Technology Guidance

Amivantamab

for previously treated, locally advanced or metastatic EGFR exon 19 deletion or exon 21 L858R substitution mutation-positive non-small-cell lung cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended amivantamab, in combination with platinum-based chemotherapy, for inclusion on the MOH List of Subsidised Drugs for previously treated, locally advanced or metastatic epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutation-positive non-small-cell lung cancer. The decision was based on the uncertain extent of clinical benefit, unfavourable cost-effectiveness compared with platinum-based chemotherapy, and the unacceptable price-volume agreement proposed by the company.

Clinical indication, subsidy class and MediShield Life claim limit for amivantamab are provided in the Annex.

Published: 6 February 2026

Technology evaluation

1.1. At the November 2025 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of amivantamab, in combination with platinum-based chemotherapy, for previously treated, locally advanced or metastatic epidermal growth factor receptor exon 19 deletion or exon 21 L858R substitution mutation-positive non-small-cell lung cancer ("advanced EGFR ex19del/ex21 L858R substitution NSCLC"). The evaluation considered the company's evidence submission for amivantamab (Rybrevant) by Johnson & Johnson, and a review conducted by one of ACE's evidence review centres.

1.2. Expert opinion from clinicians at public healthcare institutions, the MOH Cancer Drug Subcommittee, and patient experts from local patient and voluntary organisations helped ACE ascertain the clinical value of amivantamab.

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. EGFR mutations are one of the most common activating pathway events in NSCLC. Exon 19 deletions and exon 21 L858R substitutions account for the majority of these mutations. In Singapore, approximately 216 new patients are diagnosed annually with advanced EGFR ex19del/ex21 L858R substitution NSCLC.

2.2. In local practice, most patients with advanced EGFR ex19del/ex21 L858R substitution NSCLC receive osimertinib as first-line treatment. Following disease progression, patients typically receive platinum-based chemotherapy, such as carboplatin and pemetrexed, as second-line treatment. The Committee heard that there remains a clinical need for more effective second-line treatment options for these patients. Amivantamab, a bispecific antibody targeting EGFR and mesenchymal-epithelial transition (MET) receptors to overcome treatment resistance mechanisms, would be added to platinum-based chemotherapy as a second-line treatment option.

2.3. The Committee considered sixteen testimonials from local patients and carers about their lived experiences with lung cancer and the treatments they have received. They acknowledged that lung cancer had a significant negative impact on patients' emotional and mental health, with both prognostic uncertainty and symptoms affecting their ability to work, socialise and perform daily activities.

2.4. The Committee heard that ten respondents were receiving targeted therapies and reported that these treatments worked well, were easy to take, and had manageable side effects. Nearly half of these respondents had heard of amivantamab through their clinicians, patient support groups, or online sources. Some expressed hope that amivantamab could be their next treatment option should their current therapy become ineffective, while others raised concerns about its effectiveness and side effects. Most respondents were willing to accept manageable side effects from a new treatment if it effectively slowed disease progression and prolonged survival. They considered that any new treatment for lung cancer should be more affordable, prolong their lifespan, stop the cancer from worsening, and allow them to continue carrying out daily activities.

Clinical effectiveness and safety

3.1. The company requested a listing for patients with advanced EGFR ex19del/ex21 L858R substitution NSCLC previously treated with an EGFR tyrosine kinase inhibitor. The requested listing was broader than the MARIPOSA-2 trial population presented in the company's submission, which specifically enrolled patients with non-squamous cell carcinoma who had received prior osimertinib therapy. However, the Committee noted it was consistent with the HSA-approved indication. Additionally, patients with EGFR mutations and squamous cell histology are uncommon, and most would have received prior osimertinib before amivantamab treatment.

3.2. The Committee reviewed the clinical evidence presented in the company's submission, from an open-label, phase III randomised controlled trial (MARIPOSA-2) that compared amivantamab in combination with carboplatin and pemetrexed (ACP) with carboplatin and pemetrexed (CP).

3.3. At a median follow-up of 8.7 months (July 2023 data cut-off), ACP demonstrated a statistically significant improvement in progression-free survival (PFS), as assessed by blinded independent central review, compared with CP. At the second interim analysis (April 2024 data cutoff), ACP did not show a statistically significant improvement in overall survival (OS) compared with CP (Table 1).

3.4. Despite the submission's claim of a moderate to strong PFS-OS surrogacy relationship, supporting evidence relates to different settings and populations that are not applicable to the MARIPOSA-2 trial population.

Table 1: Results of PFS and OS in MARIPOSA-2 trial

Parameter	ACP (N=131)	CP (N=263)	HR (95% CI), p value[a]
PFS by blinded independent central review (data cut-off, July 2023)			
Patients with event, n (%)	74 (56.5)	171 (65.0)	-
Median PFS (95% CI), months	6.28 (5.55 to 8.41)	4.17 (4.04 to 4.44)	0.48 (0.36 to 0.64); p<0.0001
OS (data cut-off, April 2024)			
Patients with event, n (%)	65 (49.6)	143 (54.4)	-
Median OS (95% CI), months	17.74 (15.97 to 22.37)	15.34 (13.73 to16.76)	0.73 (0.54 to 0.99); p=0.0386[b]

Abbreviations: ACP, amivantamab plus carboplatin and pemetrexed; CI, confidence interval; CP, carboplatin and pemetrexed; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

[a] Obtained using log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases and Asian race.

[b] The prespecified significance threshold for OS at interim analysis 2 (2-sided alpha) was 0.0142, as determined based on the O'Brien-Fleming alpha spending approach implemented by the Lan-DeMets method.

3.5. The Committee noted that the open-label design of MARIPOSA-2 could have introduced performance and detection bias, particularly for subjective outcomes like health-related quality of life (HRQoL) and investigator-assessed outcomes.

3.6. In terms of safety, ACP was associated with higher rates of adverse events (AEs), serious AEs, and treatment discontinuations, dose reductions and drug interruptions due to AEs, compared to CP.

3.7. The submission described ACP as superior in terms of effectiveness compared with CP, with a manageable safety profile for patients with previously treated advanced EGFR ex19del/ex21 L858R substitution NSCLC. Based on the evidence submitted, the Committee concluded that while ACP demonstrated a modest improvement in PFS compared to CP, long-term OS benefit was uncertain, and safety was likely inferior.

Cost effectiveness

4.1. The Committee considered the results of the submission's cost-utility analysis that compared ACP with CP for previously treated, advanced EGFR ex19del/ex21 L858R substitution NSCLC based on the MARIPOSA-2 trial. Key components of the base-case economic evaluation provided in the submission are summarised in Table 2.

Table 2: Key components of the company-submitted base-case economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Population	Patients with advanced EGFR ex19del/ex21 L858R substitution NSCLC previously treated with osimertinib
Outcomes	Total and incremental costs Health outcomes expressed as LYs and QALYs
Perspective	Singapore healthcare system
Type of model	Partitioned survival model
Time horizon	10 years in the base case versus a median follow-up of 18.6 months and 17.8 months for ACP and CP arm, respectively in the IA2. 20 years modelled in sensitivity analyses
Health states	Progression-free, post-progression (with separate health states for those with and those without intracranial progression), death
Cycle length	1 week
Extrapolation methods used to generate results	The submission applied parametric survival analysis for the modelling of OS, PFS and TTDD outcomes, and relied on the fitted curves during both the within-trial follow-up and extrapolation periods. In the base case, parametric models were individually fitted to each treatment arm. The following parametric distributions were selected for each outcome: • PFS: loglogistic for ACP; loglogistic for CP • OS: generalised gamma for ACP; gamma for CP • TTDD: Gompertz for ACP; Gompertz for CP No treatment waning was assumed in the submission; that is, no forced convergence of survival curves was assumed over time. For the first year of the model, the submission estimated the proportion of patients having an intracranial progression among all patients who progressed, based on the trial data. The proportion was assumed to remain constant after the first year
Health-related quality of life	Utilities for the PF and PP health states were based on analysis of EQ-5D MARIPOSA-2 trial data,. Utilities for the PP with intracranial progression were calculated by using a multiplier from the literature (Roughley et al. (2014)) to the PP health state utility value calculated from MARIPOSA-2 trial data. PF: 0.78 PP (without intracranial progression): 0.73 PP (with intracranial progression): 0.55
Types of healthcare resources included	• Drug acquisition and drug administration costs • Disease management costs • Subsequent treatment costs • AE management costs • Terminal care costs

Abbreviations: ACP, amivantamab plus carboplatin and pemetrexed; AE, adverse event; CP, carboplatin and pemetrexed; IA2, interim analysis 2; LY, life year; OS, overall survival; PF, progression-free; PP, post-progression; PFS, progression-free survival; QALY, quality-adjusted life year; TTDD, time to treatment discontinuation or death.

4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was more than SG$365,000 per quality-adjusted life year (QALY) gained. However, the Committee considered the ICER to be highly uncertain and likely underestimated given:

- The submission applied a multiplier to decrease the trial-derived post-progression utility value to estimate the utility for those with intracranial progression. The Committee considered that this approach could lead to double counting the disutility due to intracranial progression, as the trial-based utility value would have included patients with intracranial progression.

- For the first year of the model, the submission estimated the proportion of patients having an intracranial progression among all patients who progressed, based on the trial data. The proportion was assumed to remain constant after the first year. However, this resulted in a higher proportion of the cohort modelled to have an intracranial progression in the ACP arm compared to the CP arm, which raised concerns about the validity of the assumptions. Taken together with the issues on utility for those with intracranial progression, the Committee considered that there were serious validity concerns over the implementation of intracranial progression in the model.

- The submission assumed that there is no treatment waning over the entire time horizon for PFS and OS. The Committee considered that there were insufficient long-term data to confirm a sustained treatment effect over the entire time horizon, and the assumption of no treatment waning was likely to favour ACP.

- The submission used cost price of amivantamab instead of selling price.

4.3. The Committee considered the revised base case, which accounted for several uncertainties in the company's model. Key changes to the economic model included excluding a distinct health state for intracranial progression and correcting the price of amivantamab. After these changes, the ICER for ACP remained above SG$365,000 per QALY gained.

4.4. The Committee noted that based on a one-way sensitivity analysis of the revised base case, the ICER was sensitive to the time horizon and choice of ACP OS extrapolation distribution.

4.5. Overall, the Committee considered that ACP did not represent a cost-effective use of healthcare resources for previously treated, advanced EGFR ex19del/ex21 L858R substitution NSCLC at the price proposed by the company.

Estimated annual technology cost

5.1. Using an epidemiological approach, the submission estimated that the annual cost impact to the public healthcare system would increase from SG$5 million to SG$10 million in the first year, to more than SG$10 million in the fifth year of listing amivantamab on the MOH List of Subsidised Drugs for previously treated, locally advanced or metastatic EGFR ex19del/ex21 L858R substitution NSCLC.

5.2. The Committee considered that the submission estimates were uncertain as the company overestimated the proportion of patients receiving first-line systemic treatment, used an inappropriate treatment duration, excluded relative dose intensity, and applied an inappropriate incidence rate of ex19del/ex21 L858R mutations. Based on the revised budget impact model, the annual cost impact to the public healthcare system was estimated to increase from SG$3 million to SG$5 million in the first year, to SG$5 million to SG$10 million in the fifth year of listing amivantamab on the MOH List of Subsidised Drugs for previously treated, locally advanced or metastatic EGFR ex19del/ex21 L858R substitution NSCLC. The Committee also considered that the submission's price-volume agreement (PVA) caps were unacceptably high and inadequate to provide budget certainty.

Recommendations

6.1 Based on available evidence, the Committee recommended not listing amivantamab in combination with platinum-based chemotherapy on the MOH List of Subsidised Drugs for previously treated, advanced EGFR ex19del/ex21 L858R substitution NSCLC. The decision was based on the uncertain extent of clinical benefit, unfavourable cost-effectiveness compared with platinum-based chemotherapy and the unacceptable PVA proposed by the company.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Company-proposed clinical indication	Subsidy class	MediShield Life claim limit per month
Amivantamab 350 mg/7 mL concentrate for solution for infusion	Amivantamab in combination with carboplatin and pemetrexed for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer with EGFR exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with osimertinib.	Not recommended for subsidy	Not recommended for MediShield Life claims