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Reimbursement Recommendation

Amivantamab (Rybrevant)

Indication: In combination with carboplatin and pemetrexed for the treatment of patients with locally advanced (not amenable to curative therapies) or metastatic non–small cell lung cancer with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with osimertinib

Sponsor: Janssen Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Rybrevant?

Canada's Drug Agency (CDA-AMC) recommends that Rybrevant in combination with carboplatin and pemetrexed be reimbursed by public drug plans for the treatment of adult patients with locally advanced (not amenable to curative therapies) or metastatic non–small cell lung cancer (NSCLC) with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after osimertinib, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Rybrevant should only be covered to treat patients aged 18 years or older with tumours harbouring *EGFR* exon 19 deletions or exon 21 L858R substitution mutations that have returned while on or after treatment with osimertinib, who are in relatively good health and have no active interstitial lung disease or unstable brain metastases.

What Are the Conditions for Reimbursement?

Rybrevant should only be reimbursed if it is prescribed by clinicians with expertise in treating NSCLC and its price is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that Rybrevant plus chemotherapy reduces the risk of the cancer worsening or spreading and likely prolongs life compared with chemotherapy alone.
- Rybrevant plus chemotherapy may meet some important patient needs by delaying worsening or spreading of cancer, prolonging life, and maintaining quality of life, although it is associated with higher risks of reactions when the drug is infused, blood clots, and skin problems.
- Based on the CDA-AMC assessment of the health economic evidence, Rybrevant does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Rybrevant is expected to cost public drug plans approximately $46.7 million over the next 3 years.

Additional Information

What Is NSCLC?

NSCLC is the most common type of lung cancer, accounting for about 88% of all cases. *EGFR* mutations, including exon 19 deletions and exon 21 L858R substitutions, occur in about 15% of patients with NSCLC in Canada

Summary

and are associated with a poor outlook when disease progresses after initial therapy with osimertinib. Only 3% of patients with advanced disease will survive for 5 years or more. In 2024, 32,100 new lung and bronchus cancer diagnoses were predicted in Canada.

Unmet Needs in NSCLC

There are currently no well-established, effective therapies for patients with NSCL with *EGFR* exon 19 deletions or exon 21 L858R substitutions who experience disease progression on or after osimertinib. Effective and tolerable options are needed to prolong life and maintain quality of life.

How Much Does Rybrevant Cost?

Treatment with Rybrevant is expected to cost approximately $26,816 to $33,520 per patient for the first 28 days, and $11,173 to $13,408 for each subsequent 28 days.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that amivantamab in combination with carboplatin and pemetrexed be reimbursed for the treatment of patients with locally advanced (not amenable to curative therapies) or metastatic non–small cell lung cancer (NSCLC) with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with osimertinib, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 ongoing, phase III, randomized controlled trial (RCT) (the MARIPOSA-2 trial) suggested that amivantamab in combination with carboplatin and pemetrexed chemotherapy (ACP) results in a clinically important improvement in progression-free survival (PFS), and likely results in a clinically important improvement in overall survival (OS) in adult patients with locally advanced or metastatic *EGFR*-mutated NSCLC (exon 19 deletion or exon 21 L858R substitution) whose disease has progressed on or after osimertinib, when compared with carboplatin and pemetrexed chemotherapy (CP). At the first interim analysis (IA1) of the MARIPOSA-2 trial (with a July 2023 data cut-off), after a median follow-up time of 8.97 months in the ACP arm and 8.34 months in the CP arm, the study met its primary end point for PFS, as assessed by blinded independent central review (BICR), with a median PFS of 6.28 months (95% confidence interval [CI], 5.55 to 8.41) in the ACP arm and 4.17 months (95% CI, 4.04 to 4.44) in the CP arm (hazard ratio [HR] = 0.48; 95% CI, 0.36 to 0.64). The median intracranial PFS, assessed by BICR, was 12.45 months (95% CI, 10.84 to not estimable [NE]) in the ACP arm and 8.31 months (95% CI, 7.29 to 11.27) in the CP arm (HR = 0.55; 95% CI, 0.38 to 0.79). At the second interim analysis (IA2) (April 26, 2024, data cut-off), after a median follow-up of 18.6 months in the ACP arm and 17.8 months in the CP arm, the median OS was 17.74 months (95% CI, 15.97 to 22.37) in with ACP and 15.34 months (95% CI, 13.73 to 16.76) with CP (HR = 0.73; 95% CI, 0.54 to 0.99). However, pERC noted that formal statistical testing was not planned for OS at the interim analysis, and the comparison should be considered descriptive.

Patients identified a need for effective treatment options with manageable side effects for patients who experience disease progression on osimertinib, which improve disease control, prolong survival, and maintain quality of life. pERC noted that ACP meets some patient needs as it offers an additional treatment option that delays disease progression and may improve survival with no significant detriment to health-related quality of life (HRQoL) compared to CP. pERC noted that important toxicities, including infusion-related reactions (IRRs), venous thromboembolism (VTE), and dermatologic toxicities, were notably higher in the ACP arm in the MARIPOSA-2 trial. The committee agreed with the clinical experts that the toxicity profile of ACP is significant but may be manageable with prophylactic and supportive care strategies.

Using the sponsor-submitted price for ACP and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for ACP was $292,610 per quality-adjusted life-year (QALY) gained compared with CP alone. At this ICER, ACP is not cost-effective at a $50,000 per QALY gained willingness-to-pay (WTP) threshold for the treatment of patients with locally advanced (not amenable to curative therapies) or

metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with osimertinib. A price reduction is required for amivantamab to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with amivantamab plus carboplatin and pemetrexed should be reimbursed in patients with locally advanced or metastatic NSCLC who meet all of the following criteria: 1.1. age 18 years or older 1.2. tumour that harbours *EGFR* exon 19 deletions or exon 21 L858R substitution mutations 1.3. disease progression on or after osimertinib as the most recent therapy.	Evidence from the MARIPOSA-2 trial suggested that treatment with amivantamab plus carboplatin and pemetrexed resulted in a clinical benefit in patients with these characteristics.	*EGFR* exon 19 deletion or exon 21 L858R status must be determined before starting treatment with amivantamab.
2. Patients must have good performance status.	Patients with an ECOG PS score of 0 or 1 were included in the MARIPOSA-2 trial.	pERC agreed with the clinical experts that patients with an ECOG PS score greater than 1 may be treated at the discretion of the treating clinician.
3. Patients must not have any of the following: 3.1. active ILD 3.2. unstable CNS metastases.	There is no evidence to support the benefit of amivantamab plus carboplatin and pemetrexed in patients with these characteristics because they were excluded from the MARIPOSA-2 trial.	pERC agreed with the clinical experts that patients with treated or stable CNS metastases should be eligible for treatment. For patients with a history of ILD, the suitability for treatment should be at the discretion of the treating physician.
Discontinuation		
4. Treatment with amivantamab plus carboplatin and pemetrexed should be discontinued upon the occurrence of any of the following: 4.1. disease progression 4.2. unacceptable toxicity.	Patients in the MARIPOSA-2 trial discontinued treatment upon progression or unacceptable toxicity consistent with clinical practice (note that carboplatin and pemetrexed chemotherapy was administered for up to 4 [21-day] cycles, then maintenance with pemetrexed was continued until disease progression or unacceptable toxicity, or patient preference).	—
Prescribing		
5. Amivantamab plus carboplatin and pemetrexed should be prescribed by clinicians with expertise in treating NSCLC.	This is meant to ensure that amivantamab plus carboplatin and pemetrexed is prescribed for appropriate patients and that adverse	—

Reimbursement condition	Reason	Implementation guidance
	effects are managed in an optimized and timely manner.	
Pricing		
6. A reduction in price.	The ICER for amivantamab plus carboplatin and pemetrexed is $292,610 when compared with carboplatin and pemetrexed chemotherapy alone. Price reductions greater than 70% for amivantamab will be required for carboplatin and pemetrexed to achieve an ICER of $50,000 per QALY compared to carboplatin and pemetrexed chemotherapy. Price reductions for different thresholds are available in Appendix 4 in the Pharmacoeconomic Review report.	—

CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; ILD = interstitial lung disease; NSCLC = non–small cell lung cancer; QALY = quality-adjusted life-year.

Discussion Points

- **Unmet needs**: pERC discussed the input from patient groups who emphasized the need for effective therapies with reduced or manageable toxicity that improve disease control, prolong survival, and maintain quality of life. pERC acknowledged the poor treatment outcomes in patients with locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations when disease progresses on or after osimertinib, as there is no well-established standard of care (SOC) for these patients. Clinical experts consulted for this review noted that patients often experience disease progression on first-line osimertinib, with some developing *EGFR*-dependent resistance. Therefore, there is an unmet need for therapies that can address known resistance mechanisms (e.g., mesenchymal epithelial transition [MET] amplification or small cell transformation) to extend survival and maintain quality of life. The clinical experts noted that many patients are clinically stable at the time of disease progression on or after osimertinib, underscoring the importance of effective but tolerable treatment options in this setting. pERC agreed that ACP potentially meets some very important unmet needs identified by patients and clinicians.
- **Relevant comparators and place in therapy:** The clinical experts consulted for this review noted that platinum-based chemotherapy is the most commonly used treatment after progression on osimertinib in the patient population under review, due to the lack of effective treatment options in this setting. The committee agreed that the choice of pemetrexed plus carboplatin as the comparator in the pivotal trial was appropriate.
- **Toxicity profile considerations:** pERC discussed the safety profile of ACP, considering the known adverse event (AE) profile and experience with amivantamab, which includes IRRs, interstitial lung

disease (ILD), VTE, and skin reactions. pERC noted that ACP was associated with higher rates of grade 3 or higher AEs (72.3% with ACP versus 48.1% with CP), as well as higher frequencies of [redacted], IRRs (58.5% with ACP versus 0.4% with CP), and VTE (10.0% with ACP versus 4.5% with CP) primarily driven by amivantamab. pERC additionally discussed evidence from 2 ongoing phase II studies submitted by the sponsor to address gaps regarding the effectiveness of prophylactic strategies to reduce the risk of IRRs (the SKIPPirr study) and dermatologic AEs (the COCOON study) associated with amivantamab. These studies, conducted after the MARIPOSA-2 trial, suggested that IRRs and dermatologic toxicities may be manageable with appropriate prophylactic measures and could improve patient tolerability in clinical practice. However, pERC noted that prophylactic medications to reduce the risk of AEs associated with amivantamab might not be uniformly available or publicly funded across jurisdictions. Clinical experts indicated that ACP might initially need to be administered in specialized ambulatory oncology centres due to the requirement for prolonged observation and premedication during early treatment cycles. However, once patients tolerate the initial infusions and require reduced observation and monitoring, administration would be appropriate at any eligible ambulatory oncology centre.

- **HRQoL considerations**: As an outcome of importance to patients and clinicians, pERC discussed the HRQoL results from the MARIPOSA-2 trial. The patient-reported outcome (PRO) analyses showed a trend toward improved HRQoL with ACP, particularly in global health status scores measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) at 6 months and 12 months. [redacted]. However, pERC noted that these findings were associated with low certainty evidence due to the limitations of the available data, including missing outcome data and declining completion rates for PROs over time. Additionally, the observed differences did not consistently exceed the predefined minimal important difference (MID) of 10 points.
- **Testing procedure considerations**: pERC noted that *EGFR* testing is currently performed as the SOC for patients with NSCLC in Canada and acknowledged that evaluating *EGFR* status for exon 19 deletions or exon 21 L858R substitutions before the initiation of ACP would be required. pERC also noted that, considering this is already SOC, *EGFR* testing is not anticipated to be an implementation or access barrier.

Background

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death in Canada, with an estimated 32,100 new diagnoses and 20,700 deaths expected in 2024. The 5-year survival rate is 22%, dropping to 16% for patients diagnosed at stage III and 3% at Stage IV. NSCLC accounts for approximately 88% of lung cancer cases. A key mechanism of NSCLC involves driver mutations that activate progrowth signalling pathways. *EGFR* mutations — present in approximately 15% of individuals with NSCLC, mostly

nonsquamous — are the most common driver mutations. Among those with *EGFR*-mutated NSCLC in Canada, exon 19 deletions and exon 21 L858R substitutions account for 49% and 35%, respectively.

Diagnosis of NSCLC involves imaging (CT, PET-CT, MRI) and biopsy. In newly diagnosed nonsquamous NSCLC, next-generation sequencing is the SOC to identify actionable mutations. Patients with advanced or progressive NSCLC experience reduced HRQoL, with symptoms including cough, fatigue, shortness of breath, chest pain, and cognitive difficulties. Canada's Drug Agency (CDA-AMC) has previously reviewed amivantamab for 2 indications involving *EGFR* exon 20 insertion mutations, both recommended with conditions. A new submission is currently under review for the combination of lazertinib and amivantamab for the first-line treatment of locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R mutations.

Sources of Information Used by the Committee

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

- a review of 1 phase III randomized, double-blind, active-controlled study in adult patients with locally advanced or metastatic nonsquamous *EGFR*-mutated NSCLC with exon 19 deletions or exon 21 L858R substitution mutations who had progressed on or after osimertinib and platinum-based chemotherapy (no long-term extension studies or indirect treatment comparisons were submitted), and 2 ongoing phase II studies addressing gaps in the systematic review evidence
- a joint submission of patients' perspectives by 3 patient groups: Lung Cancer Canada (LCC), the Canadian Cancer Survivor Network (CCSN), and the Lung Health Foundation (LHF)
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with NSCLC
- input from 2 clinician groups: the LCC Medical Advisory Committee (MAC) and the Ontario Health (Cancer Care Ontario) (OH [CCO]) Lung Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

A joint patient group submission was received from LCC, the CCSN, and the LHF. Information provided in this submission consisted of thoughts and experiences of patients with NSCLC and their caregivers, collected through virtual interviews, or information was taken by the patient groups from previous submissions to CDA-AMC. Contributions from 5 patients located in Canada diagnosed with stage III or IV NSCLC were included in the patient group submission, including input from 2 patients with direct experience

in the MARIPOSA-2 trial and 3 other patients with experience in other trials involving amivantamab or who had received amivantamab via the sponsor's compassionate access program.

Input from 2 patients described symptoms preceding the diagnosis of NSCLC, including back pain, shortness of breath, and cough. Respondents' experiences with osimertinib before receiving amivantamab varied, ranging from no side effects and good quality of life to side effects that limited day-to-day life. Upon disease progression with osimertinib, symptoms reported by respondents included significant pain and respiratory and mobility symptoms.

The patient group submission identified an unmet need for additional treatment options for patients who have progressed on osimertinib that successfully treat their disease and delay further progression, and allow for good quality of life and for patients to make future plans for working, enjoying retirement, and spending time with loved ones. Outcomes of importance identified by patients included improved management of NSCLC-related symptoms, delaying disease progression and potentially shrinking tumours, maintaining full and worthwhile quality of life, prolonging life and allowing patients to maintain independence and the ability to function to minimize caregiver burden, and having manageable side effects.

Regarding their experience with amivantamab, respondents described it as being successful in treating their disease while being durable. Input from 3 of the patients reported significant side effects upon starting treatment with amivantamab but noted that these ultimately improved with dose reductions and prescription medications. Side effects described by patients included mouth ulcers, loss of taste, constipation, skin issues, paronychia, ingrown toenails and infections around toenails, blood clot, tingling or numbness in fingers and toes, edema, tinnitus, dizziness, and weakness. Patients who were enrolled in the MARIPOSA-2 trial commented that, while on amivantamab treatment, they were able to return to a good quality of life, enjoying their hobbies, being active, and spending time with loved ones. Another patient reported terminating treatment with amivantamab due to the impact on energy levels and quality of life. Most of the respondents agreed that they strongly preferred their experience on amivantamab over previous therapies. Some patients noted that injectable treatments requiring long infusion times in the hospital were less convenient than oral targeted therapies that can be taken at home.

Clinician Input

Input From Clinical Experts Consulted for This Review

Clinical experts consulted for this review noted that there is currently no well-established, evidence-based, second-line SOC for patients with *EGFR*-mutated NSCLC who experience disease progression on osimertinib. In practice, treatment decisions are often guided by extrapolation from first-line data, expert consensus, or access to platinum-based chemotherapy (typically CP). In certain cases of oligoprogression, local therapies such as stereotactic radiotherapy may allow continuation of osimertinib; however, these approaches are not always feasible, particularly for patients in rural settings or those lacking access to specialized testing or care.

The experts emphasized a high unmet need for therapies that can address known resistance mechanisms (e.g., MET amplification, small cell transformation), extend survival, and maintain quality of life. They noted

that many patients are clinically stable at the time of progression, underscoring the importance of effective but tolerable treatment options in this setting.

The experts identified the combination of ACP as an appropriate second-line treatment for patients with *EGFR*-mutated NSCLC following progression on osimertinib. This regimen is expected to become the new SOC for patients eligible for systemic chemotherapy, based on its demonstrated efficacy and targeted mechanism of action.

According to the clinical experts, the most appropriate candidates for amivantamab plus chemotherapy are adult patients with *EGFR* exon 19 deletion or exon 21 L858R substitution mutations whose disease has progressed on or after osimertinib and who are fit to receive systemic chemotherapy. Important factors to consider include Eastern Cooperative Oncology Group Performance Status (ECOG PS) score and the ability to tolerate corticosteroid-based premedications used to manage IRRs. In cases of suspected histological transformation (e.g., to small cell histology), repeat biopsy was recommended. Patients unable to tolerate premedications or chemotherapy-related toxicities may be less suitable for this regimen. *EGFR* mutation testing is standardized in Canada, and no additional companion diagnostic was deemed necessary.

Response to treatment is typically assessed through symptom improvement (e.g., dyspnea, fatigue, cough), radiographic imaging, and functional status. The experts considered tumour shrinkage or disease stability on imaging, alongside clinical benefit, as indicative of a meaningful response. Imaging every 3 months was noted to be common practice, and meaningful response may vary by patient but generally includes symptom control and preserved quality of life.

Treatment discontinuation should occur upon confirmed clinical or radiographic disease progression. However, the experts advised that imaging alone may not always justify discontinuation, particularly if patients are experiencing ongoing clinical benefit (e.g., symptom improvement, functional stability). Continuation of treatment in such cases may be considered until progression is confirmed or functional decline occurs. Discontinuation should also be considered in the case of nonreversible grade 3 or higher toxicities. If a patient cannot tolerate 1 component of the regimen but continues to receive benefit, the remaining components may be continued at the discretion of the treating physician.

The clinical experts noted that the regimen is typically administered in an outpatient setting by clinicians experienced in systemic therapy and managing systemic therapies and infusion reactions. Initial concerns about IRRs have been largely addressed with appropriate premedication and monitoring protocols. Experts also noted the potential for a future subcutaneous (SC) formulation of amivantamab to reduce infusion-related complications and enhance convenience. A medical oncologist is required to prescribe this treatment.

Clinician Group Input

Two clinician groups consisting of 19 clinicians from the LCC MAC and 5 clinicians from the OH (CCO) Lung Cancer Drug Advisory Committee provided input for this review.

Clinician groups noted that patients with advanced *EGFR*-mutated NSCLC following disease progression on osimertinib would currently primarily receive platinum (usually cisplatin or carboplatin) plus pemetrexed chemotherapy (followed by pemetrexed maintenance chemotherapy). The LCC MAC indicated that the

most important goals for these patients are to maximize quality of life and prolong life, and that secondary goals are to minimize toxicity and prolong control of disease. Clinician groups commented that response to chemotherapy treatment following progression on osimertinib is low, and identified an unmet need for more effective therapies with longer duration of benefit that target mechanisms of resistance that develop during osimertinib treatment.

Clinician groups agreed that, in patients with *EGFR*-mutated NSCLC, the amivantamab plus chemotherapy regimen investigated in the MARIPOSA-2 trial would be expected to replace platinum-doublet chemotherapy following progression on osimertinib (i.e., would be used as second-line treatment following progression on osimertinib). Both clinician groups agreed that patients best suited for treatment with ACP would be those with advanced or incurable *EGFR*-mutated (exon 19 deletion or L858R mutation) NSCLC who have experienced progression on osimertinib, noting other considerations such as ECOG PS.

Clinically meaningful responses to treatment were stated by clinician groups to be improvement in OS, delay in progression, and improvement in symptoms or quality of life. Clinician groups expressed that treatment with amivantamab and chemotherapy should be discontinued upon (symptomatic) disease progression, unacceptable toxicity, or patient choice.

Clinician groups stated that the appropriate setting for amivantamab and chemotherapy treatment is an outpatient unit (cancer centres or hospital setting) under the supervision of a medical oncologist and by personnel experienced in administering these agents, with the LCC MAC noting that the risk of IRRs with the current mode of administration is high but manageable.

The unmet needs, treatment goals, place in therapy, patients best suited for treatment, assessment of treatment response, and discontinuation and prescribing criteria identified by the clinician groups were generally aligned with those described by clinical experts consulted by CDA-AMC for this review.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Advice from CDA-AMC
Relevant comparators	
Issues with the choice of comparator in the submitted trial(s) The MARIPOSA-2 trial compared amivantamab-carboplatin-pemetrexed followed by amivantamab-pemetrexed maintenance vs. carboplatin-pemetrexed followed by pemetrexed maintenance in patients with locally advanced or metastatic *EGFR*-mutated (exon 19 deletion or L858R substitution) NSCLC whose disease had progressed on or after	Comment from the drug plans to inform pERC deliberations. The clinical experts agreed that docetaxel would be an appropriate comparator following first-line osimertinib-platinum-pemetrexed, particularly when pemetrexed maintenance has been stopped. They also agreed that the timing of the last platinum-based chemotherapy would be a deciding factor in the choice of comparator.

Drug program implementation questions	Advice from CDA-AMC
osimertinib monotherapy. At the time of this input, first-line osimertinib monotherapy is the funded standard of care while first-line osimertinib-pemetrexed-platinum is under consideration for funding. If the patient received first-line osimertinib, then the platinum chemotherapy (mainly platinum pemetrexed followed by pemetrexed maintenance) would be the appropriate comparator. If first-line osimertinib-pemetrexed-platinum (followed by osimertinib with or without pemetrexed maintenance) is used, then an appropriate comparator would be docetaxel.	
Considerations for initiation of therapy	
Prior therapies required for eligibility Should patients previously treated with first-line osimertinib-pemetrexed-platinum with or without osimertinib-pemetrexed maintenance be considered for amivantamab-carboplatin-pemetrexed? If yes, what is the minimum disease-free interval required between the last dose of osimertinib chemotherapy and the first dose of amivantamab chemotherapy?	pERC agreed with the clinical experts that patients previously treated with first-line osimertinib-pemetrexed-platinum with or without osimertinib-pemetrexed maintenance may be considered for treatment with amivantamab plus carboplatin-pemetrexed chemotherapy. For platinum-sensitive disease, a minimum interval of 6 months from the last platinum dose to progressive disease is generally required. pERC agreed with the clinical experts that patients must also have documented disease progression on osimertinib and be clinically fit for systemic therapy (e.g., ECOG PS score of 0 to 2, adequate renal function). pERC agreed with the clinical experts that osimertinib must be discontinued upon initiation of amivantamab-based therapy. Disease stability or response should be confirmed at restaging before starting amivantamab-carboplatin-pemetrexed.
Considerations for discontinuation of therapy	
Definition of loss of response, absence of clinical benefit, or disease progression What discontinuation criteria should be used for amivantamab-carboplatin-pemetrexed?	pERC agreed with the clinical experts that the trial criteria for discontinuation of treatment with amivantamab-carboplatin-pemetrexed would apply in clinical practice and include radiographic disease progression, clinically evident worsening, unacceptable toxicity, or absence of clinical benefit as determined by the treating physician.
Considerations for prescribing of therapy	
Dosing, schedule or frequency, dose intensity Two types of dosing are available for amivantamab depending on the patient's weight (1,400 mg weekly × 4 doses then 1,750 mg every 3 weeks if < 80 kg, vs. 1,750 mg weekly × 4 doses then 2,100 mg every 3 weeks if ≥ 80 kg).	Comment from the drug plans to inform pERC deliberations. The clinical experts confirmed that patient weight is considered in determining amivantamab dose: patients weighing < 80 kg receive 1,400 mg, and those weighing ≥ 80 kg receive 1,750 mg. The first dose is split: 350 mg on cycle 1 day 1 followed by 1,050 mg (or 1,400 mg) the same day. If tolerated, patients continue with 1,400 mg (or 1,750 mg) on cycle 1 days 8 and 15, and cycle 2 day 1. Starting on cycle 3 day 1, the dose is 1,750 mg or 2,100 mg every 3 weeks.
Drug administration Premedications are recommended before each infusion to reduce the risk of infusion-related reactions.	Comment from the drug plans to inform pERC deliberations.

Drug program implementation questions	Advice from CDA-AMC
The initial dose of amivantamab is administered as a split infusion on days 1 and 2 of cycle 1, week 1.	
Concerns related to combination usage 1. If chemotherapy has to be discontinued, should amivantamab be continued as a single agent? 2. Can amivantamab be used with cisplatin-pemetrexed followed by pemetrexed maintenance?	pERC agreed with the clinical experts that, if chemotherapy needs to be discontinued, amivantamab could be continued as a single agent. The clinical experts noted that this approach aligns with clinical trial protocol and is considered acceptable in practice if there is documented disease control. pERC agreed with the clinical experts that a combination of amivantamab plus cisplatin and pemetrexed followed by amivantamab and pemetrexed maintenance may be allowed, particularly at the discretion of the treating physician.
Generalizability	
Populations of interest matching the indication but with insufficient data Should amivantamab-pemetrexed-carboplatin be used in the following settings? • ECOG PS score > 1 • Histologies other than adenocarcinoma	The trial included only patients with ECOG PS scores of 0 and 1. pERC agreed with the clinical experts that patients with ECOG PS scores greater than 1 may be considered eligible at the discretion of the treating physician, if they are fit for systemic chemotherapy. The clinical experts advised that the use of amivantamab-pemetrexed-carboplatin should be restricted to patients with nonsquamous NSCLC, as was the case in the trial population. This would include patients with nonsquamous histology, and may allow for inclusion of those with mixed histology or large cell features. However, the experts agreed that use in squamous histology should not be supported. pERC agreed with the clinical experts.
Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review On a time-limited basis, should eligible patients on existing treatments be switched to amivantamab-pemetrexed-platinum followed by amivantamab-pemetrexed?	pERC agreed with the clinical experts that, if the addition of amivantamab is funded, eligible patients on existing active treatment should be permitted on a time-limited basis to switch to amivantamab plus carboplatin and pemetrexed followed by amivantamab-pemetrexed, in specific scenarios. The clinical experts noted that the key consideration will be the length of treatment with second-line pemetrexed-carboplatin chemotherapy that a patient has received so far. They suggested the following criteria: • Patients who are currently receiving platinum pemetrexed with no evidence of disease progression should be permitted to initiate amivantamab, provided that at least 1 to 2 cycles of platinum will still overlap with the introduction of amivantamab. • For patients who are on maintenance pemetrexed, access to amivantamab requires a case-by-case consideration and should be conditional on delivering at least 2 cycles of amivantamab in combination with platinum. (e.g., delivering amivantamab-carboplatin-pemetrexed for 2 cycles, then proceeding to maintenance therapy with amivantamab with or without pemetrexed). pERC agreed with the clinical experts.

Drug program implementation questions	Advice from CDA-AMC
Funding algorithm	
In the trial, participants who had received prior neoadjuvant and/or adjuvant treatment were eligible if the disease progressed ≥ 12 months after the last dose and the patient's disease progressed on or after osimertinib in the locally advanced or metastatic setting. Should amivantamab-platinum-pemetrexed be funded in patients who received neoadjuvant and/or adjuvant therapy but whose disease progresses to the advanced stage within 12 months of the last dose of treatment? If yes, what is the minimum disease-free interval?	pERC agreed with the clinical experts that they would consider a patient eligible if disease progression occurred at least 6 months after completion of platinum-based adjuvant chemotherapy, while the patient was still receiving adjuvant osimertinib. If a patient's disease progresses after completing adjuvant osimertinib, eligibility for amivantamab should depend on whether the patient meets criteria to rechallenge with osimertinib. If the patient is eligible for osimertinib reinitiation, they should not receive amivantamab. This eligibility scenario may become less relevant as clinical decisions and funding policies evolve in response to the broader evidence generated by the MARIPOSA trial. pERC agreed with the clinical experts.
In the trial, participants must also have progressed on or after osimertinib monotherapy (wherein osimertinib must have been given as either first-line or second-line therapy). Should patients who received adjuvant osimertinib whose disease progresses while on osimertinib or within 6 months of the last dose of osimertinib be eligible for amivantamab-platinum-pemetrexed?	pERC agreed with the clinical experts that patients whose disease progresses during adjuvant osimertinib should be eligible for amivantamab plus chemotherapy, provided that at least 6 months have passed since their last chemotherapy exposure.
At the time of this input, there is an ongoing review for osimertinib for patients with unresectable stage III NSCLC *EGFR* exon 19/21 whose disease has not progressed during or following platinum chemotherapy radiation. Should these patients be considered for downstream amivantamab chemotherapy if their disease progresses while on osimertinib or within 6 months of the last dose of osimertinib? What minimum interval would be required from completion of platinum chemotherapy radiation?	pERC agreed with the clinical experts that patients who experience disease progression while on or shortly after discontinuing osimertinib following chemoradiation or adjuvant chemotherapy may be eligible for amivantamab plus chemotherapy, provided that at least 6 months have passed since the last platinum exposure. Eligibility should be based on the same clinical criteria used for patients progressing on or after osimertinib in the metastatic setting, including a minimum of 6 months since the last platinum exposure. The clinical experts stated that, in the absence of supporting evidence, they would not recommend amivantamab for use in patients who have not received prior osimertinib. pERC agreed with the clinical experts.
Care provision issues	
Companion diagnostics (e.g., access issues, timing of testing) Confirmation of *EGFR* exon 19 deletion or exon 21 L858R substitution is required before starting treatment. *EGFR* mutation testing is part of routine clinical practice.	Comment from the drug plans to inform pERC deliberations.

CDA-AMC = Canada's Drug Agency; ECOG PS = Eastern Cooperative Oncology Group Performance Status; NSCLC = non–small cell lung cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; vs. = versus.

Clinical Evidence

Systematic Review

Description of Studies

One ongoing phase III, randomized, open-label, multicentre trial (the MARIPOSA-2 trial; N = 657) assessed the efficacy and safety of ACP compared with CP alone in adult patients with locally advanced or metastatic nonsquamous *EGFR*-mutated NSCLC (exon 19 deletion or exon 21 L858R substitution) whose disease had progressed on or after osimertinib. Patients were randomized in a 2:1:2 ratio to CP, ACP, or a third investigational arm (ACP plus lazertinib), which is not included in this review report. Results from 2 prespecified interim analyses (IA1: July 10, 2023; IA2: April 26, 2024) are included. The primary end point was PFS by BICR. Key secondary end points included OS, objective response rate (ORR), duration of response (DOR), time to symptomatic progression (TTSP), and PROs (EORTC QLQ-C30 score, non–small cell lung cancer symptom assessment questionnaire).

Patients were required to have measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, ECOG PS score of 0 or 1, and documented progression on osimertinib as the most recent line of therapy. Randomization was stratified by line of prior osimertinib (first-line versus second-line), history of brain metastases, and race (Asian versus non-Asian). Patients received 21-day treatment cycles of treatment until progression or unacceptable toxicity. The ACP regimen included weight-based IV dosing of amivantamab (split in cycle 1), carboplatin area under the curve 5 for 4 cycles, and pemetrexed 500 mg/m^2 with vitamin supplementation.

Baseline characteristics were generally well balanced between the ACP (n = 131) and CP (n = 263) arms. The mean age was [redacted]; approximately [redacted] of patients were female. Most patients were Asian ([redacted]) or white ([redacted]), other racial groups included Black or African American ([redacted]) and other or unknown ([redacted]). An ECOG PS score of 0 was reported in 42% (ACP) and 38% (CP) of patients. A history of brain metastases was present in 44% and 46% of patients, respectively. *EGFR* mutation types were exon 19 deletion (68% and 70%) and exon 21 L858R (30% and 32%). All patients had previously received osimertinib (first-line or second-line), and most had received only 1 prior line of systemic therapy in the advanced or metastatic setting.

Efficacy Results

At IA1 (data cut-off July 10, 2023), the median PFS by BICR was 6.28 months (95% CI, 5.55 to 8.41) in the ACP arm and 4.17 months (95% CI, 4.04 to 4.44) in the CP arm. At this data cut-off point, [redacted] occurred in the ACP arm and [redacted] in the CP arm. The HR for PFS was 0.63 (95% CI, 0.47 to 0.84). The PFS rates at 6 months and 12 months were [redacted] in the ACP arm, and [redacted] respectively, in the CP arm.

At IA1, the median OS was [redacted] in the ACP arm and [redacted] in the CP arm. At IA2 (data cut-off April 26, 2024), median OS was 17.74 months (95% CI, 15.97 to 22.37) for ACP and 15.34 months (95% CI, 13.73 to 16.76) for CP. OS event rates at IA2 were [redacted] (ACP) and [redacted] (CP). The HR for OS at IA2 was 0.73 (95% CI, 0.54 to

0.99). Estimated OS rates at 6, 12, and 24 months were [redacted] for ACP and [redacted] for CP, respectively.

ORR by BICR at IA1 was 63.8% (95% CI, 55.0 to 72.1) in the ACP arm and 36.2% (95% CI, 30.3 to 42.3) in the CP arm. Complete responses were reported in 2 patients (1.5%) in the ACP and 1 patient (0.4%) in the CP arm.

DOR was 6.90 months (95% CI, 5.52 to NE) in the ACP arm and 5.55 months (95% CI, 4.17 to 9.56) in the CP arm. DOR greater than or equal to 6 months was observed in [redacted] of patients receiving ACP and [redacted] of patients receiving CP; duration greater than or equal to 12 months was observed in [redacted].

At IA1, [redacted] occurred in the ACP arm and [redacted] in the CP arm. Median TTSP was 14.88 months (95% CI, 11.30 to NE) for ACP and 13.01 months (95% CI, 9.20 to NE) for CP. At IA2, median TTSP was [redacted] for ACP and [redacted] for CP. Kaplan-Meier TTSP rates at 12, 18, and 24 months were [redacted] in ACP, and [redacted] in CP, respectively.

At IA1, median intracranial PFS was 12.45 months in the ACP arm and 8.31 months in the CP arm (HR = 0.55; 95% CI, 0.38 to 0.79). [redacted].

Intracranial ORR at IA1 was [redacted] in the ACP arm and [redacted] in the CP arm. At IA2, intracranial ORR was [redacted] in the ACP arm and [redacted] in the CP arm.

Median intracranial DOR was [redacted] in the CP arm and [redacted] in the ACP arm at IA1. At IA2, median intracranial DOR was [redacted] months in the CP arm and [redacted] in the ACP arm. Median time to intracranial disease progression was [redacted] in the CP arm and [redacted] in the ACP arm at IA1, and [redacted] in the CP arm and [redacted] in the ACP arm at IA2 [redacted].

Harms Results

At IA1, treatment-emergent adverse events (TEAEs) were reported in 99.2% of patients in the ACP arm and 86.4% in the CP arm. Grade 3 or higher TEAEs occurred in 72.3% of patients in the ACP arm and 48.1% in the CP arm. Serious adverse events (SAEs) were reported in [redacted] and [redacted] of patients in the ACP and CP arms, respectively.

Discontinuation of any study treatment due to AEs occurred in 18.5% of patients receiving ACP and 3.7% of patients receiving CP. Fatal AEs were reported in 2.3% of patients in the ACP arm and 1.2% in the CP arm.

Premedication, including corticosteroids, antihistamines, and antipyretics, were used to mitigate IRRs. Discontinuation due to IRRs occurred in [redacted] of patients in the ACP arm. [redacted]

[redacted].

The safety profile of amivantamab plus chemotherapy was consistent with the known adverse effects of the individual agents.

Patient-Reported Outcomes

At IA1, median time to sustained deterioration in NSCLC-SAQ total symptom score was 11.6 months (95% CI, 10.2 to 14.9) in the ACP arm and 8.5 months (95% CI, 7.2 to 10.1) in the CP arm (HR = 0.62; 95% CI, 0.43 to 0.88; P = 0.0057). At IA2, median time to deterioration in EORTC QLQ-C30 global health status score was [redacted] in the ACP arm and [redacted] in the CP arm [redacted]. Twelve-month event-free rates for global health status were [redacted].

Critical Appraisal

Randomization and stratification were appropriately implemented in the MARIPOSA-2 trial to reduce selection bias, and key efficacy end points such as PFS were assessed by BICR, minimizing the risk of measurement bias. However, the open-label design introduced potential performance and detection bias, particularly for subjective end points such as PROs and AE assessments. The primary end point of PFS and the key secondary end point of OS were included in a hierarchical testing strategy with appropriate control for multiplicity, but multiplicity adjustments were not applied to other secondary end points such as DOR and TTSP. Missing data were minimal for PFS and OS; however, PRO data decreased over time, and missingness was not formally quantified or modelled, limiting interpretability of results from later cycles. Although censoring rates were generally balanced, the trial did not report sensitivity analyses to explore the impact of informative censoring on PROs. Postprogression treatment strategies were not explicitly defined. However, timelines for subsequent therapy suggest that patients generally received standard clinical management following disease progression, which may have introduced contamination bias and potentially underestimated the treatment effect on OS, thereby limiting the interpretability of the observed survival difference. The trial population was considered generally representative of patients anticipated by the clinical experts to receive ACP in Canadian practice settings. However, generalizability may be limited for patients with poorer performance status (ECOG PS score > 1) or comorbidities. According to the clinical experts, the inclusion of patients with treated or stable brain metastases improved external validity. The trial enrolled a globally diverse population, but representation of Black, Indigenous, and other racialized groups living in Canada was limited. The clinical experts noted that the average participant age was slightly younger than the typical patient population with *EGFR*-mutated NSCLC in Canada. Overall, the ACP regimen was considered by the clinical experts to implementable in Canada, if funded, although early administration may require access to specialized centres due to infusion-related precautions. The clinical experts also noted that supportive medications for managing IRRs and dermatologic AEs may not be uniformly covered across jurisdictions.

GRADE Summary of Findings and Certainty of the Evidence

For the MARIPOSA-2 trial, which served as the pivotal trial for this 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 CDA-AMC expert committee deliberations. Certainty was rated following the GRADE Working Group approach.

Following the GRADE approach, evidence from the RCT started as high-certainty evidence and could be rated down for concerns related to study limitations (which refer 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 was 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 assessments for OS, PFS, and SAEs were based on the presence or absence of an important effect, as informed by clinical experts consulted for this review. For the HRQoL outcomes (EORTC QLQ-C30 global health status scores), the threshold for an important effect was informed by literature cited by the sponsor.

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: PFS and OS (reported at multiple time points)
- tumour response: ORR (CR + PR)
- HRQoL: EORTC QLQ-C30 global health status scores at 6 and 12 months
- notable harms: SAEs.

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for ACP versus CP.

Table 3: Summary of Findings for ACP vs. CP in Patients With NSCLC Following Progression on Osimertinib in the MARIPOSA-2 Trial

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			CP	ACP	Difference		
PFS – full analysis set, IA1							
Probability of PFS at 6 months Median follow-up: [redacted] (ACP) and [redacted] (CP)	394 (1 RCT)	[redacted]	[redacted]	[redacted]	[redacted]	High[a]	ACP results in a clinically important increase in the probability of PFS at 6 months when compared with CP.
Probability of PFS at 12 months Median follow-up: [redacted] (ACP) and [redacted] (CP)	394 (1 RCT)	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[b]	ACP likely results in a clinically important improvement in PFS at 12 months compared to CP.
OS – full analysis set, IA2							
Probability of OS at 12 months Median follow-up: [redacted] (ACP) and [redacted] (CP)	394 (1 RCT)	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[b]	ACP likely results in a clinically important improvement in OS at 12 months compared to CP.
Probability of OS at 24 months (IA2) Median follow-up: [redacted] (ACP) and [redacted] (CP)	394 (1 RCT)	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[b]	ACP likely results in a clinically important improvement in OS at 24 months compared to CP.
ORR – full analysis set, IA1							
ORR (CR + PR) Median follow-up: [redacted] (ACP) and [redacted] (CP)	394 (1 RCT)	[redacted]	[redacted]	[redacted]	[redacted]	High[c]	ACP improves ORR compared to CP.
Health-related quality of life – full analysis set, IA2							
EORTC QLQ-C30at 6 months (IA2) Median follow-up: [redacted] (ACP) and [redacted] (CP)	394 (1 RCT)	[redacted]	[redacted]	[redacted]	[redacted]	Low[d]	ACP may result in a clinically important improvement in health-related quality of life at 6 months compared to CP.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			CP	ACP	Difference		
EORTC QLQ-C30 at 12 months (IA2) Median follow-up: [redacted] (ACP) and [redacted] (CP)	394 (1 RCT)	[redacted]	[redacted]	[redacted]	[redacted]	Low[d]	ACP may result in a clinically important improvement in health-related quality of life at 12 months compared to CP.
Harms – safety analysis set							
SAEs Median follow-up: [redacted] (ACP) and [redacted] (CP) [redacted]	394 (1 RCT)	[redacted]	[redacted]	[redacted]	[redacted]	**Moderate**[e]	ACP likely results in more SAEs when compared with CP.

ACP = amivantamab plus carboplatin and pemetrexed; CI = confidence interval; CP = carboplatin and pemetrexed; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; IA1 = interim analysis 1; IA2 = interim analysis 2; MID = minimal important difference; NA = not applicable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation; 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 table footnotes.

[a]A between-group absolute risk difference of [redacted] at 6 months was clinically important according to the clinical experts (MID > 10%). The point estimate and entire CI exceeded the threshold.

[b]Rated down 1 level for imprecision. Wide CI crossed the null and the clinical importance threshold according to the clinical experts (MID > 10%).

[c]A between-group absolute risk difference of [redacted] was clinically important according to the clinical experts (MID > 10%). The point estimate and entire CI exceeded the threshold.

[d]Rated down 2 levels, 1 for serious imprecision due to the 95% CIs for the between-group differences (| [redacted]) including the possibility of no effect and not meeting the threshold for clinical importance. The MIDs were based on a 10-point change from baseline on the EORTC QLQ-C30 global health status scale, as identified in the literature and suggested by the sponsor. Rated down 1 level for risk of bias due to missing outcome data and declining completion rates for PROs over time.

[e]Certainty of the evidence was rated down by 1 level for serious imprecision. Although the total safety population met the conservative information size, the 95% CI for the absolute risk difference ([redacted]) crossed both the null effect and the threshold for a clinically important difference (10%). The wide CI reflects uncertainty regarding the presence and magnitude of a clinically important increase in SAEs.

Source: Details included in the table are from the MARIPOSA-2 Clinical Study Report[1], and additional information provided by the sponsor.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

No indirect treatment comparisons were submitted by the sponsor.

Studies Addressing Gaps in the Evidence From the Systematic Review

The sponsor identified gaps in the systematic review evidence for which 2 studies were submitted as supportive evidence. The first evidence gap was regarding the impact of prophylactic strategies to reduce the risk of IRRs associated with amivantamab, for which results from the SKIPPirr study were submitted. The second identified evidence gap was regarding the impact of enhanced versus standard dermatologic management in patients with locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations treated with amivantamab, for which interim analysis results from the COCOON study (in patients treated with first-line amivantamab plus lazertinib) were submitted.

SKIPPirr Study

Description of Study

The SKIPPirr study (N = 68) is an ongoing phase II, open-label, multicentre study evaluating oral dexamethasone, oral montelukast, or SC methotrexate for the prevention of IRRs associated with amivantamab in adult patients with advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations who have progressed on or after osimertinib treatment and on or after platinum-based chemotherapy and who may benefit from combination therapy with amivantamab and oral lazertinib. All study participants received standard prophylaxis with an antihistamine, antipyretic, and glucocorticoid (IV dexamethasone). The study used a Simon's 2-stage design with an expansion stage where cohorts were eligible to move into subsequent stages if they met an IRR incidence criterion. The primary end point was the rate of IRRs occurring on cycle 1 day 1 following administration of lazertinib and amivantamab combination therapy. In the overall study population, the median age was 63.5 years; 65% of patients were female and 35% were male; 62% of patients were Asian, 26% were white, and 1% were Black or African American (race was not reported for 10% of patients); 75% of patients had an ECOG PS score of 1; 44% had brain metastases; and 66% had an exon 19 deletion *EGFR* mutation type. In the dexamethasone 8 mg cohort, the median age was 62.0 years; 63% of patients were female and 37% were male; 59% of patients were Asian, 24% were white, and 2% were Black or African American (race was not reported for 15% of patients); 78% of patients had an ECOG PS score of 1; 37% had brain metastases; and 71% had an exon 19 deletion *EGFR* mutation type.

Efficacy Results

Only the dexamethasone 8 mg cohort passed both stage 1 and stage 2 and proceeded to the expansion stage. In this cohort, the intervention was oral dexamethasone 8 mg twice daily on days −2 and −1 (cycle 1) and 8 mg approximately 1 hour before the start of the infusion of amivantamab IV on Cycle 1 day 1. Among the 40 patients in the dexamethasone 8 mg cohort, 9 (22.5%; [redacted]) patients reported IRRs on cycle 1 day 1; [redacted]

[redacted].

Critical Appraisal

Patients and investigators were aware of the treatment intervention in the open-label SKIPPirr study. As such, there is the potential for bias in favour of the intervention; however, many signs of IRRs are objective (e.g., hypotension, fever, tachycardia) and are not as likely as subjective symptoms to be biased. Patients in the SKIPPirr study had previously received osimertinib and platinum-based chemotherapy and received amivantamab and lazertinib as background anticancer treatment, whereas anticancer treatment for the patient population of interest for this review is ACP. Although there are differences in the anticancer treatment regimens, clinical experts consulted by CDA-AMC commented that the SKIPPirr study is relevant in addressing the issue of IRR prevention in the population of interest for this review. Clinical experts also commented that the IRR rate on cycle 1 day 1 that was observed in the dexamethasone 8 mg cohort of the SKIPPirr study is clinically meaningfully less than what is expected in clinical practice with IV administration of amivantamab.

COCOON Study

Description of Study

The COCOON study (N = 138 at interim analysis) is an ongoing phase II, randomized, open-label, multicentre study evaluating enhanced (n = 70) versus standard (n = 68) dermatologic management in adult patients with locally advanced or metastatic NSCLC with *EGFR* exon 19 deletion or L858R substitution mutations who were treatment naive for advanced disease; patients received anticancer treatment with amivantamab plus lazertinib. Enhanced dermatologic management consisted of doxycycline or minocycline 100 mg twice a day for 12 weeks; clindamycin 1% topical lotion on the scalp for 9 months starting in week 13; noncomedogenic moisturizer for 12 months; chlorhexidine 4% hand and foot wash for 12 months; and general skin prophylaxis recommendations. SOC dermatologic management consisted of general skin prophylaxis recommendations per local practice and reactive treatment, such as topical corticosteroids and systemic antibiotics. The primary end point was the incidence of grade 2 or higher dermatologic adverse events of interest (DAEIs) in the first 12 weeks after initiation of amivantamab plus lazertinib treatment. Only interim analysis results were available. In the overall study population, the median age was [redacted] years, [redacted] of patients were female [redacted] and [redacted] of patients were [redacted] respectively, [redacted] of patients had an ECOG PS score of 1 [redacted].

Efficacy Results

The results of the interim analysis show that, by week 12, the incidence of grade 2 or higher DAEIs was [redacted] patients (38.6%; [redacted]) in the enhanced dermatologic management arm and [redacted] patients (76.5%; [redacted]) in the SOC dermatologic management arm (odds ratio = 0.19; 95% CI, 0.09, to 0.40; P < 0.0001).

Critical Appraisal

Patients and investigators were aware of the treatment intervention in the open-label COCOON study. As such, there is the potential for bias in favour of enhanced dermatologic management; however, many signs of DAEIs are objective and at a lower risk of bias. In addition, the findings should be interpreted with consideration that, although the primary end point was met at the interim analysis, certain data (e.g., treatment adherence, concomitant medications) were not available for appraisal. Patients in the COCOON study received amivantamab and lazertinib as background anticancer treatment as first-line treatment for advanced disease, whereas the anticancer treatment for the patient population of interest for this review is ACP, received following disease progression with osimertinib. Although there are differences in the anticancer treatment regimens, clinical experts consulted by CDA-AMC commented that the COCOON study is relevant in addressing the issue of management of dermatologic AEs in the population of interest for this review. Clinical experts highlighted that chlorhexidine 4% availability may be limited and the skin moisturizers used in the COCOON study are expensive and can be financially preclusive for patients. Clinical experts stated that the difference in the incidence of grade 2 or higher DAEIs between the 2 arms of the COCOON study (interim analysis results) is clinically meaningful.

Economic Evidence

Cost and Cost-Effectiveness

- Amivantamab is available as a solution for infusion (50 mg/mL). At the submitted price of $1,676.00 per 50 mL, the estimated per-cycle cost of amivantamab is as follows: $26,816 to $33,520 for the first 28 days, and $11,173 to $13,408 for each subsequent 28-day cycle, based on the Health Canada–recommended dosage.
- Clinical efficacy in the economic analysis was derived from the MARIPOSA-2 trial, which compared ACP to CP alone. Evidence submitted by the sponsor indicates that ACP is likely to improve PFS and OS compared to CP alone.
- The results of the CDA-AMC base case suggest:
  - ACP will be associated with higher costs to the health care system than CP alone (incremental costs = $128,544), primarily driven by increased drug acquisition costs associated with amivantamab.
  - The results of the CDA-AMC base case suggest that ACP will result in a potential gain of 0.74 life-years compared with CP alone. When the impact on HRQoL is also considered, ACP may result in a gain of approximately 0.44 QALYs compared to CP alone.
  - The ICER of AC compared to CP alone was $292,610 per QALY gained in the CDA-AMC base case. The estimated ICER was highly sensitive to the choice of model used for long-term OS extrapolation and to assumptions regarding dose skipping.
  - Although the CDA-AMC base case estimated increased QALYs with ACP compared to CP alone (incremental QALYs = 0.44), approximately 86% of the incremental benefit was gained

in the extrapolated period. In the absence of comparative evidence beyond the trial period and uncertainty in the comparative clinical evidence, the incremental QALYs for ACP predicted in the CDA-AMC base case are highly uncertain and may be overestimated. Additional price reductions may therefore be required. Clinical experts consulted by CDA-AMC noted that amivantamab requires prolonged chair time and incurs significant administration costs, which may pose barriers to implementation in clinical practice.

- CDA-AMC estimates that the budget impact of reimbursing ACP for the indicated population will be approximately $46.7 million over the first 3 years of reimbursement compared to the amount currently spent on CP alone, with an estimated expenditure of $48 million on ACP over this period. The actual budget impact of reimbursing ACP will depend on the number of people eligible for treatment.

pERC Information

Members of the Committee

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

Meeting date: July 9, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

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