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

Reimbursement Recommendation

Reimbursement Recommendation

(Draft)

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.

Recommendation: Reimburse with Conditions

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Recommendation

The CDA-AMC pCODR Expert Review Committee (pERC) recommends that amivantamab in combination with carboplatin and pemetrexed (amivantamab plus CP) be reimbursed 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 (20ins) mutations only if the conditions listed in **Error! Reference source not found.** are met.

Rationale for the Recommendation

One phase III, open-label, randomized controlled trial (RCT; PAPILLON; N = 308) demonstrated that first-line treatment with amivantamab plus CP resulted in added clinical benefit in adults with advanced or metastatic NSCLC with *EGFR* Exon 20ins mutations. The PAPILLON trial demonstrated that, compared with CP, amivantamab plus CP 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 CP and 13.0% (95% CI, 8.0 to 19.0) for CP 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 CP also demonstrated statistically significant improvements in objective response rate (ORR) compared with CP alone (odds ratio [OR] = [redacted]). pERC considered the safety profile of amivantamab plus CP to be manageable and consistent with the known safety profile of its individual treatment components. pERC was uncertain whether amivantamab plus CP would prolong survival due to immature OS data (data maturity of 33%), a high rate of crossover of patients from the CP to the amivantamab plus CP group, and imprecision in the estimates (wide confidence intervals that crossed the null).

Patients identified a need for treatment options that improve quality of life and disease control, delay disease progression, have manageable side effects, and prolong survival. pERC concluded that amivantamab plus CP 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 CP may not have a detrimental impact on health-related quality of life (HRQoL) compared to CP 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 CP and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for amivantamab plus CP was $233,922 per quality-adjusted life-year (QALY), compared with platinum-based chemotherapy (CHT) alone. At this ICER, amivantamab plus CP is not cost-effective at a $50,000 per QALY gained willingness to pay (WTP) threshold for adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with activating *EGFR* Exon 20ins mutations receiving first-line treatment. A price reduction is required for amivantamab plus CP 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 CP should be reimbursed in adults with locally advanced or metastatic, non-squamous NSCLC who meet the following criteria: 1.1 documented primary *EGFR* Exon 20ins mutations 1.2 adequate organ and bone marrow function.	Evidence from the PAPILLON trial demonstrated that treatment with amivantamab plus CP 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 12 months prior to development of progressive disease 3.2. untreated brain metastases	There is no evidence from the PAPILLON trial to support a benefit of amivantamab plus CP treatment in patients with untreated brain metastases and patients who received prior systemic treatment for locally advanced or metastatic 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 CP if they completed adjuvant or neoadjuvant therapies at least 6 months before developing progressive disease.
Discontinuation		
4. Treatment with amivantamab plus CP 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 v1.1) 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 CP should be continued until clinically meaningful progression occurs, based on the judgment of the treating clinician.
Prescribing		
5. Amivantamab plus CP should be prescribed by clinicians with expertise in treating NSCLC.	This is meant to ensure that amivantamab plus CP 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	The PAPILLON trial provided evidence on amivantamab in combination with carboplatin and pemetrexed. pERC did not review evidence supporting the efficacy	Cisplatin may be used instead of carboplatin at the discretion of the treating clinician.

Reimbursement condition	Reason	Implementation guidance
chemotherapy (i.e., carboplatin and pemetrexed).	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 CP when initiated in combination with additional anticancer drugs or when either component is initially used as monotherapy.	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 CP is $233,922 per QALY gained when compared with CHT alone. A price reduction of 83% would be required for amivantamab plus CP to achieve an ICER of $50,000 per QALY compared to CHT alone.	—
Feasibility of adoption		
8. The feasibility of adoption of amivantamab plus CP 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).	—

CHT = platinum-based chemotherapy (comprising 70% carboplatin plus pemetrexed and 30% cisplatin plus pemetrexed); CP = carboplatin and pemetrexed; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; 20ins = 20 insertions; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; NSCLC = non–small cell lung cancer; RECIST = Response Evaluation Criteria in Solid Tumors; QALY = quality adjusted life year; TKI = tyrosine kinase inhibitors.

Discussion Points

- **Significant unmet need:** pERC deliberated on amivantamab plus CP 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* Exon 20ins mutations is an aggressive and life-threatening disease with OS among the worst for lung cancer patients. Exon 20ins NSCLC is considered a rare condition and currently there is no access to Exon 20ins - targeted treatment options. Patients with *EGFR* Exon 20ins 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 CP 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 CP and 6.7 months with CP 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 CP may have a benefit in OS compared with CP alone. The evidence was of low certainty based on GRADE assessment. Uncertainty in the OS results stemmed from immature OS data (33.3% [70/210 events] of the information fraction planned for the final analysis), a large number of patients (41.9%) who crossed over from the CP 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 (AEs) were more common in patients treated with amivantamab plus CP, mainly neutropenia, gastrointestinal disorders, and infections and infestations. According to the GRADE assessment, amivantamab plus CP likely results in an increase in rash and infusion-related reactions when compared to CP 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 AEs was expected in the amivantamab plus CP 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 CP 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* Exon 20ins NSCLC. However, the committee heard from the clinical experts that patients with *EGFR* Exon 20ins 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 non-randomized study using individual patient level data from PAPILLON and real-world evidence (RWE) cohorts to compare amivantamab CP versus *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 CP compared with *EGFR* TKIs and immunotherapy plus chemotherapy.
- **Testing procedure:** pERC discussed the requirement of testing for *EGFR* Exon 20ins mutations when determining eligibility for amivantamab. Testing for *EGFR* Exon 20ins 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 Canadians 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 Canadian patients with advanced (Stage IV) NSCLC is only 3%. Goals of treatment for advanced NSCLC include delaying progression, prolonging survival, palliation of symptoms, and improving quality of life (QoL). *EGFR* Exon 20ins is a rare mutation that is associated with aggressive, highly symptomatic disease and significant clinical burden. Multiple studies have found that patients with *EGFR* Exon 20ins-positive NSCLC are typically female, non-smokers and diagnosed with metastatic disease at approximately 60 years old. In Canada, it has been estimated that *EGFR* exon 20ins 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 (Exon 20ins mutations are more prevalent in those with East Asian ethnicity).

Currently, there are no approved targeted therapies for patients with Exon 20ins 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* Exon 20ins 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* Exon 20ins mutations. Amivantamab is a bispecific antibody that binds to both the *EGFR* and MET receptor. The recommended dose for amivantamab is a once weekly intravenous (IV) infusion, at a dose of 1400 mg (1750 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 RCT in adult patients with treatment naïve *EGFR* Exon 20ins mutated locally advanced or metastatic NSCLC; and 1 non-randomized study using individual patient level data from PAPILLON and real-world evidence (RWE) cohorts to compare amivantamab CP versus *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 (LHF)
- 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, LCC - Medical Advisory Committee (MAC) and 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 LHF. Nine patients with NSCLC provided inputs through virtual interviews by LCC and CCSN. Among them, 7 patients were from Canada, 1 from the United States, and 1 from the United Kingdom. All data were collected between May and July in 2024. Based on the input, patients with Exon 20ins 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 the *EGFR*-positive Exon 20ins mutated NSCLC. According to the patient group input, improved management of disease symptoms,

quality of life, 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 quality of life 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 Exon 20ins mutation.
- The clinical experts noted that response would be determined by serial physical/symptom assessments and imaging assessments, typically with CT scans every 8 to 12 weeks on 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 CP should be used in the first line setting and clinicians from the OH - CCO Lung Cancer Drug Advisory Committee indicated that amivantamab plus CP can replace pembrolizumab or ipilimumab and/or nivolumab. All clinicians agreed that patients with *EGFR* Exon 20ins mutations are best suited for treatment with amivantamab plus CP. 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 centers, 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 1st line treatments for patients with *EGFR* Exon 20ins 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.

Implementation issues	Response
Considerations for initiation of therapy	
The trial protocol specified non-squamous NSCLC and 99% of patients had adenocarcinoma. • Please confirm the histological types of NSCLC that would be eligible for 1st line combination with amivantamab?	The PAPILLON trial excluded patients with squamous NSCLC. pERC agreed with the clinical experts that patients with non-squamous histology should be eligible for first line combination with amivantamab. In the absence of evidence for amivantamab plus CP 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 prior. • If prior adjuvant/neoadjuvant treatment was given, what is the minimum disease-free interval in order to be eligible for 1st line combination with amivantamab?	pERC agreed with the clinical experts that is would be reasonable for patients to be eligible for first-line treatment with amivantamab plus CP 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 ECOG 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 1st line combination with amivantamab? • Should patients with CNS disease be eligible for 1st line combination with amivantamab as outlined in inclusion criteria for PAPILLON?	The clinical experts felt that patients who are ECOG 2 should be eligible for amivantamab plus CP, 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 who are ECOG 2, and that the evidence does not suggest a concerning increase in harms when adding amivantamab to platinum doublet. 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 was deriving continued clinical benefit. • What discontinuation criteria should be used for 1st line combination with amivantamab in clinical practice?	pERC agreed with the clinical experts that patients who experience unacceptable toxicity despite appropriate supportive care/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/pharmacy preparations to each treatment cycle versus comparators. Greater than or equal to 80 kg: 1750 mg weekly x 4 weeks, then 2100 mg once every three 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: 1400 mg weekly x 4 weeks, then 1750 mg once every three 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 1400 mg and	This was a comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
1750 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.	
The PAPILLON trial used chemotherapy for up to 4 cycles in combination with amivantamab. • Should there be intolerance to chemotherapy prior to completion of 4 cycles, can amivantamab be continued as monotherapy?	pERC agreed with the clinical experts that if there is intolerance to chemotherapy prior to 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 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, 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 CP if they previously had a documented lack of response to an *EGFR* TKI; these drugs have a different mechanism of action than amivantamab. The clinical experts anticipated that most patients would receive chemotherapy (single agent docetaxel) as subsequent treatment.
Care provision issues	
Available as 350 mg vials. Recommended doses and dose adjustments correspond to available vial size and should minimize wastage. 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/IV antibiotics, oral steroids).	This was a comment from the drug programs to inform pERC deliberations
Timely confirmation of *EGFR* Exon 20ins mutation is needed to confirm eligibility. • What method of testing should be used for detection of *EGFR* Exon 20ins mutations?	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 Exon 20ins mutation status has been confirmed, to switch to

Implementation issues	Response
• In the event the patient has already started alternate systemic therapy before the Exon 20ins mutation results are available, can the patient be switched to amivantamab-carboplatin-pemetrexed?	amivantamab plus CP 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 = Canadian Drug Agency; CNS = central nervous system; CP = carboplatin and pemetrexed; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non–small cell lung cancer; TKI = tyrosine kinase inhibitors

Clinical Evidence

Systematic Review

Description of Study

The PAPILLON study is an ongoing, phase 3, multi-centre open-label trial conducted in 131 centres across 25 countries, including 3 study sites in Canada. Patients were ≥ 18 years of age with treatment naïve *EGFR* Exon 20ins mutated locally advanced or metastatic NSCLC. The primary objective of the study was to assess the efficacy of amivantamab plus CP compared with CP in the first line treatment of patients with *EGFR* Exon 20ins mutated NSCLC. A total of 308 patients were randomized 1:1 to either the amivantamab plus CP or CP arm, from December 2020 to November 2022. The clinical cutoff 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 treatment visit (approximately 30 days after discontinuation of study treatment), and patients continued treatment until documented radiographic disease progression. Eligible patients in the CP 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 PAPILLON were 60 years of age, on average, and 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 CP and CP 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 cutoff 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 CP arm: 84, CP arm: 132). A treatment effect favouring amivantamab plus CP was observed with a HR of 0.395 (95% CI: 0.296, 0.528; p<0.0001). The median PFS by BICR in the amivantamab plus CP arm was 11.37 months (95% CI, 9.79 to 13.70) compared with the CP arm (6.70 months; 95% CI, 5.59 to 7.33). Pre-planned sensitivity analyses evaluating PFS as assessed by the treating investigator as well as a non-stratified analysis were consistent with the primary analysis. At the 6-month time point, the absolute difference in PFS rates between amivantamab plus CP and CP 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 CP group and 2 in the CP group) remaining at risk.

Overall Survival

As of the data cutoff in May 2023, there were a total of 70 death events reported across both groups (amivantamab plus CP arm: 28 deaths, CP arm: 42 deaths). At this point, 65 patients from the CP group had crossed over to amivantamab monotherapy, and the HR was 0.675 *(*95% CI: 0.418, 1.090*),* P = 0.106. Median OS in the amivantamab plus CP arm was not estimable, and the median

OS in the CP arm was 24.38 (95% CI: 22.08, NE) 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 CP and CP 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 CP group and 6 in the CP group) who remained at risk. The sponsor also conducted sensitivity analyses to adjust for patients who crossed over to amivantamab monotherapy from CP; inverse probability of censoring weighting (IPCW) (Adjusted HR of [redacted] two-stage estimation (TSE) (Adjusted HR of [redacted]) and rank preserving structural failure time (RPSFT) (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 CP arm (111 patients [73%]), compared with the CP arm (72 patients [47.4%]) at the data cutoff for an OR of [redacted]), favouring amivantamab plus CP. The absolute difference between groups was [redacted]. The percentage of patients with progressive disease as the best response in the amivantamab plus CP arm was [redacted] compared with [redacted] in the CP 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 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 CP group and [redacted] in the CP group. The mean difference between amivantamab plus CP and CP groups for change from baseline to 12 months was [redacted]).

Progression-free Survival After First Subsequent Therapy

At the data cutoff, there were [redacted] of 153 patients ([redacted] in the amivantamab plus CP group and [redacted] of 155 patients in the CP group ([redacted] who had a PFS2 event. 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 NE (95% CI, 22.77 to NE) in the amivantamab plus CP arm and 17.25 months (95% CI, 13.96 to 21.52) in the CP arm.

Harms Results

Adverse events

Overall, all 151 patients (100%) in the amivantamab plus CP group and 152 (98.1%) patients in the CP group experienced at least one AE. The most common AE was rash, which occurred in 81 (53.6%) patients in the amivantamab plus CP group and 12 (7.7%) patients in the CP group. Other common AEs where there were large differences between groups included dermatitis acneiform, in 47 (31.1%) patients in the amivantamab plus CP group and 5 (3.2%) patients in the CP group, hypoalbuminemia, in 62 (41.1%) patients in the amivantamab plus CP group and 15 (9.7%) patients in the CP group, peripheral edema, in 45 (29.8%) patients in the amivantamab plus CP and 16 (10.3%) in the CP group, and infusion-related reaction, in 63 (41.7%) patients in the amivantamab plus CP and 2 (1.3%) patients in the CP group.

Serious Adverse Events

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

Withdrawals Due to Adverse Events

Overall, from study initiation through the data cutoff, 36 (23.8%) patients in the amivantamab plus CP arm and 16 (10.3%) patients in the CP arm had TEAEs leading to discontinuation of at least 1 study treatment. Of the 36 patients in the amivantamab plus CP 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 CP arm. Most of the TEAEs leading to study treatment discontinuation occurred at a frequency of less than 2% in both treatment arms.

Mortality

There were 4 (2.6%) patients in the amivantamab plus CP group and 9 (5.8%) patients in the CP group who died due to an AE during the study and 3 (2.0%) patients in the amivantamab plus CP group and 4 (2.6%) patients in the CP 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 noted above, rash was the most common AE, occurring in 81 (53.6%) patients in the amivantamab plus CP group and 12 (7.7%) patients in the CP group. There were [redacted] patients in the amivantamab plus CP group and [redacted] patients in the CP group with an event identified as skin and subcutaneous disorders. Infusion-related reactions were reported in 63 (41.7%) patients in the amivantamab plus CP group and 2 (1.3%) patients in the CP 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 CP 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 CP in Canada; although they would likely consider expanding the population to ECOG 2 performance status, rather than limiting to ECOG 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, 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 CP Versus CP for Patients With NSCLC with EGFR Exon 20ins

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			CP	Amivantamab plus CP	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 CP results in a clinically important improvement in the probability of being progression free compared to CP alone.
Probability of being progression free at 12 months	308 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	High[a]	Amivantamab plus CP results in a clinically important improvement in the probability of being progression free compared to CP alone.
Probability of being progression free at 18 months	308 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	High[a]	Amivantamab plus CP likely results in a clinically important improvement in the probability of being progression free compared to CP 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 CP may result in a clinically important improvement in the probability of being alive compared to CP alone.
Probability of being alive at 18 months	308 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Low[b]	Amivantamab plus CP may result in a clinically important improvement in the probability of being alive compared to CP alone.
Probability of being alive at 24 months	308 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Low[b]	Amivantamab plus CP may result in a clinically important improvement in the probability of being alive compared to CP alone.
ORR (median follow-up of 14.9 months [range 0.3 to 27.0])							
ORR by BICR Follow-up: Data cutoff	304 (1 RCT)	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[c]	Amivantamab plus CP likely results in an improvement in ORR compared to CP alone.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			CP	Amivantamab plus CP	Difference		
							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 CP may result in little-to-no difference in HRQoL compared to CP alone.
Notable Harms							
Rash[e] Follow-up: to data cutoff	308 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[f]	Amivantamab combined with CP likely results in an increase in rash compared to CP alone. The clinical significance of the rash is unknown
Infusion-related reaction Follow-up: to data cutoff	308 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[f]	Amivantamab combined with CP likely results in an increase in infusion-related reactions compared to CP alone. The clinical significance of the infusion-related reactions is unknown.

BICR = Blinded Independent Central Review; CI = confidence interval; CP = carboplatin-pemetrexed chemotherapy; EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EGFR Exon 20ins = epidermal growth factor receptor Exon 20 insertions; NA=not applicable; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RCT = randomized controlled trial

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.

Note: * Cycle 17 day 1 and cycle 25 day 1 were selected to correspond 12- and 18-month timepoints respectively; ** 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.

Note: 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 confidence interval 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 cross-over of patients from the CP group to amivantamab monotherapy post-progression. 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 (a) lack of blinding and a subjective outcome, (b) 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: Details included in the table are from the sponsor's Summary of Clinical Evidence.[31] Source: Data Request of the Sponsor, and the Clinical Study Report for PAPILLON

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 non-randomized study and is reported in the Studies Addressing Gaps 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 non-randomized study, as it utilized individual patient data for each arm in the comparison.

Description of the Non-randomized Study

The sponsor performed a non-randomized study using IPTW. These analyses used individual patient data from PAPILLON for amivantamab plus CP 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 (TTNT).

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 Asian race, history of smoking, sex, and history of other metastases.

For the PAPILLON trial versus *EGFR* TKI comparison, prior to weighting, moderate differences (absolute 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, Asian race, sex, and history of other metastases. In the primary analysis, base case average treatment effect in the treated (ATT) weighting balanced (SMD[redacted]) all four covariates between cohorts. In the full model however, 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, history of other metastases), and substantial differences observed for the remaining two factors (history of brain metastases, Asian race). The resulting effect sample size (ESS) 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, prior to weighting, substantial (absolute SMD [redacted]) differences were observed for ECOG performance status at index date, history of liver metastases, history of brain metastases, age, Asian race, 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 two remaining factors (ECOG performance status at index date, age). The balance between populations in the full model on the other hand, remained the same (6/8 factors balanced) following weighting, although moderate differences were observed for three factors (ECOG performance status at index date, history of brain metastases, history of smoking) and substantial differences observed for the remaining three factors (history of liver metastases, Asian race, history of other metastases). The resulting ESS 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 a HR of [redacted] in favour of amivantamab plus CP. The primary analysis, using base case ATT weighting, produced results in favour of amivantamab plus CP, with an HR of [redacted]). The unadjusted comparison of OS for PAPILLON versus platinum plus immunotherapy, produced a HR of [redacted]) in favour of amivantamab plus CP. The primary analysis, using base case ATT weighting, produced a point estimate favouring amivantamab plus CP 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 a HR of [redacted] the point estimate favoured amivantamab plus CP 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 CP. The primary analysis, using base case ATT weighting, produced results in favour of amivantamab plus CP, with an HR of [redacted]).

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

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

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

Harms Results

Harms were not assessed in the non-randomized studies.

Critical Appraisal

There was no pre-defined 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 standardized mean differences, 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 ESSs were very small in the base case and in several of the full model analyses, for example the ESS 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

Table 4: Cost and Cost-Effectiveness

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* Exon 20ins mutations receiving first-line treatment.
Treatment	Amivantamab plus CP
Dose regimen	Amivantamab (RYBREVANT®), 1,400 mg (1,750 mg if body weight is ≥ 80 kg) by intravenous (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 Day 1 of each 21-day cycle, starting with Cycle 3. Administer with carboplatin (target AUC 5 maximum dose 750 mg for carboplatin for 4 cycles) and pemetrexed (500 mg/m2 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 CP was $116,093 in year 1 and $49,295 afterwards, as calculated by the sponsor (accounting for discontinuation, dose reductions and dose skipping).
Comparators	• CHT alone (comprising 70% carboplatin plus pemetrexed and 30% cisplatin plus pemetrexed) • *EGFR* TKIs (comprising 85% afatinib, 5% erlotinib, and 10% gefitinib) • IOs plus CHT (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
Key limitations	• The OS extrapolations for amivantamab plus CP and CHT alone are uncertain and clinically implausible based on feedback from clinical experts consulted. • The comparative clinical efficacy of amivantamab plus CP versus *EGFR* TKIs and IOs plus CHT is highly uncertain due to the absence of head-to-head clinical trials. The non-randomized 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 CHT are more effective than CHT alone, which remains the standard of care in Canadian clinical practice). • The modelled comparators do not reflect Canadian clinical practice. Clinical expert feedback obtained by CDA-AMC noted the lack of efficacy associated with *EGFR* TKIs in general for the treatment of patients with Exon 20ins mutations. Additionally, osimertinib, the only EGFR TKI that would potentially be considered in Canadian clinical practice for a minority of patients (due to better tolerance) was not included among the *EGFR* TKIs options. Moreover, access to IOs (pembrolizumab) plus CHT is limited due to a lack of Health Canada approval for patients with *EGFR* mutation and limited funding (i.e. restricted benefit in several participating drug plans).

Component	Description
	• 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 CP experienced nearly 9 years of additional survival relative to CHT).
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by adopting a Gompertz distribution to extrapolate OS for amivantamab plus CP. 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 CP is associated with incremental costs of $193,368 and an incremental QALY gain of 0.83 versus CHT alone, resulting in an ICER of $233,922 per QALY gained. A price reduction of 83% for amivantamab would be required for amivantamab plus CP 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 cross-over adjustment in the trial for OS, ICERs ranged from $245,355 to $308,627 per QALY gained compared to CHT alone. In this latter scenario, a price reduction of 88% for amivantamab would be required for amivantamab plus CP to be considered cost-effective at a WTP threshold of $50,000 per QALY gained.

AUC = area under the curve; CHT = platinum-based chemotherapy; CP = carboplatin plus pemetrexed; EGFR = epidermal growth factor receptor; ICER = incremental cost-effectiveness ratio; IOs = immune-oncology agents; IV = intravenous; LY = life-year; QALY = quality-adjusted life-year, TKIs = tyrosine kinase inhibitors; WTP = willingness-to-pay; RPSFT = rank-preserving structural failure time; PSM = partitioned survival model.

Budget Impact

CDA-AMC identified key limitations with the sponsor's analysis: the market uptake of amivantamab plus CP was underestimated, and the use of immune-oncology agents plus CHT 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 CP, 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 CP for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with activating *EGFR* Exon 20ins mutations was $9,490,208 in Year 1, $11,418,486 in Year 2, and $11,649,162 in Year 3, for a three-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 CP's estimated three-year budget impact to $65,906,562, demonstrating that the budget impact of amivantamab plus CP 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 Villneuve, and Danica Wasney.

Meeting date: November 13, 2024

Regrets:

None

Conflicts of interest:

None