5.01 AMIVANTAMAB
Solution concentrate for I.V. infusion 350 mg in 7 mL, Rybrevant®,
LAZERTINIB,
Tablet 80 mg (as mesylate monohydrate),
Tablet 240 mg (as mesylate monohydrate),
Lazcluze®,
JANSSEN-CILAG PTY LTD

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 (Efficient Funding of Chemotherapy Program) Authority Required Pharmaceutical Benefits Scheme (PBS) listing for amivantamab and a Section 85 Authority Required PBS listing of lazertinib used as combination therapy for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with evidence in tumour material of an activating epidermal growth factor receptor mutation (*EGFR*m) known to confer sensitivity to *EGFR* tyrosine kinase inhibitors (TKIs).

1.2 While the submission did not specify the type of *EGFR* mutation in the wording of the request, it referred to exon 19 deletions or exon 21 L858R substitution, as specified in the requested TGA indications for both amivantamab and lazertinib, and the inclusion criteria of the pivotal MARIPOSA trial.

1.3 Listing was requested on the basis of a cost-effectiveness analysis versus osimertinib. The key components of the clinical issues addressed by the submission are presented in Table 1.

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

Component	Description
Population	First-line treatment of patients with locally advanced or metastatic *EGFR* gene mutation positive NSCLC.
Intervention	Amivantamab IV infusion (QW for 4 weeks) in combination with lazertinib 240 mg oral tablet once daily, followed by amivantamab IV infusion Q2W starting at Week 5 in combination with lazertinib 240 mg oral tablet once daily until disease progression.
Comparator	Osimertinib 80 mg tablet once daily until disease progression.
Outcomes	PFS, OS, ORR, DoR, TTST, PFS2, TTSP, icPFS, HRQoL, and safety.
Clinical claim	In patients with locally advanced or metastatic *EGFR*m NSCLC, first-line treatment with amivantamab in combination with lazertinib, is superior in effectiveness and inferior but manageable in safety compared with osimertinib.

Source: Table 1.1, p20 of the submission.
DoR = duration of response, *EGFR* = epidermal growth factor receptor, HRQoL = health-related quality of life, icPFS = intracranial PFS, IV = intravenous, mg = milligram, NSCLC = non-small cell lung cancer, ORR = objective response rate, OS = overall survival, PFS = progression free survival, PFS2 = PFS after first subsequent treatment, QW = once weekly, Q2W = once every two weeks, TTSP = time to symptomatic progression, TTST = time to subsequent treatment.

1.4 The submission requested PBS listing of amivantamab plus lazertinib (A+L) for two populations:

- Primarily, for patients who have been diagnosed *de novo* with locally advanced or metastatic (stage IIIB/C or IV) *EGFR*m NSCLC;
- Additionally, for stage IB-IIIA patients who have progressed to locally advanced or metastatic disease following earlier adjuvant osimertinib therapy.

2 Background

Registration status

2.1 An application to extend the registered indication for amivantamab and a standard pathway application for the registration of lazertinib was submitted to the Therapeutics Goods Administration (TGA). Both drugs are being assessed through Project Orbis.

2.2 The requested indications are:

- Amivantamab is indicated in combination with lazertinib for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations.
- Lazertinib in combination with amivantamab is indicated for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations.

2.3 The PBAC submission was made under the TGA/PBAC Parallel Process. The Delegate's Overview for each agent signalled an inclination to approve both amivantamab and lazertinib for the requested indications, subject to additional conditions of registration related to the final dataset of the MARIPOSA trial and a safety analysis of venous thromboembolism (VTE).

2.4 The Delegate requested advice from the Advisory Committee on Medicines (ACM) for both agents at the ACM meeting that took place on 6−7 February 2025. The ACM indicated that A+L has an overall positive benefit-risk profile (ratified ACM minutes for A+L) for the requested indications shown in paragraph 2.2, with the addition of the statement "Prophylactic anticoagulation is recommended for at least the first 4 months of therapy and ongoing anticoagulation is at clinician discretion" to both the amivantamab and lazertinib indications. For lazertinib, the ACM also advised the inclusion in the Product Information (PI) of the following statement: "In the event of recurrent VTE despite therapeutic anticoagulation, withhold lazertinib and amivantamab until clinically stable. Thereafter, continuation of lazertinib monotherapy may be an option if clinically warranted."

Previous PBAC consideration

2.5 Osimertinib for the first-line treatment of locally advanced or metastatic (stage IIIB or IV) *EGFR*m positive NSCLC was considered at the July 2019 and July 2020 PBAC meetings and received a positive recommendation for its listing on the PBS at the July 2020 PBAC meeting. The PBAC was satisfied that osimertinib provided, for some patients, a significant improvement in efficacy and reduction in toxicity over PBS listed *EGFR*-TKIs. The PBAC considered that the cost effectiveness of osimertinib would be acceptable if the incremental cost effectiveness ratio (ICER) was less than $45,000−$75,000/quality adjusted life year (QALY) gained (paragraphs 7.1−7.2, osimertinib public summary document [PSD], July 2020).

2.6 Amivantamab was considered at the November 2024 PBAC meeting and received a positive recommendation for listing on the PBS for the treatment of patients with EGFR exon 20 insertion mutation positive locally advanced or metastatic NSCLC in the first- and second-line setting. The PBAC considered amivantamab would be cost-effective with an ICER of not more than $55,000 to < $75,000 per QALY gained (paragraph 7.8, amivantamab PSD, November 2024).

3 Requested listing

3.1 The requested listings for A+L are provided below. Secretariat suggestions and additions proposed are shown in italics and deletions are in strikethrough.

Amivantamab (initial)

MEDICINAL PRODUCT **Form**		**PBS item code**	**Max. Amount**	**№.of Rpts**
AMIVANTAMAB Solution concentrate for I.V. infusion, 350 mg in 7 mL		NEW (Public) NEW (Private)	1400 mg	3
Available brands				
Rybrevant amivantamab 350 mg/7 mL injection, 7 mL vial				
Restriction Summary [new1] / Treatment of Concept: [new1A]				
	Category / Program: ☒ Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
	Prescriber type: ☒Medical Practitioners			
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)			
	Administrative Advice: ~~No increase in the maximum quantity may be authorised~~ *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 arrangements 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.			
	~~**Episodicity:**~~ [blank]			
	Severity: ~~Stage IIIB or IIIC (locally advanced) or IV (metastatic)~~			

	Stage IIIB/IIIC (locally advanced) or Stage IV (metastatic)
	Condition: Non-small cell lung cancer (NSCLC)
	Indication: ~~Stage IIIB or IIIC (locally advanced) or IV (metastatic) non-small cell lung cancer (NSCLC)~~ *Stage IIIB/IIIC (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)*
	Treatment Phase: Initial *treatment*
	Clinical criteria:
	Patient must not have previously received ~~PBS-subsidised treatment with~~ this drug for this condition; ~~AND~~ *OR*
	Patient ~~grandfathering from non-PBS to PBS-subsidised supply~~ must be each of: (i) currently receiving non-PBS subsidised supply for this *combination therapy* ~~drug~~ for this PBS indication, ~~(ii) untreated with this drug at the time that non-PBS subsidised supply was commenced, (ii)~~ free of disease progression since commencing non-PBS subsidised supply.
	AND
	Clinical criteria:
	~~Patient must have a WHO performance status of 2 or less, AND~~ *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 received previous PBS-subsidised treatment with an *epidermal growth factor receptor* (*EGFR*) *tyrosine kinase inhibitor (*TKI) in the locally advanced/metastatic setting; OR
	Patient must have developed intolerance to another *epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (*TKI) of a severity necessitating permanent treatment withdrawal.
	Clinical criteria:
	~~Patient must be initiated as combination therapy consisting of: (i) amivantamab, (ii) lazertinib;, AND~~ *The treatment must be initiated in combination with lazertinib (refer to the Therapeutic Goods Administration (TGA) approved Product Information for the dosage regimens for lazertinib and amivantamab).*
	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~~
	~~**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.~~

Amivantamab (continuing)

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
AMIVANTAMAB Solution concentrate for I.V. infusion, 350 mg in 7 mL	NEW (Public) NEW (Private)	1400 mg	~~5~~ 11
Available brands			
Rybrevant amivantamab 350 mg/7 mL injection, 7 mL vial			

Restriction Summary [new2] / Treatment of Concept: [new2A]		
		Category / Program: ☒ Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
		Administrative Advice: ~~No increase in the maximum quantity may be authorised~~ *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 arrangements 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.
		Episodicity: [blank]
		Severity: ~~Stage IIIB or IIIC (locally advanced) or IV (metastatic)~~ *Stage IIIB/IIIC (locally advanced) or Stage IV (metastatic)*
		Condition: Non-small cell lung cancer (NSCLC)
		Indication: ~~Stage IIIB or IIIC (locally advanced) or IV (metastatic) non-small cell lung cancer (NSCLC)~~ *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~~
		AND
		Clinical criteria:
		Patient must not have developed disease progression while receiving treatment with this drug for this condition
		Clinical criteria:
		The treatment must be initiated in combination with lazertinib (refer to the Therapeutic Goods Administration (TGA) approved Product Information for the dosage regimens for lazertinib and amivantamab).
		~~**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.~~

Lazertinib (single listing)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
LAZERTINIB					
lazertinib 80 mg tablet, 60	NEW	1	60	5	Lacluze
lazertinib 240 mg tablet, 30	NEW	1	30	5	Lacluze
Restriction Summary [new3] / Treatment of Concept: [new3A]					
					Category / Program: ☒GENERAL - General Schedule (Code GE)
					Prescriber type: ☒Medical Practitioners
					Restriction type: ☒Authority Required (immediate assessment- telephone/online PBS authorities)
					Administrative Advice: No increase in the maximum quantity *or number of units* may be authorised.
					Administrative Advice: No increase in the maximum number of repeats may be authorised.
					Administrative Advice: Special pricing arrangements 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.
					Episodicity: [blank]

	Severity: ~~Stage IIIB or IIIC (locally advanced) or IV (metastatic)~~ *Stage IIIB/IIIC (locally advanced) or Stage IV (metastatic)*
	Condition: Non-small cell lung cancer (NSCLC)
	Indication: ~~Stage IIIB or IIIC (locally advanced) or IV (metastatic) non-small cell lung cancer (NSCLC)~~ *Stage IIIB/IIIC (locally advanced) or Stage IV (metastatic) non- small cell lung cancer (NSCLC)*
	Clinical criteria:
	The treatment must be initiated in combination with amivantamab (refer to the Therapeutic Goods Administration (TGA) approved Product Information for the dosage regimens for lazertinib and amivantamab).

3.2 The submission requested a Special Pricing Arrangement (SPA) to apply to both the amivantamab vial and the lazertinib pack.

3.3 Amivantamab is administered as one of two flat doses dictated by the weight of the patient. Each vial contains 350 mg of amivantamab. The draft amivantamab PI indicates the following with respect to dosage:

- Patients weighing less than 80 kg receive 1,050 mg per week of amivantamab for the first 4 weeks, followed by 1,050 mg every 2 weeks thereafter until disease progression.
- Patients weighing greater than or equal to 80 kg receive 1,400 mg per week of amivantamab for the first 4 weeks, followed by 1,400 mg every 2 weeks thereafter until disease progression.

In the pivotal MARIPOSA trial, the reported mean weight of patients was 63.9 kg with a range of 32 to 118 kg. While the evaluation considered it to be unclear whether the trial population reflects the PBS population with respect to weight, the submission noted that a reasonable proportion of patients (approximately 12%) were over 80 kg, and given these patients require a higher dose, the maximum amount proposed for amivantamab (1,400 mg) is in line with the dose required for a patient >80 kg (i.e. 1,400 mg per infusion in the initial and continuing phases). The number of repeats proposed in the submission for initial therapy (weekly dosing) was 3 repeats, which would appropriately cover 4 weeks of therapy; however, the submission proposed 5 repeats for continuing therapy (fortnightly dosing), which would only cover approximately 3 months of therapy. The Secretariat commented that 11 repeats would be required to provide approximately 6 months of therapy.

3.4 The submission proposed separate listings for lazertinib for initial and continuing therapy. Given that lazertinib will be taken in combination with amivantamab, and to reduce administrative burden, the Secretariat proposed a single listing for each strength of lazertinib. The PBAC considered the maximum supply should be 6 months for all three dosing options. Lazertinib 240 mg listing would provide the standard dosing of 240 mg daily with 5 repeats and that will be sufficient for 6 months. However, to provide 6 months' supply for patients using the 80 mg strength for dose reduction, the appropriate repeats should be 2. This would be sufficient for patients dosed at 80 mg once daily. For patients dosed at 160 mg daily, prescribers can request 3 more

repeats from Services Australia. A prescribing instruction can be added to facilitate this approach.

3.5 In addition to the requested listing for patients with advanced/metastatic *EGFR*m NSCLC, the submission requested a PBS restriction that would permit A+L use in patients with locally advanced/metastatic disease following earlier adjuvant osimertinib therapy. The requested listing included a criterion: 'Patient must not have received previous PBS-subsidised treatment with an *EGFR* TKI in the locally advanced/metastatic setting;' or 'Patient must have developed intolerance to another *EGFR* TKI of a severity necessitating permanent treatment withdrawal'; this would allow treatment with A+L after prior osimertinib in the adjuvant setting. The PBAC noted that under the current PBS listing for osimertinib, patients are not able to receive osimertinib in the advanced/metastatic setting if they have already received a previous *EGFR* TKI in any setting (unless intolerant).

3.6 The proposed population criterion for amivantamab ('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') is broader than the requested TGA indications and the inclusion criteria of the pivotal trial (MARIPOSA). The requested TGA indications and inclusion criteria of MARIPOSA specify the treatment of patients with the *EGFR* mutations exon 19 deletions or exon 21 L858R substitution, while the proposed PBS listing does not specify the *EGFR* mutations.

- The submission stated that the exclusion of criteria specific to exon status from the proposed PBS listing was informed by the PBAC and MSAC's acceptance of advice from an *EGFR*/TKI stakeholder meeting held on October 2012 prior to their considerations of erlotinib, gefitinib and afatinib submissions for NSCLC. The *EGFR*/TKI stakeholder meeting advised that a PBS restriction should not specify the specific *EGFR* activating mutations, noting that the strongest evidence is limited to the *EGFR* ex19del and L858R mutations, which are estimated to account for about 70% of detected *EGFR* mutations (paragraph 3.3, osimertinib PSD, November 2023).
- The submission further stated that the same population criterion as proposed by the submission (i.e. without the particular *EGFR* mutation specified) has since been recommended by the PBAC for the PBS-listing of osimertinib. The clinical evidence provided to support the claim, the FLAURA trial, specified inclusion of patients with *EGFR* ex19del and L858R, either alone or in combination with other mutations (paragraph 6.5, osimertinib PSD July 2019 and July 2020), and the recommended PBS listing did not specify the detection of those mutations (paragraph 8.1, osimertinib PSD July 2020). However, the TGA indication for osimertinib is consistent with the osimertinib PBS-listing, as it does not specify the specific mutations, stating that the 'tumours must have activating *EGFR* mutations'.

In addition to osimertinib, the proposed population criterion for amivantamab that does not specify the specific EGFR mutations is consistent with that applied to other *EGFR*-TKIs (erlotinib, gefitinib and afatinib) currently available on the PBS for treating NSCLC.

3.7 The criteria proposed for continuing treatment with A+L, 'Patient must not have developed disease progression while receiving treatment with this drug for this condition' was not consistent with treatment practice in the MARIPOSA trial, but consistent with the draft PIs. In MARIPOSA, patients who progressed on A+L were allowed to continue treatment at the discretion of the investigator: at the primary data cut off point, 53.1% of patients in the A+L arm whose disease had progressed were still receiving treatment with A+L. The potential applicability issue associated with this difference between the proposed listing and the trial evidence with regard to treatment beyond progression is discussed in paragraph 6.19. The draft PI states that A+L should be administered until progression or unacceptable toxicity or no longer tolerated by the patient.

3.8 The submission noted that approximately <500 patients are anticipated to be grandfathered from an early access program upon PBS listing. The submission did not propose a grandfather restriction and stated that wording proposed in the initial restrictions for both amivantamab and lazertinib provides access for both treatment naïve and grandfathered patients. The Secretariat has proposed amendments to the restriction wording to better facilitate this access.

3.9 According to the respective draft TGA PIs for amivantamab and lazertinib, both agents are indicated for use in combination with the other. However, the proposed initial treatment restriction for both agents states that "Patient must be initiated as a combination therapy consisting of (i) amivantamab and (ii) lazertinib". This wording would allow patients to discontinue combination therapy and continue with either agent as monotherapy (patients were allowed to continue with monotherapy in the MARIPOSA trial if a study treatment was withheld due to an adverse event or unacceptable toxicity, noting that one or both agents could be restarted upon resolution of toxicity). In the case of recurrent VTEs, the respective PIs state that treatment with one agent must be permanently discontinued, and treatment with the other agent may continue at the physician's discretion. However, the Delegate's Overview notes that neither amivantamab nor lazertinib have been approved for use as monotherapy in the proposed population; in particular, the efficacy of amivantamab monotherapy in the first-line setting for patients with *EGFR* ex91del or L858R mutated advanced NSCLC has not been established.

3.10 The submission proposed a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less as an initiation eligibility criterion. However, the inclusion criteria for the MARIPOSA trial applied a WHO ECOG status of 0 or 1. The initial treatment PBS restrictions for osimertinib, erlotinib, gefitinib and afatinib all specify that patients must have a WHO performance status of 2 or less. However, there is high level of toxicity related to A+L (paragraphs 6.37−6.39),

and therefore it may be appropriate for the proposed PBS restriction to match the trial with respect ECOG performance status.

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

4 Population and disease

4.1 Lung cancer is the fifth most common diagnosed cancer and the leading cause of mortality from cancer amongst Australians, with a significantly lower 5-year survival rate compared to other cancer types: more than half (53%) of lung cancer cases are of an advanced stage at diagnosis, (stage III, 11%; stage IV, 42%)[1]. The 5-year survival rate is approximately 15% for stage III and only 5% for stage IV disease[2].

4.2 NSCLC accounts for approximately 86.6% of all lung cancers[3] and comprises adenocarcinoma (40%), squamous cell carcinoma (25-30%) and large cell carcinoma (10-15%)[4].

4.3 Age standardised incidence rates of NSCLC have been relatively stable over the last twenty years, at 57 cases per 100,000 in 2000 to an estimated 56 cases per 100,000 in 2024[1]. However, the trend in its incidence differs between females and males: the incidence in males has been decreasing (from 84 cases/100,000 in 2000 to an estimated 61 cases/100,000 in 2024), whereas the incidence in females is increasing (36 cases/100,000 in 2000 to an estimated 52 cases/100,000 in 2024). These differences are thought to be attributed to differences in smoking behaviour[5].

4.4 *EGFR* mutations are one of the most common activating pathway events in NSCLC. Among patients with any stage NSCLC, mutations in the *EGFR* gene typically occur in exons 18 to 21. Most of these mutations comprise exon 19 deletions (ex19del) and L858R substitution mutations[2], both of which are referred to as classical/common *EGFR* mutations or sensitising mutations as they elicit a positive response to *EGFR* TKI treatment[6]. The frequency of *EGFR* ex19del and L858R substitutions, specifically

[1] NCCI, (2018). National cancer stage at diagnosis data https://ncci.canceraustralia.gov.au/features/national-cancer-stage-diagnosis-data

[2] Survival for lung cancer. (2021). Cancer Research UK. https://www.cancerresearchuk.org/about-cancer/lung-cancer/survival

[3] Zappa, C., & Mousa, S. A. (2016). Non-small cell lung cancer: current treatment and future advances. *Transl Lung Cancer Res, 5*(3), 288-300. doi:10.21037/tlcr.2016.06.07

[4] Herbst, R. S., Morgensztern, D., & Boshoff, C. (2018). The biology and management of non-small cell lung cancer. *Nature, 553*(7689), 446-454. doi:10.1038/nature25183

[5] De Matteis, S., Consonni, D., Pesatori, A. C., Bergen, A. W., Bertazzi, P. A., Caporaso, N. E et al (2013). Are women who smoke at higher risk for lung cancer than men who smoke? *Am J Epidemiol, 177*(7), 601-612. doi:10.1093/aje/kws445

[6] NCCN. (2025). Clinical Practice Guidelines in Oncology (NCCN Guidelines) Non-Small Cell Lung Cancer Version 3.2025 - January 14, 2025. Retrieved from www.nccn.org/ professionals

among patients with advanced *EGFR*m NSCLC, was reported in the submission to be around 84%[7].

4.5 In Australia, *EGFR*m NSCLC occurs predominantly in patients 60−65 years (but can be diagnosed as young as 30 years), in females, in patients who have never smoked, and in patients having Asian ethnicity[6,8].

4.6 The submission stated that the current and proposed clinical management algorithm was based on the 2023 European Society of Medical Oncology (ESMO) guidelines for *EGFR*m locally advanced or metastatic NSCLC and the recently published National Comprehensive Cancer Network (NCCN) NSCLC clinical practice guidelines. However, the PBAC noted that the treatment algorithm in the submission was not reflective of the NCCN treatment guidelines: although guidelines do include A+L as an 'other recommended regimen' for treatment of *de novo* diagnosed *EGFR*m NSCLC, osimertinib is the preferred treatment over A+L (NSCL-21 of the NCCN guidelines). The PBAC noted that the 2025 ESMO Oncogene-Addicted Metastatic Non-Small-Cell Lung Cancer Living Guidelines recommended osimertinib + chemotherapy or A+L[9], with the same level of preference. The PBAC noted that the combination of amivantamab with chemotherapy was recommended as a second line regimen following progression on osimertinib in the guidelines referred to above.

4.7 The submission considered that in both the current and proposed algorithms, patients who experience disease progression on first-line treatment, either with osimertinib or A+L, will receive chemotherapy or atezolizumab in combination with bevacizumab and platinum doublet chemotherapy (ABCP[10]). The evaluation considered that this was reasonable. The 2024 NCCN guidelines state that if progression is asymptomatic, or symptomatic but limited to the brain, subsequent therapy can include definitive local consolidative therapy and/or continuing osimertinib, noting that the latter is not permitted on the PBS. If progression is symptomatic and there are multiple lesions, recommended subsequent therapy includes amivantamab in combination with chemotherapy (not currently TGA approved) or a systemic therapy regimen (e.g., carboplatin plus paclitaxel).

4.8 There were no significant differences between the current and proposed treatment algorithms apart from the introduction of A+L as (i) a first-line treatment option for

[7] Melosky, B., Kambartel, K., Häntschel, M., Bennetts, M., Nickens, D. J., Brinkmann, J., et al (2022). Worldwide Prevalence of Epidermal Growth Factor Receptor Mutations in Non-Small Cell Lung Cancer: A Meta-Analysis. *Mol Diagn Ther, 26*(1), 7-18. doi:10.1007/s40291-021-00563-1

[8] Tan, L., Alexander, M., Officer, A., MacManus, M., Mileshkin, L., Jennens, R., et al(2018). Survival difference according to mutation status in a prospective cohort study of Australian patients with metastatic non-small-cell lung carcinoma. *Intern Med J, 48*(1), 37-44. doi:10.1111/imj.13491

[9] ESMO Oncogene-Addicted Non-Small Cell Lung Cancer Living Guideline v1.2, January 2025. Retrieved from: https://www.esmo.org/living-guidelines/esmo-oncogene-addicted-metastatic-non-small-cell-lung-cancer-living-guideline

[10] Atezolizumab, bevacizumab, carboplatin, and paclitaxel

patients with locally advanced or metastatic *EGFR*m NSCLC and (ii) for the treatment of patients who have progressed to locally advanced or metastatic disease after prior adjuvant osimertinib therapy. The submission justified their proposal for the use of A+L for osimertinib-experienced patients based on advice received from Australian clinical expect opinion, which suggests that osimertinib rechallenge may be appropriate in many instances as patients are still considered sensitive to *EGFR* TKIs. However, the current PBS restrictions do not permit retreatment with *EGFR* TKIs.

4.9 Amivantamab is a fully human, immunoglobulin G1 (IgG1) bispecific antibody with high affinity for both *EGFR* and mesenchymal-epidermal transition (MET) receptors. Lazertinib is an oral, highly potent, third generation, *EGFR* TKI. It selectively inhibits both primary activating *EGFR* mutations (exon 19 deletions and exon 21 L858R substitution mutations) and the *EGFR* T790M resistance mutation, while having less activity against wild-type *EGFR* lazertinib draft PI). A+L acts by targeting the extracellular ligand binding domain and the intracellular active site of *EGFR*, respectively, synergistically inhibiting the *EGFR* pathway more potently than either agent alone.

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

5 Comparator

5.1 The submission nominated osimertinib as the main comparator for A+L for the two requested populations. The main arguments provided in support of this nomination were as follows.

Locally advanced or metastatic population diagnosed *de novo*

5.2 The submission stated that based on Drug Utilisation Sub Committee (DUSC) data, approximately 90% of the locally advanced or metastatic *EGFR*m NSCLC population is currently treated with osimertinib (out of all the PBS-listed *EGFR* TKIs), hence it is most likely to be replaced by A+L in clinical practice once listed. Osimertinib is also recommended by NCCN clinical guidelines as the preferred first-line treatment for locally advanced/metastatic *EGFR*m NSCLC[11] (paragraph 4.6).

5.3 While the evaluation and the ESC considered that the nomination of osimertinib for this population was appropriate, they noted that osimertinib in combination with platinum and pemetrexed chemotherapy is being considered at the May 2025 PBAC meeting for the same indication and is a relevant near-market comparator. The ESC further noted that patients may already be accessing osimertinib in combination with chemotherapy given that chemotherapy is relatively inexpensive and possibly funded by hospitals or patients.

Locally advanced or metastatic population following prior adjuvant osimertinib

[11] NSCL-21 of the NCCN guidelines (first line systemic therapy).

5.4 The submission stated that the PBS-listed treatment for patients who have progressed to locally advanced or metastatic disease after prior adjuvant osimertinib therapy, ABCP, is not widely used in practice. The submission stated that osimertinib rechallenge, if allowed by the PBS, would be the preferred treatment option over chemotherapy, given the superior clinical effectiveness of osimertinib compared to chemotherapy in patients with *EGFR*m NSCLC.

5.5 The ESC considered that the nomination of osimertinib as the comparator for patients previously treated with adjuvant osimertinib was not appropriate given that it is not consistent with the current Australian clinical management algorithm and ESMO and NCCN guidelines, where amivantamab + platinum-based chemotherapy, without lazertinib, is used. Further, PBS-listed osimertinib is excluded for use in patients who have previously received PBS-subsidised treatment with osimertinib (paragraph 3.5).

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 (74), health care professionals (3) and organisations (3) via the Consumer Comments facility on the PBS website.

6.3 Rare Cancers Australia stated that the NSCLC patient population is faced with significant physical, psychological and financial challenges. The organisation stated that A+L has shown strong clinical results, with many patients reporting that their disease progression has slowed or halted. The organisation acknowledged that some patients have experienced some side effects including shortness of breath, fever, chills, and vomiting, although noted that intrusive side effects are also associated with the current treatments used in NSCLC.

6.4 Lung Foundation Australia wrote in support of A+L being listed on the PBS for NSCLC with *EGFR*m, noting the health, financial and social cost of lung cancer in patients who currently have low survival rates and limited treatment options available. The organisation emphasised that the median progression free survival (PFS) for A+L was longer than that for osimertinib in the pivotal trial for *EGFR*-mutated NSCLC [MARIPOSA], and identified this as the most important outcome for those people living with or caring for someone with lung cancer.

6.5 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the A+L submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the MARIPOSA trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit

Scale (ESMO-MCBS) for A+L, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement),[12] based on a comparison with osimertinib.

6.6 The health care professionals (HCPs) commented on the survival benefit associated with A+L over osimertinib, noting that some patients would be willing to accept the increased side effects of A+L for a potential improvement in life-expectancy. The HCPs stated that the risk benefit ratio of A+L would be considered and discussed on an individual patient basis, noting that A+L would not be suitable for all 1L metastatic *EGFR* mutant NSCLC patients.

6.7 The individuals who commented included someone with experience of taking A+L, those who would like access to A+L for NSCLC (20), a parent/partner or others directly caring for individuals with access to A+L or who would like access to A+L (12), and other interested individuals (including family members, friends, or members of the public) (41). The consumer input from those with the disease and their carers emphasised the high burden of disease and suffering associated with NSCLC, the variable effectiveness of existing treatments, including osimertinib, the side-effects experienced with current treatments and the desire for access to A+L, either because existing treatments had become ineffective and/or were seeking access to an additional line of therapy, if required. Comments described A+L as a treatment that could potentially provide more effective symptom control, improve quality of life, and ease the care-giving burden on families. Possible side effects were noted, with the one individual with access to A+L describing the need to stop amivantamab due to the side effects experienced and continue with lazertinib as monotherapy. Individuals wanting access to A+L considered that side effects were an acceptable trade-off for the potential improvement in both quality and duration of life, however they suggested they were hopeful the side effects would be less severe than those of current treatments. The current cost of A+L was noted as a significant barrier to access, particularly in the context of loss of earnings due to the disease and its treatment. The other interested individuals wrote in support of those they knew suffering the social, financial and physical burdens of either having, or caring for, someone with the disease. The PBAC also noted that a number of individuals supported the PBS listing of amivantamab-based treatment as a second-line regimen following progression on osimertinib.

Clinical trial

6.8 The submission was based on one ongoing head-to-head randomised controlled trial (RCT), MARIPOSA, comparing the efficacy and safety of A+L to osimertinib as first-line treatment in patients with locally advanced or metastatic NSCLC with evidence of an

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

EGFR gene mutation (specifically, exon 19del or exon 21 L858R substitution) (N=1,074).

6.9 Details of the trial presented in the submission are provided in Table 2.

Table 2: Studies presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
MARIPOSA NCT04487080	Primary Endpoint Analysis Clinical Study Report: A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with *EGFR*-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer - MARIPOSA. Includes protocol and SAP analyses reports. (Reports)	August 2023
	Overview of updated efficacy from 13 May 2024: A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First Line Treatment in Patients with *EGFR* Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer. (Reports)	May 2024
	Cho et al. Amivantamab plus Lazertinib in Previously Untreated *EGFR*-Mutated Advanced NSCLC. https://doi.org/10.1056/NEJMoa2403614. (Full publication)	N Engl J Med. 2024
	Cho et al. MARIPOSA: phase 3 study of first-line amivantamab + lazertinib versus osimertinib in *EGFR*-mutant non-small cell lung cancer. (Full publication)	Future Oncol. 2021. 10.2217/fon-2021-0923
	Felip et al. Amivantamab plus lazertinib versus osimertinib in first-line *EGFR*-mutant advanced non-small-cell lung cancer with biomarkers of high-risk disease: a secondary analysis from MARIPOSA. https://doi.org/10.1016/j.annonc.2024.05.541 (Full publication)	Annals of Oncol. 2024.
	Campelo et al. Effect of amivantamab dose interruptions on efficacy and safety of first-line amivantamab plus lazertinib in *EGFR* mutant advanced NSCLC: Exploratory analyses from the MARIPOSA study. (abstract and presentation).	ESMO 2024. https://doi.org/10.1016/j.esmoop.2024.102584
	Cho et al. Amivantamab plus lazertinib vs osimertinib as first-line treatment in patients with *EGFR*-mutated, advanced non-small cell lung cancer (NSCLC): Primary results from MARIPOSA, a phase III, global, randomized, controlled trial (abstract).	Annals of Oncol. 2023; 34(S2)
	Felip et al. Amivantamab plus lazertinib vs osimertinib in first-line *EGFR*-mutant advanced non-small cell lung cancer (NSCLC) with biomarkers of high-risk disease: A secondary analysis from the phase 3 MARIPOSA study. (abstract).	ASCO 2024
	Lu et al. Amivantamab plus lazertinib vs osimertinib as first-line treatment among Asian patients with *EGFR*-mutated, advanced non-small cell lung cancer (NSCLC): MARIPOSA subgroup analysis. (abstract).	Annals of Oncol. 2023; 34(S4)
	Schuler et al. Amivantamab Plus Lazertinib vs Osimertinib as First-line Treatment in Patients With *EGFR*-mutated, Advanced Non-small Cell Lung Cancer (NSCLC): Primary Results From MARIPOSA, a Phase 3, Global, Randomized, Controlled Trial (Previously presented at ESMO Congress 2023, FPN:LBA14, Byoung Chul Cho et al. - Reused with permission.) (abstract).	Oncol Res Treat 2024;47(suppl 1):260
	Shreeve et al. MARIPOSA: Randomized Phase 3 Study of First-line Amivantamab + Lazertinib vs Osimertinib vs Lazertinib in *EGFR*-mutant NSCLC.	Journal of Thoracic Oncology 2021; 16(3S): S620

Trial ID	Protocol title/ Publication title	Publication citation
	Besse et al. Mechanisms of Acquired Resistance to First-line Amivantamab Plus Lazertinib Versus Osimertinib in Patients With *EGFR*-mutant Advanced Non-Small Cell Lung Cancer An Early Analysis from the Phase 3 MARIPOSA Study. (presentation).	ESMO 2024
	Lee et al. Lazertinib vs Osimertinib in 1L *EGFR*-mutant Advanced NSCLC: A Randomized, Double-blind, Exploratory Analysis From MARIPOSA. (presentation).	WCLC 2024
	Gadgeel et al. Amivantamab Plus Lazertinib vs Osimertinib in First-line *EGFR*-mutant Advanced NSCLC: Longer Follow-up of the MARIPOSA Study. (presentation).	WCLC 2024
	Nguyen et al. Amivantamab Plus Lazertinib vs Osimertinib in First-line, *EGFR*-mutant Advanced NSCLC: Patient-relevant Outcomes From MARIPOSA. (presentation).	WCLC 2024

Source: Table 2.5, pp 57-58 of the submission.
ASCO = American Society of Clinical Oncology, *EGFR* = epidermal growth factor receptor, ESMO = European Society for Medical Oncology, NSCLC = non-small cell lung cancer, SAP = statistical action plan, WCLC = World Conference on Lung Cancer.

6.10 The key features of MARIPOSA are summarised in Table 3. The RCT comprised of three arms: A+L, osimertinib (monotherapy), and lazertinib (monotherapy). The evaluation considered data on A+L compared to osimertinib only.

6.11 The MARIPOSA trial is ongoing with the final analysis of overall survival (OS) expected to be available in the first 6 months of 2025. The submission presented results from 2 clinical cut offs (CCOs):

- Interim primary analysis (August 2023 CCO, median follow-up of 22.0 months for all reported outcomes).
- Updated efficacy summary (May 2024 CCO, median follow-up of 31.1 months, reported for OS and other key secondary efficacy outcomes). The updated efficacy analysis was unplanned; it was conducted upon request by the European regulatory authority.

6.12 The submission based its clinical claim on the primary outcome, PFS, from the August 2023 CCO, and the secondary outcome, OS, from the May 2024 CCO[13].

[13] The study met the primary endpoint in the clinical cutoff of 11 August 2023

Table 3: Key features of the included evidence

Trial	N	Design	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
MARIPOSA	1,074	MC, RCT. One treatment arm was open label, two others were double-blinded.[a]	Low	Locally advanced or metastatic NSCLC treatment naïve for advanced disease *EGFR* exon 19del or exon 21 L858R disease	Primary: PFS (BICR) Secondary: OS, ORR, DOR, PFS2, TTSP, icPFS, NSCLC-SAQ (HRQoL), EORTC-QLQ-C30 (HRQoL) Exploratory: icORR, icDOR, TTST, TTTD, EQ-5D-5L (HRQoL)	OS, PFS, TTTD, EQ-5D-5L

Source: Figure 2.2, p61 of the submission, Table 2.24, pp 85- 86 of the submission, Section 3.4.1.1 of the submission.
BICR = blinded independent central review, DOR = duration of response, *EGFR* = epidermal growth factor receptor, EQ-5D-5L = Euro-QoL 5 dimensions five-levels, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30, HRQoL = health related quality of life, icDOR = intracranial duration of response, icORR = intracranial objective response rate, icPFS = intracranial progression free survival, MC = multi-centre, NSCLC = non-small cell lung cancer, NSCLC-SAQ = Non-Small Cell Lung Cancer – Symptom Assessment Questionnaire, ORR = objective response rate, OS = overall survival, PFS = progression free survival, PFS2 = PFS after first subsequent therapy, RCT = randomised controlled trial, TTSP = time to subsequent progression, TTTD = time to treatment discontinuation.
[a] The A+L arm was open-label, while the osimertinib and lazertinib arms were double blinded. The trial investigators stated that treatment blinding for the A+L group was not feasible due to differences in routes of administration.

6.13 The submission referred to 2 non-comparative studies, CHRYSALIS-cohort E and PALOMA-3, in support of the PBS listing of A+L for the second (recurrent disease) population following osimertinib treatment in the adjuvant setting. CHRYSALIS was a phase 1, open-label dose escalation trial and PALOMA-3 was a phase 3 RCT comparing subcutaneous versus intravenous formulations of amivantamab, both combined with lazertinib. CHRYSALIS-cohort E (n=45) reported an objective response rate (ORR) of 36% and a median PFS of 4.9 months. PALOMA-3 reported an ORR of 33% and a median PFS of 4.3 months in patients receiving intravenous amivantamab combined with lazertinib (n=212). The submission estimated that the recurrent disease population represented 3% of the total requested PBS population and was included in the financial estimates. This evidence is not discussed further in the comparative effectiveness/harms sections below given it is non-comparative evidence.

Comparative effectiveness

Primary outcome (PFS)

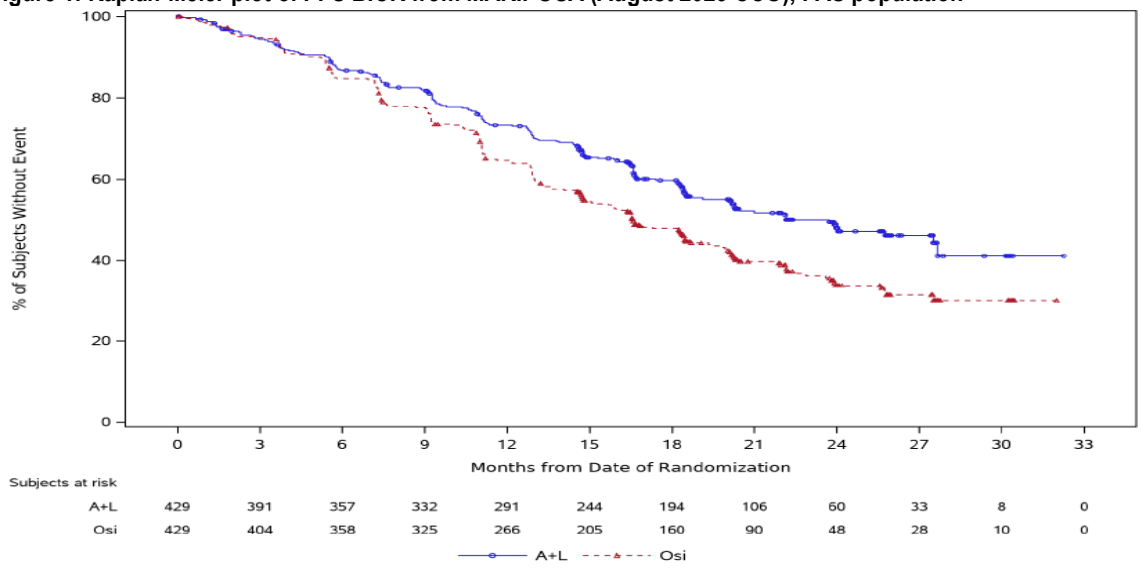
6.14 Results of PFS based on the blinded independent central review (BICR) in the full analysis set (FAS) population at the August 2023 CCO are presented in Table 4 and the corresponding Kaplan-Meier (KM) curves are presented in Figure 1.

Table 4: Summary of PFS BICR from MARIPOSA (August 2023 CCO), FAS population

MARIPOSA	A+L (N=429)	Osimertinib (N=429)
August 2023 CCO		
PFS		
Event (n)%	192 (44.8%)	252 (58.7%)
Censored (n)%	237 (55.2%)	177 (41.3%)
Time to event (months)		
Median (95% CI)	23.72 (19.12, 27.66)	16.59 (14.78, 18.46)
6-month event-free rate (95% CI)	0.87 (0.83, 0.90)	0.85 (0.81, 0.88)
12-month event-free rate (95% CI)	0.73 (0.69, 0.77)	0.65 (0.60, 0.69)
18-month event-free rate (95% CI)	0.60 (0.55, 0.64)	0.48 (0.43, 0.53)
24-month event-free rate (95% CI)	0.48 (0.42, 0.54)	0.34 (0.28, 0.39)
p-value [a]	**0.0002**	
Hazard ratio (95% CI) [b]	**0.70 (0.58, 0.85)**	

Source: Table 2.25, p93 of the submission.
A+L = amivantamab plus lazertinib, BICR = blinded independent central review, CCO = clinical cut off, CI = confidence interval, FAS = full analysis set, PFS = progression free survival.
[a] p-value is from a log-rank test stratified by mutation type (exon 19del or exon 21 L858R substitution), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favours amivantamab + lazertinib.
Bold indicates statistically significant results.

Figure 1: Kaplan-Meier plot of PFS BICR from MARIPOSA (August 2023 CCO), FAS population



Source: Figure 2.4, p94 of the submission.
A+L= amivantamab plus lazertinib, BICR = blinded independent central review, CCO = clinical cut-off, FAS = full analysis set, Osi = osimertinib, PFS = progression free survival.

6.15 There was a statistically significant improvement in PFS of A+L compared to osimertinib: a 14% improvement in the rate of disease progression or death at 24 months (48% A+L vs 34% osimertinib, hazard ratio [HR]=0.70 [95% CI: 0.58, 0.85], p=0.0002). The median PFS was 23.7 months for the A+L arm and 16.6 months for the osimertinib arm. The evaluation considered that the difference was likely to be clinically meaningful. The American Society of Clinical Oncology (ASCO) have recommended targets for meaningful clinical trial goals in NSCLC to be 4 months for

PFS for the new intervention[14].

6.16 The log(-log(S)) vs log(time) plots showed that proportional hazards assumption did not hold for PFS. The evaluation noted that under these circumstances, the HR, confidence intervals (CI) and p-values for this analysis are potentially misleading and should be interpreted with caution.

Secondary outcome (OS)

6.17 Results of the updated OS at the May 2024 CCO are summarised in Table 5 and Figure 2.

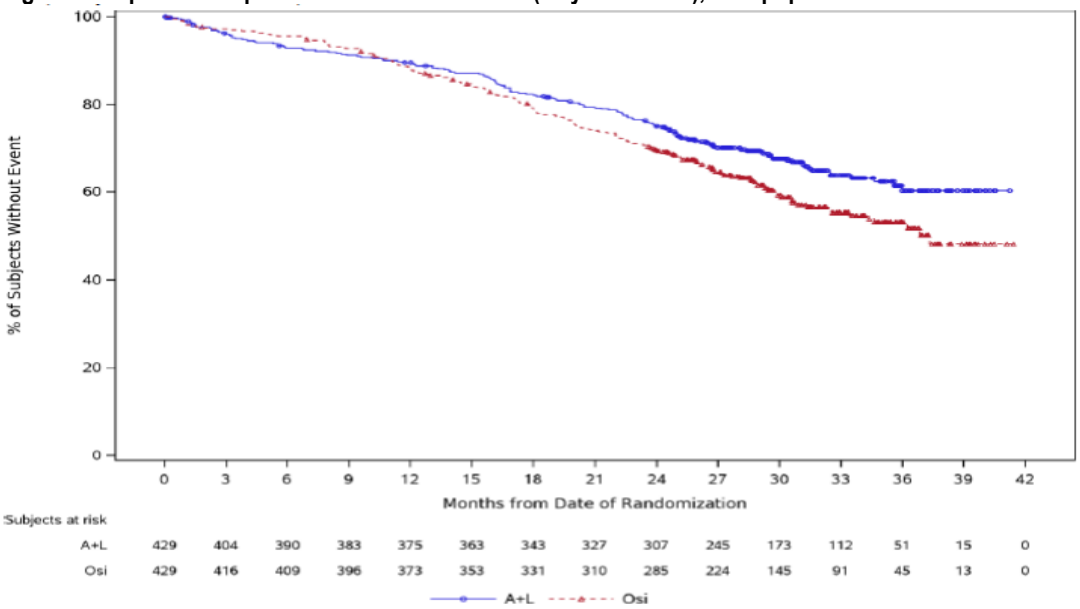
Table 5: Summary of OS from MARIPOSA (May 2024 CCO), FAS population

MARIPOSA	**A+L (N=429)**	**Osimertinib (N=429)**
May 2024 CCO		
OS		
Event (n)%	142 (33.1%)	177 (41.3%)
Censored (n)%	287 (66.9%)	252 (58.7%)
Time to event (months)		
Median (95% CI)	NE (NE, NE)	37.32 (32.53, NE)
6-month event-free rate (95% CI)	0.93 (0.90, 0.95)	0.96 (0.93, 0.97)
12-month event-free rate (95% CI)	0.90 (0.86, 0.92)	0.88 (0.84, 0.91)
18-month event-free rate (95% CI)	0.82 (0.78, 0.86)	0.79 (0.75, 0.83)
24-month event-free rate (95% CI)	0.75 (0.71, 0.79)	0.70 (0.65, 0.74)
30-month event-free rate (95% CI)	0.68 (0.63, 0.72)	0.59 (0.54, 0.64)
36-month event-free rate (95% CI)	0.61 (0.56, 0.67)	0.53 (0.47, 0.59)
p-value [a]	**0.0185** **0.0048**[c]	
Hazard ratio (95% CI) [b]	**0.77 (0.61, 0.96)** **0.75 (0.61, 0.92)**[c]	

Source: Table 2.28 p100 of the submission.
A+L = amivantamab plus lazertinib, CCO = clinical cut off, CI = confidence interval, FAS = full analysis set, NE = not estimable., OS = overall survival.
[a] p-value is from a log-rank test stratified by mutation type (exon 19del or exon 21 L858R substitution), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favours amivantamab + lazertinib.
Bold indicates statistically significant results.
[c] The PSCR stated that more mature OS data from MARIPOSA is available from the December 2024 CCO with a median follow-up of 37.8 months.

[14] Ellis, Lee M., David S. Bernstein, Emile E. Voest, Jordan D. Berlin, Daniel Sargent, Patricia Cortazar, Elizabeth Garrett-Mayer et al. "American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes." *Journal of clinical oncology* 32, no. 12 (2014): 1277-1280.

Figure 2: Kaplan-Meier plot of OS from MARIPOSA (May 2024 CCO), FAS population



Source: Figure 2.7, p101 of the submission.
A+L = amivantamab plus lazertinib, CCO = clinical cut-off, FAS = full analysis set, OS = overall survival, Osi = osimertinib.

6.18 At the median follow up of 31.1 months, 142 patients (33.1%) in the A+L arm and 177 patients (41.3%) in the osimertinib arm had died. There was a difference in OS for A+L over osimertinib, with an 8% improvement in the rate of death at 36 months (61% A+L vs 53% osimertinib, HR=0.77 [95% CI: 0.61, 0.96], p=0.0185). Median OS was not reached in the A+L arm. The Pre-Sub-Committee Response (PSCR) stated that more mature OS data from MARIPOSA is available from the December 2024 CCO with a median follow-up of 37.8 months (HR 0.75 [95% CI: 0.61, 0.92], p=0.0048).

6.19 The MARIPOSA trial protocol permitted treatment beyond disease progression. The trial results thus reflect treatment beyond progression for some patients, noting that 53.1% of A+L and 50.7% of osimertinib treated patients continued treatment post disease progression for a median of 3.9 and 3.1 months, respectively. The evaluation noted that this was inconsistent with the proposed PBS restriction. The PBAC have previously acknowledged that treatment with TKI's post progression is not permitted in the existing PBS restrictions for *EGFR*-TKIs due to the limited evidence to support the sequential use of TKIs post-progression, and that it is also not recommended by the ESMO guidelines. On this basis and given that the proposed PBS listing limits continuing treatment to those who have not experienced disease progression, the observed OS outcomes may exceed what might be expected in clinical practice in Australia. Additionally, the draft amivantamab and lazertinib PIs state that treatment may be administered [only] until disease progression, not post progression.

6.20 The submission stated that the continued use of A+L upon disease progression in MARIPOSA was similar to the post-progression use of osimertinib in the FLAURA trial. FLAURA reported a large proportion of patients continuing treatment beyond progression (67% and 70% in osimertinib and standard care arms for a median of 8 and

7 weeks, respectively) (paragraph 6.10, osimertinib PSD, July 2020). For the PBS listing of osimertinib, the ESC concluded that although treatment continuation with osimertinib after disease post progression was of reasonable concern, it was unlikely to have had a significant impact on the OS benefit of first-line osimertinib (paragraph 6.11, osimertinib PSD, July 2020).

6.21 The evaluation considered that the potential OS benefit of A+L compared to osimertinib should be interpreted with caution due to the following reasons:

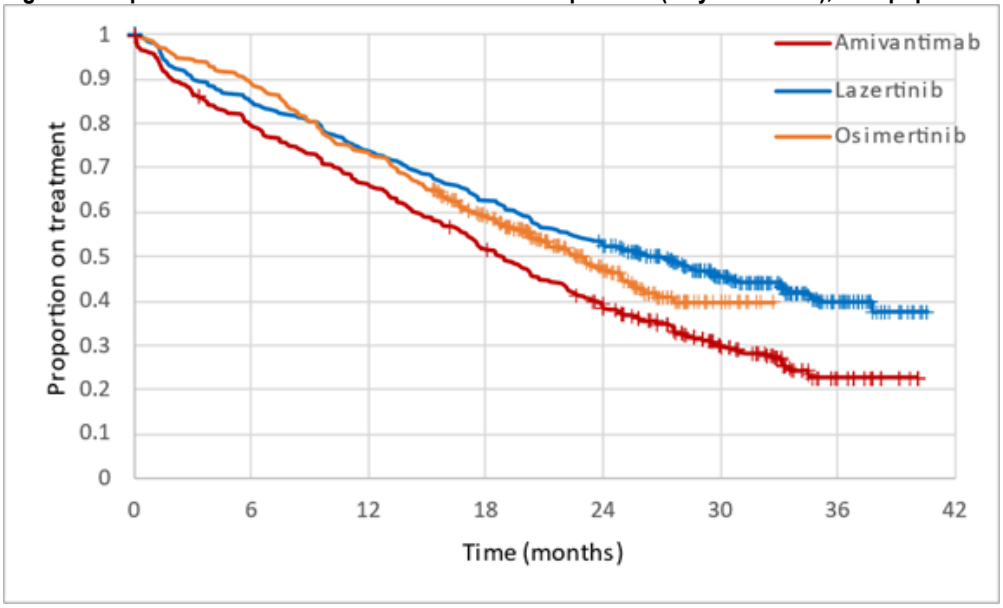
- The median OS for osimertinib was 37.3 months whilst the median OS for A+L has not yet been reached, demonstrating that the OS data remains immature.
    - The submission stated that although the median OS had not been reached for A+L, the median PFS benefit of 7.1 months observed with A+L compared to osimertinib was a surrogate, predictive of a significant improvement in OS of A+L over osimertinib over time. The submission provided findings from 2 studies in support of this claim. A study by Hashim et. al (2018) concluded that in NSCLC trials showing significant treatment effect size of >4.2 months median PFS, an OS benefit can be expected with sufficient certainty. Similarly, Johnson et. al (2006) has found that to predict a survival gain in NSCLC trials, an improvement of 3.3 months' time to progression is required in trials with 250 patients. The ASCO have recommended targets for meaningful clinical trial goals to be 4 months for PFS and a hazard rate of 0.76−0.80 for OS for a new intervention for NSCLC[15].
- The KM plot for OS initially shows there were more deaths in the A+L arm than the osimertinib arm, with the curves crossing at approximately 12 months (Figure 2), and diverging from approximately 15 months.
    - The submission described the number of deaths due to AEs during the first 6 months and concluded that only 1 death in each arm was due to an AE related to study treatment. No further analysis of those that died in the first 12 months was presented by the submission. Log(-log(S)) vs log(time) plots presented by the submission confirmed that the proportional hazards assumption did not hold. The evaluation considered that HR, CIs and p-values for this analysis should be interpreted with caution. While the submission acknowledged the violation of the proportional hazard's assumption for OS, it did not present alternative methods of evaluating OS, such as restricted mean survival time.

[15] Ellis, L. M., Bernstein, D. S., Voest, E. E., Berlin, J. D., Sargent, D., Cortazar, P., Garrett-Mayer, E., Herbst, R. S., Lilenbaum, R. C., Sima, C., Venook, A. P., Gonen, M., Schilsky, R. L., Meropol, N. J., & Schnipper, L. E. (2014). American Society of Clinical Oncology Perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. Journal of Clinical Oncology, 32(12), 1277–1280. https://doi.org/10.1200/jco.2013.53.8009

Secondary outcome (time to treatment discontinuation (TTTD), exploratory)

6.22 The KM curves of TTTD for the individual components of A+L (amivantamab and lazertinib) and for osimertinib are shown in Figure 3. TTTD was used to inform the economic model.

Figure 3: Kaplan-Meier Plot of TTTD for individual components (May 2024 CCO), FAS population



Source: Figure 2.15, p 114 of the submission.
CCO = clinical cut off, FAS = full analysis set, TTTD = time to treatment discontinuation.

6.23 A higher percentage of patients in the osimertinib arm (n= 283; 66.0%) discontinued treatment compared to the A+L arm (n= 236; 55.0%) after a follow up of 31.1 months (May 2024 CCO). Patients treated with A+L had a longer time to all treatment discontinuation than patients treated with osimertinib (median TTTD for A+L was 26.3 months vs. 22.6 months for osimertinib). Patients remained on amivantamab for a shorter duration than lazertinib and osimertinib, potentially due to higher rates of AEs observed with amivantamab.

Secondary outcomes: health-related quality of life (HRQoL) (EORTC-QLQ-C30 and EQ5D-5L)

6.24 The submission provided HRQoL data from the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30) and Euro QoL 5 dimensions five-levels (EQ-5D-5L) measures. Analysis of the EQ-5D-5L measure showed a statistically significant difference favouring the osimertinib arm. However, neither measure showed a clinically meaningful difference between treatment arms.

- For the EORTC QLQ-C30 after a median follow-up of 22.0 months, there were no meaningful differences, as per the submission's proposed minimal clinically important difference (MCID) of 10 points, from baseline or between treatment arms in the least squares mean differences. The evaluation considered it to be unclear why the submission proposed an MCID of 10 points specifically, although this value seems to be reasonable.

- Exploratory analysis of the EQ-5D-5L (using the United Kingdom value set) performed after a median follow-up of 22.0 months showed that at timepoints up to cycle 25, the least squares mean difference from baseline and least squares mean difference between A+L and osimertinib arms were statistically significant, with patients in the A+L arm experiencing a smaller improvement from baseline than patients in the osimertinib arm. The difference between the 2 arms in least squares mean change from baseline was <0.08 points and was not considered clinically meaningful by the evaluation. The lower EQ-5D-5L utility scores associated with A+L versus osimertinib may be associated with the higher rate of AEs. The submission used data from EQ-5D-5L (using the Australian value set) to inform the economic evaluation.

Comparative harms

6.25 A summary of the safety data from MARIPOSA is presented in Table 6 (August 2023 CCO). The safety data reported on the safety analysis set (SAS) consisted of all individuals within the study who received at least one dose of study treatment.

Table 6: Overall summary of TEAE incidence (August 2023, CCO), SAS population

	A+L (N=421) n (%)	Osimertinib (N=428) n (%)
Patients experiencing 1 or more TEAE	421 (100.0)	425 (99.3)
TEAEs related to study treatment [a]	414 (98.3)	378 (88.3)
Grade ≥ 3 TEAEs	316 (75.1)	183 (42.8)
Grade ≥ 3 TEAEs related to study treatment [a]	252 (59.9)	59 (13.8)
Serious TEAEs	205 (48.7)	143 (33.4)
SAEs related to study treatment [a]	97 (23.0)	24 (5.6)
TEAEs leading to discontinuation of any study treatment	147 (34.9)	58 (13.6)
TEAEs leading to death [b]	34 (8.1)	31 (7.2)
Select TEAEs Grade ≥ 3		
Rash	65 (15.4)	3 (0.7)
Paronychia	46 (10.9)	2 (0.5)
Pulmonary embolism	35 (8.3)	10 (2.3)
Dermatitis acneiform	35 (8.3)	0
Infusion related reaction	27 (6.4)	0
Deep vein thrombosis	12 (2.8)	2 (0.5)
Conjunctivitis	1 (0.2)	0
Select TEAEs of any Grade		
Pulmonary embolism	73 (17.3)	20 (4.7)
Deep vein thrombosis	61 (14.5)	11 (2.6)
Conjunctivitis	46 (10.9)	7 (1.6)
VTE TEAE		
Subjects with 1 or more VTEs of any Grade	157 (37.3)	39 (9.1)
First VTE started while on anticoagulants	5 (1.2)	0
Grade 3 VTE event	43 (10.2)	12 (2.8)
Grade 4 VTE event	2 (0.5)	2 (0.5)
Grade 5 VTE event	2 (0.5)	2 (0.5)
VTEs leading to death	2 (0.5)	2 (0.5)

Source: Table 2.41, pp120-121, Table 2.43, p 126 of the submission and Table TSFAE02bytoxpart1of2, pp 408 – 452 of Attachment 2.2 of the submission, Table 37, p136 and Table 38, p 137 of attachment 2.2 of the submission

A+L=amivantamab plus lazertinib, CCO = clinical cut-off, SAE = serious adverse event, SAS = safety analysis set, TEAE = treatment-emergent adverse event, VTE = Venous thromboembolic event.

[a] AE assessed by the investigator as related to study agent.

[b] Excludes infusion related reactions.

6.26 Treatment with A+L was associated with a higher frequency of Grade 3 or above treatment emergent adverse events (TEAEs) when compared to osimertinib (75.1% versus 42.8%). Serious TEAEs were reported more frequently for the combination of A+L (48.7%) than for osimertinib (33.4%). Based on investigator assessment, it was concluded that 23% and 5.6% of serious adverse events (SAEs) were related to A+L and osimertinib, respectively.

6.27 Infections and infestations were generally common across both arms of the trial, however the A+L arm saw a higher rates (68.4%) of paronychia than osimertinib (28.3%), and higher rates of conjunctivitis (A+L; 10.9% vs osimertinib; 1.6%). Amivantamab intravenous infusion requirements led to a high rate of infusion related reactions (62.9%). Additionally, peripheral oedema was more frequent in patients receiving A+L (35.6%) versus osimertinib (5.6%), as were pulmonary embolisms (PE; 17.3% versus 4.7%) and deep vein thrombosis (DVT; 14.5% versus 2.6%). A higher

number of VTEs of any grade were observed in the A+L arm (37.3%) versus osimertinib (9.1%).

6.28 A protocol amendment was made to recommend anticoagulation for patients in the first 4 months of treatment in the A+L arm due to the noted high rates of VTE such as DVT and PE events. At the time of the protocol amendment (August 2022), the new anticoagulation recommendation was only applicable to 12 patients receiving A+L who were within the first 4 cycles of their treatment as recruitment for the trial was completed in May 2022. Despite 37.3% of patients in the A+L arm experiencing a VTE event of any grade, only 1.2% of patients in the A+L arm experienced a 'first VTE' while on anticoagulants.

Benefits/harms

6.29 A summary of benefits and harms for A+L versus osimertinib is presented in Table 7.

Table 7: Summary of comparative benefits and harms for A+L and osimertinib

Benefits						
Progression free survival (median duration of follow up 22.0 months)						
August 2023 CCO						
Event	**A+L**	**Osimertinib**	**Absolute Difference**	**HR [b] (95% CI)**		
Progressed, n/N (%)	192/429 (44.8%)	252/429 (58.7%)	-	0.70 (0.58, 0.85) p [a] = 0.0002		
Median PFS, months (95% CI)	23.72 (19.12, 27.66)	16.59 (14.78, 18.46)	7.13			
% not progressed at 12 months (95% CI)	73 (69, 77)	65 (60, 69)	8			
% not progressed at 24 months (95% CI)	48 (42, 54)	34 (28, 39)	14			
Overall survival (median duration of follow up 31.1 months)						
May 2024 CCO						
Event	**A+L n/N (%)**	**Osimertinib n/N (%)**	**Absolute Difference**	**HR [b] (95% CI)**		
Deaths, n/N (%)	142/429 (33.1%)	177/429 (41.3%)		0.77 (0.61, 0.96) p [a] =0.0185		
Median OS, months (95% CI)	NE (NE, NE)	37.32 (32.53, NE)	NE			
6-month event-free rate (95% CI)	93 (90, 95)	96 (93, 97)	3			
% Alive at 12-month (95% CI)	90 (86, 92)	88 (84, 91)	2			
% Alive at 18-month (95% CI)	82 (78, 86)	79 (75, 83)	3			
% Alive at 24-month (95% CI)	75 (71, 79)	70 (65, 74)	5			
% Alive at 30-month (95% CI)	68 (63, 72)	59 (54, 64)	9			
% Alive at 36-month (95% CI)	61 (56, 67)	53 (47, 59)	8			
Harms						
	A+L n/N	**Osimertinib n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				A+L	**Osimertinib**	
August 2023 CCO						
Serious TEAEs	205/421	143/428	1.46 (1.23, 1.72)	48.8	33.4	15.3% (8.7%, 21.8%)
TEAEs leading to discontinuation of any study treatment	147/421	58/428	2.58 (1.96, 3.38)	34.9	13.6	21.4% (15.8%, 27.0%)
Select TEAE's with severity of Grade ≥ 3						
Infusion related reaction	27/421	0/428	0	6.4	0	6.4% (4.1%, 8.8%)
Paronychia	46/421	2/428	23.38 (5.71, 95.71)	10.9	0.5	10.5% (7.4%, 13.5%)
Rash	65/421	3/428	22.03 (6.98, 69.54)	15.4	0.7	14.7% (11.2%, 18.3%)
Select TEAEs of any grade						
Deep vein thrombosis	61/421	11/428	5.64 (3.01, 10.56)	14.5	2.6	11.9% (8.2%, 15.6%)
Pulmonary embolism	73/421	20/428	3.71 (2.31, 5.97)	17.3	4.7	12.7% (8.5%, 16.8%)
VTE TEAEs						
Subjects with 1 or more VTEs of any Grade	157/421	39/428	4.09 (2.96, 5.66)	37.3	9.1	28.2% (22.8%, 33.5%)
Grade 3 VTE	43/421	12/428	3.64 (1.95, 6.81)	10.2	2.8	7.4% (4.1%, 10.7%)

Source: Table 2.25 p 93, Table 2.28, p 100, Table 2.41, pp 120 – 121 and Table 2.43, p 126, of the submission. AE = adverse event, A+L=amivantamab plus lazertinib, CCO = clinical cut-off, CI = confidence interval, HR = hazard ratio; NE = not estimable, OS = overall survival, PFS = progression free survival, RD = risk difference; RR = risk ratio, TEAE = treatment-emergent adverse event, VTE = Venous thromboembolic event.
[a] p-value is from a log-rank test stratified by mutation type (exon 19del or exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favours amivantamab + lazertinib. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
The event experienced with the worst toxicity is used.

6.30 On the basis of direct evidence presented by the submission, for every 100 patients treated with A+L in comparison with osimertinib:

- Approximately 14 more patients would remain progression free at 24 months.
- Approximately 5 more patients would remain alive at 24 months, and 8 more patients would remain alive at 36 months.

6.31 On the basis of direct evidence presented by the submission, for every 100 patients treated with A+L in comparison with osimertinib and followed over a duration of approximately 22.0 months:

- Approximately 15 more patients would experience a treatment emergent adverse event classified with a severity of 'serious'.
- Approximately 21 more patients would experience a treatment emergent adverse event leading to discontinuation of a study treatment.
- Approximately 6 more patients would experience a Grade 3 or higher reaction related to the infusion of A+L.
- Approximately 11 more patients would experience Grade 3 or higher paronychia (nail infection).
- Approximately 15 more patients would experience Grade 3 or higher rash.
- Approximately 12 more patients would experience deep vein thrombosis (blood clot that forms in a vein) of any grade.
- Approximately 13 more patients would experience a pulmonary embolism (blood clot that forms in an artery in the lungs) of any grade.
- Approximately 28 more patients would experience 1 or more venous thrombolytic event of any grade.
- Approximately 7 more patients would experience Grade 3 venous thrombolytic event.

Clinical claim

6.32 The submission claimed that treatment with A+L was superior in efficacy, in terms of PFS and OS, and inferior but manageable in safety compared to osimertinib.

Effectiveness for locally advanced or metastatic population diagnosed *de novo*

6.33 The clinical efficacy claim was supported by statistically significant and clinically meaningful observed improvements in PFS (HR=0.70 [95% CI: 0.58, 0.85], p=0.0002) and OS (HR=0.77 [95% CI: 0.61, 0.96], p=0.02) for A+L patients compared to osimertinib; however, the ESC agreed with the evaluation that the magnitude of the OS benefit remains uncertain given that:

- The OS data provided was immature, with the median OS not yet reached for the A+L arm (paragraph 6.18).
- The proportional hazard's assumption was violated for PFS and OS (paragraphs 6.16 and 6.21); the OS curves do not appear to separate until month 15.
- The observed OS benefit may not be realised in Australian clinical practice, given that patients in MARIPOSA could continue treatment beyond progression if clinical benefit was observed (paragraph 6.19) and patients in MARIPOSA would likely have a better performance status (ECOG status of 0 or 1) than Australian patients (ECOG status of 0, 1 or 2 requested in the PBS restriction) (paragraph 3.10).

6.34 The evaluation noted that patients in the A+L arm reported statistically worse quality of life outcomes than those in the osimertinib arm, using the EQ-5D-5L, noting that the differences were on average not clinically meaningful. The observed differences were likely attributable to the higher frequency of more severe adverse events in the A+L arm than the osimertinib arm.

6.35 The PBAC acknowledged the moderate improvement in PFS and small improvement in OS of A+L over osimertinib for the locally advanced or metastatic population diagnosed *de novo*. However, it agreed with the ESC and the evaluation, that the magnitude of the clinical benefit was uncertain due to the immaturity of the OS data, the violation of the proportional hazards assumption, and quality of life favouring osimertinib.

Effectiveness for locally advanced or metastatic population following prior adjuvant osimertinib

6.36 The evaluation noted that the studies in the recurrent disease population (following adjuvant osimertinib) did not provide evidence of A+L with a relevant comparator and the trial results for the CHRYSALIS-cohort E and PALOMA-3 trials (paragraph 6.13) were not presented in the submission. Further, the inclusion of this population in the requested listing was not supported by the evidence from the pivotal trial, MARIPOSA (given that MARIPOSA excluded patients who had received any prior treatment with an EGFR TKI), nor was it accounted for in the economic evaluation. However, the ESC considered that it would be reasonable to include this small population in a potential listing, as the CHRYSALIS and PALOMA-3 trials demonstrated activity in this setting and there are few alternative options for these patients.

Safety for both *de novo* and recurrent disease populations

6.37 The submission described A+L as inferior but manageable in terms of safety compared to osimertinib. The evaluation agreed with the submission's claim of inferior safety, however considered that the safety profile may not be 'manageable'. Whilst both arms were associated with a high rate of TEAE's, the A+L arm was associated with more frequent Grade ≥3 TEAEs and more frequent severe AEs when compared with osimertinib. The ESC noted the associated management of the severe AEs seen in the A+L arm requires an escalation of care with hospitalisation, and some patients may require high-dependency and/or intensive care during management of SAEs such as Grade ≥3 pulmonary embolism. Additionally, a large proportion of patients in the A+L arm compared to osimertinib needed to discontinue treatment due to AEs (34.9% vs 13.6%). The pre-PBAC response stated that despite the inferior safety profile of A+L compared to osimertinib, there were no clinically meaningful difference in quality of life between the 2 arms.

6.38 The PSCR provided details of management such as prophylactic and reactive rash management, pre- and post-infusion medications and supportive care for infusion-related reactions, and prophylactic and reactive anticoagulation therapy for VTEs. Notwithstanding, the ESC considered that A+L was more toxic than the comparator, osimertinib, and the degree to which safety was manageable had not been demonstrated.

6.39 Overall, the ESC considered that the observed toxicity associated with A+L was an important clinical issue. Given that patients in real-world clinical practice may have poorer baseline health compared to the trial population, the incidence and severity of adverse events may be higher. This may lead to increased rates of treatment discontinuation and mortality, and ultimately reduced therapeutic effect. The PBAC agreed with the ESC that the claim of inferior but manageable safety was not supported in terms of the management of AEs.

Economic analysis

6.40 The submission presented a stepped economic cost-effectiveness and cost-utility analysis, based on the direct randomised trial, MARIPOSA. A cost-utility analysis was appropriate given that the clinical claim of superior effectiveness was reasonable. The economic evaluation compared A+L with osimertinib for the first-line treatment of patients diagnosed *de novo* with locally advanced/metastatic *EGFR*m NSCLC. The economic model did not consider stage IB-IIIA patients who progressed to locally advanced or metastatic disease following earlier adjuvant osimertinib therapy. Key components of the economic evaluation are presented in Table 8.

Table 8: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	A+L vs osimertinib
Time horizon	15 years in the model base case versus 22 months in the MARIPOSA trial in the August 2023 CCO and 31.1 months in the May 2024 CCO
Outcomes	LYG and QALY gained
Methods used to generate results	Partitioned-survival model
Health states	PFS, PD, and dead
Cycle length	1 week
Allocation to health states	OS and PFS curves from the MARIPOSA trial
Extrapolation method	Parametric models fitted to each treatment arm for PFS and OS KM estimates from the MARIPOSA trial extrapolated after the time point when < 20% of at-risk patients remained. Extrapolation functions were chosen based on goodness of fit statistics and visual inspection. Proportional hazards were not assumed. A+L • OS = Weibull • PFS = gamma • TTTD = generalised gamma 63% of QALYs and 47% of costs occur in the extrapolated period Osimertinib • OS = generalised gamma • PFS = gamma • TTTD = exponential 46% of QALYs and 43% of costs occur in the extrapolated period
Health-related quality of life	Based on the MARIPOSA trial EQ-5D-5L using an Australian algorithm (Norman et al. (2023)) PFS: pooled = 0.913; A+L = 0.900; osimertinib = 0.927 PD: pooled = 0.862; A+L = 0.860; osimertinib = 0.863 Treatment-specific utilities were applied in the PFS health state and pooled utilities applied in the PD health state
Costs	Treatment (based on TTTD curves), treatment administration, adverse event management (including rivaroxaban use to prevent pulmonary embolism) – applied as a one-off cost at the start of the model only, post-progression therapy, and end-of-life costs.

Source: Compiled from Section 3 of the submission.
A+L = amivantamab plus osimertinib, CCO = clinical cut-off, EQ-5D-5L = EuroQoL, 5 dimension, 5 level questionnaire, KM = Kaplan Meier, LYG = life-year gained, OS = overall survival, PD = progressed disease, PFS = progression-free survival, QALY = quality-adjusted life year, TTTD = time to treatment discontinuation.

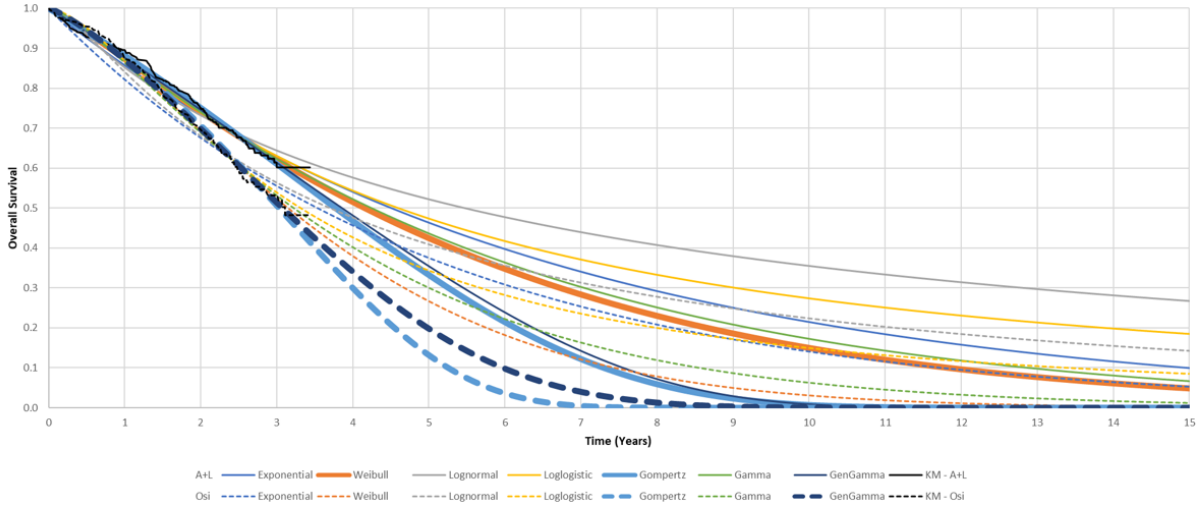
6.41 The submission used a 15-year time horizon. The evaluation considered that this was not reasonable and may overestimate A+L benefits. The MARIPOSA trial had a median follow-up of 37.8 months in the December 2024 CCO (reported in the PSCR), 31.1 months in the May 2024 CCO, and 22.0 months in the August 2023 CCO. The PBAC previously considered that the use of a 7.5-year time horizon was clinically appropriate in its consideration of osimertinib for the same indication (in treatment-naive patients with locally advanced or metastatic common *EGFR* NSCLC) (paragraph 7.11, osimertinib PSD, July 2019). The key trial for the osimertinib submission was the FLAURA trial with a median follow up of 36 months for osimertinib (paragraph 6.7, osimertinib PSD, July 2020). The submission stated that in the context of the previous

PBAC consideration for osimertinib (July 2019 & 2020 PBAC meetings), a longer time horizon would be appropriate for A+L given the additional OS benefit of A+L over osimertinib; the ESC questioned the plausibility of this argument. The evaluation considered that the magnitude of the OS benefit of A+L over osimertinib was uncertain given the immaturity of the OS data in MARIPOSA. Conversely, the PSCR argued that a longer time horizon than that accepted for osimertinib was supported given the median OS for the A+L arm was not reached after more than 3 years of follow-up.

6.42 The submission used OS and PFS KM curves from MARIPOSA to model transition probabilities, until there were fewer than 20% of patients remaining at risk, where curves become more uncertain. The submission also used TTTD curves to model the proportion of patients still on treatment. The submission did not validate the extrapolations using external data. The submission extrapolated KM curves using parametric survival analysis fitted to the observed data using exponential, Weibull, Gompertz, loglogistic, lognormal, gamma, and generalised gamma distributions (Table 8).

6.43 The OS extrapolation commenced at 34.0 months in the A+L arm and 33.4 months in the osimertinib arm, the point at which 20% of patients were at risk. The evaluation noted that extrapolations were uncertain given that the data presented by the submission had a censored data proportion of 66.9% in the A+L arm and 58.7% in the osimertinib arm in the May 2024 CCO. The long-term OS extrapolations for A+L and osimertinib are presented in Figure 4.

Figure 4: Parametric extrapolations of OS



Source: Compiled from 'Attachment 3.1 MARIPOSA *EGFR*m CEA' of the submission.
A+L = amivantamab plus lazertinib, KM = Kaplan Meier, Osi = osimertinib, OS = overall survival.
Notes: The submission chose the Weibull function to extrapolate A+L OS and the generalised gamma function for osimertinib OS. The Gompertz function had better fit for both A+L and osimertinib. Base case and better fit curves are bolded.

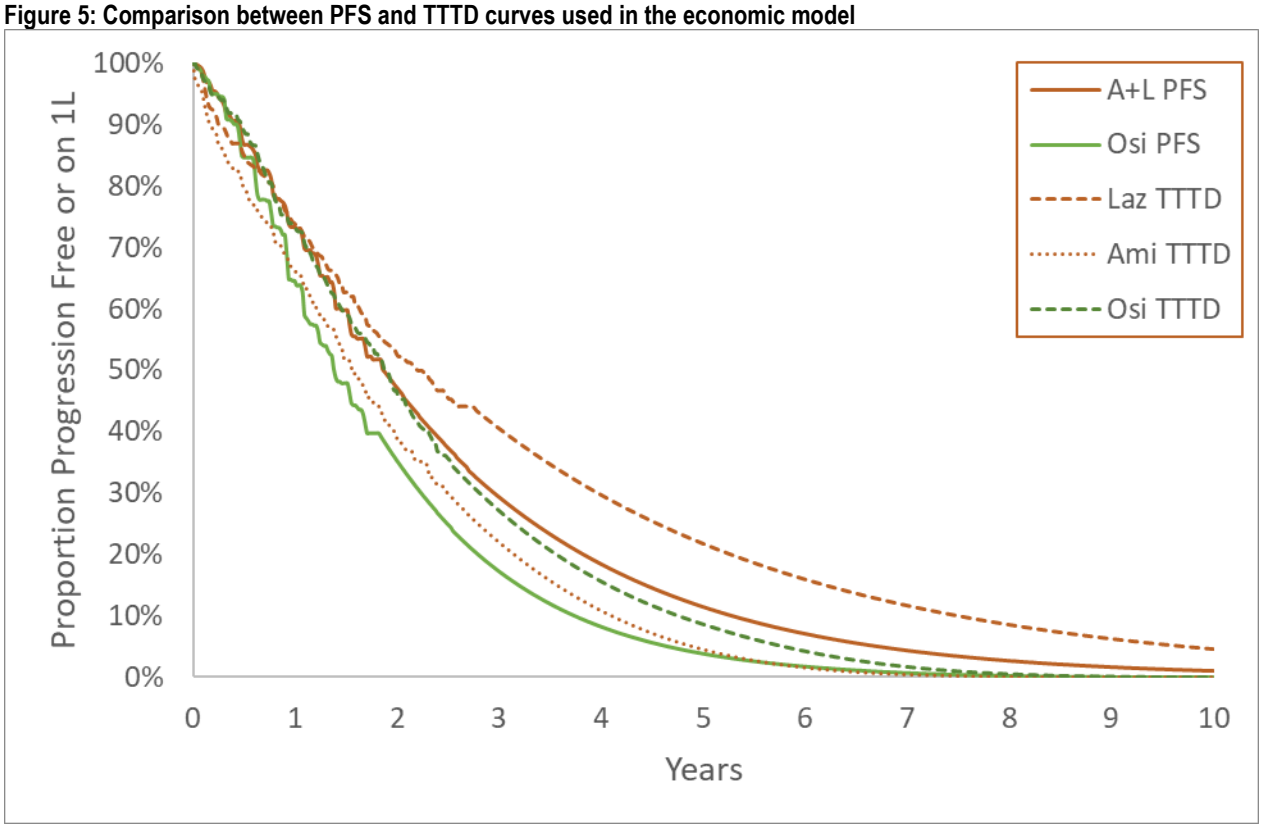
6.44 The submission chose the Weibull function to extrapolate A+L OS. The submission noted that the Gompertz function had better Akaike information criterion (AIC) and Bayesian information criterion (BIC), and that the Weibull function had the next-best statistical fit. The Weibull function had the third best statistical fit for the sum of AIC

and BIC, whereas the exponential function was second. The submission argued that when comparing 10-year survival, the Gompertz curve estimated 1% survival, which was lower compared to all other projections (except for generalised gamma), projecting survival between 15% and 36%. The evaluation and the ESC noted that this comparison was uncertain given the immaturity of the data and considered that using the Weibull function likely overestimated A+L long-term OS compared to the Gompertz function. The submission cited a review by a clinical expert advisory board that stated that curves above the Weibull were too optimistic and that Gompertz and generalised gamma were likely too conservative, but the advisory board minutes were not provided by the submission. The evaluation noted that the model was sensitive to using the Gompertz function to model A+L OS. The PSCR maintained that the Weibull function was the most appropriate choice of extrapolation for the reasons described in the submission and is further supported by the December 2024 CCO data for OS, however the extrapolation was not re-estimated using this data in the PSCR. The ESC noted that the model was sensitive to using the Gompertz function for A+L, reducing the QALYs gained from 1.1 in the base case to 0.38 (a 65% reduction) (see Table 15 below).

6.45 The submission used the generalised gamma function to extrapolate osimertinib OS. The submission noted that the Gompertz function had the best fit by AIC/BIC, followed by the Weibull and generalised gamma. However, the submission stated that upon closer inspection and considering the previously accepted 7.5-year time horizon for osimertinib in *EGFR* NSCLC, the Gompertz function was too pessimistic, whereas the Weibull function was too optimistic. The evaluation noted that the submission did not incorporate convergence of the OS curves.

6.46 The economic model used TTTD curves from the MARIPOSA trial to model medicines utilisation, which included treatment after progression. This was inconsistent with the proposed PBS restriction for continuing treatment which states that patients must not have developed disease progression while receiving treatment. However, the PBAC has noted previously that using TTTD was appropriate to model medicines utilisation (paragraph 7.13, osimertinib, PSD, July 2019). Figure 5 presents a comparison between TTTD and PFS curves used in the economic model.

Figure 5: Comparison between PFS and TTTD curves used in the economic model



Source: 'Attachment 3.1 MARIPOSA *EGFR*m CEA' of the submission.
1L = first line, A+L = amivantamab plus lazertinib, Laz = lazertinib, Osi = osimertinib, PFS = progression-free survival, TTTD = time to treatment discontinuation.

6.47 The submission used EQ-5D-5L data from the MARIPOSA trial to estimate utilities using an Australian algorithm from Norman et al. (2023). The evaluation considered that this was reasonable, although noted that the reliability of utilities derived from the MARIPOSA trial was uncertain, given that the mean utility value in the PFS health state (0.913) was higher than Australian population norms (0.86), and the applied utility value for the progressed disease (PD) health state (0.862) was similar to this value.[16] A systematic review by Jovanosky et al. (2023) studied NSCLC utilities and noted that stage III NSCLC utilities ranged from 0.27 to 0.83, lower than that reported either for PFS or PD sourced from the MARIPOSA trial.[17] 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).

[16] Redwood et al., Australian population norms for health-related quality of life measured using the EQ-5D–5L, and relationships with sociodemographic characteristics, Quality of Life Research, vol 33, issue 33, pp721-733.
[17] Jovanoski N, et al. Health State Utility Values in Early-Stage Non-small Cell Lung Cancer: A Systematic Literature Review. Pharmacoecon Open, vol 7, issue 5, pp723-738.

- osimertinib for the first-line treatment stage IIIB or IV *EGFR*m NSCLC PFS utility = 0.804, standard care (erlotinib/gefitinib) utility = 0.784, and PD utilities in patients with <180 days to death = 0.590 (Table 9, osimertinib PSD, July 2020).
- 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).
- 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).

6.48 The submission noted that the lower utilities for A+L were likely due to increased AEs. The difference in utilities between the A+L arm and the osimertinib arm was 0.027, which appears low considering that the incidence of grade ≥3 TEAE, SAE, and TEAE leading to discontinuation was higher in the A+L arm than the osimertinib arm in the MARIPOSA trial (Table 6). Therefore, the magnitude of the utility decrement for A+L compared with osimertinib was uncertain.

6.49 The submission included direct treatment costs (including administration and co-medications), AE management, subsequent therapies and end-of-life costs. The submission did not include disease management and monitoring costs as no differences would be expected in these costs between arms. Given A+L was expected to delay progression and mortality, not including disease management and monitoring costs would favour A+L, underestimating costs.

6.50 The economic model included treatment for grade 3 or 4 TEAEs that occurred in ≥5% of patients in either treatment arm, and AEs of special interest from MARIPOSA. The evaluation considered that this was reasonable. However, the evaluation noted that AE costs were applied as a one-off cost for each first-line treatment in the first cycle (not subject to discounting); applying AE management costs as a one-off likely underestimated costs as AE rates would be expected to increase the longer patients are followed-up.

6.51 The model incorrectly applied Section 100 EFC program markups to the lazertinib proposed ex-manufacturer price (EMP). Application of the correct (Section 85) markups increased the ICER by 12.6%. Results of the economic model are presented with the correct markups.

6.52 The submission estimated compliance for each drug by multiplying the percentage of doses not skipped with the dose reduction (percentage of non-skipped doses received) from the MARIPOSA trial (Table 9). The percentage of doses not skipped (1 minus [number of doses given/number of doses expected]) and the dose reduction (cumulative dose/cumulative expected dose) were calculated by the submission, however the submission did not reference where the original data were sourced, and the data were unable to be verified from the Clinical Study Report (CSR). The

submission also reported relative dose intensity, defined as the ratio of actual versus prescribed doses (prescribed doses included planned interruptions). Compliance estimated by the submission and relative dose intensity (RDI) presented in the CSR for A+L and osimertinib are presented in Table 9.

Table 9: Compliance estimated by the submission

	A+L (N=429)				Osimertinib (N=429)
	Amivantamab			Lazertinib	
	Total	Weight <80 kg	Weight ≥80 kg		
Percentage of non-skipped doses [a]	81.6%	81.4%	82.5%	93.3%	97.7%
Percentage of non-skipped doses received [b]	79.4%	79.6%	78.2%	87.6%	98.1%
Study drug compliance [c]	64.8%	65.1%	64.4%	82.1%	95.7%
Relative dose intensity per CSR	96.7%	NR	NR	93.3%	98.0%

Source: Tables 2.17 & 2.18, pp77 & 78 of the submission

A+L= amivantamab plus lazertinib, CSR = clinical study report, NR = not reported.

[a] calculated by the submission based on doses given out of doses expected given treatment duration and planned dosing schedule.

[b] calculated by the submission based on total cumulative dose divided by expected total cumulative dose, whereby expected cumulative dose for each patient was calculated from the actual administrations (i.e., non-skipped doses) and planned dosing.

[c] calculated by the submission as proportion of non-missed doses x proportion of non-missed doses received.

6.53 The submission argued that the study drug compliance shown in Table 9 was a more appropriate assessment of dose intensity than the RDI reported in the MARIPOSA trial. The submission argued that the RDI reported in the CSR related to compliance with prescribed study treatment doses and therefore excludes drug interruptions, dose reductions and discontinuations. The evaluation noted that it was not clear how the submission defined 'expected doses' used to calculate the proportion of non-skipped doses. However, there is the possibility that the methodology adopted by the submission inappropriately accounts for 'skipped doses' associated with patients who have discontinued treatment. Further, the MARIPOSA clinical trial protocol describes how dose modifications were to be captured.[18]

6.54 The CSR also reported 'dose intensity' which was calculated as the sum of total doses (mg) received divided by the number of treatment cycles. This measure of dose intensity was not referenced by the submission and should account for drug interruptions, dose reductions and discontinuations. The evaluation used these values reported in the CSR and the expected dose per cycle to calculate the estimated dose intensity percentage. Table 10 reports the alternative dose intensity estimated in the evaluation. The evaluation noted that the model was sensitive to this assumption; applying the dose intensity calculated in Table 10 increased the ICER by %.

[18] The MARIPOSA Clinical Trial Protocol states that "Dose modifications should be recorded in the eCRF as close to the scheduled dosing day as possible, in accordance with the eCRF guidelines. A change to study treatment dosing (ie, withholding doses, change in dose, change in infusion rate), and the reason for the change, must be recorded in the eCRF. For withheld doses, the duration of withholding study treatment is to be recorded. Infusion rate must also be noted for each dose of amivantamab."

Table 10: Alternative dose intensity estimated in the evaluation

	A+L (N=429)				Osimertinib (N=429)
	Amivantamab			Lazertinib	
	Total	Weight < 80 kg	Weight ≥ 80 kg		
Dose intensity as per CSR [a] (mg/28-day cycle)	1,725.5	NR	NR	5,552.4	2,136.1
Expected dose per 28-day cycle	2,193 [b]	2,100	2,800	6,720	2,240
Dose intensity [c] (calculated by the evaluation)	78.7%	NR	NR	82.6%	95.4%

Source, Table 11, pp57-58 of 'Attachment 2.2 - MARIPOSA primary CSR-CCO Aug2023' of the submission.
A+L = amivantamab plus lazertinib, CSR = clinical study report
[a] Sum of total doses (mg) received divided by the number of treatment cycles
[b] Weighted as per the proportion of weight of the MARIPOSA trial.
[c] Estimated in the evaluation by dividing dose intensity as per CSR by the expected dose.

6.55 The PSCR maintained that the submission appropriately and accurately calculated and applied compliance to each drug in the economic model; however, the ESC noted that the dose intensities used by the submission were presented in an unreferenced attachment, not in the May 2024 CCO report, and therefore the source was uncertain. The PSCR stated that the evaluation's calculation of expected dose per 28-day cycle is overly simplistic as it does not account for the induction treatment cycle where doses are higher than in maintenance cycles; however, not accounting for the induction treatment cycle means that 2 fewer doses of A+L are counted in the expected dose over 2 years, and this would lower the dose intensity by only a marginal amount in comparison to that calculated by the evaluation in Table 10. The PCSR also maintained that the rounding up of the 28-day cycle in the evaluation over-estimated the expected dose, and argued that the submission estimates are based on '..the exact number of doses (to the day) that a patient was expected to receive treatment..' rather than the cycle. The ESC noted that rounding up may overestimate the dose intensity of lazertinib and osimertinib (daily dose), however the effect on the dose intensity for amivantamab will likely be marginal and associated with the induction treatment cycle.

6.56 The submission assumed 40.6% of A+L and 49.2% of osimertinib patients who progressed received subsequent therapy based on data from the MARIPOSA trial. The model was not sensitive to the percentage of patients using subsequent therapy. The submission noted that subsequent therapies' effect on survival or HRQoL was not separately included in the model. The evaluation considered that this was reasonable, as effects in HRQoL or survival would be already captured in PFS curves, OS curves, and utilities from MARIPOSA. Subsequent PBS utilisation data of treatments used in the second-line setting were used to inform the subsequent treatment mix. Based on these data, the submission assumed all patients receiving subsequent therapy received carboplatin + pemetrexed (CP) or ABCP.

6.57 The subsequent treatments observed in MARIPOSA included chemotherapy / immunotherapy / VEGFi based regimens, and *EGFR* TKI or TKI-based regimens. The submission stated that *EGFR* TKIs are not listed as second-line *EGFR*m NSCLC on the

PBS and patients would not receive osimertinib as a second-line treatment as no patients in MARIPOSA were reported to have a T790M mutation after A+L treatment, and patients cannot receive osimertinib if it has already been used in the Australian setting. Therefore, these treatments were excluded. While this approach seems reasonable, the evaluation noted that it creates a disconnect between the therapies used to inform costs in the model (CP or ABCP) and those used in MARIPOSA, and from which post-progression outcomes were derived (e.g., TKI based regimens and immunotherapy). Both TKIs and immunotherapy have been shown to be superior to CP and ABCP in the second-line setting. The submission estimated that from those patients receiving subsequent therapy, 42.5% of patients would use ABCP. The evaluation noted that this was inconsistent with the submission's assertion that ABCP was rarely used in MARIPOSA and Australian practice. The model was not sensitive to removing ABCP as subsequent therapy.

6.58 Table 11 presents the key model drivers.

Table 11: Key drivers of the model

Description	Method/Value	Impact: Base case: dominant
Extrapolation	The function chosen to extrapolate OS in the A+L arm was the Weibull function.	High, favours A+L. The ICER remained dominant when the Gompertz function was applied. However, the absolute value increased, driven by a reduction in incremental QALYs.
Time horizon	15-year time horizon	High, favours A+L. The ICER remained dominant when a 7.5-year time horizon was applied. However, the absolute value increased, driven by a reduction in incremental QALYs.
Compliance	Using proportion of non-skipped doses and proportion of dose reductions per Table 9	High, favours A+L. Using estimates from Table 10 increased the ICER from dominant to $[redacted][1]/QALY gained [a]

Source: Source: Table 3.40, pp199-202 of the submission; 'Attachment 3.1 MARIPOSA *EGFR*m CEA' of the submission
A+L = amivantamab plus lazertinib, ICER = incremental cost-effectiveness ratio, OS = overall survival, QALY = quality-adjusted life year.
[a] Changed cells K78:83 to 100% and cells N78:83 as per table 3.6.3 in tab 'Treatment Costs' of 'Attachment 3.1 MARIPOSA *EGFR*m CEA' of the submission.
The redacted values correspond to the following ranges:
[1] $0 to < $5,000

6.59 Table 12 presents the results of the stepped economic evaluation. These results were based on the published price of osimertinib. The PBAC relied on the results of the economic evaluation incorporating the effective price of osimertinib in its assessment of the cost-effectiveness of A+L (data not shown).

Table 12: Results of the stepped economic evaluation, A+L effective price and osimertinib published price

Step and component	A+L	Osimertinib	Increment
Step 1: trial-based costs and outcomes [a]			
Costs [b]	$[redacted] ($[redacted])	$[redacted]	-$[redacted] (-$[redacted])
LYG	1.6466	1.6321	0.0145
Incremental cost/extra LYG gained			Dominant
Step 2: time horizon extended to 15 years, costs of 2L therapy and discounting			
Costs [b]	$[redacted] ($[redacted])	$[redacted]	-$[redacted] (-$[redacted])
LYG	4.4315	3.0371	1.3943
Incremental cost/extra LYG gained			Dominant
Step 3: application of utilities			
Costs [b]	$[redacted] ($[redacted])	$[redacted]	-$[redacted] (-$[redacted])
QALYs	3.8252	2.7312	1.0940
Incremental cost/extra QALY gained			Dominant

Source: Table 3.38, p194 of the submission.

2L = second line, A+L = amivantamab plus lazertinib, LYG = life-year gained, QALY = quality-adjusted life year.

[a] Includes drug costs, administration costs, and adverse event treatment costs. Uses 22 months as time horizon consistent with the median follow-up of the MARIPOSA trial.

[b] Text in brackets was estimated in the evaluation using Section 85 markups for lazertinib.

Notes: The PSCR noted the results included a small error in the assumed weight distribution of patients < 80kg (from 86.7% to 87.6%).

6.60 Table 13 presents disaggregated costs from the economic model. The results were mostly driven by first-line treatment costs, using the osimertinib published price, which overestimated the osimertinib treatment costs. The ESC noted the cost offset for end-of-life care appeared large and likely reflected in part the difference in the proportion of patients alive at the end of the model time horizon. The ESC noted that the costs associated with treating AEs appeared substantially underestimated given the toxicity observed with A+L in the trial.

Table 13: Health care resource items: disaggregated summary of cost impacts (discounted), A+L effective price and osimertinib published price

Resource item	A+L cost	Osimertinib cost	Incremental cost	% of total incremental cost [a]
Pharmaceutical products				
First-line treatment [b]	Amivantamab $[redacted] Lazertinib $[redacted] ($[redacted]) A+L $[redacted] ($[redacted])	$[redacted]	-$[redacted] (-$[redacted])	95% (94%)
Administration cost	$4,952	$0	$4,952	-26% (-30%)
Comedications [c]	$[redacted] ($[redacted])	$0	$[redacted] ($[redacted])	-2%
Subsequent treatments	$[redacted]	$[redacted]	-$[redacted]	6% (7%)
Total	$[redacted]	$[redacted]	-$[redacted]	73% (69%)
Other costs				
End-of-life cost	$47,042	$52,587	-$5,545	30% (34%)
Management of adverse events	$755	$302	$453	-2% (-3%)
Total	$47,796	$52,889	-$5,093	27% (31%)
Overall total [b]	**$[redacted] ($[redacted])**	**$[redacted]**	**-$[redacted] (-$[redacted])**	**100%**

Source: Table 3.39, p196 of the submission; tab 'Deterministic Results' of 'Attachment 3.1 MARIPOSA *EGFR*m CEA' of the submission.
A+L = amivantamab plus lazertinib.
[a] Estimated in the evaluation.
[b] Text in brackets was estimated in the evaluation using Section 85 markups for lazertinib.
[c] Sourced from tab 'Deterministic Results' of 'Attachment 3.1 MARIPOSA *EGFR*m CEA' of the submission.

6.61 Table 14 presents a summary of disaggregated health benefits from the economic model. The submission noted that health benefits were mostly driven by the PD health state. This highlights the importance of the extrapolation functions for OS. The ESC noted that the majority of the life years were gained in PD, which was counterintuitive.

Table 14: Disaggregated summary of health outcomes included in the economic evaluation (discounted)

Outcome	Outcome for A+L	Outcome for osimertinib	Incremental outcome	% of total incremental outcome
LYG				
PFS	2.289	1.742	0.547	39%
PD	2.142	1.295	0.847	61%
Total	4.431	3.037	1.394	100%
QALYs				
PFS	2.019	1.615	0.404	32%
PD	1.806	1.116	0.690	68%
Total	3.825	2.731	1.094	100%

Table 3.39, p196 of the submission; tab 'Deterministic Results' of 'Attachment 3.1 MARIPOSA *EGFR*m CEA' of the submission.
A+L = amivantamab plus lazertinib, LYG = life-year gained, PD = progressed diseases, PFS = progression-free survival, QALY = quality-adjusted life year.

6.62 The results of key univariate / multivariate sensitivity analyses are summarised in Table 15. The submission noted that drivers for both incremental costs and QALYs were the discount rate, time horizon, osimertinib price and OS extrapolation. The model was also sensitive to using compliance estimated in the evaluation. These results were based on the published price of osimertinib. The PBAC relied on the results of the economic evaluation incorporating the effective price of osimertinib in its assessment of the cost-effectiveness of A+L (data not shown).

Table 15: Sensitivity analyses, A+L effective price and osimertinib published price

Analyses	Incremental cost	Incremental QALY	ICER	% change to ICER
Base case	-$	1.094	A+L dominant	NA
Time horizon (base case: 15 years)				
5 years	-$	0.2264	A+L dominant	- %
7.5 years [1]	-$	0.6097	A+L dominant	- %
Discount rate (base case: 5%)				
0%	-$	1.6565	A+L dominant	%
3.5%	-$	1.2375	A+L dominant	%
Parametric function used for A+L OS (base case: Weibull)				
Gompertz [2]	-$	0.3796	A+L dominant	- %
Assumed discount from list price for osimertinib and atezolizumab (base case: no discount)				
25% discount from list on both	$	1.094	$[1]	%
50% discount from list on both	$	1.094	$[2]	%
Compliance (base case: Table 9) [a]				
Calculated by the evaluation (Table 10) [3]	$	1.0940	$[3]	%
Multivariate analysis				
1+2	-$	0.3356	A+L dominant	- %
1+2+3	-$	0.6097	A+L dominant	%

Source: Table 3.40, pp199-202 of the submission; 'Attachment 3.1 MARIPOSA *EGFR*m CEA' of the submission.
A+L = amivantamab plus lazertinib, ICER = incremental cost-effectiveness ratio, OS = overall survival, QALY = quality-adjusted life year.
[a] Changed cells K78:83 to 100% and cells N78:83 as per table 3.6.3 in tab 'Treatment Costs' of 'Attachment 3.1 MARIPOSA *EGFR*m CEA' of the submission.
Notes: The PSCR noted the results include a small error in the assumed weight distribution of patients < 80kg (from 86.7% to 87.6%).
The redacted values correspond to the following ranges:
[1] *$25,000 to < $35,000*
[2] *$55,000 to < $75,000*
[3] *$0 to < $5,000*

Cost/patient/year

6.63 The submission did not estimate the drug cost per patient. The evaluation assumed dose intensity as reported in Table 10 to estimate the trial mean dose per administration. Amivantamab doses were weighted by the proportion of patients weighing <80 kg and ≥80 kg. Calculations assumed whole vials, lazertinib DPMQ using Section 85 markups, and were presented as the cost per patient per year. Estimates from the economic model and financial model were consistent when comparing the costs over a one year period, however the ESC noted that a comparison of the total cost per patient per course was not presented. Table 16 presents the cost per patient per year table for A+L and osimertinib.

Table 16: Drug cost per patient for proposed and comparator drugs, A+L proposed effective price and osimertinib published price

	A+L[a]		Osimertinib	
	Trial dose and duration [b]	**Economic and financial estimates [c]**	**Trial dose and duration [b]**	**Economic and financial estimates [c]**
Mean dose per administration	Amivantamab 862.8 mg [d] Lazertinib 198.3 mg	Amivantamab 894.6 mg Lazertinib 223.92 mg	76.32 mg	78.16 mg
Vials/tablets per administration assuming wastage (whole vials/tablets)	Amivantamab 3 vials Lazertinib 1 tablet		1 tablet	
Unit cost	Amivantamab dispensed cost for 3 vials Public: $[redacted] Private: $[redacted] Weighted: $[redacted] [e] Lazertinib 30 tablets DPMQ: $[redacted]		30 tablets DPMQ: $7,581.10	
Cost/patient/week	Amivantamab $[redacted] Lazertinib $[redacted]		$1,769	
Cost/patient/year	Amivantamab Cycle 1 (4 administration per cycle): $[redacted] Cycle 2-12 (2 administrations per cycle): $[redacted] Total: $[redacted] Lazertinib $[redacted] Total $[redacted]		$91,996	

Source: Compiled in the evaluation from Section 3; 'Attachment 3.1 MARIPOSA *EGFR*m CEA' of the submission.
A+L = amivantamab plus lazertinib, DPMQ = dispensed price for maximum quantity.
[a] Using lazertinib DPMQ with Section 85 markups.
[b] Using mean dose intensity defined as mg per treatment cycle from Table 11 of 'Attachment 2.2 - MARIPOSA primary CSR-CCO Aug2023' of the submission. Amivantamab was assumed 4 administrations in cycle 1 and 2 administrations in cycles 2+.
[c] Calculated by applying % dose reductions, % doses non skipped, and weighted by </≥ 80kg for amivantamab. Given that the model assumed whole vials, % dose reductions had no effect on the estimations.
[d] 1725.51 mg divided by 2 assuming 2 administrations per 28-day cycle consistent with cycle 2+.
[e] 38% public, 62% private.

Estimated PBS usage & financial implications

6.64 This submission was not considered by DUSC.

6.65 The submission estimated the financial implications for the two cohorts separately:

- Population 1: First-line treatment of patients with locally advanced or metastatic (stage IIIB/IV) *EGFRm* NSCLC. In contrast to the usual epidemiological approach used in cost-effectiveness submissions, this submission used a market share approach due to the availability of *EGFR* TKI utilisation data provided by the DUSC Secretariat (see paragraph 6.68 below).
- Population 2: Adjuvant osimertinib-experienced patients with locally advanced or metastatic *EGFRm* NSCLC. The submission used an epidemiological approach, based on the parameters and values from the osimertinib PSD, November 2023.

6.66 Inputs and data sources used by the submission to estimate the financial implications of listing A+L are presented in Table 17.

Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Evaluation comment
Population 1		
EGFR TKI therapies for first-line *EGFR*m NSCLC	PBS 100% data Number of patients: 2019: 883 2020: 757 2021: 1,049 2022: 1,133 2023: 1,152	Data were provided by the DUSC secretariat.
Factor applied to growth rate to account for adjuvant osimertinib	Assumed -55% as it is approximately equal to the estimated number of population 2 patients each year.	This was unsupported by evidence.
Population 2		
Eligible population: osimertinib experienced	Osimertinib PSD November 2023	Data used consistent with that presented in the PSD.
Treatment utilisation		
Uptake rate population 1	Assumption from advisory board: Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4-6: [redacted]%	Based on assumption. The ESC considered the uptake to be substantially overestimated noting the toxicity of A+L and that osimertinib is the preferred treatment over A+L in the NCCN guidelines.
Uptake rate population 2	Assumption from advisory board: [redacted]%	Based on assumption.
Dose compliance	From the MARIPOSA trial using estimates from Table 9: A: 65.0% L: 82.1% O: 95.8%	Data source unclear.
Grandfathered patients	Yr 1: [redacted][1]	The submission included grandfathered patients as an additional cohort, which was not appropriate, as they would already have been included in the estimate for the A+L market share.
Duration of treatment	MARIPOSA trial and economic model: A: 100.01 weeks L: 168.58 weeks O: 115.4 weeks	Estimates could not be replicated in the evaluation but were similar to the mean base case in the economic model.
Rivaroxaban	PBS item number 11633G: $53.50	The submission assigned rivaroxaban costs to the PBS. However, rivaroxaban is not listed for VTE prevention.
MBS item 13950	Administration costs: $123.05	This was consistent with the economic model

Source: Compiled from Section 4 of the submission.

A = amivantamab, A+L = amivantamab plus lazertinib, *EGFR* = epidermal growth factor receptor, L = lazertinib, MBS = Medicare Benefits Schedule, NSCLC = non-small cell lung cancer, O = osimertinib, PBAC = Pharmaceutical Benefits Advisory Committee, PBS = Pharmaceutical Benefits Scheme, PSD = Public Summary Document, TKI = tyrosine kinase inhibitor, VTE = venous thromboembolism, Yr = year.

The redacted values correspond to the following ranges:

[1] < 500

6.67 Table 18 presents the estimated use and financial implications of listing A+L on the PBS using the A+L effective price and osimertinib published price. While Table 18 indicates that A+L is cost saving to the PBS/RBS using the osimertinib published price, the PBAC relied on the results of the cost to Government incorporating the osimertinib effective price in its assessment of the budget impact (data not shown).

Table 18: Estimated use and financial implications, A+L effective price and osimertinib published price

	2025	2026	2027	2028	2029	2030
Estimated extent of use: Population 1						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of patients grandfathered[d]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Number of scripts dispensed amivantamab [a]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Number of scripts dispensed lazertinib [b,c]	[redacted][5] + [redacted][2] = [redacted][5]	[redacted][3] + [redacted][2] = [redacted][3]	[redacted][4] + [redacted][2] = [redacted][4]	[redacted][4] + [redacted][2] = [redacted][4]	[redacted][4] + [redacted][2] = [redacted][4]	[redacted][4] + [redacted][2] = [redacted][4]
Estimated extent of use: Population 2						
Number of patients treated	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Number of scripts dispensed amivantamab [a]	[redacted][2]	[redacted][2]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed lazertinib [b,c]	[redacted][2] + [redacted][2]	[redacted][2] + [redacted][2]	[redacted][2] + [redacted][2]	[redacted][1] + [redacted][2] = [redacted][1]	[redacted][1] + [redacted][2] = [redacted][1]	[redacted][1] + [redacted][2] = [redacted][1]
Grandfathered patients[d]						
Number of scripts dispensed amivantamab [a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Number of scripts dispensed lazertinib [b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of A+L						
Cost to PBS/RPBS less copayments	[redacted][6]	[redacted][7]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
Estimated financial implications for osimertinib and rivaroxaban						
Cost to PBS/RPBS less copayments	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
Net financial implications						
Net cost to PBS/RPBS	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
Net cost to MBS	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
Net cost to the health budget	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]

Source: Compiled from Section 4 of the submission.

A+L = amivantamab plus lazertinib, MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme.

[a] Assuming 33.81 scripts per year in the first 4-week treatment cycle, then 16.91 scripts per year in subsequent cycles as estimated by the submission.

[b] Assuming 9.96 scripts per year as estimated by the submission.

[c] The submission incorrectly omitted initial scripts for lazertinib in the calculations.

[d] Twenty-nine grandfathered patients have been included in the financial totals shown in the table. The evaluation noted that grandfathered patients should not have been incorporated as a separate cohort, as they would already have been included in the estimate for the A+L market share and have thus been double-counted

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] < 500

[3] 10,000 to < 20,000

[4] 20,000 to < 30,000

[5] 5,000 to < 10,000

[6] $40 million to < $50 million

[7] $90 million to < $100 million

[8] $100 million to < $200 million

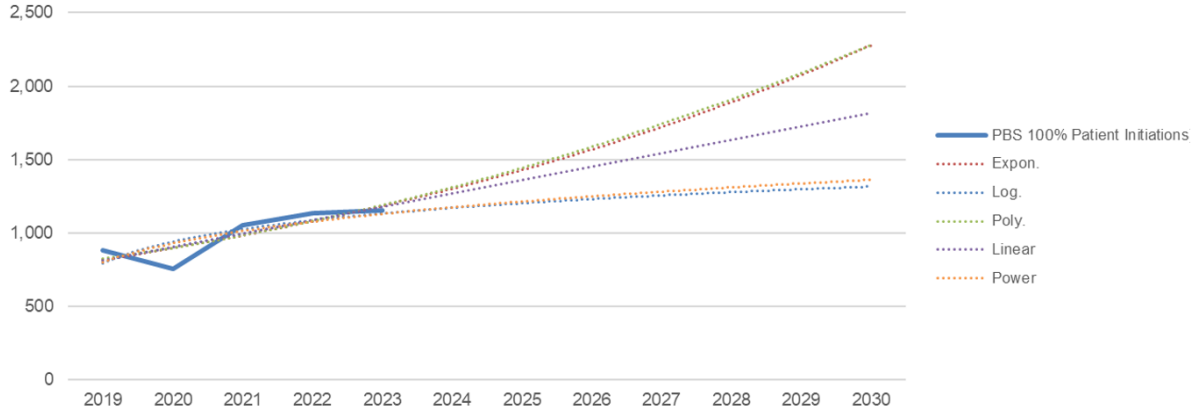
[9] net cost saving

[10] $0 to < $10 million

6.68 The submission sourced recent 100% PBS data (2019−2023) from the DUSC Secretariat on *EGFR* TKI therapies (afatinib, erlotinib, gefitinib and osimertinib) used for the first-line treatment of *EGFR*m NSCLC to estimate patients in population 1. The submission

applied a power regression to the 2019−2023 data to predict *EGFRm* TKI first-line *EGFR*m NSCLC initiations in 2023−30. The submission noted that this regression was chosen given it fitted the data well ($r^2 = 0.67$) and was visually plausible. The evaluation considered that this was uncertain. Fitting the exponential, linear and polynomial functions yielded higher r^2 of 0.724, 0.721, and 0.726, respectively. These 3 functions also predicted higher patient numbers compared to the power extrapolation. Furthermore, the power extrapolation formula applied in the financial estimates model was inconsistent with the power extrapolation reported in the main body of the submission. The extrapolation used by the submission and other extrapolations undertaken during the evaluation are presented in Figure 6.

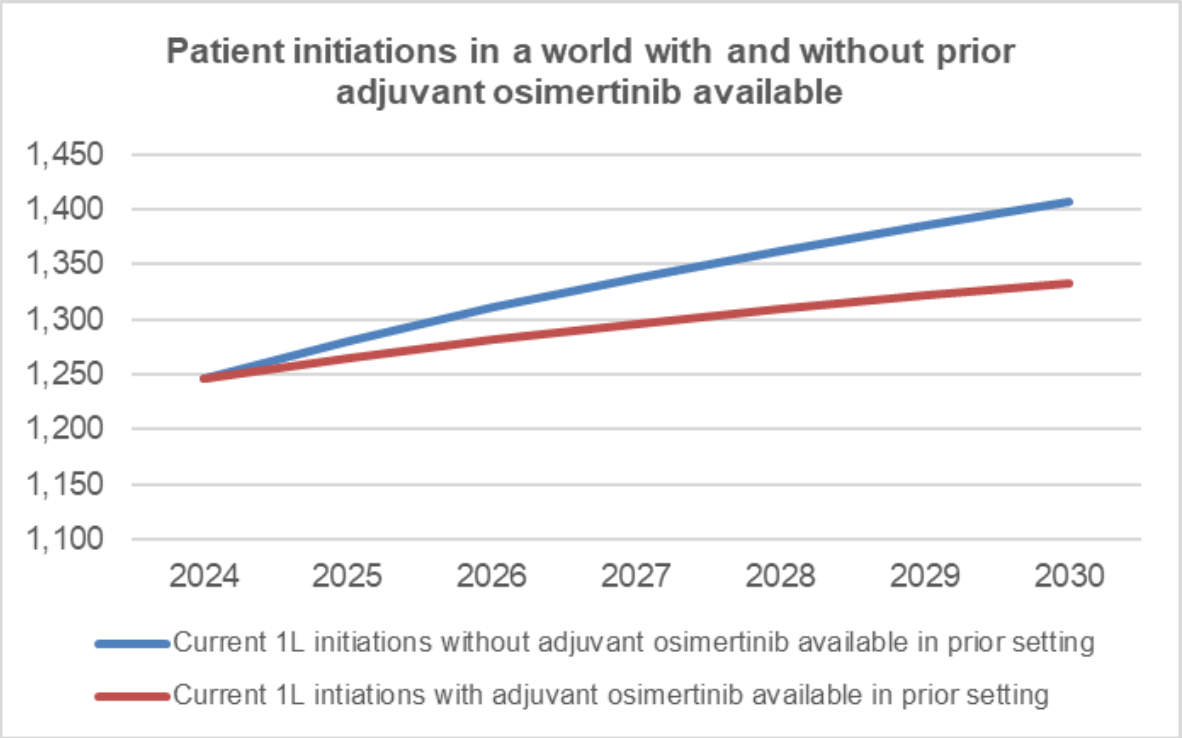
Figure 6. Number of incident first-line *EGFR*m NSCLC patients before accounting for adjuvant osimertinib impact



Source: Compiled in the evaluation.
*EGFR*m = epidermal growth factor receptor mutation, NSCLC = non-small cell lung cancer, PBS = Pharmaceutical Benefits Scheme.

6.69 The submission noted that the listing of osimertinib in the adjuvant setting would slow the growth rate of patient initiators in population 1, given its efficacy in the stage IB-IIIA setting. To account for this, the submission adjusted the estimates of the annual growth. The submission applied a 55% reduction in growth each year as it was approximately equal to the estimated number of patients in population 2 each year; however, the evaluation considered this assumption to be unsupported and uncertain. The PSCR clarified the magnitude of the reduction in the growth rate was estimated to be 55% by calibrating the percent reduction against the number of adjuvant-osimertinib experienced patients who were expected to progress to the first line metastatic setting over the 6-year forward estimates period. Figure 7 represents the difference in patient numbers when using the growth rate adjustment.

Figure 7: Number of incident first-line *EGFR*m NSCLC patients adjusted for prior adjuvant osimertinib use



Source: Figure 4.2, p222 of the submission.
1L = first-line, *EGFR*m = epidermal growth factor receptor mutation, NSCLC = non-small cell lung cancer.

6.70 The submission applied differential uptake rates for populations 1 and 2 given different clinical profiles and circumstances. The evaluation considered that this was reasonable. For population 1, the submission assumed an A+L uptake of % in Year 1, % in Year 2, % in Year 3, and % in Years 4−6 sourced from expert clinical advice from an advisory board based on superior efficacy of A+L compared to osimertinib. For population 2, the submission proposed an uptake of % given that these patients could not be re-treated with osimertinib on the PBS, and it represents the most effective treatment compared to carboplatin plus pemetrexed or ABCP based on an advisory board consensus. The submission did not provide details of how the expert opinion was sought. The ESC considered the uptake to be substantially overestimated, noting the toxicity of A+L and that the NCCN guidelines recommend osimertinib as the preferred treatment over A+L. The PBAC noted that, in contrast to the claim in the pre-PBAC response that the NCCN had changed its treatment preferences, the January 2025 update to the NSCLC guidelines maintains the recommendation to use osimertinib as the preferred 1L treatment for advanced/metastatic disease with *EGFR* exon 19 deletions or exon 21 L858R substitution.

6.71 The submission anticipated that there will be a small number of patients who will receive access to A+L prior to PBS listing through a planned expanded access program. For the financial estimates, grandfathered patients were included by the submission in addition to populations 1 and 2. The submission noted that < 500 grandfathered patients would be included in Year 1. The evaluation considered that inclusion of the

grandfathered patients was not appropriate and would double count those patients, given that they would already form part of populations 1 and 2.

6.72 The submission applied compliance estimated from MARIPOSA as per Table 9, consistent with the economic model (multiplying the proportion of doses not skipped with the dose reduction [proportion of non-skipped doses received] from the MARIPOSA trial) (paragraphs 6.52 and 6.53). However, the financial model was sensitive to applying compliance calculated during the evaluation from the CSR in Table 10, as shown in the sensitivity analyses in Table 19 below.

6.73 The submission considered cost-offsets for the reduced utilisation of osimertinib in locally advanced or metastatic *EGFR*m NSCLC, but did not consider co-medications costs and subsequent therapies. This was inconsistent with the economic model. However, given the unit cost of co-medications and subsequent treatment, mainly carboplatin + pemetrexed, the impact of not including these would be expected to be low.

6.74 The submission accounted for the expected increased usage in the PBS/RPBS of rivaroxaban for VTE prophylaxis. Rivaroxaban is listed in the PBS for the prevention of stroke or systemic embolism in the context of total knee or hip replacement, history of venous embolism, history of pulmonary embolism, and non-valvular atrial fibrillation. Therefore, rivaroxaban treatment costs for use in patients with NSCLC would likely not fall on the PBS/RPBS. Instead, rivaroxaban costs would be borne by State and Territory Governments or patients.

6.75 Table 19 presents key sensitivity analysis in the financial impact of listing A+L to PBS/RPBS using A+L effective price and osimertinib published price.

Table 19: Financial impact key sensitivity analyses, cost to PBS/RPBS A+L effective price and osimertinib published price

Cost to PBS/RPBS	2025	2026	2027	2028	2029	2030	%
Base case	[1]	[1]	[1]	[1]	[1]	[1]	-
Uptake population 1 - [redacted]%	[1]	[1]	[1]	[1]	[1]	[1]	20%
Uptake population 1 + [redacted]%	[1]	[1]	[1]	[1]	[1]	[1]	-20%
Incident first-line EGFRm NSCLC patients power extrapolation (decreased population 1 patients)[a]	[1]	[1]	[1]	[1]	[1]	[1]	6%
Removal of grandfathered patients [b]	[1]	[1]	[1]	[1]	[1]	[1]	-3%
Compliance estimated in the evaluation [c]	[1]	[1]	[1]	[1]	[1]	[1]	49%

Source: Compiled from Section 4.6 of the submission.
A+L = amivantamab plus lazertinib, *EGFR*m = endothelial growth factor receptor mutation, NSCLC = non-small cell lung cancer, PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme.
[a] Changed formulas in cells H6:N6 for y = 800.62x0.2137, and changed cells I21:N21 to account for the 55% reduction in growth rate, tab '1L *EGFR*m Market', of 'Attachment 4.1 - UCM Ami *EGFR*m BASE' of the submission.
[b] Changed cell E99 to 0 of tab '10. Registry population' of 'Attachment 4.1 - UCM Ami *EGFR*m BASE' of the submission.
[d] Changed cells J117:J121 for 78.7%, J123:J125 for 82.6% of tab '3a. Scripts – proposed', and cell J105 for 95.4% in tab '4a. Scripts – affected' of Attachment 4.1 - UCM Ami *EGFR*m BASE' of the submission.
The redacted values correspond to the following ranges:
[1] net cost saving

Quality Use of Medicines (QUM)

6.76 The submission noted that it will provide appropriate education, resources and support to promote appropriate prescribing and use of A+L to patients, prescribers, nurses and dispensers. The PSCR further stated that "since the submission, more data on AE prophylaxis have become available and provide greater reassurance to the manageability of A+L AEs and will be incorporated into QUM activities." The PBAC noted the pre-PBAC response statement that updated A+L PIs and QUM initiatives would be provided for HCP education with respect to prophylactic regimens for dermatologic/infusion reactions and VTE.

6.77 The submission did not propose a post-marketing surveillance study.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the Section 100 (Efficient Funding of Chemotherapy Program) Authority Required listing of amivantamab and a General Schedule Authority Required listing for lazertinib used in combination for the first line treatment of patients with epidermal growth factor receptor mutated (*EGFR*m) locally advanced or metastatic (Stage IIIB-IV) non-small cell lung cancer (NSCLC). The submission sought listing for two populations: (i) for the first-line treatment of locally advanced or metastatic *EGFR*m NSCLC diagnosed *de novo*; and (ii) for patients who had progressed to locally advanced or metastatic disease after prior adjuvant osimertinib therapy. The PBAC noted that the clinical place in therapy of amivantamab plus lazertinib (A+L) in

*EGFR*m NSCLC relative to osimertinib monotherapy and osimertinib in combination with chemotherapy required further consideration due to concerns regarding comparative effectiveness and safety. The PBAC considered that the magnitude of the clinical benefit of A+L over osimertinib monotherapy was uncertain and that the claim of inferior but manageable safety was not supported in terms of the management of AEs due to the toxicity associated with A+L treatment. The PBAC noted the issues associated with the economic evaluation including the uncertainty regarding the likely magnitude of benefit, and the sensitivity of the model results to the time horizon and the extrapolation function of A+L for overall survival (OS). The PBAC considered the submission's uptake rate of A+L to be to be substantially overestimated given the safety profile of the treatment.

7.2 The PBAC considered the primary reason for this outcome was due to the economic analysis provided in the submission. The PBAC also noted that the clinical place in therapy of A+L in *EGFR*m NSCLC (specifically exon 19 deletions or exon 21 L858R substitution) relative to osimertinib monotherapy and osimertinib in combination with chemotherapy required further consideration due to concerns regarding comparative effectiveness and safety.

7.3 The PBAC noted that there is a clinical need for more effective therapies for metastatic *EGFR*m NSCLC, given that there is poor survival for patients and currently PBS-listed therapies are only moderately effective. The PBAC acknowledged the unmet clinical need described in the Consumer Comments from organisations, health care professionals, and individuals, including the need for more effective second-line regimens after progression on first-line osimertinib. The PBAC also noted that the combination of amivantamab with chemotherapy was recommended in international guidelines as a second-line regimen following progression on osimertinib, however was not currently under consideration by the PBAC.

7.4 The PBAC noted that, if A+L were to be listed on the PBS for *EGFR*m locally advanced or metastatic NSCLC in the future, it may be appropriate for the amivantamab and lazertinib restrictions to:

- allow discontinuation of one therapy if a patient developed intolerance and continue treatment with the other therapy;
- remain silent on the *EGFR* mutation type, as use outside the appropriate mutation would be unlikely;
- specify an ECOG performance status of 2 or less, consistent with existing PBS listings for osimertinib, erlotinib, gefitinib and afatinib;
- allow a maximum of 6 months of treatment per script for both amivantamab and lazertinib (including dose reductions of lazertinib);
- allow treatment with A+L if a patient had received prior osimertinib in the adjuvant setting.

The PBAC noted that these suggestions would be subject to review according to the conditions of listing for any future positive recommendation for A+L.

7.5 The PBAC considered that the submission's nomination of osimertinib as the main comparator for the 1L treatment of locally advanced or metastatic *EGFR*m NSCLC diagnosed *de novo* was appropriate. However, it noted that some patients may be accessing osimertinib in combination with platinum and pemetrexed chemotherapy given that the chemotherapy is relatively inexpensive and possibly funded by hospitals or patients, and it will be considered at the May 2025 PBAC meeting for the same indication, and thus is a relevant near-market comparator. The PBAC noted that the submission did not include a comparison of A+L with osimertinib in combination with chemotherapy, however a comparison of the two PBAC submissions was included in the ESC advice for A+L. The PBAC did not accept that osimertinib is the appropriate comparator for the group of patients who have received prior osimertinib in the adjuvant setting and progressed to locally advanced or metastatic disease; it noted that platinum-based chemotherapy ± bevacizumab ± atezolizumab (ABCP) is more likely to be used in this group of Australian patients. Further, PBS-listed osimertinib is excluded for use in patients who have previously received PBS-subsidised treatment with osimertinib.

7.6 The PBAC noted the clinical evidence for A+L was based on the MARIPOSA trial, which was a head-to-head randomised controlled trial (RCT) comparing the efficacy and safety of A+L to osimertinib as 1L treatment in patients with locally advanced or metastatic *EGFR*m NSCLC. The PBAC commented on the risk of bias associated with the open label A+L arm. Further, in contrast with the requested restriction, treatment could continue in the trial beyond disease progression (53.1% of A+L and 50.7% of osimertinib treated patients continued treatment post disease progression for a median of 3.9 and 3.1 months, respectively), and patients in the trial had a better performance status (ECOG 0, 1) than that requested in the restriction (ECOG 0, 1, 2); therefore, the observed survival outcomes may exceed what might be expected in clinical practice in Australia.

7.7 The PBAC acknowledged the moderate improvement in progression free survival (PFS) and small improvement in OS of A+L over osimertinib for the locally advanced or metastatic population diagnosed *de novo*. However, it agreed with the ESC and the evaluation, that the magnitude of the clinical benefit was uncertain due to the immaturity of the OS data, the violation of the proportional hazards assumption, and quality of life favouring osimertinib.

7.8 The PBAC agreed with the ESC that that the observed toxicity associated with A+L is an important clinical issue, noting that the A+L arm of MARIPOSA was associated with more frequent Grade ≥3 treatment emergent adverse events (TEAEs) and more frequent severe adverse events (AEs) when compared with osimertinib. Despite the description of AE management offered in the submission and the PSCR, the PBAC considered the claim of inferior but manageable safety to be poorly defined and not supported in terms of the management of AEs, observing that A+L is associated with substantial toxicity for patients across a range of body systems.

7.9 The PBAC noted that the base case ICER presented in the submission used the effective price of A+L and the published price of osimertinib. The PBAC considered the uncertainty in trial effects discussed in paragraphs 7.6 and 7.7 (immature OS data, violation of the proportional hazards assumption, significantly poorer quality of life compared with osimertinib, and A+L potentially being less effective in the PBS population than the MARIPOSA trial population) potentially impacted on the reliability of the model results. The PBAC considered that the modelled benefits of A+L had low certainty, given the substantial increases in the ICER when (i) the time horizon was reduced from 15 years in the base case to 7.5 years and (ii) the extrapolation used for A+L for OS was changed from a Weibull function in the base case to a Gompertz function. The PBAC also considered that there was only moderate certainty in the modelled costs, noting that costs of A+L appeared to be underestimated and osimertinib appeared to be overestimated. The PBAC noted that it previously accepted a 7.5 year time horizon for osimertinib in the same indication, and that the Weibull function likely overestimated long-term survival in the A+L arm compared to the Gompertz function, which had the best fit for the observed data. The PBAC further noted the utility values applied appeared high and likely did not account for the toxicity of A+L, and that the utilities were higher than normal for the Australian population and values it had previously accepted for similar populations.

7.10 The PBAC noted that the financial impact of A+L is highly sensitive to the uptake by clinicians, which ranged from % to % of the market over the first 6 years of listing for the *de novo* diagnosed population. The uptake rate was sourced from an advisory board and based on the assumed superior efficacy of A+L compared to osimertinib. However, the PBAC considered this uptake rate to be substantially overestimated, noting the toxicity of A+L and that the NCCN guidelines preference for osimertinib as the preferred treatment over A+L. The PBAC considered that a reduced uptake rate of % to % over the first 6 years of listing would be appropriate, and would require further revision if 1L osimertinib + chemotherapy is recommended for PBS listing.

7.11 The PBAC considered any resubmission for A+L should address the following issues:

- The clinical place of A+L relative to osimertinib monotherapy as well as osimertinib in combination with chemotherapy;
- Availability of mature OS data to confirm the survival benefit associated with A+L;
- Economic model parameters consistent with those accepted for osimertinib for the same indication (osimertinib PSD, July 2020), including application of a 7.5 year time horizon. The PBAC considered the ICER accepted for osimertinib would likely be reasonable for A+L;
- Reduction in the A+L uptake rate as outlined in paragraph 7.10;
- Discussion of non-PBS funding for prophylactic anticoagulation and oral antibiotics for A+L patients.

The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.12 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 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.

9 Sponsor's Comment

Janssen is disappointed that the PBAC did not recommend A+L for the first-line treatment of patients with EGFRm locally advanced/metastatic non-small cell lung cancer. Janssen considers that A+L provides a substantial improvement in PFS (+ 7.1 months, HR=0.70; 95% CI: 0.58, 0.85; p=0.0002 at 22.0 months median follow-up) and OS (HR: 0.75; 95% CI: 0.61, 0.92; p=0.0048 at 37.8 months median follow-up) over osimertinib, and will work with the PBAC to make this treatment available for patients on the PBS.