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 pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Atezolizumab (Tecentriq)	
Submitted Reimbursement Request: For the treatment of patients with locally advanced or metastatic non-small cell lung cancer who have progressed on or after systemic chemotherapy until loss of clinical benefit	
Submitted By: Hoffmann-La Roche Limited	**Manufactured By:** Hoffmann-La Roche Limited
NOC Date: April 6, 2018	**Submission Date:** December 15, 2017
Initial Recommendation: June 1, 2018	**Final Recommendation:** June 20, 2018

Approximate per Patient Drug Costs, per Month (28 Days)	Atezolizumab costs $6,776.00 per 1200mg vial. At the recommended dose of 1200mg IV every 3 weeks, atezolizumab costs $322.67 per day and $9,034.67 per 28-day course.

pERC RECOMMENDATION

pERC recommends reimbursement of atezolizumab (Tecentriq) for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) and who have disease progression on or after cytotoxic chemotherapy only if the following conditions are met:

- cost-effectiveness being improved to an acceptable level and
- the drug plan cost of treatment with atezolizumab should not exceed the public drug plan cost of treatment with the least costly alternative immunotherapy.

Patients with genomic tumour driver aberrations (e.g. epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)) should first be treated with targeted agents followed by cytotoxic chemotherapy prior to receiving atezolizumab. Treatment with atezolizumab should continue until confirmed disease progression or unacceptable toxicity. pERC made this recommendation because it was satisfied that there is a net overall clinical benefit with atezolizumab compared with docetaxel, based on statistically significant and clinically meaningful improvements in overall survival, a meaningful improvement in the toxicity profile, and no detriment in quality of life. The Committee was satisfied that atezolizumab aligned with patient values in that it improved survival, had manageable side effects, it reduced disease related symptoms and would also be an additional treatment option for patients.

In the absence of a direct comparison, the Committee considered evidence provided through an indirect treatment comparison with nivolumab and pembrolizumab, the most relevant comparators in this setting. pERC

	concluded that atezolizumab is likely similar in terms of efficacy and safety compared to these agents. pERC concluded that atezolizumab, compared with docetaxel, could not be considered cost-effective in patients with metastatic NSCLC who have disease progression on or after cytotoxic chemotherapy. Given the likelihood of similarity in efficacy and safety among atezolizumab, pembrolizumab and nivolumab, pERC concluded that the price of atezolizumab should not exceed the public drug plan cost of treatment with the least costly alternative immunotherapy.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that there is a net clinical benefit of atezolizumab compared to docetaxel, jurisdictions will need to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of atezolizumab to an acceptable level. The Committee concluded that the cost-effectiveness of atezolizumab compared with pembrolizumab and with nivolumab is likely similar and, as the clinical efficacy and safety are also likely similar between these agents, pERC noted that the incremental cost-effectiveness ratio for each comparison is most sensitive to the prices of these agents. pERC noted that the price of both pembrolizumab and nivolumab are likely lower than the list price used in the submitted economic model due to pricing negotiations with the pan Canadian Pharmaceutical Alliance (pCPA) and as a consequence of drug pricing, atezolizumab was not cost-effective compared to these agents. pERC concluded that the price of atezolizumab should not exceed the public drug plan costs of the least costly immunotherapy reimbursed in this setting. **Optimal Sequencing of Atezolizumab and Other Therapies Unknown** pERC concluded that the optimal sequencing of atezolizumab and other treatments now available for the treatment of advanced or metastatic NSCLC is currently unknown. pERC was, therefore, unable to make an evidence-informed recommendation on sequencing following treatment with atezolizumab. pERC also noted that there is no direct evidence to inform the comparative efficacy of atezolizumab with PD-1 inhibitors (nivolumab and pembrolizumab). Thus, with their overlapping indications, there is no evidence to inform the choice of atezolizumab over the other available agents, or vice versa. There is also no evidence to support using PD-L1/PD-1 inhibitors in sequence (e.g., atezolizumab then nivolumab or pembrolizumab, or vice versa). **Common Approach to Determine Optimal Duration of Treatment** pERC noted that in some patients it may be reasonable to continue treatment beyond disease progression. Based on the OAK and POPLAR trials 40% of patients, considered to still derive clinical benefit by the investigators, continued treatment beyond progression. It is unclear if clinical benefit was related to continued treatment after pseudo-progression. Although there is limited evidence to determine the optimal duration of treatment, pERC agreed that it is reasonable to treat patients until loss of clinical benefit, as was done in the OAK and POPLAR trials. pERC noted that jurisdictions may want to consider developing a common approach to treatment discontinuation for atezolizumab. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

Lung cancer is the leading cause of cancer-related death worldwide, with the majority of patients presenting with non-curable disease. In Canada, an estimated 28, 600 new cases and 21,100 deaths occurred in 2017 from lung cancer, with a five-year survival rate of 18%. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. Non-squamous and squamous cell lung cancer comprise about 70% and 30% of NSCLC, respectively. Treatment decisions for advanced or metastatic NSCLC are typically dependent on the presence or absence and type of driver mutation status of patients in the first-line setting. In patients without a driver mutation, treatments in the second-line setting recently changed to include the use of the immunotherapies nivolumab or pembrolizumab. In jurisdictions where immunotherapies have not yet been implemented, single-agent chemotherapy with docetaxel or pemetrexed may be used. For patients who have a driver mutation (i.e., ALK or EGFR), targeted therapy is used upfront followed by second-line treatment with a platinum doublet and third-line treatment with immunotherapies. Pembrolizumab is also available as a front line therapy in patients with >50% PD-L1 expression level (approximately 30% of front line patients). pERC acknowledged a continued need for new and effective therapies for patients with advanced or metastatic NSCLC that provide improvements in patient survival, have more favourable toxicity profiles, and improve quality of life. However, the Committee agreed that the availability of nivolumab and pembrolizumab demonstrates that there is no urgent unmet need that can be filled by atezolizumab in this setting.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of two randomized controlled trials, OAK (Rittmeyer et al 2016) and POPLAR (Fehrenbacker et al 2016), which compared atezolizumab to docetaxel in adult patients with locally advanced or metastatic NSCLC who had progressed during or after prior platinum-containing chemotherapy regimens. Both trials demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) in favour of atezolizumab compared to docetaxel, with an absolute improvement of 4.6 months and 2.9 months in the OAK and POPLAR trials, respectively. This benefit was maintained in all subgroups except for patients with an EGFR mutation. However, because a small number of patients with an EGFR mutation entered into the trial, pERC noted that this subgroup of patients was very likely underpowered to detect a significant difference in OS. Therefore, pERC agreed that the overall trial results can be generalized to this subgroup. pERC noted that there was no difference in progression-free survival (PFS) between treatment groups. The Committee discussed this discordance between PFS and OS results and noted that this pattern has been observed in other trials evaluating immunotherapies in lung cancer. pERC agreed with the CGP assessment that PFS may be more difficult to evaluate with this class of drugs. pERC discussed the quality of life (QoL) data from the OAK and POPLAR trials and noted that atezolizumab did not result in detriment to patients' quality of life. pERC also discussed the safety data from the two trials and concluded that the toxicity profile of atezolizumab is moderate and manageable compared to docetaxel. Overall, pERC concluded that there is a net overall clinical benefit with atezolizumab in this patient population, based upon statistically significant and clinically meaningful improvements in OS, a manageable toxicity profile, and no apparent detriment in QoL compared with docetaxel. pERC further considered the results of a submitted network meta-analysis between atezolizumab, nivolumab and pembrolizumab, the most relevant comparators in this setting. Although acknowledging the limitations of making cross trial comparisons, pERC noted that the analysis found similar efficacy and safety results among the three immunotherapies. This was supported by conclusions made by the pCODR Clinical Guidance Panel (CGP) on the results of the network meta-analysis. Therefore pERC concluded that the efficacy and safety of the three agents are likely to be similar.

pERC noted that the OAK and POPLAR trials were restricted to patients with ECOG PS 0 to 1 and specifically excluded patients with ECOG PS ≥ 2. pERC discussed the fact that many patients seen in clinical practice generally have a poorer performance status than patients included in the two trials, due to advanced age and stage of disease, and that such patients would have a reduced ability to tolerate conventional chemotherapy regimens. pERC noted the Clinical Guidance Panel (CGP)'s observation that Canadian clinical practice with nivolumab and pembrolizumab has demonstrated tolerability of immunotherapies in ECOG PS 2 patients. The Committee agreed that patients with a good performance

status should be eligible for treatment with atezolizumab. pERC acknowledged the small number of patients with an EGFR or ALK mutation positive disease recruited on the trials but agreed that the overall results of the trials are generalizable to patients with ALK or EGFR mutation positive disease. pERC therefore agreed that patients with driver mutations and who would first receive targeted agents followed by cytotoxic chemotherapy should qualify for atezolizumab. pERC further agreed that atezolizumab was effective regardless of histological type and PD-L1 expression levels. Therefore, there should be no restriction on treatment based on these factors. pERC noted that the reimbursement request is broader than the Health Canada regulatory approval which specifies the use of atezolizumab in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. pERC agreed that it is reasonable to offer this treatment to patients with progression on or after cytotoxic chemotherapy as there may be instances where patients cannot tolerate the platinum portion of their treatment. In these instances, where cytotoxic chemotherapy has been administered, pERC agreed that it would be reasonable to treat patients with atezolizumab, provided they meet all other criteria within this recommendation.

pERC deliberated upon input from two patient advocacy groups concerning atezolizumab and noted that tolerable treatment side effects, control of symptoms, and control of disease progression were most important to patients. Both patient and caregiver respondents reported that the high symptom burden of lung cancer is difficult to manage. Patients expressed a need for a treatment that is both more effective and tolerable given the side effects of chemotherapy. pERC noted that the availability of nivolumab and pembrolizumab offer a more tolerable alternative to chemotherapy to patients in this setting. Based on the statistically significant improvement in overall survival, moderate side effect profile and reduced disease related symptoms, pERC agreed that atezolizumab aligned with patient values. pERC noted atezolizumab would also be an additional treatment option for patients.

pERC deliberated upon the cost-effectiveness of atezolizumab and concluded that, at the submitted price, it is not cost-effective compared to docetaxel. pERC considered estimates provided by the submitter and the reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP). The Committee agreed with the EGP's uncertainty regarding the assumption of a 1% cure rate and with the extrapolation for OS over a 10-year time horizon. pERC agreed with altering these two inputs to remove the 1% cure rate and to reduce the time horizon to 5 years, changes that resulted in a substantial reduction of the incremental gain in quality adjusted life years (QALY) and minor reduction in the incremental cost. pERC noted that this shorter time horizon is aligned with prior economic evaluation for pembrolizumab and nivolumab. pERC also deliberated upon the cost-effectiveness of atezolizumab compared with pembrolizumab and nivolumab and concluded that the effectiveness is likely similar between the three agents however since the price of atezolizumab is higher it is likely not cost effective. Based on the submitted and EGP's sequential analysis, atezolizumab is not cost-effective when compared to pembrolizumab and dominates nivolumab (i.e., more effective and less costly). Based on the submitted network meta-analysis and CGP discussions, pERC agreed that the efficacy and safety of atezolizumab is likely similar to the two other available immunotherapies. pERC agreed that minor differences reported in QALYs between the three agents are not meaningful and that cost effectiveness will largely be dependent on the pricing of each agent relative to the others. pERC therefore noted that the cost effectiveness, as presented in the submitted and EGP's sequential analysis, is very sensitive to the pricing of each available agent. Furthermore, pERC noted that the price of pembrolizumab and nivolumab is likely lower than the list price used in the submitted economic model due to pricing negotiations with the pan Canadian Pharmaceutical Alliance (pCPA) and as a consequence of drug pricing, atezolizumab was not cost-effective compared to these agents. pERC concluded that the price of atezolizumab should not exceed the public drug plan costs of the least costly immunotherapy reimbursed in this setting.

pERC considered factors affecting the feasibility of implementing a positive funding recommendation for atezolizumab. pERC noted that the submitted budget impact analysis (BIA) is most sensitive to the market share and cost of the drug. The submitted BIA reported a cost savings with the incorporation of atezolizumab into the market as the market share for atezolizumab is taken exclusively from nivolumab, the most expensive agent. pERC agreed that if the cost of nivolumab is lower (based on a negotiated price), the BIA of atezolizumab would shift away from being cost saving. As allowed in both trials, pERC agreed that patients should be able to continue treatment beyond RECIST defined disease progression if the investigator deemed the patient to have clinical benefit. In the trial, patients were assessed for progression at baseline, then every 6 weeks until week 36 and every 9 weeks thereafter. Furthermore, pERC noted that atezolizumab's 3 week dosing schedule is an enabler to implementation as it reduces inconvenience of travel and administration time for patients. pERC acknowledged this as an important

factor for patients; however, the dosing schedules of other immunotherapies (i.e. nivolumab) are likely to change in the near future reducing the inconvenience of frequent travel and administration. pERC lastly concluded that the optimal sequencing of atezolizumab and other treatments now available for advanced or metastatic NSCLC is currently unknown and there is currently no evidence to support sequencing immunotherapies such as anti PD-1 and anti PD-L1 therapies.

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
- Guidance from the pCODR clinical and economic review panels
- Input from two patient advocacy group(s) (Lung Cancer Canada (LCC) and The Lung Association – Ontario (OLA))
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One clinician group, [Cancer Care Ontario Lung DAC]
- The PAG
- The submitter [Hoffmann-La Roche Limited]

The pERC Initial Recommendation was to recommend reimbursement of atezolizumab (Tecentriq) for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) and who have disease progression on or after cytotoxic chemotherapy. Feedback on the pERC Initial Recommendation indicated that the manufacturer, PAG, and registered clinician group agreed with the Initial Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of atezolizumab (Tecentriq) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer who have progressed on or after systemic chemotherapy until loss of clinical benefit.

pERC noted that the reimbursement request is broader than the Health Canada regulatory approval which specifies the use of atezolizumab in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. pERC agreed that it is reasonable to offer treatment to patients with progression on or after cytotoxic chemotherapy as there may be instances where patients cannot tolerate the platinum portion of their treatment. In these instances, where cytotoxic chemotherapy has been administered, pERC agreed that it would be reasonable to treat patients with atezolizumab, provided they meet all other criteria within this recommendation.

Studies included: Two randomized controlled trials comparing atezolizumab to docetaxel

The pCODR systematic review included two randomized trials, OAK (N = 1225) and POPLAR (N = 287).

- OAK was a phase III international, multi-centre, open-label randomized controlled trial (RCT) that included adult patients with locally advanced or metastatic NSCLC who had progressed during or after prior platinum-containing chemotherapy regimens.
- POPLAR was a phase II international, multicenter, open-label RCT of atezolizumab versus docetaxel in adult patients with locally advanced or metastatic NSCLC who had progressed during or after prior platinum-containing chemotherapy regimens.

The pCODR review also provided contextual information on manufacturer-submitted indirect treatment comparison of pharmacological interventions used as second or higher lines of treatment for locally advanced/metastatic NSCLC. Based on the results of network meta-analyses, the overall survival hazard ratio's (HR) were similar for atezolizumab, nivolumab and pembrolizumab while all three agents

performed better than docetaxel. pERC discussed the conclusions provided by the CGP and the robustness of the manufacturer submitted network meta-analysis and indirect comparison and agreed that the efficacy and safety of the three agents are likely similar. pERC acknowledged the limitations of making cross trial comparisons but agreed that there was no major limitation that may have impacted the results.

Patient populations: Comparable populations across two trials, treatment beyond progression

Key eligibility criteria for the OAK trial required that patients have measurable disease based on the Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) criteria, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, a life expectancy of 12 weeks or longer, and adequate hematologic and end-organ function. Demographic and baseline characteristics were well balanced between the study groups. The median age in the primary population was 64 years, 61% of the patients were males, 70% were white, and 37% and 63% had an ECOG PS of 0 and 1, respectively. EGFR and ALK mutations positive patients comprised a small proportion of patients on the trial (10% and <1%, respectively). Notably, 16% and 50% of patients respectively had an unknown EGFR and ALK mutation status.

Key eligibility criteria for the POPLAR trial required that patients have measurable disease based on the RECIST (version 1.1) criteria, an ECOG PS of 0 or 1, an adequate hematologic and end-organ function, and have provided tumour specimens for central PD-L1 testing before enrolment. Demographic and baseline characteristics were well balanced between the study groups, except for a 12% greater proportion of female patients in the docetaxel compared to atezolizumab group (35% versus 47%, respectively). Overall, the median age of the patients was 62 years old; 61% male; 79% percent white; and 32% and 68% had an ECOG performance score of 0 or 1, respectively. A small proportion of patients had an EGFR or ALK mutation, 10% and 5%, respectively. pERC discussed the fact that many patients seen in clinical practice generally have a poorer performance status than patients included in the two trials, due to advanced age (if with comorbidities) and stage of disease, and that such patients would have a reduced ability to tolerate conventional chemotherapy regimens. pERC also noted the CGP's justification that Canadian clinical practice with nivolumab and pembrolizumab has demonstrated tolerability of immunotherapies in ECOG PS 2 patients and agreed that patients with a good performance status, beyond ECOG PS 1, should be eligible for treatment with atezolizumab. pERC also acknowledged the small number of patients with an EGFR or ALK mutation positive disease recruited in the trials but agreed that the overall results of the trials are generalizable to patients with ALK or EGFR mutation positive disease.

Patients in both trials were randomly assigned to receive atezolizumab (1200 mg every 3 weeks) or docetaxel (75 mg/m^2 every 3 weeks). Atezolizumab could be continued beyond disease progression in both trials with 40% and 42% of patients in the OAK and POPLAR trials continuing beyond RECIST defined progression until loss of clinical benefit as defined by the clinical investigator.

Key efficacy results: Statistically significant improvement in overall survival relative to docetaxel

The key efficacy outcome deliberated on by pERC was overall survival, the primary outcome in both trials. In the OAK study, the median OS was 13.8 compared to 9.6 months in the atezolizumab and docetaxel groups, respectively (stratified HR= 0.73; 95% CI 0.62, 0.87; p=0·0003). In the POPLAR study, the median OS was 12.6 and 9.7 months in the atezolizumab compared to docetaxel group, respectively (stratified HR 0.73; 95% CI 0.54, 0.99; p=0·040). Both trials demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS), in favour of the atezolizumab group compared to docetaxel with an absolute improvement of 4.6 and 2.9 months in the OAK and POPLAR trials, respectively. This benefit was maintained in all subgroups except for patients with an EGFR mutation. However, because a small number of patients with an EGFR mutation entered into the trial, pERC noted that this subgroup of patients was very likely underpowered to detect a significant difference in OS. Therefore, pERC agreed that the overall trial results can be generalized to this subgroup.

Secondary endpoints included investigator-assessed progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), and safety for both studies. In the OAK study, median PFS was not significantly different between groups (2.8 versus 4 months with atezolizumab and docetaxel, respectively HR = 0.95; 95% CI 0.82, 1.10; p=0.49). ORR was reported to be similar between the two treatment groups (14% in the atezolizumab group and 13% in the docetaxel group). In the POPLAR study, median PFS was not significantly different between groups (3.0 and 2.7 months in the atezolizumab and docetaxel groups, respectively HR = 0.94; 95% CI 0.72, 1.23; p=0.65) with the PFS curves crossing at about

4 months. ORR was reported to be similar between the two treatment groups (14.6% in the atezolizumab group and 14.7% in the docetaxel group). The median DOR was 14.3 months and 7.2 months in the atezolizumab and docetaxel groups (HR=0.41; 95% CI 0.18, 0.96; p=0.034). pERC noted that, as in other trials evaluating immunotherapies in lung cancer, there was no difference in progression free survival (PFS) between treatment groups. The Committee agreed with the CGP assessment that PFS may be more difficult to evaluate with this class of drugs.

Patient-reported outcomes: No quality of life detriment due to atezolizumab

pERC deliberated upon the available quality-of-life data from the OAK and POPLAR trials. In the OAK trial health-related quality of life (HRQoL) was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30 and QLQ-LC13). Based on the EORTC QLQ-C30 data, atezolizumab delayed time to deterioration (TTD) in physical functioning (HR=0.75; 95% CI 0.58, 0.98; p=0.0329) and role functioning (HR=0.79; 95% CI 0.62, 1.00; p=0.0544). However, there was no statistically significant difference between the atezolizumab and docetaxel arms in terms of time to deterioration in global QoL (HR= 0.94; 95% CI 0.72, 1.24). Patients in the atezolizumab group reported numerically improved HRQoL from baseline starting around Cycle 3 and continuing until Cycle 13 (the point at which fewer than 25% of patients who were evaluable for patient-reported outcomes had remained in the study). In the POPLAR trial HRQoL was assessed using the EORTC QLQ-C30 and LC13 questionnaires. Compliance rates for each questionnaire among patients who were still alive and on treatment were above 90% in both arms at each assessment. No clinically meaningful change (improvement or decline) from baseline was observed for patients in the atezolizumab arm during the study period in global health status, functioning (physical, role, emotional, cognitive, and social) or any of the symptom subscales, indicating that atezolizumab did not have a detrimental impact on health related quality of life (HRQoL). Deterioration of at least one lung cancer symptom (10-point or higher change from baseline) was reported in 211 patients (114 in the atezolizumab group and 97 in the docetaxel group).

pERC discussed the quality of life (QoL) data from the OAK and POPLAR trials and noted that atezolizumab significantly delayed the time to deterioration (TTD) for physical and role functioning in the OAK trial. Mean change from baseline for the EORTC-QLQ C30 questionnaire also demonstrated numerical improvements from cycle 3 to 13 in the OAK trial. In the POPLAR trial no clinically meaningful change (improvement or decline) from baseline was observed for patients in the atezolizumab arm during the study period in global health status, functioning or in any of the symptom subscales using the EORTC QLQ-C30 and QLQ-LC13 questionnaires. Overall, pERC agreed that atezolizumab did not result in detriment to patient's quality of life compared to chemotherapy.

Safety: Moderate and manageable toxicity profile

In the OAK trial mortality due to adverse events (AEs) was reported in 2% of patients in each group, and non-fatal serious AEs in 32% and 31% of patients in the atezolizumab and docetaxel groups, respectively. One treatment-related death occurred in the docetaxel group due to a respiratory tract infection. In the OAK trial, fewer patients in the atezolizumab compared to docetaxel group discontinued treatment due to AE's (19% and 31%, respectively), experienced treatment-related grade 3 or 4 AEs (15% and 43%, respectively) and experienced AEs leading to dose modifications, delays or treatment interruption (25% and 34%, respectively). Immune-related AEs (irAEs) were comparable between the two treatment groups (31% in both groups). Immune-related grade 3 or 4 AE's occurred in 6% of patients in the atezolizumab group. In the POPLAR trial, there were fewer grade 3 or 4 AEs (40.0% and 53%,), treatment-related grade 3 or 4 AEs (11% and 39%) and AE's leading to withdrawal of treatment (8% and 22%) in the atezolizumab compared to the docetaxel group, respectively. Grade 5 AE's (4% each) and non-fatal serious AE's (35% and 34%) were comparable between the atezolizumab and docetaxel groups, respectively.

pERC discussed the toxicity profile of atezolizumab and noted input from registered clinicians indicating the toxicity profile of atezolizumab is similar to what is observed with other available immunotherapies. pERC agreed that there was not major safety concern in both trials and that toxicities were lower in the atezolizumab groups compared to docetaxel. Overall, pERC agreed that that the toxicity profile of atezolizumab is moderate and manageable compared to docetaxel.

Need and burden of illness: No urgent unmet need in this setting

Lung cancer is the leading cause of cancer-related deaths worldwide, with the majority of patients presenting with non-curable disease. In Canada, an estimated 28,600 new cases and 21,100 deaths

occurred in 2017 from lung cancer with a five-year survival rate of 18%. The incidence of NSCLC rises with age and the median age at diagnosis is 70 years. NSCLC accounts for 85% of all lung cancers. Treatment decisions for advanced or metastatic NSCLC are typically dependent on the presence or absence and type of driver mutation status of patients in the first-line setting. In patients without a driver mutation, treatments in the second-line setting recently changed to include the use of the immunotherapies, nivolumab or pembrolizumab. In jurisdictions where immunotherapies have not yet been implemented, single-agent chemotherapy with docetaxel or pemetrexed may be used. For patients who have a driver mutation (i.e., ALK or EGFR) targeted therapy is used upfront followed by second-line treatment with a platinum doublet, then third-line treatment with immunotherapies. Pembrolizumab is also available as a front line therapy in patients with >50% PD-L1 expression level (approximately 30% of newly diagnosed patients).

pERC noted that the goals of treatment for patients with advanced-stage NSCLC are primarily palliative; namely, to prolong life while maintaining or improving QoL. Given that most patients have advanced age and advanced stage of disease, pERC noted that a disproportionately greater number of patients at this stage of disease have a poor performance status, as well as a higher likelihood of significant comorbidities that impact their ability to tolerate conventional chemotherapy regimens. pERC noted that nivolumab and pembrolizumab offer a more tolerable alternative to chemotherapy to patients in this setting.

pERC acknowledged a continued need for new and effective therapies for patients with advanced or metastatic NSCLC that provide improvements in patient survival, have more favourable toxicity profiles, and improve quality of life. However, the Committee agreed that the availability of nivolumab and pembrolizumab demonstrates that there is no urgent unmet need that can be filled by atezolizumab in this setting.

Registered clinician input: Atezolizumab to be a third treatment option

Registered clinician input indicated that the use of atezolizumab in NSCLC patients who have progressed beyond first-line treatment would be restricted to patients who were not previously treated with an immunotherapy agent. Those who are EGFR or ALK positive would receive a targeted therapy first line and would not receive atezolizumab until after failure of platinum doublet chemotherapy. Registered clinicians also noted that patients with driver mutations would first be treated with targeted agents before qualifying for atezolizumab.

The clinicians providing input noted that there may be some uptake in the use of atezolizumab in favour of nivolumab, in patients with metastatic adenocarcinoma of the lung who do not have a PD-L1 status or are less than 50% positive, and are EGFR and ALK wildtype. They also noted that nivolumab seems to have a more prominent efficacy profile for squamous lung cancers in clinical trial data compared to non-squamous pathologies. pERC noted input from the CGP which indicated that there is no robust data to determine the superiority of one immunotherapy over another in these subgroups of patients. pERC therefore agreed that the choice of immunotherapy to use in this setting should not be determined based on these criteria until more robust evidence is available. pERC also noted input from clinicians about differences in efficacy outcomes based on an unadjusted indirect (i.e., cross-trial)comparison of the OAK trial with the trials that evaluated nivolumab and pembrolizumab in this setting, trials with different populations and potential confounders. pERC agreed that the results of the network meta-analysis are more robust for drawing comparative conclusions in this instance and re-iterated that the efficacy and safety of the three immunotherapies (atezolizumab, nivolumab and pembrolizumab) are likely similar.

Clinicians providing input noted that in clinical practice, physicians have observed a similar side effect profile between atezolizumab, pembrolizumab and nivolumab. pERC agreed this supported the conclusions made by the CGP and aligned with the moderate toxicity profile observed in the two trials.

Registered clinicians indicated that pembrolizumab and atezolizumab are infused every three weeks while nivolumab is infused every two weeks. Clinicians therefore felt that this advantage could have a significant impact for patient time and hospital resource utilization. pERC acknowledged the convenience of less frequent administration to patients, however the dosing schedules of other immunotherapies (i.e. nivolumab) are likely to change in the near future, reducing the inconvenience of frequent travel and administration time.

PATIENT-BASED VALUES

Values of patients with NSCLC: Symptom burden and quality of life impact

pERC deliberated upon patient advocacy group input for atezolizumab and discussed the values of patients with NSCLC. Lung cancer affects many aspects of day-to-day life for people living with NSCLC. Symptoms and problems experienced by patients can be very burdensome due to their variable nature, as symptoms change frequently making them hard to manage. Both patient and caregiver respondents reported that the high symptom burden of lung cancer is difficult to manage. Some symptoms described by patients include pain, which can be very intense at times, shortness of breath, cough, weakness and extreme fatigue. Extreme fatigue and exhaustion, in particular, were symptoms that many patients reported were difficult to manage. Other symptoms include anxiety, depression, and dependence on others. Patients also described fear and anxiety as strongly associated with the experience of NSCLC.

Patients and caregivers described the impact of lung cancer on their day-to-day lives including their ability to work, travel, have a social life, their ability to participate in leisure and physical activities, relationships with friends and family, independence, emotional well-being, and their financial situation. Patients mentioned a lack of information regarding the disease, treatment options, and the eventual prognosis communicated in a way that would apply to them.

Patient values on treatment: Symptom control, reduced side effects, disease control

Patients indicated that chemotherapy is a treatment that is often faced with fear. Patients expressed a need for a treatment that is both more effective and tolerable given the side effects of chemotherapy that patients experience. pERC noted that the wide availability of nivolumab and pembrolizumab for patients who have progressed on cytotoxic chemotherapy will have reduced the prospect of receiving chemotherapy in this setting.

Key issues patients and caregivers felt needed to be addressed by a new treatment were the slowing or complete halting of disease progression, reduction of pain, fatigue, cough and shortness of breath, nausea, addressing the inability to fight infection, burning of skin, impact on mood, improvement of appetite and energy, and reduced or eliminated cost burden associated with new treatments. Based on the statistically significant improvement in overall survival, moderate side effect profile and reduced disease related symptoms, pERC agreed that atezolizumab aligned with patient values. pERC noted atezolizumab would also be an additional treatment option for patients.

Many patients also discussed the inconvenience related to schedules of treatment and the abundance of medical appointments, especially for patients who live far away from treatment centers. pERC acknowledged the 3-week dosing schedule of atezolizumab will reduce the burden of travel and scheduling for patients.

ECONOMIC EVALUATION

Economic model submitted: Cost effectiveness and cost utility analysis

The EGP assessed cost-effectiveness and cost-utility analyses comparing atezolizumab to docetaxel for patients with advanced or metastatic non-small cell lung cancer (NSCLC) after prior systemic chemotherapy. Comparisons to nivolumab and pembrolizumab were available through a manufacturer submitted network-meta analysis. Results of the cost-effectiveness analysis among all relevant comparators (nivolumab, pembrolizumab, docetaxel) were presented through a sequential analysis.

Basis of the economic model: Indirect comparison for clinical inputs

Costs included were drug acquisition cost, administration costs, supportive care costs, PD-L1 testing cost, AE management costs, subsequent treatment costs, terminal care costs and costs due to wastage.

Key clinical effect estimates considered in the analysis include OS, PFS, duration of treatment, country specific mortality rates, utilities, adverse events and time horizon. pERC noted that the clinical effect estimates between the three immunotherapies (atezolizumab, nivolumab and pembrolizumab) are likely the same. This is supported by conclusions made by the CGP and the conclusions from the network meta-analysis. pERC therefore agreed that any incremental differences modeled are likely not meaningful differences.

Drug costs: Drug cost key driver of cost-effectiveness

Atezolizumab costs $6,776.00 per 1200 mg vial. At the recommended dose of 1200 mg IV every 3 weeks, atezolizumab costs $322.67 per day and $9,034.67 per 28-day course.

Nivolumab costs $1955.56 per 100 mg vial. At the recommended dose of 3 mg/kg IV every 2 weeks, nivolumab costs $337.33 per day and $9,445.32 per 28-day course.

Pembrolizumab costs $2200.00 per 50 mg vial. At the recommended dose of 2 mg/kg IV every 3 weeks, pembrolizumab costs $293.33 per day and $8,321.33 per 28-day cycle.

Docetaxel costs $11.56 per mg. At the recommended dose of 75 mg/m^2 IV every 3 weeks, docetaxel costs $70.20 per day and $1965.64 per 28-day cycle. The cost of docetaxel used in the model is substantially cheaper than what is provided here. The EGP's reanalysis is based on this lower price.

Cost-effectiveness estimates: Very sensitive to price of drug

pERC deliberated on the cost-effectiveness of atezolizumab with relevant comparators and concluded that atezolizumab is not cost effective relative to docetaxel. pERC considered estimates provided by the submitter and reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP) and noted uncertainty regarding the approach to extrapolation for OS over a 10-year time horizon. In the submitted analysis, an assumption was made that 1% of patients would be cured, therefore a parametric curve taking this cure rate into account was used. The submitted analysis also considered a 10 year time horizon. Based on input from the CGP who agreed there is no data to support the assumption that some patients will be cured, the EGP re-analysis removed the cure rate. The EGP also shortened the time horizon to 5 years, as supported by the CGP, to better reflect clinical course of advanced or metastatic NSCLC. pERC also noted that this shorter time horizon is aligned with prior economic evaluation for pembrolizumab and nivolumab. A combined change to these two inputs resulted in a substantial reduction of the incremental gain in quality adjusted life years and minor reduction in the incremental cost.

pERC also deliberated upon the cost-effectiveness of atezolizumab compared with pembrolizumab and nivolumab and concluded that the cost effectiveness is likely similar between the three agents. Based on the submitted and EGP's sequential analysis, atezolizumab is not cost-effective when compared to pembrolizumab and dominates nivolumab (i.e., more effective and less costly). The committee agreed that the clinical effect estimates for atezolizumab, nivolumab and pembrolizumab are likely to be similar as reported in the manufacturer's submitter network meta-analysis and conclusions by CGP. pERC further noted the observed differences in the incremental QALY's (0.01-0.02 QALY's) between the three immunotherapies are not meaningful. pERC therefore noted that the cost-effectiveness of one agent relative to another, as presented in the submitted and EGP's sequential analysis, is very sensitive to the pricing of each available agent. Furthermore, pERC noted that the price of pembrolizumab and nivolumab is likely lower than the list price used in the submitted economic model due to pricing negotiations with the pan Canadian Pharmaceutical Alliance (pCPA) and as a consequence of drug pricing, atezolizumab was not cost-effective compared to these agents. If the cost of these two agents is lower than atezolizumab, the sequential analysis will be dramatically impacted with atezolizumab potentially being the least cost-effective agent. pERC therefore concluded that the price of atezolizumab should not exceed the drug plan costs of the least costly immunotherapy reimbursed in this setting.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Treatment beyond progression

pERC considered factors affecting the feasibility of implementing a positive funding recommendation for atezolizumab. pERC noted that the submitted budget impact analysis (BIA) is most sensitive to the market share and cost of the drug. The submitted BIA reported a cost saving with the incorporation of atezolizumab into the market as the market share for atezolizumab is taken exclusively from nivolumab which is the most expensive agent. pERC agreed that if the cost of nivolumab is lower (based on a negotiated price), the BIA of atezolizumab would shift away from being cost saving.

pERC agreed that patients who continue to derive clinical benefit from treatment with atezolizumab should continue to receive treatment. In both trials, patients were able to continue treatment beyond RECIST defined disease progression if the investigator deemed the patient to have clinical benefit. Based on the trial, patients are assessed for progression at baseline, then every 6 weeks until week 36 and every

9 weeks thereafter. Furthermore, pERC that the 3 week dosing schedule of atezolizumab is an enabler to implementation as it reduces inconvenience of travel and administration time for patients. pERC however acknowledged that dosing schedule of other immunotherapies (i.e. nivolumab) are likely to change in the near future further reducing the inconvenience of frequent travel and administration time. pERC lastly concluded that the optimal sequencing of atezolizumab and other treatments now available for advanced or metastatic NSCLC is currently unknown. In the absence of direct evidence to inform the comparative efficacy and safety of atezolizumab with PD-1 inhibitors (nivolumab and pembrolizumab), pERC reiterated that the efficacy and safety of atezolizumab is likely similar to these two agents. Thus, with their overlapping indications, there is no evidence to inform the choice of atezolizumab over the other available agents, or vice versa. pERC also agreed that there is no evidence to support the use of immunotherapies in sequence.

DRUG AND CONDITION INFORMATION

Drug Information	• Immunotherapy anti-PD-L1 • 1200 mg vial • 1200 mg IV every 3 weeks
Cancer Treated	• Locally advanced or metastatic non-small cell lung carcinoma
Burden of Illness	• Large prevalent and new population • Patients generally have advanced age, advanced stage of disease, poor performance status, and a higher likelihood of significant comorbidities
Current Standard Treatment	• Pembrolizumab • Nivolumab • Docetaxel
Limitations of Current Therapy	• Modest improvements in survival with chemotherapy • Poor performance status of patients makes it difficult for many patients to tolerate toxicities of chemotherapy • Two week dosing schedule with nivolumab

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:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Christopher Longo, Economist
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Dr. Kelvin Chan and Dr. Craig Earle who were not present for the meeting
- Cameron Lane who did not vote due to his role as a patient member alternate.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the 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 (Tecentriq) for NSCLC through their declarations, two members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, both 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*.

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.

Disclaimer

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking information comparing atezolizumab to nivolumab or pembrolizumab, noting that atezolizumab is a PD-L1 inhibitor (i.e. ligand) with a different mechanism of action although same pathway as nivolumab and pembrolizumab which are PD-1 inhibitors (receptor).	• pERC noted direct head to head comparisons were unavailable. Based on the results of network meta-analyses, pERC agreed that the efficacy and safety of the atezolizumab, pembrolizumab and nivolumab are likely similar. pERC acknowledged the limitations of making cross trial comparisons but agreed that there was no major limitation that may have impacted the results.
• PAG is seeking clarity on the eligible patient population as related to histology, number of previous lines of therapy, PD-L1 expression, or presence or absence of activating mutations (EGFR and ALK).	• pERC agreed that atezolizumab should be available to patients with locally advanced or metastatic NSCLC previously treated with cytotoxic chemotherapy irrespective of histology, PD-L1 expression level and presence of ALK or EGFR mutation. pERC based this decision based on the trial data which did not restrict enrollment on these criteria. Additionally, pERC agreed that the overall trial results can be generalized to these subgroups of patients.
• PAG would like confirmation that PD-1 testing is not required.	• pERC agreed that PD-L1 testing will not be required for the reimbursement of atezolizumab.
• PAG is seeking clarity on treatment duration and treatment until lack of benefit with a definition of disease progression.	• pERC agreed that patients who continue to derive benefit from treatment with atezolizumab should continue to receive treatment. In the both trials, patients were able to continue treatment beyond RECIST defined disease progression if the investigator deemed the patient to have clinical benefit. Based on the trial, patients are assessed for progression at baseline, then every 6 weeks until week 36 and every 9 weeks thereafter. For patients continuing treatment beyond progression, assessment would continue until they discontinue treatment.

PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.