pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation, the feedback from eligible stakeholders, and concerns raised in the Sponsor's Procedural Review Request (submitted on December 16, 2019). This pERC Final Recommendation supersedes the pERC Initial Recommendation and Final Recommendation dated Dec 5, 2020.

NOTE: This Recommendation supersedes the pERC Final Recommendation for this drug and indication dated December 5, 2019, as a result of a Procedural Review Request.

Drug: Atezolizumab (Tecentriq)

Submitted Reimbursement Request:
In combination with a platinum-based chemotherapy and etoposide for the first-line treatment of patients with extensive-stage small cell lung cancer. Maintenance atezolizumab should be continued until loss of clinical benefit or unacceptable toxicity.

Submitted By: Hoffmann-La Roche Limited	**Manufactured By:** Hoffmann-La Roche Limited
NOC Date: August 8, 2019	**Submission Date:** March 4, 2019
Initial Recommendation: October 3, 2019	**Final Recommendation:** December 5, 2019 **Revised:** January 30, 2020.

Approximate per Patient Drug Costs, per Month (21 Days)	Atezolizumab costs $5.65 per mg. 1,200 mg intravenously on day 1 of every 21-day cycle. Cost per 21-day cycle: $6,776.00.

pERC RECOMMENDATION

☐ **Reimburse**

☐ **Reimburse with clinical criteria and/or conditions***

☒ **Do not reimburse**

* If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC does not recommend reimbursement of atezolizumab (Tecentriq) 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).

pERC made this recommendation because it was unable to conclude that there is a clinically meaningful net benefit with atezolizumab (Tecentriq) in combination with a platinum-based chemotherapy and etoposide compared with platinum-based chemotherapy and etoposide in this patient population. While pERC noted that there is an unmet need for additional effective treatments in this setting, atezolizumab in combination with a platinum-based chemotherapy and etoposide had only a very modest overall survival (OS) and progression-free survival (PFS) benefit compared with platinum-based chemotherapy and etoposide alone. pERC expressed concerns related to whether the small improvements in OS (including the results for updated OS landmark analyses) observed with atezolizumab in combination with platinum-based chemotherapy and etoposide were

	clinically meaningful. pERC was uncertain about whether atezolizumab in combination with a platinum-based chemotherapy and etoposide adequately addresses the need for more effective therapies in this population. pERC was satisfied that atezolizumab in combination with platinum-based chemotherapy and etoposide aligns with patient values of maintaining quality of life, having manageable side effects, and providing an additional treatment choice. pERC concluded that, at the submitted price and given the small magnitude of the OS benefit, atezolizumab in combination with platinum-based chemotherapy and etoposide is not cost-effective compared with platinum-based chemotherapy and etoposide.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC noted that new clinical data comparing atezolizumab in combination with platinum-based chemotherapy and etoposide with standard of care treatments could form the basis of a resubmission to CADTH if comparative efficacy data important to decision-making, such as PFS, OS, and quality of life (QoL), are available. Specifically, trials should be designed to detect durable long-term survival benefits as has been seen with immunotherapies across multiple tumour types.

SUMMARY OF pERC DELIBERATIONS

Lung cancer represents the second most common cause of cancer among both men and women in Canada and small cell lung cancer (SCLC) accounts for 12% to 15% of lung cancer cases. Approximately one-third of patients have limited-stage (LS) SCLC at presentation, whereas two-thirds have extensive-stage (ES) disease. In ES-SCLC, the median time to progression is typically between four and five months with median overall survival (OS) between 10 to 12 months. A platinum drug (cisplatin or carboplatin) in combination with etoposide has been the standard of care systemic therapy for SCLC for several decades. A variety of new treatment options have been evaluated during the last 20 years, however, none of these have resulted in clear improvements in OS for patients with SCLC. pERC agreed with the pCODR Clinical Guidance Panel (CGP) and the registered clinicians providing input to this submission that there is an unmet need for effective and tolerable treatment options that extend survival for patients with ES-SCLC.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

Procedural Review Request

pERC issued a Final Recommendation on December 5, 2019, not to reimburse atezolizumab (Tecentriq) in combination with a platinum-based chemotherapy and etoposide for the first-line treatment of patients with ES-SCLC. 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]) 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. As part of the re-deliberations, pERC thoroughly assessed the updated OS landmark analyses at 18 months and 24 months. Following substantial discussion, pERC agreed that the data suggested a decline in the absolute improvement in OS from 18 to 24 months for patients treated with atezolizumab in combination with carboplatin and etoposide (A+C+E). pERC noted that based on these data, it could not confidently conclude that treatment with A+C+E will produce a plateau in the tail of the survival curve, signaling long-term survivors. pERC therefore maintained its Recommendation, issued on Dec 5, 2019, concluding that the available survival data were insufficient to determine the presence of long-term survivors and that there was considerable uncertainty about the magnitude of the clinical benefit of A+C+E compared with carboplatin and etoposide (C+E).

Previous pERC Recommendation

pERC deliberated on the results of one randomized, double-blind, multi-centre, phase III trial (IMpower133), that evaluated the efficacy and safety of A+C+E compared with C+E for the first-line treatment of patients with ES-SCLC. pERC noted that the absolute benefit in median OS, a co-primary outcome, between the A+C+E arm and the C+E arm was two months. Although pERC considered that the results were statistically significant, the Committee discussed that the observed difference in favour of A+C+E was modest. pERC was uncertain whether treatment with A+C+E was associated with long-term survival in treated patients as has been seen with immunotherapies across multiple tumour types. pERC debated upon the magnitude of clinical benefit that would be required to support a funding recommendation. Following substantial discussion and despite conflicting opinions, the majority of pERC members considered that there was considerable uncertainty about the magnitude of clinical benefit of A+C+E compared with C+E, considering the insufficient follow-up period of OS in the IMpower133 trial to determine the presence of long-term survivors.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed the feedback provided by the sponsor and the registered clinicians from Lung Cancer Canada (LCC) suggesting that the absolute median OS benefit alone does not adequately convey the clinical value of this regimen. While the sponsor noted that the hazard ratio (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 two months. pERC agreed with the responses provided by the CADTH Methods Team and the CADTH CGP in the final CGR, noting that in order to assess comparative OS benefit, full Kaplan-Meier curves of respective interventions need to be considered. pERC 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. It is therefore advisable to consider all three measures (i.e., HR, medians, and percentage of patients alive at a certain time point) when interpreting the survival data. pERC concluded that the available survival data were insufficient to determine the presence of long-term survivors and that there was considerable uncertainty about the magnitude of clinical benefit of A+C+E compared with C+E.

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, KEYNOTE-028, KEYNOTE-158, and CHECKMATE-331) 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 a platinum-based chemotherapy and etoposide in first-line ES-SCLC. pERC agreed with the response provided by the CGP in the final CGR noting that a patient on third-line treatment for SCLC has likely a slower growing tumour than patients in the first line (especially when prior treatments were all chemotherapy regimens). pERC also noted that studies in later lines may be prone to selection bias resulting from including patients that potentially have a more favourable biological profile than those in earlier lines. Therefore, pERC cautioned against drawing firm conclusions from cross-trial comparisons including patients on different lines of therapy for SCLC.

Furthermore, the Committee discussed feedback provided by the sponsor, the registered clinicians from LCC, and the patient advocacy group from LCC noting that pERC has recognized a similar magnitude of survival benefit as clinically meaningful in a number of tumour areas (e.g., hepatocellular carcinoma, advanced melanoma, squamous cell carcinoma of the head and neck, etc.) that are similarly difficult to treat with high unmet need. Moreover, the registered clinicians and the patient group from LCC highlighted that previous CADTH oncology reviews for immunotherapies with similar OS HR results had received conditional positive Final pERC Recommendations. pERC acknowledged that the Committee has made conditional positive Final Recommendations for previous pCODR reviews for immunotherapies for reasons that are context (drug and disease) specific. As a principle, the Committee considers a review based on its own merits and the evidence presented for the drug under consideration. pERC agreed that in addition to the trial evidence, there are other considerations that go into making recommendations, such as — but not limited to — the unmet need for alternative treatments, patient values, and economic considerations. pERC reiterated that in this instance the Committee could not confidently conclude that the modest improvement in OS in the A+C+E group compared with the C+E group was clinically meaningful, given the uncertainty in the long-term survival of patients treated with A+C+E.

pERC considered that there is an unmet need for effective treatment options with little progress seen in the management of ES-SCLC during the past 20 to 30 years. However, given the uncertainty in the long-term survival of patients treated with A+C+E, the Committee could not confidently conclude that the modest improvement in median OS in the A+C+E group compared with the C+E group was clinically meaningful and adequately addressed the need for more effective therapies for patients with ES-SCLC.

pERC deliberated on the toxicity profile of A+C+E and noted that the incidence and severity of adverse reactions were broadly similar between the two treatment groups and consistent with the safety profile of immune checkpoint inhibitor therapies in non-small cell lung cancer (NSCLC). pERC agreed with the CGP that the adverse event (AE) profile was largely driven by the expected AEs from C+E. The most common treatment-emergent adverse events (TEAEs) were of grade 3 to 4 and included neutropenia, anemia, and neutrophil count decease. Other common AEs (grade 1 to 2) included alopecia, nausea, anemia, fatigue, and neutropenia. pERC noted that the overall incidence of immune related AEs was slightly higher in the A+C+E group compared with the C+E group. The most common immune related AEs were rash followed by hypothyroidism. pERC agreed with the CGP and the registered clinicians providing input that A+C+E has a manageable toxicity profile with no new safety concerns.

pERC members discussed the available patient-reported outcomes data from the IMpower133 trial and noted that the QoL scores (physical function and health-related quality of life [HRQoL]) showed an immediate improvement, which was sustained in HRQoL scores through week 54 in patients that received

A+C+E. pERC noted that the trial data suggested that the addition of atezolizumab to C+E did not worsen the safety profile or symptom burden. However, pERC noted that the reported outcomes were descriptively analyzed and should be interpreted with caution.

pERC deliberated on input from two patient advocacy groups. Few patient respondents had direct experience using atezolizumab and those who did were mostly diagnosed with NSCLC; only one patient had received second-line treatment with atezolizumab in combination with chemotherapy and was diagnosed with SCLC. pERC was uncertain about whether the experiences of patients with NSCLC can be generalized to patients with SCLC. Moreover, pERC noted that the experience of one patient with SCLC may not be representative of the larger patient population with SCLC. Overall, pERC noted that 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. pERC considered that patients value having more treatment options, longer survival, improved QoL, fewer side effects, and no cost burden to patients. pERC concluded that A+C+E aligned with patient values because it maintains QoL, has manageable side effects, and provides an additional treatment choice. However, the magnitude of benefit of A+C+E is uncertain compared with currently available treatment options.

Upon reconsideration, pERC discussed feedback from the patient advocacy group of LCC and the sponsor noting that the Institut national d'excellence en santé et services sociaux (INESSS) had deemed the survival benefit of atezolizumab in combination with platinum-based chemotherapy and etoposide as clinically significant and had recognized its therapeutic value. pERC noted that as an independent health technology assessment (HTA) body, pERC's decisions on drug reimbursement should not be influenced by the decisions of other HTA bodies. In addition, pERC discussed feedback from the sponsor that the US FDA and Health Canada have approved the use of atezolizumab in combination with carboplatin and etoposide in the present setting. The sponsor noted that this position is further supported by recommendations in the National Comprehensive Cancer Network (NCCN) guidelines. pERC noted that regulatory agencies and organizations producing clinical practice guidelines have different objectives than HTA bodies. Regulatory agencies generally focus on the minimum efficacy level and acceptable safety profile, while the purpose of clinical practice guidelines is to optimize patient care, informed by safety and efficacy of alternative care options. HTA is broader in that it examines the comparative effectiveness of different treatment strategies looking at multiple dimensions while aiming to provide a balance between the values, needs, preferences, and perspectives of patients and those of society.

pERC deliberated upon the cost-effectiveness of A+C+E and concluded that it is not cost-effective when compared with C+E for the first-line treatment of patients with ES-SCLC. pERC noted that the sponsor's base-case incremental cost-effectiveness ratio (ICER) was lower than the pCODR Economic Guidance Panel's (EGP) reanalyzed ICER estimate. The Committee noted that the EGP made the following changes to the model to address some of its limitations: (1) replacing the health utility values for the PFS and the progressive disease (PD) states with values from the literature and applying health utility decrements due to AEs; (2) applying an alternative terminal care cost from a more recent population-based study of cancer patients in Ontario. In addition, pERC noted the uncertainty in long-term survival estimates based on extrapolation of short-term trial data from IMpower133. pERC reiterated that, based on medians for OS, it is not possible to infer the presence of long-term survivors. Furthermore, pERC deliberated on the cost-effectiveness of A+C+E compared with cisplatin and etoposide (Cis+E). pERC agreed with the EGP that, given the limitations in the submitted network meta-analysis (NMA), the comparative effectiveness of A+C+E versus Cis+E remains uncertain. pERC concluded that, at the submitted price and given the uncertainty in long-term OS benefit, atezolizumab in combination with platinum-based chemotherapy and etoposide is not cost-effective compared with platinum-based chemotherapy and etoposide.

pERC considered the feasibility of implementing a reimbursement recommendation for A+C+E for the first-line treatment of patients with ES-SCLC. pERC noted that the key factors influencing the incremental budget impact included the market share of A+C+E, treatment duration, and the percentage of patients who receive A+C+E. pERC agreed with the CGP that the market share for A+C+E had likely been underestimated, which likely resulted in an underestimate of the total budget impact associated with A+C+E reimbursement. pERC discussed the Provincial Advisory Group's (PAG) request for clarity on the appropriate definition of disease progression; whether the results of the IMpower133 trial can be

generalized to atezolizumab in combination with Cis+E; and whether treatment with A+C+E is appropriate in patients with Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or in patients requiring radiation for local symptomatic control, prophylactic cranial irradiation (PCI), or whole brain radiation. In addition, PAG identified that that there would be no drug wastage as atezolizumab is supplied as 1,200 mg vials. However, implementation of A+C+E would require additional health care resources and additional chair time.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis (BIA)
- Guidance from the pCODR clinical and economic review panels
- Input from two patient advocacy groups: Lung Cancer Canada (LCC) and the Ontario Lung Association (OLA)
- Input from registered clinicians: a joint clinician input on behalf of five clinicians from LCC and one single clinician input
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- Two patient advocacy groups, LCC and OLA
- Registered clinicians, a joint clinician input on behalf of LCC and one single clinician input
- PAG
- The sponsor, Hoffmann-La Roche Limited.

The pERC Initial Recommendation was to not recommend the reimbursement of atezolizumab (Tecentriq) 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).

Feedback on the pERC Initial Recommendation indicated that the PAG agreed with the Initial Recommendation. The patient advocacy groups, registered clinicians from LCC, and the sponsor disagreed with the Initial Recommendation. The single registered clinician agreed in part with the Initial Recommendation but did not support conversion to Final Recommendation.

pERC reconsidered its Initial Recommendation based on the feedback from eligible stakeholders in the reconsideration meeting on November 21, 2019.

Following the acceptance of a Procedural Review Request from the sponsor (submitted on December 16, 2019) by CADTH, pERC re-deliberated the clinical evidence that included new data on OS landmark analyses at 18 and 24 months, along with the other three components of the pERC deliberative framework.

The pERC Final Recommendation was to not recommend the reimbursement of atezolizumab (Tecentriq) in combination with a platinum-based chemotherapy and etoposide for the first-line treatment of patients with ES-SCLC.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the efficacy and safety of atezolizumab in combination with carboplatin plus etoposide on patient outcomes compared with appropriate comparators for the first-line treatment of patients with ES-SCLC.

Studies included: one randomized phase III trial with an active comparator

The pCODR systematic review included one ongoing, international, multi-centre, phase III, double-blind, placebo-controlled trial: IMpower133. The IMpower133 trial is evaluating the efficacy and safety of atezolizumab in combination with carboplatin plus etoposide (A+C+E) compared with carboplatin and etoposide plus placebo (C+E) as a first-line treatment for ES-SCLC.

A total of 403 patients were randomized in IMpower133, with 201 patients assigned to A+C+E and 202 patients assigned to C+E. Patients who were enrolled in the trial were treated with A+C+E during four 21-

day cycles for the induction phase (atezolizumab: 1,200 mg, administered intravenously on day 1 of each cycle; carboplatin: area under the curve of 5 mg per milliliter per minute, administered intravenously on day 1 of each cycle; etoposide: 100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle). A maintenance phase followed the induction phase where patients received either atezolizumab or placebo based on previous randomized assignment until a toxic effect or disease progression occurred according to the response evaluation criteria in solid tumours (RECIST). At the discretion of the investigator, patients were allowed to continue their trial regimen after the occurrence of disease progression during either the induction or maintenance phase if evidence of clinical benefit existed. During the maintenance phase, prophylactic cranial irradiation (PCI) was allowed, but thoracic radiation therapy was not.

The median time on treatment was longer in the A+C+E than in the C+E arm: A+C+E (atezolizumab: 4.7 months, carboplatin: 2.3 months, etoposide: 2.3 months) versus C+E: (carboplatin: 2.2 months, etoposide: 2.2 months, placebo: 4.1 months).
Patients were eligible for enrolment if they met the following criteria: aged ≥ 18 years, diagnosis of histologically or cytologically confirmed ES-SCLC defined according to the Veterans Administration Lung Study Group staging system, measurable ES-SCLC based on RECIST, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and no prior systemic treatment for ES-SCLC.

Patient population: Median age 64 years; a majority had ECOG PS of 1; and a minority received PCI in both arms

Baseline characteristics were generally well balanced between the two groups. The median age was 64 years (range 28 to 90 years) in both the A+C+E and C+E groups. The use of PCI was balanced between arms in IMpower133, 22 (10.9%) patients in the A+C+E arm and 22 (10.9%) patients in the C+E arm. The majority of patients were enrolled in the US (n = 86), Poland (n = 45), and Japan (n = 42). A total of 128 (63.7%) patients in the A+C+E arm and 135 (66.8%) patients in the C+E arm had ECOG PS of 1. The majority of patients were former smokers, 118 (58.7%) and 124 (61.4%) patients in the A+C+E and the C+E groups, respectively.

Key efficacy results: Modest benefit in Co-primary end points: OS and PFS

The primary end points were overall survival (OS) and investigator-assessed progression-free survival (PFS) 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 rigour and to protect against potential bias. Exploratory subgroup analyses for OS were conducted by age, sex, ECOG PS, presence of brain metastases, and blood tumour mutational burden.

Results reported for PFS 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 A+C+E had a statistically significant PFS compared with patients that were treated with C+E (stratified hazard ratio (HR): 0.77, 95% CI, 0.62 to 0.96, *P* = 0.017). The median PFS was 5.2 months (95% CI, 4.4 to 5.6) in patients that received A+C+E compared with a median PFS of 4.3 months (95% CI, 4.2 to 4.5) for patients that were treated with C+E.

Results reported for OS are based on a planned interim analysis. There were 104 (51.7%) patients who died in the A+C+E group compared with 134 (66.3%) patients who died in the C+E group. At a median follow-up of 13.9 months, patients who received A+C+E had statistically significantly longer OS compared with patients who were treated with C+E (stratified HR: 0.70, 95% CI, 0.54 to 0.91, *P* = 0.0069). The OS end point met the statistical boundary (HR ≤ 0.7453). OS was significantly longer in the A+C+E group (median: 12.3 months, 95% CI, 10.8 to 15.9) compared with the C+E group (median: 10.3 months, 95% CI, 9.3 to 11.3).

OS was also assessed at an updated exploration analysis with longer follow-up (data cut-off date of January 24, 2019). The results from the updated exploratory analysis of OS were consistent with the OS results of the interim analysis. The median OS was two months longer in the A+C+E group (12.3 months) compared with the C+E group (10.3 months) at a median follow-up of 22.9 months (stratified HR: 0.76, 95% CI, 0.60 to 0.94, *P = 0.0154*). The results of OS landmark analyses showed that at 12 months and 18 months there was an estimated 13% absolute improvement in OS in favour of the A+C+E group. At 24 months, the absolute improvement in OS was 5% in favour of the A+C+E group.

Patient-reported outcomes: Quality of life (QoL) descriptively analyzed; the addition of atezolizumab to C+E did not increase toxicity or symptom burden and there was greater improvement in A+C+E group compared with C+E group.

The health-related quality of life (HRQoL) end points were analyzed descriptively and therefore the interpretation of this data is limited. Patient-reported outcomes were assessed using the European Organization for the Research and Treatment of Cancer QoL 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: Disease-related symptoms, treatment-related symptoms, physical function, and HRQoL. 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. 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 three weeks." A clinically meaningful change from baseline was defined as a ≥ 10-point change within a treatment arm. The study measures 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 three months and six months after disease progression per RECIST v1.1 or after treatment discontinuation). 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 A+C+E compared with patients that received C+E. There was a delay in worsening of dyspnea symptoms for patients treated with A+C+E compared with patients who received C+E (HR: 0.75, 95% CI, 0.55 to 1.02). The data for physical function and HRQoL showed an immediate improvement in favour of patients that received A+C+E compared with patients who received C+E. The improvement in HRQoL was sustained through week 54 in patients that received A+C+E. Improvements observed in the patients treated with C+E were small and generally not clinically meaningful.

Safety: Manageable toxicity profile

The population included in the analyses of safety included 198 patients who received at least one 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.

Treatment-emergent adverse events (TEAEs) occurred in 94.9% and 92.3% of patients in the A+C+E and C+E arms, respectively. The most common TEAEs were of grade 3 to 4 and included neutropenia (A+C+E versus C+E: 22.7% versus 24.5%), anemia (A+C+E versus C+E: 14.1% versus 12.2%), and neutrophil count decease (A+C+E versus C+E: 14.1% versus 16.8%). Slightly more patients in the A+C+E arm experienced grade 1-2 TEAEs (36.9%) than in the C+E arm (34.7%). Common grade 1 or 2 TEAEs included alopecia (A+C+E versus C+E: 34.8% versus 33.7%), nausea (A+C+E versus C+E: 31.3% versus 29.6%), anemia (A+C+E versus C+E: 24.7% versus 20.9%), fatigue (A+C+E versus C+E: 19.7% versus 18.9%), and neutropenia (A+C+E versus C+E: 13.1% versus 10.2%). Similarly, there were slightly more serious TEAEs in the A+C+E arm (37.4%) than the C+E arm (34.7%), most commonly grade 3 or 4 events including neutropenia (A+C+E versus C+E: 3.0% versus 4.1%), febrile neutropenia (A+C+E versus C+E: 2.0% versus 4.6%), and thrombocytopenia (A+C+E versus C+E: 2.5% versus 2.0%).

The most commonly reported immune related adverse events (AEs) were rash followed by hypothyroidism (A+C+E versus C+E: all grades rash, 18.7% versus 10.2%; all grades hypothyroidism, 12.6% versus 0.5%).

There were 22 patients in the A+C+E group and 6 patients in the C+E group that experienced AEs that led to withdrawal from any treatment component. There were three mortalities among patients that were treated with A+C+E (death was due to neutropenia in one patient, pneumonia in one patient, and an unspecified cause in one patient) and three mortalities among patients in the C+E group (death was due to pneumonia in one patient, septic shock in one patient, and cardiopulmonary failure in one patient).

Limitations: No direct comparative data to cisplatin and etoposide (Cis+E)

The pCODR Methods Team summarized and critically appraised a sponsor-provided indirect treatment comparison (ITC). The ITC provided comparative efficacy estimates between A+C+E and C+E, Cis+E, and irinotecan plus carboplatin. Although irinotecan was included in the NMA, it was not identified as a relevant comparator for this pCODR review. According to the pCODR Clinical Guidance Panel (CGP) irinotecan is infrequently used in the initial management of SCLC because of concerns around toxicity and a lack of clear superiority. Comparative PFS and OS estimates were included in the submitted economic analysis. The pCODR Methods Team performed a critical appraisal of the NMA and noted that 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 PS. 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. Other outcomes of interest (e.g., HRQoL and safety) were not evaluated in this NMA. Finally, the submitted systematic review and NMA were completed by external consultancy groups hired by the sponsor. 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.

Need and burden of illness: High unmet need for treatments that improve survival with tolerable side effects.

In 2016, there were approximately 28,400 new cases of lung cancer and 20,800 deaths from lung cancer. Lung cancer represents the second most common cause of cancer among both men and women in Canada, and the largest cause of death from cancer. SCLC accounts for only 12% to 15% of lung cancer cases. It represents a significant health burden, with more than 4,000 cases annually across Canada. Historically a treatment-based staging system developed by the Veterans Affairs Lung Cancer Study Group was used in SCLC. 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; though most clinical trials still select patient populations based on the Veterans Affairs Lung Cancer Study Group (VALCSG) classification of LS and ES. Approximately one-third of patients have LS SCLC at presentation, whereas two-thirds have ES disease. The median age of diagnosis of SCLC is approximately 70 and this is a disease that has a strong association with tobacco usage. In ES-SCLC, the median time to progression is typically between four to five months with median OS between 10 to 12 months. Survival beyond two years is generally no more than 15%.

A platinum drug (cisplatin or carboplatin) in combination with etoposide has been the standard of care systemic therapy for SCLC for several decades. A variety of new treatment options have been evaluated during the last 20 years, however none of these have resulted in clear improvements in OS for patients with SCLC. The CGP and the registered clinicians providing input to this submission highlighted that there is a high unmet need for effective and tolerable treatment options that delay disease progression and extend survival for patients with ES-SCLC.

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. pERC agreed that there is still an unmet need for further treatment options for the first-line management of patients with ES-SCLC and acknowledged the CGP's response in the final CGR agreeing that a marginal survival benefit is clinically meaningful in this therapeutic setting. However, pERC reiterated that given the uncertainty in the long-term survival of patients treated with A+C+E, the Committee could not confidently conclude that the modest clinical benefit of A+C+E compared with C+E was clinically meaningful and adequately addressed the need for more effective therapies for patients with ES-SCLC.

Registered clinician input: high unmet need in ES-SCLC setting; IMpower133 results generalizable to atezolizumab in combination with Cis+E.
One joint clinician input on behalf of five clinicians from LCC and one single clinician input were provided for the review of atezolizumab with etoposide and a platinum-based chemotherapy for the first-line treatment of ES-SCLC. Clinicians in 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 PS of 2 or 3, as the IMpower133 trial included only patients with an ECOG PS 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 sets of clinician input. 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.

PATIENT-BASED VALUES

Values of patients with SCLC: extension of life, improvement of QoL, manageable side effects, and additional treatment choice.
Two patient advocacy groups, LCC and the OLA, provided input for atezolizumab with etoposide and a platinum-based chemotherapy for the first-line treatment of patients with 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 a patient's ability to engage with family and friends, and to take part in daily activities or work. Immunotherapy and chemotherapy were treatments patients had received to treat 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.

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. In addition, the following expectations for a better coordinated health system were expressed: incorporating more respiratory and lung cancer specialists and administration of treatments at home rather than in the hospital to remove the need for patients and caregivers to take time off work.

Patient values on treatment: Atezolizumab is effective and tolerable, enabling patients to resume an active life-style; most patient respondents were diagnosed with non-small cell lung cancer (NSCLC) and not SCLC.
Few patient respondents had direct experience using atezolizumab and those who did were mostly diagnosed with NSCLC; only one patient had received second-line treatment with 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 that 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.

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.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility and cost-effectiveness analyses

The EGP assessed one cost-utility analysis (clinical effects measured by quality-adjusted life-years [QALYs] gained) and one cost-effectiveness analysis (clinical effects measured by life-years gained) of A+C+E compared with C+E for the first-line treatment of patients with ES-SCLC.

Basis of the economic model: Clinical and economic inputs

The key clinical outcomes considered in the cost-utility analysis were PFS, OS, time to off treatment, and utilities.

Costs considered in the analysis included those related to drug acquisition and administration, pre-medication, health care resource utilization, subsequent treatment, AEs, PCI, and terminal care.

Drug costs: Treatment cost of atezolizumab, carboplatin, cisplatin, and etoposide

- Atezolizumab (intravenous) costs $5.65 per mg.
  Dosage schedule: 1,200 mg intravenously on day 1 of every 21-day cycle.
  Cost per 21-day cycle: $6,776.00.

- Carboplatin (intravenous) costs $1.73 per mg.
  Dosage schedule: Area under the curve (AUC) 5 intravenously on day 1 of every 21-day cycle.
  Cost per 21-day cycle: $779.00.

- Cisplatin (intravenous) costs $2.70 per mg.
  Dosage schedule: 75 mg/m^2 intravenously on day 1 of every 21-day cycle.
  Cost per 21-day cycle: $351.00.

- Etoposide (intravenously) costs $0.75 per mg.
  Dosage schedule: 100 mg/m^2 intravenously on days 1 to 3 of every 21-day cycle.
  Cost per 21-day cycle: $450.00.

Cost-effectiveness estimates: Not cost-effective at the submitted price; uncertainty in comparative effect estimates derived from the NMA

The sponsor-provided an economic analysis that assessed the cost-effectiveness of A+C+E compared with C+E and Cis+E. The submitted base-case ICERs were lower than the EGP's reanalyzed ICER estimates (A+C+E versus C+E: submitted probabilistic ICER versus EGP's reanalyzed probabilistic ICER: $390,378.00 versus $474,333.00). EGP made the following changes to the model to address some of its limitations:

- Health utility values for the PFS and progressive disease (PD) states were replaced with values from the literature (Labbe et al., 2016) and health utility decrements due to AEs were applied. Health utility values estimated from the IMpower133 trial were significantly higher than the health utilities of Canadian patients with metastatic SCLC reported in Labbe et al. (2017). The EGP noted that the higher health utility values observed from the trial may be a result of selection and reporting bias, as patients who were able to respond to the EQ-5D may be those with better health.

- An alternative terminal care cost was used from a more recent population-based study of cancer patients in Ontario (Horn et al., 2018). Terminal care cost for patients with lung cancer used in the submitted model was outdated (i.e., based on 2002-2003 data by Walker et al., 2011). Additionally, the study cited in the pharmacoeconomic report did not include a control group; therefore, the cost estimate may not represent the costs attributable to the terminal care phase.

In addition, the EGP noted the uncertainty in the comparative efficacy and safety of A+C+E compared with Cis+E. The submitted model assumed Cis+E to have the same efficacy (i.e., PFS) and safety profile as C+E. The HR for OS was derived from an NMA provided by the sponsor. The EGP noted that, given the limitations in the submitted NMA (for more details on the NMA see paragraph on "limitations"), the comparative effectiveness of A+C+E compared with Cis+E remains uncertain.

Key factors that influenced effectiveness included the choice of parametric survival models used to predict OS data and approaches used to estimate health utility values. Key factors that influenced costs included the choice of models to predict treatment duration and shortening the time horizon to 21 months.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact likely underestimated

Considerations with regard to the feasibility of implementing a reimbursement recommendation for A+C+E for the first-line treatment of patients with ES-SCLC: PAG requested clarity on the appropriate definition of disease progression; whether the results of the IMpower133 trial can be generalized to atezolizumab in combination with Cis+E; and whether treatment with A+C+E is appropriate in patients with ECOG PS of 2 or in patients requiring radiation for local symptomatic control, PCI, or whole brain radiation. In addition, PAG identified that that there would be no drug wastage as atezolizumab is supplied as 1,200 mg vials. However, implementation of A+C+E would require additional health care resources and additional chair time. Key factors influencing the Canada-wide incremental budget impact over three years included the market share of A+C+E, treatment duration, and the percentage of patients who receive A+C+E.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

pERC Membership During Deliberation of the Initial Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Matthew Cheung, who did not vote as he was absent from the meeting.
- Dr. Anil Abraham Joy and Dr. Henry Conter, who were excluded from voting due to a conflict of interest.
- Daryl Bell, who did not vote due to his role as a patient member alternate.

pERC Membership During Deliberation of the Final Recommendation (issued Dec 5, 2010)

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Michael Crump, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Anil Abraham Joy and Dr. Henry Conter, who were excluded from voting due to a conflict of interest.
- Daryl Bell, who did not vote due to his role as a patient member alternate.

pERC Membership During Deliberation of the Final Recommendation (issued Jan 30, 2020) in response to the Procedural Review Request

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Winson Cheung, Oncologist
Dr. Michael Crump, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr Michael Crump and Dr Catherine Moltzan, who were not present at the meeting.
- Dr. Maureen Trudeau who did not vote due to her role as the pERC Chair.
- Dr. Anil Abraham Joy, who was excluded from voting due to a conflict of interest.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of atezolizumab in combination with a platinum-based chemotherapy and etoposide for the first-line treatment of patients with extensive-stage small cell lung cancer, through their declarations, four of the members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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