CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Osimertinib (Tagrisso)

Indication: As adjuvant therapy after tumour resection in patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations

Recommendation: Reimburse with Conditions

Version:	1.0
Publication Date:	September 2021
Report Length:	14 Pages

Single Technology

CADTH

OSIMERTINIB (TAGRISSO — ASTRAZENECA CANADA INC.)

Therapeutic Area: Non-small cell lung cancer

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that osimertinib should be reimbursed as adjuvant therapy after tumour resection in patients with stage IB-IIIA (American Joint Committee on Cancer [AJCC] 7th edition staging system) non-small cell lung cancer (NSCLC) whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, double-blind, randomized placebo-controlled trial (ADAURA, N=682) in adult patients with completely resected stage IB-IIIA EGFR mutation-positive (defined as EGFR exon 19 deletions or exon 21 [L858R] substitution mutations) NSCLC, demonstrated that adjuvant treatment with osimertinib resulted in a statistically significant and clinically meaningful prolongation in disease-free survival (DFS) compared to placebo. In patients with stage II-IIIA NSCLC, the primary analysis population, median DFS was not reached in the osimertinib group and was 19.6 months (95% CI, 16.6 to 24.5) in the placebo group (hazard ratio [HR] = 0.17; 95% CI, 0.12 to 0.23; *P*<0.0001). In the overall population of stage IB-IIIA patients, the median DFS was not reached in the osimertinib group and was 27.5 months (95% CI, 22.0 to 35.0) in the placebo group (HR = 0.20; 95% CI, 0.15 to 0.27; *P*<0.0001). The DFS benefit was observed regardless of whether patients had received post-operative adjuvant chemotherapy. Patients identified a need for treatments that delay disease recurrence and improve DFS, and pERC agreed that osimertinib meets this need. Patients also expressed a need for adjuvant treatments that provide a cure and maintain quality of life with limited side effects. The ADAURA trial results were based on an interim analysis at which time the data on overall survival (OS) and health-related quality of life (HRQoL) were considered immature; therefore, no conclusions could be drawn on the effect of osimertinib on these outcomes based on the available evidence. However, pERC acknowledged that a DFS benefit of the magnitude observed in the ADAURA trial is likely to be associated with positive impacts such as improvement in patient quality of life by delaying the presentation of advanced or metastatic disease which is associated with substantial morbidity. Although the overall incidence of adverse events (AEs) was higher in patients treated with osimertinib, the toxicities observed were consistent with the known safety profile of osimertinib and pERC considered them manageable for clinicians who have experience with the drug from its use in the metastatic setting.

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 $328,026 per quality-adjusted life-year (QALY) compared to active surveillance. At this ICER, osimertinib for adult patients (aged ≥18 years) with completely resected, early-stage EGFR mutation–positive NSCLC is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold. A reduction in price of at least 82% is required for osimertinib to be considered cost-effective at a $50,000 per QALY threshold. Due to immature data on OS, there is a high degree of uncertainty regarding QALY gains meaning that a further price reduction may be required if these have been overestimated by the CADTH base case.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Adult patients (≥18 years) must have completely resected stage IB-IIIA (AJCC 7th edition) or stage IIA to IIIB (AJCC 8th edition) NSCLC with a confirmed sensitizing EGFR mutation (exon 19 deletion and/or exon 21 L858R substitution mutation), with or without post-operative adjuvant chemotherapy.	Patients enrolled in the ADAURA trial had a confirmed common sensitizing EGFR mutation, which was defined as an exon 19 deletion and/or exon 21 substitution mutation (L858R), either alone or in combination with other EGFR mutations. The trial excluded patients who had received any other prior treatment (i.e., pre-operative chemotherapy, pre- or post-operative radiation therapy, and EGFR tyrosine kinase inhibitors [TKIs]).
2. Patients should initiate treatment with osimertinib within 10 weeks of complete surgical resection if adjuvant chemotherapy was not administered, or within 26 weeks if adjuvant chemotherapy (platinum-based doublet chemotherapy, maximum of 4 cycles) was administered.	Patients enrolled in the ADAURA trial were required to initiate treatment with osimertinib within 10 weeks of complete resection if they did not receive chemotherapy to ensure complete post-operative healing had occurred, and within 26 weeks if they received chemotherapy to ensure patients recovered from toxicities of therapy.
3. Patients should have a WHO performance status of 0 or 1 (equivalent to ECOG 0 or 1) and have no significant comorbidities.	Patients enrolled in the ADAURA trial had a WHO performance status of 0 or 1. The trial excluded patients with a WHO performance status >1 and patients with significant cardiac or lung disease (e.g., QTc interval prolongation, interstitial lung disease).
Renewal	
4. Osimertinib should be reimbursed for a total duration of 3 years in patients who continue to receive clinical benefit from treatment and do not have intolerable toxicity.	In the ADAURA trial, treatment continued until disease recurrence, unacceptable toxicity, or until a maximum treatment duration of 3 years was reached.
5. Patients should be regularly monitored for toxicity and disease recurrence.	In the ADAURA trial, patients were monitored for safety at baseline and at weeks 2, 4, and 12, and then every 12 weeks until treatment was completed or discontinued. Radiological assessments for disease recurrence occurred at 12 and 24 weeks, and then every 24 weeks up to year 5, and then annually.
Discontinuation	
6. Treatment with osimertinib should be discontinued upon disease recurrence or unacceptable toxicity.	In the ADAURA trial, treatment was discontinued upon disease recurrence or if a discontinuation criterion was met (i.e., patient decision, unacceptable toxicity, an AE, pregnancy). Determination of disease recurrence was based on evidence of local or distant recurrence on CT or MRI scan and/or pathological disease on biopsy.
Prescribing	
7. Osimertinib should only be prescribed and monitored by clinicians trained in oncology and experienced in the treatment of NSCLC.	This condition is required to ensure that osimertinib is prescribed only for appropriate patients and that patients receive optimal care for toxicity management.
Pricing	
8. Reduction in price.	The ICER for osimertinib is $328,026 per QALY when compared with active surveillance.

Reimbursement Condition	Reason
	A price reduction of 82% would be required for osimertinib to be able to achieve an ICER of $50,000 per QALY compared to active surveillance. Due to immature data on OS, there is a high degree of uncertainty regarding QALY gains. The CADTH base case estimates may therefore overestimate OS benefit, meaning that further price reductions may be required to ensure cost-effectiveness.

Implementation Guidance

1. pERC discussed that the ADAURA trial included patients with or without prior receipt of adjuvant chemotherapy, and the magnitude of DFS benefit was similar in each of these patient subgroups. The clinical experts consulted by CADTH indicated that osimertinib is not intended to replace adjuvant chemotherapy. Adjuvant chemotherapy is offered to patients with good performance status and who have tumours ≥4 cm or with nodal involvement. Osimertinib would be used after standard adjuvant chemotherapy, if chemotherapy was indicated, to further reduce the risk of disease recurrence and can also be offered to patients who are considered unfit for adjuvant chemotherapy. The clinical experts noted that platinum-based adjuvant chemotherapy can be challenging to administer because it requires adequate performance status and renal function, and it also has substantial toxicity (e.g., chronic renal failure, future blood dyscrasias, neuropathy, hearing loss) making it unsuitable or contraindicated in some patients.
2. The ADAURA trial enrolled patients with a WHO performance status of 0 and 1. The clinical experts consulted by CADTH indicated that many patients in Canada with resected stage IB-IIIA NSCLC have a performance status of 2. pERC agreed with the clinical experts that the exclusion of patients with a poorer performance status from the ADAURA trial does not limit the generalizability of the trial results and therefore it would be reasonable to offer osimertinib to patients with a performance status of 2.
3. Patients treated with adjuvant osimertinib should be monitored regularly for toxicity management and disease recurrence. The clinical experts consulted by CADTH suggested a more frequent monitoring schedule for disease recurrence near the initiation of treatment with osimertinib (i.e., years 1 and 2) and a less frequent monitoring schedule near the end and after treatment (i.e., years 3 to 5). They also indicated they would likely perform annual CT imaging after 5 years for additional follow-up.
4. Osimertinib is indicated and reimbursed as first-line treatment for patients with locally advanced (unresectable) or metastatic NSCLC whose tumours harbor EGFR mutations (exon 19 deletions or exon 21 [L858R] substitutions). pERC agreed that in the absence of evidence, retreatment with osimertinib in the metastatic setting would be reasonable if patients experienced disease relapse off treatment after either discontinuing osimertinib due to toxicity or completing 3 years of adjuvant osimertinib. pERC also agreed with the clinical experts that rechallenge with osimertinib after a 6-month off-treatment interval is reasonable unless the patient experiences a recurrence. Retreatment with osimertinib in the metastatic setting would not be indicated in patients who progressed on osimertinib in the adjuvant treatment setting.
5. The 3-year total budget impact of funding osimertinib was estimated to be $130,498,368.

pERC's responses to the implementation questions submitted from the public drug plans are also summarized in tabular format in Appendix 1.

Discussion Points

- pERC discussed that the goal of adjuvant treatment is to reduce the risk of disease recurrence and improve the chance of cure and survival as well as quality of life. The clinical experts consulted by CADTH noted that although adjuvant chemotherapy provides some clinical benefit, recurrence rates remain high in patients with stage IB-IIIA EGFR mutation-positive NSCLC, and that adjuvant chemotherapy is declined by at least a third of patients due to the small magnitude of clinical benefit and associated toxicity. Further, the experts noted that when NSCLC recurs, it typically is at a stage that is no longer curable, and the focus of further treatment is palliative. The clinical experts estimated that approximately 50-60% of patients relapse with incurable disease. pERC agreed with the clinician and patient groups' input to CADTH that there is

an unmet need for more effective adjuvant therapies, particularly targeted therapies, which are not currently available in the adjuvant treatment setting.

- Due to the immaturity of the ADAURA trial data, pERC could not draw any conclusions on the effect of osimertinib on OS, PFS, and time to next treatment. Therefore, based on the available trial evidence, there is uncertainty whether the significant DFS benefit observed will translate to a clinically meaningful improvement in OS in this patient population.
- pERC discussed that DFS is an outcome of interest to patients and clinicians, since a DFS benefit delays the presentation of advanced or metastatic disease which is associated with substantial morbidity (e.g., new brain metastases) and negatively impacts quality of life. pERC noted that the patient and clinician groups emphasized that maintenance of quality of life is an important consideration for deciding treatment in the adjuvant setting. The available trial data showed no difference between the treatment groups in the time to deterioration (TTD) in the HRQoL measures assessed and thus suggested quality of life was maintained in patients treated with osimertinib, however these data are considered immature and treatment comparisons were not adjusted for multiple comparison testing.
- pERC discussed the toxicity profile of osimertinib and noted that compared to placebo, a greater proportion of patients treated with osimertinib experienced AEs, discontinued study treatment due to AEs, and experienced serious AEs. Interstitial lung disease, pneumonitis, cardiac disorders, and skin and subcutaneous tissue disorders were more common in the osimertinib group. pERC agreed these toxicities are consistent with the known safety profile of osimertinib and can be managed by clinicians who have experience with the drug from its use in the metastatic setting.
- pERC discussed that EGFR testing is routinely done in patients with late-stage NSCLC, and thus the use of osimertinib in the adjuvant setting would necessitate a change in the timing for EGFR testing for NSCLC patients in Canada. pERC noted that testing earlier in the course of lung cancer may increase the rate of testing compared to the rate observed in the metastatic setting since some patients might not experience a recurrence. Thus, pERC agreed with the clinical experts consulted by CADTH that there is a potential added cost to treatment if EGFR testing occurs earlier in the treatment course. However, the clinical experts also noted that a subset of early-stage patients (e.g., IB) would be cured with resection and adjuvant chemotherapy, and thus never need testing for metastatic disease when most testing occurs.
- pERC discussed that the oral administration of osimertinib permits patients to better manage their own care and, in turn, reduces the burden on caregivers. However, pERC noted that the high cost of this treatment might render it inaccessible for some patients, and further acknowledged that there is unequal access to oral treatment options in Canada.
- pERC acknowledged that there is substantial uncertainty regarding the appropriate osimertinib free interval for re-treatment of osimertinib in the first-line distant metastatic setting. Re-treatment and the potential impact on efficacy of re-treatment will influence the budget impact and cost-effectiveness of osimertinib in the adjuvant setting.

Background

Osimertinib (Tagrisso) has a Health Canada indication for adjuvant therapy after tumour resection in patients with stage IB-IIIA (AJCC 7th edition) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Osimertinib is an oral EGFR tyrosine kinase inhibitor (TKI). It is available as 40 mg and 80 mg tablets and the Health Canada–approved dose is 80 mg taken once a day.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 1 phase III randomized controlled trial (RCT) in adult patients with stage IB-IIIA (AJCC 7th edition) NSCLC with a centrally confirmed common sensitizing EGFR mutation (exon 19 deletion and/or exon 21 L858R substitution mutations, either alone or in combination with other EGFR mutations), who have undergone complete tumour resection, with or without postoperative adjuvant chemotherapy.
- Patient perspectives gathered by 4 patient groups, including Canadian Cancer Survivor Network (CCSN), Lung Cancer Canada (LCC), Lung Health Foundation (LHF), and CanCertainty.
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Input from 4 clinical specialists with expertise diagnosing and treating patients with lung cancer
- Input from 2 clinician groups, including Ontario Health (Cancer Care Ontario)'s Lung Cancer Drug Advisory Committee (OH-CCO's L-DAC) and LCC.

- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received 4 submissions from patient groups for this review from the CCSN, LCC, LHF (formerly Ontario Lung Association), and CanCertainty. The CCSN is a national network of patients, families, friends, community partners, and sponsors who promote the best standards of care regarding early diagnosis, timely treatment, follow-up care, support, survivorship, and quality of end-of-life care. LCC is a national, charitable organization that provides resources for lung cancer education, patient support, research, and advocacy. The LHF is a charity that focuses on respiratory illness and lung health that provides programs and services to patients and health care providers, invests in lung research, and advocates for improved policies on lung health. CanCertainty is made up of more than 30 Canadian patient groups, cancer health charities, and caregiver organizations who, along with oncologists and cancer care professionals, work to improve the affordability and accessibility of cancer treatments. For their submissions, CCSN and LCC conducted interviews with Canadian patients (n=18 and n=6, respectively) diagnosed with stages IB to IIIA NSCLC. The LHF conducted an online survey, for which they received responses from 11 patients with lung cancer and 2 family caregivers, and online focus groups including 7 patients and 3 caregivers. CanCertainty developed their submission based on published reports relating to lung cancer statistics and Canadian drug coverage as well as a past survey the group had conducted of over 1600 Nova Scotia residents from the general population.

The symptoms and challenges of lung cancer patients noted as being most significant were fatigue, shortness of breath, cough, difficulty fighting infection, and chest tightness. Other health issues that were mentioned include pain, wheezing, reduced appetite, weight loss, anxiety, and sadness. Patients reported that having lung cancer interfered with their daily lives and their ability to work, complete household chores, exercise, enjoy leisure activities, and socialize. Patients also noted the negative impact cancer had on taking day trips, thinking positively about the future, mental health, relationships with others, and the time spent both managing symptoms and attending appointments.

The patients surveyed by CCSN, LCC, and LHF identified improvements in the following outcomes as important: cure, delaying disease recurrence, limiting side effects, and maintaining quality of life. Further, patients surveyed by CanCertainty emphasized the need for a treatment that is accessible and affordable. The CCSN felt that patients valued DFS and its association with improved quality of life. Patients from the LCC submission felt that new medications for lung cancer should not interfere with daily living and should allow individuals to maintain their independence similar to before having cancer. The LHF patient respondents also emphasized better symptom reduction and management along with improving quality of life and not just extension of life.

Clinician Input

Input from clinical experts consulted by CADTH

The clinical panel reported that current treatment for Canadian patients with surgically resected stage IB-IIIA (AJCC 7th edition), EGFR-mutated NSCLC is adjuvant chemotherapy followed by active surveillance or active surveillance alone. The goal of adjuvant treatment is to treat microscopic metastatic disease, reduce the risk of recurrence, improve the chance for a cure, and improve OS. The clinical experts noted that while adjuvant chemotherapy is beneficial, recurrence rates are high in these patients. The clinical experts reported that when NSCLC recurs it is typically in a setting where it is no longer curable and treatment intent is palliative. The clinical panel indicated that better treatments are needed to decrease disease recurrence and improve OS. In the absence of improved longevity, the clinical experts noted that other important outcomes of adjuvant therapy may be to delay the presentation of advanced disease, in the context where presenting with advanced disease has high morbidity (e.g., new brain metastasis). The clinical panel indicated that adjuvant therapy is not intended to improve symptoms.

The clinical panel thought that osimertinib would be indicated for all surgically resected stage IB-IIIA EGFR-mutated NSCLC patients for 3 years. The panel also indicated that osimertinib is not intended to replace adjuvant chemotherapy; osimertinib would be used after standard chemotherapy (if chemotherapy was indicated). The clinical panel thought that higher risk patients who decline or are unfit to receive standard chemotherapy may be best suited to receive treatment with osimertinib. The panel also thought that patients

with later stage disease may have a larger benefit than those with earlier stage disease. The clinical panel indicated that patients without an EGFR mutation or intolerable toxicity (e.g., interstitial lung disease or cardiac dysfunction) to the drug would not be suitable for osimertinib. The clinical panel thought that patients with stage IB disease may be less suitable for treatment because they may have a smaller benefit from adjuvant treatment, higher cure rate from surgery, and may not want to commit to 3 years of osimertinib. The clinical panel noted that there are no data on the efficacy of osimertinib in patients with resistance mutations.

The clinical panel thought that the frequency at which response to treatment is assessed should be at the clinician's discretion. For follow-up and toxicity management, the clinical panel indicated that they would have visits at 2 weeks and 4 weeks, blood work every 3 months, CT scans every 3 to 6 months for the first 2 years, then CT scans annually for years 3 to 5. The clinical panel indicated that they would likely perform annual CT scans and visits after 5 years for additional follow-up and treatment with osimertinib should be discontinued if the patient experiences disease recurrence or unacceptable toxicity.

Clinician group input

Input was received from 2 clinician groups: the OH-CCO's L-DAC and LCC. The OH-CCO's L-DAC submission included input from 5 clinicians and the LCC submission included input from 16 clinicians. Input from the clinician groups was generally consistent with the clinical panel consulted by CADTH. The clinician groups indicated that there is a need to improve DFS and OS in patients with resected EGFR-mutated stage IB-IIIA NSCLC. The clinician groups agreed that osimertinib would not replace adjuvant chemotherapy. The clinician groups thought that patients who complete 3 years of adjuvant osimertinib and relapse at least 6 months following completion of therapy would be considered for retreatment with osimertinib therapy for advanced/metastatic disease. Like the clinical panel, the clinician groups agreed that retreatment with osimertinib in the advanced/metastatic setting after use in the adjuvant setting is a consideration, but data are not available to inform on retreatment.

Drug Program Input

The drug programs noted that osimertinib has the potential for drug-drug interactions, which could potentially increase pharmacy resource use. They also indicated that osimertinib adjuvant therapy may change the place in therapy of comparator drugs and drugs reimbursed in subsequent lines of treatment. The drug plans reported that EGFR testing is not reflexively completed for early-stage NSCLC across most Canadian jurisdictions, thus expansion of testing would be required to identify eligible patients. Lastly, the drug programs expressed concerns that the budget impact may be substantial because the duration of therapy per patient is 3 years.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

The systematic review of osimertinib included 1 phase III randomized controlled trial (RCT). The ADAURA trial (N=682) is an ongoing international, multi-centre, double-blind, placebo-controlled RCT investigating the efficacy and safety of osimertinib in patients with stage IB-IIIA NSCLC with a centrally confirmed common sensitizing EGFR mutation (exon 19 deletion and/or exon 21 L858R substitution mutations, either alone or in combination with other EGFR mutations) who have undergone complete tumour resection with or without postoperative adjuvant chemotherapy. Patients were randomized in a 1:1 ratio to either 80 mg of osimertinib orally per day (N=339) or matching placebo (N=343). The primary outcome of the ADAURA trial is DFS by investigator assessment. Secondary outcomes are OS and HRQoL by the 36-Item Short Form Survey version 2 (SF-36 v2). The main HRQoL outcome measures of interest were time to deterioration (TTD) of the 2 summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), in the stage II-IIIA population. Exploratory endpoints included central nervous system CNS DFS, disease recurrence rate, progression-free survival (PFS), time to next treatment, and TTD in PCS and MCS in the overall population (i.e., stage IB-IIIA).

The results from the ADAURA trial presented in this review are from an unplanned interim analysis with a data cut-off date of January 17, 2020. The median follow-up for OS in the stage II-IIIA population was 26.1 months and 24.6 months in the osimertinib and placebo arms, respectively; and the median follow-up for OS in the overall population was 26.1 months and 25.9 months in the osimertinib and placebo arms, respectively. The median follow-up time for DFS in the stage II-IIIA population was 22.1 months and

14.9 months in the osimertinib and placebo arms, respectively; and the median follow-up time for DFS in the overall population was 22.1 months and 16.6 months in the osimertinib and placebo arms, respectively. The study protocol and statistical analysis plan were amended to incorporate a multiple testing procedure to account for the interim analysis, which controls the type I error for the endpoints of DFS and OS in the stage II-IIIA population and the overall population.

The baseline characteristics of patients were balanced between the treatment arms. In the overall population (stage IB-IIIA), the mean age of the patients was 62.1 years. The majority of patients had stage II-IIIA disease (68.3%), a WHO performance status of 0 (63.6%), adenocarcinoma histology type (96.5%), had undergone a lobectomy (95.3%), were Asian (63.6%), and female (70.1%). Most patients had received post-operative adjuvant chemotherapy (60.0%). Overall, 54.7% of patients had exon 19 deletions and 45.2% had exon 21 L858R substitution mutations.

Efficacy results

As of the interim analysis, OS data were immature per the sponsor's assessment. Per the trial's multiple testing procedure, OS was formally tested in the stage II-IIIA population at the interim analysis. At the data cut-off date, 25 deaths had occurred in the stage II-IIIA patient population (5.3% maturity), comprising 8 deaths (3.4%) in the osimertinib arm and 17 deaths (7.2%) in the placebo arm. The HR was 0.40 (95% CI: 0.18, 0.89; *P* = 0.0244), which did not reach statistical significance (*P* value < 0.0002 required). Since OS did not reach statistical significance in the stage II-IIIA primary analysis population, OS in the overall population was not formally tested for statistical significance per the multiple testing procedure. A total of 29 patients (4.3%) in the overall population had died as of the interim analysis, comprising 9 patients (2.7%) in the osimertinib arm and 20 patients (5.8%) in the placebo arm. The HR was 0.48 (95% CI: 0.23, 1.02).

The primary endpoint of DFS was met at the interim analysis. In the stage II-IIIA population, 26 patients (11.2%) in the osimertinib arm and 130 patients (54.9%) in the placebo arm had experienced a DFS event. The HR was 0.17 (95% CI: 0.12, 0.23), which was statistically significant (*P* < 0.0001). In the overall population, 37 patients (10.9%) in the osimertinib arm and 159 patients (46.6%) in the placebo arm had experienced a DFS event. The HR was 0.20 (95% CI: 0.15, 0.27), which was also statistically significant (*P* < 0.0001). The results of the pre-specified subgroup analyses were consistent with the primary analysis of DFS in showing a benefit of osimertinib (HR of < 0.4) for all subgroups. A post-hoc exploratory analysis of DFS with disease recurrence in the CNS only also suggested an improvement with osimertinib compared to placebo (HR: 0.14; 95% CI: 0.07, 0.27).

As of the interim analysis, the disease recurrence rate was 10.9% in the osimertinib arm and 45.8% in the placebo arm. In the osimertinib arm, disease recurrence was local/regional only in 6.8% of patients, distant only in 2.9% of patients, and both local/regional and distant in 1.2% patients. In the placebo arm, disease recurrence was local/regional only in 17.8% of patients, distant only in 22.7% of patients, and both local/regional and distant in 5.2% patients. Data on PFS and time to next treatment were immature per the sponsor's assessment and the comparisons for these endpoints have not been controlled for multiple comparisons. As of the data cut-off date, [redacted] patients ([redacted]%) in the osimertinib arm and [redacted] patients ([redacted]%) in the placebo arm had experienced a PFS event. [redacted] patients ([redacted]%) in the osimertinib arm and [redacted] patients ([redacted]%) in the placebo arm had experienced a first subsequent anti-cancer therapy or death event. Of these events, [redacted] patients ([redacted]%) in the osimertinib arm and [redacted] patients ([redacted]%) in the placebo arm received a subsequent anti-cancer treatment.

In the pre-specified TTD analyses of PCS and MCS in the stage II-IIIA population, comparisons were made without adjustment for multiple comparison testing. For the PCS score, 58 (24.9%) patients in the osimertinib arm experienced confirmed deterioration by ≥ 3.1 points or death compared to 39 (16.5%) patients in the placebo arm (HR: 1.43; 95% CI: 0.96, 2.13). For the MCS score, 52 (22.3%) patients in the osimertinib arm and 52 (21.9) patients in the placebo arm experienced confirmed deterioration by ≥ 3.8 points or death (HR: 0.90; 95% CI: 0.61, 1.33). The TTD in PCS and MCS scores in the overall population were analyzed as post-hoc exploratory analyses and the results were consistent with the stage II-IIIA population.

Harms results

The median total exposure time to study drug was 22.5 months in the osimertinib arm and 18.7 months in the placebo arm. As of the data cut-off date, 40 (12%) patients in the osimertinib arm and 33 (10%) patients in the placebo arm had completed 3 years of treatment.

A total of 329 patients (97.6%) in the osimertinib arm and 306 patients (89.2%) in the placebo arm experienced at least 1 treatment-emergent adverse event (any grade) as of the interim analysis. The most frequently reported AEs in the osimertinib and placebo arms were diarrhea (46.3% and 19.8%, respectively), paronychia (25.2% and 1.5%, respectively), dry skin (23.4% and 6.4%, respectively), pruritis (19.3% and 8.7%, respectively), and cough (18.4% and 16.6%, respectively).

In the ADAURA trial, 54 patients (16.0%) in the osimertinib arm and 42 patients (12.2%) in the placebo arm experienced a serious adverse event (SAE) as of the interim analysis. The most frequently reported SAEs in the osimertinib and placebo arms were pneumonia (1.5% and 1.2%, respectively), cataracts (0.9% and 0%, respectively), diarrhea (0.6% and 0%, respectively), acute kidney injury (0.6% and 0%, respectively), ureterolithiasis (0.6% and 0%, respectively), and femur fracture (0.6% and 0.3%, respectively).

Withdrawals specifically due to AEs were not reported. As of the data cut-off date, a total of 33 patients (4.8%) had withdrawn from the ADAURA trial: 19 (5.6%) in the osimertinib arm and 14 (4.1%) in the placebo arm. Thirty-six patients (10.7%) in the osimertinib arm and 10 patients (2.9%) in the placebo arm had discontinued study treatment due to AEs. The most common AEs leading to treatment discontinuation in the osimertinib arm were interstitial lung disease (n=8, 2.4%), diarrhea (n=3, 0.9%), and decreased appetite (n=3, 0.9%). The most common AE leading to treatment discontinuation in the placebo arm was decreased ejection fraction (n=3, 0.9%).

A total of 29 (4.3%) patients had died as of the interim analysis: 9 patients (2.7%) in the osimertinib arm, 20 patients (5.8%) in the placebo arm.

Regarding notable harms, 8 patients (2.4%) experienced interstitial lung disease and 2 patients (0.6%) experienced pneumonitis in the osimertinib arm as of the interim analysis. No patients in the placebo arm experienced interstitial lung disease or pneumonitis. The frequency of cardiac disorder AEs was greater in the osimertinib arm compared to the placebo arm (11.0% vs. 5.2%, respectively). In the osimertinib arm, 6.5% patients experienced QT interval prolongation compared to 1.2% in the placebo arm. Four patients (1.2%) in the osimertinib arm experienced congestive heart failure/cardiac failure/left ventricular dysfunction compared to zero in the placebo arm. Four patients (1.2%) in the osimertinib arm experienced atrial fibrillation compared to 1 (0.3%) in the placebo arm; 6 patients (1.8%) in the osimertinib arm experienced an arrhythmia other than atrial fibrillation compared to zero in the placebo arm. Overall, 3 patients (0.4%) experienced keratitis: 2 (0.6%) in the osimertinib arm, and 1 (0.3%) in the placebo arm. In the osimertinib arm, 70.6% experienced a skin and subcutaneous tissue disorder compared to 35.6% of patients in the placebo arm. The most common skin disorders in the osimertinib and placebo arms were paronychia (25.2% and 1.5%, respectively), dry skin (23.4% and 6.4%, respectively), pruritis (19.3% and 8.7%, respectively), and dermatitis acneiform (11.0% and 4.7%, respectively).

Critical appraisal

The ADAURA trial was a double-blind RCT to minimize bias. Baseline characteristics were balanced between treatment arms and few randomized patients had been lost to follow-up as of the data cut-off date. The interim analysis was not planned, and the trial is ongoing. A multiple testing procedure was employed to control overall type I error at the 5% 2-sided level for the endpoints of DFS and OS, which was modified to account for the unplanned interim analyses. The primary endpoint was met at the interim analysis since the log-rank test for DFS in patients with stage II-IIIA disease met the prespecified threshold for statistical significance. The log-rank test for DFS in the overall population also met statistical significance for this analysis. Due to early reporting of the study, data maturity is lower than planned at the interim analysis. At the data cut-off date, the sponsor assessed the OS data to be immature. Furthermore, the comparison for OS in the stage II-IIIA population was not statistically significantly different between the treatment arms. Thus, it cannot be concluded that osimertinib confers an OS benefit compared to placebo at the time of this CADTH review. In addition, data on time to next treatment and PFS were considered of limited clinical significance by the sponsor at the time of the interim analysis due to the immaturity of the data on patients who experienced a disease recurrence event, and comparisons for these endpoints were not controlled for multiple comparisons. The results did not support conclusions for an effect of osimertinib on PFS and time to next treatment, and any potential clinical benefit for these outcomes is associated with uncertainty due to the immaturity of the data and lack of control from type I error. Conclusions could not be drawn for the effect of osimertinib on HRQoL endpoints as these endpoints were not adjusted for multiple comparisons. In addition, most patients have not had the opportunity to receive the planned study treatment duration of 3 years.

The osimertinib dose and treatment regimen used in the ADAURA trial aligns with the Health Canada indication. The ADAURA trial included patients who had received standard-of-care adjuvant chemotherapy, which is commonly used in Canadian practice. This also aligns with the intended use of osimertinib in Canada per the clinical experts consulted by CADTH and clinician groups that provided input, who indicated that osimertinib is not intended to replace adjuvant chemotherapy. The clinical experts consulted by CADTH thought that the eligibility criteria used in the trial were appropriate and generally reflected the characteristics of the intended patient population in Canada. However, the trial limited enrollment to patients with a WHO performance status of 0 to 1 and the clinical experts reported that many patients in their practice with resected stage IA-IIIB NSCLC have a performance status of 2. The clinical experts did not think that exclusion of patients with worse performance status limits the generalizability of the trial results. The proportion of Asian patients in the trial was higher than in the Canadian NSCLC population per the clinical experts consulted by CADTH. In addition, the ADAURA trial reported a higher EGFR mutation positive rate than currently seen in Canada, where EGFR testing is routinely offered to patients with locally advanced and not amenable to curative intent therapy or metastatic NSCLC only.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients (aged ≥18 years) with completely resected, early-stage EGFR mutation–positive, NSCLC
Treatment	Osimertinib
Submitted drug price	Osimertinib, 40 mg: $294.68 per tablet Osimertinib, 80 mg: $294.68 per tablet
Annual cost	At the sponsor's submitted price of $294.68 per 80 mg tablet, the annual cost of osimertinib adjuvant therapy would be $107,557 if patients remained on therapy for a full year.
Comparator	Active surveillance, consisting of no active treatment
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (38 years)
Key data source	ADAURA trial, a randomized, double blind, placebo-controlled, multicenter phase III study evaluating the efficacy of osimertinib as adjuvant therapy following complete tumour resection with curative intent with or without adjuvant chemotherapy.
Key limitations	• As overall survival in the ADAURA trial was immature, it is unknown whether osimertinib confers an OS benefit compared to placebo. The impact of osimertinib adjuvant therapy on long-term disease-free survival and the subsequent impact on OS is highly uncertain. • The time to establish cure used in the model was felt to be shorter than what was considered by CADTH clinical experts. • CADTH clinical experts felt that the distribution of patients across subsequent therapies used upon transitioning to local regional is not aligned with clinical practice. Additionally, cisplatin-pemetrexed was noted as the more commonly used chemoradiotherapy regimen for LR progression. • Annual disease management costs for LR did not meet face validity as they were higher than those for distant metastatic disease, which was deemed inappropriate by CADTH clinical experts. • AEs were assumed to only occur in the first month of treatment, which is uncertain and favours osimertinib. • Health state utility values do not meet face validity, as the utility for patients who are disease free or with local regional recurrence was estimated to be higher than that of the general Canadian population in the sponsor's submission. • Time to retreatment with osimertinib upon progression to distant metastatic disease is uncertain. • A relative dose intensity (RDI) sourced from osimertinib trials in the distant metastatic setting was applied in the adjuvant setting.

Component	Description
	• Survival outcomes in the 2L DM setting were potentially influenced by treatment crossover in the FLAURA trial. This is likely not reflective of survival outcomes in current practice.
CADTH reanalysis results	• CADTH undertook reanalyses to address limitations relating to: survival extrapolations relating to transitions from DF to LR and DF to 1L DM; extending the time to establish cure to 5 years; aligning the distribution and type of subsequent treatments used in LR progression with Canadian clinical practice; adjusting LR disease management costs to be equal to those used in the distant metastatic health states; removing radiotherapy costs and dialysis costs for those in DF and LR; using trial-based and age-adjusted utility values; adjusting the RDI to 100% and altering 2L DM to death transition probabilities. • Compared to active surveillance, the ICER for osimertinib is $328,026 per QALY. • For osimertinib to be considered cost-effective at a willingness to pay threshold of $50,000 per QALY compared to active surveillance, a price reduction of at least 82% would be required.

Budget Impact

CADTH reanalyses: assumed all patients in the new drug scenario will undergo EGFRm testing at the time of resection; assumed 95% of patients in the reference scenario who progress to DM will receive EGFRm testing and have a valid result, changed the RDI to 100%, increased osimertinib uptake in Year 1 and 2 and, aligned the distribution of patients across subsequent therapies for LR with the pharmacoeconomic analysis. Based on the CADTH reanalyses, the budget impact from the introduction of osimertinib adjuvant therapy is expected to be $21,723,455 in Year 1, $43,365,781 in Year 2 and $65,409,131 in Year 3 with a 3-year total budget impact of $130,498,368.

pERC Members

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

August 11, 2021 Meeting

Regrets

Three expert committee members did not attend.

Conflicts of Interest

None.

Appendix 1: CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) Responses to Drug Program Implementation Questions

Implementation Questions from the Drug Programs	
Implementation Issues	**Response from Expert Committee**
Considerations for Initiation of Therapy	
In ADAURA, osimertinib demonstrated a DFS benefit in patients with or without post-operative adjuvant chemotherapy. • When would adjuvant chemotherapy benefit patients that may be considered for osimertinib? • Can pERC clarify the eligible patient population based on the AJCC 8th edition staging system?	pERC discussed that the ADAURA trial included patients with or without prior receipt of adjuvant chemotherapy, and the magnitude of DFS benefit was similar in each of these patient subgroups. The clinical experts consulted by CADTH indicated that osimertinib is not intended to replace adjuvant chemotherapy. Adjuvant chemotherapy is offered to patients with good performance status and who have tumours ≥4 cm or with nodal involvement. Osimertinib would be used after standard adjuvant chemotherapy, if chemotherapy was indicated, to further reduce the risk of disease recurrence and can also be offered to patients who are considered unfit for adjuvant chemotherapy. The clinical experts noted that platinum-based adjuvant chemotherapy can be challenging to administer because it requires adequate performance status and renal function, and it also has substantial toxicity (e.g., chronic renal failure, future blood dyscrasias, neuropathy, hearing loss) making it unsuitable or contraindicated in some patients. The reimbursement request is for stage IB-IIIA NSCLC using the AJCC 7th edition. The equivalent stages using the AJCC 8th edition are stages IIA to IIIB.
Generalizability	
The submitted economic model incorporated possible retreatment with osimertinib in the metastatic setting if disease relapse occurred 48 months after the start of adjuvant osimertinib (e.g., 12 months have elapsed since the completion of adjuvant osimertinib). • Should patients who receive osimertinib in the adjuvant setting and experience disease relapse off treatment be eligible for retreatment with osimertinib in the metastatic setting? • What time frame after the completion of adjuvant therapy is appropriate in order to be eligible for re-treatment?	Osimertinib is indicated and reimbursed as first-line treatment for patients with locally advanced (unresectable) or metastatic NSCLC whose tumours harbor EGFR mutations (exon 19 deletions or exon 21 [L858R] substitutions). pERC agreed that in the absence of evidence, retreatment with osimertinib in the metastatic setting would be reasonable if patients experienced disease relapse off treatment after either discontinuing osimertinib due to toxicity or completing 3 years of adjuvant osimertinib. pERC also agreed with the clinical experts that rechallenge with osimertinib after a 6- month off-treatment interval is reasonable unless the patient experiences a recurrence. Retreatment with osimertinib in the metastatic setting would not be indicated in patients who progressed on osimertinib in the adjuvant treatment setting.

AJCC = American Joint Committee on Cancer; CT = computed tomography; DFS = disease-free survival; NSCLC = non-small cell lung cancer; pERC = pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.

CADTH

Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines*.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.