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Reimbursement Recommendation

Osimertinib (Tagrisso)

Indication: For the treatment of patients with locally advanced, unresectable (stage III) non–small cell lung cancer (NSCLC) whose tumours have *EGFR* exon 19 deletions or exon 21 L858R substitution mutations (either alone or in combination with other *EGFR* mutations) and whose disease has not progressed during or following platinum-based chemoradiation therapy

Sponsor: AstraZeneca Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Tagrisso?

Canada's Drug Agency (CDA-AMC) recommends that Tagrisso be reimbursed by public drug plans for the treatment of patients with locally advanced, unresectable (stage III) non–small cell lung cancer (NSCLC) — a stage at which the cancer has spread to nearby areas but cannot be removed by surgery. This applies only to patients whose tumours have specific changes in the *EGFR* gene, such as exon 19 deletions (Ex19del) or exon 21 L858R substitutions (either alone or in combination with other *EGFR* mutations), and whose disease has not progressed during or following platinum-based chemoradiation therapy, provided certain conditions are met.

Which Patients Are Eligible for Coverage?

Tagrisso should only be covered to treat adult patients with locally advanced unresectable (stage III) nonsquamous NSCLC (the most common subtype of NSCLS, which begins in gland-like cells in the lungs) with documented Ex19del or exon 21 L858R substitutions and who have not had disease progression during or following platinum-based chemoradiation therapy. Only patients who have a good performance status should be eligible for Tagrisso.

What Are the Conditions for Reimbursement?

Tagrisso should only be reimbursed if it is prescribed by clinicians with expertise in treating NSCLC and the cost of Tagrisso is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that patients treated with Tagrisso experienced a delay in their cancer growing or spreading compared to those with no active medicine (i.e., placebo).
- Tagrisso addresses some unmet needs of patients by delaying the growth and spread of their cancer, offering a manageable toxicity profile, and having a convenient oral route of administration. Tagrisso has potential to prolong survival and maintain health-related quality of life.
- Based on the CDA-AMC assessment of the health economic evidence, Tagrisso does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Tagrisso is estimated to cost the public drug plans approximately $19.6 million over the next 3 years.

Summary

Additional Information

What Is Unresectable (Stage III) NSCLC?

NSCLC is the most common type of lung cancer that occurs when cells in the lungs or lining of the airways grow abnormally and form a tumour. In 2024 alone, approximately 32,100 people living in Canada were expected to be diagnosed with lung cancer. In approximately 15 of every 100 people with NSCLC living in Canada there is a change in the *EGFR* gene, most of which are Ex19del or exon 21 L858R substitutions. It is estimated that approximately 1 in 21 people living in Canada will die of lung cancer during their lifetime.

Unmet Needs in Unresectable (Stage III) NSCLC

After successful completion of chemoradiation therapy, patients are usually monitored without active treatment (i.e., watchful waiting); however, this approach is frequently associated with cancer recurrence. A key unmet need is to reduce the risk of disease recurrence.

How Much Does Tagrisso Cost?

Treatment with Tagrisso is expected to cost approximately $9,020 per 28-day cycle.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that osimertinib be reimbursed for the treatment of patients with locally advanced, unresectable (stage III) non–small cell lung cancer (NSCLC) whose tumours have *EGFR* mutation exon 19 deletions (Ex19del) or exon 21 L858R substitution mutations (either alone or in combination with other *EGFR* mutations) and whose disease has not progressed during or following platinum-based chemoradiation therapy (CRT) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, double-blinded, placebo-controlled trial (the LAURA trial; N = 216) demonstrated that osimertinib maintenance therapy resulted in a clinical benefit in adults with locally advanced, unresectable (stage III) NSCLC with *EGFR* mutations (Ex19del and exon 21 L858R) whose disease has not progressed during or following platinum-based definitive CRT. The LAURA trial demonstrated that, compared with placebo, osimertinib resulted in statistically significant and clinically meaningful improvements in the primary analysis of progression-free survival (PFS) (median PFS = 39.1 months for osimertinib versus 5.6 months for placebo; hazard ratio [HR] = 0.16; 95% confidence interval [CI], 0.10 to 0.24). The results for the central nervous system (CNS) PFS outcome were supportive of the primary analyses (HR = 0.17; 95% CI, 0.09 to 0.32). pERC acknowledged that 4-year overall survival (OS) rates at an updated analysis suggested a trend in favour of osimertinib (between-group difference = [redacted]; data cut-off (DCO) date: November 29, 2024). The interpretation of OS data was limited by low data maturity (30.6%), a high rate of crossover of patients from the placebo to the osimertinib group, and imprecision in between-group estimates (wide CIs that included small effects close to or crossed the null). The health-related quality of life (HRQoL) outcome was descriptive in nature, limited by low completion rates, and did not suggest that treatment with osimertinib resulted in a statistically significant improvement in HRQoL from baseline to week 40. The committee considered that the safety profile of osimertinib appeared consistent with its known safety profile.

Patients identified a need for effective treatment options that delay disease progression, prolong survival, have manageable side effects, allow patients to experience improved HRQoL, and offer a convenient route of administration. pERC concluded that osimertinib met some patient needs because it delays disease progression, may prolong survival, has manageable side effects, may maintain HRQoL, and has an oral route of administration that can be administered in a patient's home.

Using the sponsor-submitted price for osimertinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for osimertinib was $203,741 per quality-adjusted life-year (QALY) gained compared with placebo. At this ICER, osimertinib is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained for the submitted indication. A price reduction is required for osimertinib to be considered cost-effective at a threshold of $50,000 per QALY gained.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with osimertinib should be reimbursed in adult patients who meet all the following criteria: 1.1. locally advanced, unresectable (stage III) nonsquamous NSCLC 1.2. documented *EGFR* mutations (Ex19del or exon 21 L858R) 1.3. disease has not progressed during or following definitive platinum-based CRT.	Evidence from the LAURA trial showed that osimertinib maintenance therapy compared to placebo resulted in clinical benefit in patients with these characteristics.	—
2. Patients should have a good performance status.	Patients with an ECOG performance status of 0 to 1 were included in the LAURA trial.	Patients with an ECOG performance status of 2 may be treated at the discretion of the treating clinician.
3. Patients must not have any of the following criteria: 3.1. history of ILD before CRT 3.2. QT prolongation or active cardiac arrhythmia 3.3. prior treatment with *EGFR* TKI therapy, except adjuvant therapy if completed at least 6 months prior.	The LAURA trial excluded patients with a history of ILD, QT prolongation or any clinically important abnormalities in cardiac rhythm, or prior treatment with *EGFR* TKI therapy or other systemic therapy for NSCLC outside of that received in the definitive setting for stage III disease.	pERC considered it reasonable for patients to be eligible for osimertinib if patients completed an adjuvant TKI therapy (including adjuvant treatment with osimertinib for stage I/II disease) at least 6 months prior.
Discontinuation		
4. Reimbursement of osimertinib should continue until disease progression or unacceptable toxicity, whichever occurs first.	Patients in the LAURA trial discontinued treatment upon disease progression or unacceptable toxicity. Continuation of study treatment after confirmed disease progression was allowed in the LAURA trial if the investigator believed the patient was deriving clinical benefit.	pERC agreed that treatment with osimertinib could be continued until clinically meaningful progression occurs based on the judgment of the treating clinician.
Prescribing		
5. Osimertinib should be prescribed by a clinician with expertise in treating NSCLC.	This is meant to ensure that osimertinib is prescribed for appropriate patients and that adverse effects are managed in an optimal and timely manner.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
6. A reduction in price.	The ICER for osimertinib is $203,741 per QALY gained compared with active surveillance. A price reduction of > 40% would be required for osimertinib to achieve an ICER of $50,000 per QALY gained compared to placebo. Price reductions for different thresholds are available in Appendix 4 in the Pharmacoeconomic Review report. Notably, the base-case analysis may overestimate QALY gains and cost savings, meaning further price reductions than those presented may be required.	—

CRT = chemoradiation therapy; ECOG = Eastern Cooperative Oncology Group; Ex19del = exon 19 deletion; ICER = incremental cost-effectiveness ratio; ILD = interstitial lung disease; NSCLC = non–small cell lung cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year; TKI = tyrosine kinase inhibitor.

Discussion Points

- **Unmet need:** pERC acknowledged input from patient groups and clinician groups highlighting that locally advanced stage III NSCLC is an aggressive disease with poor prognosis. Despite current treatment options, long-term survival and cure are still rare, with an estimated 16% of patients surviving for 5 years or longer. The clinical experts consulted by Canada's Drug Agency (CDA-AMC) noted that, following completion of CRT, patients with *EGFR*-mutated NSCLC have no established active treatment options and are typically managed with active surveillance. If the disease relapses, it is generally considered incurable. pERC heard from the clinical experts that patients with the *EGFR* mutations are at increased risk of developing CNS metastasis, which is associated with a decrease in HRQoL and poor prognosis. pERC agreed with the clinical experts that there is an unmet need for effective and safe therapy options in the requested patient population.
- **Efficacy outcomes:** The committee noted that, compared to placebo, osimertinib resulted in statistically significant and clinically meaningful improvements in PFS, the primary outcome in the LAURA trial. These improvements were associated with high to moderate levels of certainty per the CDA-AMC Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment. The benefit of osimertinib observed in the primary analyses was supported by a clinically meaningful improvement in the secondary outcome CNS PFS with high to moderate levels of certainty. The committee discussed that the OS results in the LAURA trial showed that osimertinib may prolong OS with low levels of certainty. Uncertainty in the OS results stemmed from immature data (30.6% [92 of 120 events] of the information fraction planned for the final OS analysis), a large number of patients (74%) who crossed over from the placebo to the osimertinib group, and [redacted]. pERC discussed the clinical meaningfulness of PFS in the patient target

population. pERC agreed with the clinical experts that the transition to relapsed disease is a clinically relevant event that indicates a shift from curative to noncurative treatment intent. pERC agreed with the clinical experts that the improvements in PFS and CNS PFS of the magnitude observed in the LAURA trial are of clinical importance in a patient population for which there are currently no standard treatments.

- **Adverse events:** pERC noted that patients with NSCLC identified a need for alternative treatment options with manageable side effects. Comparative safety from the LAURA trial indicated that any adverse events (AEs), serious AEs (SAEs), and AEs leading to treatment discontinuation, were more common in patients treated with osimertinib than those treated with placebo. The most commonly reported AEs occurring with higher incidence in the osimertinib group were radiation pneumonitis, diarrhea, and rash. The most commonly reported SAE was radiation pneumonitis. pERC acknowledged clinical expert input that the safety profile of osimertinib in the current setting appeared consistent with, and as manageable as, its known safety profile in patients with NSCLC.
- **Testing procedure considerations:** pERC noted that *EGFR* testing is currently performed as the standard of care for patients with NSCLC in Canada and acknowledged that evaluating *EGFR* status for Ex19del or exon 21 L858R before the initiation of osimertinib would be required. pERC also noted that considering this is already standard of care, *EGFR* testing is not anticipated to be an implementation or access barrier.
- **Uncertainty in cost-effectiveness:** Osimertinib has been reviewed previously by CDA-AMC and has a letter of intent with the pan-Canadian Pharmaceutical Alliance (pCPA). In the economic analysis, there are cost savings associated with not using osimertinib in subsequent treatment lines because most patients are not retreated if they receive osimertinib in an earlier setting. A lower price of osimertinib in subsequent treatment lines reduces these cost savings, therefore increasing the ICER and the required price reduction to achieve cost-effectiveness in the first-line setting.

Background

Lung cancer is the most commonly diagnosed cancer in Canada and the leading cause of cancer-related deaths. In 2024 alone, approximately 32,100 people living in Canada were expected to be diagnosed with lung cancer, with 20,700 annual deaths attributed to lung cancer. Survival from lung cancer of all stages and histologies is poor, with an overall 5-year net survival of 22%. Lung cancer is classified into NSCLC or small cell lung cancer; with NSCLC accounts for approximately 88% of cases in Canada, excluding Quebec. One of the most prominent NSCLC molecular alterations are *EGFR* mutations which cause abnormal signalling pathways that drive tumour growth. *EGFR* mutations are more frequently observed in people who never smoked, people of Asian ethnicity, patients with adenocarcinoma, and female patients. The most common *EGFR* mutations are Ex19del and the exon 21 codon 858 point mutation L858R, accounting for 70% to 90% of *EGFR* mutations. The most common symptoms of NSCLC include unspecific cough, chest and shoulder pain, hemoptysis, weight loss, dyspnea, hoarseness, bone pain, fever, and recurring infections

with bronchitis and pneumonia. Diagnostic procedures include imaging of the lungs, sputum cytology, and tissue biopsy.

The treatment goals for locally advanced, unresectable stage III NSCLC are to cure the disease; prevent local recurrence, distant metastases, and disease progression; and improve quality of life. The current conventional treatment in the front-line setting for patients presenting with unresectable stage III NSCLC, irrespective of *EGFR* mutation status, is definitive concurrent CRT, with sequential CRT used for patients who cannot tolerate concurrent CRT. In Canada, durvalumab, a PD-L1 inhibitor, is currently reimbursed for the treatment of patients whose disease has not progressed following concurrent platinum-based CRT. However, clinical experts consulted for this review with experience in the diagnosis and management of NSCLC revealed durvalumab is rarely used in clinical practice in Canada for the treatment of *EGFR*-mutated NSCLC because of its limited efficacy and higher incidence of AEs compared with placebo. In the absence of an effective and available consolidation therapy (also referred to as maintenance therapy) for unresectable *EGFR*-mutated NSCLC in Canada, clinical experts consulted for this review indicated that active surveillance (i.e., regular imaging and clinical monitoring) is the current standard of care for these patients.

Osimertinib received conditional Health Canada authorization for the treatment of patients with locally advanced, unresectable (stage III) NSCLC whose tumours have *EGFR* Ex19del or exon 21 L858R substitution mutations (either alone or in combination with other *EGFR* mutations) and whose disease has not progressed during or following platinum-based CRT. Health Canada's authorization is conditional on the final OS results from the LAURA trial (at approximately 60% maturity), which will be used to confirm clinical benefit of osimertinib observed in the primary end point: PFS for the intention-to-treat target population. The final OS analysis is event driven and anticipated to occur in the first half of 2027.

The recommended dose of osimertinib is 80 mg tablet taken orally once a day.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 placebo-controlled randomized trial in adults with locally advanced, unresectable *EGFR*-mutated (Ex19del and exon 21 L858R) NSCLC whose disease has not progressed during or following definitive platinum-based CRT
- patients' perspectives from 1 joint input gathered by 3 patient groups, Lung Health Foundation (LHF), Lung Cancer Canada (LCC), and the Canadian Cancer Survivor Network (CCSN)
- input from public drug plans that participate in the reimbursement review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with NSCLC
- input from 2 clinician groups, Lung Cancer Canada Medical Advisory Committee (LCC MAC) and Ontario Health (Cancer Care Ontario) (OH [CCO]) Lung Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups that responded to our call for input and from clinical experts consulted for the purpose of this review.

Patient Input

CDA-AMC received 1 joint patient input submission from LHF, LCC, and CCSN. LHF is a registered charity that assists and empowers people living with or caring for others with lung disease. LCC is a registered national charitable organization that supports patients through providing education, research, and advocacy. CCSN is a national network that promotes the best standard of care and provides support for cancer patients on issues related to survivorship or quality of end-of-life care.

The information was gathered through an online survey conducted from July to December 2024. There were 23 respondents from Canada who identified as living with lung cancer. These included 20 patients and 3 caregivers, all of whom had experience with osimertinib. Additionally, LFH conducted interviews with 6 patients (5 female and 1 male) who completed the online survey in January 2025. Interviewees ranged in age from 49 to 72 years. Four interviewees were diagnosed with stage IV NSCLC with an *EGFR* exon 19 mutation. One interviewee was diagnosed with stage IV lung cancer with the same mutation, and another was diagnosed with stage IIIC adenocarcinoma.

Based on the patient group input, fatigue was the most detrimental physical symptom of lung cancer, which was reported by 81% of survey respondents. This was followed by reduced appetite or weight loss (47.6%), cough (33.3%), pain (28.6%), and shortness of breath (23.8%). Additionally, 39.1% of survey respondents specifically cited fatigue and 26.1% cited shortness of breath as the primary reasons they were unable to perform daily activities. Interviewees also identified fatigue as the most detrimental physical symptom , with 3 of 6 interviewees noting fatigue and weakness as the reason they had to stop working.

In the input, lung cancer was noted to impact multiple aspects of patients' daily life. The most impacted daily activity was the ability to work (57.1% of survey respondents and 67% of interviewees), followed by participation in sports (38.1% of respondents), travel (33.3% of respondents), leisure or hobbies (28.6% of respondents), and housework (23.8% of respondents). Survey respondents felt their experiences with lung cancer led to negative impacts on their emotional well-being (43.5%), feeling cold (43.5%), feeling isolated (34.8%), and impacted their family relationships (26.1%). The interviewees noted that the negative impacts of having lung cancer included emotional distress, mental health challenges, concerns regarding insurance coverage (e.g., travel and car insurance), changing medications and managing side effects, and job limitations due to infection risks (e.g., exposure to viruses).

The patient groups noted that concerns surrounding personal health, financial burdens, and concern for family members were some of the reasons for experiencing anxiety. These experiences highlight the profound and intertwined physical, emotional, and social toll of lung cancer on patients, their families, and their caregivers. Many respondents noted that both their symptoms and the time it took to manage their treatments negatively impacted their ability to continue working.

Survey respondents tried a range of treatments, included targeted therapy (47.6%), chemotherapies (33.3%; such as pemetrexed-carboplatin, double platinum, and others), surgery (4.8%; such as lobectomy), radiation (4.8%), immunotherapy (4.8%), and clinical trials (4.8%). Side effects were frequently associated with current treatment options, with 81.0% of survey respondents mentioning fatigue as a side effect associated with lung cancer treatments. Two interviewees who shared their experiences with lung cancer medications reported adverse effects including fatigue, anemia, bothersome mouth feel or altered taste, joint pain, edema in extremities, nausea, and constipation. Additionally, both interviewees noted that while additional medications could be taken to manage side effects, such medications were costly. The patient groups highlighted that while current lung cancer treatments extend patients' lives, there are still concerns regarding HRQoL, with patients continuing to experience residual symptoms and debilitating side effects.

When considering a new medication to treat lung cancer, survey respondents identified the most important outcomes as improved HRQoL (78.3%), reduced symptoms (60.9%), improved energy (43.5%), improved symptom management (39.1%), improved and/or prolonged efficacy (26.0%), reduced cost (21.7%), reduced travel time to obtain medication or treatment (8.7%), and zero cost (4.3%). The most important outcomes reported by 2 interviewees included treatment effectiveness (i.e., extending life), improved quality of life, ability to effectively manage lung cancer without destroying healthy cells, ease of administration (daily oral pill is preferred over an IV infusion), manageable side effects, and affordability.

The patient groups stated that most respondents had positive experiences with osimertinib, with 90.8% preferring or strongly preferring it to other treatments or medications they had tried. Two interviewees reported a substantial change in quality of life with osimertinib, stating that it gave them the ability to have a normal life and to be able to return to work. The 3 most common side effects of osimertinib reported by survey respondents were negative changes in appearance (e.g., hair and nail issues) (73.9%), fatigue (69.6%), and diarrhea (69.6%); however, 95.7% of respondents felt their side effects were manageable. The top 10 benefits of osimertinib reported by survey respondents included reduced or eliminated pain (36.4%), stabilization of cancer or prolonged life (27.3%), ability to exercise (27.3%), increased energy (22.7%), reduced fatigue (18.2%), increased participation in daily activities (18.2%), reduced shortness of breath (18.2%), improved appetite or weight gain (18.2%), reduced cough (13.6%), and improved mood (13.6%).

Overall, the patient groups highlighted that there is an unmet need for lung cancer therapies that delay disease progression, prolong survival, improve HRQoL, and have manageable side effects. Patients also raised considerations about accessibility and needs for equity across all provinces in diagnoses and treatments. In addition, respondents expressed concerns about their continued ability to access medications due to costs, lack of availability, and the development of resistance to those medications that work for them.

Clinician Input

Input From Clinical Experts Consulted for This Review

Two clinical experts with expertise in the diagnosis and management of NSCLC provided input for this review.

Both experts felt the overarching goal of treatment for unresectable NSCLC in patients whose tumours have *EGFR* mutations is to reduce the risk of recurrence, increase the proportion of patients who remain cancer-free in the long-term, improve survival and, in doing so, enhance HRQoL. The clinical experts noted that conventional treatments (e.g., CRT) often lead to high rates of disease recurrence, and relapsed stage III NSCLC is generally considered incurable. Additionally, the experts flagged that patients with *EGFR* mutations are more likely to develop CNS metastases compared to those without driver mutations, which increases the risk of symptoms at recurrence. Therefore, reducing relapse risk in patients with unresectable NSCLC and *EGFR* mutations was identified as a critical unmet need by the clinical experts consulted for this review.

Although patients with unresectable NSCLC are eligible for consolidation treatment with durvalumab after CRT, the clinical experts consulted for this review indicated that most oncologists in Canada would not administer durvalumab after CRT in patients with an *EGFR* mutation due to its limited efficacy and increased toxicity.

The experts believed that using osimertinib after successful completion of platinum-based CRT would provide a new therapeutic option for patients with unresectable NSCLC with *EGFR* mutations. Since osimertinib is currently reimbursed for relapsing cases, the clinical experts noted that using it in the current setting would cause a shift in the current treatment paradigm. Patients using osimertinib in the current setting would no longer be eligible for osimertinib as first-line treatment with palliative intent, assuming recurrence occurs on maintenance osimertinib or within 6 months of stopping therapy.

The clinical experts noted that patients with unresectable stage III NSCLC whose tumours contain a common *EGFR* mutation (i.e., Ex19del or exon 21 L858R substitution) and who have not progressed following platinum-based CRT would be best suited for maintenance treatment with osimertinib. The clinical experts felt that any patient who received non–platinum-based CRT should not be routinely eligible for osimertinib treatment but felt there should be mechanisms for individual patient requests. The experts noted that *EGFR* mutations are identified throughout molecular testing, either using polymerase chain reaction or next-generation sequencing, which should be performed at diagnosis or during CRT treatment. Following platinum-based CRT, a CT scan should be performed to evaluate disease response or progression before initiating treatment with osimertinib.

Outcome metrics used in clinical practice are generally aligned with those used in clinical trials. The clinical experts consulted for this review noted that the metrics most often used in clinical practice include disease progression, OS, quality of life (e.g., symptoms and the patients' overall impression), and prevention of brain metastases. The experts noted that, in current clinical practice, imaging is performed every 3 to 6 months for the first 2 years following CRT and then annually thereafter. If osimertinib is reimbursed for patients with unresectable *EGFR*-mutated NSCLC whose disease has not progressed during or following platinum-based CRT, the experts anticipated that more frequent visits would be required when starting treatment (e.g., assessments approximately every 4 weeks for the first 3 months) and then every 3 months thereafter for the duration of treatment.

Clinical experts consulted for this review indicated that osimertinib should be discontinued in the event of disease progression or significant toxicities that cannot be safely managed with dose reductions or modifications. The clinical experts consulted for this review felt that, in the event of disease progression that is not amenable to any other local therapies, patients should be able to continue treatment with osimertinib if there is evidence of ongoing clinical benefit. The clinical experts noted that if a patient discontinued maintenance osimertinib treatment in the absence of recurrence, they should be eligible for first-line palliative-intent osimertinib treatment if at least 6 months have elapsed since discontinuation at the time of recurrence.

The experts indicated that treatment with osimertinib should be prescribed and managed by a physician familiar with managing systemic lung cancers (i.e., medical oncologist or pulmonologist). In some regions, care may be supervised by another physician (e.g., a general practitioner) under the direction from a physician trained in managing systemic anticancer therapies.

Clinician Group Input

CDA-AMC received 2 clinician group input submissions from LCC MAC and the OH (CCO) Lung Cancer Drug Advisory Committee. LCC is a national charity with the purpose of increasing awareness about lung cancer, providing support to lung cancer patients, research, and advocacy. The LCC MAC consists of clinicians in the field of lung cancer across the country. The OH (CCO) Lung Cancer Drug Advisory Committee provides timely evidence-based clinical and health system guidance on drug-related issues in support of the OH (CCO) mandate. In total, 27 clinicians contributed to this submission, 23 from LCC MAC and 4 from the OH (CCO) Lung Cancer Drug Advisory Committee.

Both clinician groups and the clinical experts consulted for this review agreed that the current standard treatment for patients with unresectable, locally advanced NSCLC with *EGFR* mutations is concurrent CRT. Clinician groups agreed that while consolidation immunotherapy with durvalumab is currently approved by Health Canada and provincially funded for unresectable NSCLC agnostic of PD-L1 expression or *EGFR* mutation, it is not used in practice or recommended as conventional treatment for patients with *EGFR* mutations. Post hoc subgroup analyses of the PACIFIC trial revealed that patients with *EGFR* mutations receiving durvalumab had similar efficacy and increased toxicity compared to those receiving placebo. As such, both clinician groups agreed that there are no targetable treatments currently approved for patients with unresectable stage III NSCLC with *EGFR* mutations. Clinician groups noted that the goal of treatment is to cure the disease, as measured by OS, PFS, and disease-free survival; LCC MAC added delaying disease progression in extrathoracic sites as a critical secondary goal.

The OH (CCO) Lung Cancer Drug Advisory Committee explained patients with stage III (per standard Canadian staging techniques) unresectable NSCLC with *EGFR* Ex19del or exon 21 L858R substitution mutations who do not to have disease progression by standard restaging techniques within 6 weeks of completion of platinum-based CRT (either concurrently or sequentially), with no contraindication to *EGFR* tyrosine kinase inhibitors, no history of interstitial lung disease before CRT, and no evidence of symptomatic pneumonitis following definitive CRT are best suited for treatment with osimertinib. The OH (CCO) flagged that although 1 of the criteria is restaging within 6 weeks of completion of CRT, there should be some

flexibility in this criterion because some centres have issues with CT waiting time. Although the OH (CCO) Lung Cancer Drug Advisory Committee indicated that reimbursement of molecular *EGFR* testing may not be universal across the country and that additional funding may be needed in provinces without provincial reimbursement, the LCC MAC indicated that they did not anticipate any increase in the cost of testing for *EGFR* rearrangements to accommodate maintenance use of osimertinib.

LCC MAC stated that the outcomes to determine whether a patient is responding to treatment in clinical practice include PFS. LCC MAC suggested including the use of scans (CT of the body with or without brain imaging) and symptoms to monitor recurrence or progression with a frequency of every 3 to 4 months whereas the OH (CCO) Lung Cancer Drug Advisory Committee suggested restaging investigations every 3 to 6 months.

Both clinician groups agreed that treatment should be discontinued if there is disease recurrence or progression, intolerance, or clinically important toxicity. The OH (CCO) Lung Cancer Drug Advisory Committee further added that treatment should be discontinued upon patient request.

Clinician groups agreed that osimertinib can be delivered in a medical oncology outpatient setting. The OH (COO) Lung Cancer Drug Advisory Committee further specified that osimertinib should be managed under the supervision of a medical oncologist with training in systemic therapy for thoracic malignancies.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The LAURA trial randomized patients to osimertinib or placebo in a 2:1 ratio. Observation is an appropriate comparator for patients with *EGFR* mutation–positive NSCLC after chemoradiation is complete for unresectable stage III NSCLC.	This was a comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
1. In the LAURA trial, patients were required to be randomized within 6 weeks of completing chemoradiation. In patients who require more time to recover from toxicities, would it be appropriate for patients to start osimertinib beyond 6 weeks? If so, is there a maximum amount of time that would be recommended (i.e., if patient has more than 12 weeks since completion chemoradiation would not be eligible for osimertinib)? 2. Should patients who receive sequential chemotherapy and radiation be eligible for osimertinib?	1. pERC agreed with the clinical experts consulted for this review that every effort should be made to initiate osimertinib within 6 weeks of completing CRT. In addition, pERC agreed with the clinical experts that the period of time between completing platinum-based CRT and initiating osimertinib should be extended to 10 weeks in patients who have not recovered from their CRT or cannot receive reimaging scans within 6 weeks. 2. The experts noted that although subgroup analyses among patients receiving platinum-based sequential CRT were not performed in the LAURA trial due to the small sample size, the efficacy of osimertinib in those receiving platinum-based

Implementation issues	Response
	sequential CRT is expected to be similar as in those receiving platinum-based concurrent CRT and no restriction should be made on the type of platinum-based CRT received. pERC agreed with the clinical experts.
Please confirm that only patients with Ex19del and exon 21 L858R *EGFR*-positive disease would be eligible for osimertinib and that patients with other *EGFR* exon positivity would not be included (i.e., exon 20).	pERC noted that the Health Canada–approved indication and reimbursement request are specific to patients whose tumours have Ex19del or exon 21 L858R substitution mutations (either alone or in combination with other *EGFR* mutations), and pERC did not review any evidence supporting the use of osimertinib maintenance therapy in patients with other *EGFR* mutations. Therefore, pERC could not comment on effectiveness in patients with other *EGFR* mutations.
Considerations for discontinuation of therapy	
In the trial, participants were able to continue osimertinib beyond disease progression if the investigator thought there was continued clinical benefit. What should the discontinuation criteria for osimertinib be?	The clinical experts consulted for this review felt that, in the event of disease progression that is not amenable to any other local therapies, patients should be able to continue treatment with osimertinib if there is evidence of ongoing clinical benefit. Patients in the LAURA trial were able to continue to receive osimertinib after BICR-confirmed progression if, in the opinion of the treating physician, they were continuing to derive clinical benefit. Therefore, the experts felt that osimertinib should be discontinued in the event of significant toxicities that cannot be safely managed with dose reductions or modifications or disease progression that is deemed by the treating physician to be amenable to other local therapies. pERC agreed that treatment with osimertinib should be continued until clinically meaningful progression occurs based on the judgment of the treating clinician. pERC noted that the decision to stop or continue treatment should also be a joint decision between the treating clinician and patient, considering the severity of side effects and the patient's symptoms, values, and preferences.
Considerations for prescribing of therapy	
Osimertinib is dosed at 80 mg orally once daily. Jurisdictions have familiarity with osimertinib as it is currently used in early stage and metastatic *EGFR*-positive NSCLC. This is to enable implementation.	This was a comment from the drug programs to inform pERC deliberations.
Generalizability	
1. Patients enrolled in the LAURA trial had an ECOG PS of 0 or 1. Are patients with an ECOG PS of 2 eligible for osimertinib? 2. The trial excluded patients with prior *EGFR* TKI. Should patients who receive prior adjuvant osimertinib for stage I/II disease be considered for osimertinib post CRT?	1. Although the LAURA trial restricted enrolment to patients with an ECOG PS of 0 or 1, pERC agrees with the clinical experts consulted for this review that the results could be generalized to patients with an ECOG PS of 2. 2. pERC agreed with the clinical experts consulted for this review that patients should be eligible to receive osimertinib per the current reimbursement request if a period of at least 6 months has elapsed since receipt of a prior EGFR TKI (including treatment with osimertinib for stage I/II disease) and there is no evidence of progressive disease during osimertinib therapy.

Implementation issues	Response
At time of implementation: For patients who have completed chemoradiation and are now on observation, is there a maximum time frame that has to elapse between end of chemoradiation and start of osimertinib?	The clinical experts consulted for this review felt that treatment with osimertinib should begin within 10 weeks of completing platinum-based CRT because this time frame would allow for sufficient time for patients to recover from CRT and receive reimaging scans while still allowing for maximum clinical benefit. pERC agreed with the clinical experts. However, at the time of funding (i.e., on a time-limited basis), patients who have completed chemoradiation should be eligible for funded treatment with osimertinib as long as they do not have evidence of disease progression.
Funding algorithm	
Request initiation of a rapid provisional funding algorithm.	This was a comment from the drug programs to inform pERC deliberations.
Drug may change place in therapy of drugs reimbursed in subsequent lines.	This was a comment from the drug programs to inform pERC deliberations.
Please note that a patient who has progressed while on osimertinib therapy or progressed within 6 months of stopping osimertinib for this indication under review, will not be eligible for osimertinib in stage IV setting.	This was a comment from the drug programs to inform pERC deliberations.
Care provision issues	
Osimertinib requires monitoring of adverse events and ECG monitoring.	This was a comment from the drug programs to inform pERC deliberations.
EGFR mutation testing is required to identify eligible patients for osimertinib.	This was a comment from the drug programs to inform pERC deliberations.
System and economic issues	
PAG is identifying osimertinib for the reimbursement requested indication to have a high budget impact.	This was a comment from the drug programs to inform pERC deliberations.

BICR = blinded independent central review; CRT = chemoradiation therapy; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; Ex19del = exon 19 deletion; NSCLC = non–small cell lung cancer; PAG = Provincial Advisory Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; TKI = tyrosine kinase inhibitor.

Clinical Evidence

Systematic Review

Description of Studies

The LAURA trial is an ongoing, multinational, phase III, double-blinded, placebo-controlled, randomized study that met the inclusion criteria for the systematic review conducted by the sponsor. This trial has no sites in Canada. The LAURA trial is aimed at evaluating the efficacy and safety of osimertinib as maintenance therapy in patients with locally advanced, unresectable (stage III) NSCLC with centrally confirmed *EGFR* mutations (Ex19del or exon 21 L858R substitution) whose disease has not progressed during or following definitive platinum-based CRT. Following confirmation of eligibility, patients were randomized in a 2:1 ratio to receive either osimertinib 80 mg orally once daily or placebo until objective

radiological disease progression (defined by Response Evaluation Criteria in Solid Tumours Version 1.1 [RECIST 1.1] and confirmed by blinded independent central review) or until another discontinuation criterion is met (e.g., patient decision or unacceptable toxicity). Randomization was stratified by prior chemoradiation strategy (concurrent versus sequential CRT), tumour stage before chemoradiation (IIIA versus IIIB/IIIC), and China versus non-China cohort (enrolled at a Chinese site and the patient declared themself of Chinese ethnicity versus enrolled at a site outside China or the patient declared themself of non-Chinese ethnicity). Overall, 216 patients were randomized to either the osimertinib group (n = 143 patients) or the placebo group (n = 73 patients) and included in the full analysis set. The outcomes relevant to this review include OS, PFS, CNS PFS, response outcomes, time to death or distant metastasis (TTDM), time to treatment discontinuation or death (TTD), patient-reported outcomes, and harms data. These were all collected at the planned DCO of January 5, 2024, and OS was additionally collected at an unplanned, updated analysis using the DCO of November 29, 2024.

In the full analysis set of the LAURA trial, slightly more patients were female (132 of 216; 61.1%) than male (84 of 216; 38.9%), the mean age of patients was 61.4 years (standard deviation [SD] = 10.95 years), and patients were primarily Asian (82.4%), followed by white (13.9%), American Indian or Alaska Native (1.4%), or another race (2.3%), as classified within the study. At baseline, patients primarily had stage IIIA (35.2%) or stage IIIB (48.6%) NSCLC, with 16.2% of patients classified as having stage IIIC NSCLC. At screening, fewer patients in the osimertinib group were positive for Ex19del (74 of 143; 51.7%) and more were positive for exon 21 L858R substitutions (47.6%) compared to the placebo group (43 of 73 [58.9%] and 30 of 73 [41.1%], respectively). Notable differences in baseline characteristics across treatment groups included fewer former smokers in the osimertinib group (25.9%) than in the placebo group (31.5%). There were more patients in the osimertinib group (55.9%) with a WHO performance status of 0 than in the placebo group (42.5%), and more patients in the osimertinib group were receiving concurrent CRT (91.6%) than in the placebo group (84.9%).

Efficacy Results

Efficacy outcomes presented are from the most recent DCOs (OS: November 29, 2024; PFS, CNS PFS, TTDM, TTD, and HRQoL: January 5, 2024).

Overall Survival

OS was tested at the January 2024 DCO and did not meet the prespecified boundary for declaring statistical significance.

At the November 2024 DCO, the median OS follow-up time for all patients was 39.36 months ([redacted]) in the osimertinib group and 35.15 months ([redacted]) in the placebo group, at which point death occurred in 40 of 143 patients (28.0%) in the osimertinib group and 26 of 73 patients (35.6%) in the placebo group. The Kaplan-Meier (KM) estimate for median OS was 58.81 months (95% CI, 54.08 months to not calculable [NC]) in the osimertinib group and 53.98 months (95% CI, 42.05 months to NC) in the placebo group, with a stratified HR of 0.67 (95% CI, 0.40 to 1.14). The between-group difference in the probability of survival for the osimertinib group versus the placebo group was [redacted]) at 36 months and [redacted]) at 48 months.

Progression-Free Survival

The median PFS follow-up time for all patients was 21.98 months (range, 0.03 to 60.55 months) in the osimertinib group and 5.55 months (range, 0.03 to 49.71 months) in the placebo group, at which point progression events had occurred in 57 of 143 patients (39.9%) in the osimertinib group and 63 of 73 patients (86.3%) in the placebo group. The KM estimate for median PFS was 39.13 months (95% CI, 31.51 months to NC) in the osimertinib group and 5.55 months (95% CI, 3.71 to 7.43 months) in the placebo group with a stratified HR of 0.16 (95% CI, 0.10 to 0.24) favouring the osimertinib group. The between-group difference in the probability of PFS for the osimertinib group versus the placebo group was [redacted] at 12 months and [redacted]) at 36 months.

CNS Progression-Free Survival

At the January 2024 DCO, CNS PFS was not eligible for statistical testing (OS was not statistically significant therefore CNS PFS was not formally tested based on the multiple testing procedure).

The median CNS PFS follow-up time for all patients was 24.64 months ([redacted]) in the osimertinib group and 5.72 months ([redacted]) in the placebo group, at which point CNS progression events had occurred in 29 of 143 patients (20.3%) in the osimertinib group and 30 of 73 patients (41.1%) in the placebo group. The KM estimate for median CNS PFS was NC in the osimertinib group and 14.88 months (95% CI, 7.36 months to NC) in the placebo group with a stratified HR of 0.17 (95% CI, 0.09 to 0.32). The between-group difference in the probability of CNS PFS for the osimertinib group versus the placebo group was [redacted] at 12 months and [redacted]) at 24 months.

Time to Death or Distant Metastases

TTDM was a secondary end point and not adjusted for multiplicity in the LAURA trial.

By the January 2024 DCO, death or distant metastases events had occurred in 33 of 143 patients (23.1%) in the osimertinib group and 31 of 73 patients (42.5%) in the placebo group. The median TTDM was not reported (95% CI, 39.29 months to NC) in the osimertinib group and 13.04 months (95% CI, 9.03 months to NC) in the placebo group, with a stratified HR of 0.21 (95% CI, 0.11 to 0.38) favouring the osimertinib group.

Time to Treatment Discontinuation or Death

TTD was a secondary end point and not adjusted for multiplicity in the LAURA trial.

By the January 2024 DCO, a death or treatment discontinuation event had occurred in 63 of 143 patients (44.1%) in the osimertinib group compared to 66 of 73 patients (90.4%) in the placebo group. The median TTD was 40.28 months (95% CI, 32.72 months to NC) in the osimertinib group compared to 8.31 months (95% CI, 6.14 to 11.10 months) in the placebo group, with a stratified HR of 0.21 (95% CI, 0.14 to 0.32) favouring the osimertinib group.

EORTC QLQ-C30 Global Health Status/Quality of Life

Outcomes based on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) were secondary end points and not adjusted for multiplicity in the LAURA trial.

The between-group difference for the mean change from baseline across all visits to week 40 in the EORTC QLQ-C30 global health status/quality of life did not meet the MID threshold of 4 points; however, the confidence interval crosses the minimally important difference threshold of −4 points for deterioration (−1.9 points; 95% CI, −5.89 to 2.00 points).

Harms Results

Safety outcomes presented are from the January 2024 DCO and are reported for the safety analysis set (i.e., all randomized patients who received at least 1 dose of study treatment).

Any Adverse Event

More patients in the osimertinib group experienced an AE (140 of 143; 97.9%) than in the placebo group (64 of 73; 87.7%). In both groups, the 3 most frequently reported AEs were radiation pneumonitis (47.6% in the osimertinib group and 38.4% in the placebo group), diarrhea (35.7% and 13.7%, respectively), and rash (23.8% and 13.7%, respectively).

Serious Adverse Events

More patients in the osimertinib group experienced an SAE (55 of 143; 38.5%) than in the placebo group (11 of 73; 15.1%). In the osimertinib group, the most frequently reported SAEs were radiation pneumonitis (10.5%), pneumonia (4.9%), and gastroenteritis (1.4%) and pneumonitis (1.4%). In comparison, the most frequently reported SAEs in the placebo group were pneumonia (4.1%) and radiation pneumonitis (2.7%); all other SAEs were reported by 1 patient.

Withdrawals Due to Adverse Events

More patients in the osimertinib group prematurely stopped treatment due to an AE ([redacted]) than in the placebo group ([redacted]). In the osimertinib group, the 3 most common AEs leading to treatment discontinuation were radiation pneumonitis (4.9%), [redacted].

Death Due to Adverse Events

A similar percentage of patients in both the osimertinib and placebo groups experienced an AE with an outcome of death ([redacted]in the osimertinib group and [redacted] in the placebo group). In the osimertinib group, the fatal AEs were due to pneumonia ([redacted]), pneumonitis ([redacted]), and a road traffic accident ([redacted]). In the placebo group, the fatal AEs were due to myocardial infarction (1.4%) and aortic aneurysm rupture ([redacted]).

Notable Harms

Generally, a higher percentage of patients in the osimertinib group experienced AEs of special interest identified in the product monograph and highlighted as important by clinical experts consulted for this review. In both treatment groups, radiation pneumonitis was the most common AE of special interest (68 of 143 [47.6%] in the osimertinib group and 28 of 73 [38.5%] in the placebo group), [redacted], and interstitial lung disease or pneumonitis (7.7% and 1.4%, respectively). Pneumonitis occurred in slightly more patients in the osimertinib group ([redacted]) than in the placebo group

([redacted]). Similarly, grade 3 or higher diarrhea occurred in [redacted] of patients in the osimertinib group and [redacted] in the placebo group.

Critical Appraisal

Despite the use of stratified randomization, differences in baseline characteristics across treatment groups poses questions about the comparability of the 2 groups. Notably, there was a higher percentage of patients with a WHO performance status of 0 at baseline in the osimertinib group (55.3%) versus the placebo group (42.5%) and fewer former smokers in the osimertinib group (25.9%) than in the placebo group (31.5%). These differences may indicate that patients in the osimertinib group had a more favourable prognosis, which could introduce confounding and bias the results in favour of osimertinib. It is acknowledged that between-group differences in baseline characteristics may occur in trials with smaller sample sizes (e.g., fewer than 100 patients per group) and multiple strata per covariates, which may apply to the LAURA trial. Subgroup analyses among current and former smokers were similar to the overall population. The sponsor conducted a post hoc subgroup analysis on baseline WHO performance status that was consistent with the PFS benefit for osimertinib in the primary analysis, and the clinical experts consulted for this review did not anticipate the differences in WHO performance status to substantially impact the results. Nonetheless, the potential for residual confounding due to baseline imbalances remains a limitation in the internal validity of the trial.

Date of death, start and end dates for concomitant medication, radiotherapy, and AEs, and subsequent anticancer treatment dates were imputed if missing. Instances where only partial information was available relied on assumptions of noninformative missingness (i.e., data missing completely at random or missing at random), which may introduce bias if missing-not-at-random mechanisms are present. Additionally, this approach may not capture uncertainty in the imputed values, resulting in an underestimation in the variability and narrowing the resulting CIs. [redacted] it does not fully mitigate the risk of bias. It assumes progression occurs uniformly and does not account for differences in assessment schedules or missing data patterns between treatment groups. Importantly, the extent of missing data leading to imputation for these critical time-dependent variables was not reported, making it difficult to assess the overall impact of this approach on potential bias in the results.

PFS assessed by blinded independent central review, followed by OS, and CNS PFS assessed by blinded independent central review were addressed using a hierarchical multiple testing procedure that controlled for type I error at the January 2024 DCO. At this time, PFS met the prespecified threshold for statistical significance. Per the testing procedure, the interim analysis of OS was also conducted at this DCO; however, OS did not reach statistical significance. Consequently, the CNS PFS end point, which was next in the hierarchy, could not be formally tested. In this case, the reporting of a nominal P value for CNS PFS can be misleading and does not follow the statistical analysis plan; however, there is a substantial between-group difference that is unlikely attributable to chance or inflated type I error.

The OS analysis was based on the intention-to-treat approach, which assumes postprogression therapies are nondifferentially distributed between groups — a condition that may not hold given the observed disparities in postrelapse therapy used. A higher percentage of patients in the placebo group used subsequent anticancer treatments ( ) than in the osimertinib group) by November 2024 DCO date. . This imbalance challenges the intention-to-treat assumption and introduces potential bias in the OS analysis. The trial did not implement methods to adjust for treatment switching (e.g., rank-preserving structural failure time models). The crossover for patients on placebo who had progression potentially leads to an underestimation of the between-group difference in OS; however, the findings align with clinical practice because osimertinib is the standard of care for disease that has progressed.

OS results from the LAURA trial are based on interim analyses, which may overestimate treatment effects. At the November 2024 DCO, the OS analysis included 66 events (40 of 143 [28.0%] in the osimertinib group and 26 of 73 [35.6%] in the placebo group), corresponding to approximately 30.6% of the total number of events required for the final analysis (120 events). This DCO date was not part of the prespecified analysis plan. Results from this time point may therefore be more susceptible to bias due to early data truncation and post hoc decision-making. This DCO date was conducted as part of regulatory marketing requirements.

Stratified Cox proportional hazards models were used to estimate the HRs and CIs for OS, PFS, and CNS PFS. The proportional hazards assumption is likely not met for OS based on the KM curves that cross several times over the duration of follow-up. Although this suggests that the HRs may not reflect the treatment effect over time for OS, it may be partially explained by the frequent use of osimertinib in patients in the placebo group whose disease progressed. Clinical experts consulted for this review felt that the OS KM curves accurately reflected the natural history of *EGFR*-mutated NSCLC, with a typical median survival of 3 to 4 years after recurrence. Alternative methods of analysis that do not rely on the proportional hazards assumption were not conducted for any of the time to event analyses, which makes it more difficult to assess the robustness of the results.

Visual inspection of KM plots indicated that fewer than 20% of patients in the placebo group remained at risk beyond 45 months for OS and beyond 12 months for PFS and CNS PFS. In the osimertinib group, fewer than 20% of patients were at risk beyond 51 months for OS and beyond 33 months for PFS and CNS PFS. Under such conditions, standard assumptions used in survival analysis (e.g., noninformative censoring) may be violated, which limits the reliability of survival estimates at later time points.

The FDA and the European Medicines Agency (EMA) consider OS the gold standard primary outcome in trials, including NSCLC trials. However, PFS is considered to be an important cancer end point by the FDA in situations in which survival may be prolonged, making an OS end point impractical. When observed differences in PFS are substantial in magnitude (viewed in the context of toxicities, the relatively short survival of patients with NSCLC, availability of alternative therapies, histologic or genetic subtype of NSCLC, and extent of prior treatment), the FDA and EMA considered PFS to provide clinical evidence to support approvals. Although a correlation between PFS and OS in patients with locally advanced NSCLC has been

shown, no correlation has been established for the current setting (i.e., unresectable *EGFR*-mutated NSCLC) and thus the validity of PFS as a surrogate for OS is unclear in the current context.

The completion rates for the EORTC QLQ-C30 and QLQ-LC13 scales declined over time, particularly in the placebo group, reducing the certainty of the treatment effects at the later time points.

The clinical experts with expertise in the diagnosis and management of patients with NSCLC felt the inclusion and exclusion criteria used in the LAURA trial were generally aligned with those typically used in NSCLC trials and the sponsor's reimbursement request. The clinical experts felt the reimbursement of osimertinib should include those with a WHO performance status of 0 to 2 (rather than only those with a WHO performance status of 0 and 1 as included in the trial).

The clinical experts consulted for this review indicated the baseline characteristics of the study population were representative of patients seen in clinical practice in Canada. Notably, a high percentage of patients enrolled in the LAURA trial identified as Asian (82.4%); however, this was partially expected because *EGFR* mutations are more common in patients of Asian ethnicity. The clinical experts consulted for this review did not expect racial differences to significantly impact treatment effects.

The clinical experts consulted for this review noted that the prior platinum-based CRT regimens used for treatment in the definitive setting for stage III disease in the LAURA trial were representative of those used to treat unresectable *EGFR*-mutated NSCLC in Canada. The same clinical experts also felt that watchful waiting was the most relevant comparator.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The selection of outcomes for the GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with the expert committee members:

- OS (probabilities at 36 and 48 months), PFS (probabilities at 12 and 36 months), CNS PFS (probabilities at 12 and 24 months)

- HRQoL (average change in EORTC QLQ-C30 Global Health Status/Quality of Life score from baseline across all visits)
- harms (pneumonitis, grade 3 or higher diarrhea, withdrawal due to AEs, and fatal AEs).

Table 3 presents the GRADE summary of findings for osimertinib versus placebo for patients with locally advanced, unresectable (stage III) NSCLC whose tumours have *EGFR* Ex19del or exon 21 L858R substitution mutations and have not progressed during or following platinum-based CRT.

Table 3: Summary of Findings for Osimertinib vs. Placebo for Patients With Locally Advanced, Unresectable (Stage III) NSCLC That Has *EGFR* Exon 19 Deletions or Exon 21 L858R Substitution Mutations and Has Not Progressed During or Following Platinum-Based CRT

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Osimertinib	Difference[a]		
Overall survival							
Probability of OS at 36 months Follow-up (months), median (range): 39.36 months ([redacted]) in the osimertinib group and 35.15 months ([redacted]) in the placebo group	216 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Low[b]	Osimertinib may result in a clinically important increase in the probability of being alive at 36 months compared to placebo.
Probability of OS at 48 months Follow-up (months), median (range): 39.36 months ([redacted]) in the osimertinib group and 35.15 months ([redacted]) in the placebo group	216 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Low[c]	Osimertinib may result in a clinically important increased probability of being alive at 48 months compared to placebo.
Progression-free survival							
Probability of PFS at 12 months Follow-up (months), median (range):	216 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	High[d]	Osimertinib results in a clinically important increase in the probability of being progression-free at 12

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Osimertinib	Difference[a]		
22.18 months (0.03 to 60.55 months) in the osimertinib group and 5.55 months (0.03 to 49.71 months) in the placebo group.							months compared to placebo.
Probability of PFS at 36 months Follow-up (months), median (range): 22.18 months (0.03 to 60.55 months) in the osimertinib group and 5.55 months (0.03 to 49.71 months) in the placebo group.	216 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[e]	Osimertinib likely results in a clinically important increase in the probability of being progression-free at 36 months compared to placebo.
Central nervous system progression-free survival							
Probability of CNS PFS at 12 months Follow-up (months), median (range): 24.64 months ([redacted]) in the osimertinib group and 5.72 months ([redacted] in the placebo group	216 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	High[f]	Osimertinib results in a clinically important increase in the probability of CNS PFS at 12 months compared to placebo.
Probability of CNS PFS at 24 months Follow-up (months), median (range): 24.64 months ([redacted]) in the osimertinib group and 5.72	216 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[g]	Osimertinib likely results in a clinically important increase in the probability of CNS PFS at 24 months compared to placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Osimertinib	Difference[a]		
months ([redacted]) in the placebo group							
EORTC QLQ-C30 global health status/ quality of life							
Mean change from baseline over all visits (baseline to week 40)	195 (1 RCT)	NR	−2.0	−3.9 (−5.98 to −1.82)	−1.9 (−5.89 to 2.00)	Low[h]	Osimertinib may result in little to no difference in quality of life compared to placebo.
Harms (DCO: January 5, 2024)							
Withdrawal due to AEs	216 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[i]	Osimertinib likely results in little to no difference in the frequency of withdrawal due to AEs compared to placebo.
Fatal AEs	216 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Low[j]	Osimertinib may result in little to no difference in the frequency of fatal AEs compared to placebo.
Pneumonitis	216 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Low[k]	Osimertinib may result in little to no difference in the frequency of pneumonitis compared to placebo.
Grade ≥ 3 diarrhea	216 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[l]	Osimertinib likely results in little to no difference in the frequency of grade 3 or greater diarrhea compared to placebo.

AE = adverse event; CI = confidence interval; CNS = central nervous system; DCO = data cut-off; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; NR = not reported; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]The between-group differences were requested from the sponsor to aid in the interpretation of the results for these end points.

[b]Certainty was rated down 1 level for risk of bias. A planned interim analysis of OS was conducted at the January 5, 2024, DCO, and could have been used to avoid concerns related to post hoc decision-making; however, this analysis was based on a shorter duration of follow-up and fewer events (43 OS events), reducing its reliability for drawing robust conclusions. The later OS results, using the November 29, 2024, DCO, provide a longer follow-up and more events (OS analysis included 66 events: 40 of 143 [28.0%] in the osimertinib group and 26 of 73 [35.6%] in the placebo group), but were from an unplanned, interim analysis, increasing the risk of post hoc decisions and the potential for inflated treatment effects. In both analyses, the presence of time-varying treatment effects, including a delayed separation and crossing of Kaplan-Meier curves, which limit the validity and reliability of the estimate of absolute difference between groups. Differences in postprogression anticancer therapies, including 74% of patients in the placebo group receiving osimertinib, also likely influenced the between-group OS difference. No empirically derived and validated minimally important difference (MID) was identified for the between-group difference in the probability of OS. The clinical experts consulted for this review suggested that a 5% to

10% between-group difference would be clinically meaningful and this value was used as the threshold. Certainty was rated down 1 level for imprecision. Using the 5% between-group difference threshold, the point estimate suggests a clinically meaningful effect on OS at 36 months, while the lower bound of the 95% CI crossed the between-group difference threshold of 5%.

[c]Certainty was rated down 1 level for risk of bias. A planned interim analysis of OS was conducted at the January 5, 2024, DCO date and could have been used to avoid concerns related to post hoc decision-making; however, this analysis was based on a shorter duration of follow-up and fewer events (43 OS events), reducing its reliability for drawing robust conclusions. The later OS results, using the November 29, 2024, DCO, provide longer follow-up and more events, but were from an unplanned analysis, increasing the risk of post hoc decisions and the potential for inflated treatment effects. In both analyses, the presence of time-varying treatment effects, including a higher probability of OS with placebo during the first 18 months and delayed separation and crossing of Kaplan-Meier curves, limit the validity and reliability of the estimate of absolute difference between groups. Differences in postprogression anticancer therapies, including 74% of placebo group patients receiving osimertinib, also likely influence the between-group OS difference. In addition, there was high attrition in the placebo group (n = 11) at 48 months, which may result in informative censoring and bias the between-group difference in OS at this time point. No empirically derived and validated MID was identified for the between-group difference in the probability of survival. The clinical experts consulted for this review suggested that a 5% to 10% between-group difference would be clinically meaningful and this value was used as the threshold. Certainty was rated down 1 level for imprecision. Although the point estimate suggests a clinically meaningful effect on OS at 48 months, the lower bound of the 95% CI did not cross the threshold, suggesting little to no difference.

[d]Certainty was not rated down for indirectness for PFS as a surrogate outcome for OS. Although direct validation of PFS as a surrogate for OS in the setting of unresectable *EGFR*-mutated NSCLC treated with maintenance therapy is lacking, the clinical experts considered PFS to be of clinical relevance for patients in delaying progression to metastatic disease administration of more toxic treatment. Certainty was not rated down for imprecision. No empirically derived and validated MID was identified for the between-group difference in the probability of PFS. The clinical experts consulted for this review suggested that a 10% to 15% between-group difference would be clinically meaningful. The effect estimate as well as both lower and upper boundaries of the 95% CI of the between-group difference exceeded the threshold and suggested a benefit.

[e]Certainty was not rated down for indirectness for PFS as a surrogate outcome for OS. Although direct validation of PFS as a surrogate for OS in the setting of unresectable *EGFR*-mutated NSCLC treated with maintenance therapy is lacking, PFS is a clinically relevant end point in oncology trials, including NSCLC, especially because patient input signalled value in therapies that prevent disease progression. Certainty was rated down 1 level for risk of bias due to high attrition at 36 months (n = 28 in the osimertinib group and n = 3 in the placebo group), which may result in informative censoring and bias the between-group difference in OS at this time point. No empirically derived and validated MID was identified for the between-group difference in the probability of PFS. The clinical experts consulted for this review suggested that a 10% to 15% between-group difference would be clinically meaningful and this value was used as the threshold. The effect estimate and both lower and upper boundaries of the 95% CI of the between-group difference exceeded the threshold and suggested a benefit.

[f]CNS PFS is not a validated surrogate for OS and does not capture extracranial progression. However, it is a clinically important outcome in the context of *EGFR*-mutated NSCLC, given the incidence and burden of CNS metastases in this population. The end point provides direct information on intracranial disease control that is relevant to patients and clinicians. No empirically derived and validated MID was identified for the between-group difference in the probability of CNS PFS. The clinical experts consulted for this review suggested that a 10% between-group difference would be clinically meaningful, and this value was used as the threshold. The effect estimate and both lower and upper boundaries of the 95% CI of the between-group difference exceeded the threshold and suggested a benefit.

[g]CNS PFS is not a validated surrogate for OS and does not capture extracranial progression. However, it is a clinically important outcome in the context of *EGFR*-mutated NSCLC, given the incidence and burden of CNS metastases in this population. The end point provides direct information on intracranial disease control that is relevant to patients and clinicians. Certainty was rated down 1 level for risk of bias due to high attrition in the placebo group at 24 months (n = 8), which may result in informative censoring and bias the between-group difference in CNS PFS at this time point. No empirically derived and validated MID was identified for the between-group difference in the probability of CNS PFS. The clinical experts consulted for this review suggested that a 10% between-group difference would be clinically meaningful, and this value was used as the threshold. The effect estimate and both lower and upper boundaries of the 95% CI of the between-group difference exceeded the threshold and suggested a benefit.

[h]Certainty was rated down 1 level for risk of bias. Beyond week 16, fewer than 50% of patients in the placebo group were available to contributed to the analysis. Certainty was rated down 1 level for imprecision. A MID for the EORTC QLQ C30 Global Health Status scale has not been definitively established, although a difference of 10 points is often cited. One recent review estimated the MID for the scale may be 4 points in patients with lung cancer, and 4 points was adopted as the MID for this assessment. Although the point estimate suggests little to no difference in HRQoL, the lower CI crosses the MID for deterioration and the possibility of a negative effect cannot be ruled out. EORTC QLQ-C30 was not adjusted for multiplicity in the trial and should be considered as supportive evidence.

[i]No empirically derived and validated MID was identified for the between-group difference in the frequency of withdrawals due to AEs. The clinical experts consulted for this review suggested that a 10% between-group difference would be clinically meaningful, and this value was used as the threshold. Certainty was rated down 1 level for imprecision. The between-group difference suggests no clinically meaningful effect on the frequency of withdrawal due to AEs at the January 5, 2024, DCO, while the upper bound of the 95% CI crosses the between-group difference threshold of 10%.

[j]No empirically derived and validated MID was identified for the between-group difference in the frequency in fatal AEs. The clinical experts consulted for this review suggested that a 5% between-group difference would be clinically meaningful, and this value was used as the threshold. Certainty was rated down 2 levels for imprecision. The between-group difference suggests no clinically meaningful effect on the frequency of fatal AEs at the January 5, 2024, DCO, while the lower bound of the 95% CI crosses the between-group difference threshold of 5%. Additionally, the absolute number of events was low in both groups, contributing to the uncertainty.

[k]No empirically derived and validated MID was identified for the between-group difference in the frequency of pneumonitis. The clinical experts consulted for this review suggested that a 5% between-group difference would be clinically meaningful and this value was used as the threshold. Certainty was rated down 2 levels for imprecision. The between-group difference suggests no clinically meaningful effect on the frequency of pneumonitis at the January 5, 2024, DCO, while the upper bound of the 95% CI crosses the between-group difference threshold of 5%. Additionally, the absolute number of events was low in both groups, contributing to the uncertainty.

[l]No empirically derived and validated MID was identified for the between-group difference in the frequency of grade 3 or higher diarrhea. The clinical experts consulted for this review suggested that a 10% between-group difference would be clinically meaningful, and this value was used as the threshold. Certainty was rated down 1 level for imprecision. The absolute number of events was low in both groups, contributing to the uncertainty.

Sources: LAURA Clinical Study Report and LAURA Overall Survival Analysis Update. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies
No long-term extension studies were submitted by the sponsor.

Indirect Comparisons
No indirect comparisons were submitted by the sponsor.

Studies Addressing Gaps in the Evidence From the Systematic Review
No studies addressing gaps in the evidence from the systematic review evidence were submitted by the sponsor.

Economic Evidence

Economic Evaluation and Budget Impact
- Osimertinib is available as an oral tablet (40 mg or 80 mg). At the submitted price of $322.13 per 40 mg or 80 mg tablet, the cost of osimertinib is expected to be $9,020 per 28-day cycle, based on the Health Canada–recommended dosage.
- Clinical efficacy in the economic analysis was derived from the LAURA trial, which compared osimertinib with placebo in patients with locally advanced, unresectable NSCLC. Evidence submitted by the sponsor indicates that osimertinib is likely to improve PFS at 36 months and may improve OS at 48 months compared to placebo in this patient population.
- The results of the CDA-AMC base case suggest:
  - Osimertinib is predicted to be associated with higher costs to the health care system than active surveillance (incremental costs = $288,697), primarily driven by drug acquisition costs for osimertinib, although there will likely be some cost savings because of reduced subsequent treatment costs.
  - Osimertinib is predicted to be associated with a gain of 1.56 life-years compared to active surveillance, resulting in a gain of 1.42 QALYs compared to active surveillance.
  - The ICER of osimertinib compared to placebo is $203,741 per QALY gained in the CDA-AMC base case.
  - The degree of life extension associated with osimertinib versus active surveillance is dependent on the long-term efficacy of osimertinib. If the benefits provided by osimertinib wane over time (e.g., due to treatment resistance), then the degree of life extension will be reduced and osimertinib becomes less cost-effective. There is no long-term evidence regarding the efficacy of osimertinib, meaning that long-term predictions of OS benefit are uncertain.
- CDA-AMC estimates that the budget impact of reimbursing osimertinib for the indicated population will be approximately $19.6 million over the first 3 years of reimbursement compared to the amount currently spent on active surveillance, with an estimated expenditure of $45.1 million on osimertinib

over this period. The budget impact of reimbursing osimertinib will depend on the number of people eligible for treatment, the uptake of osimertinib, and subsequent treatment costs.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Kelvin Chan (Vice-Chair), Dr. Phillip Blanchette, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: July 9, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

Canada's Drug Agency
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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.