Canadian Journal of Health Technologies

Canada's Drug Agency
L'Agence des médicaments du Canada

January 2025 Volume 5 Issue 1

Drugs Health Technologies Health Systems

Reimbursement Review

Osimertinib (Tagrisso)

Sponsor: AstraZeneca Canada Inc.
Therapeutic area: Non–small cell lung cancer

Table of Contents

Clinical Review

List of Tables

List of Figures

Abbreviations

AE adverse event

AJCC American Joint Committee on Cancer

BICR blinded independent central review

CI confidence interval

CNS central nervous system

EGFRm EGFR–mutated

EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

EORTC QLQ-LC13 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module

ex19del exon 19 deletion

GRADE Grading of Recommendations Assessment, Development, and Evaluation

HR hazard ratio

HRQoL health-related quality of life

ILD interstitial lung disease

L858R L858R substitution

LCC Lung Cancer Canada

MID minimal importance difference

NC not calculable

NSCLC non–small cell lung cancer

OH-CCO Ontario Health (Cancer Care Ontario)

OS overall survival

PFS progression-free survival

PPS post-progression survival

QoL quality of life

RCT randomized controlled trial

RECIST Response Evaluation Criteria in Solid Tumors

RECIST 1.1 Response Evaluation Criteria in Solid Tumors Version 1.1

SAE serious adverse event

TKI tyrosine kinase inhibitor

TSST time to second subsequent therapy

TTP time to progression

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Background Information of Application Submitted for Review

Item	Description
Drug product	Osimertinib (Tagrisso) tablets, 40 mg and 80 mg (as osimertinib mesylate), oral
Sponsor	AstraZeneca Canada Inc.
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
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Priority review and Project Orbis
NOC date	July 10, 2024
Recommended dose	80 mg tablet taken orally once a day

NOC = Notice of Compliance; NSCLC = non–small cell lung cancer.

Source: Sponsor's Summary of Clinical Evidence[1] and product monograph.[2]

Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths in Canada.[3,4] 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.[4] It is estimated that 1 in 21 Canadians (4.8%) will die from lung cancer.[4] Lung cancer is classified into non–small cell lung cancer (NSCLC) or small cell lung cancer, with NSCLC accounting for approximately 88% of cases in Canada.[3] Approximately half of all lung cancer cases in Canada are stage I to III at diagnosis, defined by the American Joint Committee on Cancer (AJCC) staging criteria.[3] Advanced disease, as defined by the AJCC, includes stage IV (metastatic) and unresectable stage IIIB and IIIC (locally advanced) cancer. Approximately 15% of patients in Canada with NSCLC have an EGFR-activating mutation in the region encoding the tyrosine kinase domain.[5-7] EGFR mutations are more frequently observed in never-smokers, people of Asian ethnicity, patients with adenocarcinoma, and females.[5,8] The most common EGFR mutations are the exon 19 deletion (ex19del) and L858R substitution (L858R).[6,7] A common feature of EGFR–mutated (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 of diagnosis.[9] Brain metastases are associated with a decreased quality of life (QoL) and poor prognosis, and are a significant cause of cancer-related mortality.[10,11]

For patients diagnosed with locally advanced or metastatic NSCLC who harbour EGFRm (i.e., an ex19del 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 noneligible EGFR mutations that cannot be treated with osimertinib.[7]

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of osimertinib (oral tablets, 40 mg and 80 mg) in combination with pemetrexed and platinum-based chemotherapy, for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations. Osimertinib has been previously reviewed by the review team.

Perspectives of Patients, Clinicians, and Drug Programs

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

Patient Input

Two patient groups, Lung Cancer Canada (LCC) and the Lung Health Foundation (formerly the Ontario Lung Association), provided input for osimertinib in combination with pemetrexed and platinum-based chemotherapy (osimertinib plus chemotherapy) for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations. Patient input was gathered from interviews and surveys, conducted in January 2021 and October 2023 by the Lung Health Foundation, and in December 2023 by LCC. The Lung Health Foundation conducted 2 interviews and gathered 15 responses from an online survey, and 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 has negative impacts on their day-to-day life, affecting their ability to participate in leisure activities and hobbies, use stairs, shop, and travel. Family members and caregivers of those living with lung cancer shared the same psychosocial burdens described by patients in this input. In addition, LCC reported that patients living with lung cancer have repeatedly stated in interviews that they desire a treatment that can improve their QoL while also effectively managing their disease.

Respondents from the Lung Health Foundation mentioned some benefits experienced with the currently available treatments, such as reduced coughing, 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, although chemotherapy and radiation may be clinically beneficial, they come with well-documented side effects that often reduce a patient's QoL. The input added that osimertinib as a monotherapy has been 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, a full and worthwhile QoL, manageable side effects, longer lifespans, independence and functionality that minimizes the burden on their caregivers and loved ones, delayed disease progression, and the ability to settle into long-term management for improved survivorship.

Clinician Input

Input From Clinical Experts Consulted for This Review

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 ex19del or L858R mutations included improving overall survival (OS), controlling disease progression (including prevention and disease control of CNS metastasis), and maintaining QoL. The clinical experts consulted by the review team noted that needs are not met in patients who are younger, who present with significant disease burden, or who have CNS metastases.

The clinical experts consulted by the review team noted that osimertinib plus chemotherapy may be offered as an alternative to osimertinib monotherapy in the first-line setting to patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations. The clinical experts consulted by the review team also noted that osimertinib monotherapy should be a first-line treatment option. The clinical experts consulted by the review team further noted that if the osimertinib plus chemotherapy was adopted in the first line with maintenance pemetrexed, second-line treatment options would include rechallenge with platinum doublet chemotherapy or docetaxel.

The clinical experts consulted by the review team noted that osimertinib plus chemotherapy may preferentially be considered in younger patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations and in patients with CNS metastases. However, the clinical experts noted that older patients with fewer disease-related symptoms may choose not to receive osimertinib plus chemotherapy because of the additive toxicity associated with the combination.

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 patient symptoms and conditions, radiographic imaging results, toxicities, and 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 Response Evaluation Criteria in Solid Tumors (RECIST) may not necessarily indicate the deficiency of treatment, and 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 centre, academic institution, or

community setting, and patients should be treated by medical oncologists well versed in the management of EGFR TKIs and platinum chemotherapy toxicity.

Clinician Group Input

Clinician group input on the review of osimertinib plus chemotherapy for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations was received from 2 clinician groups: the Lung Cancer Drug Advisory Committee of Ontario Health (Cancer Care Ontario) (OH-CCO) and the LCC Medical Advisory Committee. A total of 28 clinicians provided input for this review.

The OH-CCO input 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 are not curative. Both clinician groups emphasized need for improved therapies that result in longer control of the cancer, better QoL, and longer survival. Similar to the clinical experts consulted by the review team, the clinician groups mentioned the need for therapies that target specific patient populations, i.e., young patients and those with brain metastases. Both clinician groups noted that a treatment for brain metastases in EGFR-driven lung cancer is an urgent unmet need.

Both clinician groups noted that the combination of osimertinib and chemotherapy would be an option in patients with NSCLC with sensitizing EGFR mutations. The OH-CCO group emphasized the need for OS data before drawing any conclusions regarding the shift in the current treatment paradigm. They also mentioned that the addition of platinum-based chemotherapy to osimertinib is associated with an increase in chemotherapy-associated toxicities, which results in more inconvenience to patients, who are required to attend cancer centres more frequently because of the need for IV therapy. Similar to the input from the clinical experts consulted by the review team, both clinician groups noted that single-drug osimertinib would remain an option in first-line therapy.

The OH-CCO emphasized that all patients who have classic EGFR mutations would be suitable for osimertinib therapy if they can tolerate and have not had prior adjuvant osimertinib within the last several months. The group also mentioned that patients suitable for receiving the additional chemotherapy 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 input from 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 Reimbursement Review process. The following were identified as key factors that could potentially affect the implementation of a recommendation for osimertinib plus chemotherapy:

- relevant comparators
- consideration for initiation of therapy
- consideration of discontinuation of therapy
- consideration for prescribing of therapy
- generalizability
- funding algorithm
- care provision issues
- system and economic issues.

Clinical Evidence

Systematic Review

Description of Studies

One ongoing phase III, open-label randomized controlled trial (RCT), FLAURA2 (N = 557, including 13 patients in Canada), was included in the systematic literature search conducted by the sponsor. The FLAURA2 trial enrolled adult patients who were diagnosed with pathologically confirmed nonsquamous NSCLC that was locally advanced (clinical stage IIIB or IIIC), metastatic (clinical stage IVA or IVB), or recurrent (as defined by version 8 of the International Association for the Study of Lung Cancer *Staging Manual in Thoracic Oncology*) and whose tumours harboured an ex19del or L858R mutation, either alone or in combination with other EGFR mutations. Patients were randomized to the osimertinib plus chemotherapy group (n = 279) and the osimertinib monotherapy group (n = 278), stratified by race, WHO Performance Status, and methods used for tissue testing. The primary objective was to compare the treatment effect between osimertinib plus chemotherapy versus osimertinib monotherapy, measured by progression-free survival (PFS) according to investigator assessment. Other efficacy and safety outcomes included OS, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module (EORTC QLQ-LC13), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), and harms (i.e., adverse events [AEs], serious adverse events [SAEs], withdrawal, deaths, and 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%), an exon 19 deletion (53.1% by central cobas tissue test), and metastatic NSCLC at baseline (96.2%).

Efficacy Results

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

Overall Survival

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 plus chemotherapy group and 126 OS events (45.3%) in the osimertinib monotherapy group. The hazard ratio (HR) for OS was 0.75 (95% confidence interval [CI], 0.57 to 0.97). The differences in the probability of being alive between osimertinib plus chemotherapy and osimertinib monotherapy at 24 and 36 months were 7.6 (95% CI, [redacted] to [redacted]) and 13.5% (95% CI, [redacted] to [redacted]), respectively. The median OS was 36.7 months in the osimertinib monotherapy group but it was not reached in the osimertinib plus 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 after randomization.

PFS According to Investigator Assessment

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

Results for PFS according to a blinded independent central review (BICR) assessment were generally consistent with the PFS results according to investigator assessment. Analysis of concordance between investigator and BICR assessment of PFS showed that there was an 82.1% agreement on progressions and nonprogressions in the osimertinib plus chemotherapy group, and a 75.6% agreement on progressions and nonprogressions 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 plus chemotherapy group and the osimertinib monotherapy group favoured osimertinib plus 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 plus 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 plus chemotherapy (100%) and patients treated with osimertinib monotherapy (97.5%). However, a higher proportion of patients treated with osimertinib plus chemotherapy experienced the most common AEs (those reported in ≥ 20% patients in either treatment group) compared with those treated with osimertinib monotherapy. Such AEs included anemia (46.4% versus 8.0%, respectively), nausea (43.1% versus 10.2%, respectively), and neutropenia (24.6% versus 3.3%). Moreover, a higher proportion of patients treated with osimertinib plus chemotherapy experienced AEs of grade 3 or higher compared with the proportion of patients treated with osimertinib monotherapy (63.8% versus 27.3%, respectively). The most common AE of grade 3 or higher in those treated with osimertinib plus chemotherapy was anemia (19.9%).

Higher percentages of patients in the osimertinib plus 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 plus chemotherapy group and 6.2% of the patients receiving osimertinib monotherapy. Within the osimertinib plus chemotherapy group, 45.3% of the patients discontinued chemotherapy, of whom 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 plus chemotherapy group and 2.9% of the patients in the osimertinib monotherapy group. Of the patients in the osimertinib plus chemotherapy group 1.1% died due to pulmonary embolism, 1.11% due to pneumonia, and 0.7% due to cardiac failure.

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

Critical Appraisal

The FLAURA2 trial used central randomization and concealed patient allocation during the randomization process.[12] Overall, the baseline characteristics were balanced between the treatment groups. Generally, no serious concerns were identified in the protocol amendments and protocol deviations. As an open-label trial, investigators and patients were aware of the assigned treatment.[12] The primary outcome in the FLAURA2 trial was PFS according to investigator assessment, which was susceptible to detection bias because of the open-label design. However, the potential risk of detection bias in PFS according to investigator assessment was considered relatively low by the review team because results were consistent with those of PFS according to BICR assessment, and the analysis of concordance between PFS according to investigator and PFS according to BICR showed an acceptable agreement. Similarly, for health-related quality of life (HRQoL) outcomes (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 that 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, 230 of 279 patients in the osimertinib plus chemotherapy group were expected to return a form, but only 180 forms were received and evaluated, for a compliance rate of 78.3%. It remains unclear how the missingness in data would affect the HRQoL assessment, resulting in increased uncertainty. The Kaplan-Meier curves for OS obtained from the April 3, 2023, data cut-off crossed several times, which violated the proportional hazards assumption for OS and affected 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 of January 8, 2024) was observed during visual inspection of the Kaplan-Meier curves (i.e., they did not separate until approximately 16 months after randomization). According to the clinical experts consulted by the review team, delayed separation of survival curves is acceptable in clinical practice as it is often seen in patients receiving a combination therapy including chemotherapy. However, the late divergence of survival curves may have implications for the statistical analysis used in the FLAURA2 trial (i.e., whether the proportional hazards assumption was violated), which introduced uncertainty to the OS evidence. When 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).

The generalizability of the FLAURA2 trial is subject to several considerations. The clinical experts consulted by the review team noted that the patient eligibility criteria of the FLAURA2 trials were appropriate overall in clinical trials involving patients with NSCLC and aligned with the selection criteria used in treatment settings in Canada when identifying suitable candidates for osimertinib plus chemotherapy. However, the clinical experts consulted by the review team noted that, in real-world settings, patients are generally sicker in terms of performance status. Second, the FLAURA2 trial did not allow eligible patients to have prior treatment with an EGFR TKI. Also, the FLAURA2 trial required eligible patients to be off other adjuvant and neoadjuvant therapies (e.g., chemotherapy, radiotherapy, immunotherapy, biologic therapy, and investigational drugs) at least 12 months before the development of recurrent disease. According to the clinical experts consulted by the review team, because osimertinib monotherapy has become a first-line treatment for EGFRm, patients who had received a prior EGFR TKI should also be considered for osimertinib plus chemotherapy. Third, the histology type of most patients enrolled in the FLAURA2 trial (> 98% for both groups) was adenocarcinoma. According to the clinical experts consulted by the review team, findings from the FLAURA2 trial could still be generalizable to patients with other histology types (e.g., adenosquamous carcinoma) because it is the existence of the driving mutation that determines whether osimertinib should be used. The clinical experts consulted by the review team noted that it is plausible that the treatment effects of osimertinib plus chemotherapy would likely not differ among patients with the same driving mutation but a 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, Grading of Recommendations Assessment, Development, and Evaluation (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.[13,14]

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 the 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 estimate of the minimal important difference (MID). The MID for the Global Health Status/QoL of EORTC QLQ-C30 was based on estimates published in the literature.[15] 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)
- HRQoL 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, and 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 2 presents the GRADE summary of findings for osimertinib plus chemotherapy versus osimertinib monotherapy in patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations.

Table 2: Summary of Findings for Osimertinib Plus Chemotherapy vs. Osimertinib Monotherapy for Patients With Locally Advanced (Not Amenable to Curative Therapies) or Metastatic NSCLC Whose Tumours Have EGFR Exon 19 Deletions or L858R Substitution Mutations

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Osimertinib monotherapy	Osimertinib + chemotherapy (95% CI)	Difference (95% CI)		
Overall survival — randomization phase, FAS (data cut-off date: January 8, 2024)							
Probability of being alive at 24 months 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 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 according to investigator assessment — randomization phase, FAS (data cut-off date: June 1, 2021)							
Probability of being progression-free at 12 months 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 results in an increase in the probability of being progression-free at 12 months, compared to osimertinib monotherapy

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Osimertinib monotherapy	Osimertinib + chemotherapy (95% CI)	Difference (95% CI)		
Probability of being progression-free at 24 months 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 results 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 (0 [best] to 100 [worst]) Follow-up: week 52	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 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 (0 [best] to 100 [worst]) 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 EORTC QLQ-LC13 at week 52, compared to osimertinib monotherapy
Dyspnea symptom subscale of the EORTC QLQ-LC13 (0 [best] to 100 [worst]) 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 EORTC

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Osimertinib monotherapy	Osimertinib + chemotherapy (95% CI)	Difference (95% CI)		
							QLQ-LC13 at week 52, compared to osimertinib monotherapy
Global Health Status/QoL of the EORTC QLQ-C30 (0 [worst] to 100 [best]) 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 regarding the effect of osimertinib + chemotherapy on the Global Health Status/QoL of 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 Osimertinib monotherapy: 4 per 1,000				High[g]	Osimertinib + chemotherapy results in an increase in anemia of grade 3 or higher, compared to osimertinib monotherapy
SAEs	551 (1 RCT)	Osimertinib + chemotherapy: 377 per 1,000 Osimertinib monotherapy: 193 per 1,000				High[g]	Osimertinib + chemotherapy results 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 Osimertinib monotherapy: 62 per 1,000				High[g]	Osimertinib + chemotherapy results in an increase in discontinuation of any treatment due to AEs, compared to osimertinib monotherapy

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Osimertinib monotherapy	Osimertinib + chemotherapy (95% CI)	Difference (95% CI)		
Deaths	551 (1 RCT)	Osimertinib + chemotherapy: 65 per 1,000 Osimertinib monotherapy: 29 per 1,000				Moderate[h]	Osimertinib + chemotherapy likely results in an increase in deaths, compared to osimertinib monotherapy
ILD or pneumonitis[i]	551 (1 RCT)	Osimertinib + chemotherapy: 33 per 1,000 Osimertinib monotherapy: 36 per 1,000				Moderate[h]	Osimertinib + chemotherapy likely results in no or little difference in ILD or pneumonitis, compared to osimertinib monotherapy
Cardiac failure	551 (1 RCT)	Osimertinib + chemotherapy: 91 per 1,000 Osimertinib monotherapy: 36 per 1,000				Moderate[h]	Osimertinib + chemotherapy likely results in an increase in cardiac effects, compared to osimertinib monotherapy

AE = adverse event; CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13 = European Organisation 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; MID = minimal important difference; NR = not reported; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy; NSCLC = non–small cell lung cancer; PFS = progression-free survival; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus.

Notes: The start point for the study design of the FLAURA2 trial (i.e., an 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 hazards 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 overall survival was not identified. According to the clinical experts consulted by the review team, a between-group difference in the probability of being alive of between 5% and 10% may 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 a benefit and no meaningful benefit. In addition, the overall survival 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 hazards 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 overall survival was not identified. According to the clinical experts consulted by the review team, a between-group difference in the probability of being alive of between 5% and 10% may 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. The 95% CI for the between-group difference crossed both 5% and 10%, indicating the possibility of both a benefit and no meaningful benefit. In addition, the overall survival data were not mature as of January 8, 2024 (40.6% maturity).

[c]The 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 due uncertainty associated with missingness in data. For EORTC QLQ-LC13 assessments at week 52, out of 279 patients in the osimertinib plus chemotherapy group, 221 forms were expected, and 179 forms were received and evaluated, for a compliance rate of 81%. The type of data missing (e.g., completely at random, at random, or not at random) remains unclear, as does how the missingness in data would affect the HRQoL assessment. The risk of performance bias associated with the open-label design and the subjective nature of the measure was considered relatively low as no evidence in the data indicated that 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 levels 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. Because the clinical experts consulted by the review team were uncertain as to the exact threshold for clinical importance, the null was used as the threshold for clinical significance. The 95% CI of the between-group difference included the null or 0, indicating the possibility of both a 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 assessments at week 52, out of 279 patients in the osimertinib plus chemotherapy group, 221 forms were expected, and 179 forms were received and evaluated, for a compliance rate of 81%. The type of data missing (e.g., completely at random, at random, or not at random) remains unclear, as does how the missingness in data would affect the HRQoL assessment. The risk of performance bias associated with the open-label design and the subjective nature of the measure was considered relatively low as no evidence in the data indicated that 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 levels 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. Because the clinical experts consulted by the review team were uncertain as to the exact threshold for clinical importance, the null was used as the threshold for clinical significance. The lower bound of the 95% CI was greater than but close to the null, suggesting the 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 assessments at week 52, out of 279 patients in the osimertinib plus chemotherapy group, 230 forms were expected, and 180 forms were received and evaluated, for a compliance rate of 78.3%. The type of data missing (e.g., completely at random, at random, or not at random) and how the missingness in data would affect the HRQoL assessment remain unclear. The risk of performance bias associated with the open-label design and the subjective nature of the measure was considered relatively low as no evidence in the data indicated that 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 levels 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 was adopted as the MID for this assessment.[15] The between-group estimate is less than 5 points at week 52. The upper bound of the 95% CI crosses the null. Estimates therefore include both a 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 Medical Dictionary for Regulatory Activities 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.

Sources: FLAURA2 Clinical Study Report[16] and Drug Reimbursement Review sponsor submission.[17]

Conclusions

The pivotal FLAURA2 trial is an ongoing, phase III, open-label RCT comparing the efficacy and safety of osimertinib plus chemotherapy and osimertinib monotherapy in patients with locally advanced, metastatic, or recurrent EGFRm (ex19del or L858R) NSCLC. Overall, efficacy evidence from the FLAURA2 trials suggests that osimertinib plus chemotherapy showed added clinical benefits in OS and PFS in the intention-to-treat trial population, compared with osimertinib monotherapy. Results of these clinically relevant efficacy end points were generally in favour of osimertinib plus chemotherapy over osimertinib monotherapy. Osimertinib plus chemotherapy may result in an increase in the probability of being alive at 24 and 36 months (low certainty) and likely lead to an increase in the probability of being progression-free at 12 and 24 months (moderate certainty), compared to osimertinib monotherapy. Because of the immaturity of the OS data (40.6%) and the fact that the median OS was not reached as of January 8, 2024, uncertainty remains in the OS results. The study subgroup analyses suggested the potential for greater benefit with osimertinib plus chemotherapy versus osimertinib monotherapy in patients with CNS metastases at baseline compared with patients without CNS metastases at baseline. However, uncertainty related to the trial design and analysis of these subgroups (including no formal interaction tests) prevented drawing a definitive conclusion. The review team concluded with moderate to high certainty that the combination use of osimertinib plus chemotherapy is associated with an increased frequency of grade 3 or higher AEs, SAEs, WDAEs, and deaths reported as AEs compared to osimertinib monotherapy.

Introduction

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of osimertinib (oral tablets, 40 mg and 80 mg), 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 L858R substitution mutations.

Disease Background

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following have been summarized and validated by the review team.

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths in Canada.[3,4] Survival rates from lung cancer of all stages and histologies are poor, with an overall 5-year net survival of 22%,[4,18] and only 3% for those diagnosed with stage IV disease.[4] In 2023, it was estimated that 31,000 cases of lung cancer would be diagnosed and 20,600 deaths from lung cancer would occur that year.[4] It is estimated that 1 in 21 Canadians (4.8%) will die from lung cancer.[4]

Lung cancer is classified into NSCLC or small cell lung cancer, with NSCLC accounting for approximately 88% of cases in Canada.[3] NSCLC is further classified into 3 main histologic subtypes: adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma.[3] To determine a patient's prognosis and treatment,

NSCLC is staged using the AJCC criteria, which involves tumour-node-metastasis classification of the disease based on the size and spread of the primary tumour, lymph node involvement, and occurrence of metastasis.[19] Approximately half of all lung cancer cases in Canada are stage I to III at diagnosis.[3] Advanced disease as defined by the AJCC, includes stage IV (metastatic) and unresectable stage IIIB and IIIC (locally advanced) patients. NSCLC is often asymptomatic, and patients may live for several years before presentation due to its insidious nature.[20] The most common symptoms include unspecific coughing, chest and shoulder pain, hemoptysis, weight loss, dyspnea, hoarseness, bone pain, fever, and recurring infections with bronchitis and pneumonia.[20,21] Diagnostic procedures include imaging of the lungs, sputum cytology, and tissue biopsy.[22] Approximately one-third of patients with NSCLC have operable disease.[22]

Approximately 15% of Canadians with NSCLC have an EGFR-activating mutation in the region of the genome encoding the tyrosine kinase domain.[5-7] EGFR mutations are more frequently observed in never-smokers, people of Asian ethnicity, patients with adenocarcinoma, and females.[5,8] The most common EGFR mutations are ex19del and L858R.[6,7] A common feature of EGFRm NSCLC is the development of CNS metastases, which are detected in approximately 25% of patients at diagnosis and can affect approximately 50% of all patients within 3 years of diagnosis.[9] Brain metastases are associated with decreased QoL and poor prognosis and are a significant cause of cancer-related mortality.[10,11]

Standards of Therapy

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following have been summarized and validated by the review team.

According to the clinical experts consulted by the review team, the goal of therapy in patients with advanced EGFRm NSCLC is to improve QoL and prolong survival while delaying disease progression.

For patients diagnosed with locally advanced or metastatic NSCLC who harbour EGFR mutations (i.e., ex19del and/or L858R), according to the clinical experts consulted by the review team, the current first-line treatment in Canada is osimertinib, which is a third-generation EGFR TKI. Alternative treatment options in the first-line setting include first- and second-generation EGFR 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.

Osimertinib is the preferred first-line treatment for EGFRm NSCLC based on a Canadian consensus and various provincial guidelines.[7,23] 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 noneligible EGFR mutations that cannot be treated with osimertinib, as the Canadian consensus[7] states "… gefitinib and erlotinib are not recommended in the first-line setting unless access to osimertinib is limited or unless they are combined with other drugs."

The clinical experts consulted by the review team noted that amivantamab plus lazertinib could also be a first-line treatment option for patients with locally advanced or metastatic NSCLC who harbour EGFR mutations. However, amivantamab plus lazertinib is currently not available in Canada.

Drug Under Review

Key characteristics of osimertinib in combination with pemetrexed and platinum-based chemotherapy are summarized in Table 3, along with other treatments available for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations. The recommended dose of osimertinib is 80 mg, once a day with pemetrexed and platinum-based chemotherapy.[2]

Osimertinib, is an irreversible TKI of both an EGFRm and T790M resistance mutation that has limited activity against wild-type EGFR.[24] Osimertinib can readily cross the intact blood-brain barrier compared with earlier-generation EGFR TKIs.[25-27]

Table 3: Key Characteristics of Osimertinib Plus Chemotherapy and Osimertinib Monotherapy

Characteristic	Osimertinib + chemotherapy	Osimertinib monotherapy
Mechanism of action	An irreversible TKI of both EGFRm and T790M resistance mutation that has limited activity against wild-type EGFR	Same
Indication[a]	For the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or L858R substitution mutations	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 L858R substitution mutations (either alone or in combination with other EGFR mutations)
Route of administration	For osimertinib: oral; for pemetrexed + platinum-based chemotherapy: IV	Oral
Recommended dose	For osimertinib: 80 mg tablet taken once a day, in combination with pemetrexed and platinum-based chemotherapy for 4 cycles, followed by osimertinib plus pemetrexed maintenance Dosing of pemetrexed + platinum-based chemotherapy: the recommended dose of pemetrexed is 500 mg/m^2 administered over 10 minutes on day 1 of each 21-day cycle The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours beginning approximately 30 minutes after completion of the pemetrexed administration; patients should receive appropriate hydration before and/or after receiving cisplatin The recommended dose of carboplatin is 5 mg/mL/min (AUC 5)	80 mg tablet taken once a day
Serious adverse effects or safety issues	**Osimertinib:** Interstitial lung disease (e.g., pneumonitis), including fatal cases; QTcF interval prolongation; left ventricular dysfunction and cardiomyopathy	**Osimertinib:** Interstitial lung disease (e.g., pneumonitis), including fatal cases; QTcF interval prolongation;

Characteristic	Osimertinib + chemotherapy	Osimertinib monotherapy
	Chemotherapy **Pemetrexed:** Serious hepatobiliary toxicity and rare cases of fatal hepatic failure; gastrointestinal toxicity such as stomatitis, nausea, vomiting, and diarrhea; suppression of bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia); cases of hypersensitivity, including anaphylaxis; serious renal events, including acute renal failure; interstitial pneumonitis with respiratory insufficiency; rare cases of bullous epidermolysis including Stevens-Johnson syndrome and toxic epidermal necrolysis **Platinum-based** **Cisplatin:** Anaphylactic-like reactions; infections, such as sepsis; myelosupression such as neutropenia, leukopenia, thrombocytopenia; neurotoxicity (leukoencephalopathy; peripheral neuropathy; posterior reversible encephalopathy syndrome); renal toxicity; cardiovascular toxicity, such as venous thromboembolic events and pulmonary embolism **Carboplatin:** Highly toxic drug with a narrow therapeutic index; serious and fatal infections following administration of live or live-attenuated vaccines in patients treated with carboplatin; hypersensitivity reactions; bone marrow suppression; fatal veno-occlusive disease; fatal hemolytic anemia; fatal hemolytic-uremic syndrome	left ventricular dysfunction and cardiomyopathy
Other	**Chemotherapy** **Pemetrexed**: May cause fetal harm when administered to a pregnant patient; contraindicated for concomitant yellow fever vaccine **Cisplatin:** Contraindicated in patients with pre-existing renal impairment and hearing impairment **Carboplatin:** Contraindicated in the following conditions: severe myelosuppression; pre-existing severe renal impairment; history of severe allergic reactions to carboplatin, or other platinum-containing compounds	NA

AUC = area under the concentration-time curve during any dosing interval; EGFRm = EGFR–mutated; NSCLC = non–small cell lung cancer; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy; NA = not applicable; TKI = tyrosine kinase inhibitor.

[a]Health Canada–approved indication.

Sources: Product monographs.[2,28-30]

Perspectives of Patients, Clinicians, and Drug Programs

Patient Group Input

The full patient and clinician group submissions received are available in the consolidated patient and clinician group input document for this review on the project website.

Two patient groups, LCC and the Lung Health Foundation (formerly the Ontario Lung Association), provided input on osimertinib plus chemotherapy for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations. Patient input was gathered from interviews and surveys, conducted in January 2021 and October 2023 by the Lung Health Foundation, and in December 2023 by LCC. The Lung Health Foundation conducted 2 interviews and gathered 15 responses from online survey, while LCC conducted 13 interviews with patients and/or caregivers.

When asked about disease experience and its impact on day-to-day activities, respondents in the Lung Health Foundation input mentioned having varying experiences with their lung cancer diagnosis. Some symptoms and challenges these patients experienced because of their lung cancer were shortness of breath (80%), fatigue (60%), depression (25%), difficulty fighting infection (21%), and chest tightness (14%). Weight loss, diminished appetite, low mood, and challenges with physical and emotional intimacy were also noted by a few respondents. Respondents in this input indicated that the disease has negative impacts on their day-to-day life, affecting their ability to participate in leisure activities and hobbies, use stairs, shop, and travel. 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 their primary need is a treatment that improves their QoL while also managing their disease effectively.

Respondents from the Lung Health Foundation mentioned some benefits experienced with the currently available treatments, such as reduced coughing, 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 input also noted that patients on oral drugs value the flexibility they provide in allowing them to work and travel without restrictions. Some patients from this input reported struggling with lingering side effects. Some of the side effects with medications mentioned in this input were extreme itching affecting sleep, brain fog, fatigue, nausea, vomiting, mood changes, diminished appetite, weight loss, hair loss, anemia, and neuropathy. The input also noted that side effects from chemotherapy severely affected the patients' QoL, ability to work and in some cases, the ability to perform activities of daily living. Respondents who received surgery reported deconditioning and chronic fatigue. Some of the side effects reported from radiation were fatigue, skin changes, hair loss, and tissue scarring. When asked about challenges with access to treatment, the respondents from the Lung Health Foundation reported that they struggled with the cost associated with some treatments. They also found it challenging to navigate the health care system and, in some cases, they were unsure where to go for information and support. The LCC input mentioned that, although chemotherapy and radiation may be clinically beneficial, both come with well-documented side effects that often negatively affect a patient's QoL. The input added that osimertinib as a monotherapy has been 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. Patients in this input also expressed frustration with the speed at which treatments are approved in Canada, compared to other countries. Patients and caregivers perceive that fewer treatment options are available to them and that the drug approval process is a barrier to quick access. When choosing a therapy, some of the most crucial outcomes that patients in the LCC input wanted to have include improved management of their symptoms of EGFR NSCLC, a full and worthwhile QoL, manageable side effects, longer lives, independence and functionality to minimize the burden on their caregivers and loved ones, delayed disease progression, and the ability to settle into long-term management for improved survivorship.

Three patients from the Lung Health Foundation survey had experience with the drug under review. However, it was not clear if these patients were taking the drug as a monotherapy or in combination with chemotherapy. Some benefits reported by the patients include reduced coughing, reduced shortness of breath, improved ability to exercise, and increased participation in daily activities. Some of the side effects experienced on the drug by these patients include fatigue, appetite loss, low energy, nausea, and mild face rash. All 13 respondents from the LCC input had experience with osimertinib, 10 had received first-line and 3 had received second-line treatment. Respondents reported osimertinib to be effective at treating tumours and managing symptoms. Patients reported being able to maintain or improve their QoL, and function while on osimertinib. They also reported some frequent but manageable side effects. The most common side effects that patients interviewed by LCC recalled include diarrhea, muscle pain or spasms, lack of appetite, skin dryness or cracking, and fragile nails.

Clinician Input

Input From Clinical Experts Consulted for This Review

All CDA-AMC review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations.

Unmet Needs

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 ex19del or L858R mutations included improving OS, controlling disease progression, and maintaining QoL. In addition, according to the clinical experts consulted by the review team, prevention and disease control of CNS metastasis are important aspects of the treatment goals. The clinical experts consulted by the review team noted that needs are not met in patients who are younger, present with significant disease burden, or have CNS metastases.

Place in Therapy

The clinical experts consulted by the review team noted that osimertinib plus chemotherapy may be offered as an alternative to osimertinib monotherapy as first-line treatment for patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations. The clinical experts consulted by the review team 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 plus platinum chemotherapy was adopted in the first line with maintenance pemetrexed, second-line treatment options would include rechallenge with platinum doublet chemotherapy or docetaxel.

Patient Population

The clinical experts consulted by the review team noted that osimertinib plus chemotherapy may preferentially be considered in younger patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations. The clinical experts consulted by the review team noted that osimertinib plus chemotherapy may also be offered to patients with CNS metastases. However, according to the clinical experts consulted by the review team older patients with fewer disease-related symptoms may choose not to receive osimertinib plus chemotherapy because of the additive toxicity associated with osimertinib plus chemotherapy (compared to monotherapy).

Assessing the Response Treatment

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 disease progression determined by RECIST would not necessarily result in a change in therapy, and patients may be considered for oligo-progression management with radiotherapy and continue on treatment. Alternatively, the patient and physician may discuss ongoing therapy, acknowledging that there is incomplete disease control. The clinical experts consulted by the review team noted that, in clinical practice patients may continue on osimertinib therapy for several months, even though they have met criteria for RECIST-determined progressive disease, if there is a good tolerance of osimertinib.

Discontinuing Treatment

According to the clinical experts consulted by the review team, overall, the decision to discontinue the therapy should be made jointly by the clinician and patient and be based on a combination of factors, such as patients' symptoms and conditions, radiographic imaging results, toxicities, and laboratory parameters, as well as the balance against clinical benefit for that patient. The clinical experts consulted by the review team noted that it is reasonable to continue treatment as long as there is clinical benefit with respect to the targeted therapy component. In clinical practice, clinically meaningful symptomatic disease progression (rather than progression defined by RECIST) or toxicity would the rationale for stopping therapy.

Prescribing Considerations

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 centre, academic facility,

or community setting. According to the clinical experts consulted by the review team, patients should be treated by medical oncologists who are well versed in the management of EGFR TKIs and platinum chemotherapy toxicity.

Clinician Group Input

This section was prepared by the review team based on the input provided by clinician groups.

Clinician group input on the review of osimertinib plus chemotherapy for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations, was received from 2 clinician groups: the OH-CCO Lung Cancer Drug Advisory Committee and LLC's Medical Advisory Committee. A total of 28 clinicians provided input for this review.

The OH-CCO committee 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 are not curative. Both clinician groups emphasized need for improved therapies that result in longer control of the cancer, better QoL and longer survival. The clinician groups mentioned the need to have therapies targeting specific patient populations, i.e., young patients and those with brain metastases, as did the clinical experts consulted by the review team. Both clinician groups described treatment for brain metastases in EGFR-driven lung cancer as an urgent unmet need.

Both clinician groups noted that the combination of osimertinib with chemotherapy would be an option in patients with NSCLC with sensitizing EGFR mutations. The OH-CCO group highlighted the need for OS data before drawing any conclusion regarding a shift in the current treatment paradigm. They also mentioned that the addition of platinum-based chemotherapy to osimertinib results in more inconvenience to patients due to the increase in chemotherapy-associated toxicities that require patients to attend a cancer centre more frequently for IV therapy. Similar to the clinical experts consulted by the review team, both clinician groups noted that single-drug osimertinib would remain an option in first-line therapy.

The OH-CCO committee pointed out that all patients who have classic EGFR mutations would be suitable for osimertinib therapy if they can tolerate and 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 there is a need for osimertinib plus chemotherapy among younger patients and patients with CNS metastases to gain survival benefits and improve QoL. Both clinician groups agreed that treatment would be discontinued in cases of disease progression or undue toxicity.

Drug Program Input

The drug programs provide input on each drug being reviewed the Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The implementation

questions and corresponding responses from the clinical experts consulted by the review team are summarized in Table 4.

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
The FLAURA-2 trial compared osimertinib-pemetrexed-platinum × 4 cycles followed by osimertinib and pemetrexed maintenance every 3 weeks with osimertinib alone, which is a relevant funded comparator in this setting. Other EGFR TKIs (erlotinib, gefitinib and afatinib) could potentially be used in this setting, but osimertinib is generally preferred, so there is 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	
The FLAURA-2 trial enrolled patients with nonsquamous NSCLC, locally advanced (clinical stage IIIB, IIIC) or metastatic (clinical stage IVA or IVB), or recurrent NSCLC (according to version 8 of the IASLC staging manual), not amenable to curative surgery or radiotherapy. • The vast majority of patients enrolled in the FLAURA2 trial had adenocarcinoma (99% in both arms). Should other histology (e.g., adenosquamous carcinoma) be eligible for this treatment? • 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. The clinical experts indicated that it is plausible that the treatment effects of osimertinib + chemotherapy would likely not differ among patients with the same driving mutation but a different histology. According to the clinical experts consulted by the review team, osimertinib + chemotherapy should therefore be considered for patients with EGFR mutations in the proposed indication regardless of the histology of their lung cancer. According to the clinical experts consulted by the review team, some studies have demonstrated the effects of osimertinib in patients with NSCLC with uncommon EGFR mutations (e.g., L861q). The review team notes that these studies were not included in this submission and have not been reviewed in this report. In addition, the clinical experts consulted by the review team noted that to their knowledge, using osimertinib for patients with NSCLC with these uncommon EGFR mutations is not on-label in Canada.
The FLAURA-2 trial allowed prior adjuvant and neoadjuvant therapies provided that the treatment was completed 12 months before the development of recurrent disease. • What is the appropriate disease-free interval following completion of adjuvant osimertinib during which 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 before the development of recurrent disease is not 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 the clinicians should decide whether a patient with a disease-free interval of less than 6 months would be eligible for osimertinib + chemotherapy.
Considerations for discontinuation of therapy	
The FLAURA2 trial allowed treatment until disease progression or occurrence of unacceptable or clinically significant toxic	Overall, it should be the clinician's decision to discontinue the therapy based on a combination of factors, such as patients'

Drug program implementation questions	Clinical expert response
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. • What are the discontinuation criteria for osimertinib?	symptoms and conditions, radiographic imaging results, toxicities, and laboratory parameters, as well as the balance against clinical benefit for that patient. The clinical experts consulted by the review team noted that continuing on treatment as long as there is clinical benefit with the targeted therapy component is generally 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 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 decisions to stop osimertinib and chemotherapy should be dissociated, and it is not necessary to stop both osimertinib and chemotherapy at the same time.
Generalizability	
Should patients with a 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, a patient should be considered eligible if the patient has a good status in term of being suitable for chemotherapy.
Funding algorithm	
The drug plans noted the following items that may require the development of a provisional funding algorithm: • Drug may change place in therapy of comparator drugs • 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.
As EGFR mutation testing is part of routine clinical practice, 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 has an additional impact on 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.

NSCLC = non–small cell lung cancer; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; RECIST = Response Evaluation Criteria in Solid Tumors; TKI = tyrosine kinase inhibitor; vs. = versus; WHO PS = WHO Performance Status.

Clinical Evidence

The objective of the Clinical Review Report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of osimertinib (oral tablets, 40 mg and 80 mg), 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 ex19del or L858R mutations. The focus will be placed on comparing osimertinib plus chemotherapy to relevant comparators and identifying gaps in the current evidence.

A summary of the clinical evidence included by the sponsor in the review of osimertinib plus chemotherapy is presented in 1 section, with the critical appraisal of the evidence included at the end. The only section, a systematic review, includes pivotal studies and RCTs that were selected according to the sponsor's systematic review protocol. Our assessment of the certainty of the evidence in this first section using the GRADE approach follows the critical appraisal of the evidence.

Included Studies

Clinical evidence from 1 phase III, open-label RCT, FLAURA2, is included in the review and appraised in this document.

Systematic Review

Contents within this section have been informed by materials submitted by the sponsor. The following summary was validated by the review team.

Description of Studies

One study conducted by the sponsor, FLAURA2,[16,31] met the inclusion criteria of the sponsor-submitted systematic literature review. Characteristics of the included study are summarized in Table 5.

Table 5: Details of Studies Included in the Systematic Review

Detail	FLAURA2
Designs and populations	
Study design	Multinational, open-label, randomized, phase III trial
Locations	Patients were enrolled in 151 sites in 21 countries across Europe, Asia-Pacific, North America, South America, and Africa. There were 3 sites in Canada that enrolled a total of 13 patients in Canada.
Key dates	Patient enrolment start date: May 15, 2020 Patient enrolment end date: November 30, 2021
Randomized (N)	Randomization phase: full analysis set, N = 557 • Osimertinib + chemotherapy (n = 279) • Osimertinib monotherapy (n = 278)
Inclusion criteria	• Male or female, at least 18 years of age; patients from Japan at least 20 years of age • Pathologically confirmed nonsquamous NSCLC; NSCLC of mixed histology is allowed • Newly diagnosed locally advanced (clinical stage IIIB, IIIC) or metastatic NSCLC

Detail	FLAURA2
	(clinical stage IVA or IVB) or recurrent NSCLC (according to version 8 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), not amenable to curative surgery or radiotherapy • Tumour that harbours 1 of the 2 common EGFR mutations known to be associated with EGFR TKI sensitivity (exon 19 deletion or L858R substitution), either alone or in combination with other EGFR mutations, which may include T790M, assessed by a CLIA-certified (at US sites) or an accredited (outside of the US) local laboratory or by central prospective tissue testing • Mandatory provision of a baseline plasma sample and an unstained, archival tumour tissue sample in a quantity sufficient to allow for central confirmation of the EGFR mutation status • Patients must have untreated advanced NSCLC not amenable to curative surgery or radiotherapy. Prior adjuvant and neoadjuvant therapies (chemotherapy, radiotherapy, immunotherapy, biologic therapy, and investigational drugs), or definitive radiation/ chemoradiation with or without regimens including immunotherapy, biologic therapy, and investigational drugs, were permitted as long as treatment was completed at least 12 months before the development of recurrent disease • WHO PS of 0 to 1 at screening with no clinically significant deterioration in the previous 2 weeks • Life expectancy > 12 weeks at day 1 • At least 1 lesion, not previously irradiated, that could be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have had a short axis of ≥ 15 mm) with CT or MRI, and that was suitable for accurate repeated measurements; if only 1 measurable lesion existed, it could be used (as a target lesion) if it had not been previously irradiated and had not been biopsied within 14 days of the baseline tumour assessment scans • Willing to use contraception as appropriate during the study and for a period of time after discontinuing study treatment
Exclusion criteria	• Spinal cord compression and unstable brain metastases, with stable brain metastases in those who have completed definitive therapy, are not on steroids, and have a stable neurologic status for at least 2 weeks after completion of the definitive therapy and steroids can be enrolled; patients with asymptomatic brain metastases could be eligible for inclusion if, in the opinion of the investigator, immediate definitive treatment is not indicated • Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis that required steroid treatment, or any evidence of clinically active interstitial lung disease • Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol, or active infection including hepatitis B, hepatitis C, and HIV; screening for chronic conditions was not required • QT prolongation or any clinically important abnormalities in rhythm • Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: ◦ Absolute neutrophil count < LLN ◦ Platelet count < LLN ◦ Hemoglobin < 90 g/L; use of granulocyte colony stimulating factor support, platelet

Detail	FLAURA2
	transfusion and blood transfusions to meet these criteria is not permitted ◦ ALT > 2.5 × ULN if no demonstrable liver metastases or > 5 × ULN in the presence of liver metastases ◦ AST > 2.5 × ULN if no demonstrable liver metastases or > 5 × ULN in the presence of liver metastases ◦ Total bilirubin > 1.5 × ULN if no liver metastases or > 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases ◦ Creatinine clearance < 60 mL/min calculated by Cockcroft and Gault equation or 24-hour urine collection ● Any concurrent and/or other active malignancy that required treatment within 2 years of first dose of investigational product ● Any unresolved toxicities from prior systemic therapy (e.g., adjuvant chemotherapy) greater than CTCAE grade 1 at the time of starting study treatment, with the exception of alopecia and grade 2 prior platinum-therapy related neuropathy ● Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of osimertinib ● Prior treatment with any systemic anticancer therapy for advanced NSCLC not amenable to curative surgery or radiation including chemotherapy, biologic therapy, immunotherapy, or any investigational drug; prior adjuvant and neoadjuvant therapies (chemotherapy, radiotherapy, immunotherapy, biologic therapy, investigational drugs), or definitive radiation/chemoradiation with or without regimens including immunotherapy, biologic therapies, and investigational drugs are permitted as long as treatment was completed at least 12 months before the development of recurrent disease ● Prior treatment with an EGFR TKI ● Major surgery within 4 weeks of the first dose of investigational product; procedures such as placement of vascular access, biopsy via mediastinoscopy or biopsy via video-assisted thoracoscopic surgery are permitted ● Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of investigational product ● History of hypersensitivity to active or inactive excipients of investigational product or drugs with a similar chemical structure or class to investigational product
Drugs	
Intervention	Osimertinib 80 mg oral tablets once daily in combination with pemetrexed (500 mg/m^2) and either cisplatin (75 mg/m^2) or carboplatin (AUC of 5 mg/mL/min), with both treatments administered by IV infusion on day 1 of 21-day cycles for 4 cycles, followed by osimertinib 80 mg once daily plus pemetrexed maintenance (500 mg/m^2) every 3 weeks, until disease progression as defined by RECIST 1.1, unacceptable toxicity, or until a treatment discontinuation criterion was met
Comparator(s)	Osimertinib 80 mg oral tablets once daily, until disease progression as defined by RECIST 1.1, unacceptable toxicity, or until a treatment discontinuation criterion was met
Study duration	
Screening phase	28 days

Detail	FLAURA2
Safety run-in phase	Until RECIST 1.1–defined progression or another discontinuation criterion was met; the safety run-in was conducted before the randomized period; patients included in the safety run-in were not included in the randomized phase
Randomized phase	Until RECIST 1.1–defined progression by the investigator, or until another discontinuation criterion was met; following RECIST 1.1–defined progression, patients were followed for second progression on a subsequent treatment (according to local standard clinical practice) every 12 weeks, and for survival
Follow-up phase	RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1–defined radiological disease progression or other withdrawal criteria were met. Brain imaging mandatory at baseline and progression for all patients, and at scheduled assessments until progression for patients with baseline CNS metastases
Outcomes	
Primary end point	PFS based on investigator assessment Time frame: until the date of objective disease progression (based on RECIST 1.1) or death (by any cause in the absence of progression), regardless of whether the patient withdrew from study treatment or received another anticancer therapy before progression
Secondary and exploratory end points	**Secondary:** • OS; time frame: from the date of randomization until death due to any cause; landmark OS at 1, 2, and 3 years • ORR; time frame: not applicable; obtained up until progression, or last evaluable assessment in the absence of progression • DCR; time frame: not applicable • DoR; time frame: from the date of first documented response until date of documented progression or death in the absence of disease progression • Depth of response; time frame: not applicable • TFST; time frame: from the date of randomization to the earlier of the date of anticancer therapy start date following study treatment discontinuation or death • PFS2; time frame: from the date of randomization to the earliest of the progression event subsequent to first subsequent therapy or death • TSST; time frame: from the date of randomization to the earlier of the date of second subsequent anticancer therapy start date following study treatment discontinuation or death **HRQoL:** • Change from baseline and time to deterioration in EORTC QLQ-C30; time frame: from randomization until the date of the first clinically meaningful worsening (a change in the score from baseline of ≥ 10) • Change from baseline and time to deterioration in EORTC QLQ-LC13; time frame: from randomization until the date of the first clinically meaningful worsening (a change in the score from baseline of ≥ 10) **Safety:** • AEs, summarized by treatment group, graded by CTCAE; time frame: from time of signature of informed consent form throughout the treatment period and including the 28-day follow-up period **Exploratory:** • CNS PFS; time frame: from randomization until the date of objective CNS progression

Detail	FLAURA2
	or death • CNS ORR; time frame: not applicable • CNS DoR; time frame: from the date of first documented CNS response of PR or CR by CNS BICR assessment until the date of objective CNS progression or death • CNS DCR; time frame: not applicable • Best percentage change in CNS tumour size; time frame: not applicable
Publication status	
Publications	8 publications[12,32-38] 1 clinical trial registry entry (NCT04035486)

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; AUC = area under the concentration-time curve; BICR = blinded independent central review; CLIA = Clinical Laboratory Improvement Amendments; CNS = central nervous system; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DoR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module; HRQoL = health-related quality of life; LLN = lower limit of normal; NSCLC = non–small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = time to second progression; PR = partial response; PS = performance status; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; TFST = time to first subsequent therapy; TKI = tyrosine kinase inhibitor; TSST = time to second subsequent therapy; ULN = upper limit of normal.

Sources: FLAURA2 Clinical Study Protocol,[39] FLAURA2 Clinical Study Reports.[16,31] (Details included in the table are from the sponsor's Summary of Clinical Evidence.[1])

The FLAURA2 study is a phase III, open-label RCT investigating the use of osimertinib plus chemotherapy in patients with locally advanced, metastatic, or recurrent EGFRm (ex19del and/or L858R) NSCLC, not amenable to surgery or radiotherapy. The FLAURA2 trial was conducted in 557 patients from 21 countries worldwide, including patients in Canada. Patients were randomized to the osimertinib plus chemotherapy group (n = 279) or 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 plus chemotherapy treatment versus osimertinib monotherapy, measured by PFS according to investigator assessment. Assessment of OS was a key secondary objective. The trial is ongoing, and the data cut-off date was April 3, 2023. Of note, OS data were updated on January 8, 2024, and assessed in this report. The schematic of the study design of the FLAURA2 trial is shown in Figure 1. Before randomization, there was a safety run-in period involving 30 patients with the aim of assessing the safety and tolerability of osimertinib plus chemotherapy. The safety run-in period has been completed with a data cut-off date of February 19, 2020.

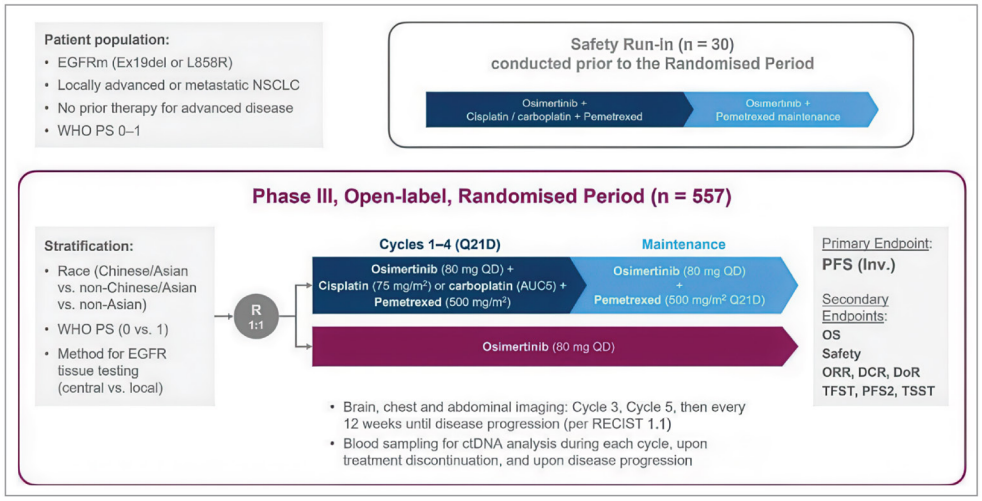
Populations

Inclusion and Exclusion Criteria

The FLAURA2 trial included adult patients with pathologically confirmed nonsquamous NSCLC that was locally advanced (clinical stage IIIB, IIIC), metastatic (clinical stage IVA or IVB), recurrent (according to version 8 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or not amenable to curative surgery or radiotherapy, including chemotherapy, biologic therapy, immunotherapy, or any investigational drug. The tumour of the eligible patients must harbour 1 of the 2 common EGFR mutations known to be associated with EGFR TKI sensitivity (i.e., ex19del or L858R), either alone or in combination with other EGFR mutations. Eligible patients should also have a WHO PS of 0 or 1. Prior adjuvant and neoadjuvant therapies (e.g., chemotherapy, radiotherapy, immunotherapy, biologic

therapy, or investigational drugs), or definitive radiation and/or chemoradiation with or without regimens, including immunotherapy, biologic therapies, investigational drugs, were permitted as long as the treatment had been completed at least 12 months before the development of recurrent disease.

Figure 1: Schematic of the FLAURA2 Study Design



AUC5 = area under the concentration-time curve of 5 mg/mL/min; CNS = central nervous system; ctDNA = circulating tumour DNA; DCR = disease control rate; DoR = duration of response; EGFRm = eGFR–mutated; Inv. = investigator NSCLC = non–small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = time to second progression; Q21D = every 21 days; QD = once daily; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; TFST = time to first subsequent therapy; TSST = time to second subsequent therapy; WHO PS = WHO Performance Status.

Note: The safety run-in and randomized periods of the study were separate. Crossover between treatment groups was not permitted. Brain scans were performed in all patients at baseline and at progression. Patients with CNS metastases identified at baseline scan, or with a history of CNS metastases, had brain scans at each tumour assessment (baseline, 6 weeks, 12 weeks, and then every 12 weeks) until disease progression.

Sources: FLAURA2 Clinical Study Reports.[16] (Details included in the table are from the sponsor's Summary of Clinical Evidence.[1])

Interventions

In the FLAURA2 trial, patients were randomized to 1 of 2 treatment groups:

- osimertinib plus chemotherapy in the form of 80 mg oral tablets once daily with pemetrexed (500 mg/m^2) and either cisplatin (75 mg/m^2) or carboplatin (area under the concentration-time curve during any dosing interval of 5 mg/mL/min), with both treatments administered on day 1 of 21-day cycles for 4 cycles, followed by osimertinib 80 mg daily and pemetrexed maintenance (500 mg/m^2), every 3 weeks
- osimertinib monotherapy in the form of 80 mg oral tablets once daily.

In both treatment groups, osimertinib doses were to be taken approximately 24 hours apart at the same time each day. Doses were not to be missed. If a patient missed a scheduled dose, they could take the dose within a window of 12 hours. If the delay was more than 12 hours after the scheduled administration time, the missed dose was not to be taken, and the patient was advised to take the next dose at the next scheduled time. The initial dose of osimertinib 80 mg once daily could be reduced to 40 mg once daily to manage toxicities. However, once the dose of osimertinib was reduced to 40 mg once per day, the patient was to remain on the reduced dose until termination from study treatment. Rechallenge at 80 mg was not allowed.

In terms of chemotherapy (pemetrexed and platinum-based therapy), investigators could choose either carboplatin or cisplatin as the platinum-based therapy for patients according to local clinical practice, and patients could be switched to the alternative platinum drug.

Pemetrexed was administered at a dose of 500 mg/m^2 as an IV infusion over 10 minutes on day 1 of each 21-day cycle according to local practice and labels until Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)-defined progression or another discontinuation criterion was met. To reduce the severity of hematologic and gastrointestinal toxicity of pemetrexed, patients also received vitamin supplements. Patients were given oral folic acid or a multivitamin containing folic acid (350 mcg to 1,000 mcg) daily, and an intramuscular injection of vitamin B12 (1,000 mcg) in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections were given on the same day as pemetrexed. An oral corticosteroid (equivalent to 4 mg of dexamethasone administered orally twice a day) was given the day before, on the day of, and the day after pemetrexed administration to reduce the occurrence and severity of skin reactions.

Cisplatin was given at a dose of 75 mg/m^2 as an IV infusion, according to local practice and labels approximately 30 minutes after the pemetrexed infusion, every 3 weeks for 4 cycles, and immediately preceded and followed by hydration.

Carboplatin was administered at a dose for a target area under the concentration-time curve during any dosing interval of 5 mg/mL/min over 15 to 60 minutes, after the pemetrexed infusion, every 3 weeks for 4 cycles, according to local practice and labels. Carboplatin dose was calculated using the Calvert formula. The carboplatin dose was not to exceed 750 mg.

Patients were to continue their randomized treatment until disease progression as defined by RECIST 1.1, unacceptable toxicity, or until a treatment discontinuation criterion was met. The criteria of discontinuation of study treatment included RECIST 1.1–defined progression if the patient was no longer receiving clinical benefit, patient decision, investigator decision, AEs, severe noncompliance with the study protocol, incorrect initiation on investigational product, and pregnancy. Patients were allowed to continue receiving their study treatment beyond RECIST 1.1–defined progression if, in the judgment of the investigator, they were receiving a clinical benefit and did not meet any of the discontinuation criteria. However, if the patient was deemed to have clinically significant unacceptable or irreversible toxicities, rapid tumour progression, or symptomatic progression requiring urgent medical intervention (e.g., CNS metastases, respiratory failure, spinal cord compression), the treatment was to be discontinued.

To maintain the dose intensity of osimertinib monotherapy and manage potential overlapping toxicities, it was recommended that, if clinically appropriate and where osimertinib interruption is not mandated, dose interruption or reduction of chemotherapy was prioritized above dose interruption or dose reduction of osimertinib. A maximum of 2 dose reductions for each component of chemotherapy treatment (i.e., cisplatin, carboplatin, or pemetrexed) was allowed. If a patient experienced toxicity that warranted a third dose reduction for any component of chemotherapy, that drug was to be discontinued. Only 1 dose reduction was permitted for osimertinib treatment. If a patient experienced a toxicity associated with osimertinib that would

warrant a second dose reduction, osimertinib was to be discontinued. If a dose reduction for toxicity occurred with any drug, the dose of that drug might not have been re-escalated.

Outcomes

A list of efficacy end points assessed in this Clinical Review Report is provided in Table 6, followed by descriptions of the outcome measures. Summarized end points are based on outcomes included in the sponsor's Summary of Clinical Evidence as well as any outcomes identified as important to this review according to the clinical expert(s) consulted for this review and input from patient and clinician groups and public drug plans. Using the same considerations, we selected end points that were considered to be most relevant to inform expert committee deliberations and finalized this list of end points in consultation with members of the expert committee. All summarized efficacy end points were assessed using GRADE. Select notable harms outcomes considered important for informing expert committee deliberations were also assessed using GRADE.

Table 6: Outcomes Summarized From FLAURA2

Outcome measure	Time point	FLAURA2
Overall survival: • First interim analysis (data cut-off date: April 3, 2023)[a] • Second interim analysis (data cut-off date: January 8, 2024)[a]	Time from the date of randomization until death due to any cause	Key secondary
Progression-free survival[a,b]	Time from randomization until the date of objective disease progression or death (by any cause in the absence of progression)	Primary
EORTC QLQ-LC13 • Coughing symptom subscale • Pain in chest subscale • Dyspnea symptom subscale	Week 52 posttreatment Week 82 posttreatment Average[c]	Secondary
EORTC QLQ-C30 • Global Health Status/QoL subscale	Week 52 posttreatment Week 82 posttreatment Average[c]	Secondary

BICR = blinded independent central review; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module; MMRM = mixed-effects model for repeated measures; QoL = quality of life.

[a]Statistical testing for these end points was adjusted for multiple comparisons (e.g., hierarchal testing).

[b]PFS according to investigator assessment was prespecified as the primary outcome for FLAURA2; PFS according to BICR was presented as a sensitivity analysis.

[c]Average included all patients contributing to the MMRM model over all visits (i.e., over 19 months or until progression disease). The score values are calculated by averaging across patients overall mean across all visits.

Sources: FLAURA2 Clinical Study Protocol version 2.0,[39] FLAURA2 Statistical Analysis Plan version 2.0,[40] FLAURA2 Clinical Study Report.[16] (Details included in the table are from the sponsor's Summary of Clinical Evidence.[1])

Descriptions of efficacy and safety outcomes presented in FLAURA2 and appraised in the Clinical Review Report follow.[16,39,40]

Efficacy Outcomes

Overall Survival

Overall survival was defined as the time from the date of randomization until death due to any cause, regardless of whether the patient withdrew from study treatment or received another anticancer therapy (i.e., date of death or censoring – date of randomization + 1). Any patient not known to have died at the time of analysis was censored based on the last recorded date.

Progression-Free Survival

Progression-free survival according to investigator was specified as the primary outcome for the FLAURA2 trial, while PFS according to BICR was presented as a sensitivity analysis. PFS was defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy before progression.

Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progressed or died after 2 or more missed visits, the patient was censored at the time of the latest evaluable RECIST assessment. Patients who had no evaluable visits or who did not have baseline RECIST data were censored at study day 1 unless they died within 2 visits of baseline, in which case their date of death was used as an event. The following rules were applied. First, the date of progression was determined based on the earliest of the dates of the component that triggered the progression; second, when censoring a patient for PFS, the patient was censored at the latest of the dates contributing to a particular overall visit assessment.

Details of censoring for primary PFS analysis are presented in Table 7.

Health-Related Quality of Life

A summary of EORTC QLQ-LC13 results is shown in Table 8.

Table 7: Censoring Rules for Primary PFS in FLAURA2

Situation	Event or censored	Event date or censored date
No evaluable postbaseline visits or does not have baseline RECIST 1.1 data, and did not die within 2 visits of baseline	Censored	Randomization date (study day 1)
No evaluable postbaseline visits or does not have baseline RECIST 1.1 data, and died within 2 visits of baseline	Event	Death date
Progresses or died immediately after 2 or more consecutive missed visits	Censored	Latest evaluable RECIST 1.1 assessment before the 2 missed visits
Disease progression or death (by any cause in the absence of progression) without 2 or more consecutive missed visits regardless of whether the patient withdrew from randomized therapy	Event	Disease progression date, or death date if no progressive disease

Situation	Event or censored	Event date or censored date
or received another anticancer therapy before progression		
Not progressed or died at the time of analysis	Censored	Latest date of assessment from their last evaluable RECIST 1.1 assessment

PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.
Source: FLAURA2 Statistical Analysis Plan version 2.0.[40]

Table 8: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	Minimal important difference
EORTC QLQ-C30	Cancer-specific self-reported measure of HRQoL 30-item questionnaire, consisting of 5 functional scales (physical, role, emotional, social, and cognitive), 9 symptom scales (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a Global Health Status scale A higher score for functional scales and for Global Health Status represents better functioning ability or HRQoL; a higher score for symptom scales represents a worsening of symptoms[41]	In studies with lung cancer patients: **Validity:** Moderate to strong correlations between the 5 EORTC QLQ-C30 functioning scales (r = 0.41 to 0.77); FACT-G and EORTC QLQ-C30 scales (r = 0.64 to 0.76);[42] HADS with all EORTC QLQ-C30 functioning scales (r = 0.28 to 0.75); BPI scales with all EORTC QLQ-C30 scales except for nausea/vomiting (r = 0.20 to 0.72),[43] supporting convergent validity **Known-groups approach:** Able to differentiate across different measures of cancer severity: cancer stages (d = 0.49); ECOG PS (d = 0.65); and self-reported health status (d = 1.36)[42] **Reliability:** Cronbach alpha ranging from 0.56 to 0.93 with 7 scales having acceptable internal consistency (alpha > 0.70)[44] **Responsiveness:** Group differences (improved vs. deteriorated ECOG PS) over 28 days between pre- and on-treatment periods showed a statistically significant difference in global quality of life (P < 0.01) scale; no such difference was identified in patients whose ECOG PS remained unchanged[41]	In a study with patients with NSCLC: MID estimates for improvement (deterioration) using the ECOG PS and weight change as anchors: **Physical functioning**: 9 and 5 (4 and 6) **Role functioning**: 14 and 7 (5 and 5) **Social functioning**: 5 and 7 (7 and 9) **Global Health Status**: 9 and 4 (4 and 4) **Fatigue**: 14 and 5 (6 and 11) **Pain**: 16 and 2 (3 and 7).[45] In a study of lung cancer patients: an anchor-based approach in which patients who reported "a little" change on the SSQ had subsequent changes on a scale of the EORTC QLQ-C30 of 5 to 10 points[46] The sponsor's submission indicated a minimum clinically relevant change was defined as a change in the score from baseline of ≥ 10 for scales/items from the EORTC QLQ-C30
EORTC QLQ-LC13	A tumour-specific questionnaire used to supplement the EORTC QLQ-C30 that contains 13 items related to lung cancer symptoms and treatment side	**Validity:** Construct validity has been established between pain score and disease type (P < 0.001); based on ECOG PS, construct validity was confirmed in dyspnea,	No relevant studies identified in patients with NSCLC For the sponsor-submitted study, a minimum clinically relevant

Outcome measure	Type	Conclusions about measurement properties	Minimal important difference
	effects including: a 3-item scale assessing dyspnea and 9 single items: pain in chest, pain in arm or shoulder, pain in other parts, coughing, hemoptysis, sore mouth or tongue, dysphagia, peripheral neuropathy, and alopecia[41] Higher scores on the symptom scales indicate worse symptoms[41]	coughing, and pain (P < 0.001) scores;[47] correlation between spirometry result and dyspnea score was found to be weak (r = 0.24); BPI intensity score and QLQ-LC13 pain score were found to be modestly correlated (r > 0.4)[43] **Reliability:** Good internal consistency reliability for the dyspnea multi-item scale (alpha = 0.81);[47] however, internal consistency was found to be unacceptable for pain scores (alpha = 0.53 to 0.54) when EORTC QLQ-LC13 was used alone without questionnaire pain items;[47] reliability estimate for dyspnea scale has been confirmed to be acceptable, i.e., alpha = 0.76 in another study[43] **Responsiveness:** Dyspnea, coughing, and pain scores improved significantly over time between pre-treatment and on-treatment period (P < 0.001 for all except for extrathoracic pain which showed P < 0.05); responsiveness of chest pain (P < 0.01), dyspnea (P < 0.001) and coughing (P < 0.001) to change in ECOG PS was also noted[47]	change was defined as a change in the score from baseline of ≥ 10 for scales/items from the EORTC QLQ-LC13

BPI = Brief Pain Inventory; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module; FACT-G = Functional Assessment of Cancer Therapy–General; HADS = Hospital Anxiety and Depression Scale; HRQoL = health-related quality of life; MID = minimal important difference; NSCLC = non–small cell lung cancer; SSQ = subjective significance questionnaire; vs. = versus.

Harms Outcomes

The harms outcomes assessed in the FLAURA2 trial included AEs, SAEs, deaths, withdrawals due to AEs, and notable harms (e.g., ILD, pneumonitis, cardiac failure, and hematological toxicities).

An AE was defined as treatment-emergent if the onset or worsening (according to an investigator's report of a change in intensity) occurred after the first dose of study treatment and within 28 days of discontinuation (i.e., the last dose of study treatment) but before or on the start date of a subsequent anticancer treatment). AEs were coded based on the Medical Dictionary for Regulatory Activities (version 25.1) and graded for severity according to the Common Terminology Criteria for Adverse Events (version 5.0).

An SAE is an AE occurring during any study phase (including treatment and follow-up) that fulfilled 1 or more of the following criteria: resulted in death, was immediately life-threatening, required inpatient hospitalization

or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital abnormality or birth defect, was an important medical event that might jeopardize the patient or might require medical treatment to prevent 1 of the outcomes listed.

Statistical Analysis

Sample Size and Power Calculation

In the FLAURA2 trial, the sample size was estimated based on the primary end point of PFS according to investigator assessment, which was initially planned to be analyzed when approximately 278 PFS events (approximately 50% maturity) had occurred. This was expected to occur approximately 33 months after the first patient was randomized (under an assumed 15-month exponential recruitment). As such, an overall sample size of approximately 556 patients was planned for randomization in a 1:1 ratio.

Assuming the PFS HR for the comparison of osimertinib plus chemotherapy versus osimertinib monotherapy was 0.68, 278 progression events would provide 90% power to demonstrate a statistically significant difference in PFS at a 5% 2-sided significance level. This translates to an improvement in median PFS from 19 months to 28 months, assuming exponential distribution and proportional hazards. The minimum critical HR was 0.79, which translated to an approximate median PFS improvement from 19 months to 24 months.

Statistical Testing

Details of the statistical analysis of selected efficacy end points are summarized in Table 9.

The assumption of proportionality was assessed for OS, PFS according to investigator assessment, and PFS according to BICR. Proportional hazards were tested first by examining plots of complementary log-log (event times) versus log (time) and, if these raised concerns, by fitting a time-dependent covariate (adding a treatment-by-time or treatment-by-ln[time] interaction term) to assess the extent to which this represented random variation. If a lack of proportionality was evident, the variation in treatment effect could be described by presenting a piecewise HR calculated over distinct time periods (e.g., 0 to 6 months, 6 to 12 months). For nonproportionality, the HR was interpreted as an average over the observed extent of follow-up unless there was extensive crossing of the survival curves. Treatment-by-covariate interaction was investigated if a lack of proportionality was found.

To control the type I error rate (alpha = 0.05, 2-sided), OS and PFS were tested in sequential order. If the previous analysis in the sequence was not statistically significant, the alpha would not be transferred to subsequent analyses. At the time of the primary analysis of PFS, if the PFS analysis was statistically significant, then subsequent hypothesis testing for OS would be performed at an overall 2-sided alpha significance level of 0.05 using the O'Brien and Fleming spending function. If the results of the PFS analysis were not statistically significant at the time of the PFS analysis, then no hypothesis testing for OS would be performed. The OS was tested in a hierarchical procedure, at the time of the PFS analysis and after the primary PFS analysis when the OS data were approximately 60% mature (approximately 334 death events across both groups).

Table 9: Statistical Analysis of Efficacy End Points in FLAURA2

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity and/or subgroup analyses
OS	• OS was analyzed using a stratified log-rank test, provided there were sufficient events (≥ 20 deaths) available for a meaningful analysis; otherwise, descriptive summaries would be provided • Effect was estimated by a HR and 2-sided 95% CI	Stratified by race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1), and method used for tissue testing (central vs. local)	Any patient not known to have died at the time of analysis was censored based on the last recorded date from the survival case report form page only	Not performed
PFS	• PFS according to investigator assessment and PFS according to BICR were analyzed using stratified log-rank test • Effect was estimated by a HR and 2-sided 95% CI using a Cox proportional hazards model	Stratified by race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1), and method used for tissue testing (central vs. local)	• Patients who have not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST assessment • If the patient progressed or died after 2 or more missed visits, the patient was censored at the time of the latest evaluable RECIST assessment • Patients who had no evaluable visits or who do not have baseline RECIST data were censored at study day 1 unless they die within 2 visits of baseline, in which case their date of death was used as an event	**Sensitivity analyses** • A Cox proportional hazards model was employed to assess to assess the effect of the prespecified covariates on the PFS HR estimate • PFS according to BICR assessment • To assess possible evaluation-time bias that might have been introduced if scans were not performed at the protocol-scheduled time points, the midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) was analyzed using a stratified log-rank test • Attrition bias (by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity and/or subgroup analyses
				immediately following 2 or more nonevaluable tumour assessments) • Quantitative interaction (assessed by means of an overall global interaction test) **Subgroup analyses** • Sex (male, female) • Race (Chinese/Asian, non-Chinese/Asian, non-Asian) • Method used for tissue testing (central vs. local) • Age at screening (< 65 years, ≥ 65 years) • Smoking history (yes, no) • EGFR mutation type (exon 19 deletion, L858R substitution) • EGFR by central ctDNA cobas test (positive, negative, missing) • EGFR mutations by central cobas tissue test (positive, negative, missing) • WHO PS (0, 1) • CNS status at baseline (yes, no) • Central confirmation of EGFR mutation (centrally confirmed tissue or ctDNA EGFR–positive result, no central confirmation)
EORTC QLQ-LC13	Change from baseline was analyzed using the MMRM analysis with all data from baseline up to	NA	Missing data were not imputed and handled through the mechanism of MMRM itself	Not performed

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity and/or subgroup analyses
	progressive disease or 19 months posttreatment, whichever was earlier, of randomization			
EORTC QLQ-C30	Change from baseline was analyzed using the MMRM analysis with all data from baseline up to progressive disease or 19 months posttreatment, whichever was earlier, of randomization	NA	Missing data were not imputed and handled through the mechanism of MMRM itself	Not performed

BICR = blinded independent central review; CI = confidence interval; CNS = central nervous system; ctDNA = circulating tumour DNA; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module; HR = hazard ratio; MMRM = mixed-effects model for repeated measures; NA = not applicable; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; vs. = versus; WHO PS = WHO Performance Status.

Sources: FLAURA2 Clinical Study Protocol version 2.0,[39] FLAURA2 Statistical Analysis Plan version 2.0,[40] FLAURA2 Clinical Study Report.[16] (Details included in the table are from the sponsor's Summary of Clinical Evidence.[1])

Analysis Populations

Analysis populations of the FLAURA2 trial are summarized in Table 10.

Table 10: Analysis Populations of FLAURA2

Population	Definition	Application
Full analysis set	The full analysis set includes all randomized patients	The FAS is used for all efficacy analyses, and treatment groups are compared based on randomized study treatment, regardless of the treatment actually received
Safety analysis set	The safety analysis set consists of all randomized patients who received at least 1 dose of study treatment	Safety data are not formally analyzed but are summarized descriptively according to treatment actually received (e.g., a patient who was randomized to osimertinib + chemotherapy but who received only osimertinib was summarized under the osimertinib monotherapy group)
CNS full analysis set	The CNS full analysis set includes all patients who undertook a brain scan in the screening/baseline period, had their scan sent for CNS BICR review, and were identified by that review as having nonmeasurable and/or measurable brain disease at baseline (i.e., at least 1 nonmeasurable and/or 1 measurable brain lesion noted at baseline)	The CNS full analysis set is used for all CNS efficacy analyses

BICR = blinded independent central review; CNS = central nervous system; FAS = full analysis set; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy.

Sources: FLAURA2 Clinical Study Protocol version 2.0,[39] FLAURA2 Statistical Analysis Plan version 2.0,[40] FLAURA2 Clinical Study Report.[16] (Details included in the table are from the sponsor's Summary of Clinical Evidence.[1])

Protocol Amendments and Deviations

In total, there were 2 versions of the clinical study protocol. The original study protocol was issued on March 19, 2019, and the amended protocol on August 26, 2021. In the amended protocol, the timing of the primary analysis was revised to include the requirement for at least a 16-month follow-up from the time of last participant in, in addition to approximately 278 PFS events. This was due to COVID-19, which had impacted study enrolment in non-Asian countries. The primary analysis was not conducted until at least 16-month follow-up had been reached to ensure a sufficient time frame to observe disease progression events.

A summary of protocol deviations in the FLAURA2 trial is presented in Table 11. Overall, 6.8% of randomized patients (38 of 557) had at least 1 protocol deviation. The most common reason was noncompliance with a RECIST 1.1 assessment (3.6%, 20 of 557).

Table 11: Summary of Protocol Deviations in FLAURA2 (Randomized Period — FAS)

Protocol deviation	Number (%) of patients	
	Osimertinib + chemotherapy	Osimertinib monotherapy
Number of patients with at least 1 protocol deviation	19 (6.8)	19 (6.8)
Patient failed inclusion criteria	1 (0.4)	2 (0.7)
Patient met exclusion criteria	2 (0.7)	2 (0.7)
Incorrect investigational product administration and/or treatment	3 (1.1)	4 (1.4)
Patient received prohibited concomitant therapy	2 (0.7)	3 (1.1)
Noncompliance with RECIST 1.1 assessment	11 (3.9)	9 (3.2)

FAS = full analysis set; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.

Source: FLAURA2 Clinical Study Report.[16]

Results

Patient Disposition

A summary of patient disposition in the FLAURA2 trial is presented in Table 12. Of 887 participants screened, 330 (37.2%) were excluded. There were 279 and 278 eligible patients randomized to the osimertinib plus chemotherapy group and the osimertinib monotherapy group, respectively. The proportions of patients who discontinued from the FLAURA2 trial were 29.4% for the osimertinib plus chemotherapy group and 31.3% for the osimertinib monotherapy group, with death the most common reason for discontinuation from the trial (25.1% versus 27.7%, respectively).

Table 12: Summary of Patient Disposition in FLAURA2

Patient disposition	Osimertinib + chemotherapy	Osimertinib monotherapy
Screened, N	887	
Patients excluded, N (%)	330 (37.2)	
Reason for exclusion, N (%)[a]		
Screen failure	319 (35.9)	
Patient decision	6 (0.7)	
Death	5 (0.6)	
Randomized (FAS), N	279	278
Patients ongoing study at data cut-off, N (%)[b]	197 (70.6)	191 (68.7)
Patients who discontinued from study, N (%)[b]	82 (29.4)	87 (31.3)
Death	70 (25.1)	77 (27.7)
Lost to follow-up	0	0
Withdrawal by patients	11 (3.9)	9 (3.2)
Screen failure	1 (0.4)	1 (0.4)
Patients who received any study treatment, N (%)[b]	276 (98.9)	275 (98.9)
Patients ongoing any study treatment, N (%)[c]	154 (55.8)	123 (44.7)
Patients who discontinued all study products, N (%)[c]	122 (44.2)	152 (55.3)
Patients who discontinued any study products, N (%)[c]	210 (76.1)	152 (55.3)
Patients who received osimertinib, N (%)[c]	276 (100)	275 (100)
Patients ongoing osimertinib, N (%)[d]	154 (55.8)	123 (44.7)
Patients who discontinued osimertinib, N (%)[d]	122 (44.2)	152 (55.3)
Reason for osimertinib discontinuation, N (%)[d]		
Progression	68 (24.6)	118 (42.9)
Adverse event	30 (10.9)	17 (6.2)
Patient decision	8 (2.9)	6 (2.2)
Study-specific discontinuation criteria	2 (0.7)	1 (0.4)
Other	14 (5.1)	8 (2.9)
Patients who received carboplatin/cisplatin treatment, N (%)[c]	276 (100)	NA
Patients who completed 4 cycles of carboplatin/cisplatin treatment, N (%)[d]	212 (76.8)	NA
Patients ongoing carboplatin/cisplatin treatment, N (%)[d]	0	NA
Patients who discontinued carboplatin/cisplatin treatment, N (%)[d]	64 (23.2)	NA
Reason for carboplatin/cisplatin discontinuation, N (%)[d]		
Progression	1 (0.4)	NA

Patient disposition	Osimertinib + chemotherapy	Osimertinib monotherapy
Adverse event	47 (17.0)	NA
Patient decision	6 (2.2)	NA
Study-specific discontinuation criteria	2 (0.7)	NA
Other	8 (2.9)	NA
Patients who received pemetrexed treatment, N (%)[c]	276 (100)	NA
Patients ongoing pemetrexed treatment, N (%)[d]	68 (24.6)	NA
Patients who discontinued pemetrexed treatment, N (%)[d]	208 (75.4)	NA
Reason for pemetrexed discontinuation, N (%)[d]		
Progression	31 (11.2)	NA
Adverse event	119 (43.1)	NA
Patient decision	30 (10.9)	NA
Study-specific discontinuation criteria	11 (4.0)	NA
Severe noncompliance to protocol	1 (0.4)	NA
Condition under investigation improved or patient recovered	1 (0.4)	NA
Other	15 (5.4)	NA
Patients ingoing study at data cut-off		
FAS, N	279	278
Safety analysis set, N	276	275

FAS = full analysis set; NA = not applicable; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy.

Note: Data cut-off: April 3, 2023.

[a]Percentages are based on the total number of patients enrolled.

[b]Percentages are based on the FAS.

[c]Percentages are based on the Safety analysis set. One patient was randomized to the osimertinib plus chemotherapy group, but only received osimertinib and was therefore included in the osimertinib group for the safety analysis set.

[d]Percentages are based on the number of patients who received one dose of the corresponding study drug.

Sources: FLAURA2 Clinical Study Report[16] and Drug Reimbursement Review sponsor submission.[17]

Baseline Characteristics

The baseline characteristics outlined in Table 13 are limited to those that are most relevant to this review or were felt to affect the outcomes or interpretation of the study results. Baseline demographics and disease characteristics were generally balanced between the osimertinib plus chemotherapy group and the osimertinib monotherapy group. Overall, the median age of enrolled patients was 61.0 years (range = 26 to 85 years). In total, 30.5% of patients were aged 65 years or older to younger than 75 years, and 8.4% of patients were aged 75 years or older. The majority of enrolled patients were female (61.4%), Asian (63.7%), with a WHO PS of 1 (62.8%), an ex19del mutation (53.1% by central cobas tissue test), and metastatic NSCLC at baseline (96.2%).

Exposure to Study Treatments

Details on the extent of exposure to study treatments in the FLAURA2 trials are summarized in Table 14. As of April 3, 2023, the overall duration of exposure to any study treatment across treatment groups in the safety analysis set ranged from 0.1 months to 33.8 months (median = 21.09). Patients in the osimertinib plus chemotherapy group had a longer exposure than those in the osimertinib monotherapy group (e.g., total exposure = 455.3 treatment-years versus 415.3 treatment-years).

In the osimertinib plus chemotherapy group, the median number of cisplatin or carboplatin treatment cycles was 4 (range = 1 to 6); 76.4% (211 of 276) and 0.7% of patients (2 of 276) received 4 or more cycles of cisplatin or 5 or more cycles of carboplatin. The median number of pemetrexed treatment cycles was 12 (range = 1 to 48); 80.1% (221 of 276) and 24.6% of patients (68 of 276) received 4 or more or 30 or more cycles of pemetrexed treatment, respectively.

Table 13: Summary of Baseline Characteristics in FLAURA2 (Randomized Period — FAS)

Characteristic	FLAURA2	
	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)
Age (years)[a]		
Mean (SD)	61.0 (10.03)	60.7 (10.57)
Median	61.0	61.5
Minimum to maximum	26 to 83	30 to 85
Sex, n (%)		
Male	106 (38.0)	109 (39.2)
Female	173 (62.0)	169 (60.8)
Race, n (%)		
Asian	179 (64.2)	176 (63.3)
White	74 (26.5)	83 (29.9)
American Indian or Alaska Native	11 (3.9)	6 (2.2)
Black or African	2 (0.7)	3 (1.1)
Other	13 (4.7)	10 (3.6)
Body mass index, kg/m^2		
n	275	271
Mean (SD)	24.36 (4.403)	24.39 (4.374)
Smoking status, n (%)		
Never	188 (67.4)	181 (65.1)
Smoker	91 (32.6)	97 (34.9)
Current	4 (1.4)	4 (1.4)

Characteristic	FLAURA2	
	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)
Former	87 (31.2)	93 (33.5)
WHO PS, n (%)		
0 (Normal activity)	104 (37.3)	102 (36.7)
1 (Restricted activity)	174 (62.4)	176 (63.3)
2 (In bed ≤ 50% of the time)[b]	1 (0.4)	0
AJCC stage (8th edition) at initial diagnosis, n (%)		
Stage IIIB	9 (3.2)	4 (1.4)
Stage IIIC	4 (1.4)	3 (1.1)
Stage IVA	98 (35.1)	104 (37.4)
Stage IVB	168 (60.2)	167 (60.1)
EGFR testing method/mutation type, n (%)		
Central test	123 (44.1)	117 (42.1)
Exon 19 deletion	75 (26.9)	67 (24.1)
L858R	47 (16.8)	49 (17.6)
Unknown or not detected[c]	1 (0.4)	1 (0.4)
Local test	156 (55.9)	161 (57.9)
Exon 19 deletion	94 (33.7)	101 (36.3)
L858R	59 (21.1)	58 (20.9)
Both exon 19 deletion and L858R substitution	3 (1.1)	1 (0.4)
Not detected[d]	0	1 (0.4)
Overall extent of disease at study entry, n (%)		
Metastatic[e]	265 (95.0)	271 (97.5)
Locally advanced[f]	14 (5.0)	7 (2.5)
Histology type, n (%)		
Adenocarcinoma[g]	275 (98.6)	275 (98.9)
Adenosquamous carcinoma	2 (0.7)	0
Other	2 (0.7)	3 (1.1)
Number of patients with metastases (by location), n (%)[h]		
Central nervous system	116 (41.6)	110 (39.6)
Liver	43 (15.4)	66 (23.7)
Lung/pleura	196 (70.3)	216 (77.7)
Lymph nodes	160 (57.3)	170 (61.2)

Characteristic	FLAURA2	
	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)
Bone + locomotive	132 (47.3)	142 (51.1)
Extrathoracic	147 (52.7)	149 (53.6)
Other	64 (22.9)	58 (20.9)
Time from initial diagnosis to the first dose, months		
n	277	274
Mean (SD)	3.6 (12.03)	3.6 (16.20)
Median	1.1	1.1
Baseline target lesion tumour size, mm[i]		
n	278	277
Mean (SD)	65.1 (42.36)	64.1 (38.87)
Median	57.0	57.0

AJCC = American Joint Committee on Cancer; ctDNA = circulating tumour DNA; EGFRm = EGFR–mutated; FAS = full analysis set; L816Q = exon 21 codon 816; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy; SD = standard deviation; WHO PS = WHO Performance Status.

Note: Data cut-off date: April 3, 2023.

[a]Age at study entry.

[b]The patient had a WHO PS of 1 at the time of randomization but before study drug administration had a record of WHO PS 2.

[c]One patient was randomized based on an invalid central tissue result (and was therefore categorized as having an EGFRm status of unknown); a retrospective baseline ctDNA result was exon 19 deletion–positive. The other patient was randomized based on a negative central tissue result (and was therefore categorized as EGFRm status not detected); a retrospective baseline ctDNA result was L858R-positive.

[d]The patient was randomized based on local result of L858R substitution–positive, which was subsequently updated to exon 21 L861Q–positive and confirmed by central test result.

[e]Metastatic disease: patient had any metastatic site of disease.

[f]Locally advanced: patient had only locally advanced sites of disease.

[g]Represents a combination of the following adenocarcinoma categories: not otherwise specified, acinar, papillary, bronchiolo-alveolar, and solid with mucous formation.

[h]This is a programmatically derived composite end point with a list of contributing data sources.

[i]Sum of longest diameters of target lesions at baseline.

Source: FLAURA2 Clinical Study Report.[16] (Details included in the table are from the sponsor's Summary of Clinical Evidence.[1])

Concomitant Medications

Details about commonly reported concomitant medications (used in ≥ 20% of patients in either group) are shown in Table 15. As of April 3, 2023, most of the patients (549 patients [98.9%]) received at least 1 permitted concomitant medication during the study.

Table 14: Summary of Patient Exposure in FLAURA2 (Randomized Period — Safety Analysis Set)

Exposure	Osimertinib + chemotherapy (N = 279)				Osimertinib monotherapy (N = 278)
	Osimertinib (n = 276)	Carboplatin or cisplatin (n = 276)	Pemetrexed (n = 276)	Overall (n = 276)[a]	
Total exposure (months)[b, c]					
Duration, mean (SD)	19.67 (9.053)	2.58 (0.742)	12.06 (9.836)	19.80 (9.016)	18.12 (8.908)
Duration, median	22.26	2.76	8.28	22.31	19.32
Minimum to maximum	0.1 to 33.8	0.7 to 4.1	0.7 to 33.8	0.7 to 33.8	0.1 to 33.8
Total treatment-years[d]	452.3	59.3	277.3	455.3	415.3
Actual exposure (months)[e]					
Duration, mean (SD)	19.32 (9.032)	—	—	19.36 (9.004)	17.95 (8.904)
Duration, median	21.83	—	—	21.83	19.02
Minimum to maximum	0.1 to 33.4	—	—	0.1 to 33.4	0.1 to 33.8
Total treatment-years[d]	444.5	—	—	445.3	411.3

osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy; SD = standard deviation.

Note: Data cut-off date: April 3, 2023.

[a]Patient received any of the study drugs (osimertinib, cisplatin, carboplatin, or pemetrexed).

[b]For osimertinib, total exposure = (min [last dose date where dose > 0 mg, date of death, date of data cut-off] – first dose date + 1) / 30.4375.

[c]For pemetrexed, cisplatin, and carboplatin, total exposure = (min [last dose date where dose > 0 mg, date of death, date of data cut-off] – first dose date + 21) / 30.4375.

[d]Total treatment-years is the sum of treatment durations of all patients by treatment group.

[e]Actual exposure = (total exposure – total duration of dose interruptions [i.e., number of days with dose = 0 mg]) / 30.4375.

Source: FLAURA2 Clinical Study Report.[16] (Details included in the table are from the sponsor's Summary of Clinical Evidence.[1])

Table 15: Concomitant Medications (20% or More of Patients in Either Treatment Group) in FLAURA2 (Randomized Period — FAS)

Concomitant medication	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)
Number of patients with a concomitant medication, n (%)	**276 (98.9)**	**273 (98.2)**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Concomitant medication	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

FAS = full analysis set; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy.

Note: Data cut-off date: April 3, 2023.

Source: FLAURA2 Clinical Study Report.[16] (Details included in the table are from the sponsor's Summary of Clinical Evidence.[1])

Subsequent Treatment

A summary of subsequent treatment in the FLAURA2 trial is shown in Table 16. As of the data cut-off date (April 3, 2023), 20.4% of the patients in the osimertinib plus chemotherapy group and 32.7%% of the patients in the osimertinib monotherapy group received any post-treatment anticancer therapy.

Efficacy

Key efficacy results in the FAS during the randomized period are presented in Table 17.

Table 16: Summary of Subsequent Treatment in FLAURA2 (Randomized Period — FAS)

Subsequent treatment	April 3, 2023		January 8, 2024	
	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)
Discontinued randomized study treatment, n (%)	123 (44.1)	151 (54.3)	155 (55.6)	187 (67.3)
Any posttreatment anticancer therapy	57 (20.4)	91 (32.7)	74 (26.5)	115 (41.4)
No posttreatment anticancer therapy	66 (23.7)	60 (21.6)	81 (29.0)	72 (25.9)
Ongoing randomized study treatment, n (%)	154 (55.2)	123 (44.2)	122 (43.7)	87 (31.3)
Did not receive study treatment, n (%)	2 (0.7)	4 (1.4)	2 (0.7)	4 (1.4)
Types of posttreatment anticancer therapy received, n (%) [%][a]				
Cytotoxic chemotherapy	41 (14.7) [33.3]	81 (29.1) [53.6]	51 (18.3) [32.9]	100 (36.0) [53.5]
Platinum compounds	19 (6.8) [15.4]	78 (28.1) [51.7]	27 (9.7) [17.4]	96 (34.5) [51.3]
Folic acid analogues (pemetrexed)	8 (2.9) [6.5]	55 (19.8) [36.4]	12 (4.3) [7.7]	72 (25.9) [38.5]

Subsequent treatment	April 3, 2023		January 8, 2024	
	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)
Taxanes	26 (9.3) [21.1]	39 (14.0) [25.8]	34 (12.2) [21.9]	48 (17.3) [25.7]
Other[b]	14 (5.0) [11.4]	16 (5.8) [10.6]	20 (7.2) [12.9]	18 (6.5) [9.6]
EGFR TKI	18 (6.5) [14.6]	39 (14.0) [25.8]	29 (10.4) [18.7]	51 (18.3) [27.3]
First- or second-generation EGFR TKI	12 (4.3) [9.8]	22 (7.9) [14.6]	17 (6.1) [11.0]	27 (9.7) [14.4]
Third-generation EGFR TKI	6 (2.2) [4.9]	22 (7.9) [14.6]	13 (4.7) [8.4]	29 (10.4) [15.5]
Osimertinib	6 (2.2) [4.9]	19 (6.8) [12.6]	10 (3.6) [6.5]	24 (8.6) [12.8]
Aumolertinib	0	3 (1.1) [2.0]	1 (0.4) [0.6]	1 (0.4) [0.5]
Furmonertinib	0	0	2 (0.7) [1.3]	1 (0.4) [0.5]
VEGF inhibitor — monoclonal antibody	14 (5.0) [11.4]	38 (13.7) [25.2]	21 (7.5) [13.5]	46 (16.5) [24.6]
PD-1 or PD-L1 inhibitor — immunotherapy	10 (3.6) [8.1]	22 (7.9) [14.6]	13 (4.7) [8.4]	25 (9.0) [13.4]
Radiotherapy	13 (4.7)	30 (10.8)	NR	NR
Other	11 (3.9) [8.9]	19 (6.8) [12.6]	17 (6.1) [11.0]	24 (8.6) [12.8]

FAS = full analysis set; NR = not reported; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

Note: Treatment beyond progression was not counted as a subsequent anticancer therapy. A patient may be counted in multiple rows if they receive more than 1 posttreatment anticancer therapy. Includes anticancer therapies with a start date after the last dose date of study treatment.

[a]The number of patients is shown with percentages calculated as the proportion of patients in the FAS and second as the proportion of patients who discontinued randomized study treatment. A patient may be counted in multiple rows if they receive more than 1 posttreatment anticancer therapy. Includes anticancer therapies with a start date after the last dose date of study treatment.

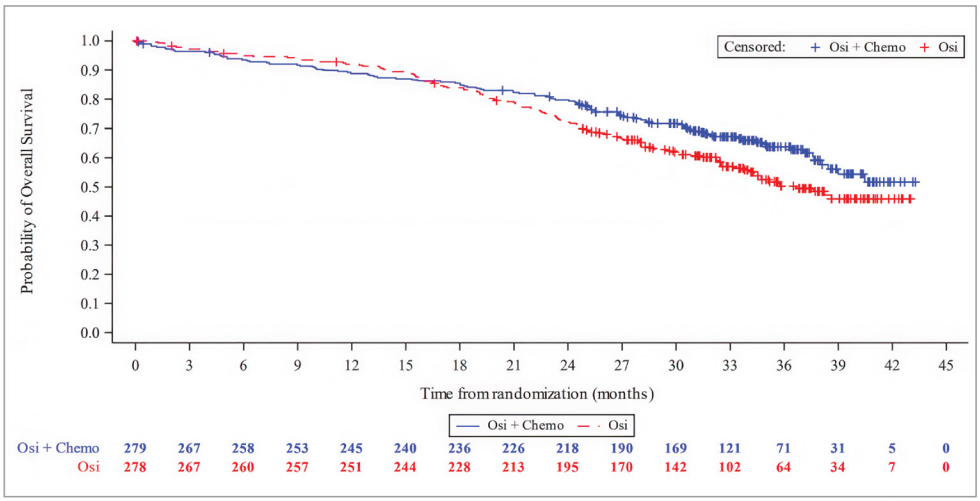
[b]Including pyrimidine analogues, vinca alcaloids, anthracyclines, podophyllotoxin derivatives.

Sources: FLAURA2 Clinical Study Report[16] and Drug Reimbursement Review sponsor submission.[17]

Overall Survival

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 plus 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 differences in the probability of being alive between osimertinib plus chemotherapy and osimertinib monotherapy at 24 and 36 months were 7.6 (95% CI, [redacted] to [redacted]) and 13.5% (95% CI, [redacted] to [redacted]), respectively. The median OS was 36.7 months in the osimertinib monotherapy group, but it was not reached in the osimertinib plus chemotherapy group. The Kaplan-Meier curves of the 2 treatment groups did not separate until about 16 months after randomization (Figure 2).

Figure 2: Kaplan-Meier Plot of OS in FLAURA2 (Randomized Period — FAS, Data Cut-Off Date: January 8, 2024)



FAS = full analysis set; OS = overall survival; Osi = osimertinib; Osi + Chemo = osimertinib in combination with pemetrexed and platinum-based chemotherapy.
Note: The values at the base of the figure indicate number of patients at risk.
Source: Drug Reimbursement Review sponsor submission.[17]

Table 17: Summary of Key Efficacy Results in FLAURA2 (Randomized Period – FAS)

Efficacy outcome	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)
OS (data cut-off: January 8, 2024)		
Number (%) of deaths as of data cut-off date	100 (35.8)	126 (45.3)
Median OS, months (95% CI)[a]	NC (38.0 to NC)	36.7 (33.2 to NC)
HR (95% CI) [2-sided P value][b]	0.75 (0.57 to 0.97) [0.0280]	
Probability of being alive at 24 months, % (95% CI)[a]	79.7 (74.5 to 84.0)	72.1 (66.4 to 77.0)
Difference in survival probability, % (95% CI)	7.6 ([redacted] to [redacted])	
Probability of being alive at 36 months, % (95% CI)[a]	63.7 (57.2 to 69.5)	50.3 (43.4 to 56.7)
Difference in survival probability, % (95% CI)	13.5 ([redacted] to [redacted])	
Still in survival follow-up, n (%)[c]	169 (60.6)	143 (51.4)
Terminated before death, n (%)[d]	10 (3.6)	9 (3.2)
Completed	0	0
Withdrawal by patient	9 (3.2)	8 (2.9)
Lost to follow-up	0	0
Other	1 (0.4)	1 (0.4)
Median follow-up (minimum to maximum) for OS in all patients, months	31.7 (0.1 to 43.3)	30.5 (0.1 to 43.0)

Efficacy outcome	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)
Median follow-up (minimum to maximum) for OS in censored patients, months	34.0 (0.2 to 43.3)	34.2 (0.1 to 43.0)
PFS according to investigator assessment (data cut-off: April 3, 2023)		
Number (%) of PFS events	120 (43.0)	166 (59.7)
Median PFS, months (95% CI)[a]	25.5 (24.7 to NC)	16.7 (14.1 to 21.3)
HR (95% CI) [2-sided P value][e]	0.62 (0.49 to 0.79) [< 0.0001]	
Probability of being progression-free at 12 months, % (95% CI)[a]	79.7 (74.3 to 84.1)	65.5 (59.5 to 70.8)
Difference in survival probability, % (95% CI)	14.2 ([redacted] to [redacted])	
Probability of being progression-free at 24 months, % (95% CI)[a]	57.2 (50.4 to 63.3)	40.8 (34.7 to 46.9)
Difference in survival probability, % (95% CI)	16.4 ([redacted] to [redacted])	
Progression, n (%)	120 (43.0)	166 (59.7)
RECIST progression[f]	95 (34.1)	158 (56.8)
Target lesions[g]	51 (18.3)	75 (27.0)
Nontarget lesions[g]	31 (11.1)	68 (24.5)
New lesions[g]	46 (16.5)	73 (26.3)
Death[h]	25 (9.0)	8 (2.9)
No progression, n (%)	159 (57.0)	112 (40.3)
Censored RECIST progression due to missing visits[i]	1 (0.4)	0
Censored death due to missing visits[i]	6 (2.2)	2 (0.7)
Progression-free at time of analysis[j]	143 (51.3)	106 (38.1)
Lost to follow-up[k]	0	0
Withdrew consent[k]	8 (2.9)	3 (1.1)
Discontinued study for other reasons[k]	1 (0.4)	1 (0.4)
Median follow-up (minimum to maximum) for PFS in all patients, months	19.5 (0 to 33.3)	16.5 (0 to 33.1)
Median follow-up (minimum to maximum) for PFS in censored patients, months	22.2 (0 to 33.1)	23.7 (0 to 33.1)
EORTC QLQ-LC13 (coughing symptoms subscale)[l] (data cut-off: April 3, 2023)		
Baseline		
n	253	252
Mean (SD)	32.4 (27.44)	31.3 (28.55)
Week 52		
n	169	139
Change from baseline LS mean (95% CI)	−14.08 (−16.69 to −11.48)	−13.03 (−15.83 to −10.23)

Efficacy outcome	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)
LS mean difference [95% CI]	−1.05 (−4.87 to 2.77)	
Average[m]		
n	253	251
Change from baseline LS mean (95% CI)	−13.23 (−14.85 to −11.62)	−11.19 (−12.83 to −9.55)
LS mean difference [95% CI]	−2.04 (−4.35 to 0.26)	
EORTC QLQ-LC13 (pain in chest subscale)[l] (data cut-off: April 3, 2023)		
Baseline		
n	253	252
Mean (SD)	16.9 (20.49)	21.2 (25.46)
Week 52		
n	169	139
Change from baseline LS mean (95% CI)	−6.65 (−8.92 to −4.38)	−7.03 (−9.47 to −4.59)
LS mean difference (95% CI)	0.38 (−2.96 to 3.72)	
Average[m]		
n	253	252
Change from baseline LS mean (95% CI)	−6.33 (−7.66 to −4.99)	−6.61 (−7.98 to −5.25)
LS mean difference (95% CI)	0.29 (−1.62 to 2.20)	
EORTC QLQ-LC13 (dyspnea symptom subscale)[l] (data cut-off: April 3, 2023)		
Baseline		
n	258	256
Mean (SD)	25.2 (26.27)	29.8 (29.09)
Week 52		
n	169	139
Change from baseline LS mean (95% CI)	−3.92 (−5.93 to −1.91)	−7.49 (−9.60 to −5.38)
LS mean difference [95% CI]	3.57 (0.65 to 6.48)	
Average[m]		
n	253	251
Change from baseline LS mean (95% CI)	−3.09 (−4.70 to −1.49)	−5.67 (−7.30 to −4.04)
LS mean difference (95% CI)	2.57 (0.28 to 4.86)	
EORTC QLQ-C30 (Global Health Status/QoL)[n] (data cut-off: April 3, 2023)		
Baseline		
n	258	256
Mean (SD)	65.7 (19.63)	63.5 (21.72)

Efficacy outcome	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)
Week 52		
n	170	143
Change from baseline LS mean (95% CI)	5.34 (3.17 to 7.51)	9.25 (6.99 to 11.51)
LS mean difference (95% CI)	−3.91 (−7.04 to −0.77)	
Average[m]		
n	253	253
Change from baseline LS mean (95% CI)	3.32 (1.67 to 4.98)	7.38 (5.70 to 9.07)
LS mean difference (95% CI)	−4.06 (−6.42 to −1.69)	

CI = confidence interval; EGFRm = EGFR–mutated; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module; FAS = full analysis set; HR = hazard ratio; LS = least squares; MMRM = mixed-effects model for repeated measures; NC = not calculable; OS = overall survival; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy; PFS = progression-free survival; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SD = standard deviation; vs. = versus.

[a]Calculated using the Kaplan-Meier method.

[b]The analysis was performed using a log-rank test stratified by race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO Performance Status (0 vs. 1), and method used for EGFRm tissue testing (central vs. local). An HR of less than 1 favours osimertinib plus chemotherapy. The efficacy boundary for significance for the first interim OS analysis (data cut-off date: April 3, 2023) was 0.00158, and the efficacy boundary for significance for the second interim OS analysis (data cut-off date: January 8, 2024) was 0.000001.

[c]Included patients known to be alive at the data cut-off date.

[d]Included patients with unknown survival status or patients who were lost to follow-up.

[e]The analysis was performed using a log-rank test stratified by race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1), and method used for EGFRm tissue testing (central vs. local). An HR of less than 1 favours osimertinib plus chemotherapy.

[f]Only included progression events that occurred within 2 consecutive scheduled visits (plus visit window) of the last evaluable assessment (or randomization).

[g]Target lesions, nontarget lesions, and new lesions were not necessarily mutually exclusive categories.

[h]Death in absence of RECIST progression, within 2 visits of baseline or last RECIST assessment (not evaluable is not considered a missing visit).

[i]RECIST progression or death occurred more than 2 consecutive scheduled visits (plus visit window) after last previous evaluable RECIST assessment or baseline if no valid postbaseline assessment. Patients were censored at last previous evaluable RECIST assessment or randomization date.

[j]Included patients known to be alive with no evaluable baseline RECIST assessment (censored at day 1) or censored at last evaluable assessment.

[k]Patients censored at last evaluable RECIST assessment or randomization.

[l]EORTC QLQ-LC13 negative-change scores from baseline represented less symptom severity, and thus improvement on symptom status. As a result, a negative difference in change scores between osimertinib plus chemotherapy and osimertinib monotherapy on EORTC QLQ-LC13 would favour osimertinib plus chemotherapy, and a positive difference in change scores would favour osimertinib monotherapy.

[m]Average included all patients contributing to the MMRM model over all visits (i.e., over 19 months or until progression disease). The score values were calculated by averaging across patients' overall mean across all visits. The analysis was performed using an MMRM analysis on the change from baseline in patient-reported outcome symptom score or functional at each visit up to 19 months (579 days), including treatment (as a random effect), visit (as fixed effect and repeated measure), and treatment by visit interaction as explanatory variables, with the baseline patient-reported outcome score as a covariate along with the baseline patient-reported outcome score by assessment interaction.

[n]EORTC QLQ-C30 positive-change scores on the Global Health Status/QoL subscales indicate improvement on health status/function, and therefore improvement in symptom status. As a result, positive difference in change scores between osimertinib plus chemotherapy and osimertinib monotherapy on Global Health Status/QoL would favour osimertinib plus chemotherapy.

Sources: FLAURA2 Clinical Study Report[16] and Drug Reimbursement Review sponsor submission.[17]

The OS was evaluated in patient subgroups by CNS metastases at baseline. As of January 8, 2024, in patients who had CNS metastases at baseline, the numbers of patients who had OS events were 44 of 116 (37.9%) patients treated with osimertinib plus chemotherapy and 62 of 110 (56.4%) patients treated with osimertinib monotherapy. The HR for OS in patients who had CNS metastases at baseline was 0.59 (95% CI, 0.40 to 0.87). In patients who did not have CNS metastases at baseline, the numbers of patients who had OS events were 56 of 163 (34.4%) treated with osimertinib plus chemotherapy and 64 of 168 (38.1%) treated

with osimertinib monotherapy. The HR for OS in patients who did not have CNS metastases at baseline was 0.89 (95% CI, 0.62 to 1.28).

The OS results from the previous data cut-off date (i.e., April 3, 2023) are shown in Appendix 1. The OS data were immature (26.8% maturity of data) as of April 3, 2023, and tested following the hierarchical testing procedure. There were 71 OS events (25.4%) in the osimertinib plus chemotherapy group versus 78 (28.1%) in the osimertinib monotherapy group. The HR for OS was 0.90 (95% CI, 0.65 to 1.24). The differences in the probability of being alive between osimertinib plus chemotherapy and osimertinib monotherapy at 12 and 24 months were −3.2% and 5.9%, respectively (95% CIs were not reported). Median OS was not reached in either treatment group. The Kaplan-Meier curves of the 2 treatment groups crossed multiple times.

Progression-Free Survival According to Investigator Assessment

As the data cut-off date April 3, 2023, with an overall data maturity of 51.3%, 120 PFS events (43.0%) according to investigator assessment were reported in the osimertinib plus chemotherapy group versus 166 PFS events (59.7%) according to investigator assessment in the osimertinib monotherapy group. The HR for PFS according to investigator assessment was 0.62 (95% CI, 0.49 to 0.79), in favour of osimertinib plus chemotherapy. The differences in the probability of being progression-free between osimertinib plus chemotherapy and osimertinib monotherapy 12 and 24 months were 14.2% (95% CI, [redacted] to [redacted]) and 16.4% (95% CI, [redacted] to [redacted]), respectively. The median PFS according to investigator assessment was 25.5 months (95% CI, 24.7 to NC) in the osimertinib plus chemotherapy group versus 16.7 (95% CI, 14.1 to 21.3) in the osimertinib monotherapy group. The Kaplan-Meier plots of OS are shown in Figure 3.

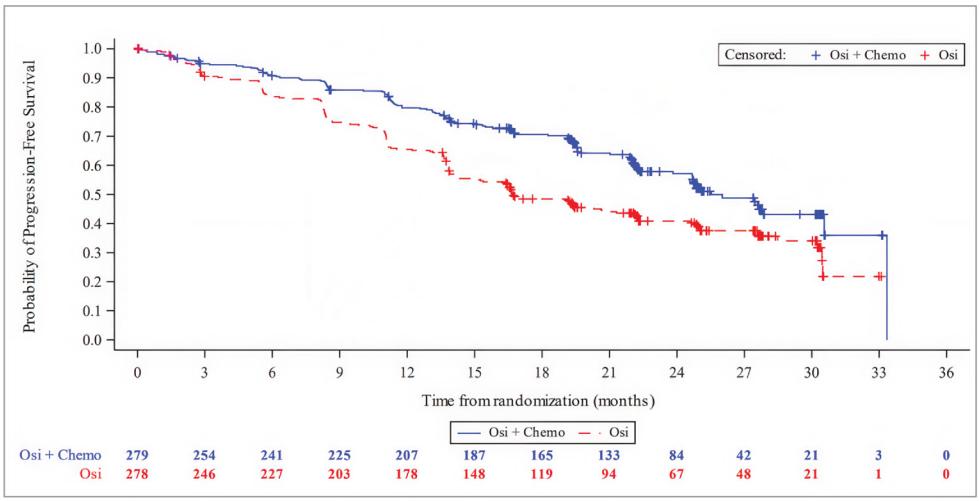
The results for PFS according to BICR were assessed as a sensitivity analysis (Appendix 1). As of April 3, 2023 (data maturity of 43.1%), there were 102 PFS events (36.6%) according to BICR in the osimertinib plus chemotherapy group versus 138 PFS events (49.6%) according to BICR in the osimertinib monotherapy group. The HR for PFS according to BICR was 0.62 (95% CI, 0.48 to 0.80), favouring osimertinib plus chemotherapy. The differences in the probability of being progression-free between osimertinib plus chemotherapy and osimertinib monotherapy at 12 and 24 months were 12.5% and 14.8%, respectively (95% CIs were not reported). The median PFS value according to BICR was 29.4 (25.1 to NC) months in the osimertinib plus chemotherapy group versus 19.9 (16.6 to 25.3) in the osimertinib monotherapy group. For PFS according to BICR, the Kaplan-Meier curves showed an early separation and did not cross throughout the remaining duration of follow-up (plot not shown).

Analysis of concordance between investigator and BICR assessment of PFS revealed an 82.1% agreement on progressions and nonprogressions in the osimertinib plus chemotherapy group, and a 75.6% agreement on progressions and nonprogressions in the osimertinib monotherapy group.

The results for PFS according to investigator assessment were also evaluated in patient subgroups by CNS metastases at baseline. As of April 3, 2023, in patients who had CNS metastases at baseline, the numbers of patients who had PFS events were 52 of 116 (44.8%) treated with osimertinib plus chemotherapy and 79 of 110 (71.8%) treated with osimertinib monotherapy. The HR for PFS according to investigator assessment in patients who had CNS metastases at baseline was 0.47 (95% CI, 0.33 to 0.66). In patients who did not have CNS metastases at baseline, the numbers of patients who had PFS events were 68 of 163 (41.7%) treated

with osimertinib plus chemotherapy and 87 of 168 (51.8%) treated with osimertinib monotherapy. The HR for PFS according to investigator assessment in patients who did not have CNS metastases at baseline was 0.75 (95% CI, 0.55 to 1.03).

Figure 3: Kaplan-Meier Plot of PFS According to Investigator Assessment in FLAURA2 (Randomized Period — FAS, Data Cut-Off Date: April 3, 2023)



Chemo = pemetrexed and platinum-based chemotherapy; FAS = full analysis set; Osi = osimertinib; PFS = progression-free survival.
Note: Values at the base of the figure indicate number of patients at risk.
Source: FLAURA2 Clinical Study Report[16] and Drug Reimbursement Review sponsor submission.[17]

EORTC QLQ-LC13

EORTC QLQ-LC13 negative-change scores from baseline represented less symptom severity, and therefore improvement in symptom status. As a result, a negative difference in change scores between osimertinib plus chemotherapy and osimertinib monotherapy on EORTC QLQ-LC13 would favour osimertinib plus chemotherapy.

The point estimates of difference in change from baseline scores of the coughing symptoms subscale between the osimertinib plus chemotherapy group and the osimertinib monotherapy group favoured osimertinib plus 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

EORTC QLQ-C30 positive-change scores on the Global Health Status/QoL subscales indicate improvement on health status/function, and therefore improvement on symptom status. As a result, a positive difference in change scores between osimertinib plus chemotherapy and osimertinib monotherapy on Global Health Status/QoL would favour osimertinib plus chemotherapy.

The point estimates of difference in change from baseline scores of the Global Health Status/QoL between the osimertinib plus chemotherapy and osimertinib monotherapy groups favoured osimertinib monotherapy at week 52 and across all visits (i.e., average).

Harms

During the safety run-in period (data cut-off date: February 19, 2020) of the FLAURA2 trial, 30 patients were involved, among whom 15 received osimertinib plus carboplatin-pemetrexed treatment and 15 received osimertinib plus cisplatin-pemetrexed treatment. AEs were reported in 90% (27 of 30) of the patients during the safety run-in period. All patients who received osimertinib plus carboplatin-pemetrexed had AEs, and 80% of the patients who received osimertinib plus cisplatin-pemetrexed treatment had AEs. The most common AEs were constipation (60%) for those on osimertinib plus carboplatin-pemetrexed treatment, and nausea (60%) for those on osimertinib plus cisplatin-pemetrexed. AEs of Common Terminology Criteria for Adverse Events grade 3 or higher were reported in 53.3% of the patients with osimertinib plus carboplatin-pemetrexed treatment and 20% of the patients with osimertinib plus cisplatin-pemetrexed treatment. SAEs were reported in 6 patients, 3 for each group. One patient with osimertinib plus carboplatin-pemetrexed treatment died. The cause was reported as suspected hypovolemic shock secondary to tumour-associated hemorrhage.

Harms data from the randomized period in the FLAURA2 trial are shown in Table 18. The data cut-off date was April 3, 2023.

Adverse Events

The proportions of patients experiencing AEs were similar between patients treated with osimertinib plus chemotherapy (100%) and patients treated with osimertinib monotherapy (97.5%). However, the proportion of patients experiencing the most common AEs (those reported in ≥ 20% patients in either treatment group), was greater among those treated with osimertinib plus chemotherapy compared with those treated with osimertinib monotherapy. Examples include anemia (46.4% versus 8.0%, respectively), nausea (43.1% versus 10.2%, respectively), and neutropenia (24.6% versus 3.3%, respectively). Moreover, a much higher proportion of patients treated with osimertinib plus chemotherapy experienced AEs of grade 3 or higher, compared with patients treated with osimertinib monotherapy (63.8% versus 27.3%, respectively). The most common AE of grade 3 and higher in patients treated with osimertinib plus chemotherapy was anemia (19.9%).

Serious Adverse Events

Higher percentages of patients in the osimertinib plus chemotherapy group experienced SAEs, compared to the percentages of patients in the osimertinib monotherapy group (37.7% versus 19.3%, respectively).

Discontinuation Due to Adverse Events

Discontinuation of osimertinib occurred in 10.9% of the patients in the osimertinib plus chemotherapy group and 6.2% of the patients in the osimertinib monotherapy. Within the osimertinib plus chemotherapy group, 45.3% of the patients discontinued chemotherapy, of whom 16.7% discontinued carboplatin or cisplatin treatment and 43.1% discontinued pemetrexed treatment.

Mortality

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

Notable Harms

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

Table 18: Summary of Harms Results in FLAURA2 (Randomized Period — Safety Analysis Set)

Adverse events	Osimertinib + chemotherapy (N = 276)	Osimertinib monotherapy (N = 275)
Most common AEs, n (%)		
Patients with any AE (reported in ≥ 20% patients in either treatment group)	276 (100)	268 (97.5)
Anemia	128 (46.4)	22 (8.0)
Diarrhea	120 (43.5)	112 (40.7)
Nausea	119 (43.1)	28 (10.2)
Decreased appetite	85 (30.8)	26 (9.5)
Constipation	81 (29.3)	28 (10.2)
Rash	77 (27.9)	57 (20.7)
Fatigue	76 (27.5)	26 (9.5)
Vomiting	73 (26.4)	17 (6.2)
Neutropenia	68 (24.6)	9 (3.3)
Stomatitis	68 (24.6)	50 (18.2)
Paronychia	65 (23.6)	73 (26.5)
Decreased neutrophil count	62 (22.5)	16 (5.8)
Increased alanine aminotransferase	56 (20.3)	21 (7.6)
COVID-19	57 (20.7)	39 (14.2)
Patients with any AE of CTCAE grade 3 or higher (reported in ≥ 5% of patients in either treatment)	176 (63.8)	75 (27.3)
Anemia	55 (19.9)	1 (0.4)
Neutropenia	37 (13.4)	2 (0.7)
Decreased neutrophil count	31 (11.2)	2 (0.7)

Adverse events	Osimertinib + chemotherapy (N = 276)	Osimertinib monotherapy (N = 275)
Decreased platelet count	21 (7.6)	0
Thrombocytopenia	19 (6.9)	3 (1.1)
SAEs, n (%)		
Patients with any SAE (reported in ≥ 2% of patients in either treatment group)	104 (37.7)	53 (19.3)
Anemia	9 (3.3)	0
COVID-19	7 (2.5)	2 (0.7)
Pneumonia	7 (2.5)	6 (2.2)
Febrile neutropenia	6 (2.2)	0
Platelet count decreased	6 (2.2)	0
Pulmonary embolism	6 (2.2)	2 (0.7)
Patients who discontinued treatment due to AEs, n (%)		
Patients with any AE leading to discontinuation of any study treatment	132 (47.8)	17 (6.2)
Patients with any AE leading to discontinuation of osimertinib	30 (10.9)	17 (6.2)
Patients with any AE leading to discontinuation of chemotherapy	125 (45.3)	NA
Discontinuation of carboplatin/cisplatin treatment	46 (16.7)	NA
Discontinuation of pemetrexed treatment	119 (43.1)	NA
Deaths, n (%)		
Patients with AE with outcome of death (reported in ≥ 2 patients in either treatment group)	18 (6.5)	8 (2.9)
Pulmonary embolism	3 (1.1)	0
Pneumonia	3 (1.1)	0
Cardiac failure	2 (0.7)	0
COVID-19 pneumonia	0	4 (1.5)
Notable harm, n (%)		
ILD or pneumonitis[a]	9 (3.3)	10 (3.6)
Cardiac failure	25 (9.1)	10 (3.6)
Hematological toxicities		
Febrile neutropenia	11 (4.0)	0
Thrombocytopenia	51 (18.5)	12 (4.4)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ILD = interstitial lung disease; NA = not applicable; SAE = serious adverse event.

Note: Data cut-off date: April 3, 2023.

[a]Included the following Medical Dictionary for Regulatory Activities 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.

Source: FLAURA2 Clinical Study Report,[16] Drug Reimbursement Review sponsor submission.[17] (Details included in the table are from the sponsor's Summary of Clinical Evidence.[1])

Critical Appraisal

Internal Validity

The FLAURA2 trial investigated the use of osimertinib plus chemotherapy in patients with locally advanced, metastatic, or recurrent EGFRm (ex19del and/or L858R) NSCLC compared to osimertinib monotherapy. A total of 557 patients were randomized to the osimertinib plus chemotherapy group (n = 279) and the osimertinib monotherapy group (n = 278), stratified by race (Chinese/Asian versus non-Chinese/Asian versus non-Asian), WHO PS (0 versus 1), and methods used for tissue testing (central versus local EGFR method) to minimize potential imbalances between the study groups that might bias the results. The trial used central randomization and concealed patient allocation during the randomization process.[12] Overall, the baseline characteristics presented in the Clinical Study Report were similar and balanced between the treatment groups.

Generally, no serious concerns were identified in protocol amendments and protocol deviations. According to the clinical experts consulted by the review team, the use of concomitant medications reflected the clinical practice settings, and the types of medications used were not expected to modify treatment effects. In the FLAURA2 trial, patients were allowed to receive subsequent anticancer treatment at the investigator's discretion following discontinuation of the randomized treatment. Overall, 20.4% of patients in the osimertinib plus chemotherapy group and 32.7% of patients in the osimertinib monotherapy group received subsequent anticancer therapy, among whom 14.7% of the osimertinib plus chemotherapy group and 29.1% of the osimertinib monotherapy group received subsequent chemotherapy. According to the clinical experts consulted by the review team, these differences were not a concern because platinum chemotherapy is not typically expected to be used in patients who have received osimertinib plus chemotherapy. The review team also determined that, because the percentage of patients who had subsequent therapies was lower in the osimertinib plus chemotherapy group than in the osimertinib monotherapy group, the risk of bias leading to overestimation of treatment effects (the OS effect) was low.

Because the FLAURA2 trial was open-label, investigators and patients were aware of the assigned treatment.[12] The primary outcome was PFS according to 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 according to investigator assessment was considered relatively low by the review team. First, results of PFS according to investigator assessment were consistent with those of PFS according to BICR assessment. Second, the analysis of concordance between PFS according to investigator and according to BICR assessment showed that there was an 82.1% agreement on progressions and nonprogressions in the osimertinib plus chemotherapy group, and a 75.6% agreement on progressions and nonprogressions in the osimertinib monotherapy group, suggesting acceptable agreement between the ways of assessment. Similarly, for HRQoL outcomes (i.e., EORTC QLQ LC-13 and EORTC QLQ-C30), which had unblinded assessment, the risk of performance bias also was considered relatively low, and no evidence in the data indicated that 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 plus chemotherapy group, 230 forms were expected and 180 forms were received and evaluated, for a

compliance rate of 78.3%). The type of data missing (e.g., completely at random, at random, or not at random) is unclear, as is how the missingness in data would affect the HRQoL assessment, resulting in increased uncertainty.

The OS was considered by the clinical experts consulted by the review team as the most clinically relevant efficacy end point for patients with NSCLC. The OS data at the data cut-off dates of April 3, 2023 (26.8% maturity of data) and January 8, 2024 (40.6% maturity of data) were evaluated by the review team. Multiplicity was controlled using the hierarchal statistical testing for OS and PFS only. The efficacy boundary for statistical significance for the updated OS analysis (data cut-off date: January 8, 2024) was 0.000001. Although the P value was 0.028 for the HR of the updated OS analysis, there was therefore no statistical significance. 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 made the OS estimates as of April 3, 2023, less valid. A late divergence of the Kaplan-Meier curves of the updated OS (data cut-off date: January 8, 2024) was observed during visual inspection of the Kaplan-Meier curves; the curves of the osimertinib plus chemotherapy group and the osimertinib monotherapy group did not separate until approximately 16 months after randomization. According to the clinical experts consulted by the review team, the delayed separation of survival curves reflected what they expected, as is often seen in patients receiving a combination therapy consisting of chemotherapy. However, the late divergence of survival curves may have implications for the statistical analysis used in the FLAURA2 trial (i.e., whether the proportional hazards assumption was violated), which introduced uncertainty to the OS evidence. Where there is a delayed separation of survival curves, a sensitivity analyses that assesses 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).

External Validity

The clinical experts consulted by the review team noted that the chemotherapy protocols were appropriate and generally reflective of the standard dose schedules used for adult patients in Canada. The clinical experts also noted that, overall, the patient eligibility criteria of the FLAURA2 trial were appropriate in clinical trials for patients with NSCLC and aligned with the selection criteria in settings in Canada when identifying suitable candidates for osimertinib plus chemotherapy. However, the clinical experts noted that, in real-world settings, patients generally have a poorer performance status at the start of therapy. In other words, patients with a performance status of 2 could also be considered for osimertinib plus chemotherapy.

The FLAURA2 trial did not allow eligible patients to have prior treatment with an EGFR TKI. Also, the trial required eligible patients to be off other adjuvant and neoadjuvant therapies (e.g., chemotherapy, radiotherapy, immunotherapy, biologic therapy, and investigational drugs) at least 12 months before the development of recurrent disease. According to the clinical experts consulted by the review team, because osimertinib monotherapy has become first-line treatment for EGFRm, patients who had received prior EGFR TKI should also be considered for osimertinib plus chemotherapy. The clinical experts consulted by the review team also noted that, following completion of adjuvant chemotherapy alone or adjuvant osimertinib, patients with a 6-month disease-free interval before the development of recurrent disease could

be considered eligible for osimertinib plus chemotherapy. The clinical experts consulted by the review team further noted that patients with a disease-free interval of less than 6 months may be eligible for osimertinib plus chemotherapy at the discretion of the treating physician.

The histology type of most patients enrolled in the FLAURA2 trial (> 98% for both groups) was adenocarcinoma. According to the clinical experts consulted by the review team, findings from the trial could still be generalizable to patients with other histology types (e.g., adenosquamous carcinoma) because it is the existence of the driving mutation that 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 plus 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:[13,14]

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate — the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. We use the word "likely" for evidence of moderate certainty (e.g., "X intervention likely results in Y outcome").
- **Low certainty**: Our confidence in the effect estimate is limited — the true effect may be substantially different from the estimate of the effect. We use the word "may" for evidence of low certainty (e.g., "X intervention may result in Y outcome").
- **Very low certainty**: We have very little confidence in the effect estimate — the true effect is likely to be substantially different from the estimate of effect. We describe evidence of very low certainty as "very uncertain."

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. 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 estimates published in the literature.[15] For harm events due to the unavailability of the absolute difference in effects, the certainty of evidence was summarized narratively.

Results of GRADE Assessments

Table 2 presents the GRADE summary of findings for osimertinib plus chemotherapy versus osimertinib monotherapy in patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations.

Long-Term Extension Studies

No long-term extension studies were identified for this review.

Indirect Evidence

No indirect evidence was identified for this review.

Studies Addressing Gaps in the Systematic Review Evidence

No studies addressing gaps in the pivotal and RCT evidence were identified for this review.

Discussion

Summary of Available Evidence

One phase III, open-label RCT, FLAURA2, (N = 557, including 13 patients in Canada) was included in the systematic literature review conducted by the sponsor. FLAURA2 enrolled adult patients who were diagnosed with pathologically confirmed nonsquamous NSCLC that was locally advanced (clinical stage IIIB, IIIC), metastatic (clinical stage IVA or IVB), or recurrent (according to version 8 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology) and whose tumour harboured 1 of the 2 common EGFR mutations — ex19del or L858R — either alone or in combination with other EGFR mutations. Patients were randomized to the osimertinib plus chemotherapy group (n = 279) and the osimertinib monotherapy group (n = 278), stratified by ethnicity, WHO PS, and methods used for tissue testing. The primary objective was to compare the treatment effect between osimertinib plus chemotherapy versus osimertinib monotherapy, measured by PFS according to 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 FLAURA2 trial is ongoing, and the data cut-off date was April 3, 2023. OS data were updated on January 8, 2024, and assessed in this report. The median age of enrolled patients was 61.0 years (range = 26 to 85). The majority (61.4%) of enrolled patients were female, 63.7% were Asian, 62.8% had a WHO PS of 1, 53.1% had an ex19del mutation (as determined by a central cobas tissue test), and 96.2% had metastatic NSCLC at baseline.

Interpretation of Results

Efficacy

Prolonging life, controlling disease progression, and improving HRQoL were highlighted by both patients and clinicians as critical treatment goals in advanced NSCLC. In the FLAURA2 pivotal trial, these needs were captured by the evaluation of efficacy outcomes such as OS, PFS, EORTC QLQ LC-13, as well as EORTC QLQ LC-C30.

The OS was considered the most clinically relevant efficacy end point by the clinical experts consulted by the review team. The maturity of OS data as of the data cut-off date of April 3, 2023, was only 26.8%. As a small number of events can lead to unstable and unreliable estimates of OS, the review team did not consider these data at the first interim analysis for the outcome as interpretable. The clinical experts consulted by the review team agreed that the immature results limited the applicability to clinical practice.

[redacted]. The HR for the updated OS was 0.75 (95% CI, 0.57 to 0.97; P = 0.028) in favour of osimertinib plus chemotherapy. The sponsor controlled for multiple statistical testing, and the efficacy boundary for statistical significance for the updated OS analysis was 0.000001; as a result, the updated analysis for OS did not reach statistical significance. The differences in the probability of being alive between the osimertinib plus chemotherapy group and the osimertinib monotherapy group at 24 and 36 months were 7.6 (95% CI, [redacted] to [redacted]) and 13.5% (95% CI, [redacted] to [redacted]), respectively. Although the sponsor did not submit an empirically validated MID for OS, the clinical experts consulted by the review team noted that a 10% or higher between-group difference in the probability of being alive at 24 and 36 months would be clinically significant, and a between-group difference between 5% and 10% would suggest that the treatment effect may be clinically relevant. Although the point estimate at 36 months exceeded 10% and the point estimate at 24 months fell between 5% and 10%, which favoured the osimertinib plus chemotherapy group, the certainty of OS evidence was affected by concerns about imprecision as the lower bound of the 95% CIs included the 5% threshold. The 36-month OS estimate had further imprecision associated with the reduction in the number of patients remaining at risk. For example, there was a high percentage of censoring (approximately

40% in each group) between month 33 and month 36. Moreover, according to the clinical experts consulted by the review team, although the OS findings were encouraging, a longer follow-up is warranted as the median OS for the osimertinib plus chemotherapy group was not reached.

The results of the primary efficacy end point in the FLAURA2 trial, PFS according to investigator assessment (data cut-off date: April 3, 2023; data maturity: 51.3%), revealed that osimertinib plus chemotherapy was more efficacious compared with osimertinib monotherapy in terms of delaying disease progression. The results of the sensitivity analysis of PFS according to BICR were generally consistent with the results of PFS according to investigator assessment. The HR for PFS according to investigator assessment was 0.62 (95% CI, 0.49 to 0.79; P < 0.0001), favouring osimertinib plus chemotherapy. The differences in the probability of being progression-free between osimertinib plus chemotherapy and osimertinib monotherapy 12 and 24 months were 14.2% (95% CI, [redacted] to [redacted]) and 16.4% (95% CI, [redacted] to [redacted]), respectively. According to the clinical experts consulted by the review team, the threshold to determine the clinical importance could be 10% or higher for the between-group difference in the probability of being progression-free at 24 and 36 months. Although the point estimates at 12 and 24 months were both higher than 10%, the lower bound of the 95% CIs crossed the threshold, indicating the possibility of both benefits and little to no benefit with osimertinib plus chemotherapy versus osimertinib monotherapy for PFS, thereby lowering the certainty of PFS evidence to moderate.

A closer examination of the PFS events identified other potential sources of uncertainty. In total, 43% and 59.7% of the patients had PFS events in the osimertinib plus chemotherapy group and the osimertinib monotherapy group, respectively. Out of these patients, 34.1% in the osimertinib plus chemotherapy group versus 56.8% in the osimertinib monotherapy group had RECIST-defined progression. However, a higher percentage of deaths in the osimertinib plus chemotherapy group contributed to PFS events compared with the osimertinib monotherapy group (9% versus 2.9%). Upon request, the sponsor provided further information on the patients who died during the follow-up of PFS (as of April 3, 2023). After examining the additional information (i.e., individual patient deaths), the review team in consultation with clinical experts noted that 9 deaths occurred within the 63 days since the start of the FLAURA2 trial in the osimertinib plus chemotherapy group versus only 1 death in the osimertinib monotherapy group during the same time period. However, the relatively small number of patients and limited information provided in the descriptions of the circumstances surrounding the deaths made it difficult to identify a clear association between treatment and an AE leading to death. The disparity in death occurrence at an early study stage between the osimertinib plus chemotherapy group and the osimertinib monotherapy group could not be explained with the available information. However, after weighing these deaths against the fewer total deaths with osimertinib plus chemotherapy versus osimertinib monotherapy, the review team determined that the results of the FLAURA2 trial suggest that the combination treatment likely leads to fewer PFS events.

Data on HRQoL were assessed based on the least squares mean 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). The certainty of the HRQoL evidence from the FLAURA2 trial is considered very low, and the evidence is uncertain about the effect of osimertinib plus chemotherapy on the coughing symptoms subscale, pain in chest subscale, and dyspnea symptom subscale of EORTC

QLQ-LC13 as well as on the Global Health Status/QoL of EORTC QLQ-LC13 at week 52, compared to osimertinib monotherapy. From a clinical perspective, the clinical experts consulted by the review team expected within-group improvement of HRQoL in both the osimertinib plus chemotherapy group and the osimertinib monotherapy group but they did not expect a between-group improvement. The HRQoL results generally met the expectation of the clinical experts. All within-group differences indicated improvements. 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 across all visits (i.e., average) showed non-null improvements, favouring the osimertinib monotherapy group.

According to the clinical experts consulted by the review team, CNS metastasis prevention and disease control in patients with NSCLC are important aspects of treatment goals as NSCLC is associated with CNS disease, resulting in morbidity and disease progression. In the FLAURA2 trial, 11 subgroups were prespecified, 1 of which was CNS metastases at baseline (yes or no). Both OS and PFS according to investigator assessment were evaluated in the CNS metastases subgroup, with the results suggesting that osimertinib plus chemotherapy is more efficacious than monotherapy in patients with CNS metastases than in those who do not have CNS metastases at baseline. For example, the HR for PFS according to investigator assessment in patients who had CNS metastases at baseline was 0.47 (95% CI, 0.33 to 0.66), whereas the HR for PFS in patients who did not have CNS metastases at baseline was 0.75 (95% CI, 0.55 to 1.03). However, despite differences in the percentages of events and point estimates for the HRs between the subgroups suggesting patients with CNS metastases may have greater benefit than those without CNS metastases, the subgroup results are inconclusive due to important uncertainties. The study was not adequately designed for subgroup analyses by CNS metastases at baseline (CNS metastases were not included in the sample size calculation and were not a stratification factor for randomization) and no formal testing for subgroup interaction was available. As a result, any difference identified may be due to chance and not a true difference in treatment effect.

Harms

The combination osimertinib plus chemotherapy in the first-line treatment setting likely results in an increase in the occurrence of harms outcomes among patients with NSCLC, compared to the osimertinib monotherapy. As of the April 3, 2023, data cut-off, the FLAURA2 trial showed that a higher percentage of patients treated with osimertinib plus chemotherapy experienced AEs of grade 3 or higher (63.8% versus 27.3%, respectively), SAEs (37.7% versus 19.3%, respectively), discontinuation of any study treatment (47.8% versus 6.2%, respectively), and death (6.5% versus 2.9%), compared to the percentage of patients treated with osimertinib monotherapy. ILD or pneumonitis, cardiac failure, and hematological toxicities (i.e., febrile neutropenia and thrombocytopenia) were considered notable harms. While the percentages of patients who had ILD or pneumonitis in the osimertinib plus chemotherapy group and the osimertinib monotherapy group were similar (3.3% versus 3.6%, respectively), higher proportions of patients in the osimertinib plus chemotherapy group experienced cardiac failure (9.1% versus 3.6%, respectively), febrile neutropenia (4.0% versus 0.0%, respectively), and thrombocytopenia (18.5% versus 4.4%).

The clinical experts consulted by the review team noted that the higher percentage of patients who discontinued any study treatment in the osimertinib plus chemotherapy group compared with the osimertinib monotherapy group was what they would expect to see in clinical practice, and therefore was not a serious concern. According to the clinical experts consulted by the review team, ILD or pneumonitis, which is a documented AE associated with osimertinib (the product monograph includes a serious warnings and precautions box), was similar between groups (3.3% versus 3.6%, respectively), as expected. The clinical experts consulted by the review team expressed concerns about anemia of grade 3 or higher (19.9% in the osimertinib plus chemotherapy group versus 0.4% in the osimertinib monotherapy group) as anemia-associated symptoms (e.g., feeling tired) would have a substantial impact on patients.

The patient input for this review noted that, in addition to being effective, osimertinib plus chemotherapy was also expected to have manageable side effects. After weighing the potential benefits and harms with the updated OS data, the clinical experts consulted by the review team noted that the AE profile in the osimertinib plus chemotherapy group was generally expected to be seen in clinical practice when using a combination therapy consisting of chemotherapy, there were no serious concerns with managing these AEs in clinical practice, and overall the evidence with updated OS data from the FLAURA2 trial suggests that the benefits of using osimertinib plus chemotherapy outweigh its potential harms. The clinical experts consulted by the review team also noted that patients who had received osimertinib monotherapy as first-line treatment typically would receive chemotherapy upon experiencing progressive disease in the second-line setting and would likely experience chemotherapy-associated harms at that time. Still, the clinical experts consulted by the review team noted that they predicted that the total harms would be similar between patients who received osimertinib plus chemotherapy as a combination therapy and patients who received osimertinib and chemotherapy in a sequential order. The clinical experts consulted by the review team further noted that, in clinical practice, clinicians need to determine patient eligibility with caution and on a case-by-case basis, particularly for patients who are more susceptible to the increased toxicity of osimertinib plus chemotherapy, such as older patients, patients with multiple comorbidities, and/or those with poorer performance status.

Conclusion

The pivotal FLAURA2 trial is an ongoing, phase III, open-label RCT comparing the efficacy and safety of osimertinib plus chemotherapy and osimertinib monotherapy in patients with locally advanced, metastatic, or recurrent EGFRm (ex19del or L858R) NSCLC. Overall, efficacy evidence from the FLAURA2 trials suggests that osimertinib plus chemotherapy showed added clinical benefits in OS and PFS in the intention-to-treat trial population, compared with osimertinib monotherapy. Results of these clinically relevant efficacy end points were generally in favour of osimertinib plus chemotherapy over osimertinib monotherapy. Osimertinib plus chemotherapy may result in an increase in the probability of being alive at 24 and 36 months (low certainty) and likely lead to an increase in the probability of being progression-free at 12 and 24 months (moderate certainty), compared to osimertinib monotherapy. Because of the immaturity of the OS data (40.6%) and the fact that the median OS was not reached as of January 8, 2024, uncertainty remains in the OS results. The study subgroup analyses suggested the potential for greater benefit with osimertinib plus

chemotherapy versus osimertinib monotherapy in patients with CNS metastases at baseline compared with patients without CNS metastases at baseline. However, uncertainty related to the trial design and analysis of these subgroups (including no formal interaction tests) prevented drawing a definitive conclusion. The review team concluded with moderate to high certainty that the combination use of osimertinib plus chemotherapy is associated with an increased frequency of grade 3 or higher AEs, SAEs, WDAEs, and deaths reported as AEs compared to osimertinib monotherapy.

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Appendix 1: Detailed Outcome Data

Please note that this appendix has not been copy-edited.

Table 19: OS in FLAURA2 (Randomized Period — FAS, Data Cut-off Date: April 3, 2023)

Efficacy outcome	FLAURA2	
	Osimertinib + chemotherapy (N = 279)	Osimertinib monotherapy (N = 278)
OS (data cut-off: April 3, 2023)		
Number (%) of deaths as of data cut-off date	71 (25.4)	78 (28.1)
Median OS (months) (95% CI)[a]	NC (31.9 to NC)	NC (NC to NC)
HR (95% CI) [2-sided P value][b]	0.90 (0.65 to 1.24) [0.5238]	
Still in survival follow-up, n (%)[c]	197 (70.6)	191 (68.7)
Terminated before death, n (%)[d]	11 (3.9)	9 (3.2)
Completed	0	0
Withdrawal by patients	10 (3.6)	8 (2.9)
Lost to follow-up	0	0
Other	1 (0.4)	1 (0.4)
Median (min, max) follow-up for OS in all patients, months	23.9 (0.1 to 34.1)	23.7 (0.1 to 33.9)
Median (min, max) follow-up for OS in censored patients, months	25.0 (0.2 to 34.1)	25.1 (0.1 to 33.9)

CI = confidence interval; FAS = full analysis set; HR = hazard ratio; NC = not calculable; NR = not reported; OS = overall survival; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy

[a]Calculated using the Kaplan-Meier method.

[b]The analysis was performed using a log-rank test stratified by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non Asian), WHO PS (0 vs. 1), and method used for EGFRm tissue testing (central vs. local). An HR < 1 favours osimertinib plus chemotherapy. The efficacy boundary for significance for the first interim OS analysis (data cut-off date: April 3, 2023) was 0.00158, and the efficacy boundary for significance for the second interim OS analysis (data cut-off date: January 8, 2024) was 0.000001.

[c]Included patients known to be alive at the data cut-off date.

[d]Included patients with unknown survival status or patients who were lost to follow-up.

Source: FLAURA2 Clinical Study Report,[16] Drug Reimbursement Review sponsor submission.[17]

Table 20: Sensitivity Analysis of PFS According to BICR in FLAURA2 (Randomized Period — FAS, Data Cut-off Date: April 3, 2023)

Efficacy outcome	FLAURA2	
	Osimertinib + chemotherapy (N = 279)	Osimertinib (N = 278)
PFS according to BICR in FAS		
Number (%) of PFS events	102 (36.6)	138 (49.6)
Median PFS (months) (95% CI)[a]	29.4 (25.1 to NC)	19.9 (16.6 to 25.3)
HR (95% CI) [2-sided P value][b,c]	0.62 (0.48 to 0.80) [0.0002]	
Probability of being progression-free at 12 months (%) (95% CI)[a]	79.8 (74.5 to 84.2)	67.3 (61.2 to 72.6)
Difference in probability (%) (95% CI)	12.5 (NR)	
Probability of being progression-free at 24 months (%) (95% CI)[a]	61.6 (54.8 to 67.7)	46.8 (40.2 to 53.2)
Difference in probability (%) (95% CI)	14.8 (NR)	
Progression, n (%)	102 (36.6)	138 (49.6)
RECIST progression[d]	75 (26.9)	124 (44.6)
Target lesions[e]	48 (17.2)	79 (28.4)
Nontarget lesions[e]	21 (7.5)	34 (12.2)
New lesions[e]	23 (8.2)	47 (16.9)
Death[f]	27 (9.7)	14 (5.0)
No progression, n (%)	177 (63.4)	140 (50.4)
Censored RECIST progression due to missing visits[g]	1 (0.4)	0
Censored death due to missing visits[g]	11 (3.9)	16 (5.8)
Progression-free at time of analysis[h]	154 (55.2)	119 (42.8)
Lost to follow-up[i]	0	0
Withdrawn consent[i]	10 (3.6)	4 (1.4)
Discontinued study for other reasons[i]	1 (0.4)	1 (0.4)

BICR = blinded independent central review; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; NC = not calculable; NR = not reported; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

[a]Calculated using the Kaplan-Meier method.

[b]The analysis was performed using a log-rank test stratified by race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1), and method used for EGFRm tissue testing (central vs. local). An HR < 1 favours osimertinib plus chemotherapy.

[c]Nominal P value.

[d]Only included progression events that occurred within 2 consecutive scheduled visits (plus visit window) of the last evaluable assessment (or randomization).

[e]Target lesions, nontarget lesions, and new lesions were not necessarily mutually exclusive categories.

[f]Death in the absence of RECIST progression, within 2 visits of baseline or last RECIST assessment (Not Evaluable is not considered as missing visit).

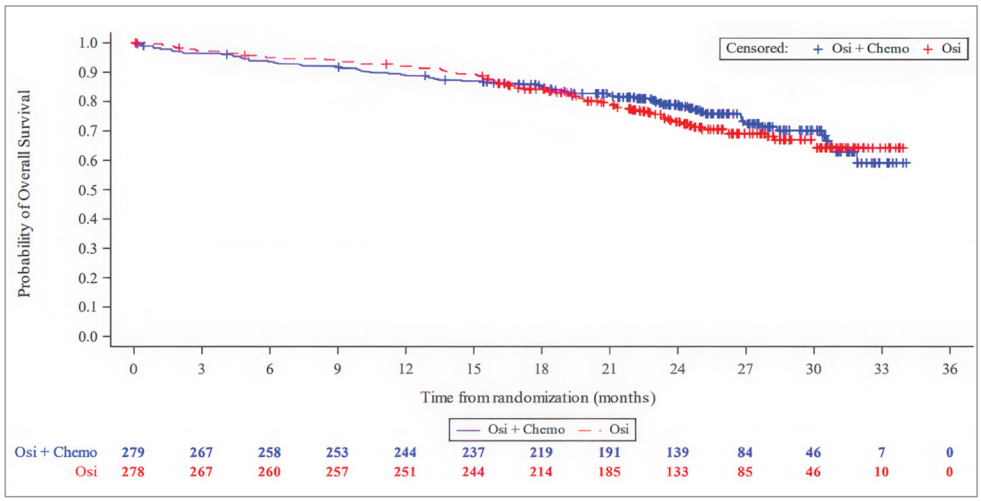
[g]RECIST progression or death occurred more than 2 consecutive scheduled visits (plus visit window) after last previous evaluable RECIST assessment or baseline if no valid postbaseline assessment. Patients are censored at last previous evaluable RECIST assessment or randomization date.

[h]Included patients, known to be alive, with no evaluable baseline RECIST assessment (censored at Day 1) or censored at last evaluable RECIST assessment.

[i]Patients censored at last evaluable RECIST assessment or randomization.

Sources: FLAURA2 Clinical Study Report[16] and Drug Reimbursement Review sponsor submission.[17]

Figure 4: Kaplan-Meier Plot of OS in FLAURA2 (Randomized Period — FAS, Data Cut-off Date: April 3, 2023)

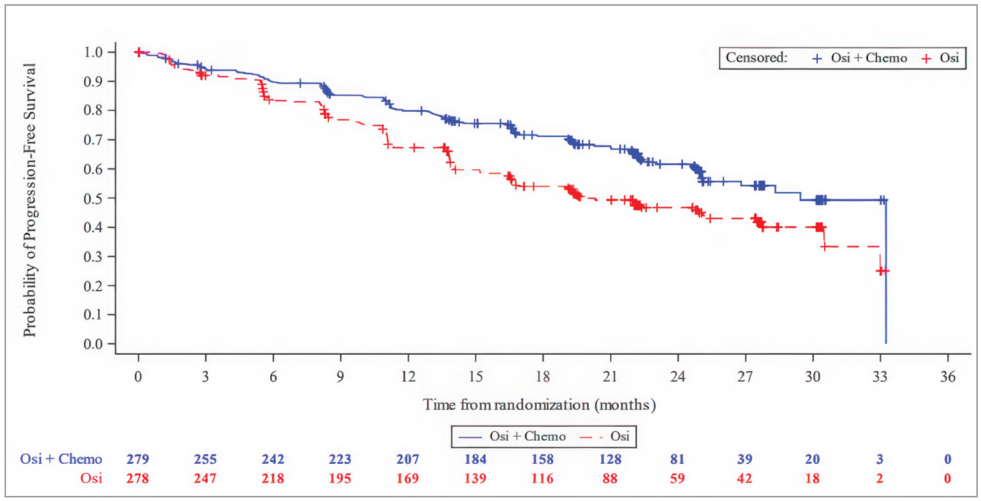


Note: Osimertinib + chemotherapy was denoted as Osi + Chemo, and osimertinib monotherapy as Osi in sponsor's Clinical Study Report. The values at the base of the figure indicate number of patients at risk.

OS = overall survival; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy

Source: FLAURA2 Clinical Study Report,[16] Drug Reimbursement Review sponsor submission[17]

Figure 5: Kaplan-Meier Plot of PFS According to BICR in FLAURA2 (Randomized Period — FAS, Data Cut-Off Date: April 3, 2023)



BICR = blinded independent central review; osimertinib + chemotherapy = osimertinib in combination with pemetrexed and platinum-based chemotherapy; PFS = progression-free survival.

Note: Osimertinib + chemotherapy was denoted as Osi + Chemo, and osimertinib monotherapy as Osi in sponsor's Clinical Study Report. The values at the base of the figure indicate number of patients at risk.

Sources: FLAURA2 Clinical Study Report[16] and Drug Reimbursement Review sponsor submission.[17]

Appendix 2: Post-Progression Survival and Time to Progression

Please note that this appendix has not been copy-edited.

In the correspondence with the review team,[48] the sponsor provided 2 systematic reviews with meta-analyses[49,50] and 2 retrospective studies[51,52] that suggested a correlation ($r > 0.8$) between post-progression survival (PPS) and OS in patients in first-line setting for advanced or metastatic NSCLC. Two meta-analyses[53,54] indicated that time to progression (TTP) accounted for only one-fifth to one-third ($R^2 = 0.19$ and $R^2 = 0.33$) of the variance in OS in patients with advanced NSCLC.

The methods used in the provided studies aligned with those that are recommended. For example, meta-analytic approaches that provide estimates of trial level correlation (often measured using r and R^2) are recommended by several HTA agencies as part of determining end point surrogacy,[55] but there is no consensus – currently – on what values of these measures constitute strong evidence or that an end point is a "good surrogate." As well, establishing an end point as a surrogate for a patient important clinical outcome is multidimensional and there is increasingly emphasis to not rely on statistical correlation alone.[56-60] Hotta et al.[53] in discussing the results of their meta-analysis on the correlation between TTP and OS acknowledged the need for studies that specifically study the interplay between causal pathways of NSCLC, the mechanism of action of the treatment of interest, and the links between intermediate and terminal outcomes.

Additionally, correlation and regression methods do not comprehensively account for relevant uncertainty, including the variability and other sources of uncertainty associated with the treatment effect on the surrogate end point.[57] This limitation was acknowledged in some of the provided articles. Moreover, assessing the certainty and precision of the correlation results was hampered by the lack of reporting of confidence intervals in most of the published articles. Thus, the reported values represent a summary statistic and do not provide information on the distribution of the correlations. This is important given the variability in the correlation between each of PPS and TTP with OS based on the subgroups and factors analyzed in the reviewed studies. For example, 1 meta-analysis reported an overall R^2 for the correlation between the median TTP ratio (between trial arms) and the median OS ratio of 0.33, but the estimate varied across subgroups ($R^2 = 0.16$ in trials with no description of the primary end point definition to 0.51 in studies[53] that used cisplatin as part of the initial treatment).

Other important limitations with the provided evidence for surrogacy of PPS and TTP include, but are not limited to:

- Retrospective design of the individual studies that were set at a single cancer centre in Japan with relatively smaller sample sizes ($N < 100$ patients).[51,52]
- It was difficult to assess the systematic reviews and meta-analytic methods due to limited reporting of the search strategies, eligibility criteria (including intervention, intervention, comparison, outcome, study design [PICOS]), and statistical analyses including assessments of the robustness of the results (e.g., lack of assessments for publication bias). Reviewers could not conclude with confidence that the methods used aligned with those that are accepted.

- Most of the analyses did not (or could not for lack of information) account for differences in and the effects of therapies received after progression, which could impact PPS and its association with OS.
- The studies were published between 2006 and 2019 and therefore the evidence is likely more representative of the situation at those time frames, including patients' risk of progression and/or response to first-line treatment. Moreover, the systematic reviews (all published before 2013) included studies from previous decades. The meta-analyses that examined the effects of trial initiation or publication date on the association between PPS and OS[49,50] and TTP and OS[53] reported this factor had an important impact on the correlations, generally with the older trials associated with weaker correlations.
- There were also the weaker correlations in targeted therapy trials than in chemotherapy regimen trials which indicates initial treatment type is an important factor. It is acknowledged that the number of trials on targeted therapies was smaller than for chemotherapy regimens, likely related to the dates the trials were conducted.
- Each of the meta-analyses identified variation in outcome definitions and assessments. As well, trials often did not report definitions of outcomes. For example, Hotta et al.[53] noted that 44% of the 54 included trials did not describe the definition of TTP and 65% of the trials provided a definition of OS. In addition, the retrospective studies identified the potential for bias related to variation on the date on which a tumour response was recorded by each physician. While, as the authors identify, this was not unique to their studies it is a key limitation especially because the determination of the duration of PPS would be based on this date (i.e., OS = PFS + PPS). The impact of outcome definition on the results of the meta-analyses and retrospective studies was not reported, except by Hayashi et al.[49] who only reported on their assumption to consider TTP and PFS as the same outcome from the trials.
- Some of the analyses adjusted for potentially confounding factors such as (but not limited to) patient age, performance status, tumour histology, molecular biomarkers, year of trial, and subsequent lines of therapy. However, there was variation in which covariates were modelled and the choice of these was not well-described. There is a potential for the failure to account for confounding variables to influence the relationship between PPS and OS or TTP and OS.
- The included populations impact the accuracy of the estimates for the relationship between the surrogate end points and OS, but also the generalizability. As mentioned, there was limited information provided about the PICOS in the systematic reviews and the eligibility criteria for the retrospective studies. The meta-analyses included patients with advanced or metastatic NSCLC who received first-line therapy, generally either with cytotoxic chemotherapy or molecular targeted drugs. Patients with EGFR mutations were not specifically selected for these analyses. The retrospective studies, however, specifically included patients with EGFR mutation–positive advanced or metastatic NSCLC. The sponsor provided studies[61-68] in other patient populations (e.g., anaplastic lymphoma kinase–positive NSCLC and/or later lines of therapy) as supportive evidence. The studies had similar limitations as those already described in addition the uncertainty of how the results in these increasingly heterogeneous populations apply to the target population for this review. Therefore,

there is limited evidence for the strength of the surrogacy of PPS and TTP with OS in the population of interest.

The sponsor provided The European Lung Cancer Working Party (ELCWP) 2012 guidelines that reported on surrogate markers as adequate predictive of OS in patients with lung cancer.[69] It was highlighted that the ELCWP issued a strong recommendation (based on "moderate quality evidence") about TTP as a surrogate end point for OS based on the results of the aforementioned meta-analyses.[53,54] The recommendation was: "TTP is an intermediate marker for overall survival in advanced NSCLC treated with first-line chemotherapy."[69] It is notable that Hotta et al. concluded based on their meta-analysis that:

"…our findings indicate that TTP in our collection of relevant trials is too weakly correlated with survival to use as a surrogate for survival in first-line chemotherapy for advanced NSCLC. With the increasing number of active compounds available for the treatment of NSCLC, even in second-line or later settings, the role of surrogate markers, including TTP, should be investigated extensively."[53]

Another important consideration, relating to the use of PPS and TTP in the health economic model, is that both were determined post hoc.

In summary, while the studies provided by the sponsor suggest PPS and TTP as surrogate end points for OS in advanced NSCLC, the limitations and multiple sources of uncertainty complicate the interpretation of the results. The review team determined that currently available evidence is not a strong support for the sponsor's claim of surrogacy.

Pharmacoeconomic Review

List of Tables

List of Figures

Abbreviations

AE	adverse event
BSA	body surface area
CDA-AMC	Canada's Drug Agency
ex19del	exon 19 deletion
ICER	incremental cost-effectiveness ratio
L858R	L858R substitution
LCC	Lung Cancer Canada
NSCLC	non–small cell lung cancer
OH-CCO	Ontario Health (Cancer Care Ontario)
OS	overall survival
PD	progressed disease
PF	progression-free
PFS	progression-free survival
PPS	post-progression survival
QALY	quality-adjusted life-year
RECIST	Response Evaluation Criteria in Solid Tumors
TTD	time to treatment discontinuation
TTP	time to progression

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Osimertinib (Tagrisso) oral tablets, 40 mg and 80 mg
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.
Health Canada approval status	NOC
Health Canada review pathway	Priority review and Project Orbis
NOC date	July 10, 2024
Reimbursement request	As per indication
Sponsor	AstraZeneca Canada Inc.
Submission history	Previously reviewed: Yes Indication: Adjuvant therapy after tumour resection in patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or L858R substitution mutations • Recommendation date: January 10, 2022 • Recommendation: Reimburse with clinical criteria and/or conditions Indication: NSCLC (first line) • Recommendation date: January 4, 2019 • Recommendation: Reimburse with clinical criteria and/or conditions Indication: NSCLC • Recommendation date: May 4, 2017 • Recommendation: Reimburse with clinical criteria and/or conditions

NOC = Notice of Compliance; NSCLC = non–small cell lung cancer.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	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
Treatment	Osimertinib in combination with pemetrexed and platinum-based chemotherapy

Dose regimen	Osimertinib plus chemotherapy:
	• Osimertinib: 80 mg orally once daily until treatment discontinuation.
	• Chemotherapy:
	  ◦ Induction phase:
	  ▪ Cisplatin: 75 mg/m^2 via IV infusion on day 1 of each 21-day cycle (4 cycles) or carboplatin: AUC 5

Component	Description
	via IV infusion on day 1 of each 21-day cycle (4 cycles) ▪ Pemetrexed: 500 mg/m^2 via IV infusion on day 1 of each 21-day cycle (4 cycles) ◦ Maintenance phase: ▪ Pemetrexed: 500 mg/m^2 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, life-years
Time horizon	Lifetime (15 years)
Key data source	FLAURA2: 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 QALYs = 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 data) and the limited ability of the FLAURA2 trial's surrogate end points such as TTP and PPS to predict long-term survival outcomes, make the model's predictions of long-term survival difficult to interpret. • During the on-trial period of the model, OS was lower among patients receiving osimertinib plus chemotherapy compared with osimertinib monotherapy, which reflected the results of the FLAURA2 trial. 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 favoured combination therapy, potentially introducing a bias that favours osimertinib plus chemotherapy. • The utility value selected by the sponsor for the PD state lacks face validity. They assumed a significant drop in 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.
CDA-AMC reanalysis results	• CDA-AMC 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. • In the CDA-AMC 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). • Because of the cost of chemotherapy and the presence of osimertinib in both modelled 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.

AUC = area under the concentration-time curve during any dosing interval; CDA-AMC = Canada's Drug Agency; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = progressed disease; PF = progression-free; PPS = post-progression survival; QALY = quality-adjusted life-year; TTP = time to progression.

Conclusions

Our Clinical Review found that no conclusions could be drawn about the effect of osimertinib plus chemotherapy on overall survival (OS) because of the immaturity of the data from the FLAURA2 trial (26.8% overall data maturity). Despite these limitations, clinical experts consulted by the review team noted that the findings appear to be favourable and may be clinically important. These data were used to inform the economic analysis, and the underlying uncertainties in the clinical findings translate to uncertainty within the economic results, most specifically the interpretation of the survival benefit estimated by the sponsor's model. While the difference in OS at the data cut point was not statistically significant, the sponsor's model predicted 0.44 additional years of life for patients receiving osimertinib plus chemotherapy. More than 100% of incremental survival in the sponsor's model was generated by extrapolating beyond the observation period of the FLAURA2 trial.

The review team identified several limitations in the economic analyses submitted by the sponsor, beyond the uncertainty regarding the impact of osimertinib plus chemotherapy on OS. In the review team's base case, osimertinib plus chemotherapy is associated with an incremental cost of $57,897 and 0.246 incremental quality-adjusted life-years (QALYs) compared to osimertinib monotherapy, resulting in an incremental cost-effectiveness ratio (ICER) of $235,123 per QALY gained. These findings were broadly similar to the sponsor's, insofar as osimertinib plus chemotherapy was expected to yield higher quality-adjusted survival at a higher cost compared to osimertinib monotherapy. If the price of osimertinib was reduced to $0, the resulting ICER would be $75,865 due to the fact that the price of osimertinib is reduced in both modelled treatment arms, while the cost of chemotherapy remains in the osimertinib plus chemotherapy arm.

Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, clinician groups, and drug plans that participated in the review conducted by Canada's Drug Agency (CDA-AMC).

Patient input was received by 2 patient groups: Lung Cancer Canada (LCC) and the Ontario Lung Association (now the Lung Health Foundation). Patient input was gathered from interviews and surveys conducted in January 2021 and October 2023 by the Lung Health Foundation and December 2023 by LCC. The Lung Health Foundation conducted 2 interviews and gathered 15 responses from online surveys and LCC conducted 13 interviews with patients and/or caregivers. Respondents indicated that the disease negatively affected their ability to participate in leisure activities, hobbies, shopping, and travel. Respondents in the LCC interviews reported that patients living with lung cancer require a treatment that improves their quality of life while also managing their disease effectively. Some benefits from currently available treatments included reduced coughing and shortness of breath, ability to exercise, delayed disease progression, reduction in disease-related symptoms, and prolonged life, as reported by the Lung Health Foundation. Input from the LCC patient group emphasized that respondents had experience with osimertinib, noting that the treatment has been effective at treating patients' tumours and managing symptoms, and that side effects

such as diarrhea, muscle pain and spasms, skin issues, and lack of appetite were frequent at treatment onset, but are generally manageable. Patients noted they were able to maintain or improve their quality of life and functionality while on osimertinib. One respondent from the Lung Health Foundation noted that, while the treatment is effective, it is costly, and they hope that the next treatment option is approved and funded.

Clinician input was received from the Ontario Health (Cancer Care Ontario) (OH-CCO) Lung Cancer Drug Advisory Committee and LCC, with a total of 28 clinicians providing input on osimertinib plus chemotherapy. The OH-CCO committee 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 are not curative. Both clinician groups emphasized the need for improved therapies that result in longer control of the cancer, a better quality of life, and longer survival. Both clinician groups noted that the combination of osimertinib and chemotherapy would be an option in patients with non–small cell lung cancer (NSCLC) with sensitizing EGFR mutations. The OH-CCO group highlighted the need for OS data before drawing any conclusion regarding a shift in the current treatment paradigm. They further mentioned that the addition of platinum-based chemotherapy to osimertinib is associated with more inconvenience to patients due to an increase in chemotherapy-associated toxicities, which require the patients to attend cancer centres more frequently for IV therapy. Both clinician groups noted that single-drug osimertinib would remain an option for first-line therapy, as did the clinical experts consulted by the review team.

Drug plan input received by the review team noted that initial chemotherapy and maintenance of pemetrexed requires IV drug preparation and ambulatory treatment appointments every 3 weeks, which will have an additional impact on resources and may increase incremental costs. The plans questioned if patients with an Eastern Cooperative Oncology Group Performance Status greater than 1 should be eligible for treatment, an inclusion that may affect overall drug costs. Plans noted that EGFR mutation testing is a part of routine clinical practice for this reimbursement population and therefore is not expected to result in an incremental difference in costs.

Several of these concerns were addressed in the sponsor's model:

- Health-state utilities that captured lung cancer symptoms and quality of life were included.
- Adverse events (AEs) associated with osimertinib plus chemotherapy were included.
- The cost of chemotherapy and associated costs related to administration, disease management, and monitoring were included.

The review team was unable to address the following concerns raised from patient and clinician group input:

- No conclusions could be drawn about the effect of osimertinib plus chemotherapy on OS because of the immaturity of the data.
- The inconvenience experienced by patients receiving osimertinib plus chemotherapy due to more frequent visits to a cancer centre for IV therapy was not captured in the analysis.

Economic Review

The current review is for osimertinib (Tagrisso) 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 deletion (ex19del) or L858R substitution (L858R) mutations.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis of osimertinib in combination with pemetrexed and platinum-based chemotherapy (osimertinib plus chemotherapy), for the first-line treatment of adult patients (aged ≥ 18 years) with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations, compared with osimertinib monotherapy.[1] The model population comprised the same target population and was aligned with the Health Canada indication.[2]

Osimertinib is available as a 40 mg or 80 mg tablet. The recommended dose is 80 mg, to be taken orally once daily until disease progression or unacceptable toxicity.[2] Patients in both the intervention and comparator arm of the model receive osimertinib via once-daily oral administration until treatment discontinuation. At the sponsor's submitted price of $322.13 per 80 mg tablet, the 21-day cost of osimertinib monotherapy is $6,764.69. In the osimertinib plus chemotherapy arm, chemotherapy treatment consists of an induction phase and maintenance phase. During the induction phase patients either receive cisplatin (75 mg/m^2) or carboplatin (area under the concentration-time curve during any dosing interval of 5 mg/mL/min) in combination with pemetrexed (500 mg/m^2) on day 1 of each 21-day cycle (every 3 weeks) for 4 cycles, with both treatments administered via IV infusion. This is followed by a maintenance phase during which pemetrexed (500 mg/m^2) is administered every 3 weeks. The dosing of the chemotherapy regimens was based on the patient's body surface area (BSA), which was assumed to be consistent with target population observed in the FLAURA2 trial (BSA = 1.71 m^2).[3] In the base case, the sponsors assumed a 50:50 split of patients receiving cisplatin or carboplatin during the induction chemotherapy phase. The treatment-acquisition costs of chemotherapy per 21-day treatment cycle included wastage and were estimated by the sponsor to be $405.00 for cisplatin, $775.00 for carboplatin, and $450.00 for pemetrexed. At the sponsor's submitted price for osimertinib and the public price for the chemotherapy regiments, the 21-day cost of osimertinib plus chemotherapy is $10,703.84 during the induction phase (assuming a 50:50 split between cisplatin and carboplatin) and $10,113.84 during the maintenance phase.

The model also included subsequent (second- and third-line) treatment-acquisition costs following treatment discontinuation of osimertinib in both study arms. Patients were assumed to receive either platinum doublet chemotherapy, pemetrexed, docetaxel, or immuno-oncology therapies.

The clinical outcomes of interest were QALYs and life-years. The economic analysis was undertaken over a lifetime time horizon of 15 years from the perspective of a Canadian public health care payer. Discounting at 1.5% annually was applied to both costs and outcomes.[1]

Model Structure

The sponsor submitted a Markov model with 3 mutually exclusive states: progression-free (PF), progressed disease (PD), and dead. Transitions between states occurred on a monthly cycle (Figure 1, Appendix 3). From the PF state, patients could transition to the PD state, the dead state, or remain PF. Patients in the PD state could remain in the PD state or transition to the dead state. In the model the proportion of patients on treatment (first-line and subsequent treatment) are determined according to time to treatment discontinuation (TTD) curves, regardless of statement membership.

Model Inputs

The model's baseline population characteristics and clinical efficacy parameters were characterized by the FLAURA2 trial, a multinational, open-label, randomized phase III trial evaluating the efficacy of osimertinib with or without pemetrexed and platinum-based chemotherapy in patients with previously untreated EGFR-mutated (ex19del or L858R) locally advanced or metastatic NSCLC.[3] The sponsor assumed that the FLAURA2 population (baseline characteristics: mean age = 60.8 years; proportion male = 38.6%) reflected the Canadian population.[1]

All transition probabilities in the model were derived from the FLAURA2 trial, using the April 3, 2023, data cut-off date. Investigator-assessed progression-free survival (PFS) was the primary outcome in the FLAURA2 trial. PFS was defined as objective disease progression (according to Response Evaluation Criteria in Solid Tumors [RECIST]) or death (by any cause in the absence of progression), regardless of whether the patient withdrew from study treatment or received another anticancer therapy before progression. OS was the secondary end point in the FLAURA2 trial and was defined as the time from the date of randomization until death due to any cause. As OS maturity was not observed (the overall maturity of data was 26.8% and the median OS was not reached) the modelled transition probabilities were assumed to be aligned with the data reported in post hoc analyses of the FLAURA2 trial. Specifically, transitions from PF to PD were modelled using time to progression (TTP) data, PD to dead was modelled using post-progression survival (PPS) data, and PF to dead was modelled using a combination of PFS and TTP data. TTP was defined as disease progression according to RECIST only, while PPS was defined as a patient experiencing death, with prior record of disease progression according to RECIST.

Parametric survival modelling was used to extrapolate health-state transition probabilities beyond the trial period (30 months of follow-up). Survival distributions were selected based on clinical plausibility of long-term projections, visual inspection of fit, and the Akaike information criterion and Bayesian information criterion.[1]

Because of the limited number of mortality events in the available FLAURA2 data and associated uncertainty in the relative extrapolated hazards, the hazards for PPS were assumed to be identical in both study arms. The sponsors used the PPS data in the osimertinib monotherapy arm to estimate the transition from PD to dead in the model for both study arms. Kaplan-Meier estimates of OS data from the FLAURA trial were used to guide selection of clinically plausible curves fitted to the FLAURA2 post-progression data.[4]

The grade 3 or greater AEs observed in the FLAURA2 trial were incorporated into the model with an associated cost and disutility.[3] These were applied for the first month (i.e., model cycle); after 1 month, no additional AEs were applied.

Health-state utility values were sourced from EQ-5D-5L data collected in the FLAURA2 trial and published estimates. The EQ-5D-5L data collected in the FLAURA2 trial were used to derive utility values for the PF ([redacted]) and PD ([redacted]) health states. EQ-5D scores were converted to a utility value using the Canadian value set for the EQ-5D-5L questionnaire.[5] However, in its base-case analysis the sponsor used a PD utility of 0.70, which was sourced from a real-world study of health-state utilities in patients in Canada with lung cancer.[6] Scenario analyses were also conducted to explore the impact of alternative sets of health-state utility values on the resulting ICERs. An age adjustment was also applied to each health-state utility by applying a multiplier based on general population utilities.[7] Disutilities for AEs were either sourced from the literature or based on assumptions and incorporated as a single disutility as a one-off in the first cycle.[1]

The model incorporated treatment-acquisition costs for osimertinib, chemotherapy, and subsequent therapies. Dosing details were sourced from Health Canada product monographs, with acquisition costs for osimertinib derived from the sponsor's submitted price[1] and IQVIA Delta Price for other treatments.[8] The dosage of treatments, including chemotherapy regimens, were estimated from the average BSA estimates (1.71 m^2) from the FLAURA2 trial's patient population.[3] IV treatment vial sizes were chosen based on the lowest monthly acquisition cost and assumed wastage in the base case.

In the model treatment duration, for all treatments, was determined regardless of state membership. Treatment duration was determined by treatment discontinuation data from the FLAURA2 trial, which was available separately for osimertinib and pemetrexed. Extrapolations of this data were used to estimate the proportion of patients on treatment in each model cycle. In the base case, no treatment stopping rules were applied in either study arm, although the model allows for application of stopping rules.

In both study arms, the cost of subsequent treatments was applied upon discontinuation of osimertinib, regardless of state membership. Subsequent treatments included both second- and third-line therapies. The distribution of patients across these treatments was based on reported estimates from the FLAURA2 study, and it was assumed that all treatments had the same duration in both second- and third-line settings. The total cost of subsequent treatment was estimated by calculating a weighted average cost for each arm, accounting for the proportion of patients receiving subsequent treatments and the duration of those treatments.

Other costs included those for monitoring, treatment administration, disease management, central nervous system metastases-related expenses, AEs, and end-of-life costs. Monitoring costs related solely to chemotherapy treatments were applied only in the osimertinib plus chemotherapy arm. Administration costs were included for each treatment based on administration frequency according to the respective product monographs.

Resources for disease management of patients in the PF and PD states were sourced from studies conducted in the UK,[9-12] while unit costs were primarily informed by the Ontario Ministry of Health and

Long-Term Care Schedule of Benefits.[13] Disease management costs for patients with central nervous system metastases were assumed to be 1.2 times higher.[14] Additionally, the model included a one-off end-of-life cost valued at $17,334.08 and costs associated with managing AEs for each study arm.[15]

Summary of Sponsor's Economic Evaluation Results

The base-case analysis was run probabilistically (2,000 iterations). The deterministic and probabilistic results were similar. The probabilistic findings are presented in the following section.

Base-Case Results

Osimertinib plus chemotherapy was associated with a gain of 0.402 QALYs at an additional cost of $59,009, resulting in an ICER of $146,769 compared with osimertinib monotherapy. Compared with osimertinib monotherapy, osimertinib plus chemotherapy was cost-effective at a willingness-to-pay threshold of $50,000 per QALY in approximately 16% of iterations. Drug acquisition contributed to 90% (67% for osimertinib, 23% chemotherapy) of the incremental costs. In both study arms, more than half of the accrued QALYs were derived within the observed trial period of 30 months. Because of the increased mortality due to chemotherapy-associated AEs observed in the FLAURA2 trial data, incremental life-years were 0.4% lower for osimertinib plus chemotherapy (i.e., osimertinib monotherapy was associated with more life-years) during the observed period of the trial, and 11.49% of the incremental QALYs accrued during the observed trial period.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. osimertinib monotherapy ($ per QALY)
Osimertinib monotherapy	327,912	Reference	2.67	Reference	Reference
Osimertinib plus chemotherapy	386,921	59,009	3.07	0.40	146,770

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.
Source: Sponsor's pharmacoeconomic submission.[1]

Additional results from the sponsor's submitted economic evaluation base case are presented in Appendix 3.

Sensitivity and Scenario Analysis Results

The sponsor assessed several model parameters in deterministic sensitivity and scenario analyses. The model results were most sensitive to assumptions around the choice of extrapolated curves for TTD for osimertinib monotherapy and alternative utility values used in the PD and PF states. No scenario analysis used a perspective other than that of the health care payer.

Appraisal of the Sponsor's Economic Evaluation

The review team identified several key limitations to the sponsor's economic analysis that have notable implications.

- **The impact of osimertinib plus chemotherapy on long-term OS is uncertain:** The FLAURA2 data used within the sponsor's submitted model did not include statistical significantly different estimates of OS between patients receiving osimertinib plus chemotherapy compared to those receiving

osimertinib monotherapy. Transition probabilities between the model states was informed by a post hoc analysis of TTP data and PPS data available from the FLAURA2 trial in each study arm. Further, the sponsor's model assumed that the PPS in the osimertinib plus chemotherapy arm is identical to the PPS in the osimertinib monotherapy arm.

As the available trial follow-up data at the time of this analysis was 30 months and data maturity was not reached, the sponsor relied on parametric survival modelling to extrapolate the TTP and PPS beyond the observed time points in the trial. The sponsor fitted separate gamma distributions to the observed TTP Kaplan-Meier curves to determine the time spent in the PF state over the 15-year time horizon for combination therapy relative to monotherapy. Transitions between PF and dead were calculated from PFS and TTP data, assuming that preprogression survival data are approximated by the difference between PFS and TTP. This approach was used because the preprogression survival data from the FLAURA2 trial were less than [redacted]% mature. The sponsor's model therefore assumes that the probability of death is lower in the PF state, and that a longer time spent in the PF state leads to an increased survival time. Although the updated OS data from January 8, 2024, from the FLAURA2 trial (not included in the model) generally favoured osimertinib plus chemotherapy over osimertinib alone, uncertainty remains in the OS results, as the median OS was not reached as of January 8, 2024, and the OS data were 40.6% mature.

Other important considerations include the use of TTP and PPS as surrogate end points for OS in advanced NSCLC, and the post hoc estimation of TTP and PPS. The Clinical Review, which assessed the sponsor's submitted studies in support of this claim, determined that there is limited evidence for the strength of the surrogacy of PPS and TTP with OS in the population of interest. Furthermore, post hoc estimation of these outcomes could have introduced an additional layer of bias, which is of concern as these data were used to extrapolate TTP and PPS for the entire lifetime horizon in the model. Together, these limitations add another source of uncertainty when interpreting the evidence used in the model.

According to the clinical experts consulted for this review and the most recent OS data (i.e., those available at January 8, 2024), a benefit with combination therapy was deemed plausible. However, the magnitude of such a benefit was uncertain without more robust evidence. Alternative parametric distributions for TTP and PPS, along with assumptions about different PPS between the study arms, were considered more plausible.

  - Given these limitations, and consistent with clinical expert opinion, the review team's reanalysis adopted alternate assumptions for OS and PFS extrapolation. The team selected the Weibull distribution for TTP in both modelled cohorts (i.e., patients receiving osimertinib plus chemotherapy and those receiving osimertinib monotherapy). Additionally, it was assumed that PPS would differ between the study arms, with the Weibull distribution selected in both modelled cohorts.

- **The impact of healthy-participant bias on the observed benefits is uncertain:** The sponsor's model predicted an additional 0.56 PF life-years, which translates to 0.44 additional predicted life-years for patients receiving osimertinib plus chemotherapy compared to those receiving osimertinib

monotherapy over the 15-year lifetime horizon. These estimated survival benefits are not realized until 22 months in the modelled time horizon. Instead, based on the clinical data, a higher number of deaths were observed for patients receiving combination treatment over the first 22 months (refer to Figure 2). This observation arises given the increased harms and deaths reported from AEs for patients receiving osimertinib plus chemotherapy compared to those receiving osimertinib monotherapy.

The clinical experts consulted for this review described the harms observed in the FLAURA2 trial as what they would expect for the addition of chemotherapy to osimertinib. A higher number of deaths observed in the combination therapy arm relative to the monotherapy arm during the early months of the trial could suggest that "sicker" patients experience mortality due to chemotherapy AEs. The remaining "healthier" patients would then be left to experience the long-term survival benefit of the treatment. Assuming perfect randomization, meaning the percentage of "sicker" individuals was equal in both study arms, continued survival of the "sicker" individuals in the monotherapy arm of FLAURA2 could indicate that the benefits of osimertinib plus chemotherapy are overestimated compared to the outcomes that would occur in the general population. This phenomenon would introduce a bias of unknown size into the economic model that favours osimertinib plus chemotherapy.

  - CDA-AMC was not able to address this limitation, as quantifying the exact impact of the healthy-participant bias on the incremental benefits was not possible.

- **Utility in the PD state lacks face validity:** The sponsor's base case assumed that patients' health-related utility decreases at disease progression, from a utility of [redacted] in the PF state to 0.70 in the PD state. Data from FLAURA2 trial suggest a smaller utility drop of [redacted] when transitioning from PF to PD. The sponsors used utilities obtained from 2 different sources to inform the health-state utility value of PF and PD states in the model. This is methodologically inappropriate and limits comparability of the utility measures across studies, as it is unclear if they measure the same construct and are derived from similar patient populations using similar methodologies. Differences in measurement tools, populations studied, and valuation techniques can lead to inconsistencies and bias in the model. According to the clinical experts consulted for this review, the decline in utility may not be as pronounced, particularly considering that patients continue treatment post-progression.
  - The review team's reanalysis used the utility estimates from the FLAURA2 trial for both PF and PD states.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CDA-AMC (Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CDA-AMC comment
Treatment duration occurs regardless of state membership.	According to the clinicians consulted, patients continue taking osimertinib following disease progression. The sponsor's approach to modelling TTD is therefore appropriate. The clinicians also indicated that the TTD curves used were in line with their expectations for this clinical population.
AEs were assumed to occur only in the first month of treatment.	AEs were incorporated in the sponsor's model as a one-off cost, and the disutility was applied only during the first cycle of the model. With this approach the sponsor is assuming that the patients on osimertinib plus chemotherapy do not have ongoing toxicity associated with chemotherapy. When considered over the model's time horizon, and the proportion of patients who continue treatment on pemetrexed, this assumption is not likely to have a significant impact on overall cost-effectiveness.

AE = adverse event; CDA-AMC = Canada's Drug Agency; TTD = time to treatment discontinuation.

CDA-AMC Reanalyses of the Economic Evaluation

Base-Case Results

The CDA-AMC base case was derived by making changes in model parameter values and assumptions, in consultation with clinical experts. The review team undertook a stepped analysis, incorporating each change detailed in Table 5 into the sponsor's model to highlight the impact of each change. The summary results of the CDA-AMC reanalyses for the weighted population are presented in Table 6.

Table 5: CDA-AMC Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CDA-AMC value or assumption
Changes to derive the CDA-AMC base case		
1. Parametric extrapolation of TTP and OS	Parametric distribution of TTP: • osimertinib plus chemotherapy: gamma • osimertinib monotherapy: gamma	Parametric distribution of TTP: • osimertinib plus chemotherapy: Weibull • osimertinib monotherapy: Weibull
2. Assumption of equal relationship of PPS between osimertinib plus chemotherapy and osimertinib monotherapy	Assumed equivalence of osimertinib monotherapy for PPS: Yes Parametric distribution of PPS: • osimertinib monotherapy: Weibull	Assumed equivalence of osimertinib monotherapy for PPS: No Parametric distribution of PPS: • osimertinib plus chemotherapy: Weibull • osimertinib monotherapy: Weibull
3. Health utility in PF state	Health-state utilities: PF: [redacted] PD: 0.70	Health-state utilities: PF: [redacted] PD: 0.80
CDA-AMC base case	—	Reanalysis 1 + 2 + 3

CDA-AMC = Canada's Drug Agency; PD = progressed disease; PF = progression-free; OS = overall survival; PPS = post-progression survival; TTP = time to progression.

Results from the CDA-AMC reanalysis demonstrate that osimertinib plus chemotherapy was associated with $57,897 in incremental costs and an incremental gain of 0.246 QALYs compared to osimertinib monotherapy, resulting in an ICER of $235,123 per QALY gained. Selecting the Weibull distribution for TTP in both

study arms resulted in the largest change to the sponsor's base case (Table 7). Based on results from the review team's reanalysis, 91% of the total costs for osimertinib plus chemotherapy are related to treatment acquisition (67% osimertinib, 24% chemotherapy). Approximately −7% of the incremental life-years and less than 1% of the incremental QALYs accrued during the observed trial period. The probability that osimertinib plus chemotherapy is cost-effective at a willingness-to-pay threshold of $50,000 per QALY is 10.35%.

Table 6: Summary of the Stepped Analysis of the CDA-AMC Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($ per QALY)
Sponsor's base case (deterministic)	Osimertinib + chemotherapy	382,430	3.08	Reference
	Osimertinib monotherapy	328,530	2.73	150,081
CDA-AMC reanalysis 1	Osimertinib + chemotherapy	381,711	2.90	Reference
	Osimertinib monotherapy	327,515	2.68	247,249
CDA-AMC reanalysis 2	Osimertinib + chemotherapy	382,323	3.07	Reference
	Osimertinib monotherapy	328,530	2.73	155,210
CDA-AMC reanalysis 3	Osimertinib + chemotherapy	382,430	3.22	Reference
	Osimertinib monotherapy	328,530	2. 88	156,165
CDA-AMC base case 1 + 2 + 3 (deterministic)	Osimertinib + chemotherapy	381,606	3.02	Reference
	Osimertinib monotherapy	327,515	2.83	282,754
CDA-AMC base case 1 + 2 + 3 (probabilistic)	Osimertinib + chemotherapy	383,306	3.03	Reference
	Osimertinib monotherapy	325,408	2.78	235,123

CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: The CDA-AMC reanalysis is based on publicly available prices of the comparator treatments. The results of all steps are presented deterministically unless otherwise indicated, while the cumulative CDA-AMC base case is always presented both deterministically and probabilistically.

Scenario Analysis Results

A scenario analysis was conducted in which the TTP curves were assumed to reach equivalence between osimertinib plus chemotherapy and osimertinib monotherapy after 60 months. This analysis resulted in an ICER of $260,330 per QALY gained.

The review team undertook price-reduction analyses based on the CDA-AMC base case. At a 100% price reduction, osimertinib plus chemotherapy reached an ICER of $75,585 compared to osimertinib monotherapy. This occurred because any reduction in the price of osimertinib will necessarily result in a corresponding decrease in the cost of osimertinib monotherapy. There remained an additional $19,033 of additional costs, due primarily to the additional cost of chemotherapy. A scenario analysis was conducted in which the price of osimertinib and the price of chemotherapy were both reduced. In this scenario, a 91% reduction in the price of all drugs was necessary to achieve an ICER below a willingness-to-pay threshold of $50,000 per QALY.

Table 7: CDA-AMC Price-Reduction Analyses

Analysis	Unit drug cost ($)	ICERs for osimertinib plus chemotherapy vs. osimertinib monotherapy ($ per QALY)	
Price reduction	**$**	**Sponsor base case**	**CDA-AMC reanalysis**
No price reduction	322.13	**146,769**	**235,123**
10%	289.92	136,765	214,474
20%	257.71	127,359	192,334
30%	225.49	116,312	180,115
40%	193.28	107,063	172,451
50%	161.07	99,010	149,582
60%	128.85	87,620	134,010
70%	96.64	77,859	122,208
80%	64.43	68,257	107,706
90%	32.21	58,941	91,916
100%	0	47,913	75,585

vs. = versus; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Issues for Consideration

- Osimertinib has been previously reviewed by CADTH for the treatment of patients with locally advanced or metastatic NSCLC that is positive for the amino acid substitution from a threonine to a methionine at position 790 in EGFR (the EGFR T790M mutation) that has progressed on or after therapy with an EGFR tyrosine kinase inhibitor,[16] for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have other EGFR mutations,[10] and as adjuvant therapy after tumour resection in patients with stage IB to stage III NSCLC whose tumours have EGFR ex19del or L858R mutations.[17] These reviews were at the submitted price of $294.68 per 40 mg or 80 mg tablet. All reviews received a recommendation for reimbursement with clinical criteria and/or conditions.[9,10,17] These conditions included improvement of the cost-effectiveness of osimertinib.[9,10,17]
- As in all CDA-AMC pharmacoeconomic reports, the economic evaluation presented in this report is based on publicly available list prices for all comparators, including osimertinib and all chemotherapy drugs. Negotiated prices are in place for all drugs in this evaluation. The finding that osimertinib plus chemotherapy is not cost-effective at a 100% price reduction may be sensitive to changes in the cost of chemotherapy, if negotiated prices are meaningfully lower than the list prices.

Overall Conclusions

Based on the evidence from the FLAURA2 trial, osimertinib plus chemotherapy showed added clinical benefits in OS and PFS in the intention-to-treat trial population compared with osimertinib monotherapy. However, because of the interim nature of the analyses (i.e., the OS data were immature at 40.6% and the median OS was not reached as of January 8, 2024), uncertainty remains in the OS results. This is

concerning as these data were used in the post hoc analysis to estimate the surrogate outcomes used in the model (i.e., PPS and TTP), which were then extrapolated over the lifetime horizon. No conclusions could be drawn about the effect of osimertinib plus chemotherapy on OS because of data immaturity. Despite these limitations, the clinical experts consulted for this review noted that the findings appear to be favourable and may be clinically important. While there was no statistically significant difference in OS at the data cut point, the sponsor's model predicted 0.44 additional years of life for patients receiving osimertinib plus chemotherapy. More than 100% of incremental survival in the sponsor's model was generated by extrapolating beyond the observation period of the FLAURA2 trial.

The review team identified several limitations in the economic analyses submitted by the sponsor, beyond the uncertainty regarding the impact of osimertinib plus chemotherapy on OS. These key limitations included uncertainty about the use of surrogate outcomes (PPS and TTP) to inform model transitions, the unknown impact of healthy-participant bias on the observed benefits, the misalignment of the assumed utility drop from PF to PD with trial data or clinical expert opinion, and the potential for introducing bias because of differences in utility measurement sources. In its reanalysis, the review team included changes to TTP extrapolations, different rates of PPS in study arms, and the use of FLAURA2 utility estimates. The reanalysis found that osimertinib plus chemotherapy is $57,898 more costly and yields 0.246 more QALYs compared with osimertinib monotherapy, resulting in an ICER of $235,123 per QALY gained. If the price of osimertinib was reduced to $0, the resulting ICER would be $75,865 because the price of osimertinib is reduced in both modelled treatment arms, while the cost of chemotherapy remains in the osimertinib plus chemotherapy arm.

The results are contingent on TTP and PPS extrapolation from the observed trial data and whether this translates into improvement in OS. Although the sponsor's approach to modelling the relationship between TTP and OS is appropriate, longer-term evidence is required to validate OS for patients receiving osimertinib plus chemotherapy. The CDA-AMC reanalysis adopted a conservative assumption that osimertinib plus chemotherapy would confer more modest long-term TTP and corresponding PFS and OS benefits relative to osimertinib monotherapy. The clinical experts consulted for this review deemed the parametric extrapolations used in the CDA-AMC base case to model transition probabilities from TTP and PPS more plausible than those used in the sponsor's base case. As such, relative to the sponsor's base case, the CDA-AMC reanalysis resulted in a reduction of life-year gains from 3.8 to 3.6 in this patient population. However, due to the small magnitude of the incremental benefits, the cost-effectiveness of osimertinib plus chemotherapy varied significantly when more optimistic and pessimistic TTP extrapolations were considered.

CDA-AMC was unable to address limitations related to the use of surrogate outcomes and the potential impact of healthy-participant bias on model outcomes. However, even without accounting for these uncertainties, the sponsor's submitted base case was not cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

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Appendix 1: Cost-Comparison Table

Please note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts and drug plan. Comparators may be recommended (appropriate) practice or actual practice. Existing product listing agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CDA-AMC Cost-Comparison Table for First-Line Treatment of Patients With Locally Advanced or Metastatic Non–Small Cell Lung Cancer

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	21-day cost ($)
Osimertinib (Tagrisso)	**80 mg**	**Tablet**	**322.1320[a]**	**80 mg daily until disease progression or unacceptable toxicity**	**322.13**	**6,765**
CISPPME + osimertinib					**362.84**	**7,620**
CRBPPME + osimertinib					**390.46**	**8,200**
CISPPME						
Cisplatin (Generic)	50 mg/50 mL 100 mg/100 mL	Vial for IV infusion	135.0000 270.0000	75 mg/m^2 q.3.w.	19.29	405
Pemetrexed (Generic)	100 mg 500 mg 1,000 mg	Powder for solution for infusion	50.0000 250.0000 4,290.0000	500 mg/m^2 q.3.w.	21.43	450
CISPPME					40.71	855
CRBPPME						
Carboplatin (Generic)	50 mg/5 mL 150 mg/15 mL 450 mg/45 mL 600 mg/60 mL	Vial for IV infusion	70.0000 210.0000 599.9985 775.0020	Target AUC 5 on day 1 q.3.w., 750 mg/mL	46.90	985
Pemetrexed (Generic)	100 mg 500 mg 1,000 mg	Powder for solution for infusion	50.0000 250.0000 4,290.0000	500 mg/m^2 q.3.w.	21.43	450
CRBPPME					68.33	1,435

CISPPME = cisplatin and pemetrexed regimen; CRBPPME = carboplatin and pemetrexed regimen; q.3.w. = every 3 weeks.

Note: All prices are from IQVIA Delta PA (accessed January 2024),[8] unless otherwise indicated, and do not include dispensing fees. Dosing is based on Cancer Care Ontario product monographs.[18] For treatments using weight-based or GFR-based dosing, CDA-AMC assumed 64.8 kg, 1.71m^2 and 125 mL/min based on the FLAURA2 trial.[3]

[a]Sponsor-submitted pricing.[1]

Appendix 2: Submission Quality

Please note that this appendix has not been copy-edited.

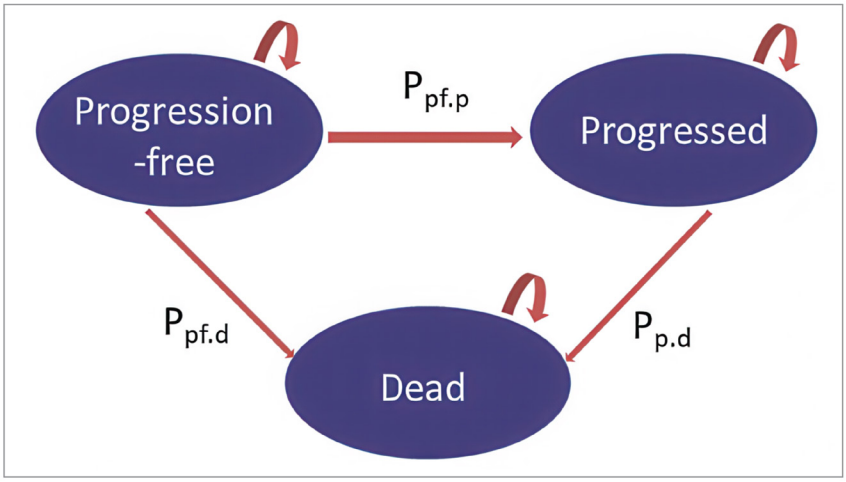
Table 9: Submission Quality

Description	Yes or No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	Yes	No comment
Model has been adequately programmed and has sufficient face validity	Yes	No comment
Model structure is adequate for decision problem	Yes	No comment
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	No comment
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	No comment
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	Yes	No comment

Appendix 3: Additional Information on the Submitted Economic Evaluation

Please note that this appendix has not been copy-edited.

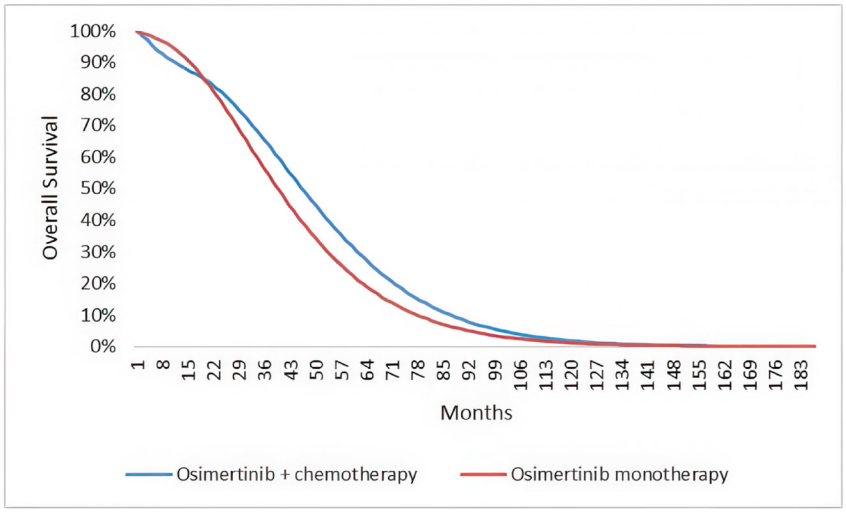
Figure 1: Model Structure



PD = progressed disease; PF = progression-free; STM = state transition model; Pff.p = transition probability PF to PD; Pp.d = transition probability PD to Death; Pfd.d = transition probability PF to Death.

Source: Sponsor's pharmacoeconomic submission.[1]

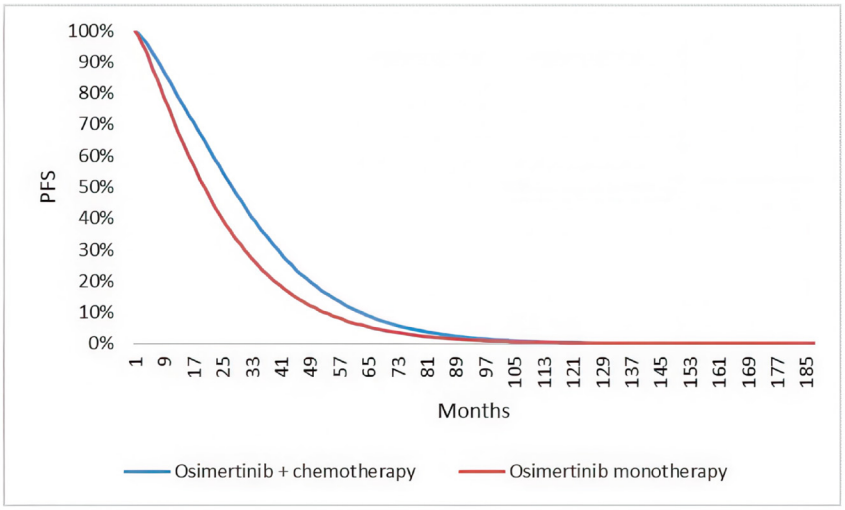
Figure 2: Predicted Overall Survival Outcomes Based on Sponsor's Parametric Survival Extrapolation Choices for TTP (Gamma)



TTP = Time to progression.

Source: Sponsor's pharmacoeconomic submission.[1]

Figure 3: Predicted Progression-Free Survival Outcomes Based on Sponsor's Parametric Survival Extrapolation Choices for PFS (Gamma)



PFS = Progression-free survival.

Source: Sponsor's pharmacoeconomic submission.[1]

Table 10: Benefits Accrued in the Extrapolated vs. Observed Data Period

Benefit accrued	Osimertinib plus chemotherapy	Osimertinib monotherapy
Discounted Lys		
Total	3.84	3.44
PF observed period	1.81	1.53
PF extrapolated period	0.70	0.44
PD observed period	0.36	0.64
PD extrapolated period	0.97	0.83
Discounted QALYs		
Total	3.08	2.73
PF observed period	1.55	1.31
PF extrapolated period	0.60	0.38
PD observed period	0.25	0.45
PD extrapolated period	0.69	0.59

PD = progressed disease; PF = progression-free; AE = adverse event; LY = life-year; QALY = quality-adjusted life-year; vs. = versus.

Table 11: Disaggregated Summary of the Sponsor's Probabilistic Base Case

Parameter	Osimertinib + chemotherapy	Osimertinib monotherapy
Discounted Lys		
Total	3.82	3.37
Progression-free	2.49	1.93
Progressed disease	1.33	1.44
Discounted QALYs		
Total	3.70	2.67
Progression-free	2.13	1.65
Progressed disease	0.94	1.01
AE	−0.00	−0.00
Discounted costs ($)		
Total	**$386,921**	**$327,912**
Primary Treatment Acquisition-Total cost	$343,073	$289,970
Osimertinib	$329,381	$289,970
carboplatin + cisplatin	$2,432	—
Pemetrexed	$11,260	—
Administration – Total cost	$5,991	$289
Administration (osimertinib)	$340	$289
Administration (carboplatin + cisplatin)	$928	—
Administration (pemetrexed)	$4,724	—
Subsequent Treatment Acquisition costs	$2,069	$5,034
Disease management -Total cost	$33,489	$32,207
Progression-free	$9,242	$7,170
Progressed disease	$7,761	$8,431
Terminal care	$16,486	$16,606
Monitoring	$310	—
AE	$1,990	$412

AE = Adverse events; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[1]

Appendix 4: Additional Details on the CDA-AMC Reanalyses and Sensitivity Analyses of the Economic Evaluation

Please note that this appendix has not been copy-edited.

Detailed Results of CDA-AMC Base Case

Table 12: Disaggregated Summary of CDA-AMC Economic Evaluation Probabilistic Results

Parameter	Osimertinib + chemotherapy	Osimertinib monotherapy
Discounted LYs		
Total	3.61	3.33
Progression-free	2.28	1.33
Progressed disease	1.88	1.45
Discounted QALYs		
Total	3.03	2.78
Progression-free	1.94	1.61
Progressed disease	1.08	1.17
AE	−0.00	−0.00
Discounted costs		
Total	**$383,306**	**$325,408**
Primary Treatment Acquisition-Total cost	$340,205	$287,656
Osimertinib	$326,501	$287,656
carboplatin + cisplatin	$2,432	—
Pemetrexed	$11,272	—
Subsequent Treatment Aquisition costs	$2,073	$5,033
Administration — Total cost	$6,002	$285
Administration (osimertinib)	$335	$285
Administration (carboplatin + cisplatin)	$931	—
Administration (pemetrexed)	$4,736	—
Disease management -Total cost	$32,725	$32,021
Progression-free	$8,438	$6,971
Progressed disease	$7,779	$8,462
Terminal care	$16,509	$16,588
Monitoring	$311	—
AE	$1,989	$412

AE = adverse event; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

A scenario analysis was performed to examine the impact of reductions in the price of osimertinib and chemotherapy. The results of this scenario analysis are described in Table 13. These results suggest that osimertinib plus chemotherapy would be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY if the price of osimertinib and the price of chemotherapy drugs were reduced by 91%.

Table 13: Price-Reduction Scenario Analysis for all Therapies

Analysis	Unit drug cost ($)				ICERs for osimertinib plus chemotherapy vs. osimertinib monotherapy ($ per QALY)	
Price reduction	**Osimertinib**	**Cisplatin**	**Carboplatin (AUC5)**	**Pemetrexed**	**Sponsor base case**	**CDA-AMC reanalysis**
No price reduction	**$322.13**	**$135.00**	**$775.00**	**$50.00**	**$150,081**	**$282,754**
10%	$290	$122	$698	$45	$136,679	$257,158
20%	$258	$108	$620	$40	$123,277	$231,562
30%	$225	$95	$543	$35	$109,874	$206,801
40%	$193	$81	$465	$30	$96,472	$180,370
50%	$161	$68	$388	$25	$83,070	$154,774
60%	$129	$54	$310	$20	$69,667	$129,178
70%	$97	$41	$233	$15	$56,265	$103,581
80%	$64	$27	$155	$10	$42,863	$77,985
90%	$32	$14	$78	$5	$29,461	$52,389
100%	$0	$0	$0	$0	$16,058	$26,793

QALY = quality-adjusted life-year; vs. = versus.

A second scenario analysis was performed to estimate the impact of negotiation on the price of osimertinib, compared to the current price of osimertinib. This scenario recognizes that osimertinib currently has a negotiated price that is unlikely to be renegotiated. While the CDA-AMC standard approach to price reduction considers the reduction in price on 'both sides' of the decision problem (i.e., both in the comparator arm and in the new drug arm), this review presents the unusual circumstance in which a drug is being compared to itself in the identical setting. Accordingly, this scenario analysis considers an osimertinib price reduction in the new drug arm, but keeps the price of osimertinib the same in the comparator arm.

In this analysis, a 14% reduction in the price of osimertinib was required to reach an ICER of $50,000 per QALY gained. At an 18% price reduction, the total health care system costs associated with osimertinib plus chemotherapy were lower than the total health care system costs associated with osimertinib monotherapy (i.e., osimertinib plus chemotherapy was dominant).

Table 14: Price-Reduction Scenario Analysis for Osimertinib Alone

Analysis	Unit drug cost ($)		ICERs for osimertinib plus chemotherapy vs. osimertinib monotherapy ($ per QALY)	
Price reduction	**Osimertinib (in new drug arm)**	**Osimertinib (in comparator arm)**	**Sponsor base case**	**CDA-AMC reanalysis**
No price reduction	**322.13**	**322.13**	**150,081**	235,123
10%	290	**322.13**	59,656	102,531
12%	283	**322.13**	41,570	76,013
14%	277	**322.13**	23,485	49,495
18%	264	**322.13**	Osimertinib plus chemotherapy dominates osimertinib monotherapy	Osimertinib plus chemotherapy dominates osimertinib monotherapy

Appendix 5: Submitted Budget Impact Analysis and CDA-AMC Appraisal

Please note that this appendix has not been copy-edited.

Table 15: Summary of Key Take-Aways

Key take-aways of the budget impact analysis
• CDA-AMC identified the following key limitation with the sponsor's analysis: ◦ Estimates of drug plan coverage were uncertain. • CDA-AMC 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**. • CDA-AMC 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.**

Summary of Sponsor's Budget Impact Analysis

The sponsor's submitted budget impact analysis (BIA) assessed the impact resulting from reimbursing osimertinib in combination with pemetrexed and platinum-based chemotherapy for first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations. The BIA was conducted from the perspective of the Canadian public drug plans over a 3-year (2025 to 2027) time horizon with 2024 as the base year, using an epidemiologic approach. The sponsor's pan-Canadian estimates reflect the aggregated results from provincial budgets (excluding Quebec) as well as the Non-Insured Health Benefits (NIHB) program. Adjustments were made to the provincial populations to remove NIHB patients to estimate the provincial public plan population. The sponsor's base case included drug acquisition costs only and no mark-ups or dispensing fees were included in the cost calculations. TTD curves from the FLAURA2 trial were applied to each cycle to determine the proportion of patient who discontinued treatment. Patients who discontinued from osimertinib + chemotherapy and osimertinib monotherapy were eligible to receive subsequent treatment. Market share inputs were estimated based on sponsor-submitted patient and physician preferences published in a FLAURA2 editorial.[19] Key inputs to the BIA are documented in Table 16.

The following key assumptions were made by the sponsor:

- An average BSA of 1.71m^2 was used in the drug acquisition calculations and was derived from the FLAURA2 trial.
- The sponsor assumed that 100% of patients in the reference scenario would receive osimertinib monotherapy.

Table 16: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Target population	
Annual incidence of lung cancer	0.088%[20,21]
Proportion of NSCLC	88.0%[22]
Stage IIB, IIC or IV at diagnosis	52.7%[23]
Incident population with early-stage disease	47.3%[22]
Annual recurrence to metastatic disease	5.1%[24]
Total patients with de novo metastasis or distance recurrence	10,796
Proportion tested for EGFR mutations	77.4%[25,26]
Proportion positive for EGFR mutations	15.2%[27]
Proportion with exon 19 deletions or exon 21 L858R mutations	18.3%[27]
Proportion receiving first-line systemic treatment	87.6%[27]
Drug plan eligibility	77.9%[28]
Number of patients eligible for drug under review	740 / 752 / 764
Market uptake (3 years)	
Uptake (reference scenario) Osimertinib monotherapy	 100% / 100% / 100%
Uptake (new drug scenario) Osimertinib + chemotherapy Osimertinib monotherapy	 [redacted] / 27% [redacted] / 73%
Cost of treatment (per patient, per 21-day cycle)[a]	
Osimertinib + chemotherapy [induction]	$7,653
Osimertinib + chemotherapy [maintenance]	$7,265
Osimertinib monotherapy[b]	$6,765

NSCLC = non–small cell lung cancer.

[a]Costs of treatment were calculated per 21-day cycle to align with the dosing cycles for platinum induction and pemetrexed.

[b]Osimertinib monotherapy does not differ in cost between induction and maintenance.

Summary of the Sponsor's BIA Results

The sponsor's base case reported that the reimbursement for osimertinib + chemotherapy for the treatment for first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR ex19del or L858R mutations would result in an incremental budget impact of $589,350 in year 1, $2,162,331 in year 2, $4,379,040 in year 3. The total 3-year incremental cost of reimbursing osimertinib + chemotherapy is $7,130,721.

CDA-AMC Appraisal of the Sponsor's BIA

CDA-AMC identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **The proportion of patients eligible for public coverage is uncertain.** The sponsor's base case used age and jurisdiction-specific public coverage rates for all medications. IV oncology drugs are likely to be fully covered. Depending on the jurisdiction, oral oncology drugs may be fully reimbursed or may only be reimbursed by regular public drug plans, as assumed in the sponsor's base case.
    - To address uncertainty regarding the proportion eligible for public drug coverage, CDA-AMC assumed 100% coverage across jurisdictions and age as a scenario analysis.

CDA-AMC Reanalyses of the BIA

CDA-AMC Did not undertake a base-case reanalysis and accepted the sponsor's submitted base case.

Table 17: CDA-AMC Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CDA-AMC value or assumption
Changes to derive the CDA-AMC base case		
No changes.	—	—

CDA-AMC conducted the following scenario analyses to address remaining uncertainty, using the CDA-AMC base case (results are provided in Table 18):

1. Assuming 100% drug plan coverage.

Table 18: Detailed Breakdown of the CDA-AMC Reanalyses of the Budget Impact Analysis

Stepped analysis	Scenario	Year 0 (current situation) ($)	Year 1 ($)	Year 2 ($)	Year 3 ($)	Three-year total ($)
Submitted base case	Reference	41,159,894	102,891,320	144,461,484	171,833,373	419,186,177
	New drug	41,159,894	103,480,670	146,623,815	176,212,413	426,316,898
	Budget impact	0	589,350	2,162,331	4,379,040	7,130,721
CDA-AMC scenario analysis 1: 100% Drug Plan Coverage	Reference	53,114,451	132,775,086	186,413,877	221,726,395	540,915,358
	New drug	53,114,451	133,538,718	189,212,449	227,395,190	550,146,357
	Budget impact	0	763,631	2,798,573	5,668,796	9,230,999

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ISSN: 2563-6596

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.