and etoposide plus cisplatin.

In the base case, atezolizumab in combination with etoposide plus carboplatin was associated with a statistically significantly longer OS benefit compared with etoposide plus carboplatin (HR=0.70, 95% CrI 0.54-0.91). Atezolizumab in combination with etoposide plus carboplatin is associated with a statistically significantly higher odds of OS at 1 year compared with etoposide and carboplatin (OR=1.75, 95% CrI 1.17-2.61). There appears to be no difference in treatment between atezolizumab in combination with etoposide plus carboplatin compared with etoposide plus cisplatin at 1 year as the upper limit of the 95% CrI is close to the value of 1 (OR=0.67, 95% CrI 0.44-1.01).

The validity of the NMA is based on three assumptions (i.e., similarity, homogeneity, and consistency) which were assessed in this review. It is important to note that the NMA base case result of PFS is the same as the PFS result reported in the IMpower133 trial. Thus, the base case for PFS did not provide any new data. Heterogeneity was not assessed due to the small size of the evidence networks. However, a qualitative assessment of heterogeneity revealed that there was variability both across the trials and within treatment groups for gender and ECOG performance status. Thus, the homogeneity assumption was violated. The quality assessment of the included studies in the evidence network revealed that the highest risk of bias across the studies was associated with study blinding and randomisation which may introduce selection bias. Furthermore, the robustness of the analysis is unclear as one trial included in the network of evidence involved an elderly, high-risk population and a sensitivity analysis was not conducted to exclude this trial. Due to a lack of a closed loop in the evidence network, the consistency between direct and indirect comparisons

could not be assessed. Members of CGP noted within the Canadian landscape, irinotecan is infrequently used in the initial management of SCLC because of concerns around toxicity and a lack of clear superiority. While a sensitivity analysis with the exclusion of irinotecan trials may have informed how the effect estimates varied, the evidence network is sparse and this may not have been feasible. Other outcomes of interest (e.g., health related quality of life and safety) were not evaluated in this NMA. Finally, the submitted systematic review and NMA were completed by external consultancy groups hired by the submitter. As a result, the information provided in the reports should be viewed considering this potential conflict of interest and lack of peer-review. Based on the aforementioned limitations, the comparative efficacy estimates may be biased. Thus, the certainty in the results reported for PFS and OS is limited and should be interpreted with caution.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.3 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity)

Table 1.3. Assessment of generalizability of evidence for atezolizumab in combination with carboplatin plus etoposide as first-line treatment for extensive-stage small-cell lung cancer

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(IMpower133 trial)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Stage of disease</td><td>IMpower133 trial included patients with extensive-stage SCLC, according to Response Evaluation Criteria in Solid Tumors (RECIST). Patients with limited-stage SCLC were not included.</td><td>Does stage limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Interpretation of the trial results applies to extensive-stage SCLC.

There is no data to support the use of atezolizumab in patients with other stages than the one observed in the Impower133 trial.</td></tr>
<tr><td>Performance Status</td><td>Patients were included in the IMpower133 trial if they had ECOG status of 0 or 1.
The majority of patients in the atezolizumab (plus carboplatin and etoposide) and the placebo (plus carboplatin and etoposide) arm had an ECOG performance score of 1 (64% and 67% respectively).

<table>
<tr><td colspan="3">ECOG score, n(%)</td></tr>
<tr><td></td><td>Atezolizumab n=201</td><td>Carboplatin and etoposide n=202</td></tr>
<tr><td>0</td><td>73 (36%)</td><td>67 (33%)</td></tr>
<tr><td>1</td><td>128 (64%)</td><td>135(67%)</td></tr>
</table>
</td><td>Are the trial results generalizable to patients with an ECOG score of 2 or higher?</td><td>IMpower133 allowed patients with ECOG 0-1 only. Most treatment algorithms, including ASCO guidelines for advanced NSCLC recommend treatment be considered in patients with a performance status of ECOG 2 as well. In NSCLC, the use of immune checkpoint inhibitors has been extended to patients with ECOG 2. It would also be appropriate to treat ECOG 2 patients with ES SCLC with platinum, etoposide and atezolizumab. The submission from LCC suggested that patients with poor performance status who improve rapidly on treatment should be allowed to add atezolizumab into the treatment in subsequent</td></tr>
</table>

Domain	Factor	Evidence (IMpower133 trial)	Generalizability Question	CGP Assessment of Generalizability
				cycles. Given the modest benefit overall from the addition of atezolizumab to carboplatin and etoposide, the CGP would not recommend atezolizumab in patients with ECOG 3 or 4.
	Organ dysfunction	The Impower133 trial limited eligibility to patients with adequate hematologic and organ function.	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	The use of atezolizumab should be limited to patients with adequate hematologic, hepatic and renal function as determined by the treating oncologist.
	CNS Metastases	Patients with treated asymptomatic central nervous system metastases were eligible. Prophylactic cranial irradiation (PCI) was allowed per local standard of care. Definitive thoracic radiation was not allowed per protocol; palliative radiation was permitted. During the maintenance phase of treatment, prophylactic cranial irradiation (PCI) was permitted as per local standard-of-care. The use of PCI was balanced between arms in IMpower133, 22 (10.9%) patients in the atezolizumab containing treatment arm and 22 (10.9%) patients in the placebo control arm received PCI.[7]	Are the trial results generalizable to patients requiring radiation for local symptomatic control, prophylactic cranial irradiation, or whole brain radiation?	IMpower133 allowed patients with asymptomatic treated brain metastases to enter the trial. Therefore, the CGP believes atezolizumab should be available to patients with asymptomatic treated brain metastases. Prophylactic cranial irradiation (PCI) was allowed on the trial and therefore patients receiving PCI should be allowed to continue maintenance atezolizumab. Patients requiring palliative radiation for symptom management

Domain	Factor	Evidence (IMpower133 trial)	Generalizability Question	CGP Assessment of Generalizability
				prior to commencing systemic therapy should be eligible for the addition of atezolizumab to chemotherapy.
	Biomarkers	Exploratory Tumor Mutational Burden in Blood (bTMB) biomarker analyses were performed using pre-specified cut-offs of ▫ 10 versus < 10, and ▫ 16 versus <16 separately, in an effort to investigate the association of this marker with clinical outcomes.	Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?	There are no biomarkers to help in the selection of patients for the addition of atezolizumab to platinum-based chemotherapy. Therefore, there should be no indication for PD-L1, or TMB testing in SCLC.
Intervention	Combination drug	The IMpower133 trial assessed carboplatin plus etoposide with or without atezolizumab. In some jurisdictions cisplatin plus etoposide is commonly used.	Can the trial results be generalized to cisplatin plus etoposide with Atezolizumab?	Although the IMpower133 trial did not evaluate atezolizumab in combination with cisplatin + etoposide, the CGP agreed that the results for atezolizumab in combination with carboplatin and etoposide should be generalized to atezolizumab in combination with cisplatin and etoposide in first-line ES-SCLC. Most clinicians would consider cisplatin and carboplatin as interchangeable in the management of SCLC.
	Line of therapy	The Impower133 trial limited eligibility to patients with no prior systemic treatment for extensive stage-SCLC.	Are the results of the trial generalizable to other lines of	Interpretation of the trial results applies to first-line extensive stage-SCLC.

Domain	Factor	Evidence (IMpower133 trial)	Generalizability Question	CGP Assessment of Generalizability
		Patients who have received prior chemoradiotherapy for limited-stage 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 limited-stage SCLC.	therapy (e.g., to second-line setting as monotherapy or in combination with topotecan following progression on platinum-based chemotherapy?	There is no data to support the use of atezolizumab in patients in other lines of therapy than the one observed in the IMpower133 trial.
	Dose and Schedule	In the IMpower133 trial patients were assigned to an induction phase (four 21-day cycles) of a 3-drug combination: • atezolizumab at a dose of 1200 mg (fixed dose) every 3 weeks as an intravenous infusion. • carboplatin (area under the curve of 5 mg per milliliter per minute, administered intravenously on day 1 of each cycle); and • etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle) The induction phase was followed by a maintenance phase, in which patients received atezolizumab (dosing as above) until the occurrence of unacceptable toxic effects or disease progression according to RECIST.	Is the trial dosage generalizable to patients in Ontario? Across Canada?	The dosing schedule of the trial is applicable to current Canadian clinical practice. Most places will administer 4 cycles of chemotherapy. Some centres may administer 6 instead of 4 cycles. The CGP agreed that the Impower133 trial results are generalizable to centres that administer 6 cycles of chemotherapy.
Outcomes	Appropriateness of Primary and Secondary Outcomes	Primary: • OS • PFS using RECIST (investigator – assessed) Secondary: • ORR using RECIST (investigator-assessed) • DOR		OS and PFS are the most important outcomes to clinicians and therefore appropriate primary outcomes have been measured in the Impower133 trial. Given the primary outcomes are the most important and both demonstrate significant improvements for the addition of atezolizumab to carboplatin and etoposide, the lack of improvement

Domain	Factor	Evidence (IMpower133 trial)	Generalizability Question	CGP Assessment of Generalizability
				in secondary outcomes (ORR) become less important.
	Assessment of Key Outcomes	PFS was measured using RECIST as assessed by Investigator.	If the trial used a different method of assessment than that used in Canadian clinical practice, are the results of the trial applicable to the Canadian setting?	CGP agreed that outcomes were assessed appropriately and applicable to the Canadian context. CGP did not express concern regarding the lack of blinded radiology review.
Setting	Countries participating in the Trial	Canada was not included. There were 25 study sites in the United States, 7 in Australia, 53 in Europe, and 33 in Asia.	If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.	Even though the IMpower133 trial did not include Canada there is no reason to believe that the results would be different in the Canadian population of patients with extensive-stage SCLC
	Supportive medications, procedures, or care	Nearly all patients received at least one concomitant medication initiated on or after randomization date, and this was balanced between both treatment arms. The most commonly used classes of drugs included: 5-HT3 antagonists, steroids, colony stimulating factors, supplements, antiemetics not elsewhere classifiable (NEC), opioid analgesics, non-steroidal anti-inflammatories, laxatives and stool softeners, and antihistamines.[2]	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	There is no reason to believe that the supportive care management of these patients differed from the usual care provided within the Canadian health care system. IMpower133 did not allow the use of thoracic radiation. Given the lack of safety data for concurrent administration of thoracic radiation and

Domain	Factor	Evidence (IMpower133 trial)	Generalizability Question	CGP Assessment of Generalizability
				atezolizumab, the CGP would not recommend thoracic radiation be administered concurrently with atezolizumab.

1.2.4 Interpretation

Burden of Illness

There is a strong need for improved therapies in ES SCLC. SCLC is a common problem, accounting for 15% of lung cancer cases, representing over 4000 cases annually in Canada. Despite multiple randomized trials evaluating a variety of strategies, no real advances in systemic therapy for SCLC have been made in the last three decades.[8] The combination of cisplatin, or carboplatin with etoposide has remained the standard of care therapy.[9] The median survival of ES SCLC remains poor at 10-12 months, with 15% or fewer patients surviving beyond two years.[10]

In recent years, immune checkpoint inhibitors have changed the outlook of advanced and metastatic non small cell lung cancer (NSCLC). Nivolumab, pembrolizumab and atezolizumab are now routinely incorporated into treatment algorithms for this disease. In the second-line setting, all three agents have been shown to improve overall survival compared with docetaxel.[11-15] In the first-line setting, single agent pembrolizumab in patients with tumours demonstrating strong expression of PD-L1 (> 50% of cells),[16] or the addition of pembrolizumab to platinum-based chemotherapy,[17,18] for patients with PD-L1 positive or negative tumours, has improved overall survival in comparison to platinum-based chemotherapy alone.

Progress in immune checkpoint inhibitor therapy in SCLC though, has been much slower. The addition of ipilimumab to platinum and etoposide failed to improve overall survival (HR 0.94, 95%CI 0.81-1.09, median OS 11.0 vs 10.9m).[19] Some activity has been observed from both single agent nivolumab and the combination of nivolumab plus ipilimumab in heavily pretreated patients with SCLC.[20] Single agent pembrolizumab in patients with previously treated SCLC has shown modest activity.[21] Nevertheless, immune checkpoint inhibitors are not currently included in treatment algorithms for SCLC in Canada.

Effectiveness

Building on the success observed in NSCLC, with combination chemotherapy and immune checkpoint inhibitor, IMpower133 evaluated the addition of atezolizumab to standard first-line therapy for ES SCLC with carboplatin and etoposide.[1] Previously untreated patients with ES SCLC, good performance status (ECOG 0-1) and measurable disease were randomized to carboplatin, etoposide and placebo, or carboplatin, etoposide and atezolizumab. Patients with asymptomatic treated brain metastases were eligible for study entry. However, patients with significant co-morbid medical problems, or contraindications to immune checkpoint inhibitor therapy, such as autoimmune diseases, were not eligible. The trial allowed prophylactic cranial irradiation (PCI) but not thoracic radiation (TRT). Carboplatin and etoposide were administered for up to four cycles. Atezolizumab, or placebo, was started with cycle 1 of chemotherapy and continued until disease progression, or unacceptable toxicity. The primary outcomes were OS and investigator assessed PFS. Key secondary outcomes included investigator assessed ORR, duration of response and safety. Exploratory biomarker analyses examined the association of tumour mutation burden (TMB) and PD-L1 expression with key outcomes.

There were 202 patients with ES SCLC randomized to carboplatin, etoposide and placebo and 201 to carboplatin, etoposide and atezolizumab. The median age was 64, which is about 7 years younger than the median age of SCLC patients in Canada. This is typical of clinical trial populations. The other baseline patient characteristics were well balanced. Median follow up at the time of the primary analysis was relatively short at 13.9 months.

This makes interpretation of the long term benefits of atezolizumab challenging. The trial met both primary outcomes.

There was a significant improvement in OS (median OS 10.3m vs 12.3m, HR 0.70, 95%CI 0.54-0.91). PFS was modestly improved (median PFS 4.3m vs 5.2m, HR 0.77, 95%CI 0.62-0.96). There was no significant difference in ORR (64.4% vs 60.2%), which numerically was slightly higher in the control arm. One should not draw any conclusions from this as it likely represents chance variation. The median duration of response was similar between the two groups (3.9m vs 4.2m), although the proportion of patients with ongoing response at 12 months was more than double in the atezolizumab arm (14.9% vs 6.2%). Health related quality of life (QoL) improved in both arms, but there was a greater improvement in QoL observed in patients randomized to the addition of atezolizumab to carboplatin and etoposide.

Sub group analyses for OS showed a consistent improvement in OS for patients randomized to atezolizumab for most sub groups. However, these sub group analyses were exploratory and therefore the interpretation of the results is limited.

The HR for patients with brain metastases was 1.07 (95%CI 0.47-2.43). However, the number of patients was very small and it would not be appropriate to draw any firm conclusions from this. TMB using thresholds of 10 mutations per megabase (Mb), or 16 mutations/Mb was not predictive of a differential benefit from atezolizumab. Therefore, it is not possible to identify sub groups of patients who would not benefit from the addition of atezolizumab.

Safety

The adverse event (AE) profile is largely driven by the expected AEs from carboplatin and etoposide. The most common AEs include neutropenia, anemia, alopecia, hair loss, nausea, fatigue and were occurred with similar frequency between the two groups. As would be expected, there were more immune related AE (irAE) in patients randomized to atezolizumab (39.9% vs 24.5%). There were no new safety signals from atezolizumab observed in this trial. Given the familiarity already with immune checkpoint inhibitors in the management of NSCLC, there would be no new safety concerns in implementing atezolizumab in the treatment of SCLC.

Network meta-analysis

A network meta-analysis was conducted looking at alternate treatment options to carboplatin and etoposide. This identified only four studies and is of limited utility. Most clinicians would consider cisplatin and carboplatin as interchangeable in the management of SCLC. The focus on carboplatin-based regimens in the network meta-analysis was at the exclusion of other trials evaluating cisplatin and irinotecan and therefore somewhat incomplete. Additionally, several of the trials evaluating irinotecan in SCLC have been conducted in Japanese or other Asian countries, where pharmacogenomic differences exist that may account for improved efficacy of irinotecan. Within the Canadian landscape, irinotecan is infrequently used in the initial management of SCLC because of concerns around toxicity and a lack of clear superiority. That said, the network meta-analysis favoured carboplatin, etoposide and atezolizumab for OS, which is the outcome most valued by clinicians.

Overall, the data from IMpower133 support the implementation of atezolizumab in combination with platinum and etoposide chemotherapy as first-line therapy for ES SCLC.

The data on OS and PFS favour the addition of atezolizumab. The improvement in PFS was small. However, this has also been observed in other trials of immunotherapy in lung cancer, where significant improvements in OS were observed.[11] The improvement in OS is more meaningful than the improvement in PFS. There are some advantages in global health related QoL favouring atezolizumab. There is no increase in overall incidence of AEs, although there is a predictable increase in the risk of irAE of approximately 15-20%.[17,18] This seems acceptable in the setting of improved OS. The magnitude of benefit for OS appears modest at present. However, the HR of 0.70 is greater than the minimum clinically significant benefit (HR<0.76-0.80) as defined by ASCO, although the absolute difference is less than 2.5-3.0 months.[22] The survival of patients with SCLC though, is typically less than NSCLC and the relative improvement in OS is more important. The median follow-up is still short and so the estimates of OS beyond 15 months are imprecise. Longer follow up will be required to understand if these findings translate into a meaningful difference in OS beyond two years, as has been observed in trials of immune checkpoint inhibitors in NSCLC.[23]

There is a strong need for improved treatments in SCLC. The addition of atezolizumab represents the first improvement in systemic treatment options for SCLC in over 20 years. A large number of patients have potential for improved treatment, given the prevalence of SCLC in the Canadian population.

There are some questions that cannot be answered directly from the IMpower133 trial data:

- Canadian patients with ES SCLC are frequently treated with cisplatin and etoposide, instead of carboplatin and etoposide. These regimens are considered to be similarly effective. There is no reason to not extrapolate the IMpower133 data to patients receiving cisplatin and etoposide, as well as carboplatin and etoposide. Additionally the standard of care is to administer four to six cycles of chemotherapy. There should be flexibility to allow up to six cycles of chemotherapy in combination with atezolizumab.
- LCC suggested that there are some patients who may not have received atezolizumab in the first-line setting, or did not receive maintenance atezolizumab and these patients might be candidates for atezolizumab together with carboplatin and etoposide at relapse. The CGP believes there are no data to answer that question, but would not recommend atezolizumab in the second-line setting.

1.3 Conclusions

The Clinical Guidance Panel believes there is a net clinical benefit for atezolizumab in combination with platinum and etoposide chemotherapy compared with platinum plus etoposide as first-line therapy for ES SCLC. There is a modest improvement in median OS (10.3m vs 12.3m, HR 0.70, 95%CI 0.54-0.91) for patients treated with carboplatin, etoposide and atezolizumab, compared with carboplatin and etoposide. The median follow-up is short and the OS estimates beyond 15 months are imprecise. Therefore, it is difficult to know whether there will be a proportion of patients deriving longer term benefit, as has been seen in trials of immune checkpoint inhibitors in NSCLC. Modest improvements in PFS (median PFS 4.3m vs 5.2m, HR 0.77, 95%CI 0.62-0.96) and health related QoL are supportive of the recommendation. The improved efficacy is observed with an acceptable toxicity profile that is largely reflective of the expected AE profile for carboplatin and etoposide. These are expected immune related AEs that oncologists are already familiar with managing. SCLC represents are significant health burden. Estimates

are that over 1600 patients annually across Canada might benefit from the addition of atezolizumab to platinum and etoposide chemotherapy. Therefore, this new option for treatment has the potential to improve on a significant unmet need. Atezolizumab would insert into the existing first-line treatment of ES SCLC, in combination with a platinum agent plus etoposide, with ECOG PS 0-2, stable treated brain metastases and no contraindications to the use of an immune checkpoint inhibitor.

In their feedback on the Initial Recommendation, the sponsor, the patient groups from LCC and OLA, and the registered clinicians from LCC highlighted the high unmet need in the present target population. It was noted that given the aggressive and fast-growing nature of ES-SCLC, which is associated with poor survival, the lack of advancement in treatments for ES-SCLC in the past 20 years and the fact that atezolizumab did not introduce new safety concerns, even a marginal survival benefit is considered significant in this therapeutic context. In response to the stakeholders' feedback, the CGP agreed with the feedback noting that there is a significant, albeit modest, improvement in OS which is clinically meaningful.

CADTH received a procedural review request from the sponsor on December 16, 2019. The procedural review request was accepted by CADTH, and it was determined that the submission needed to be re-deliberated by pERC at its next available meeting on January 16, 2020 (for more details see pages 4 and 5 of this CGR). In response to the procedural review request from the sponsor, the CGP has reconsidered their CGP conclusion in the context of OS landmark analyses at 18 and 24 months. These OS data had previously not been included in the materials that form the 'pERC Brief'. The Clinical Guidance Panel noted that at 18 months there was an estimated 13% absolute improvement in OS in favour of the atezolizumab treated patients (34% vs 21%). At 24 months, the absolute improvement in OS was 5% (22% vs 17%).[6] The CGP agreed that these data support their initial opinion that, compared with platinum plus etoposide, there is a real but modest improvement in survival for patients treated with atezolizumab in combination with carboplatin and etoposide as first-line therapy for ES-SCLC. The CGP agreed to uphold their initial conclusion.

Provincial Advisory Group's (PAG's) Implementation Questions:

1. If recommended for reimbursement, PAG noted that patients currently receiving platinum-based chemotherapy (cisplatin/carboplatin plus etoposide) would need to be addressed on a time-limited basis. Please confirm.
    - **Response:** At the time of implementation of atezolizumab, there will be a pool of patients currently receiving first-line therapy with platinum and etoposide. The CGP believes that patients still receiving first-line chemotherapy should be allowed to add atezolizumab into their treatment. This would be a time limited need

2. There is a potential for indication creep, as clinicians may want to use atezolizumab in the second-line setting as monotherapy or in combination with topotecan following progression on platinum-based chemotherapy.
    - **Response:** PAG raised the issue of the potential for creep in indications. There are no data on the use of atezolizumab in LS SCLC, or as second-line therapy. The CGP would not recommend the use of atezolizumab in LS SCLC or second-line therapy at this time.
3. PAG is seeking clarity on treatment duration and treatment until "loss of clinical benefit"

with a definition of disease progression. What stopping rules should be used for atezolizumab in the maintenance setting and are the usual immunotherapy stopping rules appropriate (10% increase in total tumour burden confirmed with a second CT scan 6-8 weeks following the last scan if progression is suspected)?

- **Response:** In IMpower133 treatment was continued until progression, or unacceptable toxicity. Treatment beyond progression was allowed if the patient had ongoing clinical benefit. In practice, only a small proportion of patients continued treatment beyond one year. There may be some patients who do benefit from treatment beyond progression, although SCLC typically progresses rapidly. While we do not have specific data on how long treatment was continued beyond progression, it is likely to be only a few months. The CGP believes some discretion should be allowed to the treating physician to continue atezolizumab beyond progression. It is hard to define discreet criteria for this though.

4. Atezolizumab is an add-on therapy which would require additional healthcare resources such as nursing, pharmacy, clinic visits, and supportive care. Additional resources would be required for drug preparation, drug administration, and monitoring and management of infusion related reactions as well as immune related adverse events.

   Response: The addition of atezolizumab may add an extra hour of chair time to existing chemotherapy treatments. For patients continuing on to maintenance atezolizumab, this would represent incremental use of chemotherapy suite, clinic and pharmacy resources. However, the median number of doses of atezolizumab was only 7, with a median number of four cycles of chemotherapy. Therefore, the incremental use of resources is modest.

5. PAG is seeking guidance on second-line treatment options following platinum-based chemotherapy with atezolizumab.

   Response: The addition of atezolizumab to platinum and etoposide therapy is unlikely to influence second line treatment options. At present patients with potentially sensitive disease (relapse > three months from completion of treatment) may be retreated with platinum and etoposide. Alternative treatment options include cyclophosphamide, doxorubicin and vincristine, or topotecan (not funded in all provinces). These options should not change.

2 BACKGROUND CLINICAL INFORMATION

This section is completed early in the review. In addition to providing context for pERC, it can provide direction to the Methods Team and the Economic Guidance Panel on important points to consider while conducting the systematic review and economic evaluation. It is not intended to be a full systematic review; however, it should be evidence- based and thoroughly referenced.
This section was prepared by the pCODR Lung Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Lung cancer represents the second most common cause of cancer among both men and women in Canada, but the largest cause of death from cancer. In 2016, there were approximately 28,400 new cases of lung cancer and 20,800 deaths from lung cancer.[24] Small cell lung cancer (SCLC) accounts for only 12-15% of lung cancer cases.[10,25] Nevertheless, this still represents a significant health burden, with over 4,000 cases annually across Canada.[26] Historically a treatment based staging system developed by the Veterans Affairs Lung Cancer Study Group (VALCSG) was used in SCLC.[27] Patients with disease confined to one hemithorax that could be encompassed in a single radiation field, were classified as limited stage (LS) disease, and everything else was classified as extensive stage (ES) disease. In recent years, there is some movement toward anatomic staging, using the Tumour, Node (lymph node), and Metastasis (TNM) system.[28] Most clinical trials though, still select patient populations based on the VALCSG classification of LS and ES.

Approximately one third of patients have LS SCLC at presentation, whereas two thirds have ES disease.[10] The median age of diagnosis of SCLC is approximately 70 and this is a disease with a strong association with tobacco usage. The expected five year survival of LS SCLC is approximately 20-25%. However, there are few five year survivors with ES SCLC and the median survival is between 10-12 months.

2.2 Accepted Clinical Practice

Typically, surgery does not have a major role to play in the management of SCLC,[29] although there is some controversy about surgery in patients with small tumours less than 2-3cm. In general, patients with LS SCLC are treated with a combination of platinum-based chemotherapy together with thoracic radiation (TRT), whereas patients with ES SCLC are treated with chemotherapy alone.[9] While there is a high likelihood of response to therapy, the risk of recurrence is high. In ES SCLC, the median time to progression is typically between 4 to 5 months with median OS between 10-12 months. Survival beyond 2 years is generally no more than 15%. Patients with SCLC are also at high risk for the development of brain metastases and a meta-analysis of randomized trials supports the use of prophylactic cranial irradiation (PCI) in LS SCLC patients achieving a complete response to their initial chemoradiation therapy.[30] There has been an expanded role for radiation in ES SCLC in the last decade with randomized trials demonstrating a modest improvement in overall survival (OS) from PCI in patients responding to initial chemotherapy[31] and a suggestion of improved OS from thoracic radiation.[32] The gains in OS from these treatments are modest and selection of patients most likely to benefit remains challenging.

A platinum agent (cisplatin or carboplatin) in combination with etoposide has been the standard of care systemic therapy for SCLC for several decades.[9,33,34] However, little

progress has been made recently in the systemic treatment and outcomes for ES SCLC.[8] A variety of strategies have been evaluated over the last 20 years including the use of non cross-resistant chemotherapy,[35] intense weekly chemotherapy,[36,37] maintenance chemotherapy[38] and high dose chemotherapy with transplantation.[39] None of these strategies have resulted in clear improvements in OS for patients with SCLC. Unlike NSCLC, where molecularly targeted therapies have significantly improved treatment outcomes for patients with advanced disease, multiple trials of agents targeting a variety of molecular abnormalities have all failed to show any improvement in treatment outcomes for patients with SCLC.

The majority of patients with SCLC will relapse. Further chemotherapy is frequently given at the time of relapse. Modest improvements in OS were observed in a trial of oral topotecan versus best supportive care.[40] Combination chemotherapy with cyclophosphamide, doxorubicin and vincristine (CAV), or alternatively intravenous topotecan represent the most common second-line chemotherapy options.[41] Additional agents such as amrubicin have failed to show any improvement in OS over topotecan.[42] Therefore there is a real need for improved treatment for SCLC.

Given the success of immune checkpoint inhibitors (ICI) in NSCLC, there is much interest in evaluating these agents in SCLC as well. A randomized phase II trial of carboplatin, paclitaxel with or without ipilimumab as initial therapy in patients with ES SCLC demonstrated some improvement in progression free survival (PFS) for the triplet regimen (HR 0.64, 95%CI 0.40-1.02), however the difference in median PFS was only 6.4 months versus 5.3 months.[43] A subsequent randomized phase III trial of cisplatin, etoposide with, or without ipilimumab failed to demonstrate any improvement in OS for the addition of ipilimumab (HR 0.94, 95%CI 0.81-1.09, median OS 11.0 vs 10.9m).[19] In the relapsed SCLC setting, the data from a non randomized trial shows activity for the combination of nivolumab plus ipilimumab.[20] Objective responses (ORR) were observed for both single agent nivolumab (10%, 95%CI 5-18%), as well as the combination of nivolumab plus ipilimumab (23%, 95%CI 13-36%). Median PFS figures ranged from only 1.4 to 2.6 months and median OS ranged from 4.4 to 7.7 months. However, a smaller proportion of patients appeared to derive longer term benefit, with 30% of patients treated with nivolumab plus ipilimumab remaining alive at two years. Further evaluation of nivolumab plus ipilimumab is ongoing. There are additional trials ongoing evaluating other immune checkpoint inhibitors in combination with platinum-based chemotherapy, or as maintenance therapy following platinum-based chemotherapy.

In their feedback on the initial recommendation, the sponsor noted that immunotherapies in later lines of SCLC have demonstrated a promising flattening of the survival curves (CHECKMATE-032[20], KEYNOTE-028[44], KEYNOTE-158[21], and CHECKMATE-331[55]) suggesting that there is a durable and long-term survival benefit in some treated patients. The sponsor further noted that it appears reasonable to predict that a similar plateauing of survival curves would be seen in patients treated with atezolizumab in combination with with a platinum-based chemotherapy and etoposide in first-line ES-SCLC. In response to the sponsor's feedback the CGP noted that a patient on 3rd line treatment for SCLC has likely a slower growing tumor than patients in the first line (especially when prior treatments were all chemotherapy regimens). Therefore, the CGP cautioned against drawing firm conclusions from cross-trial comparisons including patients on different lines of therapy for SCLC.

Several trials in patients with NSCLC support the addition of an ICI to chemotherapy.[17,18,45] The Impower133 trial evaluated the addition of atezolizumab to carboplatin, and

etoposide chemotherapy in good performance status patients with ES SCLC. There were 403 patients with ES SCLC randomized to carboplatin, etoposide and placebo, or carboplatin, etoposide and atezolizumab. There was no significant difference in ORR (64.4% vs 60.2%). PFS was modestly improved (median PFS 4.3m vs 5.2m, HR 0.77, 95%CI 0.62-0.96) and there was a significant improvement in OS (median OS 10.3m vs 12.3m, HR 0.70, 95%CI 0.54-0.91). Some increased immune related adverse events (irAE) were observed, but no major differences in expected chemotherapy related AEs. Biomarker testing, did not identify a subgroup more likely to benefit. The improvement in OS is modest but this represents the first trial to demonstrate an improvement in OS in ES SCLC in several decades. Atezolizumab would represent an additional agent added into the first line therapy of ES SCLC.

Patients with extensive stage small cell lung cancer		
Line of Therapy	Current state	Proposed future sate
1st-Line	Platinum agent (cisplatin or carboplatin) plus etoposide	Platinum agent (cisplatin or carboplatin) plus etoposide plus atezolizumab
2nd-Line	Cyclophosphamide, doxorubicin and vincristine or topotecan	Cyclophosphamide, doxorubicin and vincristine or topotecan
3rd -Line	No established third line therapy	No established third line therapy

It is acceptable to use clinical practice guidelines as references for this section. Evidence-based guidelines should be used whenever possible and levels of evidence should be indicated.

2.3 Evidence-Based Considerations for a Funding Population

There are approximately 28,800 new cases of lung cancer annually in Canada.

Proportion of SCLC (15%)	4,320
Proportion with ES SCLC (67%)	2,895
Proportion receiving treatment (73%)[10]	2,113
Proportion with ECOG PS 0-2 (75%)	1585

Based on the above assumptions, there are approximately 4320 patients annually in Canada with SCLC. If two thirds of these patients have ES SCLC and 73% of patients receive some systemic therapy (based on Ontario data from ICES),[10] there are approximately 2113 patients with ES SCLC who receive systemic therapy. From Ontario data, 20% of patients initiate chemotherapy in hospital. Assuming this is a surrogate for poor performance status, then there are approximately 1585 patients with ES SCLC who could be eligible for the addition of atezolizumab to platinum plus etoposide chemotherapy. There are no biomarkers for selection of patients for chemotherapy plus atezolizumab. The number treated will likely be lower, as some of these patients may have contraindications to the use of atezolizumab.

2.4 Other Patient Populations in Whom the Drug May Be Used

There are currently no approved indications for an immune checkpoint inhibitor in SCLC. The Impower133 trial was limited to patients with ES SCLC and performance status 0-1. These patients are easily identified. There is no clear reason not to consider this therapy in PS 2 patients and this would be consistent with guideline recommendations for the treatment of patients with lung cancer.

There is some potential for creep in the patient population offered atezolizumab. Poor PS patients often respond rapidly to therapy with an associated improvement in PS. There will be some potential for physicians to extrapolate the Impower133 data to these patients. The data does not apply to LS SCLC. There is some potential to extrapolate to patients with LS SCLC. However, these patients are also treated with radiation and there is a paucity of data for combinations of radiation and an ICI, so this is less likely.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Lung Cancer Canada (LCC) and the Ontario Lung Association (OLA), provided input for atezolizumab (Tecentriq) with etoposide and a platinum-based chemotherapy for the first-line treatment of patients with small cell lung cancer (SCLC).

OLA obtained information from four phone interviews: one with a patient living with lung cancer completed in November 2018, one with a caregiver of a patient living with lung cancer completed in March 2019, and two with patients living with chronic lung conditions completed in March 2019; upon follow-up with OLA it was confirmed that the two patients with chronic lung conditions were living with chronic obstructive pulmonary disease (COPD). OLA also included input obtained from online surveys completed by 115 respondents living with a chronic lung condition, or their caregivers between December 2018 and February 2019. Most respondents (88%) indicated living with a chronic lung disease; three of the 115 respondents indicated living with lung cancer. OLA also incorporated input from a certified respiratory educator who reviewed sections related to disease experience and experiences with available treatments and outcomes. All data gathered by OLA were from Canadian respondents. None of the respondents on behalf of OLA reported experience with atezolizumab.

LCC obtained information from respondents via the following sources:

- The Faces of Lung Cancer Survey is a nationally conducted survey on lung cancer patients and caregivers completed in August 2015. A total of 91 patients, all of whom were currently living with or previously had lung cancer, and 72 caregivers, who were currently caring for had cared for patients with lung cancer, completed the survey.
- Two previous submissions provided to pCODR on behalf of patients with non-small cell lung cancer (NSCLC) who were treated with chemotherapy and immunotherapy, and patients with NSCLC who were treated with atezolizumab.
- An environmental scan retrieving input from five caregivers, three of whom were male and two who were female, and one male patient. The one male patient had experience with chemotherapy as a treatment. The ages of these respondents were unknown, except for one female caregiver who was 48 years old.
- Interviews of one female patient aged 62 and one female caregiver whose age was unknown. The patient and caregiver interviewed had experience with combination therapy of atezolizumab and chemotherapy as a second-line treatment.

In total, LCC incorporated input from eight participants. LCC noted that they experienced difficulty sourcing patients for this submission. Section 3.2 discusses patients with NSCLC who had experience with single agent atezolizumab. LCC stated that experiences of NSCLC patients would still be relevant to discuss regarding SCLC patients. One patient with SCLC was interviewed by LCC who had experience receiving the combination treatment of atezolizumab and chemotherapy.

LCC and OLA noted that, from a patient's perspective, SCLC is an aggressive condition with limited treatment options available for patients. The fear and stress experienced by patients and caregivers related to receiving a diagnosis of SCLC was mentioned by both LCC and OLA, as SCLC is associated with poor survival. Symptoms of lung cancer were stated to impact patient's ability to engage with family and friends, take part in daily activities or work. Immunotherapy and chemotherapy were treatments patients had received to treat their SCLC. Both chemotherapy and immunotherapy were stated to be effective, however, side effects of immunotherapy were much more tolerable, with some patients being able to resume their daily tasks. Only patients on behalf of LCC reported having experience with atezolizumab, however, quotes and experiences were mostly reported by patients diagnosed with NSCLC; only one patient had received atezolizumab in combination with chemotherapy and was diagnosed with SCLC. LCC stated that they did not

believe there to be any reason why experiences would differ greatly between patients with NSCLC and SCLC, however, no evidence was provided to support their belief. Patients with NSCLC reported that atezolizumab was effective, with some patients experiencing positive responses relatively quickly. Side effects were reported to be few, tolerable and manageable. In general, patients found that they were able to engage in daily activities, including going back to work. The patient who was diagnosed with SCLC and received atezolizumab in combination with chemotherapy reported significant tumour shrinkage, but experienced significant side effects that required hospitalization. Despite the experienced side effects and hospitalization, this patient expressed that receiving atezolizumab was a good opportunity.

In terms of expectations for alternative treatment options, OLA and LCC highlighted the following patient values: extension of life, improvement of QoL, manageable side effects, and additional and affordable treatment choices. An overarching theme of hope was discussed, as patients and caregivers felt grateful to have a treatment that allowed them to partake in normal daily tasks and allowed them to live longer in hopes of receiving a new treatment if needed in the future.

Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Lung Cancer

LCC highlighted the aggressive nature of SCLC and the few treatments available for patients. Both LCC and OLA indicated that fear and stress patients and their families feel when diagnosed with SCLC as SCLC carries poor survival outcomes for patients. OLA highlighted feelings of frustration expressed by patients and caregivers related to the number of appointments and length of time it takes to receive an accurate diagnosis. *"It took close to a year, with many appointments and referrals to finally get to the right specialist and receive a proper diagnosis and learn about my prognosis."* In addition, respondents expressed feeling rushed during appointments, and would appreciate receiving information in a language that is understandable to them with a clear idea of their treatment choices.

Symptoms of lung cancer identified by LCC and OLA include pain, which could be very intense at times, chest pain and chest tightness, shortness of breath, hoarseness and coughing up blood, sleep disturbances, increased triggers within the air or to allergens, weakness, extreme fatigue or exhaustion. Due to the rapid progression of the SCLC, LCC stated that patients usually present early with fatigue and weight loss. Some symptoms were stated to be dependent on the location or organs affected. Symptoms were also stated to be fluctuating frequently, rather than fixed or consistent, making them difficult to manage. Specifically, extreme fatigue was described as difficult to handle, as patients had to plan their day around managing their exhaustion. *"If I go out in the morning, that's it for the day. I do not have the energy to do anything else."* Managing symptoms of loved was also takes a toll on caregivers, as one caregiver stated, *"Before my husband passed away from his lung cancer, all I did was care for him. It was an all-consuming job."*

OLA identified aspects of daily living affected by lung cancer, such as the ability to work, travel, socialize and participate in leisure and physical activities. In addition, relationships with family and friends, independence, the emotional well-being and the financial situation of patients and families are affected. *"it affects every aspect of my day to day life. It takes longer to get dressed and do my personal hygiene. My ability to carry out*

daily tasks and activities is greatly reduced and I can no longer lift heavy objects. I can't walk distances and get tired very quickly."

Patients interviewed by OLA expressed a need for greater information to help with understanding the disease and making decisions about next steps. Respondents expressed that they did not receive sufficient information about lung cancer or cancer in general, treatment options, and the eventual prognosis in terms that would apply to them. LCC highlighted an unmet need among SCLC patients as they currently have limited treatment options with poor prognosis for survival.

3.1.2 Patients' Experiences with Current Therapy for Lung Cancer

The following treatments were reported by respondents of OLA: Spiriva, Advair, Symbicort, Daxas, Prednisone, Ventolin as needed, Atrovent, Serevent, Onbrez, and Tudorza. One patient was unable to list all medications as the list of medications they were on was so extensive. One patient was undergoing radiation, while another had received a double lung transplant in early 2018. These treatments were stated to be effective at providing some relief for symptoms of lung cancer, including fatigue, shortness of breath, cough, appetite loss and low energy. However, other symptoms were stated to require better management, including palpitations, dry mouth, mouth sores, "light-headedness" or "dizziness", shakiness and impact on mood. Other side effects reported were loose bowels, headaches and difficulty sleeping.

LCC reported patient experiences with immunotherapy and chemotherapy. Patients with SCLC were seemed to report that chemotherapy was effective at treating their cancer. Three patients were reported to respond well to chemotherapy, with patients experiencing reductions in tumour size and improvement in symptoms; these patients did eventually experience progression. One patient recently had a clear scan after treatment with chemotherapy. Another patient was also reported to experience tumour shrinkage with chemotherapy and were able to engage in activities, such as bowling, golfing and riding; however, this patient does worry about the possibility of progression. According to LCC, side effects of chemotherapy are well-documented with some patients experiencing minimal symptoms while others report symptoms consistent with other cases of patients on chemotherapy including nausea, vomiting and fatigue. One respondent commented that her mother experienced some sickness and hair loss, but found the symptoms to be manageable overall. Alternatively, another patient reported feeling very sick while receiving chemotherapy, describing it as "awful" and was bedridden for two months. Some respondents on behalf of LCC reported experiencing nausea, fatigue, dizziness, shortness of breath and hair loss. Anti-emetics helped one patient cope with the nausea. Patients' ability to work can also be affected while receiving chemotherapy, which can affect the financial stability of patients and their families. Chemotherapy was also stated to impact patients' immune systems, in some cases completely whipping out patients' white and red blood cells. The immune related side effects were stated to inhibit a patients' ability to go out, return to work, have visitors and spend quality time with friends and family. One patient with NSCLC was admitted for ten days and had to stop treatment with chemotherapy as their white and red blood cell levels were so low.

LCC commented on the efficacy of immunotherapy based on input from NSCLC patients obtained from previous submissions made to pCODR. Overall, comments stated immunotherapy was effective at controlling the cancer. Responses ranged from no change in tumour size but disease control, to no evidence of disease. Despite seeing no change in tumour size, one patient stated that scans showed she was stable; this patient stated, *"This was my new normal"* and *"better than the alternative."* This patient was able to get

"back to the basics of life" and resume completing small chores. Symptoms of disease were stated to improve within days of patients' first treatment. One patient, who had a severe cough and lost weight, experienced improvement in his cough which allowed him to have a more normal family life. Side effects of immunotherapy were stated to be mild and easily manageable. Stronger side effects reported by some were managed by over the counter medications or prescription drugs. Management of side effects were in general tolerable, did not interfere with day-to-day life, and allowed for patient to have a *"good"* quality of life. One SCLC patient stated that immunotherapy was easier to tolerate compared to previous treatments, with her only side effect being a rash which was treated with antihistamines.

OLA highlighted that patients would appreciate treatments with fewer adverse events and the ability to maintain quality of life. Training for general practitioners was suggested to help reduce unnecessary delays in diagnosis of patients, and better communication between doctors and patients so patients can understand their diagnosis and prognosis in terms that apply to them. Finally, OLA identified the solitude, and feelings of isolation and loss independence leading to depression for patients.

3.1.3 Impact of Lung Cancer and Current Therapy on Caregivers

The emotional and physical toll of caregiving affects caregiver's ability to fulfil familial roles, work and engage in activities they enjoy leading to chronic stress. LCC also identified the stigma experienced by caregivers due to the negative implications associated with lung cancer. Caregivers may feel isolated due to the burden of experiencing unconscious attitudes directed towards the patient or their loved ones. The isolation felt by caregivers could lead to anxiety, worry and even depression. As both chemotherapy and immunotherapy are given to patients intravenously, caregivers must also balance work and family tasks with appointments. Overall, caregivers are affected psychologically, behaviourally and physiologically, and must juggle competing priorities with caregiving potentially impacting family finances due to taking time off work to take their loved ones to appointments, or help with other caregiving tasks.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Atezolizumab

No patients from the OLA submission reported experience with atezolizumab. LCC included input from NSCLC patients who received single agent atezolizumab as they experienced difficulty finding SCLC patients who had experience with atezolizumab. However, LCC stated that they did not believe there would be any reason as to why this group of patients would be any different.

According to LCC, patients not only responded to atezolizumab, but did so relatively quickly. The following are quotes from two separate NSCLC patients: *"It obviously worked. In my case, my tumours reduced 65% in 6 weeks." "(Atezolizumab) worked. My hair grew back thicker (after losing it to chemotherapy) and everything started to get back to normal."* One patient stated that within three months of treatment, he was 95%-100% of how felt before his diagnosis. Atezolizumab was effective at treating patient's lung cancer, with results ranging from slight shrinkage of tumours up to around 60% reduction in size, and in some cases patients showed no evidence of disease.

On behalf of patients with NSCLC, side effects were fewer, tolerable and more manageable and allowed patients to return to life. One patient reported side effects including having no appetite and severe fatigue, however found atezolizumab to be overall effective at treating his cancer. Two patients stopped treatment due to side effects of hyperthyroidism and a serious auto-immune condition; both patients were declared No Evidence of Disease (NED) at the point of their discontinuation of atezolizumab. Patients reported being able to return to work while receiving treatment and were able to drive themselves to treatments. LCC highlighted that atezolizumab allowed patients to live longer, spend time with loved ones and provided them with hope.

One female patient 62 years of age with SCLC with experience with atezolizumab and chemotherapy in combination was interviewed by LCC. The patient was given four cycles of the combination therapy and demonstrated significant tumour shrinkage at a follow-up scan. The patient is currently receiving atezolizumab maintenance therapy. Side effects experienced by this patient included flu like symptoms, pneumonia, anemia which required a blood transfusion, and shingles. The patient was weak and had to be taken to the emergency for treatment. LCC reported that the patient was glad to have the opportunity to receive atezolizumab combined with chemotherapy despite having experienced side effects.

3.3 Additional Information

While LCC had difficulty finding patients for this submission, they identified the following needs expected from new treatments for SCLC patients: improved symptoms, better survival rates, better quality of life and more manageable side effects. OLA stated that stopping or slowing of progression, reduction of pain, fatigue, cough and shortness of breath, and improvement in appetite and energy were key treatment outcomes patients and caregivers would like addressed. Specifically, emphasis was placed on energy levels, as all patients OLA spoke to via telephone expressed a desire for more energy. Patients and caregivers would like the following side effects reduced or eliminated: pain, fatigue, nausea, shortness of breath, appetite loss, low energy, inability to fight infection, burning of skin, and impacts on mood. Patients and caregivers would also appreciate reduced or no cost burden associated with new treatments.

In addition to expectations for new treatments, OLA described expectations for a better coordinated health system incorporating more respiratory and lung cancer specialists. Patients would like the option of conducting treatments at home, removing the need for patients and caregivers to take time off work, and reducing the disruption of the daily routine. Similarly to LCC, OLA also identified the importance of maintaining quality of life for patients.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a reimbursement recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Generalizability of trial results to cisplatin/etoposide

Economic factors:

- Treatment duration and stopping rules for maintenance atezolizumab

Please see below for more details.

4.1 Currently Funded Treatments

The current standard of care for chemotherapy-naïve patients with extensive stage small cell lung cancer (SCLC) is platinum-based chemotherapy (e.g., cisplatin/etoposide; carboplatin/etoposide). The IMpower133 trial assessed carboplatin/etoposide with or without atezolizumab. In some jurisdictions cisplatin/etoposide is commonly used, PAG is seeking generalizability of trial results to cisplatin/etoposide with atezolizumab.

4.2 Eligible Patient Population

The IMpower133 trial included patients with extensive-stage SCLC as well as ECOG PS of 0-1, PAG is seeking guidance on whether atezolizumab would be limited to these patients or whether atezolizumab would be offered to patients with limited-stage SCLC or ECOG PS of 2. The pivotal trial also included patients with a history of treated asymptomatic CNS metastases. PAG is seeking guidance whether patients requiring radiation for local symptomatic control, prophylactic cranial irradiation, or whole brain radiation, would be eligible for atezolizumab.

If recommended for reimbursement, PAG noted that patients currently receiving platinum-based chemotherapy (cisplatin/carboplatin plus etoposide) would need to be addressed on a time-limited basis.

There is a potential for indication creep, as clinicians may want to use atezolizumab in the second-line setting as monotherapy or in combination with topotecan following progression on platinum-based chemotherapy.

4.3 Implementation Factors

Atezolizumab is administered every three weeks and at the same dose (1200mg) for all patients. Maintenance atezolizumab is recommended to be continued until loss of clinical benefit or unacceptable toxicity. PAG noted that there would be no drug wastage as atezolizumab is supplied as 1200mg vials.

PAG is seeking clarity on treatment duration and treatment until “loss of clinical benefit” with a definition of disease progression. What stopping rules should be used for

atezolizumab in the maintenance setting and are the usual immunotherapy stopping rules appropriate (10% increase in total tumour burden confirmed with a second CT scan 6-8 weeks following the last scan if progression is suspected)?

Additional chair time is required during the maintenance phase as patients treated with platinum-based chemotherapy do not currently receive any maintenance treatment following four cycles of therapy.

Atezolizumab is an add-on therapy which would require additional healthcare resources such as nursing, pharmacy, clinic visits, and supportive care. Additional resources would be required for drug preparation, drug administration, and monitoring and management of infusion related reactions as well as immune related adverse events.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on second-line treatment options following platinum-based chemotherapy with atezolizumab.

4.5 Companion Diagnostic Testing

PAG would like confirmation that PD-L1 testing is not required.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One joint clinician input on behalf of five clinicians from Lung Cancer Canada (LCC) and one single clinician input were provided for the review of atezolizumab (Tecentriq) in combination with chemotherapy for first-line treatment of extensive stage small cell lung cancer (ES-SCLC). A total of six clinicians provided information and their input is summarized below. Both inputs indicated having experience with using atezolizumab. The current standard of care for patients with ES-SCLC in the first-line was stated to be platinum-based chemotherapy. Eligibility criteria for patients from the IMpower133 trial were stated to be reasonable and reflective of clinical practice. However, the clinicians expressed a desire to extrapolate evidence from the IMpower133 trial to patients with an ECOG performance status of 2 or 3, as the IMpower133 trial included only patients with an ECOG performance status of 0 or 1. The IMpower133 trial also only included patients who received carboplatin, whereas the clinicians providing input suggested that patients receiving cisplatin should also be eligible for atezolizumab. Finally, treatment with atezolizumab and chemotherapy for patients with brain metastases was supported by both clinician inputs. General stopping rules for immunotherapy were stated to be reasonable stopping rules for atezolizumab in this setting. Unmet need among patients with ES-SCLC was highlighted by both LCC and the single clinician input, as the condition is an aggressive subtype of lung cancer with a median survival of less than one year, and with little significant advances in treatments for decades.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatment(s) for Small Cell Lung Cancer

Both clinician inputs identified platinum-based chemotherapy as the standard of care; specifically, etoposide with either cisplatin or carboplatin, for between four to six cycles. Patients who cannot receive platinum-based chemotherapy regimens may also receive anthracycline-based treatments, of which the combination treatment of cyclophosphamide, Adriamycin (doxorubicin) and vincristine (CAV) was stated to be the most common.

5.2 Eligible Patient Population

The single clinician input noted the inclusion criteria from the trial were reasonable and aligned with needs of clinical practice. LCC highlighted the following inclusion criteria: patients with good performance status as per ECOG performance score of 0 or 1, good organ function, and treatment prior to enrolment if patients presented with brain metastases. The single clinician input agreed that eligible patients should include those with ECOG performance status of 0 or 1, however stated that they would like to include patients with an ECOG performance status of 2. LCC agreed with extrapolating the use of atezolizumab in combination with chemotherapy among a wider population than defined by the study, specifically: patients receiving either cisplatin or carboplatin should be eligible for atezolizumab, and patients with an ECOG performance status of 2 or 3 at diagnosis should receive induction chemotherapy with the option of adding atezolizumab if an early response is achieved with a concurrent improvement in performance status. According to clinicians from LCC, clinicians are willing to treat SCLC patients with a poor performance status and poorer organ function because patients experience a rapid and predictable response to treatment.

All patients in the trial received carboplatin, representing a sizable subset of patients in clinical practice. However, LCC identified a substantial group of patients that could be treated with etoposide and platinum chemotherapy that could not have been eligible for the study. In general, the variation of using cisplatin or carboplatin with etoposide is well established in practice, and both platinum agents are available in new treatment algorithms.

5.3 Relevance to Clinical Practice

Unmet need among patients with ES-SCLC was highlighted by both LCC and the single clinician input, as the condition is an aggressive subtype of lung cancer with a median survival of less than one year, and with little significant advances in treatments for decades. Atezolizumab is used in Canada as a second-line treatment for NSCLC and available through a compassionate access program. Clinicians on the joint input stated to have experience with atezolizumab through clinical trials. The joint input stated that atezolizumab combined with chemotherapy significantly improves survival compared to the current standard platinum etoposide doublet. The safety and tolerability of chemotherapy and immunotherapy agents have been well-established, and clinicians now have broad experience with chemotherapy and immunotherapy agents, alone or in combination. The single clinician input stated that benefits of atezolizumab were modest, with minimal increase in adverse events, and that there are currently no superior treatment options.

According to LCC, contraindications to atezolizumab combined with chemotherapy are standard contraindications with immunotherapy, for example pre-existing and active autoimmune conditions. For patients with a contraindication to chemotherapy, it is unlikely that immunotherapy would be provided to patients as a monotherapy unless it was through a clinical trial. The single clinician input also recognized that immune-related contraindications will be important to consider.

5.4 Sequencing and Priority of Treatments with Atezolizumab

The single clinician input stated that atezolizumab would not replace any current treatments, but that it would be given to patients concurrently with available therapies. LCC agreed that sequencing would not be an issue with atezolizumab, as it would be added to first-line platinum and etoposide chemotherapy. Further lines of therapy would be unchanged from current standards of practice. Anthracycline-based treatment or topotecan are currently included as second-line practice. The single clinician input stated that if patients do not begin treatment with atezolizumab in their first cycle, they should be given atezolizumab during the second cycle of treatment.

The joint clinician input acknowledged that there are some patients who respond well to first-line platinum and etoposide chemotherapy in the first-line and experience a durable period of response. When patients experience progression, LCC stated that they are rechallenged successfully with platinum and etoposide. In the IMpower133 study, after patients received initial chemotherapy they were provided atezolizumab maintenance treatment. The joint clinician input state that if patients progress while receiving atezolizumab maintenance, they could still be rechallenged with platinum and etoposide alone in the second-line setting. There may be rare situations where patients receive platinum etoposide chemotherapy and atezolizumab in the first-line setting, but do not receive maintenance with atezolizumab. In such scenarios, it was suggested that if these patients are rechallenged with platinum etoposide chemotherapy, atezolizumab could reasonably be added in again.

5.5 Companion Diagnostic Testing

Not applicable.

5.6 Implementation Questions

5.6.1 In some jurisdictions cisplatin/etoposide is commonly used, are the results from the Impower133 trial generalizable to cisplatin/etoposide with atezolizumab?

Both inputs agreed that results from the Impower133 trial would be generalizable to cisplatin-etoposide with atezolizumab.

5.6.2 If atezolizumab was available, in clinical practice what stopping rules should be used for atezolizumab in the maintenance setting? Are the usual immunotherapy stopping rules appropriate (10% increase in total tumour burden confirmed with a second CT scan 6-8 weeks following the last scan if progression is suspected)?

The single clinician input stated that the above criteria are appropriate. The joint clinician input stated that atezolizumab should be stopped as per the clinical trial criteria, either due to unacceptable toxic effects, disease progression or no additional clinical benefit.

5.6.3 In clinical practice, is there evidence to treat patients with brain metastases requiring radiation for local symptomatic control, prophylactic cranial irradiation, or whole brain radiation, at the same time that they are receiving treatment with atezolizumab?

The single clinician input stated that treating patients with brain metastases was reasonable as the pharmacokinetics of the drug should not be affected. The joint clinician input acknowledged that the IMpower133 trial did not address the issue of treatment of patients with brain metastases. The joint clinician input suggested that radiotherapy could be sequenced between cycles of chemotherapy and atezolizumab for patients with de novo brain metastases who also require urgent systemic therapy. For patients who progress with central nervous system disease only while receiving chemotherapy with atezolizumab or during atezolizumab maintenance therapy, radiotherapy may be appropriately offered for local control while a patient continues to receive systemic treatment. As prophylactic brain radiotherapy was included in the IMpower133 study, the joint clinician input recommended that this remain the case in clinical practice. However, it was noted that currently prophylactic cranial irradiation (PCI) in ES-SCLC is less frequently used due to other studies that questioned its efficacy. Treatment was suggested to be discontinued for patients who progress in the central nervous system and systemically.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the safety and effect of atezolizumab in combination with carboplatin plus etoposide on patient outcomes compared to appropriate comparators for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC). The selection criteria table is presented in Section 6.2.1.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7. Section 7 includes a critical appraisal of a network meta-analysis (NMA) assessing the relative efficacy of atezolizumab in combination with etoposide plus platinum-based chemotherapy versus relevant platinum doublet therapies used in clinical practice globally for the first-line treatment of ES-SCLC.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs, conference abstracts, posters	Adult patients with ES-SCLC	The dose for atezolizumab is 1200 mg (Fixed dose) every 3 weeks as an intravenous infusion Four 21-day cycles of carboplatin (area under the curve of 5 mg per milliliter per minute, administered intravenously on day 1 of each cycle) and etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1	Cisplatin or carboplatin and Etoposide	<u>Primary Outcome</u> -Overall Survival -Investigator-assessed Progression Free Survival <u>Secondary Outcomes</u> -Investigator-assessed objective response rate -Duration of Response -Safety -Overall Survival -Quality of life

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
		through 3 of each cycle)		
RCT: Randomized Control Trial; ES-SCLC: extensive stage-small cell lung cancer				

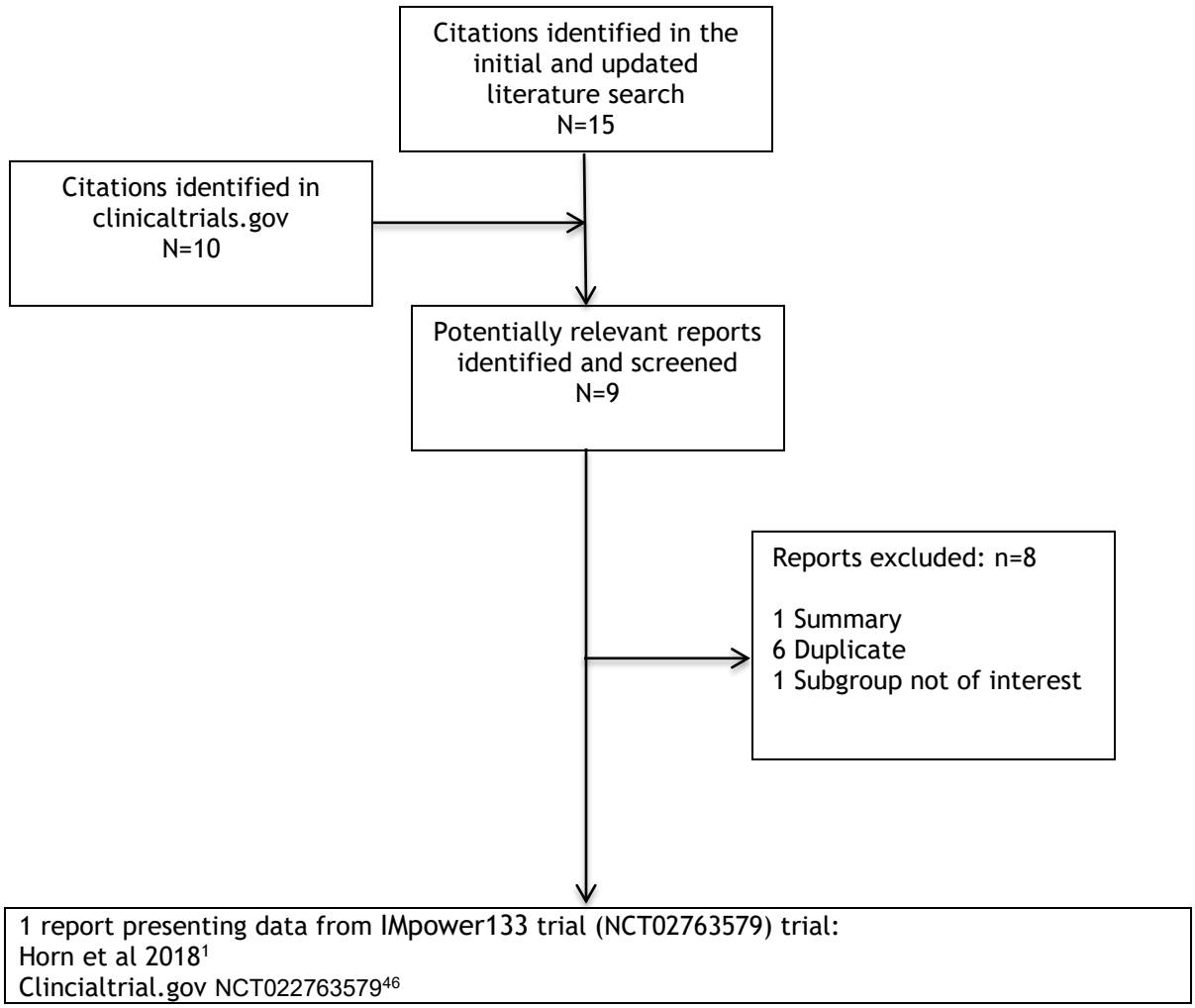
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Fifteen citations were screened. Among the 8 potentially relevant reports identified by the search, one study[1] was included in the pCODR systematic review and 8 studies were excluded.

Figure 6.1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to studies including Checkpoint Meeting responses,[7] and clinical study report[2] were also obtained through requests to the Submitter by pCODR.

6.3.2 Summary of Included Studies

One clinical trial (IMpower133) was included in this systematic review. The key characteristics of this trial are summarized in Table 6.2 and specific aspects of trial quality are summarized in Table 6.3.

6.3.2.1 Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of the Impower133 trial.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
IMpower133 trial (NCT02763579)[46] Multinational phase III ongoing double-blind, randomized, placebo-controlled trial N=403 at 106 sites in 21 countries (Enrolment between June 6, 2016 and May 31, 2017) Funded by F. Hoffmann–La Roche/Genentech, a member of the Roche Group. Clinical data cut-off April 24, 2018 Updated Clinical data cut-off January 24, 2019 The estimated study completion date is March 24, 2020.	Key Inclusion Criteria: • Adults with histologically or cytological confirmed ES-SCLC defined according to the Veterans Administration Lung Study Group staging system • Measurable ES-SCLC based on RECIST • An ECOG performance-status score of 0 or 1 • Patients with treated asymptomatic central nervous system metastases were eligible Key Exclusion Criteria: • patients with a history of autoimmune disease • previous treatment with CD 137 agonists or immune-checkpoint blockage therapies	<u>Intervention</u> in the induction phase, four 21-day cycles of carboplatin (administered intravenously on day 1 of each cycle) and etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle) with either atezolizumab (at a dose of 1200 mg, administered intravenously on day 1 of each cycle) or placebo followed by a maintenance phase during which they received either atezolizumab or placebo <u>Comparators</u> carboplatin and etoposide plus placebo	<u>Primary Outcome</u> -Overall Survival -Investigator-assessed Progression Free Survival <u>Secondary Outcomes</u> -Investigator-assessed objective response rate -Duration of Response -Safety all Survival (OS) ▪ Safety

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
ES-SCLC extensive stage small cell lung cancer; ECOG Eastern Cooperative Oncology Group; RECIST Response Evaluation Criteria in Solid Tumors			

Table 6.3: Select quality characteristics of included studies of Atezolizumab in combination with carboplatin and etoposide in patients with ES-SCLC

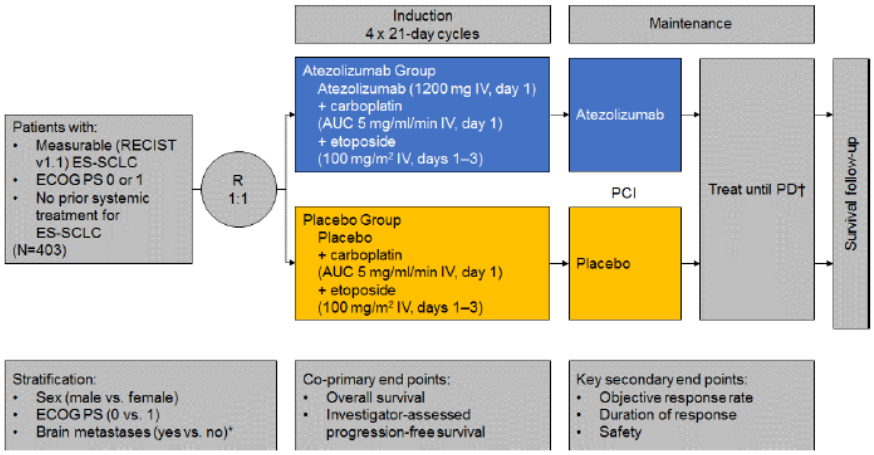
Study	IMpower133 trial
Treatment vs. Comparator	Atezolizumab in combination with carboplatin plus etoposide vs carboplatin plus etoposide plus placebo
Primary outcomes	PFS OS
Required sample size	The estimated enrollment is 403 patients.[46] The sample size of the trial was calculated on the basis of the overall survival analysis. It was determined that 306 deaths in the intention-to-treat population would be needed to provide 91% power at a two-sided significance level of 0.045 to detect a hazard ratio for death with atezolizumab as compared with placebo of 0.68, with the use of a log-rank test.[1]
Sample size	201 (atezolizumab plus carboplatin plus etoposide group) vs. 202 (carboplatin plus etoposide plus placebo) "The sample size calculation of the study is determined by the analysis of OS."[3] In order to achieve an improvement of HR= 0.68 in OS using a log-rank test, approximately 280 deaths in the ITT population will be required to achieve 88% power at a two-sided significance level of 0.045. A study amendment was made from 298 deaths to 280 deaths and 90% to 88% power.[1] One OS interim analysis will be performed when approximately 220 OS events in the ITT population are observed, at approximately 23 months after the first patient is randomized. For PFS the primary analysis is planned to be conducted during the time of the OS interim analysis, and is estimated to be when approximately 275 PFS events in the ITT population have occurred. A study amendment was made from 233 to 275 events. This is estimated to occur at approximately 23 months after the first patient is randomized. A study amendment was made from 21 months to 23 months. This provides 98% power to detect an improvement of HR= 0.55 in PFS at a two-sided significance level of 0.005."[3]
Randomization method	Stratified according to sex, ECOG performance- status score (0 or 1), and presence of brain metastases (yes or no). 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 tumor cells, and the lack of an association between response and PD-L1 expression in the phase 1 trial of atezolizumab in ES-SCLC.[1]
Allocation concealment	Yes. The Submitter stated that by using blinded kit numbers to assign study drug, the drug allocation was concealed.[7]
Blinding	The Sponsor study team, investigator/study site personnel, and the patient were blinded to treatment assignment. The study site obtained the patient's identification number and treatment assignment from the interactive voice or Web response system (IxRS) for eligible patients. The IxRS system is programmed to have blinded and unblinded reports, which are separated out into the separate role types in the system (blinded/unblinded users). All site users were granted blinded access only, and study team members directly involved in monitoring data collection and conducting data review were only able to access blinded information in the IxRS system.[7] Safety data was not blinded and reviewed by an independent data and safety monitoring committee for assessment of the side-effect profile.
ITT Analysis	Yes
Final analysis	No. As of the data cut-off, January 24, 2019, the study was ongoing for additional overall survival data. The estimated study completion date is March 24, 2020.
Early termination	The IMpower133 study was not terminated early and continued as per pre-specified study plan.
Ethics Approval	Yes

ECOG = Eastern Cooperative Oncology Group OS = overall survival; PFS = progression-free survival (PFS); ISS = International Staging System; ITT = Intention to Treat

a) Trials

One randomized, ongoing, multinational, phase III double-blind, placebo-controlled trial met the inclusion criteria. The aim of this trial was to examine the efficacy and safety of adding atezolizumab to first line treatment with carboplatin and etoposide compare to carboplatin and etoposide plus placebo in patients with ES-SCLC. The IMpower133 trial enrolled 403 patients across 21 countries from 106 sites. The following countries were included: Australia, Austria, Brazil, Chile, China, Czechia, France, Germany, Greece, Hong Kong, Hungary, Italy, Japan, Korea, Republic of, Mexico, Poland, Russian Federation, Serbia, Spain, Taiwan, United Kingdom, United States. There were 25 study sites in the United States, 7 in Australia, 53 in Europe and 33 in Asia. Randomization was performed with the use of a permuted-block randomization method to randomly assign patients in a 1:1 ratio to atezolizumab in combination with carboplatin or carboplatin and etoposide plus placebo and stratified according to sex, ECOG performance- status score (0 or 1), and presence of brain metastases (yes or no). 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 tumor cells, and the lack of an association between response and PD-L1 expression in the phase 1 trial of atezolizumab in ES-SCLC. IMpower133 trial was funded by F. Hoffmann–La Roche/Genentech. An employee from F. Hoffmann-La Roche and an employee from Genentech analyzed the data. According to the Submitter, data were recorded on case report forms in the clinical database (i.e., CRF data), and data were collected outside of the clinical database (i.e., non-CRF data). At study start-up, the study team reviewed and approved the CRF to ensure that the correct data was designated to be collected in the electronic data capture system and that data are collected per formal data standards as dictated by the Data Standards Office and data characteristics precisely meet protocol and team specifications. Figure 6.2 illustrates the study design.[4]

Figure 6.2. Study design[4]



* Only patients with treated brain metastases were eligible; due to the low number of patients with brain metastases, the presence of brain metastases was excluded as a stratification factor in stratified data analyses.

† Patients who met prespecified criteria (see Supplementary Methods) were allowed to be treated beyond disease progression per RECIST v1.1 criteria until loss of clinical benefit in a blinded fashion.

PCI, prophylactic cranial irradiation; PD, disease progression.

Source: Califano R, Każarnowicz A, Karaseva N, et al. IMpower133: Patient-reported outcomes (PROs) in a Ph1/3 study of first-line (1L) atezolizumab + carboplatin + etoposide (CP/ET) in extensive-stage SCLC (ES-SCLC) [slide deck]. ESMO 2018.[4]

The primary efficacy endpoints of IMpower133 were OS defined as the time from randomization to death from any cause measured at 1 and 2 years. As well as investigator-assessed PFS defined as the time from randomization to disease progression according to RECIST or death from any cause measured at 6 months and 1 year.

For OS, one interim efficacy analysis was planned when approximately 240 OS events had been observed. The primary analysis of PFS was conducted at the same time as the interim OS analysis, however, the timing of the analysis depended on when 240 OS events in the ITT population had occurred.[3]
The final OS analysis was planned to be conducted when approximately 306 OS events in the ITT population had occurred. This was estimated at approximately 36 months after the first patient was randomized, however, the timing of this analysis is dependent on the actual number of OS events.[3]

Secondary outcomes included investigator-assessed objective response rate (ORR) (according to RECIST) and the duration of response (DOR) defined as time from the first documented objective response to documented PD or death from any cause, whichever occurred first which was analyzed similar to Kaplan-Meier methodology.[2] Confirmation of responses was not required, but confirmed response rates were reported to avoid potential bias. The Clopper-Pearson method for 95% CI of response rates was applied. 95% CI for the difference in ORRs between the two treatment arms was estimated using the normal approximation to the binomial distribution method.[2] Safety (e.g., adverse events) were assessed according to National Cancer Institute Common Terminology Criteria for Adverse

Events, version 4.0. The investigators determined whether adverse events were related to the trial regimen.

Patient reported outcomes were assessed using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), the supplemental lung cancer module (QLQ-LC13), and the EuroQol 5 Dimensions 5-Level (EQ-5D-5L) questionnaire. The EORTC QLQ-C30 and EORTC QLQ-LC13 instruments measured the following four criteria: (1) Disease-related symptoms, (2) treatment-related symptoms, (3) physical function, and (4) health-related quality of life.[4] The EQ-5D-5L instrument is used to elicit utility scores for the submitted cost-effectiveness evaluation. Patient reported outcomes were descriptively analyzed using time to deterioration (TTD) in patient-reported lung cancer-related symptoms and change from baseline in lung cancer- and treatment-related symptoms.[4] The TTD outcome was defined as the "time from randomization to deterioration (10-point change) on each of the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom subscales maintained for two assessments or one assessment followed by death from any cause within 3 weeks."[2] A clinically meaningful change from baseline was defined as a ≥ 10-point change within a treatment arm.[4] The EORTC QLQ-C30 is a validated and reliable self-report measure scale. There are 30 questions that that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scores ranges from 0-100 and higher scores represent higher response level: Either worse symptoms, better function, or better HRQoL.[2] The patient reported questionnaires were administered during the study treatment phase (induction and maintenance phases: every 21 days at the scheduled study treatment visits until treatment discontinuation) and during survival follow-up (at 3 months and 6 months after disease progression per RECIST v1.1 or after treatment discontinuation).

The EORTC QLQ-LC13 module encompassed one multiple-item scale that evaluated dyspnea and various single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. The EORTC QLQ-LC13 module was completed by patients following the same time intervals as the EORTC QLQ-C30 questionnaire.[3]

Statistical analysis

Kaplan–Meier methodology was performed to determine OS and PFS, as well as to calculate the median time from randomization to death (for OS) and the median time from randomization to disease progression or death (for PFS) for each group. 95% confidence intervals for the median time were obtained via the Brookmeyer and Crowley method. A similar approach was used for the analysis of the duration of response. A stratified Cox regression model was used to calculate the hazard ratios and 95% confidence intervals for OS and PFS with the same stratification factors that were used in the stratified log-rank test. In order to assess whether treatment benefit varied for patients based on age, the variable of age, age as a continuous variable and age by treatment, interaction terms were added to the Cox regression model for the OS endpoint.[7]

As there are two primary co-endpoints for this trial, in order to adjust for multiplicity, a group sequential Holm's procedure was implemented. The hypothesis test for PFS was conducted at a two-sided alpha of 0.005 and OS would be tested at a two-sided alpha of 0.045. If the primary analysis of PFS was deemed significant, then the two-sided 0.005 alpha would be applied to OS. If the interim or final analysis for OS was significant, the

two-sided 0.045 alpha would be used for PFS. In order to control for the Type I error for OS, the stopping boundaries for OS interim and final analyses will be computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundary. The analysis timing and stopping boundary of OS is presented in Table 6.4.[1]

Table 6.4. Analysis Timing and Stopping Boundary of Overall Survival[1]

Analysis Timing	Information Fraction (Number of Events)	Estimated Time from First Patient In (months)	Stopping Boundary in HR (two-sided p-value) PFS is Statistically Significant	Stopping Boundary in HR (two-sided p-value) PFS is Not Statistically Significant
OS interim analysis	78.4% (240)	25	HR≤0.7453 (p≤0.0228)	HR≤0.7405 (p≤0.02)
OS final analysis	100% (306)	36	HR≤0.7937 (p≤0.0433)	HR≤0.7899 (p≤0.039)

HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

Source: NEJM, Horn et al., First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer, 379:2220-2229. © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

As part of an exploratory analyses of PFS and OS outlined in the protocol, the duration of OS in the subgroups characterized 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 PD-L1 tumor expression status was examined. Cox proportional hazards models were conducted and unstratified HRs and Kaplan-Meier estimates of median survival time were generated for each level of the categorical variables for assessment between treatment groups.[1]

Data on patient reported outcomes (i.e., physical function and health-related quality of life) were prespecified as secondary and exploratory endpoints in the ITT. Descriptive analyses were conducted (e.g., change from baseline).[47]

a) ***Populations***

IMpower133 randomized 201 patients to the atezolizumab in combination with carboplatin plus etoposide group and 202 patients to the carboplatin and etoposide plus placebo group. According to the study authors, the baseline patient characteristics are well balanced between the atezolizumab in combination with carboplatin plus etoposide and the carboplatin and etoposide plus placebo groups and representative of ES-SCLC. The median age was 64 years (range 28-90 years) in both, the atezolizumab in combination with carboplatin and etoposide and carboplatin and etoposide plus placebo groups. The use of prophylactic cranial irradiation (PCI) was balanced between arms in IMpower133, 22 (10.9%) patients in the atezolizumab containing treatment arm and 22 (10.9%) patients in the carboplatin and etoposide plus placebo arm received PCI.[7] The majority of patients were enrolled in the United States (n=86), Poland (n=45) and Japan (n=42). The patient demographics and baseline disease characteristics of all enrolled patients in the ITT population are presented in Table 6.5.

Table 6.5: Patient demographics and baseline disease characteristics of the ITT population[1]

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 enrollment — no. (%)†	17 (8.5)	18 (8.9)
Blood-based tumor 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)

* The date of data cutoff was April 24, 2018.
† The data were determined from electronic case-report forms.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status 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 tumor mutational burden; 351 of the samples (173 in the atezolizumab group and 178 in the placebo group) yielded high-quality data for analysis of tumor 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).

Source: NEJM, Horn et al., First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer, 379:2220-2229. © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

b) Interventions

Treatment assignments were blinded. In the induction phase, four 21-day cycles of carboplatin (area under the curve of 5 mg per milliliter per minute, administered intravenously on day 1 of each cycle) and etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle) with either atezolizumab (at a dose of 1200 mg, administered intravenously on day 1 of each cycle) or placebo. Maintenance phase followed the induction phase whereby patients received either atezolizumab or placebo based on previous randomized assignment until a toxic effect or disease progression occurred according to RECIST.[1] At the discretion of the investigator, patients were allowed to continue their trial regimen after the occurrence of disease progression during either the induction of maintenance phase if evidence of clinical benefit existed. During the maintenance phase, prophylactic cranial irradiation was allowed, but thoracic radiation therapy was not.[1]

Among patients that received atezolizumab in combination with carboplatin and etoposide, the median duration of treatment was 4.7 months (range, 0 to 21), and the median number of atezolizumab doses received was 7 (range, 1 to 30).[3] Among patients that received atezolizumab in combination with carboplatin and etoposide compared with carboplatin and etoposide plus placebo, the median number of doses of chemotherapy was identical. The median dose intensity and total cumulative dose of chemotherapy were similar among patients that received atezolizumab in combination with carboplatin and etoposide compared with carboplatin and etoposide plus placebo.[1]

For patients with concomitant conditions present at baseline, dose modifications will be applied according to the corresponding shift in toxicity grade, based on the investigator's discretion.[2] The most commonly used classes of drugs included: [redacted].[2] (*Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by sponsor that it can be publicly disclosed.*)

No dose reductions were permitted for patients that received either atezolizumab in combination with carboplatin and etoposide or carboplatin and etoposide plus cisplatin.[3] In the event a patient experienced an adverse event that required a dose to be held, study treatment may be suspended for up to 105 days following the last dose. The patient will be discontinued from either atezolizumab in combination with carboplatin and etoposide or carboplatin and etoposide plus placebo if the adverse event due to treatment exceeds 105 days following the last dose.[2] For the management of adverse events associated with atezolizumab, toxicities should be treated adhering to standard medical practice. However, additional tests (e.g., autoimmune serology or biopsies) should be used to identify a possible immunogenic etiology.

c) Patient Disposition

Among patients in the atezolizumab and carboplatin plus etoposide group, the proportion of adverse events leading to withdrawal from any treatment was 11.1% compared to 3.1% in the carboplatin and etoposide plus placebo group. Additional results are outlined in Table 6.6.

Table 6.6: *Patient Disposition*

Category	Atezolizumab and Carboplatin and Etoposide Group, n	Placebo and Carboplatin and Etoposide Group, n
Randomized	201	202
Discontinued	124	142
Died	101	132
Lost to follow-up	3	1
Withdrew by physician	2[b]	0[b]
Withdrawals	18	9
AEs leading to withdrawal from any treatment[a]	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)

[a] Incidence of treatment-related AEs and AEs leading to withdrawal from any treatment are for any treatment component; [b]Source: checkpoint responses[7]
AE, adverse event.

The subsequent anti-cancer therapies received by patients after discontinuation of study treatment are summarized in the following. The reported percentages are based on the number of patients in the atezolizumab in combination with carboplatin and etoposide group (n=201) and carboplatin and etoposide plus placebo (n=202) groups at the data cut-off date: April 24, 2018. The percentages of patients who received at least one subsequent cancer therapy were similar in the two treatment groups (51.7% in the atezolizumab in combination with carboplatin and etoposide group; and 57.4% in the carboplatin and etoposide plus placebo group), with chemotherapy/non-anthracycline being the most common subsequent treatment in both groups (40.3% and 43.6%, respectively). Other subsequent cancer therapies received included: (atezolizumab in combination with carboplatin and etoposide vs. carboplatin and etoposide plus placebo) chemotherapy/anthracycline (15.4% vs. 22.8%), immunotherapy (3.0% vs. 7.4%), Other (1.0% vs. 1.0%), and targeted therapy (1.0% vs. 0.5%).[3]

d) Limitations/Sources of Bias

Although this phase III trial was a randomized, double-blinded study, there are limitations associated with the study design and methodology. While the sample size of the trial was based on the analysis of OS, the secondary efficacy endpoints and subgroup analyses were not adequately powered to determine statistical significance. Specifically, sample size calculations were outlined for OS and investigator assessed PFS. Thus, the results for secondary endpoints should be interpreted with caution. In addition, an amendment was made to the stopping boundary for OS interim and final analyses from HR ≤ 0.665 to HR ≤ 0.745 to observe a smaller effect size, however, the rationale provided in the protocol is unclear. The amendment was dated May 14, 2018 following the first data cut-off on April 24, 2018. Although methods for testing for multiplicity were outlined in the protocol for primary endpoints, it is unclear whether these were carried out in the statistical analysis for secondary endpoints. Results related to patient-reported outcomes were descriptive only. In addition, the proportion of patients that did not complete the EORTC QLQ C30 and whether these patients may have responded differently to patients that completed the questionnaire is unclear. Lastly, due to the sponsor involved in various aspects of the trial

(e.g., data collection, performing data analysis, authorship), there is a possible conflict of interest.

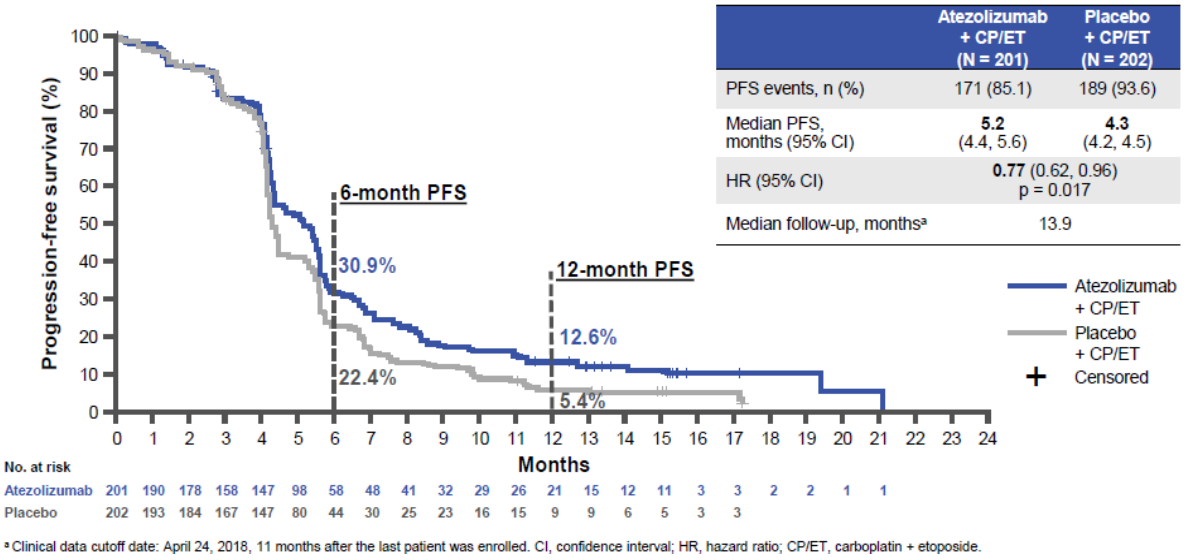
6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Progression Free Survival (PFS)- investigator assessed

Results reported for investigator assessed PFS are based on the primary analysis and considered the final analysis for PFS. At a median follow-up of 13.9 months (data cut-off date: April 24, 2018), patients that received atezolizumab combined with carboplatin plus etoposide had statistically significant PFS compared to patients that were treated with carboplatin and etoposide plus placebo (stratified HR: 0.77, 95% CI 0.62-0.96, p=0.017).[3] The median PFS was 5.2 months (95% CI 4.4 to 5.6) and 4.3 months (95% CI 4.2 to 4.5) in the atezolizumab in combination with carboplatin plus etoposide and carboplatin and etoposide plus placebo groups respectively.

Figure 6.3. Kaplan-Meier curve results for Progression Free Survival[48] (Clinical Data Cut-off April 24, 2018)



	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	**5.2** (4.4, 5.6)	**4.3** (4.2, 4.5)
HR (95% CI)	**0.77** (0.62, 0.96) p = 0.017	
Median follow-up, months[a]	13.9	

[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

Source: Liu SV, Mansfield A, Szczesna A, et al. IMpower133: primary PFS, OS, and safety in a Ph1/3 study of 1L atezolizumab+ carboplatin + etoposide in extensive-stage SCLC [slide deck]. IASLC 2018.[48]

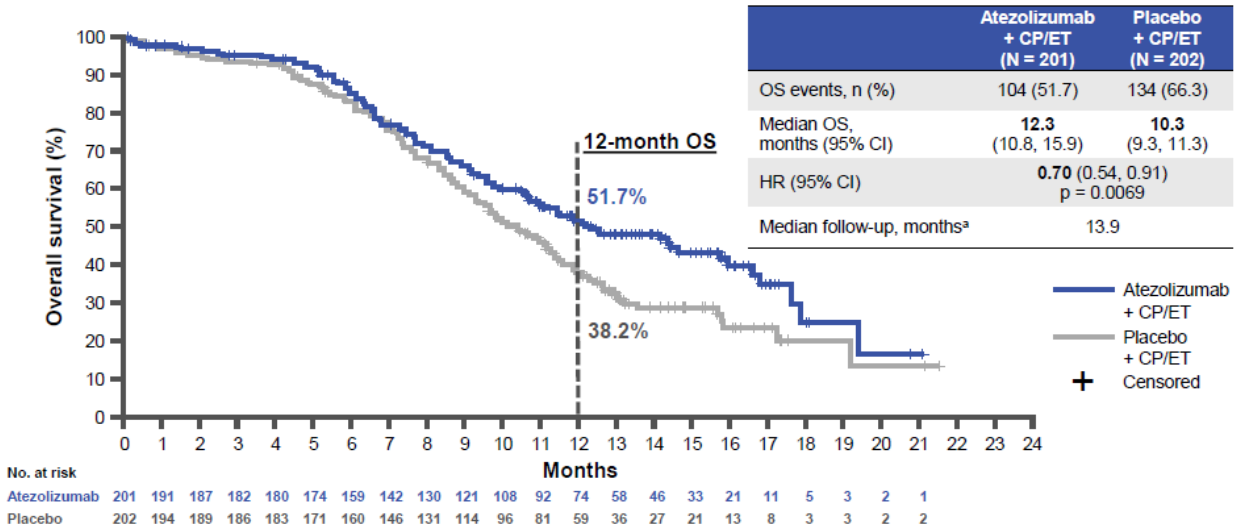
Results from the exploratory subgroup analyses of PFS suggest the following subgroups of patients: females, ECOG performance status = 1 and patients with no liver and brain metastases may likely benefit from treatment with atezolizumab in combination with carboplatin and etoposide.

Overall Survival

Results reported for overall survival are based on an interim (data cut-off date: April 24, 2018) and updated exploratory analysis (data cut: January 24, 2019). There were 104 (51.7%) patients that died in the atezolizumab in combination with carboplatin plus etoposide group compared to 134 (66.3%) patients that died in the placebo plus carboplatin plus etoposide group. The stratified HR at a median follow-up of 13.9 months was 0.70, 95% CI 0.54-0.91, p=0.0069).[3] At the planned interim OS analysis, the OS endpoint met the statistical boundary (HR ≤ 0.7453). Overall survival was statistically significantly longer in the atezolizumab and carboplatin plus etoposide group (median, 12.3 months; 95% CI: 10.8 -15.9) than in the carboplatin and etoposide plus placebo group (median, 10.3 months; 95% CI: 9.3 - 11.3).

At the updated analysis, clinical data cut-off date January 24, 2019, 302 of the planned 306 death events for the analysis of OS had occurred at a median follow-up of 22.9 months. The stratified HR at a median follow-up of 22.9 months was 0.76 (95% CI: 0.601-0.949). The results from the updated exploratory analysis of OS with longer follow-up were consistent with the OS results of the interim analysis.[7] Median OS was 2 months longer in the atezolizumab in combination with carboplatin and etoposide group compared with the carboplatin and etoposide plus placebo group (median OS of 12.3 months versus 10.3 months).[49] Figure 6.4 and Figure 6.5 presents results for overall survival.

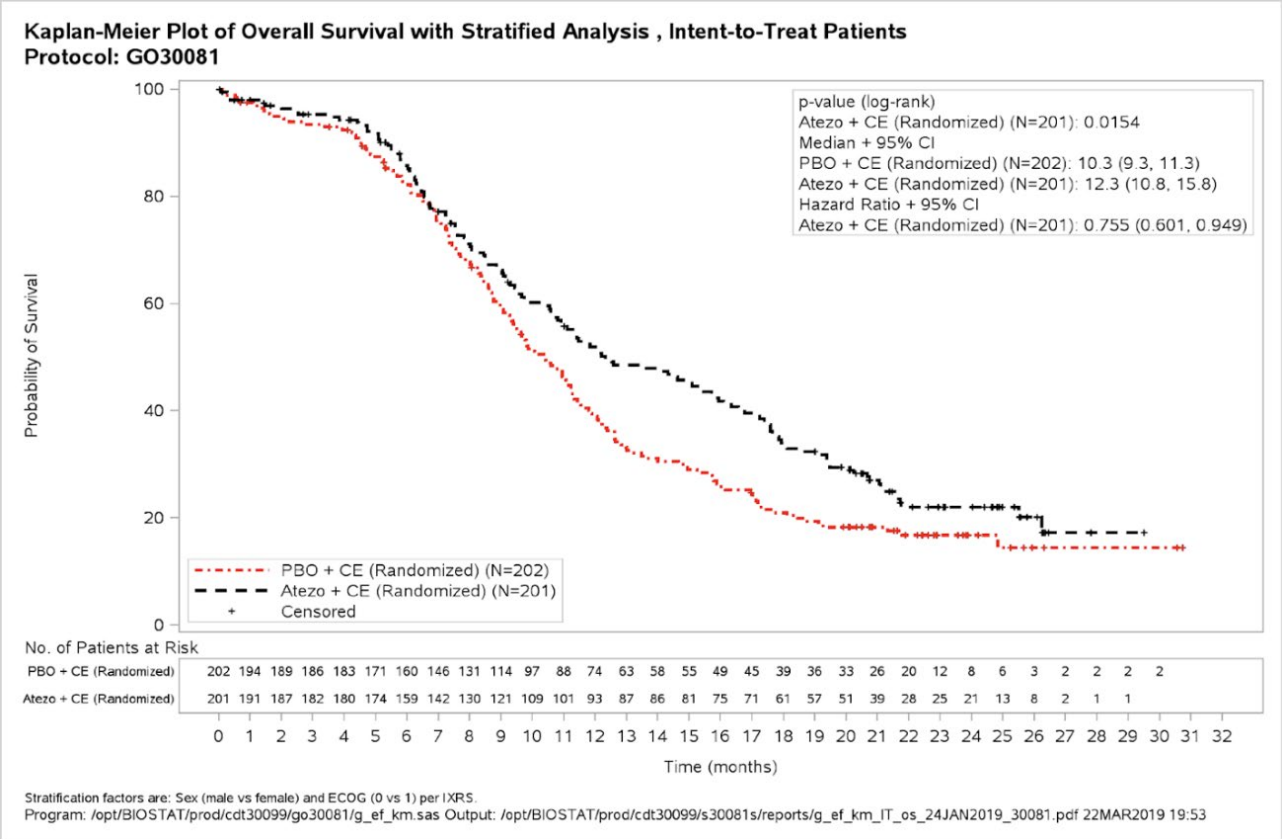
Figure 6.4. Kaplan-Meier curve for Overall Survival (Clinical Data Cut off April 24, 2018)[48]



[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

Source: Liu SV, Mansfield A, Szczesna A, et al. IMpower133: primary PFS, OS, and safety in a Ph1/3 study of 1L atezolizumab+ carboplatin + etoposide in extensive-stage SCLC [slide deck]. IASLC 2018.[48]

Figure 6.5. Kaplan-Meier curve for Overall Survival (Clinical Data Cut off January 24, 2019)[7]



Source: Hoffmann-La Roche response to pCODR checkpoint meeting questions on Tecentriq (atezolizumab).[7]

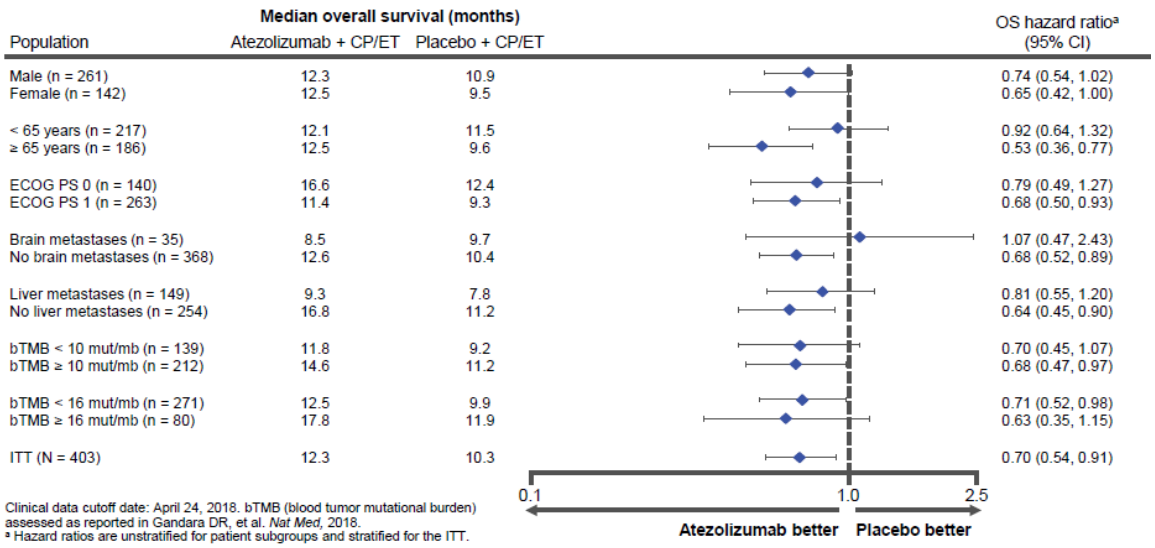
In their feedback on the initial recommendation, the sponsor and the registered clinicians providing feedback noted that the absolute median OS benefit alone does not adequately convey the clinical value of this regimen. It was noted that information required to assess survival benefit includes the medians, landmark analyses, and HRs. While the sponsor noted that the HR is the most appropriate and statistically valid way to evaluate clinical benefit, the registered clinicians noted that the HR of 0.7 and the survival benefit at 12 and 18 months carry more weight than the median absolute OS benefit of 2 months. In response to the sponsor's and registered clinicians' feedback the CADTH Methods Team and the CADTH Clinical Guidance Panel (CGP) agreed that in order to assess comparative OS benefit full Kaplan-Meier curves of respective interventions need to be considered. The Methods team also noted that while the HR provides an estimate of the relative efficacy between the treatment options in a clinical trial, comparing medians and percentage of patients alive at different time points for each treatment group can provide an absolute measure of improvement in efficacy. Therefore, it is advisable to consider all three measures (i.e., HR, medians, and landmark analyses) when interpreting the survival data.

CADTH received a procedural review request from the sponsor for atezolizumab for ES-SCLC on December 16, 2019, which CADTH accepted on the grounds that it failed to act in accordance with its procedures in conducting the review. Specifically, the sponsor alleged that data from a recent publication (Reck et al. [2019])[5] regarding 18-month survival rates were not new data and should have been considered by pERC at the reconsideration

meeting on November 21, 2019. The sponsor also noted that this information had been provided as part of the Checkpoint Meeting Responses dated May 6, 2019. CADTH acknowledged that the relevant data had been provided in the Checkpoint Meeting Responses. In view of this finding, it was determined that the submission needed to be re-deliberated by pERC at its next available meeting on January 16, 2020. The data for the OS landmark analysis at 18 months are as follows: at 18 months, 61/201 patients (30%) were alive in the atezolizumab in combination with carboplatin plus etoposide group, when compared with 39/202 patients (19%) in the placebo plus carboplatin and etoposide group (January 2019 data cut off date).[50] The OS rate at 18 months reported by the sponsor was 34% in the atezolizumab in combination with carboplatin plus etoposide group compared to 21% in the placebo plus carboplatin and etoposide group.[50] The OS landmark analysis results at 24 months (January 2019 data cut off date) were also provided in the Checkpoint meeting material. The European Public Assessment Report[6] (EPAR) on atezolizumab (Tecentriq) for ES-SCLC was published on October 23, 2019 after the posting of the initial recommendation (October 3, 2019), and outlines the OS landmark analysis results for 12, 18, and 24 months. At 24 months, 21/201 (10%) patients were alive in the atezolizumab in combination with carboplatin and etoposide group, when compared with 8/202 (4%) patients in the placebo plus carboplatin and etoposide group.[6] The 24 months OS rate reported in the EPAR was 22% in the atezolizumab in combination with carboplatin plus etoposide group, compared to 17% in the placebo plus carboplatin and etoposide group.[6] See Table 1.1, page 6 of this CGR, for further details.

The exploratory subgroup analyses of OS shown in Table 6.7 suggests the following subgroups of patients: age ≥ 65 years, ECOG performance status = 1 and patients with no liver and brain metastases may likely benefit from treatment with atezolizumab in combination with carboplatin and etoposide. While treatment benefit in OS was mostly consistent across the subgroups, there was a noticeable difference for patients with baseline brain metastases and patients <65 years old. It is important to note that the number of patients with a presence of brain metastases is low and the interpretation of these results is limited. The p-value for the interaction term from this model suggested that the treatment effect is not affected by patient's age. When the non-significant interaction term was removed from the model, the HR was equal to 0.70 (95% CI: 0.538, 0.901), which was consistent with what is observed in the primary analysis in the overall ITT population.[51] Table 6.7 presents the OS results for baseline characteristics.

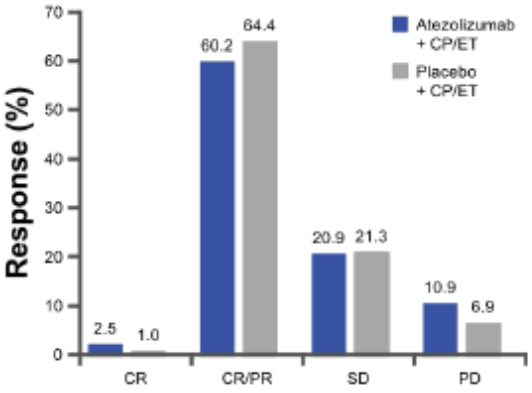
Table 6.7. Subgroup Analysis of Overall Survival according to baseline characteristics[48]



Overall Response Rate

The overall response rate was assessed at the April 24, 2018 data cut and was similar for patients that received atezolizumab in combination with carboplatin plus etoposide (60.2%) compared to patients that received carboplatin and etoposide plus placebo (64.4%).[47] There were five patients (2.5%) in the atezolizumab group and two patients (1.0%) in the carboplatin and etoposide plus placebo group who had a complete response.

Figure 6.5. Confirmed Response[48]



Duration of response	Atezolizumab + CP/ET (N = 121)	Placebo + CP/ET (N = 130)
Median duration, months (range)	4.2 (1.4[a] to 19.5)	3.9 (2.0 to 16.1[a])
HR (95% CI)	0.70 (0.53, 0.92)	
6-month event-free rate — %	32.2	17.1
12-month event-free rate — %	14.9	6.2
Patients with ongoing response — no. (%)[b]	18 (14.9)	7 (5.4)

Source: Liu SV et al. IMpower133: primary PFS, OS, and safety in a Ph1/3 study of 1L atezolizumab+ carboplatin + etoposide in extensive-stage SCLC [slide deck]. IASLC 2018.[48]

Duration of Response

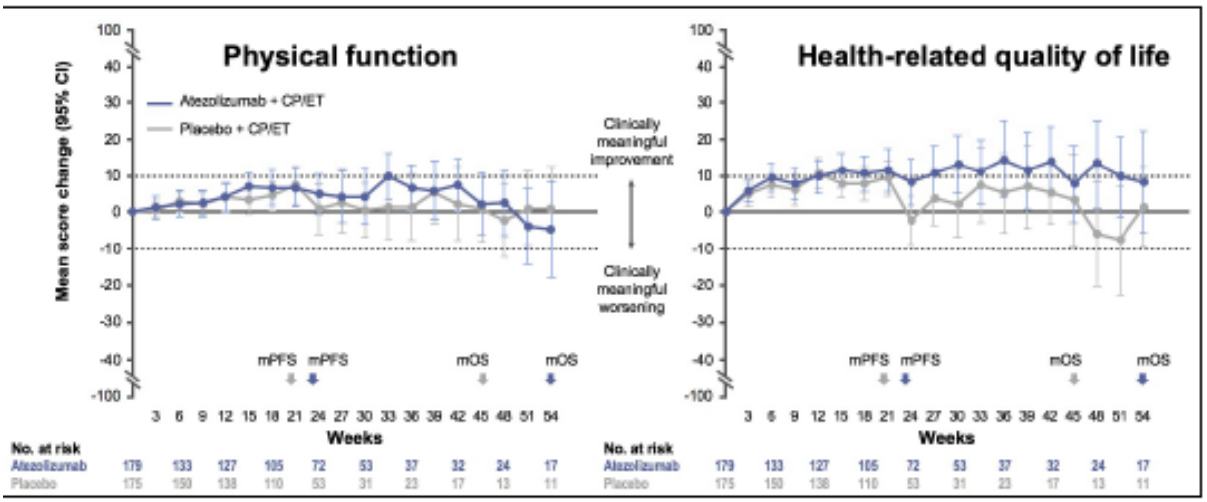
The median duration of the objective response for patients that received atezolizumab in combination with carboplatin and etoposide was 4.2 months (95% CI1.4-19.5 months) and 3.9 months (95% CI 2.0 -16.1 months) for patients treated with carboplatin and etoposide plus placebo at the clinical Data cut-off date: April 24, 2018.[48]

Quality of Life

Physical functioning and health related quality of life

Physical functioning and health related quality of life were measured using patient reported outcomes data from the IMpower133 trial based on the April 24, 2018 data cut-off date[4]. The data showed an immediate improvement in physical function and HRQoL in favour of patients that received atezolizumab plus carboplatin and etoposide arm versus placebo and carboplatin and etoposide. While the improvement in HRQoL was sustained through Week 54, as shown in Figure 6.6, the improvements observed in the carboplatin and etoposide plus placebo arm were small and generally not clinically meaningful.[47] The completion rate defined as the number of patients who completed the assessment divided by the number of patients expected to complete the assessment was ≥ 85% at baseline and ≥ 70% in both arms until Week 75 (n = 6). The compliance rate was not reported.[4]

Figure 6.6. Change from baseline for Physical Function and Health Related Quality of Life[4]



Source: Califano R, Każarnowicz A, Karaseva N, et al. IMpower133: patient-reported outcomes (PROs) in a Ph1/3 study of first-line (1L) atezolizumab + carboplatin + etoposide (CP/ET) in extensive-stage SCLC (ES-SCLC) [slide deck]. ESMO 2018.[4]

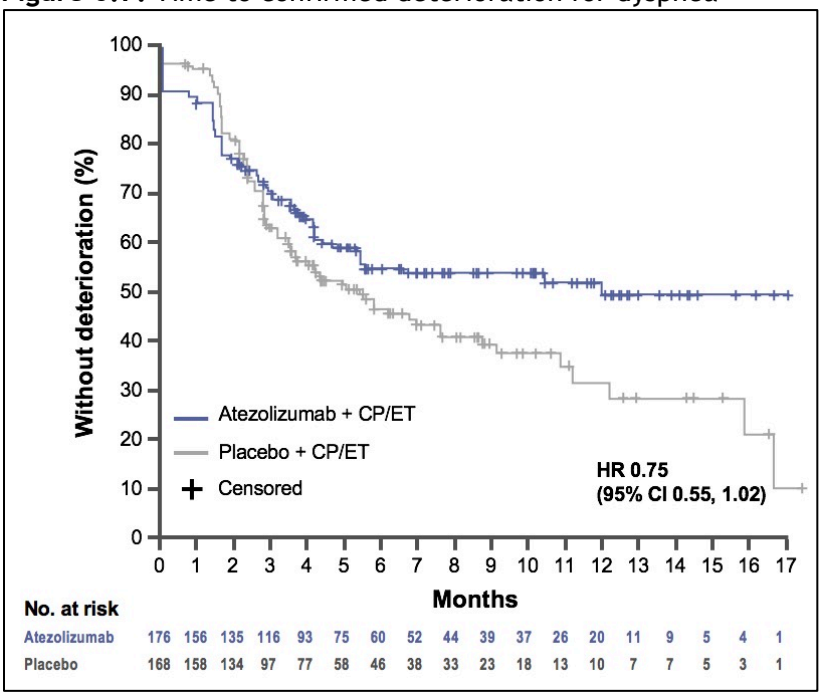
Lung Cancer and Treatment Related Symptoms

There was a greater improvement from baseline in patient-reported lung cancer-related symptoms (chest pain, dyspnea, arm/shoulder pain) for patients that received treatment with atezolizumab in combination with carboplatin plus etoposide compared to patients that received carboplatin and etoposide plus placebo.

Times to deterioration in cough, chest pain, and arm/shoulder pain was similar between groups. There was a delay in worsening of dyspnea symptoms for patients treated with atezolizumab in combination with carboplatin and etoposide compared to patients that received carboplatin and etoposide plus placebo (HR; 0.75, 95% CI 0.55, 1.02). Results for

time to deterioration (TTD) are shown in Figure 6.7. The median TTD was not evaluable in the atezolizumab in combination with carboplatin plus etoposide arm versus 5.6 months in the carboplatin and etoposide plus placebo.[4]

Figure 6.7. Time to confirmed deterioration for dyspnea[4]



Source: Califano R, Każarnowicz A, Karaseva N, et al. IMpower133: patient-reported outcomes (PROs) in a Ph1/3 study of first-line (1L) atezolizumab + carboplatin + etoposide (CP/ET) in extensive-stage SCLC (ES-SCLC) [slide deck]. ESMO 2018.[4]

Safety Outcomes

The population included in the analyses of safety included 198 patients who received at least 1 dose of atezolizumab and 196 patients who received placebo. Safety data were not blinded and reviewed by an independent data and safety monitoring committee for assessment of the side-effect profile. There were 22 patients in the atezolizumab in combination with carboplatin and etoposide group and 6 patients in the carboplatin and etoposide plus placebo group that experienced AEs that led to withdrawal from any treatment component.[3] There were 3 mortalities among patients that were treated with atezolizumab in combination with carboplatin plus etoposide (death was due to neutropenia in 1 patient, pneumonia in 1 patient, and an unspecified cause in 1 patient) and 3 mortalities among patients in the carboplatin and etoposide plus placebo group (death was due to pneumonia in 1 patient, septic shock in 1 patient, and cardiopulmonary failure in 1 patient).[3] There were 112 patients (56.6%) that experienced treatment-related Grade 3-4 adverse events in the atezolizumab in combination with carboplatin and etoposide compared to 110 patients (56.1%) in the carboplatin and etoposide plus placebo group. Serious adverse events occurred in 74 patients (37.4%) that received atezolizumab in combination with carboplatin and etoposide compared to 68 patients (34.71%) in the carboplatin and etoposide plus placebo group. There were 45 patients (22.7%) that experienced Grade 3-4 neutropenia that received treatment with atezolizumab in combination with carboplatin plus etoposide compared to 48 patients (24.5%) that received carboplatin and etoposide plus placebo. Table 6.8 presents the safety data.

Table 6.8. Adverse events related to trial regimen[1]

Event	Atezolizumab Group (N=198)			Placebo Group (N=196)		
	Grade 1 or 2	Grade 3 or 4	Grade 5	Grade 1 or 2	Grade 3 or 4	Grade 5
	number of patients (percent)					
Any adverse event	73 (36.9)	112 (56.6)	3 (1.5)	68 (34.7)	110 (56.1)	3 (1.5)
Adverse events with an incidence of ≥10% in any grade category or events of grade 3 or 4 with an incidence of ≥2% in either group						
Neutropenia	26 (13.1)	45 (22.7)	1 (0.5)	20 (10.2)	48 (24.5)	0
Anemia	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
Decreased neutrophil count	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
Decreased platelet count	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
Decreased white-cell count	10 (5.1)	6 (3.0)	0	16 (8.2)	9 (4.6)	0
Diarrhea	15 (7.6)	4 (2.0)	0	18 (9.2)	1 (0.5)	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

[a] The date of data cutoff was April 24, 2018. Multiple occurrences of the same adverse event in one patient were counted once at the highest grade for the preferred term. The incidence of treatment-related adverse events associated with any component of the trial regimen is shown.

Source: NEJM, Horn et al., First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer, 379:2220-2229. © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

The most commonly reported immune related adverse events were rash followed by hypothyroidism (atezolizumab in combination with carboplatin plus etoposide vs. carboplatin and etoposide plus placebo: all grades rush 18.7% vs. 10.2%; all grades hypothyroidisms: 12.6% vs. 0.5%).[47] Table 6.9 outlines immune related adverse events.

Table 6.9. Immune related adverse events[47]

Immune-related AEs, n (%) > 1% Grade 3–4 AEs in either treatment group	Atezolizumab (N=198)		Placebo (N=196)	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Rash	37 (18.7)	4 (2.0)	20 (10.2)	0
Hypothyroidism	25 (12.6)	0	1 (0.5)	0
Hepatitis (diagnosis)	14 (7.1)	3 (1.5)	9 (4.6)	0
Hepatitis (laboratory abnormalities)	14 (7.1)	3 (1.5)	9 (4.6)	0
Infusion-related reaction	11 (5.6)	4 (2.0)	10 (5.1)	1 (0.5)
Hyperthyroidism	11 (5.6)	0	5 (2.6)	0
Pneumonitis	4 (2.0)	1 (0.5)	5 (2.6)	2 (1.0)
Colitis	3 (1.5)	2 (1.0)	0	0
Pancreatitis	1 (0.5)	1 (0.5)	2 (1.0)	2 (1.0)
Severe cutaneous reaction	2 (1.0)	0	0	0
Adrenal insufficiency	0	0	2 (1.0)	0
Rhabdomyolysis	2 (1.0)	1 (0.5)	0	0
Nephritis	1 (0.5)	1 (0.5)	1 (0.5)	0
Hypophysitis	1 (0.5)	0	0	0
Vasculitis	0	0	1 (0.5)	0
Diabetes mellitus	1 (0.5)	0	0	0
Guillain-Barre Syndrome	1 (0.5)	1 (0.5)	0	0

AE, adverse event.
Horn, et al. NEJM 2018.

Source: Clinical summary: Tecentriq® (atezolizumab): for the first-line treatment of 14 patients with extensive stage small cell lung cancer 15 (ES-SCLC) in combination with a platinum-based 16 chemotherapy and etoposide.[47]

6.4 Ongoing Trials

No ongoing trial were identified as being relevant to this review.

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of the network meta-analysis

The following supplemental issues were identified during development of the review protocol as relevant to the pCODR review of atezolizumab for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).:

- Summary and Critical appraisal of the network meta-analysis (NMA) comparing the efficacy and safety of atezolizumab in combination with etoposide plus platinum-based chemotherapy

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1.1 Background

The Submitter conducted a systematic literature review which provided input for the network meta-analysis (NMA) which was also provided by the Submitter. The primary objective of the NMA was to compare atezolizumab in combination with etoposide/platinum-based chemotherapy for the first-line treatment of extensive stage small cell lung cancer (ES-SCLC) with relevant platinum doublet therapies used in clinical practice globally.

7.1.2 Methods

Search and study selection of SLR

The following electronic databases were searched including Medline®, Medline® Epub Ahead of Print (In-Process & Other Non-Indexed Citations), Embase and the Cochrane library on July 1, 2018.[52] An additional search of congress proceedings, reference lists of included publications, Health Technology Assessment (HTA) bodies, and the International Clinical Trials Registry Platform (ICTRP) was conducted from the past 3 years to identify relevant evidence. A systematic review and meta-analysis feasibility assessment of treatments in untreated ES-SCLC was conducted.[52]

Meta-analysis feasibility assessment

This included a review of previously published meta-analyses, generation of a best-case scenario evidence network, assessment of trial comparability, and generation of outcome-specific evidence networks.[52] Note that the current meta-analysis feasibility assessment is based on the April 2018 data cut for the IMpower133 trial taken from the primary clinical study report (data cut off 28 April 2018), dated 7th September 2018. The feasibility assessment explored additional outcomes including the duration of response, time in response, time to deterioration, grade 3-5 adverse events (AEs), serious AEs (SAEs), and treatment-related SAEs, but no evidence networks were feasible for these outcomes.[52]

Quality (risk of bias) assessment of RCTs assessed the following items: randomization allocation, if groups were similar at the outset of the study, blinding, attrition, statistical analysis and conflicts of interest.[52]

Table 7.1: Inclusion and exclusion criteria for systematic review

Clinical effectiveness	Inclusion Criteria
Study design	Prospective RCTs (phase 2-4) with active or placebo or best supportive care (BSC) controls with no restriction on blinding. While single-arm designs were not eligible for data extraction or feasibility assessment, these were tagged and relevant citations were provided in the Submitter's appendix.
Population	Adult patients (≥ 18 years) with histologically or cytologically confirmed ES-SCLC with no prior systemic treatment for ES-SCLC.
Intervention	Atezolizumab, carboplatin or cisplatin plus etoposide, carboplatin plus irinotecan or paclitaxel, and BSC.
Comparators	• Cisplatin plus etoposide • Carboplatin plus irinotecan • Carboplatin plus paclitaxel • Best supportive care
Outcomes	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) Safety • All-grade treatment related adverse events (AE) • Treatment related Grade 3 or 4 AEs • Treatment related serious adverse events (SAE) • Tolerability: Dose reductions and interruptions, discontinuation (any reason), discontinuation (due to AEs) HRQoL • Details of HRQoL and patient reported outcomes measures administered as part of clinical trials were captured
Language Restriction	No restriction. The primary focus was English language publications or non-English language publications with an English abstract.

NMA methodology

A Bayesian approach was used to conduct the NMA analyses which encompassed the formal combination of a prior probability distribution.[53] Since the evidence networks included up to

five trials, there was insufficient data to apply the random effects model correctly. Therefore, it was not feasible to assess heterogeneity using meta-regression and subgroup analyses in the current project. Fixed effects models were applied for all analyses. Median hazard ratios (HRs) and associated 95% credible intervals (CrIs) were reported for time-to-event outcomes. Statistical significance of the data is based on our interpretation of the 95% CrIs. The outcomes investigated included progression free survival (PFS) at 6 months, 2 years, overall survival (OS) at 1 year and 2 years and objective response rate. For the purpose of alignment with the pharmacoeconomic evaluation, data for PFS and OS are reported below.

Based on the few studies included in the current network, the Submitter acknowledged that meta-regression could not be assessed. The Submitter further stated that there were no subgroup analyses appropriate for time to event outcomes as a result of limited subgroup data across the trials of the networks.[53]

For each outcome, the surface under the cumulative ranking (SUCRA) was calculated for each treatment. A SUCRA value of 1 was deemed to be the best treatment whereas a treatment certain to be the worst had a value of 0.[53]

7.1.3 Results

Systematic literature review

The systematic literature review search revealed 8,291 articles and 7,848 articles were excluded. Reasons for exclusions were outlined in the PRISMA flow diagram. Based on the 112 articles identified as potentially relevant, a total of 72 publications met the inclusion criteria for the systematic review.[52] Four publications[54-57] formed a connected evidence network with the IMpower133 trial.[1] The study design and patient characteristics are provided below in Table 7.2.

Table 7.2. Patient characteristics of included studies in the evidence network[52]

Study	Inclusion criteria	Treatment arms	N	Male, n (%)	Age, median (IQR)	ECOG PS, n (%)		Presence of brain metastases, n (%)	Non-protocol follow-up cancer therapies, n (%)
						0	1		
IMpower133 (5) Phase III, double-blind RCT 135 sites globally NCT02763579	• ES-SCLC • Age ≥18 years • ECOG PS 0 or 1 • No prior systemic therapy for ES-SCLC	**Induction** • Atezolizumab 1200 mg on day 1 • Carboplatin at a dose of AUC 5 mg/ml/min on day 1 • Etoposide 100 mg/m2 administered on days 1, 2, and 3 • Treatment administered every 3 weeks up to a total of 4 cycles **Maintenance** • From cycle 5 onwards, atezolizumab 1200 mg given on day 1 of every 21-day cycle *Treat to PD or loss of clinical benefit*	201	130 (64.7)	111 (55.2%) of patients aged <65	73 (36.3)	128 (63.7)	16 (8.0)	• Second-line therapy, 101 (50.2%) • Third-line therapy, 29 (14.4%) • Fourth-line therapy, 3 (1.5%) • Total number of treatments, 138 • Immunotherapy, 6 (3.0%)
		Induction • Placebo 1200 mg on day 1 • Carboplatin at a dose of AUC 5mg/ml/min on day 1 • Etoposide 100 mg/m2 administered on days 1, 2, and 3 • Treatment administered every 3 weeks up to a total of 4 cycles **Maintenance** • From cycle 5 onwards, placebo 1200 mg was given on day 1 of every 21-day cycle (maintenance) *Treat to PD or loss of clinical benefit*	202	132 (65.3)	106 (52.5%) of patients aged <65	72 (35.6)	130 (64.4)	16 (7.9)	• Second-line therapy, 116 (57.4%) • Third-line therapy, 38 (18.8%) • Fourth-line therapy, 15 (7.4%) • Total number of treatments, 176 • Immunotherapy, 15 (7.4%)

Hermes 2008 (57) Phase III, open-label RCT Norway and Sweden	• ES-SCLC • Age ≥18 years • No prior systemic anticancer therapy (Brain metastases not an exclusion criteria)	• Irinotecan at a dose of 175 mg/m2 administered on day 1 • Carboplatin at a dose of AUC 5 mg/ml/min on day 1 • Cycles were repeated on day 21 days for 4 cycles	105	66 (63)	67 (46-81)	56 (63)	NR	49 patients received second-line chemotherapy (13 reinduction)
		• Etoposide at a dose of 120 mg/m2 administered on day 1 to 5 • Carboplatin at a dose of AUC 5 mg/ml/min on day 1 • Cycles were repeated on day 21 days for 4 cycles	104	72 (69)	68 (42-82)	54 (52)	NR	48 patients received second-line chemotherapy (17 reinduction)
Okamoto 2007 (38) Phase III RCT (unclear blinding) Japan JCOG 9702	• ES-SCLC • ECOG PS 0 -2 (age ≥70 years) • ECOG 3 PS (age<70) • Chemotherapy naïve • Expected survival ≥2 months	• Etoposide 80 mg/m2 administered on days 1, 2, and 3 • Carboplatin AUC 5 mg/ml/min on day 1 • Cycles repeated every 3-4 weeks for up to 4 cycles	110	95	74 (56-86)	81	18	68 (62%) patients received second-line chemotherapy after relapse
		• Etoposide 80 mg/m2 administered on days 1, 2, and 3 • Cisplatin at a dose of 25 mg/m2 of BSA on day 1, 2 and 3 • Cycles repeated every 3-4 weeks for up to 4 cycles	110	98	73.5 (55-85)	81	18	62 (56%) patients received second-line chemotherapy after relapse
Schmittel 2011 (22) Phase III, open-label RCT Germany NCT00168896	• ES-SCLC • Age ≥18 years • ECOG PS 0 or 1 • No prior therapy • Life expectancy > 3 months • Karnofsky PS ≥50%	• Irinotecan at a dose of 50 mg/m2 administered on days 1, 8, and 15 • Carboplatin at a dose of AUC 5 mg/ml/min on day 1 • Cycles were repeated on day 29 up to 6 cycles	106	70 (66)	60 (34-80)	NR	(25)	13 patients received additional chemotherapy after disease progression (second and third-line)
		• Etoposide 140 mg/m2 administered on days 1, 2, and 3 • Carboplatin at a dose of AUC 5 mg/ml/min on day 1 • Cycles were repeated on day 22 up to 6 cycles	110	71 (65)	63 (39-80)	NR		23 patients received additional chemotherapy after disease progression (second and third-line)
Skarlos 1994 (16) RCT (unclear phase and blinding) Greece	• Previously untreated SCLC • Age <75 years • WHO PS <3 Data reported for ES-SCLC subgroup-baseline characteristics provided for total SCLC trial population	• Etoposide 100 mg/m2 administered on days 1, 2, and 3 • Cisplatin at a dose of 50 mg/m2 of BSA on day 1 and 2 • Treatment administered every 3 weeks up to a total of 6 cycles	73 (30 ES-SCLC)	66	60 (34-78)	6	52	NR	NR
		• Etoposide 100 mg/m2 administered on days 1, 2, and 3 • Carboplatin at a dose of 300 mg/m2 of BSA on day 1 • Treatment administered every 3 weeks up to a total of 6 cycles	74 (31 ES-SCLC)	67	60 (36-76)	10	43	NR	NR

Abbreviations: AUC, area under curve; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; ES-SCLC; extensive stage SCLC; IQR, interquartile range; NR, not reported; PD, progressed disease; PS, performance status; SCLC, small cell lung cancer; WHO, World Health Organisation.

The quality assessment of the included studies in the evidence network revealed that the highest risk of bias across the studies was associated with study blinding and randomisation.

Meta-analysis feasibility assessment

Of the 72 publications included in the SR, 68 were excluded from the meta-analysis feasibility assessment. There were 61 studies that included comparators not of interest and 7 studies that assessed etoposide plus cisplatin in all arms of the trials at either different doses, number of cycles or schedules and these were not comparisons of interest. Although one study[54] included in the evidence network involved a SCLC population, relevant outcome data for ES-SCLC subgroup was available. Four studies included in the SLR formed a connected evidence network together with the IMpower133 trial. A qualitative assessment of heterogeneity across the five studies included in the evidence network was performed. The Submitter stated that the studies appeared to be homogeneous to combine, however, confirmation from clinicians would be preferred. An indirect comparison of atezolizumab and etoposide and carboplatin versus irinotecan plus carboplatin and etoposide plus cisplatin was investigated in the evidence networks. It was not feasible to include best supportive care and paclitaxel plus cisplatin in the networks due to insufficient data.

Included Studies

The data for PFS across the five trials of the evidence network is presented in Table 7.3.

NMA Results

The NMA reported comparative efficacy results for the following comparators: atezolizumab in combination with etoposide and carboplatin, etoposide plus carboplatin, etoposide and cisplatin, and irinotecan plus carboplatin. However, for the purpose of alignment with the pharmacoeconomic evaluation, results for irinotecan plus carboplatin are not reported here. Within the Canadian landscape, irinotecan is infrequently used in the initial management of SCLC because of concerns around toxicity and a lack of clear superiority. The Submitter conducted two scenario analyses for PFS and OS.[53] A base-case using the adjusted/stratified HRs and a scenario 1 analysis using unadjusted/unstratified HRs were reported across the trials. The results for the base-case using adjusted/stratified HRs are reported below where specified.[53]

Progression-free Survival (PFS)

Two studies were included in the evidence network for PFS shown in Figure 7.1. Other studies in the network did not report a PFS HR. Therefore, the comparison of atezolizumab in combination with carboplatin plus etoposide versus cisplatin plus etoposide was not available.

Figure 7.1. Evidence network for PFS[53]

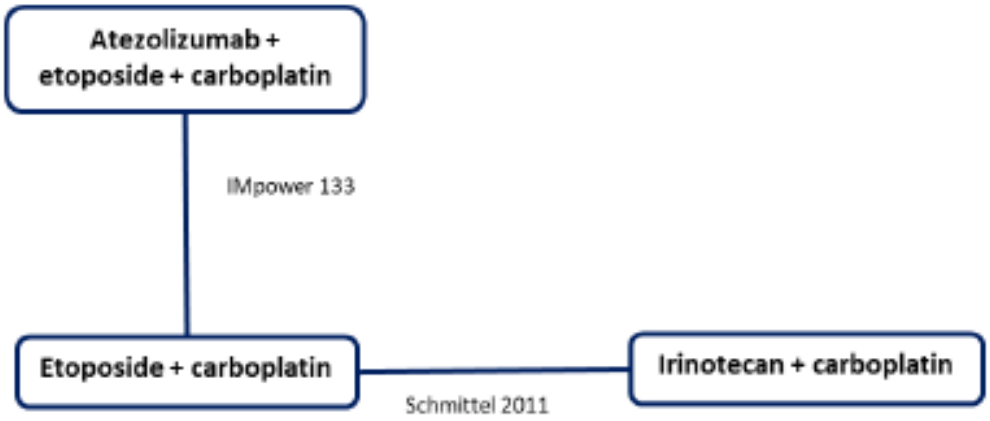


Table 7.3 presents the base-case analysis of PFS adjusted/stratified HRs and SUCRA ranks[53]

Treatment A	Treatment B			SUCRA
	Etoposide plus carboplatin	Etoposide plus carboplatin plus atezolizumab	Irinotecan plus carboplatin	
Etoposide plus carboplatin		1.30 (1.05, 1.60)	1.35 (1.03, 1.77)	0.012
Etoposide plus carboplatin plus atezolizumab	0.77 (0.62, 0.95)		1.04 (0.74, 1.47)	0.701
Irinotecan plus carboplatin	0.74 (0.57, 0.98)	0.96 (0.68, 1.36)		0.787

N.B HRs (95% CrI) are presented for treatment A (row) versus treatment B (column). SUCRA treatment rankings relate to the treatment listed in column 1 (treatment A). Abbreviations: CrI, credible interval; FE, fixed effect; HR, hazard ratio; SUCRA, surface under cumulative ranking curve.

Atezolizumab in combination with etoposide plus carboplatin is associated with a statistically significantly longer PFS compared with etoposide plus carboplatin.

Based on the SUCRA value provided for PFS, treatment with irinotecan and carboplatin was considered the best, however, this treatment is not relevant in the Canadian scope. Treatment with atezolizumab in combination with carboplatin plus etoposide was considered to be the next best.

The results of the NMA from scenario 1 are consistent with the base-case NMA.

PFS at 6 months and 1 year

Three trials reported data for odds ratios (ORs) PFS at 6 months and 12 months shown in Figure 7.2.

Figure 7.2. Evidence network for PFS at 6 months and 1 year[53]

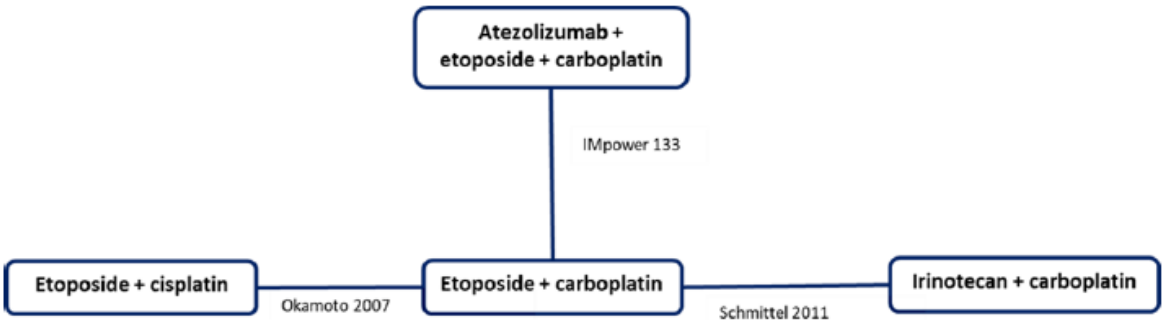


Table 7.4. PFS at 6 months: Matrix of odds ratios (ORs) and SUCRA ranks[53]

Treatment A	Treatment B				SUCRA
	Etoposide plus carboplatin	Etoposide plus carboplatin plus atezolizumab	Etoposide plus cisplatin	Irinotecan plus carboplatin	
Etoposide plus carboplatin		0.64 (0.41, 1.00)	1.19 (0.66, 2.15)	1.87 (0.89, 3.9)	0.26
Etoposide plus carboplatin plus atezolizumab	1.57 (1.00, 2.46)		0.59 (0.34, 1.02)	0.93 (0.46, 1.88)	0.78
Etoposide plus cisplatin	0.84 (0.47, 1.51)	0.54 (0.26, 1.12)		0.50 (0.22, 1.1)	0.12
Irinotecan plus carboplatin	1.69 (0.98, 2.92)	1.08 (0.53, 2.19)	2.01 (0.91, 4.49)		0.84

N.B OR (95% CrIs) are presented for treatment A (row) versus treatment B (column). SUCRA treatment rankings relate to the treatment listed in column 1 (treatment A). Abbreviations: CrI, credible interval; FE, fixed effect; OR, odds ratio; SUCRA, surface under cumulative ranking curve.

Atezolizumab in combination with etoposide plus carboplatin is associated with a higher odds of PFS at 6 months compared with etoposide plus carboplatin. However, this is not statistically significant.

There is no statically significant difference in PFS at 6 months between atezolizumab in combination with etoposide plus carboplatin and etoposide plus cisplatin.

There is no statistically significant difference in PFS at 6 months between etoposide plus carboplatin and etoposide plus cisplatin.

Based on the SUCRA value provided for PFS, treatment with irinotecan and carboplatin was considered the best, however, this treatment is not relevant in the Canadian scope. Treatment with atezolizumab in combination with carboplatin plus etoposide was considered to be the next best.

Table 7.5. PFS at 1 year: Matrix of odds ratios (ORs) and SUCRA ranks[53]

Treatment A	Treatment B				SUCRA
	Etoposide plus carboplatin	Etoposide plus carboplatin plus atezolizumab	Etoposide plus cisplatin	Irinotecan plus carboplatin	
Etoposide plus carboplatin		0.40 (0.18, 0.82)	1.00 (0.58, 1.73)	2.51 (1.02, 6.51)	0.19
Etoposide plus carboplatin plus atezolizumab	2.51 (1.22, 5.45)		0.47 (0.17, 1.23)	1.19 (0.34, 4.05)	0.86
Etoposide plus cisplatin	1.00 (0.58, 1.73)	0.40 (0.15, 0.99)		0.47 (0.15, 1.42)	0.20
Irinotecan plus carboplatin	2.11 (0.81, 5.87)	0.84 (0.25, 2.94)	2.12 (0.70, 6.70)		0.75

N.B OR (95% CrIs) are presented for treatment A (row) versus treatment B (column). SUCRA treatment rankings relate to the treatment listed in column 1 (treatment A). Abbreviations: CrI, credible interval; FE, fixed effect; OR, odds ratio; SUCRA, surface under cumulative ranking curve.

Atezolizumab in combination with etoposide plus carboplatin is associated with a statistically significantly higher odds of PFS at 1 year compared with etoposide plus carboplatin.

There is no statically significant difference in PFS at 1 year between atezolizumab in combination with etoposide plus carboplatin and etoposide plus cisplatin.

There is no statistically significant difference in PFS at 1 year between etoposide plus carboplatin and etoposide plus cisplatin.

Based on the SUCRA value provided for PFS, treatment with irinotecan and carboplatin was considered the best, however, this treatment is not relevant in the Canadian scope. Treatment with atezolizumab in combination with carboplatin plus etoposide was considered to be the next best.

Overall Survival (OS)

Three trials reported data in the evidence network for OS base-case shown in Figure 7.3

Figure 7.3. Evidence network for OS[53]

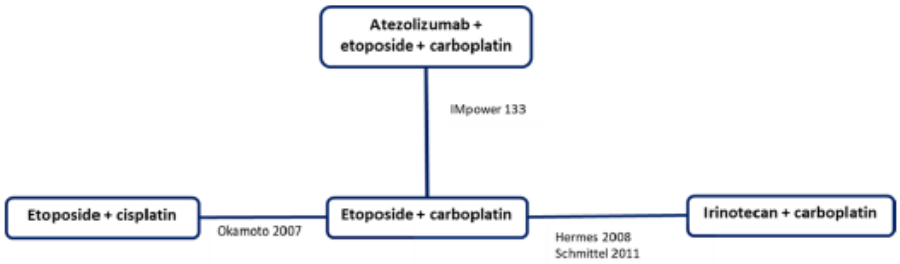


Table 7.6 Base-case analysis of OS stratified/adjusted HRs[53]

Treatment A	Treatment B				SUCRA
	Etoposide plus carboplatin	Etoposide plus carboplatin plus atezolizumab	Etoposide plus cisplatin	Irinotecan plus carboplatin	
Etoposide plus carboplatin		1.43 (1.10, 1.84)	0.99 (0.74, 1.32)	1.41 (1.14, 1.74)	0.18
Etoposide plus carboplatin plus atezolizumab	0.70 (0.54, 0.91)		0.69 (0.47, 1.02)	0.99 (0.71, 1.38)	0.83
Etoposide plus cisplatin	1.01 (0.76, 1.34)	1.44 (0.98, 2.11)		1.42 (0.99, 2.03)	0.18
Irinotecan plus carboplatin	0.71 (0.57, 0.88)	1.01 (0.72, 1.41)	0.70 (0.49, 1.01)		0.81

N.B HR (95% CrIs) are presented for treatment A (row) versus treatment B (column). SUCRA treatment rankings relate to the treatment listed in column 1 (treatment A). Abbreviations: CrI, credible interval; FE, fixed effect; HR, hazard ratio; SUCRA, surface under cumulative ranking curve.

Atezolizumab in combination with etoposide plus carboplatin is associated with a statistically significantly longer OS compared to patients that received etoposide plus carboplatin.

There is no statistically significant difference in OS between atezolizumab in combination with etoposide plus carboplatin and etoposide plus cisplatin.

There is no statistically significant difference in OS between etoposide plus carboplatin and etoposide plus cisplatin.

Based on the SUCRA value provided for OS, treatment with atezolizumab in combination with carboplatin plus etoposide was considered to be the best.

The results of the NMA from scenario 1 are consistent with the base-case NMA

<u>OS at 1 or 2 years</u>

Four trials reported data for OS at 1 or 2 years base-case shown in Figure 7.4. Due to insufficient follow up for 2 years OS data in the IMpower133 trial, the NMA was conducted for OS at 1 year only.

Figure 7.4. Evidence network for OS at 1 year[53]

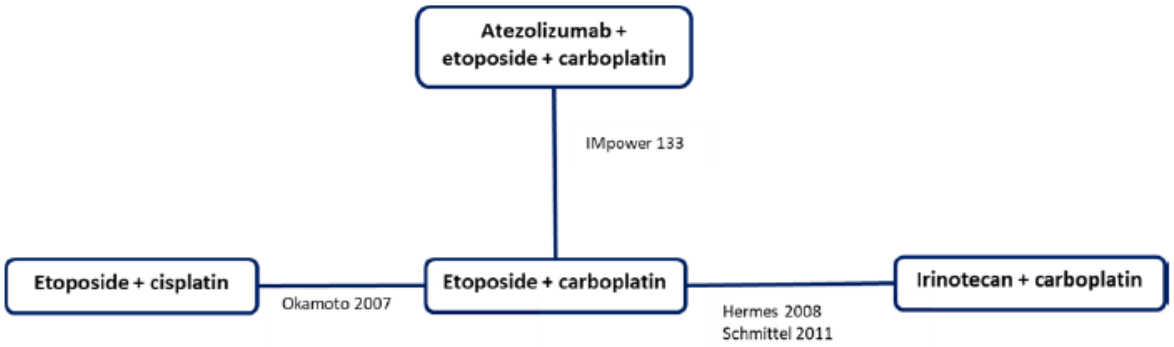


Table 7.7. NMA for OS results at 1 year; Matrix of ORs (95% CrI) and SUCRA ranks[53]

Treatment A	Treatment B				SUCRA
	Etoposide plus carboplatin	Etoposide plus carboplatin plus atezolizumab	Etoposide plus cisplatin	Irinotecan plus carboplatin	
Etoposide plus carboplatin		0.57 (0.38, 0.85)	1.26 (0.73, 2.19)	2.2 (1.12, 4.35)	0.28
Etoposide plus carboplatin plus atezolizumab	1.75 (1.17, 2.61)		0.67 (0.44, 1.01)	1.17 (0.66, 2.07)	0.90
Etoposide plus cisplatin	0.79 (0.46, 1.38)	0.45 (0.23, 0.90)		0.53 (0.27, 1.06)	0.08
Irinotecan plus carboplatin	1.50 (0.99, 2.26)	0.86 (0.48, 1.53)	1.88 (0.95, 3.75)		0.74

N.B OR (95% CrIs) are presented for treatment A (row) versus treatment B (column). SUCRA treatment rankings relate to the treatment listed in column 1 (treatment A). Abbreviations: CrI, credible interval; FE, fixed effect; OR, odds ratio; SUCRA, surface under cumulative ranking curve.

Atezolizumab in combination with etoposide plus carboplatin is associated with a statistically significantly higher odds of OS at 1 year compared with etoposide plus carboplatin.

There appears to be no difference in treatment between etoposide plus carboplatin plus atezolizumab with etoposide plus cisplatin at 1 year as the upper limit of the 95% CrI is close to the value of 1.

There is no statistically significant difference in OS at 1 year between etoposide plus carboplatin and etoposide plus cisplatin.

Based on the SUCRA value provided for OS, treatment with atezolizumab in combination with carboplatin plus etoposide was considered to be the best.

7.1.4 Critical Appraisal of the ITC

The quality of the NMA provided by the Submitter was assessed according to the recommendations made by the ISPOR Task Force on Indirect Treatment Comparisons.[58] Details of the critical appraisal are presented below.

Table 7.8 Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis adapted from Jansen et al.[58]

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	Yes
2. Are any critical interventions missing?	No. Members of CGP stated that within the Canadian landscape, irinotecan is infrequently used in the initial management of SCLC because of concerns around toxicity and a lack of clear superiority.
3. Are any relevant outcomes missing?	Yes. Health related quality of life and safety was not reported in the NMA. The following outcomes were assessed: PFS, OS and ORR.

ISPOR Questions	Details and Comments‡
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes. A summary of the systematic literature review used to conduct the NMA was reported. The information sources, search strategy and study selection criteria were clearly reported.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	N/A. There is no closed loop.
7. Is it apparent that poor quality studies were included thereby leading to bias?	Potentially. A risk of bias assessment of RCTs was conducted using the seven-criteria checklist outlined in the NICE single technology appraisal (STA) user guide. The highest risk of bias across the studies was associated study blinding and randomisation.[52]
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Unlikely. All studies were published at the time the SLR and NMA were completed. All studies included appear to report their planned outcomes.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Yes. In the Skarlos 2004 trial, baseline characteristics are reported for the SCLC population and not the ES-SCLC subgroup of interest for this review. Okamoto 2007 included an elderly, high-risk population and included patients with an age range of 55-86 years and 92% of patients were ≥70 years whereas 54% of the trial patient population in the IMpower133 trial was <65 years. Patients with ECOG PS 0-1 ranged from 50% to 100%, with a mean of 77% across the trials which suggests moderate variation across the included trials.[52]
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Yes. Age, gender, ECOG performance status, metastatic sites, ethnicity and smoking history were identified as potential treatment effect modifiers. The Submitter did acknowledge there was variability across the trials and within the treatment groups for the treatment effect modifiers of gender and ECOG performance status.[52]
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Yes. The use of Bayesian network preserves within study randomization
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Not possible. There was no closed loop.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	Not applicable.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Yes. The Submitter stated that only fixed effects models were applied for the analyses because of insufficient number of trials.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable. Since the evidence networks included up to five trials, there was insufficient data to apply the random effects model correctly.
17. If there are indications of heterogeneity, were subgroup analyses or meta-	No. The Submitter noted there was insufficient data to investigate heterogeneity via meta-regression due to the small

ISPOR Questions	Details and Comments‡
regression analysis with pre-specified covariates performed?	number of trials and there was limited availability of comparable subgroup data across the trials of the network.[53]
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes. The NMA evidence networks are presented
19. Are the individual study results reported?	Yes. The Submitter provided the base case for PFS, OS, and ORR in the NMA.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Not applicable. There was no closed loop.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes. Measures of uncertainty were reported for each hazard ratio.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**Yes.** The submitter provided the surface under the cumulative ranking (SUCRA) for each treatment. A SUCRA value of 1 was deemed to be the best treatment whereas a treatment certain to be the worst had a value of 0
23. Is the impact of important patient characteristics on treatment effects reported?	**No.**
24. Are the conclusions fair and balanced?	**Yes.** Reasonably interpreted the results considering the limitations of the analysis.
25. Were there any potential conflicts of interest?	**Unclear.** The submitted systematic literature review and NMA were completed by an external consultancy group hired by the submitter.
26. If yes, were steps taken to address these?	**Unclear.** Potential conflicts of interest were outlined.

7.1.5 Conclusions

Progression Free Survival

Atezolizumab in combination with etoposide plus carboplatin is associated with a statistically significantly longer PFS compared with etoposide plus carboplatin. The NMA base case result of PFS is the same as the PFS result reported in IMpower133 trial (HR = 0.77, 95% CI 0.62-0.96).[53] Atezolizumab in combination with etoposide plus carboplatin is associated with a higher odds of PFS at 6 months compared with etoposide plus carboplatin (OR= 1.57, 95% CrI 1.00- 2.46). There was a statistically significant higher odds of PFS at 1 year in favour of atezolizumab in combination with etoposide plus carboplatin compared with etoposide plus carboplatin (OR=2.51, 95% CrI 1.22, 5.45). There was no statically significant difference in PFS at 6 months (OR=0.59, 95% CrI 0.34-1.02) and 1 year (OR=0.47, 95% CrI 0.17-1.23) between atezolizumab in combination with etoposide plus carboplatin and etoposide plus cisplatin.[53]

Overall Survival

In the base case, atezolizumab in combination with etoposide plus carboplatin was associated with a statistically significantly longer OS benefit compared with etoposide plus carboplatin (HR=0.70, 95% CrI 0.54-0.91).[53] Atezolizumab in combination with etoposide plus carboplatin was associated with a statistically significantly higher odds of OS at 1 year compared with etoposide plus carboplatin (OR=1.75, 95% CrI 1.17-2.61). There appears to be no difference in treatment between atezolizumab in combination with etoposide plus carboplatin compared with etoposide plus cisplatin at 1 year as the upper limit of the 95% CrI is close to the value of 1 (OR=0.67, 95% CrI 0.44-1.01).[53]

The validity of the NMA is based on three assumptions (i.e., similarity, homogeneity, and consistency) which were assessed in this review. It is important to note that the NMA base case result of PFS is the same as the PFS result reported in the IMpower133 trial. Thus, the base case for PFS did not provide any new data. Heterogeneity was not assessed due to the small size of the evidence networks. However, a qualitative assessment of heterogeneity revealed that there was variability both across the trials and within treatment groups for gender and ECOG performance status.[52] Thus, the homogeneity assumption was violated. The quality assessment of the included studies in the evidence network revealed that the highest risk of bias across the studies was associated with study blinding and randomisation which may introduce selection bias.[52] Furthermore, the robustness of the analysis is unclear as one trial included in the network of evidence involved an elderly, high-risk population and a sensitivity analysis was not conducted to exclude this trial. Due to a lack of a closed loop in the evidence network, the consistency between direct and indirect comparisons could not be assessed. Members of CGP noted within the Canadian landscape, irinotecan is infrequently used in the initial management of SCLC because of concerns around toxicity and a lack of clear superiority. While a sensitivity analysis with the exclusion of irinotecan trials may have informed how the effect estimates varied, the evidence network is sparse and this may not have been feasible. Other outcomes of interest (e.g., health related quality of life and safety) were not evaluated in this NMA. Finally, the submitted systematic review and NMA were completed by external consultancy groups hired by the submitter. As a result, the information provided in the reports should be viewed considering this potential conflict of interest and lack of peer-review. Based on the aforementioned limitations, the comparative efficacy estimates may be biased. Thus, the certainty in the results reported for PFS and OS is limited and should be interpreted with caution.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Method Team did not identify other relevant literature proving supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lung Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on atezolizumab (Tecentriq) in combination with carboplatin and etoposide for extensive stage small cell lung cancer (ES-SCLC) Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. Sponsor, as the primary data owner, did not agree to the disclosure of Clinical information, therefore, this information has been redacted in this Recommendation and publicly available guidance report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Lung Clinical Guidance Panel is comprised of three clinical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2019**, Embase** 1974 to 2019 March 14**, Ovid MEDLINE(R) ALL** 1946 to March 14, 2019

#	Searches	Results
1	(atezolizumab* or Tecentriq* or tecntriq or MPDL3280A or MPDL-3280A or RG7446 or RG-7446 or 52CMI0WC3Y).ti,ab,ot,kf,kw,hw,rn,nm.	3919
2	Carboplatin/	75995
3	Carboplatin/ or (carboplat* or Diammine* or Paraplatin* or Blastocarb* or Carbosin* or Carbotec* or Ercar* or Neocarbo* or Platinwas* or Ribocarbo* or Nealorin* or boplatex* or carplan* or cycloplatin* or erbakar* or ifacap* or kemocarb* or JM8 or JM 8 or oncocarbin* or paraplatin* or CBDCA or CCRIS 3404 or CCRIS3404 or EINECS 255-446-0 or HSDB 6957 or HSDB6957 or NSC 201345 or NSC201345 or NSC 241240 or NSC241240 or BG3F62OND5).ti,ab,ot,kf,kw,hw,rn,nm.	93427
4	2 or 3	93427
5	Etoposide/	100398
6	Etoposide/ or (etopos* or Lastet* or Toposar* or Vepesid* or Zuyeyidal* or Eposide* or Eto-GRY or Exitop* or Onkoposid* or Riboposid* or Celitop* or Etomedac* or Eposin* or HSDB 6517 or Celltop* or citodax* or citodox* or epsidox* or etomedac* or etomedec* or etophos* or etopol* or etopoxan* or etopophos* or etopofos* or etosid* or fastet* or nexvep* or posid* or topresid* or vespid* or vp tec* or HSDB6517 or NK 171 or NK171 or NSC 141540 or NSC141540 or VP 16* or VP16* or 6PLQ3CP4P3).ti,ab,ot,kf,kw,hw,rn,nm.	120592
7	5 or 6	120592
8	1 and 4 and 7	63
9	8 use medall	2
10	8 use cctr	10
11	*atezolizumab/	552
12	(atezolizumab* or Tecentriq* or tecntriq or MPDL3280A or MPDL-3280A or RG7446 or RG-7446).ti,ab,kw,dq.	2057
13	11 or 12	2148
14	*carboplatin/	16095
15	*carboplatin/ or (carboplat* or Diammine* or Paraplatin* or Blastocarb* or Carbosin* or Carbotec* or Ercar* or Neocarbo* or Platinwas* or Ribocarbo* or Nealorin* or boplatex* or carplan* or cycloplatin* or erbakar* or ifacap* or kemocarb* or JM8 or JM 8 or oncocarbin* or paraplatin* or CBDCA or CCRIS 3404 or CCRIS3404 or EINECS 255-446-0 or HSDB 6957 or HSDB6957 or NSC 201345 or NSC201345 or NSC 241240 or NSC241240).ti,ab,kw,dq.	52567
16	14 or 15	52567
17	*etoposide/	20315

18	*etoposide/ or (etopos* or Lastet* or Toposar* or Vepesid* or Zuyeyidal* or Eposide* or Eto-GRY or Exitop* or Onkoposid* or Riboposid* or Celitop* or Etomedac* or Eposin* or HSDB 6517 or Celltop* or citodax* or citodox* or epsidox* or etomedac* or etomedec* or etophos* or etopol* or etopoxan* or etopophos* or etopofos* or etosid* or fastet* or nexvep* or posid* or topresid* or vespid* or vp tec* or HSDB6517 or NK 171 or NK171 or NSC 141540 or NSC141540 or VP 16* or VP16*).ti,ab,kw,dq.	65514
19	17 or 18	65514
20	13 and 16 and 19	28
21	20 use oemezd	16
22	21 not conference abstract.pt.	4
23	9 or 10 or 22	16
24	remove duplicates from 23	13
25	21 and conference abstract.pt.	12
26	limit 25 to yr="2014 -Current"	12
27	24 or 26	25
28	limit 27 to english language	21

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#58	Search #57 AND publisher[sb]	1
#57	Search #54 AND #55 AND #56	2
#56	Search Etoposide[mh] OR etopos*[tiab] OR Lastet*[tiab] OR Toposar*[tiab] OR Vepesid*[tiab] OR Zuyeyidal*[tiab] OR Eposide*[tiab] OR Eto-GRY[tiab] OR Exitop*[tiab] OR Onkoposid*[tiab] OR Riboposid*[tiab] OR Celitop*[tiab] OR Etomedac*[tiab] OR Eposin*[tiab] OR HSDB 6517[tiab] OR Celltop*[tiab] OR citodax*[tiab] OR citodox*[tiab] OR epsidox*[tiab] OR etomedac*[tiab] OR etomedec*[tiab] OR etophos*[tiab] OR etopophos*[tiab] OR etopofos*[tiab] OR etopol*[tiab] OR etopoxan*[tiab] OR etosid*[tiab] OR fastet*[tiab] OR nexvep*[tiab] OR posid* [tiab] OR topresid* [tiab] OR vespid*[tiab] OR vp tec*[tiab] OR HSDB6517[tiab] OR NK 171[tiab] OR NK171[tiab] OR NSC 141540[tiab] OR NSC141540[tiab] OR VP 16*[tiab] OR VP16*[tiab] OR 6PLQ3CP4P3[rn]	28039
#55	Search Carboplatin[mh] OR carboplat*[tiab] OR Diammine*[tiab] OR Paraplatin*[tiab] OR Blastocarb*[tiab] OR	19678

Search	Query	Items found
	Carbosin*[tiab] OR Carbotec*[tiab] OR Ercar*[tiab] OR Neocarbo*[tiab] OR Platinwas*[tiab] OR Ribocarbo*[tiab] OR Nealorin*[tiab] OR boplatex* [tiab] OR carplan*[tiab] OR cycloplatin*[tiab] OR erbakar* [tiab] OR ifacap*[tiab] OR kemocarb*[tiab] OR JM8[tiab] OR JM 8[tiab] OR oncocarbin*[tiab] OR paraplatin*[tiab] OR CBDCA[tiab] OR CCRIS 3404[tiab] OR CCRIS3404[tiab] OR EINECS 255-446-0[tiab] OR HSDB 6957[tiab] OR HSDB6957[tiab] OR NSC 201345[tiab] OR NSC201345[tiab] OR NSC 241240[tiab] OR NSC241240[tiab] OR BG3F62OND5[rn]	
#54	Search Atezolizumab[supplementary concept] or atezolizumab*[tiab] OR Tecentriq*[tiab] OR tecntriq*[tiab] OR MPDL3280A[tiab] OR MPDL-3280A[tiab] OR RG7446[tiab] OR RG-7446[tiab] OR 52CMI0WC3Y[rn]	612

3. Cochrane Central Register of Controlled Trials (Central)
   Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

World Health Organization
http://apps.who.int/trialsearch/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Tecentriq/atezolizumab, small-cell lung cancer

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Tecentriq/atezolizumab, small-cell lung cancer

Conference abstracts:

American Society of Clinical Oncology (ASCO)

http://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Tecentriq/atezolizumab, small-cell lung cancer-last 5 years

Detailed Methodology

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-Mar 14, 2019) with in-process records & daily updates via Ovid; Embase (1974-Mar 14, 2019) via Ovid; The Cochrane Central Register of Controlled Trials (February 2019) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Tecentriq, atezolizumab, carboplatin and etoposide.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of August 22, 2019.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov, World Health Organization International Clinical Trials Registry and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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