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Reimbursement Recommendation

Amivantamab (Rybrevant)

Indication: In combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations

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 should be reimbursed by public drug plans when used in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic non–small cell lung cancer (NSCLC) with activating *EGFR* exon 20 insertion (ex20ins) mutations if certain conditions are met.

Which Patients Are Eligible for Coverage?

Rybrevant in combination with carboplatin and pemetrexed should only be covered to treat patients who have NSCLC with a specific *EGFR* gene mutation called ex20ins, have a good performance status, and the cancer has spread to other parts of the body or cannot be removed by surgery.

What Are the Conditions for Reimbursement?

Rybrevant in combination with carboplatin and pemetrexed should only be reimbursed when started in combination with platinum-based chemotherapy (i.e., carboplatin and pemetrexed), and the cost of Rybrevant is reduced. It should not be reimbursed for patients with untreated brain metastases or those who have had previous systemic therapy, adjuvant treatment (given after surgery), or neoadjuvant treatment (given before surgery) if those treatments were completed less than 6 months before the cancer worsened. Rybrevant in combination with carboplatin and pemetrexed must be prescribed by specialists with experience managing NSCLC.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that treatment with Rybrevant in combination with carboplatin and pemetrexed reduced the risk of the cancer worsening or spreading compared to chemotherapy alone.
- 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.
- Rybrevant in combination with carboplatin and pemetrexed meets patients' needs as it delays the cancer worsening or spreading, improves disease control, and has a manageable toxicity profile.
- Based on public list prices, Rybrevant is estimated to cost the public drug plans approximately $32.6 million over the next 3 years. However,

Summary

the actual budget impact is uncertain and depends on how many patients are eligible for treatment.

Additional Information

What Is *EGFR* ex20ins Mutation-Positive NSCLC?

NSCLCs are types of cancers that occur when the cells in the lungs change and grow and form a tumour. Cancer is considered metastatic when cancer cells have spread to other parts of the body. There are approximately 30,000 new cases of NSCLC diagnosed each year in Canada, and up to 0.6% of patients have NSCLC with a specific *EGFR* gene mutation called ex20ins, which can cause cancers to grow and spread.

Unmet Needs

Patients with NSCLC with *EGFR* ex20ins mutations are treated with chemotherapy and immunotherapy; however, most patients' disease does not respond to these available treatments. There is a need for new, life-extending treatments that improve quality of life (QoL).

How Much Does Rybrevant Cost?

Treatment with Rybrevant in combination with carboplatin and pemetrexed is expected to cost approximately $16,083 per patient per 21-day cycle for cycles 1 and 2, $10,076 for cycles 3 and 4, and $9,091 for cycles 5 and beyond, assuming an average patient weight of 66 kg.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that amivantamab in combination with carboplatin and pemetrexed (amivantamab plus carboplatin-pemetrexed) be reimbursed for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with activating *EGFR* ex20ins mutations only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, open-label, randomized controlled trial (the PAPILLON trial; N = 308) demonstrated that first-line treatment with amivantamab plus carboplatin-pemetrexed resulted in added clinical benefit in adults with advanced or metastatic NSCLC with *EGFR* ex20ins mutations. The PAPILLON trial demonstrated that, compared with carboplatin-pemetrexed, amivantamab plus carboplatin-pemetrexed resulted in statistically significant and clinically meaningful improvements in median progression-free survival (PFS) after a median follow-up time of 14.92 months (11.37 months versus 6.70 months; hazard ratio [HR] = 0.40; 95% confidence interval [CI], 0.30 to 0.53; P < 0.0001). PFS rates at 12 months were 48.0% (95% CI, 39.0 to 56.0) for amivantamab plus carboplatin-pemetrexed and 13.0% (95% CI, 8.0 to 19.0) for carboplatin-pemetrexed alone; PFS rates at 18 months were 31.0% (95% CI, 22.0 to 40.0) and 3.0% (95% CI, 1.0 to 9.0), respectively. Amivantamab plus carboplatin-pemetrexed also demonstrated statistically significant improvements in objective response rate (ORR) compared with carboplatin-pemetrexed alone (odds ratio [OR] = [redacted]). pERC considered the safety profile of amivantamab plus carboplatin-pemetrexed to be manageable and consistent with the known safety profile of its individual treatment components. pERC was uncertain whether amivantamab plus carboplatin-pemetrexed would prolong survival due to immature overall survival (OS) data (data maturity of 33%), a high rate of crossover of patients from the carboplatin-pemetrexed group to amivantamab monotherapy, and imprecision in the estimates (wide CIs that crossed the null).

Patients identified a need for treatment options that improve QoL and disease control, delay disease progression, have manageable side effects, and prolong survival. pERC concluded that amivantamab plus carboplatin-pemetrexed met some of the patients' needs, as it delays disease progression, improves disease control, and has a manageable toxicity profile. pERC considered that amivantamab plus carboplatin-pemetrexed may not have a detrimental impact on health-related quality of life (HRQoL) compared to carboplatin-pemetrexed alone; however, the evidence is of low certainty due to the open-label trial design and the decline in the number of patients available to provide assessments over time.

Using the sponsor-submitted price for amivantamab plus carboplatin-pemetrexed and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for amivantamab plus carboplatin-pemetrexed was $233,922 per quality-adjusted life-year (QALY), compared with platinum-based chemotherapy alone. At this incremental cost-effectiveness ratio, amivantamab plus carboplatin-pemetrexed is not cost-effective at a $50,000 per QALY gained willingness to pay threshold for adult patients with locally

advanced (not amenable to curative therapy) or metastatic NSCLC with activating *EGFR* ex20ins mutations receiving first-line treatment. A price reduction is required for amivantamab plus carboplatin-pemetrexed 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-pemetrexed should be reimbursed in adults with locally advanced or metastatic, nonsquamous NSCLC who meet the following criteria: 1.1. documented primary *EGFR* ex20ins mutations 1.2. adequate organ and bone marrow function.	Evidence from the PAPILLON trial demonstrated that treatment with amivantamab plus carboplatin-pemetrexed resulted in clinical benefit in patients with these characteristics.	—
2. Patients should have a good performance status.	Patients with an ECOG performance status of 0 to 1 were included in the PAPILLON trial.	Patients with an ECOG performance status of 2 may be treated at the discretion of the treating clinician.
3. Patients must not have any of the following: 3.1. prior systemic treatment for locally advanced or metastatic disease; prior adjuvant or neoadjuvant chemotherapy is permitted, if completed at least 6 months before development of progressive disease 3.2. untreated brain metastases.	There is no evidence from the PAPILLON trial to support a benefit of amivantamab plus carboplatin-pemetrexed treatment in patients with untreated brain metastases. Participants were allowed to receive prior adjuvant or neoadjuvant platinum-based doublet chemotherapy if completed at least 12 months before developing progressive disease.	Patients with treated or stable CNS metastases should be eligible for treatment. pERC considered it reasonable for patients to be eligible for amivantamab plus carboplatin-pemetrexed if they completed adjuvant or neoadjuvant therapies at least 6 months before developing progressive disease.
Discontinuation		
4. Treatment with amivantamab plus carboplatin-pemetrexed should be discontinued upon disease progression or unacceptable toxicity, whichever occurs first.	In the PAPILLON study criteria for discontinuation of study treatment included documented radiographic (RECIST version 1.1) disease progression, unacceptable toxicity, or meeting another criterion for treatment discontinuation. Continuation of study treatment after confirmed disease progression was allowed in the PAPILLON study, if the investigator believed the patient was deriving clinical benefit.	pERC agreed that treatment with amivantamab plus carboplatin-pemetrexed should be continued until clinically meaningful progression occurs, based on the judgment of the treating clinician.

Reimbursement condition	Reason	Implementation guidance
Prescribing		
5. Amivantamab plus carboplatin-pemetrexed should be prescribed by clinicians with expertise in treating NSCLC.	This is meant to ensure that amivantamab plus carboplatin-pemetrexed is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
6. Amivantamab should only be reimbursed when started in combination with platinum-based chemotherapy (i.e., carboplatin and pemetrexed).	The PAPILLON trial provided evidence on amivantamab in combination with carboplatin-pemetrexed. pERC did not review evidence supporting the efficacy and safety of amivantamab when used in combination with other anticancer drugs. There is no evidence from the PAPILLON trial to support the efficacy and safety of amivantamab plus carboplatin-pemetrexed when initiated in combination with additional anticancer drugs or when either component is initially used as monotherapy.	Cisplatin may be used instead of carboplatin at the discretion of the treating clinician. Amivantamab may be continued as monotherapy once the disease is responding even if chemotherapy is discontinued because of side effects or toxicity.
Pricing		
7. A reduction in price.	The ICER for amivantamab plus carboplatin-pemetrexed is $233,922 per QALY gained when compared with platinum-based chemotherapy alone. A price reduction of 83% would be required for amivantamab plus carboplatin-pemetrexed to achieve an ICER of $50,000 per QALY compared to platinum-based chemotherapy alone.	—
Feasibility of adoption		
8. The feasibility of adoption of amivantamab plus carboplatin-pemetrexed must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate(s).	—

CDA-AMC = Canada's Drug Agency; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; NSCLC = non–small cell lung cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; RECIST = Response Evaluation Criteria in Solid Tumours; QALY = quality-adjusted life-year.

Discussion Points

- **Significant unmet need:** pERC deliberated on amivantamab plus carboplatin-pemetrexed considering the criteria for significant unmet need that are described in section 9.3.1 of the Procedures for Reimbursement Reviews. pERC noted that NSCLC with *EGFR* ex20ins mutations is an aggressive and life-threatening disease with OS among the worst for patients with lung cancer. *EGFR* ex20ins NSCLC is considered a rare condition and currently there is no access to targeted

treatment options for ex20ins. Patients with *EGFR* ex20ins have not benefited from available *EGFR*-targeted therapy or immunotherapy and represent a population with significant unmet need. The available evidence demonstrated that amivantamab plus carboplatin-pemetrexed resulted in clinically meaningful improvements in PFS; at a median follow-up time of 14.9 months, median PFS was 11.4 months with amivantamab plus carboplatin-pemetrexed and 6.7 months with carboplatin-pemetrexed alone. The evidence was rated as being of high certainty, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

- **Overall survival:** Patients identified a need for treatments that prolong survival. pERC discussed that based on the evidence from the PAPILLON trial, amivantamab plus carboplatin-pemetrexed may have a benefit in OS compared with carboplatin-pemetrexed alone. The evidence was of low certainty based on GRADE assessment. Uncertainty in the OS results stemmed from immature OS data (33.3% [70 of 210 events] of the information fraction planned for the final analysis), a large number of patients (41.9%) who crossed over from the carboplatin-pemetrexed group to amivantamab monotherapy, and imprecision in the estimates (i.e., wide CIs that included the possibility of little-to-no difference and in some cases potential harm). Given the limitations, pERC could not draw definitive conclusions on the comparative OS results from the PAPILLON trial.
- **Adverse effects**: pERC discussed patients' desire for treatments with manageable adverse effects. Comparative safety from the PAPILLON trial indicated that grade 3 or higher and serious adverse events (SAEs) were more common in patients treated with amivantamab plus carboplatin-pemetrexed, mainly neutropenia, gastrointestinal disorders, and infections and infestations. According to the GRADE assessment, amivantamab plus carboplatin-pemetrexed likely results in an increase in rash and infusion-related reactions when compared to carboplatin-pemetrexed alone. However, the majority of these reactions were low grade and treatment discontinuation as a consequence was relatively rare. pERC heard from the clinical experts that a higher proportion of adverse events (AEs) was expected in the amivantamab plus carboplatin-pemetrexed group, given that a combination therapy was being evaluated in comparison to chemotherapy only. pERC acknowledged clinical expert input that the safety profile of amivantamab plus carboplatin-pemetrexed appeared manageable and consistent with the known safety profile of its individual treatment components. Patient input stated that hope of survival outweighed the negatives of drug side effects.
- **Indirect evidence**: pERC noted that in addition to platinum-based chemotherapy, *EGFR* tyrosine kinase inhibitors (TKIs) as well as immunotherapies are currently available as first-line treatment for patients with *EGFR* ex20ins NSCLC. However, the committee heard from the clinical experts that patients with *EGFR* ex20ins are resistant to *EGFR* TKIs and have low response rates to immunotherapies; therefore, first-line platinum-based chemotherapy remains the most relevant and routinely used therapy option in the present target patient population. pERC reviewed a sponsor-submitted nonrandomized study using individual patient level data from the PAPILLON trial and real-world evidence cohorts to compare amivantamab plus carboplatin-pemetrexed to *EGFR* TKIs and immunotherapy plus chemotherapy. The committee noted several limitations with the submitted comparative analysis, notably heterogeneity across study designs and populations, risk

of residual confounding, small effective sample sizes in the comparator groups, and imprecision. pERC concluded that the comparative evidence was insufficient to draw definitive conclusions on the relative efficacy (i.e., OS, PFS, real-world PFS, and time to next treatment) of amivantamab plus carboplatin-pemetrexed compared with *EGFR* TKIs and immunotherapy plus chemotherapy.

- **Testing procedure:** pERC discussed the requirement of testing for *EGFR* ex20ins mutations when determining eligibility for amivantamab. Testing for *EGFR* ex20ins mutations is currently performed as part of the standard of care for locally advanced or metastatic NSCLC in Canada and is not anticipated to be an implementation or access barrier.
- **Economic considerations:** pERC discussed that the economic evidence is highly uncertain due to limitations with the clinical evidence, and that CDA-AMC was unable to resolve some identified limitations through reanalysis. To account for the outstanding uncertainty in the economic evidence, pERC noted that a greater price reduction than noted in Table 1 may be warranted.

Background

Canadian Cancer Statistics 2023 estimate that 1 in 14 people in Canada will be diagnosed with lung cancer in their lifetime and that 1 in 4 cancer-related deaths in Canada will be attributed to the disease. The overwhelming majority of newly diagnosed lung cancer cases in Canada are attributed to NSCLC (88%), and the 5-year net survival rates for patients in Canada with advanced (stage IV) NSCLC is only 3%. Goals of treatment for advanced NSCLC include delaying progression, prolonging survival, palliation of symptoms, and improving QoL. *EGFR* ex20ins is a rare mutation that is associated with aggressive, highly symptomatic disease, and significant clinical burden. Multiple studies have found that patients with positive *EGFR* ex20ins NSCLC are typically female, nonsmokers, and diagnosed with metastatic disease at approximately 60 years of age. In Canada, it has been estimated that *EGFR* ex20ins account for approximately 5% of *EGFR* mutations and between 0.4% to 1.2% of all NSCLC cases, with provincial variation likely being driven by differences in population demographics (ex20ins mutations are more prevalent in patients of East Asian ethnicity).

Currently, there are no approved targeted therapies for patients with ex20ins mutations in the first-line setting. The current recommended standard of care remains chemotherapy (cisplatin or carboplatin generally in combination with pemetrexed followed by pemetrexed maintenance). Treatment with chemotherapy alone does not provide a durable treatment benefit for patients with *EGFR* ex20ins and is associated with poor survival outcomes (median PFS ranging from 4.2 to 6.9 months and median OS from 16.1 to 22.4 months).

Amivantamab has received Health Canada approval for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with activating *EGFR* ex20ins mutations. Amivantamab is a bispecific antibody that binds to both the *EGFR* and *MET* receptor. The recommended dose for amivantamab is a once weekly IV infusion, at a dose of 1,400 mg (1,750 mg if body weight is 80 kg or greater) for 4 weeks (first dose split on days 1 and 2), then 1,750 mg (2,100 mg if body weight is ≥ 80 kg) on day 1 of each 21-day cycle, starting with cycle 3.

Sources of Information Used by the Committee

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

- a review of 1 phase III randomized controlled trial in adult patients with treatment naive *EGFR* ex20ins mutated locally advanced or metastatic NSCLC; and 1 nonrandomized study using individual patient level data from the PAPILLON trial and real-world evidence cohorts to compare amivantamab plus carboplatin-pemetrexed to *EGFR* TKIs and immunotherapy plus chemotherapy
- patients' perspectives gathered by 1 joint submission from 3 patient groups, Lung Cancer Canada (LCC), the Canadian Cancer Survivor Network (CCSN), and the Lung Health Foundation
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with locally advanced or metastatic 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

The patient input submission was jointly submitted by LCC, the CCSN, and the Lung Health Foundation. Nine patients with NSCLC provided input through virtual interviews by LCC and CCSN. Among them, 7 patients were from Canada, 1 from the US, and 1 from the UK. All data were collected between May and July in 2024. Based on the input, patients with ex20ins mutations face a unique challenge as the mutation is insensitive to conventional TKIs and thus face a poorer prognosis, necessitating different treatment options. Patient groups indicated that there is an urgent unmet need for novel treatment options for patients with positive *EGFR* ex20ins mutated NSCLC. According to the patient group input, improved management of disease symptoms, QoL, and survival, as well as delayed disease progression and manageable side effects are considered important outcomes by patients with NSCLC. All 9 participants had experience with amivantamab. Generally, patients indicated that amivantamab was effective in stabilizing disease and maintaining QoL with manageable side effects. The most common side effects reported included facial and scalp rashes, cuts on fingers and toes, paronychia, eye dryness, sensitivity to the sun, fatigue, skin sensitivity, and nausea.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

- The clinical experts consulted by CDA-AMC on this review noted the toxicities associated with cytotoxic chemotherapy and its limited efficacy, and that targeted therapies with better efficacy are needed.
- The clinical experts noted that amivantamab would be added to current standard doublet therapy in the first-line setting. The clinical experts believed that the patients most likely to respond to amivantamab are those with the ex20ins mutation.
- The clinical experts noted that response would be determined by serial physical and symptom assessments and imaging assessments, typically with CT scans every 8 to 12 weeks while receiving therapy or if there were new symptoms suggesting progression. The clinical experts believed that treatment should be discontinued in patients with unacceptable toxicity, significant progression, or patient choice.

Clinician Group Input

Two clinician groups submitted inputs, the LCC-MAC and the OH-CCO Lung Cancer Drug Advisory Committee. In total, 32 clinicians from LCC-MAC and 7 clinicians from OH-CCO Lung Cancer Drug Advisory Committee provided input to the submissions.

The clinician groups agreed with the clinical experts consulted by CDA-AMC that because of poor outcomes with current available treatments, there is a significant unmet need for novel targeted therapies with better efficacy. The clinician groups agreed with the clinical experts consulted by CDA-AMC that amivantamab plus carboplatin-pemetrexed should be used in the first-line setting and clinicians from the OH-CCO Lung Cancer Drug Advisory Committee indicated that amivantamab plus carboplatin-pemetrexed can replace pembrolizumab or ipilimumab and/or nivolumab. All clinicians agreed that patients with *EGFR* ex20ins mutations are best suited for treatment with amivantamab plus carboplatin-pemetrexed. Clinicians from LCC-MAC suggested radiological response assessments every 6 to 9 weeks and clinicians from the OH-CCO Lung Cancer Drug Advisory Committee suggested response assessments every 9 to 12 weeks. All clinicians agreed that disease progression and unacceptable toxicities should be considered when deciding to discontinue treatment. All clinicians agreed that specialists with experience in using systemic therapy in cancer care are required for the treatment with amivantamab; outpatient cancer centres, satellite facilities, or hospitals would be appropriate settings.

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 trial compared amivantamab-pemetrexed-carboplatin against pemetrexed-carboplatin. The currently funded first-line treatments for patients with *EGFR* ex20ins mutations are platinum-doublet chemotherapy (usually cisplatin or carboplatin plus pemetrexed, followed by pemetrexed maintenance). • Is there evidence to inform the use of amivantamab in combination with alternate platinum-doublet chemotherapy options?	The PAPILLON trial provided evidence on amivantamab in combination with carboplatin and pemetrexed; no evidence was available for amivantamab in combination with other platinum-doublet options for the patient target population. pERC agreed with the clinical experts that it would be reasonable to use cisplatin instead of carboplatin at the discretion of the treating clinician.
Considerations for initiation of therapy	
The trial protocol specified nonsquamous NSCLC and 99% of patients had adenocarcinoma. • Please confirm the histological types of NSCLC that would be eligible for first-line combination with amivantamab?	The PAPILLON trial excluded patients with squamous NSCLC. pERC agreed with the clinical experts that patients with nonsquamous histology should be eligible for first-line combination with amivantamab. In the absence of evidence for amivantamab plus carboplatin-pemetrexed in patients with other histological types of NSCLC, there is insufficient information to guide a recommendation on generalizing the PAPILLON study results to these patients.
The trial protocol allowed neoadjuvant or adjuvant treatments only if given 12 months before. • If prior adjuvant or neoadjuvant treatment was given, what is the minimum disease-free interval to be eligible for first-line combination with amivantamab?	pERC agreed with the clinical experts that it would be reasonable for patients to be eligible for first-line treatment with amivantamab plus carboplatin-pemetrexed if they completed adjuvant or neoadjuvant therapies at least 6 months before developing recurrent disease; this is aligned with the 2023 CDA-AMC provisional funding algorithm for advanced or metastatic NSCLC with activating *EGFR* mutations.
The trial only included patients with an ECOG of 0 or 1. Patients with treated brain metastases were eligible if they were asymptomatic, if their condition was clinically stable, and if they had received no glucocorticoid treatment for at least 2 weeks before randomization. • Should patients with ECOG > 1 be considered for first-line combination with amivantamab? • Should patients with CNS disease be eligible for first-line combination with amivantamab as outlined in inclusion criteria for the PAPILLON trial?	The clinical experts felt that patients with an ECOG of 2 should be eligible for amivantamab plus carboplatin-pemetrexed, noting that in clinical trials the patient populations selected tend to be healthier than those seen in clinical practice. The clinical experts noted that they typically offer platinum-doublet chemotherapy to patients with an ECOG of 2, and that the evidence does not suggest a concerning increase in harms when adding amivantamab to platinum-doublet chemotherapy. Patients with untreated brain metastases were excluded from the PAPILLON trial. A total of 23.1% of patients had a history of brain metastasis. According to the clinical experts, patients with stable or treated metastases should be eligible for amivantamab. Further, the experts agreed that patients with unstable or new and clinically relevant CNS metastasis, should not be eligible to receive amivantamab before receiving treatment for the CNS metastases. pERC agreed with the clinical experts.
Considerations for discontinuation of therapy	
In the trial, treatment beyond confirmed disease progression was allowed if the investigator deemed that the participant	pERC agreed with the clinical experts that patients who experience unacceptable toxicity despite appropriate supportive

Implementation issues	Response
was deriving continued clinical benefit. • What discontinuation criteria should be used for first-line combination with amivantamab in clinical practice?	care or dose reductions, who experience significant progression, or those who choose to do so, should discontinue therapy.
Considerations for prescribing of therapy	
Amivantamab adds multiple treatment visits and pharmacy preparations to each treatment cycle versus comparators. Greater than or equal to 80 kg: 1,750 mg weekly for 4 weeks, then 2,100 mg once every 3 weeks starting at week 7 and continued until disease progression or unacceptable toxicity. Week 1 dose given as split infusion on day 1 and day 2 Less than 80 kg: 1,400 mg weekly for 4 weeks, then 1,750 mg once every 3 weeks starting at week 7 and continued until disease progression or unacceptable toxicity. Week 1 dose given as split infusion on day 1 and day 2.	This was a comment from the drug programs to inform pERC deliberations.
Administration rates for amivantamab follow an escalation schedule for the first few doses (rates vary for 1,400 mg and 1,750 mg doses). These escalating infusion rate schedules will require additional monitoring by nursing. Target doses are administered over 2 hours at a fixed rate. The administration of the first dose is split over 2 days. This represents a notable increase in resources versus comparator therapies and has an impact on patients, the chemotherapy treatment room, and pharmacy.	This was a comment from the drug programs to inform pERC deliberations.
The PAPILLON trial used chemotherapy for up to 4 cycles in combination with amivantamab. • Should there be intolerance to chemotherapy before completion of 4 cycles, can amivantamab be continued as monotherapy?	pERC agreed with the clinical experts that if there is intolerance to chemotherapy before completion of 4 cycles, amivantamab can be continued as monotherapy, noting that the mechanism of amivantamab is distinct from that of cytotoxic chemotherapy, and that there is evidence for its use as monotherapy from second-line trials.
Generalizability	
• On a time-limited basis, for patients currently receiving first-line therapy or recently completed first-line therapy, should amivantamab in combination with platinum-doublet chemotherapy be funded for patients provided that disease progression has not occurred to alternate first-line therapy?	pERC agreed with the clinical experts that for patients who are currently receiving first-line therapy, including platinum-doublet chemotherapy (cisplatin or carboplatin generally in combination with pemetrexed followed by pemetrexed maintenance), a time-limited transition period should be implemented to allow for switching.
Funding algorithm	
• Are patients eligible for amivantamab if they received *EGFR* TKI therapy for a duration of less than 8 weeks with a documented lack of response? • What are the subsequent treatment options after patients progress on amivantamab?	According to the PAPILLON trial eligibility criteria, monotherapy with an approved *EGFR* TKI (i.e., gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib) for the treatment of locally advanced or metastatic disease was allowed, if treatment duration did not exceed 8 weeks. pERC agreed with the clinical experts that patients should be eligible for amivantamab plus carboplatin-pemetrexed if they previously had a documented lack of response to an *EGFR* TKI in first-line therapy; these drugs have a different mechanism of action than amivantamab.

Implementation issues	Response
	The clinical experts anticipated that most patients would receive chemotherapy (single drug docetaxel) as subsequent treatment.
Care provision issues	
Recommended doses and dose adjustments correspond to available vial size and should minimize wastage (available as 350 mg vials). The product monograph indicates a need to withdraw a volume from the infusion bag equal to the volume of drug being added and the volume in the infusion bag should be 250 mL. It is extra work to ensure a final volume of exactly 250 mL.	This was a comment from the drug programs to inform pERC deliberations.
Additional therapies may be required for the management of skin toxicities (e.g., emollient creams, topical corticosteroids, oral or IV antibiotics, or oral steroids).	This was a comment from the drug programs to inform pERC deliberations.
Timely confirmation of *EGFR* ex20ins mutation is needed to confirm eligibility. • What method of testing should be used for detection of *EGFR* ex20ins mutations? • In the event the patient has already started alternate systemic therapy before the ex20ins mutation results are available, can the patient be switched to amivantamab-carboplatin-pemetrexed?	The clinical experts noted that NGS testing is the current standard; however, there are emerging technologies such as rapid tests that are being used in some jurisdictions. The clinical experts noted that it would be reasonable to allow patients who have started alternate systemic therapy before ex20ins mutation status has been confirmed, to switch to amivantamab plus carboplatin-pemetrexed once their status is confirmed, at the discretion of the treating clinician.
System and economic issues	
There are confidential prices for comparators (chemotherapy).	This was a comment from the drug programs to inform pERC deliberations.

ALK = anaplastic lymphoma kinase; CDA-AMC = Canada's Drug Agency; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; NGS = next-generation sequencing; NSCLC = non–small cell lung cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; TKI = tyrosine kinase inhibitor.

Clinical Evidence

Systematic Review

Description of Study

The PAPILLON study is an ongoing, phase III, multicentre open-label trial conducted in 131 centres across 25 countries, including 3 study sites in Canada. Patients were aged 18 years or older with treatment naive *EGFR* ex20ins mutated locally advanced or metastatic NSCLC. The primary objective of the study was to assess the efficacy of amivantamab plus carboplatin-pemetrexed compared with carboplatin-pemetrexed in the first-line treatment of patients with *EGFR* ex20ins mutated NSCLC. A total of 308 patients were randomized 1:1 to either the amivantamab plus carboplatin-pemetrexed or carboplatin-pemetrexed arm, from December 2020 to November 2022. The clinical cut-off date for data inclusion was May 2023. The treatment phase for each participant started at cycle 1 day 1 and continued in 21-day cycles until the end of the treatment visit (approximately 30 days after discontinuation of study treatment), and patients continued

treatment until documented radiographic disease progression. Eligible patients in the carboplatin-pemetrexed arm who experienced disease progression were given the option to enter the crossover phase and receive amivantamab monotherapy in 21-day cycles. The primary outcome was PFS assessed by blinded independent committee review (BICR) and secondary outcomes included OS and OR.

Patients in the PAPILLON trial were aged 60 years on average, the majority were female (56%), and had no smoking history (58%). There were 65% of patients with an ECOG of 1; the remainder had an ECOG score of 0. The majority of patients (77%) had no history of brain metastases. Almost all patients had adenocarcinoma and had not used prior *EGFR* inhibitors (99% each). Almost all patients had either stage IVA [redacted] or IVB [redacted] disease at screening. [redacted] patients had prior surgery for lung cancer and [redacted] had prior radiotherapy. Although there were some differences in specific baseline characteristics between amivantamab plus carboplatin-pemetrexed and carboplatin-pemetrexed groups, the clinical experts consulted by CDA-AMC on this review did not believe them to be clinically relevant.

Efficacy Results

As of the data cut-off in May 2023, there was a median follow-up of 14.92 months.

Progression-Free Survival

Analyses were performed after 216 events had been observed (amivantamab plus carboplatin-pemetrexed arm: 84, carboplatin-pemetrexed arm: 132). A treatment effect favouring amivantamab plus carboplatin-pemetrexed was observed with an HR of 0.395 (95% CI, 0.296 to 0.528; P < 0.0001). The median PFS by BICR in the amivantamab plus carboplatin-pemetrexed arm was 11.37 months (95% CI, 9.79 to 13.70) compared with the carboplatin-pemetrexed arm (6.70 months; 95% CI, 5.59 to 7.33). Preplanned sensitivity analyses evaluating PFS as assessed by the treating investigator as well as a nonstratified analysis were consistent with the primary analysis. At the 6-month time point, the absolute difference in PFS rates between amivantamab plus carboplatin-pemetrexed and carboplatin-pemetrexed groups was [redacted] at 12 months it was [redacted] and at 18 months it was [redacted]). Note that by 18 months there were only 17 patients (15 in the amivantamab plus carboplatin-pemetrexed group and 2 in the carboplatin-pemetrexed group) remaining at risk.

Overall Survival

As of the data cut-off in May 2023, there were a total of 70 deaths reported across both groups (amivantamab plus carboplatin-pemetrexed arm: 28 deaths, carboplatin-pemetrexed arm: 42 deaths). At this point, 65 patients from the carboplatin-pemetrexed group had crossed over to amivantamab monotherapy, and the HR was 0.675 (95% CI, 0.418 to 1.090; P = 0.106). Median OS in the amivantamab plus carboplatin-pemetrexed arm was not estimable, and the median OS in the carboplatin-pemetrexed arm was 24.38 (95% CI, 22.08 to not estimable) months. The final planned OS analysis will be conducted on more mature OS data, approximately 48 months after the first participant was randomized, when approximately 210 deaths overall are anticipated. Results of the stratified sensitivity analysis were consistent with unstratified analysis. At the 12-month time point, the absolute difference in OS rates between amivantamab plus carboplatin-pemetrexed and carboplatin-pemetrexed groups was [redacted]); at 18 months

it was [redacted] and at 24 months it was [redacted]). Note that by 18 months there were only 11 patients (5 in the amivantamab plus carboplatin-pemetrexed group and 6 in the carboplatin-pemetrexed group) who remained at risk. The sponsor also conducted sensitivity analyses to adjust for patients who crossed over to amivantamab monotherapy from carboplatin-pemetrexed; inverse probability of censoring weighting (adjusted HR of [redacted] 2-stage estimation (adjusted HR of [redacted]) and rank-preserving structural failure time (adjusted HR [redacted]) analyses.

Objective Response Rates

Based on BICR assessment in patients with measurable disease at baseline (n = 304), there was a higher percentage of responders in the amivantamab plus carboplatin-pemetrexed arm (111 patients [73%]), compared with the carboplatin-pemetrexed arm (72 patients [47.4%]) at the data cut-off for an OR of [redacted]), favouring amivantamab plus carboplatin-pemetrexed. The absolute difference between groups was [redacted]. The percentage of patients with progressive disease as the best response in the amivantamab plus carboplatin-pemetrexed arm was [redacted] compared with [redacted] in the carboplatin-pemetrexed arm. Results of the sensitivity analysis evaluating ORR as assessed by the treating investigator were consistent with the assessment by BICR.

Health-Related Quality of Life

For the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Global Health Status (range: 0 [worst] to 100 [best] points), the mean change from baseline to 12 months was [redacted]) in the amivantamab plus carboplatin-pemetrexed group and [redacted] in the carboplatin-pemetrexed group. The mean difference between amivantamab plus carboplatin-pemetrexed and carboplatin-pemetrexed groups for change from baseline to 12 months was [redacted]).

PFS After First Subsequent Therapy

At the data cut-off, there were [redacted] of 153 patients ([redacted] in the amivantamab plus carboplatin-pemetrexed group and [redacted] of 155 patients in the carboplatin-pemetrexed group ([redacted] who had a PFS event after first subsequent therapy (PFS2). The HR was 0.493 (95% CI, 0.32 to 0.759; P = 0.001). This analysis was not adjusted for multiplicity. The median PFS2 was not estimable (95% CI, 22.77 to not estimable) in the amivantamab plus carboplatin-pemetrexed arm and 17.25 months (95% CI, 13.96 to 21.52) in the carboplatin-pemetrexed arm.

Harms Results

Adverse Events

Overall, all 151 patients (100%) in the amivantamab plus carboplatin-pemetrexed group and 152 patients (98.1%) in the carboplatin-pemetrexed group experienced at least 1 AE. The most common AE was rash, which occurred in 81 patients (53.6%) in the amivantamab plus carboplatin-pemetrexed group and 12 patients (7.7%) in the carboplatin-pemetrexed group. Other common AEs where there were large differences between groups included dermatitis acneiform in 47 patients (31.1%) in the amivantamab plus

carboplatin-pemetrexed group and 5 patients (3.2%) in the carboplatin-pemetrexed group; hypoalbuminemia in 62 patients (41.1%) in the amivantamab plus carboplatin-pemetrexed group and 15 patients (9.7%) in the carboplatin-pemetrexed group; peripheral edema in 45 patients (29.8%) in the amivantamab plus carboplatin-pemetrexed and 16 patients (10.3%) in the carboplatin-pemetrexed group; and infusion-related reaction in 63 patients (41.7%) in the amivantamab plus carboplatin-pemetrexed and 2 patients (1.3%) in the carboplatin-pemetrexed group.

Serious Adverse Events

Treatment-emergent SAEs were reported in 56 patients (37.1%) in the amivantamab plus carboplatin-pemetrexed group and 48 patients (31.0%) in the carboplatin-pemetrexed group. The most common SAEs in the amivantamab plus carboplatin-pemetrexed group were due to pneumonia (6 patients [4.0%] versus 4 patients [2.6%] in the carboplatin-pemetrexed group), pneumonitis (4 patients [2.6%] and no patients in the carboplatin-pemetrexed group), and pulmonary embolism (4 patients [2.6%] in each group). All other SAEs in the amivantamab plus carboplatin-pemetrexed group had an incidence of less than 2%. The most common SAE in the carboplatin-pemetrexed arm was anemia (6 patients [3.9%] and 1 patient [0.7%] in the amivantamab plus carboplatin-pemetrexed group).

Withdrawals Due to Adverse Events

Overall, from study initiation through the data cut-off, 36 patients (23.8%) in the amivantamab plus carboplatin-pemetrexed arm and 16 patients (10.3%) in the carboplatin-pemetrexed arm had treatment-emergent AEs leading to discontinuation of at least 1 study treatment. Of the 36 patients in the amivantamab plus carboplatin-pemetrexed arm who discontinued any study treatment, 17 discontinued amivantamab. Pneumonitis was the most common cause of discontinuation of amivantamab (4 patients [2.6%]), followed by dermatitis acneiform ([redacted]). Thrombocytopenia (3 patients [1.9%]) and neutropenia (2 patients [1.3%]) were the most common reasons for treatment discontinuation of either carboplatin or pemetrexed in the carboplatin-pemetrexed arm. Most of the treatment-emergent AEs leading to study treatment discontinuation occurred at a frequency of less than 2% in both treatment arms.

Mortality

There were 4 patients (2.6%) in the amivantamab plus carboplatin-pemetrexed group and 9 patients (5.8%) in the carboplatin-pemetrexed group who died due to an AE during the study and 3 patients (2.0%) in the amivantamab plus carboplatin-pemetrexed group and 4 patients (2.6%) in the carboplatin-pemetrexed group who died due to an AE within 30 days of the last dose.

Notable Harms

The notable harms identified for this review were rash and infusion reactions. As previously mentioned, rash was the most common AE, occurring in 81 patients (53.6%) in the amivantamab plus carboplatin-pemetrexed group and 12 patients (7.7%) in the carboplatin-pemetrexed group. There were [redacted] patients in the amivantamab plus carboplatin-pemetrexed group and [redacted] patients in the carboplatin-pemetrexed group with an event identified as skin and subcutaneous disorders. Infusion-related reactions were reported in 63 patients (41.7%) in the amivantamab plus carboplatin-pemetrexed group and 2 patients (1.3%) in the carboplatin-pemetrexed group.

Critical Appraisal

- The lack of blinding in the PAPILLON trial introduced significant potential for bias in the assessment of patient-reported outcomes such as HRQoL. There were a large number of patients (42%) who crossed over from the carboplatin-pemetrexed group to amivantamab monotherapy after disease progression, which is a major confounder when assessing OS. Another limitation of assessment of OS was that the data are not yet mature.
- With respect to external validity, the clinical experts consulted by CDA-AMC on this review believed the population enrolled in the PAPILLON trial to be generalizable to the patients they expect to be treated with amivantamab plus carboplatin-pemetrexed in Canada; although they would likely consider expanding the population to an ECOG of 2 performance status, rather than limiting to an ECOG of 0 or 1 performance status, as was seen in the trial.

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 expert committee members:

- PFS
- OS
- ORR
- HRQoL (EORTC QLQ-C30 Global Health Status)
- notable harms: rash and infusion-related reactions.

The target of the certainty of evidence assessment was the presence or absence of a clinically important effect based on thresholds informed by the clinical experts consulted for this review for PFS and OS. The literature-based minimally important difference (MID) of 10 points was used for the EORTC QLQ-C30 Global Health Status. This MID has been estimated for within-group changes and was applied in the absence of an estimate of the MID for a between-group difference. The target of the certainty of evidence was the presence or absence of any (non-null) effect for the ORR because a threshold for a clinically important between-group difference could not be estimated.

Table 3: Summary of Findings for Amivantamab Plus Carboplatin-Pemetrexed Versus Carboplatin-Pemetrexed for Patients With NSCLC With *EGFR* ex20ins

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Carboplatin-pemetrexed	Amivantamab plus carboplatin-pemetrexed	Difference		
PFS (median follow-up of 14.9 months [range 0.3 to 27.0])							
Probability of being progression free at 6 months	308 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	High[a]	Amivantamab plus carboplatin-pemetrexed results in a clinically important improvement in the probability of being progression free compared to carboplatin-pemetrexed alone.
Probability of being progression free at 12 months	308 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	High[a]	Amivantamab plus carboplatin-pemetrexed results in a clinically important improvement in the probability of being progression free compared to carboplatin-pemetrexed alone.
Probability of being progression free at 18 months	308 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	High[a]	Amivantamab plus carboplatin-pemetrexed likely results in a clinically important improvement in the probability of being progression free compared to carboplatin-pemetrexed alone.
OS (median follow-up of 14.9 months [range 0.3 to 27.0])							
Probability of being alive at 12 months	308 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Low[b]	Amivantamab plus carboplatin-pemetrexed may result in a clinically important improvement in the probability of being alive compared to carboplatin-pemetrexed alone.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Carboplatin-pemetrexed	Amivantamab plus carboplatin-pemetrexed	Difference		
Probability of being alive at 18 months	308 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Low[b]	Amivantamab plus carboplatin-pemetrexed may result in a clinically important improvement in the probability of being alive compared to carboplatin-pemetrexed alone.
Probability of being alive at 24 months	308 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Low[b]	Amivantamab plus carboplatin-pemetrexed may result in a clinically important improvement in the probability of being alive compared to carboplatin-pemetrexed alone.
ORR (median follow-up of 14.9 months [range 0.3 to 27.0])							
ORR by BICR Follow-up: Data cut-off	304 (1 RCT)	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[c]	Amivantamab plus carboplatin-pemetrexed likely results in an improvement in ORR compared to carboplatin-pemetrexed alone. The clinical importance is uncertain.
HRQoL: EORTC QLQ-C30 Global Health Status							
EORTC QLQ-C30 Global Health Status, mean change from baseline (0 [worst] to 100 [best] points) Follow-up: 12 months	308 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Low[d]	Amivantamab plus carboplatin-pemetrexed may result in little-to-no difference in HRQoL compared to carboplatin-pemetrexed alone.
Notable harms							
Rash[e] Follow-up: to data cut-off	308 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[f]	Amivantamab combined with carboplatin-pemetrexed likely results in an increase in rash compared to carboplatin--

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Carboplatin-pemetrexed	Amivantamab plus carboplatin-pemetrexed	Difference		
							pemetrexed alone. The clinical significance of the rash is unknown.
Infusion-related reaction Follow-up: to data cut-off	308 (1 RCT)	NR				Moderate[f]	Amivantamab combined with carboplatin-pemetrexed likely results in an increase in infusion-related reactions compared to carboplatin-pemetrexed alone. The clinical significance of the infusion-related reactions is unknown.

BICR = Blinded Independent Central Review; CI = confidence interval; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HRQoL = health-related quality of life; MID = minimally important difference; NA = not applicable; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial.

Notes: 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.

For the EORTC QLQ-C30 Global Health Status, means and 95% CIs are derived based on the mixed effects model with repeated measures, in which the dependent variable is change from baseline in score, and independent variables are baseline, visit, treatment, and visit by treatment interaction as fixed effects and individual patient as random effect.

The between-group differences for PFS, OS, HRQoL, and notable harms were not part of the sponsor's statistical analysis plan and were requested by the review team to facilitate interpretation.

[a]The clinical experts consulted by the review team considered that both the point estimate and lower bound of the CI constituted clinically meaningful benefit.

[b]Rated down 1 level for study limitations; results are from an interim analysis and there is a risk of bias due to confounding as a result of crossover of patients from the carboplatin-pemetrexed group to amivantamab monotherapy postprogression. Rated down 1 level for imprecision; the point estimate suggests benefit and CI includes little-to-no difference and in some cases, potential harm (threshold of 5% suggested by clinical experts).

[c]No threshold of clinical importance could be established; effects were appraised using the null. Rated down 1 level for indirectness; this is a surrogate end point without strong evidence that it predicts the treatment effect on OS.

[d]Rated down 2 levels for study limitations; there is risk of bias due to lack of blinding and a subjective outcome and substantial missing outcome data. Based on a MID of 10 points, the point estimate and both bounds of the CI suggest little-to-no difference. The 10-point MID has been estimated for within-group changes, and was applied in the absence of an estimate of a between-group MID. However, both within- and between- group differences were smaller than the MID.

[e]Lower-level rash was used instead of higher-level rash because it was thought to capture rash events more specifically.

[f]Rated down 1 level for study limitations; there is a risk of bias due to lack of blinding and potential subjectivity in the outcomes.

Source: Data request of the sponsor, and the Clinical Study Report for the PAPILLON trial. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

No long-term extension studies were submitted.

Indirect Comparisons

The sponsor submitted an indirect treatment comparison (ITC) report that included analyses that used individual patient data from the PAPILLON trial and real-world databases, and inverse probability of treatment weighting (IPTW) methods to reduce the risk of bias due to confounding. This was considered by the review team as a nonrandomized study and is reported in the following section.

Studies Addressing Gaps in the Evidence From the Systematic Review

This section includes the content of the ITC report submitted by the sponsor, which was considered by the review team to be a nonrandomized study, as it used individual patient data for each arm in the comparison.

Description of the Nonrandomized Study

The sponsor performed a nonrandomized study using IPTW. These analyses used individual patient data from the PAPILLON trial for amivantamab plus carboplatin-pemetrexed and from real-world databases (COTA and ConcertAI) for *EGFR* TKI monotherapy and platinum chemotherapy plus immunotherapy. The analyses examined the outcomes of OS, PFS, real-world PFS, and time to next treatment.

Covariates were identified by the sponsor which were considered treatment effect modifiers or prognostic factors. The base case results were adjusted for ECOG performance status at index date, history of brain metastases, history of liver metastases, and age at index date. The full model adjusted for all the variables in the base case, plus East Asian ethnicity, history of smoking, sex, and history of other metastases.

For the PAPILLON trial versus *EGFR* TKI comparison, before weighting, moderate differences (absolute standardized mean difference [SMD] [redacted]) were observed for ECOG performance status at index date and history of smoking. Substantial differences (absolute SMD [redacted]) were seen for history of liver metastases, age, East Asian ethnicity, sex, and history of other metastases. In the primary analysis, base case average treatment effect on the treated (ATT) weighting balanced (SMD[redacted]) all 4 covariates between cohorts. However, in the full model all 8 of the included factors had absolute SMDs[redacted], indicating a lack of balance, with moderate differences observed for 6 factors (ECOG performance status at index date, history of liver metastases, age, history of smoking, sex, and history of other metastases), and substantial differences observed for the 2 remaining factors (history of brain metastases and East Asian ethnicity). The resulting effect sample size in the *EGFR* TKI cohort was [redacted] for the base case and full model, respectively, compared to the original [redacted] observations.

For the PAPILLON trial versus platinum plus immunotherapy comparison, before weighting, substantial (absolute SMD [redacted]) differences were observed for ECOG performance status at index date, history of liver metastases, history of brain metastases, age, East Asian ethnicity, and history of other metastases. In the primary analysis, ATT weighting reduced the proportion of categories with absolute SMDs[redacted] from [redacted]), with only moderate differences observed for the 2 remaining factors (ECOG performance status at index date and age). Conversely, the balance between populations in the full

model remained the same (6 of 8 factors balanced) following weighting, although moderate differences were observed for 3 factors (ECOG performance status at index date, history of brain metastases, and history of smoking) and substantial differences observed for the remaining 3 factors (history of liver metastases, East Asian ethnicity, and history of other metastases). The resulting effect sample size in the platinum plus immunotherapy cohort was [redacted] for the base case and full model, respectively, compared to the original [redacted] observations.

Efficacy Results

The unadjusted comparison of OS for the PAPILLON trial versus *EGFR* TKI, produced an HR of [redacted] in favour of amivantamab plus carboplatin-pemetrexed. The primary analysis, using base case ATT weighting, produced results in favour of amivantamab plus carboplatin-pemetrexed, with an HR of [redacted]). The unadjusted comparison of OS for the PAPILLON trial versus platinum plus immunotherapy, produced an HR of [redacted]) in favour of amivantamab plus carboplatin-pemetrexed. The primary analysis, using base case ATT weighting, produced a point estimate favouring amivantamab plus carboplatin-pemetrexed but the 95% CI crossed the null, with an HR of [redacted]).

The unadjusted comparison of PFS for the PAPILLON trial versus *EGFR* TKI, produced an HR of [redacted] the point estimate favoured amivantamab plus carboplatin-pemetrexed but the 95% CI crossed the null. Similarly, the primary analysis, using base case ATT weighting, produced an HR of [redacted]). The unadjusted comparison of PFS for the PAPILLON trial versus platinum plus immunotherapy, produced a HR of [redacted]) favouring amivantamab plus carboplatin-pemetrexed. The primary analysis, using base case ATT weighting, produced results in favour of amivantamab plus carboplatin-pemetrexed, with an HR of [redacted]).

The unadjusted comparison of real-world PFS for PAPILLON versus *EGFR* TKI, produced an HR of [redacted] favouring amivantamab plus carboplatin-pemetrexed. The primary analysis, using base case ATT weighting, produced results in favour of amivantamab plus carboplatin-pemetrexed, with an HR of [redacted]). The unadjusted comparison of real-world PFS for the PAPILLON trial versus platinum plus immunotherapy, produced an HR of [redacted]) favouring amivantamab plus carboplatin-pemetrexed. The primary analysis, using base case ATT weighting, produced results in favour of amivantamab plus carboplatin-pemetrexed, with an HR of [redacted]).

The unadjusted comparison of time to next treatment for the PAPILLON trial versus *EGFR* TKI, produced an HR of [redacted]) favouring amivantamab plus carboplatin-pemetrexed. The primary analysis, using base case ATT weighting, produced results in favour of amivantamab plus carboplatin-pemetrexed, with an HR of [redacted]). The unadjusted comparison of time to next treatment for the PAPILLON trial versus platinum plus immunotherapy, produced an HR of [redacted]) favouring

amivantamab plus carboplatin-pemetrexed. The primary analysis, using base case ATT weighting, produced results in favour of amivantamab plus carboplatin-pemetrexed, with an HR of [redacted]).

Results of the other sensitivity analyses (not shown) were mostly in the direction of favouring amivantamab plus carboplatin-pemetrexed, but in some cases the results were imprecise, with CIs that crossed the null.

Harms Results

Harms were not assessed in the nonrandomized studies.

Critical Appraisal

There was no predefined protocol available and the search and selection criteria, data extraction, and methods to appraise the risk of bias were not described. There was minimal information related to the real-world data source regarding data quality and completeness, suitability, and validity of any algorithms used to identify patients and classify outcomes. Additionally, due to the lack of protocol, there is an increased risk of bias in the selection of the reported results.

Propensity score-based methods aim to reduce the risk of bias due to confounding; however, it is important to note that no comparisons using data from randomized cohorts were used in the sponsor's analysis. Lack of randomization within the datasets introduces the possibility of imbalance of patient characteristics which could lead to comparing groups of patients who do not possess the similar prognostic risk. While the methods used by the sponsor serve to reduce confounding, the results indicate that a high risk of residual confounding is present in the analyses, even after the adjustments that were made on prognostic and effect-modifying covariates. While a sensitivity analysis of the full model including all 8 factors was conducted, the primary analysis of the base case only adjusted for 4 factors; it is unlikely that this represents all relevant prognostic and effect-modifying variables. In many cases, the full model was associated with high SMDs, indicating evidence of differences in baseline characteristics between the groups being compared. The base case model which used 4 factors also had notable imbalances.

The use of real-world data has several limitations. Participants in the PAPILLON trial were monitored more strictly than were the patients included in the ITC from the real-world databases. Monitoring of patients in the real-world databases was likely to be less rigorous. OS measurements may include errors or missing deaths, or censoring may differ between the clinical and real-world data sources. The sponsor suggested that missing deaths in real-world data may result in an overestimation of OS. The handling of missing data in the databases and in the analyses was not clearly described in the sponsor's report.

The effect sample sizes were very small in the base case and in several of the full model analyses, for example the effect sample size was [redacted] in the IPTW-ATT full model for the *EGFR* TKI group. In the full model, the majority of the 8 included factors remained unbalanced (SMDs[redacted]) following ATT weighting, for both the PAPILLON trial versus *EGFR* TKI (all 8 factors imbalanced) and platinum plus immunotherapy comparisons (5 of 8 factors were imbalanced). Therefore, the reliability of the results from the full model is expected to be low due to risk of bias and the small sample size. The results of the base case model are based on populations that have greater similarity to one another (in comparison to the full model); however,

imbalances remained, and the base case model did not control for all the important baseline prognostic covariates.

The selection of comparators in the analyses lack clinical relevance in the Canadian context. The relevance is also limited by the lack of analyses including patient-reported outcomes such as HRQoL.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of the Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with activating *EGFR* ex20ins mutations receiving first-line treatment.
Treatment	Amivantamab plus carboplatin-pemetrexed
Dose regimen	Amivantamab (Rybrevant), 1,400 mg (1,750 mg if body weight is ≥ 80 kg) by IV infusion once weekly for 4 weeks (first dose split on days 1 and 2), then 1,750 mg (2,100 mg if body weight is ≥ 80 kg) on ay 1 of each 21-day cycle, starting with cycle 3. Administer with carboplatin (target AUC 5 maximum dose of 750 mg for carboplatin for 4 cycles) and pemetrexed (500 mg/m^2 IV until disease progression) on a 21-day cycle.
Submitted price	Amivantamab, 350 mg/7 mL vial: $1,676
Submitted treatment cost	First 28 days: $21,481 (less than 80 kg) to $27,606 (80 kg or more) Thereafter, per 21 days: $6,713 (less than 80 kg) to $8,282 (80 kg or more) Amivantamab is administered in combination with carboplatin ($1,099 per 21-day cycle for 4 cycles) and pemetrexed ($372 per 21-day cycle until disease progression). The annual cost of amivantamab plus carboplatin-pemetrexed was $116,093 in year 1 and $49,295 afterwards, as calculated by the sponsor (accounting for discontinuation, dose reductions, and dose skipping).
Comparators	• platinum-based chemotherapy alone (comprising 70% carboplatin plus pemetrexed and 30% cisplatin plus pemetrexed) • *EGFR* TKIs (comprising 85% afatinib, 5% erlotinib, and 10% gefitinib) • IOs plus platinum-based chemotherapy (comprising 70% pembrolizumab plus carboplatin plus pemetrexed and 30% pembrolizumab plus cisplatin plus pemetrexed)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (15 years)
Key data source	PAPILLON trial, phase III open-label RCT

Component	Description
Key limitations	• The OS extrapolations for amivantamab plus carboplatin-pemetrexed and platinum-based chemotherapy alone are uncertain and clinically implausible based on feedback from clinical experts consulted. • The comparative clinical efficacy of amivantamab plus carboplatin-pemetrexed versus *EGFR* TKIs and IOs plus platinum-based chemotherapy is highly uncertain due to the absence of head-to-head clinical trials. The nonrandomized study results used to inform comparative clinical effects in the submitted model produce results that lack face validity (i.e., *EGFR* TKIs and IOs plus platinum-based chemotherapy are more effective than platinum-based chemotherapy alone, which remains the standard of care in Canadian clinical practice). • The modelled comparators do not reflect clinical practice in Canada. Clinical expert feedback obtained by CDA-AMC noted the lack of efficacy associated with *EGFR* TKIs in general for the treatment of patients with ex20ins mutations. Additionally, osimertinib, the only *EGFR* TKI that would potentially be considered in clinical practice in Canada for a minority of patients (due to better tolerance) was not included among the *EGFR* TKI options. Moreover, access to IOs (pembrolizumab) plus platinum-based chemotherapy is limited due to lack of Health Canada approval for patients with *EGFR* mutation and limited funding (i.e., restricted benefit in several participating drug plans). • Decision uncertainty cannot be accurately characterized by the PSM structure. When using the only OS extrapolation deemed clinically plausible, probabilistic results did not align with deterministic results and still produced implausible scenarios (e.g., the average patient receiving amivantamab plus carboplatin-pemetrexed experienced nearly 9 years of additional survival relative to platinum-based chemotherapy).
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by adopting a Gompertz distribution to extrapolate OS for amivantamab plus carboplatin-pemetrexed. CDA-AMC was unable to address uncertainty related to comparative clinical data or the relevance of modelled comparators. Due to the limitations associated with the clinical evidence and model structure, the CDA-AMC base case was restricted to results generated from the deterministic analysis of the revised model. • In the CDA-AMC base case, amivantamab plus carboplatin-pemetrexed is associated with incremental costs of $193,368 and an incremental QALY gain of 0.83 versus platinum-based chemotherapy alone, resulting in an ICER of $233,922 per QALY gained. A price reduction of 83% for amivantamab would be required for amivantamab plus carboplatin-pemetrexed to be considered cost-effective at a WTP threshold of $50,000 per QALY gained. • When accounting for clinical uncertainty related to the persistence of long-term treatment effect and methods for crossover adjustment in the trial for OS, ICERs ranged from $245,355 to $308,627 per QALY gained compared to platinum-based chemotherapy alone. In this latter scenario, a price reduction of 88% for amivantamab would be required for amivantamab plus carboplatin-pemetrexed to be considered cost-effective at a WTP threshold of $50,000 per QALY gained.

AUC = area under the curve; CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; IO = immune-oncology drug; LY = life-year; NSCLC = non–small cell lung cancer; OS = overall survival; PSM = partitioned survival model; QALY = quality-adjusted life-year, RCT = randomized controlled trial; TKI = tyrosine kinase inhibitor; WTP = willingness to pay.

Budget Impact

CDA-AMC identified key limitations with the sponsor's analysis: the market uptake of amivantamab plus carboplatin-pemetrexed was underestimated, the use of immune-oncology drugs plus platinum-based chemotherapy and *EGFR* TKIs was deemed overestimated by clinical expert feedback obtained by CDA-AMC, the number of eligible patients is uncertain and the sponsor likely underestimated the proportion of patients tested for *EGFR* mutations, and subsequent treatment was not considered in the analysis.

CDA-AMC reanalysis increased the market share of amivantamab plus carboplatin-pemetrexed, revised the base year market shares for comparators, and adjusted the *EGFR* mutations testing rate to 100%. In the CDA-AMC base case, the estimated budget impact of funding amivantamab plus carboplatin-pemetrexed for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with activating *EGFR* ex20ins mutations was $9,490,208 in year 1, $11,418,486 in year 2, and $11,649,162 in year 3, for a 3-year total of $32,557,856.

CDA-AMC conducted scenario analyses to address remaining uncertainty. Assuming that there are 200 incident patients per year increased amivantamab plus carboplatin-pemetrexed estimated 3-year budget impact to $65,906,562, demonstrating that the budget impact of amivantamab plus carboplatin-pemetrexed is highly sensitive to the number of eligible patients for treatment.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, 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: November 13, 2024

Regrets: None

Conflicts of interest: None

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