pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL 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.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available and will supersede this Initial Recommendation.

Drugs: Atezolizumab (Tecentriq) and Bevacizumab (Avastin)

Submitted Reimbursement Request:
Atezolizumab in combination with bevacizumab and platinum-based chemotherapy for the treatment of metastatic epidermal growth factor receptor (EGFR) and/or anaplastic lymphoma kinase (ALK)-positive non-squamous non-small cell lung cancer (NSCLC) in patients who have progressed on treatment with targeted therapies. Maintenance atezolizumab should be continued until loss of clinical benefit or unacceptable toxicity. Maintenance bevacizumab should be continued until disease progression or unacceptable toxicity.

Submitted by: Hoffmann-La Roche Limited

Manufactured by: Hoffmann-La Roche Limited

NOC Date: May 24, 2019

Submission Date: November 18, 2019

Initial Recommendation Issued: April 30, 2020

Approximate per Patient Drug Costs, per Month	Atezolizumab costs $6,776 per 1,200 mg vial and bevacizumab costs $519.18 per 100 mg vial or $2,076.71 per 400 mg vial. At the recommended doses of 1,200 mg and 15 mg/kg for atezolizumab and bevacizumab, respectively, given every three weeks for up to six cycles, atezolizumab costs $6,776 per cycle and bevacizumab costs $5,711 per cycle (assuming a patient weight of 71.9 kg). • Atezolizumab and bevacizumab maintenance costs $12,487 per cycle • Atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) costs $17,547 per cycle • Platinum doublet plus pemetrexed costs $6,160 per cycle • Platinum doublet costs $5,610 per cycle

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	pERC does not recommend reimbursement of atezolizumab in combination with bevacizumab and platinum-based chemotherapy, followed by atezolizumab and bevacizumab maintenance, for the treatment of metastatic EGFR and/or ALK-positive non-squamous NSCLC in patients who have progressed on targeted therapies. pERC made this recommendation because it was unable to conclude, based on the submitted evidence from the IMpower150 trial, that there is a net clinical benefit of atezolizumab and bevacizumab in combination with carboplatin and paclitaxel (ABCP) chemotherapy compared to bevacizumab, carboplatin, and paclitaxel (BCP), in patients with metastatic EGFR and/or ALK-positive non-squamous NSCLC. The Committee noted there was uncertainty around the progression-free survival (PFS) and overall survival (OS) results since treatment effect estimates were based on post-hoc analyses of a small subgroup of EGFR- and/or ALK-positive patients that may

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reimbursement request.	have been influenced by imbalances in baseline patient characteristics between treatment groups and the effects of multiple comparison testing. pERC agreed there is a need for additional treatment options in patients with EGFR and/or ALK-positive metastatic non-squamous NSCLC who have progressed on targeted treatments; however, given the post-hoc nature of the submitted evidence, pERC was uncertain whether ABCP adequately addresses the need for more effective therapies in this subgroup of patients. pERC agreed that ABCP aligns with patient values in that it is an additional treatment option with a manageable side-effect profile and no apparent detriment in quality of life (QoL). However, pERC noted the addition of atezolizumab to BCP is associated with increased but manageable toxicity, has an uncertain effect on OS, and does not offer an easier form of treatment administration, which are factors identified as important to patients. pERC concluded that, at the submitted price, ABCP is not cost-effective when compared to the current standard of care of platinum-based chemotherapy combined with pemetrexed. pERC considered the uncertainty in cost-effectiveness to be high and related to the results of the comparative efficacy of ABCP to pemetrexed and platinum-based chemotherapy based on the submitted network meta-analysis that included a broader patient population and excluded key comparators. pERC also noted the results of the cost-effectiveness analysis were driven by the high cost of atezolizumab and bevacizumab, and that even with a substantial price reduction for each drug, it is highly unlikely ABCP would become cost-effective.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC agreed that a resubmission of atezolizumab and bevacizumab combined with platinum-based chemotherapy could be considered based on prospective comparative evidence from trials designed to detect a difference in meaningful outcomes important to decision-making such as PFS, OS, and QoL in the population requested for reimbursement. Future trials should consider evaluating atezolizumab and bevacizumab combined with standard of care chemotherapy treatments available in Canada.

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SUMMARY OF pERC DELIBERATIONS

In Canada, lung cancer represents the second most common cause of cancer among both men and women, and the largest cause of death from cancer, with approximately 29,300 new cases and 21,000 deaths estimated in 2019. Non–small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases. Multiple randomized trials have established immune checkpoint inhibitor therapy, either alone, or in combination with chemotherapy, as standard of care for the initial management of advanced and metastatic NSCLC, extending median survival from around one year, to up to 18 to 24 months. Identification of molecular drivers in lung adenocarcinomas, such as mutations of the epidermal growth factor receptor (EGFR) and/or translocations of the anaplastic lymphoma kinase (ALK) genes have resulted in oral targeted therapy treatment options for 20% of patients (approximately 2,500 patients annually) with advanced and metastatic non-squamous NSCLC. Oral tyrosine kinase inhibitors (TKIs) represent the most effective initial treatment for these patients; however, molecularly driven NSCLC will eventually become resistant to targeted therapies and many patients will be considered for other systemic therapies The role of immune checkpoint inhibitors combined with chemotherapy remains uncertain in patients with EGFR mutations and/or ALK translocations, as these patients have mostly been excluded from trials of platinum-based chemotherapy and immunotherapy. pERC agreed with the pCODR Clinical Guidance Panel (CGP) and registered clinicians and patients providing input to this submission that there is a need for additional treatment options in patients with EGFR and ALK-positive non-squamous NSCLC who have progressed on targeted therapies.

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

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated on the results of subgroup analyses performed on data from one randomized, open-label, three-group, multi-centre, phase III randomized controlled trial, IMpower150. This trial evaluated atezolizumab with (ABCP) and without bevacizumab (ACP) in combination with carboplatin and paclitaxel compared to bevacizumab, carboplatin, and paclitaxel (BCP) in patients with stage IV NSCLC who had received no prior chemotherapy for metastatic disease. pERC's deliberations focused on the ABCP versus BCP comparison. Patients with known EGFR mutations or ALK translocations were eligible for IMpower150 if they had experienced progression with one or more lines of targeted therapy. pERC noted that following a protocol amendment, the pre-specified primary analysis of the trial, which assessed the co-primary outcomes of overall survival (OS) and progression-free survival (PFS) in all trial patients, was changed to exclude patients with EGFR mutations and ALK translocations, and therefore was restricted to a wild-type patient population. The protocol amendment was informed by the results of external trials that suggested atezolizumab and other programmed death ligand-1 (PD-L1) inhibitors did not show benefit in EGFR/ALK-positive patients compared to chemotherapy. Separate analyses were conducted for the small number of patients in the IMpower150 trial who were EGFR and/or ALK positive, EGFR-only positive, had EGFR sensitizing mutations (mutations in Exon 19 of the EGFR gene or Leu858Arg substitution), and EGFR sensitizing mutations with prior targeted treatment; however, with the exception of the EGFR-only positive subgroup, these analyses were not pre-specified and were analyzed as post-hoc exploratory subgroups. pERC focused their deliberations to these subgroup analyses and noted that the patient population for which reimbursement is being sought, those with EGFR mutations and/or ALK translocations who have progressed on targeted therapies, was excluded from the Health Canada indication for atezolizumab and bevacizumab based on their exclusion from the primary analysis of the IMpower150 trial.

pERC discussed the results of the subgroup analyses that were based on a small group of 104 patients, 41 in the ABCP group and 63 in the BCP group, which showed that PFS was significantly longer in patients who received ABCP; while OS, although numerically favoured ABCP, showed no statistically significant difference between treatment groups except for the subgroup of patients with sensitizing EGFR mutations. pERC noted that the median OS has not yet been reached in the ABCP group for any EGFR/ALK patient subgroup. pERC expressed concern over the quality of the submitted evidence and agreed with the pCODR Methods Team's appraisal that the subgroup analysis results are descriptive in nature (hypothesis generating), are at risk of bias due to a lack of stratification by mutation status and resulting imbalance in baseline patient characteristics between treatment groups, and are at risk of false-positive

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findings due to the effects of multiple comparison testing. Further, pERC discussed that the EGFR and/or ALK-positive subgroup was small, which decreased the precision of treatment effect estimates and the ability to detect a difference in treatment effect between groups. Considering these limitations, pERC agreed that there is high uncertainty in the results of the subgroup analyses and thus concluded that the magnitude of clinical benefit associated with ABCP is unclear in this patient subgroup.

pERC discussed that platinum doublet therapies (i.e., pemetrexed plus cisplatin/carboplatin) are the current standard of care for patients with metastatic EGFR and/or ALK-positive non-squamous NSCLC who have progressed on targeted therapies and that the comparator group in the IMpower150 trial, BCP, is not funded in any jurisdiction in Canada. In order to assess the comparative efficacy of BCP to relevant comparators the sponsor provided an indirect treatment comparison (ITC) in the form of a network meta-analysis (NMA) and match-adjusted indirect comparison (MAIC) based on a systematic review of treatments for stage IV non-squamous NSCLC. The results of these analyses, however, were highly uncertain and difficult to interpret due to the inclusion of a broader patient population in comparator trials (i.e., not necessarily EGFR/ALK-positive) and the exclusion of important comparators (i.e., immunotherapy with and without chemotherapy).

pERC acknowledged that there is a need for additional treatment options in patients with EGFR and/or ALK-positive metastatic non-squamous NSCLC who have progressed on targeted therapies; however, given the post-hoc nature of the submitted evidence and the uncertainty around the magnitude of the clinical benefit in PFS and OS, pERC was uncertain whether ABCP adequately addresses the need for more effective therapies in this subgroup of patients. pERC commented that randomized trials have been conducted specifically in EGFR mutated and ALK rearranged patient populations; therefore, randomized controlled trials focused to patients with non-squamous NSCLC who have EGFR mutations and/or ALK rearrangements and progressed on targeted therapies is feasible.

pERC deliberated on the toxicity profile of ABCP and noted that the incidence and severity of adverse events (AEs) were broadly similar between the ABCP and BCP treatment groups and primarily reflected toxicities associated with chemotherapy and bevacizumab. pERC noted, however, the addition of atezolizumab to BCP did result in more grade 3-4 treatment-related AEs and immune-related AEs (irAEs), as well as a higher proportion of patients who discontinued treatment due to AEs when compared to patients who received BCP. Nonetheless, pERC agreed with the CGP that overall, the safety profile is manageable and familiar to clinicians who are experienced in administering immunotherapy, and no new safety concerns were identified in the IMpower150 trial.

pERC discussed the patient-reported outcome data available from the IMpower150 trial for the EGFR/ALK-positive subgroup that was provided by the sponsor for the global health status and physical functioning subscales of the European Organization for the Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 (EORTC QLQ-C30). pERC noted there was no clinically significant decrease in the mean change from baseline in either global health status or physical functioning in both treatment groups (≥ 10 points) at any assessment time point in the trial; therefore, based on these limited data, pERC agreed ABCP appears to have no detriment on patient quality of life (QoL).

pERC deliberated on input from one patient advocacy group, Lung Cancer Canada (LCC), who provided input from a small number of patients with non-squamous NSCLC (n = 3) and one caregiver (n = 1) who had direct experience with atezolizumab and bevacizumab combined with platinum-based chemotherapy. Patients indicated they value access to alternative treatment options and pERC considered this an important value in this subpopulation of non-squamous NSCLC patients who have progressed through and exhausted all available targeted treatment options. pERC agreed that the combination treatment aligns with the patient values of an additional treatment option and manageable side effects; however, pERC also agreed that the combination shows no difference in QoL, its effect on OS is uncertain, and it does not offer an easier form of treatment administration, which are other factors identified as being important to patients.

pERC deliberated on the cost-effectiveness of ABCP compared with platinum-based chemotherapy in combination with pemetrexed. pERC discussed the limitations of the submitted model described by the Economic Guidance Panel (EGP) and noted that due to key limitations with the underlying evidence supporting the comparative efficacy of ABCP based on the submitted NMA and its long-term extrapolation, the magnitude of benefit associated with ABCP was considered uncertain. pERC considered the reanalyses conducted by the EGP. The scenarios considering price reductions for both atezolizumab and biosimilar bevacizumab were of interest, with pERC highlighting the high cost of treatment as the key driver of ABCP's cost-effectiveness. pERC concluded ABCP was not cost-effective at the submitted price for

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atezolizumab and bevacizumab (nor if biosimilar bevacizumab was considered). They also noted that ABCP was unlikely to be cost-effective at conventional willingness-to-pay thresholds, even with substantial price reductions to both atezolizumab and bevacizumab.

pERC discussed the factors that could impact the feasibility of implementing a reimbursement recommendation for ABCP as treatment for patients with EGFR and/or ALK-positive non-squamous NSCLC. The Committee highlighted that bevacizumab is not currently funded for NSCLC and therefore funding would be required for both atezolizumab and bevacizumab. pERC commented that although a bevacizumab biosimilar could be considered for potential cost savings, the reanalyses performed by the EGP indicated cost savings obtained by using a biosimilar would be insufficient. pERC also discussed the budget impact analysis (BIA) and noted that the factor most influencing the estimated budget impact was the eligible population size. pERC noted that the EGP considered the eligible population size calculated by the sponsor to be underestimated, and that the use of an updated estimate by the EGP yielded a higher overall budget impact when compared to the sponsor's estimate. pERC also discussed factors raised by the Provincial Advisory Group (PAG), which related to the eligible patient population, the appropriateness of adding the combination to any platinum-based chemotherapy, treatment beyond disease progression, additional health care resources that would be required with the combination regimen, and sequencing of all available treatments.

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 sponsor's economic model and BIA
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group (LCC)
- input from registered clinicians (CCO and LCC)
- input from pCODR's PAG.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the efficacy and safety of atezolizumab and bevacizumab in combination with platinum-based chemotherapy for the treatment of metastatic EGFR and/or ALK-positive non-squamous NSCLC in patients who have progressed on treatment with targeted therapies.

Studies included: Post-hoc subgroup analyses from one randomized phase III trial

The pCODR review included one trial, IMpower150, which is an international, multi-centre, open-label three-group, phase III randomized trial that evaluated ABCP compared to ACP and BCP in patients with stage IV NSCLC who had received no prior chemotherapy for metastatic disease. The trial was conducted at 240 sites in 26 countries including Canada. The comparison of ABCP versus BCP was the focus of the pCODR review and pERC deliberation.

Eligible patients were randomized to ABCP or BCP and received six cycles of induction therapy and then continued maintenance therapy (AB for the ABCP group; and B for the BCP group) until disease progression, unacceptable toxicity, or loss of clinical benefit (atezolizumab) as assessed by the investigator. Atezolizumab and bevacizumab were administered IV at doses of 1,200 mg and 15 mg/kg, respectively, on a 21-day cycle. Paclitaxel given at dose of 200 mg/m^2 IV (175 mg/m^2 IV for patients of Asian race or ethnicity) and carboplatin given as an AUC (area under the drug concentration-time curve) of 6 IV were also administered on a 21-day cycle. Randomization was stratified by sex, presence of liver metastases at baseline, and by level of PD-L1 expression. A total of 1202 patients were randomized in the three treatment groups, 400 to ABCP and 400 to BCP. Following a protocol amendment, the pre-defined primary efficacy analysis of the trial, which assessed the co-primary outcomes of OS and PFS, excluded patients with EGFR mutations or ALK translocations and therefore was restricted to patients with wild-type non-squamous NSCLC. The protocol amendment was informed by the results of external trials that

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suggested atezolizumab and other single-drug PD-LI inhibitors (i.e., nivolumab and pembrolizumab) did not show clinical benefit in EGFR/ALK-positive patients compared to chemotherapy. Secondary end points of the IMpower150 trial included objective response rate (ORR), duration of response, health-related QoL (HRQoL), and safety. Separate subgroup analyses were conducted (and published separately) for the trial patients who were EGFR and/or ALK-positive, EGFR-positive, had sensitizing EGFR mutations (mutations in Exon 19 of the EGFR gene or Leu858Arg substitution), and sensitizing EGFR mutations with prior targeted treatment. Except for the EGFR-only positive subgroup, these subgroup analyses were neither formally prespecified nor tested a priori, and therefore are considered descriptive, post-hoc analyses with no adjustments made for multiple comparison testing. Further, because EGFR/ALK-positive status or TKI pre-treatment status were not used as stratification variables in randomization, there was no a priori expectation of balance in baseline characteristics between the treatment groups.

The pCODR review also included a summary and critical appraisal of two sponsor-submitted ITCs: one NMA comparing ABCP to other chemotherapy-based treatments for stage IV non-squamous NSCLC and one MAIC of ABCP to pembrolizumab monotherapy. The ITCs provided the comparative efficacy inputs for the pharmacoeconomic model in order to evaluate the cost-effectiveness and budget impact of ABCP compared to other treatments.

Patient population: Median age 63 years; Eastern Cooperative Oncology Group Performance Status performance status 0-1; majority of patients had prior TKI treatment; imbalances in patient characteristics between treatment groups

Patients with known EGFR mutations or ALK translocations were eligible for the IMpower150 trial if they had disease progression with, or intolerance of, one or more targeted therapies (TKIs or ALK inhibitors). Patients could have any level of PD-L1 expression. Excluded from the trial were patients with active or untreated central nervous system metastases, leptomeningeal disease, uncontrolled pleural effusion, pericardial effusion or ascites needing frequent drainage, and uncontrolled tumour-related pain. The trial also excluded patients with a history of autoimmune disease, lung parenchymal disease, severe cardiovascular disease, severe active infections (including HIV and hepatitis B or C), hypertension or severe vascular disease. Prohibited medications included systemic immunosuppressant medications within two weeks prior to randomization and other approved anti-cancer treatments within three to six weeks before randomization, except for TKIs, which had to be discontinued greater than seven days before randomization.

In the ABCP group, 34 (9%) of patients were EGFR-positive, 11 (3%) were ALK-positive, and four patients had both types of mutation, for a total of 41 patients who comprised the EGFR and/or ALK-positive subgroup. In the BCP group, 45 (11%) of patients were EGFR-positive, 20 (5%) were ALK-positive, and two patients had both types of mutation, for a total of 63 patients who comprised the EGFR/ALK-positive subgroup. The EGFR/ALK-positive subgroup had a similar age to the intent-to-treat (ITT) population of the trial (63 years), though the relative proportion of patients who were female or Asian was higher (48.8% to 60.4% female, 31.7% to 39.6% Asian). The Eastern Cooperative Oncology Group (ECOG) performance status was 0 for 45.3% to 57.1% of patients, depending on the treatment group. A higher proportion of patients in the subgroup had not used tobacco (42.9% to 60.4%); and the proportion of patients who were categorized as having a tumour cell score of 3 (PD-L1 expression ≥ 50%) was smaller (3.8% to 7.3%). When the ABCP and BCP groups were compared, a number of imbalances were observed. A higher proportion of patients in the BCP group had an ECOG score of 0 (57.1% versus 46.3%), liver metastases at baseline (15.9% versus 12.2%), and ALK rearrangements (31.7% versus 26.8%). Conversely, a higher proportion of patients in the ABCP group had EGFR mutations (82.9% versus 71.4%). It is difficult to assess the potential overall direction of bias arising from the imbalances in patient characteristics, as individual prognostic factors may bias in opposite directions (e.g., liver metastases and ECOG). Approximately 85% of sensitizing EGFR-positive patients on the ABCP regimen received at least one prior treatment. In the ALK-positive patient population who received the ABCP regimen, approximately 27% received at least one prior treatment. Lack of prior TKI treatment among some patients may have been due to accessibility issues in certain geographic regions, or because the patients were centrally tested and randomized prior to knowing their mutation status. The most common TKIs received by patients were erlotinib and gefitinib.

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Key efficacy results: Uncertainty in treatment efficacy due to exploratory assessment of subgroup data

pERC deliberated on key efficacy outcomes including OS and PFS. Tumour assessment occurred at baseline and every six weeks for 48 weeks following cycle 1 (day 1), then every nine weeks after week 48, until disease progression as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, or loss of clinical benefit for patients receiving atezolizumab. At the most recent data cut-off date (January 22, 2019), the median length of follow-up was approximately 20 months (ITT population).

For the EGFR/ALK-positive population (104 patients), the median survival for patients treated with ABCP had not been reached, while the median survival for those patients treated with BCP was 17.5 months (95% confidence interval [CI], 10.4 months with a non-estimable upper limit). The hazard ratio (HR) for mortality was 0.54 (95% CI, 0.29 to 1.03) with the upper limit of the CI crossing the null value (no effect) of 1.0. Similar results were seen for the individual mutation subgroups of patients (i.e., EGFR-positive, patients with EGFR mutations who received prior TKI treatment, and patients with ALK-positive rearrangements). In patients with EGFR sensitizing mutations, the median survival for patients treated with ABCP was not reached, while for patients treated with BCP the median survival was 17.5 months (95% CI, 11.7 months with upper limit not estimable). In this subgroup the HR was 0.31 (95% CI, 0.11 to 0.83), which favoured ABCP and was considered statistically significant.

For PFS, the median PFS of patients treated with ABCP was 10.0 months (95% CI, 7.9 to 15.2 months), while the median PFS for those treated with BCP was 6.1 months (95% CI, 5.6 to 8.4 months). The comparison favoured ABCP, stratified HR of 0.55 (95% CI 0.35 to 0.87), unstratified HR of 0.55 (95% CI, 0.34 to 0.90), which was considered statistically significant. Similar results were observed for the individual mutation subgroups of patients who were EGFR-positive, patients with EGFR sensitizing mutations, patients with EGFR sensitizing mutations and TKI pre-treatment, and patients with ALK-positive mutations. In the subgroup of patients with EGFR sensitizing mutations, the median PFS for patients treated with ABCP was 10.3 months, while for patients treated with BCP the median PFS was 6.1 months (HR of 0.41; 95% CI, 0.23 to 0.75). In the subgroup of patients with sensitizing EGFR mutations who had previously received TKI inhibitors, the comparison also favoured ABCP (HR of 0.42; 95 % CI, 0.22 to 0.80).

Patient-reported outcomes: Limited data on patient-reported outcomes show no deterioration in QoL

Patient completion rates of EORTC QLQ-C30 questionnaires in the IMpower150 trial were not available for the EGFR/ALK-positive subgroup but were reported for the ITT-wild-type population (who comprised 86.5% of the ITT population), where 91.8% and 91.9% of questionnaires were completed at baseline for the ABCP and BCP groups, respectively, with ≥ 70% participation through cycle 23. Data on HRQoL were provided by the sponsor for two subscales of the EORTC QLQ-C30: global health status and physical functioning. For global health status, the median baseline values for both groups were 66.7 (range, 0.0 to 100.0). In both groups, scores were maintained over time for surviving patients who provided data (e.g., scores for ABCP were derived from 36 patients at cycle 1, and 22 patients at cycle 13, and scores for BCP were derived from 55 patients at cycle 1 and 16 patients at cycle 13). There was no clinically significant decrease in the mean change from baseline in global health status score in either treatment group (≥ 10 points) at any time point. For physical functioning, the median baseline value for both groups was 86.7 (range, 20.0 to 100.0). In both groups, scores were maintained over time for surviving patients who provided data (e.g., scores for ABCP were derived from 36 patients at cycle 1, and 22 patients at cycle 13, and scores for BCP were derived from 55 patients at cycle 1, and 16 patients at cycle 13). There was no clinically significant decrease in the mean change from baseline in physical function score in either treatment group (≥ 10 points) at any time point.

Limitations: Lack of robust ITCs to inform comparative efficacy and safety of ABCP to relevant comparators

The sponsor provided two ITCs based on a systematic review of treatments for stage IV, non-squamous NSCLC. The first ITC was an NMA based on 11 trials that included comparisons between ABCP and combinations of gemcitabine, paclitaxel, pemetrexed, bevacizumab, cisplatin, and carboplatin. The results from the NMA provide evidence that ABCP had longer expected survival than the majority of comparators when extrapolated over a 60-month time frame with more than 95% probability. However, for some comparators (pemetrexed plus cisplatin/carboplatin plus bevacizumab with bevacizumab maintenance, pemetrexed plus cisplatin/carboplatin plus bevacizumab with bevacizumab plus

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pemetrexed maintenance, pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance, and carboplatin/cisplatin plus vinorelbine with vinorelbine maintenance), the estimated difference in OS favoured ABCP but the 95% credible intervals (CrIs) included zero, that is no difference between treatment groups. The PFS results provide evidence that ABCP had longer PFS than all but one comparator (carboplatin/cisplatin plus vinorelbine with vinorelbine maintenance). For ORR, the results provide evidence that ABCP had greater odds of overall response compared to all of the other comparators; and for treatment discontinuation due to AEs, the results provide evidence that ABCP has greater odds of treatment discontinuation than most of the comparators. A number of important limitations of the NMA were identified by the pCODR Methods Team that raise concern about the validity of the results, which include the following: lack of comparators that included immunotherapy or combinations of immunotherapy and chemotherapy; the data for the subgroup of interest to this review (EGFR/ALK-positive) were only available for the IMpower150 trial, so the comparison of this subgroup to the ITT populations of all other included trials required the assumption that the presence of EGFR mutations or ALK translocations would not affect response to comparator therapy; survival data were immature, resulting in the need to extrapolate survival, with results that are uncertain and sensitive to model selection; and the dataset was relatively sparse, leading to broad CrIs and potential failure to detect real differences.

The second ITC was a separate unanchored MAIC of ABCP with pembrolizumab monotherapy. Data were not available for the comparison of pembrolizumab monotherapy with any of the individual treatments included in the NMA, so a separate unanchored MAIC was conducted for this comparison using data from the KEYNOTE-024 trial. Compared with pembrolizumab monotherapy, ABCP showed longer estimated OS and PFS, but for both outcomes the CrIs crossed the boundary of no effect. Overall response rate and the proportion of AEs that were treatment-related, led to withdrawal, or were grade 3 and above all favoured ABCP. The principal limitation of this ITC (as appraised by the pCODR Methods Team) was the use of an unanchored MAIC, with its attendant high risk of bias, the lack of matching on histological subtype and mutation status, the small number of patients available, and the uncertainties around the extrapolation of survival curves. The trial of pembrolizumab monotherapy excluded EGFR/ALK-positive patients and selected for patients high PD-L1 expression and data for the non-squamous subgroup of patients were not separately reported.

Safety: Slight increase in toxicity with ABCP compared to BCP

The median treatment exposure of atezolizumab (safety population) in the ABCP group was 8.3 months; and exposure to bevacizumab was 6.7 months and 5.1 months in the ABCP and BCP groups, respectively. In the EGFR/ALK-positive subgroup, 16 (39.0%) patients who received ABCP continued to receive atezolizumab following disease progression for a median 2.36 months (range, 0.1 to 10.6 months).

All patients in both treatment groups experienced at least one AE, and almost all patients had at least one treatment-related AE. Of the patients who received ABCP, 39 (97.5%) had one or more treatment-related AEs, 25 (62.5%) of which were grade 3 or 4, and 1 (2.5%) was grade 5 (fatal). Of the patients who received BCP, 59 (95.2%) had one or more treatment-related AEs, 34 (54.8%) of which were grade 3 or 4, and two (3.2%) were grade 5. More patients who received ABCP had AEs leading to withdrawal from any treatment, and had AEs leading to any dose modification or interruption. Of the patients who had received ABCP, 14 (35.0%) had one or more AEs leading to withdrawal, and 25 (62.5%) had one or more AEs leading to dose modification or interruption. Of the patients who received BCP, 10 (16.1%) had one or more AEs leading to withdrawal, and 29 (46.8%) had one or more AEs leading to dose modification or interruption. More patients who received ABCP had irAEs compared to those who received BCP. Nineteen (47.5%) patients who received ABCP had one or more AEs compared with 10 (16.1%) patients who received BCP. The most common irAEs were rash (27.5% in ABCP versus 9.7% in BCP), hepatitis (10.0% versus 11.3%), and hypothyroidism (15% versus 3.2%). Other low-frequency AEs involved multiple systems, although individual patients could contribute multiple AEs. A higher proportion of patients who received ABCP had AEs of interest for bevacizumab, 62.5% compared with 53.2% for all AEs. Eight (20.0%) patients who received ABCP and nine patients (14.5%) who received BCP had grade 3 to 4 AEs. The difference appeared across multiple categories of AEs, however the numbers for individual AEs were small, so incidence would be influenced by single patients.

Need and burden of illness: Unmet need for additional treatment options

Significant advancements have been made in the last decade in the management of NSCLC, and multiple randomized trials have now established immune checkpoint inhibitor therapy, either alone, or in combination with chemotherapy, as standard of care for the initial management of advanced and

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metastatic NSCLC, extending median survival from around one year, to up to 18 to 24 months. Nevertheless, NSCLC is still considered to be an incurable illness and better treatment options are needed. Identification of molecular drivers in lung adenocarcinomas, such as mutations of the EGFR and translocations of the ALK genes have resulted in oral targeted therapy treatment options in 20% of patients with advanced and metastatic non-squamous NSCLC, which represents nearly 2,500 patients annually across Canada. However, the role of immune checkpoint inhibitors remains uncertain in these subpopulations of patients. Recent data supports the use of pembrolizumab in combination with platinum-based chemotherapy as initial therapy for non-squamous NSCLC, but these trials did not include patients with EGFR mutations and ALK translocations. These patients have been included in trials evaluating atezolizumab in combination with platinum-based chemotherapy, although the primary analyses were conducted in wild-type populations and clinical benefit was not shown in the EGFR or ALK patient subgroups. This highlights the need for further evaluation of immunotherapy and chemotherapy regimens in patients with metastatic EGFR/ALK-positive non-squamous NSCLC patients who have progressed and exhausted all targeted therapy options.

Registered clinician input: Unmet need for additional treatment options after progression on targeted treatments; mixed clinician opinion on efficacy of ABCP

Two clinician submissions were received for the review of atezolizumab in combination with bevacizumab and platinum-based chemotherapy; one individual clinician input submission from the Cancer Care Ontario Lung Drug Advisory Committee (CCO DAC) and one joint input submission on behalf of 13 clinicians from LCC. Registered clinicians from both submissions reported that there is a significant unmet need for patients with EGFR and ALK-positive mutations, as patients invariably progress after targeted therapies and require further effective treatment options. Clinicians from LCC noted the improvements in PFS, OS, and response rate in patients with EGFR- and ALK mutations based on exploratory subgroup analyses of the IMpower150 trial data and considered the observed benefits to be clinically meaningful and an improvement over what would be expected for the sequence of doublet chemotherapy alone followed by immunotherapy. These clinicians stated that chemotherapy and immunotherapy are standard treatments for patients with EGFR/ALK driver tumours and that many practitioners are well experienced in managing their side effects. They also noted that bevacizumab is associated with a new side-effect profile related to vascular endothelial growth factor inhibition and therefore may be contraindicated in certain patients with uncontrolled hypertension, hemoptysis, and patients who have a recent history of a myocardial infarction or stroke. The other clinician providing input did not recommend the use of ABCP citing concerns about the exploratory efficacy analyses (only a trend to OS improvement) and tolerability of ABCP. Clinicians from LCC noted that the use of bevacizumab introduces a new set of side effects and could lead to contraindication in patients with certain cardiovascular conditions or a history of cardiovascular events. The availability of biosimilar bevacizumab was mentioned as a potential means to reduce treatment-related costs. Clinicians from LCC indicated that it would be reasonable to initiate ABCP at any point of the three months following initiation of doublet chemotherapy for patients who have not yet transitioned to maintenance therapy. Both groups of clinicians support the use of maintenance pemetrexed in addition to atezolizumab in combination with bevacizumab for patients treated with first-line platinum-based chemotherapy (pemetrexed plus carboplatin/cisplatin).

PATIENT-BASED VALUES

Values of patients with non-squamous NSCLC: Physical and emotional impacts on daily living; unmet need for additional treatments after targeted therapy

One patient group, LCC, provided input on atezolizumab and bevacizumab plus platinum-based chemotherapy for the treatment of metastatic EGFR and/or ALK-positive non-squamous NSCLC in patients who have progressed on treatment with targeted therapies. Patient (n = 94) and caregiver (n = 73) respondents providing input stated a diagnosis of lung cancer has a significant physical and emotional impact on their lives, limiting their ability to carry on with their daily lives. Patients commented that current chemotherapies are efficacious but are associated with side effects including nausea, vomiting, and fatigue, while noting that immunotherapies are more tolerable and do not interrupt daily life. Patients expressed that despite the availability of more targeted treatments in recent years, there is a high unmet need as many patients eventually progress on current treatments.

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Patient values on treatment: Improvement in OS and QoL, and an easier form of treatment modality

Patients and caregivers expect improvement in survival and quality of life and an easier form of treatment modality from new therapies. Four patients reported having experience with atezolizumab and bevacizumab, three of whom had an EFGR/ALK mutation. All four patients reported increased independence, better tolerability, reduction of tumour size and increased survival (relative to initial prognosis) with ABCP. Three out of the four patients reported some side effects, the most common being fatigue; and two patients reported neuropathy in hands and feet. Other side effects included nausea, hair loss, occasional constipation, dry heaving, and body aches.

ECONOMIC EVALUATION

Atezolizumab is supplied as 1,200 mg vials for IV infusion and bevacizumab is supplied as either 100 mg or 400 mg vials for IV infusion. The recommended doses of atezolizumab and bevacizumab are 1,200 mg and 15 mg/kg, respectively, given by IV infusion every three weeks in combination with a platinum-based doublet chemotherapy regimen, for up to six cycles, followed by maintenance with atezolizumab and bevacizumab until loss of clinical benefit. At the sponsor's submitted price of $6,776 per vial for 1,200 mg of atezolizumab, the cost per cycle is $6,776, while at the submitted price of $519.18 per 100 mg vial or $2,076.71 per 400 mg vial, the cost of bevacizumab is $5,711 per cycle (assuming a patient weight of 71.9 kg).

The sponsor submitted a partitioned survival analysis comparing ABCP against pemetrexed in combination with platinum-based chemotherapy. The target population was patients with locally advanced or metastatic non-squamous NSCLC with EGFR or ALK genomic tumour aberrations, in whom targeted therapies have failed. The sponsor modelled the costs and quality-adjusted life-years (QALYs) over a lifetime time horizon (10 years) from the public health care payer perspective. The proportion of patients who were progression-free, experienced progressive disease, or were dead at any time over the model time horizon was derived from non-mutually exclusive survival curves. PFS and OS for ABCP were modelled based on the IMpower150 trial and extrapolated using survival analysis techniques. PFS and OS for the comparator arm were derived by applying hazard ratios to ABCP survival curves. These hazard ratios were obtained from the NMA commissioned by the sponsor. The model captured AEs related to treatment, but only considered their costs and not their impact on utility. Health state utility values in the model were based on a patient's proximity to death, with changes in patient utility occurring independently of progression, as of 30 weeks from death. Costs captured in the model related primarily to drug acquisition and administration; subsequent therapy costs were also captured. The proportion of patients receiving subsequent therapy, and the distribution of subsequent therapies, was based on clinical expert opinion. The sponsor reported a probabilistic incremental cost-effectiveness ratio (ICER) of $362,346 per QALY gained for ABCP compared with platinum-based chemotherapy plus pemetrexed.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- Uncertainty exists as to the comparative efficacy of ABCP and platinum-based chemotherapy in combination with pemetrexed. The NMA used data from populations that may not be comparable and excluded key comparators and trials.
- Several issues were identified with the implementation and extrapolation of the clinical data within the submitted economic evaluation. This included median OS not being reached in the observed period; a long plateau in the OS curve being informed by fewer than 10 patients; and the OS and PFS curves crossing. This led to uncertainty with the approximation and extrapolation of the observed data within the model, particularly given much of the benefit observed with ABCP was over the extrapolation period.
- A proximity-to-death approach was used to describe patient health states. Clinical expert feedback indicated that taking a patient off treatment would be the event associated with the largest impact on patient utility. Additionally, the sponsor excluded adverse event disutilities, the impact of which would likely not be captured in routine utility questionnaires.
- The proportion of patients in each treatment group receiving subsequent therapy following discontinuation, as well as the distribution of subsequent therapies, was not representative of the Canadian setting.

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- Biosimilar bevacizumab is less costly than the sponsor-submitted price for branded bevacizumab, likely overestimating costs associated with ABCP. Clinical expert feedback indicated biosimilar bevacizumab was likely to be used in clinical practice instead of the branded option.

CADTH undertook reanalyses which included using alternative utility values based on being on or off treatment, including treatment-related adverse events, using the biosimilar price for bevacizumab, as well as updating estimates of the proportion of patients receiving subsequent therapy and the distribution of those therapies to be more representative of Canadian clinical practice.

Based on these revisions, CADTH concluded similar results to the sponsor in that ABCP is not cost-effective compared to platinum-based chemotherapy plus pemetrexed, at conventionally accepted thresholds, with an ICER of $430,339 per QALY gained. The probability that ABCP was cost-effective at a willingness-to-pay threshold of $100,000 per QALY gained was 0%. It was also estimated that approximately 65% of the incremental QALYs gained were from the extrapolation period for which there is substantial uncertainty.

The results were primarily driven by the substantially high cost of combined treatment. If the cost of atezolizumab was reduced by 99%, the high cost of even biosimilar bevacizumab prevents the treatment from being cost-effective at even an $100,000 per QALY threshold. Along with a 99% price reduction for atezolizumab, the price of biosimilar bevacizumab would need to be approximately 46% below current list price for the ICER to fall below $100,000 per QALY or approximately 85% to fall below $50,000 per QALY.

Overall it is highly unlikely that ABCP would be considered a cost-effective use of Canadian health care resources, at a $50,000 or $100,000 per QALY threshold, even if substantial price reductions were obtained for both atezolizumab and bevacizumab.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: submitted BIA is underestimated

The Provincial Advisory Group (PAG) identified considerations related to the feasibility of reimbursement of ABCP, which included the following: lack of funding for bevacizumab, available funded treatments for EGFR and ALK-positive patients, the eligible patient population (patients with progression on all versus one TKI; patients with an ECOG performance status of 2; patients with untreated or active CNS metastases; and patients with ROS-1 mutations), the appropriateness of adding atezolizumab and bevacizumab to any platinum-based chemotherapy, treatment duration (criteria for treating beyond disease progression), the additional health care resources that would be required with the combination regimen (nursing, pharmacy, and clinic visits/monitoring), and sequencing of all available treatments (targeted treatments and PD-L1 inhibitors). PAG noted that there would be no drug wastage for atezolizumab and minimal wastage for bevacizumab since it is used for other tumour indications and vial sharing could be implemented.

The EGP noted that the key factor influencing the incremental budget impact was the estimated eligible population size. Several limitations with the steps to derive the eligible population were identified, which likely led to an underestimation of the eligible population size. This included inappropriate input values related to the proportion of non-squamous NSCLC patients with locally advanced or metastatic cancer, as well as the proportion of patients initiating treatment. An update to assumptions relating to the target population size indicated that the total budget impact was underestimated. This re-analysis also included the use of the biosimilar price for bevacizumab, which is less costly than the sponsor-submitted price for branded bevacizumab.

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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)
Daryl Bell, Patient Member
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, 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. Christopher Longo who was not present for the meeting
- Dr. Anil Abraham Joy who abstained from voting due to a potential conflict of interest
- Dr. Maureen Trudeau who did not vote due to her role as the pERC Chair.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee 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 and bevacizumab for EGFR and/or ALK-positive metastatic non-squamous NSCLC, through their declarations, two members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, one member 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*. Hoffmann-La Roche Limited, as the primary data owner, did not agree to the disclosure of all data related to the patient population being considered for reimbursement; therefore, this information has been redacted in the publicly available guidance reports.

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 policymakers 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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