

## pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

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

### pERC Final Recommendation

This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

**Drug:** Osimertinib (Tagrisso)

**Submitted Reimbursement Request:**

For the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer whose tumours have epidermal growth factor receptor mutations.

**Submitted By:**  
AstraZeneca Canada Inc

**Manufactured By:**  
AstraZeneca Canada Inc

**NOC Date:**  
July 10, 2018

**Submission Date:**  
May 16, 2018

**Initial Recommendation:**  
November 1, 2018

**Final Recommendation:**  
January 04, 2019

**Approximate per Patient Drug Costs, per Month (28 Days)**

Osimertinib costs \$294.68 per day for the 40 mg or 80 mg tablet.

- At the recommended dose of 80 mg once daily, osimertinib costs \$294.68 per day and \$8,250.94 per 28-day course.

### pERC RECOMMENDATION

pERC recommends reimbursement of osimertinib (Tagrisso) in the first-line treatment of patients with locally advanced (not amenable to curative intent therapy) or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations (exon 19 deletions [exon 19 del] or exon 21 [L858R]) only if both of the following conditions are met:

- Cost-effectiveness is improved to an acceptable level.
- Feasibility of adoption (budget impact) is addressed.

If the aforementioned conditions cannot be met, pERC does not recommend reimbursement of osimertinib. Eligible patients should be previously untreated in the locally advanced or metastatic setting and have a good performance status. Treatment should continue until clinically meaningful disease progression or unacceptable toxicity.

pERC made this recommendation because the Committee was confident of the net clinical benefit of osimertinib based on a considerable improvement in progression-free survival (PFS) that was statistically significant and clinically meaningful. Osimertinib also had a manageable toxicity profile and, based on the available data, treatment did not result in a decrement in patients’ quality of life (QoL). Osimertinib aligned with the patient values of maintaining QoL, being an effective first-line treatment option, and potentially providing an improvement in PFS for patients with central nervous system (CNS) metastases.

The Committee concluded that, at the submitted price, osimertinib was not cost-effective compared with standard tyrosine kinase inhibitors (TKIs) and

	<p>would require a substantial price reduction. pERC also highlighted that the potential budget impact of osimertinib was underestimated, and that the actual budget impact would be substantially greater given that the market share was underestimated and only the Ontario perspective was considered. pERC therefore had significant concerns about the capacity for jurisdictions to implement the therapy due to the high cost of osimertinib.</p>
<p><b>POTENTIAL NEXT STEPS FOR STAKEHOLDERS</b></p>	<p><b>Pricing Arrangements to Improve Cost-Effectiveness of Osimertinib</b> Given that pERC concluded that there is a net clinical benefit with osimertinib in patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations (exon 19 del or L858R), jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and affordability of osimertinib compared with EGFR TKIs.</p> <p><b>Optimal Sequencing of Osimertinib and Other Therapies</b> pERC noted that there is no clinical trial evidence to inform the optimal sequencing of osimertinib and other treatments now available for the treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations (exon 19 del or L858R). However, pERC agreed that treatment with osimertinib is likely to be followed by doublet chemotherapy as second-line treatment. Upon implementation of osimertinib reimbursement, pERC recognized that collaboration among provinces to develop a common approach for treatment sequencing would be of value.</p> <p><b>Time-Limited Need for Patients Currently on Treatment with a First or Second Generation EGFR TKI or Chemotherapy</b> When implementing a funding recommendation for osimertinib, jurisdictions may wish to consider addressing the time-limited need for this treatment in patients currently receiving targeted agents or chemotherapy in the first-line setting and who have not experienced disease progression. pERC noted that this time-limited access should be for patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations (exon 19 del or L858R) and who would otherwise meet the eligibility criteria outlined in this recommendation.</p> <p><b>Please note:</b> Provincial Advisory Group questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.</p>

## SUMMARY OF pERC DELIBERATIONS

In Canada, an estimated 28,400 new cases and 20,800 deaths occurred in 2016 from lung cancer, with a five-year survival rate of 18%. The treatment decision regarding advanced or metastatic NSCLC is typically dependent on the presence or absence and type of driver mutation status of patients. Current estimates of the incidence of the EGFR mutation range from 10% to 15% in Western populations. In patients with Asian backgrounds, the incidence can increase to 30% to 40%. pERC noted that about 2,000 Canadian patients would present in this setting per year. Two common mutations, a deletion in exon 19 (exon 19 del) or a point mutation in exon 21 (L858R), account for almost 90% of EGFR gene mutations. For patients with an EGFR mutation, treatment regimens consist of oral targeted therapies, such as gefitinib and erlotinib, directed at the tyrosine kinase domain. The second-generation EGFR TKI afatinib has been shown to have relatively small and significant absolute improvements in PFS when compared with first-generation TKIs such as gefitinib. Despite the high efficacy of EGFR TKIs observed in advanced NSCLC patients, resistance emerges in the majority of patients. Although treatment options are available in this setting, pERC agreed that there is a continued need for more effective and tolerable treatments for patients who harbour EGFR sensitizing and T790 resistance mutations, especially in patients with brain metastases.

[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 one randomized controlled trial (RCT), FLAURA, which assessed the efficacy and safety of osimertinib compared with physician's choice of EGFR TKIs (erlotinib or gefitinib) in patients with locally advanced or metastatic NSCLC with EGFR mutations (Ex19del or L858R). pERC agreed that osimertinib demonstrated statistically significant and clinically meaningful improvements in investigator-assessed PFS in favour of osimertinib (hazard ratio = 0.46 (0.37 to 0.57)  $P < 0.001$ ). pERC agreed that an absolute magnitude of PFS benefit of 8.7 months in favour of the osimertinib group (median PFS of 18.9 months versus 10.2 months) was very meaningful in patients with advanced or metastatic disease. pERC also noted that the PFS results were consistent with a blinded independent central review and that the PFS benefit was consistent across all subgroups. The results for overall survival (a secondary outcome) were not yet mature; however, the Committee noted that the available data are promising. pERC considered the results for patient-reported outcomes and agreed that osimertinib did not result in a decrement to patients' QoL overall, and a minimally important improvement was reported for cough. pERC agreed that the toxicity profile of osimertinib was manageable compared with gefitinib or erlotinib. The proportion of patients experiencing grade 3 or 4 adverse events and serious adverse events was lower in the osimertinib group compared with patients in the gefitinib or erlotinib group. However, pERC noted that some caution may be needed when administering osimertinib to patients as QT prolongations occurred more frequently with the osimertinib group. In addition to the results of the FLAURA trial, pERC also discussed input from registered clinicians indicating that osimertinib represents a major advance in the treatment of EGFR mutation-positive NSCLC. Overall, pERC agreed that osimertinib provides a net clinical benefit to patients.

pERC noted that treatment continuation beyond progression, defined by Response Evaluation Criteria in Solid Tumors (RECIST), which was allowed on the FLAURA trial, may provide disease control and reduced disease burden for patients. Therefore, the Committee agreed that treatment with osimertinib should be continued until clinically meaningful progression occurs, based on the judgment of the treating oncologist. pERC considered the generalizability of the trial results in patients with PS 2 and recognized that a reduction in disease burden with treatment can improve PS. pERC therefore agreed that osimertinib should be used in patients with good PS and the decision to treat should be left to the treating oncologist. pERC also considered that results in the subgroup of patients with stable CNS metastases, although exploratory in nature, were similar to the overall trial results, leading pERC to conclude that osimertinib is beneficial to patients with stable CNS metastases. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from registered clinicians related to the use of osimertinib in the first-line setting for patients who present with de novo T790M mutations and patients who may be pre-treated with chemotherapy due to an urgent need for treatment. pERC noted that patients with de novo T790M are currently eligible for reimbursement based on a previous decision

for osimertinib (second-line review) in which pERC concluded that patients with de novo T790M mutation should be considered for reimbursement of osimertinib given the lack of effective treatment options in this population, lack of feasibility of an RCT, and biological plausibility supporting the efficacy of osimertinib in this population. pERC further noted that patients who may receive one or two cycles of chemotherapy due to urgent need as they await the results of their molecular profiling should remain eligible for treatment with osimertinib.

pERC deliberated upon input from one patient group and noted that patients with advanced NSCLC often have a high symptom burden and value improvements in symptom control and QoL. Patients who had experience with osimertinib reported having a fast response and symptom relief, which pERC considered to be meaningful. Considering the impact of cough on patients' QoL, pERC noted that improvement in cough within the FLAURA trial was meaningful to patients. pERC, however, noted that fatigue was the most debilitating and important symptom to control for patients. Fatigue was not improved based on the FLAURA trial and was the most common symptom reported by patients providing input and who had experience with osimertinib. Overall, pERC considered patient values and agreed that the results of the FLAURA trial, which demonstrated improvements in PFS, particularly in patients with CNS metastases; manageable toxicity profile compared with gefitinib and erlotinib; and no detrimental impact on QoL, were outcomes meaningful to patients and in alignment with patient values.

pERC deliberated upon the cost-effectiveness of osimertinib compared with gefitinib based on the submitted economic evaluation and reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP). pERC agreed that the incremental cost-effectiveness ratios (ICER) for both comparisons were high at the submitted and EGP reanalysis estimates (osimertinib versus gefitinib and osimertinib versus afatinib). A factor that had a large impact on the ICERs was the method of extrapolating the PFS curves. pERC agreed with the variety of alterations made to the method of extrapolation by the EGP. Where appropriate, the EGP used the best fitting parametric curve. In other instances, where there was no best fitting curve, the EGP explored the impact of using an alternative parametric curve on the ICER. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the submitter related to the use of a Weibull curve in a previous second-line review evaluating osimertinib compared with the EGP's use of a different curve in the current review. pERC noted input from the EGP detailing that different sources of data were used to inform the second-line setting of the previous review compared with the current review. Therefore, the curve with the best fit was chosen for the submitted source of data in the current review. pERC was satisfied with the rationale provided by the EGP and concluded that a change was not required. Other factors that had an impact on the ICER were the treatment duration (both in first and second line) and the time horizon. pERC agreed with the pCODR Clinical Guidance Panel (CGP) that it is more reasonable to use time-to-treatment discontinuation curve to model duration of treatment as patients are likely to remain on treatment beyond progression. Of note, using the time-to-treatment curves reduced the ICER in favour of osimertinib. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the submitter related to the use of a 10-year time horizon to be consistent with other reviews conducted in similar indications. pERC noted that the EGP and CGP agreed with the submitter's rationale and removed modifications to the time horizon. pERC, however, noted that the 10-year time horizon is making long-term projections from relatively short follow-up in the FLAURA clinical trial (15 months for osimertinib and 9.7 months for control). pERC agreed with the EGP that long-term extrapolation of survival data with short follow-up introduces the risk of overestimating the actual benefit gained with osimertinib. When these factors were combined, the ICER increased by about \$50,000 to \$100,000 for both the presented comparisons, leading pERC to conclude that osimertinib is not cost-effective either at the submitted or the EGP reanalysis estimates. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the submitter related to the availability of additional QoL data for patients following progression on chemotherapy or an EGFR TKI. pERC noted that these data were not made available to pCODR during the review and agreed with the EGP that it would be inappropriate to comment on any potential impact this information may have on the ICER.

pERC deliberated upon the feasibility of implementing a funding recommendation for osimertinib. pERC agreed that there will be a time-limited need for osimertinib in patients who are currently on a first-generation EGFR TKI and have not experienced disease progression or patients who are currently on chemotherapy and are found to harbour a sensitizing or resistance mutation. pERC agreed these patients should be allowed to switch to osimertinib therapy. pERC agreed with the CGP that treatment should be continued beyond RECIST-defined progression at the discretion of the treating oncologist. pERC further noted that there is no evidence to guide the sequencing of available agents subsequent to first-line



osimertinib. pERC, however, noted the CGP's comment, which indicated that available evidence does not support the use of current EGFR TKIs subsequent to osimertinib.

pERC was particularly concerned with the potential budget impact of osimertinib. pERC noted that the budget impact analysis was based on an Ontario perspective and used reimbursement claims data. pERC agreed that the use of claims data may not accurately reflect the budget impact in all jurisdictions as mechanisms of take home cancer drug coverage differ among provinces. Furthermore, the market share estimates in the reference scenario were only for the Ontario population and the assumptions for drug uptake once osimertinib becomes available were unjustifiably low given the efficacy of osimertinib compared with available EGFR TKIs in this population. Based on these factors, pERC noted that the budget impact analysis is substantially underestimated. When taking into account the market share in the Canadian population and a more plausible estimate of uptake, together with the high costs of the drug, osimertinib is likely to have a significant effect on the budget impact and, therefore, on the affordability of the therapy. Given the potentially substantial budget impact of osimertinib, the provinces should consider taking steps to limit the budget impact.

## EVIDENCE IN BRIEF

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

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis (BIA)
- Guidance from the pCODR clinical and economic review panels
- Input from one patient advocacy group (Lung Cancer Canada [LCC])
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, (Lung Cancer Canada)
- Two clinician groups (Cancer Care Ontario Lung Drug Advisory Committee and Lung Cancer Canada Medical Advisory Committee)
- PAG
- The submitter [AstraZeneca Canada Inc.].

The pERC Initial Recommendation was to recommend reimbursement of osimertinib (Tagrisso) in the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations (exon 19 deletions [exon 19 del] or exon 21 [L858R]). Feedback on the pERC Initial Recommendation indicated that the manufacturer and PAG agreed with the Initial Recommendation, while the patient advocacy group and registered clinician groups agreed in part with the Initial Recommendation.

### **pCODR review scope**

The purpose of the review is to evaluate the safety and efficacy of osimertinib for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations.

### **Studies included: Randomized phase III study**

The pCODR systematic review include one randomized, double-blind, controlled trial, FLAURA, which compared osimertinib or standard EGFR tyrosine kinase inhibitors (TKI) (gefitinib or erlotinib) in patients with previously untreated EGFR mutation-positive (Ex19del or L858R) advanced NSCLC.

The pCODR review also provided contextual information on a critical appraisal of a manufacturer-submitted indirect treatment comparison (ITC) of osimertinib versus afatinib for advanced/metastatic EGFR mutation-positive NSCLC patients. According to the submitter, the results of the ITC suggest that osimertinib improved both progression-free survival (PFS) and overall survival (OS) compared with afatinib in the overall population (patients with EGFR mutation-positive NSCLC receiving treatment at first line) and for each subgroup (central nervous system [CNS] metastases, EGFR mutation type, and ethnicity). A fundamental assumption of the ITC was that erlotinib is of equivalent efficacy to gefitinib. Overall, there is moderate uncertainty in the reported ITC results.

### **Patient populations: Treatment beyond progression, CNS metastasis**

Key eligibility criteria included that patients be at least 18 years old (with the exception of Japan, at least 20 years old); patients have locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy; tumour harbours one of the two common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del or L858R), either alone or in combination with other EGFR mutations; and that patients have a World Health Organization (WHO) performance status (PS) of 0 to 1. Patients with symptomatic and unstable brain metastases were excluded.

A total of 556 patients were randomized across 132 sites and 29 countries, including Canada; 279 were allocated to osimertinib and 277 were allocated to standard EGFR TKI (gefitinib or erlotinib). The majority of patients had metastatic disease and about 20% of patients had CNS metastasis. Most patients were Asian (62%), never smokers (63% to 65%), and had a WHO PS of 1 (58% to 60%) at the time of trial entry. The median age of patients was 64 and CNS metastases were present in 19% and 23% of patients in the osimertinib and standard EGFR-TKI group, respectively. All patients enrolled could have treatment

continuation beyond progression, defined by Response Evaluation Criteria in Solid Tumors (RECIST), which was allowed in the trial since both treatment groups had the exon 19 deletion or L858R mutation. Overall, baseline characteristics of patients were well balanced. pERC considered the generalizability of the trial results and recognized that PS of 2 may be reversible with a reduction in disease burden. pERC therefore agreed that osimertinib should be used in patients with good PS and the decision to treat should be left to the treating oncologist.

Patients in the osimertinib group received osimertinib at a dose of 80 mg once daily and patients in the standard EGFR-TKI group received gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily. The type of standard EGFR TKI was determined at the site/country level. The median duration of treatment exposure was 16.2 months for the osimertinib group and 11.5 months for the standard EGFR-TKI group. Of note, afatinib was not a standard EGFR TKI included in the comparator group in the FLAURA trial. According to the authors of the publication, at the time the trial was conducted, afatinib was not widely used, nor had it been made available internationally as the standard EGFR TKI.

Treatment beyond disease progression was allowed as long as the investigator judged that there was continued clinical benefit. A total of 91 patients (67%) in the osimertinib group and 145 patients (70%) in the standard EGFR-TKI group remained on treatment beyond investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) progression and the median duration of continued treatment was eight weeks compared with seven weeks, respectively. pERC agreed that treatment with osimertinib should be continued until clinically meaningful progression occurs, based on the judgment of the treating oncologist.

Patients in the standard EGFR-TKI group could cross over to open-label osimertinib after confirmation of objective disease progression (by blinded independent central review) and post-progression documentation of T790 resistance mutation (T790M)-positive mutation status. In total, 48 patients in the standard EGFR-TKI group crossed over to receive osimertinib.

#### **Key efficacy results: Significant and clinically meaningful improvement in PFS**

The key efficacy outcome deliberated on by pERC included investigator-assessed PFS as the primary outcome. Only one analysis for PFS was planned. At the time of the analysis, the median PFS was 18.9 months in the osimertinib group compared with 10.2 months in the standard EGFR-TKI group (hazard ratio for disease progression or death, 0.46; 95% confidence interval [CI], 0.37 to 0.57;  $P < 0.001$ ). Sensitivity analysis based on blinded independent central review and all pre-defined subgroup analyses were consistent with those for primary PFS analysis. pERC agreed that osimertinib demonstrated a statistically significant and clinically meaningful improvement in investigator-assessed PFS in favour of osimertinib. pERC also agreed that an absolute magnitude of PFS benefit of 8.7 months in favour of the osimertinib group was very meaningful in the metastatic patient population. Subgroup analysis for PFS in patients with CNS metastasis demonstrated similar benefit in favour of the osimertinib group. pERC considered that results in the subgroup of patients with stable CNS metastases, although exploratory in nature, were similar to the overall trial results, leading pERC to conclude that osimertinib is beneficial to patients with stable CNS metastases.

Key secondary outcomes included OS. One interim analysis for OS was planned and a final analysis at 60% maturity. At the interim analysis, the data were immature (25% maturity; hazard ratio of 0.63 [95% CI, 0.45 to 0.88]  $P = 0.007$ ). pERC noted that the results for OS were not yet mature and could be impacted by crossover; however, the Committee noted that the available data are promising.

#### **Patient-reported outcomes: Minimally important improvement in cough only**

Patient-reported outcomes were measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) (at baseline and followed by every six weeks) and the Quality of Life Questionnaire-Lung Cancer (QLQ-LC13) (at baseline, then weekly for six weeks, and followed by every three weeks). Among key symptoms (dyspnea, chest pain, fatigue, and appetite loss), only cough in the osimertinib group demonstrated a clinically important improvement.

There were no clinically meaningful improvements in QLQ-C30 global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. Median time from randomization to the first recorded clinically relevant deterioration of key lung cancer symptoms was also similar between the two treatment groups. Overall, pERC agreed that osimertinib did not result in decrement to patients' quality of life (QoL) while a minimally important improvement was reported for cough.

### **Safety: Monitoring for QT prolongation**

pERC deliberated on the safety profile of osimertinib and noted that the incidence of grade 3 or 4 and higher adverse (AEs), serious AEs and withdrawal due to AEs were higher in the standard EGFR-TKI group. Fatal AEs were low in both groups but numerically higher in the standard EGFR-TKI group. Changes in QT interval occurred in 10% of patients in the osimertinib group, with one serious event of QT interval prolongation. Dose interruptions and dose reductions due to AEs were driven mostly by QT prolongation in the osimertinib group. pERC agreed that the toxicity profile of osimertinib was manageable compared with gefitinib or erlotinib. pERC noted that some caution may be needed when administering osimertinib to patients as QT prolongations occurred more frequently with the osimertinib group.

### **Need and burden of illness: More effective treatment options**

In Canada, an estimated 28,400 new cases and 20,800 deaths occurred in 2016 from lung cancer, with a five-year survival rate of 18%. The treatment decision regarding advanced or metastatic NSCLC is typically dependent on the presence or absence and type of driver mutation status of patients in the first-line setting. Two common mutations, exon 19 del or L858R, account for almost 90% of EGFR gene mutations. Molecular profiling of lung adenocarcinomas for EGFR mutations and anaplastic lymphoma kinase translocations is now routinely performed at the time of initial lung cancer diagnosis. Current estimates of the incidence of the EGFR mutation range from 10% to 15% in Western populations. In patients with Asian backgrounds, the incidence can increase to 30% to 40%. pERC noted that about 2,000 Canadian patients would present in this setting per year.

For patients with an EGFR mutation, treatment regimens consist of targeted therapy upfront. Oral targeted therapies directed at the tyrosine kinase domain of the EGFR have shown higher overall response rate, improved PFS, and improved QoL compared with standard chemotherapy options, and have been incorporated into treatment algorithms. A trial comparing the second-generation EGFR TKI (afatinib) with a first-generation EGFR TKI (gefitinib) showed significantly higher overall response rate and PFS compared with gefitinib, although the absolute improvement in PFS was relatively small. Osimertinib is a third-generation EGFR TKI that irreversibly binds the EGFR sensitizing mutations and T790Ms and promotes significantly greater activity for CNS metastases. pERC therefore agreed that there is a continued need for more effective and tolerable treatments for patients who harbour EGFR sensitizing and T790Ms, especially in patients with brain metastases.

### **Registered clinician input: Effective first-line option**

pERC noted input from registered clinicians indicating that current treatments in the patient population under review are erlotinib, gefitinib, and afatinib, although there is variability in how some of these agents are reimbursed across jurisdictions. Registered clinicians indicate that osimertinib is superior in efficacy to these available EGFR TKIs based on a substantially longer PFS as well as improved CNS activity, and because the initial survival data looks promising. Based on the results of the trial, registered clinicians also indicated that osimertinib is associated with fewer side effects (such as rash and diarrhea) than standard EGFR TKIs.

pERC further noted input from registered clinicians indicating that osimertinib would be prescribed as first-line treatment for patients with EGFR-positive (exon 19 deletion or exon 21 L858R) stage IIIB or IV NSCLC who have an ECOG PS of 0 to 2. Osimertinib would also be used in patients with CNS metastases as it crosses the blood brain barrier and has demonstrated activity in this population. Registered clinicians indicated that the sequencing of agents following progression on osimertinib is unknown. One clinician indicated that platinum chemotherapy may be used after progression on osimertinib. Lastly, clinicians noted that upfront use of osimertinib would allow patients to avoid the need for biopsies in the second-line setting to determine T790M status and eligibility for second-line osimertinib. pERC noted input from registered clinicians indicating that osimertinib represents a major advance in the treatment of EGFR mutation-positive NSCLC.

## **PATIENT-BASED VALUES**

### **Values of patients with NSCLC: Symptom control, income security, disease control**

pERC deliberated upon input from LCC, which included input from 91 patients with lung cancer and 72 caregivers. Input from LCC noted that patients with lung cancer have a lower likelihood of surviving at least



five years compared with other types of cancer. Lung cancer also results in more deaths than breast, prostate, and colorectal cancers combined.

pERC noted input from LCC that stated that lung cancer patients face the highest symptom burden compared with all other cancer patients. Fatigue, loss of appetite, shortness of breath, cough, pain, and blood in sputum were reported with loss of appetite, cough, pain, and shortness of breath being found to be significant QoL predictors. According to a Canadian survey of patients with advanced lung cancer, two-thirds of lung cancer patients felt their symptoms interfered with daily activities and a third noted experiencing frequent or constant feelings of anxiety or worry. Other considerations by patients were financial hardship, significant impact on those close to them, and feelings of stigma associated with lung cancer related to negative attitudes regarding smoking.

Caregivers expressed the need to justify and advocate for their loved one's lung cancer diagnosis due to the stigma associated with lung cancer. The additional stress due to the late diagnosis of lung cancer is also a concern for caregivers as the majority of diagnoses occur in stage IV. The demands of caregiving are highest and most stressful at this stage. Loss of income is burdensome, especially for younger patients, as caregivers are forced to take time off work, resulting in the loss of two incomes within a household. Caregivers note that symptoms and quick decline of patients are sources of distress for them. Fatigue and lack of energy was the most common symptom experienced by lung cancer patients, and is the symptom most difficult to manage and with the greatest impact on QoL life on both patients and caregivers.

### **Patient values on treatment: Symptom control, efficacy in brain metastasis, manageable side effects of treatment**

With current targeted oral therapies, input indicated that patients were able to continue to stay active and spend time with family. Patients with brain metastases do not currently have oral targeted treatment options. Brain metastasis also places an additional burden on lung cancer patients, as it significantly negatively impacts patients' prognosis. Current treatments for these patients include chemotherapy or radiation. Stereotactic radiation or whole brain radiation (WBR), which involves risk of permanent cognitive damage, are considered unfavourable treatment options.

Experiences with osimertinib were positive, as it was reported to have worked quickly and effectively, was effective against brain metastases, showed manageable side effects and allowed patients to remain hopeful and return to their lives. Five patients who were treated with osimertinib in first line all reported tumour shrinkage with one patient reporting that the primary tumour was almost gone. A total of eight patients who received osimertinib as first-line reported brain metastases prior to the beginning of their treatment. Half of these patients were treated with stereotactic radiation or WBR before they began treatment with osimertinib. The remaining four patients were only treated with osimertinib and showed signs of tumour shrinkage, which LCC mentioned was significant as treatment with osimertinib allows for avoidance of WBR, which is associated with permanent cognitive side effects.

The most commonly reported side effects of osimertinib were fatigue and a change in appetite. pERC noted that fatigue is a symptom that is most difficult for patients to manage. Many patients reported few side effects and said that, of the side effects experienced, they were mostly manageable. Tumour shrinkages reflected great feelings of hope among patients.

## **ECONOMIC EVALUATION**

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

The EGP assessed cost-effectiveness and cost-utility analyses comparing osimertinib with gefitinib or afatinib for the treatment of patients with EGFR mutation-positive, locally advanced or metastatic NSCLC that are treatment-naïve and eligible for first-line treatment with an EGFR TKI.

### **Basis of the economic model: Clinical and cost inputs**

Costs included were drug acquisition costs, administration costs, dose intensity, second- and third-line treatment costs, duration of treatment in all lines, disease monitoring costs, AE costs, and end-of-life care costs.

Key clinical effect estimates considered in the analysis include PFS in first- and second-line setting, time-to-progression in the first- and second-line setting, and disutilities due to AEs.

### **Drug costs: High drug acquisition cost, flat dosing**

Osimertinib costs \$294.68 per day for the 40 mg or 80 mg tablet. At the recommended dose of 80 mg once daily, osimertinib costs \$294.68 per day and \$8,250.94 per 28-day course.

Afatinib costs \$73.30 per 250 mg tablet. At the recommended dose of 250 mg once daily, afatinib costs \$73.30 per day and \$2,052.40 per 28-day course.

Gefitinib costs \$73.30 per 250 mg tablet. At the recommended dose of 250 mg once daily, gefitinib costs \$73.30 per day and \$2,052.40 per 28-day course.

Erlotinib costs \$68.00 per 150 mg tablet. At the recommended dose of 150 mg once daily, erlotinib costs \$68.00 per day and \$1,904.00 per 28-day course.

### **Cost-effectiveness estimates: ICER sensitive to method of data extrapolation**

pERC deliberated upon the cost-effectiveness of osimertinib compared with gefitinib based on the submitted economic evaluation and reanalysis estimates provided by the EGP. pERC noted that an assumption of similar efficacy between gefitinib and erlotinib is reasonable as multiple clinical trials have demonstrated consistent findings among first-generation TKIs. pERC further noted that there is no strong evidence to suggest that there is a meaningful difference in efficacy between afatinib and gefitinib or erlotinib. Given the absence of a head-to-head comparison between osimertinib and afatinib, pERC agreed that the use of the gefitinib/erlotinib PFS curves from the FLAURA trial to model the afatinib PFS curves was reasonable.

pERC agreed that the incremental cost-effectiveness ratio (ICER) for both comparisons between osimertinib versus gefitinib and osimertinib versus afatinib were high at both the submitted and the EGP reanalysis estimates. A factor that had a large impact on the ICERs was the method of extrapolating the PFS curves. pERC noted a variety of alterations made to the method of extrapolation by the EGP. In several instances the best fitting curve was not used in the base case and the EGP used the best fitting parametric curve. In other instances, where there was no best fitting curve, the EGP explored the impact of using an alternative parametric curve on the ICER. The choice of parametric curve had the largest impact on the ICER. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the submitter related to the use of a Weibull curve in a previous second-line review evaluating osimertinib compared with the EGP's use of a different curve in the current review. pERC noted input from the EGP detailing that different sources of data were used to inform the second-line data in the previous review compared with the current one. Therefore, the best fit was chosen for the submitted source of data in the current review. pERC was satisfied with the rationale provided by the EGP and agreed that a change was not required. Other factors that impacted the ICER were treatment duration (both in first and second line) and the time horizon. pERC agreed with the pCODR Clinical Guidance Panel (CGP) that it is more reasonable to use the time-to-treatment discontinuation (TTD) curve to model duration of treatment as patients are likely to remain on treatment beyond progression. Of note, using the TTD curves reduced the ICER in favour of osimertinib. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the submitter related to the use of a 10-year time horizon to be consistent with other reviews conducted in similar indications. pERC noted that the EGP and CGP agreed with the submitter's rationale and removed modifications to the time horizon. pERC, however, noted that the 10-year time horizon is making long-term projections from relatively short follow-up in the FLAURA clinical trial (15 months for osimertinib and 9.7 months for control). pERC agreed with the EGP that long-term extrapolation of survival data with short follow-up introduces the risk of overestimating the actual benefit gained with osimertinib. When these factors were combined, ICER increased by about \$50,000 to \$100,000 for both the presented comparisons, leading pERC to conclude that osimertinib is not cost-effective either at the submitted or the EGP reanalysis estimates. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the submitter related to the availability of additional QoL data for patients following progression on chemotherapy or an EGFR TKI. pERC noted that these data were not made available to pCODR during the review and agreed with the EGP that it would be inappropriate to comment on any potential impact this information may have on the ICER.

## **ADOPTION FEASIBILITY**

### **Considerations for implementation and budget impact: Budget impact substantially underestimated**

pERC deliberated upon the feasibility of implementing a funding recommendation for osimertinib. pERC discussed that gefitinib and erlotinib were appropriate comparators at the time the FLAURA trial was conducted. pERC further noted that afatinib is now a relevant comparator in this setting; however, there is no head-to-head trial comparing osimertinib with afatinib. Input from the CGP indicated that there is a marginal difference in efficacy between these first- and second-generation TKIs. Notwithstanding limitations of ITCs, pERC noted that the 2013 pCODR review for afatinib had assessed an ITC between afatinib, gefitinib, and erlotinib, and made similar conclusions. Furthermore, a small randomized trial has demonstrated marginal yet significant differences between gefitinib and afatinib. pERC therefore agreed that the assumption of similar efficacy between gefitinib and afatinib is reasonable.

pERC agreed that there will be a time-limited need for osimertinib in patients who are currently on a first-generation EGFR TKI who have not experienced disease progression or patients who are currently on chemotherapy and are found to harbour a sensitizing or resistance mutation. pERC agreed that these patients should be allowed to switch to osimertinib therapy. pERC also agreed with the CGP that treatment should be continued beyond RECIST-defined progression at the discretion of the treating oncologist. pERC further noted that there is no evidence to guide the sequencing of available agents subsequent to first-line osimertinib. pERC, however, noted the CGP's comment, which indicated that available evidence does not support the use of current EGFR TKIs subsequent to osimertinib. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from registered clinicians related to the use of osimertinib in the first-line setting for patients who present with de novo T790M mutations and patients who may be pre-treated with chemotherapy due to an urgent need for treatment. pERC noted that patients with de novo T790M are currently eligible for reimbursement based on a previous decision for osimertinib (second-line review) in which pERC concluded that patients with de novo T790M mutation should be considered for reimbursement of osimertinib given the lack of effective treatment options in this population, lack of feasibility of a randomized controlled trial, and biological plausibility supporting the efficacy of osimertinib in this population. pERC further agreed that patients who may receive one or two cycles of chemotherapy due to urgent need as they await the results of their molecular profiling should remain eligible for treatment with osimertinib.

pERC members had an extensive discussion on the potential budget impact of osimertinib and noted that the BIA was based on an Ontario perspective and using reimbursement claims data. pERC agreed that the use of claims data may not accurately reflect the budget impact in all jurisdictions as mechanisms of drug coverage differ among provinces. Furthermore, the market share estimates in the reference scenario were only for the Ontario population and the assumptions for drug uptake once osimertinib becomes available were unjustifiably low given the efficacy of osimertinib compared with available EGFR TKIs in this population. Based on these factors, pERC noted that the BIA is substantially underestimated. When taking into account the market share in the Canadian population and a more plausible estimate of uptake, together with the high costs of the drug, osimertinib is likely to have a significant effect on the budget impact and, therefore, on the affordability of the therapy. Given the potentially substantial budget impact of osimertinib, the provinces should consider taking steps to limit the budget impact.

## DRUG AND CONDITION INFORMATION

<b>Drug Information</b>	<ul style="list-style-type: none"> <li>• Selective tyrosine kinase inhibitor</li> <li>• 40 mg and 80 mg oral tablet</li> <li>• 80 mg per day orally</li> </ul>
<b>Cancer Treated</b>	<ul style="list-style-type: none"> <li>• Epidermal growth factor receptor (EGFR) sensitizing and resistance mutation-positive non-small cell lung cancer</li> </ul>
<b>Burden of Illness</b>	<ul style="list-style-type: none"> <li>• Leading cause of cancer-related deaths</li> <li>• In 2016, 28,400 new cases and 20,800 deaths occurred from lung cancer in the Canadian population</li> <li>• EGFR mutant population ranges from 10% to 15%</li> </ul>
<b>Current Standard Treatment</b>	<ul style="list-style-type: none"> <li>• Afatinib</li> <li>• Gefitinib</li> <li>• Erlotinib</li> </ul>
<b>Limitations of Current Therapy</b>	<ul style="list-style-type: none"> <li>• Resistance develops with available EGFR tyrosine kinase inhibitors</li> <li>• Toxicity of whole brain radiation</li> </ul>

## 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 Alternate  
 Dr. Kelvin Chan, Oncologist  
 Lauren Flay Charbonneau, Pharmacist  
 Dr. Matthew Cheung, 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  
 Dr. Christopher Longo, Health Economist  
 Cameron Lane, Patient Member  
 Valerie McDonald, Patient Member  
 Dr. Marianne Taylor, Oncologist  
 Dr. Dominika Wranik, Health Economist

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

- Dr. Winson Cheung and Dr. Anil Abraham Joy who were not present for the meeting
- Dr. Kelvin Chan, who was excluded from voting due to a conflict of interest
- Daryl Bell, who did not vote due to his role as a patient member alternate.

Dr. Maureen Trudeau, Oncologist (Chair)  
Dr. Catherine Moltzan, Oncologist (Vice-Chair)  
Daryl Bell, Patient Member Alternate  
Dr. Kelvin Chan, Oncologist  
Lauren Flay Charbonneau, Pharmacist  
Dr. Matthew Cheung, Oncologist  
Dr. Winson Cheung, Oncologist  
Dr. Henry Conter, Oncologist  
Dr. Avram Denburg, Pediatric Oncologist

Dr. Leela John, Pharmacist  
Dr. Anil Abraham Joy, Oncologist  
Dr. Christine Kennedy, Family Physician  
Dr. Christian Kollmannsberger  
Dr. Christopher Longo, Health Economist  
Cameron Lane, Patient Member  
Valerie McDonald, Patient Member  
Dr. Marianne Taylor, Oncologist  
Dr. Dominika Wranik, Health Economist

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

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

### **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 osimertinib (Tagrisso) for advanced or metastatic non-small cell lung cancer, through their declarations, five members had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

### **Information sources used**

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

### **Consulting publicly disclosed information**

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

### **Use of this Recommendation**

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

### **Disclaimer**

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).



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

PAG Implementation Questions	pERC Recommendation
<ul style="list-style-type: none"> <li>PAG is seeking information comparing osimertinib with afatinib.</li> </ul>	<ul style="list-style-type: none"> <li>pERC noted that there is no head-to-head trial comparing osimertinib with afatinib. CGP input indicated that a small randomized trial has demonstrated marginal yet significant differences between gefitinib and afatinib. Notwithstanding limitations of indirect treatment comparisons, pERC noted that the 2013 pCODR review for afatinib had assessed an indirect treatment comparison between afatinib, gefitinib, and erlotinib and made similar conclusions. pERC therefore agreed that the assumption of similar efficacy between gefitinib and afatinib is reasonable.</li> </ul>
<ul style="list-style-type: none"> <li>PAG is seeking clarity on the subgroup of patients with EGFR mutations who would be eligible for treatment with osimertinib. PAG noted that the trial enrolled patients with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.</li> </ul>	<ul style="list-style-type: none"> <li>Given that all patients included in the FLAURA trial had the Ex19del or L858R mutation, pERC agreed that eligibility for treatment with osimertinib should be restricted to the subgroup of patients with locally advanced or metastatic NSCLC who have EGFR mutations (Ex19del or L858R). pERC agreed that this is the majority of patients with an EGFR mutation.</li> </ul>
<ul style="list-style-type: none"> <li>PAG is seeking guidance on whether patients who have started chemotherapy but have not progressed could be switched to osimertinib.</li> <li>PAG is also seeking guidance on switching patients who have started therapy with gefitinib, erlotinib, or afatinib but have not progressed.</li> </ul>	<ul style="list-style-type: none"> <li>When implementing a funding recommendation for osimertinib, jurisdictions may consider addressing the time-limited need for this treatment in patients currently receiving a targeted agent or chemotherapy in the first-line setting and who have not experienced disease progression. pERC noted that this time-limited access should be for patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations (exon 19 del or L858R) and who would otherwise meet the eligibility criteria outlined in this Recommendation.</li> </ul>
<ul style="list-style-type: none"> <li>PAG is also seeking guidance on whether or not osimertinib could be given second line at the time of disease progression for those who completed first-line chemotherapy that was started before the results of EGFR mutation status were known.</li> </ul>	<ul style="list-style-type: none"> <li>pERC noted that for patients who complete first-line treatment with chemotherapy and have disease progression, second-line osimertinib is already available but limited to patients who harbour the T790M mutation. There is no evidence to use osimertinib in the broader EGFR population as a second-line treatment option.</li> </ul>
<ul style="list-style-type: none"> <li>PAG is seeking information on the mean duration of treatment.</li> </ul>	<ul style="list-style-type: none"> <li>pERC noted that the median duration of treatment was 16.2 months for the osimertinib group and 11.5 months for the standard EGFR-TKI group. The FLAURA trial allowed treatment beyond disease progression and patients received a median of eight and seven weeks of treatment beyond progression in the osimertinib and standard EGFR-TKI groups, respectively. pERC agreed that treatment with osimertinib should be continued until clinically meaningful progression occurs, based on the judgment of the treating oncologist.</li> </ul>

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