

Amivantamab

for previously untreated, locally advanced or metastatic EGFR exon 20 insertion 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 untreated, locally advanced or metastatic epidermal growth factor receptor (EGFR) exon 20 insertion 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.

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 untreated, locally advanced or metastatic epidermal growth factor receptor exon 20 insertion mutation-positive non-small-cell lung cancer (“advanced EGFR ex20ins NSCLC”). The evaluation considered the company’s evidence submission by Johnson & Johnson for amivantamab (Rybrevant), and a review 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 ex20ins mutations are an uncommon subset of EGFR mutations. They account for 4.6% of non-squamous NSCLC cases in Singapore. Approximately 57 new patients are diagnosed with advanced EGFR ex20ins NSCLC each year, with the majority expected to receive first-line therapy.
- 2.2. Patients with EGFR ex20ins mutations have poorer prognoses compared with more common EGFR mutations. They have demonstrated resistance to standard tyrosine kinase inhibitors and limited treatment benefit with immunotherapies. Consequently, current treatment is largely restricted to platinum-based chemotherapy, such as carboplatin with pemetrexed, as first-line treatment. The Committee therefore acknowledged the high clinical need for additional treatment options in this patient population. Amivantamab, a bispecific antibody targeting EGFR and mesenchymal–epithelial transition factor (MET) receptors to block signalling pathways that drive tumour growth and resistance, would be added to platinum-based chemotherapy as a first-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 nearly half of the respondents had heard of amivantamab from their clinicians, patient support groups, or online sources. Some expressed hope that amivantamab could be a treatment option, while others had 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 previously untreated advanced EGFR ex20ins NSCLC. This listing was broader than the PAPILLON trial population presented in the company's submission, which specifically enrolled patients with non-squamous histology. However, the Committee noted it was consistent with the HSA-approved indication, and that patients with EGFR ex20ins NSCLC with squamous histology are relatively rare.
- 3.2. The Committee reviewed the clinical evidence presented in the company's submission, from an open-label, phase III randomised controlled trial (PAPILLON), that compared amivantamab in combination with carboplatin and pemetrexed (ACP) with carboplatin and pemetrexed (CP). The trial allowed patients to crossover from the CP arm to receive amivantamab monotherapy upon disease progression.
- 3.3. At a median follow-up of 14.9 months (May 2023 data cut-off), ACP was associated with statistically significant improvements in progression-free survival (PFS) as assessed by blinded independent central review, compared with CP (Table 1).
- 3.4. Overall survival (OS) data were immature, with no statistically significant difference between the two treatment groups. The difference in OS was less pronounced at the October 2023 data cut-off compared to the May 2023 data cut-off (Table 1). While the submission proposed PFS as a surrogate endpoint for OS, the Committee considered the PFS-OS surrogacy relationship uncertain, as the studies presented in the submission were not specific to advanced EGFR ex20ins NSCLC and differed in treatments administered and lines of treatment. The submission applied a crossover adjustment to the CP OS data to estimate the counterfactual survival outcomes in the absence of treatment switching. However, the use of crossover adjustment was not adequately justified, as the crossover rate observed in the trial reflected the current

use of second-line amivantamab in local practice. Additionally, the adjusted results had wide confidence intervals that approached or crossed the null, and all adjustment methods had significant limitations that compromised the interpretability of these results.

Table 1: Results of PFS and OS in PAPILLON trial

Parameter	ACP (N=153)	CP (N=155)	HR (95% CI), p value
Primary analysis (data cut-off, May 2023)			
PFS by blinded independent central review			
Patients with event, n (%)	84 (54.9)	132 (85.2)	-
Median PFS (95% CI), months	11.37 (9.79 to 13.70)	6.70 (5.59 to 7.33)	0.40 (0.30 to 0.53), p<0.0001
Unadjusted OS			
Patients with event, n (%)	28 (18.3)	42 (27.1)	-
Median OS (95% CI), months	NE (NE to NE)	24.38 (22.08 to NE)	0.68 (0.42 to 1.09), p=0.1056
Adjusted OS^b			
IPCW	-	-	0.52 (0.28 to 0.94) ^a
TSE	-	-	0.55 (0.31 to 0.92) ^a
RPSFT model	-	-	0.60 (0.32 to 1.12) ^a
Updated OS analysis (data cut-off, October 2023)			
Unadjusted OS			
Patients with event, n (%)	40 (26.1)	52 (33.5)	-
Median OS (95% CI), months	NE (28.32, NE)	28.58 (24.38 to NE)	0.76 (0.50 to 1.14), p=0.1825

Abbreviations: ACP, amivantamab plus carboplatin and pemetrexed; CI, confidence interval; CP, carboplatin and pemetrexed; HR, hazard ratio; IPCW, inverse probability of censoring weighting; NE, not estimable; OS, overall survival; PFS, progression-free survival. RPSFT, rank preserving survival failure time; TSE, two-stage estimation.

^a p-values not reported for adjusted analyses.

^b Crossover adjustment methods applied to CP arm to estimate counterfactual OS in absence of treatment switching to amivantamab. These adjusted analyses had significant limitations (paragraph 3.4).

- 3.5. In terms of safety, ACP was associated with higher incidence of grade ≥ 3 treatment-emergent adverse events (TEAEs), and TEAEs leading to discontinuations, dose reductions, and dose interruptions of any study agent compared to CP, suggesting poorer tolerability.
- 3.6. The submission described ACP as superior in terms of effectiveness compared with CP, with a manageable safety profile for patients with previously untreated EGFR ex20ins NSCLC. Based on the evidence submitted, the Committee concluded that while ACP demonstrated improved PFS compared to CP, the long-term OS benefit remained uncertain due to immature data, uncertainty in the PFS-OS surrogacy relationship, and limitations in crossover adjustment. In terms of safety, the Committee considered ACP to have an inferior safety profile compared to CP.

Cost effectiveness

4.1. The Committee considered the results of the submission's cost-utility analysis that compared ACP with CP for previously untreated, advanced EGFR ex20ins NSCLC, based on the PAPILLON 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 previously untreated advanced EGFR ex20ins NSCLC
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 14.9 months in the primary analysis and 20.9 months in the updated OS analysis. 5 to 40 years modelled in sensitivity analyses
Health states	Pre-progression; post-progression; death
Cycle length	1 week
Extrapolation methods used to generate results	<p>The submission used independent modelling extrapolations based on the KM data from PAPILLON for each treatment arm on the basis that the proportional hazard assumption did not hold. A standardised approach was applied to select the most appropriate parametric models, including visual inspection, statistical goodness-of-fit, and assessment of clinical plausibility.</p> <p>The following parametric distributions were selected for each outcome:</p> <ul style="list-style-type: none"> • PFS: loglogistic for ACP; gamma for CP • OS: generalised gamma for ACP; gamma for CP • TTDD: Weibull for ACP; gamma for CP <p>No treatment waning was assumed in the submission; that is, no forced convergence of survival curves was assumed over time.</p> <p>To adjust for crossover, a TSE method was used to adjust OS for CP arm in the base case with RPSFT model also presented as a scenario.</p>
Health-related quality of life	Estimated based on EQ-5D data from the PAPILLON trial. PF = 0.81 PP = 0.72
Types of healthcare resources included	<ul style="list-style-type: none"> • Drug acquisition and drug administration costs • Disease management cost • Subsequent treatment costs • AE management costs • Terminal care costs

Abbreviations: ACP, amivantamab plus carboplatin and pemetrexed; AE, adverse event; CP, carboplatin and pemetrexed; KM, Kaplan-Meier; LY, life year; OS, overall survival; PF, progression free; PP, post-progression; PFS, progression-free survival; QALY, quality-adjusted life year; RPSFT, rank preserving structural failure time; TSE, two-stage estimation; TTDD, time to treatment discontinuation or death.

- 4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG\$165,000 and SG\$205,000 per quality-adjusted life year (QALY) gained. However, the Committee considered the ICER to be highly uncertain and likely underestimated given:
- The OS data were immature with less than 30% of patients in each arm having died at the May 2023 data cut-off. The submission did not include the October 2023 data cut-off in the model.
 - The submission applied a crossover adjustment which was inadequately justified and highly uncertain (see para 3.4). The Committee noted that this compounded the uncertainty of OS extrapolations arising from the immature OS data.
 - The submission assumed that there is no treatment waning over the entire 10-year 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 the 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 removing the crossover adjustment and correcting the price of amivantamab. These changes substantially increased the ICER to between SG\$245,000 and SG\$285,000 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 price of amivantamab, 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 untreated, advanced EGFR ex20ins 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 be between SG\$3 million and SG\$5 million over the first five years of listing amivantamab on the MOH List of Subsidised Drugs previously untreated, advanced EGFR ex20ins NSCLC.

- 5.2. The Committee considered that the submission estimates were uncertain as the company did not apply the estimated incidence of ex20ins mutations appropriately, excluded relative dose intensity, and used an inappropriate treatment duration. Based on the revised budget impact model, the annual cost impact to the public healthcare system was estimated to be less than SG\$1 million in the first year, and between SG\$1 million and SG\$3 million in the fifth year of listing. 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 untreated, advanced EGFR ex20ins 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	First-line treatment of adult patients (≥ 18 years old) with locally advanced or metastatic non-small cell lung cancer with activating epidermal growth factor receptor exon 20 insertion mutations	Not recommended for subsidy	Not recommended for MediShield Life claims

 Agency for Care Effectiveness - ACE
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As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

The guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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