

5.04 AMIVANTAMAB, Solution concentrate for I.V. infusion 350 mg in 7 mL, Rybrevant[®], Janssen-Cilag Pty Ltd.

1 Purpose of submission

- 1.1 The Category 1 submission requested Section 100 (Efficient Funding of Chemotherapy Program) Authority Required (Telephone/Online) listing for amivantamab for the treatment of patients with epidermal growth factor receptor (*EGFR*) exon 20 insertion (ex20ins) mutation positive treatment naïve (first-line) locally advanced or metastatic non-small cell lung cancer (NSCLC), used in combination with platinum-based chemotherapy (PBC).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis of amivantamab plus carboplatin and pemetrexed (ACP) versus carboplatin and pemetrexed (CP) alone. CP was the PBC used in the clinical trial evidence and was used to represent PBC in this submission.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with treatment naïve, locally advanced or metastatic NSCLC with evidence of <i>EGFR</i> ex20ins mutation.
Intervention	Amivantamab IV infusion in combination with PBC every 3 weeks for up to 6 cycles followed by amivantamab IV infusion and pemetrexed IV infusion every 3 weeks until disease progression.
Comparator	PBC (represented in the clinical trial evidence by carboplatin and pemetrexed)
Outcomes	PFS, OS, ORR, DoR, TTST, PFS2, HRQoL and safety
Clinical claim	In patients with treatment naïve, locally advanced or metastatic NSCLC with evidence of <i>EGFR</i> ex20ins mutation, amivantamab in combination with PBC for up to 6 cycles followed by amivantamab and pemetrexed until disease progression, is superior in effectiveness and inferior but manageable in safety compared with PBC.

Source: Table 1.1, p18 of the submission

Abbreviations: DoR, duration of response; *EGFR*, epidermal growth factor receptor; ex20ins, exon 20 insertion; HRQoL, health related quality of life; IV, intravenous; NSCLC, non-small cell lung cancer; OS, overall survival; ORR, objective response rate; PBC, platinum-based chemotherapy; PFS, progression free survival; PFS2, PFS after first subsequent therapy; TTST, time to subsequent therapy.

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** not registered. The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration the Delegate's Overview was available.
- 2.2 The proposed indication for amivantamab in combination with platinum-based chemotherapy is for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating *EGFR* exon 20 insertion mutations.

- 2.3 The Delegate was inclined to approve registration. The Delegate considered that based on the PAPILLON clinical trial the addition of amivantamab to first-line chemotherapy in ex20ins EGFRm NSCLC increased progression-free survival (PFS) and objective response rate (ORR). The Delegate also considered that the immature overall survival (OS) data from PAPILLON trial were of limited interpretability but were not suggestive of a detriment. The Delegate advised that final survival analysis should be required as a condition of registration.
- 2.4 Amivantamab also has provisional approval for the treatment of patients with locally advanced or metastatic NSCLC that has an activating *EGFR* exon 20 insertion mutation, whose disease has progressed on or after PBC. The Delegate considered the results of PAPILLON were adequate to confirm the clinical benefit of amivantamab for the later-line treatment, after disease progression on (or after) platinum-based chemotherapy, such that this usage was considered appropriate for full registration.

Previous PBAC consideration

- 2.5 The PBAC previously considered mobocertinib at the November 2022 and July 2023 PBAC meetings for the treatment of adults with *EGFR* ex20ins positive locally advanced or metastatic NSCLC who have received PBC (i.e., second-line treatment). Mobocertinib was recommended at the July 2023 meeting, however, the submission stated it did not proceed with listing due to the deregistration of mobocertinib.

3 Requested listing

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount	№.of Rpts
AMIVANTAMAB Solution for infusion, 350 mg/vial	Published price: Public: \$8,994.13 Private: \$9,163.46 Effective price: Public: \$■■■■ Private: \$■■■■	2,100 mg (6 vials)	5 initial 7 continuing
Available brands			
Rybrevant® (amivantamab 350 mg injection, 1 vial)			

Category / Program: Section 100 – Efficient Funding of Chemotherapy
Prescriber type: Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Administrative Advice: No increase in the maximum quantity may be authorised. No increase in the maximum number of repeats may be authorised.
Indication: Stage III B/C locally advanced or Stage IV metastatic NSCLC
Treatment Phase: Initial PBS subsidised treatment
Clinical criteria: Patient must have evidence in tumour material of an activating epidermal growth factor receptor (<i>EGFR</i>) exon20 insertion mutation
AND Patient must not have received systemic therapy for this condition in the metastatic setting prior to initiation of this drug

AND
The treatment must be initiated with platinum-based chemotherapy
AND
The patient must have a WHO performance status of 2 or less prior to initiation with this drug for this condition
Administrative Advice:
A patient may only qualify for PBS-subsidised treatment under this restriction once. Following completion of the initial PBS-subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.
A maximum quantity of a weight-based dose of up to six vials (of 350 mg) is authorised for each administration of amivantamab. The prescriber should specify the number of vials (of 350 mg) required to make up the total dose of amivantamab for each administration at the time of the application.
Special Pricing Arrangements apply
Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Category / Program: Section 100 – Efficient Funding of Chemotherapy
Prescriber type: Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Administrative Advice:
No increase in the maximum quantity may be authorised. No increase in the maximum number of repeats may be authorised.
Indication: Stage III B/C locally advanced or Stage IV metastatic NSCLC
Treatment Phase: Continuing PBS subsidised treatment
Clinical criteria:
Patient must have previously received treatment with this drug for this condition
AND
Patient must not have developed disease progression while receiving treatment with this drug for this condition
Administrative Advice:
A maximum quantity of a weight-based dose of up to six vials (of 350 mg) is authorised for each administration of amivantamab. The prescriber should specify the number of vials (of 350 mg) required to make up the total dose of amivantamab for each administration at the time of the application.
Special Pricing Arrangements apply
Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

- 3.1 The sponsor requested a special pricing arrangement (SPA). The submission requested a published approved ex-manufacturer price (AEMP) per 350 mg vial of \$1,458.00 (corrected to \$1,484.00 in the pre-subcommittee response [PSCR]) with an effective AEMP of \$.
- 3.2 Patients with Eastern Cooperative Oncology Group (ECOG) status of 2 were excluded from the clinical evidence base, PAPILLON trial, however, were included in the requested listing for amivantamab (WHO performance status of 2 or less). The PBAC noted that there was no clinical data to support the use of amivantamab in patients with ECOG performance status of 2. However, the PBAC considered that the inclusion of patients with a WHO performance status of 2 or less was reasonable and consistent with other targeted NSCLC treatment listings (e.g., tepotinib and gefitinib).
- 3.3 The PAPILLON trial mostly enrolled patients with Stage IV (97.4%) at screening. Therefore, the applicability of the trial data to Stage III B/C patients included in the proposed restriction was uncertain. The PBAC agreed with the ESC that the inclusion

of Stage III B/C patients in the proposed restriction was likely reasonable despite their small representation in the PAPILLION trial, and noted this would be consistent with other recommended PBS listings in NSCLC (i.e. osimertinib Public Summary Document [PSD], July 2020 PBAC Meeting; Soria et al 2018¹).

- 3.4 The submission stated that the sponsor intends to provide access to amivantamab via a patient access program for approximately 20 patients. A grandfathering restriction was proposed in the submission. The PSCR accepted the amended wording proposed by the Secretariat for the initial treatment phase to accommodate access to both new patients who had not been treated with amivantamab before and grandfathered patients.
- 3.5 The submission proposed an administrative advice in the restriction requiring the prescribers to specify the number of vials requested to make up the total dose for each administration, as amivantamab is weight-based (<80 kg or ≥80 kg at baseline). This administrative advice is not needed, as according to medicines listed under EFC, authorised prescribers are required to identify the dose of the chemotherapy drug and for an infusion prescription the number of times that supply of the infusion is to be repeated. They are not required to identify the quantity or number of units of a pharmaceutical benefit to be supplied. Pharmacists upon dispensing the EFC algorithms will be directed on the efficient number of vials of a chemotherapy drug that they can use to make up the final dose. Prescribers are expected to refer to the TGA Product Information (PI) for any information regarding dosing schedule. The PSCR accepted the removal of the proposed administrative advice.
- 3.6 The submission also requested for amivantamab monotherapy to be considered for second-line use (i.e., on or after progression on PBC) using alternative restriction wording that allows patients to receive treatment in the first- or second-line setting. The justification provided for this included: high unmet need in this population, recognising that amivantamab monotherapy is provisionally TGA approved for use (as second-line treatment following disease progression on or after PBC) in this population and is recommended as a second-line treatment option in international treatment guidelines. The clinical criterion stating that a 'patient must not have received systemic therapy for this condition in the metastatic setting prior to initiation of this drug' from the initial treatment restriction is omitted from the proposed alternative restriction. The clinical evidence presented in the submission for the second-line setting were descriptive and based on single-arm studies. This consideration was not included in the economic model but presented in the financial estimates. The first-line population as outlined in the PICO as the primary information provided herein, however summarised evidence for second-line use is also presented. The PBAC considered the clinical evidence presented were adequate to confirm the clinical benefit of amivantamab after disease progression on (or after) PBC. The PBAC

¹ Soria J-C, Ohe Y, Vansteenkiste J, et al. (2018). Osimertinib in untreated *EGFR*-mutated advanced non-small-cell lung cancer. *N Engl J Med*; 378: 113-25.

also noted the high unmet need for this patient population and that the TGA Delegate was inclined to approve this indication for full registration (see paragraph 2.4). The PBAC therefore agreed with ESC and were supportive of a listing that allows access in the first-line (treatment naïve) and second line (i.e. on or after progression on PBC) treatment setting.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Lung cancer is the fifth most commonly diagnosed cancer in Australia, with an estimated 14,782 people diagnosed in 2023.² It is the most common cause of cancer-related death, with a 5-year survival of 24%. *EGFR* mutations are the most common type of mutation in NSCLC, with approximately 30% of NSCLC patients carrying *EGFR* mutations.³ Among these patients, approximately 4–15% of patients have *EGFR* ex20ins mutations, making it less common than *EGFR* exon 19 deletion (ex19del) mutations (46%) and *EGFR* L858R point mutation (38%).^{4,5,6} Patients with *EGFR* 20ins mutations have poorer prognosis and outcomes compared to patients with more common forms of *EGFR* mutations.
- 4.2 Consistent with the patient population in the PAPILLON pivotal study, the proposed position of amivantamab in combination with PBC is in the *EGFR* ex20ins mutation positive treatment-naïve (first-line) locally advanced or metastatic NSCLC setting.
- 4.3 The National Comprehensive Cancer Network (NCCN) clinical NSCLC guidelines were recently updated to recommend ACP as the preferred first-line treatment option for patients with advanced or metastatic non-squamous *EGFR* exon 20 insertion mutation-positive NSCLC,⁷ while the European Society for Medical Oncology (ESMO) clinical guidelines suggest PBC as first-line treatment.⁸ The submission noted that the ESMO guidelines were published prior to the PAPILLON trial results.
- 4.4 Amivantamab is a fully human, immunoglobulin G1 (IgG1) bispecific antibody with high affinity for both *EGFR* and mesenchymal-epidermal transition (MET) receptors. These characteristics bypass resistance to tyrosine kinase inhibitors (TKIs) and have

² Australian Institute of Health and Welfare, (2023), 'Cancer data in Australia', retrieved from <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/summary>

³ Jordan et al, (2017), 'Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies', *Cancer discovery* 7.6: 596-609.

⁴ Lea et al, (2021), '*EGFR* Exon 20 Insertion Mutations: Clinicopathological Characteristics and Treatment Outcomes in Advanced Non-Small Cell Lung Cancer', *Clinical lung cancer* 22.6: e859-e869.

⁵ Arcila et al, (2013), '*EGFR* exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics', *Molecular cancer therapeutics* 12.2: 220-229.

⁶ Gazdar, (2009), 'Activating and resistance mutations of *EGFR* in non-small-cell lung cancer: role in clinical response to *EGFR* tyrosine kinase inhibitors', *Oncogene* 28.1: S24-S31.

⁷ Riely et al. "Non-Small Cell Lung Cancer, Version 4.2024, NCCN Clinical Practice Guidelines in Oncology." *Journal of the National Comprehensive Cancer Network* 22.4 (2024): 249-274.

⁸ Hendriks et al, (2023), 'Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up', *Annals of Oncology*, 34.4 (2023): 339-357

immune cell directing activity conferring a potential treatment advantage over other *EGFR* therapies in those with co-mutations. *EGFR* ex20ins mutations have been found to be resistant to TKIs and have been shown to have limited treatment benefit with immunotherapies.^{9,10}

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The proposed comparator was PBC. The main reasons provided by the submission in support of this were that prior to the availability of amivantamab, PBC was the recommended first-line treatment in patients with *EGFR* ex20ins-positive NSCLC to whom TKIs and immunotherapies confer limited treatment benefit.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (14), health care professionals (2) and organisations (4) via the Consumer Comments facility on the PBS website.
- 6.3 The PBAC noted the advice received from the Rare Cancers Australia, Lung Foundation Australia and the International Cancer Advocacy Network's Exon 20 Group supported the PBS listing of amivantamab for the treatment of patients with *EGFR* ex20ins mutation positive locally advanced or metastatic NSCLC.
- 6.4 The organisations noted that patients with *EGFR* ex20ins mutation positive NSCLC currently face particularly low survival rates and have limited treatment options, creating a significant burden for patients and their carers and relatives. The organisations noted that amivantamab was associated with increased PFS, as shown in the PAPHILLON trial, and considered this to be a clinically meaningful benefit for patients with this uncommon and often refractory form of NSCLC. The organisations noted that amivantamab was associated with adverse side effects, including fatigue and rash, however considered these to be manageable with few patients discontinuing treatment due to adverse events. The organisations also highlighted the substantial financial pressures experienced by patients with NSCLC, pointing out that patients often face reduced income due to an inability to work, coupled with the cost

⁹ Girard et al. "Comparative clinical outcomes between *EGFR* ex20ins and wildtype NSCLC treated with immune checkpoint inhibitors." *Clinical lung cancer* 23.7 (2022): 571-577.

¹⁰ Ettinger et al, (2024), National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology – Non-small cell lung cancer.

of treatment. The organisations considered the PBS listing of amivantamab would reduce the financial pressures experienced by patients.

- 6.5 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the amivantamab submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the PAPILLON trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for amivantamab in combination with chemotherapy, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement),¹¹ based on a comparison with PBC.
- 6.6 The PBAC noted comments from health care professionals supporting the PBS listing of amivantamab in both the first- and second-line settings. The health care professionals considered that although the OS data remains immature, amivantamab was associated with improved PFS compared with PBC in the PAPILLON trial and considered that this improvement was likely to extend to OS benefits. It was also noted that amivantamab was associated with a high risk of infusion reactions and venous thrombosis requiring prophylactic anticoagulation.
- 6.7 The PBAC noted comments from individuals wanting access to amivantamab described experiencing several side effects from current treatment options that resulted in hospitalisation. In addition to the physical toll, individuals described the significant emotional and psychological challenges associated with having a form of NSCLC with limited treatment options. The individuals considered amivantamab would likely extend and improve their quality of life. However, the individuals considered the current cost of amivantamab was a significant barrier to treatment.
- 6.8 The comments from carers noted the side effects experienced included rashes and diarrhoea which were controlled effectively through medication. The comments from other interested individuals noted that many people are diagnosed between the ages of 40 and 60 years while raising children and considered that amivantamab had the potential to extend the duration and quality of life of patients, significantly benefiting both them and their families.

Clinical trial

- 6.9 The submission was based on one ongoing head-to-head randomised trial comparing ACP to CP (N=308), the PAPILLON trial.
- 6.10 Details of the trial presented in the submission are provided in Table 2.

¹¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
PAPILLON NCT04538664	A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared with Carboplatin-Pemetrexed, in Patients with <i>EGFR</i> Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer - PAPILLON.	Clinical Study Report (Primary Analysis) September 2023
	A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared with Carboplatin-Pemetrexed, in Patients with <i>EGFR</i> Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer – PAPILLON.	Clinical Study Report (Crossover Phase) September 2023
	Zhou et al. Amivantamab plus Chemotherapy in NSCLC with <i>EGFR</i> Exon 20 Insertions.	<i>NEJM</i> 2023; 30;389(22):2039-2051.

Source: Table 2.4, p53 of the submission

Abbreviations: NSCLC, non-small cell lung cancer; *EGFR*, epidermal growth factor receptor tyrosine kinase; Exon 20ins, exon-20 insertion mutations.

6.11 The key features of the direct randomised trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
ACP vs CP						
PAPILLON	308	R, OL, MC 14.9 months (median)	Some concerns ^a	Treatment-naïve with locally-advanced or metastatic NSCLC and <i>EGFR</i> ex20ins	Primary: PFS Secondary: OS, ORR, DoR, TTST, PFS2, TTSP, HRQoL	PFS, OS, HRQoL

Source: Table 2.5, p56 of the submission

Abbreviations: DoR, duration of response; *EGFR*, epidermal growth factor receptor; ex20ins, exon 20 insertion; HRQoL, health related quality of life; MC, multi-centre; NSCLC, non-small cell lung cancer; OL, open label; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression free survival after first subsequent therapy; R, randomised; TTSP, time to symptomatic progression; TTST, time to subsequent therapy

^a This was revised from low (as presented in the submission) to some concerns during the evaluation due to introduction of bias relating to the treatment switching and high levels of censoring.

6.12 Evidence presented in the submission was based on a data cutoff date of 3 May 2023 (median duration of follow-up of 14.9 months) with 46% of patients in the ACP arm and 15% of patients in the CP arm still receiving treatment. The final analysis is expected at the end of 2025 and no further interim analyses are planned. At the time of data cutoff, median OS for the ACP arm was not yet known.

6.13 Patients in the CP arm were given the option to enter a crossover phase after blinded independent central review (BICR) confirmed progression where participants received amivantamab monotherapy in a 21-day cycle. The crossover phase was neither randomised nor controlled, and all disease assessments were investigator-assessed. 65 patients (42%) from the CP arm crossed over to amivantamab monotherapy following disease progression. There is significant potential for bias in data generated after crossover. Crossover limits the rigor of longer term follow up comparisons of OS outcomes between the CP and ACP groups. The Pre-PBAC Response acknowledged

the potential for bias in the data after cross-over, however highlighted that the cross-over biases against ACP rather than CP.

- 6.14 Results from the crossover phase (alongside data from a Phase I, single-arm study, CHRYSALIS) were included in the submission to support the request for amivantamab as second-line therapy (alternative PBS listing, paragraph 3.6). CHRYSALIS is a phase I, open-label, dose-escalation, and dose-expansion study, which included a post-platinum population with *EGFR* exon20ins NSCLC. The dose regimen of amivantamab monotherapy during the crossover phase of the PAPILLON trial differed from the draft Product Information (PI) dosing for amivantamab monotherapy (1050 mg for <80 kg or 1400 mg for ≥80 kg, every 2 weeks from week 5, based on the CHRYSALIS study).
- 6.15 The overall risk of bias associated with the PAPILLON trial was rated by the evaluation as prompting ‘some concerns’ because:
- Although the crossover phase was consistent with the trial protocol, allowing patients to switch treatments introduces possible selection effects in comparing longer term outcomes between the CP and ACP groups.
 - The open-label nature (non-blinding of study participants and treating clinicians) of the PAPILLON trial may have introduced performance and detection biases. All outcomes were investigator-assessed apart from PFS and ORR which were assessed by BICR.
 - The results presented in the submission were based on a data cutoff that was planned for the primary outcome (PFS) analysis. The evaluation considered that the assessment of secondary outcomes appeared premature, as evidenced by the failure to reach median OS within the 14.9 months follow up period leading to high levels of censoring (OS: 81.7% in ACP and 72.9% in CP). High levels of censoring could lead to bias if the participants censored are different from those who remain in the analysis.
 - The higher proportion of patients in the ACP arm discontinuing treatment due to non-progression or death events (10.6% vs 5.8%) and the higher proportion with at least one missing scheduled disease evaluation (7.2% vs 3.9%) compared to the CP arm raises some concerns of attrition bias. Additionally, the incidence of drug-related treatment emergent adverse events (TEAEs) leading to discontinuation was substantially higher in the ACP arm than the CP arm (23.8% vs 10.3%).

Comparative effectiveness

- 6.16 A summary of the efficacy results for PFS, OS and ORR from the full analysis set (FAS) population in PAPILLON at data cutoff date of 3 May 2023 is presented in Table 4.

Table 4: Summary of PFS, OS and ORR outcomes in PAPILLON trial (FAS)

	ACP (N=153)	CP (N=155)
Median follow-up (months)	14.9	
Progression-free survival (BICR)		
Events (progression or death), n (%)	84 (54.9%)	132 (85.2%)
Censored	69 (45.1%) ^e	23 (14.8%) ^e
Median PFS, months (95% CI)	11.37 (9.79, 13.70)	6.70 (5.59, 7.33)
p-value ^a	<0.0001	
Hazard ratio (95% CI) ^b	0.395 (0.296, 0.528)	
Overall survival		
Event (death)	28 (18.3%)	42 (27.1%)
Censored	125 (81.7%)	113 (72.9%)
Median OS, months (95% CI)	NE (NE, NE)	24.38 (22.08, NE)
6-month event-free rate (95% CI)	0.94 (0.89, 0.97)	0.97 (0.92, 0.99)
12-month event-free rate (95% CI)	0.86 (0.79, 0.91)	0.82 (0.74, 0.87)
18-month event-free rate (95% CI)	0.74 (0.64, 0.82)	0.68 (0.58, 0.76)
24-month event-free rate (95% CI)	0.72 (0.61, 0.81)	0.54 (0.37, 0.68)
p-value ^c	0.1056	
Hazard ratio (95% CI) ^b	0.675 (0.418, 1.090)	
Objective response rate (BICR)		
Number of subjects with measurable disease at baseline	152	152
Responders (CR + PR)	111	72
Objective response rate	73.0%	47.4%
p-value ^a	<0.0001	
Odds ratio (95% CI) ^d	2.971 (1.844, 4.787)	
Best Overall Response (n, [%])		
Complete Response (CR)	6 (3.9%)	1 (0.7%)
Partial Response (PR)	105 (69.1%)	71 (46.7%)
Stable Disease (SD)	29 (19.1%)	62 (40.8%)
Progressive Disease (PD)	4 (2.6%)	16 (10.5%)
Not Evaluable (NE)	8 (5.3%)	2 (1.3%)

Source: Tables 2.24 and 2.26, p94 of the submission

Abbreviations: ACP, amivantamab plus carboplatin/ pemetrexed; BICR, blinded independent central review; CI, confidence interval; CP, carboplatin/ pemetrexed; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; n/N, number; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; PFS, progression free survival; PS, performance status.

^a p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

^b Hazard ratio is from stratified (PFS)/unstratified (OS) proportional hazards model. Hazard ratio <1 favours ACP.

^c p-value is from a log-rank test.

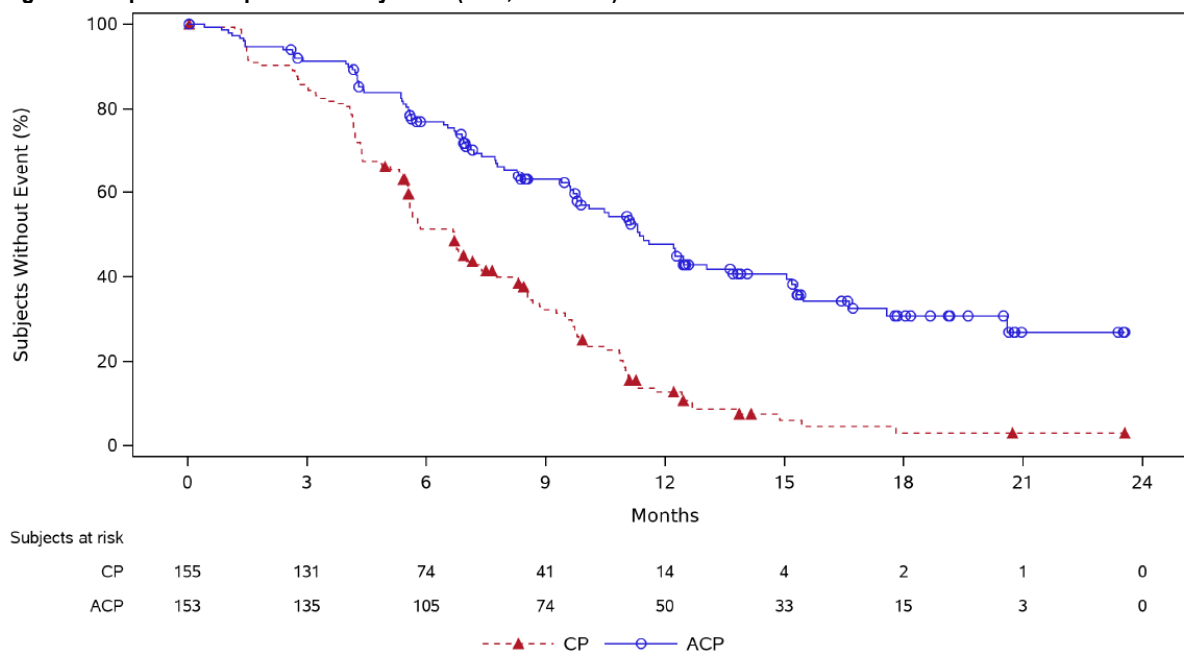
^d Odds ratio >1 favours ACP.

^e 39.2% in ACP arm and 12.9% in CP arm censored due to study cut-off

Bold text indicates statistically significant results.

6.17 The primary outcome for the PAPILLON trial was PFS. After an overall median follow up of 14.9 months, significantly fewer patients in the ACP arm had disease progression or death compared to the CP arm (54.9% in ACP, 85.2% in CP). The median PFS for the ACP and CP arms were 11.37 and 6.70 months, respectively, and this was a statistically significant difference (hazard ratio (HR) 0.395 (95% confidence interval [CI] 0.296, 0.528). The Kaplan Meier (KM) curves for PFS in the PAPILLON trial are presented in Figure 1.

Figure 1: Kaplan-Meier plot of PFS by BICR (FAS, stratified)



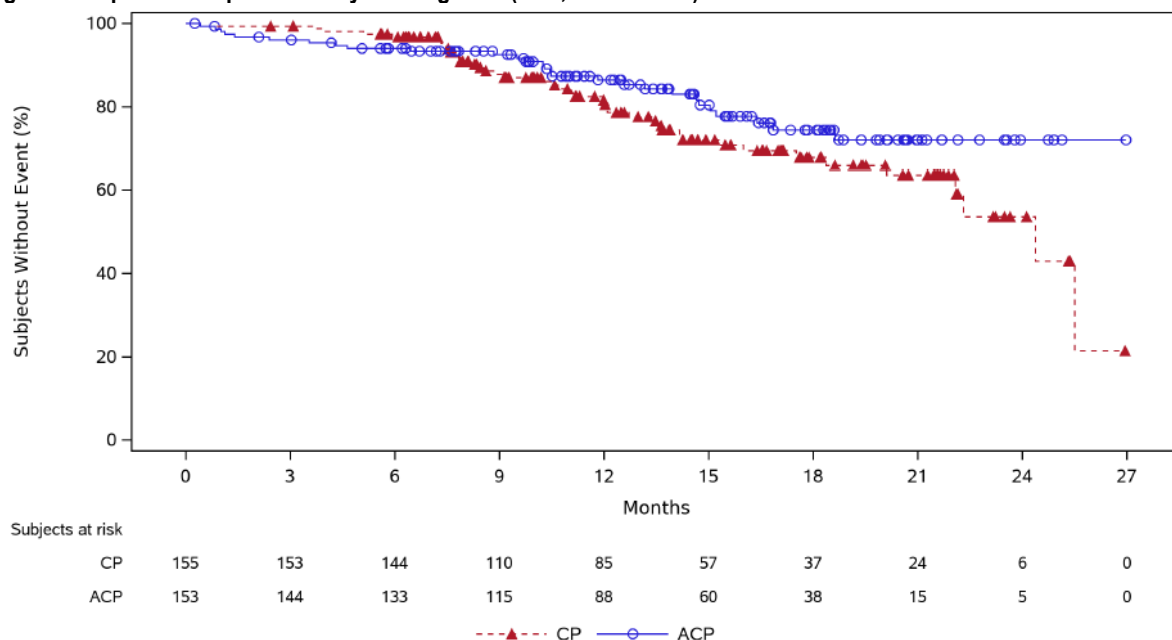
Source: Figure 2.4, p90 of the submission

Abbreviations: ACP, amivantamab plus carboplatin/ pemetrexed; CP, carboplatin/ pemetrexed; BICR, blinded independent central review; FAS, full analysis set; PFS, progression free survival.

6.18 For PFS, the superior treatment effect for ACP over CP was consistent across subgroups, including age, sex, race, weight, history of brain metastasis, ECOG performance status score and history of smoking. Likely due to small sample sizes, HR estimates were not statistically significant among two subgroups: patients age ≥ 75 years (HR=0.59; 95% CI 0.22, 1.58) and history of brain metastasis (HR=0.63; 95% CI 0.38, 1.06), though HR estimates were consistent with the overall effect.

6.19 Secondary outcomes included OS and ORR. At the time of cutoff for data analysis, median OS was not reached in the ACP arm and was 24.4 months in the CP arm. The submission stated that there was a strong trend towards improved survival in the ACP arm (HR=0.676; 95% CI 0.418, 1.090). The KM curves for OS in the PAPILLON trial are presented in Figure 2.

Figure 2: Kaplan-Meier plot of OS by investigators (FAS, unstratified)



Source: Figure 2.7, p94 of the submission

Abbreviations: ACP, amivantamab plus carboplatin/ pemetrexed; CP, carboplatin/ pemetrexed; BICR, blinded independent central review; FAS, full analysis set; OS, overall survival.

- 6.20 Literature demonstrating the correlation between PFS and OS in NSCLC remain mixed. Evidence suggests that the association between these outcomes is weak (low to medium correlation) particularly for metastatic lung cancer.^{12,13} Conversely, among studies that report a surrogate threshold effect (STE), suggested PFS differences of 3.3 months (with a trial size of 250 patients)¹⁴ and 4.2 months¹⁵ are required to predict OS. The reported difference in median PFS of 4.67 months between the ACP and CP arms in the PAPILLON trial is above these STEs.
- 6.21 The submission used three methods to adjust the OS outcome for treatment switching: i) two-stage estimation (TSE), (ii) inverse probability of censoring weight (IPCW) and (iii) rank preserving structural failure time (RPSFT). IPCW and RPSFT were pre-specified in the protocol as supplementary analyses to adjust for confounding from treatment crossover. The ESC noted that pre-specified adjustments were typically more robust compared with post-hoc adjustments.
- 6.22 Each of the approaches applied have their merits and limitations and each method relies on a specific set of assumptions. While the submission described the steps of

¹² Sia et al. "A review of cancer related surrogate outcomes used for PBAC decision making." (2023).

¹³ Blumenthal et al. "Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses." *Journal of Clinical Oncology* 33.9 (2015): 1008-1014.

¹⁴ Johnson et al. "Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis." *The Lancet Oncology* 7.9 (2006): 741-746.

¹⁵ Hashim et al. "Do surrogate endpoints better correlate with overall survival in studies that did not allow for crossover or reported balanced post progression treatments? An application in advanced non-small cell lung cancer." *Value in Health* 21.1 (2018): 9-17.

conducting the respective analyses, the submission lacked details on how models were selected, no tests (and results) were presented to demonstrate how the models performed and empirical results regarding assumptions being met or violated were not presented.

- 6.23 The submission stated that the RPSFT approach might not be the most appropriate method given that the ‘common treatment effect’ assumption was not met as there was uncertainty in the magnitude of treatment effect of amivantamab as first-line use (ACP arm) compared to the treatment effect in those who have progressed on PBC. Simulation studies testing different methods for adjusting for treatment switching have shown that the RPSFT method produces results with low bias provided that the common treatment effect assumption holds but may be subject to high bias when this assumption is violated.¹⁶ The ESC agreed with the submission that given the common treatment effect assumption was not met for the RPSFT approach, it was likely subject to bias and a less reliable estimate of the treatment effect.
- 6.24 The submission favoured the TSE and IPCW approaches over the RPSFT on the basis that key prognostic factors were identified and included in the analyses thus (somewhat) satisfying the ‘no unmeasured confounders’ assumption. Details of the systematic literature and Delphi panel used to identify prognostic factors were not included in the submission. Although the submission likely included relevant covariates, other important prognostic variables identified from the literature such as body mass index (BMI)^{17,18} were not considered.
- 6.25 The OS results adjusted for treatment switching are presented in Table 5.

Table 5: Results for OS unadjusted and adjusted for treatment switching

	HR (95% CI)
Unadjusted	
FAS, unstratified	0.68 (0.42, 1.09)
FAS, stratified	0.72 (0.44, 1.17)
Adjusted for treatment switching	
TSE	0.55 (0.34, 0.89)
IPCW	0.52 (0.28, 0.94)
RPSFT	0.60 (0.32, 1.12)

Source: Compiled during the evaluation from Table 2.26, 2.58, p94, 139 of the submission

Abbreviations: CI, confidence interval; ECOG PS; European Cooperative Oncology Group performance status; OS, overall survival; HR, hazard ratio; FAS, full analysis set; IPCW, inverse probability of censoring weighting; TSE, two-stage estimation; RPSFT, rank preserving survival failure time.

^a Stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

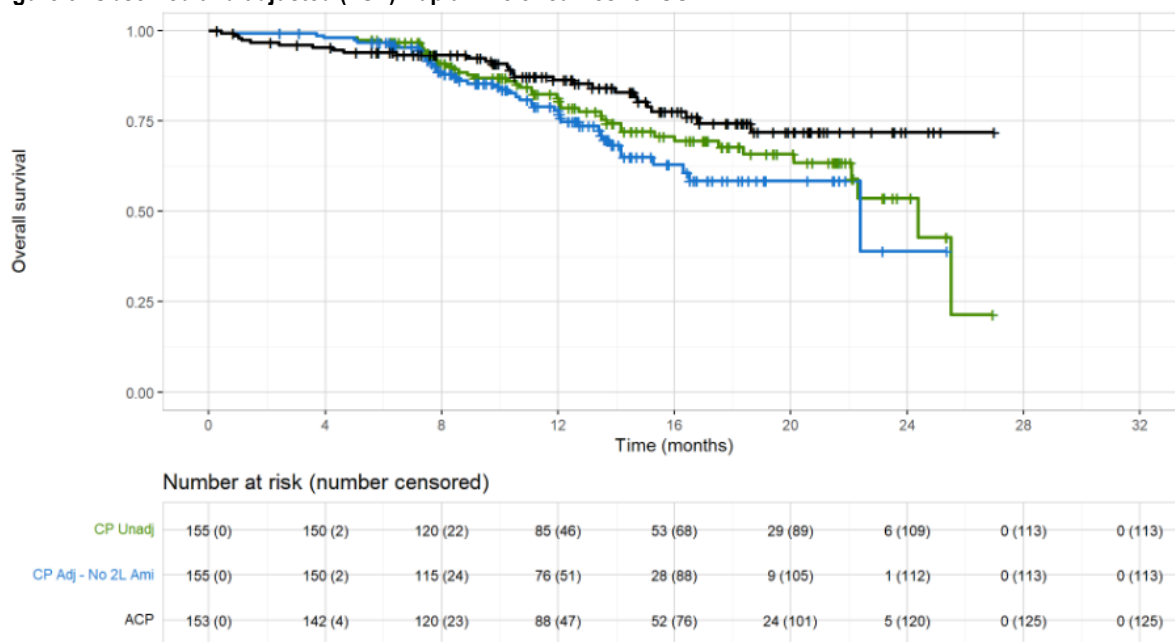
¹⁶ Morden et al. "Assessing methods for dealing with treatment switching in randomised controlled trials: a simulation study." *BMC medical research methodology* 11 (2011): 1-20.

¹⁷ Yuan et al. "Postdiagnosis BMI Change Is Associated with Non–Small Cell Lung Cancer Survival." *Cancer Epidemiology, Biomarkers & Prevention* 31.1 (2022): 262-268.

¹⁸ Jiang et al. "The relationship between body-mass index and overall survival in non-small cell lung cancer by sex, smoking status, and race: A pooled analysis of 20,937 International lung Cancer consortium (ILCCO) patients." *Lung Cancer* 152 (2021): 58-65.

6.26 The results from the TSE approach were applied as the base case in the economic model. Figure 3 shows the OS KM curves from the PAPILLON trial and the TSE-adjusted OS KM curve for CP. As noted in paragraph 6.15, the assessment of OS appears premature as median OS for the ACP arm had not been reached at data cutoff (median of 14.9 months follow-up) and a large proportion of patients censored (81.7% in ACP and 72.9% in CP) for analysis. This meant that the analysis was informed by a small number of events (Table 4).

Figure 3: Observed and adjusted (TSE) Kaplan-Meier curves for OS



Source: Figure 3.12, p178 of the submission

Abbreviations: 2L, second line; ACP, amivantamab plus carboplatin / pemetrexed; Adj, adjusted; CP, carboplatin / pemetrexed; OS, overall survival, TSE, two-stage estimation; Unadj, unadjusted.

6.27 The evaluation considered that theoretically the TSE approach was an appropriate adjustment method as it is less sensitive to data requirements and the ‘common treatment effect’ assumption that is relevant to IPCW and RPSFT methods. However, the TSE approach does rely on the assumptions that treatment switching occurs soon after disease progression and that at the time of switching, patients are all at a similar stage of disease at the time of progression. These assumptions could not be verified based on the data/results presented in the submission.

6.28 The ESC noted that additional information and sensitivity analyses to support the selection of the TSE approach were provided in the PSCR. The ESC considered the TSE assumptions (no unmeasured confounders, no time-dependent confounding after secondary baseline until treatment switching, all identified/measured confounders included and correctly specified in the regression adjustment based on a relatively well-fitting parametric AFT model to the observed post-progression survival data) were likely met and had increased confidence in the robustness of the TSE-adjusted OS results.

- 6.29 The patient-reported outcome measures included in the PAPILLON trial included the EuroQol 5 Dimension 5 Level (EQ-5D-5L) and were analysed as an exploratory endpoint. EQ-5D-5L utility scores (based on the UK value set) were maintained across all treatment cycles and differences between treatment arms were not statistically significant ($p>0.05$).
- 6.30 The submission also included data from a Phase I, single-arm study (CHRYSALIS; N=153) and data from the PAPILLON trial crossover phase (N=65) to demonstrate the use of amivantamab monotherapy as second-line treatment (following progression on or after PBC) to support the submission's request for an alternative PBS restriction that allows patients to receive treatment in the first- or second-line setting (see paragraph 3.6).
- 6.31 Table 6 presents a summary of the efficacy results from CHRYSALIS and PAPILLON crossover phase.

Table 6: Summary of key results from CHRYSALIS and PAPILLON crossover phase for amivantamab

	CHRYSALIS		PAPILLON crossover (N=65)
	Efficacy population (N=81) ^a	Additional efficacy population (N=124) ^b	
Median follow up, months	14.5	11.9	11.9
Progression-free survival			
Events (progression or death), n %	57 (70.4%)	90 (72.6%)	35 (53.8%)
Median time to event, months (95% CI)	8.25 (5.49, 12.32)	6.80 (5.55, 8.28)	6.77 (4.40, 9.59)
Overall survival			
Events (death), n %	31 (38.3%)	44 (35.5%)	17 (26.2%)
Median time to event, months (95% CI)	22.77 (17.48, NE)	22.77 (17.48, NE)	17.68 (12.09, NE)
Objective response rate			
Responders (CR + PR)	31	45	22
Overall response rate, % (95% CI)	38.3 (27.7, 49.7)	36.3 (27.8, 45.4)	39.3 (26.5, 53.2)

Source: Table 11, Appendix 1 of the submission.

Abbreviations: CI, confidence interval; CR, complete responder; NE, not evaluable; PR, partial responder.

^a Primary efficacy population included patients who had undergone ≥ 3 post-baseline disease assessments or discontinued treatment for any reason, including disease progression/death, prior to the cut-off of 8 June 2020.

^b Additional efficacy analysis included patients who had >6 months of follow-up from the last subject enrolled date (29 September 2020) at the cut-off of 30 March 2021.

Note: The dose and frequency of amivantamab between the CHRYSALIS and PAPILLON crossover phase differed. For instance, for those weighing <80 kg, patients in CHRYSALIS received a lower dose of amivantamab (1,050 mg for patients) every two weeks while in PAPILLON, patients were treated with 1,750 mg of amivantamab every three weeks.

Comparative harms

- 6.32 A summary of the comparative harms for ACP vs CP from the PAPILLON trial after a median follow-up for 14.9 months is presented in Table 7. Patients in the ACP arm had a greater risk of experiencing any drug-related TEAE, a greater risk of experiencing grade 3 or higher AEs and a greater risk of experiencing an AE requiring dose discontinuation, reduction or interruption.

Table 7: Summary of key adverse events in the trials

	ACP N=151	CP N=155	Risk difference (95% CI) ^d	Relative risk (95% CI) ^e
Median follow-up (months)	14.6	15.5	-	-
Any TEAE, n (%)	151 (100.0%)	152 (98.1%)	0.02 (0, 0.04)	1.02 (0.99, 1.05)
Drug-related ^a	151 (100.0%)	146 (94.2%)	0.06 (0.02, 0.09)	1.06 (1.02, 1.11)
Any Grade ≥3 TEAE, n (%)	114 (75.5%)	83 (53.5%)	0.22 (0.12, 0.32)	1.41 (1.19, 1.68)
Drug-related ^a	100 (66.2%)	57 (36.8%)	0.29 (0.19, 0.4)	1.8 (1.42, 2.28)
Any SAE, n (%)	56 (37.1%)	48 (31.0%)	0.06 (-0.04, 0.17)	1.20 (0.88, 1.64)
Drug-related ^a	36 (23.8%)	16 (10.3%)	0.14 (0.05, 0.22)	2.31 (1.34, 3.98)
TEAE leading to discontinuation of any study treatment, n (%)	36 (23.8%)	16 (10.3%)	0.14 (0.05, 0.22)	2.31 (1.34, 3.98)
AE leading to discontinuation of A	17 (11.3%)	N/A	N/A	N/A
Related to ACP ^a	10 (6.6%)	N/A	N/A	N/A
TEAE leading to death, n (%) ^b	7 (4.6%)	4 (2.6%)	0.02 (-0.02, 0.06)	1.8 (0.54, 6.01)
Drug-related ^a	3 (2.0%)	2 (1.3%)	0.01 (-0.02, 0.04)	1.54 (0.26, 9.09)
Total no. of deaths within 30 days of last dose (excluding deaths during crossover phase), n (%) ^c	7 (4.6%)	4 (2.6%)	0.02 (-0.02, 0.06)	1.8 (0.54, 6.01)
AE	3 (2.0%)	2 (1.3%)	0.01 (-0.02, 0.04)	1.54 (0.26, 9.09)
Progressive disease	1 (0.7%)	1 (0.6%)	0 (-0.02, 0.02)	1.03 (0.06, 16.26)
Most commonly reported (>5%) toxicity Grade 3 or 4 TEAEs				
Neutropenia	50 (33.1%)	35 (22.6%)	0.11 (0.01, 0.21)	1.47 (1.01, 2.12)
Rash	17 (11.3%)	0	0.11 (0.06, 0.16)	35.9 (2.1, 592.0)
Leukopenia	17 (11.3%)	5 (3.2%)	0.08 (0.02, 0.14)	3.49 (1.32, 9.22)
Anaemia	16 (10.6%)	19 (12.3%)	-0.02 (-0.09, 0.05)	0.86 (0.46, 1.62)
Thrombocytopenia	15 (9.9%)	16 (10.3%)	0 (-0.07, 0.06)	0.96 (0.49, 1.88)
Hypokalaemia	13 (8.6%)	2 (1.3%)	0.07 (0.03, 0.12)	6.67 (1.53, 29.07)
Paronychia	10 (6.6%)	0	0.07 (0.02, 0.11)	21.6 (1.3, 364.6)
Asthenia	8 (5.3%)	4 (2.6%)	0.03 (-0.02, 0.07)	2.05 (0.63, 6.68)

Source: Table 2.41, p114 of the submission

Abbreviations: ACP, amivantamab plus carboplatin / pemetrexed; AE, adverse events; CI, confidence interval; CP, carboplatin / pemetrexed; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

^a AE is assessed by the investigator as related to study treatment

^b AEs leading to death are based on AE outcome of Fatal. Per protocol, all deaths within 30 days of last dose were required to have an associated AE reported, even if due to progressive disease

^c In full analysis set population

^d Values >0 favour the CP arm

^e Values >1 favour the CP arm

Bold text indicates significant results.

Note: The risk difference and relative risk were calculated by the submission and were not pre-specified.

- 6.33 Rash, infusion-related reactions (IRRs) and pneumonitis / interstitial lung disease (ILD) were pre-identified AEs of special interest. Rash was the most common (89.4% in ACP vs 18.1% in CP). Among these, 19.2% were classified as Grade 3 and four patients (2.6%) discontinued treatment.
- 6.34 There were substantially more patients in the ACP treatment group experiencing Grade ≥3 TEAEs compared to CP (75.5% vs 53.5% respectively). The most common Grade ≥3 TEAEs were rash, paronychia, hypokalaemia, neutropenia and leukopenia.
- 6.35 The incidence of TEAEs leading to discontinuation was substantially higher in the ACP arm than the CP arm (23.8% vs 10.3%). Similarly, the incidence of TEAEs resulting in

treatment dose reductions (48.3% vs 22.6%) or treatment dose interruptions (68.9% vs 36.1%) was substantially higher with ACP.

Benefits/harms

6.36 A summary of the comparative benefits and harms for ACP vs CP based on data from the PAPHILLON trial is presented in Table 8.

Table 8: Summary of comparative benefits and harms for ACP and CP

Benefits						
PFS (median duration of follow up 14.9 months)						
Event	ACP	CP	Absolute Difference	HR (95% CI)		
Progressed, n (%)	84/153 (55%)	132/155 (85%)	-	0.395 (0.296, 0.528) P<0.0001		
Median PFS, months (95% CI)	11.37 (9.79, 13.70)	6.70 (5.59, 7.33)	4.67			
% not progressed at 6 months (95% CI)	77 (69, 83)	51 (43, 59)	26			
% not progressed at 12 months (95% CI)	48 (39, 56)	13 (8, 19)	35			
% not progressed at 18 months (95% CI)	31 (22, 40)	3 (1, 9)	28			
OS survival (median duration of follow up 14.9 months)						
Deaths, n/N (%)	28/153 (18%)	42/155 (27%)	-	0.675 (0.418, 1.090) P=0.1056		
Median OS, months (95% CI)	NE (NE, NE)	24.38 (22.08, NE)	-			
% Alive at 6 months (95% CI)	94 (89, 97)	97 (92, 99)	-3			
% Alive at 12 months (95% CI)	86 (79, 91)	82 (74, 87)	4			
% Alive at 18 months (95% CI)	74 (64, 82)	68 (58, 76)	6			
% Alive at 24 months (95% CI)	72 (61, 81)	54 (37, 68)	18			
Harms						
	ACP n/N	CP n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				ACP	CP	
Any drug-related TEAE	151/151	146/155	1.06 (1.02, 1.11)	100	94	0.06 (0.02, 0.09)
Drug-related AEs grade ≥3	100/151	57/155	1.8 (1.42, 2.28)	66	37	0.29 (0.19, 0.4)
Grade ≥3 Neutropenia	50/151	35/153	1.47 (1.01, 2.12)	33	23	0.11 (0.01, 0.21)
Grade ≥3 Rash	17/151	0/155	35.9 (2.1, 592.0)	11	0	0.11 (0.06, 0.16)
Grade ≥3 Leukopenia	17/151	5/155	3.49 (1.32, 9.22)	11	3	0.08 (0.02, 0.14)
TEAEs leading to drug discontinuation	36/151	16/155	2.31 (1.34, 3.98)	24	10	0.14 (0.05, 0.22)
TEAEs leading to dose reduction	73/151	35/155	2.14 (1.53, 2.99)	48	23	0.26 (0.15, 0.36)
TEAEs leading to treatment interruption	104/151	56/155	1.91 (1.51, 2.41)	69	36	0.33 (0.22, 0.43)

Source: Tables 2.24, 2.26, 2.45, 2.46, 2.47, 2.48 p90, 94, 120, 122-124 of the submission

Abbreviations: ACP, amivantamab plus carboplatin/ pemetrexed; AE, adverse events; BICR, blinded independent central review; CI, confidence interval; CP, carboplatin/ pemetrexed; ECOG, Eastern Cooperative Oncology Group; HR, Hazard Ratio; NE, not estimable; PFS, progression free survival; PS, performance status; RD, risk difference; RR, relative risk; TEAE = treatment-emergent adverse event

^a p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

^b Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favours ACP.

Note: + = censored observation, NE = not estimable

Bold text indicates significant results.

- 6.37 Based on the direct evidence presented by the submission, for every 100 patients with *EGFR* ex20ins mutation positive treatment naïve (first-line) NSCLC treated with ACP instead of CP:
- Approximately 26 additional patients would remain progression-free at six months.
- 6.38 Based on the direct evidence presented by the submission, for every 100 patients with *EGFR* ex20ins mutation positive treatment naïve (first-line) NSCLC treated with ACP instead of CP for a median follow-up of 14.9 months:
- Approximately 6 additional patients would have a TEAE.
 - Approximately 29 additional patients would have a grade 3 or 4 toxicity drug-related AE.
 - Approximately 11 additional patients would be diagnosed with neutropenia grade 3 or 4.
 - Approximately 11 additional patients would be diagnosed with a rash grade 3 or 4.
 - Approximately 8 additional patients would be diagnosed with leukopenia (a decrease in the white blood cell count) grade 3 or 4.
 - Approximately 14 additional patients would discontinue all study treatment due to TEAE.

Clinical claim

- 6.39 The submission claimed that in patients with treatment-naïve, locally advanced or metastatic NSCLC with evidence of *EGFR* ex20ins mutation, ACP was superior in effectiveness and inferior but manageable in safety compared to CP.
- 6.40 The PBAC agreed with the ESC that the claim of superior effectiveness in patients with metastatic (Stage IV) NSCLC was adequately supported based on the primary outcome, PFS, in the PAPILLON trial.
- 6.41 The PBAC considered that the clinical evidence supported an OS advantage for ACP vs CP, though the magnitude of this benefit remained uncertain due to immature data, bias caused from cross-over and high levels of censored data.
- 6.42 The submission described ACP as inferior but manageable in terms of safety compared to CP. The PBAC agreed with ESC that the claim of inferior safety was adequately supported. However, the PBAC considered the term 'manageable safety' to be misleading and minimised the severity of drug-related toxicity, as it does not appropriately capture the full extent of the patient experience.

Economic analysis

6.43 The submission presented a stepped economic cost-effectiveness and cost-utility analysis based on the direct randomised trial, PAPILLON. A summary of the key components of the economic evaluation is presented in Table 9.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	ACP vs CP
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Time horizon	7.5 years in the economic model vs 14.9 months (median follow up) in the PAPILLON trial
Outcomes	Quality-adjusted life years gained; Life years gained
Methods used to generate results	Partitioned survival model.
Health states	The model included three health states: Pre-progression; Post-progression; Dead
Cycle length	3 weeks
Transition probabilities or Allocation to health states (if partitioned survival model)	<p>Health state allocations in the model were informed by PFS and OS time to event data from the PAPILLON trial.</p> <p>Pre-Progression PFS KM curves from the PAPILLON trial were used to establish the proportion of patients that remained in the Pre-progression health state over time. Parametric extrapolation began when 10% of patients remained at risk, i.e. extrapolation began at 18 months in the ACP arm and 11.5 months in the CP arm.</p> <p>Post-progression OS KM curves from the PAPILLON trial were used to establish the proportion of patients remaining in the Post-progression health state, until 10% of the population remained at risk, at which point parametric extrapolation was applied. Extrapolation began at 21 months in the ACP arm and 18.3 months in the CP arm. The PAPILLON trial allowed for crossover of patients in the CP arm after progression, so OS estimates were based on a two-stage estimation (TSE) adjustment.</p>
Extrapolation method	<p>PFS and OS KM data from the PAPILLON trial were truncated at the point where 10% of patients remained at-risk. Parametric extrapolations were fit to each of the individual KM curves for the time horizon of 7.5 years. Parametric distributions applied to each curve were based on goodness of fit, as judged by AIC and BIC, and clinical plausibility.</p> <p>The submission assumed a continued treatment effect of PFS and OS throughout the time horizon and no treatment waning was applied.</p> <p>The submission assumed treatment until progression which aligned with the trial protocol.</p> <p>The percentage of costs that occurred in the extrapolated period were 38% and 49% in the ACP and CP arms, respectively. The percentage of QALYs that were gained in the extrapolated period were 55% and 37% for the ACP and CP arms, respectively, and the percentage of LYs gained were 56% and 38% in the ACP and CP arms, respectively.</p>
Health related quality of life	<p>EQ-5D-5L data collected in the PAPILLON trial were used to inform the utility estimates in the Pre-progression and Post-progression health states. Scores were valued using the Australian tariff from Norman (2023). In the Post-progression health state, a pooled utility estimate of 0.839 was applied.</p> <p>With the intention of capturing differences in the safety profiles of the medications, the submission applied treatment specific Pre-progression utility estimates: 0.913 in the</p>

Component	Summary
	ACP arm and 0.916 in the CP arm.
Costs related to AEs	Adverse events from the PAPILLON trial were included as costs in the economic model if they were Grade 3 or 4 in severity, had occurred in at least 5% of patients in either treatment arm, and were significantly different. The difference in adverse event profiles of the two treatment arms was captured by applying a one-off cost of \$64.63 in the ACP arm and \$23.38 in the CP arm.

Source: Table 3.1, p154 of the submission and compiled during the evaluation

Abbreviations: ACP, amivantamab plus carboplatin and pemetrexed, AE, adverse event; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; CP, carboplatin and pemetrexed; EQ-5D-5L, EuroQol 5 Dimension 5 Level; KM, Kaplan-Meier; LY, life year; OS, overall survival, PFS, progression free survival; QALY, quality-adjusted life year

6.44 The allocation of patients to Pre-progression, Post-progression, and Dead health states in the model was based on time-to-event data for PFS and OS from the PAPILLON trial. The PAPILLON trial is ongoing, and the OS data remain immature (para 2.3).

6.45 A time horizon of 7.5 years was applied in the model. The submission stated that this was sufficient to capture all the important differences in costs and outcomes. The evaluation considered that the time horizon was long relative to the PAPILLON trial duration of 14.9 months (median follow-up period at primary analysis). The submission referenced 2 previous PBAC considerations to support the time horizon applied, however the period of extrapolation exceeds those of previous PBAC considerations and is more uncertain. The previous PBAC considerations were as follows:

- The PBAC previously accepted that the use of a 7.5-year time horizon was clinically appropriate in its consideration of osimertinib in treatment-naïve patients with locally advanced or metastatic common EGFR NSCLC (para 7.11, osimertinib PSD, July 2019 PBAC meeting). Osimertinib was subsequently recommended at the July 2020 meeting. The key trial for the osimertinib submission was the FLAURA trial with a median follow up of 36 months for osimertinib, which was longer than the median follow-up of the PAPILLON trial. Furthermore, patients with EGFR ex20ins NSCLC had shorter median OS and PFS compared to patients with common EGFR NSCLC, thus the time frame was able to capture a larger proportion of clinical end points in that trial (Bazhenova et al., 2021).
- The PBAC previously recommended mobocertinib for the treatment of EGFR exon20ins NSCLC in patients who had progressed on PBC based on a time horizon of 5 years. The submission claimed that as mobocertinib was a second-line therapy for patients post progression on PBC, expanding the time horizon for first line therapy was appropriate. The median follow-up from the key trial for mobocertinib was 25.8 months.

The PSCR noted that the time horizon was further supported by observational long-term survival data of treatment-naïve metastatic ex20ins NSCLC patients where the 5-year real world OS with currently available therapies (i.e. platinum-based

chemotherapy) is 8% (Bazhenova et al., 2021¹⁹). As ACP is shown to be superior in efficacy to CP, the PSCR considered an extrapolation to 7.5 years was reasonable. The ESC noted the median follow-up of the PAPILLON trial was 14.9 months and that the OS data informing the model remained immature. The ESC therefore considered the base case time horizon (7.5 years) introduced uncertainty and considered a 5-year time horizon may have been more conservative, given the short duration of follow-up. The pre-PBAC response maintained that a 7.5-year time horizon was appropriate reiterating the points above and noted the data informing the extrapolation of OS in the economic model was based on a robust Phase 3 randomised control trial.

- 6.46 The submission assumed a continued treatment effect of PFS and OS throughout the time horizon, i.e., no forced convergence was applied in the economic model. Although the difference in treatment effect reduced as time progressed, the PFS functions did not converge until 8.77 years and the OS functions did not converge until 8.11 years, which was beyond the 7.5-year time horizon. The evaluation considered that the assumption of continued treatment effect was not well supported. The PAPILLON trial is ongoing and 46% and 15% of patients in the ACP and CP arms respectively were still receiving treatment at the data cutoff date. Although the OS KM curves appear to slightly separate (favouring ACP) after 12 months, the OS data remains too immature for definitive conclusions to be drawn.
- 6.47 The OS KM applied in the economic model was adjusted using the TSE approach (HR=0.55; 95% CI 0.34, 0.89) to account for treatment switching to amivantamab monotherapy in the CP arm. The ESC considered adjusting for treatment switching in the PAPILLON trial was reasonable. Of the three adjustment methods proposed, TSE was applied to the base case. The ESC considered this was likely reasonable, however noted that the incremental cost-effectiveness ratio (ICER) was sensitive to the adjustment method used (Table 13).

Extrapolation time points

- 6.48 The submission applied the KM data from the PAPILLON trial for both PFS and OS up until the point where 10% of patients remained at risk. The submission reported that based on this, the extrapolation of PFS began at 18 months in the ACP arm and at 11.5 months in the CP arm. The extrapolation of OS began at 21 months in the ACP arm and 18.3 months in the CP arm.

Extrapolation of PFS

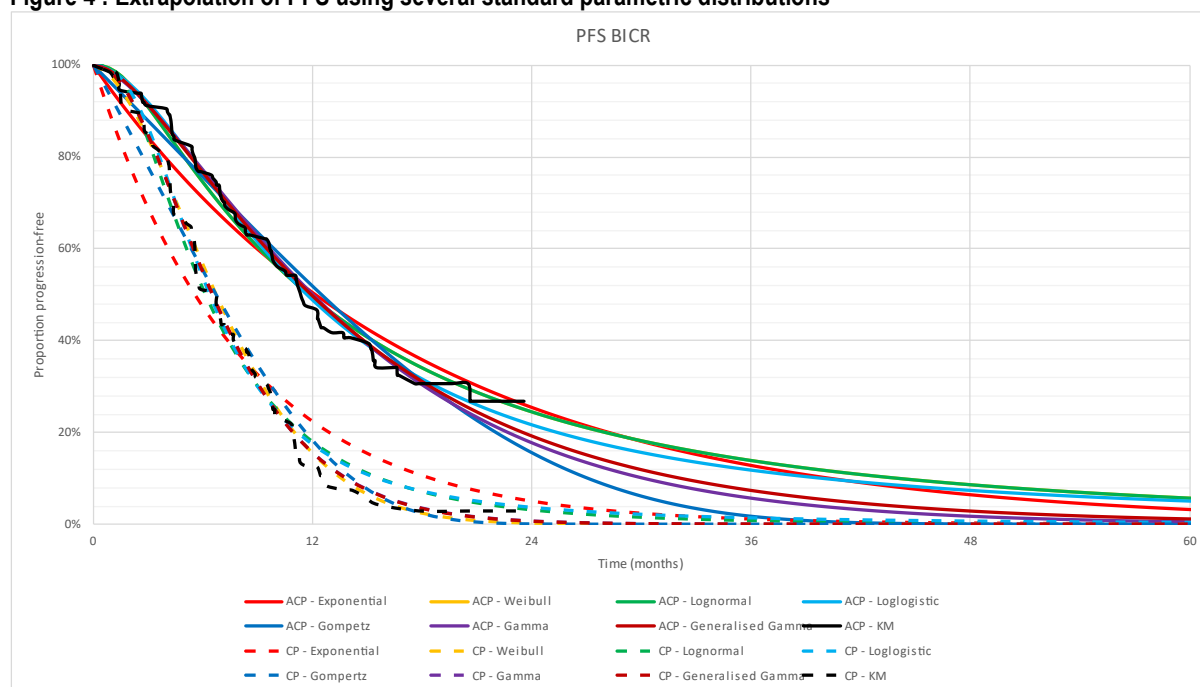
- 6.49 Figure 4 shows the extrapolation curves using different parametric distributions and the PFS KM curve from the PAPILLON trial. The gamma distribution (solid purple and dashed purple) was selected to extrapolate PFS for both the ACP and CP arms as it was

¹⁹ Bazhenova, L., Minchom, A., Viteri, S., Bauml, J. M., Ou, S. I., Gadgeel, S. M., Girard, N. (2021). Comparative clinical outcomes for patients with advanced NSCLC harboring *EGFR* exon 20 insertion mutations and common *EGFR* mutations. *Lung Cancer*, 162, 154-161.

the best fitting for CP according to the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) and second-best fitting for ACP.

6.50 The submission noted that the other distributions either did not provide the best statistical fit (exponential and Gompertz) or resulted in clinically implausible scenarios (e.g. log-logistic where 5.17% of patients would remain at-risk at 5 years). The selection of the gamma distribution appeared to be the best fitting curve among those tested. The choice of distribution for PFS for the ACP arm of the model had a moderate impact on the ICER which ranged between \$75,000 to < \$95,000/QALY gained (-6% change from base case of \$75,000 to < \$95,000/QALY gained) when the Gompertz distribution was applied and \$75,000 to < \$95,000/QALY gained (+16%) when the lognormal distribution was applied.

Figure 4 : Extrapolation of PFS using several standard parametric distributions



Source: Figure 3.7, p171 of the submission

Abbreviations: ACP, amivantamab plus carboplatin/ pemetrexed; BICR, after blinded independent central review; CP, carboplatin/ pemetrexed; KM, Kaplan-Meier; PFS, progression free survival

6.51 The submission assumed a continued treatment effect of PFS throughout the time horizon; i.e., no treatment waning was applied. The extrapolation in the ACP arm begins at 18 months, and visually it can be seen that the gamma ACP curve begins to flatten out at approximately this point while the CP gamma trace is 0% by 24 months. Due to the tails in the extrapolation curve, a difference in PFS is maintained at 5 years where 0.5% of patients in the ACP arm and 0% in the CP arm remain in PFS. The ESC considered the base case extrapolation of PFS was likely reasonable, however noted that the ICER was sensitive to the PFS extrapolation function applied to the ACP arm.

Extrapolation of OS

- 6.52 For the ACP arm, a generalised gamma distribution was applied, and in the CP arm a log-logistic distribution was applied to extrapolate OS. The submission stated that due to violation of the proportional hazards assumption independent curve fitting for each arm of the PAPHILLON trial data was performed. The evaluation considered that this was reasonable.
- 6.53 In the ACP arm of the model the best fit according to the BIC and AIC was the exponential curve, however the generalised gamma curve was selected for the base case. The submission considered that the generalised gamma curve better matched the empiric hazard data from the PAPHILLON trial and also considered it provided conservative 5-year and median survival estimates (22.65% and 36 months, respectively). For CP, the submission reported that the log-logistic curve was most appropriate compared to the other TSE-adjusted extrapolations which estimated $\leq 3\%$ (Weibull, Gompertz, Gamma, and generalised gamma) or $\geq 10\%$ (exponential and log-normal) survival at 5 years. Survival at 5 years with the log-logistic curve was 7.6%, which the submission argued was consistent with the 8% reported by Bazhenova et al (2021). The evaluation considered the selected parametric distributions appeared reasonable.
- 6.54 In the ACP arm, applying a log-logistic function would have resulted in an estimated 5year OS of 42% (likely clinically implausible), compared to 23% OS estimated with the applied generalised gamma distribution for this arm. For the CP arm, the log-logistic distribution resulted in a 5-year OS of 7%, compared to 11% if the generalised gamma function had been applied.
- 6.55 The economic model assumed that ACP has a treatment advantage in OS over CP with a continued treatment effect throughout the time horizon. The evaluation considered that this assumption and the ongoing OS treatment effect were not well supported given the immaturity of the data. The ICER was highly sensitive to both the method chosen to adjust for treatment switching and the distributions selected for extrapolation of OS.
- 6.56 Table 10 displays the mean and median OS in the economic model when each of the parametric functions were applied. In the ACP arm mean OS ranged from 2.84 years (Gompertz) to 5.34 years (Lognormal). In the CP arm mean OS ranged from 1.65 years (Gompertz) to 3.01 (exponential). Median real-world OS reported in Bazhenova et al. (2021) was 1.45 years and in Ou et al. (2023) it was 1.42 years, which seems to indicate that survival of patients in the CP arm of the PAPHILLON trial was better than those observed from real-world evidence. The reasons for this were unclear but may be related to the characteristics of patients recruited to the trial (likely younger and healthier populations) and related to the trial settings.

Table 10: Overall survival over the 7.5-year time horizon estimated by parametric distributions in the model

Parametric function	ACP		CP	
	Median OS (years)	Mean OS (years)	Median OS (years)	Mean OS (years)
Exponential	4.02	4.21	2.13	3.01
Weibull	3.51	3.89	1.72	1.83
Lognormal	5.34	4.66	1.86	2.59
Log-logistic (base case: CP arm)	3.97	4.28	1.76	2.25
Gompertz	2.84	2.91	1.69	1.65
Gamma	3.58	3.99	1.75	2.02
Generalised gamma (base case: ACP arm)	3.13	3.39	1.73	1.92

Source: Compiled during the evaluation from information in the economic model included with the submission.

Abbreviations: ACP, amivantamab plus carboplatin and pemetrexed; CP carboplatin and pemetrexed; OS, overall survival.

Note: These estimates were based on OS Kaplan-Meier data until 10% of the patient population remained at risk.

Health state utilities

- 6.57 Quality of life data using the EQ-5D-5L from the PAPILLON trial were used to inform the utility values for the Pre-progression and Post-progression health states in the base case analysis. In the Pre-progression health state, treatment-specific utilities were applied (0.913 for ACP and 0.916 for CP) while in the Post-progression health state, a pooled utility estimate (0.839) was applied irrespective of treatment group.
- 6.58 The submission claimed that while there was no statistically significant difference in EQ-5D by treatment group, there were numerical differences with a slightly lower pre-progression utility reported in the ACP arm due to the increased rate of AEs seen in patients treated with ACP vs CP in the PAPILLON trial. As such, the submission assumed treatment-specific utility in the Pre-progression state to account for patients' disutility associated with any AEs while they were receiving treatment.
- 6.59 The utility values were high compared to utilities previously accepted by the PBAC, including:
- osimertinib for the adjuvant treatment of Stage IB to IIIA NSCLC: first-line distant metastatic utility = 0.794; second-line distant metastatic utility = 0.64 (Table 9, osimertinib PSD, November 2023 PBAC Meeting). Base case QALY gained = 1.956 / PBAC scenario QALY gained = 1.014.
 - selpercatinib for the treatment of advanced or metastatic rearranged during transfection (RET) fusion-positive NSCLC: pre-progression = 0.776; post-progression = 0.714 (Table 10, selpercatinib PSD, July 2024 PBAC Meeting). Base case QALY gained = 1.27 / multivariate sensitivity analysis QALY gained = 1.02.
 - larotrectinib for the treatment of locally advanced or metastatic NSCLC or soft tissue sarcoma (STS) harbouring neurotrophic tropomyosin receptor kinase (NTRK) gene fusions: pre-progression = 0.713; post-progression = 0.688 (Table 12, larotrectinib PSD, March 2024 PBAC Meeting). Base case QALY gained = 1.95.

- 6.60 Furthermore, a systematic review of health state utility values for late-stage NSCLC showed that the highest reported pre-progression utility used was 0.84.²⁰ The ESC noted that utility data from the PAPILLON trial could not be verified during the evaluation and that the ICER was relatively sensitive to the utility values.

Costs

- 6.61 To calculate the per cycle cost of amivantamab, the submission factored in the proportion of skipped/reduced doses, the proportion of patients over/under 80 kg, and the dose intensity for initial/maintenance treatment based on the PAPILLON trial. The submission also assumed treatment until progression.
- 6.62 Adverse events from the PAPILLON trial were included as costs in the model if they were Grade 3 or 4 severity, had occurred in at least 5% of patients in either treatment arm, and were significantly different. The decision criteria for inclusion in the economic model appeared reasonable, however it meant that rarer (expensive) adverse events such as deep vein thrombosis were excluded from the model. This would have a disproportionate impact favouring the intervention arm, given that 23.8% of ACP patients experienced a TEAE that led to discontinuation of a study treatment, compared to 10.3% in the comparator arm (relative risk: 2.31, 95% CI 1.34 to 3.98) (Table 7).
- 6.63 Weighted average MBS access statistics were used to value each of the AEs with costs ranging from \$0.00 for asthenia to \$124.11 for neutropenia. These costs are low and do not capture the cost of hospital admission. Sensitivity analysis conducted during the evaluation considering alternate costs for managing Grade 3/4 AEs had a small impact on the ICER, increasing it from \$75,000 to < \$95,000/QALY gained to \$75,000 to < \$95,000/QALY (+1%).
- 6.64 The economic model applied a one-time cost of \$52,873.20 for end-of-life care based on Langton 2016. The end-of-life cost applied in the model appears high. Previous PBAC considerations have applied a cost of approximately \$38,000 based on the same source (para 6.43, pembrolizumab for oesophageal carcinoma PSD, November 2021 PBAC meeting; para 6.46, nivolumab PSD, November 2021 PBAC meeting). Excluding end-of-life costs from the economic model increased the ICER from \$75,000 to < \$95,000/QALY gained to \$75,000 to < \$95,000/QALY gained (+5%). Given the uncertainty of the OS data, it is likely not reasonable that the economic model be driven, in-part, by a high end-of-life cost associated with earlier deaths in the CP arm, particularly as discounting is lower compared to when the deaths are assumed to occur in the ACP arm.
- 6.65 A summary of the key drivers of the economic model is presented in Table 11.

²⁰ Paracha et al. "Systematic review of health state utility values in metastatic non-small cell lung cancer with a focus on previously treated patients." Health and quality of life outcomes 16 (2018): 1-30

Table 11: Key drivers of the model

Description	Method/Value	Impact Base case: \$11/QALY gained.
OS parametric functions	<p>ACP: generalised gamma, CP: log-logistic (TSE adjusted)</p> <p>The parametric distribution for CP was based on best fit according to AIC/BIC, while the generalised gamma function for ACP was based on clinical plausibility.</p>	<p>Very high, favours comparator.</p> <p>The extrapolation of OS is highly uncertain given the premature OS data in the PAPILLON trial. The submission assumed a large and continued treatment effect applied throughout the time horizon. This is highly uncertain.</p>
OS adjustments for treatment switching	<p>TSE: HR 0.55</p> <p>Alternative adjustments: IPCW: HR 0.52 RPSFT: HR 0.60</p>	<p>Very high, favours amivantamab.</p> <p>When the IPCW adjustment was applied, the ICER reduced to \$²/QALY gained (-24%) and when using the RPSFT adjustment, the ICER increased to \$¹/QALY gained (+17%)</p>
Utilities	<p>The utility values applied were based on EQ-5D-5L data from the PAPILLON trial. Pre-progression utility was 0.913 in the ACP arm and 0.916 in the CP arm. Post-progression utility was pooled 0.839. These utility values could not be verified during the evaluation and were higher than in other recent studies.</p>	<p>Moderate, favours intervention</p> <p>When a pre-progression utility of 0.794 and post-progression utility of 0.64 (osimertinib PSD, November 2023 PBAC meeting) were applied, the ICER increased to \$³ (+20%). The osimertinib submission was in the adjuvant setting, in patients with Stage IB-III A NSCLC, who would likely have better quality of life.</p>

Source: Table 3.35, pp199-200 of the submission and compiled during the commentary

Abbreviations: ACP, amivantamab plus carboplatin and pemetrexed; AIC Akaike information criterion; BIC, Bayesian information criterion; CP, carboplatin and pemetrexed; EQ-5D-5L, EuroQol 5 Dimension 5 Level; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weight; NSCLC, non-small cell lung cancer; OS, overall survival; PSD, public summary document; QALY, quality-adjusted life year; RPSFT, rank preserving structural failure time; TSE, two-stage estimation

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$55,000 to < \$75,000

³ \$95,000 to < \$115,000

6.66 The results of the stepped economic evaluation are presented in Table 12.

Table 12: Results of the stepped economic evaluation

Step and component	ACP	CP	Increment
Step 1: trial-based costs and outcomes (14.9 months follow up, no discounting for costs and outcomes)^a			
Costs	\$█	\$4,319	\$█
LY gained	1.1717	1.1562	0.0156
Incremental cost/extra LY gained			\$ ¹
Step 2: extrapolated analysis (7.5 year time horizon, 5% discounting for costs and outcomes, and adjustment for treatment switching)			
Costs	\$█	\$52,572	\$█
LY gained	3.1120	2.1222	0.9898
Incremental cost/extra LY gained			\$ ²
Step 3: utility weights applied (7.5 year time horizon, 5% discounting for costs and outcomes and adjustment for treatment switching)			
Costs	\$█	\$52,572	\$█
QALYs gained	2.6493	1.8330	0.8164
Incremental cost/extra QALY gained			\$ ³

Source: Table 3.33, p196 of the submission

Abbreviations: ACP, amivantamab plus carboplatin and pemetrexed; CP, carboplatin/ pemetrexed; LY, life years; QALYs, quality-adjusted life-years.

^a In Step 1, Costs: Drug and drug administration costs & costs of treating adverse events; Time horizon: 14.9 months (median follow-up in PAPILLON); No discounting applied; Full analysis set, no adjustment for treatment switching.

The redacted values correspond to the following ranges:

¹ > \$1,055,000

² \$55,000 to < \$75,000

³ \$75,000 to < \$95,000

6.67 The ESC noted that the extrapolation step (Step 2) was an important driver of the ICER. The ICER reduced from > \$1,055,000 per LY gained (trial-based analysis) to \$55,000 to < \$75,000 per LY gained when the time horizon was extended to 7.5 years.

6.68 Overall, the ESC considered that the results of the economic evaluation were associated with the following uncertainties:

- The data that informed the transitions in this model from the PAPILLON trial were immature with a median follow up of 14.9 months. The time horizon in the model was 7.5 years and subsequently there was substantial uncertainty about the ongoing effectiveness of amivantamab beyond the trial period, particularly in relation to differences in overall survival. At the data cutoff point, median OS for ACP had not been reached. Although there appeared to be a trend towards improved survival in the ACP arm, data for OS remained immature for definitive conclusions. A large proportion of patients were censored (81.7% in ACP and 72.9% in CP) at the data cutoff date for analysis and this might impact on the interpretation of results. Therefore, the assumption of a superior (extrapolated and continued) OS treatment effect was highly uncertain. The economic model demonstrated a large, continued treatment effect and most effectiveness gains occurred between 2 and 5 years.
- Similarly, the extrapolation functions applied to estimate OS were informed by limited event data. The type of parametric distribution applied to the OS data had a very large impact on the ICER.

6.69 The results of key univariate sensitivity analyses are summarised in Table 13.

Table 13: Sensitivity analyses

Variables altered in the sensitivity analysis	Incremental costs	Incremental QALYs	ICER	Change to ICER (%)
Base case results	\$█	0.8164	\$█ ¹	█
Discount rate (base case: 5%)				
0%	\$█	1.0015	\$█ ²	█
3.5%	\$█	0.8675	\$█ ¹	█
Time horizon (base case: 7.5 years)				
5 years	\$█	0.6960	\$█ ¹	█
10 years	\$█	0.8176	\$█ ¹	█
Parametric function used for ACP OS (base case: Generalised gamma)				
Weibull	\$█	1.1462	\$█ ³	█
Gompertz	\$█	0.5372	\$█ ⁴	█
Gamma	\$█	1.2091	\$█ ³	█
Log-logistic	\$█	1.3960	\$█ ⁵	█
Adjustment method for treatment switching used for CP OS & best-fit extrapolation (base case: TSE + log-logistic)				
No adjustment – FAS + log-logistic	\$█	0.4143	\$█ ⁶	█
IPCW + log-logistic	\$█	1.0561	\$█ ²	█
RPSFT + log-logistic	\$█	0.7038	\$█ ¹	█
Extrapolation point for switching from KM data to parametric functions (base-case: at-risk = 10%)				
Use parametric fit only (from time 0)	\$█	0.9113	\$█ ²	█
20% at-risk remaining	\$█	0.7913	\$█ ¹	█
Cost of adverse events				
Revised to include hospitalisations for Grade 3/4 AEs ^a	\$█	0.816	\$█ ¹	█
Utility (base case: pre progression, ACP=0.913, CP=0.916; post progression pooled=0.839)				
Pre-progression utility of 0.794 and post-progression utility of 0.64 (osimertinib PSD November 2023) ^b	\$█	0.6782	\$█ ⁷	█

Source: Table 3.35, pp 199-200 of the submission and added to during the evaluation

Abbreviations: ACP, amivantamab plus carboplatin/ pemetrexed; AE, adverse event; AIC, Akaike information criterion; BIC Bayesian information criterion; CP, carboplatin/ pemetrexed; FAS, full analysis set; ICER, incremental cost effectiveness ratio; IPCW, inverse probability of censoring weight; KM, Kaplan-Meier, PSD, public summary document; OS, overall survival; QALYs, quality-adjusted life-years; RPSFT, rank-preserving structural failure time; TSE, two stage estimation.

^a Costs applied include (\$3,974.10 for asthenia based on DRGX63 for minor complexity admission, \$461.44 for neutropenia based on PBS item 2784L filgrastim 480 microgram/0.5 mL injection, \$3,245 for paronychia, based on DRG J68B, major skin disorder, minor complexity, and \$25.35 for hypokalaemia based on PBS item 3012M.

^b Reported incorrectly in the commentary and ESC Advice. Corrected prior to the finalisations of the PBAC minutes.

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$55,000 to < \$75,000

³ \$45,000 to < \$55,000

⁴ \$115,000 to < \$135,000

⁵ \$35,000 to < \$45,000

⁶ \$155,000 to < \$255,000

⁷ \$95,000 to < \$115,000

6.70 The PBAC recalled it had previously recommended targeted therapies for NSCLC with an ICER of < \$55,000 to < \$75,000 per QALY (paragraph 7.13, selpercatinib PSD, July 2024 PBAC meeting).

Drug cost/patient/course

Table 14: Drug cost per patient for amivantamab when used in combination with PBC (using requested effective price)

	ACP			CP		
	Trial	Model	Financial estimates	Trial	Model	Financial estimates
Mean duration (months)	10.19 ^a	15.42	15.38	C: 2.17 P: 7.32	C: 2.8 P: 8.16 ^e	NI
Cost/patient/cycle [Initiating]	\$ (Cycle 1) \$ (Cycle 2-4) ^b	\$ (Cycle 1) \$ (Cycle 2-4) ^b	\$ ^c	C: \$149 ^b P: \$141 ^b	C: \$149 ^b P: \$141 ^b	NI
Cost/patient/cycle [Continuing]	\$ ^b	\$ ^b	\$ ^d	P: \$141 ^b	P: \$141 ^b	NI
Cost/patient/course	\$ ^f	\$ ^f	\$ ^f	C: \$580 P: \$1,489	C: \$574 P: \$1,888 ^g	NI

Source: Compiled based on PAPILLON trial data (CSR), Attachment 3.1 (economic model) and Attachment 4.1 (financial estimates) of the submission

Abbreviations: ACP, amivantamab plus carboplatin/ pemetrexed; CP, carboplatin/ pemetrexed; C, carboplatin; DPMQ, dispensed price for maximum quantity; EFC, Efficient Funding of Chemotherapy; NI, not included; P, pemetrexed; PBC, platinum-based chemotherapy; PFS, progression free survival.

^a Based on the amivantamab component only as reported in the PAPILLON trial

^b Calculated based on the recommended doses as product information adjusted to proportion of patients above and below 80 kg, skipped doses and dose reduction as per PAPILLON trial, relevant EFC fees and adjusted for private/public split. As per undiscounted costs presented in the economic model.

^c Based on the number per year of 20.92 this was multiplied by (12/52) to get the number of scripts for the initiating period, multiplied by the DPMQ effective price for initiating treatment, divided by 4 to get the per cycle cost. The number of scripts per year is adjusted to capture the proportion of patients over/under 80kg of 84.4%/15.6%, non-skipped doses (85.5% in the under 80kg group and 88.1% in the above 80kg group) a private/public split of 61%/39% and dose reduction (93.7% for patients below 80kg, 93.5% for patient above 80kg)

^d Based on number of doses per year 13.95 for continuing treatment, multiplied by continuing treatment period of 54.84 weeks and DPMQ cell J273' of impact proposed eff tab of financial model. Divided by 18.28 to get the price per cycle, adjustments include those outlined in footnote c.

^e Based on treatment to progression (mean PFS in the CP arm of the economic model 0.68 years)

^f Reported incorrectly in the commentary and ESC Advice. Corrected prior to the finalisations of the PBAC minutes.

^g Based on an adjustment of 98.4% non-skipped doses and a dose reduction of 99.1%

6.71 The cost per patient on amivantamab second-line monotherapy would be different as the (truncated) mean treatment duration with amivantamab monotherapy is shorter (5.66 months) in the PAPILLON crossover phase. Based on a mean duration of treatment (median follow-up of 11.9 months) and adjusting for dose reduction (87.7%) and treatment interruptions (66.2%), the course per treatment is estimated to be \$ per patient.

Estimated PBS usage & financial implications

6.72 This submission was considered by DUSC.

6.73 The submission used an epidemiological approach to estimate the financial implications associated with proposed listing of amivantamab. The epidemiological model estimated the number of patients with *EGFR* ex20ins NSCLC likely to receive amivantamab based on Australian lung cancer incidence, prevalence of exon20ins mutations, and uptake rates for first line therapy.

6.74 A summary of the key inputs in the financial analysis are presented in Table 15.

Table 15: Key inputs for financial estimates

Data	Value	Source	Comment
Proportions of NSCLC and Stage IIIB/IV disease	86.6% & 65.5%	Mitchell et al., 2013; mobocertinib PSD.	The evaluation considered this was reasonable and consistent with that previously accepted for mobocertinib (mobocertinib PSD July 2023 PBAC meeting), and entrectinib (entrectinib PSD, March 2020 PBAC meeting).
Proportions with Stage IIIA disease and those who would progress to Stage IIIB or Stage IV	11.8% & 60%	Mitchell et al., 2013. Aligned to mobocertinib submission, which was based on Table 17, pembrolizumab PSD, November 2018 PBAC meeting.	The evaluation considered this was reasonable and consistent with that previously accepted for mobocertinib (mobocertinib PSD, July 2023 PBAC meeting),
Proportion of patients diagnosed at stage I-II disease and those who would progress to Stage IIIB or Stage IV	22.7% & 10%	Mitchell et al. 2013; osimertinib PSD, November 2023 PBAC Meeting, Figure 2.	Although Mitchell et al. 2013 is now more than 10-years old, the evaluation considered it was likely a reasonable source for Australian data. A more recent Editorial by John et al. 2020 estimated that the proportion of patients diagnosed with Stage I-II disease was 19%.
Patients with EGFR mutations	17.90%	DUSC review on erlotinib and gefitinib (2017).	The evaluation considered that this was reasonable and consistent with the mobocertinib submission (Table 14, mobocertinib PSD, July 2023 PBAC meeting).
Proportion of EGFR-positive NSCLC patients with ex20ins	8.96%	Moore et al., 2018	The evaluation considered that this was reasonable and consistent with the mobocertinib submission (Table 14, mobocertinib PSD, July 2023 PBAC meeting). The financial estimates were highly sensitive to this parameter. Decreasing the proportion to 7% decreased the financial estimates by 21%. Given that diagnosis techniques have improved recently, the DUSC considered that 8.96% was likely to be a reasonable estimate.
Proportion with ECOG performance status of 0-2 in 1L	80.1%	Mitchell et al., 2013	The evaluation considered that this was reasonable and consistent with the mobocertinib submission (Table 14, mobocertinib PSD, July 2023 PBAC meeting)
Proportion who elect 1L systemic therapy (2025–2030)	100%	Assumption	The evaluation considered that this input was uncertain and an overestimate as, some patients with Stage IIIB/IV disease may elect for best-supportive care, particularly given the adverse event profile of amivantamab. The DUSC noted that the mobocertinib submission estimated 85% of patients would elect first-line PBC. The DUSC considered this input was overestimated and would likely range between 80–85%.
Proportion who elect 1L systemic	84%	AURORA registry	The DUSC considered that if an alternative listing that allowed patient to receive treatment in the

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Data	Value	Source	Comment
therapy (2023–2024)			first- or second-line setting was recommended, the proportion of patients who would elect first-line PBC may be lower than 80-85%, if some patients elect to preserve amivantamab for later line treatment.
Uptake rate	95%	Daratumumab PSD, November 2021 PBAC Meeting with May 2022 Addendum	The submission claimed that the uptake rate applied in the daratumumab amyloidosis submission was reasonable as it was a condition with high unmet need. The evaluation considered that the uptake assumed was uncertain; given the inferior safety profile. However, it might be reasonable to assume that the rate will be high due to the lack of effective therapies available within this cohort. The model was sensitive to this parameter, decreasing the proportion to 80% decreased the financial estimates by 16%. The DUSC considered there would be a proportion of patients who would be too frail to attempt treatment with amivantamab plus PBC and a more reasonable estimate would be 80%.
Treatment duration	1L: 66.84 weeks GF: 54.84 weeks 2L: 40.08 weeks	Based on PFS curves from the economic model.	The submission indicated that the treatment duration for 2L treatment was based on a lognormal extrapolation of PFS in the crossover phase of PAPILLON, however this could not be verified during the evaluation. For grandfathered patients the submission assumed patients would have completed initial treatment prior to PBS listing, thus the treatment duration was an estimate. The DUSC considered that PBS patients were likely to have shorter treatment durations than patients treated in the pivotal trial, due to the toxicity of amivantamab, and considered the treatment duration was likely overestimated. The DUSC agreed that it was reasonable for a shorter duration to be applied to grandfathered patients, however considered this duration may remain overestimated.
Average vials per script	Initial 4.5 Continuing 5.2	Product of the recommended dose, the average weight of patients from the PAPILLON trial, and the proportion of skipped/reduced doses.	The DUSC considered that dose reductions may be more likely in the PBS population and the average vials per script may be overestimated.

Source: Table 4.1, pp208-209 of the submission

Abbreviations: 1L, first line; 2L, second line; DUSC, Drug Utilisation Sub-Committee; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; ex20in, exon 20 insertion; GF, grandfathered; NSCLC, non-small cell lung cancer; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PFS, progression free survival; PSD, public summary document; RPBS, Repatriation Pharmaceutical Benefits Scheme.

6.75 The number of patients treated, the estimated use and the financial implications for the proposed PBS listing of amivantamab are summarised in Table 16.

Table 16: Estimated use and financial implications (using proposed effective prices for amivantamab)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients 1L	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of patients 1L (grandfathered)	█ ^{b 1}	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of patients 2L	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of patients treated 1L	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of patients treated total	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed 1L ^a	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Number of scripts dispensed grandfathered ^a	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed 2L ^a	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated financial implications of amivantamab						
Cost to PBS/RPBS less copayments 1L	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Cost to PBS/RPBS less copayments 1L (including grandfathered)	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Cost to PBS/RPBS less copayments 1L & 2L	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³

Source: Tables 4.5, 4.7 and 4.11, pp217, 219, 220 and 223-224 of the submission.

Abbreviations: 1L, first-line; 2L, second-line; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme

^a The number of scripts was estimated based on the proportion of patients under and above 80 kg, skipped doses and reduced doses as reported in the PAPILLON trial.

^b Based on submission's assumptions on the number of patients accessing amivantamab via a patient access program.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

- 6.76 The total cost to the PBS/RPBS of listing amivantamab was estimated to be \$0 to < \$10 million in Year 6, and a total of \$40 million to < \$50 million in the first 6 years of listing for first line therapy including grandfathered patients.
- 6.77 The submission applied a treatment duration of 66.84 weeks (15.43 months; 12 weeks initiating followed by 54.84 weeks continuing) based on the mean of the extrapolated PFS curve from the economic model. The financial estimates assume that treatment will continue until disease progression. The assumed treatment duration for amivantamab was long and uncertain given the adverse event profile of amivantamab and that it was dependent on the extrapolation functions applied in the economic model. This also did not align with the treatment duration of 67.03 weeks from the economic model. Duration of treatment was expected to be an important driver of the financial estimates.
- 6.78 The submission included additional incident patients with Stage I-II (< 500 patients over six years) and IIIA (< 500 patients over six years) disease that were expected to progress to Stage IIIB or Stage IV within the year. While it might be reasonable to assume that a proportion of Stage III A patients might progress within the year, the proportion of patients with Stage I-II disease that might progress remained uncertain. Sensitivity analysis conducted during the evaluation showed that decreasing the proportion of patients who develop later stage disease from Stage I-II disease to 0%

decreased the financial impact from \$50 million to < \$60 million to \$40 million to < \$50 million (-3%).

- 6.79 The submission did not present any changes in the use and financial impact of other medicines claiming that the proposed population does not respond well to currently available targeted therapies including TKIs and immune checkpoint inhibitors (ICIs).
- 6.80 The submission also did not consider the potential impact on other PBS-listed medications that might be used to manage the adverse events arising from treatment with amivantamab. In the PAPILLON trial, patients in the ACP arm received more concomitant medications (including antimicrobials, corticosteroids, blood substitutes such as albumin human and antithrombotic agents) during the treatment period. Compared to the proposed unit price of amivantamab, these concomitant medications are of relatively low cost and their exclusion from the financial estimates would likely have a small impact on the financial implications.
- 6.81 The submission claimed that the listing of amivantamab would not have an impact on any MBS items including biomarker testing for NSCLC and chemotherapy administration costs.
- 6.82 The submission assumed that 100% of patients would elect first-line systemic therapy with an uptake rate of 95%. These estimates appeared high as best supportive care could be a valid option, particularly given the inferior safety profile of amivantamab and the poor prognosis for this patient group. The financial estimates were highly sensitive to the uptake rate. A reduction in uptake rate from 95% to 80% led to a 15% decrease (from \$40 million to < \$50 million to \$40 million to < \$50 million) in the financial estimates over the 6 years. Revising the proportion of patients electing first-line therapy to 85% and uptake to 80% concurrently, reduced the financial estimates to \$30 million to < \$40 million (28% reduction).
- 6.83 To support the submission's proposal for an alternative PBS restriction (to include amivantamab monotherapy for second-line use after progression on PBC), the submission estimated that an additional < 500 patients would receive amivantamab across 6 years resulting in an additional \$0 to < \$10 million (+5%) to the PBS/RPBS. This estimate is based on the dosing frequency of first-line patients which is inconsistent with the TGA PI. When the dosing frequency from the TGA PI the inclusion of the additional < 500 patients increased the financial estimated by \$0 to < \$10 million (+6%). Some key uncertainties that might impact these estimates include:
- The treatment duration in this population was based on parametric extrapolation of the crossover patients in the PAPILLON trial. This extrapolation was not described in the submission.
 - The submission assumed that 70.3% of patients would progress from first-line treatment to second-line, based on the proportion of patients who received subsequent systemic therapy in the PAPILLON trial. Although 70.3% of patients in

the CP arm of the PAPILLON trial had subsequent therapy, only 41.9% of patients in the CP arm received amivantamab monotherapy. As such, this may be an overestimate as not all patients would opt to be treated with amivantamab or be eligible.

6.84 Overall, the DUSC considered that the estimates presented in the submission were overestimated. The main issues were as follows:

- The assumed percentage of patients who would elect first-line systemic therapy (100%; 2025–2030) was overestimated and a more reasonable estimate would be in the range of 80–85%. The Pre-PBAC Response argued that ACP will be the first effective targeted therapy for patients with ex20ins mutations and therefore maintained that nearly all patients would elect to receive first-line systemic therapy. However, the Response presented updated financial estimates that assumed the proportion of patients who would elect first-line systemic therapy to be 93%, i.e., the midpoint of 85% and 100%. The impact of this change is a reduction to the cost for PBS/RPBS of \$0 to < \$10 million in Year 1, \$0 to < \$10 million in Year 6, totalling \$0 to < \$10 million across 6 years.
- The submission assumed that 84% of patients would elect first-line systemic treatment (2023–2024), based on the AURORA final report ex20ins July 2024, and that the remaining 16% would elect to have radiotherapy or surgery. If an alternative listing was recommended that allows patients to receive treatment in the first- or second-line setting, the proportion who would likely elect first-line amivantamab plus PBC may be lower than 80–85%, if some patients elect to preserve amivantamab for later line treatment. The Pre-PBAC Response argued that given the extremely poor prognosis of patients diagnosed with ex20ins, many do not survive to receive second-line treatment, and therefore considered that it was unlikely that amivantamab would be preserved for a later line treatment.
- The assumed uptake of amivantamab (95%) was overestimated as a proportion of patients would be too frail to attempt treatment with amivantamab plus PBC and a more reasonable estimate would be 80%. The Pre-PBAC Response maintained that the assumed update was appropriate as fragility had already been accounted for in the financial estimates through the proportion of patients who elect first-line systemic therapy (as frail patients would not elect treatment), and secondly, through the proportion of patients with an ECOG performance status of 0–2.
- The number of scripts was overestimated as the assumed treatment duration and dose were overestimated. The DUSC considered that PBS patients were likely to experience an increased number of adverse effects and are therefore more likely to be reduced to a lower dose or discontinued than patients treated in the pivotal trial. The Pre-PBAC Response maintained that data from the PAPILLON trial were appropriate to inform dose and treatment reduction and do not overestimate the number of scripts in the financial model.

Quality Use of Medicines

- 6.85 The submission acknowledged that the quality use of amivantamab will be underpinned by ensuring that clinicians are aware of the appropriate patient profile and circumstances of use for which amivantamab may be prescribed. The submission outlined four groups of stakeholders who play a fundamental role in the appropriate use of amivantamab: patients, prescribers, nursing staff and dispensers. Each of these stakeholder groups will be provided with appropriate education, resources and support from the sponsor to promote appropriate prescribing and use of amivantamab. The education and resources provided by the sponsor will focus on key quality use of medication discussion points, including: identifying the appropriate patients for amivantamab therapy; promoting appropriate level of awareness of amivantamab and relevance to other clinical decisions; education on potential drug-drug interactions; education on patient assessment prior to dosing, with reference to a patients' medical history and comorbidities; education on the appropriate dosing and IV infusion support as per the recommendations in the draft PI.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of amivantamab, for the treatment of patients with epidermal growth factor receptor (*EGFR*) exon 20 insertion (ex20ins) mutation positive locally advanced or metastatic non-small cell lung cancer (NSCLC). The PBAC considered it was reasonable for amivantamab to be available for patients in the first- and second-line setting. The PBAC recognised there was a high clinical need for additional treatment options for patients with this rare form of *EGFR* mutation, which has shown to have a limited response to conventional treatments. The PBAC considered the evidence presented demonstrated a progression-free and overall survival (OS) benefit over the comparator (platinum-based chemotherapy) but the magnitude of benefit in terms of OS was uncertain. The PBAC considered amivantamab would be cost-effective with an incremental cost-effectiveness ratio (ICER) of \$55,000 to < \$75,000 per quality adjusted life year (QALY) gained. The PBAC considered the financial estimates remained overestimated and should be revised based on advice provided by the Drug Utilisation Subcommittee (DUSC).
- 7.2 The PBAC noted the input from individuals, health care professionals, Lung Foundation Australia, the International Cancer Advocacy Network's Exon 20 Group, and Rare Cancers Australia emphasising the clinical need for effective treatment options for this population, given that patients have a poor prognosis and there is currently no other therapy that targets the *EGFR* ex20ins mutation. The PBAC noted the consumer comments outlining the clinical benefits associated with amivantamab, based on the results of the PAPHILLON trial. The PBAC noted comments stating that the cost of amivantamab remained a financial burden to patients and that a PBS listing would

ensure equity of access. In addition, the PBAC noted the Medical Oncology Group of Australia's support for the submission.

7.3 With regards to the requested restriction, the PBAC advised that:

- The clinical evidence presented by the submission were adequate to confirm the clinical benefit of amivantamab after disease progression on (or after) platinum-based chemotherapy (PBC). The PBAC also noted the high unmet need for this patient population and that the TGA Delegate was inclined to approve the second-line indication for full registration (see paragraph 2.4). The PBAC agreed with ESC and were supportive of a listing that allows patients to receive treatment in the first- or second-line setting. Therefore, the PBAC considered it reasonable to remove the following criteria: 'Patients must not have received systemic therapy for this condition in the metastatic setting prior to initiation of this drug' and 'the treatment must be initiated with platinum-based chemotherapy.' However, noted that to avoid inappropriate use of amivantamab monotherapy in the first-line setting, the restriction should include a criterion limiting treatment to be either in combination with platinum-based chemotherapy where the patient has not previously received systemic therapy for this condition in the metastatic setting prior to initiation of this drug (i.e. used in combination with PBC in the first line setting) or be the sole PBS subsidised therapy where the condition has progressed following treatment with platinum-based chemotherapy (i.e. used as monotherapy in the second-line setting).
- Owing to the lack of efficacy of EGFR TKIs in patients with ex20in mutations (insensitive to ex20in mutations), the PBAC recommended flow-on amendments to the existing initial PBS listings items for gefitinib, erlotinib and afatinib for Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC. The flow-on amendments are intended to exclude patients with EGFR ex20ins-positive NSCLC with the addition of the clinical criterion: 'Patient must not have evidence in tumour material of an activating epidermal growth factor receptor (EGFR) exon 20 insertion mutation.' The PBAC noted this would be consistent with the July 2023 PBAC recommendation for mobocertinib. The PBAC considered that these flow-on changes should also apply to the initial treatment restrictions of osimertinib in the first-line setting. The PBAC considered that it was not necessary for the second-line listing of osimertinib, as it already specifies the mutation type of T790K.
- The PBAC considered that the current amended wording in the initial phase will allow access to both new patients who had not been treated with amivantamab before and grandfathered patients.

7.4 The PBAC considered the nominated comparator, PBC (represented in the clinical trial evidence by carboplatin and pemetrexed), was appropriate.

7.5 The PBAC noted the submission was based on the PAPHON trial, an open-label, randomised, controlled trial comparing amivantamab and carboplatin-pemetrexed therapy (ACP) (n=153) to carboplatin-pemetrexed (CP) (n=155), in patients with *EGFR*

exon20in locally advanced or metastatic NSCLC. The PBAC noted the various limitations with the PAPILLON trial (paragraph 6.15). While acknowledging these limitations, the PBAC considered the trial adequately demonstrated that the addition of amivantamab to first-line chemotherapy increased progression-free survival (PFS) (hazard ratio [HR] 0.395, 95% CI: 0.296, 0.528) and objective response rate (ORR) (odds ratio 2.971, 95% CI: 1.844, 4.787) (data cutoff May 2023 with a median follow-up of 14.9 months). Overall, the PBAC considered that based on the PFS and ORR clinical outcomes, the claim of superior comparative effectiveness of ACP over CP was supported. The PBAC also considered the clinical evidence supported an OS advantage for ACP over CP, though due to the limitations of the PAPILLON trial, the magnitude of this benefit remained uncertain.

- 7.6 The PBAC noted the submission provided additional data to support a listing that allows patients to receive treatment in the first- or second-line setting, including data from the PAPILLON crossover phase for amivantamab and the CHRYSALIS study, a phase I, open-label, dose-escalation, and dose-expansion single-arm study, which included a post-platinum population with *EGFR* exon20ins NSCLC. The PBAC considered these data were adequate to confirm the clinical benefit of amivantamab for second-line treatment, after disease progression on (or after) platinum-based chemotherapy.
- 7.7 The PBAC considered the claim of inferior safety of ACP vs. CP was reasonable. The PBAC noted patients in the ACP arm experienced approximately twice as many Grade ≥ 3 treatment emergent adverse events (TEAEs) and TEAEs that resulted in treatment discontinuation or death compared to the CP arm. The PBAC also considered the difference in thrombosis incidence (pulmonary embolism 7.9% ACP vs. 4.5% CP, deep vein thrombosis 6.6% ACP vs. 1.9% CP) was clinically important and raised potential concern regarding patient management.
- 7.8 The submission presented a cost-utility analysis to support the cost-effectiveness of ACP vs. CP, with the economic model reporting an ICER of \$75,000 to < \$95,000 per QALY gained. The PBAC noted the ESC considered that the results of the economic evaluation were associated with a number of uncertainties, as discussed in paragraphs 6.45 and 6.68. The PBAC also noted that the utilities applied to the model were high; however, the PBAC noted that the incremental QALYs gained in the ACP arm vs. CP arm (0.8164) appeared largely consistent with that observed for other targeted therapies. Further, the PBAC noted the impact of changing utilities was not large and it was likely amivantamab would remain cost effective if alternative utilities were used. In this context, the PBAC advised that an ICER of not more than \$55,000 to < \$75,000 per QALY gained with the exclusion of end-of-life care costs (as discussed in paragraph 6.64) would be appropriate and noted that a price reduction would be required for amivantamab to be considered cost-effective.
- 7.9 The PBAC considered that the financial estimates were likely overestimated:

- The PBAC agreed with the DUSC that the proportion of patients with Stage IIIB/IV disease electing first-line systemic therapy (submission assumed 100% 2025–2030) was overestimated – the PBAC considered that 85% was more reasonable as some patients might elect best supportive care given the adverse event profile of amivantamab.
- While noting that patient frailty would also be accounted for through the proportion of patients who elect first-line systemic therapy and through the proportion of patients with an ECOG performance status of 0–2, the PBAC agreed with the DUSC that the uptake rate remained overestimated (submission assumed 95%) – the PBAC considered that an uptake of 85% was more reasonable.

The PBAC noted that DUSC considered that the assumed treatment dose and treatment duration for the first- and second-line settings were likely overestimated but considered the assumptions were reasonable.

- 7.10 The PBAC considered the financial impact moderate for this rare malignancy. The PBAC noted the DUSC’s advice that minor changes to the methods used to derive the utilisation and financial estimates and structure of the estimates model should be considered. The PBAC advised that the financial estimates should be revised as per the DUSC advice noted in paragraph 7.9.
- 7.11 The PBAC recommended that amivantamab should not be treated as interchangeable with any other drugs.
- 7.12 The PBAC advised that amivantamab is suitable for prescribing by medical practitioners only.
- 7.13 The PBAC recommended that the Early Supply Rule should not apply to amivantamab.
- 7.14 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for amivantamab:
- a) The treatment is not expected to provide a substantial improvement in efficacy compared to PBC but is expected to provide a moderate benefit in terms of PFS;
 - b) The treatment is not expected to address an urgent clinical need because alternative therapies (PBC) are PBS listed;
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT	PBS item code	Max. Amount	No. of Rpts
AMIVANTAMAB	New (Public) New (Private)	2100 mg	5
Available brands			
Rybrevent amivantamab 350 mg/7 mL injection, 7 mL vial			
Category / Program: Section 100 – Efficient Funding of Chemotherapy – Public (HB)/ Private (HS)			
Prescriber type: Medical Practitioners			
Benefit type: Authority Required (immediate assessment- telephone/online application avenues)			
Administrative Advice: No increase in the maximum amount or number of units may be authorised.			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Administrative Advice: Special Pricing Arrangement apply.			
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.			
Restriction Summary [new 1] / Treatment of Concept: [new 2]			
Indication: Stage IIIB/ IIIC (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)			
Treatment Phase: Initial treatment			
Clinical criteria:			
Patient must have evidence in tumour material of an activating epidermal growth factor receptor (EGFR) exon 20 insertion mutation			
AND			
Clinical criteria:			
Patient must have/have had a WHO performance status of no greater than 2 at treatment initiation with this drug for this condition.			
AND			
Clinical criteria:			
Patient must not have previously received this drug for this condition; OR			
Patient must be each of: (i) currently receiving non-PBS subsidised supply for this drug for this PBS indication, (ii) free of disease progression since commencing non-PBS subsidised supply.			
AND			
Clinical criteria:			
The treatment must be/have been in combination with platinum-based chemotherapy (PBC) where the patient has not previously received systemic therapy for this condition in the metastatic setting, (i.e. used in combination with PBC in the first line setting) OR			
The treatment must be/have been the sole PBS subsidised therapy at the time of treatment initiation where the condition has progressed following treatment with platinum-based chemotherapy, (i.e. used as monotherapy in the second line setting).			
Administrative Advice:			
A patient may only qualify for PBS-subsidised treatment under this restriction once. Following completion of the initial PBS-subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.			

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MEDICINAL PRODUCT	PBS item code	Max. Amount	No. of Rpts
AMIVANTAMAB	New (Public) New (Private)	2100 mg	7
Available brands			
Rybrevant amivantamab 350 mg/7 mL injection, 7 mL vial			
Category / Program: Section 100 – Efficient Funding of Chemotherapy – Public (HB)/ Private (HS)			
Prescriber type: Medical Practitioners			
Benefit type: Authority Required (immediate assessment- telephone/online application avenues))			
Administrative Advice: No increase in the maximum amount or number of units may be authorised.			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Administrative Advice: Special Pricing Arrangement apply.			
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.			
Restriction Summary [new 3] / Treatment of Concept: [new 4]			
Indication: Stage IIIB/ IIIC (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)			
Treatment Phase: Continuing treatment			
Clinical criteria			
Patient must have previously received PBS-subsidised treatment with this drug for this condition			
AND			
Clinical criteria			
Patient must not have developed disease progression while receiving treatment with this drug for this condition			

8.2 Flow on changes:

1. Amend initial treatment phase of gefitinib (8769M), erlotinib (25 mg 10022L, 100 mg 10020J, 150 mg 10014C) and afatinib (20 mg 11335N, 30 mg 11341X, 40 mg 11359W, 50 mg 11329G) for Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC listings as follows:

Population criteria
Patient must have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors in tumour material; AND
Population criteria
Patient must not have evidence in tumour material of an activating epidermal growth factor receptor (EGFR) exon 20 insertion mutation

2. Amend initial treatment phase of osimertinib 80 mg (12232T,) as first-line EGFR tyrosine kinase inhibitor therapy for Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC listings as follows:

Population criteria
Patient must have evidence in tumour material of an activating epidermal growth factor receptor (EGFR) gene mutation known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors; AND
Population criteria
Patient must not have evidence in tumour material of an activating epidermal growth factor receptor (EGFR) exon 20 insertion mutation.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.