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Reimbursement Recommendation

Lazertinib and Amivantamab (Lazcluze and Rybrevant)

Indication: For the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations.

Sponsor: Janssen Inc.

Final Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Lazcluze Plus Rybrevant?

Canada's Drug Agency (CDA-AMC) recommends that Lazcluze plus Rybrevant be reimbursed by public drug plans for the treatment of locally advanced (not amenable to curative therapy) or metastatic non–small cell lung cancer (NSCLC) with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations if certain conditions are met.

Which Patients Are Eligible for Coverage?

Lazcluze plus Rybrevant should only be covered to treat adults (≥ 18 years) with newly diagnosed NSCLC whose tumours have spread to other parts of the body, returned after treatment, or cannot be removed by surgery or chemoradiation; whose tumours harbour *EGFR* exon 19 deletions or L858R substitution mutations; and who are in relatively good health.

What Are the Conditions for Reimbursement?

Lazcluze plus Rybrevant should only be reimbursed for patients who have not had any prior anticancer treatment for advanced or metastatic disease, if prescribed by clinicians with expertise in treating NSCLC, and the cost of Lazcluze plus Rybrevant does not exceed the total cost of treatment with osimertinib plus platinum-based chemotherapy (PBC).

Why Did CDA-AMC Make This Recommendation?

- Evidence from an ongoing clinical trial demonstrated that Lazcluze plus Rybrevant delays cancer progression and may extend life compared with osimertinib alone.
- Lazcluze plus Rybrevant may meet some important patient needs by providing another treatment option that delays disease progression and potentially prolonging life; however, there was not enough evidence to show that Lazcluze plus Rybrevant would improve quality of life.
- Based on the CDA-AMC assessment of the health economic evidence, Lazcluze plus Rybrevant does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Lazcluze plus Rybrevant than osimertinib plus PBC.
- Based on public list prices, Lazcluze plus Rybrevant is estimated to cost the public drug plans approximately $34.8 million over the next 3 years.

Summary

Additional Information

What Is NSCLC?

Lung cancer is the most common cancer and is the leading cause of cancer deaths in Canada. Approximately 88% of patients with lung cancer in Canada have NSCLC, of which about 15% have an *EGFR* mutation. In 2024, 32,100 new cases of lung and bronchus cancer were predicted to be diagnosed. NSCLC has a poor prognosis, with only 3% of patients with advanced disease (stage IV) surviving for 5 years.

Unmet Needs in NSCLC

There are limited treatment options available for patients with NSCLC with *EGFR* mutations that can effectively prolong survival, prevent disease progression (particularly tumours that spread to the brain or spinal cord), and maintain quality of life.

How Much Does Lazcluze and Rybrevant Cost?

Treatment with Lazcluze plus Rybrevant is expected to cost approximately $12,135 per 28-day cycle.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that lazertinib in combination with amivantamab be reimbursed for the first-line treatment of adults with locally advanced (not amenable to curative therapy) or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 ongoing, phase III, randomized controlled trial (RCT) (MARIPOSA) demonstrated that amivantamab plus lazertinib resulted in added clinical benefit in progression-free survival (PFS) compared with osimertinib monotherapy in adults with locally advanced or metastatic NSCLC whose tumour harboured *EGFR* exon 19 deletions or exon 21 L858R substitution mutations. At the preplanned interim analysis (data cut-off date of August 11, 2023), the median PFS was 23.72 months (95% confidence interval [CI], 19.12 to 27.66) in the amivantamab plus lazertinib group compared to 16.59 months (95% CI, 14.78 to 18.46) in the osimertinib group, with a hazard ratio (HR) of 0.70 (95% CI, 0.58 to 0.85). The difference in the probability of being progression-free at 12 months and 24 months was [redacted] and [redacted], in favour of amivantamab plus lazertinib. As of the updated efficacy analysis (data cut-off date of May 13, 2024), the median overall survival (OS) was not reached in the amivantamab plus lazertinib arm and was 37.32 months (95% CI, 32.53 to not estimable) in the osimertinib arm, in favour of amivantamab plus lazertinib (HR = 0.77; 95% CI, 0.61 to 0.96); however, pERC noted that the results for OS were immature and uncertain. pERC also noted the significant harms associated with amivantamab plus lazertinib. A total of 75.1% of patients in the amivantamab plus lazertinib arm and 42.8% in the osimertinib arm experienced a grade 3 or higher adverse event (AE). Compared to osimertinib, more patients in the amivantamab plus lazertinib arm reported clinically important AEs of rash (88.6% versus 49.1%), infusion-related reaction (IRR) (62.9% versus 0), and venous thromboembolism (VTE) (37.3% versus 9.1%). In the absence of direct comparative evidence with osimertinib plus chemotherapy, the sponsor submitted indirect evidence in the form of a network meta-analysis (NMA). pERC concluded that there was insufficient evidence to detect a difference between amivantamab plus lazertinib and osimertinib plus PBC [redacted] and the limitations of the NMA increased the uncertainty in the results.

Patients identified a need for treatments that delay progression, prolong survival, have manageable side effects, and allow them to experience improved quality of life. pERC concluded that, compared to osimertinib monotherapy, amivantamab plus lazertinib likely meets the need for improved PFS and may improve OS. However, pERC noted that treatment with amivantamab plus lazertinib was associated with significant side effects, and the committee was unable to draw conclusions on health-related quality of life (HRQoL) due to the high amount of missing data.

Using the sponsor-submitted price for amivantamab plus lazertinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for amivantamab plus lazertinib was $305,328

per quality-adjusted life-year (QALY) compared with osimertinib monotherapy. At this ICER, amivantamab plus lazertinib is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for adults with locally advanced (not amenable to curative therapy) or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations in the first-line setting. A price reduction is required for amivantamab plus lazertinib to be considered cost-effective at a $50,000 per QALY threshold compared to osimertinib monotherapy. There was insufficient clinical evidence to justify a price premium for amivantamab plus lazertinib over osimertinib plus PBC.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with amivantamab plus lazertinib should be reimbursed in adults (≥ 18 years) with: 1.1. newly diagnosed locally advanced or metastatic NSCLC not amenable to curative surgery or chemoradiation 1.2. a tumour that harbours *EGFR* exon 19 deletions or exon 21 L858R substitution mutations.	Evidence from the MARIPOSA trial suggested that treatment with amivantamab plus lazertinib resulted in a clinical benefit in patients with these characteristics.	*EGFR* exon 19 deletions or exon 21 L858R status must be determined before starting treatment with amivantamab plus lazertinib.
2. Patients must have good performance status.	Patients with an ECOG Performance Status of 0 or 1 were included in the MARIPOSA trial.	Patients with an ECOG Performance Status greater than 1 may be treated at the discretion of the treating clinician.
3. Patients must not have any of the following: 3.1. history of ILD 3.2. any prior systemic treatment for locally advanced stage III or metastatic stage IV disease, except for adjuvant or neoadjuvant therapy received at least 6 months before locally advanced or metastatic disease developed 3.3. unstable CNS metastases.	There is no evidence to support the benefit of amivantamab plus lazertinib in patients with these characteristics because they were excluded from the MARIPOSA trial.	—
Discontinuation		
4. Treatment with amivantamab plus lazertinib should be discontinued upon disease progression or unacceptable toxicity.	Patients in the MARIPOSA trial discontinued treatment upon progression or unacceptable toxicity consistent with clinical practice.	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
5. Amivantamab plus lazertinib should be prescribed by clinicians with expertise in treating NSCLC.	This is meant to ensure that amivantamab plus lazertinib is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. Amivantamab plus lazertinib should be negotiated so that it does not exceed the drug program cost of treatment with the least costly most relevant comparator reimbursed for the treatment of adults with locally advanced (not amenable to curative therapy) or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations in the first-line setting.	The CDA-AMC Clinical Review noted inconsistent timing of disease assessments between the MARIPOSA and FLAURA2 trials, along with factors such as heterogeneity in the presence of brain metastases and unknown information on 2 potential prognostic factors. As such, there is insufficient evidence to justify a cost premium for amivantamab plus lazertinib over osimertinib plus PBC.	—

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; ILD = interstitial lung disease; NSCLC = non–small cell lung cancer; PBC = platinum-based chemotherapy.

Discussion Points

- **Unmet needs:** pERC discussed the input from patient groups, which emphasized the need for treatments that improve survival, maintain quality of life, and have reduced or manageable side effects. pERC and the clinical experts also noted the need for treatments that prevent central nervous system (CNS) metastasis and offer CNS disease control in patients with NSCLC. pERC acknowledged the substantial morbidity and mortality associated with NSCLC and agreed that amivantamab plus lazertinib potentially meets some very important unmet needs identified by patients compared to osimertinib monotherapy. However, pERC was unable to conclude whether amivantamab plus lazertinib met the identified unmet needs versus osimertinib plus chemotherapy due to a lack of direct comparative evidence and limitations associated with the submitted indirect evidence.
- **Relevant comparators and place in therapy:** pERC discussed the relevance of the comparator in the MARIPOSA trial (osimertinib monotherapy), noting that osimertinib plus chemotherapy concluded negotiations with the pan-Canadian Pharmaceutical Alliance on January 29, 2025, receiving a letter of intent. In consultation with the clinical experts, pERC noted that there is no evidence to choose 1 treatment over another but highlighted that treatments would be chosen in consultation with the patient considering multiple factors, including, but not limited to, the mode of administration (oral versus IV), underlying comorbidities, frailty, and patient preference regarding potential increased toxicities (e.g., VTE).

- **Adverse events:** pERC discussed the safety profile of amivantamab plus lazertinib given the known AE profile and experience with amivantamab, which includes IRRs, interstitial lung disease (ILD), and skin and nail reactions. pERC noted that, compared to osimertinib, amivantamab plus lazertinib was associated with higher rates of grade 3 or higher AEs (75.1% versus 42.8%), as well as higher frequencies of paronychia (68.4% versus 28.3%), IRRs (62.9% versus 0%), and VTE (37.3% versus 9.1%), which were primarily driven by amivantamab. pERC and the clinical experts emphasized the considerable patient morbidity associated with nail and skin toxicity, as well as the requirement for prophylaxis for VTEs. pERC also noted that the medications associated with amivantamab to reduce the risk of IRRs and VTE may not be publicly funded or available in all jurisdictions. pERC also discussed 2 studies addressing gaps submitted by the sponsor — the SKIPPirr and PALOMA-3 studies — for the purpose of addressing IRR prophylaxis and management of VTEs, respectively, which pERC noted mitigate some concerns with the AE profile of amivantamab plus lazertinib. pERC also discussed the high proportion of AEs leading to dose interruptions with amivantamab plus lazertinib relative to osimertinib (83.1% versus 38.6%), as well as the discontinuation from all study drugs (in the amivantamab plus lazertinib arm [for amivantamab and 45.4% for lazertinib], and for the osimertinib arm). pERC emphasized the tolerability concerns of the regimen, as in the amivantamab plus lazertinib arm, 34.0% of patients discontinued treatment with amivantamab due to AEs, while 20.7% of patients discontinued the lazertinib component of the regimen due to AEs. Conversely, pERC noted that 11.7% of patients in the osimertinib group and 13.6% of patients in the lazertinib monotherapy group discontinued due to AEs. pERC noted the increased monitoring requirements for the notable AEs associated with this regimen.
- **Treatment efficacy:** pERC discussed the pivotal evidence submitted for this review, which consisted of 1 phase III, RCT (MARIPOSA) and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) certainty of evidence assessment. pERC noted that, compared to osimertinib, amivantamab plus lazertinib resulted in statistically significant improvements in PFS (HR = 0.70; 95% CI, 0.58 to 0.85), which was associated with a moderate level of certainty. pERC noted that the clinical meaningfulness of the improvement in PFS was uncertain. pERC also discussed the prespecified subgroup analyses in patients with or without a history of CNS metastases, which suggested similar benefits in the subgroup of patients with brain metastases compared to the primary analysis population. pERC deliberated on the results for OS, noting that the results were supportive of a potential survival advantage with amivantamab plus lazertinib over osimertinib; however, the evidence was of low certainty and the data were considered immature.
- **Quality of life considerations:** As an outcome of importance to patients and clinicians, pERC discussed the HRQoL results of the MARIPOSA trial. Despite the suggestion that there was no improvement or detriment to HRQoL with amivantamab plus lazertinib compared to osimertinib, pERC emphasized that the results for HRQoL generally favoured osimertinib; however, the committee noted the uncertainty in comparative HRQoL results due to high levels of attrition.
- **Indirect evidence:** pERC noted that only 1 active comparator currently available in Canada (i.e., osimertinib monotherapy) was assessed in the clinical trial evidence. pERC discussed the indirect

evidence submitted for this review, which consisted of NMAs comparing amivantamab plus lazertinib with osimertinib plus chemotherapy. The results of the NMA suggested [redacted]. pERC noted the substantial uncertainty in the results of the NMA given the wide 95% credible intervals likely driven by the between-study clinical and methodological heterogeneity.

- **Economic considerations:** In the absence of clear evidence to quantify the difference in survival outcomes between amivantamab plus lazertinib and osimertinib plus PBC, there is insufficient evidence to support a price premium for amivantamab plus lazertinib compared to osimertinib plus PBC. The price of amivantamab and lazertinib in this indicated population should be negotiated such that the total cost of treatment is no greater than the total cost of treatment with osimertinib plus PBC. pERC also discussed the existence of potential costs and impacts to patient quality of life (including financial toxicity) that may not have been captured in the economic evaluation related to the management of AEs and other toxicities associated with amivantamab, lazertinib, osimertinib, and PBC.
- **Cost-effectiveness compared to osimertinib:** The ICER for amivantamab plus lazertinib is $305,328 when compared with osimertinib monotherapy. A price reduction of 87% would be required for amivantamab plus lazertinib to achieve an ICER of $50,000 per QALY compared to osimertinib monotherapy.
- **Testing procedure considerations:** pERC noted that *EGFR* testing is currently performed as the standard of care for patients with NSCLC in Canada and acknowledged that evaluating *EGFR* status for exon 19 deletions or exon 21 L858R substitution mutations before the initiation of amivantamab plus lazertinib would be required. pERC also noted that considering this is already standard of care, *EGFR* testing is not anticipated to be an implementation or access barrier.

Background

Lung cancer is the most diagnosed cancer and leading cause of cancer-related deaths in Canada; it is estimated that 1 in 14 people in Canada will develop lung cancer, which accounts for 1 in 4 cancer-related deaths. In 2024, 32,100 new cases of lung and bronchus cancer were projected. NSCLC comprises 88% of cases and has a poor prognosis, with a 5-year survival rate of only 3% for advanced disease (stage IV). A key mechanism involves driver mutations that activate progrowth signalling pathways, most commonly in the *EGFR* gene. These driver mutations are found more frequently in patients with adenocarcinomas, those who are nonsmokers, patients of Asian ethnicity, and those who are female. According to the clinical experts consulted by the review team, testing for *EGFR* mutations, including exon 19 deletions and exon 21 L858R substitution mutations, is currently performed as part of the standard of care for locally advanced or metastatic nonsquamous NSCLC in Canada.

According to the experts consulted for this review, osimertinib is the current standard treatment for NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations, based on the FLAURA trial, which demonstrated superior PFS and OS compared to erlotinib and gefitinib. It is taken daily until disease progression or intolerance and has a favourable safety profile, making it suitable for the vast majority of patients, including older adults. Osimertinib plus PBC is also recommended for reimbursement as a first-line treatment of adults with locally advanced or metastatic NSCLC whose tumours have *EGFR* exon 19 deletions or exon 21 L858R mutations. It is currently undergoing price negotiations and therefore is not widely available yet.

Amivantamab plus lazertinib has been approved by Health Canada for the first-line treatment of adults with locally advanced (not amenable to curative therapy) or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations. Lazertinib is a highly selective CNS-penetrant, oral, third-generation *EGFR* tyrosine kinase inhibitor (TKI) and amivantamab is a bispecific antibody. Lazertinib is available as 80 mg and 240 mg tablets and the dosage recommended in the product monograph is 240 mg once daily, taken orally, in combination with amivantamab until disease progression or no longer tolerated by the patient. Amivantamab is available as a 350 mg/7 mL (50 mg/mL) single use vial for IV infusion and the dosage recommended in the lazertinib product monograph is 1,050 mg (if body weight < 80 kg) or 1,400 mg (if body weight ≥ 80 kg) administered by IV infusion in 28-day cycles, once weekly for the first 4 weeks (with a split dose on days 1 and 2) and then once every 2 weeks at week 5 onward.

Sources of Information Used by the Committee

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

- a review of 1 RCT in patients aged 18 years or older with newly diagnosed locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations that was treatment naive and not amenable to curative therapy; 5 indirect treatment comparisons; 1 phase II trial in patients with advanced or metastatic NSCLC and *EGFR* exon 19 deletions or exon 21 L858R mutations with disease progression on or after sequential osimertinib plus PBC; and 1 phase III trial in patients with *EGFR*-mutated locally advanced or metastatic NSCLC whose disease progressed after osimertinib plus PBC
- patients' perspectives gathered by 3 patient group(s), Lung Cancer Canada, the Canadian Cancer Survivor Network, and the Lung Health Foundation
- input from the public drug plans and cancer agencies that participated in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations
- input from 2 clinician groups, the Ontario Health - Cancer Care Ontario (OH-CCO) Lung and Thoracic Cancer Drug Advisory Committee (DAC) and the Lung Cancer Canada Medical Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

For this review, patient input was jointly submitted by 3 organizations: Lung Cancer Canada, the Canadian Cancer Survivor Network, and the Lung Health Foundation. Information was gathered from 4 patients in Canada diagnosed with stage IV NSCLC with treatment experience with amivantamab (N = 3) or lazertinib plus amivantamab combination therapy (N = 1). Data were collected through virtual interviews and from previous patient input submissions to CDA-AMC.

The patient group input described the initial shock patients experienced by their diagnosis, as they noted minimal initial symptoms (e.g., back pain, a persistent cough, or shortness of breath). Three of the patients reported experience with currently available *EGFR*-targeted therapies, including osimertinib, gefitinib, and afatinib, with limited side effects (e.g., significantly dry skin, thinning hair, and diarrhea) before their disease progressed. As such, progression and treatment resistance remain a critical concern for patients. The input noted that patients desire a treatment that can improve the management of their disease symptoms, delay further progression, shrink their tumours, improve their quality of life, prolong survival with independence and functionality, and have manageable side effects.

Three of the patients included in the input each had a different mutation (exon 20, exon 19, or exon 21 L858R) and reported successful tumour shrinkage and stable metastases after receiving amivantamab as a first-line, third-line, or later-line treatment. One patient developed additional metastases approximately 3 years after initiating third-line amivantamab and has since passed away. The patient who received lazertinib and amivantamab combination therapy as a second-line treatment for more than 2.5 years to date had initial shrinking in their primary tumour and is currently experiencing stable metastases. Two patients reported significant side effects at treatment onset, including severe dry scalp and bleeding due to dryness; [redacted]; painful acne; and rashes on their scalp, back, and chest. The patient input noted that these side effects reduced in severity over time, were controlled with prescription medications, were not as severe as those experienced with chemotherapy, and were deemed worthwhile if the treatment was working. Two patients reported that they were able to return to a good quality of life and could pursue hobbies, travel, and spending time with family. The input also noted that patients preferred the ease and convenience of oral targeted therapies that can be taken at home versus the long infusion times in the hospital needed with amivantamab.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts noted that, ultimately, all patients with NSCLC will experience disease progression; thus, there is a need for treatments that delay progression, extend survival, and have manageable side effects. The clinical experts noted that there is a risk of relapse with current therapies, particularly in the case of CNS disease as *EGFR*-mutated NSCLC tends to present with brain metastases or have a high risk of their development. The current standard of care (osimertinib monotherapy) is generally well tolerated, relieves disease-related symptoms quickly, can be administered to older adults, is an oral medication, and can be

more convenient for patients. The clinical experts noted that there is a risk of added toxicity and potential inconvenience of IV chemotherapy administered every 3 weeks for the recently recommended osimertinib plus chemotherapy combination. Additionally, *EGFR* inhibitors are generally associated with serious toxicities (e.g., pneumonitis) that can impact quality of life.

The experts indicated that amivantamab plus lazertinib, osimertinib alone, or osimertinib plus chemotherapy could all be considered first-line options for patients with the *EGFR* mutations relevant to this review. Amivantamab plus lazertinib and osimertinib plus chemotherapy would offer the opportunity for more efficacy over osimertinib alone, although with trade-offs such as the risk of greater toxicity and more clinic visits. Amivantamab plus lazertinib could be an alternate option to osimertinib plus chemotherapy for a proportion of patients, particularly those who are younger and more fit but have some poorer prognostic features, including CNS metastases. The experts emphasized, however, that similar to other treatments for *EGFR*-mutated NSCLC, amivantamab plus lazertinib would not be curative.

The clinical experts noted that *EGFR* detection is routine across Canada and therefore misdiagnosis is unlikely. Patients with newly diagnosed locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations who were young, fit, or felt to be at high risk of poorer outcomes (e.g., those with liver metastases, brain metastases, or p53 mutations) would be most likely to be considered for this therapy. The experts noted that not all patients would be suitable for amivantamab plus lazertinib, potentially due to underlying comorbidities, frailty, lack of desire for IV treatment or increased toxicities, including thromboembolism. They stated that patient preference would be important to consider, and that the choice of treatment would routinely involve a discussion with patients regarding their treatment options. The experts noted that patients with prior *EGFR* TKI experience were excluded from the pivotal trial; however, there is a possibility that osimertinib may be used as an adjuvant therapy after tumour resection. These patients (estimated by the experts to be approximately 10% to 15% of patients) would not have been included in the pivotal trial; therefore, it is unclear whether they would be considered candidates for amivantamab plus lazertinib. The experts also noted that older patients (i.e., those older than aged 75 years) were not highly represented in the trial and may also be less tolerant of a more aggressive regimen.

The experts noted that patients are typically evaluated by their physician every 3 to 4 weeks and imaging is conducted every 8 to 12 weeks, depending on their treatment regimen. Objective response criteria (e.g., radiological assessment every 2 to 3 months to determine disease progression) can be used to ensure disease response or control, along with clinical assessments of disease-related symptoms (e.g., cough, shortness of breath) and HRQoL, which the experts noted is not routinely assessed in clinical practice using standardized tools. The clinical experts stated that the discontinuation criteria for amivantamab plus lazertinib should be the same as other anticancer therapies, for which disease progression, intolerable toxicity, toxicity associated with deteriorating quality of life, and patient choice would all be grounds to discontinue. The experts noted that amivantamab plus lazertinib should only be prescribed under the care of oncology specialists in a cancer centre.

Clinician Group Input

Two clinician groups, OH-CCO DAC and the Lung Cancer Canada Medical Advisory Committee, provided input. They emphasized that the primary treatment goals for patients with stage IV NSCLC include prolonging survival, improving symptoms, and delaying disease progression. Osimertinib remains the standard first-line treatment for *EGFR*-mutated NSCLC, but resistance inevitably develops and no publicly funded targeted therapies exist for patients whose disease progresses on osimertinib in Canada. The input noted that to address resistance, intensified first-line regimens, such as osimertinib plus chemotherapy, have been explored. However, according to the clinician groups, not all patients have disease that responds to these therapies, highlighting the need for additional, intensified treatments in the first-line setting that improve survival, symptom control, and brain protection while maintaining manageable toxicity and convenience. OH-CCO DAC noted that amivantamab and lazertinib do not fully meet the criteria of convenience or low toxicity.

Both clinician groups agreed that amivantamab plus lazertinib would be used as a first-line treatment in the population under review. Single-drug osimertinib will still be considered a first-line option as there will be patients who do not want to receive IV systemic therapy or prefer the logistics involved with an oral drug alone. In the event there is access to combination osimertinib plus chemotherapy in the future, this regimen would add an additional first-line therapeutic option. Following these regimens, chemotherapy would remain a viable second-line option. The patients best suited for amivantamab plus lazertinib are those with advanced *EGFR*-mutated NSCLC who can tolerate intensified treatment and increased monitoring. The input noted that it is not yet possible to identify specific patients whose disease is more likely to respond to this therapy or which patients should receive osimertinib plus chemotherapy versus amivantamab plus lazertinib. The input stated that treatment response is assessed through side effect profiles, clinical outcomes, and imaging at regular intervals. Patients will require close monitoring, particularly for dermatologic side effects, with evaluations typically occurring every 2 to 4 months. Lazertinib is taken at home, while amivantamab is administered in outpatient oncology units or hospitals by experienced personnel.

Drug Program Input

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The comparator in the MARIPOSA trial is osimertinib monotherapy, but osimertinib plus chemotherapy has also been recommended for reimbursement by CDA-AMC and both are potential comparators.	This is a comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
The MARIPOSA trial included patients with an ECOG Performance Status of 0 or 1. Would it be appropriate to	Select patients with an ECOG Performance Status of 2 could be considered for treatment especially if the Performance Status is at least in part related to disease-related factors. This would be

Implementation issues	Response
allow patients with another ECOG Performance Status (e.g., 2) to be treated with amivantamab plus lazertinib?	based on clinical judgment. pERC agreed with the clinical experts.
The MARIPOSA trial eligibility included previous adjuvant or neoadjuvant therapy for stage I and II disease if treatment was completed at least 12 months ago. Could treatment with amivantamab plus lazertinib be considered in patients who had a shorter than 12 months interval of treatment?	If the treatment received in the adjuvant or neoadjuvant setting was a non-*EGFR* inhibitor (e.g., cytotoxic chemotherapy), a period of 6 months could be considered. The experts also noted that osimertinib in the adjuvant setting is standard of care and that this would only apply to a rare subset of patients. There is no data on prior *EGFR* inhibitors in the adjuvant setting as patients with prior TKI use were excluded from the MARIPOSA trial. pERC agreed with the clinical experts but noted that a 6-month interval is acceptable for patients who also received osimertinib in the adjuvant setting.
Alignment of the initiation criteria with osimertinib plus chemotherapy should be considered.	This is a comment from the drug programs to inform pERC deliberations.
Considerations for prescribing of therapy	
The combination contains an oral and IV drug and, depending on jurisdiction, these may be funded differently.	This is a comment from the drug programs to inform pERC deliberations.
Generalizability	
When initially funded, would it be appropriate to switch patients from osimertinib (plus chemotherapy) to amivantamab plus lazertinib, assuming no disease progression?	The clinical experts noted that patients would not switch therapies unless there was a lack of efficacy, at which point switching therapies would be considered a new line of therapy. Assuming no progression, patients might also switch if they were unable to tolerate osimertinib plus chemotherapy and a more intensive approach was indicated, or the patient was not considered to be a suitable candidate for osimertinib plus chemotherapy, in which case this would not be considered a new line of therapy. pERC agreed with the clinical experts.
If there is toxicity, would it be appropriate to switch patients from osimertinib (plus chemotherapy) to amivantamab plus lazertinib or vice versa?	The clinical experts noted that switching would be appropriate if the toxicity was not considered related to the *EGFR* inhibitor, as the side effects of *EGFR* inhibitors will not be improved by switching to amivantamab plus lazertinib. pERC agreed with the clinical experts and noted that this would only be in the absence of disease progression.
If there is toxicity, would it be appropriate to discontinue 1 of the drugs in the regimen (amivantamab or lazertinib) and continue on the other one?	The clinical experts noted that the decision to discontinue a component of the regimen would depend on factors such as the nature of the toxicity and the timing the toxicity occurred (e.g., late or early in treatment). pERC agreed with the clinical experts, noting this was done in the MARIPOSA trial and would be appropriate depending on the nature of the toxicity, but could be done at the discretion of the treating clinician.
Funding algorithm	
The initiation of a rapid provisional funding algorithm has been requested.	This is a comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
Care provision issues	
VTE has a higher incidence in the amivantamab plus lazertinib arm. Prophylaxis for the first 4 months is recommended, though funding of anticoagulants may be variable across jurisdictions and may include patient self-pay.	This is a comment from the drug programs to inform pERC deliberations. The experts commented that VTE can be associated with considerable morbidity and favoured longer prophylactic treatment but noted that most of the events in the trial occurred early on. pERC agreed and emphasized the availability and accessibility requirements for prophylactic treatment options given that anticoagulant prophylaxis may need to continue throughout treatment with amivantamab plus lazertinib.
System and economic issues	
Confidential pricing exists for osimertinib.	This is a comment from the drug programs to inform pERC deliberations.

CDA-AMC = Canada's Drug Agency; ECOG = Eastern Cooperative Oncology Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; TKI = tyrosine kinase inhibitor; VTE = venous thromboembolism.

Clinical Evidence

Systematic Review

Description of Studies

MARIPOSA is an ongoing randomized, multicentre, phase III trial comparing the efficacy and safety of first-line amivantamab plus lazertinib to osimertinib monotherapy in adults with *EGFR*-mutated NSCLC. The data contained in the submission were from a data cut-off date of August 11, 2023, which represented the cut-off for the primary analysis of PFS and interim analysis of OS. An updated clinical efficacy analysis of major secondary end points (i.e., OS) and exploratory end points with longer-term follow-up was conducted using a data cut-off date of May 13, 2024. The MARIPOSA trial enrolled adults (aged ≥ 18 years) with newly diagnosed, histologically or cytologically confirmed, locally advanced or metastatic NSCLC that was treatment naive and not amenable to any curative therapy, including surgical resection or chemotherapy. Patients also had to meet specific organ function thresholds and have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. The tumour also had to have evidence of either the *EGFR* exon 19 deletion mutation or the *EGFR* exon 21 L858R substitution mutation, as well as at least 1 lesion measurable by Response Evaluation Criteria for Solid Tumors (RECIST) 1.1 that had not been previously irradiated. Notable exclusion criteria included prior treatment for any locally advanced (stage III) or metastatic (stage IV) cancer, symptomatic brain metastases, and any prior *EGFR* TKI therapy.

A total of 1,074 patients were randomized 2:2:1 to either open-label amivantamab plus lazertinib (arm A; N = 429), double-blinded osimertinib (arm B; N = 429), or double-blinded lazertinib (arm C; N = 216), respectively. Randomization was stratified by mutation type (exon 19 deletion versus exon 21 L858R substitution mutation), race (Asian versus not Asian), and history of brain metastases (present versus absent). Those in arm A received amivantamab 1,050 mg (1,400 mg if body weight ≥ 80 kg) by IV infusion in

28-day cycles, once weekly for the first 4 weeks (with a split dose on days 1 to 2 in week 1) and then once every 2 weeks, and three 80 mg lazertinib tablets once daily. Those in arm B received osimertinib 80 mg plus 3 lazertinib placebo tablets once daily. Those in arm C received 1 osimertinib placebo capsule plus three 80 mg lazertinib tablets (240 mg total) once daily. The primary end point of the MARIPOSA trial was PFS by blinded independent central review (BICR), with secondary end points including OS, objective response rate (ORR), duration of response (DOR), and HRQoL measures.

Efficacy Results

The results of the prespecified primary analysis of PFS and interim analysis of OS (August 11, 2023, data cut-off; median duration of follow-up of 22.01 months), as well as results from OS, ORR, and DOR from the additional May 13, 2024, reanalysis (median follow-up of approximately 31 months) were reported.

Progression-Free Survival by BICR

As of the August 11, 2023, data cut-off, there were a total of 192 PFS events (44.8%) in the amivantamab plus lazertinib arm, and 252 PFS events (58.7%) in the osimertinib arm. Of these, 148 (77.1%) and 228 (90.5%) were due to progressive disease, and 44 (22.9%) and 24 (9.5%) were due to death without progressive disease in the amivantamab plus lazertinib and osimertinib arms, respectively. The median PFS in the amivantamab plus lazertinib arm was 23.72 months (95% CI, 19.12 to 27.66), and in the osimertinib arm was 16.59 months (95% CI, 14.78 to 18.46), in favour of amivantamab plus lazertinib (HR = 0.70; 95% CI, 0.58 to 0.85; P = 0.0002). The differences in the probability of having disease that was progression-free between amivantamab plus lazertinib and osimertinib at 6 months, 12 months, 18 months, and 24 months was [redacted], respectively.

PFS was not reanalyzed with data from the May 13, 2024, data cut-off as the primary end point was met in the primary analysis of PFS (August 11, 2023, data cut-off).

Overall Survival

As of the August 11, 2023, data cut-off, with 214 deaths observed in the amivantamab plus lazertinib and osimertinib arms combined at the data cut-off, the interim analysis of OS was evaluated at a 2-sided significance level of 0.0050. There was a total of 97 deaths (22.6%) in the amivantamab plus lazertinib arm, and 117 deaths (27.3%) in the osimertinib arm. The median OS was not reached in either study arm as of the data cut-off (HR = 0.80; 95% CI, 0.61 to 1.05; P = 0.1099). The OS event-free probability between study arms for the proportion of patients who were alive at 6 months, 12 months, 18 months, and 24 months was [redacted], respectively.

As of the May 13, 2024, data cut-off, there were 142 deaths (33.1%) in the amivantamab plus lazertinib arm and 177 deaths (41.3%) in the osimertinib arm. The median OS was not reached in the amivantamab plus lazertinib arm. The median OS was 37.32 months (95% CI, 32.53 to not estimable) in the osimertinib arm, in favour of amivantamab plus lazertinib (HR = 0.77; 95% CI, 0.61 to 0.96; P = 0.0185). The OS event-free probability between study arms for the proportion of patients who were alive at 12 months, 24 months, and

36 months was [redacted], respectively.

Objective Response Rate

As of the August 11, 2023, data cut-off, a total of 336 patients (79.8%; 95% CI, 75.7% to 83.5%) in the amivantamab plus lazertinib arm and 314 patients (75.8%; 95% CI, 71.4% to 79.9%) in the osimertinib arm had an objective response ([redacted], respectively). The odds ratio for response when compared to the osimertinib arm was 1.27 (95% CI, 0.91 to 1.77).

As of the May 13, 2024, data cut-off, a total of [redacted] in the amivantamab plus lazertinib arm and [redacted] in the osimertinib arm had an objective response. The odds ratio for response was [redacted].

Duration of Response

As of the August 11, 2023, data cut-off, there were 336 confirmed responders (i.e., individuals whose disease showed response to the treatment) in the amivantamab plus lazertinib arm and 314 in the osimertinib arm. The median DOR in the amivantamab plus lazertinib arm was 25.76 months (95% CI, 20.14 to not estimable), and in the osimertinib arm the median DOR was 16.76 months (95% CI, 14.75 to 18.53). The difference between study arms in the proportion of responders with DOR of 6 months, 12 months, 18 months, and 24 months was [redacted], respectively.

As of the May 13, 2024, data cut-off, there were [redacted] confirmed responders in the amivantamab plus lazertinib arm and [redacted] in the osimertinib arm. The median DOR in the amivantamab plus lazertinib arm was 25.76 months (95% CI, 20.34 to 33.87), and in the osimertinib arm the median DOR was 18.14 months (95% CI, 14.78 to 20.14). The difference between study arms in the proportion of responders with DOR of 12 months, 24 months, and 30 months was [redacted] respectively.

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) functional scales range from 0 to 100, with higher scores indicating better functioning. As of the August 11, 2023, data cut-off, the mean baseline EORTC QLQ-C30 Global Health Status score was [redacted] in the amivantamab plus lazertinib arm and [redacted] in the osimertinib arm. At cycle 13, day 1, the least squares (LS) mean change from baseline was [redacted] in the amivantamab plus lazertinib arm and [redacted] in the osimertinib arm, representing an LS mean difference of [redacted]

[redacted]). At cycle 21, day 1, the LS mean change from baseline was [redacted] in the amivantamab plus lazertinib arm and [redacted] in the osimertinib arm, representing an LS mean difference of [redacted]. At cycle 27, day 1, the LS mean change from baseline was [redacted] in the amivantamab plus lazertinib arm and [redacted] in the osimertinib arm, representing an LS mean difference of [redacted].

The results for EORTC QLQ-C30 Global Health Status were not assessed at the May 13, 2024, data cut-off.

Non–Small Cell Lung Cancer – Symptom Assessment Questionnaire Total Score

The Non–Small Cell Lung Cancer – Symptom Assessment Questionnaire (NSCLC-SAQ) contains 5 domains and the total score ranges from 0 to 20, with higher scores indicating more severe symptoms. As of the August 11, 2023, data cut-off, the mean baseline NSCLC-SAQ total score was [redacted] in the amivantamab plus lazertinib arm and [redacted] in the osimertinib arm. At cycle 13, day 1, the LS mean change from baseline was [redacted] in the amivantamab plus lazertinib arm and [redacted] in the osimertinib arm, representing an LS mean difference of [redacted]. At cycle 21, day 1, the LS mean change from baseline was [redacted] in the amivantamab plus lazertinib arm and [redacted] in the osimertinib arm, representing an LS mean difference of [redacted]). At cycle 27, day 1, the LS mean change from baseline was [redacted] in the amivantamab plus lazertinib arm and [redacted] in the osimertinib arm, representing an LS mean difference of [redacted].

The results for NSCLC-SAQ total score were not assessed at the May 13, 2024, data cut-off.

Harms Results

Harms from the lazertinib monotherapy arm were also reported to provide additional context into the harms associated with amivantamab.

Adverse Events

As of the August 11, 2023, data cut-off, all patients in the amivantamab plus lazertinib arm and lazertinib monotherapy arm, and 99.3% of patients in the osimertinib arm experienced an AE. In addition, 75.1% of patients in the amivantamab plus lazertinib arm, 42.8% in the osimertinib arm, and 45.5% in the lazertinib arm experienced a grade 3 or higher AE. The most commonly reported AEs were paronychia (68.4% in the amivantamab plus lazertinib arm, 28.3% in the osimertinib arm, and [redacted] in the lazertinib arm); infusion-related reactions (62.9% in the amivantamab plus lazertinib arm, 0% in the osimertinib arm, and [redacted] in the lazertinib arm); rash (61.8% in the amivantamab plus lazertinib arm, 30.6% in the osimertinib arm, and [redacted] in the lazertinib arm); hypoalbuminemia (48.5% in the amivantamab plus lazertinib arm, 6.1% in the osimertinib arm, and [redacted] in the lazertinib arm); increased alanine aminotransferase (36.1% in the

amivantamab plus lazertinib arm, 13.3% in the osimertinib arm, and [redacted] in the lazertinib arm); and peripheral edema (35.6% in the amivantamab plus lazertinib arm, 5.6% in the osimertinib arm, and [redacted] in the lazertinib arm).

Additional AEs that were reported in a numerically higher proportion of patients in the osimertinib arm relative to the other 2 study arms were diarrhea (44.4% in the osimertinib arm, 29.2% in the amivantamab plus lazertinib arm, and [redacted] in the lazertinib arm); leukopenia (15.4% in the osimertinib arm, 6.2% in the amivantamab plus lazertinib arm, and [redacted] in the lazertinib arm); and neutropenia ([redacted] in the osimertinib arm, [redacted] in the amivantamab plus lazertinib arm, and [redacted] in the lazertinib arm).

Serious Adverse Events

As of the August 11, 2023, data cut-off, a total of 48.7% of patients in the amivantamab plus lazertinib arm, 33.4% of patients in the osimertinib arm, and 35.2% of patients in the lazertinib arm reported serious AEs. The most common serious AEs (occurring in more than 1.5% of patients) that were also reported in numerically higher proportions in the amivantamab plus lazertinib arm relative to the osimertinib and lazertinib arms were pulmonary embolism (26 [6.2%] in the amivantamab plus lazertinib arm, 10 [2.3%] in the osimertinib arm, and [redacted] in the lazertinib arm); deep vein thrombosis (12 [2.9%] in the amivantamab plus lazertinib arm, 2 [0.5%] in the osimertinib arm, and [redacted] in the lazertinib arm); IRR (9 [2.1%] in the amivantamab plus lazertinib arm and 0 in the osimertinib [redacted]); respiratory failure (6 [1.4%] in the amivantamab plus lazertinib arm, 2 [0.5%] in the osimertinib arm, and [redacted] in the lazertinib arm); rash (7 [1.7%] in the amivantamab plus lazertinib arm and 0 in the osimertinib [redacted]).

Withdrawals Due to Adverse Events

As of the August 11, 2023, data cut-off, a total of 34.9% of patients in the amivantamab plus lazertinib arm, 13.6% in the osimertinib arm, and [redacted] in the lazertinib arm had discontinued any study treatment due to AEs. The most common reason for study treatment discontinuation in the amivantamab plus lazertinib arm was [redacted]); in the osimertinib arm the most common reason for discontinuation was [redacted]).

Mortality

The proportion of patients who died was numerically similar across the study arms (96 patients [22.8%] in the amivantamab plus lazertinib arm, 116 patients [27.1%] in the osimertinib arm, and [redacted] patients in the lazertinib arm). The most common reason for death was disease progression (11.6% of patients in the amivantamab plus lazertinib arm, 18.9% of patients in the osimertinib arm, and [redacted] of patients in the lazertinib arm), followed by AEs (9.3% of patients in the amivantamab plus lazertinib arm, 6.8% of patients in the osimertinib arm, and [redacted] of patients in the lazertinib arm).

Notable Harms

The AEs of special interest (AESIs) of rash, IRR, and pneumonitis or ILD were prospectively identified based on the safety profile of amivantamab, and VTE was added as an AESI during the conduct of the study. A

numerically higher proportion of patients in the amivantamab plus lazertinib arm reported rash (88.6% versus 49.1% in the osimertinib arm and [redacted] in the lazertinib arm), IRR (62.9% versus 0 in the osimertinib [redacted]), and VTE (37.3% versus 9.1% in the osimertinib arm and [redacted] in the lazertinib arm). A total of 3.1% of patients in the amivantamab plus lazertinib arm, 3.0% of patients in the osimertinib arm, and [redacted] of patients in the lazertinib arm reported pneumonitis or ILD.

Critical Appraisal

The amivantamab plus lazertinib arm was open label, which would impact the assessment of HRQoL outcomes due to participants knowing that they were receiving treatment with amivantamab plus lazertinib. It is also possible that patients randomized to the osimertinib or lazertinib monotherapy arms, while double-blinded, would also be aware that they were not receiving amivantamab plus lazertinib as amivantamab is an IV infusion and there was no matching placebo IV. In addition, the study protocol was amended several times after patient enrolment started, including the addition of AESIs and updating the inclusion and exclusion criteria; therefore, there is an unknown risk of bias due to these changes, which impacts an unknown number of patients. The OS results of the study were based on an interim analysis; thus, there is a risk of overestimating the true treatment effect. The median OS and DOR were not estimable at the time of the prespecified data cut-off date. While data with longer-term follow-up were provided for OS, ORR, and DOR, this did not represent a prespecified data cut-off date and should be considered exploratory. The median OS was not reached in either the August or May data cut-offs. As of the August 11, 2023, data cut-off (median follow-up of 22.01 months), a total of 25% of OS events had occurred across both study arms, but as of the May 13, 2024, data cut-off, a total of [redacted] of OS events had occurred, suggesting that the data are largely immature for OS. The 75th percentile for the DOR result was likewise not estimable at the May 2024 data cut-off, suggesting the data are immature for this outcome as well. The long-term results associated with amivantamab plus lazertinib are therefore unclear for OS and DOR. In addition, ORR and DOR were not controlled for multiple comparisons and are only considered supportive of the overall effect of amivantamab and lazertinib. In general, the stratification factors used in randomization and other potential prognostic factors identified by the experts, such as age, smoking status, ECOG status, and sex, were balanced between the study arms. The HRQoL end points were secondary in the MARIPOSA trial and the results were not adjusted for multiple comparisons; therefore, there is an increased risk of type I error, and these results can only be considered supportive. HRQoL estimates had a substantial amount of missing data and were modelled using a mixed model for repeated measures, which assumes the data are missing at random. However, the nature of the disease means that, because patients are censored at disease progression or death, among other reasons, it is likely that patients who remained on study were systematically different from patients who did not provide data, and there is a likelihood of bias in the results. While the NSCLC-SAQ analysis required that all 5 domains be complete to compute a total score, no methods to account for missing responses for the EORTC QLQ-C30 were reported, which also may impart a bias of unknown direction and degree.

There are also limitations impacting the external validity of the study. Per the clinical experts consulted for this review, the study inclusion and exclusion criteria and baseline characteristics were broadly representative of the patients in clinical practice settings in Canada, apart from the fact that the racial

breakdown in the MARIPOSA trial was slightly different than the typical patient population in a clinical setting in Canada. However, they noted that the MARIPOSA trial limited enrolment to an ECOG Performance Status of 0 or 1, and patients with an ECOG Performance Status of 2 or greater may be considered for this therapy. In addition, patients with a history of adjuvant therapy were enrolled if the therapy was more than 12 months prior; the experts noted that if the treatment received in the adjuvant or neoadjuvant setting was a non-*EGFR* inhibitor (e.g., cytotoxic chemotherapy), then a period of 6 months could be considered. They also noted that patients who had any prior experience with *EGFR* TKIs were excluded, which might preclude patients from receiving amivantamab plus lazertinib if they had received osimertinib in the adjuvant setting given its use for earlier-stage NSCLC in Canada. The clinical experts estimated that this might affect approximately 10% or 15% of patients. The results of the trial would therefore not be generalizable to these patients. In addition, the median follow-up at the time of the May 13, 2024, data cut-off was approximately 31 months; however, the trial is still ongoing and longer-term results on efficacy and harms are not available; it is uncertain whether the results are generalizable to a longer treatment duration.

Table 3: Summary of Findings for Amivantamab Plus Lazertinib Versus Osimertinib for Patients With Locally Advanced or Metastatic Non–Small Cell Lung Cancer

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	What happens
		Amivantamab plus lazertinib	Osimertinib	Difference		
Survival outcomes						
Progression-free survival by BICR: August 11, 2023, data cut-off						
Proportion of patients who are progression-free at 24 months Median follow-up: 23.72 months vs. 16.59 months[a]	858 (1 RCT)	[redacted]	[redacted]	[redacted]	Moderate[b]	Amivantamab plus lazertinib likely results in an increase in the proportion of patients who are progression-free at 24 months when compared with osimertinib.
Overall survival: May 13, 2024, data cut-off[c]						
Proportion of patients who are alive at 24 months Median follow-up: [redacted]	858 (1 RCT)	[redacted]	[redacted]	[redacted]	Low[d,e]	Amivantamab plus lazertinib may result in an increase in the proportion of patients who are alive at 24 months when compared with osimertinib.
Proportion of patients who are alive at 30 months	858 (1 RCT)	[redacted]	[redacted]	[redacted]	Low[d,e]	Amivantamab plus lazertinib may result in an increase in the proportion of patients who are

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	What happens
		Amivantamab plus lazertinib	Osimertinib	Difference		
Median follow-up: [redacted]						alive at 30 months when compared with osimertinib.
Proportion of patients who are alive at 36 months Median follow-up: [redacted]	858 (1 RCT)	[redacted]	[redacted]	[redacted]	Low[d,e]	Amivantamab plus lazertinib may result in an increase in the proportion of patients who are alive at 36 months when compared with osimertinib.
Health-related quality of life outcomes: August 11, 2023, data cut-off[f]						
EORTC QLQ-C30 Global Health Status score (100 [best] to 0 [worst])						
LS mean change from baseline to cycle 13, day 1 Median follow-up: 22.01 months	858 (1 RCT)	[redacted]	[redacted]	[redacted]	Very low[g,h]	The evidence is very uncertain about the effect of amivantamab plus lazertinib on the change from baseline to cycle 13, day 1, in EORTC QLQ-C30 Global Health Status when compared with osimertinib.
LS mean change from baseline to cycle 27, day 1 Median follow-up: 22.01 months	858 (1 RCT)	[redacted]	[redacted]	[redacted]	Very low[g,h]	The evidence is very uncertain about the effect of amivantamab plus lazertinib on the change from baseline to cycle 27, day 1, in EORTC QLQ-C30 Global Health Status when compared with osimertinib.
NSCLC-SAQ total score (0 [best] to 20 [worst])						
LS mean change from baseline to cycle 13, day 1 Median follow-up: 22.01 months	858 (1 RCT)	[redacted]	[redacted]	[redacted]	Very low[g,i]	The evidence is very uncertain about the effect of amivantamab plus lazertinib on the change

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	What happens
		Amivantamab plus lazertinib	Osimertinib	Difference		
						from baseline to cycle 13, day 1, in NSCLC-SAQ total score when compared with osimertinib.
LS mean change from baseline to cycle 27, day 1 Median follow-up: 22.01 months	858 (1 RCT)	[redacted]	[redacted]	[redacted]	Very low[g,i]	The evidence is very uncertain about the effect of amivantamab plus lazertinib on the change from baseline to cycle 27, day 1, in NSCLC-SAQ total score when compared with osimertinib.
Harms: August 11, 2023, data cut-off						
Proportion of patients with a rash Median follow-up: 22.01 months	858 (1 RCT)	[redacted]	[redacted]	[redacted]	Low[j]	Amivantamab plus lazertinib may result in an increase in the proportion of patients with a rash when compared with osimertinib.
Proportion of patients with VTE Median follow-up: 22.01 months	858 (1 RCT)	[redacted]	[redacted]	[redacted]	Low[j]	Amivantamab plus lazertinib may result in an increase in the proportion of patients with VTE when compared with osimertinib.
Proportion of patients with an infusion reaction Median follow-up: 22.01 months:	858 (1 RCT)	[redacted]	[redacted]	[redacted]	Low[j]	Amivantamab plus lazertinib may result in an increase in the proportion of patients with an infusion reaction when compared with osimertinib.
Proportion of patients with pneumonitis or interstitial lung disease	858 (1 RCT)	[redacted]	[redacted]	[redacted]	Low[k]	Amivantamab plus lazertinib may result in an increase in the proportion of patients with pneumonitis or

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	What happens
		Amivantamab plus lazertinib	Osimertinib	Difference		
Median follow-up: 22.01 months						interstitial lung disease when compared with osimertinib.

BICR = blinded independent central review; CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LS = least squares; MID = minimal important difference; NSCLC-SAQ = Non–Small Cell Lung Cancer – Symptom Assessment Questionnaire; OS = overall survival; RCT = randomized controlled trial; vs. = versus.

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

[a]Follow-up presented as amivantamab plus lazertinib vs. osimertinib.

[b]Rated down 1 level for serious imprecision. Based on an MID of a 20% (200 per 1,000) difference between study arms provided by the clinical experts consulted for this review, the point estimate and lower bound of the CI are below the threshold for clinically meaningful benefit.

[c]The May 13, 2024, efficacy update was done at the request of the European Medicines Agency and does not represent a preplanned analysis.

[d]Rated down 1 level for serious limitations. Median OS was not reached at the time of the PFS-triggered interim analysis (August 11, 2023) [redacted]. This implies that the OS data are immature and there is high uncertainty in the trends observed to date; therefore, the confidence with which the results predict the outcome in the long term is not clear.

[e]Rated down 1 level for serious imprecision. Based on an MID of a 10% difference (100 per 1,000) between study arms provided by the clinical experts consulted for this review, the point estimate and lower bound of the CI are below the threshold for clinically meaningful benefit.

[f]The results for this outcome were not controlled for multiple comparisons and are considered supportive evidence.

[g]Rated down 2 levels for serious study limitations. A considerable amount of patient data was missing at the time points and, based on the study design, it is likely that the missingness is informative. The open-label design of the amivantamab plus lazertinib arm also imparts bias to these subjective study measures, as patients would be aware that they are randomized to the treatment arm, and patients randomized to the osimertinib arm may also be aware of their treatment assignment due to the lack of placebo IV administered in the study.

[h]Rated down 1 level for serious imprecision. Based on an MID of 10 points provided by the sponsor, the point estimate and lower bound of the CI are below the MID.

[i]Rated down 1 level for serious imprecision. Based on an MID of a 2-point increase (worsening) or 3-point decrease (improvement) in total score provided by the sponsor, the point estimate and lower bound of the CI are below the MID.

[j]Rated down 2 levels for serious limitations due to a lack of CI estimates and lack of absolute differences between study arms.

Sources: Details included in the table are from the sponsor's Summary of Clinical Evidence, the MARIPOSA CSR (August 11, 2023, data cut-off), the MARIPOSA Efficacy Update (May 13, 2024, data cut-off), and additional information provided by the sponsor.

GRADE Summary of Findings and Certainty of the Evidence

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 the expert committee members.

- Clinical outcomes:
  - PFS at 24 months
  - OS at 24, 30, and 36 months
- HRQoL outcomes:
  - Change from baseline to cycle 13, day 1, in EORTC QLQ-C30 Global Health Status and NSCLC-SAQ total score
  - Change from baseline to cycle 27, day 1, in EORTC QLQ-C30 Global Health Status and NSCLC-SAQ total score
- Harms:

- Rash
- VTE
- IRRs
- Pneumonitis or ILD

Long-Term Extension Studies

The submission did not include any long-term extension studies.

Indirect Comparisons

The MARIPOSA trial compared amivantamab plus lazertinib with osimertinib monotherapy; however, there was no other head-to-head trial that assessed the relative effectiveness and safety of amivantamab plus lazertinib compared to other potentially relevant first-line treatment options. In addition, the results from the indirect evidence were incorporated into the pharmacoeconomic model, meriting a review of the indirect evidence. The body of indirect evidence consisted of 5 NMAs informed by a systematic literature review (SLR).

Description of Studies

An SLR was conducted in May 2020 and updated in July 2022; it searched for therapeutic or palliative options for patients with metastatic or surgically unresectable common *EGFR*-mutated NSCLC; the common *EGFR* mutations included exon 21 L858R substitutions and exon 19 deletions, T790M in exon 20, and C797S in exon 20.

On completion of the SLR, the feasibility of conducting NMAs to compare amivantamab plus lazertinib with key comparators was assessed. The feasibility assessment appraised studies on the following factors:

- their alignment with the prespecified scope
- similarity of patient characteristics
- similarity of study characteristics
- reported outcome measures
- data availability and network connectivity.

All interventions were considered either as monotherapy or in combination with others, unless the combination was deemed not of interest. Exclusions on the basis of interventions were initially made considering network connectivity. Interventions that had come onto the market but were discontinued or deemed unlikely to come to market were excluded. The submission therefore included first-generation TKIs (i.e., erlotinib, gefitinib, icotinib), second-generation TKIs (i.e., afatinib, dacomitinib), third-generation TKIs (i.e., osimertinib, lazertinib, aumolertinib, furmonertinib), chemotherapy, and monoclonal antibodies (i.e., bevacizumab, ramucirumab, cetuximab, and amivantamab). The clinical experts consulted for this review highlighted osimertinib and osimertinib plus chemotherapy as relevant comparators in Canada, and a deviation request to exclude first- and second-generation *EGFR* TKIs (i.e., afatinib, erlotinib, gefitinib) plus PBC was accepted by CDA-AMC. The results from the comparison to osimertinib monotherapy and

osimertinib plus chemotherapy were therefore included in the review. Though other treatments were included in the network, they were not considered appropriate or relevant comparators; thus, results for them were not reported.

Treatment effect modifiers were identified by the sponsor during the feasibility assessment based on the available baseline characteristics (supplemented by searching ClinicalTrials.gov), through reference to published literature or treatment appraisals, and discussion with experts.

Efficacy and Harms Results

Critical Appraisal

The indirect evidence consisted of 5 NMAs informed by an SLR. The SLR was conducted in 2022; therefore, it is not known whether the most recent publications on other relevant comparators (or OS updates to publications) would have been captured in the search. In addition to this, while the study exclusion list and reasons for exclusion were provided, 14 studies were excluded on the basis of not having an intervention of interest or useful connection; these terms were not defined in the report and it is not known whether the criteria for a “useful connection” might bias the NMA network. Furthermore, while the steps for the quality assessment were provided, the results of the quality assessment were not; therefore, the specific risks of bias in the individual studies are not known. As the 3 studies included in the NMA had different designs (open label, mixed open label and double blind, and double blind), this could represent a source of bias and adds uncertainty to the results of the NMA.

The NMA methods themselves are also subject to minor limitations: the use of fixed-effect models over random-effect models increases the uncertainty as it does not account fully for potential heterogeneity between studies. In addition, the nature of the network meant that it was not possible to evaluate pairwise contrasts, and consistency was not evaluated in the submission. Although the impact of these is likely minor given all 3 trials were phase III RCTs, these limitations also contribute to increasing the general uncertainty in the results.

The submission provided the criteria by which treatment effect modifiers were identified in the studies forming the NMA network and identified ECOG Performance Status, cancer histology, presence of brain metastases, race or ethnicity, and common *EGFR* mutation as treatment effect modifiers. According to clinical experts consulted for this review, the list of effect modifiers was generally representative of important

indicators in the disease, and the list of additional prognostic factors (age, sex, smoking status) also included factors that would interact with the effect modifiers or represented prognostic factors on their own. Treatment effect modifiers were generally balanced across the 3 studies included in the appraisal with the exception of brain metastases, for which FLAURA reported lower proportions of patients with CNS metastases. In addition, smoking status and cancer stage at screening were not reported in either the FLAURA or FLAURA2 trials. These represent potential prognostic indicators that could interact with treatment effect modifiers. Overall, the heterogeneities in these 3 areas increased the uncertainty in the results.

There were additional differences noted with regards to study design and inclusion criteria that were highlighted in the submission. The duration of follow-up in the studies was shorter for the FLAURA trial (at the time the SLR was conducted) than for the MARIPOSA and FLAURA2 trials, with a shorter period of time over which events can accrue; this could bias the results in favour of the comparators in the FLAURA trial (osimertinib). A more recent publication of OS results for the FLAURA trial has been published, but was not included in the network. In addition, there were numeric differences noted in the frequency of assessments between the 3 studies: assessments were done at baseline, every 6 weeks (± 1 week) for 18 months, then every 12 weeks in the FLAURA trial; every 8 weeks (± 1 week) for the first 30 months followed by every 12 weeks (± 1 week) thereafter in the MARIPOSA trial; and at baseline, week 6, week 12, then every 12 weeks for the FLAURA2 trial. While there is potential for overestimating treatment effects when disease assessments occur less frequently,[16] the nature of this bias is that the interval within which an event occurred is known, but the exact time of the event is not known. For survival outcomes, this bias is more likely to impact the median estimates, as the median considers the number of events in individual arms of the study at a particular time and may be sensitive to the timing of the assessment. The direction of bias of the HR estimates are less likely to be materially impacted by the frequency of assessment, and while there is increased uncertainty in the estimates and CIs, the extent and direction of this bias in the NMA network is unclear.

Additional design differences included the ascertainment of results by BICR versus investigator: the FLAURA2 and MARIPOSA trials reported sensitivity analyses for PFS by BICR and PFS by investigator, respectively, and the results were consistent with the primary analyses;[17] therefore, this bias was also not considered to impact the results. The FLAURA2 trial also required a minimum life expectancy for enrolment, but the clinical experts consulted for this review noted that this was unlikely to have an impact on the results or comparability of the studies as patients with fewer than 12 weeks' life expectancy would be considered unsuitable for treatment with interventions such as chemotherapy or amivantamab due to toxicity concerns. Lastly, while the sponsor noted that there were also differences in the frequency of serial brain imaging and the criteria for conducting serial brain imaging, CNS outcomes were not appraised in the report. Overall, the differences in study design have the potential for bias but the degree of bias is unknown; therefore, this increases the uncertainty in the results but was not deemed likely to change the conclusions from the NMA.

Studies Addressing Gaps in the Evidence From the Systematic Review

The sponsor submitted 2 studies (SKIPPirr and PALOMA-3) that did not meet the eligibility criteria for inclusion in the systematic review.

The sponsor noted that systemic IRRs, including severe reactions, that occur with the introduction of a new protein therapeutic infusion are frequently observed. The SKIPPirr study evaluated the potential of prophylactic strategies in reducing amivantamab-associated IRRs.

Following observed increases in VTE events with the combination of amivantamab plus lazertinib in the MARIPOSA trial, a mitigation strategy involving prophylactic anticoagulation therapy per local guidelines during the first 4 months of therapy with enhanced monitoring was implemented in 2022 and integrated into the PALOMA-3 study protocol.

SKIPPirr Study — IRRs

SKIPPirr is an ongoing phase II study evaluating prophylactic strategies to reduce IRRs associated with amivantamab in patients with *EGFR*-mutated (exon 19 deletion or exon 21 L858R substitution) advanced or metastatic NSCLC. The SKIPPirr study included patients with disease progression on or after sequential osimertinib plus PBC. The study uses Simon's 2-stage design with 4 cohorts receiving different prophylactic treatments. Cohorts are as follows: oral dexamethasone on varying schedules (cohorts A and A2), oral montelukast (cohort B), or subcutaneous methotrexate (cohort C). Only the dexamethasone 8 mg cohort met both stage 1 and stage 2 criteria, reducing IRR incidence to 22.5% (versus 67.4% with standard management). The regimen was well tolerated, with no grade 3 or higher IRRs or new safety signals. The most common symptoms were nausea, dyspnea, and hypotension.

PALOMA-3 Study — VTE Prevention

PALOMA-3 is a phase III study comparing subcutaneous (SC) and IV amivantamab plus lazertinib in patients with *EGFR*-mutated locally advanced or metastatic NSCLC who progressed after osimertinib plus PBC. As such, all patients had at least 1 prior therapy, with the majority (89%) having had at least 2 lines of prior therapy. Following increased VTE events in the MARIPOSA trial, prophylactic anticoagulation was integrated into the PALOMA-3 study and recommended for the first 4 months of treatment per local guidelines. The overall VTE incidence was 11.8%, mostly grade 1 or 2. Prophylactic anticoagulation use was similar between the SC and IV groups (approximately 80%), but VTE rates were lower with SC administration (9.2% versus 14.3% for IV). Among patients with anticoagulation, VTEs occurred in 7.3% (SC) and 11.7% (IV), while nonusers had higher rates (16.7% SC; 25.6% IV). Bleeding events were more frequent with anticoagulation. Overall, SC amivantamab plus lazertinib showed a lower VTE incidence than IV, regardless of anticoagulation use.

Critical Appraisal

The SKIPPirr and PALOMA-3 studies provided data on prophylactic treatments for preventing IRRs and VTE events, respectively, in patients with *EGFR*-mutated advanced or metastatic NSCLC. However, both studies had limitations that impact the generalizability and interpretability of their findings. SKIPPirr was an open-label, nonrandomized study with a small sample size, increasing the risk of bias, particularly in comparison to the rigour of standardized RCTs. Patients were aware of their treatment, which may have contributed to detection and performance bias, and the open-label design may influence the reporting of AEs. Similarly, the PALOMA-3 study, while randomized and stratified based on key clinical factors, also had an open-label design, introducing similar biases. In both studies, patients had disease that progressed on or

after prior treatment with osimertinib plus PBC, which does not align with the Health Canada indication as a first-line treatment. Additionally, included patients had an ECOG Performance Status of 0 or 1, meaning they were relatively healthy, which may not fully represent the broader population that would receive prophylactic treatment in real-world clinical practice in Canada.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adults with locally advanced (not amenable to curative therapy) or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations in the first-line setting
Treatments	Amivantamab plus lazertinib
Dose regimen	Amivantamab: Body weight < 80 kg: 1,050 mg weekly for 4 weeks, then every 2 weeks Body weight ≥ 80 kg: 1,400 mg weekly for 4 weeks, then every 2 weeks Lazertinib: 240 mg once daily until disease progression or no longer tolerated by the patient
Submitted price	Amivantamab liquid concentrate for IV fusion, 50 mg/mL: $1,676.00 Lazertinib tablets, 80 mg: $103.60 and 240 mg: $310.82
Submitted treatment cost	$12,135 per 28-day cycle
Comparators	• Osimertinib • Osimertinib plus PBC (carboplatin or cisplatin plus pemetrexed)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (15 years)
Key data sources	MARIPOSA trial: amivantamab plus lazertinib compared with osimertinib monotherapy NMA: amivantamab plus lazertinib compared with osimertinib plus PBC
Key limitations	• The comparative efficacy of amivantamab plus lazertinib compared to osimertinib plus PBC is uncertain due to the lack of head-to-head evidence and limitations with the sponsor's NMA, particularly due to the inconsistencies in disease assessment between the MARIPOSA and FLUARA2 trials. Other factors, such as heterogeneity in the presence of brain metastases and unknown information on 2 potential prognostic factors, also contributed to the uncertainty in the modelled OS, PFS, AEs, and SAEs for osimertinib plus PBC. As such, in the CDA-AMC base case, equivalent clinical efficacy between amivantamab plus lazertinib and osimertinib plus PBC was assumed. • The long-term OS benefit of amivantamab plus lazertinib is highly uncertain due to immature data from the MARIPOSA trial and reliance on extrapolated survival projections. These projections suggest a significant survival benefit, although median OS had not been reached at the time of data cut-off (31 months).

Component	Description
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by assuming equal OS and PFS efficacy for osimertinib plus PBC compared to amivantamab plus lazertinib and assuming a Gompertz function to extrapolate long-term OS for amivantamab plus lazertinib compared to osimertinib monotherapy. • In the CDA-AMC base case, amivantamab plus lazertinib was more costly than osimertinib plus PBC (incremental cost = $81,302) and was equally effective (based on assumption). • Amivantamab plus lazertinib was associated with an ICER of $305,328 per QALY gained (incremental cost = $201,023; incremental QALY = 0.66) compared to osimertinib monotherapy. The CDA-AMC base case suggested that an 87% price reduction for amivantamab plus lazertinib would be required for the regimen to achieve cost-effectiveness relative to osimertinib monotherapy at a WTP threshold of $50,000 per QALY gained.

AE = adverse event; CDA-AMC = Canada's drug Agency; ICER = incremental cost-effectiveness ratio; LY = life-year; NMA = network meta-analysis; NSCLC = non–small cell lung cancer; OS = overall survival; PBC = platinum-based chemotherapy; PFS = progression-free survival; QALY = quality-adjusted life-year; SAE = serious adverse event; WTP = willingness to pay.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the percentage of patients tested for *EGFR* mutations is uncertain, the market uptake of osimertinib may be overestimated, and the market uptake of osimertinib plus PBC may be underestimated.

The CDA-AMC budget impact analysis base case changed the market uptake for osimertinib and osimertinib plus PBC in both the reference and new drug scenarios to align with clinical expectations. The analysis indicates that funding amivantamab plus lazertinib for the first-line treatment of locally advanced (not amenable to curative therapy) or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations would result in an incremental budget impact of $3,881,198 in year 1, $10,459,802 in year 2, and $20,500,384 in year 3. This results in a 3-year budgetary impact of $34,841,383.

pERC Information

Members of the Committee

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

Meeting date: May 14, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

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