Canada's Drug and Health Technology Agency

**CADTH Reimbursement Review**

# CADTH Reimbursement Recommendation

(Draft)

osimertinib (Tagrisso)

Indication: In combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of patients with locally advanced (not amenable to curative therapies) or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

Sponsor: AstraZeneca Canada Inc.

Recommendation: Reimburse with Conditions


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**Single Technology**



**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.

## Recommendation

The pCODR Expert Review Committee (pERC) recommends that osimertinib in combination with pemetrexed and platinum-based chemotherapy (osimertinib + chemotherapy) be reimbursed for the first-line treatment of patients with locally advanced (not amenable to curative therapies) or metastatic non-small cell lung cancer (NSCLC) whose tumours have *EGFR* exon 19 deletions (Ex19del) or exon 21 (L858R) substitution mutations only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

One ongoing phase III, open-label randomized controlled trial (RCT; FLAURA2) demonstrated that osimertinib + chemotherapy resulted in added clinical benefit in progression-free survival (PFS) compared to osimertinib monotherapy in adult patients with locally advanced, metastatic, or recurrent non-squamous NSCLC and whose tumour harboured Ex19del or L858R, either alone or in combination with other *EGFR* mutations. Median PFS per investigator assessment was 25.5 months (95% confidence interval [CI]: 24.7 months to not calculable [NC]) in the osimertinib + chemotherapy group versus 16.7 months (95% CI: 14.1 to 21.3 months) in the osimertinib monotherapy group, with a hazard ratio (HR) of 0.62 (95% CI: 0.49 to 0.79) at the data cut-off date of April 3, 2023. The difference between groups in the probability of being progression-free and alive at 12 and 24 months was 14.2% (95% CI: [redacted] to [redacted]) and 16.4% (95% CI: [redacted] to [redacted]), respectively, in favour of osimertinib + chemotherapy. In addition, osimertinib + chemotherapy may have a benefit in overall survival (OS) compared to osimertinib monotherapy, although this evidence is of low certainty due to the data being imprecise (i.e., wide CIs that indicated the possibility of both benefit and no meaningful benefit) and the OS data had a data maturity of 40.6%. As of the updated OS analysis (data cut-off date of January 8, 2024), median OS was 36.7 months in the osimertinib monotherapy group and not reached in the osimertinib + chemotherapy group, with a HR of 0.75 (95% CI: 0.57 to 0.97). The difference between groups in the probability of being alive at 24 and 36 months was 7.6% (95% CI: [redacted] to [redacted]) and 13.5% (95% CI: [redacted] to [redacted]), respectively, in favour of osimertinib + chemotherapy.

Patients identified a need for treatments that improved OS and PFS, reduced side effects, improved quality of life, and were easily accessed (i.e., patients value the convenience of oral drugs). pERC concluded that osimertinib + chemotherapy likely meets their need for improved PFS and may improve OS.

Using the sponsor submitted price for osimertinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for osimertinib plus chemotherapy was $235,123 per quality-adjusted life-year (QALY) gained compared with osimertinib monotherapy. At this ICER, osimertinib plus chemotherapy is not cost-effective at a $50,000 per QALY gained willingness to pay (WTP) threshold for patients with locally advanced or metastatic NSCLC. 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. Osimertinib + chemotherapy should only be reimbursed in adult patients (≥18 years) who meet all the following criteria:<br>1.1. Locally advanced, metastatic, or recurrent non-squamous NSCLC not amenable to curative surgery or radiation<br>1.2. Tumour that harbours *EGFR* Ex19del or L858R substitution mutations, either alone or in | The FLAURA2 trial demonstrated clinical benefit in adult patients with newly diagnosed locally advanced (clinical stage IIIB, IIIC) or metastatic NSCLC (clinical stage IVA or IVB) or recurrent NSCLC (per version 8 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), not amenable to curative surgery or radiotherapy. Patients' tumours harbored Ex19del or L858R, either alone or in combination with other *EGFR* mutations, which may include T790M. Patients in the | Based on the toxicity observed in patients treated with osimertinib + chemotherapy in the FLAURA2 trial, patients with ECOG ≥2 are not appropriate candidates for this treatment. |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| combination with other *EGFR* mutations<br>1.3. ECOG performance status of 0 or 1 | FLAURA2 trial had a WHO performance status of 0 to 1. | |
| 2. Osimertinib + chemotherapy should not be reimbursed in patients who meet any of the following criteria:<br>2.1. History of ILD<br>2.2. QT prolongation or active cardiac arrhythmia<br>2.3. Prior systemic therapy for advanced NSCLC, except for adjuvant or neoadjuvant therapies received at least 6 months prior to developing recurrent disease | Patients with a history of ILD; QT prolongation or any clinically important abnormalities in rhythm; or prior treatment with any systemic anti-cancer therapy for advanced NSCLC not amenable to curative surgery or radiation were excluded from the FLAURA2 trial. Prior adjuvant and neo-adjuvant therapies, or definitive radiation/chemoradiation were permitted as long as treatment was completed at least 12 months prior to the development of recurrent disease. | pERC considered it reasonable for patients to be eligible for osimertinib + chemotherapy if they completed adjuvant or neoadjuvant therapies at least 6 months prior to developing recurrent disease to align with the 2023 CADTH Provisional Funding Algorithm for advanced or metastatic NSCLC with activating *EGFR* mutations. |
| **Discontinuation** | | |
| 3. Treatment with osimertinib + chemotherapy should be discontinued upon disease progression or unacceptable toxicity, whichever occurs first. | Treatment with osimertinib + chemotherapy in the FLAURA2 trial was given until disease progression, unacceptable toxicity, or a treatment discontinuation criterion was met, whichever occurred first. Study treatment discontinuation criteria in the FLAURA2 trial included RECIST v1.1-defined progression if the patient was no longer receiving clinical benefit based on the investigators' judgement, patient decision, or investigator decision. | In the FLAURA2 trial, patients were allowed to continue receiving their study treatment beyond RECIST v1.1-defined progression if they were receiving clinical benefit based on the investigators' judgement. pERC agreed that treatment with osimertinib + chemotherapy should be continued until clinically meaningful progression occurs, based on the judgement of the treating clinician. |
| **Prescribing** | | |
| 4. Osimertinib + chemotherapy should be prescribed by clinicians with expertise in treating NSCLC. | This is meant to ensure that osimertinib + chemotherapy is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner. | — |
| 5. Osimertinib should only be prescribed in combination with pemetrexed and platinum-based (i.e., cisplatin or carboplatin) chemotherapy. | The FLAURA2 trial provided evidence on the osimertinib in combination with pemetrexed and either cisplatin or carboplatin for 4 cycles followed by osimertinib and pemetrexed maintenance therapy every 3 weeks. pERC did not review evidence supporting the efficacy and safety of osimertinib when used in combination with other anticancer drugs. | Osimertinib may be continued as monotherapy once the disease is responding even if chemotherapy is discontinued due to side effects or toxicity. |
| **Pricing** | | |
| 6. A reduction in price. | The ICER for osimertinib plus chemotherapy is $235,123 per QALY gained when compared with osimertinib monotherapy. | In addition to CADTH's standard approach, alternative approaches to calculating price reduction were considered: a price reduction for all drugs including |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| | Osimertinib plus chemotherapy is associated with an additional 0.25 QALYs compared to osimertinib monotherapy and with incremental costs of $57,897. The results are driven by the cost of osimertinib and chemotherapy. Price reductions required to achieve cost-effectiveness at given willingness-to-pay thresholds are reported in Tables 7, 13, and 14 of the Pharmacoeconomic Report. | chemotherapy; and a reduction in price for osimertinib plus chemotherapy but not osimertinib monotherapy. Price reduction for all drugs in the regimen (including chemotherapy) may be required for osimertinib to provide optimal value to the health system. |

CNS = central nervous system; EGFR = epidermal growth factor receptor; ICER = incremental cost-effectiveness ratio; ILD = interstitial lung disease; NSCLC = non-small cell lung cancer; QALY = quality-adjusted life year; RECIST = Response Evaluation Criteria in Solid Tumours; TKI = tyrosine kinase inhibitor; WHO = World Health Organization.

## Discussion Points

- pERC noted that prevention of central nervous system (CNS) metastasis and CNS disease control are important treatment goals in patients with NSCLC, and acknowledged the specific needs of patients with CNS metastases due to the associated morbidity. Patients with stable brain metastases and patients with asymptomatic brain metastases for which immediate definitive treatment was not indicated could be enrolled In the FLAURA2 trial. Prespecified subgroup analyses suggested the potential for greater benefit with osimertinib + chemotherapy in patients with CNS metastases at baseline compared with patients without CNS metastases at baseline, although there was uncertainty related to the trial design and analysis of these subgroups (i.e., not included in the sample size calculation and not a stratification factor for randomization, no formal testing for subgroup interaction available). pERC concluded that osimertinib + chemotherapy is beneficial to patients with stable CNS metastases.
- Patients expressed a need for treatments with reduced or manageable side effects. pERC noted that the combination use of osimertinib + chemotherapy in the first-line setting likely results in an increase in the occurrence of adverse events (AEs) compared to the osimertinib monotherapy. The FLAURA2 trial showed a higher percentage of patients treated with osimertinib + chemotherapy experienced AEs of grade 3 or higher, serious adverse events (SAEs), discontinuation of any study treatment, and deaths reported as AEs, compared to patients treated with osimertinib monotherapy. pERC noted that clinicians will need to consider the toxicity of osimertinib + chemotherapy when selecting optimal patients for whom to offer this treatment. Eligible patients should be informed about the associated risks, and the side effects of this treatment will need to be managed by a clinician with expertise in treating NSCLC.
- Improving health-related quality of life (HRQoL) was highlighted by both patients and clinicians as a critical treatment goal in advanced NSCLC. HRQoL was assessed in the FLAURA2 trial based the change from baseline in EORTC QLQ-LC13 (e.g., Coughing Symptoms Subscale, Pain in Chest Subscale, and Dyspnea Symptom Subscale) and EORTC QLQ-C30 (e.g., Global Health Status/QoL). pERC noted that within-group differences indicated improvements in both the osimertinib + chemotherapy and osimertinib monotherapy groups. pERC concluded that the evidence suggested there was no detriment in patients' HRQoL when treated with osimertinib + chemotherapy or osimertinib monotherapy. In terms of between-group differences, only the point estimates of difference of the Dyspnea Symptom Subscale of EORTC QLQ-LC13 and the Global Health Status/QoL of EORTC QLQ-C30 at Week 52 and averaged across all visits showed non-null improvement favouring the osimertinib monotherapy group. pERC noted that the comparative HRQoL evidence was uncertain due to risk of bias from missing data and imprecision in the results.
- Using CADTH's typical approach to price reduction, there was no price at which osimertinib plus chemotherapy achieved an ICER at or below $50,000 per QALY gained compared to osimertinib plus chemotherapy. This was principally due to the additional cost of chemotherapy and changes in health state occupancy in the pharmacoeconomic model. A scenario analysis was performed in which a price reduction was applied to all drugs including chemotherapy. This scenario analysis suggested that a 91% reduction in the price of osimertinib and chemotherapy would be necessary to reach an ICER of $50,000 per QALY gained. A second scenario analysis was conducted in which osimertinib plus chemotherapy was treated the same way as a wholly new regimen, meaning that the price reduction was only applied on 'one side' of the comparison (i.e., osimertinib monotherapy was not affected by the reduction in price). In this second analysis, a 14% reduction in the price of osimertinib was required to achieve an ICER below $50,000 per QALY gained. All drugs included in the economic analysis have currently

negotiated prices. The negotiated prices may exert considerable influence over the price reduction needed to achieve cost-effectiveness, and are not reflected in CADTH's analyses.

## Background

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths in Canada. In 2023, it was estimated that there would be 31,000 cases of lung cancer diagnosed and 20,600 deaths from lung cancer that year. It is estimated that 1 in 21 (4.8%) Canadians will die from lung cancer. Lung cancer is classified into NSCLC or small cell lung cancer, with NSCLC accounting for approximately 88% of cases in Canada. Approximately half of all lung cancer cases in Canada are stage I-III at diagnosis, defined by the American Joint Committee on Cancer (AJCC) staging criteria. Advanced disease as defined by AJCC, includes stage IV (metastatic) and unresectable stage IIIB,C (locally advanced) patients. Approximately 15% of Canadians with NSCLC have an epidermal growth factor receptor (EGFR) activating mutation in the region encoding the tyrosine kinase domain. EGFR mutations are more frequently observed in never-smokers, people of Asian ethnicity, patients with adenocarcinoma, and females. The most common EGFR mutations are exon 19 deletions and the exon 21 codon 858 point mutation (L858R). A common feature of EGFRm NSCLC is the development of central nervous system (CNS) metastases, which are detected in approximately 25% of patients at diagnosis and can affect approximately 50% of all patients within 3 years from diagnosis. Brain metastases are associated with decreased quality of life and poor prognosis and are a significant cause of cancer-related mortality.

For patients diagnosed with locally advanced or metastatic NSCLC who harbour EGFR mutations (i.e., Exon 19 deletion and/or L858R mutation), according to the clinical experts consulted by the review team, the current first line treatment in Canada is osimertinib. Alternative treatment options in the first line setting include first- and second- generation EGFR-tyrosine kinase inhibitors (TKIs) (i.e., gefitinib, erlotinib, and afatinib) as well as platinum doublet chemotherapy. The clinical experts consulted by the review team also noted that patients would receive platinum doublet chemotherapy upon progressive disease after they had received osimertinib monotherapy. Since osimertinib became available, gefitinib, erlotinib and afatinib have had limited utilization in the first-line treatment setting in Canada and instead are reserved for the small number of patients whose tumours have non-eligible EGFR mutations that cannot be treated with osimertinib.

Osimertinib has been approved by Health Canada in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of patients with locally advanced (not amenable to curative therapies) or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Osimertinib is a TKI. It is available as tablets, 40 mg and 80 mg, and the dosage recommended in the product monograph 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 phase III, open-label, RCT (FLAURA2) in adult patients with locally advanced, metastatic, or recurrent EGFRm (Ex19del and/or L858R) NSCLC, not amenable to surgery or radiotherapy
- patients' perspectives gathered by 2 patient groups, Lung Cancer Canada (LCC) and Lung Health Foundation
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with NSCLC
- input from 2 clinician groups, Ontario Health-Cancer Care Ontario (OH-CCO) Lung Cancer Drug Advisory Committee and Lung Cancer Canada – Medical Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor

## Stakeholder Perspectives

### Patient Input

Two patient groups, LCC and the Lung Health Foundation (formerly known as Ontario Lung Association), provided input for osimertinib in combination with pemetrexed and platinum-based chemotherapy (osimertinib + chemotherapy) for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) mutations. Patient input was gathered from interviews and surveys, conducted from January 2021 and October 2023 by the Lung Health Foundation, and in December 2023 by LCC. While the Lung Health Foundation conducted 2 interviews and gathered 15 responses from online survey, LCC conducted 13 interviews with patients and/or caregivers.

When asked about disease experience and its impact on day-to-day activities, respondents indicated that the disease have negative impacts on their day-to-day life, impacting their ability to participate in leisure activities and hobbies, use stairs, go shopping, travel etc. Family members and caregivers of those living with lung cancer shared the same psychosocial burdens as the patients in this input. In addition, LCC reported that patients living with lung cancer have repeatedly stated in interviews that the key value they want in a treatment is one that improves their quality of life while also managing their disease effectively.

Respondents from the Lung Health Foundation mentioned some benefits experienced with the currently available treatments, such as - reduced cough, reduced shortness of breath increased participation in daily activities, ability to exercise, prolonged life, delayed disease progression and a reduction in the severity of other disease-related symptoms. The LCC input mentioned that though chemotherapy and radiation may be clinically beneficial, they come with well-documented side effects that often negatively impact a patient's quality of life. The input added that osimertinib as a monotherapy has been very well-received by patients interviewed for this submission.

Respondents from the Lung Health Foundation reported that key treatment outcomes to consider when evaluating new therapies included stopping or slowing the progression of the disease with minimal side effects, as well as medications that are effective for advanced disease. When choosing a therapy, some of the most crucial outcomes that patients from the LCC input wanted to have include - improved management of their symptoms of EGFR NSCLC, allowing them to have a full and worthwhile quality of life, having manageable side effects, allowing patients to live longer and maintain their independence and functionality to minimize the burden on their caregivers and loved ones, and delaying disease progression and settling patients into long-term management for improved survivorship.

### Clinician Input

#### *Input From Clinical Experts Consulted by the Review Team*

According to the clinical experts consulted by the review team, the key treatment goals for patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations included improving OS, controlling disease progression (including prevention and disease control of CNS metastasis), and maintaining quality of life. The clinical experts consulted by the review team noted that needs are not met in patients who are younger, who are present with significant disease burden, or who have CNS metastases.

The clinical experts consulted by the review team noted that osimertinib + chemotherapy may be offered as an alternative to osimertinib monotherapy in the first line setting for patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. The clinical experts consulted by CADTH also noted that osimertinib monotherapy should remain as a first line treatment option. The clinical experts consulted by the review team further noted that if the osimertinib + chemotherapy was adopted in first line with maintenance pemetrexed, second line treatment options would include rechallenge with platinum doublet or docetaxel.

The clinical experts consulted by the review team noted that osimertinib + chemotherapy may preferentially be considered in younger patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and in patients with CNS metastases. However, the clinical experts consulted by the review team noted that older patients

with fewer disease related symptoms may choose not to receive osimertinib + chemotherapy due to the additive toxicity associated with osimertinib + chemotherapy.

According to the clinical experts consulted by the review team, outcomes to determine whether a patient is responding in clinical practice focus on functional status, disease related symptoms, and radiographic imaging. Depending on local resources and time on treatment, radiographic imaging may be conducted every 2 to 4 months to confirm benefit.

The clinical experts consulted by the review team noted that, overall, it should be the clinician's decision to discontinue the therapy based on a combination of factors, such as patients' symptoms/conditions, radiographic imaging results, toxicities, laboratory parameters, as well as the balance against clinical benefit for that patient. According to the clinical experts consulted by the review team, patients with progression defined by RECIST may not necessarily indicate the deficiency of treatment, and thus, in clinical practice, clinicians tend to make decisions regarding discontinuing treatment based on whether patients have clinically meaningful symptomatic disease progression.

The clinical experts consulted by the review team noted that the planned combination of osimertinib and chemotherapy would appropriately be delivered in any cancer treatment center, academic to community setting, and patients should be treated by medical oncologists who are well versed in the management of EGFR TKI and platinum chemotherapy toxicity management.

### *Clinician Group Input*

Clinician group input on the review of osimertinib + chemotherapy for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) mutations, was received from 2 clinician groups: OH-CCO Lung Cancer Drug Advisory Committee and Lung Cancer Canada – Medical Advisory Committee. A total of 28 clinicians provided input for this review.

OH-CCO mentioned that current treatments target shrinking the cancer, improvement in disease related symptoms, and maximizing control of the disease to prevent or delay symptoms and prolong life. However, both clinician groups indicated that the current treatment options with osimertinib monotherapy and/or sequential therapy with osimertinib followed by chemotherapy is not curative. Both clinician groups highlighted need for improved therapies that result in longer control of the cancer, better quality of life and longer survival. Similar to the clinical experts consulted by the review team, the clinician groups mentioned the need to have therapies targeting specific patient populations, i.e., young patients and those with brain metastases. Both clinician groups emphasized that brain metastases in EGFR driven lung cancer are an urgent unmet need.

Both clinician groups noted that the combination of osimertinib with chemotherapy would be an option in NSCLC patients with sensitizing EGFR mutations. The OH-CCO group highlighted the need to have overall survival data to draw any conclusion regarding the shift in the current treatment paradigm. They further mentioned that the addition of platinum-based chemotherapy to osimertinib is associated with an increase in chemotherapy associated toxicities, thus requiring the patients to attend the cancer centre more frequently because of the need for IV therapy, resulting in more inconvenience to patients. Similar to the clinical experts consulted by the review team, both clinician groups noted that single agent osimertinib would remain an option in first line therapy.

OH-CCO group highlighted that all patients who have EGFR classic mutations would be suitable for osimertinib therapy who can tolerate and who have not had prior adjuvant osimertinib within the last several months. They also mentioned that for the addition of chemotherapy, suitable patients would be those for whom IV chemotherapy will be well tolerated or safe, and who have adverse features of their EGFR mutation positive cancer. Similar to the clinical experts consulted by the review team, the clinician groups noted that younger patients and patients with CNS metastases would benefit from the combination regimen. Both clinician groups agreed that treatment would be discontinued in cases of disease progression or undue toxicity.

## Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for osimertinib. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

## Table 2: Responses to Questions from the Drug Programs

| Implementation Issues | Response |
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| **Relevant comparators** | |
| FLAURA-2 compared osimertinib-pemetrexed-platinum for 4 cycles followed by osimertinib and pemetrexed maintenance every 3 weeks with osimertinib alone, which is a relevant funded comparator in this setting.<br><br>Other EGFR TKI's (erlotinib, gefitinib and afatinib) could potentially be used in this setting, but osimertinib is generally preferred, so no issue with the choice of comparator. No downstream treatment options would be affected. | This is a comment from the drug plans to inform pERC deliberations. |
| **Considerations for Initiation of Therapy** | |
| FLAURA-2 enrolled patients with non-squamous NSCLC, locally advanced (clinical stage IIIB, IIIC) or metastatic (clinical stage IVA or IVB), or recurrent NSCLC (per version 8 of the IASLC staging manual), not amenable to curative surgery or radiotherapy.<br><br>• The vast majority of patients enrolled on the FLAURA2 study had adenocarcinoma (99% in both arms). Should other histology (e.g. adenosquamous carcinoma) be eligible for this treatment?<br><br>• Are there any uncommon *EGFR* mutations that would have better potential for effectiveness that should be considered for eligibility for treatment with osimertinib/pemetrexed-platinum? | According to the clinical experts consulted by the review team, it is the driver mutation rather than histology that determines whether osimertinib should be used or not. The clinical experts indicated that it is plausible to believe that the treatment effects of osimertinib + chemotherapy would likely not differ among patients with the same driving mutation but different histology. Therefore, according to the clinical experts consulted by the review team, osimertinib + chemotherapy should be considered for patients with *EGFR* mutations in the proposed indication regardless of the histology of their lung cancer.<br><br>pERC agreed with the clinical experts that patients with NSCLC whose tumour harbours the eligible *EGFR* mutations should be considered for this treatment and notes a small number of patients with adenosquamous histology were included in the FLAURA2 clinical trial.<br><br>pERC noted that the Health Canada approved indication and reimbursement request were specific to patients whose tumours have *EGFR* exon 19 deletions 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 this treatment in patients with other uncommon *EGFR* mutations. Therefore, pERC could not comment on effectiveness in patients with other *EGFR* mutations. |
| FLAURA-2 allowed prior adjuvant and neoadjuvant therapies provided that the treatment was completed 12 months prior to the development of recurrent disease.<br><br>• What is the appropriate disease-free interval following completion of adjuvant osimertinib where patients would be considered eligible for osimertinib-pemetrexed-platinum in the recurrent advanced/metastatic setting? | The clinical experts consulted by the review team did not consider a 12-month interval prior to the development of recurrent disease appropriate in clinical practice. According to the clinical experts consulted by the review team, patients with a 6-month disease-free interval following completion of adjuvant chemotherapy alone or adjuvant osimertinib could be considered eligible for osimertinib + chemotherapy. The clinical experts consulted by the review team further noted that it should be the clinician's judgement to decide whether a patient with less than 6-month disease-free interval would be eligible for osimertinib + chemotherapy.<br><br>pERC considered it reasonable for patients to be eligible for osimertinib + chemotherapy if they completed adjuvant or neoadjuvant therapies at least 6 months prior to developing |

| Implementation Issues | Response |
|---|---|
| | recurrent disease to align with the 2023 CADTH Provisional Funding Algorithm for advanced or metastatic NSCLC with activating *EGFR* mutations. |
| **Considerations for discontinuation of therapy** | |
| FLAURA2 allowed treatment until disease progression or occurrence of unacceptable or clinically significant toxic effects. However, it was also noted that treatment beyond disease progression was permitted if the patient had a continued clinical benefit, according to the judgment of the investigator.<br><br>• What are the discontinuation criteria for osimertinib? | According to the clinical experts consulted by the review team, overall, it should be the clinician's decision to discontinue the therapy based on a combination of factors, such as patients' symptoms/conditions, radiographic imaging results, toxicities, laboratory parameters, as well as the balance against clinical benefit for that patient. The clinical experts consulted by the review team noted that generally continuing on treatment as long as there is clinical benefit is reasonable. In clinical practice, symptomatic disease progression or toxicity would be the rationale for stopping therapy. Of note, the clinical experts consulted by the review team clarified that patients with progression defined by RECIST may not necessarily indicate the deficiency of treatment, and thus, in clinical practice, clinicians tend to make decisions regarding discontinuing treatment based on whether patients have clinically meaningful symptomatic disease progression.<br><br>The clinical experts consulted by the review team noted that the decisions to stop osimertinib and chemotherapy should be dissociated, and it is not necessary to stop both osimertinib and chemotherapy at the same time.<br><br>pERC determined that treatment with osimertinib + chemotherapy should be discontinued upon disease progression or unacceptable toxicity, whichever occurs first, in alignment with the FLAURA2 trial. pERC agreed that treatment with osimertinib + chemotherapy should be continued until clinically meaningful progression occurs, based on the judgement of the treating clinician. Osimertinib may be continued as monotherapy once the disease is responding even if chemotherapy is discontinued due to side effects or toxicity. pERC noted that the decision to stop or continue the treatment should also be based on a joint decision-making between the treating clinician and patient, considering the severity of side effects, and patient symptoms, values, and preferences. |
| **Generalizability** | |
| Should patients with WHO PS > 1 be eligible? | The clinical experts consulted by the review team noted that rather than using rating of performance status to decide patient eligibility, they will consider a patient eligible if the patient have a good performance status in term of being suitable for chemotherapy.<br><br>pERC determined that, based on the toxicity observed in patients treated with osimertinib + chemotherapy in the FLAURA2 trial, patients with WHO or ECOG performance status ≥2 are not appropriate candidates for this treatment. |

| Implementation Issues | Response |
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| **Funding algorithm** | |
| The drug plans noted the following items that may require the development of a provisional funding algorithm:<br><br>• Drug may change place in therapy of comparator drugs<br>• Drug may change place in therapy of drugs reimbursed in subsequent lines | This is a comment from the drug plans to inform pERC deliberations. |
| **Care provision issues** | |
| Additional toxicity is expected with the osimertinib/pemetrexed/platinum treatment (grade 3 or higher: 64% vs 27%) - e.g., hematological toxicity 71% vs 24%, cardiac toxicity (9% vs 4%) | This is a comment from the drug plans to inform pERC deliberations. |
| EGFR mutation testing is part of routine clinical practice, so it is not expected that there would be any incremental impact. | This is a comment from the drug plans to inform pERC deliberations. |
| **System and economic issues** | |
| Initial chemotherapy and maintenance pemetrexed require IV drug preparation and ambulatory treatment appointments every 3 weeks, which is an additional impact to resources. | This is a comment from the drug plans to inform pERC deliberations. |
| There is a confidential negotiated prices for osimertinib, pemetrexed and cisplatin. | This is a comment from the drug plans to inform pERC deliberations. |

EGFR = epidermal growth factor receptor; IV = intravenous; NSCLC = non-small cell lung cancer; osimertinib + chemotherapy = osimertinib + in combination with pemetrexed and platinum-based chemotherapy; RECIST = Response Evaluation Criteria in Solid Tumours; TKI = tyrosine kinase inhibitor; WHO PS = World Health Organization performance status; Clinical Evidence

One ongoing phase III, open-label RCT (FLAURA2, N = 557, including 13 patients in Canada) was included in the systematic literature search (SLR) conducted by the sponsor. FLAURA2 enrolled adult patients who were diagnosed with pathologically confirmed non-squamous NSCLC that was locally advanced (clinical stage IIIB, IIIC), m; etastatic (clinical stage IVA or IVB), or recurrent (per version 8 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology) and whose tumour harboured Ex19del or L858R, either alone or in combination with other EGFR mutations. Patients were randomized to the osimertinib + chemotherapy group (n = 279) and the osimertinib monotherapy group (n = 278), stratified by race, WHO PS, and methods used for tissue testing. The primary objective was to compare the treatment effect between osimertinib + chemotherapy versus osimertinib monotherapy, measured by PFS per investigator assessment. Other efficacy and safety outcomes included OS, EORTC QLQ-LC13, EORTC QLQ-C30, and harms (i.e., AEs, SAEs, withdrawal, deaths, notable harms).

The median age of enrolled patients was 61.0 years (range: 26 to 85 years). The majority of enrolled patients were female (61.4%), Asian (63.7%), with a WHO PS of 1 (62.8%), with Exon 19 deletion (53.1% by central cobas tissue test) as well as had a metastatic NSCLC at baseline (96.2%).

*Efficacy Results*

FLAURA2 is ongoing, and the data cut-off date all efficacy endpoints was April 3, 2023, except for OS which were updated on January 8, 2024.

**OS**

As of the data cut-off date of January 8, 2024, the OS data had a data maturity of 40.6% and were adjusted for multiple statistical testing. There were 100 OS events (35.8%) in the osimertinib + chemotherapy group and 126 OS events (45.3%) in the osimertinib monotherapy group. The HR for OS was 0.75 (95% CI: 0.57 to 0.97). The difference in the probability of being alive between osimertinib + chemotherapy and osimertinib monotherapy at 24 and 36 months was 7.6 (95% CI: [redacted] to [redacted]) and 13.5% (95% CI: [redacted] to [redacted]), respectively. Median OS was 36.7 months in the osimertinib monotherapy group but not reached in the osimertinib + chemotherapy group. There was a delayed separation of the Kaplan-Meier curves of the 2 treatment groups, which did not separate until about 16 months post randomization.

**PFS per investigator assessment**

As the data cut-off date April 3, 2023, with an overall data maturity of 51.3%, 120 PFS events (43.0%) per investigator assessment were reported in the osimertinib + chemotherapy group versus 166 PFS events (59.7%) per investigator assessment in the osimertinib monotherapy group. The HR (95% CI) for PFS per investigator assessment was 0.62 (0.49 to 0.79), in favour of osimertinib + chemotherapy. The difference in the probability of being progression free between osimertinib + chemotherapy and osimertinib monotherapy 12 and 24 months was 14.2% (95% CI: [redacted] to [redacted]) and 16.4% (95% CI: [redacted] to [redacted]), respectively. Median PFS (95% CI) per investigator assessment was 25.5 (24.7 to not calculable [NC]) months in the osimertinib + chemotherapy group versus 16.7 (14.1 to 21.3) in the osimertinib monotherapy group.

Results of PFS per BICR assessment were generally consistent with the results of PFS per investigator assessment. Analysis of concordance between investigator and BICR assessment of PFS showed that there was an [redacted]% agreement on progressions and non-progressions in the osimertinib + chemotherapy group, and a [redacted]% agreement on progressions and non-progressions in the osimertinib monotherapy group.

**EORTC QLQ-LC13**

The data cut-off date for EORTC QLQ-LC13 was April 3, 2023. The point estimates of difference in change from baseline scores of the Coughing Symptoms Subscale between the osimertinib + chemotherapy group and the osimertinib monotherapy group favoured osimertinib + chemotherapy at Week 52 and across all visits (i.e., average), while the point estimates of difference of the Pain in Chest Subscale or the Dyspnea Symptom Subscale favoured the osimertinib monotherapy group at Week 52 and across all visits (i.e., average).

**EORTC QLQ-C30**

The data cut-off date for EORTC QLQ-C30 was April 3, 2023. The point estimates of difference in change from baseline scores of the Global Health Status/QoL between the osimertinib + chemotherapy group and the osimertinib monotherapy group favoured osimertinib monotherapy at Week 52 and across all visits (i.e., average).

*Harms Results*

The data cut-off date for harms data in the FLAURA2 trial was April 3, 2023. The proportions of patients experiencing at least 1 AE of any grade were similar between patients treated with osimertinib + chemotherapy (100%) and patients treated with osimertinib monotherapy (97.5%). However, in most AEs (reported in ≥ 20% patients in either treatment group), a higher proportion of patients was found in those treated with osimertinib + chemotherapy than those treated with osimertinib monotherapy, such as anemia (46.4% versus 8.0%), nausea (43.1% versus 10.2%), neutropenia (24.6% versus 3.3%). Moreover, a higher proportion of patients treated with osimertinib + chemotherapy experienced AEs of grade 3 or higher, compared with the proportion of patients treated with osimertinib monotherapy (63.8% versus 27.3%). The most common AEs of grade 3 and higher in patients treated with osimertinib + chemotherapy was anemia (19.9%).

Higher percentages of patients in the osimertinib + chemotherapy group experienced SAEs, compared to the percentages of patients in the osimertinib monotherapy group (37.7% versus 19.3%). Discontinuation of any study treatment occurred in 47.8% of the patients in the osimertinib + chemotherapy group and 6.2% of the patients in the osimertinib monotherapy. Within the osimertinib + chemotherapy group, 45.3% of the patients discontinued chemotherapy, of which 16.7% discontinued carboplatin or cisplatin treatment and 43.1% discontinued pemetrexed treatment.

Deaths were reported in 6.5% of the patients in the osimertinib + chemotherapy group and 2.9% of the patients in the osimertinib monotherapy group. Patients in the osimertinib + chemotherapy group died due to pulmonary embolism (1.1%), pneumonia (1.1%), and cardiac failure (0.7%).

The proportions of patients experiencing ILD/pneumonitis were similar between patients treated with osimertinib + chemotherapy (3.3%) and patients treated with osimertinib monotherapy (3.6%). A higher proportion of patients in the osimertinib + chemotherapy group experienced cardiac failure (9.1% versus 3.6%), febrile neutropenia (4.0% versus 0.0%), and thrombocytopenia (18.5% versus 4.4%), compared to patients in the osimertinib monotherapy group.

### *Critical Appraisal*

The FLAURA2 trial utilized central randomization and concealed patient allocation during the randomization process. The baseline characteristics were overall balanced between the treatment groups. Generally, no serious concerns were identified in protocol amendments and protocol deviations. As an open-label trial, investigators and patients were aware of the assigned treatment. The primary outcome in FLAURA2 was PFS per investigator assessment, which was prone to the impact of detection bias due to the open-label design. However, the potential risk of detection bias in PFS per investigator assessment was considered relatively low by the review team because results were consistent with those of PFS per BICR assessment and, the analysis of concordance between PFS per investigator and PFS per BICR assessment showed an acceptable agreement. Similarly, for HRQoL outcomes (i.e., EORTC QLQ LC-13 and EORTC QLQ-C30) which had unblinded assessment, the risk of performance bias was also considered relatively low as there was no evidence in the data indicating knowledge of treatment assignment affected the results. However, it was more of a concern that the assessment of HRQoL outcomes at Week 52 was based on a portion of randomized patients. For example, for EORTC QLQ-C30 assessment at Week 52, out of 279 patients in the osimertinib + chemotherapy group, 230 forms were expected, and 180 forms were received and evaluated (compliance rate: 78.3%, 180/230). It remains unclear how the missingness in data would affect the HRQoL assessment, thus resulting in increased uncertainty. The Kaplan-Meier curves of OS obtained from the April 3, 2023, data cut-off crossed several times, which violated the proportional hazards assumption for OS and impacted the validity of the OS estimates as of April 3, 2023. A late divergence of the Kaplan-Meier curves of the updated OS (data cut-off date: January 8, 2024) was observed during the visual inspection of the Kaplan-Meier curves (i.e., did not separate until approximately 16 months post randomization). According to the clinical experts consulted by the review team, in clinical practice the delayed separation of survival curves was acceptable as it is often seen in patients receiving a combination therapy consisting of chemotherapy. However, the late divergence of survival curves might have implications for the statistical analysis used in FLAURA2 (i.e., whether the proportional hazards assumption was violated), which introduced uncertainty to the OS evidence. In the situation where there is a delayed separation of survival curves, sensitivity analyses to assess whether the proportional hazards assumption was satisfied would have been appropriate (e.g., using survival analyses that do not rely on the proportional hazards assumption).

There are several considerations related to the generalizability of the FLAURA2 trial. The clinical experts consulted by the review team noted that the patient eligibility criteria of FLAURA2 were overall appropriate in clinical trials for patients with NSCLC and aligned with the selection criteria used in the Canadian treatment settings when identifying suitable candidates for osimertinib + chemotherapy. However, the clinical experts consulted by the review team noted that in the real-world settings, patients are generally sicker in terms of performance status. Second, FLAURA2 did not allow eligible patients to have prior treatment with an EGFR-TKI. Also, FLAURA2 required eligible patients to be off other adjuvant and neo-adjuvant therapies (e.g., chemotherapy, radiotherapy, immunotherapy, biologic therapy, investigational agents) at least 12 months prior to the development of recurrent disease. According to the clinical experts consulted by the review team, since osimertinib monotherapy had become first-line treatment for EGFRm, patients who had received prior EGFR-TKI should also be considered for osimertinib + chemotherapy. Third, the histology type of most patients enrolled in FLAURA2 (> 98% for both groups) was adenocarcinoma. According to the clinical experts consulted by the review team, findings from FLAURA2 could still be generalizable to patients with other histology types (e.g., adenosquamous carcinoma) because it is the existence of the driving mutation which decides whether osimertinib should be used. The clinical experts consulted by the review team noted that it was plausible to believe that the treatment effects of osimertinib + chemotherapy would likely not differ among patients with the same driving mutation but different histology.

### *GRADE Summary of Findings and Certainty of the Evidence*

**Methods for Assessing the 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 our 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 reference points for the certainty of evidence assessment for OS and PFS were set according to the presence of an important effect based on thresholds agreed upon by clinical experts consulted by the review team for this review. The target of the certainty of evidence assessment was the presence of any (non-null) effect for EORTC QLQ-LC13 due to the lack of a formal MID estimate. The MID for the Global Health Status/QoL of EORTC QLQ-C30 was based on estimate published in the literature. For harm events due to the unavailability of the absolute difference in effects, the certainty of evidence was summarized narratively.

The selection of outcomes for 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 expert committee members:

- Survival outcomes (OS, PFS),
- Health related quality of life outcome (Coughing Symptoms Subscale of the EORTC QLQ-LC13, Pain in Chest Subscale of the EORTC QLQ-LC13, Dyspnea Symptom Subscale of the EORTC QLQ-LC13, Global Health Status/QoL of the EORTC QLQ-C30)
- Harms (AEs of Grade 3 or higher, SAEs, discontinuation of any treatment due to AEs, deaths, notable harms including ILD/pneumonitis, cardiac effects, hematological toxicities)

**Results of GRADE Assessments**

Table 3 presents the GRADE summary of findings for osimertinib + chemotherapy versus osimertinib monotherapy in patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

## Table 3: Summary of Findings for Osimertinib + Chemotherapy Versus Osimertinib Monotherapy for Patients with Locally Advanced (Not Amenable to Curative Therapies) or Metastatic NSCLC Whose Tumours Have EGFR Exon 19 Deletions or Exon 21 (L858R) Substitution Mutations

| Outcome and follow-up | Patients (studies), N | Relative Effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Osimertinib Monotherapy | Osimertinib + Chemotherapy | Difference | | |
| **OS – Randomization Phase, FAS (Data Cut-off Date: January 8, 2024)** | | | | | | | |
| **Probability of being alive at 24 months**<br><br>Median follow-up duration (months): 31.7 for Osimertinib + Chemotherapy group; 30.5 for Osimertinib Monotherapy group | 557 (1 RCT) | NR | [redacted] per 1,000 | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | [redacted] more per 1,000 ([redacted] more to [redacted] more per 1,000) | Low[a] | Osimertinib + chemotherapy may result in an increase in the probability of being alive at 24 months, compared to osimertinib monotherapy. |
| **Probability of being alive at 36 months**<br><br>Median follow-up duration (months): 31.7 for Osimertinib + Chemotherapy group; 30.5 for Osimertinib Monotherapy group | 557 (1 RCT) | NR | [redacted] per 1,000 | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | [redacted] more per 1,000 ([redacted] more to [redacted] more per 1,000) | Low[b] | Osimertinib + chemotherapy may result in an increase in the probability of being alive at 36 months, compared to osimertinib monotherapy. |
| **PFS per Investigator Assessment – Randomization Phase, FAS (Data Cut-off Date: June 1, 2021)** | | | | | | | |
| **Probability of being progression free at 12 months**<br><br>Median follow-up duration (months): 19.5 for Osimertinib + Chemotherapy group; 16.5 for Osimertinib Monotherapy group | 557 (1 RCT) | NR | [redacted] per 1,000 | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | [redacted] more per 1,000 ([redacted] more to [redacted] more per 1,000) | Moderate[c] | Osimertinib + chemotherapy likely result in an increase in the probability of being progression free at 12 months, compared to osimertinib monotherapy. |
| **Probability of being progression free at 24 months**<br><br>Median follow-up duration (months): 19.5 for Osimertinib + Chemotherapy group; 16.5 for Osimertinib Monotherapy group | 557 (1 RCT) | NR | [redacted] per 1,000 | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | [redacted] more per 1,000 ([redacted] more to [redacted] more per 1,000) | Moderate[c] | Osimertinib + chemotherapy likely result in an increase in the probability of being progression free at 24 months, compared to osimertinib monotherapy. |
| **HRQoL – Randomization Phase, FAS (Data Cut-off Date: June 1, 2021)** | | | | | | | |
| Coughing Symptoms Subscale of the EORTC QLQ-LC13 | 557 (1 RCT) | NR | -13.03 | -14.08 (-16.69 to -11.48) | -1.05 (-4.87 to 2.77) | Very Low[d] | The evidence is uncertain about the effect of |

| Outcome and follow-up | Patients (studies), N | Relative Effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Osimertinib Monotherapy | Osimertinib + Chemotherapy | Difference | | |
| (0 [best] to 100 [worst])<br><br>Follow-up: Week 52 | | | | | | | osimertinib + chemotherapy on the Coughing Symptoms Subscale of the EORTC QLQ-LC13 at Week 52, compared to osimertinib monotherapy. |
| Pain in Chest Subscale of the EORTC QLQ-LC13<br>(0 [best] to 100 [worst])<br><br>Follow-up: Week 52 | 557 (1 RCT) | NR | -7.03 | -6.65 (-8.92 to -4.38) | 0.38 (-2.96 to 3.72) | Very Low[d] | The evidence is uncertain about the effect of osimertinib + chemotherapy on the Pain in Chest Subscale of the EORTC QLQ-LC13 at Week 52, compared to osimertinib monotherapy. |
| Dyspnea Symptom Subscale of the EORTC QLQ-LC13<br>(0 [best] to 100 [worst])<br><br>Follow-up: Week 52 | 557 (1 RCT) | NR | -7.49 | -3.92 (-5.93 to -1.91) | 3.57 (0.65 to 6.48) | Very Low[e] | The evidence is uncertain about the effect of osimertinib + chemotherapy on the Dyspnea Symptom Subscale of the EORTC QLQ-LC13 at Week 52, compared to osimertinib monotherapy. |
| Global Health Status/QoL of the EORTC QLQ-C30<br>(0 [worst] to 100 [best])<br><br>Follow-up: Week 52 | 557 (1 RCT) | NR | 9.25 | 5.34 (3.17 to 7.51) | -3.91 (-7.04 to -0.77) | Very Low[f] | The evidence is uncertain about the effect of osimertinib + chemotherapy on the Global Health Status/QoL of the EORTC QLQ-LC13 at Week 52, compared to osimertinib monotherapy. |
| **Harms, Safety Analysis Set (Data Cut-off Date: April 3, 2023)** | | | | | | | |
| Anemia of Grade 3 or higher | 551 (1 RCT) | Osimertinib + chemotherapy: 199 per 1,000<br>Osimertinib monotherapy: 4 per 1,000 | | | | High[g] | Osimertinib + chemotherapy result in an increase in anemia of Grade 3 or higher, |

| Outcome and follow-up | Patients (studies), N | Relative Effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Osimertinib Monotherapy | Osimertinib + Chemotherapy | Difference | | |
| | | | | | | | compared to osimertinib monotherapy. |
| SAEs | 551 (1 RCT) | Osimertinib + chemotherapy: 377 per 1,000<br>Osimertinib monotherapy: 193 per 1,000 | | | | High[g] | Osimertinib + chemotherapy result in an increase in SAEs, compared to osimertinib monotherapy. |
| Discontinuation of any treatment due to AEs | 551 (1 RCT) | Osimertinib + chemotherapy: 478 per 1,000<br>Osimertinib monotherapy: 62 per 1,000 | | | | High[g] | Osimertinib + chemotherapy result in an increase in discontinuation of any treatment due to AEs, compared to osimertinib monotherapy. |
| Deaths | 551 (1 RCT) | Osimertinib + chemotherapy: 65 per 1,000<br>Osimertinib monotherapy: 29 per 1,000 | | | | Moderate[h] | Osimertinib + chemotherapy likely result in an increase in deaths, compared to osimertinib monotherapy. |
| ILD/pneumonitis[i] | 551 (1 RCT) | Osimertinib + chemotherapy: 33 per 1,000<br>Osimertinib monotherapy: 36 per 1,000 | | | | Moderate[h] | Osimertinib + chemotherapy likely result in no or little difference in ILD/pneumonitis, compared to osimertinib monotherapy. |
| Cardiac failure | 551 (1 RCT) | Osimertinib + chemotherapy: 91 per 1,000<br>Osimertinib monotherapy: 36 per 1,000 | | | | Moderate[h] | Osimertinib + chemotherapy likely result in an increase in cardiac effects, compared to osimertinib monotherapy. |

Notes: The start point for the study design of FLAURA2 (i.e., RCT) was high certainty. 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] Certainty was not rated down for risk of bias despite uncertainty about whether the proportional hazard assumption was met. Although the survival curves crossed over at earlier time points, there was clear separation at later time points. Indirectness was not rated down as the differences between patients in the indication and patients in the pivotal trial were not considered sufficient by the clinical experts consulted by the review team to result in important differences in the observed effect. Rated down 2 levels for very serious imprecision due to the following reasons. An empirically derived and validated between group MID for OS was not identified. According to the clinical experts consulted by the review team, a between-group difference in the probability of being alive between 5% and 10% might be clinically meaningful, and a difference of 10% or greater would indicate clinical significance. At 24 months, the point estimate of the between-group difference was between 5% and 10%, and the 95% CI for

the between-group difference crossed both 5% and 10%, which indicated the possibility of both benefit and no meaningful benefit. In addition, the OS data were not mature as of January 8, 2024 (40.6% maturity).

[b] Certainty was not rated down for risk of bias despite uncertainty about whether the proportional hazard assumption was met. Although the survival curves crossed over at earlier time points, there was clear separation at later time points. Indirectness was not rated down as the differences between patients in the indication and patients in the pivotal trial were not considered sufficient by the clinical experts consulted by the review team to result in important differences in the observed effect. Rated down 2 levels for very serious imprecision due to the following reasons. An empirically derived and validated between group MID for OS was not identified. According to the clinical experts consulted by the review team, a between-group difference in the probability of being alive between 5% and 10% might be clinically meaningful, and a difference of 10% or greater would indicate clinical significance. At 36 months, the point estimate of the between-group difference was greater than 10%, however, this was based on a large degree of uncertainty from few events and a high percentage of censoring (approximately 40% per group) between Month 33 and Month 36. Moreover, the 95% CI for the between-group difference crossed both 5% and 10%, which indicated the possibility of both benefit and no meaningful benefit. In addition, the OS data were not mature as of January 8, 2024 (40.6% maturity).

[c] Risk of bias was not rated down. Indirectness was not rated down as the differences between patients in the indication and patients in the pivotal trial were not considered sufficient by the clinical experts consulted by the review team to result in important differences in the observed effect. Rated down 1 level for serious imprecision. An empirically derived and validated between group MID for PFS was not identified. According to the clinical experts consulted by the review team, a between-group difference of 10% or greater in the probability of being progression free would indicate clinical significance. The 95% CI for the between-group difference included 10%, which indicated the possibility of both benefits and no meaningful benefit.

[d] Rated 1 level down for risk of bias Similarly due uncertainty associated with missingness in data. For EORTC QLQ-LC13 assessment at Week 52, out of 279 patients in the osimertinib + chemotherapy group, 221 forms were expected, and 179 forms were received and evaluated (compliance rate: 81%, 179/221). It remains unclear about the type of data missing (e.g., missing completely at random, missing at random, or missing not at random) and how the missingness in data would affect the HRQoL assessment. The risk of performance bias associated to the open-label design and the subjective nature of the measure was considered relatively low as there was no evidence in the data indicating knowledge of treatment assignment affected the results. Indirectness was not rated down as the differences between patients in the indication and patients in the pivotal trial were not considered sufficient by the clinical experts consulted by the review team to result in important differences in the observed effect. Rated down 2 level for very serious imprecision. An empirically derived and validated between group MID for the Coughing Symptoms and Chest Pain subscales of the EORTC QLQ-LC13 was not identified. The clinical experts consulted by the review team were uncertain of what the exact threshold for clinical importance would be, therefore the null was used as the threshold for clinical significance. As the 95% CI of the between-group difference included the null or 0, indicating the possibility of both benefit and little or no difference.

[e] Rated 1 level down for risk of bias due to uncertainty associated with missingness in data. For EORTC QLQ-LC13 assessment at Week 52, out of 279 patients in the osimertinib + chemotherapy group, 221 forms were expected, and 179 forms were received and evaluated (compliance rate: 81%, 179/221). It remains unclear about the type of data missing (e.g., missing completely at random, missing at random, or missing not at random) and how the missingness in data would affect the HRQoL assessment. The risk of performance bias associated to the open-label design and the subjective nature of the measure was considered relatively low as there was no evidence in the data indicating knowledge of treatment assignment affected the results. Indirectness was not rated down as the differences between patients in the indication and patients in the pivotal trial were not considered sufficient by the clinical experts consulted by the review team to result in important differences in the observed effect. Rated down 2 level for very serious imprecision. An empirically derived and validated between group MID for the Dyspnea Symptom Subscale of the EORTC QLQ-LC13 was not identified. The clinical experts consulted by the review team were uncertain of what the exact threshold for clinical importance would be, therefore the null was used as the threshold for clinical significance. The lower bound of the 95% CI was above the null but very close to it, suggesting magnitude of the effect was imprecisely estimated.

[f] Rated 1 level down for serious risk of bias due to uncertainty associated with missingness in data. For EORTC QLQ-C30 assessment at Week 52, out of 279 patients in the osimertinib + chemotherapy group, 230 forms were expected, and 180 forms were received and evaluated (compliance rate: 78.3%, 180/230). It remains unclear about the type of data missing (e.g., missing completely at random, missing at random, or missing not at random) and how the missingness in data would affect the HRQoL assessment. The risk of performance bias associated to the open-label design and the subjective nature of the measure was considered relatively low as there was no evidence in the data indicating knowledge of treatment assignment affected the results. Indirectness was not rated down as the differences between patients in the indication and patients in the pivotal trial were not considered sufficient by the clinical experts consulted by the review team to result in important differences in the observed effect. Rated down 2 level for very serious imprecision. An 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 review estimated the MID for the scale may be 5 points or greater in patients with lung cancer, and 5 points were adopted as MID for this assessment. The between group estimate is less than 5 points at week 52. The upper bound of the 95% CI crosses the null. Therefore, estimate includes both trivial benefit and no benefit.

[g] Risk of bias was not rated down. Indirectness was not rated down as the differences between patients in the indication and patients in the pivotal trial were not considered sufficient by the clinical experts consulted by the review team to result in important differences in the observed effect. Imprecision was not rated down.

[h] Risk of bias was not rated down. Indirectness was not rated down as the differences between patients in the indication and patients in the pivotal trial were not considered sufficient by the clinical experts consulted by the review team to result in important differences in the observed effect. Rated down 1 level due to relatively smaller numbers of events.

[i] Included the following MedDRA Preferred Terms: interstitial lung disease, pneumonitis, acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, idiopathic pulmonary fibrosis, lung disorder, organizing pneumonia, pulmonary toxicity, and pulmonary fibrosis.

AE = adverse event; CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer - Quality of Life Questionnaire - Core 30; EORTC QLQ-LC13 = European Organization for Research and Treatment of Cancer - Quality of Life Questionnaire - Lung Cancer Module; FAS = full analysis set; HRQoL = health related quality of life; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; MID = minimal important difference; MMRM = mixed-effects model for repeated measures; NR = not reported; osimertinib + chemotherapy = osimertinib + in combination with pemetrexed and platinum-based chemotherapy; RCT = randomized controlled trial; SAE = serious adverse event

## Economic Evidence

Cost and Cost-Effectiveness

### Table 4: Summary of Economic Evaluation

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis<br>Markov model |
| **Target population** | Patients with locally advanced (not amenable to curative therapies), or metastatic NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations |
| **Treatment** | Osimertinib in combination with pemetrexed and platinum-based chemotherapy |
| **Dose regimen** | Osimertinib plus chemotherapy:<br>• Osimertinib: 80 mg orally once daily until treatment discontinuation.<br>• Chemotherapy:<br>  ○ Induction Phase:<br>  ▪ Cisplatin: 75 mg/m² via IV infusion on Day 1 of each 21-day cycle (4 cycles) *or* Carboplatin: AUC 5 via IV infusion on Day 1 of each 21-day cycle (4 cycles).<br>  ▪ Pemetrexed: 500 mg/m² via IV infusion on Day 1 of each 21-day cycle (4 cycles).<br>  ○ Maintenance Phase:<br>  ▪ Pemetrexed: 500 mg/m² via IV infusion every 21 days. |
| **Submitted price** | Per tablet (80 mg), $322.13 |
| **Submitted treatment cost** | The 21-day per patient cost of osimertinib plus chemotherapy is $10,704 during the induction phase (assuming a 50:50 split between Cisplatin and Carboplatin) and $10,114 during the maintenance phase. |
| **Comparator** | Osimertinib monotherapy (80 mg once daily) |
| **Perspective** | Canadian publicly funded health care payer |
| **Outcomes** | QALYs, LYs |
| **Time horizon** | Lifetime (15 years) |
| **Key data source** | FLAURA2 trial: Multinational, open-label, randomized phase III trial evaluating the efficacy of osimertinib with or without pemetrexed and platinum-based chemotherapy |
| **Submitted results** | ICER = $146,769 per QALY gained (incremental costs = $59,009; incremental QALY = 0.40) |
| **Key limitations** | • The long-term impact of osimertinib plus chemotherapy on OS is uncertain. OS was estimated from a post-hoc analysis of the FLAURA2 trial, which introduces uncertainties into the economic model. These uncertainties, compounded by incomplete OS data (lack of mature OS data) and the limited ability of the FLAURA2 trial's surrogate endpoints like TTP and PPS to predict long-term survival outcomes, make the model's predictions of long-term survival difficult to interpret.<br>• During the on-trial period of the model, OS was lower among patients receiving osimertinib plus chemotherapy than osimertinib monotherapy, which reflected the results of FLAURA2. The long-term survival benefits of osimertinib plus chemotherapy were all generated through extrapolation beyond the period for which observational evidence exists. In addition to the uncertainty created by extrapolation, this pattern of results could suggest that "sicker" patients may experience mortality due to chemotherapy AEs, leaving "healthier" patients to experience the long-term survival benefit of the treatment. Assumptions regarding patient characteristics determining chemotherapy tolerance likely favored combination therapy, potentially introducing a bias that favours osimertinib plus chemotherapy. |

| Component | Description |
|---|---|
| | • The utility value selected by the sponsor for the progressive disease (PD) state lacks face validity. They assumed a significant drop in health-related quality of life (HRQoL) after disease progression, but FLAURA2 trial data suggested a smaller utility drop. Additionally, using utilities from different sources for PF and PD states limits comparability. |
| **CADTH reanalysis results** | • CADTH conducted a reanalysis that included: selecting an alternative parametric survival extrapolation of TTP; allowing for a difference in PPS between the study arms; selecting an alternative survival extrapolation of PPS for osimertinib plus chemotherapy; and, using utility estimates from FLAURA2 for both PF and PD states.<br>• In the CADTH base case, the ICER for osimertinib plus chemotherapy relative to osimertinib monotherapy was $235,123 per QALY gained (incremental costs = $57,897; incremental QALYs = 0.25).<br>• Due to the cost of chemotherapy and the presence of osimertinib in both modeled treatment cohorts, no price reduction could be calculated that resulted in osimertinib plus chemotherapy being cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. |

ICER = incremental cost-effectiveness ratio; HRQoL = health-related quality of life; LY = life-year; PD = Progressed disease; PF = Progression free; PPS = Post progression survival; QALY= quality-adjusted life-year; TTP = Time to treatment discontinuation

## Budget Impact

CADTH did not conduct a base-case analysis, as the sponsor's submission provided an adequate presentation of the budget impact for osimertinib. The sponsor's base case suggested a 3-year budgetary impact of $7,130,721. However, CADTH noted that the estimates of public drug plan coverage were uncertain. CADTH presented a scenario analysis to test the impact of 100% drug plan coverage on the estimated budget impact. The scenario analysis resulted in a 3-year budgetary impact of $9,230,999.

## pERC Information

### Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

### Meeting date: August 14, 2024

### Regrets:

Two expert committee members did not attend.

### Conflicts of interest:

None