Technology Guidance

Pembrolizumab

for treating persistent, recurrent, or metastatic cervical cancer

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 chemotherapy, with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in patients whose tumours express programmed death-ligand 1 with a combined positive score greater than or equal to 1. The decision was based on the uncertain extent of clinical benefit and unfavourable cost-effectiveness of pembrolizumab at the price proposed by 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 October 2023 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence submitted by the company and a review of the submission by one of ACE's evidence review centres for the technology evaluation of pembrolizumab when used in combination with chemotherapy, with or without bevacizumab, for treating persistent, recurrent, or metastatic cervical cancer in patients whose tumours express programmed death-ligand 1 (PD-L1) with a combined positive score greater than or equal to 1 (CPS ≥1).

1.2. Expert opinion was obtained from the MOH Cancer Drug Subcommittee and patient experts from local patient and voluntary organisations, who assisted ACE to ascertain the clinical value of pembrolizumab.

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. Approximately 95 patients are diagnosed with persistent, recurrent, or metastatic cervical cancer each year in Singapore. Most cervical cancer tumours express PD-L1, and the company requested a listing for patients whose tumours express PD-L1 with a CPS ≥1. The Committee noted that the company's requested listing for pembrolizumab was aligned with the approved HSA indication.

2.2. In local practice, most patients who have persistent, recurrent, or metastatic cervical cancer are treated with chemotherapy (cisplatin or carboplatin plus paclitaxel), with or without bevacizumab. While cisplatin, carboplatin, paclitaxel and some brand(s) of bevacizumab biosimilar are already subsidised, the Committee acknowledged the clinical need to consider pembrolizumab for funding, to improve treatment affordability and ensure appropriate patient care.

2.3. The Committee considered a testimonial from a local patient expert about how recurrent cervical cancer had negatively impacted her daily life physically, mentally and emotionally, and prevented her from working. The Committee noted that the fear of disease recurrence and the impact of her condition on her relationship with her partner were the patient's greatest concerns. The Committee also acknowledged that the patient had undergone surgery to remove a part of her cervix and had received chemotherapy at diagnosis and at first relapse. However, the chemotherapy was not effective, and the patient experienced side effects that significantly affected her confidence, self-esteem, and ability to rest. In addition, the patient had a colostomy and received immunotherapy in combination with chemotherapy at second relapse. The Committee heard that the patient considered any new treatments for recurrent cervical cancer should have fewer side effects, improve quality of life, have less impact on daily activities, and enable independent living.

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-826) that compared pembrolizumab with placebo in patients with PD-L1 CPS ≥1, who were also receiving chemotherapy, with or without bevacizumab. The submission presented results from the first interim analysis of KEYNOTE-826 (May 2021 data cut-off). At a median follow-up of 22 months, the results showed that progression-free survival (PFS) and overall survival (OS) were significantly longer in the pembrolizumab versus placebo group (Table 1 and Figure 1). However, the OS data were immature, as median OS was not reached in the pembrolizumab group at interim analysis.

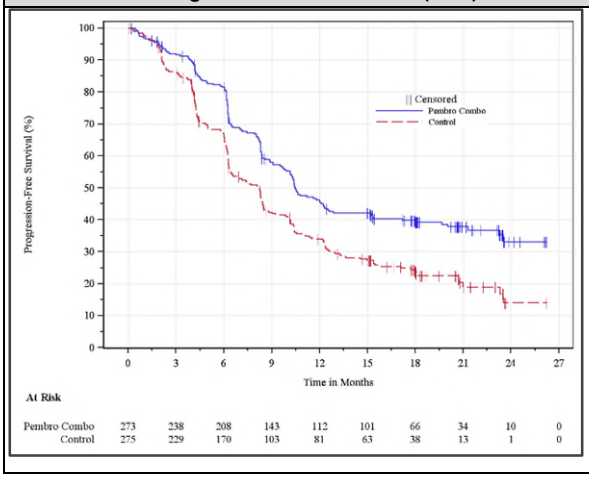
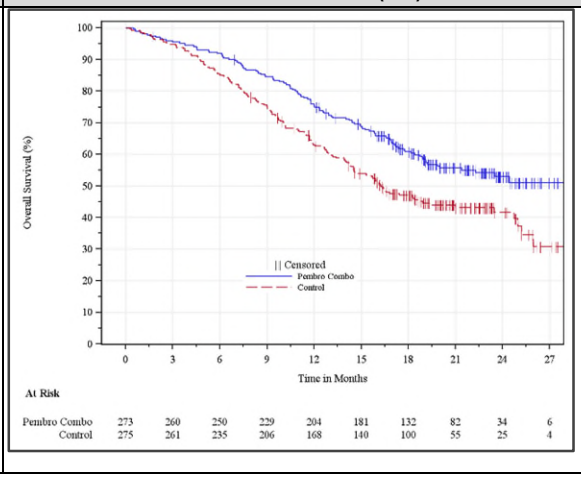
3.2. The Committee noted that clinical benefit in terms of OS was likely for the pembrolizumab group, given the separation of Kaplan-Meier (KM) curves between treatment groups (Figure 1). However, the duration and size of long-term benefit beyond the trial follow-up duration was uncertain, based on the immature OS data submitted. There was also no evidence in the submission nor literature to demonstrate a surrogate relationship between PFS and OS in cervical cancer. The Committee noted that the company had released the final OS results from KEYNOTE-826 recently. However, the results were not included in the submission, hence the Committee was unable to verify the updated findings. Overall, the Committee considered that uncertainty remained about the long-term survival resulting from pembrolizumab in combination with chemotherapy, with or without bevacizumab.

Table 1: Results of PFS and OS for patients with PD-L1 CPS ≥1 in KEYNOTE-826

May 2021 data cut-off	Pembrolizumab + chemotherapy ± bevacizumab (N=273)	Placebo + chemotherapy ± bevacizumab (N=275)
Progression-free survival (PFS)		
PFS events, n (%)	157 (57.5)	198 (72.0)
Median PFS, months (95% CI)	10.4 (9.7 to 12.3)	8.2 (6.3 to 8.5)
HR (95% CI)	**0.62 (0.50 to 0.77), p<0.0001**	
Overall survival (OS)		
Deaths, n (%)	118 (43.2)	154 (56.0)
Median OS, months (95% CI)	NR (19.8 to NR)	16.3 (14.5 to 19.4)
HR (95% CI)	**0.64 (0.50 to 0.81), p=0.0001**	

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached.
Bold indicates statistically significant result.

Figure 1: Kaplan-Meier curves for patients with PD-L1 CPS ≥1 in KEYNOTE-826

Progression-free survival (PFS)	Overall survival (OS)
	

3.3. In terms of safety, the trial showed that compared with placebo, more patients in the pembrolizumab group experienced grade 3 to 5 treatment-related adverse events (TRAEs; 68.4% vs 64.1%), serious TRAEs (30.3% vs 23%), and potentially immune-mediated adverse events (33.9% vs 15.2%). Nonetheless, the Committee noted that the safety profile of pembrolizumab in combination with chemotherapy, with or without bevacizumab, was consistent with the known safety profile of the individual treatments, and no new safety signals were observed.

3.4. Overall, the Committee considered the submission's claim of superior clinical effectiveness for pembrolizumab in combination with chemotherapy compared with chemotherapy (both with or without bevacizumab) was reasonable. However, long-term data was required to reliably determine the magnitude of survival benefit associated with pembrolizumab. The Committee also considered that the addition of pembrolizumab to chemotherapy, with or without bevacizumab, resulted in an inferior safety profile.

Cost effectiveness

4.1. The submission presented an economic evaluation based on the KEYNOTE-826 trial, in patients with persistent, recurrent, or metastatic cervical cancer, whose tumours express PD-L1 with a CPS ≥1. Pembrolizumab in combination with chemotherapy was compared with chemotherapy (both with or without bevacizumab) using a cost-utility analysis based on a semi-Markov state transition model with three health states. 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 persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 with a CPS ≥1
Outcomes	Total and incremental costs, total and incremental LYs gained, total and incremental QALYs gained, ICER
Perspective	Singapore healthcare system
Type of model	Semi-Markov state transition model
Time horizon	10 years in the model base case, based on a median follow-up of 22 months in KN826 trial
Health states	Three health states: • Progression-free • Progressed disease • Death
Cycle length	3 weeks (21 days)
Extrapolation methods used to generate results	A piecewise approach was used to extrapolate PFS and TTP for both treatment arms. The submission informed PFS and TTP using KM data from KN826 up to a specified cut-off point, after which parametric distributions were fitted. Cut-off points were identified from turning points in the hazard plots and the cumulative hazard plots. The submission selected a 37-week cut-off point, based on plausible visual fit and to align time points with the completion of tumour imaging assessment schedules. For PFS and TTP, the submission stated that the proportional hazards assumption did not hold and independently fitted log-logistic distributions to extrapolate the curves after 37 weeks in both treatment arms. For PPS, the submission stated that the proportional hazards assumption did not hold and fitted the curve independently using generalised gamma distributions to each arm. The selection of parametric survival distributions was based on AIC/BIC statistics, visual fit and clinical plausibility. No treatment waning was applied in the base case.
Health-related quality of life	Utility values were informed by EQ-5D-5L data from KN826 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: • 0-30 days: 0.431 • 30-90 days: 0.507 • 90-180 days: 0.640 • 180-360 days: 0.705 • ≥360 days: 0.760

Component	Description
	• Grade 3 disutility: -0.033
Types of healthcare resources included	• Drug and drug administration • Disease management costs • Subsequent treatment costs • AE management costs • Terminal care costs

Abbreviations: AE, adverse event; AIC, Akaike information criterion; BIC, Bayesian information criterion; CPS, combined positive score; EQ-5D-3L, EuroQoL 5 Dimension 3 Level; EQ-5D-5L, EuroQoL 5 Dimension 5 Level; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; KN826, KEYNOTE-826; LY, life year; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PPS, post-progression survival; TTP, time-to-progression; QALY, quality-adjusted life year.

4.2. In the submission, the base-case incremental cost-effectiveness ratio (ICER) was between SG$75,000 and SG$105,000 per quality-adjusted life year (QALY) gained. However, the Committee considered the ICER to be highly uncertain and likely underestimated, given the following:

- The model was highly sensitive to the extrapolation of time-to-progression (TTP) and PFS. Extrapolation in the submission's base case used the two-piece approach, where KM data from KEYNOTE-826 was applied up to 37 weeks and log-logistic parametric survival models were fitted to the remaining observed data. The Committee noted that this approach resulted in the estimation of substantial PFS and OS gains, which local clinical experts considered were overly optimistic. There was also limited OS evidence to support the long-term survival benefit modelled. The Committee acknowledged the limitations of the alternative one-piece extrapolation and maintained that the use of a piecewise approach to extrapolate the clinical trial data was a source of uncertainty in the model.

- To inform the risk of death after progression, the submission extrapolated post-progression survival (PPS) data from KEYNOTE-826 by fitting independent survival models to each treatment group. The Committee noted the uncertain clinical plausibility of the long 'tails' predicted in the model, especially in the context of immature OS evidence being used to support the extrapolated PPS data. Hence, a more conservative assumption was considered, where no treatment effect was assumed to persist beyond progression. Based on the totality of evidence submitted, the Committee concluded that it was more appropriate to use pooled PPS curves for both treatment groups in the base-case analysis.

- The submission assumed that, despite stopping pembrolizumab after a maximum of two years, the treatment effect would be maintained over the entire time horizon. The Committee acknowledged that results at the first interim analysis of KEYNOTE-826 showed no indication of treatment benefit decreasing over 17.2 months of follow-up. However, the overall immaturity of the OS data submitted suggested that the claim of sustained treatment effect for pembrolizumab was highly uncertain.

- In the submitted base-case analysis, health-state utilities were estimated using a time-to-death approach, in which utilities were applied based on the distribution of patients across different categories of time-to-death. However, the Committee noted that this approach potentially severed the link between progression status and health-related quality of life. Hence, the Committee considered it was more appropriate to inform utilities in the base case using the progression status approach, which categorised utilities based on each health state in the model.

4.3. The Committee considered the revised base case, which accounted for several uncertainties in the company's model. Key changes included using alternative extrapolation approaches for TTP and PFS, pooled PPS curves in both treatment groups, incorporating treatment waning, and applying utilities based on a progression status approach. These changes substantially increased the ICER to between SG$165,000 and SG$205,000 per QALY gained.

4.4. The Committee noted that, based on a one-way sensitivity analysis of the revised base case, the key model drivers were the discount rate for QALYs, health state utilities for the progression-free state, and time horizon. The Committee also noted that the use of different survival extrapolations and treatment waning assumptions resulted in a wide range of ICERs.

4.5. Overall, the Committee considered that pembrolizumab did not represent a cost-effective use of healthcare resources when used in combination with chemotherapy, with or without bevacizumab, for treating persistent, recurrent, or metastatic cervical cancer in patients whose tumours express PD-L1 with a CPS ≥1 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$5 million and SG$10 million over the first five years of listing pembrolizumab on the MOH List of Subsidised Drugs for treating persistent, recurrent, or metastatic cervical cancer in patients whose tumours express PD-L1 with a CPS ≥1.

5.2. The Committee considered that the submission's financial estimates were high, due to an overestimation of the number of eligible patients, treatment duration, and an optimistic uptake rate for pembrolizumab. 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, increasing to between SG$1 million and SG$3 million in the fifth year of listing.

Recommendations

6.1. Based on the evidence submitted, the Committee recommended not listing pembrolizumab on the MOH List of Subsidised Drugs, for use in combination with chemotherapy, with or without bevacizumab, for treating persistent, recurrent, or metastatic cervical cancer in patients whose tumours express PD-L1 with a CPS ≥1. The decision was based on the uncertain extent of clinical benefit and unfavourable cost-effectiveness of pembrolizumab at the price proposed by the company.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indication	Subsidy class	Eligible for MediShield Life claims (implementation date)
Pembrolizumab 100 mg/4 mL solution for infusion	Pembrolizumab, in combination with chemotherapy, for treating patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 with a CPS ≥1.‡	Not recommended for subsidy	Yes[1] (1 Mar 2024)
Pembrolizumab 100 mg/4 mL solution for infusion plus bevacizumab 100 mg/4 mL and 400 mg/16 mL concentrate for solution for infusion	Pembrolizumab, in combination with chemotherapy and bevacizumab, for treating patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 with a CPS ≥1.‡	Not recommended for subsidy	Yes[1] (1 Mar 2024)

‡revised clinical indication with effect from 1 Aug 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 persistent, recurrent, or metastatic cervical cancer

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 2 Jan 2024

2. **Guidance updated to revise the clinical indication for pembrolizumab**

   Date of Publication 1 Aug 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/