

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.

Drug:
Osimertinib (Tagrisso)

Submitted Funding Request:
For the treatment of patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy

Submitted by:
Astra Zeneca Canada Inc.

Manufactured by:
Astra Zeneca Canada Inc.

NOC Date:
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Submission Date:
April 1, 2016

Initial Recommendation Issued:
March 3, 2017

pERC RECOMMENDATION

pERC recommends reimbursement of osimertinib (Tagrisso) in patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on EGFR tyrosine kinase inhibitor (TKI) therapy conditional on the cost-effectiveness being improved to an acceptable level.

pERC made this recommendation because the Committee was confident of the net clinical benefit of osimertinib based on a substantial 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, did not result in a decrement or an improvement in patients' quality of life. Osimertinib also aligned with patient values.

The Committee concluded that, at the submitted price, osimertinib was not cost-effective compared with chemotherapy and would require a substantial price reduction.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Generalizability of Results in Patients With WHO PS 2, central nervous system metastases, and *de novo* T790M mutation
pERC noted that osimertinib should be reimbursed for patients with a good performance status. pERC considered that patients with declining performance status (i.e., World Health Organization Performance Status [WHO PS] of 2 or more) may benefit from treatment with osimertinib if the factors affecting PS are lung cancer-related and are considered to be reversible with treatment. pERC also noted that one-third of patients in the trial had stable central nervous system (CNS) metastases at baseline and that the results of the AURA3 trial were consistent between this subgroup of patients and those in the overall study population. pERC therefore agreed that the overall

trial results are generalizable in patients with stable CNS metastases. Lastly, pERC agreed that patients with *de novo* T790M mutation represent a small group of patients (< 2%) who have limited treatment options. After considering the lack of feasibility of conducting a randomized controlled trial in this population as well as the plausibility that osimertinib would be active in this population because of its mechanism of action, pERC agreed that patients with *de novo* T790M mutation should be considered for inclusion in the reimbursement population.

Time-Limited Need for Patients Currently on or Having Recently Completed Treatment With Chemotherapy or an Immune Checkpoint Inhibitor

At the time of implementing a reimbursement recommendation for osimertinib, jurisdictions may want to consider addressing the short-term, time-limited need for osimertinib for patients with T790M mutation-positive NSCLC who have progressed on EGFR TKI therapy and who are currently on or have recently completed treatment with chemotherapy or an immune checkpoint inhibitor.

Optimal Sequencing of Osimertinib and Other Therapies

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 epidermal growth factor receptor (EGFR) T790M mutation-positive NSCLC. However, pERC agreed that treatment with osimertinib is likely to be followed by doublet chemotherapy as third line treatment (second line in patients with *de novo* T790M mutation) and subsequently with immune checkpoint inhibitors. Upon implementation of osimertinib reimbursement, pERC recognized that collaboration among provinces to develop a common approach for treatment sequencing would be of value.

Pricing Arrangements to Improve Cost-Effectiveness

Given that pERC was satisfied that there is a net clinical benefit with osimertinib compared with chemotherapy, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of osimertinib.

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 15% to 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. Current estimates of the incidence of the EGFR mutation in Canadian NSCLC patients range from 10% to 15%. For these patients, treatment regimens consist of targeted therapy upfront. Approximately half of these patients with acquired EGFR kinase resistance harbour EGFR T790M resistance mutations in their cancer when they progress on first-line therapy. Approximately 2% of patients have the EGFR T790M mutation at presentation. Current second-line treatment consists of a platinum doublet chemotherapy. Immune checkpoint inhibitors have recently become available for patients who progress on or after treatment with a cytotoxic chemotherapy. Treatment options for patients with *de novo* EGFR T790M mutation consist of first- or second-generation EGFR TKI, despite poor outcomes, or initial toxic chemotherapy. pERC therefore agreed that there is a continued need for more effective and tolerable treatments for patients who harbour EGFR T790M resistance mutations.

[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 RCT, AURA3, which assessed the efficacy and safety of osimertinib compared with platinum-doublet chemotherapy in patients with advanced EGFR T790M mutation-positive NSCLC, who had progressed following treatment with an approved EGFR TKI agent. pERC considered the hazard ratio (HR) of 0.30 (95% confidence interval [CI], 0.23 to 0.41; $P < 0.001$) to be impressive and agreed that it demonstrated a statistically significant and clinically meaningful relative improvement in investigator-assessed PFS in favour of osimertinib. pERC agreed that an absolute magnitude of PFS benefit of 5.7 months in favour of the osimertinib group (median PFS of 10.1 versus 4.4 months) was meaningful in this patient population. pERC also noted that the PFS results were consistent with a blinded independent central review and that the PFS benefit was maintained across all calculated HRs in subgroups. The results for overall survival (OS) (a secondary outcome) were not yet mature and are likely to be confounded because of the high rate of crossover from the chemotherapy group to osimertinib upon disease progression. pERC considered the results for patient-reported outcomes (PROs) and agreed that osimertinib did not result in detriment to patients' quality of life. However, the available results were limited because of the amount of data available for assessment. pERC considered that the select reporting of five symptoms from a 13-item validated questionnaire (Quality of Life Questionnaire-Lung Cancer Module: QLQ-LC13) made it difficult for the Committee to understand the full impact of osimertinib on patients' quality of life. Four out of the five scales reported were not meaningfully different from baseline or between groups. Results from the Quality of Life Questionnaire-Core 30-Item (QLQ-C30) scale also indicated that there was no clinically meaningful improvement or decline with the use of osimertinib. pERC agreed that the toxicity profile of osimertinib was manageable compared with chemotherapy. Although the median duration of exposure in the osimertinib group was double that of the chemotherapy group, the proportion of patients experiencing grade 3 or 4 adverse events (AEs) and serious AEs was lower in the osimertinib group compared with chemotherapy. Osimertinib was also associated with a lower rate of AEs leading to permanent discontinuation, compared with chemotherapy. Furthermore, pERC noted input from registered clinicians indicating that osimertinib represents a major advance in the treatment of EGFR mutation-positive NSCLC. Registered clinicians expect that a high proportion of patients will benefit from osimertinib treatment, with minimal concerns about toxicity. Overall, pERC agreed that osimertinib provides a net clinical benefit to patients. pERC noted that treatment continuation beyond Response Evaluation Criteria in Solid Tumors (RECIST)-defined progression 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 a number of patient populations. pERC recognized that poor PS (i.e., WHO PS ≥ 2) may be reversible when a reduction in disease burden with treatment can improve PS. pERC therefore agreed that some patients with poorer PS may benefit from treatment with osimertinib and the decision to treat should be left to the treating oncologist. pERC also considered that results in a large subgroup of patients with stable CNS

metastases were similar to the overall trial results, leading pERC to conclude that osimertinib should be made available to patients with stable CNS metastases. Furthermore, pERC noted that patients with *de novo* T790M mutation were not included in the trial. 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 agreed that patients with *de novo* T790M mutation should be considered for funding of osimertinib.

pERC deliberated upon input from two patient groups and noted that patients with advanced NSCLC often have a high symptom burden and value improvements in symptom control and quality of life. Patients who had experience with osimertinib also reported having fast response and symptom relief, which pERC considered to be meaningful. The oral route of administration of osimertinib also aligned with patient values of improved independence and fewer medical appointments. Considering the impact of cough on patients' quality of life, pERC noted that clinically meaningful improvement in cough within the AURA3 trial was meaningful to patients. Overall, pERC considered patient values and agreed that the results of the AURA3 trial, which demonstrated improvements in PFS, manageable toxicity profile compared with chemotherapy, and no detrimental impact on quality of life, were outcomes meaningful to patients and in alignment with patient values.

pERC deliberated upon the cost-effectiveness of osimertinib compared with chemotherapy based on the submitted economic evaluation and reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP). pERC agreed that limitations in the maturity of the clinical trial data for OS created great uncertainty in the results for OS. In discussing the plausibility of accruing benefit in the post-progression state, pERC considered that upon progression, patients would likely go on to chemotherapy and some clinical benefit would likely be accrued. However, in discussion, pERC stated that as patients progress between lines of therapy, their responsiveness diminishes. In the absence of evidence to determine the magnitude of benefit patients would accrue in the post-progression state, pERC accepted the EGP's reanalysis limiting post-progression benefit. Furthermore, regardless of the anticipated benefit due to subsequent therapies, pERC agreed that it is unlikely that two-thirds of the quality-adjusted life-years would be gained after progression. pERC also noted that changes were made to the time horizon to better align with the clinical course of the disease and the cost of generic pemetrexed was used. When incorporating all three factors into the analysis, pERC agreed that the incremental cost-effectiveness ratio (ICER) was more than triple the base-case results provided by the submitter; therefore, pERC concluded that, at the submitted price, osimertinib is not cost-effective.

pERC deliberated upon the feasibility of implementing a funding recommendation for osimertinib and agreed that a biopsy would be required to determine eligibility for treatment with osimertinib. Based on input from the pCODR Clinical Guidance Panel (CGP) and registered clinicians, pERC noted that testing for the T790M mutation is currently available in most jurisdictions. However, pERC acknowledged the burden of testing to confirm the presence of the T790M mutation in patients will require an invasive rebiopsy as reliable and validated plasma based tests are not yet available. With the availability of osimertinib in the second-line setting for patients who fail on EGFR TKIs (afatinib or gefitinib) in the front-line setting, pERC agreed that platinum doublet chemotherapy will likely shift to third-line therapy followed by immune checkpoint inhibitors. pERC agreed that there will be a time-limited need for osimertinib in patients who are currently on or who have recently completed or progressed on chemotherapy or an immune checkpoint inhibitor. pERC considered the budget impact of osimertinib and agreed that it is likely underestimated, as more patients who are progressing on first-line treatment, and who would typically not be eligible for chemotherapy, will be eligible to receive osimertinib because of the more favourable toxicity profile.

EVIDENCE IN BRIEF

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

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

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of osimertinib for the treatment of patients with advanced epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), who have progressed following treatment with an approved EGFR tyrosine kinase inhibitor (TKI) agent.

Studies included: Crossover allowed, central nervous system metastases included

The pCODR systematic review included one randomized controlled trial (RCT), AURA3, which assessed the efficacy of osimertinib compared with platinum-doublet chemotherapy in patients with advanced EGFR T790M mutation-positive NSCLC, who had progressed following treatment with an approved EGFR TKI agent.

Key inclusion criteria specified that patients be 18 years or older (> 20 years in Japan), have documented EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, and L861Q), central confirmation of tumour T790M mutation status positive from a tissue biopsy sample taken after documented disease progression, World Health Organization performance status (WHO PS) 0 to 1 with no deterioration over the previous two weeks and minimum life expectancy of 12 weeks. Patients with asymptomatic, stable central nervous system (CNS) metastases not requiring steroids use for at least four weeks prior to start of study treatment were also allowed to enrol in the trial.

Patients in the AURA3 trial were randomized 2:1 to receive osimertinib 80 mg daily (n = 279) or platinum-based doublet chemotherapy (n = 140). In the chemotherapy group 136/140 went on to receive treatment. A combination of pemetrexed plus carboplatin was administered to 94/136 (69.1%) patients and a combination of pemetrexed plus cisplatin was administered to 42/136 (30.9%) patients. In patients randomized to the platinum-chemotherapy group and who received at least one dose of chemotherapy, 73 (54%) went on to receive maintenance pemetrexed monotherapy.

Patient populations: Treatment beyond disease progression

Baseline characteristics were mostly balanced between treatment groups. More patients enrolled on the trial were female (61.6% and 69.3%), in second line of therapy (96.4% and 95.7%), and of Asian background (65.2% and 65.7%) in both the osimertinib and platinum-doublet groups, respectively. Patients were stratified based on ethnicity (Asian or Non-Asian). All patients had previously received an EGFR TKI and had a WHO PS of 0 (36.6% and 40.0%) or 1 (63.4% and 60.0%), in the osimertinib and platinum-doublet treatment groups, respectively. Patients with CNS metastases were also enrolled (33.3% and 36.4% in the two treatment groups, respectively).

In the osimertinib arm, patients could continue to receive osimertinib beyond Response Evaluation Criteria in Solid Tumors (RECIST) v1.1-defined progression as long as they were continuing to show clinical benefit, as judged by the investigator. The trial reported that among patients in the osimertinib group who had RECIST-defined progression and were still alive, 64% (82/129) continued treatment with osimertinib beyond progression for a median of 4.1 months. pERC noted input from the pCODR Clinical Guidance Panel (CGP) suggesting that RECIST-defined progression may not always indicate deterioration in patients, as continued treatment may provide disease control and reduced disease burden for patients.

Given this, pERC was comfortable with concluding that treatment with osimertinib should be continued based on the judgment of the treating oncologist, until clinically meaningful progression occurs.

In the chemotherapy arm, patients could receive up to six cycles of pemetrexed plus cisplatin or carboplatin as initial treatment. Those patients whose disease had not progressed after four cycles of chemotherapy could continue. Upon RECIST v1.1-defined progression, patients in the chemotherapy arm were given the opportunity to begin treatment with osimertinib. At the time of data cut-off, 166 patients (59%) in the osimertinib group and 16 (12%) in the chemotherapy group were still receiving the assigned treatment. Furthermore, 82 (58.6%) patients randomized to the chemotherapy arm and who had discontinued their randomized treatment had crossed over to receive osimertinib.

Key efficacy results: Clinically meaningful improvement in progression-free survival and objective response rate

The key efficacy outcome deliberated on by pERC was investigator evaluated progression-free survival (PFS), the primary outcome for the trial. At the data cut-off of April 15, 2016, median follow-up for all patients was 8.3 months with 250 progression events (59.7% maturity) having occurred. pERC noted a statistically significant improvement in investigator-assessed median PFS in favour of osimertinib (10.1 versus 4.4 months) with an impressive hazard ratio (HR) of 0.30; 95% confidence interval (CI), 0.23 to 0.41; $P < 0.001$. At 12 months, 44.0% and 9.8% of patients had not experienced disease progression in the osimertinib and platinum-doublet groups, respectively. These results are consistent with the blinded independent central review assessment. All calculated HRs for PFS in subgroups were ≤ 0.50 , indicating a minimum of a 50% reduction in the risk of progression or death for the assessed subgroups, including patients who had a CNS metastases at enrolment, where the HR for PFS was 0.32 (95% CI, 0.21 to 0.49). Overall survival (OS) and objective response rate (ORR) were secondary outcomes in the trial. Median OS was not reported, as a sufficient number of events had not occurred. At the first interim analysis (April 15, 2016), the study reported that 14.6% and 17.6% of patients had died. Given that a large proportion of patients who progressed on the chemotherapy arm crossed over to receive osimertinib (58.6%), pERC agreed that the OS results are likely to be confounded. A second interim analysis will be performed after 50% of events and a final analysis after 70% of events. ORR was statistically improved in favour of the osimertinib group (70.6% and 31.4%). The majority of responses were partial responses (69.2% and 30.0%) in the osimertinib and platinum-doublet groups, respectively. Duration of response was also longer in the osimertinib groups compared with chemotherapy (9.7% and 4.1 months, respectively).

pERC considered the generalizability of the trial results in a number of patient populations. Although the trial was limited to patients with a WHO PS of 0 to 1, pERC recognized that poorer PS in patients may be reversible where a reduction in disease burden with treatment can improve PS. pERC therefore agreed that some patients with poorer PS may benefit from treatment with osimertinib and the decision to treat should be left to the treating oncologist. pERC also considered the fact that one-third of patients in the trial had stable CNS metastases at baseline. Subgroup analysis in these patients demonstrated results similar to the overall trial results (HR, 0.32; 95% CI, 0.21 to 0.49), leading pERC to conclude that osimertinib should be made available to patients with stable CNS metastases. Furthermore, pERC noted that patients with *de novo* T790M mutation were not included in the trial. The Committee considered the CGP's conclusions and agreed that an RCT is likely not feasible in this population. pERC further considered lack of response with first- and second-generation EGFR TKIs in this population and noted a need for effective treatment options. As a therapy that targets the T790M mutation, pERC agreed that biological plausibility supports the efficacy of osimertinib in this population. Overall, given the lack of effective treatment options, lack of feasibility of an RCT and biological plausibility, pERC agreed that patients with *de novo* T790M mutation should be eligible for treatment with osimertinib.

Patient-reported outcomes: Selected reporting of symptom scales

Patient-reported outcomes (PROs) were measured using European Organisation for Research and Treatment of Cancer Core 30-item Quality of Life Questionnaire (EORTC QLQ-C30) and the 13-item Quality of Life Questionnaire-Lung Cancer Module (QLQ-LC13). A minimal clinically meaningful change was defined as a change in score from baseline of ≥ 10 . The primary analyses for PROs were performed using a mixed-effects model for repeated measures (MMRM) analyses of change from baseline from randomization until six months in five key lung cancer symptoms (dyspnea, appetite loss, fatigue, cough, and pain in chest).

The submitter reported that a statistically significant difference in mean change from baseline until six months follow-up for all five pre-specified PRO symptoms (cough, dyspnea, chest pain, fatigue, and

appetite loss, chosen based on qualitative evidence that the submitter gathered, and identifying key symptoms of concern for NSCLC patients). pERC considered the select reporting of only five symptoms from a 13-item validated questionnaire (QLQ-LC13) made it difficult for the Committee to understand the full impact of osimertinib on patients' quality of life. From among the five scales reported, clinically meaningful within-group improvements (≥ 10 difference) were demonstrated only for cough, and between-group changes were clinically meaningful for fatigue. The remaining four scales were not meaningfully different from baseline or between groups. Results from the QLQ-C30 scale indicated that there was no clinically meaningful improvement or decline. Overall, based on the available data for assessment, pERC agreed that osimertinib did not result in a detriment to patients' quality of life.

Safety: Manageable toxicity profile

pERC agreed that the toxicity profile of osimertinib was manageable compared with chemotherapy. Adverse events (AEs) with the outcome of death (fatal AEs) were reported in four (1.4%) and 1 (0.7%) patients in the osimertinib group compared with the chemotherapy group, respectively. One death (pneumonitis) was considered to possibly be related to osimertinib. The one death in the chemotherapy group occurred due to hypovolemic shock and was considered to be possibly related to treatment. Although the median duration of exposure in the osimertinib group was double that of chemotherapy group (8.1 and 4.2 months, respectively), the proportion of patients experiencing grade 3 or 4 AEs (22.6% and 47.1%) and serious AEs (17.9% and 25.7%) was lower in the osimertinib group compared with chemotherapy, respectively. pERC noted that the registered clinician input acknowledged that osimertinib has a manageable toxicity profile. Osimertinib was also associated with a lower rate of AEs leading to permanent discontinuation compared with chemotherapy (7% and 10%). pERC noted that there were elevations in the QT interval prolongation, left ventricular ejection fraction (LVEF), and interstitial lung disease; however, the CGP agreed the increases were not clinically meaningful. It is notable that warnings and precautions were issued for these AEs of interest within the Health Canada Product Monograph. Overall, pERC agreed that the toxicity profile of osimertinib was manageable.

Need and burden of illness: More effective and tolerable options

Lung cancer is the leading cause of cancer-related deaths worldwide, with the majority of patients presenting with non-curable disease. In Canada, an estimated 28,400 new cases and 20,800 deaths occurred in 2016 from lung cancer, with a five-year survival rate of 15% to 18%. NSCLC accounts for 85% of all lung cancers. Treatment decisions for advanced or metastatic NSCLC are typically dependent on the presence or absence and type of driver mutation status of patients in the first-line setting. Current estimates of the EGFR mutant population range from 10% to 15%. For patients who have this driver mutation, treatment regimens consist of targeted therapy upfront. Approximately half of these patients with acquired EGFR kinase resistance harbour EGFR T790M resistance mutations in their cancer when they progress on first-line therapy. Second-line treatment consists of a platinum doublet chemotherapy and third-line pemetrexed in those who maintain a good PS. Approximately 2% of patients also have the EGFR T790M mutation at presentation. Treatment options in these patients consist of first- or second-generation EGFR TKI despite the poor outcomes, while others receive initial toxic chemotherapy. pERC noted that immune checkpoint inhibitors have recently become available for patients who have previously progressed on or after treatment with a cytotoxic chemotherapy. In patients with the driver mutation, eligibility for treatment with an immunotherapy requires that patients have also had prior targeted therapy. pERC therefore agreed that there is a continued need for more effective and tolerable treatment options in patients who harbour the EGFR T790M resistance mutations.

Registered clinician input: Manageable toxicity, superior to chemotherapy

Clinicians providing input noted that standard treatment in patients who develop the T790M mutation following upfront EGFR TKI therapy consists of platinum-doublet chemotherapy or best supportive care. Tumour response rates are around 20% to 30%, with a PFS of three to six months. It is therefore expected that the majority of patients progressing on upfront targeted therapy will be eligible for osimertinib. Clinicians providing input agreed that osimertinib represents a major advance in the treatment of EGFR mutation-positive NSCLC, and a high proportion of patients will benefit.

Clinicians providing input agreed that no significant concerns were noted with the use of osimertinib. Furthermore, the observed toxicities such as rash and diarrhea may be lower than those observed with first-generation TKIs. Based on a combined total of 15 patients whom they have treated with osimertinib, the clinicians providing input noted that the clinical trial data were in alignment with their own experience of using osimertinib in patients. Their patients described osimertinib as being tolerable, and the majority had excellent responses, with marked and dramatic improvement in symptoms within days to

weeks of starting therapy. This response includes significant reduction in pain and dyspnea, and improved quality of life. Overall, clinicians providing input noted that osimertinib is clinically superior to the current standard treatment (platinum-based chemotherapy or best supportive care).

Clinicians providing input agreed that patients eligible for osimertinib treatment would require a new biopsy to confirm the T790M mutation. In many provinces, T790M mutation is being tested routinely even in the EGFR TKI-naïve population and the infrastructure is already in place, so repeat testing is both reasonable and realistic. Clinicians do acknowledge the burden of testing in patients as it requires an invasive rebiopsy and acknowledged the development of new methods (cell-free DNA, which is currently being validated and which uses plasma samples) that are expected to reduce both costs and burden of rebiopsy on patients. With the availability of osimertinib, current second-line treatments (platinum doublet) would then move to third line.

PATIENT-BASED VALUES

Values of patients with lung cancer: Highly symptomatic, with a substantial impact on daily living

ERC deliberated upon input from Lung Cancer Canada and the Ontario Lung Association. pERC noted that lung cancer affects many aspects of patients' day-to-day life, such as the ability to work, travel, socialize, and participate in leisure and physical activities. Patients' relationships with family and friends, independence, emotional well-being, and financial situation are also affected. Many of the patients who provided input were younger and in the prime of their lives and had experienced shock at their diagnosis and associated poor prognosis. pERC noted that patients often have a high symptom burden, such as loss of appetite, cough, pain, and shortness of breath, all of which were found to be significant predictors of quality-of-life. Symptoms are not fixed or consistent, but rather change frequently, which can also be difficult to manage. Patients also experience anxiety and worry because of their disease. A literature review found that lung cancer patients often experience higher depression rates compared with other cancers. Furthermore, pERC noted that patients with lung cancer are often burdened with the stigma associated with smoking, even though EGFR mutation-positive NSCLC more often occurs in never-smokers.

Patients providing input indicated that current treatments provide some relief for symptoms, but side effects such as palpitations, dry mouth, mouth sores, vision and urinary problems and impact on mood need to be better managed. pERC, therefore, agreed that improvements in symptom control and quality of life were important to patients. Based on the results of the AURA3 trial, pERC agreed that osimertinib did not result in deterioration of patients' quality of life.

pERC also noted the tremendous burden on patients and their caregivers. Caregivers experience stigma unique to lung cancer, which places an additional emotional burden on them. The late diagnosis of lung cancer, often in stage IV, can also be very stressful, particularly when dealing with the declining health of family members or friends. Caregivers reported a significant economic toll on household finances as a result of lung cancer and difficulty in managing the high symptom burden of lung cancer, both for patients and caregivers.

Patient values on treatment: Management of disease and treatment side effects, progression-free survival, improved quality of life

Patients with EGFR mutations reported having received first-generation TKIs as first-line treatment. The oral targeted agents were associated with a high quality of life and were highly tolerable. After progression on front-line therapy, patients describe feeling dread and anxiety that chemotherapy may be their only option. Those patients who had experience with chemotherapy equated their treatment experience with suffering. Chemotherapy is associated with severe side effects, including nausea, vomiting, hair loss, fatigue, and the risk of fever and infection. According to patients, the burden of chemotherapy was felt during all stages of the treatment. pERC noted that patients desire treatments that have improved convenience and improved side effect profile over current therapies. Patients also desire treatments that allow them to have improved independence and less assistance from others. Patients also desire fewer medical appointments, and less financial cost burden.

Among patients who did not have direct experience with osimertinib, desired treatment outcomes include stopping or slowing the progression of the disease, reducing side effects (e.g., pain, burning of skin, fatigue, cough, and shortness of breath), and improving appetite and energy. Patients would also like to

access treatments they can take at home to reduce the need for patient or the caregiver to take time off work and decrease disrupt daily routine. pERC agreed that the oral route of administration of osimertinib aligned with patient values.

Seven patients and five caregivers who had experience with osimertinib provided input. Patients reported that osimertinib started working within days, allowing them to feel better and experience relief from symptoms. Osimertinib allowed patients to get back to their normal lives. Patients understand that their disease is terminal, but expressed that regaining the ability to get back to normal life to do meaningful activities with their families, to fulfill everyday family obligations, and get their affairs in order was of great value. Patients expressed having gained genuine hope and the ability to look to the future with the use of osimertinib. For respondents whose cough was particularly severe, being on osimertinib resolved their cough so they were able to sleep better. Regaining the ability to sleep through the night was very important to patients, as it helped increase energy and helped patients feel better. Patients also reported having gained back their appetite and the ability to get back to eating solid foods. Side effects associated with osimertinib were manageable and resolved within a reasonable amount of time. pERC considered patient values and agreed that the results of the AURA3 trial, which demonstrated improvements in PFS, manageable toxicity profile, and no detrimental impact on quality of life, compared to chemotherapy, to be outcomes meaningful to patients. Considering the impact of cough on patients' quality of life, pERC noted that clinically meaningful improvements in cough within the AURA3 trial were in alignment with the patient experiences, reported in the patient input submission.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis comparing osimertinib with a platinum-doublet chemotherapy for patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Basis of the economic model: Indirect clinical inputs for overall survival, high drug cost

Costs considered in the analysis include drug acquisition costs, post-progression treatment costs, AE management, and end-of-life care costs. The clinical effects considered in the analysis were based on PFS data from the AURA3 trial, OS estimates from other sources (naive indirect comparison), utilities in the progression-free and post-progression states, and disutilities.

Drug costs: High drug acquisition cost, generic pemetrexed available

At the list price, osimertinib costs \$294.6764 for the 40 mg or 80 mg tablet. At the recommended dose of 80 mg once daily, osimertinib costs \$294.6764 per day and \$8,250.94 per 28-day course.

At the list generic price, pemetrexed costs \$0.8318 per mg. At the recommended dose of 500 mg/m² every 21 days, pemetrexed costs \$33.67 per day and \$942.66 per 28-day course. Cisplatin costs \$2.70 per mg. At the recommended dose of 75 mg/m² every 21 days, cisplatin costs \$16.39 per day and \$459.00 per 28-day course.

Cost-effectiveness estimates: Long-term extrapolation, immature trial data

pERC deliberated upon the cost-effectiveness of osimertinib compared with chemotherapy based on the submitted economic evaluation and reanalysis estimates provided by the EGP. pERC agreed that limitations in the maturity of the clinical trial data for OS created a large amount of uncertainty in the results for OS. However, the submitted analysis reported that the majority of benefit that patients accrued (more than two-thirds) was in the post-progression state. The EGP attempted to account for this by removing all post-progression benefit from the reanalysis estimates. In discussing the plausibility of accruing benefit in the post-progression state, pERC considered the fact that upon progression, patients would likely receive chemotherapy and some clinical benefit would be accrued. The Committee also considered that as patients progress between lines of therapy, their responsiveness diminishes. In the absence of evidence to determine the magnitude of benefit patients would accrue in the post-progression state, pERC accepted the EGP's reanalysis limiting post-progression benefit. Furthermore, regardless of the anticipated benefit due to subsequent therapies, pERC agreed that it is unlikely that two-thirds of the quality-adjusted life-years would be gained after progression. pERC also noted that changes were made to the submitted 10-year time horizon to better align with the clinical course of the disease where, based on the opinion of the CGP, a five-year time horizon would be more appropriate in this population. Lastly,

given the availability of generic pemetrexed, pERC agreed that the cost reflected in the cost-effectiveness analysis should reflect the generic price. When incorporating all three factors into the analysis, pERC agreed that the incremental cost-effectiveness ratio (ICER) was more than triple the base-case results provided by the submitter. pERC therefore concluded that osimertinib is not cost-effective.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Biopsy required, flat pricing

pERC discussed the feasibility of implementing a funding recommendation for osimertinib. pERC agreed that a biopsy would be required to determine eligibility for treatment with osimertinib. Based on input from the CGP and registered clinicians, pERC noted that testing is currently available in most jurisdictions. While the majority of patients eligible for treatment with osimertinib can be identified with the plasma-based test, for those who test negative on the plasma test, a more invasive tissue biopsy will be required. Based on registered clinician input, pERC noted that plasma-based tests are currently being validated and are expected to be available in the near future; these will have the advantage of reducing the burden of invasive biopsies to patients. With the availability of osimertinib in the second-line setting for patients who fail on EGFR TKIs (afatinib or gefitinib) in the front-line setting, pERC agreed that platinum doublet will likely shift to third-line therapy, followed by immune checkpoint inhibitors (nivolumab or pembrolizumab) in the fourth-line setting. pERC noted that erlotinib would be available as a first-line option in some jurisdictions for patients who are intolerant to afatinib and gefitinib. pERC agreed that there will be a time-limited need for osimertinib in patients who are currently on or who have recently completed or progressed on chemotherapy or an immune checkpoint inhibitor.

pERC noted that the oral route of administration is an enabler; however, in jurisdictions where applications are required for pharmacare programs, which can be associated with co-payments and deductibles, patients may experience some limited accessibility and financial burden. The flat pricing of osimertinib will also be a barrier to implementation. pERC considered the budget impact of osimertinib and agreed it is likely underestimated, as more patients who are progressing on first-line treatment, and who would typically not be eligible for chemotherapy, will be eligible to receive osimertinib.

DRUG AND CONDITION INFORMATION

Drug Information	<ul style="list-style-type: none"> • Selective tyrosine kinase inhibitor (TKI) • 40 mg and 80 mg oral tablet • 80 mg per day orally
Cancer Treated	<ul style="list-style-type: none"> • EGFR T790 mutation-positive non-small cell lung cancer (NSCLC)
Burden of Illness	<ul style="list-style-type: none"> • Leading cause of cancer-related deaths • In 2016, 28,400 new cases and 20,800 deaths occurred from lung cancer in the Canadian population • EGFR mutant population ranges from 10% to 15%. Approximately half of these will develop EGFR T790M resistance mutations • Approximately 2% of patients also develop the EGFR T790M mutation at presentation
Current Standard Treatment	<ul style="list-style-type: none"> • Platinum doublet • Best supportive care • First-generation TKIs (in 2% of patients who develop <i>de novo</i> T790M mutation)
Limitations of Current Therapy	<ul style="list-style-type: none"> • Toxicity of chemotherapy • Tumour response rates are around 20% to 30%, with a progression-free survival of three to six months • First-generation TKIs ineffective in <i>de novo</i> T790M mutation-positive patients

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. Paul Hoskins, Oncologist (Vice-Chair)
 Dr. Scott Berry, Oncologist
 Dr. Kelvin Chan, Oncologist
 Dr. Matthew Cheung, Oncologist
 Dr. Craig Earle, Oncologist
 Dr. Allan Grill, Family Physician
 Don Husereau, Health Economist

Dr. Anil Abraham Joy, Oncologist
 Karen MacCurdy Thompson, Pharmacist
 Valerie McDonald, Patient Member Alternate
 Carole McMahon, Patient Member
 Dr. Catherine Moltzan, Oncologist
 Jo Nanson, Patient Member
 Dr. Marianne Taylor, Oncologist
 Danica Wasney, Pharmacist

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

- Craig Earle, Allan Grill, and Danica Wasney, who were not present for the meeting
- Anil Abraham Joy, who was excluded from voting due to a conflict of interest
- Valerie McDonald, who did not vote due to her role as a patient member alternate.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of

interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of osimertinib (Tagrisso) for 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*.

Use of this Recommendation

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

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