Technology Guidance

Pembrolizumab

for treating locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended pembrolizumab for inclusion on the MOH List of Subsidised Drugs, when used in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for patients with untreated locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric or gastroesophageal junction adenocarcinoma, whose tumours express programmed death-ligand 1 with a combined positive score greater than or equal to 1. The decision was based on the unfavourable cost-effectiveness of pembrolizumab and an unacceptable pricing proposal from the company.

Clinical indication, subsidy class and MediShield Life claims eligibility for pembrolizumab are provided in the Annex.

Updated: 1 June 2026

Factors considered to inform the recommendations for funding

Company-led submission

1.1. At the November 2024 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum- containing chemotherapy, for untreated locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, in patients whose tumours express programmed death-ligand 1 (PD-L1) with a combined positive score greater than or equal to 1 (CPS ≥1). The evaluation included the company's evidence submission and a review by one of ACE's evidence review centres.

1.2. Expert opinion obtained from the MOH Cancer Drug Subcommittee assisted ACE in ascertaining the clinical value of pembrolizumab. Local patient and voluntary organisations were invited to provide their lived experiences to inform the evaluation, however, no submissions were received.

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. In Singapore, gastric cancer is the eighth most common cancer among males and the tenth among females. The disease can be classified based on staging and tumour biomarkers, including HER2 and PD-L1 expression. Approximately 29 patients are diagnosed each year in Singapore with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma, with tumours that express PD-L1 (CPS ≥1).

2.2. In local practice, most patients are treated with trastuzumab plus chemotherapy, which comprises capecitabine and oxaliplatin (CAPOX) or 5-fluorouracil, oxaliplatin and folinic acid (FOLFOX). While these treatments are already subsidised, the Committee acknowledged the clinical need to consider pembrolizumab for funding, to improve treatment affordability and ensure appropriate patient care.

Clinical effectiveness and safety

3.1. The Committee reviewed the clinical evidence in the submission, which was based on a phase III randomised controlled trial (KEYNOTE-811) that compared pembrolizumab with placebo in patients with previously untreated locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma. Patients in the trial also received standard of care (SOC) treatment comprising trastuzumab in combination with either CAPOX or 5-fluorouracil and cisplatin (FP). The submission presented results for patients whose tumours expressed PD-L1 (CPS ≥1), which aligned with the company's requested listing and the approved HSA indication.

3.2. At the third interim analysis of the KEYNOTE-811 trial (March 2023 data cut-off), pembrolizumab plus SOC led to improvements in progression-free survival (PFS) and overall survival (OS) compared with placebo plus SOC (Table 1). However, the Committee noted the results may not be generalisable to local practice due to the following issues. Firstly, the FP chemotherapy backbone in KEYNOTE-811 differed from what is used in local practice (FOLFOX), and there was no data comparing their efficacy when used with pembrolizumab and trastuzumab. Secondly, the OS results did not show a clear benefit in favour of pembrolizumab among Asian patients whose tumours expressed PD-L1 (CPS ≥1). While the Committee acknowledged that the Asian subgroup was small and not statistically powered to detect differences in OS between treatment groups, this finding suggested heterogeneity in treatment effect across all patients. Overall, the Committee found the generalisability of the trial results to local practice to be uncertain.

Table 1: Results of PFS and OS for patients with PD-L1 (CPS≥1) in KEYNOTE-811 at IA3

March 2023 data cut-off	Pembrolizumab + SOC (n=298)	Placebo + SOC (n=296)
PFS by BICR		
PFS events, n (%)	217 (72.8)	225 (76.0)
Median PFS, months (95% CI)	10.9 (8.5 to 12.5)	7.3 (6.8 to 8.5)
HR (95% CI)	0.71 (0.59 to 0.86), nominal p=0.0002	
OS		
Deaths, n (%)	204 (68.5)	218 (73.6)
Median OS, months (95% CI)	20.0 (17.9 to 22.7)	15.7 (13.5 to 18.5)
HR (95% CI)	0.81 (0.67 to 0.98), nominal p=0.0142	

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; IA3, third interim analysis; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SOC, standard of care.

3.3. In terms of safety, the Committee heard that compared with placebo plus SOC, pembrolizumab plus SOC was associated with a higher incidence of serious treatment-related adverse events (TRAEs; 26.0% vs 22.8%) and grade 3-5 TRAEs (58.9% vs 50.9%). Nonetheless, the Committee noted that the safety profile of pembrolizumab plus SOC was generally consistent with known adverse events of the individual treatments.

3.4. The submission described pembrolizumab, in combination with SOC, as superior in terms of effectiveness compared with SOC alone. Based on the evidence submitted, the Committee concluded that the submission's claim of superior effectiveness was reasonable. In terms of safety, the Committee concluded that the addition of pembrolizumab to SOC resulted in an inferior safety profile.

Cost effectiveness

4.1. The Committee considered the results of the submission's cost-utility analysis comparing pembrolizumab plus SOC with placebo plus SOC for patients with untreated locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma, whose tumours express PD-L1 (CPS ≥1). 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 locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma, whose tumours express PD-L1 (CPS ≥1)
Outcomes	Total and incremental direct medical costs, total and incremental LYs gained, total and incremental QALYs gained, ICER
Perspective	Singapore healthcare system
Type of model	Partitioned survival model
Time horizon	10 years in the base case, 20 years modelled in sensitivity analysis
Health states	Progression-free, progressed, and death
Cycle length	1 week with half cycle correction
Extrapolation methods used to generate results	Spline models with 1, 2 and 3 knots, as well as parametric models, were fitted to each treatment arm for OS and PFS. In the base case, jointly fitted, spline models with 2 knots (hazards) were applied to OS, and independently fitted spline models with 2 knots (hazards) were applied to PFS. These were selected based on statistical fit and visual inspection. Time-on-treatment curves were mature enough and did not require extrapolating. Treatment effect was assumed to be consistent over the time horizon (no treatment waning).
Health-related quality of life	Utility values were informed by EQ-5D-5L data from KEYNOTE-811 using the UK algorithm and cross walked to EQ-5D-3L using van Hout (2012). Utilities were analysed using the time-to-death approach in the base case, based on the following values: • 0 to 30 days: 0.501 • 30 to 180 days: 0.769 • 180 to 360 days: 0.821 • ≥360 days: 0.865 • Grade 3 disutility: -0.042
Types of healthcare resources included	• Drug and drug administration • Disease management costs • Subsequent treatment costs • AE management costs • Terminal care costs

Abbreviations: AE, adverse events; CPS, combined positive score; EQ-5D-3L, EuroQoL 5 Dimension 3 Level; EQ-5D-5L, EuroQoL 5 Dimension 5 Level; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICER, incremental cost-effectiveness ratio; LY, life year; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QALY, quality-adjusted life year.

4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$135,000 and SG$165,000 per quality-adjusted life year (QALY) gained. The Committee considered the ICER to be uncertain and likely underestimated, in view of the following:

- The lack of OS benefit in the Asian subgroup raised uncertainty in the efficacy of pembrolizumab plus SOC. The Committee noted that this uncertainty could not be adequately addressed in the revised base case.

- The OS extrapolations in the model were considered optimistic. The jointly fitted spline model assumed that the treatment benefit of pembrolizumab plus SOC would persist over the entire time horizon. The Committee noted that the choice of extrapolation neither aligned with goodness-of-fit statistics nor clinical opinion.

- In the submission's base-case analysis, health utilities were estimated using a time-to-death approach, which applied utilities based on the length of time before death. The Committee noted this approach may not fully capture patients' experiences, as deteriorations in quality of life are often associated with both the stage and symptoms of the disease. Given these uncertainties, the Committee considered a health-state approach was more appropriate as it categorises utilities based on health states in the model.

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 alternative extrapolation approaches and application of utilities using the health-state approach, which further increased the base-case ICER.

4.4. The Committee noted that one-way sensitivity analysis and scenario analyses of the revised base case resulted in ICERs that remained unfavourably high. The key model drivers were the duration of subsequent treatment, health state utilities, and the relative dose intensity of pembrolizumab.

4.5. Overall, at the price proposed by the company, the Committee concluded that pembrolizumab plus SOC did not represent a cost-effective use of healthcare resources for patients with untreated locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma, whose tumours express PD-L1 (CPS ≥1).

Estimated annual technology cost

5.1. The Committee considered that the submission's financial estimates were uncertain due to inappropriate inputs, including an overestimation of the proportion of gastric and GEJ cancers that are adenocarcinomas.

5.2. 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.

5.3. Additionally, the Committee reviewed the company's proposed price-volume agreement (PVA) and concluded that its terms were unacceptable, as it would undermine the PVA's ability to provide budget certainty for payors.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing pembrolizumab on the MOH List of Subsidised Drugs, for use in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for patients with untreated locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma, whose tumours express PD-L1 (CPS ≥1). The decision was based on the unfavourable cost-effectiveness of pembrolizumab and an unacceptable pricing proposal from the company.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Approved clinical indication	Subsidy class	Eligible for MediShield Life claims (implementation date)
Pembrolizumab 100 mg/4 mL solution for infusion	Pembrolizumab in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for patients with untreated locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, whose tumours express PD-L1 (CPS≥1).	Not recommended for subsidy	Yes[1] (1 August 2025)

[1] Please refer to MOH's website for the MediShield Life claim limit starting from the implementation date.

VERSION HISTORY

Guidance on pembrolizumab for treating locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1. **Publication of guidance**

   Date of Publication 17 Feb 2025

2. **Guidance updated to include pembrolizumab on the Cancer Drug List**

   Date of Publication 4 Jun 2025

3. **Guidance updated to reflect MediShield Life claims eligibility**

   Date of Publication 1 Jun 2026

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

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 https://www.ace-hta.gov.sg/about-us/